BOOK OF ABSTRACTS

11th CONFERENCE ON FAST FIELD CYCLING NMR RELAXOMETRY

"Le Benedettine" Conference Center

Pisa, 5-7 June 2019

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National Research Council of Italy

Department of Chemical Sciences and Materials Technology

Gruppo Italiano Discussione Risonanze Magnetiche

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21 Years of Fast Field Cycling NMR Relaxometry conferences

Since the first meeting, which was held in Berlin in 1998, the Fast Field Cycling NMR Relaxometry community has grown in number and interests and we have come a long way since then. The past conferences have managed to strengthen the interactions among researchers from different scientific areas (chemists, physicists, engineers, biologists, physicians), which have brought advancements in the theory and the experiment and have extended the fields of application of the technique to a variety of disciplines, such as materials science, earth sciences, medicine, just to cite a few.

Building on the success of the previous conferences and thanks to the numerous participants, the 11th conference has gathered stimulating contributions on the development of new experimental methods, easy-to-use data interpretation tools and suitable theoretical models, in order to be able to face issues regarding new societal challenges, as health, food security, clean energy and environment.

We thank all the participants for their stimulating contributions which are collected in this book of abstracts, certain that they will arouse the interest of the reader and will give rise to fruitful discussions and collaborations.

Lucia Calucci and Marco Geppi
Chairs of the Local Organizing Committee

Keynote Lectures

PROTEIN AGGREGATION AND RELAXATION DISPERSION

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Protein aggregation in protein solutions causes changes in the shape and amplitude of the water-proton-nuclear-spin-lattice-relaxation rates. In the simplest case, the aggregation of monomer units creates solution species of increased size with a distribution of rotational correlation times proportional to the distribution of molecular volume. The distribution of correlation times leads to a superposition of relaxation rate profiles that in principle contains the information about the size distribution of the aggregates. Several of the key analytical markers of the MRD profile will be examined quantitatively. However, the coupling between the water-proton-relaxation rate and the protein-particle size involves labile exchange between protein sites and the water pool that may be altered by the aggregation. If this change is significant, it will compromise simple analysis of the relaxation dispersion profiles. Nevertheless, several interesting and possibly useful approaches will be discussed for modeling the relaxation profiles.

ON TIME AND FREQUENCY SCALES OF MOLECULAR DYNAMICS TO BE PROBED BY NMR TECHNIQUES

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The field-cycling technique is usually applied to probe the frequency scale of non-secular dipolar couplings fluctuating due to molecular dynamics in a wide range. The physical and technical limits of the experimental frequency window will be discussed. As concerns low frequencies or long time scales, spin-lattice relaxation dispersion can favorably be supplemented by studying the secular part of dipolar interactions. As a favorable technique the so-called dipolar correlation effect will be presented. The scheme in Fig. 1 shows the combined dynamic range of molecular motions that is accessible on this basis in principle.

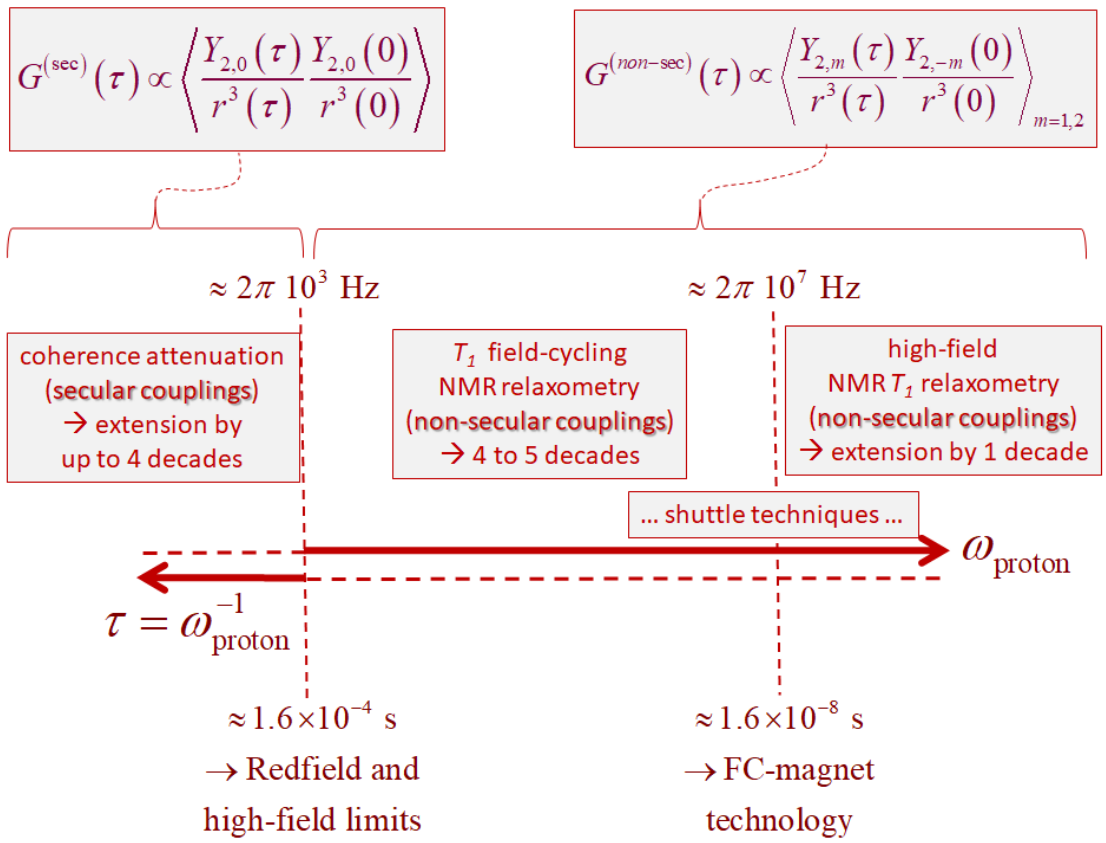

Fig. 1. Secular and non-secular dipolar correlation functions and the time and frequency scales to be probed by respective NMR techniques [1].

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MOLECULAR IMAGING OF CANCER USING FIELD CYCLING

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Molecular imaging with MRI often relies on contrast agents that are targeted to bind or accumulate in tissues increasing local imaging contrast. However, specificity of these agents to their targets is often limited due to inherent contrast from unehanced tissue or contrast enhancement from unbound agent. For contrast agents whose relaxivity is strongly field-dependent, R_1-dispersion imaging using fast field-cycling (FFC) can improve agent specificity albeit at the expense of reduced SNR. This can facilitate quantification of imaging contrast without the necessity of comparing pre- and post-injection imaging. Our laboratory uses FFC relaxometry to assess relaxation for novel contrast agents and methods for molecular MRI of cancer. We have also developed FFC hardware for R_1-dispersion imaging of mice at 1.5 Tesla [1] to study longitudinal changes in the tumor microenvironment (TME) such as macrophage invasion.

Macrophages are the most abundant immune cell in the TME. The presence of tumor-associated macrophages (TAMs) is linked with tumor cell invasion, metastasis and is strongly predictive of poor treatment outcomes for breast cancer. Macrophages readily phagocytose superparmagnetic iron oxide nanoparticles (SPIONs) such as Ferumoxytol, a drug for treatment of iron-deficiency associated with chronic kidney disease. Ferumoxytol has a significant R_1 dispersion, which can be exploited at 1.5 Tesla using FFC (Fig. 1). SPIONs are very effective agents for relaxation, producing very short T_2^* values in tissues resulting in signal loss or "*negative*" MRI contrast, which is difficult to quantify. Conversely R_1-dispersion imaging produces a "*positive*" contrast for SPION imaging facilitating quantification of SPION concentration and the presence of TAMS (Fig 2.) Imaging of tumor-associated inflammation using SPIONs may "*serve as a new biomarker for long-term prognosis and related treatment decision that will support ongoing development of new immune-targeted therapies*" [2].

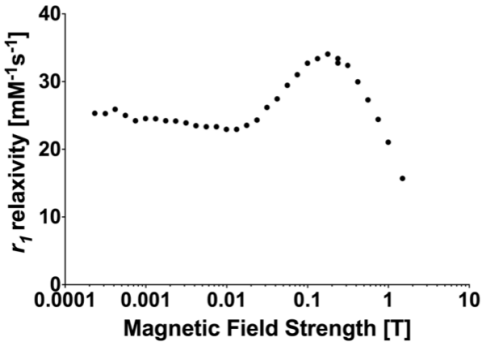

Fig. 1. Proton nuclear magnetic relaxation dispersion of Ferumoxytol (Feraheme) measured at 37°C.

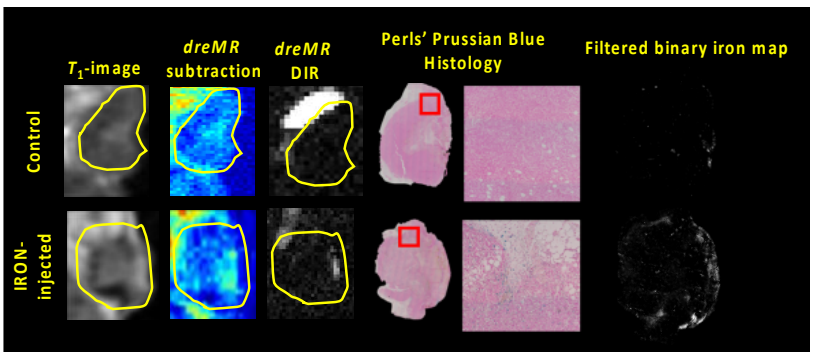

Fig. 2. R_1-dispersion imaging of Ferumoxytol-labeled macrophages in a mouse breast tumor. Comparison of control (no injection) and iron-injected mouse. The tumor is outlined in yellow.

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IMPROVING SELECTIVITY IN FAST FIELD CYCLING: MULTIDIMENSIONAL EXPERIMENTS AND TAILORED PROBES

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Traditionally, FFC relaxometry used to suffer not only from low sensitivity due to inherently low magnetic field strengths, but also from a lack of options to extract specific information among a multitude of spin interactions in complex systems if spectral resolution were not available. This contribution surveys several approaches that have been carried out in the last decade to improve this situation and allow for a better distinction of relaxation mechanisms and spin pools.

An obvious strategy is the removal of the intermolecular contribution to relaxation by either isotopic dilution with deuterons, or by measuring ^{2}H relaxation dispersion directly which is dominated in almost all cases by intramolecular processes. For instance, monitoring ^{1}H signals of polymers in a deuterated matrix allows one to isolate the intramolecular contribution and, indirectly, to extract the important information of mean-squared displacements of the polymer segments [1]. While biexponential [2] and multiexponential relaxation fits [3] have been demonstrated to identify different fractions of nuclei either inside a molecule or in a complex matrix, the full potential of separation is exploited by generating 2D plots of T_1-T_2 correlation by integrating CPMG acquisition into the FFC sequence [4].

In porous media, the interaction of adsorbates with the surface depends on the chemical properties of both partners: while polar liquids on polar interfaces show strong NMR dispersion, the same is found for hydrocarbons on non-polar organic interfaces [5]. This provides an approach to quantify wetting behaviour in rocks or soils where the surface conventionally interacts stronger with water, but becomes locally or globally oil-wet after extensive treatment with hydrocarbons – NMRD will differ between the wetting and non-wetting phases. Exploiting the presence of naturally occurring free radicals at the interface by means of DNP to the adsorbed species can be used for assessing the local distribution of water and oil in mixed-wet samples, and even to distinguish between the aromatic and aliphatic components in oil due to their differential interaction properties with organic interfaces [6]. By taking the chemical interactions of certain radicals with molecules into account, the individual reorientational dynamics of different moieties of macromolecules have successfully been analyzed [7].

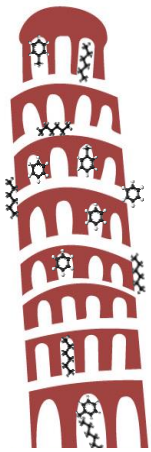

Fig. 1. Aromatic and aliphatic molecules possess different adsorption properties in a porous medium; T_1-T_2 2D correlation maps or localized DNP are strategies to differentiate between them.

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Invited Lectures

SURFACE EFFECT ON THE MOLECULAR DYNAMICS INSIDE CARBON XEROGEL MESOPORES

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Low field nuclear magnetic resonance (NMR) relaxometry and diffusometry techniques are widely used for the characterization of porous materials. NMR relaxometry techniques exploit the proportionality between the relaxation rate of the confined molecules and the surface to volume ratio of the investigated pores. The proportionality constant, also called relaxivity, is determined by the adsorption properties of molecules on the pore surface [1], the magnetic impurity content of the solid matrix [2] and the magnitude of the external magnetic field [1-3]. Consequently, the relaxation experiments provide access to the pore size distribution and the wettability of the confined molecules [1-3]. NMR diffusometry techniques [4] use pulse field gradients to encode and decode position of the investigated molecules and thus allow determination of the effective diffusion coefficients as a function of the diffusion time. This, in turn, provides information about the transport properties of the pore system.
In our contribution, low-field NMR relaxometry and diffusometry techniques are employed to extract information about the effects introduced by the interaction with the surface on the rotational and translational dynamics of molecules confined inside mesoporous carbon xerogels. The molecules under study were water, cyclohexane and hexane. They were chosen due to their different interaction strength with the carbonaceous matrix [3]. Frequency dependent longitudinal relaxation measurements, using the fast field cycling technique [5], allowed extraction of the fractal dimension for the carbon xerogel surface. It was observed that the measured value is influenced by the molecule affinity to the surface. Diffusion measurements, using the pulse field gradient technique, have revealed that the stronger interaction with the surface of cyclohexane and hexane molecules leads to an increased diffusive tortuosity, as compared with water.

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FIRST CLINICAL STUDIES WITH FFC-MRI: EARLY RESULTS

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Our lab has recently commissionned a resistive whole-body FFC-MRI scanner operating between 200 mT and 20 μT, opening the way to *in-vivo* application of FFC methods. Several clinical pilot studies are under way and early results in stroke and cancer show great potential for clinical applications.
The PUFFINS study (Potential Use of Fast Field cycling IN Stroke) led by Dr Mary-Joan Macleod shows large contrast in brain stroke from 0.2 T to 200 μT, opening the way to ultra-low field stroke imaging devices (see Fig. 1).
Previous results on breast cancer ressections showed biomarkers of tumour aggressiveness [1], which have been linked to water exchange through the membrane [2,3]. Similar results are also seen in colorectal cancer, including in the peritumoural area. Brain glioma also showed a variety of patterns, which are still to be understood. We have started breast and brain scans and obtained the first *in vivo* dispersion images of volunteers, showing excellent ability for image segmentation (see Fig 2).
These studies should continue for 1 to 2 years but early results demonstrate the capabilities of FFC-MRI for image processing and data extraction. This presentation will expose the methods used for image analysis in our labs and how the data collected has been exploited to date.

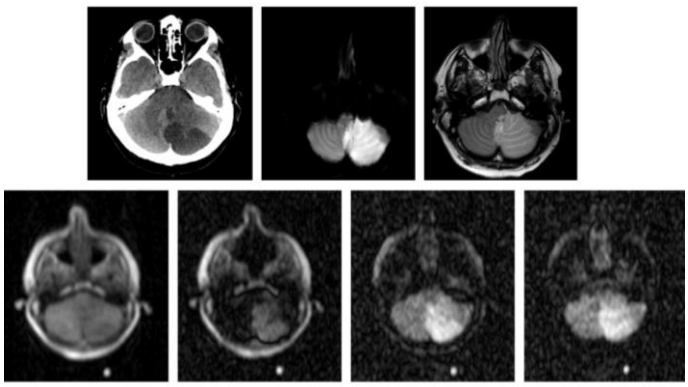

Fig. 1. Images of brain stroke from CT (top left), DWI at 3 T (top middle) and T2 at 3T (top right), as well as FFC-MRI at 200, 20, 2 and 0.2 mT (bottom line). A contrast is clearly visible down to the lowest attainable field.

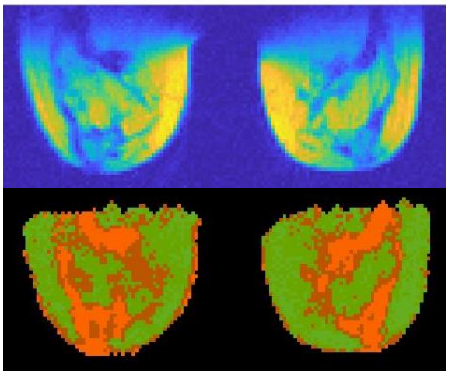

Fig. 2. Top: magnitude images of an FFC-MRI scan at 200 mT from a healthy volunteer. Bottom: composite image using dispersion data at low and high field as well as quadrupolar peak amplitude.

Acknowledgements: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 668119 (project "IDentIFY").

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FAST FIELD CYCLING NMR RELAXOMETRY IN ENVIRONMENTAL SCIENCE

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Environmental issues are nowadays the main concerns in scientific discussions due to their relevance for the evaluation of the strategies needed to protect all the forms of life. Soil desertification, water and air pollution are the main problems that we are all called to solve to ensure sustainable living conditions to all the future generations.
Fast field cycling (FFC) NMR relaxometry can play a very important role for the aforementioned issues due to its powerfulness as a technique used for monitoring purposes.
Here, different case studies are discussed in order to show how FFC NMR relaxometry can be applied to reveal environmental problems and suggest possible remediation strategies.

FAST-FIELD CYCLING MAGNETIC RESONANCE IMAGING AROUND 1.5T TO MAP NMR RELAXATION DISPERSION IN VIVO

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Fast-field cycling magnetic resonance imaging (FFC-MRI) [1] provides new means to localize contrasts based on NMR relaxation dispersion which may lead to useful biomarkers of diseases. In the last decade [2], clinical FFC-MRI was shown feasible at low field [3,4], and pre-clinical FFC-MRI at high field (up to 3T) [5-8]. Here, we synthesize the instrumental developments of an FFC insert designed for mice, and present the first in vivo quantitative NMRD mapping study on a kidney cancer model.
The system (Fig.1a) comprises a resistive insert (Stelar s.r.l, Mede, Italy) centred into a 1.5T clinical MRI. Inversion recovery as well as fast steady-state incoherent FFC sequences [9] were implemented for R_1-NMRD measurement, and a multiple spin-echo FFC sequences for R_2-NMRD measurement [10], validated against literature on Gd chelates, iron oxides particles, and ferritin solutions. An in vivo MRI protocol was defined comprising localisation, proton density, T_1w and T_2w scans at fixed field, and the acquisition of inversion recovery images processed to get R_1-NMRD images (validated on phantoms).
The imaging protocol was applied to 27 anesthetised NSG mice grafted on the left kidney with patient biopsy of kidney cancers (pediatric nephroblastoma and clear cell renal cell carcinoma) [8] (Fig.1b-c).

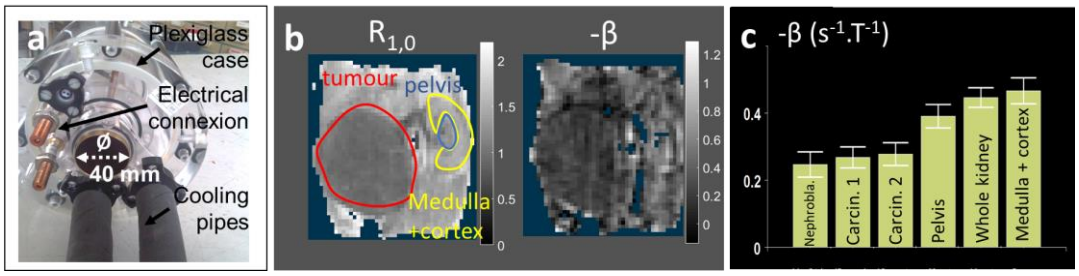

Fig. 1. FFC-MRI setup (a), typical 1.5T $R_{1,0}$ and –β (slope of NMRD profile) of the abdomen (b) and average over the population for 1 nephroblastoma and 2 carcinomas showing significant differences between tumours and healthy kidneys (c).

In summary, new ways to generate dispersive contrast were proposed. R_1 dispersive contrast could be generated using fast steady-state sequences, and strong R_2 dispersive contrast could be obtained on ferritin, a protein relevant in liver and brain diseases. Reproducible imaging results were obtained in vivo, displaying endogenous dispersive properties and difference with tumours, opening the way to preclinical studies with the FFC-MRI system.

Acknowledgements: Work supported by the CA15209 COST Action (EURELAX). France Life Imaging (grant ANR-11-INBS-0006). Stelar s.r.l provided technical support. Nephroblastoma samples available thanks to N. Assoun, E. Daudigeos-Dubus, B. Geoerger, MAPPYACTS project, Gustave Roussy.

