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# **Fast Field Cycling NMR Relaxometry**

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# **Keynote Lectures**

## A BRIEF HISTORY OF FIELD-CYCLING IMAGING

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This lecture will discuss the timeline of magnetic field-cycling in MRI; it will concentrate on the development of field-cycling imaging at Aberdeen, in the context of work carried out elsewhere.

In the mid-1980s I started to work on low-field MRI with Jim Hutchison, whose team had recently performed the world's first clinical whole-body scan [1]. The Head of Department, Prof. John Mallard, suggested that I investigate double-resonance methods in imaging. The most promising was a combination of electron and nuclear resonance (the Overhauser effect), with the aim of imaging the distribution of free radicals. This worked in samples [2] and *in vivo* [3], but sample heating was problematic due to RF power absorption from the high-frequency electron irradiation. Jim Hutchison suggested using field-cycling – switching to low field for electron irradiation (low frequency, low power) and higher field for NMR detection and imaging (improved SNR). In 1989 we built a Helmholtz field-cycling insert for our resistive MRI magnet and demonstrated the method [4]; this was our first use of field-cycling with MRI. We developed the technology and built a large-scale version, using a human-sized resistive field-offset coil inside a 60 mT permanent magnet, with field switching in *ca.* 20 ms [5].

In 1992, Carlson in San Francisco had demonstrated the feasibility of localised field-cycling relaxometric imaging, using a head-sized offset coil inside a clinical permanent-magnet MRI system [6]; that team was able to generate dispersion plots from the human brain *in vivo*, showing quadrupolar dips [7]. This work, together with Jiao and Bryant's paper showing that the dips could be used for protein quantitation [8] inspired us to use our existing whole-body field-cycling scanner for relaxometric MRI, results of which were presented at the first FFC-NMR relaxometry conference in Berlin, in 1998 [9].

In recent years the team at Aberdeen has built a new human-sized scanner, using a resistive magnet with a maximum field strength of 0.2 T [10]; the device has been used for studies of patients clinical conditions, including stroke [11] and cancer [12]. A number of studies are taking place to expand the range of clinical conditions, with the aim of determining the clinical benefit of field-cycling imaging (FCI). Construction of a new, clinical FCI scanner is currently underway, within the University teaching hospital.

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## FFC-NMR AND THE DEVELOPMENT OF MRI CONTRAST AGENTS: FROM SMALL COMPLEXES TO NANOSYSTEMS

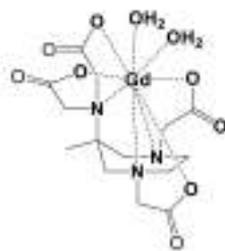
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Gadolinium-based contrast agents (GBCAs) are widely used with clinical magnetic resonance imaging (MRI) and tens of millions of doses of GBCAs are administered annually worldwide [1]. Increasing attention is paid also to biologically relevant metal ions such as Mn(II) or Fe(III) as alternatives to Gd(III), leading to a greater interest in the aqueous coordination chemistry of their complexes. The best technique to access to fundamental information on the solution structure and dynamics of these metal-based contrast agents appears to be fast field-cycling relaxometry. The acquisition of Nuclear Magnetic Relaxation Dispersion profiles of aqueous solutions of paramagnetic metal complexes and their analysis with the established theory of paramagnetic relaxation allows getting reliable estimation of several structural, electronic and dynamic parameters [2]. These include the number of water molecules in the inner, second and outer coordination spheres, their distance from the paramagnetic centre, the relationship between electronic relaxation and structural properties of the complex, the exchange lifetime of the coordinated water molecule(s) and the overall molecular tumbling time.

In combination with other complementary techniques, FFC-NMR also allows to highlight other relevant details associated with molecular dynamics, presence of hydration equilibria, occurrence of prototropic exchange, and dependence of the water exchange rate on coordination sites. These aspects will be discussed by showing the most recent results related to a model compound:  $[\text{Gd}(\text{AAZTA})(\text{H}_2\text{O})_2]^-$ , both as a free complex and as a building block of multimers and dendrimers or encapsulated into nanogels [3,4].



**Fig. 1.** Chemical Structure of  $[\text{Gd}(\text{AAZTA})(\text{H}_2\text{O})_2]^-$ .

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## NMR RELAXOMETRY ACCESSING THE RELAXATION SPECTRUM IN SIMPLE AND POLYMER GLASS FORMERS

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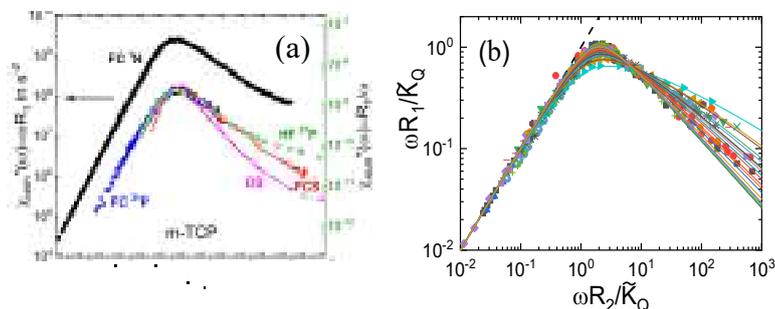
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One of the great issues of FC NMR relaxometry is revealing the nature of the dynamics in complex systems, for example, addressing details of the spectral density/susceptibility in systems like polymer or dendrimer melts. Important results were presented by previous FC studies and we will add some more on polymer rubbers establishing FC NMR as a tool of molecular rheology. Here, accessing NMR frequencies below the earth field by employing a home-built relaxometer is particularly useful.

Simple liquids still provide challenges for FC NMR either. Since the work of Bloembergen et al. understanding the <sup>1</sup>H relaxation remained an unsettled issue. Due to the experimentally accessible frequency range of FC NMR, liquids are studied in the moderate-to-high viscosity regime. Such liquids undergo the glass transition. With the advent of new NMR relaxometers one is able to re-address the NMR relaxation from  $T_m$  down to the glass state. We present a quantitative description of the <sup>1</sup>H spin-lattice relaxation rate  $R_1(T, \omega)$  of various liquids and demonstrate that master curves in terms of the susceptibility representation  $\omega R_1(T, \omega)$  can be constructed extending over many decades in  $\omega$  [1]. They are described by contributions reflecting translational and rotational dynamics mediated by inter- and intramolecular pathways. The rotational part shows high similarity with those reported by dielectric spectroscopy or light scattering (Fig. 1a). The translational contribution is fit by applying the force-free hard sphere model describing diffusion of dipolarly coupled spins and allows to determine the diffusion coefficient. The results are compared to atomistic MD simulations reproducing both relaxation contributions [2]. We show how high-field (HF) data can be included in constructing the master curves (Fig. 1a). Moreover, measuring also the spin-spin relaxation rate  $R_2(T)$  in addition to  $R_1(T)$  allows one to directly estimate the relaxation spectrum (Fig. 1b) [3].

An advantage of NMR is its selectivity, which allows one to probe site-specific dynamics. It can be done by labelling of different molecular sites by a single NMR nucleus or by a simultaneous study using various NMR probes. The latter is demonstrated by applying FC <sup>1</sup>H and FC <sup>31</sup>P NMR in the case of a molecular liquid (Fig. 1a) and by <sup>1</sup>H and <sup>7</sup>Li NMR in the case of a salt solution.

**Fig. 1.** (a) NMR susceptibilities of a phosphororganic liquid as probed by FC <sup>1</sup>H and FC <sup>31</sup>P relaxometry compared to data from HF <sup>31</sup>P NMR (determined by CSA interaction), dielectric spectroscopy (DS) and light scattering (PCS). (b) <sup>2</sup>H  $R_1(T)$  such plotted against  $R_2(T)$  to remove the effect of differences in the coupling constants  $\tilde{K}_Q$  and  $\omega$ ; the relaxation peak is revealed indicating differences among the liquids.



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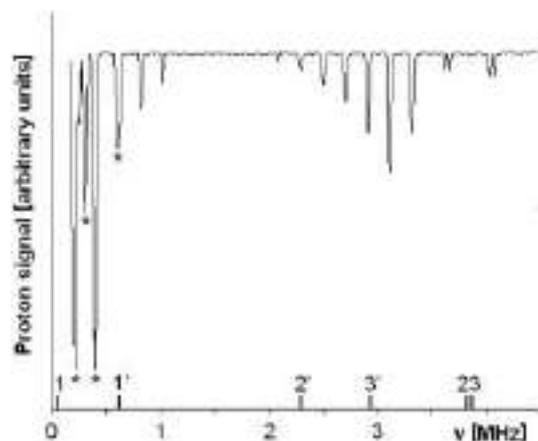
# **Invited Lectures**

## Field Cycling NMR of Pharmaceuticals

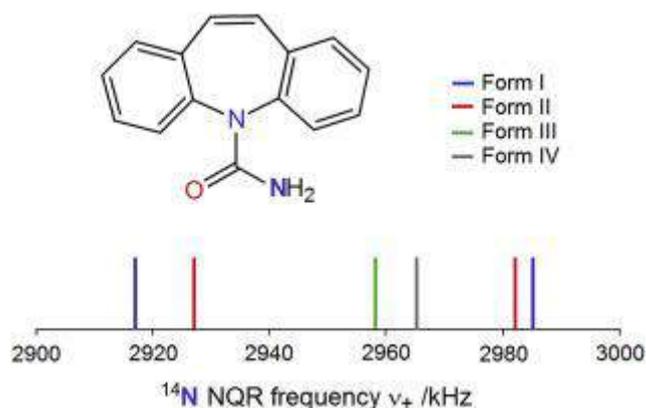
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Modern medicines are very precisely defined mixtures of different components with the aim of producing a final dosage form with accurately defined characteristics. Most of active pharmaceutical ingredients (APIs), excipients and packaging materials are used in solid forms. Solubility, dissolution profiles, absorption rates, bioactivity, shelf life and other properties of pharmaceutical ingredients critically depend on crystalline packing of molecules. It is thus very important to be able to distinguish between different amorphous, crystalline, polymorphic, co-crystalline or hydrate forms.[1] The most successful analytical methods here are XRD and solid state NMR. However, due powder nature of pharmaceutical ingredients and line broadening, high resolution ssNMR is challenging. As an alternative, pure nuclear quadrupole resonance of nitrogen nuclei, which is present in almost 90% of solid medicines, can directly measure electric field gradients at the nuclei site and thus distinguish between different crystalline forms. However, nitrogen quadrupole resonance lines lie below 5 MHz so direct detection is often not possible due low sensitivity. Here we show experimental results of indirect detection of nitrogen quadrupole resonances in pharmaceutically relevant materials using field cycling, cross relaxation and nuclear quadrupole double resonance methods.



**Fig. 1.**  $^1\text{H}$ - $^{14}\text{N}$  NQDR solid-effect spectrum of carbamazepine Form III at  $T = 295$  K. [2]



**Fig. 2.**  $^{14}\text{N}$  NQR  $\nu_+$  frequencies at the amide nitrogen positions in polymorphs of carbamazepine. [2]

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## MAGNETIC LOCKING INTO KEROGEN: IMPACT ON FLUID DYNAMICS

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How the transport of fluids in a confined and complex mixed organic/inorganic matrix can be far below the expected value from topological aspect? A good example of this situation is oil shales. Oil and gas shales are source rocks in which organic matter has matured to form hydrocarbons. They exhibit a dual porous network formed by the intertwining of mineral and organic pores that leads to very low permeability. Still, the exact origin of this extremely low permeability remains somehow unclear. The present communication addresses this important question and provides novel insights on the mechanisms that strongly hinder fluid diffusion in such materials [1]. By combining nuclear relaxation ( $T_1$ - $T_2$  and FFC-NMR) and electronic magnetic resonance (1D and 2D ESR) techniques combined with SEM imaging, we evidence that magnetic locking occurs into kerogen. This locking results from a magnetic coupling between vanadyl present in porphyrins and the organic matrix. We demonstrate that such coupling retards fluid diffusion and is reversible. This key dynamical feature explains the extremely low mobility of oil in shale rocks. This phenomenon may be a more general feature occurring in several systems where fluids are confined in a complex hierarchical matrix that embeds both organic and inorganic radicals resulting from ageing process.

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## MULTIMODAL ANALYSIS OF CONFINED WATER DYNAMICS IN A MESOPOROUS CATALYST PRECURSOR: FOCUS ON NMRD

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Porous Boehmite is a precursor of a catalytic support. A topotactic transformation allows to obtain  $\gamma$   $\text{Al}_2\text{O}_3$  catalyst support which inherits most of morphological properties of this precursor. Understanding and optimizing molecular transport inside Boehmite pore network is a key parameter to improve molecular accessibility to the pore surface of either the precursor or  $\gamma$   $\text{Al}_2\text{O}_3$ .

In this talk, we present a multimodal analysis of confined water dynamics inside this material with a special focus on NMRD.

3D morphology and topology of the boehmite pore network were formerly investigated by electron tomography [1] and small angle scattering, providing a 3D representation of the pore network at the nanometer scale. Moreover, bulk concentration of atoms such as  $\text{Fe}^{3+}$  was determined by X band ESR.

Interfacial water dynamics at very short time (less of few ns) was analyzed during preliminary QENS experiments, pointing to a very low  $^1\text{H}$  surface self-diffusion coefficient. At the mesoscopic time scale (from 1 ns to 10  $\mu\text{s}$ ), water dynamics was probed by NMRD of  $^1\text{H}$  and  $^2\text{H}$  at different levels of water saturation of the pore network. In all cases, dispersion curves  $R_1(\omega)$  follow a very similar algebraic law, highlighting the determinant contribution of the water dynamics on surface [2].

In order to evaluate respective contributions of intra I-I, inter I-I and I-S dipolar interactions, numerical simulations are conducted using the 3D reconstruction of the pore network, as it was formerly done in the case of the Vycor glass [2]. Contribution of each Hamiltonian is computed and compared to NMRD experimental data. Respective roles of surface interaction and surface geometry on water dynamics are finally discussed.

