



13th FFC NMR Conference

BOOK OF ABSTRACTS

10-13 Sep. 2024

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Agricultural, Food and Forest Sciences

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CONFERENCE PROGRAM

Tue 10/09		
8.30-12.30	• Arrivals, welcoming • Late registrations	
13.30-13.45	Congress opening and Institutional addresses	
	Theory and Tutorial session opening – Chair S. STAPF	
13.45-14.45	Prof. Danuta Kruk – (University of Warmia and Mazury in Olsztyn, Poland): "Theoretical background of relaxation (I(w), G(t), different relaxation mechanisms."	T1
14.45-15.45	Prof. Esteban Anoardo – (LaRTE- FaMAF – Instituto de Física Enrique Gaviola) CONICET, Universidad Nacional de Córdoba, Argentina: "Hardware and technical issues, problems, limitations, hands-on experience FFC theoretical introduction."	T2
15.45-16.15	Coffee break and Poster session	
16.15-17.15	Prof. Giacomo Parigi – (Magnetic Resonance Center and Department of Chemistry, University of Florence): "Fast Field Cycling application (I): contrast agents and paramagnetic systems."	T3
17.15-18.15	Prof. Pellegrino Conte – (Department of Agricultural, Food and Forestry Sciences, University of Palermo): "Fast Field Cycling application (II): environmental topics."	T4
Wed 11/09		
8.30-8.45	Welcoming - Scientific program presentation Chair: G. Ferrante & A.L. Rollett	
8.45-9.30	Opening plenary lecture – Professor Emeritus Silvio Aime (Department of Molecular Biotechnology and Health Sciences – University of Turin): "Through several decades of FFC NMR relaxometry, from research to applications and beyond... <i>Quo Vadis Relaxometry?</i> "	PL1
9.30.-10.15	Invited lecture - Eva Jakab Toth (Centre de Biophysique Moléculaire – CNRS, Orléans, France): "Towards safer and more specific MRI agents."	IL1
10.15-10.30	Oral presentation – Marco Ricci (Department of Science and Technological Innovation of the University of Eastern Piedmont "A. Avogadro", Alessandria, Italy): "Paramagnetic chelates embedded in nanogels as MRI probes."	O1
10.30 -10.45	Oral presentation – Giacomo Parigi (Magnetic Resonance Center and Department of Chemistry, University of Florence): "NMR Relaxometry of paramagnetic proteins as MRI contrast agents."	O2
10.45-11.15	Coffee break and Poster session Chair E. Anoardo & D. Brougham	
11.15-11.30	Oral presentation – Quoc Lam Vuong (University of Mons, Belgium): "Theory of proton relaxation induced by superparamagnetic nanoparticle: a classical approach to NMRD."	O3
11.30-11.45	Oral presentation – Adam Kubrak (Magnetic Resonance Center and Department of Chemistry, University of Florence):	O4



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	"Relaxometric studies to reveal potential theranostic properties of human transthyretin conjugated with GD(iii) complexes."	
11.45-12.15	Keynote lecture – Lionel Broche (School of Medicine, Medical Sciences and Nutrition - University of Aberdeen, Scotland): "FCI hardware and applications"	KL1
12.15-12.30	Oral presentation – Faisal Sheraz Shah (University of Warmia and Mazury in Olsztyn, Poland): "Spin Relaxation Dynamics in Haemoglobin Solutions: A Study of Molecular Interactions."	O5
12.30-12.45	Oral presentation – Kahinga Kamau (University of Warmia and Mazury in Olsztyn, Poland): "NMR insights into trypsin's molecular dynamics."	O6
12.45-13.00	Oral presentation – Evrin Umut (Dokuz Eylul University, School of Healthcare, Department of Medical Imaging Techniques, Turkey): "slow diffusion in sucrose hydrogel microparticles as potential sustained drug delivery vehicles."	O7
13.00-14.00	Lunch	
	Chair D. Faux & A. Strate	
14.00-14.45	Invited lecture: Carlos Mattea (Technische Universität Ilmenau, Germany): "Fast Field Cycling studies of molecular dynamics in soft matter materials."	IL2
14.45-15.00	Oral presentation – Emilia Pelegano-Titmuss (Hunter College – CUNY, New York): "Type IV Eutectic Electrolytes for Lithium-Ion Batteries."	O8
15.00-15.15	Oral presentation – Paolo Arosio (Department of Physics, University of Milan): "Modulation of the nuclear relaxation properties in iron oxide core-shell nanoparticles."	O9
15.15-15.30	Oral presentation – Giselle de Araujo Lima e Souza (Hunter College – CUNY, New York): "Understanding ion dynamics in boron nitride ionogel electrolytes."	O10
15.30 –16.00	Keynote lecture – Villiam Bortolotti (Department of Civil, Chemical, Environmental and Materials Engineering, University of Bologna): "Introduction to the FFC NMR relaxometry applied to confined fluid"	KL2
16.00-16.30	Coffee break and Poster session	
	Chair C. Mattea & J. Ward-Williams	
16.30-16.45	Oral presentation – Elzbieta Masiewicz (University of Warmia and Mazury in Olsztyn, Poland): " ¹ H NMR relaxometry and a variety of "simple" ionic liquids."	O11
16.45-17.00	Oral presentation – Anne Strate (University of Rostock, Germany): "Exploring rotational and translational dynamics in ionic liquids: Insights from FFC NMR relaxometry and MD simulations."	O12
17.00-17.15	Oral presentation – Corentin Boulogne (University of Lorraine, France): "NMR methods to characterize structure and dynamics of supramolecular hydrogels."	O13
17.15-17.30	Oral presentation – Bulat Gizatullin (Technische Universität Ilmenau, Germany): "Anomalous ¹ H and ² H NMR relaxation in conventional porous silica."	O14
17.30-17.45	Oral presentation – Anastasia Nagmutdinova (Department of Civil, Chemical, Environmental and Materials Engineering, University of Bologna): "Cement hydration of a different composition followed by FFC NMR."	O15
18.00–20.00	Excursion (optional) – Guided walking evening tour Palermo Historical center	



Thu 12/09		
8.30-8.45	Welcoming - Scientific program presentation Chair R. Anedda & S. Baroni	
8.45-9.30	Invited lecture - Mecit Halil Oztop (Department of Food Engineering, Middle East Technical University, Turkey): "Can FFC NMR Relaxometry Substitute Conventional Food Analysis Techniques?"	IL3
9.30.-9.45	Oral presentation – Madeleine Rhodes (University of Aberdeen, Scotland): "Surface topology of fibrin network from FFC-NMR dispersion profiles."	O16
9.45-10.00	Oral presentation – Tomaž Apih (J. Stefan Institute, Slovenia): "Cross relaxation spectroscopy on Fast-Field Cycling Relaxometer"	O17
10.00-10.15	Oral presentation – Sigfried Stapf (Technische Universität Ilmenau, Germany): "Relaxation, diffusion, and DNP approach to binary liquids in porous glass: to mix or to demix?"	O18
10.15-10.30	Oral presentation – Anne Laure Rollet (PHENIX – Sorbonne University, Paris, France): "Evidence of the change of transport mechanism in ionic liquids containing Li ⁺ and La ³⁺ ."	O19
10:30-11:00	Coffee break and Poster session	
	Chair G. Parigi & E. Toth	
11.00-11.30	Keynote lecture – Roberto Anedda (Porto Conte Ricerche srl, Alghero SS): "NMR relaxometry for dairy quality control: opportunities and challenges"	KL3
11.30-11.45	Oral presentation – Zlenseu Ruth Tan (PHENIX- Sorbonne University, Paris, France): "Tips and tricks for investigating water proton dynamics in hydrogel/clay composite materials through Nuclear Magnetic Relaxation Dispersion (NMRD)."	O20
11.45-12.00	Oral presentation – Simona Baroni (Department of Molecular Biotechnology and Health Sciences, University of Turin): "Cancer assessment by relaxometry."	O21
12.00-12.15	Oral presentation – Lyns Verel Che Dji (University of Lorraine, France): "Longitudinal NMRD profile as a tool to characterize and predict the efficacy of phosphonate based-SPIONs as MRI contrast agents."	O22
12.15-12.30	Oral presentation – Amnah Alamri (University of Aberdeen, Scotland): "IN-VIVO and EX-VIVO detection of colorectal cancer at ultra-low field using Fast Field-Cycling methods."	O23
12:30-14:00	Lunch	
	Chair D. Kruk & P. Lo Meo	
14.00-14.40	Invited lecture – Pellegrino Conte (Department of Agricultural, Food and Forestry Sciences, University of Palermo): "Environmental applications of Fast Field Cycling NMR relaxometry."	IL4
14.40-15.00	Oral presentation – Alessandro Nucera (Department of Science and Technological Innovation of the University of Eastern Piedmont "A. Avogadro", Alessandria, Italy): "Relaxometric investigations of Fe(III)-based complexes as T ₁ -weighted Contrast Agents."	O24
15.00-15.15	Oral presentation – Giovanni Vito Spinelli (Department of Mathematics, University of Bologna): "Advancing NMR Analysis: Deep Neural Network Solutions for Inverting NMRD Profiles with Quadrupolar Dips"	O25



15:15-15:30	Oral presentation – Stan Sykora (Extra-Byte S.r.l.) “Evaluation of relaxometric data by rex: classical and modern procedures.”	O26
15.30-16.00	Coffee break and Poster session	
	Panel discussion – Participation at the Round Table Chair: Dr. Manoj Nimbalkar	
16.00-17.20	Dialogue with Invited speaker – Silvio Aime, Eva Toth, Carlos Mattea, Mecit Halil Oztop, Pellegrino Conte	
17.20-17.30	Panel discussion conclusion	
17.30-18.00	<i>Celebration of the 40th Stelar’s anniversary</i>	
18.45-19.00	Meeting on the way for a social dinner	
19.30-20.30	Happy hour + Social dinner at Hotel Borsa	
Fri 13/09		
8.30-8.45	Welcoming - Scientific program presentation Chair P. Conte & D. Chillura Martino	
9.00-9.15	Oral presentation – Danuta Kruk (University of Warmia and Mazury in Olsztyn, Poland): “Understanding NMR relaxation theory – how to create new equations and what for?”	O27
9.15-9.30	Oral presentation – Lucas Siemons (Department of Chemistry, LBM, CNRS, École Normale Supérieure, PSL University, Sorbonne University, Paris, France): “Ultrafast High-Resolution Relaxometry from 100 μ T to 23.5 T to unravel internal motions in proteins and nucleic acids.”	O28
9.30-9.45	Oral presentation – Michele Pierigé (University of Pisa): “Effect of tackifying resins on SBR dynamics by means of ^1H Field cycling NMR relaxometry.”	O29
9.45-10.00	Oral presentation – David Faux (School of Mathematics and Physics, University of Surrey, UK): “Maximising value from Fast Field Cycling NMR with the 3TM software.”	O30
10:00-10:30	Coffee break and Poster session	
10.30-11.00	Best poster award ceremony Greetings	
11.00-11.50	Closing	



POSTER SESSION

NMR relaxometry to monitor in situ the loading of ion exchange resins with Ni^{2+} and Cu^{2+} ions during a column experiment	P1
Developing Copper(II) and Gadolinium(III) Coiled Coils as MRI Contrast Agent	P2
FFC NMR Relaxometry to unveil structural and functional features of Ceramic raw materials from North Morocco	P3
Exploring the competitive Adsorption of water in mesoporous with NMR relaxometry	P4
Simulation of transverse nuclear magnetic relaxation induced by superparamagnetic nanoparticles with a semipermeable coating	P5
Monte Carlo simulations of the T_2 relaxivity induced by cubic shaped superparamagnetic nanoparticles	P6
Fast-field-cycling NMR Relaxometry and Biometric Analyses for the Evaluation of Hemp Inflorescences Traceability	P7
Impact of Simulated Fire on Soil Properties: A FFC-NMR Investigation	P8
Activated carbons from cherry stones: a green strategy for organic pollutants photodegradation	P9
Oxidative functionalization assessment of a poplar biochar	P10
FFC-NMR studies on Sicilian dairy products	P11
FFC-NMR characterization of nanosponge materials	P12
The TRL scale and the development of FFC-NMR apparatus	P13
Optimized sulfamido-carborane-conjugated Gd complex as a theranostic probe for MRI-guided BNCT in mesothelioma therapy	P14
Inverse temperature dependence of water relaxation in inulin and karragennan microgels: a chemical exchange dominated regime	P15
FFC NMR relaxometry as a tool for detecting the quality of biotechnological drugs	P16
Latest achievements of the DNP FFC technique to study complex systems	P17
FFC-NMR Relaxometry of Perfluorosulfonic Acid Ionomers and Their Perfluorosulfonyl Fluoride Precursors Membranes	P18
Myoglobin in motion: ^1H relaxation techniques unveiled	P19
Non-invasive Characterization of Cholesterol Solid; T_1 Relaxation, Solid Content, and Phase Transition Using TD-NMR	P20
Evaluation of radical degraded lubricant	P21
Dynamical properties of biomaterials - Insight from ^1H FFC-NMR and TD-NMR Relaxation	P22
Comparison of Natural and Agglomerated Cork Stoppers in Dry and Soaked States	P23
Towards FFC probing samples at shorter echo and FID times	P24
^1H relaxation features of endometrium tissues	P25
Molecular insights into milk composition using nuclear magnetic resonance relaxometry	P26



OPENING PLENARY LECTURE



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Through several decades of FFC NMR relaxometry, from research to applications and beyond... Quo Vadis Relaxometry?