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NANOSECOND PROTEIN MOTIONS IN PROTEINS REVEALED BY HIGH-RESOLUTION RELAXOMETRY

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Understanding of the physics and chemistry that underlie the function of biological macromolecules requires an atomic-resolution description of their conformational space and the timescales of the motions in this space. The measurement of nuclear spin relaxation gives access to motions on multiple timescales between the tens of picoseconds and nanoseconds. However, the analysis of motions has, so far, relied on limited experimental data and used simple model-free approaches. High-resolution relaxometry, as introduced by Redfield [1], is a powerful technique to quantify nuclear spin relaxation over a broad range of magnetic fields and provides unprecedented experimental data to quantify accurately picosecond to nanosecond motions in proteins. Two studies of backbone nitrogen-15 by high-resolution relaxometry of folded proteins have revealed motions on nanosecond/picosecond time scales [2,3].

Here, we present carbon-13 relaxation rates recorded between 0.2 and 22.3 T on methyl groups in ubiquitin. The resulting extensive ensemble of experimental constraints allows the analysis of internal motions with up to three correlation times spanning three orders of magnitude from picoseconds to nanoseconds. Experimental results were compared to the analysis of a 1 μs trajectory calculated by molecular dynamics (MD), which we use to provide a mechanistic interpretation of the detected motions when the two approaches agree. The methodology was developed to study isoleucine side-chains [4] and recently adapted to valine and leucine sidechains. Nanosecond motions in such sidechains quantified with unprecedented accuracy. We also show that the amplitude of ps-ns motions in protein sidechain has been underestimated by conventional high-field deuterium relaxation approaches.

We also show that high-resolution relaxometry offers a refined description of ps-ns motions in intrinsically disordered proteins (IDP's). Nitrogen-15 relaxation rates were measured between 0.33 and 14.1 T on the protein osteopontin. Relaxation rates at low field correlate with the degree of local ordering as shown by the distributions of correlation times reconstructed using regularization techniques. Motions in the low tens of nanoseconds, to which high-field relaxation is blind, are clearly identified.

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ANALYTICAL EXPRESSIONS AND SIMULATION OF NUCLEAR SPIN RELAXATION IN 3D LIQUID SYSTEMS

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The Redfield approximation provides an analytical description of the relaxation of the observed nuclear spins in terms of relaxation rates expressed as sums of Laplace-Fourier transforms of time correlation functions (TCF) of the positions and orientations of the species which carry the observed spins and the other nuclear or electronic spins causing their relaxation. Despite the many forces of various intensities and ranges acting on those species, the relaxation rates often have analytical expressions or even closed algebraic forms in the case of reference ideal situations [1,2]. However, when a perturbing Hamiltonian causing the spin relaxation fluctuates at a rate lower than its magnitude, the Redfield formalism is no longer valid. Then, the magnetization evolution can strongly deviate from a regular decay (e.g., Fig. 1). One has to resort either to sophisticated approaches such as the Sweedish slow-motion theory [3] and adiabatic approximation [4] or to simulations [3] which are rather direct, but often computer demanding. We discuss why the deviations from the Redfield approximation of slowly-fluctuating perturbing Hamiltonians show up mainly in the low field domain revealed by FFC-NMR relaxometry and propose strategies for computing the nuclear relaxation involving such perturbing Hamiltonians.

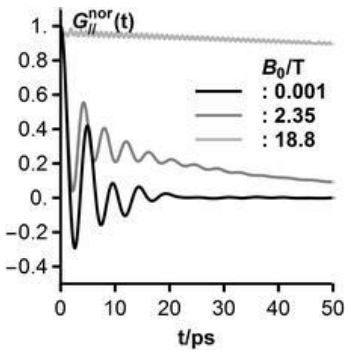

Fig. 1. Longitudinal relaxation function $G_{//}^{nor}(t) = \langle S_z(t)S_z \rangle / \langle S_z(0)S_z \rangle$ of an electronic spin $S = 1$ with static and transient ZFS parameters $\Delta_S = 5\ \text{cm}^{-1}$, $\Delta_T = 2\text{cm}^{-1}$, rotational and vibrational correlation times $\tau_R =$ 100 ps, $\tau_v = 5$ ps [3].

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EVIDENCE FOR THE ROLE OF INTRACELLULAR WATER LIFETIME AS A TUMOUR BIOMARKER OBTAINED BY IN VIVO FIELD-CYCLING RELAXOMETRY

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Conventional diagnostic magnetic resonance imaging (MRI) techniques have focused on the improvement of the spatial resolution by using high magnetic fields (1-7 T). High field allows the visualization of small tumour mass but lacks to give a precise evaluation of tumour grading and metastatic potential. Recently, we showed that the intracellular water lifetime represents a hallmark of tumour tissue cells status that can be easily monitored by measuring T_1 at different and relatively low magnetic field strengths, ranging from 0.2 to 200 mT [1,2]. A fast exchange through cell membranes indicates a high metabolic rate and thus a high activity of the tumor cells. Thus it is possible to measure the high metabolic pressure by an enhance water exchange with the exterior of the cell. Therefore, intracellular water lifetime can be considered an important tumour biomarker directly depending on the rate of cell proliferation, cell migration and in responding to external stimuli as hypoxia or extracellular acidosis. Moreover, currently tumour responses to therapy are monitored primarily by imaging evaluating essentially the decrease of tumor size. This approach, however, lacks sensitivity and can only give a delayed indication of a positive response to treatment. In our study, we propose the use of FFC-NMR to provide relevant information about response to treatment by monitoring changes of water exchange rates through cell membranes that are directly dependent on the metabolism alterations caused by the chemo- or radio-therapy.

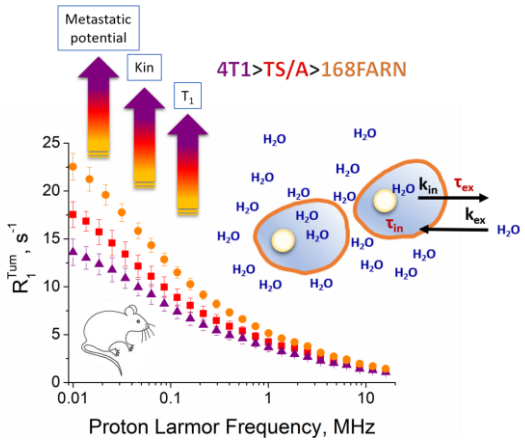

Fig. 1. NMRD profiles of the tumour tissues grown on hind limbs: 4T1 (▲), TS/A (■), and 168FARN (●).

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APPLICATIONS OF FFC-NMR RELAXOMETRY TO PETROLEUM POROUS MATERIALS

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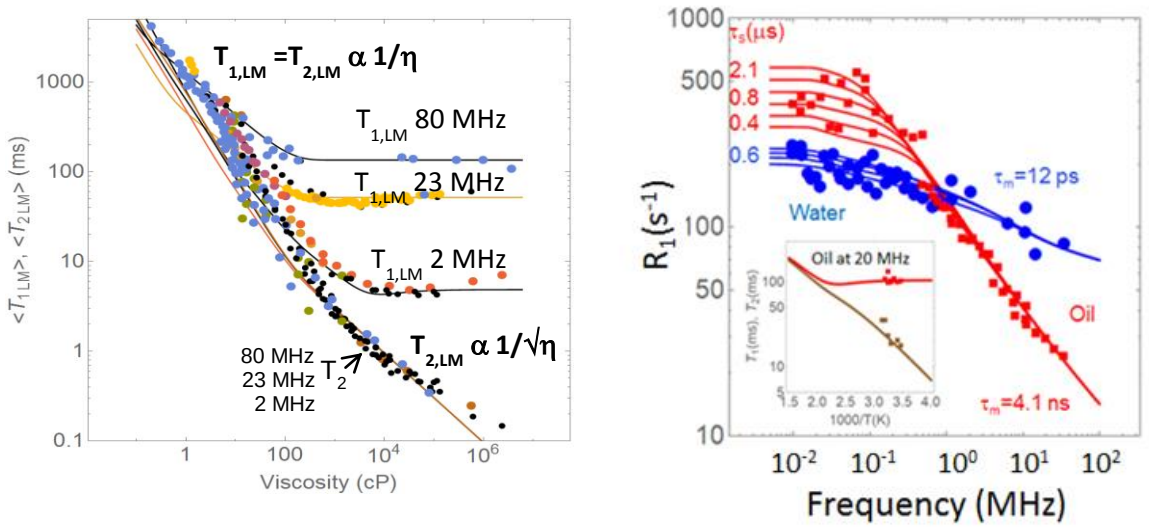
We present our last results on nuclear magnetic relaxation dispersion technique (FFC-NMR) and 2D spin correlation T_1-T_2 for characterizing the molecular dynamics of hydrocarbons in petroleum industry. A first example is given on the viscosity dependencies of T_1 and T_2 of heavy crude oils (Fig. 1a) modeled as the hydrocarbons dynamics at proximity of asphaltene nanoaggregates and macroaggregates. Other examples are presented on the multiscale nuclear magnetic relaxation (Fig. 1b) for characterizing non-invasively the structure, dynamics and wettability of petroleum fluids (brine and oil) embedded in the dual microstructures (kerogen and clays) of as received shale rocks. The activated diffusive nature of these fluids has been evidenced as well as their respective wettabilities. The convergence in the modeling of these multiscale experiments gives a comprehensive understanding of fluid transport in these extremely low permeable rock samples.



(a) (b)

Fig. 1. (a) Comparison experiments-theory of the viscosity dependencies of several heavy crude oils. (b) Comparison experiments-theory of the NMRD profiles of brine (blue) and oil (red) in as received shale rock at room temperature. In inset are given the temperature dependencies of T_1 (red) and T_2 (brown) of oil in shale rock.

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RELAXOMETRY AND OVERHAUSER DYNAMIC NUCLEAR POLARIZATION

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One of the most severe limitations of NMR is the inherent low sensitivity. Among extensive efforts to overcome this limitation, dynamic nuclear polarization (DNP) is emerging as a promising tool to hyperpolarize nuclear spins for NMR. Overhauser DNP is ascribed to the magnetization transfer occurring in a magnetic field from unpaired electrons to nuclei through stochastic modulation of the magnetic hyperfine interaction between electron and nuclear spins. The transfer requires a non-Boltzmann distribution of the populations of electronic and nuclear spin energy levels, which is achieved by microwave irradiation at the electron Larmor frequency. The Overhauser DNP enhancements strongly depend on the correlation times modulating the dipole-dipole interaction between nuclei and unpaired electrons. The analysis of the relaxation profiles of polarizing agents thus represents a valuable tool for their characterization, because they can provide information on these parameters.

DNP is usually performed using nitroxide radicals as polarizing agents, characterized by sharp EPR lines, fast rotation, fast diffusion, and favourable distribution of the unpaired electron. The relaxation profiles of solvent water protons in the presence of nitroxide radicals or paramagnetic metal complexes have been collected and analyzed to obtain the correlation times and the coupling factors [1-5], which report on the largest Overhauser DNP enhancements achievable at full electron saturation, as a function of the applied magnetic field.

For ^{1}H, molecular motion leads predominantly to a modulation of the magnetic electron-nuclear dipole-dipole interaction at a time scale of tens of ps. This makes the Overhauser DNP enhancements achievable at room temperature, and magnetic fields > 1 T, relatively small (< 10^2). On the other hand, the enhancement of ^{13}C nuclei in $CHCl_3$ or CCl_4 solutions can be up to 1000 at magnetic fields of 3 Tesla [6]. ^{13}C relaxometry indicated that ^{13}C relaxation is dominated by the contact interaction with the nitroxide radicals, with a correlation time of about 1 ps. A higher relaxivity was measured at low fields for $CHCl_3$ than for CCl_4, as the result of the additional contribution arising from the H atom in $CHCl_3$. Notably, the ^{13}C relaxation profile of $CHCl_3$ could be reproduced with the same parameters as CCl_4 plus an additional contribution mediated by the H-atom. In both solvents, a dipolar contribution to the total relaxivity should also be included. The best-fit values of the parameters obtained from the ^{13}C relaxation profiles can account for coupling factors of -0.47 (CCl_4) and -0.37 ($CHCl_3$), as measured at 3.35 T.

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FFC, A LOOK TO THE PAST

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This non-exhaustive presentation will evoke the evolution of the FFCR over the years, trying to pay credit to the major contributors to its development [1].
A special emphasis will be put on the role of FFCR in the context of the development of contrast agents for magnetic resonance imaging.

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TEMPERATURE AND WATER-ASSOCIATED CHANGES OF CEREAL PRODUCTS MONITORED BY TD-NMR

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Based on spin-spin T_2 relaxation time measurements, the time-domain NMR (TD-NMR) spectroscopy has been used to provide relevant information on the water and biopolymer motion and transfer in bread [1,2]. This technique permits to characterize molecular interaction and transformations in a non-invasive and non-destructive way, in real time during a process (heating, freezing, hydration …). In bread, proteins of gluten when hydrated form a viscous mass that confers to the dough, structure, viscosity, mixing tolerance and gas holding ability [3]. On the other hand, starch, in presence of water and increasing temperature, undergoes a series of changes known as swelling, gelatinization and retrogradation that induce variations in water distribution, in starch structure and interactions between them [4,5]. Our studies aims at understanding and ranking the contribution of these biochemical transformations that contribute to the crumb structure and the textural properties of bread made with cereal flour or a gluten free mix [6]. The water transfers and the extent of starch gelatinization in dough and crumb were studied by TD-NMR during and after the heating/cooling process of dough at various water levels. Preliminary fast field cycling NMR experiments make it possible to envisage further works in order to understand the role of water in the formation of bread crumbs.

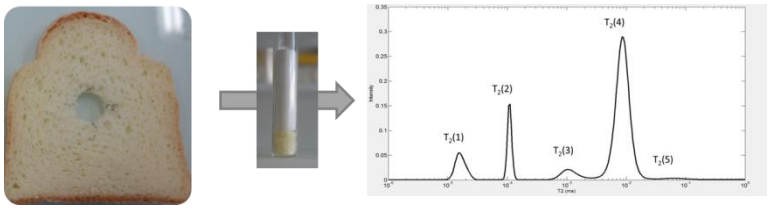

Fig. 1. TD-NMR of bread crumb

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^{1}H NMR STUDY OF MOLECULAR ORDER AND DYNAMICS IN CBC9CB LIQUID CRYSTAL

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Molecular order and dynamics of the CB-C9-CB liquid crystalline dimer exhibiting the nematic (N) and the twist bend nematic (Ntb) phases [1-2] were investigated by proton NMR spectroscopy, using fields of 0.78 T and 7.04 T, and relaxometry. The first relaxometry experiments for a very wide Larmor frequency domain (8 kHz–300 MHz) on this system, using a combination of standard and fast field cycling NMR techniques, were performed. The spectroscopy results in the Ntb phase allowed us to probe the local molecular orientation relative to the Ntb helix axis. The relaxation data were analyzed considering order director fluctuations (ODF), molecular self-diffusion (SD) and local molecular rotations/reorientations (R) relaxation mechanisms. Global fits of theoretical relaxation models, as a function of temperature and Larmor frequency, for the phases under investigation, allowed for the determination of rotational correlation times [3], diffusion coefficients, viscoelastic parameters, correlation lengths and activation energies (in the case of thermally activated mechanisms) [4]. A clear difference between the structures of the N and Ntb phases was detected from the results of proton spin–lattice relaxation through distinct temperature and frequency dependencies' signatures of the collective modes. Significant pre-transitional effects were observed at the N–Ntb phase transition both from relaxometry and spectroscopy data. The experimental results correlate to data and models for comparable liquid crystalline systems.

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Oral Communications

FIELD-CYCLING NMR RELAXOMETRY AS A TOOL FOR THE CHARACTERIZATION OF THE ELASTIC PROPERTIES OF LIPOSOMES

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It has been clearly established that liposomes with enhanced membrane elasticity favor the penetration of drugs through the skin [1-4]. However, details of the underplaying mechanisms have not been clearly understood so far [2,3,5-7]. The elasticity of liposome membranes has been mainly characterized through two different approaches: vesicle deformability as observed in extrusion experiments [8-10], and measurements of the bending elastic constant [11-13]. A discussion about the equivalence of these two approaches has been considered [14]. Moreover, the measurement of the bending elastic constant (or modulus) showed a marked dependence on the used experimental technique [15]. This fact has a close relationship on how the physics involved in each experimental protocol & technology interacts with the sample system, which in turn strongly depends on how it was manipulated according to the needs and requirements of the used technique. In this context, field-cycling NMR relaxometry can be considered as a promising alternative [16]. It is hardly invasive, while the information on the elastic properties can be obtained from the nuclear magnetic relaxation of the lipid protons (liposomes suspended in deuterated water). In this opportunity we present a general overview of the problem, and some new results that support a deeper analysis about the pros and cons of the FFC-relaxometry technique in confront with other experimental approaches.

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UTILITY OF FAST FIELD CYCLING RELAXOMETRY AND NUCLEAR QUADRUPOLE RESONANCE STUDIES OF ACTIVE PHARMACEUTICAL INGREDIENTS (FFCR and NQR of API)

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Nuclear quadrupole resonance (NQR) frequencies are determined by the interaction of nuclear quadrupole moment of $I > \frac{1}{2}$ nuclei such as ^{14}N or ^{37}Cl with electric field gradient (EFG) tensor at the nuclei site. Further, the EFG tensor in molecular crystals is determined by charge distribution around the nuclei, thus primarily by the intramolecular bonds of the nuclei's atom, secondary with intermolecular bonds between the nuclei molecule and neighboring molecules, and tertiary by the arrangements of surrounding molecules. The NQR is often sensitive enough to detect any subtle structure change, even due to small external pressure or change of temperature for a fraction of a degree. This makes NQR a very interesting tool to confirm or discriminate between various forms of solids. Due to lack of broadening of NQR lines in powders due to zero external field, NQR spectroscopy is advantageous over solid state NMR in many cases. For solid pharmaceuticals, polymorphic, co-crystalline, hydride, amorphous, etc. forms of active pharmaceutical ingredients (API) can all be distinguished, at least in principle. In recent years, the powerful DFT methods allow for better and better calculation of EDF tensors parameters, which is helping both in the prediction of NQR frequencies, as well as in verification and optimization of calculated structures.
Experimentally, pure ^{14}N NQR is often not possible due to low signal to noise ratio. Therefore cross-relaxation spectroscopy using the quadrupole enhancement relaxation measured by fast field cycling relaxometry can be used to determine the NQR frequencies, albeit at the loss of resolution. We describe some recent results using NQR, CR and NQDR methods.

IN VIVO FFC-NMR OF TUMOR-ASSOCIATED MACROPHAGES (TAMs) IN MURINE MELANOMA WITH ASSESSMENT OF INTRA-CELLULAR LOCALIZATION OF IRON OXIDE PARTICLES

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Tumour associated macrophages (TAMs) are forced by the cancer cells to adopt an anti-inflammatory phenotype and secrete factors to promote angiogenesis and tumor invasion [1]. For these reasons, sensitive and non invasive methods to detect TAMs are needed for tumour classification and individual patient stratification to stronger or targeted therapies.
Herein we propose a new, alternative diagnostic protocol to assess the localization of an USPIO-NP (ferumoxytol) in TAMs in melanoma tumours. The method is based on the acquisition of *in vivo* NMRD profiles on a FFC relaxometer endowed with a wide bore magnet and a dedicated transmitter/receiver solenoid detection coil placed around the mouse's leg [2]. The slopes of the obtained R_1^{POST}-R_1^{PRE} profiles acquired 3 and 24 h after ferumoxytol injection (Fig.1) appear the most significant parameter that can act as an unequivocal reporter of nanoparticle intra- or extracellular localization thus allowing an unambiguous TAM quantification. In fact, 24h after the injection the remaining ferumoxytol is taken up by macrophages as confirmed by histological analysis (Pearls assay). This finding open new horizons for the field of cell tracking applications [3].

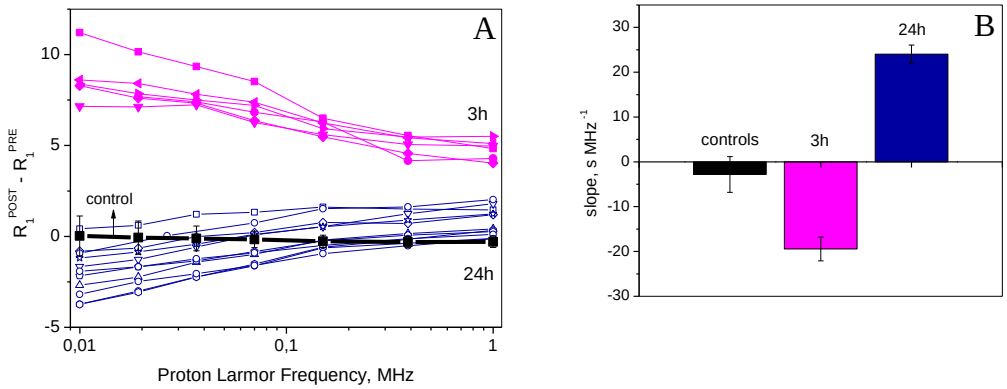

Fig. 1. A) NMRD profile differences, obtained by subtracting PRE profiles to the corresponding POST profiles acquired 3 h and 24 h after ferumoxytol injection. Black square points correspond to POST-PRE control profiles acquired 24 h after the injection of a physiological solution; B) Average slopes of R_1 profiles calculated at low field.

