Theory of MR Signal Decay in the Presence of Superparamagnetic Nanoparticles.

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Here we present a theoretical analysis of the MR signal formation in the presence of mesoscopic inhomogeneous magnetic field induced by MR superparamagnetic contrast agent. The contrast agent is considered as a set of spherical magnetized inclusions of radius R occupying a volume fraction ζ. The theory is based on a Gaussian approximation for the distribution of phases accumulated by diffusing spins.

A superparamagnetic iron oxide nanoparticle (MION, etc.) (1, 2) consists of a single-crystal inner core of R about 2.3 nm, containing about n = 2000 atoms of Fe organized in the inverse spinel-type lattice, covered by a shell of surface-bound dextran molecules. The configuration of dextran molecules is rather flexible and may allow some water diffusion within the shell but outside the core. As the characteristic diffusion time $t_D = R^2/D$ (D is the water diffusion coefficient) ranges in nanoseconds, the signal decay can be described in terms of a standard relaxation rate ΔR_2 for SE signal (ΔR_2^* for FID signal). Assuming an average magnetic moment μ per Fe atom, the following expression for the relaxation rate can be derived:

[1] $$\Delta R_2 \; ; \; \Delta R_2^* = \frac{\pi}{15}\left(\frac{8\gamma\mu}{3}\right)^2 \frac{\lambda N_a n}{D R}.$$

In [1] N_a is Avogadro's number, λ is a molar concentration of Fe in the solution, γ is the gyromagnetic ratio.

Using experimentally found (1) the relaxation rate of MION in the aqueous solution ΔR_2 =34.8 (mM·sec)$^{-1}$, and R=2.3 nm, $\gamma = 2.675\cdot 10^8$ (sec·T)$^{-1}$, D = 2.5 μm^2/msec, n=2000, we estimate the magnetic moment per 1 atom Fe: $\mu = 1.34\mu_B$ ($\mu_B = 0.93\cdot 10^{-20}$ erg/Gauss is Bohr's magneton) which is typical for spinel-type ferrites.

By making use of numerical Monte-Carlo simulations of the signal, we calculate a mean square error ε introduced by the Gaussian approximation and propose the validity criterion of the latter. To achieve an accuracy of ε < 10%, the following condition should be met:

[2] $$\frac{3\zeta D}{4\pi\gamma M R^2} > 0.01.$$

In [2] $\zeta = \lambda N_a v_0 / n$ is the volume fraction of magnetized particles, $M = n\mu / v_0$ is the particle's magnetization, $v_0 = 4\pi R^3/3$ is a single particle volume.

For fixed M and R, the inequality [2] sets a lower limit for the volume fraction: $\zeta > 10^{-3}$,. or λ > 60 mM.

If nanoparticles are compartmentalized within cells with impermeable membranes, a cell loaded by nanoparticles can be considered as a single magnetized "particle" with an average magnetization $M_c = \zeta M$ within a cell. For μm-size cells, the characteristic diffusion time t_D is on the order of milliseconds and the MR signal from the extracellular space should be described by means of general expression for the attenuation function $\Gamma = -\ln(S/S_0)$ rather than ΔR_2. The short- and long-time expansions of the function $\Gamma(t)$ for the FID and SE signals have the form:

[3]
$$\Gamma_{FID}(t) \; ; \; \Gamma_0 \cdot \left[\frac{1}{2}\tau^2 - \frac{3}{2}\tau^3 + \frac{144}{35\pi^{1/2}}\tau^{7/2}\right]$$
$$\Gamma_{SE}(t) \; ; \; \Gamma_0 \cdot \left[\frac{3}{4}\tau^3 - \frac{36(4-\sqrt{2})}{35\pi^{1/2}}\tau^{7/2}\right] \qquad \tau < 1;$$

$$\Gamma_{FID}(t) = \Gamma_0 \cdot \left[\frac{4\tau}{9} - \frac{2}{3}\left(\frac{\tau}{\pi}\right)^{1/2} + \frac{11}{81}\right],$$
$$\Gamma_{SE}(t) = \Gamma_0 \cdot \left[\frac{4\tau}{9} - \frac{2(\sqrt{8}-1)}{3}\left(\frac{\tau}{\pi}\right)^{1/2} + \frac{11}{27}\right] \qquad \tau > 1,$$

where $\tau = t/t_D$, t is time after a RF pulse for FID and echo time for SE signal, $\Gamma_0 = 4/45\cdot(4\pi\gamma M_c R_c^2/D)^2$, R_c is the cell radius. Note that these expressions qualitatively and quantitatively differ from those obtained for the inclusions with permeable surfaces (3). It is important to emphasize that even for very large τ the second term ($\sim \tau^{1/2}$) in the long-time expansions may substantially contribute to $\Gamma(t)$. For fixed cell's size and volume fraction, the validity condition of the Gaussian approximation sets an upper limit on M_c: $M_c < 75\zeta_c D/\pi\gamma R_c^2$, ζ_c is a cells' volume fraction. For example, for R_c = 3 μm, ζ_c = 0.01, D =1 μm^2/msec, M_c should be less than 1 mG. For higher magnetization, the Gaussian approximation fails and the signal can be described in the framework of the static dephasing regime (4). This was recently demonstrated in experiments with superparamagnetic nanoparticles (SHU 555A, SHU 555C) compartmentalized within THP-1 cells (5).

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