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The acquisition of the longitudinal relaxation times over an extended range of magnetic field strength (NMRD profiles) paves the way to the identification of the motions that drive spin relaxation. The access to Fast Field Cycling (FFC) relaxometers allows to obtain unique information on the molecular dynamics in a number of substances and materials. The application of FFC relaxometry has brought important achievements in many research fields from biomedicine to material sciences. In particular the study of the molecular dynamics of water protons brings fundamental information to the development of the MRI field. A paradigmatic example is represented by the *in vitro* characterization of MRI contrast agents whose NMRD profiles allows the accurate assessment of the determinants of their relaxivity (the relaxation enhancement brought to water protons by the contrast agent). These studies are at the basis of the optimized design of the new generation of relaxation enhancers [1] Moreover the measurement of T1 at low magnetic fields allows to extract relevant information on the exchange of water across the cellular membrane, an information hardly accessible by other techniques that is associated to the cellular metabolism, an information of paramount importance in the characterization of tumor's aggressiveness [2]. The NMRD profiles of biological tissues provides also the access to the occurrence of *quadrupole peaks* (QPs) – significant increases in the measured relaxation rate ($R1 = 1/T1$) in the presence of immobilized protein molecules, at magnetic fields where the proton NMR frequency and the ¹⁴N nuclear quadrupole resonance (NQR) frequency coincide. This peculiar feature has been investigated either to extract new information on the pathophysiology of the investigated tissues either for the design of a new class of metal-free, frequency encoding MRI contrast agents [3]. Another area where the information related to water proton dynamics brought seminal contributions is represented by the characterization of foodstuffs (cheese, wines, vineyards, etc..) whose NMRD fingerprint provides a unique contribution to define their origin.

FFC relaxometry still have to show its potential in many other fields. One may foresee that important results may come from the detection of heteronuclei, in particular when associated to hyperpolarization as well as its ability to report on water dynamics may prompt further studies in the field of hydrogel based devices, a field currently under intense scrutiny. Finally the improved knowledge that will be gained about the molecular interactions and cycling across different compartments is expected to advance our understanding on the origin of the endogenous contrast in MR images.

References

- [1] F.Hasallari, C.Carrera, E. Cavallari, E.Gianolio and S. Aime *Inorg. Chem. Front.*, 2024 and refs therein.
- [2] E. Di Gregorio, C.Papi, L.Conti, A.Di Lorenzo, E.Cavallari, M. Salvatore, C. Cavaliere, G.Ferrauto, S.Aime. *Angew Chem Int Ed Engl.* 2024 Feb 5;63(6):e202313485
- [3] S. Geninatti Crich, S. Baroni, R.Stefania, L. M. Broche, N. Senn, D. J. Lurie, J. J. Ross, and S.Aime. *Angew. Chem. Int. Ed.* 10.1002/anie.202011513



INVITED LECTURES

TOWARDS SAFER AND MORE SPECIFIC MRI AGENTS

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Metal complexes are widely used as imaging probes in various imaging modalities. One important field in molecular imaging involves the detection of physico-chemical parameters of tissues, concentration of ions, metabolites, etc. by applying smart, activatable imaging probes that are responsive to the specific parameter to detect. Magnetic Resonance Imaging is particularly well adapted to the design of responsive probes. The efficacy (relaxivity) of the probe has to be selectively influenced, based on coordination chemistry concepts, by the particular biomarker that we wish to detect. We have been developing potential smart contrast agents to detect metal ions, redox state and enzyme activity [1].

Following recent toxicity concerns related to the use of Gd³⁺ complexes in MRI, there is an active research for more biocompatible alternatives. Among these, Mn²⁺ chelates have great promise. However, the lower charge and the lack of ligand-field stabilization energy for Mn²⁺ are not favorable to achieve high thermodynamic stability, and the highly labile nature of Mn²⁺ sets an even more difficult challenge to meet. We have been exploring rigid and pre-organized ligand structures which are particularly interesting in this respect [2].

In this talk, some representative examples from these fields will be discussed, with an emphasis on the importance of FFC relaxometric approaches for the characterization of the probes.

References

- [1] (a) S. M. A. Pinto, M. J. F. Calvete, M. E. Ghica, S. Soler, I. Gallardo, A. Pallier, M. B. Laranjo, A. M.S. Cardoso, M. M. C. A. Castro, C.M.A. Brett, M. M. Pereira, É. Tóth, and C. F. G. C. Galdes, A Biocompatible Redox MRI Probe Based on a Mn(II)/Mn(III) Porphyrin, *Dalton Trans.* 2019, 48, 3249-3262. (b) M. Bödenler, K. P. Malikidogo, J.-F. Morfin, C. S. Aigner, É. Tóth, C. S. Bonnet, H. Scharfetter, High-Field Detection of Biomarkers with Fast Field-Cycling MRI: The Example of Zinc Sensing, *Chem. Eur. J.* 2019, 25, 8236 –8239. (c) S. M.A. Pinto, A. R.R. Ferreira, D. S.S. Teixeira, S. C.C. Nunes, A. L.M. Batista de Carvalho, J. M. S. Almeida, Z. Garda, A. Pallier, A. A.C.C. Pais, C. M.A. Brett, É. Tóth, M. P.M. Marques, M. M. Pereira and C. F.G.C. Galdes, Fluorinated Mn(III)/(II)-Porphyrin with Redox-Responsive 1H and 19F Relaxation Properties, *Chem. Eur. J.* 2023, 29, e202301442. (d) R. Jouclas, S. Laine, S. V. Eliseeva, J. Mandel, F. Szeremeta, P. Retailleau, J. He, J.-F. Gallard, A. Pallier, C. S. Bonnet, S. Petoud, P. Durand and É. Tóth Lanthanide-Based Probes for Imaging Detection of Enzyme Activities by NIR Luminescence, T1- and ParaCEST MRI *Angew. Chem. Int. Ed.* 2024, doi.org/10.1002/anie.202317728.
- [2] (a) D. Ndiaye, M. Sy, A. Pallier, S. Mème, I. de Silva, S. Lacerda, A. M. Nonat, L. J. Charbonnière and É. Tóth, *Angew. Chem. Int. Ed.* 2020, 59, 11958. (b) P. Cieslik, P. Comba, B. Dittmar, D. Ndiaye, É. Tóth, G. Velmurugan, H. Wadepohl, *Angew. Chem. Int. Ed.* 2022, 61, e202115580, (c) D. Ndiaye, P. Cieslik, H. Wadepohl, A. Pallier, S. Mème, P. Comba, É. Tóth, Mn²⁺ bispidine complex combining exceptional stability, inertness and MRI efficiency, *J. Am. Chem. Soc.* 2022, 144, 22212. (d) Z. Garda, F. Szeremeta, O. Quin, E. Molnár, B. Váradi, R. Cléménçon, S. Mème, C. Pichon, G. Tircsó, E. Toth, Small, Fluorinated Mn²⁺ Chelate as an Efficient 1H and 19F MRI Probe, *Angew. Chem. Int. Ed.* 2024, <https://doi.org/10.1002/anie.202410998>



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FAST FIELD CYCLING STUDIES OF MOLECULAR DYNAMICS IN SOFT MATTER MATERIALS

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This Fast field cycling (FFC) NMR is a powerful technique in material science, offering detailed insights into molecular dynamics, structural properties, and phase behavior in various materials, including polymers, liquid crystals, porous structures and nanomaterials. FFC provides valuable insights into the relaxation mechanisms of materials by studying NMR relaxation times as a function of the magnetic field, making it particularly useful for investigating molecular dynamics over a wide range of timescales, providing a unique technique to probe molecular motion and structural changes in confined and complex fluids, giving a broader picture of molecular dynamics than conventional NMR. However, FFC NMR requires specialized and sometimes costly instrumentation, and the interpretation of its data can be complex, necessitating detailed models of molecular dynamics and relaxation mechanisms.

In this contribution, applications related to our work in polymer dynamics, and molecular dynamics in liquids under confinement will be shown. Ionic liquid (ILs) solvents combined with polymers offers the possibility of new applications in the field of material science for energy storage (batteries, electrolytes, supercapacitors). ILs can be used in polymer electrolyte membrane fuel cells and solid batteries. The confinement of ILs in polymer matrices, retaining transport and flexibility inside these systems, remains still as an important challenge. FFC applied to the study of molecular dynamics of several ILs consisting of organic cations and different types of anions incorporated in polymer matrices will be shown, together with studies of the mobility and interactions of stable organic radicals (nitroxide) with polymers and ILs, with the help of FFC, EPR and DNP, showing mechanisms of electron polarization transfer to the NMR active nuclei in the system.

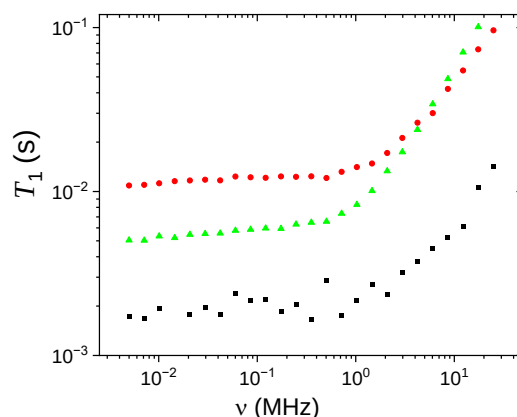


Fig. 1. ¹H (red), ¹⁹F (green) and ⁷Li (black) NMRD experiments LiTf₂N salt with the IL Emim TF₂N with TEMPO radical.

References

- [1] B. Gizatullin, C. Mattea, S. Stapf, T. Wissel, G. Buntkowsky, NMR Relaxation Dispersion of Liquids Adsorbed on Modified Surfaces of SBA-15 Mesoporous Silica, *J. Phys. Chem. C*, 128, 8785-8796 (2024)
- [2] B. Phani Kumar, N. Lobo, C. Mattea, S. Stapf, Exploring Crystal-Phase Molecular Dynamics of the Low-Viscous Mesogen 6CHBT: A Combined FFC and High-Field NMR Relaxometry Investigation, *J. Phys. Chem. B*, 128, 3997-4007 (2024)
- [3] K. Lindt, N. Fatkullin, C. Mattea, J. Allgaier, S. Stapf, M. Kruteva, Spin Relaxation and Dynamics of Ring Poly(ethylene oxide) in Melts, *Macromolecules*, 57, 3765-3775 (2024)
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- [5] B. Gizatullin, C. Mattea, I. Shikhov, C. Arns, S. Stapf, Modelling molecular interactions with wetting and non-wetting rock surfaces by combining Electron Paramagnetic Resonance and NMR relaxometry, *Langmuir* 38, 11033 (2022)

Can FFC NMR Relaxometry Substitute Conventional Food Analysis Techniques?

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Food quality, safety, and authenticity are critical concerns in the food industry, necessitating precise and reliable analytical techniques. Traditional methods, including chromatography and various forms of spectroscopy such as Near-Infrared (NIR), Mid-Infrared (Mid-IR), Raman, and Fourier Transform Infrared (FTIR) spectroscopy, have been widely employed to analyze food composition and structure. These techniques, along with Time-Domain Nuclear Magnetic Resonance (TD-NMR), are non-destructive and provide valuable insights into food properties. However, they may not offer a comprehensive understanding of the complex nature of food matrices. Fast Field Cycling Nuclear Magnetic Resonance (FFC NMR) Relaxometry is emerging as an innovative alternative, offering detailed insights into molecular dynamics and structural properties while retaining the non-destructive advantage. FFC NMR Relaxometry may have the potential to replace or complement conventional food analysis techniques, including both non-destructive methods like spectroscopy and TD-NMR, and destructive techniques such as chromatography. As a non-destructive technique, FFC NMR provides comprehensive data on moisture content, fat composition, protein structures, and carbohydrate dynamics within food matrices. Its ability to characterize food microstructure and molecular interactions distinguishes it from other techniques. However, challenges remain, including high costs, complex data interpretation, and difficulties in standardizing methods across diverse food types. The inherent complexity of food systems further complicates the development of universal models, presenting a significant barrier to the widespread adoption of FFC NMR. In this talk, we will discuss the advantages of FFC NMR, alongside its current limitations compared to traditional methods. We will also address the challenges involved in standardizing FFC NMR methods and improving data analysis to better model complex food systems. Overcoming these barriers is crucial for advancing the application of FFC NMR in routine food quality control. We will present examples, discuss the challenges, and discuss the steps needed to further develop and integrate this technique into the food industry.

Environmental applications of Fast field cycling NMR relaxometry

Pellegrino Conte^{1*}, Calogero Librici¹, Ettore Madonia¹, Antonella Di Vincenzo², Paola Bambina², Elena Piacenza², Delia Francesca Chillura Martino², Paolo Lo Meo²

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Fast Field Cycling (FFC) Nuclear Magnetic Resonance (NMR) relaxometry is an advanced technique with significant applications in environmental science. FFC NMR relaxometry allows for the measurement of nuclear spin relaxation over a wide range of magnetic field strengths, offering insights into molecular dynamics and interactions in heterogeneous systems. This versatility makes it particularly useful in studying soils, sediments, and aquatic systems, where complex interactions between water, organic matter, and minerals play crucial roles in environmental processes.