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MOLECULAR DYNAMICS STUDY OF PEG-BASED MIXTURES WITH GADOLINIUM, MANGANESE AND COBALT METALLIC COMPLEXES BY NMR RELAXOMETRY, DIFFUSOMETRY AND X-RAY DIFFRACTION

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We present a study of the molecular dynamics in PEG-based non-ionic magnetic complexes by means of ^{1}H NMR relaxometry and diffusometry. This study was complemented with small angle X-ray diffraction measurements to characterize the local molecular organization. Previous NMR relaxometry studies on Aliquat and P_{66614}-based magnetic ionic liquid mixtures have put in evidence a strong paramagnetic relaxation enhancement as well as a considerable diffusion coefficient and viscosity response to the applied external magnetic fields [1-3]. In order to complement those studies and enable the unveiling of the mechanisms which are behind the observed enhanced paramagnetic properties, a new set of PEG-based non-ionic magnetic complexes were analyzed. The Manganese and Gadolinium-based metalic complexes clearly present enhanced paramagnetic properties for concentrations below 1% (m/m). The analogous cobalt-based complex, however, did not show the same properties for similar concentrations. In the case of cobalt it was even possible to study the pure metallic complex, which is generally impossible due to hardware limitations of FFC spectrometers, namely, the switching time, which do not allow for the measurement of T_1 values smaller than approximately 5 milliseconds. Diffusometry was performed at 300 and 400MHz and allowed the conclusion that, in these non-ionic mixtures, magnetic field does not have an appreciable effect on the diffusion coefficient, unlike what was observed for the previously studied ionic systems [1-3]. The small angle x-ray diffraction results are discussed in terms of the local order degree evaluation in comparisson with other systems.

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RELAXOMETRIC CHARACTERIZATION OF POTENTIAL Mn^{2+}-BASED MRI CONTRAST AGENTS

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Mn(II) shows several favourable magnetic properties and much better toxicity profile respect to the Gd^{3+} ion. For these reasons, Mn(II)-chelates can be considered a viable alternative to the Gd(III)-based MRI contrast agents currently used in clinics.[1] A considerable amount of Mn(II)-probes have been studied by the relaxometric point of view, aiming to determine the molecular parameters responsible of their MRI contrast efficiency.

In this work, we investigated two types of complexes based on an acyclic polydentate ligand containing a picolinate group ($PAADA^{3-}$) and a cyclic 1,4,7-triazacyclononane-1,4-diacetic acid (H_2NO2A) (Fig. 1).

The rotational correlation time (τ_R) and the electronic parameters of the Mn(II)-PAADA were extrapolated by the simultaneous best-fitting of the ^1H nuclear magnetic relaxation dispersion profiles (NMRD) and ^{17}O NMR relaxation and shift data.[2] The modification of the rotational dynamics was achieved through the functionalization of the pyridyl unit of the ligand with a lipophilic dodecyloxo group (Fig. 1A). The functionalized chelate shows enhanced relaxivity compared to Mn(II)-PAADA, as a consequence of the reduced mobility of the complex in aqueous solution, and a high affinity with bovine serum albumin.

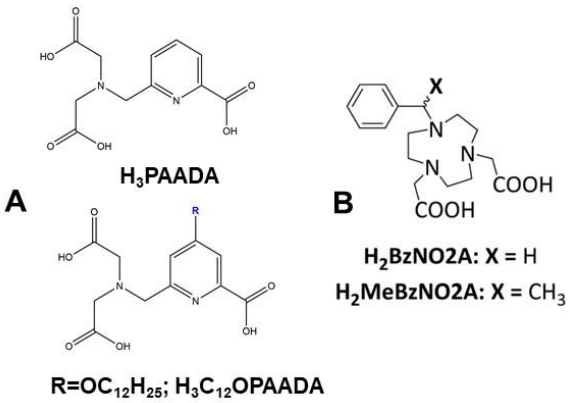

Fig. 1. The structures of the ligands used for the preparation of the corresponding Mn^{2+}-chelates.

In the second study, Mn(II) complexes based on derivative NO2A pentadentate ligands containing different substituents (X) attached to the third nitrogen atom of the macrocyclic unit (Bz and MeBz) were investigated (Fig. 1B).[3] We observed that the water exchange rate of the coordinated water molecule in these complexes is influenced by the nature of the substituent (Me, $k^{298}_{ex} = 62.6 \times 10^7\ s^{-1}$; Bz, $k^{298}_{ex} = 4.4 \times 10^7\ s^{-1}$; MeBz, $k^{298}_{ex} = 2.6 \times 10^7\ s^{-1}$).[3] The decreasing exchange rates are explained by the increasing bulkiness of the substituent, which limits the approach of the entering water molecule in an associative water exchange mechanism.

The results reported here provide insight into important molecular parameters that control the efficiency of Mn^{2+} complexes as MRI contrast agents.

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NMR RELAXOMETRY EXPERIMENTS IN BOVINE AND HUMAN CARTILAGE - SIMULATING THE EFFECTS OF OSTEOARTHRITIS

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Cartilage is an essential part of the vertebrate body. It can be viewed as a fiber-reinforced, permeable composite gel within a physiological salt solution. Most of it is composed of extracellular matrix, at around 98% of volume. The major fibrous component of cartilage, type II collagen, provides the tensile strength of cartilage. Proteoglycan aggregates, which generate a high osmotic pressure in the cartilage, are found between the collagen fibers. Osteoarthritis (OA) is a disease that affects the cartilage in joints, leading to pain of increasing intensity, joint stiffness and even loss of mobility [1]. Developing a method for the early detection of OA starts with understanding the healthy tissue and the effects of various treatments on its properties, as well as the investigation of ex-vivo specimens of healthy and diseased cartilage. Low-field NMR relaxometry provides a different perspective from the clinical MRI currently in use [2]. It offers information on the molecular dynamics inside the tissue, before and after it has been subjected to various conditions, such as degradation by trypsin, which affects the capacity of cartilage to sustain pressure. In the current work, bovine articular cartilage has been used as a model tissue to reveal the influence of drying (Fig. 1a), aging and trypsin treatement on the relaxation dispersion curves. The same technique has been applied on samples extracted from patients who underwent knee replacement surgery, revealing different characteristics of the dispersion curve depending on the severity of the disease (Fig. 1b). Histology and Mankin grading of these and future samples will allow a correlation between the properties of the relaxation dispersion and the severity of the disease.

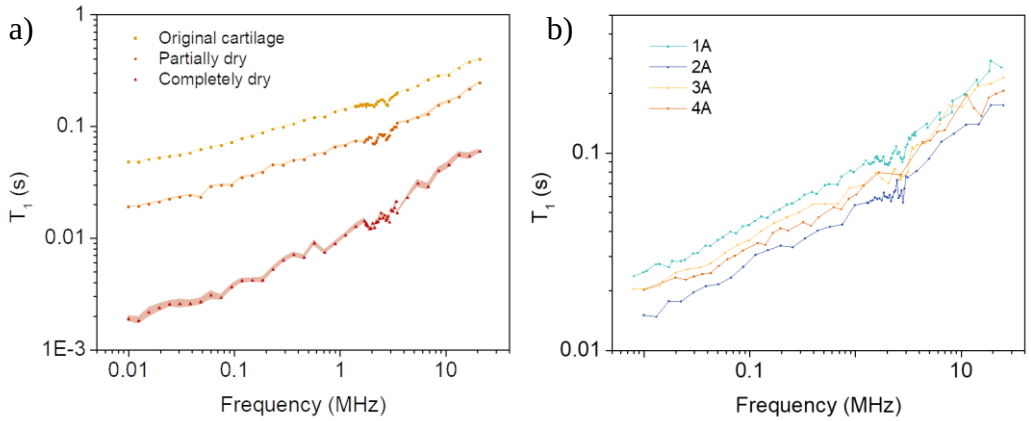

Fig. 1. a) Dispersion curves of bovine cartilage undergoing drying, b) Dispersion curves of four samples extracted from the same human joint, at different locations.

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MULTICOMPONENT DIPOLAR RELAXATION TIME (T_{1D}) ASSESSMENT IN MYELIN USING INHOMOGENEOUS MAGNETIZATION TRANSFER (ihMT) MRI

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Assessing myelin (a lipid-protein lamellar membrane) fluidity may yield further understanding of demyelinating diseases, such as multiple sclerosis [1]. The fluidity, related to collective motions of membranes may potentially be probed by T_{1D}, the relaxation time of the dipolar order, which is built due to the local fields of dipolar-coupled spins [2], much weaker than the external magnetic fields. Hence, T_{1D} is more sensitive to slower motional processes. IhMT (inhomogeneous Magnetization Transfer) [3], is a new T_{1D}-weighted MRI technique, whose measurement sequence can be tailored to enable *in vivo* T_{1D} measurement [4]. The model used in [4] considers a single dipolar compartment, which fails to fully characterize membrane systems associated with multiple T_{1D}s. In this work, we extent the previous ihMT model by including a second dipolar reservoir. We have applied the matrix formalism to the ihMT theory [3]bnand solved the differential equations at the steady-state by using the matrix exponential solution [5]. IhMT RARE images of an excised rat spinal cord were acquired at 7T (Bruker, Pharmascan with cryoprobe) with the modified ihMT sequence and Δt values of 0.8; 1.6; 4; 8; 16; 20 ms, and mean RF power, B_{1RMS} of 3.5; 5.8; 6.7; 8.0; 9.0 μT.

Results: ihMT data fitted to the proposed model allowed measuring a long component (T_{1D1}~10 ms) and a short component (T_{1D2} ~ 400µs). In white matter, the fraction of short T_{1D} component, (1-f_D), increases with B_{1RMS}, and the short T_{1D2} map was more resolved at high power, in agreement with the theory [6].

Conclusion: the hypothesis of multi-T_{1D} components in complex membranes such as myelin is reasonable, because myelin has a complex and dynamically heterogeneous organization. Future work will link the actual T_{1D} values to membrane properties, such as angular-dependence with B_0 and fluidity.

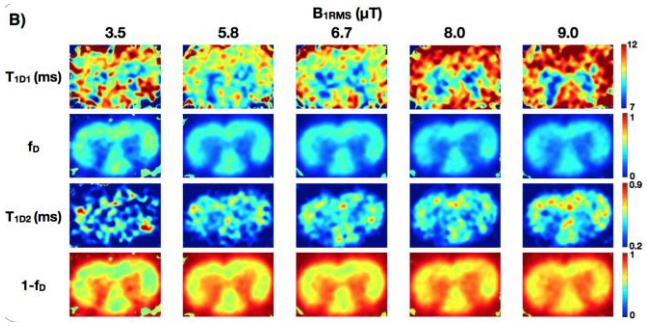

Fig. 1. Long T_{1D1}, short T_{1D2}, fractions f_D and $1\text{-}f_D$ maps acquired with different B_{1RMS} on excised rat spinal cord. Observe that the short component T_{1D2} map, is revealed as B_{1RMS} is increased. Shorter T_{1D} values were found in grey matter (GM) allowing strong contrast between highly myelinated WM and less myelinated GM.

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GETTING THE MOST FROM A FFC-NMR DISPERSION CURVE FROM A POROUS MATERIAL

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The interpretation of T_1^{-1} relaxation rate dispersion curves obtained from FFC-NMR experiments on porous material is challenging. Models used to fit to experimental data over the full frequency range must describe spin diffusion over timescales spanning many orders of magnitude. The 3τ model [1,2] calculates the diffusion correlation functions and Fourier transformations numerically and evolves from Korb's earlier models [3]. The outcome is that the 3τ model can be fit to T_1^{-1} relaxation rate dispersion curves from porous systems with or without paramagnetic impurity spins over the full frequency range (see Fig. 1). Fits yield three characteristic diffusion time constants plus estimates of the characteristic pore dimension and, if relevant, paramagnetic impurity concentration. However, a disadvantage is that the numerical computations are challenging. Now, however, pre-calculated datasets and front-end graphical fitting software are available to the FFC-NMR community allowing least squares fits to T_1^{-1} relaxation rate dispersion curves with uncertainty estimation. The underpinning science behind the 3τ model will be described and analysis software will be demonstrated.

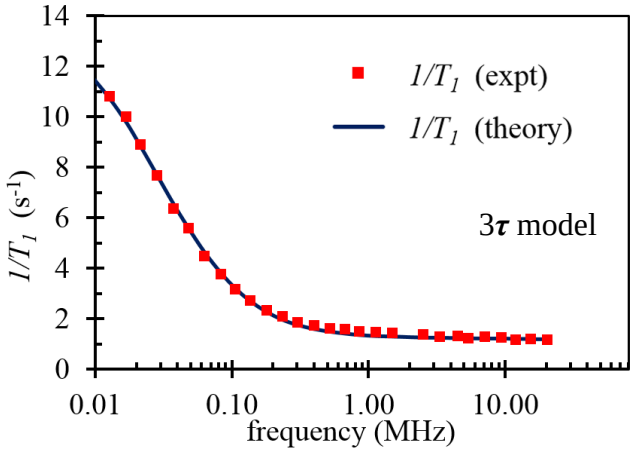

Fig. 1. The spin-lattice relaxation rate T_1^{-1} is presented as a function of frequency for a plaster paste sample from [3]. The solid line is the fit based on the 3τ model.

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FFC-NMRD RELAXOMETRY FOR EARLY DETECTION AND CHARACTERIZATION OF *EX-VIVO* MURINE BREAST CANCER

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Breast Cancer is a multifactorial disease, considered a major public-health issue worldwide. It is the most diffuse cancer among women and the treatment outcome is strongly influenced by the possibility to detect it at a very early development stage and to evaluate the metastatic potential. Quick and detailed diagnostic tests able to provide a detailed characterization of tumor are still needed in order to further improve the chances of curing this disease. It evolves through a multistep progression process, starting from epithelial simple hyperplasia, to atypical hyperplasia, to carcinoma in situ (CIS) and finally to metastatic carcinomas. Herein, Balb-NeuT mice at different ages (7, 15, 21 and 30 weeks) have been used [1]. They are transgenic mice in which breast cancer spontaneously develop in all mammary glands and closely recapitulate human breast cancer development. The onset of cancer is triggered by the overexpression of the activated form of the rat ErbB2 (Her/2-neu) oncogene, whose amplification is typically observed in 20–30% of human breast. In this work, for the first time, it has been reported that Fast Field Cycling Nuclear Magnetic Resonance Dispersion (FFC-NMRD) profiles can be used for the detection of cancer in murine breast tissues biopsies [2]. In particular, from the analysis of longitudinal water relaxation time (T_1) at variable magnetic field (FFC relaxometry), it has been possible to detect the presence of tumor in NeuT mice at a very early stage (7-weeks) when the disease is not detectable by common high resolution MRI and shows minimal and not diffuse histological modifications. Tumor progression is strongly correlated with significant changes in T_1 values and of the overall shape of NMRD profiles (Fig.1A). By fitting with a line the log/log NMRD profiles, it has been possible to quantify the slope of the curve. This parameter is strongly correlated to the tumor stage (Fig.1B). In particular, the slope is small in healthy control (ca. 0.1) and it increases at late stages of tumor (up to *ca*. 0.35 for 30weeks NeuT mice).
In addition, ^{14}N-quadrupolar peaks (^{14}N-QPs) have been analyzed. They are not present in healthy mammary tissue (Fig.1A) but are clearly detectable in presence of the tumor, at all stages of development. Therefore, the presence of ^{14}N-QPs is an early biomarker of tumor onset.
In such a way, NMRD profiles can be suitable for i) making detectable breast tumor at a very early stage (by investigating the presence of ^{14}N-QPs) and ii) making possible to assess tumor stage (by investigating the overall NMRD profile shape). Importantly, both the information can be gained without the administration of exogenous contrast agents.

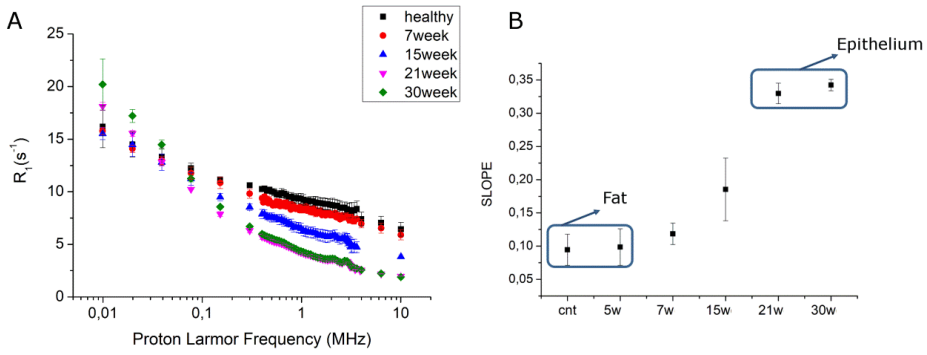

Fig. 1. (A) NMRD profiles of ex vivo breast tissue of NeuT at different stages (7, 15, 21 and 30 weeks) compared with healthy mice. (B) Slope of NMRD profiles at different stages of NeuT.

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PLASTICALLY CRYSTALLINE PHASES STUDIED BY FIELD-CYCLING NMR RELAXOMETRY

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In many cases, the FID in molecular solids becomes rather short, however, there is a class of systems, namely plastically crystalline (PC) phases, which through their dynamic orientational disorder exhibit motionally averaged spectra and thus the corresponding FID is sufficiently long to allow reliable measurements of the dispersion of the spin-lattice relaxation times in the solid state.
In the present study, we demonstrate the potential of FC NMR relaxometry characterizing the various motional processes in PC phases. A paradigmatic case is cyano adamantine [1], which we investigated in the temperature range 4 K - 420 K including FC as well as conventionally measured T_1 data. The molecule is rigid and of globular shape. It forms a PC phase below the melting point T_m = 462 K in which the molecules perform isotropic reorientation on a cubic lattice. At T_t = 280 K a transition to an ordered phase is observed. Super-cooling the PC phase below T_t, however, leads to a slow-down of the overall reorientation. In addition to the overall reorientation of the molecule, a (faster) uniaxial reorientation around the main (C3) axis of the molecule is found.
Almost full reproduction of $T_1(T)$ at the different frequencies is achieved. In the case of the uni-axial rotation persisting at low temperatures, we demonstrate that a distribution of activation energies $g(E)$ reproduces the salient features of $T_1(T)$ down to 4 K. Preliminary results on other PC phases like DABCO and m-carborane are presented, too.

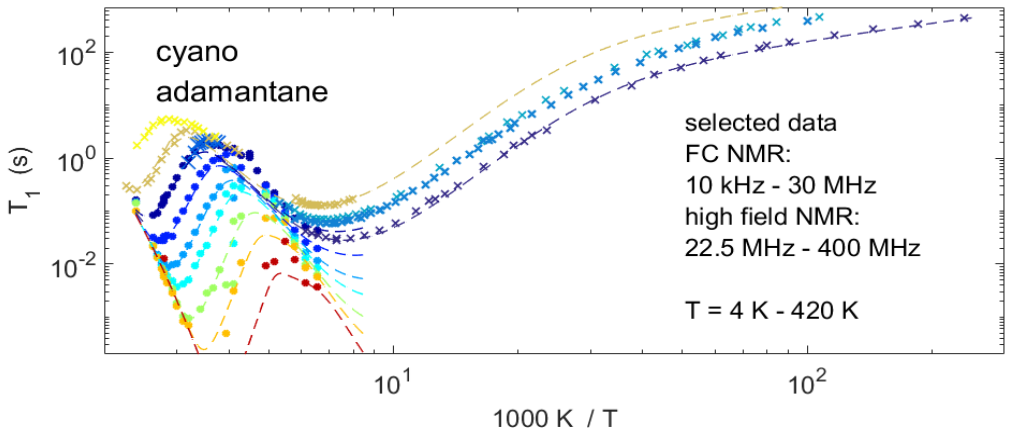

Fig. 1. Spin-lattice relaxation time T_1 of cyano adamantane in its plastically crystalline phase plotted versus the logarithm of inverse temperature T. High-field data from ref. [1] was included.

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NMR RELAXOMETRY STUDIES OF ELECTROLYTES MODEL COMPOUNDS

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The development of the new generation of electrolytes for energy storage, which simultaneously enable substantial improvements in energy and power density, safety and reductions of environmental impacts and cost, is a big challenge at the present time. In this work, two types of electrolytes were explored using the fast filed-cycling NMR relaxometry technique (FFC): ionogels (IGs) and deep eutectic solvents (DES).

