On the Monte-Carlo simulation of hundreds of biological cells charged with lots of hundreds of superparamagnetic nanoparticles

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Synopsis

Simulation of superparamagnetic-particle charged cells is a challenge for Monte Carlo (MC) simulations. Especially the high number of particles involved pose a problem when practical limits in computational power is to be considered. We discuss the replacement of many cells charged with particles by fewer cells. We show that the diffusion regime then may be conserved by proper scaling of the MC model.

Introduction

Superparamagnetic (nano-) particles used as contrast agents in magnetic resonance imaging may open the window towards molecular imaging as, e.g., cell tracking. The MR contrast is given by effects due to the susceptibility of the particles (signal extinction due to intra-voxel dephasing) and, in the slow diffusion regime up to the motional averaging diffusion regime, by effects due to diffusion of the particles behind the particles [1]. To account for diffusion effects, Monte-Carlo (MC) simulations have been proposed and performed in the past. However, the nanoparticles are much smaller than the cells; they are even too small to be modeled individually. When modeling a charged cell charges with nanoparticles, the question arises which susceptibility is to be chosen. The answer might be simply guessed by smearing out the particles across the cell. However, taking into account the diffusion mechanism, the equation describing the diffusion regime is to be fulfilled and the answer is more complicated than it looks at a first glance. The scope of the presented work is to established an appropriate theory for correct MC modeling..

Methods

The diffusion regime is determined by the product of the transverse correlation time τ_D and the magnetic frequency $\Delta\omega_r$ i.e. $\Delta\omega_r \cdot \tau_D \propto \chi R^2/D = \text{const.}$ [Eq. 1]. Here χ is the susceptibility of the superparamagnetic charged cell and D is the diffusion constant of water protons. The dipole strength of an iron-charged cell of volume ΔV and magnetization M is given by $p_m = M\,\Delta V \propto N\,\chi\,R^3$ [Eq. 2] where N is the number of particles in the cell and R is their radius.

To conserve the diffusion-regime while replacing N particles with radius R in the cell by one charged cell of radius R' with an effective susceptibility $\tilde{\chi}$ and an effective diffusion constant $\tilde{D}$, the following set of equations has to be fulfilled:

$$N\,\chi\,R^3 = \tilde{\chi}\,R'^3 \quad \text{[Eq. 3a]} \qquad \chi R^2/D = \tilde{\chi}\,R'^2/\tilde{D} \quad \text{[Eq. 3b]}$$

For both Eqs. [3] to hold, $\tilde{\chi}$ and $\tilde{D}$ have to be regarded as dependent variables, and the Eqs. [3] have to be solved for them. The result is easily found as

$$\tilde{\chi} = N\,\chi\left(\frac{R}{R'}\right)^3 \quad \text{[Eq. 4a]} \qquad \tilde{D} = N\,\frac{R}{R'}\,D \quad \text{[Eq. 4b]}$$

Due to the larger step size $\Delta\lambda = \sqrt{6\,\tilde{D}\,\Delta t}$ in the model, the Gradient G also has to be corrected by $G\,\alpha\;\; G\times\sqrt{D/\tilde{D}}$ [Eq. 4c]. Eqs. (4a-c) constitute the set of equation which corrects for the smearing out of SPIO particles among the charged cells.

Computations have been performed using a CPMG Sequence with R = 12.5 nm (describing a nanoparticle), R' = 5 µm (as an order of magnitude for the cell sizes of interest). About 3.000.000 magnetic particles have been distributed randomly in the first case among Nc = 31 cells and in the second case among Nc = 306 cells.

In a first experiment we investigated the effect of different numbers of cells using the same diffusion coefficient. R was hold constant and N was decreased by a factor 10. This was modeled in the first experiment by dividing $\tilde{\chi}$ by a factor 10. The effective diffusion coefficient was computed according to Eq. 4b for 31 cells, each one charged with 100.000 nanoparticles.