One of the primary applications of FFC NMR in environmental science is the investigation of soil properties and water content. By analyzing the relaxation rates of hydrogen nuclei in water, it is possible to infer soil moisture levels, pore size distribution, and interaction of water with organic and mineral components. This is essential for understanding water retention and movement in soils, which are critical for agricultural productivity and groundwater management.

Additionally, FFC NMR relaxometry is employed to study the binding of pollutants, such as heavy metals and organic contaminants, to soil and sediment particles. By examining the relaxation behavior of nuclei associated with these pollutants, it is possible to assess their mobility, bioavailability, and potential environmental impact. This information is crucial for developing strategies for soil remediation and pollution mitigation.

Moreover, FFC NMR can be used to monitor the degradation of organic matter in natural waters, providing insights into carbon cycling and the health of aquatic ecosystems. The technique's ability to distinguish between different types of molecular environments makes it invaluable for characterizing the composition and dynamics of natural organic matter in water bodies.

Overall, FFC NMR relaxometry is a powerful tool in environmental science, enabling detailed studies of complex systems that are vital for environmental monitoring and management.



KEYNOTE LECTURES

FCI HARDWARE AND APPLICATIONS

Dr Lionel M Broche

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Field-Cycling Imaging (FCI) makes it possible to measure T1 NMR dispersion profiles in vivo and non-invasively directly on patients. This technology derives from MRI but requires radical design changes that impact almost all aspects of the device¹. While this brings some important challenges, it also opens wide avenues for clinical applications. This presentation will provide an overview of the state of our FCI research to date.

We have been using our Mark 2 prototype system successfully over the past 6 years, with continuously improving methodology and image quality. Current FCI examinations last between 45 and 60 minutes to measure four magnet fields in the NMR dispersion profiles, with five evolution times each. This has shown increased contrast levels at fields typically below 20 mT, as shown in the analysis of brain stroke² and various cancers.

In brain stroke, T1 contrast below 20 mT can differentiate between ischemic and haemorrhagic strokes and can also separate areas affected by small vessel diseases, a common stroke mimic on MRI scans. FCI of cancer shows different types of image contrast for different tumour types depending on the organ and, for some tumour types, on the invasiveness of the tumour. The interpretation of the NMRD profiles remain challenging but various works by other groups has shown that transmembrane water exchanges explain some of these observations^{3,4}, and recent results in colorectal cancer indicates some links with protein production and ATP.

Data analysis methods have also improved, with the integration of advances fitting methods to improve image quality, as well as deep learning methods for noise filtering. This showed large improvements in the quality of the T1 maps.

Finally, a new FCI scanner has been commissioned in the Aberdeen Royal Infirmary that overcomes some of the major technical limitations of the Mark 2 scanner. In particular, it shows large improvements in image quality thanks to an improved flexible coil array system that operates at 8.5 MHz⁵, as well as a 60 cm diameter bore that compares with standard clinical MRI scanners. This system has been developed to be integrated in clinical settings and can be replicated.

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Introduction to the FFC NMR relaxometry applied to confined fluids

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As it has been demonstrated in several scientific works, the investigation of the dependence on the Zeeman field (external polarization magnetic field B_0) of the Nuclear Magnetic Resonance (NMR) longitudinal relaxation time, as well as the transverse relaxation time, offers a rather direct and detailed insight into events at the molecular level (i.e. molecular dynamics) that cannot be obtained with other standard techniques, especially in the case of slow dynamics processes.

This approach, implemented with the Fast Field Cycling (FFC) NMR relaxometry technique, allows the creation of Nuclear Magnetic Resonance Dispersion (NMRD) profiles that can be effectively used to study fluids confined in complex systems.

Every kind of porous medium presents (at a specified temperature) a peculiar NMRD profile that fully characterizes it. Therefore, the NMRD profile is a useful “fingerprinting” tool to characterize many substances.

The FFC technique applies to several fields, including, just to list a few, material science (polymers, saturated porous media), food science (meat, milk-based products), pharmaceutical, and many more. Using a very generalized and simplified definition of a porous medium as a material consisting of a skeletal portion (often called the “matrix” or “frame”) containing pores (voids), typically filled with a fluid (either liquid or gas), then many everyday materials can be categorized as porous media and FFC-NMR is a useful non-invasive and non-destructive tool for their characterization.

Together with proper data acquisition, the data inversion is also a key factor to correctly identify and understand molecular dynamics phenomena occurring in a substance. Over time, a wide variety of mathematical models have been developed to interpret the results of FFC measurements performed on samples of different natures[1].

In a nutshell, this presentation aims to highlight the basic principles of FFC-NMR and to provide some insight into the physical background of a limited and arbitrary list of FFC models effective in practical applications. Such models are currently used to interpret NMRD profiles related to molecular dynamics in complex systems, arising mainly from dipole-dipole or quadrupole interactions.

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NMR RELAXOMETRY FOR DAIRY QUALITY CONTROL: OPPORTUNITIES AND CHALLENGES

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Despite its power to reveal unique microstructural and dynamic details in dairy products, NMR relaxometry –specifically Fast Field Cycling (FFC-NMR) relaxometry - remains underutilized in the dairy industry. This presentation aims to provide critical insights into bridging the gap, leveraging a decade of industrial research and statistically robust data from thousands of samples [1-5]. We will explore how NMR relaxometry, particularly FFC-NMR, combined with dairy science expertise, offers a deeper understanding of dairy systems – from milk to aged cheeses. We will discuss some proposed interpretative models for FFC-NMR Nuclear Magnetic Relaxation Dispersion (NMRD) data [3,6,7] on cheese, highlighting their potential for practical applications in quality control. This includes novel approaches for authentication, fraud detection, and process monitoring (e.g., milk heat treatment, cheese ripening). Finally, we will address challenges like the inherent complexity of dairy systems and propose solutions for integrating FFC-NMR with existing control measures. This presentation will showcase the transformative potential of FFC-NMR for the dairy industry.

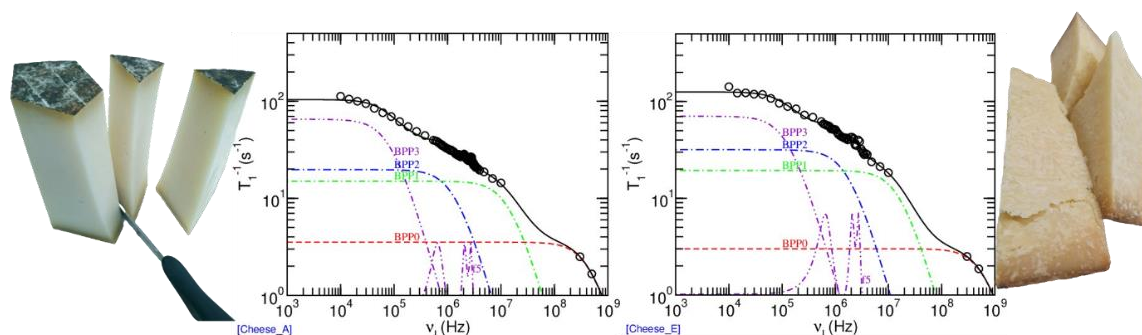


Fig. 1. Photographs and BPP-model fitting of FFC-NMR NMRDs from two ~6-months ripened hard cheeses produced according with the same official protocol but differing for some details of the cheesemaking process. Clear differences, not detectable by conventional control plans, appear from both visual inspection and FFC-NMR data.

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ORAL PRESENTATIONS



PARAMAGNETIC CHELATES EMBEDDED IN NANOGELS AS MRI PROBES

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Nanogels (NGs) offer a promising strategy for highly sensitive MRI probes because of their exceptional biocompatibility, versatility in synthesis, and hydrophilic properties. Notably, when contrast agents (CAs) are confined within NGs, their relaxivity is significantly boosted. This enhancement results from the constraints imposed on the rotational dynamics of the encapsulated CA, the abundance of confined water within the NGs, and the increased viscosity of the entrapped water molecules within the polymer network. In an initial investigation, we prepared nanogels (NGs) through the use of electrostatic interactions between biocompatible chitosan and hyaluronic acid. These NGs were designed to incorporate Gd^{3+} -chelates with varying hydration state and charges.¹ Of particular interest were the NGs functionalized with the $[\text{Gd}(\text{DOTP})]^{5-}$ complex, which, despite lacking water molecules coordinated to Gd^{3+} , exhibited an impressive relaxivity value of $78.0 \text{ mM}^{-1} \text{ s}^{-1}$ at 0.5 T and 298 K.² However, an in vivo MRI study revealed the limited stability of the NG formulation. To address this limitation, an alternative, more stable nanogel was proposed. This nanogel is based on chitosan covalently functionalized with a bisamide-derivative of *t*-CDTA, which can effectively coordinate paramagnetic Mn^{2+} ions (Fig. 1).³ The new NG offers several advantages in terms of stability, high relaxivity and good biocompatibility. Building on these promising outcomes, the same synthetic approach was utilized to develop other NGs that incorporate Gd^{3+} or Dy^{3+} -based chelates. The aim was to produce nanoprobes for MRI applications with T_1 or T_2 shortening capabilities (Fig. 1). The molecular and dynamic parameters responsible of the relaxivity for these NGs were analyzed by measuring the relaxivity values as a function of the applied magnetic field, temperature and pH.

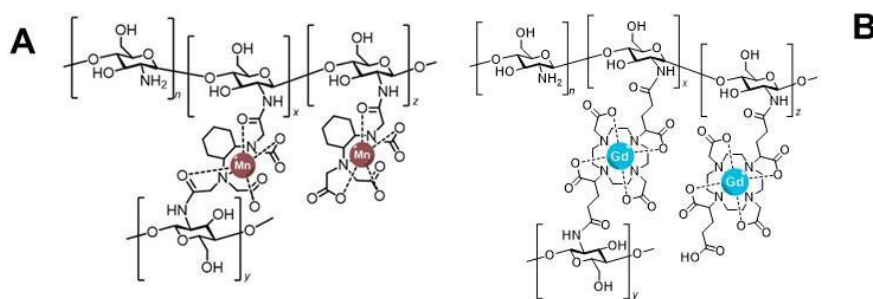


Fig. 1. Schematic illustration of nanogel functionalized with Mn(II) (A) and Gd(III)-chelates (B).

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NMR RELAXOMETRY OF PARAMAGNETIC PROTEINS AS MRI CONTRAST AGENTS

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Field-cycling relaxometry can provide direct access to spectral density functions, so that information on molecular structure and dynamics of macromolecules in solution can be obtained. ¹H relaxometry profiles are very useful for the characterization of paramagnetic molecules, especially in the field of the development of contrast agents for MRI [1].

The strategy to reduce the risks associated with the administration of MRI gadolinium(III) contrast agents can pass through the use of complexes with higher efficiency, i.e. higher relaxivity, so that the injected dose can be sizably reduced. The paramagnetic relaxivity is defined as the relaxation rate enhancement due to the presence of 1 mmol/dm³ concentration of the paramagnetic species. Molecular reorientation times in the nanosecond timescale are needed to achieve the highest efficiency at the fields of MRI scanners. This can be achieved by functionalizing low molecular weight gadolinium(III) complexes to bind noncovalently to macromolecules, by confining them within nanosized matrices, like nanogels [2], or by exploiting nanosized Gd³⁺-based compounds.

The interaction of paramagnetic complexes with macromolecules present in biological systems can cause an increase of the paramagnetic relaxivity [3], which in turn increases the MRI contrast. For instance, the Gd³⁺ caspase probe 1 (CP1) complex has been proposed to detect the activation of caspase-3/7 [4], normally activated during apoptosis: the caspase cleaves the peptide DEVD, causing aggregation of the remaining gadolinium(III) conjugate, and thus an increased relaxivity.

The relaxivity profiles of Gd-labeled large protein assemblies, as the tetrameric protein asparaginase [5] or the protein cages AaLS-13 and OP [6], show a remarkably high relaxivity at MRI fields, ca. five times higher than that of clinically used contrast agents. The analysis of the relaxivity profiles can shed light on the origin of the observed relaxivity enhancement, mainly ascribed to a correlation time modulating the proton-electron dipole-dipole interaction of few nanoseconds.

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THEORY OF PROTON RELAXATION INDUCED BY SUPERPARAMAGNETIC NANOPARTICLE: A CLASSICAL APPROACH TO NMRD

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Superparamagnetic nanoparticles are particles that are smaller than a magnetic Weiss domain. They have no remnant magnetization and become highly magnetized under a magnetic field. Their properties render them ideal for a broad spectrum of applications, such as hyperthermia, where they act as nanoheaters to kill tumor cells, or magnetic particle imaging, an imaging technique where they are used as tracers. They have been widely used in magnetic resonance imaging (MRI) as negative contrast agents: they produce a strong dipolar magnetic field which interacts with proton spins and accelerates their relaxation [1].

The magnetic moment of these particles is aligned along a preferential axis called the "anisotropy axis" to which an anisotropy energy is associated. Another important parameter is the Néel time, which characterizes the alternation of the magnetic moment between the two directions of the anisotropy axis. These properties influence the dipolar magnetic field produced by these particles and consequently affect proton relaxation. Thus, the proton NMRD of an aqueous solution containing superparamagnetic nanoparticles is significantly impacted by the anisotropy energy, the Néel time, as well as the nanoparticle size and magnetization.