The IGs, prepared by B. Dunn and D. Ashby (UCLA), are pseudo-solid-state electrolytes composed of an ionic liquid (IL) confined within the mesoporous network of a sol-gel-derived inorganix matrix [1], therefore they combine the high mechanical and thermal stability of a solid electrolyte with the large ionic conductivity of the ILs [2]. The effect of confinement on ILs dynamics was analyzed by measuring ^{1}H, ^{19}F and ^{7}Li spin-lattice relaxation rate dispersions of IGs made of BMIM-TFSI (1-butyl-3-methylimidazolium–bis-(trifluoromethanesulfon)imide) with 1M Li TFSI into a silica matrix at different temperatures. The analysis of the experimental data was performed assuming the existence of two fractions of the liquid: a core fraction (near the pore center) and a surface fraction (near the confining walls) and using two different models based on translational and rotational diffusion and reorentation mediated by translational displacements (RMTD) [3-5].

DES are formed from two different constituents that do not have to be ionic liquids, but whose mixture has a lower melting point compared to its parents and one of them is hydrogen bond donor (HBD) and the other acceptor (HBA) [6]. They feature a large variety of potential starting materials available to design billions of chemically distinct materials with tailored properties for different applications, among them, electrochemical energy storage [7]. However, fundamental studies that address the relation between chemical structure and physical-electrochemical properties of DES are limited. In this work, the molecular dynamics of DES composed of choline chloride (ChCl) and glycerol was studied by measuring proton spin lattice relaxation rate dispersions at different molar concentrations of ChCl and at different temperatures. Dynamics extracted from the relaxation profiles are compared with results obtained by other techniques, including broadband dielectric spectroscopy.

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THE USE OF LOW RANK APPROXIMATION FOR NOISE REDUCTION IN LOW FIELD NMR: A FLEXIBLE METHOD FOR THE ACCELERATION OF MULTIDIMENSIONAL STUDIES AND THE IMPROVEMENT OF TIME RESOLUTION IN REACTION MONITORING

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Low field time-domain NMR is a flexible technique to investigate several kinds of materials, exploring their physical properties. One of its limitations lies in the low Signal-to-Noise Ratio which is usually overcome by signal accumulation. Unfortunately, there are two settings in which this strategy could be troublesome: multi-dimensional experiments and analysis of evolving systems.
In the case of multi-dimensional experiments, we incur in the "curse of dimensionality": due to the high dimension of the parameter space the number of experiments needed to fit them is very high. This makes accumulating multiple acquisitions particularly time consuming.
For the study of evolving system, the signal accumulation framework is limited by the evolving rate of the system. In fact, the state of the system can significantly change during the time required for multiple acquisitions.
In this work we present the preliminary results for the low rank approximation of complex matrices using Truncated Singular Value Decomposition (TSVD) and we investigate its performance and limits, in the settings of low field NMR (e.g. double quantum filter sequences, reaction monitoring, T_1 dispersion curves).
Let **A** be the *N*x*M* signal matrix, the rows of which are made by the *N* acquired signal. The presence of additive noise makes **A** full rank, so it is possible to reduce the noise by searching for a low rank approximation of **A**.
The truncation of the last *N-k* singular value gives the best approximation in Frobenius norm with rank *k* for **A**. The choice of *k* is related to the a-priori knowledge on the number of signal components and to the variation of the singular value.
Our preliminary results show that the low rank approximation by SVD on complex signal matrix is a useful noise reduction method for accelerating multidimensional experiments and to preserve time resolution in the monitoring of evolving system.

TOWARDS A MODEL-BASED FIELD-FREQUENCY LOCK FOR FAST FIELD CYCLING NMR: EXPERIMENTAL VALIDATION

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Fast Field Cycling Nuclear Magnetic Resonance (FFC NMR) relaxometry allows to investigate molecular dynamics of complex materials. FFC relaxometry experiments require the magnetic field to reach different values in few milliseconds and field oscillations to stay within few ppms during signal acquisition. Such specifications require the introduction of a novel Field-Frequency Lock (FFL) system. In fact, control schemes based only on current feedback may not guarantee field stability, while standard FFLs are designed to handle very slow field fluctuations, such as thermal derives, and may be ineffective in rejecting faster ones. The aim of this work is then to propose a methodology for the synthesis of a regulator that guarantees rejection of field fluctuations and short settling time. Experimental trials are performed for both model validation and evaluation of the closed-loop performances. Relaxometry experiments are performed to verify the improvement obtained with the new FFL. The results highlight the reliability of the model and the effectiveness of the overall approach.

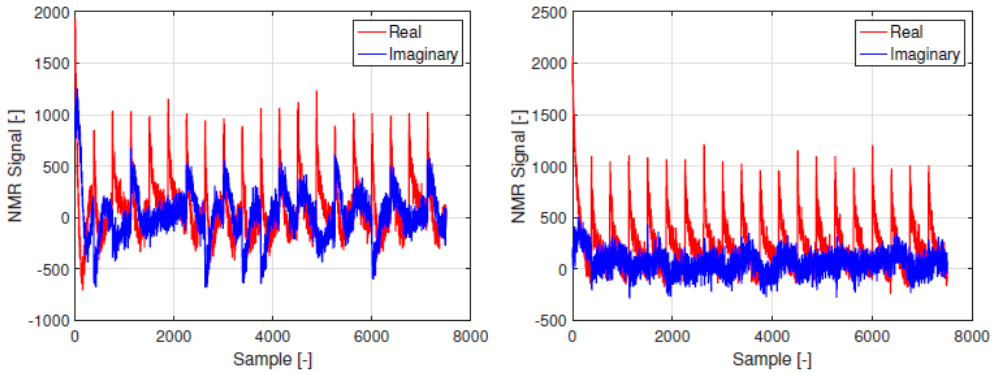

Fig. 1. FFC NMR experiment without lock system (a) and with lock system (b), in presence of a 10 Hz sinusoidal current disturbance.

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DIFFERENCE APPROACH TO ELIMINATING RADICAL RELAXIVITY IN DNP FFC RELAXATION STUDY

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The combination of the well-established DNP and FFC techniques has recently been reported [1] to obtain DNP enhanced T_1 relaxation time dispersion to study molecular dynamics in various systems [2, 3]. Additional relaxivity, i.e., a significant decrease of the relaxation time due to the addition of radicals in the system of interest, inducing drastic changes in the spin-lattice relaxation dispersion, usually renders the analysis of molecular dynamics properties difficult or impossible. Using a new difference approach [4], the dynamics in the system without radicals can be recovered, and the radical relaxation effects can be isolated. The main area of interest for the implementation of the difference approach is the study of molecular dynamics in systems with exhibit low thermal polarization. X nuclei systems are one of the focus areas of interest due to the low natural abundance of some isotopes, such as ^{13}C (~1%), and relatively low gyromagnetic ratio of nuclei, such as ^{2}H, ^{7}Li etc.
In this contribution the proof of principle is discussed based on the molecular dynamics study of a block-copolymer (PS-PB-PS), while the first results of actual X nuclei systems, such as deuterated benzene in nanosilica (see Fig.1), are presented.

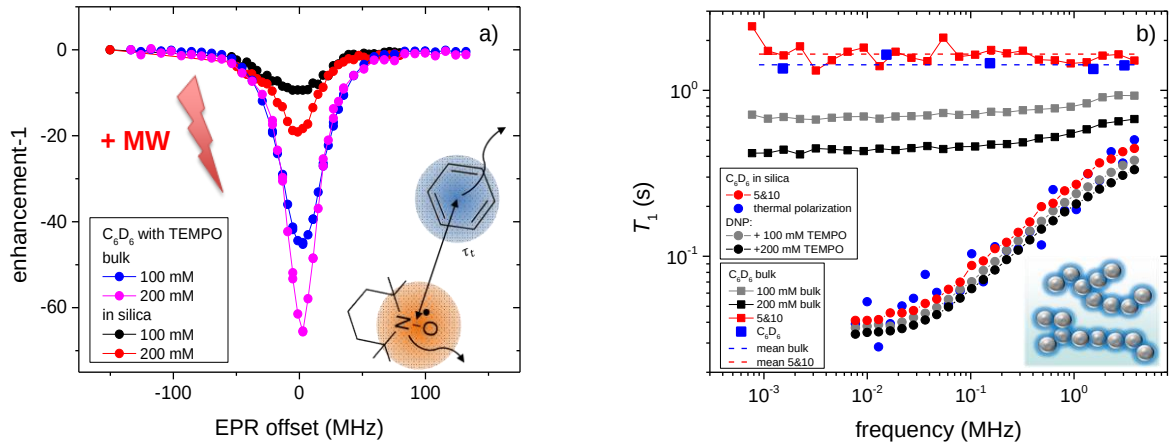

Fig. 1. ^{2}H DNP spectra (a) at 1W microwave power and NMRD (b) of deuterated benzene in bulk and adsorbed in silica without radicals and with 100 and 200 mM of TEMPO in comparison with data recovered with the difference approach.

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NMR RELAXOMETRY FOR ADSORPTION STUDIES: PROOF OF CONCEPT WITH COPPER ADSORPTION ON ACTIVATED ALUMINA

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Water pollution by heavy metal is a major environmental problem [1]. Adsorption is one of the most used and promising heavy metal removal techniques. The development and evaluation of new adsorbents is thus an important topic. Some heavy metal ions - like Cu^{2+}, Mn^{2+}, Cr^{3+}… - are paramagnetic and known to affect the Nuclear Magnetic Resonance (NMR) relaxation times T_1 and T_2 of water protons in aqueous solutions. These relaxation times can be used to evaluate the paramagnetic ion concentration in solution. For the adsorption of Cu^{2+}on activated alumina, we show, after a comparison with conventional methods, that NMR T_2 relaxometry can be used to perform kinetics study and obtain a Langmuir isotherm [2]. The T_2 relaxometric experiment is performed at 0.47 T directly in an NMR tube with 350 µl of solution and 45 mg of adsorbent (Fig.1). For the kinetics study, a single tube is used since the measurement is nondestructive. The NMR experiments allow to determine a maximum Cu^{2+} adsorption capacity q_{max} = 4.32 mg(Cu)/g(Al_2O_3) and an equilibrium adsorption constant K = 0.61 mM^{-1}. T_1 based relaxometry can also be used to evaluate the amount of Cu^{2+} adsorbed on alumina, directly on the wet sorbent. Even if it is limited to paramagnetic heavy metal ions and necessitates rather high metal concentration, NMR relaxometry could become an interesting additional tool for the study of heavy metal adsorption.

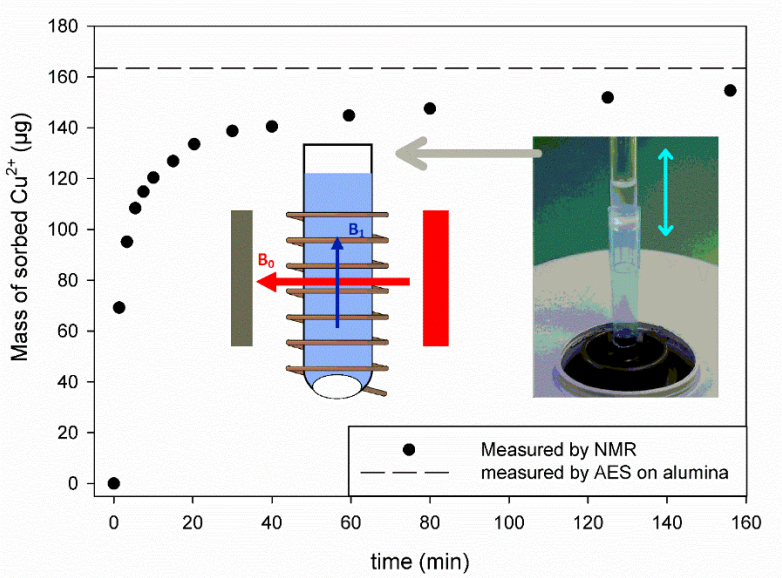

Fig. 1. Principle of the adsorption follow-up by NMR relaxometry

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SYNTHESIS AND RELAXOMETRIC CHARACTERIZATION OF MRI CONTRAST AGENTS BASED ON PYCLEN STRUCTURE AND COMPLEXED WITH MANGANESE

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Magnetic resonance imaging (MRI) has a leading place amongst all the imaging techniques thanks to its high spatial resolution and its non invasiveness. It suffers however from a low sensitivity and requires in some cases the use of contrast agents. Currently clinically used contrast agents are gadolinium complexes but their safety is more and more called into question. They are indeed involved in the NSF (nephrogenic systemic fibrosis) disease for patients with renal dysfunctionment and recent studies have shown a potential accumulation of gadolinium in the brain of patients after several injection, especially for the linear gadolinium complexes [1]. Alternatives are thus more and more investigated, and we propose here the synthesis of manganese contrast agents. These are based on the pyclen structure, with or not an additional arm on the pyridine moiety, allowing a further coupling of the Mn-complex on another entity. These complexes were fully characterized by proton relaxometry and ^{17}O NMR to evaluate their efficacy as MRI contrast agents.

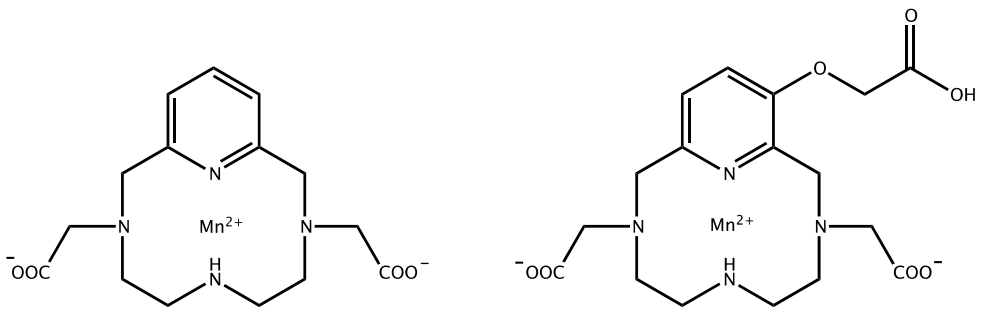

Fig. 1. Mn-complexes derivated from pyclen used in this work.

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SALT SPECIFIC EFFECTS ON NMRD PROFILES OF PROTEIN SOLUTIONS

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The chemical nature of salts can tune the stability of aqueous protein solutions. However, it is difficult to probe salt effects unambiguously. NMRD studies offers a unique and non-invasive way for studying ion-specific effects and their influences on water dynamics. Here, we present R_1 NMRD results for aqueous formulations of bovine serum albumine (BSA) and lysozyme (LZM) with and without added univalent salts (NaCl and NaI). We show that salt addition increases the water proton R_1 in LZM but decreases it in BSA solutions [1]. Original relaxation equations are proposed for reproducing the essential features of the observed ^{1}H-water R_1-NMRD profiles (Fig. 1). Basically, at low frequencies R_1 is dominated by the intramolecular relaxation induced by the reorientational dynamics of a few long-lived water molecules trapped in deep wells that exchange among other less trapped wells of the protein interfacial energy landscape. At high frequencies, R_1 is dominated by the intermolecular relaxation induced by the fast water translational diffusion on the protein surface or its proximity [2]. We believe that the presented NMRD results (Fig. 1) enable a better understanding of water dynamics near the protein surface in solutions with and without salts.

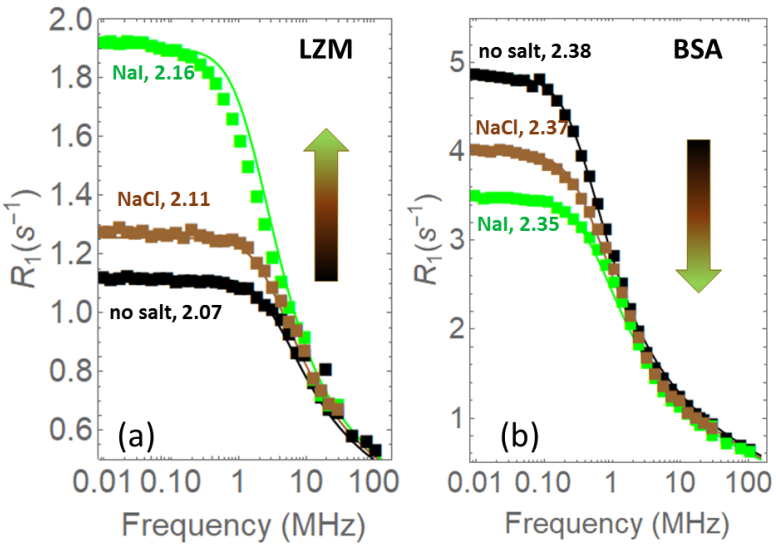

Fig. 1. Water proton R_1 NMRD profiles in LZM **(a)** and BSA **(b)** solutions with and without salts. Symbols represent experiments while solid lines represent the best fits obtained with our relaxation theoretical model varying protein surface fractal dimension (d_f values are indicated in the figures). R_1 in LZM solutions increases as "no salt > NaCl > NaI" while the ordering is reversed for BSA (see arrows).

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NMRD OF WATER IN CONFINED NANOPOROUS NETWORK: INTERMITTENT DYNAMICS VERSUS PORE SURFACE CURVATURE

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The confined dynamics of water molecules inside a pore is an intermittence of adsorption steps near the interface with the possibility of a surface diffusion and excursions in the pore network [1]. Depending of the strength of the interaction in the layer(s) close to the surface and the dynamical confinement of the distal bulk liquid, the exchange dynamics can be more or less fast. The average time spend in the surface proximal region (also called the adsorption layer) between a first entry and a consecutive exit allows to estimate the level of "nanowettablity" of water. As shown in several seminal works, the NMRD is an affective experimental method to follow this type of intermittent dynamics near an interface.
In this conference, the intermittent dynamic of a confined fluid inside nanoporous materials is discussed [2]. A special attention is given to the interplay between bulk diffusion, adsorption and surface diffusion on curved pore interfaces. Taking into account the nano or meso lengthscale confinement of the pore network, an analytical model of the intra-dipolar spin-lattice relaxation dispersion curves is proposed. In the low frequency regime (50KHz-100MHz), this model is successfully compared with numerical simulations performed using a 3D-off lattice reconstruction of the Vycor glass. Comparison with experimental data available in the literature is finally discussed.

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WHAT DO WE KNOW ABOUT ^{14}N QUADRUPOLE RELAXATION ENHANCEMENT?

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The possibility of performing spin relaxation experiments versus magnetic field has lead to revealing several relaxation effects originating from a quantum-mechanical interplay between different types of spin interactions. One of them is Quadrupole Relaxation Enhancement (QRE).
A very "superficial" description of the QRE effect is as follows. Tis effect involves at least one nucleus of spin-quantum number I=1/2 (typically ^{1}H) and one nucleus of spin quantum number $S \geq 1$; let us think about ^{14}N ($S = 1$) as Nitrogen is one of the fundamental components of organic matter, from simple molecules, via proteins to tissues. The two nuclei (^{1}H and ^{14}N) have to be mutually coupled by ^{1}H-^{14}N dipole-dipole interactions. The energy level structure of ^{1}H is fully determined by its Zeeman interaction and, hence, its magnetic spin quantum number, $m_I = \pm 1/2$. ^{14}N nucleus experiences two kinds of interactions: Zeeman interaction and quadrupole coupling – *i.e.* a coupling with the electric field gradient tensor at its position. When the orientation of the electric field gradient tensor is fixed with respect to the direction of the external magnetic field (*i.e.* the molecular dynamics is slow), the energy level structure of ^{14}N is determined by a superposition of the two interactions. This implies that at some magnetic fields the ^{1}H resonance frequency (the transition frequency between the ^{1}H energy levels) matches one of the ^{14}N transition frequencies between its energy levels, the ^{1}H polarization can be "taken over" by ^{14}N leading to a frequency specific enhancement of the ^{1}H spin-lattice relaxation rate, often referred to as "quadrupole peaks". As the positions of the quadrupole peaks depend on the quadrupole parameters which are determined by the electric field gradient tensor at the ^{14}N site, the positions shift in response to even subtle changes in the electric field gradient. Moreover, the presence of the quadrupole peaks can serve as a proof of slow dynamical processes in the system. In consequence, QRE is a very sensitive fingerprint of molecular arrangement exploited in material science, biology and medicine. In the last case the position and the shape of the quadrupole peaks can potentially reflect pathological changes in tissues (*e.g.* early stage tumors).
The mechanism outlined above is, however, very confusing. It does not provide answers to numerous pertinent questions, like:

- Why QRE effects are observed for molecular motion occuring on an intermediate time scale (not only for slow dynamics)?
- Is is possible to precisely formulate the conditions under which they become visible?
- Why in some cases the quadrupole peaks are of Lorentzian shape and in some others not?
- Is their amplitude indeed a measure of an immobilized fraction of protons in the system?
- May one reveal the QRE effects by a simple "extracting" of the relaxation background from the overall relaxation dispersion profiles?
- Why the relative amplitudes of the quadrupolar peaks are different for different systems?