To preserve the diffusion regime, in a second experiment N was decreased by a factor 10 in the model by dividing both $\tilde{\chi}$ and $\tilde{D}$ by a factor 10.

We studied the signal decay in a cubic voxel of size 1 mm³ with and without bipolar gradient using a MC model. A benchmark test not shown here without particles also has been performed showing that the diffusion has been correctly simulated by the model using eqs. (4 a-c).

Results

The Figs. 1 and 2 show the signal decay for a CPMG sequence with different numbers of cells. In Fig. 1 the diffusion constant is preserved, in Fig. 2 the diffusion regime is preserved. For both figures, a bipolar gradient of 30 mT/m was applied over 50 ms per echo time. Figs. 3 and 4 show the corresponding results for the bipolar gradient switched off. The number of cells, susceptibilities, diffusion constants and number of nanoparticles per cell are summed up in Table 1.

Discussion

The computations are valid in the case that nanoparticle-charged cells are distributed with a volume fraction f being of the order of at most a few percent. This is the case e.g. for charged Kupffer cells of the liver or spleen. In the first case we discuss the computational effort (summation over 31 cells) is much less than in our second case (summation over 306 cells). If the diffusion regime is preserved as in our second experiment, the resulting signal decay, evaluated at the signal maximum at multiples of TE in a CPMG sequence, shows to be the same for both cases (31 cells respectively 306 cells). Both $\tilde{\chi}$ and $\tilde{D}$ therefore have to be adapted. Replacing a large number of cells by a smaller number of cells this way allows to compute T2 for very large numbers of cells, which, otherwise, would be computationally too expensive. We conclude that preserving the diffusion regime with eqs. (4a-c) seems possible. As an important implication the results thereby indicate that the simulation of the individual nanoparticles by charged cells accordingly to Eqs. (4a-c) is valid.

References

[1] K.T. Yung "Empirical Models of Transverse Relaxation for Spherical Magnetic Perturbers" MRI 21:451-463 (2003)

Nc	CHI~ [10^{-6}]	D~ [µm²/ms]	N
31	100	1040	100.000
306	10	1040 (104)	10.000

Table 1

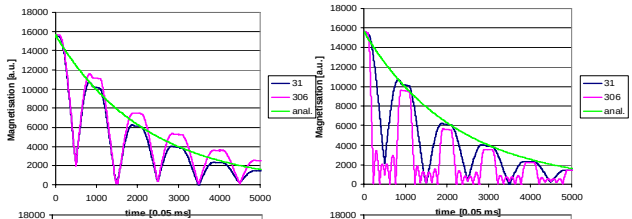

Fig. 1: CPMG Signal decay with diffusion constant being identical. Particles distributed among 31 spheres rsp. 306 spheres rsp. analytical solution without particles. Bipolar gradient 30 mT/m.

Fig. 2: CPMG Signal decay with diffusion regime being identical. Particles distributed among 31 spheres rsp. 306 spheres rsp. analytical solution without particles. Bipolar gradient 30 mT/m.

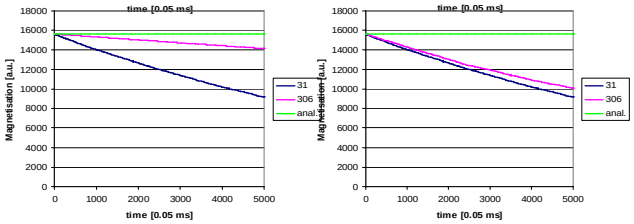

Fig. 3: CPMG Signal decay with diffusion constant being identical. Particles distributed among 31 spheres rsp. 306 spheres rsp. analytical solution without particles. Bipolar gradient switched off.

Fig. 4: CPMG Signal decay with diffusion regime being identical. Particles distributed among 31 spheres rsp. 306 spheres rsp. analytical solution without particles. Bipolar gradient switched off.