The usual approach to developing theoretical NMRD models is to use the Redfield formalism, which is a full quantum framework. The current models of NMRD induced by superparamagnetic nanoparticles are developed within this quantum formalism [2,3]. In this work, we propose to develop a full classical theory, which has the advantage of being more intuitive to understand. In this theory, the superparamagnetic spin is modeled by a classical magnetic moment that obeys the Landau-Lifshitz-Gilbert equation [4]. This equation describes the time evolution of the magnetic moment and includes thermal fluctuations. We demonstrate that this approach can reproduce the quantum NMRD, paving the way for a more general model that would include phenomena such as nanoparticle aggregation or Brownian rotational motion.

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RELAXOMETRIC STUDIES TO REVEAL POTENTIAL THERANOSTIC PROPERTIES OF HUMAN TRANSTHYRETIN CONJUGATED WITH Gd(III) COMPLEXES

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Fast Field-Cycling (FFC) NMR Relaxometry is a well-established technique that enables one to study the molecular dynamics of macromolecules as proteins by measuring relaxation rates R_1 as a function of the applied magnetic field. The characterization of paramagnetic compounds potentially useful as contrast agents in MRI is an important application of ^1H FFC-NMR Relaxometry, which can shed light on structural and dynamic properties important for the understanding of their mechanism of action. Contrast agents based on gadolinium(III) complexes are widely used in clinical diagnostics, but due to the high toxicity of the free metal ion, there are concerns about their safety [1]. Striving towards a decrease of the injected Gd(III) complex, several studies aim to enhance the relaxivity and thus the efficacy of the MRI agents. To this aim, low molecular weight Gd(III) complexes have been developed to be covalently bound to macromolecules with molecular reorientation times in the nanosecond time scale. Gd-tagged proteins, such as Gd-DOTA attached to asparaginase, show a high increase in paramagnetic relaxivity and were suggested as potential theranostic agents [2].

The analysis of the acquired relaxometry (or Nuclear Magnetic Relaxation Dispersion, NMRD) profiles is performed through the application of relaxation models able to describe interactions and motional processes occurring in the system by taking into account defined parameters and conditions. A fitting software with a graphical interface is under development, that will easily allow for the analysis of the relaxation profiles of paramagnetic molecules, proteins and nanoparticles. Potential applications and key features of the new tool are shown to demonstrate its feasibility.

Here, we investigate human transthyretin (TTR), which is a carrier protein for the delivery of cytotoxic drugs, as a potential theranostic agent [3]. The paramagnetic Gd-C4-IA complex is used as a tag. The results of our work reveal a promising relaxivity enhancement of the GdTTR conjugates, which will be presented.

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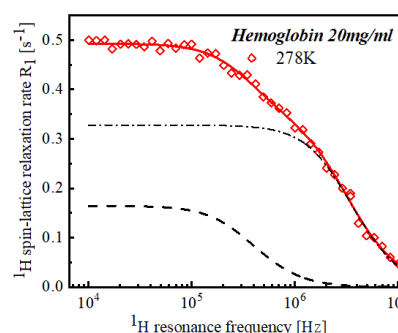
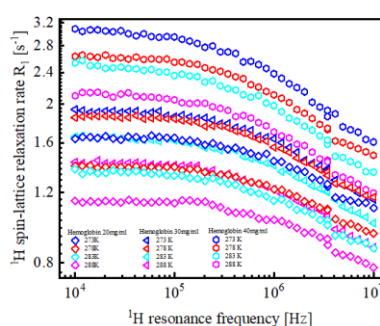
Spin Relaxation Dynamics in Haemoglobin Solutions: A Study of Molecular Interactions

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The investigation of haemoglobin dynamics and concentration dependent behaviour is crucial for understanding its biophysical properties and functionality [1]. In this experimental study, ^1H spin-lattice relaxation experiments have been performed to reveal dynamics of water molecules in haemoglobin solutions, covering a broad frequency range from about 10 kHz to 10 MHz. The studies have been performed at different haemoglobin concentration including 20mg/ml, 30mg/ml, and 40mg/ml versus temperature, from 273K to 288K. The studies have been complemented with Time-Domain NMR relaxation experiments (spin-lattice and spin-spin relaxation) performed at 18.5 MHz. Profiting from the characteristic mathematical properties of spectral density functions, depending on the mechanism of motion, the subject of water diffusion on the protein surface has been addressed. The model has been verified against the spin-spin relaxation data. Performing an analysis of ^1H spin-lattice relaxation data over a broad frequency range, one reveals several relaxation contributions associated with motional processes on different time scales. The relaxation expressions for spin-spin relaxation rates include spectral density function taken at zero-resonance frequency – this implies that the relaxation rates include contributions proportional to the correlation times and these contributions likely dominate the spin-spin relaxation rates. This implies that using incorrect motional models for the spin-lattice relaxation data, one would be not able to reproduce the spin-spin relaxation rates because the obtained correlation time would not reflect the real time scale of the motion



Acknowledgements

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NMR INSIGHTS INTO TRYPSIN'S MOLECULAR DYNAMICS

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The molecular dynamics of trypsin, a key enzyme in protein digestion within the small intestine, have been explored through an integrated approach combining ¹H spin-lattice and spin-spin relaxation experiments. By utilizing Fast Field Cycling NMR (FFC-NMR) relaxometry (STELAR s.r.l. relaxometer, Mede, Italy), we performed ¹H spin-lattice relaxation measurements over a frequency range of 10 kHz to 10 MHz at various temperatures. These investigations were complemented by time-domain spin-lattice and spin-spin relaxation experiments (TD-NMR) at 18.5 MHz (Resonance Systems GmbH, Kirchheim unter Teck, Germany) and our experiments focused on trypsin-H₂O and trypsin-D₂O mixtures.

Several models were developed to correlate the relaxation properties with the dynamic behavior of these systems. Consequently, ¹H spin-lattice relaxation data for protein systems can be interpreted using relaxation contributions expressed through Lorentzian spectral densities with varying correlation times. This approach has been successfully applied to both low-concentration protein solutions and solid proteins [1]. In solutions, the relaxation effects are attributed to water molecules interacting with distinct binding sites on the proteins, with the exchange dynamics between these sites playing a crucial role. In the case of solid, low-hydrated proteins, the observed power-law dependencies in ¹H spin-lattice relaxation have been associated with backbone dynamics [2,3].

The combined application of FFC-NMR and TD-NMR provides a detailed understanding of trypsin's molecular dynamics and structural stability in different solvent environments. Isotope substitution was used to distinguish the origins of specific relaxation contributions, which is essential given the comparable fractions of ¹H nuclei from both water and protein molecules in the system. The findings offer valuable insights into protein-solvent interactions, paving the way for future studies on protein dynamics and functionality under various conditions.

Acknowledgments/Funding

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SLOW DIFFUSION IN SUCROSE HYDROGEL MICROPARTICLES AS POTENTIAL SUSTAINED DRUG DELIVERY VEHICLES

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Hydrogel microparticles are promising for drug delivery applications for several reasons. First, they can target to the close proximity of diseased tissues a high amount of drug molecules thanks to their small size and enhanced surface/volume ratio. Second, they can release their drug content via passive diffusion in a time-controlled sustained process that the body can tolerate the released amount of drug in a certain time interval as often required in therapies with antidepressants and chemotherapeutic agents. As a measure of the efficiency of the drug delivery application, the water-binding capacity or release kinetics of any water-soluble drug molecule in a hydrogel particulate system should be clarified. In this study, water dynamics in mesoporous sucrose hydrogel microparticles was investigated by means of nuclear magnetic resonance (NMR) techniques. High-resolution ¹H NMR spectra and NMR diffusometry measurements obtained on swollen state sucrose micro/nanogel revealed the existence of different fractions of water molecules based on their interaction with the gel matrix. In addition to the translational diffusion of bulk water, two more diffusion processes characterized with self-diffusion coefficients 1 and 2 orders of magnitude smaller than that of bulk water were identified. ¹H spin-lattice relaxation dispersion profiles obtained for a broad range of Larmor frequencies using fast field cycling (FFC) and conventional NMR relaxometry techniques allowed us to further clarify the mechanisms of molecular motion.

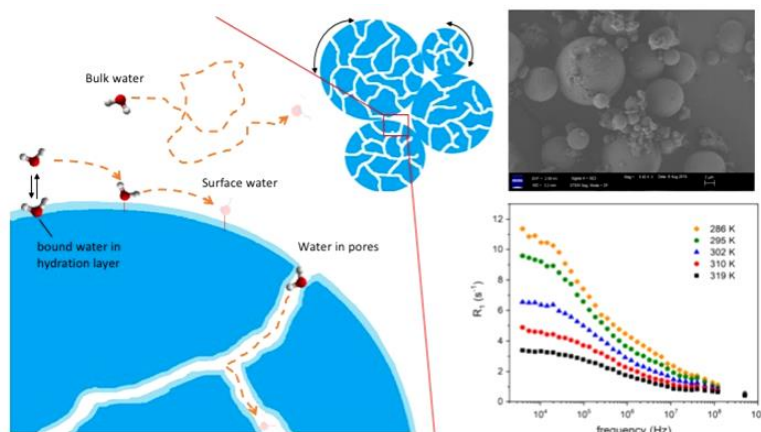


Fig. 1. Schematic showing different water fractions in sucrose microgel agglomerates and FFC data.

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Type IV Eutectic Electrolytes for Lithium-Ion Batteries

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Deep Eutectic Solvents (DESs) or eutectic solvents (ES) have emerged as promising candidates to replace conventional organic solvents in various technological applications due to their distinctive physicochemical properties, such as lower vapor pressure, low flammability, and ease of preparation at low costs compared to ionic liquids. DESs exhibit unique characteristics derived from the hydrogen-bonded network between their constituent components. Within the DES classification, Type IV DESs, formed by a molecular component and a metal salt, have recently garnered attention as electrolytes for lithium-ion batteries (LIBs) due to their potential to achieve high lithium transference numbers, enabling efficient charge-discharge cycles in LIBs.

In this work, we studied different eutectic mixtures formed by pyrazole (PYR) and lithium bis(trifluoromethane)sulfonimide (LiTFSI) at varying compositions, focusing on their transport properties. Measurements were conducted at 283 K, ensuring all systems remained liquid at this reduced temperature. Fast Field Cycling NMR Relaxometry was utilized to investigate the dynamics of the system as a function of the magnetic field, ranging from 30 kHz to 15-35 MHz in ¹H Larmor frequency. Additionally, Pulsed Field Gradient (PFG) NMR was employed to examine translational dynamics by measuring the self-diffusion coefficients. All measurements were carried out in the ¹H, ¹⁹F, and ⁷Li domains. This approach allowed us to evaluate the proposed eutectic systems as electrolyte components from a molecular perspective.

Our investigation revealed an intricate interplay between the lithium salt and pyrazole at different concentrations. Notably, the 1:2 LiTFSI:Pyrazole mixture exhibited a unique trend compared to other samples, with all nuclei relaxing faster and displaying higher R_1 values at lower frequency ranges. Additionally, PFG NMR results indicated that Li⁺ ions have two distinct diffusion coefficients, likely due to their different local environments. The underlying reasons for this behavior are currently under investigation. Furthermore, we found that the lithium transference numbers in our DESs range from 0.13 to 0.47, underscoring their potential application in lithium-ion batteries.

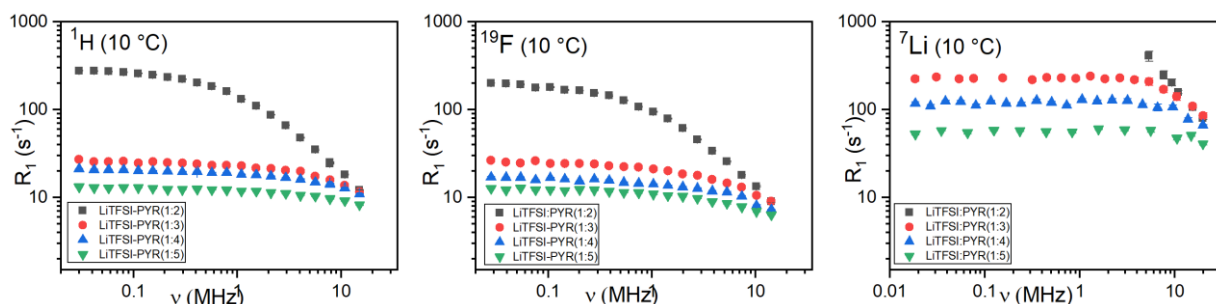


Fig. 1. R_1 relaxation profiles for ¹H, ¹⁹F and ⁷Li in LiTFSI:PYR eutectic mixtures as a function of composition.

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MODULATION OF THE NUCLEAR RELAXATION PROPERTIES IN IRON OXIDE CORE-SHELL NANOPARTICLES

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In this oral discussion a selection of some of our most significant case studies [1] on magnetic nanoparticles for potential applications in magnetic resonance is presented.