The presentation will answer to these questions and several other.

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^{1}H RELAXATION DISPERSION OF COMPOSITE WHEY PROTEIN ISOLATE HYDROGELS

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Pectin (PC), gum tragacanth (GT) and xanthan gum (XG) blended heat induced whey protein isolate (WPI) hydrogels and hydrogels containing no additional polymer (C) were loaded with black carrot extract (BC). In the presence and absence of BC, ^{1}H relaxation dispersion data of hydrogels were recorded in the frequency range of 4 kHz – 30 MHz (e.g., Fig. 1). According to the relaxation dispersion data, it was estimated that all hydrogels possessed three dynamic processes, characterized by following correlation time values: τ_1 (2.65 – 3.34 x 10^{-6}), τ_2 (3.06 – 5.63 x 10^{-7}) and τ_3 (6.7 x 10^{-9} – 12.42 x 10^{-8}). Rotational dynamics dominated the relaxation processes of all hydrogels containing 80% (w/w) water, down to very low frequencies due to the high tendency of T_1 to change in frequency [1]. Translational dynamics was observed at a small frequency independent region at very low frequency regime. Therefore, R_1 ($1/T_1$) *versus* square root of frequency graphs were plotted and the translational diffusion coefficients of the samples were calculated in the linear region. Diffusion coefficients of the all hydrogels were in the range of (1.42 – 1.90) x 10^{-14} m^2/s, showing that the diffusion of water was hindered within the hydrogel matrixes by means of interactions between entrapped liquids and surrounding gel network [2]. Since samples contained WPI, quadrupole peaks were also observed at the frequency range around 2 x 10^6 Hz [3].

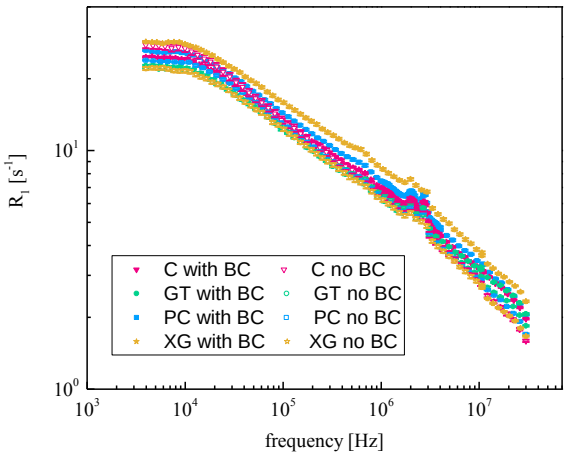

Fig. 1. ^{1}H relaxation dispersion data of hydrogels.

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LOCAL AND GLOBAL DYNAMICS IN INTRINSICALLY DISORDERED PROTEINS

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FFC relaxometry allows for the direct measurement of protein proton spectral density functions by dissolving proteins in D_2O at millimolar concentrations. This permits to collectively monitor the relaxation rates of non-exchanging protein protons as a function of the magnetic field [1]. The analysis of these profiles provides direct information on the protein reorientation time, and thus on its aggregation state, and on the collective order parameter of protein protons, and thus on internal mobility. Such analysis takes advantage of a complete relaxation matrix analysis, in order to model the distribution of the proton relaxation rates in proteins [2].

The profiles of well folded proteins are characterized by a large relaxation rate at low fields (from 100 to thousands s^{-1}), and by a Lorentzian dispersion reporting on the correlation time modulating the dipole-dipole interactions between protein protons. For a protein of about 150 amino acids, correlation times around 10 ns are expected and measured at 298 K. The low field relaxation rate is however somewhat smaller than calculated, due to the presence of local mobility, and the observed discrepancy provides an estimate of the extent of these fast motions, in the form of a model-free order parameter S_C.

For intrinsically disordered proteins (IDPs), no dispersion should be observed in the 0.01-50 MHz range of proton Larmor frequency. Instead, relaxometry measurements performed at 298 K for IDPs of 100-150 amino acids in D_2O solutions show dispersions corresponding to correlation times of about 5-8 ns, thus indicating the presence of motions occurring on a timescale much longer than that of IDP segmental motions, which are not related to specific long-range interactions between the protein residues, and thus represent an intrinsic feature of the mobility of IDPs [3]. The low field relaxation rates are however much smaller in IDPs (10-50 s^{-1}) than for well folded proteins, as a result of an S_C^2 of about 0.1.

Molecular dynamics (MD) simulations represent an ideal tool for elucidating the mobility of IDPs at an atomic level of detail. Using a very long trajectory of 34 μs recently generated for the IDP α-synuclein, we have shown that the presence of motions with correlation times of several nanoseconds is also supported by MD simulations [4]. In fact, the calculated MD trajectory shows that, although most of the conformational dynamics occurs locally, fast local motions are unable of averaging dipolar interactions completely, indicating the presence of correlation times of 6-9 ns, with S_C^2 of 0.04-0.10, in full agreement with the experimental relaxometry data.

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FAST FIELD CYCLING RELAXOMETRY OF A UNIQUE IONIC COMPOUND

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Fast-field cycling relaxometry (FFC) is a rapidly expanding NMR technique with applications in a diverse range of materials science [1]. As a case study, we discuss its use in revealing the dynamics present in an ionic compound, [$N_{10,111}$][beti], whose solid possesses a unique combination of properties. Above its melting point (31°C) [$N_{10,111}$][beti] behaves as a typical room-temperature ionic liquid [2]. Upon solidification it forms an optically clear glass-like material, yet its X-ray diffraction shows only sharp peaks and no diffuse component. After employing a number of techniques (such as X-ray diffraction, NMR high-field measurements and others) to better understand the molecular structure of this unique solid, we investigated its dynamics using FFC NMR Relaxometry. FFC is a low-field NMR technique which allows measurement of the dependence of the longitudinal relaxation rate $R_1 = 1/T_1$ of the samples over a wide range of magnetic fields using just one instrument [3]. We performed FFC measurements using Stelar's SPINMASTER 1T FFC relaxometer on ^{1}H and ^{19}F nuclei from 10 kHz up to 40 MHz). Furthermore, experiments were carried out over a wide range of temperatures (Fig.1). Temperature-dependent ^{1}H and ^{19}F FFC data in the liquid are similar and both were analyzed in terms of relaxation models used for other liquid systems [2]. In the low temperature phase, both ^{1}H-cations and anion-localized ^{19}F spin-lattice relaxation dispersions take on an additional relaxation contribution with a power-law character whose interpretation is currently under investigation.

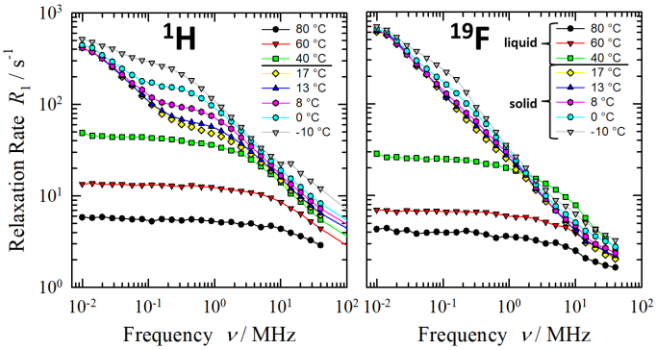

Fig. 1. FFC data for ^{1}H and ^{19}F nuclei.

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ROLE OF PORE INTERCONNECTIVITY ON MOLECULAR DIFFUSION WITHIN FAUJASITE ZEOLITE INVESTIGATED BY NMR RELAXOMETRY

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Hierarchical porous materials are present in many industrial processes, for example in petroleum industry for oil refining. In this lecture, we will discuss diffusion behavior of different molecules within the pore network of faujasite zeolite Y (fig. 1).

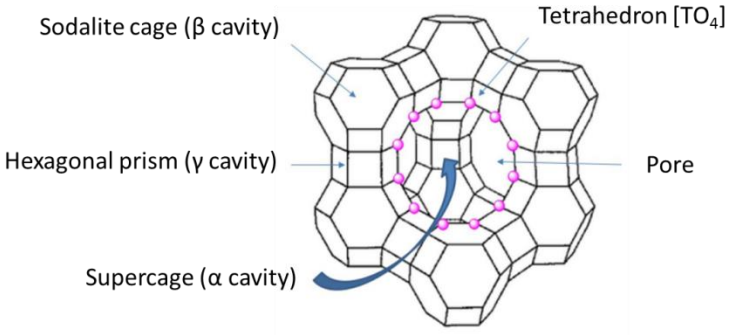

Fig. 1. Crystal structure of faujasite NaY

Zeolitic crystal pore structure contains micropores with a diameter less than 2 nm. The mesopores and macropores are created in order to improve diffusion, thus considering the studied zeolites as multi-scale materials. A fundamental problem in this system is the molecular transport to reach the reaction sites. To shed light on this phenomenon, three types of zeolites with different surfaces areas and SiO_2/Al_2O_3 mole ratios are employed. These samples are filled with various amounts of cyclohexane or dodecane using an adsorption protocol.
The molecular transport has been investigated using ^1H and ^2H NMR Relaxometry from 10 kHz up to 100 MHz allowing the observation of distinct dynamics upon the filling rate (from 0.1 of micropore to full mesopore volume) and the Si/Al ratio of zeolite.

FFC-MRI AT LOW MAGNETIC FIELD HOMOGENEITY

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The magnetic field homogeneity is an important aspect in magnetic resonance imaging (MRI). Field inhomogeneity causes distortions in both the geometry and intensity of the image [1]. The homogeneity in commercial MRI scanners is usually close to few ppm, a condition hardly achievable in fast field-cycling (FFC) NMR electromagnets (typically of the order or higher than 100 ppm). We have recently presented a FFC relaxometer with MRI capabilities [2]. Such an instrument turns ideal for the study and design of new physical and chemical contrasts agents for field-cycled MRI. A key aspect of the FFC-MRI relaxometer relays on its magnet homogeneity: there is a compromise between the ideal requirements for MRI experiments and the required performance of the power supply (surviving to a certain degree of inhomogeneity strongly reduces technical difficulties and costs). In this work we present the instrument prototype of own design, and focus the discussion on the magnetic field homogeneity. The electromagnet is a novel variable-geometry Notch-type coil [3]. The variable-geometry electromagnet endows it with magnetic field and homogeneity correction capabilities. The magnet was degraded to 4500 ppm and after adjustment of the magnet´s geometry a maximal recovery up to 1400 ppm was possible. We will show first results after implementing methods [4] to deal with such inhomogeneity that successfully conduced to images without distortions. The machine is currently in use for the design of new physical contrasts based in the low-field manipulation of the spin-system.

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TEMPERA PAINTINGS: THE EYE OF NMR RELAXOMETRY ON AN ANCIENT RECIPE

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Tempera painting is an old pictorial technique widely used from Antiquity to the advent of oil painting in the XVth century. It has been here and there used since. Several recipes have been developed over centuries and different geographical areas. This technique consists in mixing finely grinded mineral pigments with a binder that can be egg, skin glue or wax. Supplementary additives can also be used as vinegar. In this study, we will focus on *a tempera* painting based on egg yolk and green earth. This mixture was espacially as underlayer for a better representation of the skins (*verdaccio*) as it can be seen on the uncompleted painting of Michelango *The Manchester Madonna* (figure 1).

Fig. 1. The Manchester Madonna, about 1497, possibly as early as 1494, Michelangelo. The National Gallery, London.

The understanding of this technique from it properties to its artistic end, requires to understand the water dynamics at different scales and its correlation with the textural properties of tempera paintings. In this aim, rheological measurements have been carried out and compared to the ^{1}H relaxation rate (from 10 kHz to 100 MHz) for several formulations. For the latters, we have followed the recipe described in the book of Cennino Cennini "Il libro dell'Arte" written in 1437.

We have used green earths originated from several deposits. We have also compared the results of the formulations with those obtained with elemental minerals presents in the green earths (celadonite, montmorillonite, calcite, quartz, etc.) or equivalent (muscovite).

The evolution of the relaxation rate of ^{1}H with frequency is the signature of the dynamics at different scales. It reveals that in the green earth and water mixtures, the water dynamics can be described by a fast exchange between the mineral grain surface and bulk [1]. The addition of egg yolk yields to a drastic change in the rheological properties of the formulation. While the ^{1}H relaxation rate increases with the amount of minerals in the green earths/water formulations, the reverse evolution is observed with the formulations including egg yolk.

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FAST FIELD-CYCLING MRI IDENTIFIES ISCHAEMIC STROKE AT ULTRA-LOW MAGNETIC FIELD STRENGTH

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Introduction: Fast Field-Cycling MRI[1] (FFC-MRI) is a novel MRI technique in which the external magnetic field is switched during the imaging experiment. By doing this, FFC-MRI gains access to information which is invisible to conventional MRI scanners, including the variation of T_1 with magnetic field. In this work we aimed to assess whether we can identify recent cerebral infarcts at ultra-low field strength, when compared with conventional imaging.
Methods: After informed consent, a group of patients (n=24) with ischemic stroke were scanned within 24-96h of presentation. The FFC-MRI examination took 45 minutes, and included FFC images at five evolution fields (0.2 mT to 0.2 T). Patients also had CT and/or 3T MRI images available.
Results: In patients with sub-acute ischaemic stroke, T_1-weighted FFC-MRI images exhibited hyper-intense regions, with contrast increasing markedly as the evolution magnetic strength field decreased, to a maximum at the lowest field used (0.2 mT). The infarct region measured by FFC-MRI correlated well with the abnormality in CT and/or Diffusion Weighted images (DWI) (Examples in Fig. 1,2).
Discussion: This is the first-ever clinical application of this new modality, proving that FFC-MRI can generate diagnostic-quality images of ischaemic stroke at ultra-low magnetic fields (e.g. 0.2 mT), with significantly enhanced endogenous T_1-contrast compared to conventional MRI. These exciting findings have implications for future development of a new and safe imaging modality not only for stroke but many other clinical conditions.

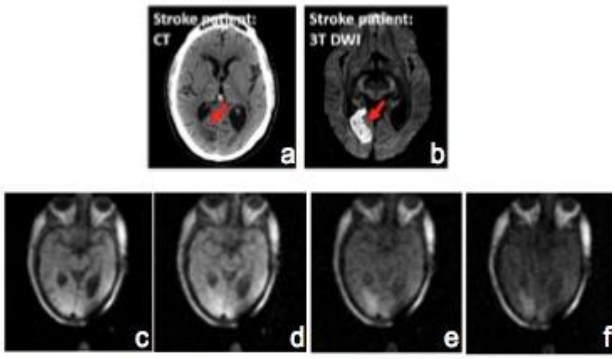

Fig. 1. CT, 3T DWI MRI and FFC MRI images from a 67 year old male admitted with a right occipital infarct. a) CT at 24 hours after onset, b) 3T DWI image at 78 hours after onset, c-f) FFC-MRI inversion-recovery images at the level of the lesion at 200mT, 50mT, 2mT and 0.2mT respectively (75 hours after onset).

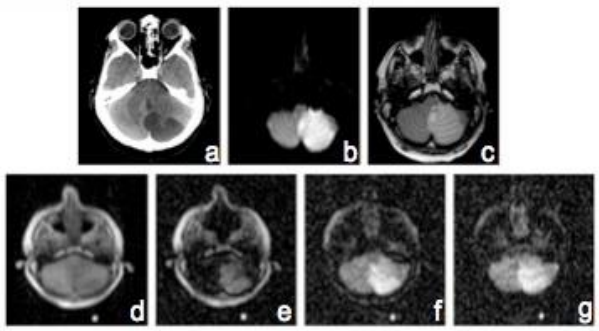

Fig. 2. CT, 3T MRI and FFC MRI images from a 50 year old male admitted with a posterior inferior cerebral artery territory infarct. a) CT at 24 hours after onset, b) 3T DWI image at 96 hours after onset, c) 3T T2 weighted image at 96 hours after onset, d-g) FFC-MRI inversion-recovery images at the level of the lesion at 200mT, 2.2mT, 2mT and 0.2mT respectively (90 hours after onset).

Acknowledgements: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 668119 (project "IDentIFY").

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FIELD CYCLING RELAXOMETRY OF POLYDISPERSED SAMPLES: SOME SPECIAL ASPECTS

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Field cycling NMR relaxometry is often used to measure the characterize solid and semi-solid samples which can be at least approximately characterized by a single longitudinal relaxation time T_1. The focus in these cases is on the field dependence of the T_1, i.e., just the apparent dispersion curve.
However, many systems of great importance both in life and materials sciences are not mono-exponential, either because they are chemically or morphologically heterogeneous or because, even though apparently homogeneous, they exhibit signal components relaxing at different rates.
When measuring such systems on instruments with fixed magnetic fields, one normally collects particularly large amounts of data (for example, hundreds of tau values in experiments like IR and SR) in order to characterize in great detail the empirical relaxation curves, and then attempts (with well-known mathematical difficulties) to extract from those data the desired quantitative distributions of the relaxation times within the sample.
Carrying out the same procedure on a field cycling instrument, with the goal of acquiring the relaxation time distributions at different field strength, while highly desirable, encounters various obstacles. Some are just annoying but otherwise relatively straightforward. In particular, this regards the fact that data acquisition times need to be much longer than under the simplified mono-exponential assumption.
Other would be problems are more subtle and are related to two facts: the various sample ‘components’,

(i) since they have different relaxation rates, exhibit different attenuation factors during the FC sequences. This leads to apparent distortions of the relaxion times distributions.
(ii) since they also exhibit different field dependencies of their relaxation rates, the relaxation times distributions vary with magnetic field in a complex way which defies correct analysis of the results.

In this presentation we will focus in particular on point (i) trying to set up a theoretical and computational framework within which the distortions can be understood and possibly even corrected. Point (ii) will be discussed, but only in a qualitative way (work in progress).

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MAGNETIC FIELD CYCLING OVER ULTRA-WIDE RANGE FOR NMR RELAXATION DISPERSION AND HYPERPOLARIZATION

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The influence of stationary spin-spin interaction on spin evolution, in particular on relaxation and polarization transfer processes becomes important in the regime of strong coupling, i.e. when the coupling strength between spins becomes comparable to (or larger than) their difference in Zeeman interaction. Accordingly, field variation is a suitable way for switching between weak and strong coupling. While in such experiments the NMR detection is usually done at high field under weak coupling conditions, spin evolution proceeds at low field. For liquids, when the leading coupling term is scalar J-coupling, the strong coupling regime can go up to several Tesla for homonuclear spin groups. In contrast, for heteronuclei with their large difference in Larmor frequency one has to reduce the field to 10^{-4} T or lower to get strong coupling. This consideration gave the motivation for devising a field-cycling set-up that covers the full range between about 10^{-9} T and 10 T. It is constructed as an add-on for standard NMR spectrometers and based on a digitally controlled shuttling system that moves the sample between the spectrometer magnet providing high resolution spectra and a shielding permalloy barrel equipped with an ancillary set of coils for shimming and field control. In this way the field amplitude is adjustable in steps of 1 nT while its total inhomogeneity across the sample volume (20 mm x 5 mm diam.) is reduced to less than 5 nT. In cases when a sudden jump into or out of the strong coupling regime is desirable, a Helmholtz pair provides this option. [1] For fields above 0.5 mT the sample is positioned in the stray field of the spectrometer magnet.

The strong influence of homo- and heteronuclear spin-spin coupling on the relaxation dispersion is demonstrated on several examples. For coupled heteronuclear spin systems relaxation with a common T_1 is found at low fields, where the spins are "strongly coupled". In some cases, experiments at ultralow fields provide access to heteronuclear long-lived spin states. Efficient coherent polarization transfer is seen for proton-carbon spin systems at ultralow fields as follows from the observation of quantum oscillations in the polarization evolution. Applications to analysis and manipulation of heteronuclear spin systems are discussed.

Likewise, the polarization transfer between para-hydrogen and ^{15}N or ^{13}C in hyperpolarization experiments strongly varies in the range down to 10^{-8} T. Features of avoided level crossings (LACs) are clearly resolved and can be used to characterize transient catalytic complexes [2].

Acknowledgements: This work was supported by the Russian Science Foundation (project No. 15-13-20035).

