Transverse Relaxation of Cells Labeled with Magnetic Nanoparticles

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We describe the NMR relaxation properties of magnetically labeled cells. The cells are labeled with magnetic nanoparticles (SPIO, USPIO), which generate susceptibility contrast. The geometry of the labeled cells and the surrounding tissue is considered. We assume that the magnetic nanoparticles accumulate to form a magnetic core of radius R_C inside the cell. The correlation time τ, which describes the motion of spins around this core, is analyzed. Using the strong collision approach, explicit expressions are derived for the transverse relaxation rate R_2^* for tissue containing labeled cells as a function of the core radius, the diffusion coefficient, and the concentration of the nanoparticles. The predictions of this model agree well with numerical simulations and experimental data. Magn Reson Med 54:702–706, 2005. © 2005 Wiley-Liss, Inc.

Key words: transverse relaxation; magnetically labeled cells; strong collision

Magnetic resonance imaging of cells, such as macrophages or stem cells, will be of paramount interest for future diagnosis and therapy of many diseases. For example, unstable atherosclerotic plaques are responsible for most myocardial infarctions or brain strokes. Unstable plaques exhibit a higher degree of inflammation, which correlates with the number of macrophages inside the plaque. As regards to stem cells, it is expected that these cells may differentiate into specialized tissue cells and possibly return normal function to the affected organ. It is important to assess the migration and mobility dynamics of stem cells non-invasively to evaluate the effectiveness of the therapy approach, for example, in the brain (1) or in a myocardial infarct (2). The cells described above may incorporate Ultrasmall SuperParamagnetic Iron Oxide (USPIO) (3,4), which makes them become visible in MRI (5) by reducing transverse relaxation times in surrounding tissue.

In the presence of an external field, the superparamagnetic particles induce an inhomogeneous magnetic field $B(\mathbf{r})$ within and around the cells. Dephasing of the spin ensemble consists of two components: a coherent component related to the differing local frequencies $\omega(\mathbf{r}) = \gamma B(\mathbf{r})$ (γ = gyromagnetic ratio) of the spins, and an incoherent component, which results from stochastic phase modulations due to diffusion within this field. The proportion of each of these components depends on the motion regime to which the spin ensemble is subjected. This regime may be characterized by two parameters (6): first, the correlation time τ, which roughly denotes the mean time a spin is affected by a certain local frequency and which is a function of the diffusion coefficient and the shape of the inhomogeneous field; and, second, the average magnitude of the inhomogeneous field, which may be quantified by the variance of the local frequencies $\langle\omega(x)^2\rangle$or some characteristic frequency. When the dynamics of stochastic field fluctuations are slow compared to the magnitude of the field, $\tau\langle\omega(x)^2\rangle^{1/2} \gg 1$, and tend to the static dephasing regime, the coherent component dominates. In the opposite case, for very fast fluctuations $\tau\langle\omega(x)^2\rangle^{1/2} \ll 1$ (motional narrowing limit), the incoherent component is more important.

Most approaches that derive transverse relaxation rate for diffusing spins within an inhomogeneous field have focused on one of the limiting motion regimes mentioned above. The literature on the motional narrowing limit is abundant. The static dephasing regime has been considered for various field distributions by Yablonskiy and Haake (7). An extension was derived by Kiselev and Posse (8), considering the diffusion of spins within local linear gradients. To our knowledge, only 2 approaches exist that focus on the whole dynamic range. One is the Gaussian approximation. This approach assumes a Gaussian shaped probability distribution of the phase angle over time. This model was first presented by Anderson and Weiss (9); it was first used in MRI by Kennan and coworkers (10). Sukstanskii and Yablonskiy (11) applied the Gaussian approximation to study MR signal formation in the presence of mesoscopic structure-specific magnetic field inhomogeneities. Another approach, presented recently (12–15), approximates the diffusion dynamics by more simple stochastic transition dynamics.

