Nuclear magnetic relaxation induced by gel-suspended cells labelled by iron-oxide nanoparticles: experimental and simulation studies

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Superparamagnetic (SPM) nanoparticles (NPs) are magnetic monodomains characterized by a great electronic magnetic moment and are used in Magnetic Resonance Imaging as negative contrast agents. Indeed, SPM NPs decrease the relaxation time of water proton spins by producing a large dipolar magnetic field [1]. While the influence of SPM NPs homogeneously distributed in water on proton spins are theoretically well understood, the modelling of realistic systems such as NPs confined in cells remains challenging. In this preliminary work, the magnetic nuclear relaxation induced by in-vitro cells labelled by SPM NPs are studied experimentally and compared to simulations.

1. Methodology

Two types of systems were studied in this work (Figure 1): (A) SPM NPs homogeneously distributed in water, (B-C) cells labelled by SPM NPs suspended in a gel. In the experimental case, each cell can contain several NPs (Figure 1B) while, in our preliminary simulations, labelled cells were modelled as spheres containing a big magnetic particle modelling the NP clustering (Figure 1C).

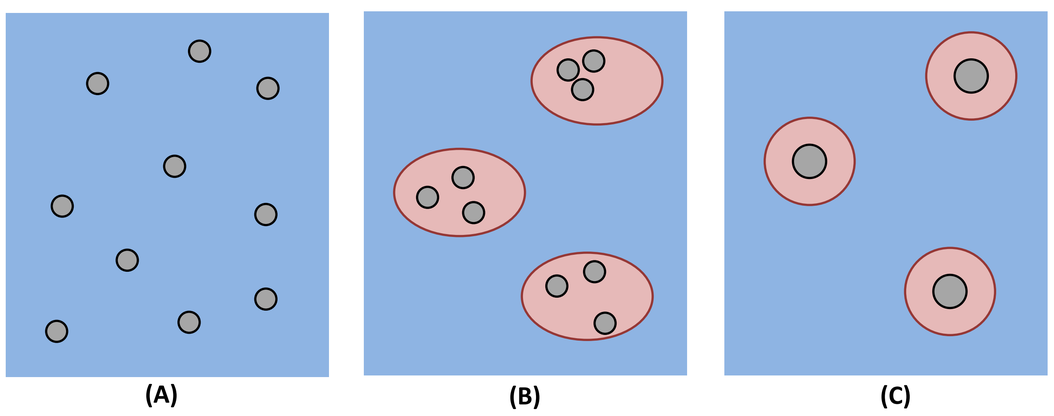

Figure 1 – 3 types of systems studied in this work. Nanoparticles are represented by grey discs, cells by red ellipses.

EXPERIMENTS : Human prostatic adenocarcinoma cells (PC3) were labelled by 7nm maghemite nanoparticles coated by anionic citrate ligand (provided by PECSA, Université Pierre-Marie Curie). The labelled cells were then suspended in a low gelling temperature gel as in ref [2]. Relaxation times were measured at a proton Larmor frequency of 20 MHz on a Bruker Minispec with a CPMG sequence (echo-time of 1 ms).

SIMULATIONS : Nanoparticles are considered as impenetrable spheres, cells are modelled as permeable spheres characterized by a permeability constant and an inner-cell viscosity producing a dipolar magnetic field. Water proton diffusion is simulated by a random walk as in ref [3]. Each proton carries a spin which rotates at the Larmor Frequency which depends on the local magnetic field (i.e. on the position of the spin in the sample). An average on all the proton spins is computed and an exponential fit of the magnetization decay provides the simulated transverse relaxation rate.

2. Results

Homogeneously distributed SPM NPs have already been extensively studied. For sufficiently small NPs (diameter < 40nm), a mono-exponential decay of the proton magnetization is observed and the corresponding relaxation rate is proportional to the NP volume fraction. In our case, the measured transverse relaxivity was 200 $s^{-1}.mM^{-1}$[Fe].

Simulation (**A** and **B**) and experimental results (**C** and **D**) are shown in Figure 2. The proton magnetization decay was bi-exponential (i.e. described by two exponential terms) in both cases: two relaxation rates (each one characterized by a normalized amplitude) were measured for each sample/simulation.

Two permeability cases were simulated: large and small permeabilities.

(a) In the case of small permeabilities, the largest relaxation rate remains constant while the lowest one increases with the cellular volume fraction. The highest one can thus be attributed to the confined inner-cellular protons while the second one can be attributed to the extracellular protons.

(b) In the case of high permeability, the exchange of protons is not negligible and the two relaxation rates increase with the cellular volume fraction.