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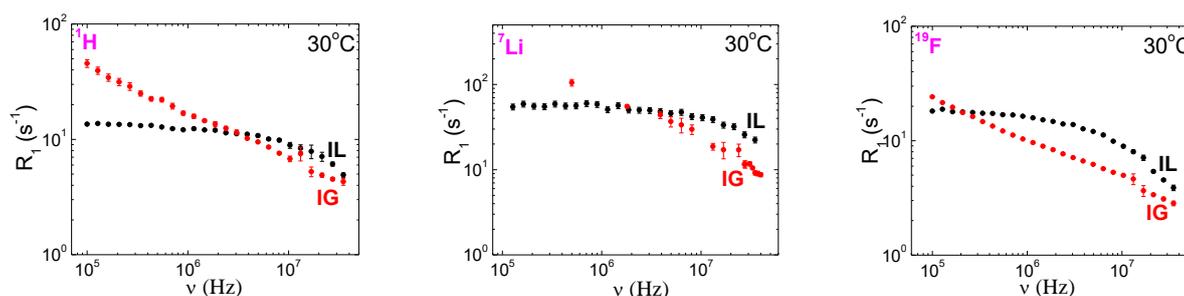
## A RELATIVE NEWCOMER'S JOURNEY IN FFC RELAXOMETRY: BATTERIES TO BRAINS

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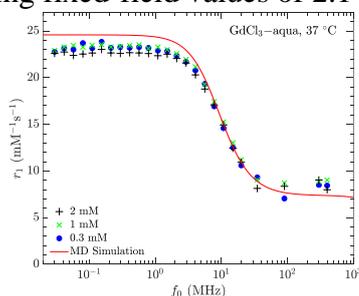
My decision in 2015 to enter the FFCNMR field has broadened my range of academic pursuits. Most of our work concerns characterization of structure and ion transport in novel liquid and solid lithium battery electrolytes. We describe here a recent study<sup>1</sup> of a pseudo-solid electrolyte (referred to as ionogel – IG) based on an ionic liquid, in which the effects of liquid confinement by a nanoporous silica matrix on all mobile ions are observed over a broad frequency range, as shown in Fig. 1.



**Fig.1** Relaxation dispersions for <sup>1</sup>H, <sup>7</sup>Li, and <sup>19</sup>F of 1 M LiTFSI in ionic liquid BMIM TFSI (IL) and corresponding ionogel (IG).

Next, we describe recent results on deep eutectic solvents based on mixtures of hydrogen bond donors and acceptors, under development for flow batteries.<sup>2</sup>

A departure from battery materials science was encouraged by our present collaboration with Rice University (P. Singer et.al.) involving Gadolinium-based contrast agents, which are currently the gold standard in clinical MRI. The Rice team has developed a molecular dynamics (MD) approach to simulate relaxation dispersions of GdCl<sub>3</sub> – aqua, that is relaxation model-independent and with no adjustable parameters. Figure 2 displays results of three different GdCl<sub>3</sub> concentrations over a broad magnetic field range, including fixed-field values of 2.1 T, 7 T, and 9.4 T, and good agreement with the MD simulation.



**Fig. 2.**  $r_1$  for GdCl<sub>3</sub>–aqua at 37 °C; measurements (data points) at various Gd<sup>3+</sup> concentrations, and MD simulation (curve).

Finally, we are collaborating with the U.S. National Institute of Standards and Technology (K. Keenan, et.al.), to develop a phantom or reference object for low-field MRI. Different materials are being assessed to replicate the relaxation properties of white and grey matter.

1. “NMR Relaxometry and Diffusometry Analysis of Dynamics in Ionic Liquids and Ionogels for Use in Lithium Ion Batteries”, Nishani Kanchana Jayakody, Carla C. Fraenza, Steven G. Greenbaum, David Ashby and Bruce S. Dunn, *Journal of Physical Chemistry, B* 2020 124 (31), 6843–6856. <https://doi.org/10.1021/acs.jpcc.0c02755>
2. “Dynamics of Glyceline and Interactions of Constituents: A Multi-technique NMR study”, Carla Fraenza, Ramez Elgammal, Mounesha Garaga, Thomas Zawodzinski and Steven Greenbaum, *Journal of Physical Chemistry B*, 2022, 126, 4, 890–905 <https://doi.org/10.1021/acs.jpcc.1c09227>



## DEFINING PHOSPHOLIPID BINDING SITES ON AMPHITROPIC PROTEINS WITH HIGH RESOLUTION <sup>31</sup>P RELAXOMETRY

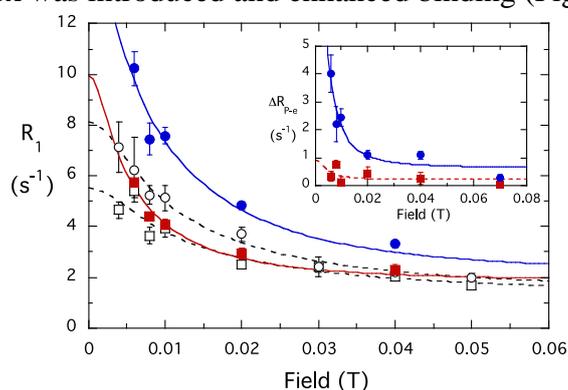
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Amphitropic proteins interact transiently with membranes. The binding can be relatively nonspecific (e.g., insertion of hydrophobic residues) or specifically require a particular phospholipid. Defining specific interactions is often difficult, particularly when the membrane contains different phospholipids. <sup>31</sup>P relaxometry is an excellent tool to identify and characterize specific protein-phospholipid interactions by spin-labeling the protein at different sites and comparing the paramagnetic relaxation enhancement over a wide range of magnetic fields. The effects of different spin-label sites on the lowest field NMRD provide distance constraints for the <sup>31</sup>P – electron interaction that together with modelling can identify specific phospholipid binding sites. Three proteins whose interactions with specific phospholipids were examined are the Akt-1 PH domain [1] and PTEN [2], both involved in phosphoinositide signaling, and a phosphatidylinositol-specific phospholipase C (PI-PLC), a bacterial virulence factor activated by phosphatidylcholine (PC) [3]. In all three cases novel *specific* phospholipid binding sites were found. The most unexpected result was that PI-PLC forms two specific PC choline cation / tyrosine- $\pi$  complexes that are critical for tight vesicle binding. As proof, two tyrosines were added to a similar protein with poor affinity for PC (no PR<sub>1</sub>E when spin-labeled and added to vesicles) [4]. <sup>31</sup>P relaxometry confirmed that a specific PC cation –  $\pi$  complex was introduced and enhanced binding (Figure 1).



**Fig. 1.** *S. aureus* PI-PLC spin-labeled at D213C preferentially enhances the <sup>31</sup>P  $R_1$  for PC (blue circles) but not PMe (red squares) compared to PC/PMe vesicles alone (dotted lines) The inset shows the  $R_1$  attributed to the spin label.

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## WIDE-RANGE RELAXOMETRY FOR PARAMAGNETIC SYSTEMS: DATA ANALYSIS AND ITS PITFALLS

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An extended set of paramagnetic relaxation enhancement (PRE) data, up to 32.9 Tesla, was recently reported for protons in acidified solutions of Ni(II) salt in the presence and in the absence of added glycerol [1]. The data were analyzed using the Swedish slow-motion theory, including the inner and outer sphere contributions. The results, supported by *ab initio* quantum chemical calculations and MD simulations, indicated difficulties in estimating relative contributions from the two mechanisms.

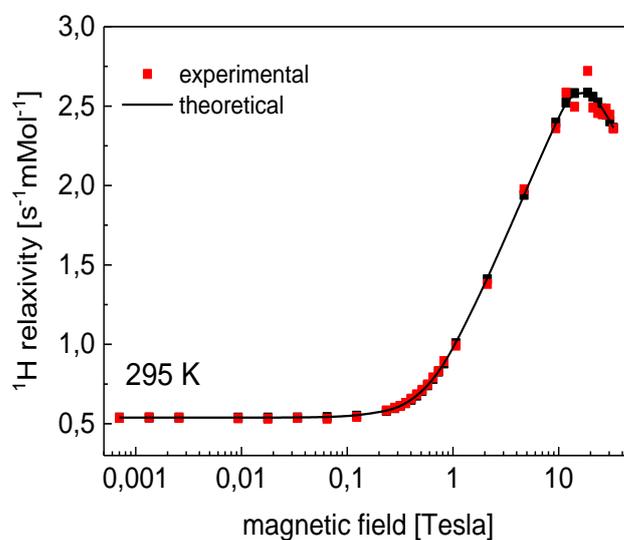


Fig. 1. Theoretical and experimental relaxivities for the glycerol-containing sample

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## Reliable description of rotational and translational motion in ionic liquids by means of field cycling NMR relaxometry and molecular dynamics simulations

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We study the rotational and translational motion in ionic liquids (ILs) by means of high-resolution NMR spectroscopy, fast field cycling (FFC) relaxometry and molecular dynamics (MD) simulations. ILs with hydrogen-bonded cation anion combinations provide extremely wide liquid ranges that allow shedding light on the validity of commonly used relaxation models. For quadrupolar (<sup>2</sup>H) as well as dipolar (<sup>1</sup>H and <sup>19</sup>F) relaxation, we validate the applicability of the Bloembergen-Purcell-Pound (BPP) approach, which assumes isotropic rotational motion [1]. Numerous examples for molecular and ionic liquids showed that the assumption of isotropic rotation is not justified, resulting in unphysically small NMR coupling parameters and too long rotational correlation times. The broad liquid ranges of suitable ILs provide sufficient temperature dependent relaxation rates for considering more sophisticated models taking anisotropic or internal rotation into account (see Fig. 1) [2-4]. Independently, we determined correlation functions, coupling parameters and relaxation rates from classical MD simulations. That allows justifying the underlying relaxation models we used for evaluating the measured relaxation data [5].

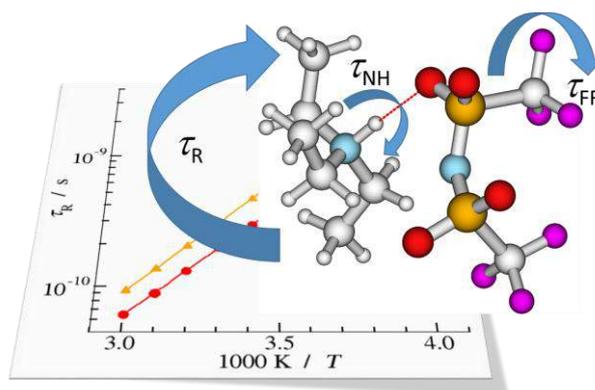


Fig. 1. Rotational correlation times for the cation and anion in the ionic liquid [TEA][NTf<sub>2</sub>].

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## DYNAMICS OF IONIC LIQUIDS BY MEANS OF NMR RELAXOMETRY

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NMR relaxometry is a unique source of information about translational and rotational dynamics of ionic liquids. Several ionic liquids are composed of  $^1\text{H}$  containing cations and  $^{19}\text{F}$  containing anions.  $^1\text{H}$  NMR relaxometry experiments give access to the relative cation-cation and cation-anion translation diffusion (via  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{19}\text{F}$  dipole-dipole, inter-ionic relaxation pathways, respectively) as well as to rotational dynamics of the cation (via intra-ionic  $^1\text{H}$ - $^1\text{H}$  dipole-dipole interactions). Analogously,  $^{19}\text{F}$  relaxation experiments probe the relative anion-anion and cation-anion translation movement (via  $^{19}\text{F}$ - $^{19}\text{F}$  and  $^1\text{H}$ - $^{19}\text{F}$  dipole-dipole, inter-ionic relaxation pathways, respectively) and rotational dynamics of the anion (via intra-ionic  $^{19}\text{F}$ - $^{19}\text{F}$  dipole-dipole interactions). This, already complex, relaxation scenario becomes even more complicated in the presence of ions including nuclei possessing quadrupole moments, such as  $^7\text{Li}$ . In such a case quadrupole interactions are the main source of  $^7\text{Li}$  relaxation associated with translation diffusion of lithium ions.

To profit from the potential of NMR relaxometry for ionic liquids it is of utmost importance to include into the description of relaxation processes all relevant relaxation pathways [1-4]. This can lead to surprising results – for instance, it has turned out that for some ionic liquids,  $^{19}\text{F}$  relaxation processes are dominated by cation-anion,  $^1\text{H}$ - $^{19}\text{F}$  dipole-dipole interactions, with the  $^{19}\text{F}$ - $^{19}\text{F}$  relaxation contribution being, in fact, negligible. As far as translation diffusion is concerned, NMR relaxometry gives access to relative translation movement of ions: cation-cation, cation-anion and cation-anion, in contrast to NMR gradient experiments (diffusometry) providing information about self-diffusion processes. Consequently, by comparing the relative and self-diffusion coefficients one can get insight into correlation effects in the ionic movement – in the case of uncorrelated dynamics the relative diffusion coefficient is given as a sum of self-diffusion coefficients of the interacting species. In this context, one should point out that any kinds of experimental evidence of correlated molecular or ionic dynamics are very rare.

The outlined subjects will be thoroughly discussed and illustrated by examples.

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## WATER DYNAMIC AND MESH SIZE DISTRIBUTION IN HETEROGENEOUS POLYGALACTURONIC ACID HYDROGELS PROBED WITH FFC NMR RELAXOMETRY

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Gels are essential materials in physics and chemistry. They are of paramount importance in medicine, pharmacy and food science, to name but a few. In this work, we performed an extensive NMR analysis of the water dynamics and mesh size of heterogeneous polygalacturonic acid (polyGalA) hydrogels [1] used for encapsulation and release of active components.

The results obtained with different dynamic models used to treat the FFC profile data are compared and put into perspective with outcomes from independent techniques (Molecular Dynamics, SANS, rheology).