In this article, we apply this strong collision approximation to determine spin dephasing in the case of magnetically labeled cells. To study the relaxation process over the whole dynamic range, we replace the exact time evolution of transverse magnetization determined by the Bloch–Torrey equation (16) by a strong collision approximation. The basic idea behind this approach is that the new generator of time evolution conserves the 2 point correlation time of the original diffusion mediated field fluctuations. The strong collision approach is the first order approximation of a systematic "extended" strong collision approximation, which retains also higher order correlation times (13). In contrast to other approaches that describe only one diffusion regime, the strong collision approximation is not based on any assumption of local field strength $\delta\omega$ or correlation time τ. The strong collision approximation leads directly to an expression for the relaxation time that

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is valid for all diffusion regimes. To illustrate the usefulness of the theory, we check the limiting cases and study the dependence of the relaxation rate on different parameters.

MODEL OF THE LABELED CELLS

We have chosen to model the situation in which small paramagnetic particles (SPIO, USPIO) have been incorporated by stem cells or macro-phages. We assume that every cell contains approximately the same number of particles and that they form a spherical impermeable core with radius R_C and volume $4/3\ \pi\ R_C^3$. Furthermore, we assume that the volume fraction of magnetic material, η, is much smaller than 1. Under these conditions the inhomogeneous field around this core is approximately that of a magnetic dipole, that is, in spherical coordinates (r,θ,φ):

$$B(\mathbf{r}) = \mu_0 \frac{\Delta M}{3} R_C^3 \frac{3\cos^2\theta - 1}{r^3}, \qquad [1]$$

where $\Delta M = M_C - M_T$ is the difference between the magnetization of the core M_C and the surrounding tissue M_T. Introducing the characteristic equatorial frequency shift $\delta\omega = \gamma|B(r = R_C,\ \theta = \pi/2)| = \gamma\mu_0\Delta M/3$ where γ is the gyromagnetic ratio, we have

$$\omega(\mathbf{r}) = \delta\omega\ R_C^3 \frac{3\cos^2\theta - 1}{r^3}. \qquad [2]$$

We now assume homogeneous diffusion properties outside the magnetic core, that is, we neglect potential diffusion restrictions by membranes or other structures. The volume of the core is considered as a forbidden region. This is an important consideration as it is known that the relaxation rate is affected by the assumed boundary condition at the core (17). Instead of considering diffusion in the whole tissue, we focus only on the mean spherical volume per labeled cell, that is, $4/3\pi R^3 = 1/c$, where c is the cell density. Diffusion is then restricted to the space between two concentric spheres with radii R_C and R, that is, periodic boundary conditions are assumed. It is important to emphasize that the sphere with radius R is only a mathematical boundary and has nothing in common with the cell nucleus or cell membrane. The rationale for this restriction and its mathematical implications for evaluation of diffusion have already been discussed in detail (18).

THEORY

We consider diffusion of spins in a medium with a uniform diffusion constant D. The diffusion takes place in an inhomogeneous magnetic field, for example, the field around a dipole given by Eq. [1]. The time evolution of the local transverse magnetization $m(\mathbf{r},t)$ is given by the Bloch–Torrey equation (16) $\partial_t m(\mathbf{r},t) = [D\nabla^2 + i\omega(\mathbf{r})]\ m(\mathbf{r},t)$ where $m(\mathbf{r},t) = m_x(\mathbf{r},t) + \mathrm{i}m_y(\mathbf{r},t)$ is the notation in polar form of the magnetization that is generated at point $\mathbf{r}$. The local precession frequency $\omega(\mathbf{r})$ is determined by the geometry of the problem, in our case by Eq. [2]. After formal time integration of the Bloch–Torrey equation, we obtain $m(\mathbf{r},t) = \exp([D\nabla^2 + i\omega(\mathbf{r})]t)\ m(\mathbf{r},0)$ and for the signal from the whole sample we get

$$M(t) = \frac{1}{V}\int_v \mathrm{d}^3\mathbf{r}\, e^{[D\nabla^2 + i\omega(r)]t}\ m(\mathbf{r},0) \qquad [3]$$

In our case the sample volume V is the space between the magnetic core and the surface of the relaxation sphere: $V = 4/3\pi(R^3 - R_C^3)$. There are a few geometrically determined functions $\omega(\mathbf{r})$ for which the Bloch–Torrey equation can be solved analytically, for example, when $\omega(\mathbf{r})$ is the local precession frequency in a linear gradient field. For more sophisticated functions $\omega(\mathbf{r})$, such as the field around cylinders and spheres, only numerical calculations or computer simulations may be applied to determine the time course of the transverse magnetization. The starting point for such calculations, for example, Monte Carlo simulations, is the integral given in Eq. [3]. A reasonable approach for describing the relaxation process over the whole dynamic range is the *strong collision approximation*, which consists in replacing the diffusion operator $D\nabla^2$ in Eq. [3] by a *strong collision operator* (14). This approach is primarily applied to processes where the relaxation time describing the contribution of field inhomogeneities is longer than the correlation time. However, it can be shown that this approach can be extended to all dynamics of field fluctuations (13) and that it is also applicable in all diffusion regimes.