For almost 10 years, our research activity focused on the comprehension of the physical mechanisms on the basis of the nuclear relaxation of magnetic nanoparticles (MNPs) in the presence of magnetic fields. Taking advantage of the insights gathered over this time span, we report on and discuss the dependence of the relaxation behavior on the chemico-physical properties of magnetic nanoparticles. In particular, an overview is carried out on the correlations between their efficiency as contrast agents in magnetic resonance imaging and the magnetic core of MNPs (mainly iron oxides), their size and shape, and the coating and solvent used for making them biocompatible and well dispersible in physiological media. Moreover, the heuristic model proposed by Roch and coworkers [2] is adopted to describe most of the experimental data sets. The amount of data analyzed allowed us to provide a partial picture of MNPs relaxation behavior and, at the same time, propose new interesting perspectives to be investigated.

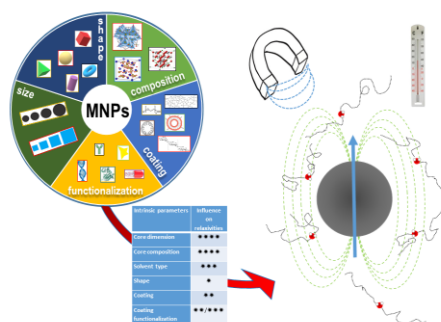


Fig. 1. Schematic representation of the principal intrinsic parameters (magnetic core composition, size, shape, coating, and surface functionalization) and extrinsic parameters (solvent, magnetic field, and temperature) relevant for describing the MNP nuclear relaxation process.

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UNDERSTANDING ION DYNAMICS IN BORON NITRIDE IONOGEL ELECTROLYTES

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Ionogels, based on hexagonal boron nitride (hBN), are promising materials for rechargeable lithium-ion batteries, enabling flexible electrochemical devices. These electrolytes, combined with imidazolium ionic liquids and hBN nanoplatelets, exhibit excellent mechanical properties and ion-conductive gel electrolyte behavior. However, a molecular-level understanding of ion dynamics within the gelling matrix is lacking.

This work presents an overview of the transport properties of hBN ionogels and their constituents. The hBN gel electrolytes consist of carbon-coated hBN nanoplatelets (40 wt%) and a lithium ionic liquid (Li-IL), 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide (EMIM-TFSI) containing 1M lithium bis-(trifluoromethylsulfonyl)imide (LiTFSI) salt by measuring the longitudinal relaxation rate (R_1) dispersions using fast field cycling NMR, and the self-diffusion coefficient of the ionic species using pulsed-field gradient NMR.

Experimental results reveal in liquid electrolytes (EMIM-TFSI and EMIM-LiTFSI), Li^+ minimally impacted the dynamics of TFSI^- and EMIM^+ ions, with the anion being slightly more affected. However, in the ionogel (EMIM-TFSI gel), fluorine relaxation was more sensitive to the hBN matrix than the EMIM^+ cation. The hBN matrix favored the dynamics of the TFSI^- anion, enhancing its mobility, likely due to structural features facilitating ion transport. In the presence of Li^+ (EMIM-LiTFSI gel), this effect was less pronounced, probably due to the anion's interaction with the Li^+ ion. PFG NMR measurements supported the enhancement of TFSI^- dynamics, revealing an increase in the anion diffusion coefficient in the gelling matrix. Overall, this work highlights the intermolecular interaction between the TFSI^- anion and the hBN matrix, driving the transport properties of these highly conductive ionogels.

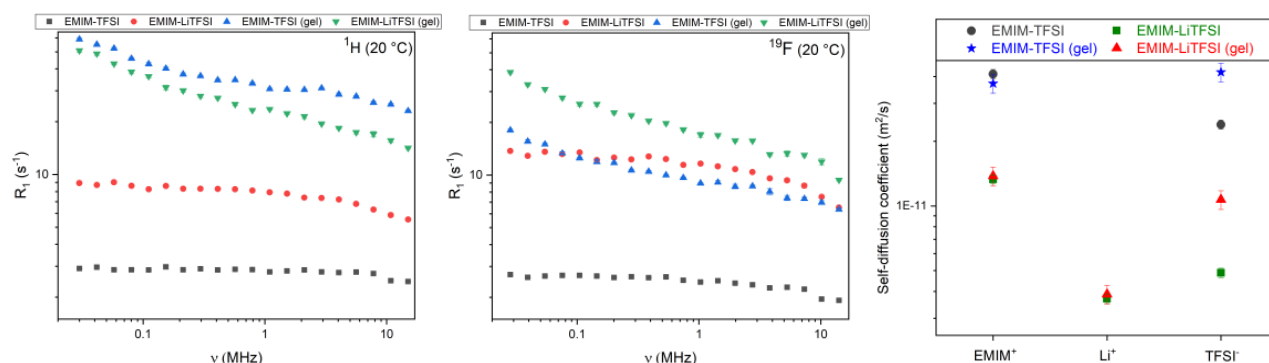


Fig. 1. ^{19}F (a), ^1H (b) relaxation rate dispersions R_1 and self-diffusion coefficients (c) of the ionic species studied

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¹H NMR RELAXOMETRY AND A VARIETY OF “SIMPLE” IONIC LIQUIDS

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In parallel to the wide range of applications of ionic liquids, their dynamical properties are of great interest from a fundamental point of view. NMR relaxometry has much to contribute to this topic. First, frequency dependent relaxation experiments make it possible to probe translational and rotational dynamics of ionic liquids in a single experiment. Second, the shape of the frequency dependencies of relaxation rates (with focus on spin-lattice relaxation) reveal the mechanism of the ionic motion. In case of ionic liquids in bulk the mechanism of the translation motion is not surprising – one expects isotropic, three - dimensional translation diffusion, however, the rotational dynamics can be complex. One should, however, point out at this stage that due to the relatively small size of ions the rotational dynamics is relatively fast and inquiring into details of this motion often requires higher resonance frequencies than those accessible in FFC NMR relaxometry. There is more to that – the rotational dynamics is modulated by internal motion of the ions, for instance cation chains (the internal motion depends on the structure of the ions). From this perspective, FFC NMR relaxometry is a relatively “low resolution” technique. The overall relaxation rates come from different chemical groups and represent an overaged effect of the complex motion. This is one of the reasons why relaxation contributions associated with intra-ionic dipole-dipole interactions often cannot be satisfactorily described in terms of Lorentzian spectral densities.

In this study, ¹H spin-lattice relaxation experiments have been carried out for ionic liquids including different types of anions: [Cl]⁻, [I]⁻ and [DCA]⁻ and cations with different chain length (e.g. [BMIM]⁺, [HMIM]⁺, [OMIM]⁺, [DMIM]⁺ etc.). The presence of hydrogen atoms only in the cation structure makes it possible to directly probe the cation dynamics – this is the reason for using the term “simple” in the title. The first subject we are going to address is the influence of the anion structure on the translation diffusion of the cations. The second subject concerns the rotational dynamics - in some cases the FFC NMR studies have been complemented by relaxation experiments performed at higher frequencies, selectively for different chemical groups present in the cations. In this way one can split the ¹H spin-lattice relaxation rates obtained in FFC NMR experiments into components associated with the internal motion.

Acknowledgments/Funding

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Exploring rotational and translational dynamics in ionic liquids: Insights from FFC NMR relaxometry and MD simulations

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Our project focuses on the study of rotational and translational motion in ionic liquids (ILs) by means of fast field cycling (FFC) NMR relaxometry over broad temperature ranges. The spectrometer frequency can be swept between 10 kHz and 40 MHz for ¹H nuclei, yielding NMR dispersion profiles which allow for the simultaneous observation of several molecular processes at different timescales in one single experiment.

Depending on the atomic composition of the ILs it is mostly possible to measure ¹H NMR dispersion profiles for the cations as well as ¹⁹F NMR dispersion profiles for the anions. In order to dissect the spin lattice relaxation rates into their inter- and intramolecular contributions, relaxation models are required. While translational diffusion coefficients can be extracted using the force free hard sphere model, the determination of rotational correlation times strongly depends on the molecular structure of the ions. As long as the rotating identity can be considered a rigid sphere, the simple Bloembergen Purcell Pound model can be applied. This is the case for example for the triethylammonium [TEA]⁺ cation. However, if the ions are better described as ellipsoids (e.g. N-pentylpyridinium [C₅Py]⁺ cation), or show additional internal rotation, (e.g. bis(trifluoromethylsulfonyl)imide [NTf₂]⁻ anion) more complex relaxation models are required. [1] Finally, molecular dynamics (MD) simulations are a useful complement to FFC NMR relaxometry, since they do not only provide comparable values for both quantities, but can also mechanistically verify the applied relaxation models by computing the inter- and intramolecular frequency-dependent dipolar NMR relaxation and reconstructing the total NMR dispersion profiles.[2]

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NMR methods to characterize structure and dynamics of supramolecular hydrogels

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Peptide-based hydrogels can form well-organized supramolecular assemblies and are widely used with various applications, e.g. in biotechnology. The design of low molecular hydrogels for specific applications require to modify their mechanical and chemical properties, with for example the grafting of nucleobases [1]. A deeper understanding of the atomic-scale structure of the hydrogels is necessary to allow the adjustment of their macroscopic properties, and Nuclear Magnetic Resonance is a major technique to gather information about structural and dynamics properties at atomic-scale. Solid-State NMR is powerful to probe the hydrogel sample structure and to investigate the molecular arrangement that forms the three-dimensional lattice of this type of gels. ¹H rotating-frame relaxation times ($T_{1\rho}^H$) can be measured for different moieties of the peptide-based molecules (Fig.1) in order to bring information about molecular interactions.

Low-field NMR techniques, such as Fast-Field Cycling Relaxometry (Fig. 2) allow the dynamical characterization of the hydrogel isotropic phase [2], and potentially highlights the existence of different water populations regarding correlation times. Furthermore, those techniques, in addition with High-Resolution NMR measures, are powerful tools to investigate the gelation kinetics of the peptide-based hydrogels.

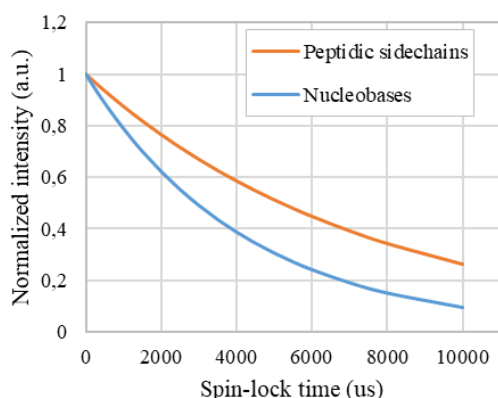


Fig. 1. $T_{1\rho}^H$ of molecule moieties

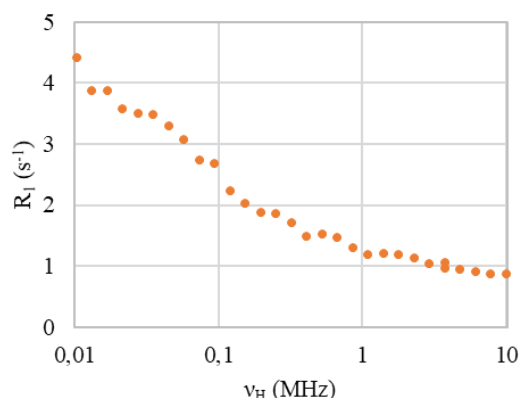


Fig. 2. ¹H NMRD profile of hydrogel

The combination of all these NMR techniques proves to be a powerful tool to characterize both structure and dynamics of peptide-based-hydrogels.

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ANOMALOUS ^1H AND ^2H NMR RELAXATION IN CONVENTIONAL POROUS SILICA

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In the current study, we conduct a detailed analysis of water dynamics on silica surfaces using fast-field cycling relaxometry [1]. For the first time, we distinguish intra- and intermolecular contributions by subtracting ^1H and ^2H NMRD of water in silica and analyze them using conventional models, such as RMTD and FFHS, respectively. One of our findings indicates that, in native silica at ambient temperature, proton exchange dynamics have minimal impact on relaxation properties, while RMTD mechanisms predominantly influence ^2H NMRD [2]. Using phosphate buffers, the most commonly used buffers for chemical reactions in silica, as a proton exchange modifier, we showed an acceleration of ^2H NMRD relaxation by up to one order of magnitude (see Figure 1). Despite this acceleration, the shape of the NMRD curve remains unchanged.

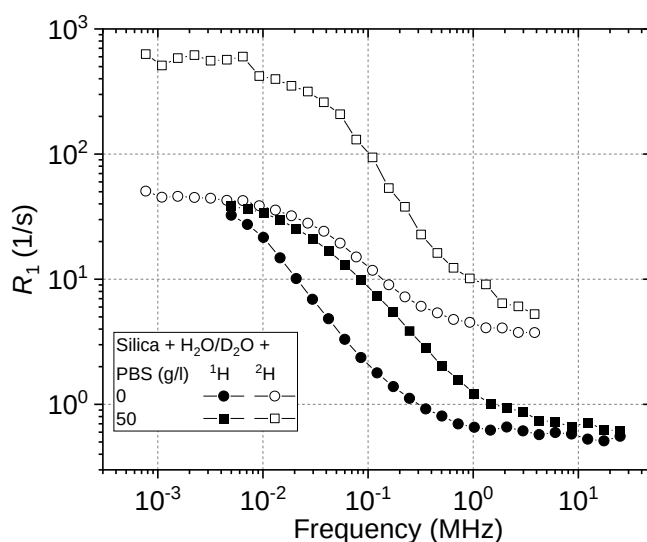


Fig. 1. ^1H (solid symbols) and ^2H (open symbols) NMRD of water in silica containing PBS buffer

The analysis of NMRD reveals that intermolecular relaxation dominates at low concentrations of PBS buffer and frequencies below 100 kHz. The intermolecular contribution to ^1H NMRD is confirmed by ^2H dilution experiments. The temperature dependence of ^2H spin-spin relaxation times shows a typical exchange pattern that scales with phosphate salts concentration. The applicability of two- and three-site exchange models is also discussed.