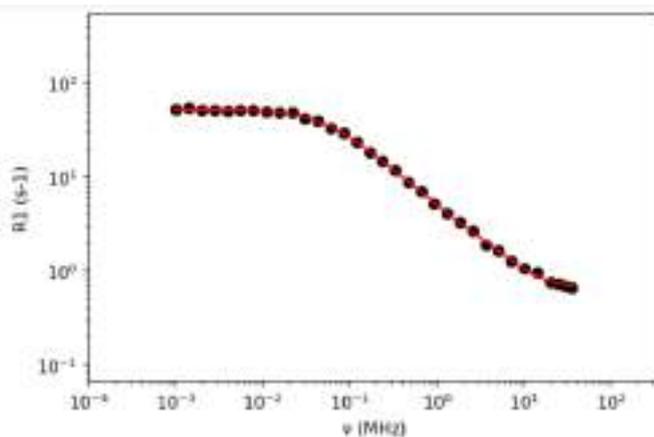


Fig. 1. <sup>1</sup>H NMRD profile of Ca-polyGal hydrogel

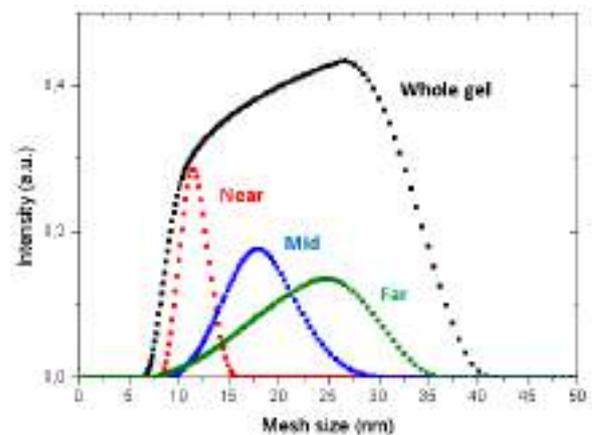


Fig. 2. Mesh size distribution in the Complete and sliced heterogeneous Ca-polyGal. hydrogel

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## FIELD-CYCLING RELAXOMETRY IN THE NANOTESLA TO MILLITESLA RANGE

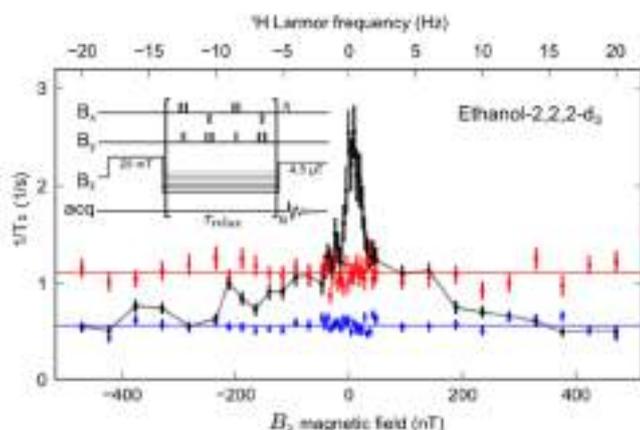
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Magnetic resonance relaxation in the Hz to kHz range can quantify slow- correlation-time ( $>1 \mu\text{s}$ ) dynamic processes in chemical systems, not limited to: liquid adsorption and diffusion on surfaces (e.g. porous materials), spin diffusion and decay mechanisms for long-lived spin states. A magnetically shielded enclosure is one route to achieving control of precise, homogeneous and repeatable fields for measurements in this frequency range, demanding that both fast-field-cycling and NMR signal detection hardware be compatible with shielding of ambient fields (e.g. MuMetal chambers). In recent years, we have developed a nT to  $\sim 20$  mT FFC-NMR system using alkali-atom vapor magnetometers to detect  $^1\text{H}$  NMR signals at Larmor frequencies from DC to 20 kHz (0.5 mT), with sensitivities comparable to traditional fast-field-cycling and inductive pickup coil detection[1]. Aside from precise field control, lower detection frequency overcomes several other technical demands of high-field FFC-NMR such as magnet refrigeration and radiofrequency electronics, opening the way to portable and even hand-held field-cycling NMR systems.

In this talk, I outline some applications enabled by ultralow-field relaxometry including dynamics studies of high-pressure supercritical and other fluids in metallic confinement, and of common solvents in sub-10 nm pore spaces. New techniques for spin control during relaxation delays are also introduced. For instance, trains of  $(90)_X(180)_Y(90)_X$  direct current (dc) composite pulses allow decoupling of one or multiple spin species from residual magnetic bias fields  $\sim 100$  nT, in effect making a true zero field, as well as decoupling heteronuclear spin species from one another[2]. We also introduce new “meridional” dc composite pulses to increase robustness of spin control, which may be useful in battery-powered FFC NMR systems.



**Fig. 1.** Field dependence of  $^1\text{H}$  spin relaxation rates in liquid  $\text{CD}_3\text{CH}_2\text{OH}$ . Apparent longitudinal relaxation rates under free decay (BLACK curve) are due to (1) H-D ( $^1\text{H}$ - $^2\text{H}$ ) scalar coupling of  $^3J_{\text{HD}} \sim 1$  Hz via scalar relaxation of the second kind; (2) residual transverse fields. The two contributions can be isolated by applying  $^1\text{H}$ -only (BLUE curve) or combined  $^1\text{H}$ - $^2\text{H}$  dynamical decoupling during the relaxation delay  $\tau_{\text{relax}}$ .

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## CHALLENGES IN OBTAINING NQR PARAMETERS FROM FENTANYL CITRATE USING FAST FIELD CYCLING RELAXOMETRY

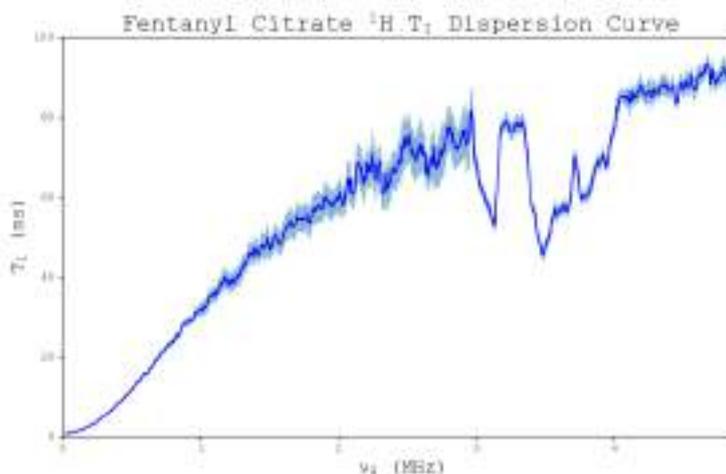
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The two most important aspects of observing the nuclear quadrupole resonance (NQR) signals of new materials are finding the NQR resonance frequencies and the sample having relaxation rates favorable for observation. Fast Field Cycling (FFC) Relaxometry provides a technique to indirectly determine both NQR frequencies and their  $T_1$  by looking for local variations in  $^1\text{H}$   $T_1$  or  $^1\text{H}$  magnetization as a function of an applied magnetic field [1]. We will discuss our FFC work in measuring the  $^1\text{H}$   $T_1$  dispersion curve of the synthetic opioid fentanyl citrate ( $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$ ) to identify its  $^{14}\text{N}$  NQR frequencies [2]. Because of the large number of  $^1\text{H}$  in this material the  $^1\text{H}$   $T_1$  isn't well defined by a single value. This obscures the interaction of the  $^{14}\text{N}$  NQR and  $^1\text{H}$  NMR systems and increases the measurement time necessary for feature discrimination. Additionally, naively extracting the  $^{14}\text{N}$  NQR  $T_1$  also obscures the underlying relaxation rates of this material. We will describe our methods for dealing with these challenges.



**Fig. 1.** The  $^1\text{H}$   $T_1$  dispersion curve of fentanyl citrate [2] shows pronounced features between 3 and 4 MHz attributed to cross relaxation between the  $^1\text{H}$  NMR and  $^{14}\text{N}$  NQR systems.

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# Lectures

## LOW FIELD RELAXOMETRY FOR MARGIN ASSESSEMENT AND TUMOUR GRADING IN BREAST-CONSERVING SURGERY

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As breast-conserving surgery is routinely applied for the treatment of breast cancer (the most common form of cancer for women), the need for new technologies to improve intraoperative margin assessment has become increasingly important [1]. In this study, the potential of Fast Field Cycling Relaxometry as a new diagnostic tool was evaluated. Small samples of freshly excised tissue from patients undergoing breast cancer surgery were collected and subjected to measurements of the proton longitudinal relaxation rate ( $R_1$ ) at very low magnetic field strengths, then sent to gold standard histopathological evaluation (H&E staining) (Fig. 1).

It was found that a good accuracy in margin assessment, i.e., a sensitivity of 93% and a specificity of 85%, could be achieved by using two quantifiers namely *i*) the slope of the line joining the  $R_1$  values measured at 0.02 and 1 MHz (the Ratio criterion) and *ii*) the sum of the  $R_1$  values measured at 0.39 and 1 MHz (the  $2R_1$  criterion). The discriminating ability is mainly based on the different lipid/protein/water content and water mobility between healthy and malignant tissues [2].

The relaxometric method is low cost, fast, and does not rely on the expertise of a pathologist or cytologist as it can be

highly automatized. Furthermore, the data analysis of tumour samples according to the 2SX exchange model [3] indicated that the extracellular volume fraction and the intracellular water lifetime may represent good biomarkers for tumour grading.

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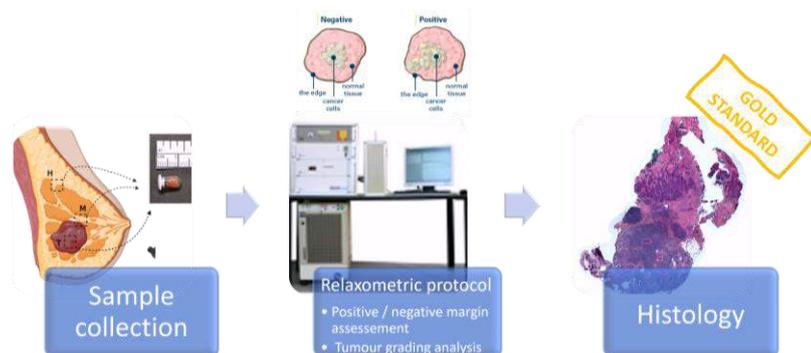


Fig. 1. Schematic representation of the relaxometric study

## Construction And Optimisation Of A Six-Channel Torso Array For Cardiac Field-Cycling Imaging At 0.2T

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### Background/Introduction

Field-Cycling Imaging (FCI) is a novel low-field MRI technique which allows  $T_1$  dispersion to be probed in vivo and exploited as a novel contrast mechanism. In this work we describe the construction of a six-channel anterior-posterior torso array and present the first in-vivo FCI cardiac images and  $T_1$  dispersion from healthy volunteers.

### Methods

Both array segments were constructed using three 2-turn 160 mm loops wound from high frequency litz and arranged in a Venn configuration with a 40 mm overlap to provide a degree of passive geometric decoupling. Additional decoupling and transmit protection was achieved by impedance matching through a lattice-balun to custom built low impedance preamplifiers.

As a proof of concept, we then used the torso array to collect short-axis cardiac images (Fig 1) from a group of healthy volunteers (N = 10, 4 males) at field strengths ranging from 0.2T to 20  $\mu$ T from which  $T_1$  dispersion information was derived from the left ventricle.

### Results

Coil-coupling measurements found that inter-coil coupling was -33 dB between adjacent elements and -35 dB for opposite coil pairs at 300 mm. The unloaded to loaded Q-factor ratio was found to be  $>2$ , indicating that the coil is body-noise dominated.

The left ventricle was readily visible in the volunteer FCI images. The derived mean  $T_1$  dispersion values were 0.2 T:  $177 \text{ ms} \pm 31.5$ , 0.02 T:  $116 \text{ ms} \pm 61$ , 0.002 T:  $48 \text{ ms} \pm 19.4$ , 0.0002 T:  $33 \text{ ms} \pm 19$  which are comparable with expected  $T_1$  values at ultra-low magnetic fields.

### Conclusions

We have demonstrated a six-channel torso array coil for imaging at 0.2T and demonstrated the first application of field-cycling cardiac imaging in humans. These results pave the way for future work into cardiac applications of field-cycling.



Figure 1. Representative in vivo FCI cardiac images from base to apex collected from a healthy volunteer at 0.2T.



## SPECIFIC SURFACE INTERACTION OF FLUIDS IN POROUS GLASS - RELAXATION DISPERSION OF BICOMPONENT SYSTEMS

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The theoretical description of the  $T_1$  dispersion of liquids in “clean” (i.e. metal-free) porous glass has been established decades ago, distinguishing between the limiting cases of strong and weak adsorption of the molecules on the native glass surface with its large amount of hydroxyl groups [1]. The model predicts vanishing  $T_1$  dispersion in the weak adsorption case, and strongly pronounced dispersion for those molecules that encounter preferential orientation on the surface, allowing for a low-frequency dispersion component by experiencing the surface curvature via anomalous diffusion. Therefore, this process is intramolecular by nature and is expected to lead to equivalent dispersions for protons and deuterons [2].

In many cases, however, the interaction of liquids with surfaces may be considered “intermediate”, which becomes particularly apparent in matrices with large internal surfaces and small pore sizes such as Vycor porous glass. With the goal of gaining more detailed insight into the relaxation processes of a wider range of liquids, we have carried out (a)  $^2\text{H}$  relaxation dispersion measurements of perdeuterated liquids and (b)  $^1\text{H}$  and  $^2\text{H}$  studies of binary systems of two fluids in Vycor that are either miscible or immiscible in the bulk. For distinguishing different mechanisms, we have chosen fluids with different polarity as well as protic (water, ethanol) and aprotic liquids (acetone, THF, cyclohexane, n-alkanes) [3,4], both as single components and in mixtures of equal amount. In addition to FFC profiles, relaxation times and diffusion coefficients were determined at a fixed field of 1.0 T. For immiscible pairs of liquids, Vycor was first saturated with the non-polar component and then allowed to be replaced by the polar component by soaking it in bulk, while the fluid distribution inside the porespace was monitored continuously employing the  $^1\text{H}$  spectrum.

It was observed that deuterated compounds in Vycor frequently featured an even stronger  $T_1$  dispersion than their undeuterated counterparts, whereas diffusion properties remained dominated by geometrical tortuosity in all cases. For mixtures in Vycor, we discuss the concept of one component preferentially or completely covering the solid interface, a situation which is in agreement with findings for systems with an unipolar liquid such as cyclohexane.