As shown in previous work (12), it is more suitable to consider the Laplace transform of the magnetization decay, that is,

$$\hat{M}(s) = \int_0^\infty \mathrm{d}t e^{-st} M(t). \qquad [4]$$

Replacing the diffusion operator in the expression for the signal from the whole sample (Eq. [3]) and performing the Laplace transformation, we find (12)

$$\hat{M}(s) = \hat{M}_0(s + \tau^{-1}) + \tau^{-1}\cdot\hat{M}_0(s + \tau^{-1})\cdot\hat{M}(s) = \frac{\hat{M}_0(s + \tau^{-1})}{1 - \tau^{-1}\cdot\hat{M}_0(s + \tau^{-1})}, \qquad [5]$$

where $\hat{M}_0(s)$ is the Laplace transform of the time course of the magnetization in the absence of diffusion (static dephasing) in a magnetic field around the sphere, where the local frequency is given by Eq. [2]. The integration over the relaxation volume is straightforward and leads us to the following expression:

$$\hat{M}_0(s) = \frac{1}{V}\int_v \mathrm{d}^3\mathbf{r}\ \frac{1}{s - \mathrm{i}\omega(\mathbf{r})} = \frac{1}{1-\eta}\frac{1}{s}\left[G\left(\eta\frac{\delta\omega}{s}\right) - \eta G\left(\frac{\delta\omega}{s}\right)\right], \qquad [6]$$

where

$$G(x) = \frac{2}{3}(1 - 2ix)\sqrt{\frac{1}{3}\left(1 - \frac{i}{x}\right)}\operatorname{arccoth}\sqrt{\frac{1}{3}\left(1 - \frac{i}{x}\right)} + \frac{1}{3}. \quad [7]$$

After an inverse Laplace transform of this expression, we arrive at the time course of the magnetization. This means that the Laplace transform $\hat{M}(s)$ provides all the information about the relaxation process. The inverse Laplace transform of Eq. [5] is not possible analytically, and to solve it numerically is cumbersome. In the limit $\eta \ll 1$, an exact time course of the magnetization $M_0(t)$ in the static dephasing regime ($D = 0$) has been determined in the publication of Yablonskiy and Haacke (7). In order to determine the transverse relaxation time T_2^*, we assume a time evolution of the magnetization of the form $M(t) = exp(-t/T_2^* + i\Omega t)$, where Ωt is an unknown phase factor. If we insert this function into the definition of the Laplace transform (Eq. (4)), we obtain $\hat{M}(s) = 1/(R_2^* - i\Omega + s)$. After setting $s = 0$, we find that

$$R_2^* = \frac{1}{T_2^*} = \mathrm{Re}\left[\frac{1}{\hat{M}(0)}\right] = \frac{1}{\tau}\mathrm{Re}\left[\frac{1-\eta}{G(\eta\tau\delta\omega) - \eta G(\tau\delta\omega)} - 1\right], \quad [8]$$

This method for determining T_2^* is well known from the mean relaxation time approximation (19), where the relaxation time is the first long-time moment of the magnetization decay, that is, $T_2^* = \mu_{-1}[M(t)]$. We use a small s limit of the Laplace transform of the magnetization decay to define R_2^*, which reflects the signal behavior for long times, although measurements of R_2^* are normally obtained with short echo times.

We determine the correlation time from relaxation dynamics in the motional narrowing limit. This range is characterized by $\tau\delta\omega \ll 1$ and the transverse relaxation rate is

$$R_2^* = \tau\langle\omega^2(\mathbf{r})\rangle. \quad [9]$$

Brooks and colleagues (20) determined the relaxation rate within this range for an impermeable core as

$$R_2^* = \frac{16}{45}\eta\delta\omega^2\frac{R_C^2}{D}. \quad [10]$$

For a permeable core, the prefactor *16/45* has to be replaced by *8/25* (21). For the correlation time that we use for determination of the relaxation rate in Eq. [8]. we obtain the result

$$\tau = \frac{4}{9}\frac{R_C^2}{D} \quad [11]$$

for an impermeable core, and for a permeable core the prefactor *4/9* has to be replaced by the prefactor *2/5*.