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SIMULATION OF THE NUCLEAR MAGNETIC RELAXATION INDUCED BY SUPERPARAMAGNETIC NANOPARTICLES TRAPPED IN A BIOLOGICAL TISSUE

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Superparamagnetic nanoparticles are generally composed of iron oxides and have the property of having a high magnetization when submitted to a high external field, and no remnant magnetization in zero field. There is a variety of theoretical models which try to quantitatively explain the relaxation induced by those types of nanoparticles: this effect can be modeled by the magnetic inhomogeneities produced by the nanoparticles and the diffusion of the water molecules around them [1].
The diffusion coefficient of water molecules is an important parameter in these models. However, they only consider relaxation in a homogeneous medium: in a biological tissue, the diffusion of the water molecules is strongly constrained by the presence of a network of cells in which water diffuses. Moreover, cellular membranes affect the water molecule movement through their permeability. Those constraints on diffusion affect the relaxation times [2].
This work aims at simulating by using Monte Carlo techniques the relaxation of water molecules in a tissue loaded by superparamagnetic nanoparticles. The tissue is modeled as a periodic layout of semi-permeable membranes. It is shown that, when all the cells are identically loaded by the nanoparticles, the simulated relaxation times do no differ from the relaxation in a homogeneous medium and do not depend on the cell permeability. If the tissue cells are not all loaded in the same way, the relaxation can greatly vary and will depend on the cell permeability and the spatial distribution of the nanoparticles. This effect should thus be taken into account for the iron quantification by MRI in vivo.

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PROBING INTERACTION STRENGTH AND LIQUID DYNAMICS IN NANOPOROUS OXIDES USING FAST FIELD CYCLING NMR

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Fast field cycling relaxometry has been shown to be a powerful tool for the analysis of adsorbate dynamics and liquid-surface interactions for a wide range of porous media [1-3]. In this study the behaviour of a simple, yet catalytically important, γ-alumina surface was studied. Significantly different NMRD profiles were obtained for six liquids, which represented many of the key chemical functionalities used in catalysis, imbibed within the alumina (Fig 1a). The NMRD profiles could be rationalized in terms of the type and strength of surface bonding, allowing a ranking of the adsorbate-surface interaction strengths. Further insights into the molecular dynamics were obtained by transforming the data into the T_1 domain. This transformation revealed minor components in the T_1 distributions of methanol and acetone (Fig 1b), the physical origins of which were shown to be functionality-specific relaxation and competitive adsorption due to stable reaction intermediates [4]. This works has led to an improved understanding of the physiochemical processes occuring within the pore space and a more robust characterisation of interaction strength. The approaches used for single component systems were applied to binary liquid mixtues imbibed within γ-alumina in order to explore the competitive adsorption process and the liquid structuring within the pore space. For both non-polar:polar and polar:polar mixtures an extreme microphase separation was observed [5].

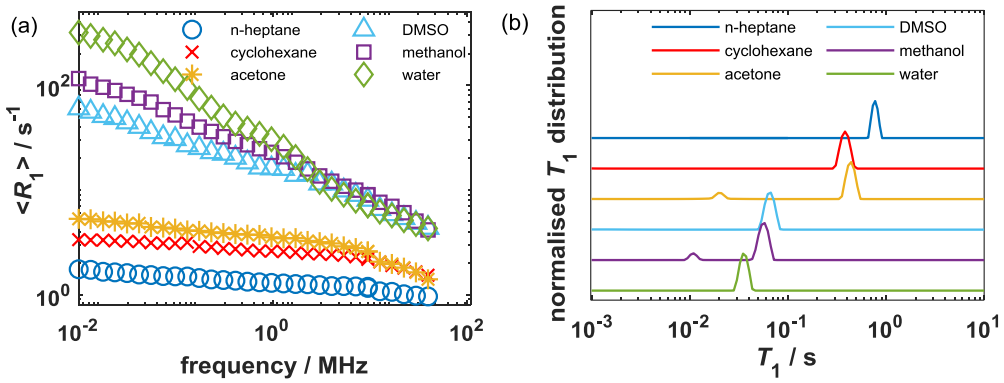

Fig. 1. The (a) NMRD profiles of six different liquids imbibed within γ-alumina and (b) the corresponding T_1 distributions obtained at 1 MHz for each liquid.

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FIELD-CYCLING STUDY OF EXCHANGE INTERACTION IN SHORT-LIVED BIRADICALS BY LIGHT-INDUCED NUCLEAR HYPERPOLARIZATION IN RIGID D-X-A DYADS

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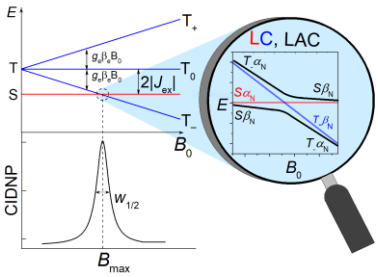
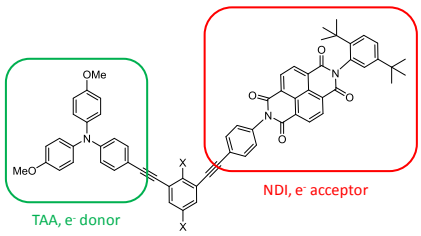
Intramolecular charge transfer is of great importance for understanding many important chemical and biochemical processes. For example, photoinduced electron transfer is the crucial step in photosynthesis or in photovoltaic cells. Model donor-bridge-acceptor compounds, which form a short lived charge-separated (CS) state under light irradiation, can be used to investigate this phenomenon [1]. As a result of spin-selective charge recombination, non-equilibrium population of nuclear Zeeman states is formed, the effect is known as chemically induced dynamic nuclear polarization (CIDNP). CIDNP is a nuclear magnetic resonance (NMR) phenomenon, which arises in spin-selective recombination of radicals and is observed as anomalous intensities and phases in the NMR spectra of diamagnetic products of radical reactions. During relaxation time in the diamagnetic ground state, the product molecules "remember" that they originated from radicals and can be detected by the conventional NMR techniques with all the advantages of NMR spectroscopy, the most important of which is spectral resolution. The polarization formed is sensitive to magnetic resonance parameters of the radicals such as g-factors of the radicals, hyperfine coupling constants, exchange interaction, and other.





Here, we present measurements of ^{1}H time-resolved and field-cycling CIDNP, as well as ^{13}C field-cycling CIDNP [2] of rigid donor-bridge-acceptor dyads, where a triarylamine moiety TAA is an electron donor, bridge is a bisethynylenebenzene (with X=Me, Cl, OMe, CN), and naphthalene diimide NDI is an electron acceptor. They represent an excellent model system for studying reversible photoinduced charge separation by CIDNP. From ^{1}H CIDNP spectra obtained with time resolution of 0.5 μs detected at 4,7 T we got the spin-density distribution in the short-lived biradicals. From the level crossing feature in the ^{1}H and ^{13}C CIDNP field dependences we obtained information on sign and magnitude of the exchange interaction, J_{ex} , hyperfine coupling constants and from $w_{1/2}$ the paramagnetic nuclear relaxation which is related to the hyperfine coupling anisotropy. A new approach for analyzing the field dependence will be presented. Having at natural abundance of ^{13}C a CIDNP enhancement around 3300 (with repect to thermal polarization at 9.4T) allowed us to detect ^{13}C-CIDNP spectra with excellent signal-to-noise ratio at biradical concentrations of less than 0.1 nM.

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Posters

FIELD-CYCLING NMR RELAXOMETRY ANALYTICS OF A LUBRICANT BASE OIL SUBJECTED TO THERMAL STRESS

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Lubricant oils are complex mixtures of hydrocarbons composed of a base oil and additives [1]. They are indispensable in most of the mechanical systems that involves mobile parts, and it is expected that their performance results progressively affected as a consequence of fulfilling its functions [2]. A variety of physical and chemical factors affect the lubricant at molecular level. Heating is present in all internal combustion engines, and has an active role in processes as, nitrogen, oxygen and sulfur incorporation, hydrocarbon chains ruptures and ramifications [3-7].
Proton fast field-cycling nuclear magnetic resonance (H^1 FFC-NMR) relaxometry can be used to study the effect of thermal stress in a lubricant base oil. In a recent paper, we show results of base oil that underwent controlled thermal degradation [8]. The relaxometric response was evaluated and interpreted in terms of self-diffusion and molecular rotations. Base oil degradation was done at T=90°C and T=270°C, and the produced degradation becomes clearly evidenced in the profiles, especially at low relaxation fields.
In this work we show new results and other experiments using Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance spectroscopy (NMRS) that support the changes observed in the relaxation dispersions curves. Oxidation, hydrocarbon chains ruptures and ramification promoted by heating were clearly evidenced.

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RELAXOMETRIC INVESTIGATION OF A BIOMIMETIC LIPID-BASED MAGNETIC NANOVECTOR

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An increasing awareness about novel medical applications of smaller, inorganic-based nanoparticles, possessing unique properties at the nanoscale, has led to a burst of research activities in the development of "nanoprobes" for diagnostic medicine and agents for novel, externally activated, therapies. In this research field, magnetic nanoparticles are prominent due to fundamental peculiar properties which make them particularly appealing to materials and biomedical applications.
At the same time, biomimetic nanomaterials made of a variety of different materials (e.g. natural polymers and lipids) and different forms (e.g. nanospheres, micelles, nanorods, nanotubes, etc) are particularly interesting for their capability to act as delivery vehicles. These nanovectors can be designed in such a way as to alter their physicochemical properties under a specific stimulus, which can be either physical, chemical, biological, or any combination thereof, enhancing their ability to release the encapsulated drug. Moreover, they demonstrate a biomimetic character with increased biocompatibility and low immunogenicity, which allows them, as mentioned above, to effectively deliver various therapeutic substances in a controlled way.
Combining the properties of these two classes of nanomaterials, we fabricated a biomimetic lipid-based magnetic nanovector with a good loading capacity of the chemotherapic temozolomide; our vector showed the ability to release heat locally after being exposed to an adequate alternating magnetic field [1].
In the perspective of obtaining a theranostic nanovector, we tested the relaxometric properties of a comparable system without the presence of the encapsulated drug.
Here we present the ^{1}H-NMR-D profiles collected in the wide frequency range 0.01-57MHz; the range was selected to allow the investigation of the physical mechanisms responsible for nuclear relaxation through the analysis of the $r_1(\nu)$ and $r_2(\nu)$ curves and to cover several frequencies associated to the fields used by most common clinical imagers, i.e., $\mu_0 H$ = 0.2, 0.5, and near 1.5 T (corresponding to ~8, 20, and 64MHz). In particular, the transverse relaxivity values, although lower than those of withdrawn (from market) Endorem® contrast agent, show a quite good relaxometric efficiency. This feature, combined with the other properties of the nanovector, make it a promising solution for further applicative developments.

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FAST FIELD CYCLING NMR RELAXOMETRY OF BURGUNDY WINES

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Proton spin-lattice relaxation in synthetic and real wines is studied by fast field cycling NMR relaxometry. The relaxation mechanism unambiguously originates from proton interaction with paramagnetic ions naturally present in wines. Proton NMRD profiles of white and red wine from Burgundy, and model wines are well reproduced by Solomon-Bloembergen-Morgan equations [1, 2]. Relaxation is primarily governed by interactions with Mn^{2+}. A straightforward model-independent quantification of the manganese ion concentration (down to few tens of µg/l) is proposed, but Fe^{3+} occurrence, and manganese complexation could also be identified in situ [3].

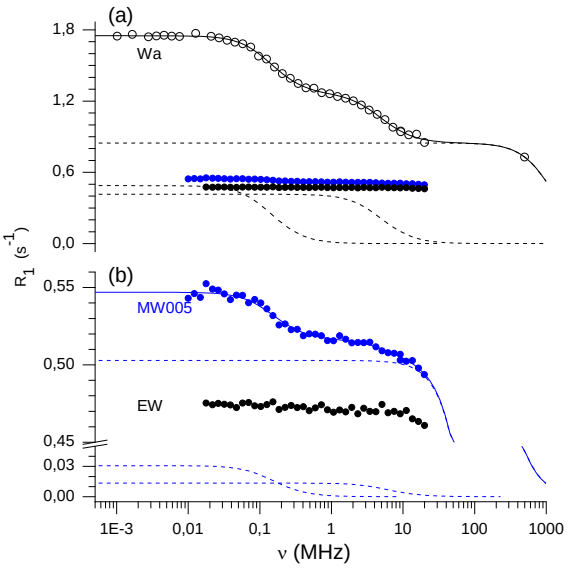

Fig. 1. Proton NMRD profiles of wine (Wa), exchanged wine (EW) and model wine (MW005) containing 50 µg/l of Mn^{2}+. Solid lines are simulataed with Solomon-Bloembergen-Morgan equations.

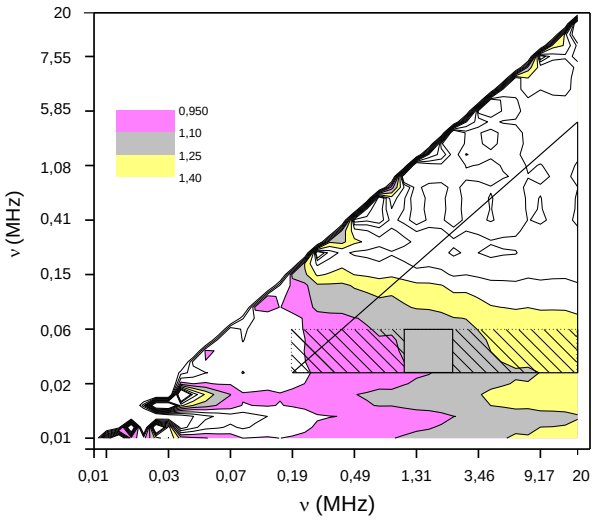

Fig. 2. Mn^{2+} concentrations of Wa for all possible frequency couples. Average concentrations of 1.17(9), 1.2(1), and 1.3(2) mg/l were calculated for the square, rectangular and tringle zone, respectively. The ICP-MS measured Mn^{2+}concentration is 1.25 mg/l .

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NMR RELAXOMETRY IN REAL AND MODEL FOOD SYSTEMS: IMPACT OF SUCROSE AND WATER CONTENT ON THE STRUCTURE AND MOLECULAR DYNAMICS IN CEREAL BASED-PRODUCTS

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Results of preliminary study concerning proton dynamic within extrudate cereal based-products are reported. The extrudates, prepared with a twin-screw extruder, are composed of wheat flour, gluten, salt, and sucrose. Differential scanning calorimetry evidenced multiple glass transitions revealing heterogeneities that could be associated with either a polymer-rich phase and/or a plasticizer (sugar)-rich phase [1, 2]. Extrudates stored at the same water activity, may present difference in the zones inside the materials with distinct water content [2]. On the basis of the assumption that proton mobility should vary in the different phases, fast field-cycling NMR relaxometry is used to follow impacts on a longitudinal relaxation rate (R1) of sucrose content (0 & 10%) and humidity (11 & 75% RH) during storage effects. Whatever the humidity of the samples is, with or without sucrose, NMRD profiles show three linear dependences on the log-log representation (Fig. 1.b). The deviation of experimental data in the lowest frequency range (below 0.1 MHz) should be considered with caution because of the limit of relaxometer switching time (3 ms). However, the slopes S1 and S2 could be associated with two different mobilities (i.e. within the domains, water at the pore surface). The relaxation rate measured for extrudates stored at 75% RH showed higher mobility than that of samples stored at 11%RH (Fig. 1a). Addition of plasticizer such as sucrose, clearly modify the low-frequency part of the NMRD profile while the high-frequency region is unchanged (Fig. 1b). These results should contribute to understand and control impact of sucrose and water on the physical properties that govern the gustative qualities of the cereals and also improve their shelf life.

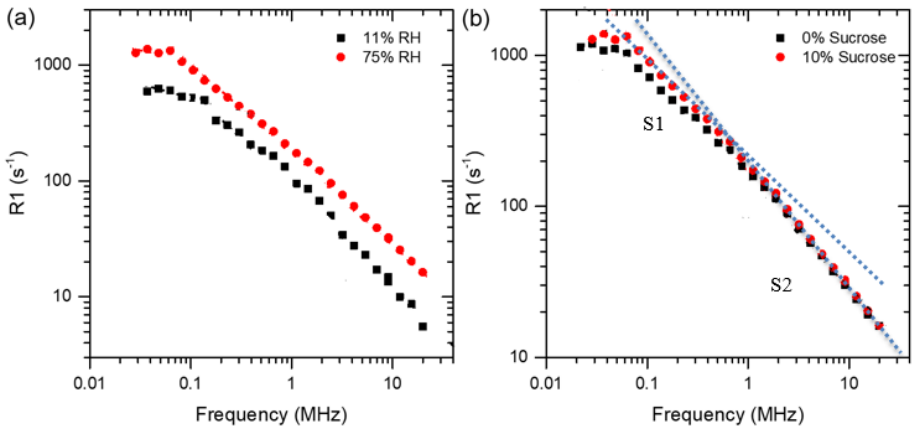

Fig. 1. Proton NMRD profiles of extrudates; (a) Extruded sample containing 10% sucrose stored at 11 and 75% relative humidity; (b) Extruded sample contained 0 and 10% sucrose stored at 75% relative humidity.

Acknowledgements: Authors are grateful to COST Action CA15209 European Network on NMR Relaxometry (EURELAX)

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DYNAMICS OF AN ANHYDROUS SOLID FORM OF Na-IBUPROFEN FROM ^{1}H AND ^{13}C NUCLEAR RELAXATION TIMES

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Ibuprofen is a very widely used non-steroidal analgesic and anti-inflammatory drug, delivered in many different solid formulations. The sodium salt of Ibuprofen has received considerable attention in pharmaceutical research and industry because, thanks to its higher water solubility, it acts more rapidly than the more common acid form of Ibuprofen. The stable form of Na-Ibuprofen at room temperature is a di-hydrated crystal, which has been widely studied and characterized [1-2].
The di-hydrated form undergoes dehydration when heated above 80°C or exposed to P_2O_5 or to N_2 atmosphere, giving rise to an anhydrous form named *form 1* [3]. The structural properties of this form at room temperature have been investigated by X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Solid State NMR (SSNMR) [4].
In this work we have investigated *form 1* by SSNMR in the temperature range 20-80°C. We have found that *form 1* is not stable upon heating and it transforms into a new phase, *form 2*, which on the contrary results to be stable after further cooling and heating steps. This prompted us to investigate the molecular dynamic properties of Na-Ibuprofen in *form 2*, also with the aim of comparing them with those of *form 1* and of the di-hydrated form.
All the internal molecular motions of *form 2* with frequencies ranging from 10^4 to 10^8 Hz have been characterized in detail by combining ^{1}H Fast Field Cycling (FFC) with the measurement of ^{13}C and ^{1}H spin-lattice relaxation times in the laboratory (T_1) and rotating frames ($T_{1\rho}$) carried out at a ^{1}H Larmor frequency of 400 MHz and in the temperature range 20-80°C. The relaxation data have been simultaneously analysed with suitable models, determining motional parameters, such as activation energies and correlation times, which have shown interesting differences with *form 1* and di-hydrated form.

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SUPERPARAMAGNETIC MULTI-CORE IRON OXIDE NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Superparamagnetic nanoparticles are efficient contrast agents for magnetic resonance imaging (MRI) and other biomedical applications owing to the interaction of their strong and reversible magnetization with the ^{1}H content of the environment [1,2]. However, many challenges remain in order to optimize the magnetic properties of nanoparticles for MRI while maintaining biocompatibility, colloidal stability in a field, degradability, and control over bio-distribution.
This study will investigate the impact of stabilizing surface ligands (PEG-grafts) on the stability and both the FFC-NMR and AC-field hyperthermic responses of selected spherical magnetic iron oxide nanoparticle and nanoflower suspensions [3] and their corresponding composite hydrogels. Significant improvements in stability in the presence of a field are reported, and the contributions of the Neel and Brownian processes to the relaxivity and to the hyperthermic efficiency, are separated using FFC-NMR analysis. For the nancomposite gels it is found that FFC-NMR confirms particle dispersion and pinpoints the formulations that optimise the MRI and hyperthermic responses. The implications for longitudinal monitoring of nancomposite implants for diagnostic and therapeutic applications are discussed.

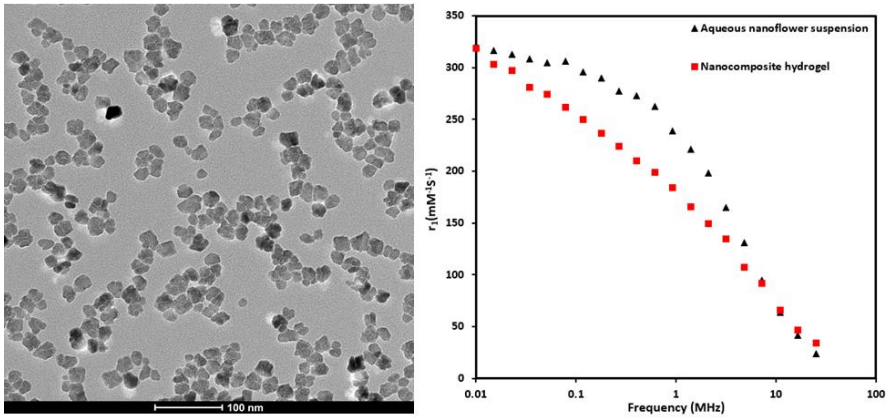

Fig. 1. Left, representative TEM image of iron oxide nanoflowers (50 kx). Right, longitudinal relaxivity (r_1) of iron oxide nanoflowers in aqueous suspension and hydrogel media (Epoxy-amine).