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## EXPLORING THE COMPETITIVE ADSORPTION OF WATER-ETHANOL MIXTURES IN MESOPOROUS SILICAS

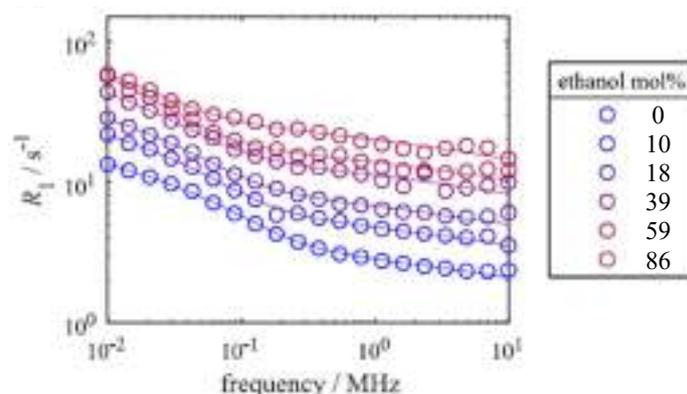
L. Rozing,<sup>a,b</sup> J. Ward-Williams,<sup>a\*</sup> J. Beckmann,<sup>a</sup> A. Sederman,<sup>a</sup> M. Mantle,<sup>a</sup> L. Gladden<sup>a</sup>

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The relaxation behaviour of liquids confined within porous materials can be strongly influenced by co-imbibed species, allowing relaxation measurements to give important insights into the dynamics and structuring of liquid mixtures within the pore space [1]. In previous studies on alumina catalyst carriers, it was shown that for binary liquid mixtures with large polarity differences the more polar species preferentially occupied the surface and forced the less polar species into the bulk pore space [2]. In this work we have explored the competitive adsorption behaviour of water-ethanol liquid mixtures within silica supports, where the difference in polarity is relatively small and both components have the potential to interact strongly with the surface. The relaxation behaviour of each component was studied as a function of composition (see Fig 1) for four different pores sizes (6-30 nm) and the adsorption behaviour was shown to differ strongly between the silica carriers. By combining a fast field cycling analysis with independent surface hydroxyl density and pore size measurements it was shown that the surface chemistry controlled the adsorption properties in this pore size range. These results provide useful insights on how to optimise the surface selectivity of silica materials for catalytic or separations based applications.



**Fig. 1.** The NMRD profiles of the water component imbibed within Q30 silica (pore size ~30 nm) as a single component and in a binary liquid mixture. For each NMRD profile the mole fraction of ethanol in the liquid mixture is shown.

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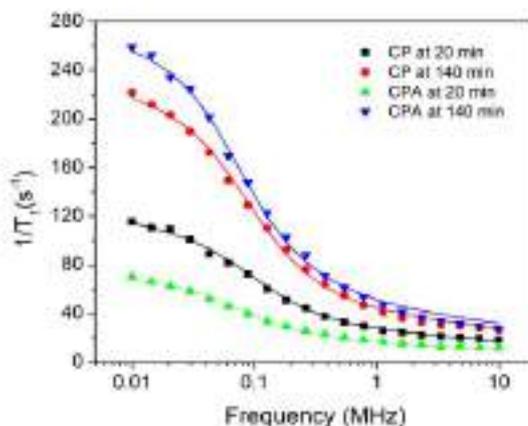
## THE EFFECT OF CALCIUM NITRATE ON CEMENT HYDRATION: FAST FIELD CYCLING NMR RELAXOMETRY INVESTIGATIONS

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In the last years, there is an increased interest for applying the 3D printing technology with cement-based composites. However, printing with cement composites is not simple, and requires a better control of the setting time. One admixture that can be used in cement composites to control the cement hydration, and consequently the setting time, is calcium nitrate [1]. It accelerates the hydration dynamics but may have negative influence on porosity and strength development. That is why, understanding its role in a cement mixture is an important objective. In our work, we study the influence of calcium nitrate on the early hydration dynamics of a white cement paste, via Fast Field Cycling NMR relaxometry (e.g., Fig.1).



**Fig. 1.** Relaxation dispersion curves recorded at different hydration times in the absence (CP) and the presence (CPA) of the accelerator. The samples were prepared with white cement, a water-to-cement ratio of 0.4, and an accelerator-to-cement ratio of 0.02. The lines are the best fits with 3-tau model [2].

The evaluation of the data is based on the 3-tau relaxation model [2]. According with this model, it is demonstrated an accelerated increase in the surface-to-volume ratio of the capillary pores in the presence of the accelerator. It is also concluded a decrease in the mobility of water molecules in the surface layer.

**Acknowledgement:** This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS - UEFISCDI, project number PN-III-P4-ID-PCE-2020-0533, within PNCDI III

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## WATER DYNAMICS IN COMPOSITE AQUEOUS SUSPENSIONS OF CELLULOSE NANOCRYSTALS AND A CLAY MINERAL STUDIED THROUGH MAGNETIC RESONANCE RELAXOMETRY

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Nanocomposites are a group of hybrid materials that offer excellent advantages in developing functional materials with desired chemical, physical, and mechanical properties. The incorporation of nanoparticles into a polymer network is a leading technique to achieve or control the properties of composite materials. Cellulose nanocrystals (CNCs) have a uniform nanorod shape, high surface area, and unique liquid crystalline character. CNCs in water, at a given concentration, have shown the ability to self-organize into a chiral nematic (cholesteric) liquid-crystalline phase with a helical arrangement. CNCs suspensions can produce structural colors, a fascinating feature of certain surfaces, mostly found in nature, that change color with illumination or by changing the viewing angle. These structural colors can be tuned by controlling the pitch of the chiral nematic structure and the preparation conditions of CNCs. The study of the dynamic properties of confined water might reveal many microscopic details regarding the interfacial relationship between the confined water molecules and the confining walls.

<sup>1</sup>H spin–lattice relaxation time (T<sub>1</sub>) measurements were performed to probe the dynamic behavior of water in aqueous suspensions of cellulose nanocrystals (CNCs) and a layered smectite clay mineral with different degrees of concentration. <sup>1</sup>H–T<sub>1</sub> experiments were carried out over a wide frequency domain, ranging from a few kilohertz to 500 MHz, with the aid of conventional and fast field cycling nuclear magnetic resonance (NMR) techniques. The experimental relaxometry data illustrate differences between the dynamic behavior of bulk water and that confined in the vicinity of CNC–clay surfaces. The modeling of the relaxation dispersions allowed the determination of dynamical processes and variables explaining the dynamic behavior of water in CNC–clay suspensions. It turned out that reorientations mediated by translational displacements are a leading NMR relaxation mechanism for water interacting with the surfaces of CNC–clay particles in the low-frequency domain. In the high-frequency regime, however, the inner-sphere paramagnetic relaxation mechanism dominates, which is caused by the interaction of water protons with dissolved Fe ions.

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## TOWARDS ANTIBODY DIRECTED HIGH-CONTRAST MRI NANOPROBES FOR DIAGNOSIS OF STROKE

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Early treatment is essential to minimise the after-effects of a Stroke; monitoring the effect of administered therapeutics would allow for adaptation of the treatment regime to optimise the clinical outcome. Traditional small molecule Gd-based contrast agents (CAs) produce insufficient contrast to allow for effective imaging of low concentration targets such as cell receptors. The construction of multimeric, nanoscale probes has been demonstrated to improve the effective contrast significantly.[1] In this work we used nanoprobcs incorporating GdCAs, fluorescent quantum dots (QDs),[2] and antibody-based targeting, to image platelets with a view to monitoring clot formation and treatment in the future.

The chelate **GdL<sub>1</sub>** has an  $r_1$  of 3.25 mM<sup>-1</sup> s<sup>-1</sup> (37 °C, 400 MHz) and the nanoconstruct **GdL<sub>1</sub>-QD** has a per Gd  $r_1$  of 3.90 mM<sup>-1</sup> s<sup>-1</sup> (37 °C, 400 MHz), resulting in, per QD, relaxivity of 376.4 mM<sup>-1</sup> s<sup>-1</sup> (37 °C, 400 MHz). The shape of the NMRD profiles for these CAs differs; **GdL<sub>1</sub>-QD** has an additional peak in the region of 10-60 MHz which is not present for **GdL<sub>1</sub>**. Attaching **GdL<sub>1</sub>** to the QD surface results in a 4.4 fold increase at 10 MHz and 2.7 fold increase at 60 MHz in the per Gd  $r_1$ . Due to the high number of GdCAs loaded on each QD, **GdL<sub>1</sub>-QD** displayed a maximum effective per QD  $r_1$  of 3203 mM<sup>-1</sup> s<sup>-1</sup> (10 MHz, 37 °C).

A number of QD surface coatings were investigated to assess their impact on platelet behaviour: InP/ZnS QDs coated in thioglycolic acid or Penicillamine had minimal effect on platelet aggregation or function and showed low uptake of the QDs by the platelets at concentrations up to 30 nM in washed platelets.

The nanoprobe, **GdL<sub>1</sub>-QD**, significantly increases the effective  $r_1$  compared to the small molecule **GdL<sub>1</sub>**. QD based fluorescent agents can be also used to study platelets without disrupting their function. These results lay the groundwork for the development of QD based GdCA for diagnosing Stroke.

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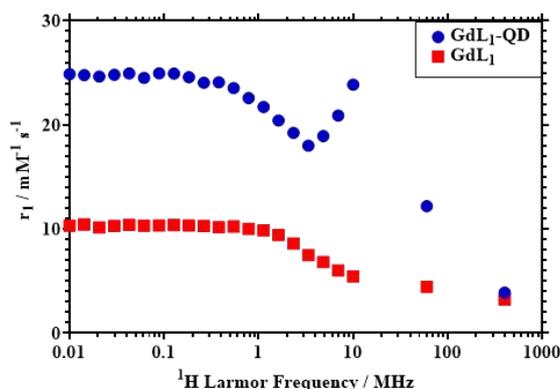


Fig. 1. NMRD profile of **GdL<sub>1</sub>** and **GdL<sub>1</sub>-QD**

## Detection Of Ischaemic Stroke In Patients Using Field Cycling Imaging

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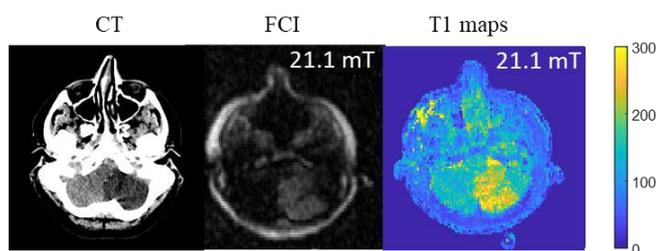
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**Purpose:** We conducted a clinical study to explore the stroke contrast in a range of low magnetic field strengths using Field-Cycling imaging (FCI) [1].

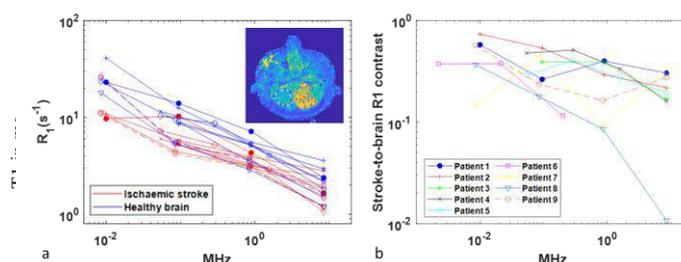
**Methods:** 38 Patients with ischemic stroke were scanned on the whole-body FCI system within 24 to 96 h after presentation (ethics approved by NoSREC, number 16/NS/0136). FCI images were acquired using a field-cycled inversion recovery spin echo sequence with three to six evolution fields typically ranging from 0.2 T to 0.2 mT (equivalent to 8.5 MHz to 0.085 MHz), five evolution times, in-plane resolution of 2 to 4 mm, slice thickness of 10 mm, one slice and no averaging. Total duration was 45 min. The results were validated using the clinical CT scan or a 3T MRI scan. Multi-field T1 quantification was performed in Python using a joint total generalised variation (TGV) regularisation [2]. Two region of interests (ROIs) were selected manually over infarct regions and contralateral normal brain for R1 dispersions.

**Results:** Nine patients were included. The infarct region in FCI and T1 maps corresponded with the clinical images (Fig. 1). The R1 dispersion profiles in stroke area differed from the normal brain tissue below 8.5 MHz and the R1 contrast (stroke to normal brain) increased with low frequencies (Fig. 2).

**Discussion:** This is the first-ever measurement of R<sub>1</sub> dispersion in patients with stroke showing that we can discriminate between healthy and ischemic brain regions below 8.5 MHz. Changes in R1 relaxation may reflect modifications of water diffusion across cell membranes due to cellular adaptation or death[3].



**Fig. 1.** CT, FCI and T1 map from a patient with ischaemic stroke. FCI was acquired 6 days after onset. The colour bar shows the T1 in ms.



**Fig. 2.** a) R1 dispersion curves plotted for all patients. The image shows an example of the ROI location. b) Contrast plotted at different frequencies for all patients.

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## INSIGHTS GLEANED FROM A REVIEW OF NMRD PROFILES

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As a part of the development of our REX utility, we have collected [1,2, ...] a large number of relaxation profile formulas, both for longitudinal and perpendicular relaxation rates, and gained a body of experience in fitting them to experimental data. While most of these were collected from literature, a few are original, based on heuristic continuous distributions of correlation times.

From a broader perspective, we are all aware that there exists a large number of “elementary” relaxation rate formulas  $R_1(f,\tau)$  and  $R_2(f,\tau)$  which can be classified primarily by a combination of a spin interaction on one side with a model of a stochastic molecular motion on the other side. Such elementary relaxation formulae then become terms of complete relaxation profile expressions that are often specific for particular families of substances and/or materials.

In most practical cases it is not easy to decide a-priori which terms need to be included to describe a given NMRD profile. This is due to facts such as (a) there is a certain repetitive tendency in the above scheme, (b) many elementary formulas have similar forms, and (c) the numbers of feasible combinations are staggering. In general, finding a convincing model requires a lot of experience in NMR relaxometry as well as a good knowledge of the studied material, combined with a versatile software that makes it easy to “play” with various hypotheses and assumptions (NMR CAR, or computer-aided-relaxometry).

Even so, the outcome is usually non-univocal, i.e., given an NMRD profile, one finds multiple plausible formulas that fit it quite well. In other words, NMR field-cycling relaxometry is very good at excluding certain models of molecular motions, but less good at proving any single one.

An important help arises from the possibility to fit multiple profiles pertinent to the same sample, one that should conform to the same model of molecular motion. Classical examples include simultaneous fits of NMRD profiles acquired at different temperatures and/or simply temperature dependencies of relaxation times at a fixed Larmor frequency. Less common cases might include dispersion profiles obtained from different nuclei in the same sample, and profiles acquired with completely different methodologies (for example NMR and dielectric). This leads to multiple sets of experimental data, the models for which necessarily share some parameters, even while differing in others. Simultaneous fitting of such multiple data sets will necessarily become a necessity in any molecular dynamics research.

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Note: this just an authoritative recent example of a vast literature containing several hundreds of titles.

## FAST FIELD CYCLING AND DYNAMIC NUCLEAR POLARIZATION: BEYOND THE ENHANCEMENT VALUE

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Since around 2015, a combination of FFC and DNP magnetic resonance techniques [1] has been established as an advanced method for studying molecular dynamics in a variety of systems: polymers and copolymers [2], petroleum materials [3], ionic liquids [4], and other complex systems [5]. The level of NMR signal enhancement achieved a value of several hundred, which made it possible to study samples where low- $\gamma$  nuclei such as  $^2\text{H}$  and  $^{13}\text{C}$  are the main targets.

On the other hand, in some cases, the DNP enhancement is low and does not produce many benefits in comparison with conventional FFC. However, the information which can be obtained from DNP data is still valuable for studying dynamics. For instance, the well-known Overhauser DNP effect is directly related to the dynamics parameters, such as correlation times and space distribution of interacting species. When solid or cross effects dominate, qualitative information about dynamics is available as well. The mixing of several DNP effects reveals unique dynamics properties of the studied system, tremendously complicating the analysis of the data though.

In the current contribution, we exhibit the last results of the DNP-FFC study of complex systems such as ionic liquids and porous media, where DNP data significantly contribute to the analysis of the dynamics, while NMR signal enhancement remains low.

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## ModelFreeFFC: a regularization approach to the analysis of NMRD profiles

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The present contribution describes a computational approach to the analysis of Nuclear Magnetic Relaxation Dispersion (NMRD) profiles, acquired by Fast Field Cycling (FFC) techniques. The aim is to develop a flexible and efficient computational framework to promote the employment of FFC in different application fields. Following [1], we represent the NMRD profile  $R_1$  as the sum of three components: an offset  $R_0$ , keeping into account very *fast* molecular motions, a term representing the normalized amplitude correlation function  $f$ , according to the *model-free* approach [2], and a term describing the occurrence of the so-called *quadrupolar dips* [1]. We express the relationship between the NMRD measurements  $R_1$  and the model parameters  $(\hat{f}, \hat{\phi}, \hat{R}_0)$  as a non-linear inverse problem, represented by the weighted sum between a quadratic fit term, and an  $L_1$  regularization term.

The model parameters are computed by the following non-linear constrained minimization problem:

$$(\hat{f}, \hat{\phi}, \hat{R}_0) = \underset{(f, \phi, R_0)}{\operatorname{argmin}} \left\{ \left\| \mathbf{R}_1 - (\mathbf{K}f + \mathbf{Q}(\phi) + R_0) \right\|_2^2 + \lambda \left\| f \right\|_1 \right\}$$

$$\text{s.t. } f \geq 0, R_0 \geq 0, \phi \in \mathbf{B}_\phi$$

where  $\mathbf{B}_\phi$  is the bound set for the parameter  $\phi$  of the quadrupolar function  $\mathbf{Q}(\phi)$ , and the matrix  $\mathbf{K}$  represents the discretized *model-free* kernel [1].

The term  $\lambda$  is the regularization parameter that weights the contribution of the  $L_1$  regularization term. We propose an automatic strategy for the computation of  $\lambda$  according to the uniform penalty principle [3, 4]. The proposed method is implemented in the ModelFreeFFC Matlab software [5] and will be presented at the Stelar *s.r.l.* exhibition booth.

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## The subtle importance of collective motions on isotropic magnetic and non-magnetic ionic liquid systems

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In recently published works aiming to study the paramagnetic properties of magnetic ionic liquids using <sup>1</sup>H NMR relaxometry and diffusometry, X-ray diffractometry revealed, for some of the studied systems, a well-defined bilayered structure motivated by the segregation of the polar and non-polar domains [1]. Although the studied compounds do not present the same degree of order as a liquid crystal, it was only possible to consistently combine the data from all experimental techniques considering local order fluctuations as a possible relaxation pathway.

The present work also combines <sup>1</sup>H NMR relaxometry and diffusometry with X-ray scattering experiments in the study of the molecular dynamics of magnetic and non-magnetic ionic liquids based on the [P6,6,6,14]<sup>+</sup> and [C8mim]<sup>+</sup>. The data from all experimental techniques corroborated the need to consider either order parameter fluctuations or layer undulations in the model fitting analysis of these ionic systems, despite their apparent isotropic nature. Ultimately, NMR relaxometry, particularly FFC NMR, is presented as a tool to assess local order dynamics and even discriminate between different types of molecular order fluctuations in isotropic liquids.

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## Molecular Dynamics of Ionic Liquids from Fast Field Cycling NMR and Molecular Dynamics Simulations

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Understanding the connection between the molecular structure of ionic liquids and their properties [1] is of paramount importance for practical applications. However, this connection can only be established if a broad range of physicochemical properties on different length- and timescales is available in the first place. Even then, the interpretation of the results often remains ambiguous due to the natural limits of experimental approaches. Here we use fast field cycling (FFC) to access both translational and rotational dynamics of ionic liquids. These combined with a comprehensive physicochemical characterization and MD simulations provide a toolkit to give insight into the mechanisms of molecular mechanics. The FFC results are consistent with the computer simulation and conventional physicochemical approaches. We show that curling of the side chains around the positively charged cationic core is essential for the properties of ether functionalized ionic liquids [2], and demonstrate that neither geometry nor polarity alone are sufficient to explain the macroscopic properties.

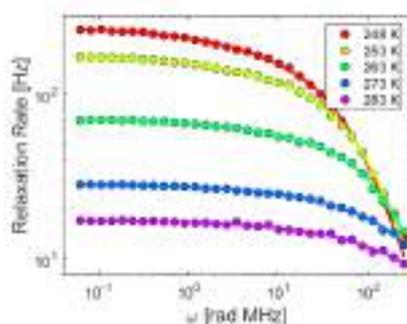


Figure 1: NMR dispersion of [P20231][NTf<sub>2</sub>] between 248 and 283 K.

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## DETECTION OF BREAST LESIONS WITHOUT USE OF CONTRAST AGENTS USING FIELD CYCLING IMAGING AT LOW FIELDS

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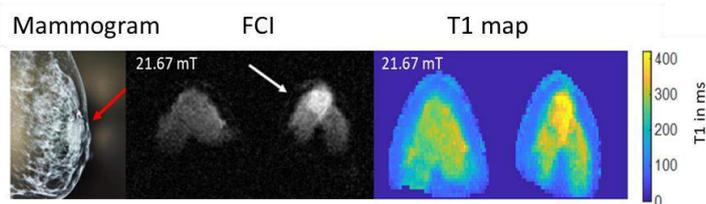
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**Purpose:** We conducted a clinical study to explore if we can detect breast tumours without the need for exogenous contrast using Field-Cycling imaging (FCI) [1] at low magnetic field strengths.

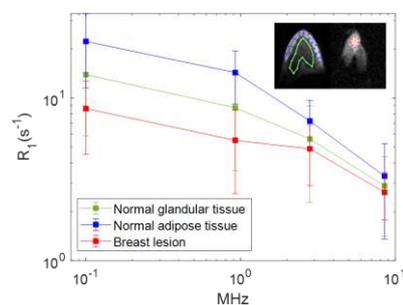
**Methods:** 26 patients with breast lesions were scanned on the whole-body FCI system before surgery (ethics approved by NoSREC, number 19/NS/0064). FCI images were acquired using a field-cycled inversion recovery spin echo sequence with four evolution fields ranging from 0.2 T to 0.23 mT (equivalent to 8.5 MHz to 0.1 KHz), five evolution times, slice thickness of 10 mm, one slice and no averaging. Total duration was 45 min. The results were validated using the clinical CT or 1.5T MRI scan. Multi-field T1 quantification was performed in Python using a joint total generalised variation (TGV) regularisation [2]. Three region of interests (ROIs) were selected manually over lesions, contralateral adipose and glandular tissue for R1 dispersions.

**Results:** Ten patients were included. The breast lesion in FCI and T1 maps corresponded with the clinical images (Fig. 1). The R1 dispersion profiles in lesions differed from the normal breast tissue with higher contrast shown at lower fields and the R1 was lower in breast lesions (Fig. 2).

**Discussion:** This is the first-ever measurement of R<sub>1</sub> dispersion in patients with breast lesions. FCI can differentiate between breast lesions and normal breast below 0.2T (8.5 MHz) without the use of contrast agents. Changes in R1 relaxation may reflect enhanced water diffusion across tumour cell membranes [3].



**Fig. 1.** Mammogram, FCI and T1 map from a patient with a borderline phyllodes lesion. The colour bar shows the T1 in ms. The arrows show the lesion.



**Fig. 2.** Averaged R1 dispersion curves. The error bars show the standard deviation across patients. The image shows an example of the ROI location.

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## EXPLORING THE CRYSTALLINITY OF TURKISH DELIGHTS BY USING MAGIC SANDWICH ECHO SEQUENCE (MSE)

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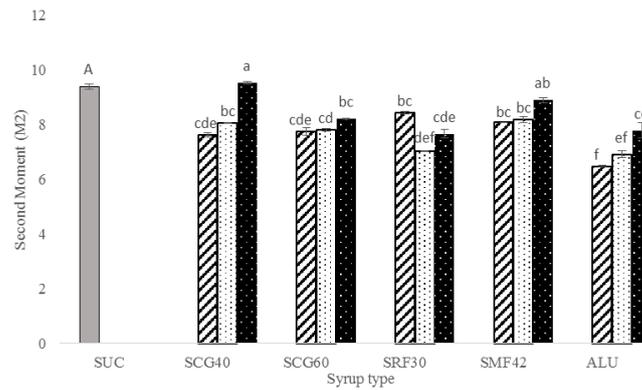
<sup>a</sup> Department of Food Engineering, Konya Food and Agriculture University, Konya, Turkey

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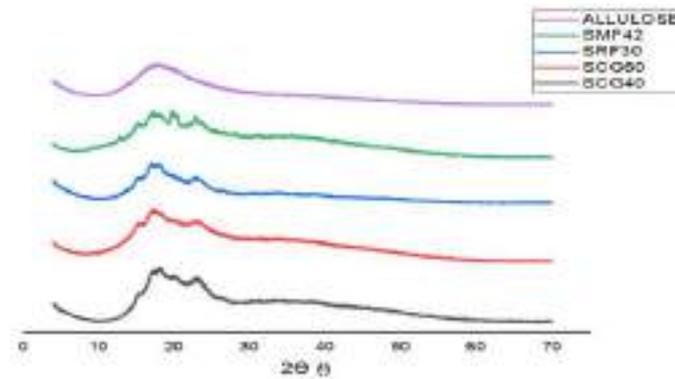
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Turkish delight (Lokum) is a traditional dessert and originates its formulation date back to 1800s. Sucrose is the main sugar source in the formulation. However, to prevent crystallization in lokum, manufacturers sometimes substitute the beet sugar with corn syrup or other type of sweeteners such as allulose syrup. At present, X-Ray Diffraction (XRD) technique is generally used to detect the crystallinity of the food samples. Since XRD technique gives more promising results for the powder samples with homogenous nature, TD-NMR reveals as an easier and alternative method to XRD for the determination of the crystallinity of Turkish delight samples. In this study, to explore the differences of crystallinities between the Turkish delights consisting of different type of sugar source, both XRD and TD-NMR experiments were performed. Lokum samples was prepared by using 4 different sugar source such as powder sucrose (SUC), different glucose syrups (SCG40&SCG60), different fructose syrups (SRF30&SMF42) and Allulose syrup (ALU) at 3 different substitution level (30%,45%,60% w/w) by considering the previous study with some modifications [1]. Samples were analyzed by using Magic Sandwich Echo (MSE) sequence which could be considered as an important non-conventional TD-NMR relaxometry technique. In order to detect the crystallinity differences among the formulations, parameters called as second moments ( $M_2$ ) were measured through MSE sequence by a system operating at  $^1\text{H}$  frequency of 20.34 MHz (Spin Track, Resonance Systems GmbH, Kirchheim/Teck, Germany). When all second moment ( $M_2$ ) results were considered, use of different type of syrups at different substitution levels showed detectable changes in  $M_2$  results indicating different crystallinities (Fig.1). The lowest  $M_2$  value was obtained for the lokum sample containing 30% allulose syrup and 30% sucrose indicating very low crystallinity for this sample while the highest  $M_2$  was obtained for the control sample containing only powder sucrose as the sugar source indicating its highest crystallinity. XRD results also validated the outcomes of TD-NMR results since diffraction peaks with “halo pattern” was obtained for the ALU samples containing 30% syrup indicating minimum crystallinity value for this sample (Fig.2). Therefore, it could be concluded that, second moment values ( $M_2$ ) measured through TD-NMR by using MSE pulse sequence, might be a possible and easier alternative to XRD method for detection of the crystallinity differences of Turkish delights containing different type and amount of sugar source.



**Fig. 1.** Second Moment (M2) results of Turkish delights containing sucrose (SUC) and different type of syrups at different concentrations (30%: ▨, 45%: ▩, 60%: ▣)



**Fig.2.** X-ray Diffraction Patterns of Turkish Delights containing different type of syrup (30% concentration)

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## Mechanism of relaxation of rat's blood, red blood cells and plasma at different temperatures.

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Infants who are born prematurely (<37 weeks), are more prone to brain hemorrhages with a relatively high rates of death and permanent physical/cognitive disabilities [1]. Although current imaging techniques such as MRI is reliable, it can seriously suffer from a lack of sensitivity, especially at the early stages of bleeding.

A promising alternative is Fast Field Cycling (FFC) which offers a unique information about the molecular dynamics of the explored system, it has already been used to study simple biological solutions such as serum albumin and even slightly complex ones such as human whole blood [2].

However, in this latter, relaxation rates have always been analyzed and reported as single exponentials (i.e. one proton population) despite that blood is composed of two distinct compartments which are the red blood cells (RBC) and the plasma.

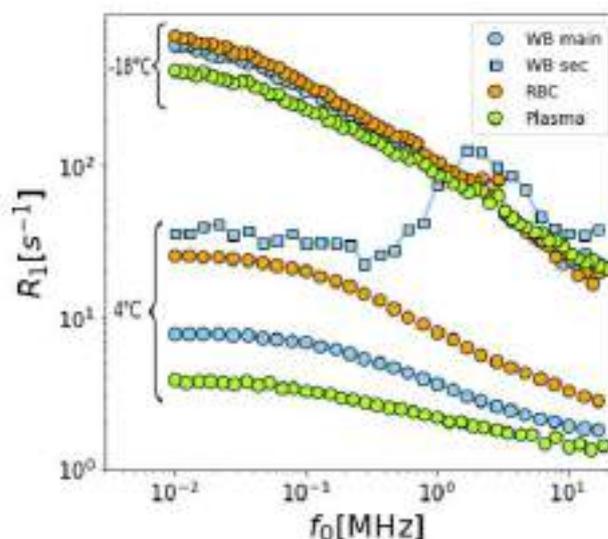
The aim of this present work is to investigate the validity of this assumption by acquiring nuclear magnetic resonance dispersion (NMRD) profiles of the rat's whole blood, RBC and plasma at different temperatures.

To that end, arterial whole blood was drawn from healthy Sprag Dewley rats, plasma and RBC were obtained by centrifugation and all samples were collected into anticoagulant coated tubes and preserved at 4°C prior to measurements. The NMRD profile for each sample was acquired between 10KHz and 20MHz at temperatures ranging from -18°C to 4°C.

We found that at low temperatures < -9°C, all samples expressed one single population and the NMRD profiles of whole blood and RBC were almost identical. When temperature increased >4°C, unlike the RBC and the plasma, the whole blood had two distinct populations.

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**Fig 1.** NMRD profiles of whole blood (WB), RBC and plasma at -18°C and 4°C. WB main : main population, WB sec : second population.

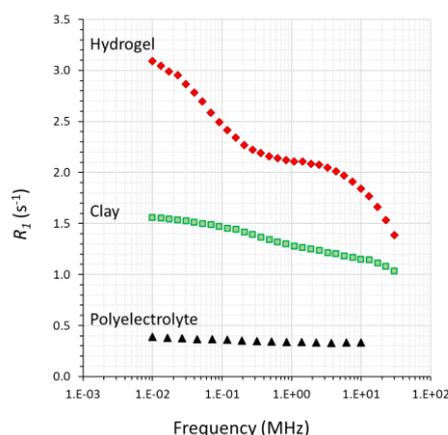
## WATER MULTISCALE DYNAMICS IN HYDROGEL-CLAY COMPOSITE

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Hydrogels are macromolecular materials made up of polymer chains linked together to form a three-dimensional network, that presents appealing properties for various domains as biomedicine, biotechnology, pharmaceutical industry, or even the food industry [1]. For instance, they make it possible to develop biomimetic artificial tissues, biosensors, new dressings and even super-absorbent materials. There are two kinds of hydrogels depending on the interactions into play between polymer chains: chemical hydrogels and physical or supramolecular hydrogels. Unlike chemical hydrogels where the polymer chains are connected by covalent bonds, supramolecular hydrogels exhibit only physical interactions. The very interesting properties of these supramolecular hydrogels lies in the reversibility of their bonds, allowing tunable applications such as the controlled release of active substances, by passing simultaneously from the solution to the gel phase and conversely. The counterpart is that most physical hydrogels possess inferior mechanical properties to chemical hydrogels. In order to be able to combine reversibility and resistance of the material, nanoparticles are added in these hydrogels. In this work, we combined cationic polyelectrolytes and clay nanoparticles to formulate anisotropic hydrogels and we investigated the dynamics of water using FFC NMR relaxometry. The NMRD profiles obtained were compared to those obtained with the individual components, i.e. the solutions of cationic polyelectrolytes and the dispersions of clays nanoparticles (Fig. 1).



**Fig. 1.** <sup>1</sup>H NMRD profiles of cationic polyelectrolyte solution, montmorillonite aqueous dispersion and of the composite hydrogel made with the two previous components.

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## FIELD-CYCLING MRI RELAXOMETRY: ACTIVE CONTRAST AND DYNAMIC IMAGING

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A prototype has been developed on the grounds of a commercial field-cycled NMR relaxometer by including/replacing additional hardware to enable MRI experiments [1]. The machine has been thought-out for concept testing of new contrasts and experiments in phantoms and small rodents. The field-cycled MRI relaxometer was based on a variable-geometry wide-bore electromagnet of own design [2], with a gradient unit including optimized longitudinal gradient coils [3]. In this opportunity, we will briefly discuss field-cycling dynamic images [4] and the concept of active contrast [5].

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# Posters



## Relaxometry as a tool to assess the magneto-crystalline state and surface modification of sub-5 nm iron oxide nanoparticles obtained through continuous flow synthesis

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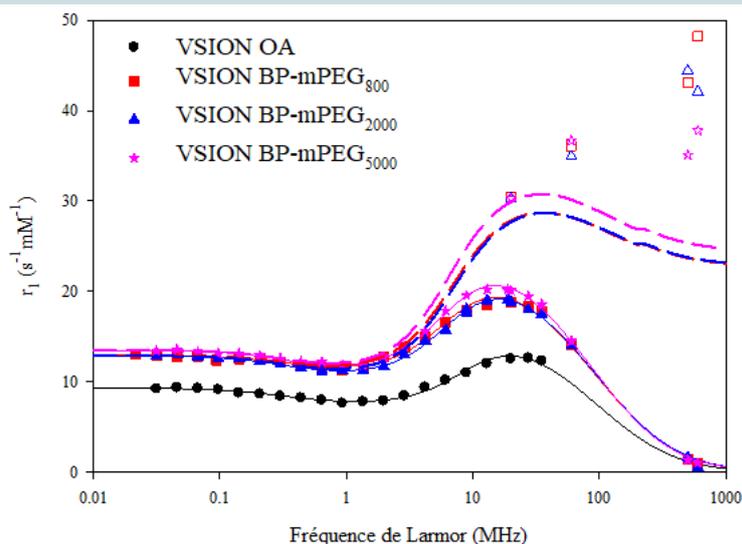
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Iron oxide nanoparticles are at the forefront of rapid development in nanotechnology. Thanks to their magnetic properties, chemical stability and their biocompatibility, colloidal suspensions of iron oxide nanoparticles gathered considerable attention, finding countless applications in the field of nanomedicine<sup>[1]</sup>. Out of all those applications, iron oxide nanoparticles are mainly known as contrast agents for MRI, enabling the modification of image contrast through their ability to speed up the relaxation of water protons. Iron oxide nanoparticles are historically known as negative ( $T_2$ ) contrast agents, providing signal suppression and therefore appearing as dark spots on MR images<sup>[2]</sup>. However, investigations performed in recent years have shown that iron oxide nanoparticles can act as positive ( $T_1$ ) contrast agents when they fulfil certain physicochemical properties. Very-small iron oxide nanoparticles (VSION), characterized by core size below 5 nm, are generally accepted as the best candidates for  $T_1$  contrast due to their reduced magnetization and the presence of a surface spin-canted layer<sup>[3]</sup>.

In recent years, continuous flow processes have emerged as reliable and robust alternatives for the preparation of inorganic nanoparticles<sup>[4-5]</sup>. In this context, a continuous flow process was adapted for the preparation of small-sized iron oxide nanoparticles obtained through a thermal decomposition method<sup>[6]</sup>. Of the studied experimental parameters (*i.e.* temperature, pressure, capillary inner diameter and flow rate), none was found to have a noticeable influence on the particle size determined by transmission electron microscopy (TEM). However, it was observed that the nanoparticle relaxometric properties, obtained by the study of their nuclear magnetic resonance dispersion (NMRD) profiles, are to a certain extent proportional to the reaction time (*i.e.* the residence time in the capillary reactor). These differences in the relaxometric properties of the iron oxide nanoparticles were attributed to changes in the crystalline state of the nano-objects. This hypothesis was corroborated by characterizing the synthesized nanoparticles with two techniques : vibrating sample magnetometry (VSM) and X-ray diffraction (XRD).

Surface modification is mandatory to provide VSION with hydrophilicity and stability in biological fluids. More specifically, the observation of  $T_1$  for such systems is only achievable for highly stable suspensions, showing no sign of clustering (as it would result in high  $r_2/r_1$  ratios, causing signal loss in MRI experiments). Hydrophobic VSION (coated with oleic acid) obtained through the thermal decomposition process were hence transferred in aqueous media using PEGylated ligands of different PEG chainlengths (*i.e.* PEG<sub>800</sub>, PEG<sub>2000</sub> and PEG<sub>5000</sub>). Various analytical methods were used, along with relaxometric measurements (NMRD profiles; Fig. 1), to fully characterize the particles properties in view of their use as positive contrast agents for  $T_1$ -weighted MRI.



**Fig. 1.** NMRD profiles (recorded at 37 °C) of OA capped VSION (in THF; filled black circles) and of VSION covered with BP-mPEG ligands in water i.e. BP-mPEG<sub>800</sub> (filled red squares), BP-mPEG<sub>2000</sub> (filled blue triangles) and BP-mPEG<sub>5000</sub> (filled pink stars). The dashed lines represent the prediction of  $r_2$  provided by the SPM model using the parameters obtained from the  $T_1$  fitting. Empty red squares, empty blue triangles and empty pink stars are experimental  $r_2$  points of VSION BP-mPEG<sub>800</sub>, BP-mPEG<sub>2000</sub> and BP-mPEG<sub>5000</sub>, respectively.

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## SHOWCASING THE 3-TAU MODEL

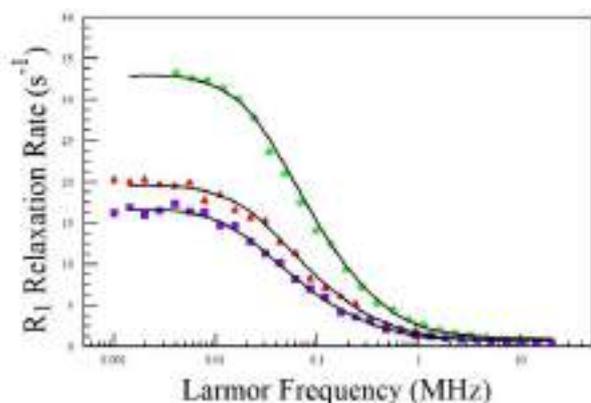
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The 3-Tau Model [1-2] is applied to NMRD profiles from four diverse porous systems: (i) a hydrogel, (ii) mozzarella cheese, (iii) a cement and (iv) murine tissue. Fits were executed using the open-source 3TM software [3-4]. In each case, the 3-Tau Model fits provide physically-meaningful dynamical time constants, structural information and insight into  $T_2$  and the ratio  $T_1/T_2$ .



Parameter	Gel slice		
	Far	Middle	Near
$\tau_\ell$ ( $\mu\text{s}$ )	0.48	0.42	0.42
$\tau_d$ ( $\mu\text{s}$ )	1.53	1.15	1.0
$\tau_b$ (ps)	5.62	7.49	8.66
$\tau_d/\tau_\ell$	3.16	2.73	2.37
$h$ (nm)	98	68	37
$T_1/T_2$	7.7	8.9	10.5

**Fig. 1.**  $T_1^{-1}$  NMRD profile where green circles, red triangles and blue squares correspond to the “near”, “middle” and “far” hydrogel slices, respectively. Black solid lines correspond to the fit based on the 3-Tau Model parameters in the table.

For illustration, Fig. 1 and the table present results for three slices through a hydrogel sample. The slices are labelled “far”, “middle” and “near” and refer to low, medium and high polymer density respectively. The density is reflected by the planar-pore-equivalent thickness  $h$  which suggests a characteristic pore size of 37nm consistent with independent experiments.

The water surface diffusion time constant  $\tau_\ell$  is only weak function of the polymer density yet the desorption time constant  $\tau_d$  shows a systematic shortening with increasing polymer density indicating that surface water spends less time at the polymer surface in the denser material. The ratio  $\tau_d/\tau_\ell$  indicates the number of surface hops before desorption.  $\tau_b$  is related to the translational diffusion coefficient of water. Room temperature pure water has  $\tau_b = 5.28$  ps so that a reduction in diffusion coefficient is observed with increasing polymer density. The model ratio  $T_1/T_2$  at 20 MHz rises with the decreasing pore size associated with increased polymer density in agreement with a previous study [5].

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## EXAMINATION OF TUMOROUS MURINE TISSUE USING THE 3-TAU MODEL

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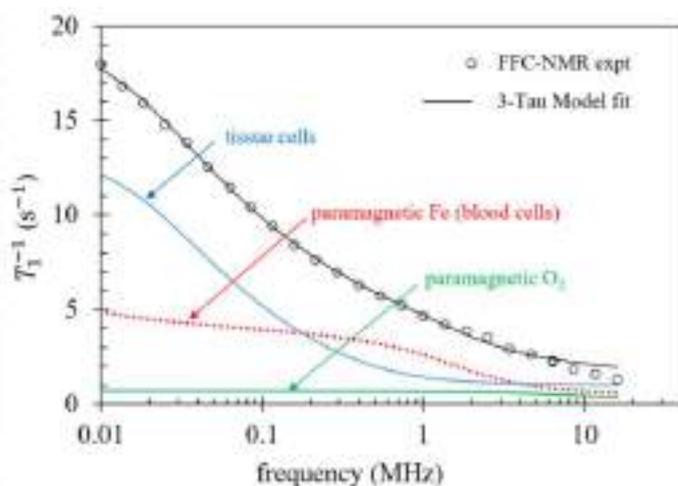
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Magnetic Resonance Imaging (MRI) provides excellent spatial resolution of healthy and pathological tissues and plays a key role in diagnosing tumour progression. However, MRI scanners do not provide sufficient  $T_1$  sensitivity to identify the tumour stage and focus has turned to low-field NMR relaxometry. Ruggiero *et al* reported that *in vivo*  $T_1$  measurements at low magnetic fields establish that tumour cells display proton  $T_1$  values markedly longer than those for healthy tissue that parallels the aggressiveness of the tumour [1]. Moreover, FFC-NMR profiles may provide valuable information on water *dynamics* in tumour tissues.



**Fig. 1.**  $T_1^{-1}$  NMRD profile of mouse leg tissue after intramuscular injection of 71% tumour cells.

The NMRD profiles from healthy and pathological murine tissue reported in [1] are re-analysed using the 3-Tau Model [2-4]. Remarkably, the fits reveal three contributions to the dispersion: (i) an *S-I* dipolar contribution associated with iron (II) and/or iron (III) in red blood cells, (ii) an *I-I* dipolar contribution due to the dynamics of water at cell surfaces and in the bulk, and (iii) a contribution due to oxygenated water.

The surface water fraction is found to change systematically with tumour progression providing an opportunity to model changes in intra-cellular and inter-cellular water content with tumour progression.

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**On the observation of  $^{14}\text{N}$  Quadrupole Resonance transitions in  
water proton NMR relaxometry dispersion curves.  
The case of a labile NH grouping in a semi-rigid molecular moiety**

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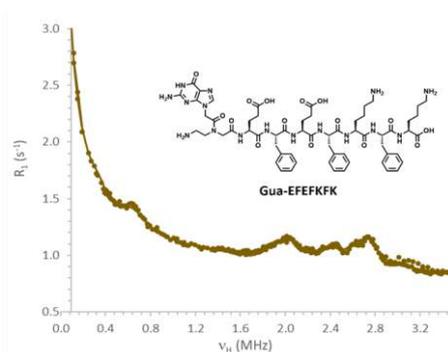
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Peptide-based hydrogels are considered as high potential supramolecular materials in the biomedical domain and open new horizons in terms of applications. We report herein on the NMRD study of hydrogels obtained by the incorporation of DNA-nucleobases into their peptide nucleic acid (PNA) forms in the octapeptide Phe-Glu-Phe-Glu-Phe-Lys-Phe-Lys [1]. Four gels could be obtained (corresponding to four different nucleobases, i.e. thymine, cytosine, adenine and guanine), and it was made possible to determine water dynamics as a function of the type of nucleobase involved, this dynamics being linked to the strength of the gel. Specifically, the role of the nucleobase in the gel formation could be enlightened and, for the gels bearing the T and G nucleobases, quadrupolar peaks could be observed on the dispersion curves measured on the water protons (figure 1). Indeed, for a partly rigid NH grouping with a labile proton, water NMR relaxometry curves may exhibit three transitions (corresponding to the frequencies of the three  $^{14}\text{N}$  NQR transitions which depend on the nuclear quadrupole coupling and on the asymmetry parameter of the electric field gradient tensor) provided that the NH grouping belongs to a moiety possessing a sufficient degree of ordering. The line-shape of the quadrupolar peaks can lead to a correlation time describing mainly the motion of the NH grouping (the proton of which being in exchange with water protons), and their amplitudes can be interpreted in terms of an effective NH distance. Furthermore, the analysis of experimental data allowed one to determine the nuclear quadrupole coupling in the protonated and deprotonated forms of this molecular moiety involving a labile NH grouping.



**Fig. 1.** Experimental NMRD data measured at 25°C on the hydrogel obtained with the molecule Gua-EFEFKFK. Continuous curve: recalculated NMRD obtained with three different water types yielding QRE.

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## APPLICATION OF FAST FIELD-CYCLING (FFC) NMR RELAXOMETRY IN COLORECTAL CANCER

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**Purpose:** Previous studies on musculoskeletal and breast cancer found promising biological biomarkers of tumours non-invasively and without using contrast media, using ultralow-field magnetic resonance<sup>1,2,3</sup>. The aim of this pilot study is to show how the R1 dispersion profiles differ in colorectal cancer versus healthy samples at magnetic fields below 100 kHz using the FFC-NMR technique.

**Methods:** All colorectal tissue samples were obtained via the Grampians Biorepository with the informed consent of the patients. In this pilot study, we examined 20 fresh resected colorectal tumour samples and corresponding normal counterparts. The dispersion profiles were acquired using a commercial Fast Field Cycling NMR Relaxometry technique (Stelar S.l.r., Italy) at a controlled temperature of 37°C +/- 0.1°C. Field-Cycling pre-polarised and non-polarised pulse sequences were used. To investigate this statistically, we compared the relaxation rate (R1) in healthy and tumour samples below 100 KHz using a related-samples Wilcoxon signed-rank test since the normality assumption has not been met.

**Results:** The ex-vivo R1 dispersion profiles revealed differences between healthy and tumour samples, and this difference increases with lower fields below 100 kHz (Fig. 1). Moreover, the average tumour R1 values were significantly higher than normal samples below 100 kHz ; this difference appeared in all study samples (Fig. 2).

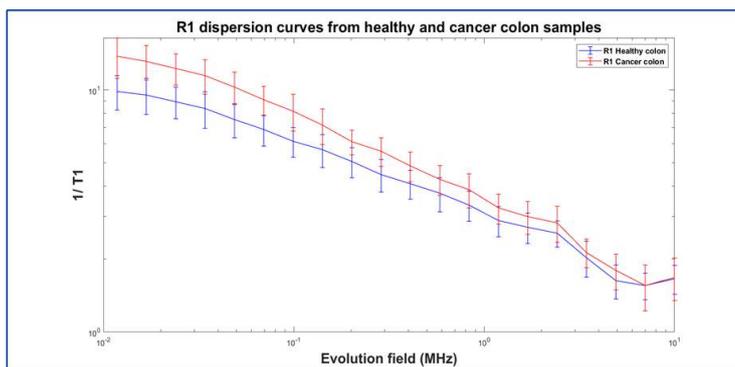


Fig. 1. R1 dispersion curves were acquired from normal and colon tumour samples.

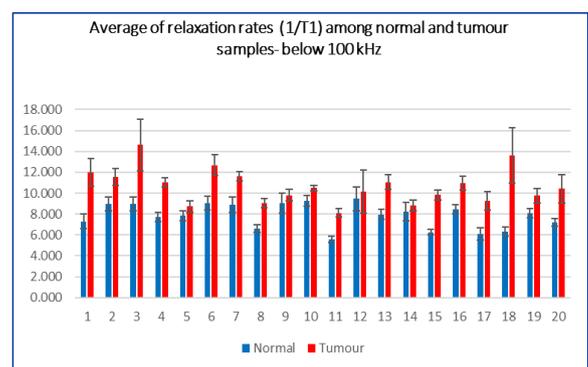


Fig. 2. The average Relaxation rates among normal and tumour samples

**Conclusion:** We showed a potential new biomarker of colorectal cancer based on R1 dispersion curves - extended to low magnetic fields below 100 kHz-. Our next project is to demonstrate this finding in vivo and acquire T1-weighted images at different low field strengths using our whole-body 0.2 T FCI scanner.

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## FAST FIELD CYCLING NMR AS A QUALITY CONTROL TOOL IN DAIRY PRODUCTS

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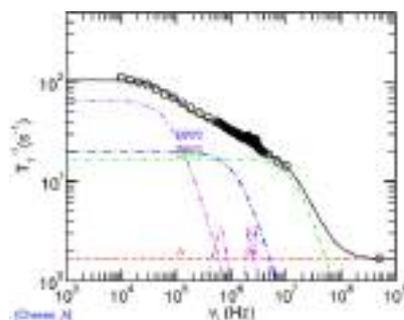
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A deeper definition of structural and dynamical changes of milk and derived products following industrial dairy processes would certainly take advantage of NMR relaxometry.

Milk pasteurization, homogenization, fermentation, pH changes, renneting, curd shrinkage and syneresis, curd heating and cheese ripening are just some of the industrial processes that play a role in defining quality features of commercial dairy products. We have collected scientific evidence on the sensitivity of NMR relaxometry to several of the abovementioned treatments.

As an example, this study aims at proposing Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR) for quality evaluation of an Italian PDO cheese of which the market offer includes artisanal and industrial products with very different characteristics. FFC-NMR is able to discriminate the production chain and also potential fraudulent products which do not comply with the official cheesemaking protocol. Six cheeses (3 artisanal and 3 industrial) were measured using an FFC-NMR relaxometer in the range 0.01-10 MHz at 10°C and 20°C (room temperature). For each sample, 30 different field points were acquired. One high field  $T_1$  measurement (500MHz) has been acquired too (Fig.1).



**Fig. 1:** Fitting of the NMRD profile of a cheese sample using Fitteia software.

NMRD profiles allowed to clearly discriminate between the PDO cheeses, especially at lower frequencies. The parameters obtained by fitting the NMRD profiles with an appropriate model [1] highlighted differences between the two cheese groups. This work confirms the capability of FFC-NMR to discriminate between dairy products produced with different processes and suggests that FFC-NMR could be used as a quality control method for the dairy industry.

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## ON THE ELASTIC PROPERTIES OF LIPOSOME MEMBRANES AND DYNAMIC REGIMES OF LIPIDS MOLECULES: A RELAXOMETRIC APPROACH.

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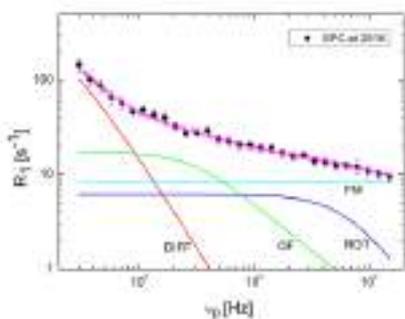
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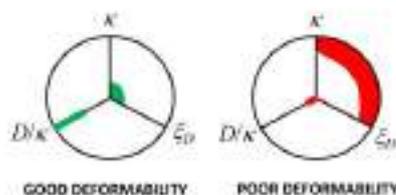
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In previous works [1-5], a model was discussed to interpret the proton spin-lattice relaxation rate dispersion measured in liposomes suspended in deuterated water (Fig. 1). In addition to providing general information on the lipid dynamics, the model allows inferring about the elastic properties of the liposomes through the bending elastic constant  $\kappa$ , and the diffusion constant  $D$ .

In this work, different liposomal formulations were considered to study the correlation between the molecular dynamical regime and the involved physical parameters that define the deformability of the vesicles. For temperatures lower than human skin temperature (HST), the elastic modulus of the membrane decreases with the addition of surfactant, as expected. However, such behaviour is neither observed at HST, nor at temperatures over it. In addition, a comparison with previous work, revealed a quite different dynamical behaviour depending on the purity of the used lipids. A deeper analysis about the relationship between  $\kappa$  and  $D$  for different formulations and temperatures, allowed us to build-up deformability performance maps (Fig. 2).



**Fig. 1.** Relaxation rate dispersion of soybean phosphatidylcholine liposomes. Experimental points ( $\bullet$ ) are compared with the optimal model curve (magenta solid line). Contributions from each type of motion are included (Fast Motions, Rotations, Order Fluctuations and Diffusion).



**Fig. 2.** Exemplary deformability performance maps for a formulation according to the values of the involved relevant physical quantities. Values increase outward from the center of the circle. The parameter  $\xi_D$  refers to a “Dynamic Regime Coefficient” (whose meaning will be explained in the poster).

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## DYNAMICS OF IONIC LIQUID/POLYMER STUDIED BY MAGNETIC RESONANCE

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We present a study of molecular dynamics in Ionic liquids (ILs) mixed with polymers. The ILs consist of organic cations based on imidazolium rings and different types of anions. Depending on the anion type, the polymers form either a rigid matrix with porous structure where the confined ILs express high mobility, or a gel-type matrix where the mobility of the ILs is reduced with respect to the bulk [1]. By studying molecular translational diffusion and NMR relaxation times, we recover information about the molecular interactions taking place in the system. In addition, we are interested in the study of the mobility and interactions of stable organic radicals such as nitroxide, porphyrins, with the polymers and ILs, with the aim of studying mechanisms of electron polarization transfer to the NMR active nuclei in the system. For this purpose, X-band EPR and DNP experiments were performed. Moreover, NMR Relaxation Dispersion (NMRD) is used to distinguish between different dynamical models expressed in terms of their spectral densities [2].

All this information is used to understanding some of the basic principles underlying charge transport processes, molecular dynamics, and physico-chemical stability in these systems. This information is essential for any practical application in the field of material science focused on sustainable energy supplies and energy storage materials. Ionic conductivity is related with translational mobility associated with diffusion and Nuclear Magnetic Relaxation (NMR) is used to assess information on microscopic rotation and translational dynamics in these systems.

The current state of our research related to the ILs emim-TFSI, emim-DCA combined with Poly(vinyl alcohol) (PVA) and nitroxide radicals will be given, specifically about molecular rotation and translation correlation times retrieved by analyzing models on the electron-nuclear spin interaction.

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## AGEING OF RESERVOIR ROCKS: A MULTINUCLEAR NMR RELAXOMETRY STUDY

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In reservoir rocks, the term “ageing” refers to extended exposition to crude oil; a typically water-wet sandstone will then gradually become oil-wet as a consequence of the deposition of insoluble fractions of oil onto the surface grains. Rocks can be aged artificially by subjecting them to oil at elevated temperature or pressure for weeks or months, possibly supported by centrifugation. Experimentally determining the wetting status of a particular rock sample remains a challenging task since most rocks will show mixed-wet behaviour globally (properties will allow both water and oil to adsorb with finite probability) and locally (different grain materials or local residue concentrations).

In this study, we discuss wettability as a means to investigate the effect of molecular interaction with surfaces onto their relaxation properties. Water and oil as the single phase in typical sandstone rocks were shown to follow qualitatively different NMRD features [1]. During coexistence, one of the two liquids will preferentially adsorb and the other will ideally behave bulk-like. By saturating native and aged sandstones and chalk we have found entirely different NMRD behaviour for water, benzene or alkanes. In order to separate the different relaxation contributions, we have studied perdeuterated and perfluorinated compounds and compared their relaxation with those of <sup>1</sup>H nuclei. Intra- and intermolecular contributions can thus be quantified. In a further step, microwave irradiation of radicals in the rock samples were employed to enhance the signal intensity of nuclei coming into close contact with these radicals. We observed that the radicals contained in the rock itself, such as Mn<sup>2+</sup> ions, may contribute to nuclear relaxation but are inefficient for DNP due to the extreme width of the EPR line; radicals embedded in the solid oil residues, on the other hand, led to significant DNP enhancement despite their overall much lower concentration [2]. The solid layer, containing predominantly asphaltenes and resins, thus has the double effect of altering the adsorption properties of maltene molecules and of providing additional relaxation sinks due to their content in stable radicals.

By comparison of T<sub>1</sub> dispersion of <sup>1</sup>H and <sup>2</sup>H nuclei of equivalent molecules, as well as T<sub>1</sub>-T<sub>2</sub> relaxation maps, we are able to identify the relative contribution of intra- and intermolecular relaxation for protic and aprotic liquids, and to distinguish the respective contribution arising from the surface diffusion and RMTD models.

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## Assessment of ultrasound drug delivery using Fast Field Cycling

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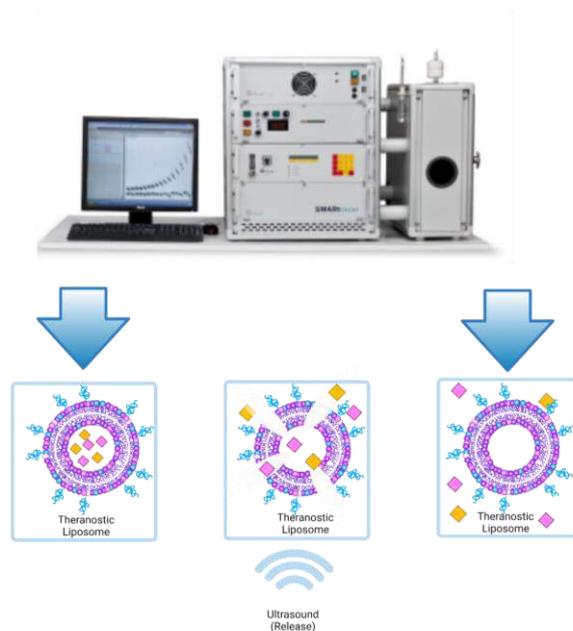
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The main focus in the development of anticancer nanomedicines is to successfully address drugs to the desired sites of therapeutic action [1].

In this study is investigated a promising strategy to induce the controlled drug release by the local application of low intensity pulsed ultrasound to theranostic liposomes loaded with the chemotherapeutic doxorubicin and a Gd-based MRI agent.

The ultrasound-induced release was assessed by both spectrofluorimetry, to quantify the doxorubicin that can be delivered, and proton relaxometry at fixed and variable magnetic fields to evaluate the  $T_1$  contrast enhancement consequent to the release of the Gd-based agent. Indeed, Fast Field cycling (FFC) is a valuable tool to study relaxivity of paramagnetic liposomes and to identify the most appropriate magnetic field to work on. Furthermore, its ability to evaluate the water dynamics in lipid bilayers could be used to investigate the ultrasound waves effects on liposome membranes permeability. To this purpose, Fast Field Cycling Nuclear Magnetic Resonance Dispersion (FFC-NMRD) profiles were acquired before and after the ultrasound stimulation, and modulating the characteristics of the acoustic waves to optimize the release efficiency (Fig.1).

The results that will be presented highlight the important contribution that FFC can provide in cancer research for the characterization of smart nanotherapeutics.



**Fig. 1.** Scheme of liposome release monitored by FFC

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## ON THE WAY TO DESIGN SUSTAINABLE FAST FIELD CYCLING RELAXOMETERS

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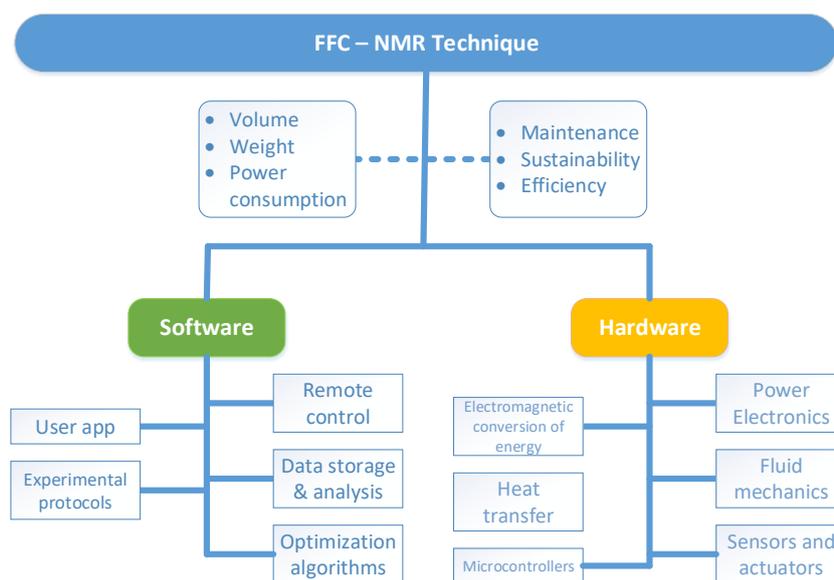
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Considering the nowadays challenges that modern societies are facing concerning mainly the power feed in tariffs and consumption, the materials costs and scarcity, and the waste produced in research labs, one important challenge related with the FFC Nuclear magnetic Resonance is how the researchers are dealing with equipment that is out of date. Starting from the comparison of 4 generations of FFC home built equipment we analyse the environmental sustainability, the technical and technological aspects, considering distinct approaches and components when designing new FFC NMR equipment (Fig. 1).



**Fig. 1.** Technological frame of the FFC-NMR technique.

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## ModelFreeFFC Tool

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ModelFreeFFC is a freeware standalone Matlab® tool, developed at the University of Bologna (Bologna, Italy), for fitting Nuclear Magnetic Relaxation Dispersion curves obtained by Fast Field Cycling Nuclear Magnetic Resonance Relaxometry measurements. The software implements a regularized inversion algorithm based on the model-free approach [1], and comes also with a graphical user interface (GUI) for Windows and Linux Oss. The present contribution aims to illustrate the ModelFreeFFC tool. Figure 1 represents the three main components of the ModelFree GUI: the data input on the left, the inversion parameters in the centre, and the output quantities and plots on the right. Some examples will be shown to assist potential users in adapting and uploading their data. The software version, presently available online [2], does not take into account the quadrupolar effect. A prototype with such an extension will be released at the Conference.



Figure 1 - ModelFreeFFC Tool Gui Interface.

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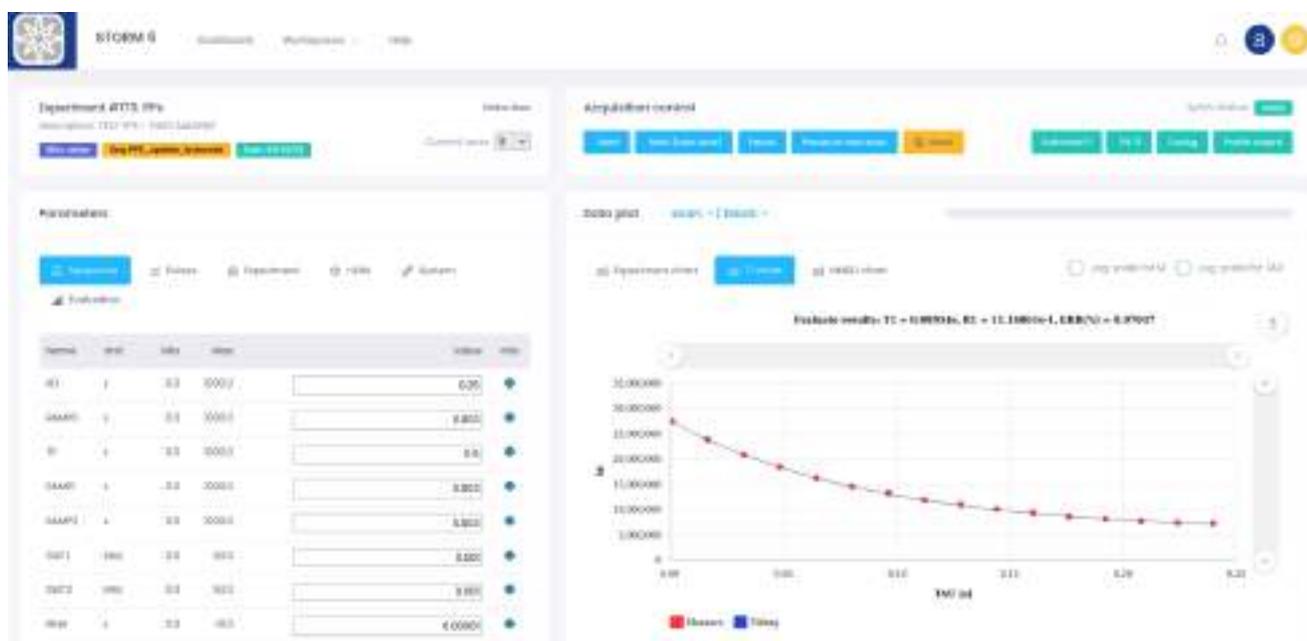
## A NEW ADVANCED SOFTWARE TOOL FOR FFC NMR COMPLEX EXPERIMENT

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The increasing availability of new digital and analogic technologies, in principle, would make possible to conceive increasingly advanced, performant and complex FFC NMR experiments, aimed at the characterization of a compound with more accurate and specific information about its molecular dynamics. For that, the availability of more suitable software tools, capable to easily manage the design of a complex experiment, the acquisition of data and the consequent capability to analyze large volume of multidimensional data would be needed. The work we present in this poster aims to provide to the FFC NMR users all these advanced software/hardware capabilities. The first challenge of the project has been to conceive a specific architecture and concepts which can allow to improve and facilitate all interaction of the user with the system, for the design and the execution of a highly complex NMR FFC experiment. Storm6 is created according to the idea of prioritizing the customization. The software acts in fact as a web server. All operations can be run from any web browser any user can get access and operate the FFC relaxometer using their own workspace. The NMR sequences are made in very simple text format. They are written as JSON script, a lightweight, text-based, language-independent data interchange format, while the main core of software package is written in Python. In combination with the recent NMR console firmware, the user would manage to design ideally infinite number of nested loops for cycling all the desired parameters. Another valuable feature is the possibility of downloading the data in different formats. Depending on the experiment, the data can be exported both as very simple CVS file or even as HDF5 file if necessary to supports large, complex, multidimensional, heterogeneous experimental data. Future next steps will be: to permit further customization, specific automations, application-oriented configuration, as well as the development of tools for improved analysis. More features, will be presented and discussed in the poster.



## MULTI - EXPONENTIALITY OF RELAXATION PROCESSES AND QUADRUPOLE RELAXATION ENHANCEMENT

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Fast Field Cycling (FFC) Nuclear Magnetic Resonance (NMR) relaxometry has led to discovering several relaxation effects that are not observed at high frequencies. The reason for that is other spin interactions (for instance quadrupole couplings of  $^{14}\text{N}$  nuclei present in biomolecules) being comparable with Zeeman interactions at lower magnetic fields. It has been observed that when the  $^1\text{H}$  resonance frequency matches one of the transitions frequencies of  $^{14}\text{N}$  (determined by the quadrupole coupling) one can observe a frequency specific enhancement of  $^1\text{H}$  spin-lattice relaxation, providing the  $^1\text{H}$ - $^{14}\text{N}$  dipole-dipole interactions fluctuate in time slow enough [1-3] – they are often referred to as “quadrupole peaks”. It has also turned out that for systems including “non-equivalent” pools of hydrogen atoms ( $^1\text{H}$  nuclei) one can observe non-exponential relaxation processes. The non-exponentiality requires a considerable experimental effort to be detected – this can be achieved by choosing logarithmic timescale for recording the time evolution of  $^1\text{H}$  magnetization (time dependencies of the magnetisation are often referred as a magnetisation curves) and performing the measurements in a broad time range, collecting many experimental points. A careful analysis of non-exponentiality effects in magnetisation curves introduces some “resolution” to NMR relaxometry experiments at low magnetic fields – a “classical” approach to the data analysis (assuming single-exponential magnetization evolution) provides only averaged relaxation rates. Therefore, independently of the experimental potential, the subject of deconvoluting magnetization curves into single-exponential components is of primary importance – otherwise one can lose the “resolution” even with excellent equipment. Following this line, the reason for the non-exponentiality can be two-fold. The first one is dynamical (and structural heterogeneity) of the system. However, the second reason stems from the quantum-mechanical scenario of relaxation processes in systems including NMR nuclei of different gyromagnetic factors mutually coupled by dipole-dipole interactions. Therefore non-exponentiality effects are more pronounced in the frequency range in which “quadrupole peaks” for biomolecular systems are observed. It is important to distinguish between those two origins of the non-exponentiality to draw proper conclusions about molecular dynamics – this subject will be illustrated by examples for selected biomolecular systems.

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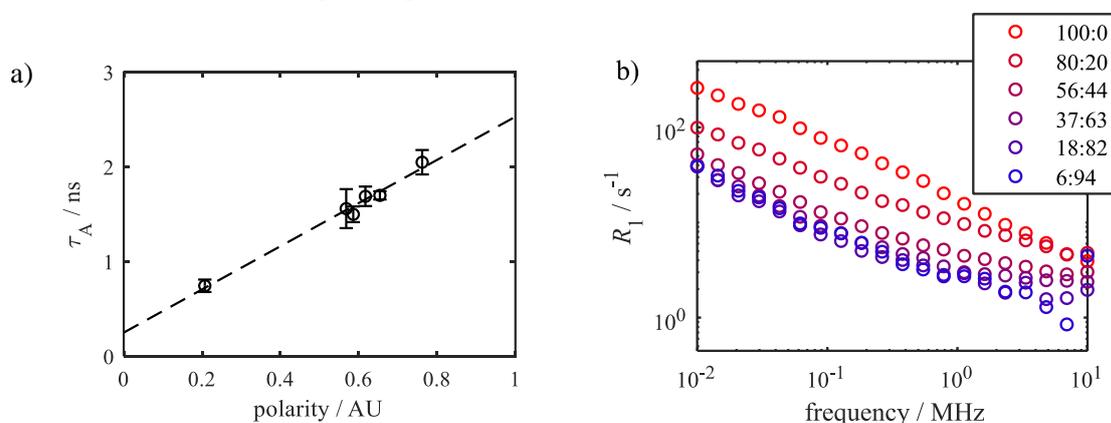
## INSIGHTS INTO THE COMPETITIVE ADSORPTION OF ALCOHOL-WATER MIXTURES IN ANATASE TITANIA USING FAST FIELD CYCLING NMR

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Liquid mixtures that are miscible in their bulk state can segregate when imbibed within a mesoporous medium, this is an effect known as microphase separation [1]. Obtaining greater insight into the dynamics of nanoconfined liquid mixtures and particularly microphase separation is essential to several fields within the chemical industry, such as catalysis, separation technologies, and oil recovery. FFC-NMR has been shown to be a useful tool for the analysis of surface-adsorbate interactions [2]. In this study, <sup>1</sup>H NMR dispersion profiles of linear alcohols and THF imbibed within a mesoporous anatase titania catalyst support were measured. Based on a Reorientations Mediated by Translational Diffusion (RMTD) approach [3], an adsorption correlation time,  $\tau_A$ , could be determined, which correlates with the polarity, and therefore the surface-alcohol interaction strength (Fig. 1a).



**Fig. 1.** a) Adsorption correlation times,  $\tau_A$ , of alcohols and THF in titania plotted against their polarity. b) Alcohol component <sup>1</sup>H NMRD profiles for ethanol-water mixtures imbibed within anatase titania, at a range of ethanol:water compositions.

Subsequently, the FFC-NMR approach was applied to a range of alcohol-water mixtures at different mixture compositions. The alcohol component relaxation rates decrease with an increase of water in the system (Fig. 1b), indicating the surface-alcohol interaction is suppressed by the addition of water. Based on the RMTD model mentioned above, the competitive adsorption of a range of alcohol-water mixtures could be quantitatively compared, providing insight into the nature of the microphase separation effects in these systems.

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