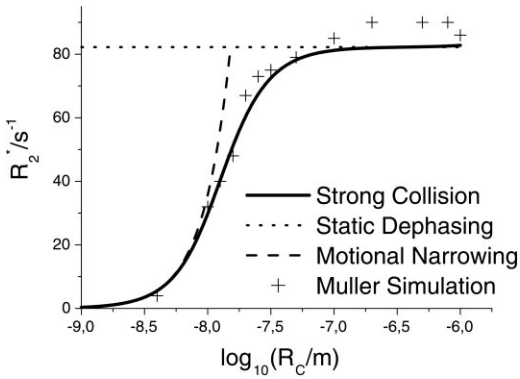

FIG. 1. R_2^* dependence for different sphere radii R_C. The continuous line is obtained from Eq. [8] using parameters $\eta = 2{\cdot}10^{-6}$, $\delta\omega = 34{\cdot}10^6$ Hz, and $D = 2.3$ μm^2 ms^{-1}. Crosses are $1/T_2^*$ versus sphere radius for Muller simulation. If the condition $log_{10}(R_C/m) \gg -6.746$ is fulfilled (12), the static dephasing regime predictions ($R_2^* = \frac{2\pi}{3\sqrt{3}}\eta\delta\omega$) coincide with our results.

APPLICATIONS

The transverse relaxation of superparamagnetic loaded cells in the static dephasing limit was studied extensively by Bowen and coworkers (22). This limit describes the effect of magnetic field variations on static spins. The spin is permanently exposed to the same magnetic field $\omega(\mathbf{r})$. This approximation is valid if stochastic field fluctuations due to diffusion are much slower than spin precession caused by local frequency variations. The condition for which the static dephasing region theory applies is given in Eq. [55] of the work by Yablonskiy and Haacke (7), as follows:

$$\frac{R_C^2}{D}\delta\omega\frac{\sqrt[3]{\eta}}{6} \gg 1. \quad [12]$$

The dependence of relaxation rate on the radius of spherical particles is the main application of our results. The diffusion regime is determined by the relative values of τ and $\delta\omega$. Since $\delta\omega$ is independent of the sphere radius, the diffusion regime depends solely on the correlation time, $\tau \propto R_C^2/D$. Therefore, for small spheres, the motional narrowing limit ($1/\tau \gg \delta\omega$) applies, and for large spheres, the static dephasing regime (12) applies. Fig. 1 shows that the results of the strong collision model (8) are in close agreement with numerical simulations by Muller and colleagues (23) and also with data obtained from the motional narrowing and static dephasing limits in the region where their approximations are valid.

To show that our results are valid over the whole dynamic range, we compare our results with those of Jensen and Chandra (24) and Yung (6). Jensen and Chandra interpolated the whole dynamic range by adding the relaxation time from the static dephasing limit $R_2^* = 3k\eta\ \delta\omega$ (with $k \approx 0.4031 \approx 2\pi/(9\sqrt{3})$for compact objects) and motional narrowing (Eq. [10]),

$$T_2^* = \frac{5}{4\eta\tau\delta\omega^2} + \frac{1}{3k\eta\delta\omega}. \quad [13]$$

The same result was found by Yung (6) empirically who considered the scaled relaxation rate $y^* = 1/(\eta\,\delta\omega\,T_2^*)$ and radius $x = \sqrt{\delta\omega/D}\,R_C$

$$y^*: = \frac{cx^2}{1 + \frac{c}{d}\,x^2}, \qquad [14]$$

with $c = 16/45$ and $d = 3k$. In Fig. 2 we compare the prediction of our strong collision model (normalization of the plot in Fig. 1) with Eq. [14].

We see a good agreement between the strong collision result and the empiric model for all values of the sphere radius R_C. For quantification of the improvement in accuracy obtained by using our theory, we compare the predictions of the strong collision theory versus the interpolation formula Eq. [13]. For example, using the data of Fig. 1, the maximum relative error of the interpolation formula is *0.222*; using the strong collision theory, we obtain a maximum relative error of *0.099*.