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^{1}H NMR RELAXIVITY OF NOVEL COLLOIDAL NANOSTRUCTURED Gd(III)-BASED POTENTIAL CONTRAST AGENTS

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Novel nanostructured potential contrast agents were prepared following a recently reported procedure [1-3] in which water insoluble Gd(III) complexes, with ligands based either on thiacalix[4]arene or tetrahydroxy-calix[4]arene (Figure 1), self-assemble into nanosized particles by precipitation from an organic to an aqueous phase and form stable colloids by coating with poly(sodium styrene sulfonate).

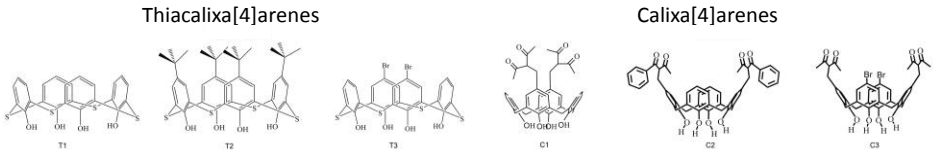

Fig. 1. Ligands used to synthesize Gd(III) complexes.

The longitudinal (r_1) and transverse (r_2) relaxivities of the colloidal systems were measured at 20.8 MHz. ^{1}H FFC NMR relaxometry was applied to determine r_1 as a function of Larmor frequency in the 10 kHz to 40 MHz range. Relaxivity dispersions, showing a maximum at around 20-30 MHz (Figure 2), clearly indicated the effective incorporation of the Gd(III) complexes into nanostructures. Their analysis allowed the mechanism at the basis of contrast enhancement and the key factors affecting the contrast efficiency to be highlighted.

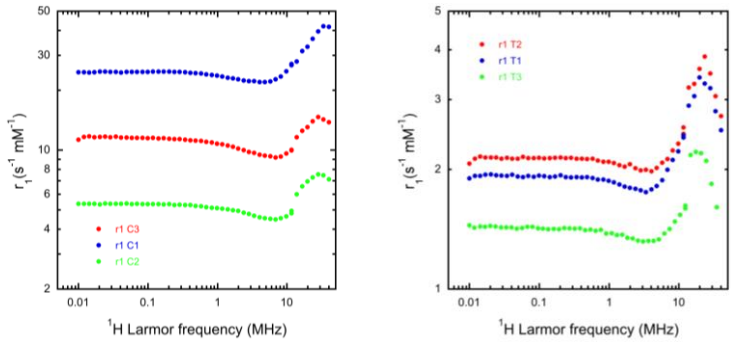

Fig. 2. Longitudinal relaxivity dispersion curves acquired at RT for the investigated nanostructured colloidal potential CAs based on Gd(III) complexes with thiacalix[4]arene (left) or calix[4]arene (right) ligands.

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LOOK LOCKER FFC NMR SEQUENCE: A TIME SAVING APPROACH IN MEASUREMENT OF LONG T_1 WITH FFC NMR EXPERIMENTS AT ANY RELAXATION FIELD

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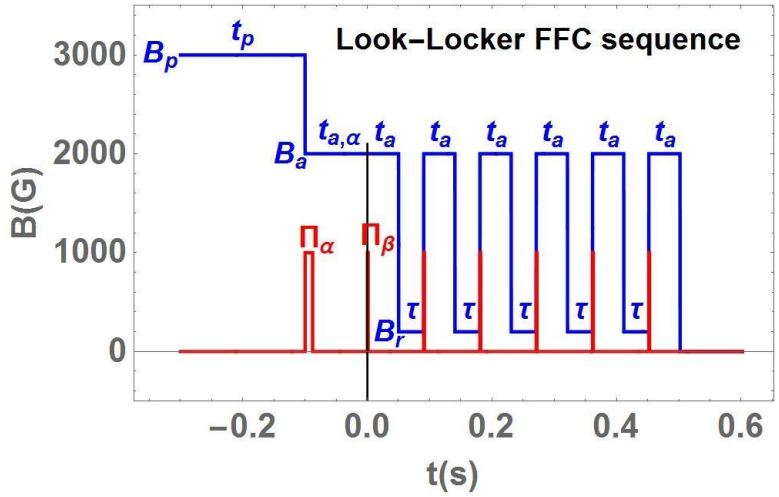
The traditional NMR time domain sequences (inversion recovery and saturation recovery) used for the determination of T1, need to be repeated for every tau used to describe the decay of the magnetization. Experiment times mainly depend on the length of the T1 to be observed and the number of tau needed to sample the decay of the magnetization in a given relaxation field. This approach, in particular for long T1's, can become quite time consuming.
The Look Locker NMR method for the determination of T1, is extensively used in MRI as a 'time-saving' approach compared with traditional inversion and saturation recovery methods.
The aim of the work described in the poster is the development and implementation of FFC Look Locker sequences on a SPINMASTER FFC relaxometer. The correct formalism for the T1 fitting of the Look Locker data will also be presented.
Advantages and limitations of the method will be demonstrated and discussed on experimental data acquired by both traditional and Look Locker methods.



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TOWARDS A MODEL-BASED FIELD-FREQUENCY LOCK FOR FAST FIELD CYCLING MRI: HANDLING THE EFFECT OF GRADIENTS

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Fast Field Cycling Magnetic Resonance Imaging (FFC MRI) aims at exploring the dependence of tissues relaxation rates on the magnetic field strength on a full-body scale, to provide unique structural information on materials in a non-invasive way. Magnetic field stability is a key issue of this challenge, since a stable magnetic field is required to guarantee precise and resolved results. Field-Frequency Lock (FFL) systems are currently under development for Fast Field Cycling Nuclear Magnetic Resonance (FFC NMR), but the presence of field gradients requires ad-hoc solutions to guarantee stability in every phase of the acquisition sequence in an MRI experiment. This work proposes two strategies to adapt FFC Field-Frequency Locks to explicitly consider the presence of field gradients. The two approaches are investigated in simulations, and the results analyzed to define which strategy could better suit the contest of a full-body FFC MRI scanner.

Acknowledgements: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 668119 (project "IDentIFY").

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STUDY OF THE PARAMAGNETIC EFFECT FROM DIVERSE LANTHANIDE IONS (Gd^{3+}, Dy^{3+}, Tb^{3+}, Eu^{3+}) ON FLUORINE RELAXATION TIMES

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Medical imaging is a dynamic area of researches whose one of the goal is the elaboration of more efficient contrast agents (CA). Those agents need to be improved to optimize the detection of affected tissues such as cancers or tumours while decreasing the injected quantity of agents. The paramagnetic contrast agents containing fluorine atoms can be used both on proton and fluorine MRI. This research field is therefore promising thanks to the ability to map the anatomy by ^{1}H MRI and locate exactly the agents by ^{19}F MRI.
One of the challenges in this domain is to synthesize a molecule containing several chemically equivalent fluorine atoms with short relaxation times to allow the record of ^{19}F MR images in good conditions. In that aim, we propose to synthesize a CA containing a paramagnetic ion and nine chemically equivalent fluorine atoms by a cycloaddition reaction between two previously synthesized molecules (figure 1).

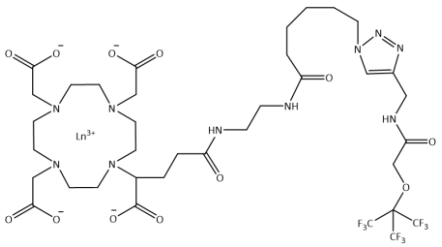

***Fig. 1**:* Chemical structure of the synthesized compound.

The structure of the fluorinated paramagnetic contrast agents (Gd^{3+}, Dy^{3+}, Tb^{3+}, Eu^{3+} complexes) was confirmed by mass spectrometry. Those fluorinated contrast agents were then characterized by ^{19}F NMR where differences were observed on the fluorine relaxation times T_1 and T_2 depending on the lanthanide ion. Compared to the fluorine relaxation times in the corresponding diamagnetic compound (T_1 around 2s), we have shown that Gd^{3+} induced a strong decrease of the relaxation times T_1 and T_2 (T_1 around 10 milliseconds) whereas Eu^{3+} is nearly inefficient (fluorine relaxation time T_1 around 1000 ms). On the other hand, Tb^{3+} and Dy^{3+} induced a moderate and appropriate decrease of T_1 (around 200 ms) which is convenient for further medical applications.
Molecular dynamic simulations have been performed in order to understand the folding of the molecule. These simulations showed that strong interactions force the molecule to fold, inducing a decrease of the distance between the paramagnetic ion and fluorines.
This study has shown the paramagnetic influence of several lanthanide ions on fluorine atoms situated close to them. Although the gadolinium ion has the highest paramagnetic effect, its influence can sometimes be too strong with a too significant decrease of the relaxation times in. An alternative can then be envisaged by the use of the dysprosium and terbium ions which allow to obtain appropriate relaxation times for clinical use.

FFC-NMR DISPERSION OF HYDRATED C_3S: A MATLAB SCRIPT FOR THE PROFILE FITTING BY THE 3τ MODEL

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Tricalcium silicate C_3S is the major component in all kinds of cementitious materials, such as white or grey Portland cement. A deep understanding of its hydration process will enlighten us on the formation of the hydrates structure, like CSH. The use of Fast Field Cycling (FFC) is a good way to perform analyses on such kind of materials. In particular, FFC dispersion profiles of the longitudinal relaxation rates (R_1) on a wide range of NMR frequencies permit to get information on the dynamics of the diffusing spins, by analysing the acquired data with a suitable spin diffusion model. In this work, the 3tau model [1] developed at the Physics Department, University of Surrey, has been used to fit our experimental data. The model is mainly based on three characteristic correlation time constants: the bulk and the surface diffusion times and the surface desorption time. To easily fit this model to the dispersion profiles, a MATLAB® script code called 3τM has been created. The fitting process implemented in the script is based on the non linear least squares method. In figure 1, an interface screenshot of the 3τM script is shown. The fitting procedure has been applied to a sample of pure C_3S [2] hydrated (water to cement ratio = 0.5) hardened for about one month. Distillated water and cement have been mixed together at 1600 rpm during 2 min. The R_1 dispersion profile was obtained with the FFC Spinmaster (Stelar, Mede, Italy). After the presentation of the script details and the FFC-NMR pulse sequence used, the results of the spins diffusion model in term of the three time constants will be briefly discussed.

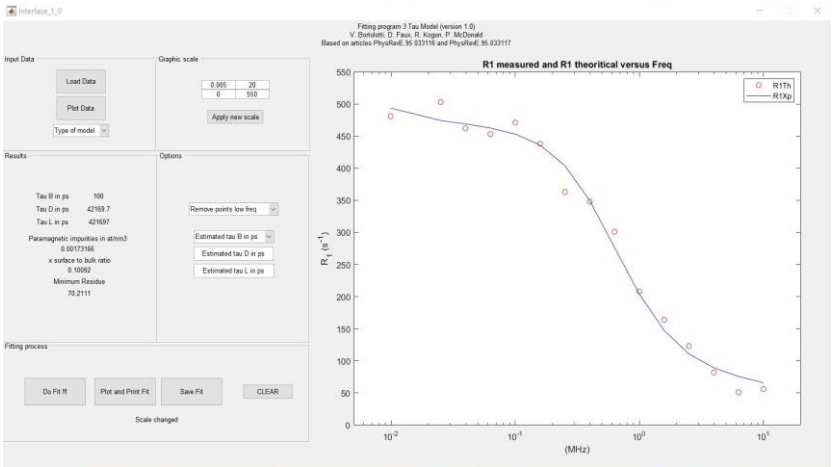

Fig. 1. Screenshot of the interface of the Matlab script 3τM. Measured R_1 relaxation rates (open circles) for pure C_3S hydrated, after one month hardening are plotted along with the fitted curve (continuous line).

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IMPROVED SECOND COORDINATION SPHERE T_1 RELAXIVITY OF RHODAMINE APPENDED Fe(III)-CATECHOLATE COMPLEX FOR NITRIC OXIDE IMAGING

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In recent years, research on Fe(III)-based MRI contrast agents (CA) has been significantly increased to overcome the limitations arising from the Gd(III)-based MRI CAs such as Nephrogenic systemic fibrosis (NSF) that leads to kidney failure [1]. We have synthesized Fe(III) complexes of an (E)-3',6'-bis(diethylamino)-2-((3,4-dihydroxybenzylidene)amino)spiro[isoindoline-1,9'-xanthen]-3-one a rhodamine-catechol ligand and studied as T_1 MRI CA for nitric oxide (NO) imaging combined with optical spectroscopy. The Fe(III) complex has been characterized as $[Fe(RhoCat)_3]^{3-}$ by HR-mass, electronic and redox methods. The EPR spectrum showed g-values of 8.74, 5.10, 4.24 and 3.92 that corresponding to high spin S = 5/2.

The longitudinal relaxivity r_1 of Fe(III) complex calculated as 4.24 $mM^{-1}s^{-1}$ in 1.41 T (25 ^oC, pH 7.32 in 25 mM of HEPES). The improved relaxivity is due to the second coordination sphere relaxivity of water proton with metal bound oxygen and imine nitrogen through hydrogen bonding. The change in r_1 values has been studied in different pH, in which, no significant change was observed up to pH 5, whereas in pH 4 about 42% decreased relaxivity observed. On the other hand, the r_1 values slightly increased to 25% from neutral to basic pH up to pH 10. The r_1 value of Fe(III) complex was enhanced to 6.88 $mM^{-1}s^{-1}$ in 4% BSA solution and showed good binding ability with protein. The rhodamine moiety is pH sensitive and upon lowering the pH resulted in an increase in fluorescence intensity. Further, upon addition of nitric oxide (NO), a reactive oxygen species (ROS) showed 'turn-on' fluorescence behavior. Other ROS, reactive nitrogen species (RNS), anions and phosphates have not produced any changes in fluorescence intensity (Fig. 1). The MRI phantom imaging and live cell fluorescence imaging of Fe(III) complex produced good results. Further, the cellular viability of the Fe(III) complex studied in the cancer cell that showed cells are viable in the required concentration for MRI [2].

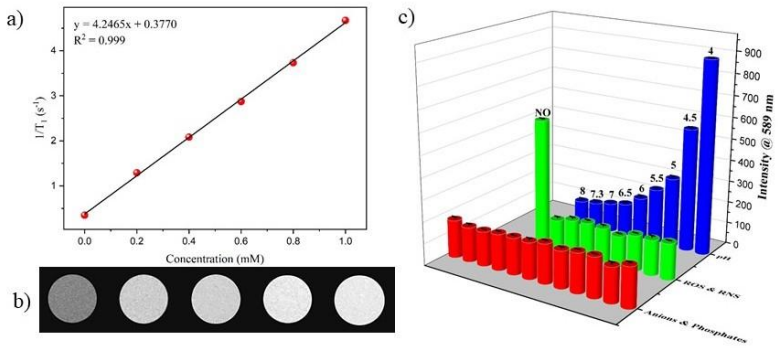

Fig. 1. The longitudinal relaxivity r_1 (a), MRI phantom images (b) and fluorescence intensity changes by pH and NO of Fe(III) complex (c).

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TWO-DIMENSIONAL WATER DIFFUSION IN HYALURONIC DERMAL FILLERS REVEALED BY NMR RELAXOMETRY

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Nuclear Magnetic Resonance (NMR) Relaxometry is one of the unique methods of supplying information about molecular dynamics and structure. According to this method, by a single experiment, one can detect motional processes in a broad range of time scales (from ms to ps). It is possible due to the fact that the relaxation rate is linked with the molecular dynamics. It depends on how fast the proton transitions between its energy levels occur. Those transitions are thanks to magnetic dipole-dipole interactions between magnetic moments of protons, which fluctuate in time due to molecular dynamics, like rotational or translational motion. The spin-lattice relaxation rate, is given as a linear combination of spectral density functions. Determination of the mechanism of the motion could be performed thanks to different mathematical form of those functions. The shape of a relaxation dispersion profile (spin-lattice relaxation rate versus the resonance frequency) is thus a fingerprint of the mechanism of the molecular motion.
In liquid systems, translation diffusion is a very important mechanism of molecular motion which can not be neglected. In most cases, it is concerned as three – dimensional (3D) process. However, when some kind of confinement is present in the system, 1D or 2D diffusion could be considered. The hyaluronic compounds used as dermal filler are an example of systems with 2D translation diffusion. They are one of the main components of the extracellular matrix and a major component of skin, where they are involved in tissue repair and regeneration. The hyaluronic acid is formed of monomers of D-glucuronic acid and N-acetyl-D-glucosamine linked by β-glycosidic bonds. At physiological pH, it occurs primarily in the form of sodium salt and has the ability to bind water. For medical purposes, the hyaluronic acid is cross-link in order to obtain gels with varying degrees of fluidity and rigidity. The water-binding capacity and the characteristics of the processes of gel volume changing after its implantation into tissues are one of the most important factors determining the medical usefulness of dermal fillers. Moreover, the time-scale and mechanism of water dynamics in the hyaluronic acid gels are of high importance. For the purposes of revealing the dynamical properties of water confined in the gel matrices, NMR relaxometry is an excellent technique.
The main purpose of this work is to reveal the mechanisms of water mobility in dermal filler with the purpose of their tailoring towards better efficiency. Moreover, in order to determine possible differences in water dynamics in healthy and pathological tissues, demonstration of the ability of NMR relaxometry to unambiguously identify the mechanism of water diffusion is needed.

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STRUCTURAL AND DYNAMIC CHARACTERIZATION OF ELASTOMERIC MATERIALS BY TIME DOMAIN NMR SPECTROSCOPY

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In the last decades, many efforts have been dedicated to the improvement of the mechanical properties of elastomeric composite materials, as they are particularly attractive for several industrial applications. As a matter of fact, these properties are mainly related to the motional constraints of the polymer network, which are due to physical entaglements and chemical cross-linking between polymer chains, and may be influenced by the presence of different additives and reinforcement fillers (carbon black, nanosilica, clays) [1,2]. Usually, the cross-link density is monitored by mechanical measurements (modulus, strain at stress, etc.); however, these methods provide only macroscopic observables, but are not suitable for a description of the topology and dynamics of the polymer network at the molecular scale. Indeed, this knowledge is required to have a more complete view of the factors that correlate with the mechanical properties of elastomers and, consequently, to better address the design of optimized materials. In this context, low field ^{1}H time domain (TD) NMR can give an important contribution [3].
In this work, we have investigated the effect of the formulation (polymer, additives, filler) and the vulcanization conditions on the structural and dynamic properties of different elastomeric materials, with application in the tyre industry, by a combination of TD NMR methods. ^{1}H Multiple Quantum (MQ) esperiments [4] were used to evaluate the residual ^{1}H-^{1}H dipolar couplings, which arise from the fast anisotropic motion of the polymer chains and are thus directly related to the amount of topological contraints within the polymer network. ^{1}H relaxation times (T_1, T_2) [5,6] were measured to probe a wide range of motional frequencies of the polymer chains. In particular, ^{1}H spin-lattice relaxation times (T_1) were evaluated by means of Fast Field Cycling [6] experiments at different temperatures, covering Larmor frequencies from 10 kHz to 35 MHz.

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ROTATIONAL CORRELATION TIMES, DIFFUSION COEFFICIENTS AND QUADRUPOLAR PEAKS IN PROTIC IONIC LIQUIDS BY MEANS OF ^{1}H FAST FIELD CYCLING NMR RELAXOMETRY

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Fast Field Cycling (FFC) NMR relaxometry is applied to study ^{1}H nuclear magnetic relaxation dispersion (NMRD) in alkylammonium- and alkylphosphonium-based protic ionic liquids (PILs) including anions of different interaction strengths by means of the Spinmaster FFC2000 (Stelar s.r.l., Mede, Italy). These PILs are characterized by the formation of hydrogen bonds between the N-H or P-H bonds of the cations and the oxygen atoms of the anions building one or three dimensional hydrogen bond networks. The ^{1}H dispersion curves were decomposed into intra- and intermolecular contributions to the spin-lattice relaxation rate R_1 to determine rotational correlation times τ_R as well as self-diffusion coefficients D_T.
Moreover, self-diffusion coefficients D_T were obtained via a low-frequency dispersion law dominated by translational motion [1,2]. These D_T were determined from the slope of a linear fit of the spin-lattice relaxation rate R_1 as a function of the square root of frequency $\nu^{1/2}$. This law can be applied provided that the dispersion at low frequencies is dominated by the intermolecular relaxation contribution. The D_T determined by full analysis of the relaxation data and by the low-frequency dispersion law are consistent and close to those measured by field-gradient NMR.
The alkylammonium-based PILs showed a local enhancement of the ^{1}H spin-lattice relaxation rates R_1 at high frequencies. This enhancement, commonly referred to as quadrupole relaxation enhancement (QRE), results from the intramolecular magnetic dipole coupling of the NH protons with the quadrupole ^{14}N nuclei. In the frequency range where the QRE appears, the resonance condition between the Zeeman transition energy of the ^{1}H spins and the energy difference of two levels of the quadrupole ^{14}N nuclei has to be fulfilled [3,4]. Consequently, the QRE disappears when the NH protons are exchanged by deuterons or when the quadrupolar nucleus ^{14}N is replaced by the dipolar nucleus ^{31}P.
Overall, we can show that Field Cycling relaxometry provides access to rotational correlation times, self-diffusion coefficients and quadrupole relaxation enhancement in one experiment.