In both cases, the amplitude of the highest relaxation rates increases with the cellular volume fraction which tends to prove that these the increase can be related to the increase of inner-cellular protons.

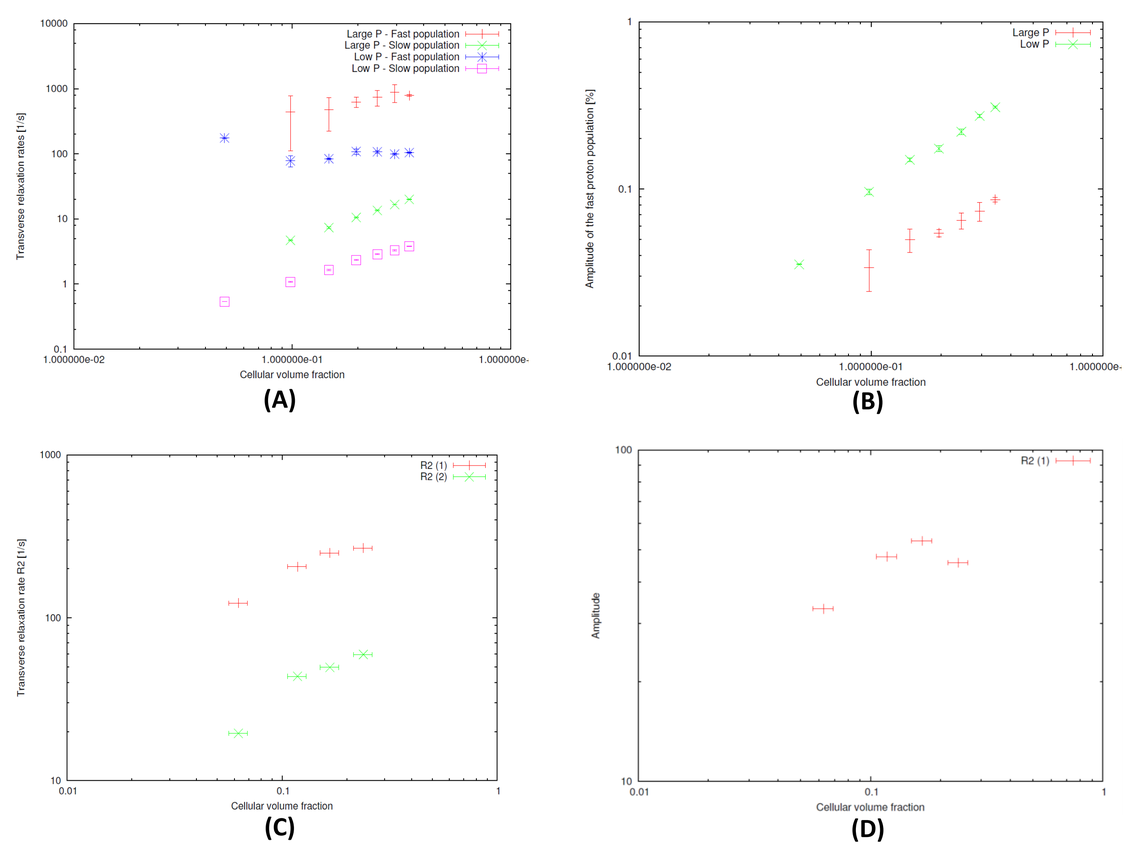

Figure 2 – Simulation and experimental results. Simulation Parameters : outer-cellular diffusion coefficient D_{out} = 3 . 10^{-9} m²/s, inner-cellular diffusion coefficient D_{in} = 10^{-9} m²/s, « Large » permeability P = 0,0085 m/s, « small » permeability P = 0 m/s (small), NP radius of R = 300 nm, cellular radius R_C = 10 µm, NP magnetization M_s = 382 000 A/m. In (B), the total amplitude is normalized to 1 while in (c) it is expressed in [%].

The experimental results seem to correspond to the predictions of the simulation results in the case of high permeability. Indeed, the relaxation rates seem to increase with the cellular volume fraction and the amplitude of the highest relaxation rate also increases with it.

3. Conclusion

The qualitative trends predicted by our simulated models (two compartimentalized protons) seem to be verified by our experimental results. However, a quantitative comparison is not possible yet: Indeed, the iron concentration of our samples has not been measured yet. This quantity is important to be able to normalize our data to make them comparable. This could lead us to make a quantitative measurement of the contribution of the inner-cellular protons and to have an estimate of the cellular viscosity and the membrane permeability.

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