To study the dependence of the relaxation rate R_2^* on the equatorial frequency shift δω, we compare in Fig. 3 our results from Eq. [8] with the limiting cases and Monte Carlo simulations of Jensen and Chandra (see Fig. 1 in (24)). We see good agreement between the strong collision result, the Jensen and Chandra simulations, and the limiting cases. In addition, the transition between the diffusion regimes can be identified, and the inflection point (see Fig. 3) agrees with the prediction of Yablonskiy and Haacke (12).

DISCUSSION AND CONCLUSIONS

Based on a simple model geometry of magnetically labeled cells and surrounding tissue, we have derived an analytical expression for the transverse relaxation rate as a function of the volume fraction of the USPIOs, the radius of the magnetic core, the magnetization difference, and the diffusion coefficient. The method that allowed this analytical approach was the application of the strong collision approach to the dynamics of spin diffusion. Based on the picture of spins diffusing around a sphere, two frequency scales characterizing the underlying relaxation mechanism are present. The dynamic frequency scale $1/\tau$ characterizes the stochastic process of diffusion using the correlation of moving spins. The magnetic frequency scale characterized by the equatorial frequency δω specifies the relaxation caused by the local field inhomogeneity of the magnetic sphere. Comparing the two frequencies, we can distinguish different diffusion regimes. Analytical expressions for the relaxation time T_2^* exist for each; the application of such an analytical expression assumes knowledge of the underlying regime. Knowing the characteristics of tissue, that is, the characteristic magnetic field shift δω and the dynamic frequency $1/\tau$, leads to a decision about which approximation should be applied. In the case of magnetic labeled cells, the analysis can be reversed. A measurement of the relaxation time T_2^* could provide information about the tissue. A quantitative description, which is valid for the whole range of frequencies and contains the two limiting cases (motional narrowing and static dephasing), has been derived in this paper.

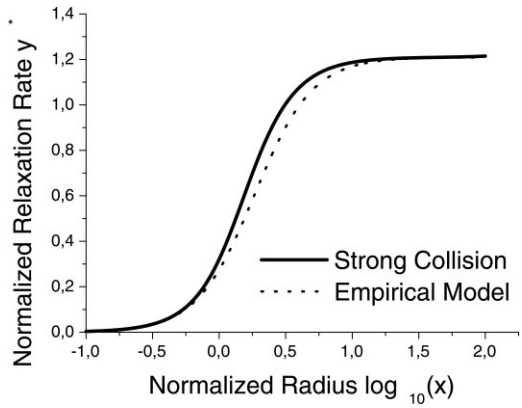

FIG. 2. Normalized R_2^* dependence on the normalized sphere radius R_C. The continuous line is obtained from Eq. [8]; the dotted curve corresponds to the interpolation model (14) with parameters $c = 16/45$ and $d = \frac{2\pi}{3\sqrt{3}}$.

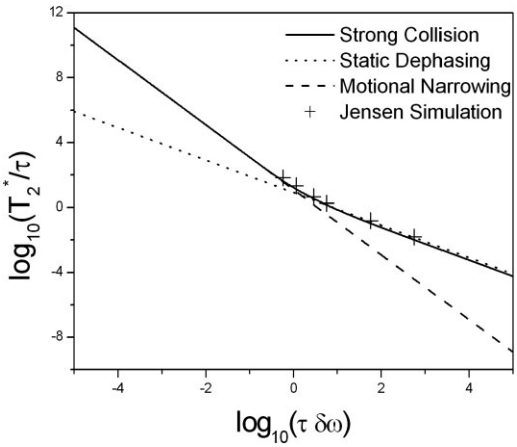

FIG. 3. Comparison of the strong collision approximation (Eq. [8]) with Jensen and Chandra simulations for a volume fraction $\eta = 0.1$. The asymptotes are the limiting cases obtained from Eq. [10] for the motional narrowing limit and $R_2^* = 3k\eta\,\delta\omega$ for the static dephasing limit. From Eq. [12] we obtain the value $log_{10}(\tau\,\delta\omega) \gg 0.76$ for the validity of the static dephasing regime.