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CEMENT HYDRATION OF A DIFFERENT COMPOSITION FOLLOWED BY FFC NMR

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Cement is a widely used material worldwide. During the last decade, cementitious material production increased by 20%. Cement production accounts for 7% of the world's CO₂ emissions [1]. Understanding processes that occur during the hydration and wetting-drying processes of the cementitious materials not only benefits cement production but also helps decrease the ecological impact.

NMR (Nuclear Magnetic Resonance) Relaxometry, a non-destructive and non-invasive, relatively fast, and inexpensive technique has been used to study cement for over 40 years. One of the first works on cement hydration studied by NMR was published in 1978 by Blinc et al [2]. However, research on Limestone Calcined Clay (LC3) cement with the NMR technique is uncommon. Moreover, studies of cement with the Fast Field Cycling (FFC) NMR technique are even more limited. We found only a few studies on mortar and synthetic cement [3, 4]. Moreover, the studies on cement using FFC NMR had limitations in the compositions of the used samples (only grey cement or white cement with silica fume as an additive) [5]. In this work, we studied cements of different compositions during the early stages of hydration. Samples used were White Portland Cement, Ordinary Portland Cement, and LC3 with a 0.5 water-to-cement ratio. FFC NMRD experiments were performed using a Stellar Bench-top Fast Field Cycling NMR Relaxometer SMARtracer over a 0.01 – 10 MHz frequency range.

We used an innovative approach to process the raw data to create the NMRD profile. For each frequency point of the NMRD profile, we inverted the T₁ relaxation curves (from both PP and NP sequences) to obtain the T₁ relaxation time distributions to separate and follow the different cement components over time. The T₁ relaxation time distributions were obtained with UpenWin [6], while the NMRD profiles were analyzed using the freeware in-house developed software ModelFreeFFC [7].

We demonstrated that the FFC NMR technique could provide additional information on the cement materials during hydration, especially at lower magnetic fields, concerning pore formation, transport, diffusion, and relaxation processes at the pore surfaces.

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Surface topology of fibrin network from FFC-NMR dispersion profiles

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Purpose: FFC-NMR is currently utilised to study biological structures. However, the influence of in-vivo molecular dynamics on nuclear magnetic relaxation dispersion profile (NMRDP) configuration lacks understanding. Literature shows that for a biological system of adsorbate molecules with fractal properties, representative of a spin-lattice relaxation mechanism of reorientation-mediated by translational displacements (RMTD), details of the surface topology of the system is described from the fractal dimension [1]. Fractal dimension is a statistical measurement of geometric complexity, shown to be retrieved from NMRDPs with application of a polymer power-law model [1]. Therefore, to validate a relationship between NMRDP of biological systems and the polymer model, a simplified model of a clot comprised of a complex network of filamentous fibrin fibres was initially utilised. Filamentous structures are a network of fractal adsorbate molecules that are biologically ubiquitous, evident in the vascular system (blood clot), cells (cytoskeleton), musculoskeletal system (tendons), and digestive system (microbiome).

Methods: Purified clot models were generated from twelve varying concentrations of thrombin (0.01 – 1 U/mL) and fibrinogen (1 – 3 mg/mL) to modify the topology of the fibrin network structure. The NMRDPs of clot models were acquired using FFC-NMR relaxometry. The protocol included pre- and non-polarised sequences at multiple field strengths ranging between 8 – 0.001 MHz. All samples were analysed at 37 °C. Clots were additionally generated with fluorescent fibrinogen in microscope chamber slides for confocal microscopy, aiding 3D visualisation of the fibrin network. The microscopy-based fractal dimensions were calculated using imaging analysis algorithms. The derivative of NMRDPs aided detection of the various relaxation regimes associated with purified clot models. Retrieval of the exponent from the polymer model applied to NMRDPs regimes facilitated calculation of NMR-based fractal dimensions [2]. Each clot model of varying thrombin or fibrinogen concentration was analysed independently.

Results: Three distinctive relaxation regimes are evident in NMRDPs of structurally altered purified clots. Comparison between NMR- and microscope-based fractal dimensions indicate the fractal dimensions measured by microscopy, which was 1.77 ($\pm$ 0.07), corresponds to the fractal dimension measurement from the second NMR relaxation regime, which was 1.74 ($\pm$ 0.09) within frequency range of 10 kHz to 300 kHz. Juxtaposition of individual clot models, with varying thrombin and fibrinogen concentrations for topological modification, shows the fractal dimensions are statistically equivalent ($p > 0.05$) (Fig 1).

Discussion: The work proposed here validate the use of the RMTD polymer power-law model in fibrin clots, within 10 kHz to 300 kHz. Application of the polymer model on NMRDP of purified filamentous networks within that frequency range can therefore inform about the fibre network. However, outside this frequency range, different motion regimes exist which have not yet been investigated. The purified clot models lack physiological relevance, therefore complexifying the



model with additional biological elements will examine if the relationship between surface topology and the NMR polymer model is biologically accurate. Biomaterials representing other physiologically filamentous structures (i.e. tendon from a network of collagen) will further explore the operational limit of this model. Moreover, the polymer model is influenced by a diffusion constant, requiring temperature dependent FFC-NMR to be achieved.

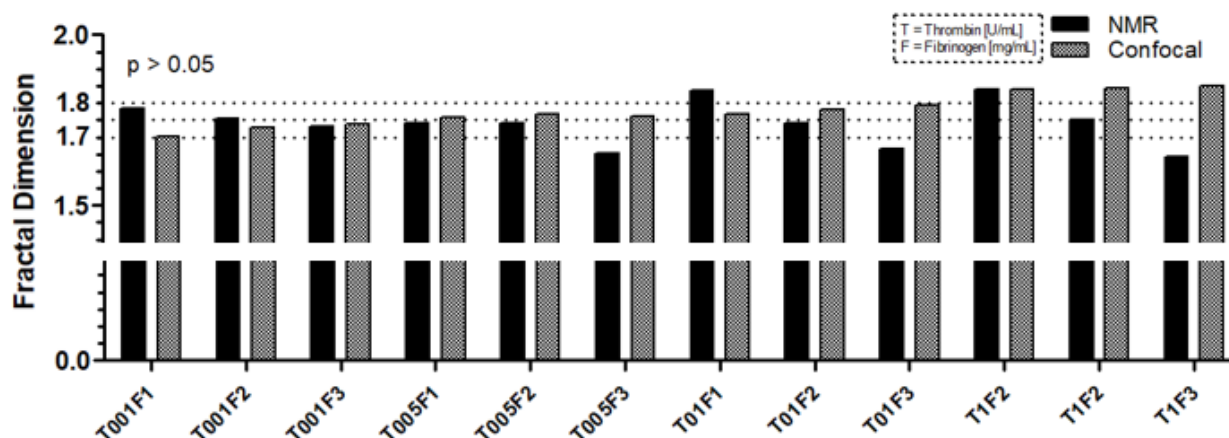


Fig. 1. Comparison of fractal dimensions from NMR (dark) and confocal microscopy (light) for all clot models generated from various concentrations of thrombin and fibrinogen.

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CROSS RELAXATION SPECTROSCOPY ON FAST-FIELD CYCLING RELAXOMETER

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The electric field gradient (EFG) tensor is a crucial parameter in the study of molecular structures and environments, particularly in the context of solid-state physics, chemistry and pharmaceuticals. The measurements and analysis of particularly ^{14}N nitrogen nuclei EFG play a significant role in the pharmaceutical industry in areas such as[1]:

- molecular structure elucidations
- polymorphic forms detection
- drugs-excipient interactions
- stability and quality control

EFG tensor is ideally determined directly by nuclear quadrupole resonance (NQR) spectroscopy, which measures transitions between nuclei quantum levels, which are split due to interaction between the nuclei quadrupole moment and the EFG at the site of the nucleus. However, in the case of ^{14}N NQR, the resonance frequencies lie below 4 MHz, and direct detection of pharmaceutically relevant samples is often not possible due to low signal to noise ratio and an indirect detection via nuclear quadrupole double resonance (NQDR) has to be used[2,3].

While NQDR techniques in general require special hardware, it is well known that fast-field cycling (FFC) relaxometer can be used to determine the ^{14}N EFG tensor in powdered solids by cross-relaxation (CR) spectroscopy. Here so called “quadrupole dips” occur in the spin-lattice relaxation dispersion curve for the values value of magnetic field where hydrogen Larmor frequency crosses field (almost) independent nitrogen quadrupole resonance frequencies.

However, a typical FFC relaxometer is optimized to measure proton NMR signals in liquids and soft matter, where NMR signals are long and nuclear relaxation is fast. So short NMR signals and long relaxation times pose some measurement challenges, which I address in this talk.

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RELAXATION, DIFFUSION, AND DNP APPROACH TO BINARY LIQUIDS IN POROUS GLASS: TO MIX OR TO DEMIX?

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Existing models for relaxation in porous media fail to describe materials with pore sizes well below 10 nm or quadrupolar spins [1,2], with vastly different dispersions between species, whereas self-diffusion is frequently observed to show identical tortuosity for all species. In this work, we shed light on the apparent discrepancy between relaxation and diffusion behavior by studying binary liquids that are miscible in the bulk but appear to demix inside mesoporous media.

Concentration series of binary mixtures were prepared in Vycor porous glass, with one component being replaced by a perdeuterated compound. Measurements of T_1 and T_2 at 1 T and 11.7 T are combined with field-cycling T_1 dispersion for ^1H nuclei in the range 10 kHz to 30 MHz. For the same systems, self-diffusion coefficients of both components were determined in bulk and in porous glass. Pronounced differences in relaxation dispersion are observed, for instance, when acetone entirely displaces cyclohexane from the surface, and when water is predominantly attracted to the surface [3,4]. In both cases, the attracted component experiences a twice larger tortuosity factor in diffusion, suggesting separation into two continuous liquid sub-phases inside the porous network. Phase separation, or de-mixing, is suggested by trends in relaxation as well as diffusion: Any liquid filling the porespace of Vycor porous glass with a polar surface shows T_1 dispersion of ^1H and ^2H nuclei, suggesting reorientational dynamics on timescales exceeding 10^{-5} s. Cyclohexane co-existing with acetone is one example where this dispersion entirely disappears (see figure), suggesting effective phase separation inside the mesopores. This concept is corroborated by a concentration-dependent apparent tortuosity obtained from the self-diffusion coefficients.

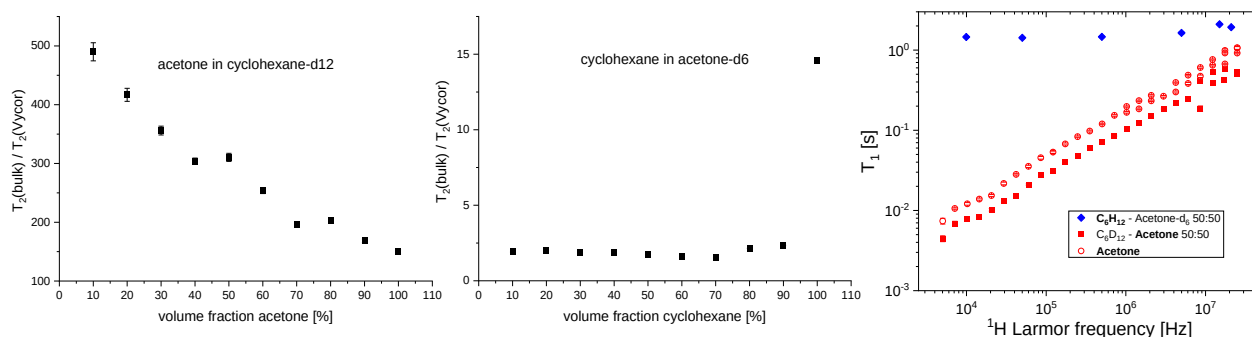


Fig. 1. (left, middle) ^1H transverse relaxation times of acetone/cyclohexane mixtures in Vycor porous glass, normalized to bulk value; (right) relaxation dispersion of the ^1H -containing species in the same mixtures.