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^{1}H RELAXATION DISPERSION OF STARCH BASED CONFECTIONS

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Soft confectionery products which were prepared with different formulations by using starch, soy protein isolate and D-allulose were examined. In order to characterize the effect of sugar type, maximum possible concentrations (30%) of sucrose and D-allulose were used in formulations. Also, starch concentration was decreased by replacement of SPI to examine the effect of soy protein addition. ^{1}H relaxation dispersion data of confectionery products were recorded in the frequency range of 4 kHz – 30 MHz and results are given in (Fig. 1). Rouse model or Renormalized Rouse Model are generally used to describe the molecular dynamics of polymers depending on molecular mass of polymers [1,2]. Therefore, renormalised Rouse Model was used to fit data. According to the dispersion data, it can be clearly seen that T_1 values for only starch and D-Allulose containing confectionery (11_R30) are longer than the other three formulations. Longer spin-lattice relaxation time refers longer correlation times which indicate slower motions of different molecular chain organizations and further intermolecular interaction [2].

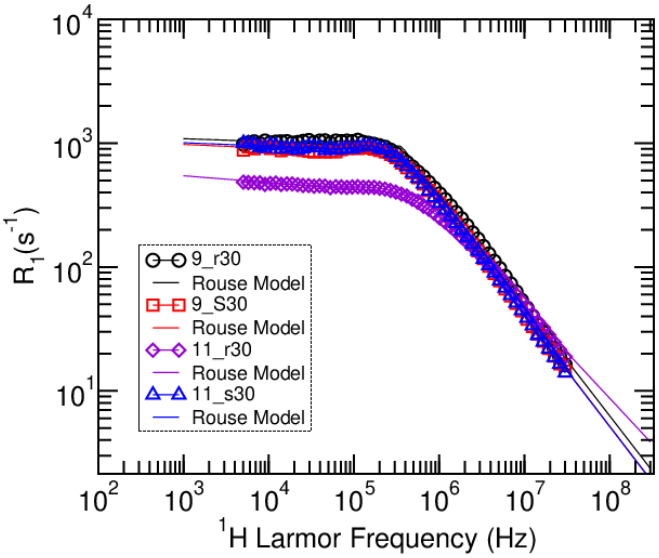

Fig. 1. ^{1}H relaxation dispersion data of starch based confectionery products.

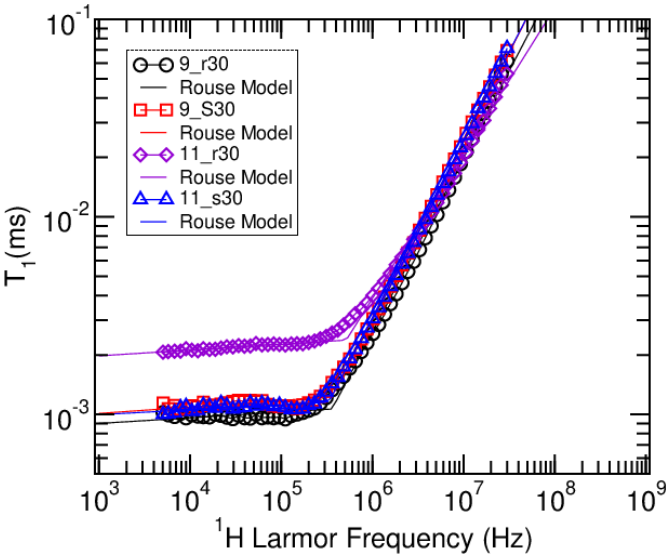

Fig. 2. ^{1}H spin-lattice relaxation time curves of starch based confectionery products.

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BATTERY ELECTROLYTES – MULTI-NUCLEAR FAST FIELD CYCLING RELAXOMETRY REVEALS IMPORTANT MOLECULAR DYNAMICS INFORMATION

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The growing need of electric energy required to power portable electronic devices and electric vehicles promote an increasing interest in research on high-performance new batteries. In the current study we consider two electrolytes: bis(trifluoromethane)sulfonimide lithium salt (C2F6LiNO4S2, LiTFSI) in solution and lithium phosphorus sulfide (Li3PS4) in solid state. We aim to characterize them from a molecular dynamics point of view using the Fast Field Cycling (FFC) NMR relaxometry technique. We performed FFC measurements using Stelar's SPINMASTER 1T FFC relaxometer on 1H, 19F, 7Li and 31P nuclei from 5 kHz up to 30 MHz (referring to 1H Larmor frequency). Experiments were also repeated over a wide range of temperatures. In this study we show how it is possible to obtain dynamics parameters for different nuclei from the experimental data (NMRD profiles) and using basic theoretical information. Investigating the transport properties of the electrolytes is fundamental for obtaining high-performance batteries and for this reason we report how to determine not only the self-diffusion coefficient (as with the NMR gradient methods), but also the relative diffusion coefficient (e.g. cation-anion) which provides information about whether the ionic dynamics are correlated [1,2]. Furthermore, we deal with other important topics such as obtaining the correlation times (rotational dynamics) and other useful information about the presence of clusters and their size [1,2,3]. The FFC NMR technique, together with the multi-nuclear capability of the Stelar SPINMASTER FFC relaxometer, constitutes a powerful tool for characterization of electrolytes giving access to an amount of particular molecular dynamics information that could otherwise only be obtained by applying, several other different techniques. For all these reasons, we believe that FFC technique could have a large economic impact on the battery industry.

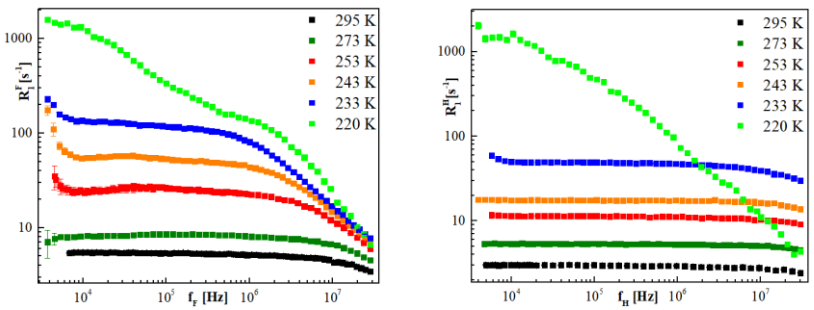

Fig. 1. NMRD profiles of $C_2F_6LiNO_4S_2$ aqueous solution aquired at different temperatures for the ^1H amd ^{19}F nuclei.

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FFC NMR APPLICATION TO PETROLEUM TIGHT SANDSTONES ROCKS

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Fast-field cycling (FFC) is an established NMR method which offers unique opportunity to characterize the molecular dynamics and transport properties of complex liquids in bulk or in confined environments [1]. Many scientific papers report the interpretation of NMRD profiles in different kind of rocks, saturated with brine and/or oil [2,3], for investigating important microscopic properties such as correlation times and NMR wettability. In this study we apply for the first time the FFC method to tight pore sandstone rocks (brine saturated) and we provide new information on pore-size distribution and surface wettability of brine confined within pores.
The bimodal pore-size distribution in tight sandstones is extended to much smaller pores compared with the quasi monomodal pore-size distribution of conventional sandstones that is usually centered on very large pores of several tens of μm. The interpretation of the NMRD profiles of tight sandstones has shown a water surface diffusion about one third of the bulk diffusion. Finally, we compare results from conventional (Fig.1) and unconventional (Fig.2) tight sandstones. Results from this study show that FFC technique is a useful method for probing the molecular dynamics of important unconventional reservoir rocks, such as tight pore-size sandstones.

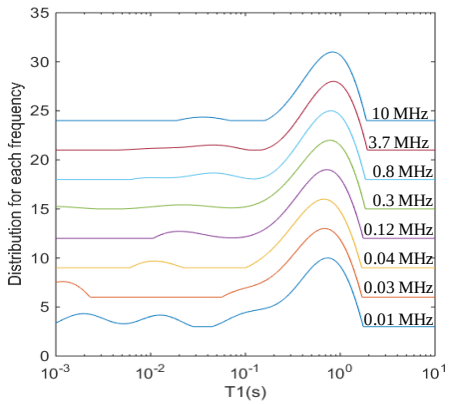

Fig.1. Conventional water saturated sandstone.

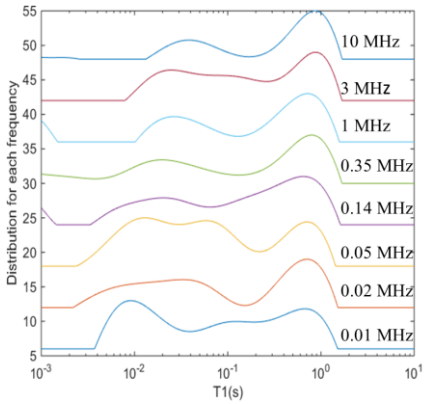

Fig.2. Unconventional water saturated sandstone.

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TRAPPING OF Gd(III) IONS BY KEPLERATE POLYANIONIC NANOCAPSULES IN WATER: A ^{1}H FAST FIELD-CYCLING NMR RELAXOMETRY STUDY

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Polyoxomolybdates of the type $[\{Mo^{VI}Mo^{VI}_5O_{21}(H_2O)_6\}_{12}\{Mo^{V}_2O_4(ligand^{n-})\}_{30}]^{(12+30n)-}$, also known as Keplerates (Kps), are polyanionic nanocapsules (diameter ~ 3 nm) bearing 20 $\{Mo_9O_9\}$ pores connected to a central cavity by 20 channels. In solution they can entrap cations in different sites of their porous structure in equilibrium with cations free in solution.
Hydrophilic colloids were prepared through the self-assembly of KpOAc or $KpHPO_4$ (i.e. Kp with ligand = acetate or hydrogen phosphate) macroanions and Gd(III) cations in water, further stabilized by F-127 Pluronics. The strongly enhanced water proton relaxivity observed at 20 MHz was postulated to derive from the trapping of Gd(III) aqua ions in the nanocapsules [1,2].

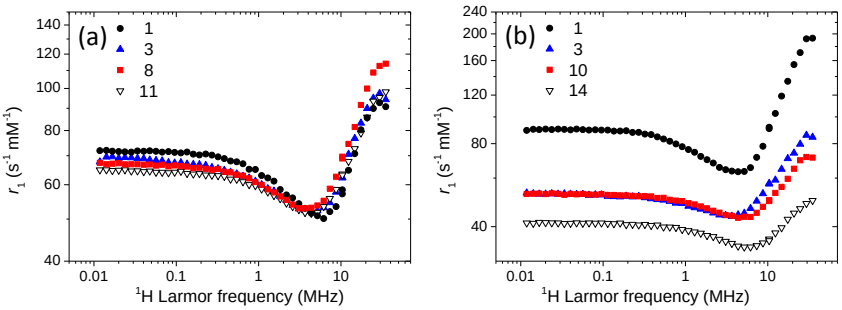

Fig. 1. r_1 curves acquired at 25°C on (a) Gd_x(KpOAc) and (b) Gd_x($KpHPO_4$) with the indicated x values.

^{1}H FFC NMR relaxometry allowed this hypothesis to be verified on aqueous suspensions containing either KpOAc or $KpHPO_4$ and Gd(III) in different proportions (Fig. 1). The analysis of ^{1}H longitudinal relaxivity vs the Larmor frequency on the basis of the theory for paramagnetic relaxation enhancement gave a detailed description of the state of $[Gd(H_2O)_8]^{3+}$ ions in dependence of the different capsule charge and Gd to Kp molar ratios [3]. $[Gd(H_2O)_8]^{3+}$ ions were found to be trapped in the KpOAc capsules, most probably located in up to 11 pores, with no evidence for free ions. On the other hand, equilibria between trapped and free $[Gd(H_2O)_8]^{3+}$ ions established in the suspensions containing $KpHPO_4$, which depended on the Gd to Kp molar ratios, and a maximum of 3-4 Gd per capsule was found. A major role of the NH_4^+ counter-ion was invoked to rationalize the different behavior of KpOAc and $KpHPO_4$.

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INSIGHTS INTO COMPETITIVE ADSORPTION OF BINARY LIQUID MIXTURES IN NANOPOROUS OXIDES USING FAST FIELD CYCLING NMR

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Fast Field Cycling (FFC) NMR has been shown to be a powerful tool for the analysis of the surface dynamics of liquids imbibed within catalytically-relevant porous media [1]. The adsorbate–surface interactions are controlled not only by the properties of the adsorbate and the surface, but can also be affected by the presence of a coadsorbate, as has been observed for binary liquid mixtures in porous media [2]. In this study, a range of tetrahydrofuran(THF):water mixture compositions were imbibed within anatase titania, specifically exploring the relaxation behaviour at sub-monolayer coverages of water, the stronger interacting species. ^{1}H NMRD profiles specific to the THF component were extracted through a multiexponential fit. These profiles could be well fitted to a phenomenological power law of the form $R_1 \propto \omega_0^{-\chi}$, the exponent of which contained information about the adsorption strength [3]. Figure 1 shows the exponent, χ, plotted against the intra-pore mixture composition (Fig. 1a) and also how the exponent varies as a function of the fraction of the surface occupied by THF, assuming that water prefentially asdorbs on the surface (Fig. 1b).

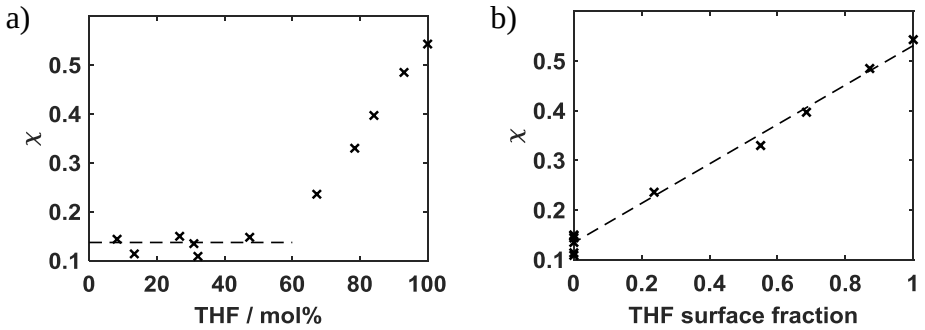

Fig. 1. THF power law exponents determined from ^{1}H NMRD profiles of a series of THF:water mixtures imbibed within anatase titania, plotted against the intra-pore mixture composition in (a) mol% and (b) the fraction of the surface that is accessible by THF. Dashed lines are included as a guide to the eye.

For a water surface coverage larger than one monolayer (<62 mol% THF), the THF power law exponents were constant at 0.14±0.02, indicating that water strongly outcompeted THF for surface binding sites. For sub-monolayer water coverage, the THF exponent increased linearly with the surface fraction of THF to 0.54, indicating that the THF-surface interaction in the binary increased monotonically with decrease in the amount of water present at these very low water concentrations. Ongoing work focuses on two areas. First the development of theoretical models to describe the data discussed in this work. Second, to extend this work to gain insight into how the composition of a binary liquid, when used as a solvent in catalysis, influences the catalytic process.

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DETERMINATION OF DEUTERON QUADRUPOLE COUPLING CONSTANTS AND REORIENTATIONAL CORRELATION TIMES FOR PROTIC IONIC LIQUIDS

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We show that deuteron quadrupole coupling constants (DQCCs), and reorientational correlations times of molecular bonds N-D that are involved in hydrogen bonding, τ_{ND}, can be determined from NMR T_1 relaxation times experiments simultaneously. For this purpose, we used tri-alkyl ammonium based protic ionic liquids (PILs) as model compounds. They exhibit high viscosities and large liquid ranges that allows measurements far beyond the extreme narrowing region. The T_1 minima already occur significantly above room temperature. However, applying the well-known Bloembergen-Purcell-Pound approach results in significantly too small DQCCs, indicating that the underlying assumption of isotropic rotation may not be justified. On the other hand, we obtain reasonable DQCCs for the liquid phase if anisotropic motion is considered. The DQCCs are very small due to attractive Coulomb interaction between cation and anion, which is further enhanced by hydrogen bonding. The DQCCs strongly depend on the interaction strength of the anion but are independent of the alkyl chain length of the tri-alkyl ammonium cations pointing to the exclusive cation-anion interaction along the hydrogen bond.

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SHUTTLE NMR RELAXOMETRY

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The chemical and physical principles underlying protein function can only be unraveled by gaining insight into both structural and dynamic features.
Relaxation measured at various lower field strengths and detected at high field with high spectral resolution provides dynamic information linked to structure.

Relaxometry with a sample shuttle:

- Polarization at high field
- Relaxation at a wide range of low fields
- Detection at high field

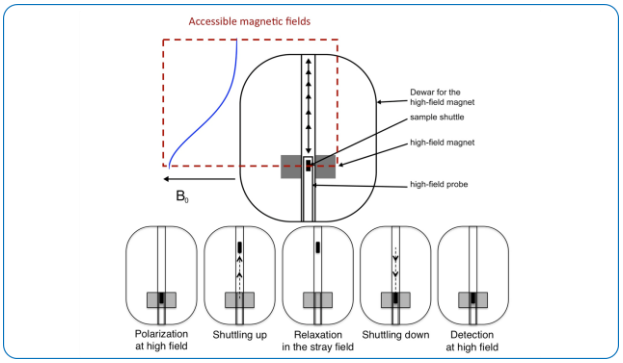

Fig. 1. Principle of high-resolution relaxometry.

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^{19}F NMR RELAXOMETRY OF AQUEOUS DISPERSIONS OF NAFION

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Perfluorosulfonic acid (PFSA) ionomers such as Nafion have been widely used to prepare proton conducting membranes as well as catalyst layers of polymer electrolyte membrane fuel cells (PEMFC). They are dispersed in polar solvents as rod-like particles and after heating at above 230 °C they are transformed into smaller and more uniform particles [1]. Recently we measured SEC, cryo-TEM and SAXS of Nafion aqueous dispersions after heating to 240 °C and showed the averaged molar masses derived from three methods are in good agreement [2]. ^{19}F FFC-NMR is expected to provide complement these structural data with dynamics of polymer chains which are important to understand their interaction and structural development by solvent evaporation.

Nafion dispersions were purchased from Chemours (DE1020, EW=1000) and Fumatech (FLA805, EW=800). While DE1020 contains elongated and interconnected rod-like particles, FLA805 contains spherical nanoparticles as shown in their cryo-TEM images. Spin-lattice relaxation rates of these dispersions were measured using a Spinmaster 2000 (Stelar s.r.l.) with a ^{19}F probe. Both of the ^{19}F NMRD profiles obey power law at > 1 MHz and almost constant at < 0.1MHz, which were successfully fitted by the one dimensional limited defect diffusion model [3] and activation energies of the diffusion coeffcients were estimated. Nature of the defects will be discussed by referring to the mobile helix reversal and conformational changes in the poly(tetrafluoroethylene) [4].

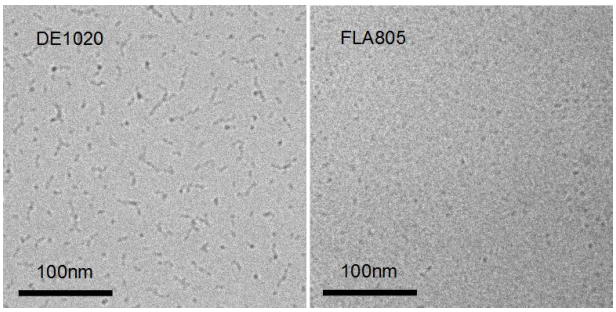

Fig. 1. Cryo-TEM images of 0.1 wt% aqueous dispersions.

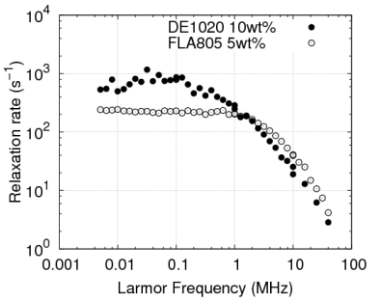

Fig. 2. Relaxation rates at 303K.

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Author Index