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REFERENCES

1. Zelivyanskaya ML, Nelson JA, Poluektova L, Uberti M, Mellon M, Gendelman HE, Boska MD. Tracking superparamagnetic iron oxide labeled monocytes in brain by high-field magnetic resonance imaging. J Neurosci Res 2003;73:284–295.
2. Kraitchman DL, Heldman AW, Atalar E, Ammado LC, Martin BJ, Pittenger MF, Hare JM, Bulte JWM. In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. Circulation 2003; 107:2290–2293.

3. Yeh TC, Zhang W, Ildstad ST, Ho C. Intracellular labeling of T-cells with superparamagnetic contrast agents. Magn Reson Med 1993;30: 617–625.
4. Yeh TC, Zhang W, Ildstad ST, Ho C. In vivo dynamic MRI tracking of rat T-cells labeled with superparamagnetic iron-oxide particles. Magn Reson Med 1995;33:200–208.
5. Weissleder R, Cheng H, Bogdanova A, Bogdanova A Jr. Magnetically labeled cells can be detected by MR imaging. J Magn Reson Imaging 1997;7:258–263.
6. Yung KT. Empirical models of transverse relaxation for spherical magnetic perturbers. Magn Reson Imaging 2003;21:451–463.
7. Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues: the static dephasing regime. Magn Reson Med 1994;32:749–763.
8. Kiselev VG, Posse S. Analytical theory of susceptibility induced NMR signal dephasing in a cerebrovascular network. Phys Rev Lett 1998;81: 5696–5699.
9. Anderson PW, Weiss PR. Exchange narrowing in paramagnetic resonance. Rev Mod Phys 1953;25:269–276.
10. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. Magn Reson Med 1994;31:9–21.
11. Sukstanskii AL, Yablonskiy DA. Gaussian approximation in the theory of MR signal formation in the presence of structure-specific magnetic field inhomogeneities. J Magn Reson 2003;163:236–247.
12. Bauer WR, Nadler W, Bock M, Schad LR, Wacker C, Hartlep A, Ertl G. Theory of the BOLD effect in the capillary region: an analytical approach for the determination of T2 in the capillary network of myocardium. Magn Reson Med 1999;41:51–62.
13. Bauer WR, Nadler W. Spin dephasing in the strong collision approximation. Phys Rev E 2002;65:066123.
14. Bauer WR, Nadler W, Bock M, Schad LR, Wacker C, Hartlep A, Ertl G. Theory of coherent and incoherent nuclear spin dephasing in the heart. Phys Rev Lett 1999;83:4215–4218.
15. Bauer WR, Nadler W, Bock M, Schad LR, Wacker C, Hartlep A, Ertl G. The relationship between T2* and T2 in myocardium. Magn Reson Med 1999;42:1004–1010.
16. Torrey HC. Bloch Equations with diffusion terms. Phys Rev 1956;104: 563–565.
17. Gossuin Y, Gillis P, Lo Bue F. Susceptibility-induced T(2)-shortening and unrestricted diffusion. Magn Reson Med 2002;47:194–195.
18. Bauer WR, Schulten K. Theory of contrast agents in magnetic resonance imaging: coupling of spin relaxation and transport. Magn Reson Med 1992;26:16–39.
19. Nadler W, Schulten K. Generalized moment expansion for Brownian relaxation processes. J Chem Phys 1985;82:151–160.
20. Brooks RA, Moiny F, Gillis P. On T2-shortening by weakly magnetized particles: the chemical exchange model. Magn Reson Med 2001;45: 1014–1020.
21. Jensen JH, Chandra R. NMR relaxation in tissues with weak magnetic inhomogeneities. Magn Reson Med 2000;44:144–156.
22. Bowen CV, Zhang X, Saab G, Gareau PJ, Rutt BK. Application of the static dephasing regime theory to superparamagnetic iron-oxide loaded cells. Magn Reson Med 2002;48:52–61.
23. Muller RN, Gillis P, Moiny F, Roch A. Transverse relaxivity of particulate MRI contrast media: from theories to experiments. Magn Reson Med 1991;22:178–182.
24. Jensen JH, Chandra R. Transverse relaxation time field dependence for tissues with microscopic magnetic susceptibility variations. Proc Int Soc Magn Reson Med 1999:656.