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Evidence of the change of transport mechanism in ionic liquids containing Li^+ and La^{3+}

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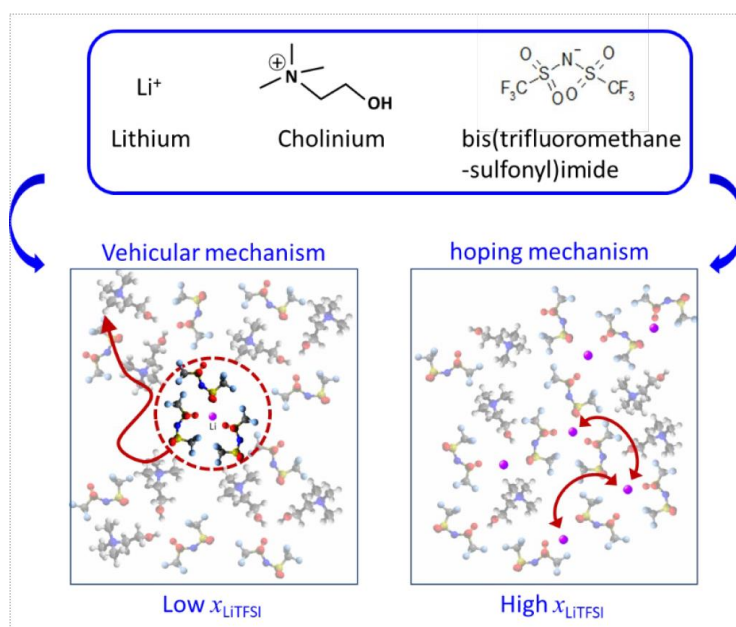
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The dynamics in mixtures of ionic liquid and monoatomic cations has been studied at different time scales ranging from the nanosecond up to the second using NMR relaxometry and diffusometry. The mixtures were composed of cholinium bis(trifluoromethanesulfonyl)imide ([Chol][TFSI]) and LiTFSI, with LiTFSI mole fraction, x_{LiTFSI} , spanning from 0 to 0.5 (saturated solution), and [Chol][TFSI] and $\text{La}(\text{TFSI})_3$ with $0 \leq x_{\text{La}(\text{TFSI})_3} \leq 0.12$. The translational self-diffusion coefficients of Chol^+ , TFSI^- and Li^+ have been measured, along with NMR their relaxation times at various magnetic fields, in order to decipher the intertwined dynamics between the ions, and to reveal how the local dynamics impact the long range translational diffusion. When the concentrations of lithium and lanthanum are increased in the liquid, the long range dynamics of all the ions drop. In the case of LiTFSI, the self-diffusion coefficient of lithium becomes higher than the one of TFSI at high concentration, revealing a change in lithium transport mechanisms. The NMR relaxation of ^7Li data confirm this change, showing a clearer transition at $x_{\text{LiTFSI}} = 0.15$. It is interpreted as a change from a vehicular transport mechanism of the lithium below $x_{\text{LiTFSI}} = 0.15$ to a hopping mechanism above. A similar crossover seems to occur in the lanthanum solutions. The hydroxyl group of the organic cation seems to be involved in this phenomenon.





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TIPS AND TRICKS FOR INVESTIGATING WATER PROTON DYNAMICS IN HYDROGEL / CLAY COMPOSITE MATERIALS THROUGH NUCLEAR MAGNETIC RELAXATION DISPERSION (NMRD) PROFILES FITTING

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Hydrogels are polymeric materials, in which the macromolecules linked together through chemical or physical bonds to form a three-dimensional network. These soft and water-swelling materials are highly attractive due to their applicability in a variety of scientific fields [1]. To enhance their properties (mechanical, optical, swelling, ...), hydrogels are often combined with colloidal suspensions (nanocomposite systems) as required [2]. Among the challenges related to these systems, water proton dynamics investigation is one of the most relevant. Indeed, it can be used as a powerful tool to reveal water-macromolecule, water-nanoparticle as well as nanoparticle-macromolecule interactions. The systems studied here are composites, consisting of a polyelectrolyte-based hydrogel (modified ionene) mixed with different clay nanoparticles suspensions (Montmorillonites and Beidellite). These clay nanoparticles contain paramagnetic impurities (Fe^{3+}) that could induce water protons relaxation in their vicinity [3-4]. By the mean of nuclear magnetic relaxation dispersion (NMRD) profiles recorded in-situ by fast-field cycling relaxometry, one can therefore easily attest that water protons approach the surface (availability of surface sites), through the increase in their relaxation rates. The interest of NMRD lies in fitting the profiles to carefully selected theoretical models, in order to access parameters related to water proton dynamics at clay particle surface. In complex systems such as those studied here, the theoretical models usually used involve a large number of critical parameters that must be constrained for an accurate and realistic description. In this work, we attempted to establish a set of good practices (tips and tricks) to accept or reject a set of theoretical parameters during the fitting procedure. This was achieved, among other things, through the analysis of correlation matrices and ensuring that the output parameters of the fit had a physical meaning. The current strategy has been applied to pure clay aqueous suspensions (first step) prior to its further extension to hydrogel/clay composites (second step). The experimental NMRD profiles have been fitted to a combination of Solomon-Morgan-Bloembergen and Jean-Pierre Korb models.

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CANCER ASSESSMENT BY RELAXOMETRY

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Our previous studies on cells and animal models have demonstrated that Field Cycling (FC) relaxometry at low magnetic field strengths (below 0.2 T) can discriminate healthy tissues from tumours according to their aggressiveness and metastatic potential [1]. Indeed, at these magnetic field intensities, the recovery of ¹H magnetisation depends on the rate of water exchange between intracellular and extracellular compartments. This, in turn, correlates with several metabolic and chemical-physical biomarkers, including protein overexpression and Na⁺/K⁺-ATPase activity. This contribution aims to show how this potentiality of FC relaxometry can be exploited to roll out study and develop methods for cancer assessment. To illustrate, the relaxometric data obtained from surgically resected tissue samples addresses the current unmet clinical need of intraoperative negative margin assessment during breast-conserving surgery [2]. Furthermore, the elaboration of these data enables the characterisation of tumour tissue with greater depth based on grading (Fig.1).

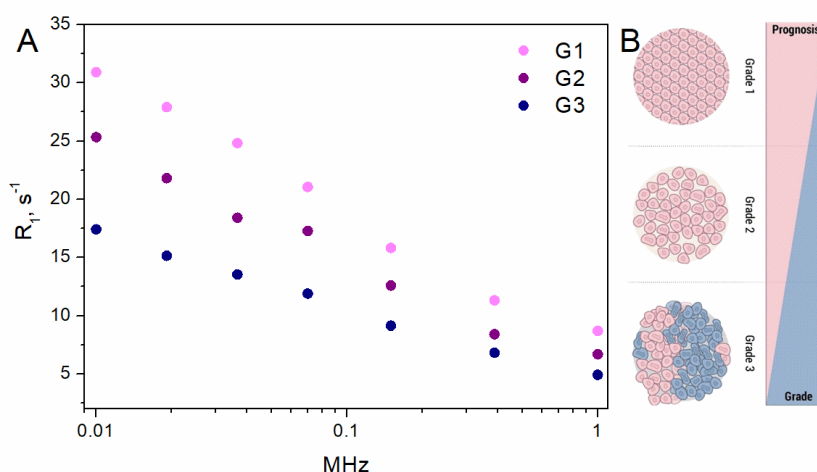


Fig. 1. A) Comparison of the proton longitudinal relaxation rate R_1 as a function of the applied magnetic field for three representative breast cancer tissue samples of different grades (G1, G2 and G3, as assigned by the anatomopathologist). B) Representative scheme of breast cancer grade.

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Longitudinal NMRD profile as a tool to characterize and predict the efficacy of phosphonate based-SPIONs as MRI contrast agents

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Superparamagnetism exhibited by iron oxide particles at the nanoscale makes them suitable as contrast agents in magnetic resonance imaging (MRI). Control over their properties is governed by a well-optimized synthesis method. The microwave method was used to yield highly crystalline and surface-functionalized nanoparticles. Surface functionalization increases biocompatibility, colloidal stability, targeting ability, and size control. These nanoparticles were capped with methylene phosphonic acid and alendronic acid ligands (commercially available) because their phosphonate groups strongly adhere to the nanoparticle surface. To characterize these nanoparticles, the fast-field cycling NMR technique was used between 5KHz-10MHz, and longitudinal NMRD profiles were obtained to show their efficacy (relaxivity) as a function of the magnetic field strength. Both longitudinal and transverse relaxivities at medically relevant magnetic field strengths are reported in this study. The influence of these nanoparticles on water proton relaxation was assessed using the Roch et al. [1] model to analyze the NMRD profiles.

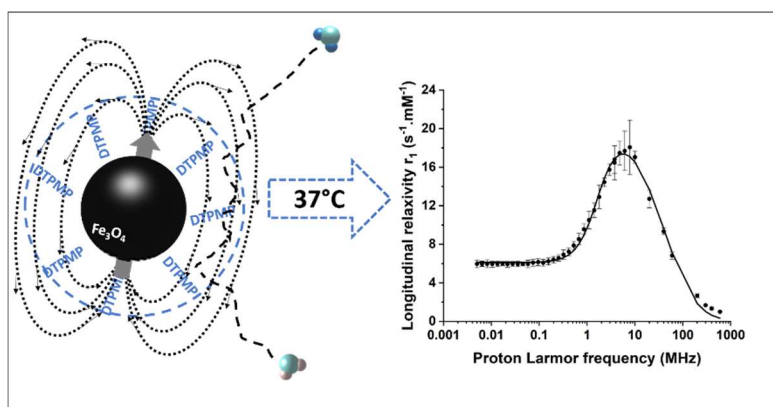


Fig. 1. Longitudinal r_1 NMRD profile of methylene phosphonic acid (DTPMP) coated superparamagnetic iron oxide nanoparticles in the frequency range 0.005-600 MHz at 37°C

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IN-VIVO AND EX-VIVO DETECTION OF COLORECTAL CANCER AT ULTRA-LOW FIELD USING FAST FIELD-CYCLING METHODS

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Introduction

R_1 ($1/T_1$) Nuclear Magnetic Relaxation Dispersion (NMRD) profiles provide promising biological biomarkers of tumours non-invasively and without using contrast media, using ultralow magnetic field (1–3). More interestingly, Field-Cycling imaging (FCI) provides images with R_1 -dispersion contrast that can offer new insights for clinical applications in a variety of pathologies. The aim of this pilot study was to acquire R_1 -dispersion profiles from fresh resected colorectal cancer samples using the FFC-NMR technique and to test the feasibility of the FCI whole-body scanner to *in vivo* detect rectal cancer.

Methods

Twenty-eight fresh resected tumour samples and corresponding peritumoral and healthy counterparts were analyzed using a commercial FFC NMR relaxometry at a controlled temperature of 37°C $\pm$ 0.1°C. A two-segment power law model was applied to fit the NMRD profiles. For imaging work, seven patients diagnosed with rectal cancer were scanned by using an FCI scanner, with four evolution fields ranging from 0.2 T to 0.2 mT, TE of 21 ms, 20 kHz bandwidth, in-plane resolution of 4.3 mm and slice thickness of 10 mm.

Results

The ex-vivo R_1 dispersion profiles revealed differences between healthy, peritumoral and tumour samples, and this difference increases with lower fields below 100 kHz (**Fig.1**). Moreover, the FCI scans analysis revealed that R_1 dispersion profiles from tumour and healthy tissue distinctly demonstrated higher R_1 values at lower magnetic fields within tumour regions across seven patient scans (**Fig.2**).

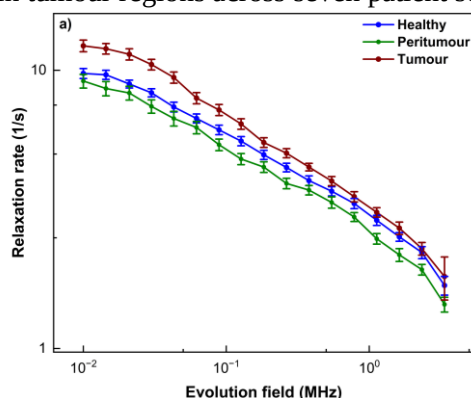


Fig.1. Average R_1 dispersion profile (log/log scale) from *ex vivo* analysis of colorectal cancer, peritumoral and corresponding healthy samples. Error bars represent the standard error of the mean.

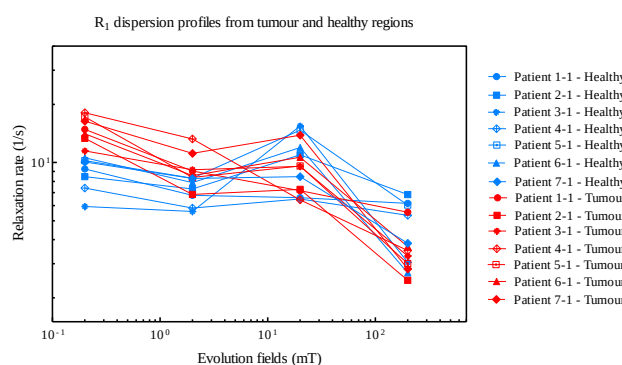


Fig.2. Average R_1 dispersion profiles (log/log scale) from *in vivo* imaging of seven rectal cancer patients, comparing tumor tissue (indicated in red) and healthy tissue in the contralateral region (indicated in blue).

