Relaxation with Diffusion near Magnetic Particles and Cells: Analytical Description and Experiment

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Introduction: A number of theoretical models have been proposed to describe the relaxation of MRI signal in the presence of mesoscopic field inhomogeneities such as capillaries carrying oxygenated blood or cells containing superparamagnetic iron oxide (SPIO). Based on the physical extent and magnitude of the field perturbations, as well as the local diffusion coefficient, signal behaviour can be classified into a number of regimes, such as the static dephasing regime (SDR) [1] in which diffusion can be neglected. For the case of spherical perturbers in the SDR, the FID has been characterized [1], as has the signal at the echo time TE of a single- or multiple-spin-echo sequence [2,3]. However, the complete signal behaviour throughout a spin echo is not well described in cases where diffusion cannot be neglected. In conjunction with high temporal resolution relaxometry techniques such as TurboSPI [4], a better understanding of the signal time course would allow additional physiological parameters (such as independent estimates of cell density and iron loading level) to be extracted while isolating unwanted effects such as macroscopic inhomogeneity. We present a revised analytical model that describes the complete spin-echo signal, and compare it to both experimental data and Monte Carlo simulations.

Theory: Our model is based on the earlier model of Kiselev and Posse [5] which was formulated for networks of cylindrical magnetic perturbers, to study diffusion in microvessels. We consider instead the case of spherical particles, which require the model to incorporate the three-dimensional field perturbation:

\[
\omega(\mathbf{r}, R, \theta) = \delta \omega R^3 \left( \frac{3 \cos^2 \theta - 1}{2} \right) \delta \omega = 4 \pi \gamma \chi B_0
\]

The main field strength is \(B_0\) and the particle susceptibility is \(\chi\). Assuming that the volume fraction \(\zeta\) occupied by the perturbers is small and that they have a uniform radius \(R\), the complete analytical expression for the time-dependent signal evolution during the spin echo due to the presence of the perturbers can be calculated:

\[
s(t) = e^{-\delta \omega F} s^{FE} = \int_0^\infty \frac{d\mathbf{r}}{2} \int_0^\infty \frac{d\theta}{\sqrt{2 \pi}} \exp \left( -i \left( 3 \cos^2 \theta - 1 \right)(t - \tau) - 3 \lambda \eta (F/2) \right) s(\mathbf{r}) \omega(\mathbf{r}, R, \theta)
\]

Asymptotic expressions for \(t >> \tau\) also match those derived in [1,2] as \(D=0\) but contain additional \(\lambda\)-dependent terms. Similar analytic approximations to eqn.2 may be found for times close to \(\tau\), which should remain valid as long as the diffusion path is sufficiently small (conditions for which are suggested in [2], [3], and [5]).

Methods: For a given set of parameters (\(D, R, \chi, \tau\)), equation 2 can be numerically integrated over an appropriate time window to give the model’s prediction of the signal behaviour. For comparison, Monte Carlo simulations were performed of diffusing protons near a network of magnetic perturbers. Impermeable spheres of radius \(R\) are randomly distributed within a cubical universe, filling it to a volume fraction \(\zeta\). Diffusion is modelled as a random walk, with each step a randomly-oriented 3D vector of length \(\sqrt{6D\Delta t}\), \(\Delta t = 100\mu s\). \(N=10^3\) protons are used in each simulation, with a new network of spheres generated every 100 protons. The magnetic field at each step is the sum of the fields from all of the spheres inside the cube, with a phase reversal at \(t=\tau\) to simulate a spin-echo pulse. The sum of all proton magnetizations becomes the simulated MRI signal. Experimental data was acquired for validation of the model and simulations, using micron-sized iron oxide particles (0.96μm diameter MPIO, Bangs Laboratories) and C3 cancer cells labelled with 35nm Molday-Ion Rhodamine B (BioPAL Inc.). Cells had an average diameter of \(8\mu m\) and a mean radius of \(7\mu m\). All data were acquired on a 3T horizontal bore MRI system with a sliceselective RF coil equipped with a 5cm i.d. NMR tubes containing labelled cells or MPIO particles (suspended in 4% gelatin) which were imaged with TurboSPI, permitting the collection of spatially-resolved relaxation data at high temporal resolution. \(T_1\), susceptibility and ADC were also measured for each tube and used as inputs for the analytical model and Monte Carlo simulations.

Results: Figure 1 shows the MR signal behaviour around the spin echo center for typical experimental data (black) as well as the analytical model predictions (blue), Monte Carlo simulations (red) and static dephasing predictions (green) with matched parameters. All tubes tested showed similar behaviour. Figure 1a shows the signal behaviour for labelled cells while Figure 1b shows the behaviour of MPIO particles. Predictions by the static dephasing model [1] agree with the data far from the echo center, but deviate significantly near TE due to diffusion effects. In particular, the spin echo peak is shifted, with a maximum somewhat earlier than TE, and this shift is more pronounced with smaller particles. This shift is larger than that predicted by the static model alone, and is reproduced by both our proposed slow diffusion model and Monte Carlo simulations.

Discussion: For both labelled cells and MPIO particles, there is good agreement between experimental data, the model output and the Monte Carlo simulations, with some deviations observed for small particles and long times away from the spin-echo center. We anticipate that the simulations will prove useful in defining the range of parameters over which the model remains valid. One advantage of this model is that it provides an exact expression for the signal throughout the entire spin echo, not just at \(t=\tau\) or \(t>>\tau\). Though this expression is not currently suitable for fitting the experimental data, we are developing approximations valid around the spin echo center which should be suitable for extracting estimates of perturber parameters (such as volume fraction and susceptibility) from TurboSPI data. In applications involving loaded cells, this may permit decoupling of cell density from the iron loading level, which is not possible with quantitative techniques that yield \(R_s^2\) alone. The ability to directly measure these quantities would be of significant use in the tracking of labelled cell populations, particularly in longitudinal studies that involve label dilution.

References: