

Fast Field Cycling NMR Relaxometry

From molecular dynamics
to practical applications



STELAR

For over 40 years Stelar has been developing, manufacturing and marketing innovative scientific electronic instruments for Nuclear Magnetic Resonance (NMR) research and industrial applications. Stelar specializes in unique analytical instrumentation using the Fast Field Cycling NMR Relaxometry (FFC NMR) technique. It's focused on continuous development of this technology, on the diffusion of the FFC NMR method for both academic and industrial research and for process and QC applications, and has invested on increasing the awareness about FFC NMR as a useful analytical technique.

We aim to provide a representative overview of key advances in material sciences, pharmaceuticals, food sciences, chemical engineering and many more research topics, with particular emphasis on the experimental and theoretical contributions that have shaped the field.

We want to acknowledge the contributions of all authors and scientists whose work has made this booklet possible.



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**Fast Field Cycling NMR Relaxometry:
From molecular dynamics to practical applications.**
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Fast Field Cycling NMR Relaxometry

From molecular dynamics
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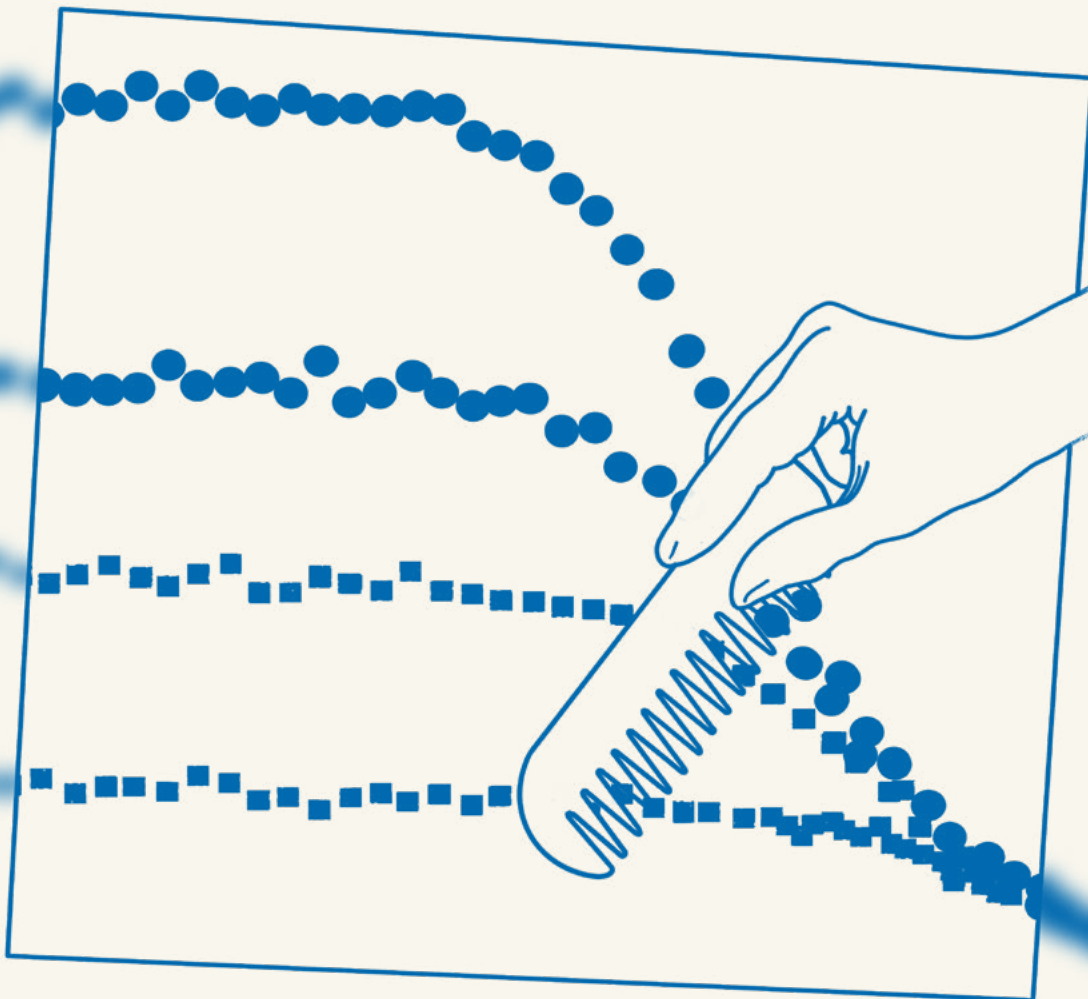


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1.1

/INTRODUCTION: FAST FIELD CYCLING RELAXOMETRY (FFC)

The Fast Field Cycling (FFC) NMR Relaxometry technique

Fast Field Cycling NMR Relaxometry is a non-destructive low-field magnetic resonance technique which is performed in the range of a few

Fast Field Cycling NMR Relaxometry is the only technique which permits the measurement of nuclear spin relaxation times over a wide range of magnetic field strengths with just one instrument, thus offering a more complete investigation of molecular dynamics in a variety of substances and materials.

kHz up to around 100 MHz, depending on the instrument. FFC NMR Relaxometry is the only low-field NMR technique which measures the longitudinal spin relaxation rate, $R_1=1/T_1$, as a function of the magnetic field strength over a wide range of frequencies using only one instrument [1-7].

The information obtained from T_1 is connected to the molecular dynamics of a substance or complex material. The technique is particularly useful in revealing information on slow molecular dynamics which can only be carried out at very low magnetic field strengths.

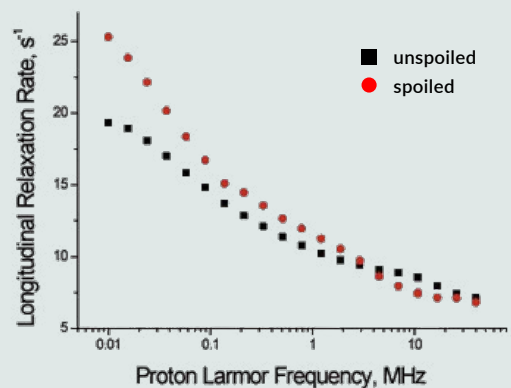
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/INTRODUCTION: FAST FIELD CYCLING RELAXOMETRY (FFC)

The NMRD profile

The magnetic field dependence of $1/T_1$ of any given substance or material is shown in the graphical form as a Nuclear Magnetic Resonance Dispersion (NMRD) profile [1, 7, 10, 11, 12].

► FIG. 1:
The NMRD profiles of a foodstuff before (unspoiled, black squares ■) and after it has expired (spoiled, red dots ●). [Stelar in-house data].



The relaxation rate $1/T_1$ of a substance or material will tend to change when there is a variation in molecular dynamics, which may be caused by the following:

- change of state (e.g. solid to liquid; phase changes in complex systems such as liquid crystals);
- concentration changes (e.g. effect on aggregation states of biomolecules);
- temperature changes;
- viscosity changes;

- cofactor interactions such as sulfur-polymer coupling or plasticizer effects;
- paramagnetic impurities;

Changes in the relaxation rate, $1/T_1$, of a substance or material, are sometimes not evident at single magnetic field strengths, but when studied over a wide range of magnetic field strengths, as with FFC NMR Relaxometry, changes are easier to identify as they are often more visible with the NMRD profile, especially at the lower magnetic field strengths. [1,6-15].

The NMRD profile is the plot of $1/T_1$ versus the Larmor frequency of the relaxation magnetic field.

1.3

/INTRODUCTION: FAST FIELD CYCLING RELAXOMETRY (FFC)

Relation of NMRD to molecular dynamics

Molecular dynamics include rotational and translational motions of molecules which occur randomly in time. These stochastic fluctuations are characterized by a time correlation function. For Brownian rotational diffusion, this correlation function is described by an exponential decay:

$$C(t) = B^2 e^{-(t/\tau_c)}$$

Molecular motions cause local fluctuating magnetic fields which induce nuclear relaxation. Any motion that causes changes in the local fields contributes to the relaxation process including rotation, translation and chemical exchange among different chemical or physical environments. For rotation this becomes,

$$J(\omega) = B^2 \int_{-\infty}^{\infty} e^{-(t/\tau_c)} e^{-i(\omega t)} dt$$

Which to within a constant has the form

$$J(\omega) = B^2 \left[\frac{\tau_c}{1 + \omega^2 \tau_c^2} \right]$$

Considering the simple case in which only one spin species is involved and isotropic motion is considered, the relaxation rate is given by:

$$\frac{1}{T_1} = J(\omega) + 4J(2\omega)$$

Molecular dynamics comprise rotational and translational motions of molecules.

Thus, the Nuclear Magnetic Resonance Dispersion (known as NMRD or MRD) as the Larmor frequency dependence of the spectral density function that is related directly, by the Fourier transform, to the time correlation function characterizing molecular motions.

A critical feature of NMRD is that it is possible to map spectral densities as low as 5-10 kHz which corresponds to a time regime in the vicinity of 30 microseconds, i.e., well into the range of chemical exchange events. Variations of the method permit exploration to lower frequencies.

ACKNOWLEDGEMENT:

Thanks to Prof. Robert G. Bryant (University of Virginia, USA) for providing some of the text for this section.

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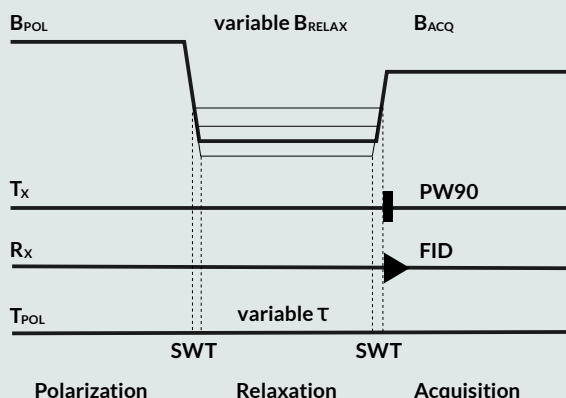
/INTRODUCTION: FAST FIELD CYCLING RELAXOMETRY (FFC)

FFC technique

The spin-lattice (or longitudinal) relaxation time T_1 , when studied over a wide range of magnetic field strengths, can furnish important information on molecular dynamics (motions) of water molecules in a variety of different environments.

FFC NMR Relaxometry requires a small amount of a solid or liquid sample (enough to fill a standard 10mm NMR tube to a volume of around 1 cm³) with no other form of preparation required. The Stellar wide-bore magnet is able to accommodate larger samples such as rock cores or even small animals.

A sketch of the FFC technique is shown in FIG. 2. The Stellar relaxometer works by fast electronic switching of the magnetic field from an initial polarizing magnetic field (B_{POL}), where the equilibrium of nuclear magnetization is attained in about $4T_1$, to a field of interest (relaxation field; B_{RELAX}) at which the nuclear spins relax to the new equilibrium state with a characteristic relaxation time constant T_1 . After a delay time, τ , the B_{RELAX} is switched to the field of acquisition (B_{ACQ}) and the NMR signal is detected after a $\pi/2$ RF pulse (FIG. 2) [1, 5, 7].



► FIG. 2: Schematic representation of the Field Cycling technique.

/ESSENTIAL DIFFERENCES BETWEEN A FFC NMR RELAXOMETER AND A FIXED FIELD TIME DOMAIN INSTRUMENT TO MEASURE NUCLEAR SPIN RELAXATION

1.5.1

Practical difference between a fixed field magnet and an FFC relaxometer

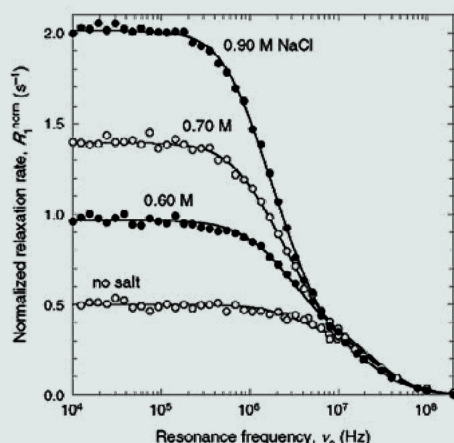
A FFC relaxometer, such as the Stellar **SPINMASTER** or **SMARTracer**, is a specialized system with a low field magnet which is able to electronically switch the magnetic field strength required, from a few kHz up to the maximum magnetic field strength allowed by the magnet (up to 42 MHz ¹H Larmor frequency with the 1 Tesla magnet) and which is able to overcome the limits of the NMR signal-to-noise ratio at low magnetic field strengths [1, 7, 10, 12, 13].

A standard fixed field magnet measures the relaxation rate constant $1/T_1$ with the limitation that it is unable to change the magnetic field strength of operation and thus is only able to measure $1/T_1$ at a single magnetic field strength. Fixed field time domain instruments generally operate at a single frequency in the range of 2–60 MHz.

The FFC relaxometer is able to measure $1/T_1$ at very low magnetic field strengths (down to a few kHz) which is of particular advantage as many molecular processes occurring in the range between nano-seconds and milliseconds (slow molecular dynamics) are very difficult to measure at higher magnetic field strengths.

Fig. 3 shows how protein aggregation can be investigated using FFC. NMRD profiles allowed the study of BTPI (Bovine Pancreatic Trypsin Inhibitor) self-association as a function of pH, salt type, salt concentration and temperature [11].

The NMRD profiles in FIG.3 show that it would be difficult to distinguish between the different samples at magnetic field strengths higher than 5 MHz.



► FIG. 3: NMRD profiles from aqueous BPTI (Bovine Pancreatic Trypsin Inhibitor) solutions at 27°C, pH 4.5 and the indicated NaCl concentrations. (From [11])

/ESSENTIAL DIFFERENCES BETWEEN A FFC NMR RELAXOMETER AND A FIXED FIELD TIME DOMAIN INSTRUMENT TO MEASURE NUCLEAR SPIN RELAXATION

1.5.2

Technical difference between the fixed field and the NMRD experiment

The key difference between the fixed field experiment and the NMRD experiment is that the NMRD profile provides a test of the theory used to interpret the data in terms of the molecular dynamics in the system.

As reported in subsection 1.3, rotational motions are a simple example [1, 7, 9, 10].

The relaxation rate constant may be written for relaxation induced by rotational Brownian motion as:

$$\frac{1}{T_1} = B^2 \left[\frac{\tau}{1 + (\omega\tau)^2} + \frac{4\tau}{1 + (2\omega\tau)^2} \right]$$

The measurement of the field dependence characterizes the rotational correlation time, τ , as well as the strength of the coupling, B^2 , driving relaxation. However, one does not need to know B^2 to extract the dynamical information because it derives from the Larmor frequency dependence entirely.

In the fixed field experiment, the Larmor frequency, ω , is fixed. In this case, to extract τ , one needs to know B^2 accurately. Further, there is no test of the assumptions in the theory for the fixed field measurement, but in the NMRD experiment, if the theory is inappropriate, it will not faithfully fit the NMRD profile.

/APPLICATIONS: MATERIAL SCIENCE

2

Applications of Fast Field Cycling NMR in Materials Science

Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR) facilitates detailed analysis of molecular dynamics and structural heterogeneity that are often inaccessible to conventional techniques. This method employs rapid switching of magnetic field strength during relaxation measurements, allowing observation of nuclear spin relaxation rates across a broad range of fields within a single experiment [1]. Unlike conventional NMR, which operates at a fixed field, FFC-NMR reveals how relaxation processes depend on the external field, offering a comprehensive perspective on molecular motion over multiple timescales [1]. By elucidating segmental mobility, ion transport, and relaxation mechanisms across various fields, FFC-NMR distinguishes materials with subtle structural differences. These insights are critical for understanding structure–property relationships and guide the design, optimisation, and performance enhancement of polymers, electrolytes, and other advanced materials [2-5].

FFC-NMR Relaxometry is widely used in academic research and in industries such as oil and polymer manufacturing [6]. This technique investigates molecular dynamics and structural organisation through field-dependent relaxation measurements, generating Nuclear Magnetic Relaxation Dispersion (NMRD) profiles that plot spin-lattice relaxation rate against field strength [7]. These profiles represent relaxation processes across different fields and help identify contributions from distinct molecular motions and interactions. The shape and features of the NMRD curve provide essential information about molecular dynamics, revealing properties that are not detectable at a single fixed field [8]. By acquiring NMRD profiles over a broad field range, including low and ultra-low fields, FFC-NMR uncovers relaxation mechanisms associated with microstructure and dynamics that are overlooked by fixed-field methods. Low-field measurements are particularly valuable because dipolar interactions and slow molecular motions dominate relaxation, increasing sensitivity to segmental mobility, ion transport, and structural heterogeneity [9, 10]. Material performance is governed primarily by molecular dynamics rather than by static structure alone [11]. Minor variations in composition or processing can significantly affect mechanical, thermal, and transport properties, even when

conventional characterisation methods reveal minimal differences [12]. FFC-NMR overcomes this limitation by providing quantitative relaxation dispersion data, enabling differentiation of materials with subtle structural variations and supporting the optimisation of functional properties. For example, in polymer electrolyte research, two samples with nearly identical chemical compositions and similar results from standard spectroscopy or thermal analysis exhibited distinct relaxation profiles when analysed by FFC-NMR. These differences reflected variations in segmental polymer mobility, which accounted for significant disparities in ion conductivity. Dispersion analysis of NMRD profiles, therefore, provides a dynamic fingerprint of materials and serves as a valuable complement to traditional characterisation techniques [13]. FFC-NMR is applicable to a broad range of materials. In polymers, field-dependent relaxation data provide insights into chain mobility and segmental dynamics, which are directly linked to mechanical properties and processing performance [14]. In electrolytes and ionic systems, low-field measurements probe ion dynamics and transport mechanisms relevant to electrochemical efficiency and energy storage [15]. The multi-nuclear capabilities of FFC-NMR further enhance its analytical utility, enabling the study of nuclei such as ^1H , ^2H , ^{13}C , ^{19}F , ^{23}Na , and ^7Li , all of which are significant in materials science [16]. Each nucleus provides specific information: ^1H and ^2H reveal polymer backbone and side-chain mobility; ^{19}F is essential for fluorinated polymers and battery electrolytes; ^7Li and ^{23}Na assess ion dynamics in energy materials; and ^{13}C offers details on polymer structure and dynamics [8]. Simultaneous examination of multiple nuclei within the same sample enables FFC-NMR to deliver comprehensive information on structure and composition, thereby increasing its versatility and analytical depth [13].

FFC-NMR complements established materials science techniques. Methods such as spectroscopy, rheology, and thermal analysis provide information on composition and macroscopic properties, whereas FFC-NMR elucidates molecular-scale processes across the relaxation spectrum. Integrating FFC-NMR with other analytical methods is particularly beneficial in research contexts [17]. For example, thermal analysis and spectroscopy can determine chemical composition and thermal transitions, followed by FFC-NMR to investigate molecular mobility and relaxation. Rheological measurements can then correlate FFC-NMR-derived dynamics with bulk mechanical properties.

FFC-NMR complements established materials science techniques.

Studies that combine these approaches yield a comprehensive understanding of structure-property relationships and material performance. This integrated methodology supports the development of optimised materials for industrial and technological applications.

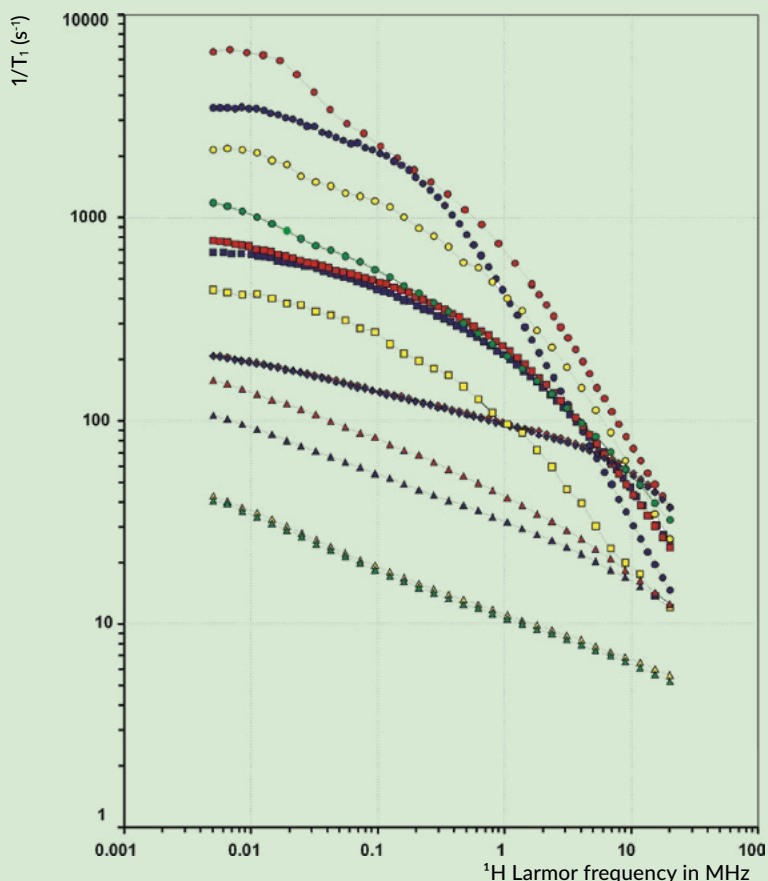
Subsequent chapters present specific applications of FFC-NMR in polymers, electrolytes, and other material systems, demonstrating how this technique provides quantitative data on molecular dynamics and structural properties across both low and high-field regimes.

2.1 /APPLICATIONS: MATERIAL SCIENCE Polymers

Several interesting applications for polymer characterization are potentially applicable to the polymer industry and could be developed to become standard analytical tools.

Listed from top down at 0.01 MHz:

- | | |
|------------------------------|---------------------------|
| CIRCLES: | DIAMONDS: |
| ● isobutylene-isoprene | ◆ polyisoprene 97% |
| ● styrene-butadiene, anionic | ◆ natural rubber |
| ● polychloroprene cis | TRIANGLES: |
| ● ethylene-propylene rubber | ▲ SBS rubber |
| SQUARES: | ▲ polybutadiene cis/trans |
| ■ styrene-butadiene | ▲ polybutadiene 97% |
| ■ styrene-butadiene, radical | ▲ polybutadiene 97.5% |
| ■ polyisoprene trans | |



▲ FIG. 4: NMRD profiles of different polymers from 0.005 MHz to 20 MHz. From in-house data.

FFC NMR Relaxometry has frequently been employed to solve problems in characterization of complex materials, including polymers [1-17].

As shown in FIG. 4, FFC NMR technique can be used for fingerprinting polymers due to the fact that the molecular dynamics of these systems presents very different behaviour, which is reflected in their NMR dispersion profiles.

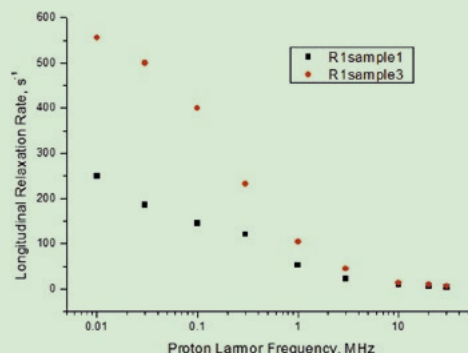
From FIG. 4, it is also evident that, at low fields, it is easier to discriminate between different kinds of polymers.

Small differences in the composition/structure of some polymers may lead to large differences in the desired physical/mechanical properties and thus it is important to be able to differentiate between these.

FIG. 5 shows an example of how FFC can be used to distinguish between two samples of the same polymer, made at two different manufacturing sites [4]. These polymers showed different mechanical properties.

The ¹H NMRD profiles of the two polymer samples revealed large differences in 1/T₁ at low magnetic field strengths, which were not revealed at the higher magnetic field strengths at which many permanent magnet (Fixed Field) relaxometers work (e.g. 5 or 20 MHz).

Moreover, FFC-NMR is very useful to investigate chain dynamics in entangled polymer systems and polymer melts [10] and can be also applied to study molecular order (dynamics slows down when the molecular weight is increased) and inter-segment interactions [10, 11].



▲ FIG. 5: ¹H NMRD profiles of two identical polymers produced by two different manufacturing sites which displayed different mechanical properties.

Furthermore, there are interesting application for polymer characterization which are exploitable by the polymer industry and that could be developed to become standard analytical tools.

Polymeric chains present dynamic processes not present in other compounds which are strongly

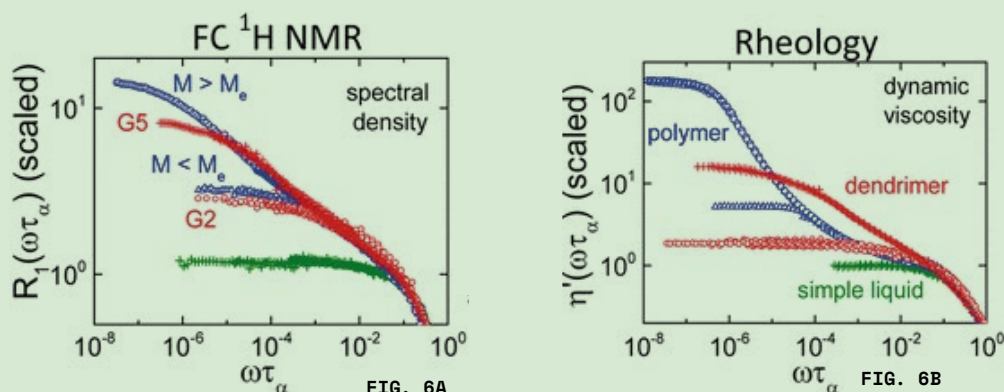
correlated to the macroscopic mechanical properties of the materials.

From a comparison with rheological studies FFC NMR emerges as method of molecular rheology (FIG. 6) to be applied to polymers, rubbers and dendrimers for which all rheological changes are reflected in the FFC dispersion curves [5, 7].

This information can be exploited to control polymer melt processing in industry.

The dynamics of polymers has huge practical interest due to the fact that most plastic objects are made from melts.

Small deviations in manufacturing procedure may lead to a polymer product not meeting the required performance parameters.



▲ FIG. 6:

Results from PPG (polypropylene glycol) and PPI (polypropyleneimine) dendrimers with different molar masses (M) investigated with FFC ^1H NMR, shear rheology (G) and dielectric spectroscopy (DS). Results are compared in a reduced spectral density representation.

The picture on the left (FIG. 6A) represents the master curve of $R_1(\omega\tau_\alpha)$ with τ_α indicating the local correlation time. The picture on the right (FIG. 6B) is instead the rescaled dynamic viscosity $\eta'(\omega\tau_\alpha)$. The close correspondence of these two functions makes the FFC NMR technique a powerful tool of molecular rheology allowing to investigate the microscopical processes behind the macroscopical rheological behaviour of complex fluids (adapted from [12]).

/APPLICATIONS: MATERIAL SCIENCE

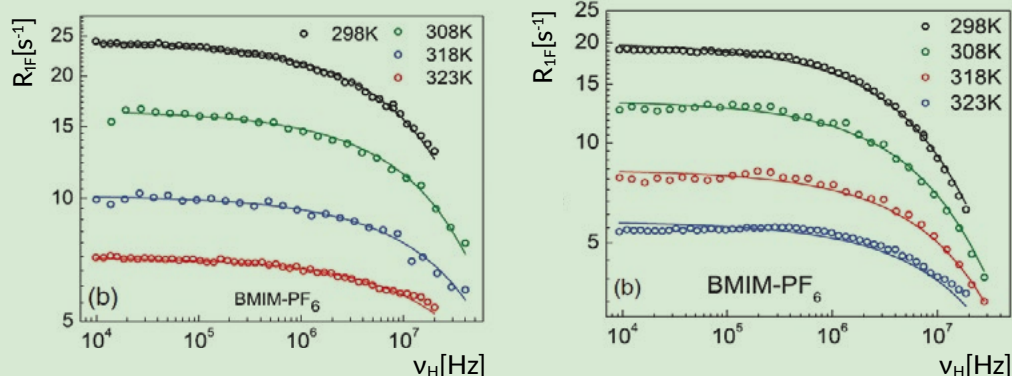
2.2

Electrolytes and Ionic Liquids: Characterisation and Dynamics

The study of ionic conductivity in electrolytes requires detailed characterisation of the transport properties of both cations and anions, which may partially aggregate. Nuclear magnetic resonance (NMR) is highly effective for this purpose due to

its sensitivity and selectivity, enabling detailed analysis of individual ion dynamics (see FIG. 7).

A comprehensive understanding of electrolyte dynamics is crucial for evaluating battery efficiency (see Chapter 6: Heteronuclei: ^7Li , ^{19}F). Fast



▶ FIG. 7:

^1H spin-lattice relaxation rate, R_{1F} , (FIG 7A) and ^{19}F spin-lattice relaxation rate, R_{1F} (FIG 26B) for the ionic liquid BMIM-PF₆ (1-butyl-3-methylimidazolium hexafluorophosphate) versus frequency at different temperatures.

(Adapted from [2]).

▲ FIG. 7A

▲ FIG. 7B

A comprehensive understanding of electrolyte dynamics is crucial for evaluating battery efficiency. FFC-NMR enables the same.

Field-Cycling Nuclear Magnetic Resonance (FFC NMR) has been employed to investigate ion dynamics in electrolytic liquids [1-12], targeting not only the ^1H nucleus [1, 6], but also ^{19}F [1, 2, 3] and ^7Li nuclei [4]. In a standard FFC NMR experiment, the sample is placed in an NMR tube, inserted into the instrument, and exposed to a sequence of magnetic field changes. The procedure includes polarising the sample at a high magnetic field, transferring it to a lower field for a defined period to allow relaxation, and then returning to a high field for signal detection. Relaxation rates are measured at various fields and subsequently analysed to elucidate the dynamics and transport properties of ions within the electrolyte.

FFC NMR functions by rapidly varying the magnetic field over a broad range during the experiment, allowing measurement of nuclear spin relaxation rates as a function of magnetic field (Larmor frequency). The sample is typically polarised at a high magnetic field, transferred to a lower field for a defined period to measure relaxation, and then returned to a high field for detection. Analysis of relaxation rates as a function of magnetic field provides information on ion dynamics across multiple time-scales. Interpre-

tation of these rates often relies on models such as the Bloembergen-Purcell-Pound (BPP) theory and associated spectral density functions, which clarify the molecular motions responsible for relaxation [13]. These models facilitate the identification of dynamic regimes and enable comparison between different electrolyte systems. This approach is particularly effective for capturing both slow and fast molecular motions related to ionic mobility and aggregation, making it highly applicable to the study of electrolytes and ionic liquids. Limitations include the requirement for adequate sensitivity for less-abundant nuclei and the risk of signal loss at very low magnetic fields. This technique is applicable to any NMR-active nucleus, provided that detection sensitivity is sufficient. A key application in electrolyte and ionic liquid research is the measurement of ion diffusion coefficients [2,3,5], as discussed in chapter 7 (see 7. FFC NMR Diffusion Measurements). Compared to methods such as pulsed-field gradient (PFG) NMR or impedance spectroscopy, FFC NMR probes ion dynamics across a wider range of time-scales and offers direct insights into molecular motion mechanisms [15]. While PFG NMR excels at measuring self-diffusion coefficients with high precision and impedance spectroscopy assesses bulk ionic conductivity, FFC NMR complements these approaches by capturing both rotational and translational dynamics, thereby providing a more comprehensive understanding of ionic transport. [14]

2.3

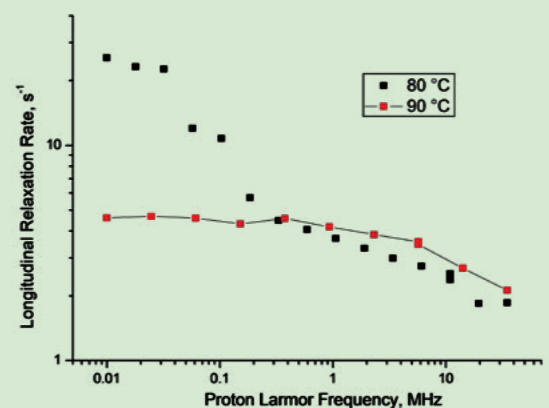
/APPLICATIONS: MATERIAL SCIENCE Liquid crystals

Liquid crystal screens are widely used in the electronics industry.

The performance of liquid crystals is closely related to their various phases and their molecular dynamics is very complex [1-5].

FFC NMR Relaxometry is a powerful and unique technique that allows the study of orientational order and molecular dynamics processes in these liquid crystalline systems over a wide range of magnetic fields (FIG. 8).

Screen development made easy.



▲ FIG. 8: ^{19}F NMRD profiles of the 4DBF₂ liquid crystal, containing two fluorine atoms, which undergoes a phase transition from isotropic to nematic phase between 67°C and 86°C: the change of phase is due to the different organization of the crystals and this is reflected in the two NMRD profiles taken at 80°C and 90°C. (Data from [1])

3 Environmental applications

FFC-NMR is becoming a very reliable technique for the evaluation of the molecular dynamics in soils, sediments and water.

Environmental sustainability is the modern scientific-field key word. For this reason, new and environmentally sustainable analytical techniques have been (and still are) produced. The main focus of these techniques is not only the use of “green” chemicals (i.e. chemical compounds showing low environmental impact), but also the reduction of waste through the simplification of the analytical procedures such as extractions and purifications. In particular, the modern analytical trend is to find procedures which allow investigation of complex systems as a whole. Fast Field Cycling (FFC) NMR Relaxometry is becoming a very reliable technique for the evaluation of the molecular dynamics in soils, sediments and water [1, 2, 13, 14]. It may allow the understanding of the fate of environmental contaminants, as well as the mechanisms of nutrient exchange between soils and plant roots. FFC NMR Relaxometry shows considerable potential for the study of environmental systems.

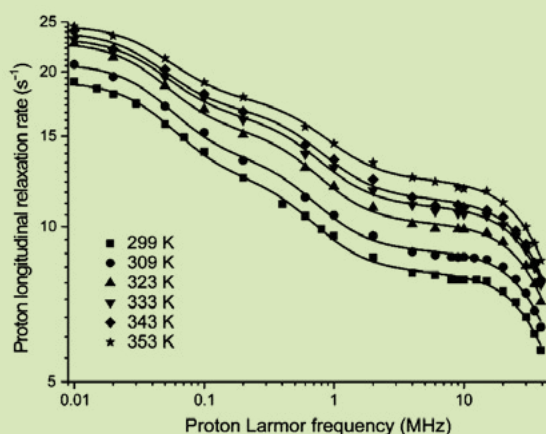
It has been applied:

- to evaluate differences among horizons of silt and sandy loam soils [3];
- to monitor pore size distribution in soils [3,4];
- to determine hydraulic properties of medium sand soil, fine sand soil, and homogeneous sand/kaolin clay mixture [4,5];
- to measure the affinity of natural organic matter for clay mineral systems [6];
- for the reconstruction of the environmental evolution of the sediments inside a saltmarsh [7];
- to monitor the changes occurring in soils after afforestation [8];
- to evaluate water availability in unsaturated soils [9];
- to study aggregate stability of biochar amended soils [10, 11];
- to reveal properties of biochar, which can affect soil fertility [11, 12].

Just to report an example, in FIG. 9 we show the NMRD profiles of water-saturated biochar at different temperatures [11]. From the analyses of the NMRD profiles it was revealed that:

1. a slow-motion regime occurs as water lays on biochar surface;
2. water molecules interact with biochar surface by weak non-conventional H-bonds with an energy in the range 2-6 kJ/mol.

► FIG. 9: Variable temperature NMRD profiles of a water saturated poplar biochar. (From [11]).



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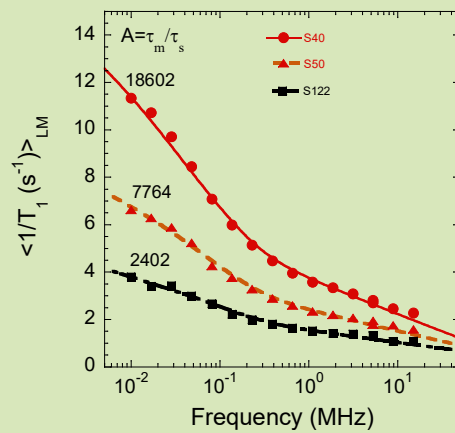
Thanks to Prof. Pellegrino Conte (University of Palermo) for his valuable help and fruitful discussions on environmental applications of FFC.

/APPLICATIONS: ENVIRONMENTAL SCIENCE

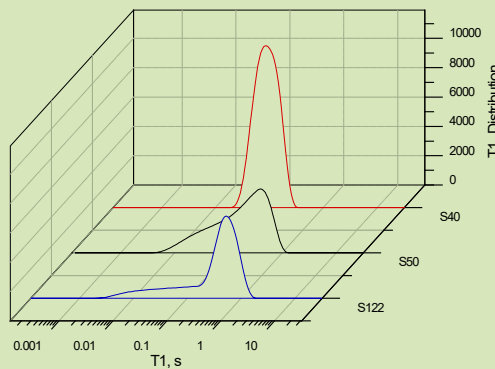
3.1 Porous materials and crude oil

Understanding the dynamics and transport properties of water and crude oil in porous rocks is crucial for the petroleum industry to improve the extraction processes and yields of crude oil.

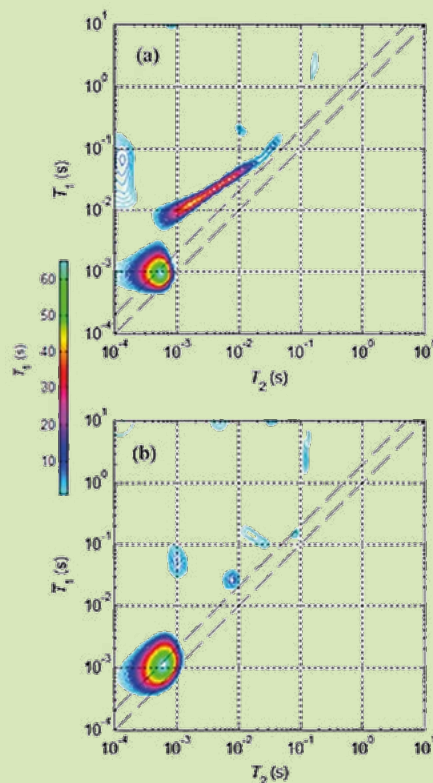
► **FIG. 10:** NMRD of the logarithmic average $\langle 1/T_1 \rangle_{LM}$ of 3 carbonate 1" rock cores. The consideration of such a logarithmic average allows quantitative comparison of the different NMRD data. The continuous lines are the best fits obtained with a bi-logarithmic surface relaxation model. The dynamical surface affinity index, A , representing the local NMR wettability is given above each fit.



► **FIG. 11:** T_1 distributions of 3 carbonate rock core samples at 0.01 MHz.



► **FIG. 12:** These pictures are taken from REF. [8, 9] and they show a 2D T_1 - T_2 spin-correlation maps of untreated oil/water/air (a) and water/air (b) shales, recorded at 2.5 MHz and 35°C. A colour code scale is given for estimating the relative intensities of the different peaks. The dashed lines correspond to $T_1=T_2$ and $T_1=2T_2$.



With crude oil reserves diminishing, it is increasingly important to extract the maximum yield of oil possible from the reservoir. Injecting various aqueous preparations is one method used to force oil to the surface.

Geological factors of importance include the type of reservoir rock, its porosity and its wettability. In rocks with small pores, wettability is a key factor for assessment of oil extraction.

The higher the **wettability** (or **dynamical surface affinity**) the higher the probability that water can displace oil at the pore surface and thus the result should be a higher yield of oil [2-8].

In a study of three samples of carbonate rocks (S40, S50, S122; 1 inch diameter rock cores studied on a dedicated 0.5T wide bore SPINMASTER FFC relaxometer) saturated with water, data from 1H NMRD was used to assess the dynamical surface affinity of water (or **wettability**, FIG. 10) and the distribution of pore sizes (porosity) [1].

It was found that the dynamical surface affinity depends critically on the pore size. In FIG. 10 the T_1 distributions of the 3 rocks at 0.01MHz are reported.

In FIG. 12 it is shown a 2D spin-correlation T_1 - T_2 study that allows to interpreting the very different T_1/T_2 ratio observed for different petroleum fluids confined in the rock pores.

In REF. [10] it is also reported that measuring the 2D spin-correlation spectra T_1 - T_2 at several frequencies would give higher confidence and better knowledge of the fluids. The importance of applying the FFC method to study the shale rocks relies on the fact that the frequency dependency of the NMRD profile gives unambiguous information on the local dynamics of fluids allowing to spotting the fluid type in the confinements of shales.

Zhou et al. have more recently shown the application of NMRD profiles to petroleum tight sandstone rocks, providing information on surface wettability within the pores and the pore

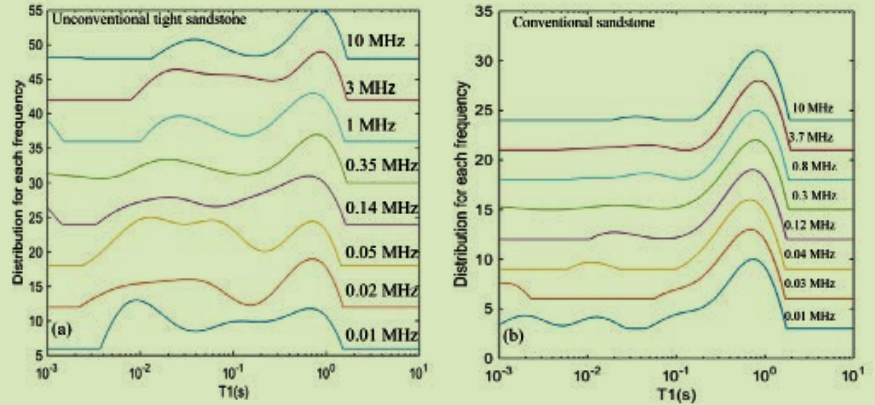
FFC NMR can be used to determine pore size distribution in porous rocks containing petroleum.

► FIG. 13A:

Stack plots of normalized T_1 -distributions obtained from 0.01 to 10 MHz at 25°C (bottom to top) of brine confined in unconventional tight sandstones. All the T_1 -distributions are normalized with the same unit surface.

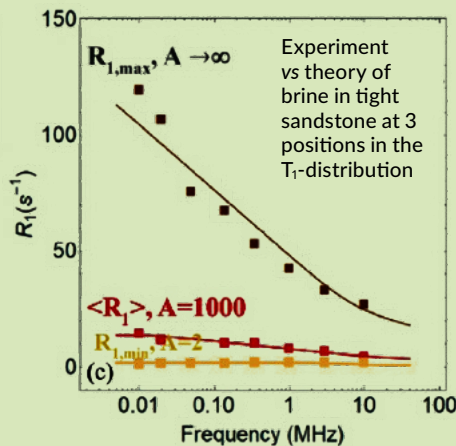
► FIG 13B:

Stack plots of normalized T_1 -distributions obtained from 0.01 to 10 MHz at 25°C (bottom to top) of brine confined in conventional sandstones



► FIG. 14:

Comparison between three experimental NMRD profiles: $\langle R_1(\omega) \rangle$ (red squares ■), $R_{1,max}(\omega)$ (brown squares ■), $R_{1,min}(\omega)$ (orange squares ■) and the best fit calculations of $R_1(\omega)$ obtained with a specific equation [11]. For each NMRD profile, the dynamical surface affinity parameter A (NMR wettability) found is indicated.



size distribution [11]. It was found that these particular unconventional sandstones. Conventional sandstones have almost monomodal pore size distribution, while this becomes bimodal in evidence for a pore-size dependence of the water wettability (see FIG. 14) in tight sandstones thus qualifying the FFC technique as a valuable technique for probing the molecular dynamics and wettability of the unconventional sandstone reservoir rocks.

3.2

/APPLICATIONS: ENVIRONMENTAL SCIENCE

Monitoring the hydration process of cement paste via FFC NMR Relaxometry

Using FFC it is possible to compare changes in the hydration dynamics of pure cement paste and cement paste containing silica fume.

The hydration of cement is a complex and irreversible chemical reaction of cement grains with water molecules leading to the formation of hydration products. The hydration process is influenced by a variety of factors such as: temperature, water-to-cement ratio, the presence of additives and admixtures, the phase composition of the clinker, etc. [1]. These internal and external factors significantly affect the cement hydration reaction, the formation of products, the hydration dynamics, the porous structure, and the properties of the manufactured cement-based materials [1,10].

Consequently, by controlling the cement hydration process, it is possible to tune the properties of the hardened concretes and mortars.

One valuable technique for monitoring the hydration process, consequently an important tool in designing new cement based materials, is Fast Field Cycling (FFC) Nuclear Magnetic Resonance (NMR) Relaxometry [3]. FFC NMR Relaxometry is sensitive to a wider range of molecular motions, as compared with relaxation measurements performed at a single frequency. Thus, in the case of liquids confined inside cement based materials, it allows better discrimination of the surface and bulk contributions to the relaxation [4-6]. Herein two applications of the FFC technique applied to cement materials prepared with grey and white Portland cement are illustrated.

FIG. 15A and FIG. 15B reveal the influences introduced by the curing temperature on the hydration process of a grey cement paste prepared at a water-to-cement (w/c) ratio of 0.3. The evolution of the proton nuclear magnetic relaxation dispersion (NMRD) curves clearly demonstrate an acceleration of the hydration process by increasing the temperature [5]. The interpretation of the NMRD curves assumes that the relaxation process is dominated by the interaction of water protons with the paramagnetic centres located on the surface of cement grains [4, 5]. Thus, it is possible to monitor the evolution of the surface-to-volume ratio of capillary pores [2] during the early hydration stages. Furthermore, the transverse diffusional correlation times at the surface of cement grains and the corresponding surface diffusion coefficients can be monitored. The results showed a slight decrease of the transverse diffusional correlation time upon increasing the temperature and a significant increase in the surface-to-volume ratio of capillary pores [5].

FIG. 15C and FIG. 15D illustrate another application of FFC NMR Relaxometry, to monitor the influence introduced by the addition of silica fume (SF)

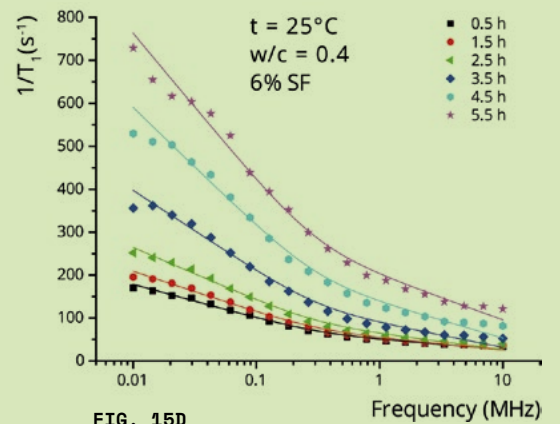
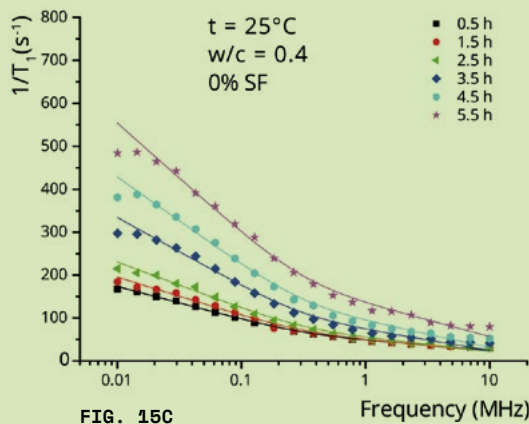
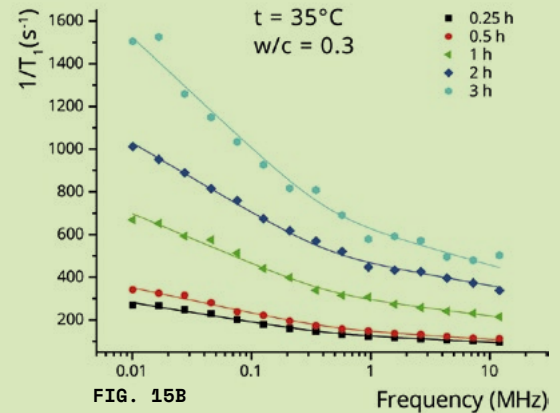
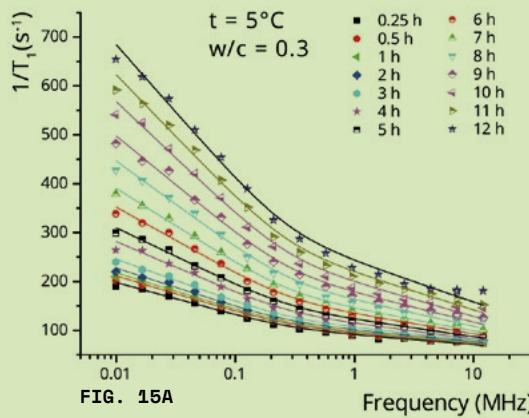
in a cement paste, prepared at a w/c=0.4 and hydrating at 25°C. Silica fume is a pozzolanic binder which is known for its beneficial properties in the concrete industry, especially in the manufacturing of high performance concrete [1]. The improvements in the strength of cement based materials, introduced by SF addition, rely on the fact that it reacts with calcium hydroxide produced during the hydration of cement or other hydraulic binders [1].

Using FFC NMR Relaxometry, it is possible to compare the changes in the hydration dynamics of a pure cement paste (FIG. 15C) and a cement paste containing silica fume (FIG. 15D). The evolution of NMRD curves during the early hydration showed accelerated dynamics in the sample containing silica fume (FIG. 15D) as compared with the simple cement paste (FIG. 15C).

Another outcome of the FFC NMR Relaxometry investigations is that the surface correlation time, and consequently the interaction of water molecules with the cement grains surface, does not change during the early hydration [6].

ACKNOWLEDGEMENT:

Thanks to Prof. Ioan Ardelean (Technical University of Cluj-Napoca, Romania) for providing the text for this section.



▲ FIG. 15:
Time evolution of the NMRD curves during of a gray cement paste hydrating at different temperatures (A, B), or a white cement paste prepared with different amounts of silica fume (C, D).
Adapted from REFS. [5] and [6].

4

/APPLICATIONS: FOOD SCIENCE

Overview of Applications of Fast Field Cycling Nuclear Magnetic Resonance in Food Analysis

Over the past decades, the use of Fast Field Cycling (FFC) Nuclear Magnetic Resonance (NMR) in food science has increased significantly, as evidenced by numerous scientific publications. FFC is a non-destructive and versatile technique that enables rapid evaluation and is applicable to a broad spectrum of food products [1-3, 6-14]. Nuclear Magnetic Relaxation Dispersion (NMRD) profiles, which are graphical representations that show how the rate of nuclear relaxation changes with varying magnetic field strengths, are obtained from FFC NMR measurements. In simple terms, these profiles depict how molecules in the food sample move and interact on a molecular level. Understanding NMRD profiles matters because they reveal details about the structure, composition, and physical properties of food, such as water mobility and the presence of different fat or protein structures. These profiles provide valuable information for food manufacturers across multiple applications [4].

The primary applications of FFC NMR in food fingerprinting and analysis include the following:

- Quality control (QC);
- Shelf-life stability;
- Assessment of ageing, varietal differences, and geographical origin
- Detection of food fraud and authentication [5].

Food products that benefit from FFC NMR analysis include for examples include cocoa butter, edible oils, authentication of vegetable oils with emphasis on rapeseed oil, fruit juices, shelf-life assessment of fruits such as dehydration of blueberries, wines, vegetables, and meats, including quality control of dry-cured ham and evaluation of meat dehydration. Dairy products such as cheese and yoghurt are also analysed. Furthermore, FFC NMR is applied to assess food storage conditions, including liquefied honey and fermentation processes [14, 16-20].

/APPLICATIONS: FOOD SCIENCE

4.1 Food fingerprinting

The NMRD profile is sensitive to dehydration, oxidation, spoilage and the addition of additives.

Food fingerprinting is an analytical approach used to verify the authenticity, composition, origin, and quality of food by identifying specific chemical, physical, and molecular characteristics. In analytical chemistry, fingerprinting generates a unique profile based on a substance's chemical composition, analogous to how a fingerprint uniquely identifies an individual. Comparing these chemical profiles enables researchers to discern differences or similarities between samples, thereby determining whether a food product is authentic or has been altered. For instance, fingerprinting techniques are commonly applied to confirm the purity of olive oil, detect adulteration in honey, and verify the origin of wine or coffee. These applications demonstrate the role of food fingerprinting in supporting scientific analysis for quality control and fraud prevention. Fast Field Cycling Nuclear Magnetic Resonance

(FFC NMR) is notable in food fingerprinting for its use of Nuclear Magnetic Relaxation Dispersion (NMRD) curves. To generate an NMRD curve, a food sample is analysed using the FFC NMR instrument, which measures changes in the nuclear magnetic relaxation rate as the external magnetic field strength is systematically varied. Recording relaxation rates at multiple magnetic fields produces the NMRD curve. In food analysis, these curves are valuable because relaxation behaviour is highly sensitive to changes in the molecular environment. For example, the NMRD profile can indicate dehydration, oxidation, spoilage, or the presence of additives. Analysis of these profiles enables detection of subtle alterations in the food matrix, facilitating early identification of spoilage or adulteration. As a result, food manufacturers and regulators can verify the authenticity and safety of food products, thereby protecting public health and maintaining consumer confidence.

Food represents a complex matrix in which NMRD has demonstrated significant diagnostic utility. The NMRD profile is sensitive to dehy-

dration, oxidation, spoilage, and the addition of additives, including adulterants that may result in fraudulent products. Compared to other fingerprinting techniques, such as chromatography or mass spectrometry, which often require extensive sample preparation and are time-consuming, NMRD enables rapid, non-destructive analysis of intact samples. Furthermore, NMRD provides unique insights into the molecular dynamics of

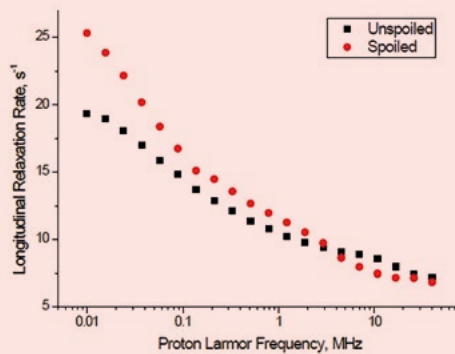
foods that are not accessible through traditional chemical profiling methods. Thus, NMRD can be effectively used to fingerprint foods, either as a stand-alone technique or in combination with other established analytical methods [9, 20-29].

The following paragraphs present selected applications of FFC NMR in food fingerprinting.

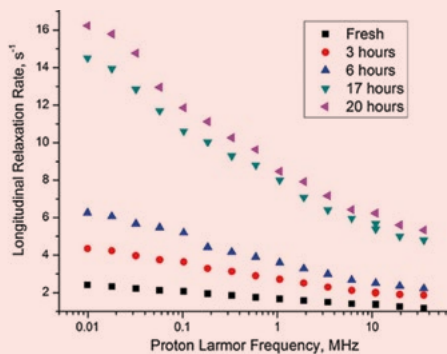
/APPLICATIONS: FOOD SCIENCE

4.2 Quality Control in Spoilage Detection and Shelf-Life Assessment

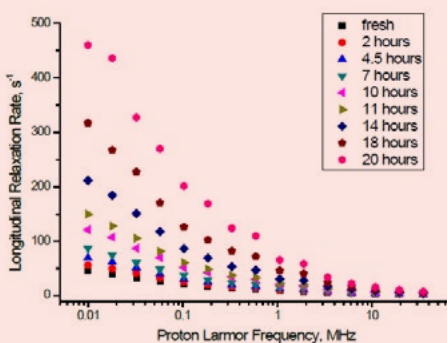
▶ **FIG. 16:** ¹H NMRD profiles of a milk-based refrigerated drink product within expiry date (unspoiled, black ■), and after induced spoilage (spoiled, red ●). (From [1])



▶ **FIG. 17:** ¹H NMRD profiles of a piece of banana measured as a function of the time with the aim to monitor the aging effects. (From [1])



▶ **FIG. 18:** ¹H NMRD profiles of pork loin open to air at ambient temperature over a twenty-hour time period. (From [10])



Spoilage detection in milk-based products, shelf-life evaluation of fruit and meat, and monitoring of the ham dry-curing process are critical aspects of food quality control [14, 16-20].

FFC showed large differences in the $1/T_1$ for spoiled and non-spoiled products at low frequencies (between 10 and 100 kHz). A large food manufacturer intended to use this data to carry out in-line production quality control checks on these products.

Discrimination between fresh and aged products can be achieved based on their water content. These results can be correlated and applied to quality control processes, including freshness and shelf-life monitoring [1, 9].

For example, FIG. 17 illustrates changes in the proton Nuclear Magnetic Relaxation Dispersion (NMRD) profile of fresh bananas over 20 hours. NMRD effectively demonstrates the rate at which meat, such as pork loins (FIG. 18), dehydrates as water is lost.

Apih and colleagues [10] demonstrated that a combined FFC NMR and quantitative Magnetisation Transfer NMR (qMT-NMR) approach, utilising the area under quadrupolar peaks, is effective for this analysis. This method, which incorporates NMRD profiles and restricted magnetisation pool size from qMT-NMR, provides a rapid, non-destructive means of characterising both fresh and dry-cured ham tissues. It is therefore a powerful tool for monitoring the dry-curing process [10].

Collectively, these results indicate that, particularly at lower magnetic fields, differences in $1/T_1$ relaxation rates enable a clear distinction between various states of the same product.

4.3

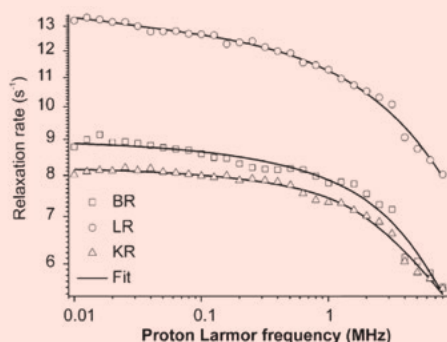
/APPLICATIONS: FOOD SCIENCE Geographical origin

Edible oils

Fast Field Cycling (FFC) is an effective analytical technique for distinguishing among various characteristics of edible oils. Conte and colleagues demonstrated that FFC can differentiate pistachio oils obtained from seeds subjected to different thermal desiccation processes, seeds of the same cultivar grown in distinct geographical

areas, and oils produced from seed cultivars sampled within the same region [11]. Additionally, a reliable correlation was established between oil kinematic viscosity and relaxation parameters measured by FFC. Based on these findings, Conte and colleagues concluded that the geographical origin of pistachio seeds is a significant factor in discriminating oils of varying quality.

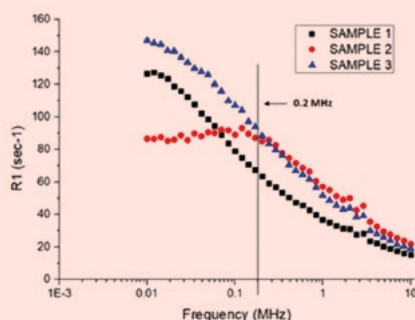
FIGURE 19 demonstrates that the results obtained at low magnetic fields (below 10 MHz) were essential for this study. Conte and colleagues also applied the FFC technique to extra-virgin olive oils [12]. Their findings indicate that olive oils are not disordered and amorphous liquids, but rather systems in which constituents are organized into well-defined supramolecular aggregates. This insight is important for advancing the understanding of absorption, transport, and metabolism of extra-virgin olive oils, which are fundamental components of the Mediterranean diet.



► FIG. 19:
 ^1H NMRD profiles allow discrimination between oils obtained from different cultivars sampled in the same geographical location. (From [11])

Comparison of Cheeses Produced from Unpasteurized and Pasteurised Milks

► FIG. 20:
 ^1H NMRD profiles can be used as a fingerprint for cheeses made from pasteurized (sample 1 ■) and unpasteurized sheep's milk (samples 2 ● and 3 ▲). Sample 3 ▲ is a more seasoned cheese than sample 2 ●. Data from Stelar in-house studies [24].

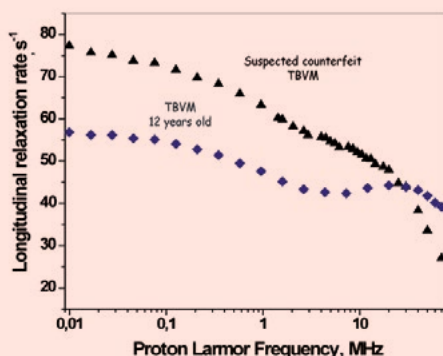


NMRD profiles can serve as a fingerprinting method to distinguish cheeses of a specific protected origin produced from unpasteurized and pasteurised sheep's milk (see FIG. 20). In cheeses made from unpasteurized milk, differences in $1/T_1$ were particularly pronounced at fields below 0.2 MHz when comparing young (fresher) and more seasoned (older) cheeses. [24]

4.4

/APPLICATIONS: FOOD SCIENCE Food fraud and authentication Balsamic vinegar and rape-seed oil

► FIG. 21:
 ^1H NMRD profiles for 12-year aged balsamic vinegar (blue ◆) and counterfeit product, with thickening agents added (black ▲). (From [13])



Food authentication represents a significant concern for the food industry. Unscrupulous producers may gain economic advantages by manufacturing fraudulent products that are sold at the premium price of authentic goods. Consumers are entitled to accurate information regarding product authenticity, which justifies higher pricing. Baroni et al. demonstrated that the NMRD profile is a highly effective tool for characterising genuine balsamic vinegars and provides valuable insights for detecting fraudulent products [13].

^1H NMRD profiles revealed substantial differences between a genuine 12-year-old TBVM and a suspected fraudulent product (TBVM, FIG. 21). TBVM is a protected designation of origin product, and its market price reflects its extensive ageing process. Rachocki et al. reported that, after determining the diffusion coefficient for a specific type of authentic rapeseed oil, it was possible to assess the authenticity of various oil samples using this parameter [14]. The diffusion coefficient is sensitive to the molecular environment, including chemical composition, production process, and the geographical origin of the cultivar. Therefore, the diffusion coefficient of rapeseed oil, as calculated from the NMRD profile, serves as a unique and characteristic parameter for that

particular oil. TBVM is a protected designation of origin product and its cost on the market is rather high in accordance with its ageing process. Rachocki et al. reported that, after calculating the diffusion coefficient for a particular type of authentic rape-seed oil, it was possible to run measurements on a series of oil samples, to check their authenticity [14]. This is due to the fact that the diffusion coefficient is sensitive to the environment in which the molecules diffuse, e.g. chemical composition, the oil production process and the geographical growth area of the cultivar. The diffusion coefficient of the rape oil, which can be calculated from the NMRD profile, becomes a unique parameter, characteristic of that particular oil.

4.5 Food ageing process

/APPLICATIONS: FOOD SCIENCE

Cheese ageing

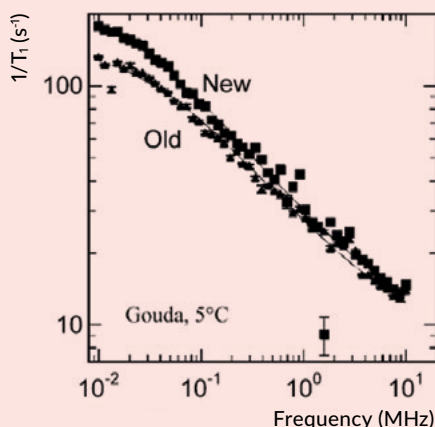
Cheeses are solid emulsions in which milk fat is dispersed within a matrix of water and proteins. Identification of these structural regions is crucial for understanding cheese composition. Monitoring changes in these regions yields insights into the structural evolution of the final cheese product. Godefroy et al. demonstrated that Fast Field

Cycling Nuclear Magnetic Resonance (FFC NMR) analysis of Gouda-type and Mozzarella-type cheeses enables the determination of protein hydration levels as a function of ageing [2].

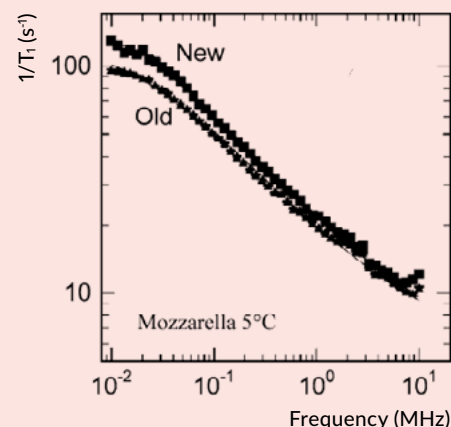
FIGURES 22 and 23 illustrate the differences observed in aged dry-salted Gouda-type and Mozzarella-type cheeses, respectively.

▶ FIG. 22:
 ^1H NMRD profiles of young and old dry salted gouda-type cheese at 5 °C. (From [2])

▶ FIG. 23:
 ^1H NMRD dispersion curves of young and old dry salted mozzarella-type cheese at 5 °C. (From [2])



▲ FIG. 22



▲ FIG. 23

4.6 Fast Field Cycling to monitor the crystallization in alimentary fat

/APPLICATIONS: FOOD SCIENCE

Case study: the fat and confectionery industry

Low-field NMR (20MHz) is currently used in the confectionery and fat industry for determining what is called solid fat content (SFC), i.e. the proportion of crystalline material present in a sample. However, this technique is not sensitive

enough at lower SFC values resulting in the need of complementary techniques if crystallization studies, rather than melting profiles, are sought. FFC NMR has been shown to be sensitive to different types of molecular motions by allowing

the access to a wider range of lower frequencies (<20 MHz) that are not usually attainable using other type of NMR instruments.

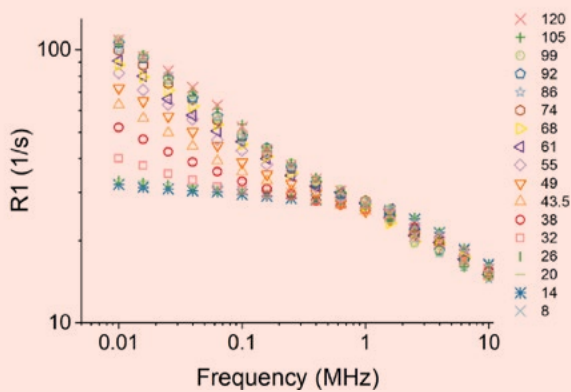
These frequencies are interesting because they show the slower molecular motions that are usu-

ally invisible using other set-ups, such as that of structuring, or orientation that occur during the formation or transformation of liquid crystal phases [2] and lipid bilayers [3]. This therefore raised the question of whether these lower frequencies would be able to detect the initial stages of crystallization that are not observable using the SFC method.

Lower frequencies might prove advantageous for studying the early stages of crystallization.

Application of FFC to detect the crystallization in chocolate butter

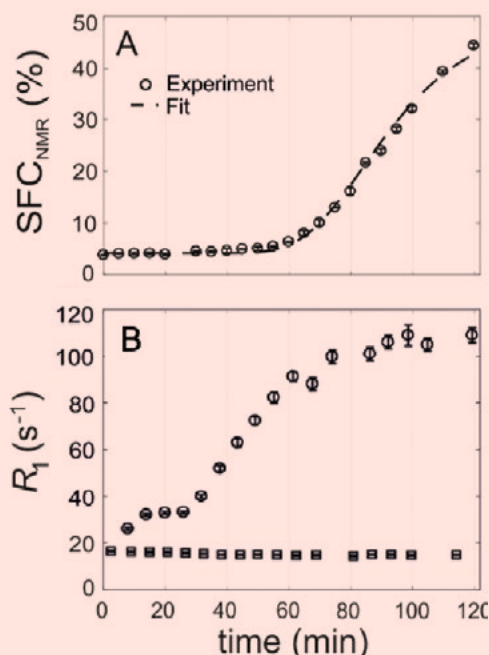
By heating cocoa butter and then cooling it step-wise, Ladd-Parada, et al. [4] were able to estimate the self-diffusion coefficient and its temperature dependence using the well-known method by Kruk, et al. [5].



▲ FIG. 24: Relaxation profile as a function of time of cocoa butter previously heated to 50°C, cooled to 20°C and held isothermally at this temperature. Time increases from the bottom (8 min) to the top (120 min), the key on the right-hand side is indicative of the time (minutes) at which the relaxation measurements finished. (Adapted from [4]).

► FIG. 25: Crystallization of cocoa butter at 22°C. [Adapted from (6)].

(A) SFC NMR turnover and the corresponding Gompertz fit.
 (B) R_1 values at 10 kHz (circles ○) and 10 MHz (squares ◻).



However, once the sample was cooled and held isothermally at 20°C, molecular motions other than self-diffusion became more dominant with time, particularly at frequencies below 1 MHz (FIG. 24). Here it was observed a strong increase in the spin-lattice relaxation rate (R_1) values, suggesting a phase transition, i.e. crystallization.

Notably, when holding the sample at 20 °C, Ladd-Parada, et al. (2019b) [6] observed that by using the standard SFC technique, they could not pick-up crystallization until after 50 mins (FIG. 24), whereas, when plotting the R_1 value at 10 KHz vs time, it was seen to increase immediately, reaching a first plateau, followed by a second increase and plateau as previously observed in literature using X-ray scattering (van Malssen, et al. (1996) [7]. It must be noted that the time-dependency of the relaxation rate is not used for modelling crystallization kinetics using the Avrami nor Gompertz models as is common in literature, when analysing DSC data, for example.

However, it is notable that when the R_1 starts plateauing for the second time, it coincides with the increase of the SFC curve, showing that measurements below 1 MHz are complementary to those at 20 MHz, helping to determine the time of start of the phase transition.

Conclusions

It has been shown that tracking the R_1 values at 10 kHz allowed the observation of the initial stages of crystallization, as it is sensitive to the amount of orientationally ordered TAG molecules (i.e. triacylglycerols, which are the main components of fats) and their associated dynamics in the sample (FIG. 25).

In summary, using lower frequencies might prove advantageous for studying the early stages of crystallization.

5 FFC NMR in Biomedical Science

The primary advantage of FFC lies in its sensitivity to biochemical and microenvironmental parameters.

Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR) Relaxometry offers a range of applications in healthcare, pharmaceuticals, cosmetics, and both preclinical and clinical research, with particular relevance for biomedical detection involving magnetic resonance imaging (MRI) contrast agents [3,4,5]. Whereas MRI provides high-resolution anatomical images and contrast based on proton density and relaxation at a single magnetic field strength, FFC-NMR evaluates the dependence of longitudinal relaxation (R_1 or T_1) across a wide spectrum of magnetic fields [1, 3]. FFC-NMR measurements are typically conducted using specialised relaxometers that rapidly switch magnetic field strengths during the pulse sequence, allowing for precise analysis of relaxation rates as a function of field. Samples are placed in dedicated holders or probes, and automated routines collect relaxation data across multiple field strengths to generate Nuclear Magnetic Resonance dispersion (NMRD) profiles. These field-dependent NMRD profiles reveal molecular dynamics, water mobility, and macromolecular interactions that are closely linked to tissue microstructure and pathological changes [1, 3, 8]. The primary advantage of FFC lies in its sensitivity to biochemical and micro-environmental parameters that are often undetectable by conventional imaging methods. Variations in relaxa-

tion dispersion can reveal differences in cellular organisation, protein concentration, membrane exchange, and tissue oxygenation [3,8]. Quadrupolar peaks and other dispersion features serve as quantitative biomarkers of molecular architecture, enabling more detailed characterisation of biological systems beyond morphological data alone [6]. FFC techniques are designed to complement, rather than replace, existing diagnostic modalities. While MRI remains the standard for spatial resolution and anatomical assessment, FFC Relaxometry provides functional and molecular insights that enhance interpretation and facilitate biomarker discovery [4, 5]. This integrated approach supports improved disease characterisation, the development of advanced contrast agents, and a more comprehensive understanding of biological processes at the molecular level [4, 5].

Subsequent sections provide a detailed examination of the medical applications of FFC-NMR, emphasising its contributions to contrast agent optimisation, *in vivo* and *ex vivo* tissue analysis, protein dynamics, pharmaceuticals, cosmetics, and forensic investigations. Recent and ongoing studies, such as those investigating novel MRI contrast agents for neuroimaging, *in-vivo* tumour characterisation, and advancements in relaxometry protocols for drug development, reflect sustained and increasing interest in this field. Each application illustrates the capacity of FFC-NMR to generate clinically and scientifically relevant data that complement and enhance conventional biomedical methodologies [7].

5.1.1 MRI contrast agents

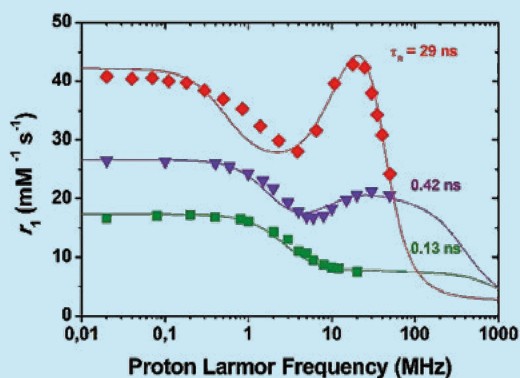
Contrast agents (CAs) are commonly injected in patients undertaking Magnetic Resonance Imaging (MRI) scans as they accelerate the relaxation rate of water molecules in the tissues, enhancing the signal contrast between different tissues in the body. The CAs currently available consist of paramagnetic complexes, most of them gadolinium (Gd(III)-based) or super-paramagnetic iron oxide particles. The efficacy of the CA is given by its “relaxivity” (r_1), which is the enhancement of the longitudinal relaxation rate (R_1) of the water protons normalized to a 1 mM concentration of the paramagnetic ions present. Proton NMRD profiles are commonly used to characterize a CA by measuring the relaxation rate of the water protons at different magnetic field strengths.

With translation to the clinical setting in mind, it is essential to measure and analyse the NMRD profiles of any potential CA.

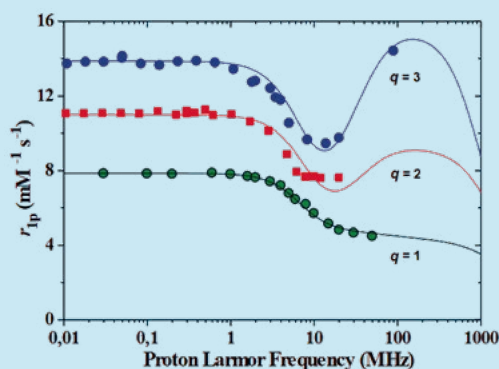
Relaxation depends on several structural and dynamics parameters of the metal system and understanding how these parameters influence the shape of the NMRD profile is important for optimizing relaxivity [1-11].

From the NMRD profile of a CA and through analysis using simulation models, such as the Solomon-Bloembergen-Morgan (SBM), several parameters of the CA can be studied [1, 2, 4, 5, 7, 8]. The design and synthesis of new CAs that improve MRI sensitivity is an important research topic. The parameters that can be obtained from fitting the NMRD profile are pivotal in designing

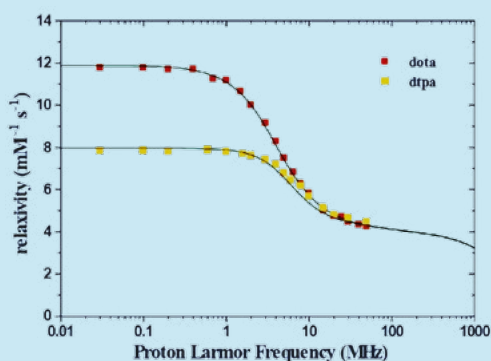
FFC NMR technique allows investigation of the interaction between metal ions and water which can be used to improve the effectiveness of a contrast agent and to optimize its design.



▲ FIG. 26:
 ^1H NMRD profile at 25°C of three Gd(III) complexes. GdDOTA-BOM3 (in green ■), its inclusion complex with β -cyclodextrin (in violet ▼) and GdDOTA-BOM3-HSA adduct (in red ◆). The different shapes and amplitudes of the profiles are mainly due to the different τ_R of the paramagnetic complexes.
[Courtesy of Prof. M. Botta from the University of Eastern Piedmont]



▲ FIG. 27:
 ^1H NMRD profile at 25°C of three Gd(III) complexes differing in the number q of inner sphere water molecules. GdDTPA (green circles ●), GdHOPY (red squares ■), GdCalix[4]arene (blue circles ●).
[Courtesy of Prof. M. Botta from the University of Eastern Piedmont].



▲ FIG. 28:
 ^1H NMRD profiles of GdDOTA and GdDTPA are well differentiated at magnetic fields <10 MHz
[Courtesy of Prof. M. Botta from the University of Eastern Piedmont].

new CAs and increasing the performance of the existing ones (FIG. 26 and FIG. 27).

These parameters are:

- r is the distance between the proton of a metal-bound water molecule and the paramagnetic ion.
- q , or *hydration number*, is the number of water molecules coordinated to the paramagnetic ion;
- τ_M is the mean residence (exchange) lifetime of a water molecule coordinated to the paramagnetic ion;
- $T_{1,2e}$ are the electronic relaxation times;
- τ_R is the rotational correlation (tumbling) time.

To effectively design a new CA or develop and study a relaxation model, the acquisition of a full NMRD profile is required. FIG. 28 reports an example of two common Gd(III)-complexes, with identical hydration states and very similar structures. At high magnetic fields (>10 MHz) the NMRD profiles of these complexes overlap, whereas at magnetic fields lower than 10 MHz the relaxivity of the two complexes is well differentiated.

The differences are strictly related to different structural and dynamic properties of the CAs. It is very difficult to fit an NMRD profile accurately with very few field points (measurements of R_1). The smaller the range of frequencies considered, the less accurate the fitting.

State-of-the-art research aims at obtaining new CAs with a higher relaxivity and a higher specificity (molecular targeting) while limiting the potential toxicity of the metal ions, which are toxic to humans when not strongly bound to an organic chelate. Novel theoretical models are being studied to improve fitting of the FFC experimental data allowing estimation of the parameters involved in relaxation.

In summary:

- Through best fit of the NMRD profile to the equation of paramagnetic relaxation, the values of the molecular parameters of the CAs can be assessed.
- Each parameter has an effect on the shape of the NMRD profile.
- FFC Relaxometry is used to interpret the behaviour of CAs in aqueous solution, elucidate the role of the various molecular parameters and guide their further refinements through rational chemical design.
- FFC indeed has a fundamental role in the continuous search for improved contrast-enhancing agents, by increasing the understanding of these agents at the molecular level.

ACKNOWLEDGEMENT:

Thanks to Prof. Mauro Botta (University of Eastern Piedmont) for his valuable help and fruitful discussions on contrast agents and NMRD profiles.

/BIOMEDICAL SCIENCE: RECENT ACHIEVEMENTS AND INNOVATIONS

5.1.2

Study of a new in-vivo application: FFC-NMRD profiles of tumour-bearing mouse leg

The acquisition of NMRD profiles on animal models is a fundamental step forward in validating the clinical effectiveness of FFC-MRI [4, 5] with the final goal of finding new biomarkers capable of characterizing different diseases for an earlier diagnosis with lower costs and new protocols responsive to changes in water mobility following therapeutic treatment [6, 7, 8].

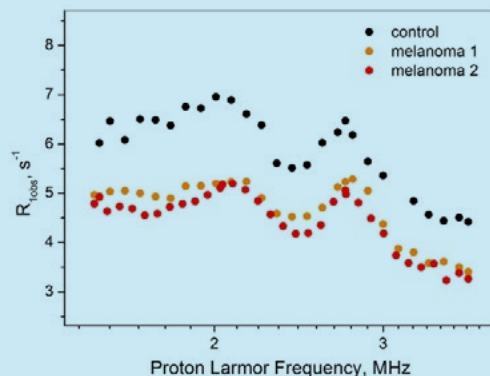
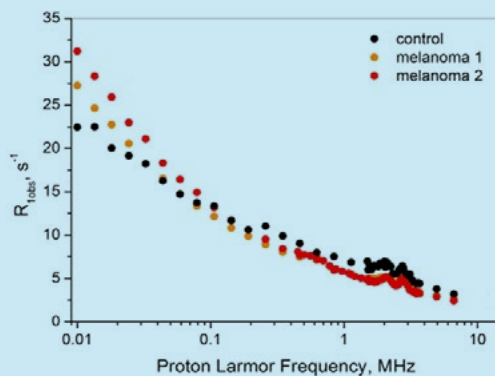


▲ FIG. 29: This MRI image shows the difference between normal and tumour bearing mouse leg.



▲ FIG. 30: Mouse in the wide bore probe.

▶ FIG. 31: Melanoma tumours have shorter T_1 than normal tissue due to the higher iron content melanin aggregates. T_1 differences are proportional to the tumour size (132 and 180 mm³ for tumour 1 and 2 respectively).



▲ FIG. 32: Quadrupolar peaks arising from protein amidic groups can be seen very clearly, centred at proton NMR frequencies of 0.65, 2.10 and 2.75 MHz. This is a phenomenon that is completely invisible to conventional (fixed-field) MRI but fully exploitable by FFC-NMR.

Many diseases are inadequately diagnosed, or not diagnosed early enough by current imaging methods.

Examples of unmet clinical needs arise in thromboembolic disease, osteoarthritis, cancer, sarcopenia, and many more areas.

Conventional magnetic resonance imaging (MRI) techniques have focused on the improvement of the spatial resolution by using high magnetic fields (1-7T).

High field allows the visualization of small tumour mass but lacks the ability to give a precise evaluation of important hallmarks of the disease such as tumour grading, oxygenation, pH and metastasization, which may affect the type of therapy chosen.

New work aims at developing an innovative diagnostic strategy, based on the measurements of longitudinal relaxation times at low and ultra-low magnetic fields with FFC NMR Relaxometry to obtain quantitative information on tumour characteristics, due to different water content and mobility, that is invisible to standard MRI [1-3].

Indeed, FFC introduces an entirely new dimension into MRI, namely the strength of the applied magnetic field.

In this study, a dedicated surface coil and a suitable RF interface has been developed for the acquisition of in-vivo NMRD profiles in an animal model (FIG. 28 and FIG. 30).

The preliminary results on mice showed that the endogenous contrast between normal and diseased tissue, due to differences in T_1 , is much greater at low field and the shape of the relaxation dispersion profiles may be used as a method for reporting the molecular dynamical processes of water (i.e. the exchange rate across membranes) that dominate the relaxation mechanism at low fields (FIG. 31).

An example of a phenomenon that is completely invisible to conventional (fixed-field) MRI but fully exploitable by FFC-NMR is the occurrence of quadrupole peaks (QPs) – significant increases in the measured relaxation rate ($R_1 = 1/T_1$) in the presence of immobilized protein molecules, at magnetic fields where the proton NMR frequency and the ¹⁴N nuclear quadrupole resonance (NQR) frequency coincide. The QPs arising from protein amide groups can be seen very clearly (FIG. 32).

Indeed, QPs of hypoxic tumour tissues are significantly less pronounced than those of normal leg tissues (FIG. 33). This pioneering work has shown that FFC NMR

Relaxometry can detect relatively small changes in tissue architecture at the cellular level, which occur early enough to provide an earlier diagnosis and non-invasive tumour characterization.

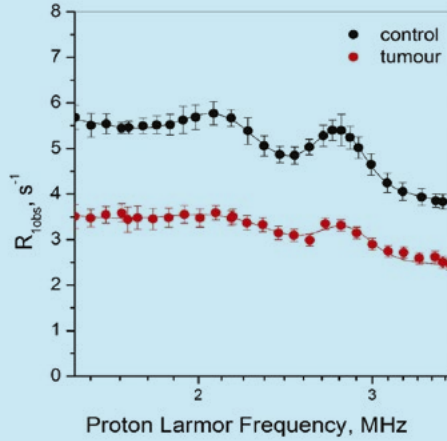


FIG. 33A

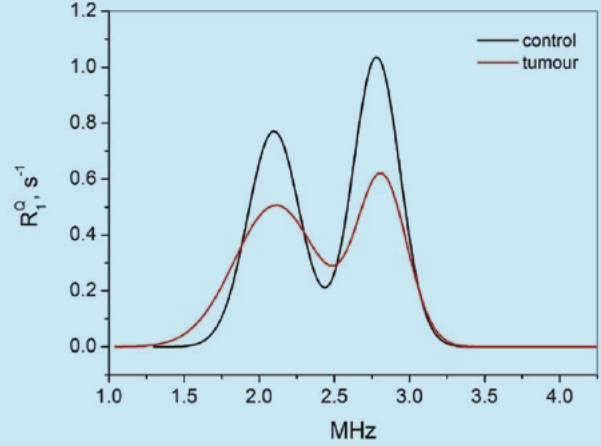


FIG. 33B

► FIG. 33: QP of hypoxic tumour tissues are significantly less pronounced than normal legs tissue.

5.1.3

/APPLICATIONS: BIOMEDICAL SCIENCE

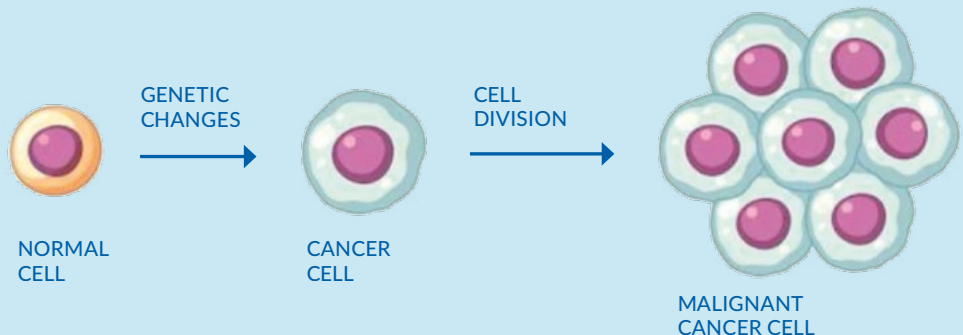
A new solution for advanced tumour tissue characterization: Revolutionizing tumour tissue analysis with Fast Field Cycling NMR Relaxometry

The future of tumour analysis

At Stelar, we are eager to propose a new cutting-edge solution in the field of cancer research, based on our expertise in Fast Field Cycling (FFC) NMR Relaxometry technology. This innovative NMR application allows a non-invasive, fast, and simple characterization of tumorous tissues, providing researchers and clinicians with a new approach for measuring a key biomarker linked to the treatment response and tumour progression. [1]

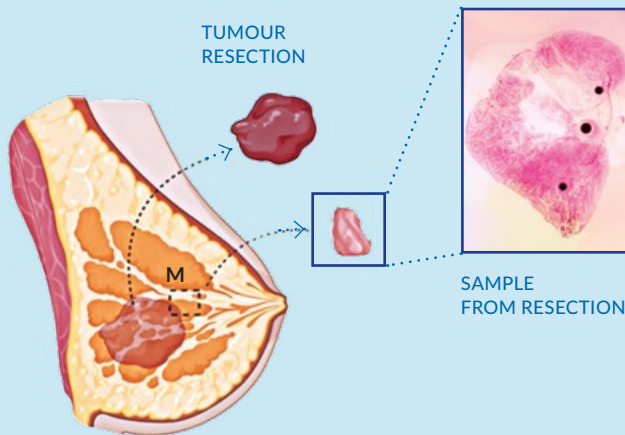
Diagnostic and pre-clinical challenge

- Accurate tumor characterization is key to understanding tumour gradation and its aggressiveness, optimizing treatments.
- Traditional imaging and biopsy methods often miss subtle changes, delaying therapy adjustments.
- Improved monitoring techniques allow for earlier, more precise treatment modifications, enhancing therapy effectiveness and patient outcomes. [2]



► FIG. 34: Cancer development process. Cancer is the uncontrolled growth of abnormal cells in the body. It can form tumors, invade nearby tissue and spread to other parts of the body.

► REMOVAL OF TUMOUR MASS.
SAMPLE COLLECTION

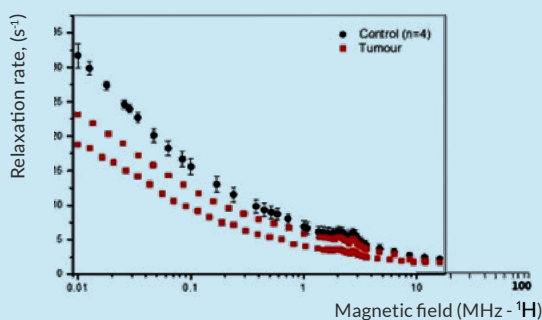


► SAMPLE MEASUREMENT
AND ANALYSIS:
A FEW MINUTES.



► NMRD PROFILES
OF THE TUMOUR TISSUE

● CONTROL
■ TUMOUR



Problem addressed

Breast cancer is the most common cancer among women, with approximately 380,000 new cases diagnosed annually in the European Union [3, 4]. Based on current trends, one in eight women will develop breast cancer in their lifetime. Early and effective surgical intervention is critical, yet challenges remain in ensuring the complete removal of cancerous tissue during breast-conserving surgery (BCS). One of the most significant risks in BCS is the recurrence of tumours due to residual cancer cells at the surgical margins. Currently, up to 40% of BCS procedures yield margins that are either positive or uncertain, leading to increased risks of locoregional recurrence. The gold standard for margin assessment—histological evaluation—requires several days for results and depends on highly specialised personnel, causing delays and higher costs in treatment [5].

The solution: Fast Field Cycling (FFC) NMR Relaxometry

Fast Field Cycling (FFC) NMR Relaxometry offers a cutting-edge, non-destructive approach to promptly measure a critical biomarker, closely linked to tumour structure, cell density, and treatment responsiveness.

Key benefits of FFC-NMR Relaxometry

- Ultra-Sensitive: detects minute changes in tumour structure before they become visible. High sensitivity and specificity.
- Early treatment insights: promptly monitor therapeutic efficacy, thus reducing response times, compared to traditional imaging techniques and other analysis methods.
- Non-destructive: characterizing tumorous tissues with a new approach, that preserves tissue integrity.

Why choose Stelar's FFC NMR Relaxometry for tumour tissue characterization?

The innovative and cutting-edge diagnostic method based on Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR) technology addresses the limitations of current histological assessment by providing real-time, high-precision analysis of tissue during surgery.

Key features include:

1. Automatised response (< 9 min),
2. High sensitivity and specificity,
3. No treatment of the sample (just inserted into a glass tube), so samples can be used for further tests.

The compact design (<1 m³) allows it to be conveniently integrated into surgical rooms, enhancing the standard of care while minimising operational disruptions [6, 7]

- Pre-clinical Diagnostic tool: detecting the staging of tumours and their level of aggressiveness, for advanced and improved preclinical diagnostics.

- World-Class Hardware: built by Stelar, trusted by leading institutions world-wide.
- Proven Scientific Validation: backed by top research institutions and key publications.

Stelar's FFC NMR system, backed by key breast cancer studies, offers crucial insights into tumour biology and treatment response, advancing personalized oncology and more effective cancer therapies [8, 9].

5.2

/APPLICATIONS: BIOMEDICAL SCIENCE

Cartilages

Fast Field-Cycling Nuclear Magnetic Resonance (FFC-NMR) is an advanced technique for investigating osteoarthritis (OA) because of its sensitivity to molecular dynamics and field-dependent relaxation mechanisms. Measuring longitudinal relaxation time (T_1) dispersion across different magnetic field strengths enables FFC-NMR to identify subtle biochemical and structural changes in articular cartilage that precede visible degeneration [1]. Research demonstrates that OA-related degradation, particularly proteoglycan loss and collagen matrix disruption, alters water-macromolecule interactions, as shown by changes in quadrupo-

lar peaks and T_1 dispersion profiles [1]. Analyses of enzymatically treated and native cartilage reveal multi-component relaxation behaviour that reflects tissue composition and integrity [2]. FFC-NMR provides direct spectroscopic biomarkers of cartilage degeneration, while FFC-MRI enables spatial mapping of these parameters *in situ* [1]. Together, these techniques offer non-invasive, molecular-level insights into cartilage pathology, facilitating early diagnosis, monitoring of disease progression, and evaluation of therapeutic interventions in osteoarthritis [3].

5.3

/APPLICATIONS: BIOMEDICAL SCIENCE

Proteins

The field dependence of the water proton relaxation rate in protein solutions reports on the reorientation motions of the protein: it reflects protein dynamics as a result of the interaction between water protons and the protein. [1-10]

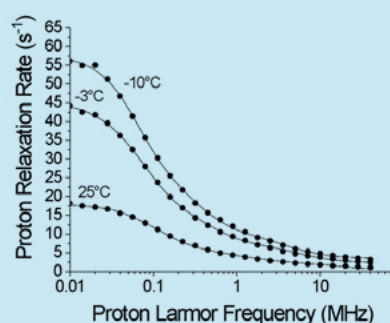
Since ¹H NMRD profiles are typically measured over a range of proton Larmor frequencies spanning from 0.01 to 50 MHz, correlation times spanning from 10⁻⁵ to 10⁻⁹ s can be accessible. This provides a direct measurement of the reorientation times of proteins from few kDa up to MDa. Aggregation would be evidenced, if present, by the occurrence of an unexpectedly large reorientation time. Reorientation correlation times of systems as large as 600 kDa (human αB-Crystallin) in 20% v/v glycerol and 360 kDa (α7α7 protea-

some from *Thermoplasma acidophilum*) in 40% v/v glycerol can be accessed, resulting as large as 1.4 and 0.9 μs, respectively, at 25 °C [1].

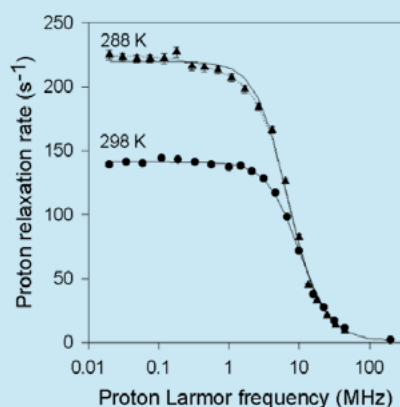
In the presence of multiple motional processes, the ¹H NMRD profiles thus result as the superposition of different spectral density functions associated with characteristic motional correlation times. Multiple correlation times are actually often needed for the analysis of the relaxation profiles, corresponding to three pools of protons experiencing different motional regimes. A first pool is constituted by fast exchanging protons with a residence lifetime shorter than the protein reorientation time: the correlation time modulating the dipole-dipole interaction is in this case the residence lifetime, and thus they do not bear in-

formation on the reorientation time. A second pool is defined for fast exchanging protons with a reorientation time larger than the residence lifetime: these are the protons bearing information on the reorientation time. The third pool of protons contains slowly exchanging protons (with a residence lifetime larger than the nuclear relaxation time): the correlation time is again the reorientation time, but the dispersion is quenched and appears distorted, seemingly shifted to higher fields, and thus yielding a smaller apparent correlation time (unless the value of the residence lifetime is properly taken into account). Possible local motions further complicate the picture, providing additional contributions. The analysis of the experimental NMRD profiles can be simplified by assuming that the data can be reproduced by the sum of Lorentzian dispersions (FIG. 35), corresponding to different correlation time values [2]. An average correlation time ($\langle\tau_c\rangle$) can be defined as the weighted average of the best fit correlation times, and for small proteins it was shown that ($\langle\tau_c\rangle$) is in good agreement with the reorientation time as calculated from the Stokes' equation.

► **FIG. 35:**
 Three-Lorentzian dispersions fit of the relaxation profiles of α B-crystallin in 20% v/v glycerol [1]



► **FIG. 36:**
 Relaxometric profiles of the protein protons of lysozyme 2.8 mM at H^* 3.5 and two different temperatures [3].



The water proton relaxation rate in protein solutions is a reporter of the protein dynamics. e.g. well-folded proteins are characterized by a large relaxation rate at low fields (100-5000 s⁻¹) while unfolded proteins have a relatively small relaxation rate at low fields (10-50 s⁻¹).

However, this does not hold in the case of protein aggregation and in large systems, where the reorientation time corresponds to the largest correlation time obtained in the fit [1]. This different behaviour can be ascribed to the large contributions of fast local motions and exchange to the correlation time modulating the dipole-dipole interactions, as the result of the increased reorientation time.

Direct measurement of protein proton spectral density functions is also possible by dissolving proteins in D₂O at millimolar concentration and collectively monitoring the protein protons themselves [3]. The analysis of such profiles provides direct information on the protein re-orientational time, and thus on its aggregation state, and on the collective order parameter of protein protons, and thus on internal mobility.

The analysis takes advantage of a complete relaxation matrix analysis of protein protons in order to model the distribution of the proton relaxation rates in proteins, which can be used to analyse the experimental profiles and extract dynamic information on the protein [4].

The profiles of well-folded proteins are characterized by a large relaxation rate at low fields (100-5000 s⁻¹), and by a dispersion in correspondence of the protein re-orientational time, which makes the relaxation rates at high fields very small (FIG. 36). The low field relaxation rate is however smaller than calculated for a rigid protein with such reorientation time, due to the presence of fast local motions, and the observed discrepancy provides an estimate of their extent, in the form of a model-free order parameter.

Unfolded proteins are characterized by a relatively small relaxation rate also at low fields (10-50s⁻¹), but they show a dispersion occurring at the same fields of globular proteins.

The measurements performed for the intrinsically disordered protein (IDP) α -synuclein as well as for a variety of other IDPs indicate that reorientation times similar to those of folded proteins, with a small collective order parameter, are also present in these biomolecules. The presence of these slow reorientation times is not affected by mutations in α -synuclein, which are related to genetic forms of Parkinson's disease, and do not depend on secondary and tertiary structural propensities.

Therefore, this suggests that long-range correlated dynamics are present as an intrinsic property of IDPs and offers a general physical mechanism of correlated motions in highly flexible biomolecular systems [5].

ACKNOWLEDGEMENT:

Thanks to Prof.s Giacomo Parigi and Claudio Luchinat (Magnetic Resonance Center (CERM) and Department of Chemistry, University of Florence, Italy) for providing the text for this section.

5.3.1

/APPLICATIONS: BIOMEDICAL SCIENCE Monoclonal antibodies

The aggregation of therapeutic proteins (e.g. monoclonal antibodies) is an important problem in the bio-pharmaceutical industry.

It is well documented that protein product aggregates are potent inducers of immune responses to therapeutic protein products, thus manufacturers of therapeutic protein products should ensure that their products contain minimal product aggregates.

Currently size exclusion chromatography (SEC) is primarily used in combination with orthogonal methods to confirm aggregate sizes present. There is a real need for new and improved analytical methods for defining protein aggregates for the benefit of the patient, to avoid constraining the production capacity of therapeutic proteins over the coming years and to prevent loss of therapeutic proteins through aggregation during the manufacturing process and storage [1, 2].

FFC NMR Relaxometry shows considerable promise for making routine assessments of protein aggregation and denaturation.

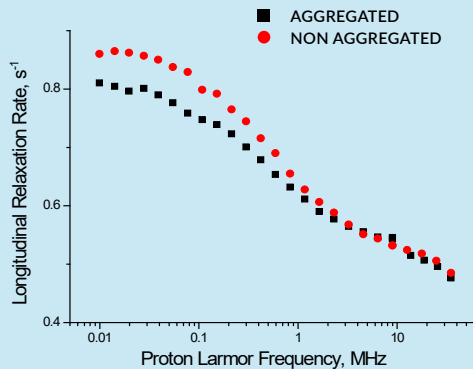
The unique feature of NMRD is that it can be used to characterize very large aggregates because of the very low frequencies achieved and does not suffer from aggregate fraction or separation as the system is measured [3].

FIG. 37 shows the ^1H NMRD profiles of a therapeutic protein (10 mg/mL) in its monomeric non-aggregated state and with artificially induced aggregation [4]. The differences between the aggregated and non-aggregated states can be most clearly seen at lower magnetic field strengths. Adoption of the FFC method for such an application in an industrial setting would not necessarily require the full NMRD profile but instead calibration at a few low field points. The main asset of FFC is that it is non-destructive.

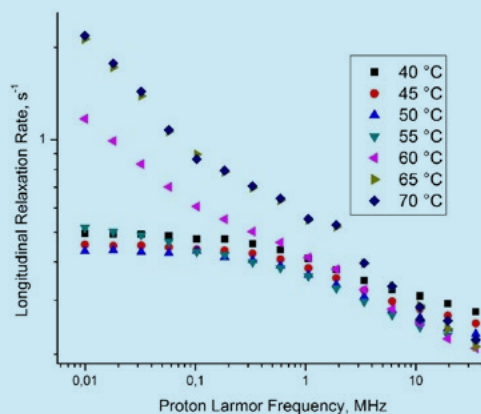
FIG. 38 shows how ^1H NMRD profiles can also show the dynamics in monomeric therapeutic proteins at different temperatures [4]. The temperature-dependent behaviour of one antibody (10 mg/mL) was studied between 40°C and 70°C. The protein initially aggregated (40-55°C) then unfolded (above 55°C).

The unfolding behaviour is clear at low magnetic field strengths.

► FIG. 37: ^1H NMRD profiles of a therapeutic monoclonal antibody in its monomeric (non-aggregated) and an artificially aggregated states.



► FIG. 38: ^1H NMRD profiles of a monomeric therapeutic protein at different temperatures corresponding to unfolding dynamics.



The aggregation of therapeutic proteins is an important issue in the bio-pharmaceutical industry. FFC NMR Relaxometry shows considerable promise for making routine assessments of therapeutic protein aggregation and denaturation.

Main topics concerning protein NMRD profiles:

- investigate the level of aggregation in proteins or a mixture of proteins;
- assess changes in protein aggregation;
- study protein-protein interactions;
- obtain information concerning molecular dynamics of proteins;
- study protein changes due to a change of solution temperature;
- obtain the fingerprint of a protein;
- evaluate the size distribution of certain protein species;
- estimate the degree of hydration of a protein;
- estimate protein concentration in a solution;
- quantify different protein species in a mixture.

5.4

/APPLICATIONS: BIOMEDICAL SCIENCE Pharmaceutical

The prevalence of counterfeit medicines has increased in many countries. These unregulated pharmaceuticals, which may contain the active ingredient as well as additional derivatives, pose significant health risks and, in severe cases, may be fatal [1]. Consequently, the development of reliable analytical methods to identify non-authentic products is essential. Fast Field Cycling

Nuclear Magnetic Resonance (FFC NMR) Relaxometry has been evaluated as a technique to distinguish between authentic and counterfeit Viagra®. Research demonstrated that relaxation was bi-exponential across the entire frequency range for the counterfeit product, whereas the original Viagra® exhibited a single exponential relaxation process [2].

5.5

/APPLICATIONS: BIOMEDICAL SCIENCE Cosmetic

Hyaluronic acid-based dermal fillers are widely used in cosmetic procedures to treat scars, tissue atrophy, and wrinkles, as well as for facial rejuvenation and volumetric enhancement.

Cross linking within the hyaluronic acid matrix is a key modification that determines the viscoelastic and rheological properties of the resulting hydro-gels, enabling customization for specific clinical applications. Commercial hydro-gels generally exhibit cross linking densities between 1 and 5 percent by weight, which correspond to storage moduli (G') of approximately 100 Pa to 600 Pa, depending on the formulation. These parameters affect the injectability, cohesiveness, and resilience of fillers *in vivo*, guiding practitioners in product selection for targeted clinical outcomes.

The study "Mechanism of Water Dynamics in Hyaluronic Dermal Fillers Revealed by Nuclear Magnetic Resonance Relaxometry" [1] examined water mobility in various hyaluronic acid dermal filler formulations using NMR Relaxometry. The results indicated that cross linking density significantly influences the dynamics and distribution of water molecules within hydrogels. Increased

cross linking densities were shown to reduce water diffusion rates, leading to improved gel stability and enhanced functional properties. These findings underscore the value of NMR Relaxometry as a sensitive technique for elucidating the effects of formulation parameters on the functional performance of dermal fillers.

Fast Field Cycling Nuclear Magnetic Resonance (FFC NMR) Relaxometry provides a quantitative approach for investigating the network architecture and dynamics of hyaluronic acid hydrogels. By analysing relaxation behaviour across different magnetic field strengths, FFC NMR yields insights into molecular mobility and cross-link density, both of which are closely associated with the macroscopic rheological properties of these materials. The study "Dynamics of hyaluronan aqueous solutions as assessed by Fast Field Cycling NMR Relaxometry" [2] demonstrated the use of FFC NMR to characterize the molecular dynamics and structural features of hyaluronan. This research offered quantitative evidence supporting the relationship between NMR relaxation behaviour and hydrogel network properties discussed above.

NMR Relaxometry is a sensitive technique for elucidating the effects of formulation parameters on the functional performance of dermal fillers.

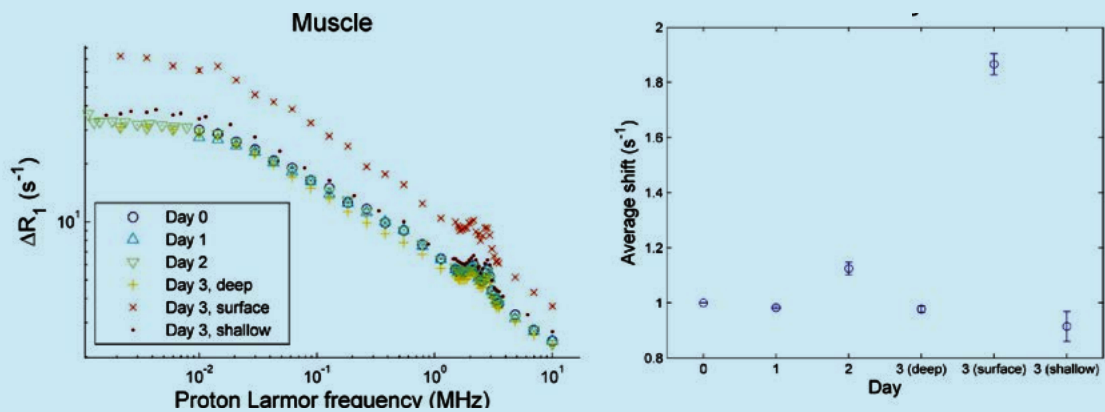
5.6

/APPLICATIONS

Forensics: case study on post-mortem

FFC NMR Relaxometry and FFC-MRI techniques have been used as non-invasive techniques to investigate post-mortem decomposition changes (and thus post-mortem interval, PMI) in swine muscle (FIG. 39A), fatty tissue (FIG. 39B) and bone marrow (FIG. 39C). PMI is critical for the forensic pathologist and investigators probing crimes and suspicious deaths.

NMRD profiles allow qualitative and quantitative analysis of tissue status through features known as quadrupolar peaks. Indeed, muscle tissues showed significant variations (p -value <0.05) over time, though limited in amplitude, while bone marrow samples showed distinct variations (p -value <0.05) with noticeable linear-like results after 24 hours.

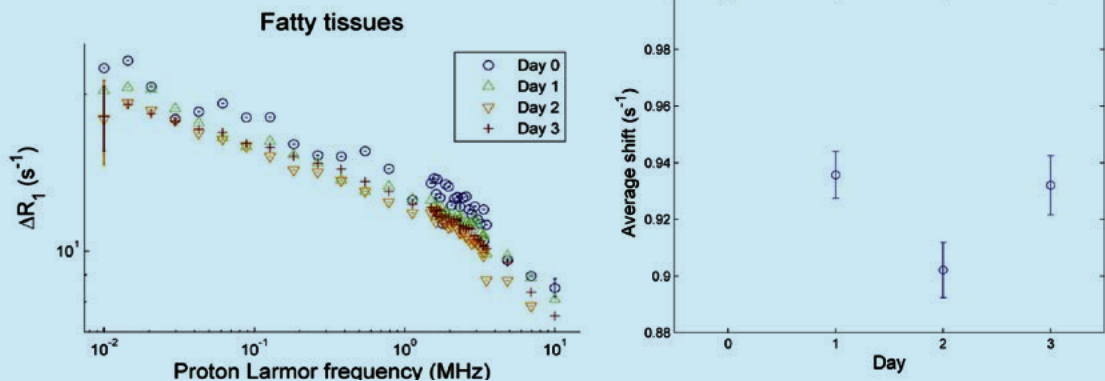


▲ FIG. 39A:

Dispersion curves from the muscles samples.

All samples follow the same trend with quadrupolar peaks around 2.5 MHz.

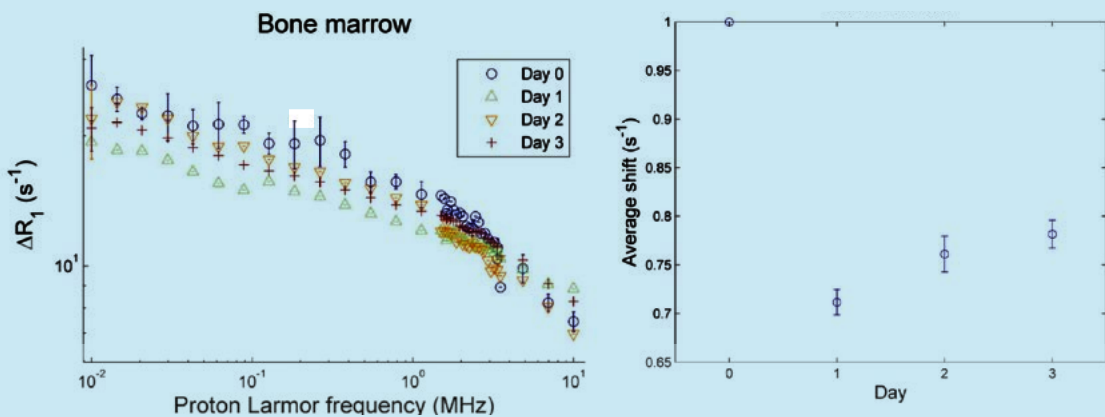
Variations were observed between the samples until day 3.



▲ FIG. 39B:

Dispersion curves of fatty tissues do not present any quadrupolar peaks.

Large variations occurred between day 0 and 1 but little changes occurred later.



▲ FIG. 39C:

Dispersion curves of bone marrow samples.

The profiles, without any significant quadrupolar peaks, look quite similar to fatty tissues.

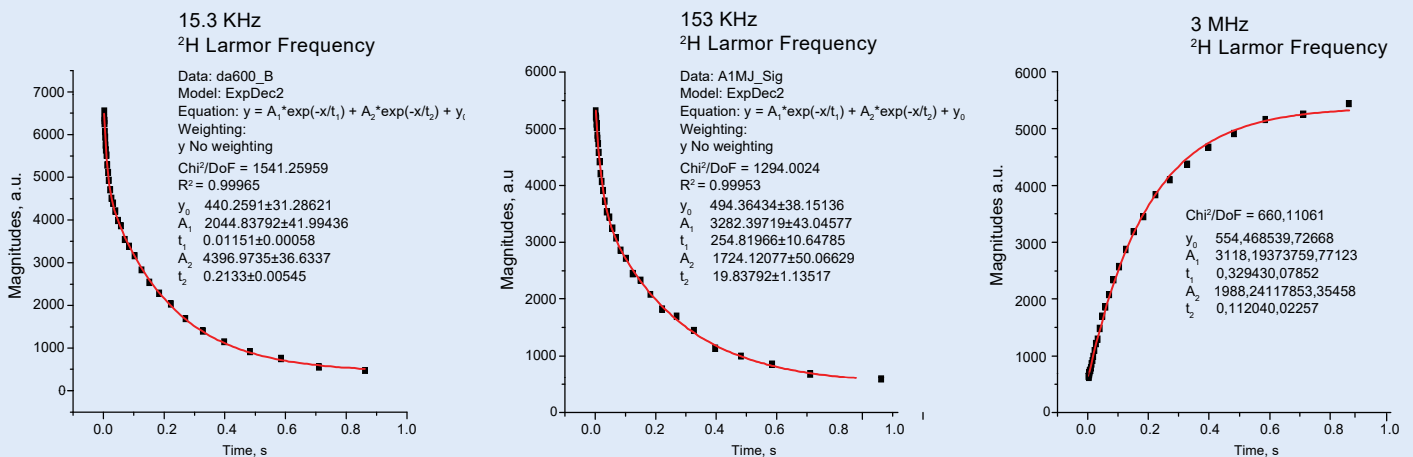
Nevertheless, results are very different from that obtained in fatty tissues.

/APPLICATIONS: HETERONUCLEI

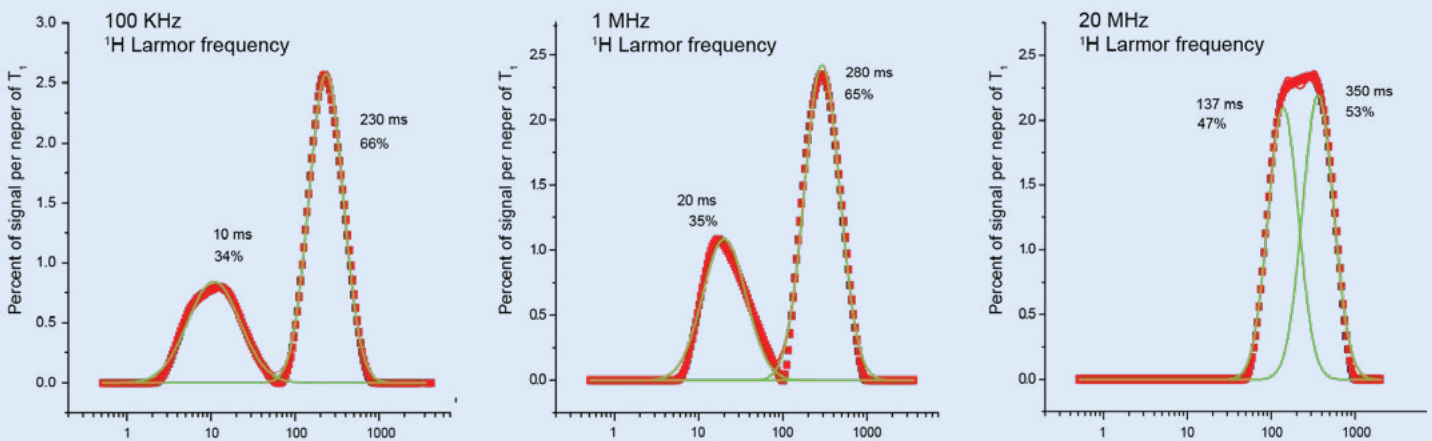
6 Heteronuclei

FFC NMR Relaxometry is mostly used for proton-based analyses (^1H nucleus).

It's possible to study dispersion curves or simpler decay curves of T_1 for other nuclei, such as deuterium (^2H), fluorine (^{19}F), lithium (^7Li), compounds enriched in carbon-13 (^{13}C) and more. Multi-nuclear measurements reveal additional relaxation mechanisms and molecular dynamics [1-3].



▲ FIG. 40: ^2H longitudinal relaxation data at different fields in fuel cell membranes fitted with a bi-exponential fitting algorithm.



▲ FIG. 41: T_1 distributions obtained by means of a Laplace inversion algorithm at 3 different fields.

The possibility to perform multi-nuclear analysis extends the potential of FFC NMR Relaxometry and may prove important for characterization of certain materials or substances and to unlock molecular dynamics information of other key nuclei [4-6].

Up to now, most applications of NMR Relaxometry involved the study of protons due to the low sensitivity of other nuclei (heteronuclei) and to technical difficulties mainly related to the signal-to-noise (S/N) ratio problems caused by the low acquisition frequency.

Fast Field Cycling technique allows the direct observation of heteronuclei with low receptivity and detectability, due to the fact that the magnetic field strength can be switched without the need to vary the frequency of the spectrometer. This multi-nuclear approach expands the potential of Fast Field Cycling NMR applications and allows exploration of the field dependence of the spin-lattice relaxation time T_1 of important heteronuclei within substances, especially at low Larmor frequencies.

This multi-nuclear approach expands the potential of Fast Field Cycling NMR applications and allows exploration of the field dependence of the spin-lattice relaxation time T_1 of important heteronuclei within substances, especially at low Larmor frequencies, where other conventional NMR experiments present severe S/N ratio degradation. The FFC Relaxometry technique allows the investigation of the content and/or the ability to characterize compounds containing important NMR-sensitive nuclei, such as ^2H , ^7Li , ^{13}C , ^{19}F , ^{31}P , ^{23}Na . The presence of such nuclei in a limited number of positions can be explored, therefore providing important structural information. The ability of measuring nuclear spin relaxation, on nuclei other than ^1H , over a wide range of frequencies presents a new advance in the possible applications of TD-NMR and the prospect of new channels of research. In the following, we show the applicability of FFC technique for the acquisition of the longitudinal relaxation rate ($R=1/T_1$) as a function of the applied magnetic field strength of some important heteronuclei.

^2H

DEUTERIUM

In the pictures below, Deuteron T_1 decay curves of fuel cell membranes acquired directly on solid sample are shown. These curves present an evident multi-exponentiality particularly at low field. The relaxation data at three different fields have been evaluated with discrete and continuous methods, using a two components traditional multi-exponential fitting (FIG. 40) as well as by means of a Laplace inversion algorithm (FIG. 41) in order to evaluate the distribution curve of T_1 (UPEN algorithm was used).

In 2016, deuteron FFC NMR Relaxometry has recently been applied for investigating molecular dynamics in molecular liquids and polymers [4].

^{13}C

CARBON

In FIG. 42 and FIG. 43 examples of ^{13}C NMR acquisition at low field are reported, demonstrating the capacity of FFC NMR to investigate the relaxometric behaviour of low NMR-sensitive nuclei at low magnetic field strengths.

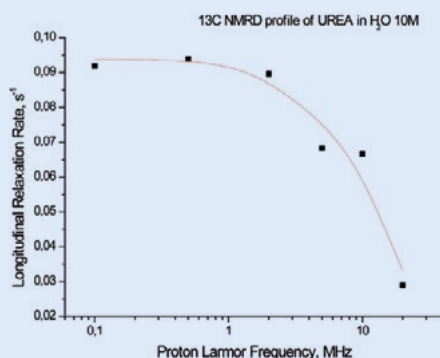
In FIG. 43, it is shown the Longitudinal Relaxation Decay of a ^{13}C -enriched sample of a carboxylic acid that was measured by acquiring a ^{13}C NMR signal at the magnetic field strength of 2.35 mT (equivalent to 0.1 ^1H MHz) and at the temperature of -120°C .

^7Li , ^{19}F

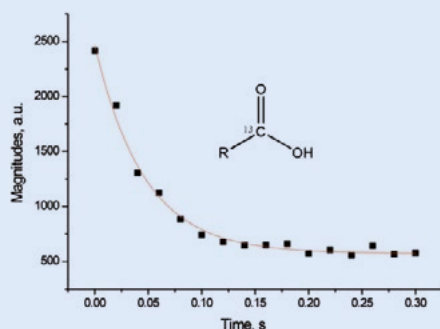
LITHIUM AND FLUORINE

Lithium is an important component of batteries in electronics industry. The fluorine nucleus is often found as part of the organic counter-ion of lithium-based electrolytes for batteries. Being able to study the relaxation rates of these important nuclei could aid the studies for new battery electrolyte and electrode materials (FIG. 44). ^{19}F FFC NMR has been applied to investigate the molecular dynamics of liquid crystals [5].

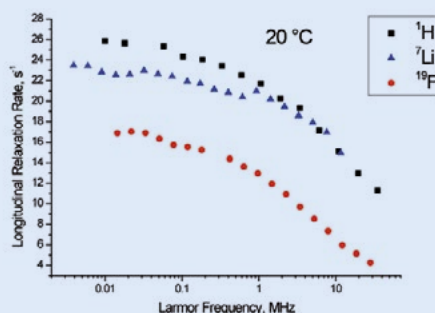
► FIG. 42:
 ^{13}C NMRD profile of urea in water.



► FIG. 43:
 ^{13}C NMR longitudinal decay curve of a carboxylic acid.



► FIG. 44:
NMRD profiles of three different nuclei (^1H , ^7Li and ^{19}F), at 20°C , belonging to the same sample of an electrolyte solution for a battery system.



/APPLICATIONS

7

FFC NMR diffusion measurements

Fast Field Cycling NMR Relaxometry is a versatile technique that can be applied as a method to calculate the diffusion coefficient in a wide range of viscous liquids [1-17] with a range around $10^{-8} > D \text{ (m}^2 \text{ s}^{-1}) > 10^{-14}$ being covered. Diffusion experiments performed on very different materials such as ionic liquids [7, 9, 11, 13], polymers [1, 10], paramagnetic systems [12], vegetable oils [6] and fats [14] confirm that the results from FFC NMR are always consistent with those from conventional pulsed-field-gradient (PFG) NMR methods [FIG. 43].

Thus, FFC NMR Relaxometry emerges as a complementary method to field-gradient NMR diffusometry and has a few advantages compared to it:

- FFC is not limited by the strength of the field gradients;
- FFC instrumentation allows low field data to be obtained that can be used not only for extracting the diffusion coefficient but also other kinds of dynamical parameters and information (obviously depending on the sample being measured);
- SMARtracer FFC relaxometer is less expensive than an NMR spectrometer equipped with gradients required for PFG measurements.

Furthermore, using FFC NMR Relaxometry:

1. One can determine not only the self-diffusion coefficient (as in the gradient methods), but also the relative diffusion coefficient (for instance cation-anion) which provides information about whether the ionic dynamics are correlated.
2. The method favourably bridges the ranges covered by field-gradient NMR diffusometry and quasi-elastic neutron scattering [4]

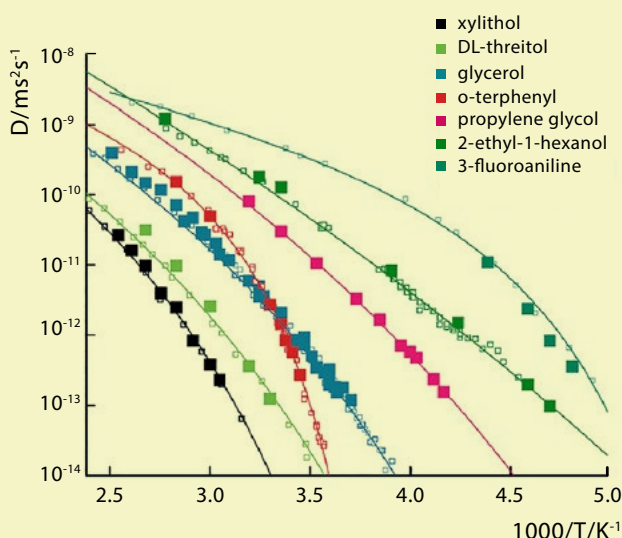
Contrary to the field-gradient techniques, the FFC method is uniquely sensitive to the NMR signal of the nuclear spins belonging to a low-abundant fraction of molecules as long as their molecular dynamics is significantly differentiated from that of the highly abundant molecules.

This is particularly in evidence for liquid molecules adsorbed at pore walls in porous materials where the NMR diffusometry applying PFG NMR plays a minor role, whereas the FFC NMR Relaxometry allows the diffusion of adsorbed molecules to be followed based on specific relaxation mechanisms [11].

Using the information from an NMRD profile it is possible to calculate the value of the diffusion coefficient easily by plotting the relaxation rate R_1 versus the square root of the resonance frequency (FIG. 44).

This dependence is linear at low frequencies and can be fitted (FIG. 44): $R_1 = A + B\sqrt{\omega}$.

Then, from the slope B of the curve, one can determine the diffusion coefficient D, using the relationship: $D = (C/B)^{2/3}$ where the proportionality constant C can be easily calculated – it includes only well-known physical constants. ■



◀ FIG. 44:
This plot shows the good agreement between Diffusion coefficient D obtained from FFC NMR (full symbols) and FG NMR (small open symbols) techniques for several liquids versus reciprocal temperature. (From [1])

Diffusion experiments performed on very different materials such as ionic liquids, polymers, paramagnetic systems and vegetable oils confirm the validity of the FFC NMR method to obtain the diffusion coefficient.

8

/APPLICATIONS: OTHER APPLICATIONS

FFC NMR Relaxometry and DNP

Overhauser Dynamic Nuclear Polarization

^1H FFC Relaxometry is an easy method for the estimation of the DNP enhancement achievable at full electron saturation, as a function of the applied magnetic field.

Dynamic nuclear polarization (DNP) is a promising tool to hyperpolarize nuclear spin, in order to increase the sensitivity of the NMR experiments. Overhauser DNP is ascribed to the magnetization transfer occurring in a magnetic field from unpaired electrons to nuclei through stochastic modulation of the magnetic hyperfine interaction between electron and nuclear spins. The magnetization transfer achievable with a polar-

izing agent, the molecule containing the unpaired electron, largely depends on its mobility. The Overhauser DNP enhancements in fact strongly depend on the correlation times modulating the dipole-dipole interaction between nuclei and unpaired electrons. Therefore, the analysis of the relaxometry profiles of polarizing agents for solution DNP experiments represents a valuable tool for the characterization of their efficiency. DNP is usually performed using nitroxide radicals as polarizing agents. The relaxation profiles of solvent water protons in the presence of nitroxide radicals have been collected (FIG. 45) and analysed to obtain the correlation times and the achievable Overhauser DNP enhancement [1-9].

^1H relaxometry thus represents an easy way to estimate the DNP enhancement achievable at full electron saturation, as a function of the applied magnetic field.

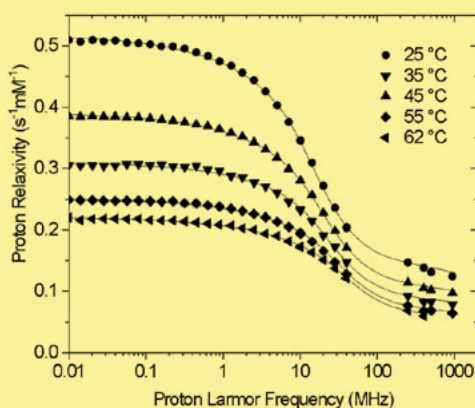
For these nitroxide complexes, correlation times of a few tens of picoseconds are found at room temperature.

These values make the Overhauser DNP enhancements achievable at magnetic fields $>1\text{T}$ relatively small. On the other hand, the enhancement of ^{13}C nuclei in CHCl_3 and CCl_4 solutions can be up to 1000 at magnetic fields of 3 Tesla [5].

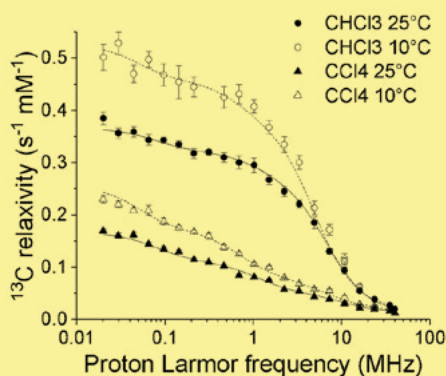
^{13}C relaxometry showed that ^{13}C relaxation of CHCl_3 and CCl_4 is dominated by the contact interaction with the nitroxide radicals occurring through the chlorine atoms, with a 1-ps correlation time (FIG. 46).

The presence of an H atom in CHCl_3 makes the low field relaxivity for CHCl_3 larger than for CCl_4 . The best fit values of the parameters obtained from the ^{13}C relaxation profiles can account for coupling factors of -0.47 (CCl_4) and -0.37 (CHCl_3), as measured at 3.35 T.

► FIG. 45: Solvent water ^1H relaxivity profiles for water solutions of TEMPOL at different temperatures. From the analysis of these profiles the efficiency of this molecule as DNP polarizer can be determined [3].



► FIG. 46: ^{13}C relaxivity of CCl_4 and CHCl_3 solutions with 200 mM TEMPONE informs on the contact terms responsible for DNP [5].



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/APPLICATIONS

9

Prospective Developments in FFC-NMR Research and Industrial Implementation

Industries and researchers are encouraged to further investigate this technology to fully realise its potential.

Beyond conventional relaxation dispersion studies, Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR) facilitates advanced analytical approaches that significantly expand its application scope. Overhauser Dynamic Nuclear Polarisation (DNP) and FFC-based diffusion measurements are robust methodologies for investigating molecular dynamics and transport phenomena. DNP utilises polarisation transfer from unpaired electron spins to nuclear spins, thereby enhancing Nuclear Magnetic Resonance (NMR) sensitivity.

When combined with field-dependent Relaxometry, this technique enables evaluation of dynamic parameters governing electron–nucleus interactions and offers insights into molecular mobility and local environments. The adaptability of FFC-NMR systems at low magnetic fields, typically from a few microtesla to several tens or hundreds of millitesla, is particularly advantageous for studying samples such as biological tissues, soft matter, and complex fluids, where high-field conventional NMR may be less effective. Optimising and characterising polarisation efficiency under these low-field conditions broadens the range of systems that can be accurately investigated.

FFC-NMR diffusion measurements provide an alternative strategy for assessing translational mobility in liquids and soft materials. Analysing the frequency dependence of longitudinal relaxation rates enables the extraction of diffusion coefficients and transport-related parameters without the need for strong magnetic field gradients.

This methodology is particularly effective in low-field regimes and in systems where conventional gradient-based techniques are limited. Collectively, these approaches demonstrate the versatility of FFC-NMR as a comprehensive platform for investigating molecular motion, transport processes, and signal enhancement mechanisms beyond standard relaxometry applications.

The applications presented in this booklet represent only a subset of the potential uses of FFC-NMR, and its full capabilities remain to be explored. Although Nuclear Magnetic Resonance Dispersion (NMRD) curve examples are included, the broader potential of FFC-NMR is often overlooked due to its association with conventional spectroscopy. FFC-NMR complements not only NMR spectroscopy but also other analytical technologies such as rheology. It can measure T_1 as a function of B_0 field, as well as T_2 and diffusion, supporting advanced mathematical data analysis and two- or multi-dimensional correlations. To extract meaningful parameters from FFC-NMR data, researchers commonly employ analysis techniques such as the inverse Laplace transform for relaxation time distributions and multivariate analysis for interpreting complex datasets. These mathematical and computational approaches enable users to fully leverage the detailed information provided by FFC-NMR measurements.

This booklet presents applications in traditional sectors such as healthcare, materials science, the chemical industry, and research, and also highlights uses in non-traditional industries, including food and agriculture, forensics, environmental science, cultural heritage, and archaeology. For instance, FFC-NMR has been used to determine water mobility and molecular composition in various samples.

Applications in emerging sectors such as quantum computing, information technology, energy storage and batteries, and space science remain largely unexplored. Preliminary studies indicate that FFC-NMR can characterise lithium-ion transport mechanisms in battery electrolytes, providing valuable insights for next-generation energy storage solutions.

FFC-NMR holds significant potential in traditional industries such as pharmaceuticals, food, feed, beverages, and cosmetics, where it can serve as a primary technology for quality control and assurance.

Industries and researchers are encouraged to further investigate this technology to fully realise its potential.

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Fast Field Cycling NMR Relaxometry Technique: an introduction

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From molecular dynamics to practical applications

2 FFC NMR in material science

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This booklet compiles selected scientific studies that exemplify the breadth of ongoing research and development in Fast Field-Cycling Nuclear Magnetic Resonance (FFC-NMR) and delineates the current scope and scientific relevance of FFC-NMR methodologies.

FFC-NMR provides a means to probe molecular motion by correlating relaxation phenomena with underlying physicochemical properties. It allows the detection of slow motional processes and the resolution of distinct dynamic regimes that remain inaccessible to standard fixed-field NMR techniques.

The studies compiled herein demonstrate the enhanced experimental versatility and scientific impact of FFC-NMR in both fundamental investigations and applied research contexts. We aim to provide a representative overview of key advances in material sciences, pharmaceuticals, food sciences, chemical engineering and many more research topics, with particular emphasis on the experimental and theoretical contributions that have shaped the field.