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Relaxometric investigations of Fe(III)-based complexes as T_1 -weighted Contrast Agents

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The rapid integration of MRI in clinical diagnostics has been greatly aided by the development of gadolinium-based contrast agents. However, recent concerns about their economic, environmental, and clinical impacts have prompted research into alternative options. Fe(III) chelates have emerged as potential substitutes, showing comparable efficacy in clinical settings. Yet, understanding the relationship between their mechanisms of action and structural influences remains an open challenge.[1] Insights into this aspects can only be accurately determined by relaxometry. Hence, a detailed examination on the relaxometric properties of several Fe(III)-based chelates was carried out by measuring ^1H longitudinal relaxation data from 0.01 up to 500 MHz and ^{17}O transverse relaxation rates (R_2) and shifts ($\Delta\omega_t$) at 11.7 T, as a function of temperature. Starting from $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$, we were able to differentiate the prototropic exchange contribution from the overall water exchange processes (Fig. 1). Furthermore, studies on monohydrated model systems such as $[\text{Fe}(\text{EDTA})]^-$ and $[\text{Fe}(\text{CDTA})]^-$ highlighted that electronic relaxation times are one of the key determinants of relaxivity, necessitating optimization efforts.[2] Consequent studies on lipophilic derivatives of $[\text{Fe}(\text{EDTA})]^-$ explored the synergy of electronic relaxation and molecular tumbling on water proton relaxation enhancement. The lipophilic nature of these chelates also allowed the study of the interaction with different macromolecules (i.e. human serum albumin). Finally, this relaxometric approach has been crucial to fully characterize the differently hydrated species defining the Fe(III)-Tiron system. These investigations may represent useful guidelines for the development of Fe(III) complexes as T_1 contrast agents with improved safety, biotolerability and efficacy.

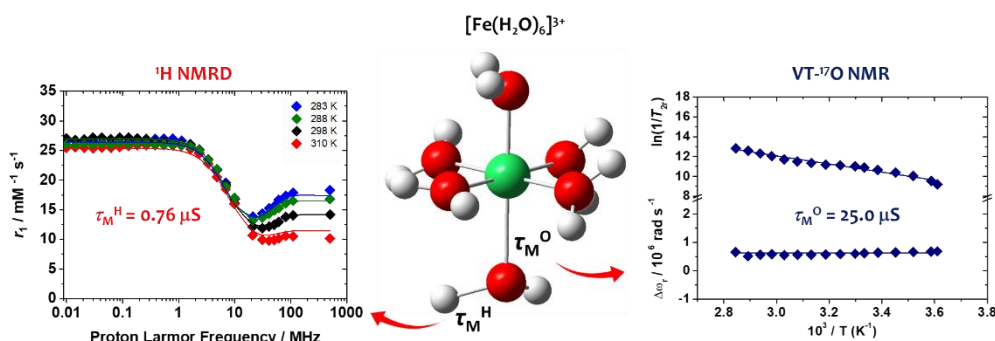


Fig. 1. Differentiation of the prototropic exchange contribution from the overall water exchange process by relaxometry for $[\text{Fe}(\text{H}_2\text{O})_6]^{3+}$.

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Advancing NMR Analysis: Deep Neural Network Solutions for Inverting NMRD Profiles with Quadrupolar Dips

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Interpreting Nuclear Magnetic Resonance Dispersion (NMRD) profiles acquired by FFC NMR relaxometry technique, especially with quadrupolar dips [1], presents significant complexity and challenges due to the intricate nature of the data [2]. Various optimization-based software tools have been explored and documented in the literature to address the parameter identification problem [2, 3]. These profiles measure the variation of the longitudinal relaxation rate, R_1 , with the angular frequency ω of the applied magnetic field, necessitating sophisticated analytical techniques to decode the information accurately:

$$R_1(\omega) = R_0 + R^{HH}(\omega) + R^{NH}(\omega) \quad \omega = 2\pi\nu$$

Here, $R_0 \geq 0$ is an offset accounting for fast correlation times. The term $R^{HH}(\omega)$ has the following expression:

$$R^{HH}(\omega) = \int_0^\infty \left(\frac{\tau}{(1+(\omega\tau)^2)} + \frac{4\tau}{(1+4(\omega\tau)^2)} \right) f(\tau) d\tau,$$

where $f(\tau)$ represents the unknown correlation time distribution describing the $^1H-^1H$ relaxation, and τ represents the correlation times, i.e., the average times required for a molecule to rotate one radian or move a distance equal to its radius of gyration.

Finally, $R^{NH}(\omega)$ describes the quadrupolar enhancement relaxation term. It is a nonlinear function depending on six physical parameters to be extracted: $\Psi = [C^{NH}, \theta, \phi, \tau_Q, \nu_-, \nu_+] \in \mathbb{R}^6$ [1,2].

To address the complexity of FFC-NMR analysis, researchers are exploring alternative strategies such as deep learning. Recent advancements in AI, particularly Deep Neural Networks (DNNs), show significant potential in efficiently inverting NMRD profiles, even when dealing with complex quadrupolar interactions. We present a computational approach employing Deep Neural Networks (DNNs) to identify model parameters in the presence of quadrupolar dips. This method integrates a numerical optimization technique with the Plug and Play (P-n-P) approach [4]. Specifically, parameter estimation is conducted using a coordinate descent method, employing the nonlinear Gauss-Seidel iterative algorithm to solve the problem in two blocks.

Two – Blocks Plug and Play Algorithm

1. Initialize $j = 0$, choose starting $((R_0, f)^{(0)}, \Psi^{(0)})$.
2. Repeat:
 - Update $(R_0, f)^{(j+1)}$ solving $\min_{R_0, f \geq 0} \{ \|R_1 - (R_0 + \mathcal{F}_1(f))\|_2^2 + \lambda \|f\|_1 \}$ using the *Truncated Newton Interior-Point method*. $\lambda > 0$ is the regularization parameter updated following the balancing principle [5].
 - Update $\Psi^{(j+1)}$ with *NMRNet*.
 - Increment j .
3. Until exit condition is met.



The first block (to extract R_0 and f) is formulated as a constrained least-squares problem with an L_1 penalty term and is solved using the Truncated Newton Interior-Point method. The second block estimates the quadrupolar parameters by a trained feed-forward neural network (referred to as NMRNet), using the P-n-P approach.

NMRNet is a feed-forward neural network with 5 hidden layers. It takes as input only the R^{NH} part of the NMRD profile. The input layer's dimension matches the NMRD profile, while the output layer has a dimension of 6, corresponding to the parameters we aim to extract. The final activation function is designed using constraints based on physical a priori information.

Furthermore, we developed a loss function that integrates the L_1 loss from output predictions and the predicted R_1 signal, which is crucial for training predictions and fitting the NMRD profile.

This contribution aims to demonstrate the effectiveness of utilizing DNNs for NMRD profile inversion by comparing the outcomes with those obtained using a previously developed robust optimization method [2]. The results indicate a strong agreement between the two approaches (as shown in Figure 1), suggesting that DNN-based methods could significantly enhance this analysis, particularly by accelerating the processing of large datasets.

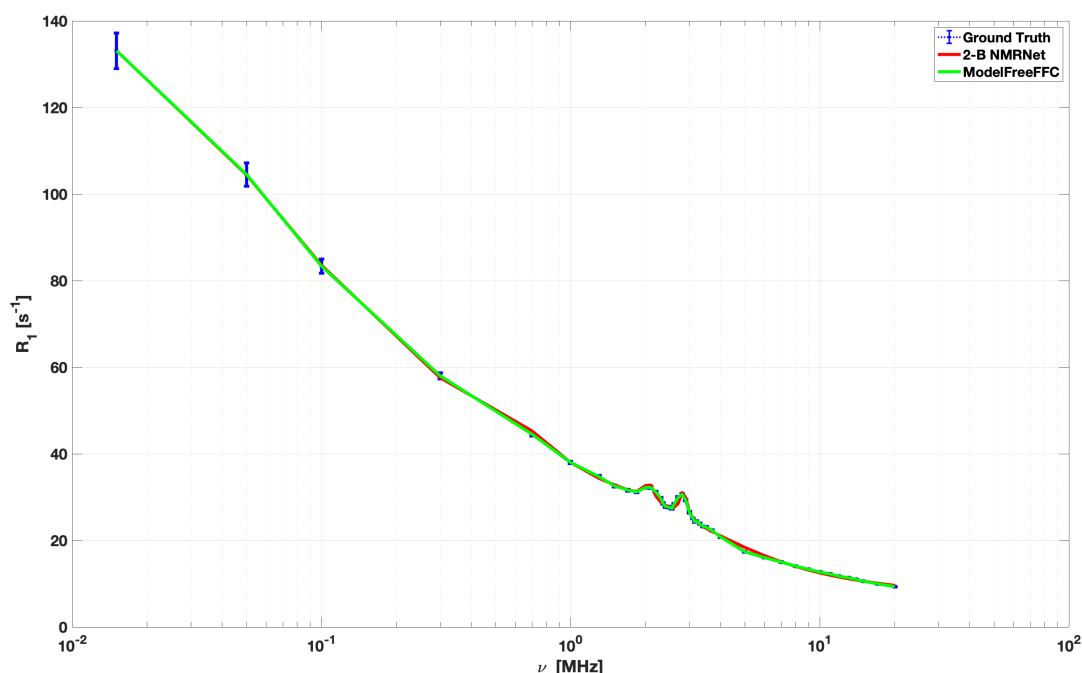


Figure 1. NMRD Profile of Parmigiano sample. In blue the experimental signal acquired, in red the results obtained by the proposed method, and in green the results obtained by a robust algorithm developed [2].

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EVALUATION OF RELAXOMETRIC DATA BY REX: CLASSICAL AND MODERN PROCEDURES

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This presentation will start with a brief review of current data-evaluation capabilities of the WinREX software, which are rapidly expanding, including many fitting and simultaneous fitting procedures (FID's, relaxation curves, discrete and continuous inversions, field and temperature profiles, arrayed experiments) with models in each category that a user can freely combine from a large variety of "elementary models". All fits are complemented by rigorous "goodness of fit" tests (we call them residues analysis), such as chi-square, Kolmogorov-Smirnov, VonMises-Cramèr, and others.

It will then proceed with two reflections:

- 1) Questions and "problems" often raised by users which have a common root: multiplicity of possible solutions due to the objective lack of complete information in the experimental data. We will reflect on why it so often happens, when it is most likely to happen, and how can we counter it.
- 2) Based partially on the previous point, as well as on "modern tendencies", we will reflect on what other performance items are needed in a relaxometry data-evaluation software, dividing them into several intersecting categories:
 - a) New procedures for preventive checking on the information content of experimental data
 - b) Better support for models involving diffusion and rheological phenomena in materials
 - c) Combining NMR relaxometry with related methods (dielectric relaxation, fluorescence, ...)
 - d) AI-types of data processing: PCA, PLS, ML, DL, ...



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Understanding NMR relaxation theory – how to create new equations and what for?

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The first expressions for spin – lattice and spin – spin relaxation rates (R_1 and R_2 , respectively) have been obtained for relaxation process caused by magnetic dipole – dipole interactions between identical, spin -1/2 nuclei, at a high magnetic field (resonance frequency). The equation: $R_1 \sim (J(\omega) + 4J(2\omega))$ has become a “golden rule” for interpreting NMR relaxation data. And then FFC NMR came along and we can vary the resonance frequency and the expressions are broken down.

The first great advantage of FFC NMR relaxometry is the possibility to probe dynamical processes occurring on much different time scales. This has, however, consequences – the overall relaxation rates include relaxation contributions originating from inter-molecular and intra-molecular dipole – dipole interactions mediated by different dynamical processes (translation, rotation, chain motion, internal dynamics). This implies that one has to identify all relevant relaxation contributions and express them in terms of spectral density functions attributed to specific mechanism of motion. The shape of the frequency dependencies of the relaxation rates are fingerprints of the mechanisms of the dynamical processes. This has proven to be a great challenge – when relaxation experiments are performed at a single (high) resonance frequency one can eliminate relaxation contributions associated with slower motion (such as translation diffusion) and claim non-Arrhenius dependencies in case of troubles.

The second great advantage of varying the resonance frequency is the possibility to reveal relaxation effects originating from different spin interactions. The relaxation scenario at a high resonance frequency is simple: dipole-dipole interactions cause transitions between Zeeman energy levels. At lower resonance frequencies one observes peculiar effects associated with quadrupole interactions (for instance for ^{14}N nuclei), while at very low resonance frequencies residual dipole-dipole interactions and scalar couplings come into play.

The third great advantage is the potential to reveal bi-exponential (multi-exponential) relaxation processes caused by the quantum-mechanical relaxation framework or/and heterogenous dynamics. Distinguishing between these origins for hetero-nuclear systems can be very demanding.

In my opinion, the most challenging systems are solid electrolytes – here one encounters all the subjects. The purpose of the lecture is to present the development in the relaxation theory, from the simplest cases to the most complex ones and show the way of tailoring the relaxation models to the specifics of the investigated systems.

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Ultrafast High-Resolution Relaxometry from 100 μ T to 23.5 T to unravel internal motions in proteins and nucleic acids.

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Bio-molecular motions are vital for biological function and determine how and when proteins and nucleic acids interact with their surroundings. High-Resolution Relaxometry (HRR) probes the spectral density function of specific inter-atomic interactions by measuring field-dependent site-specific relaxation rates, giving access to internal motions from ~ 10 ps to ~ 10 ns [1].

Here, we use HRR to study the internal motions in a 12 base-pair DNA helix (Fig. 1). We developed a theoretical framework describing: low field relaxation rates from 2 T to 23.5 T, the underlying internal motions using the Extended Model Free approach and compare them to molecular dynamics simulations. The timescales and order parameters show that despite its simple structure DNA exerts surprisingly wide motions on a pico- to nanosecond timescales.

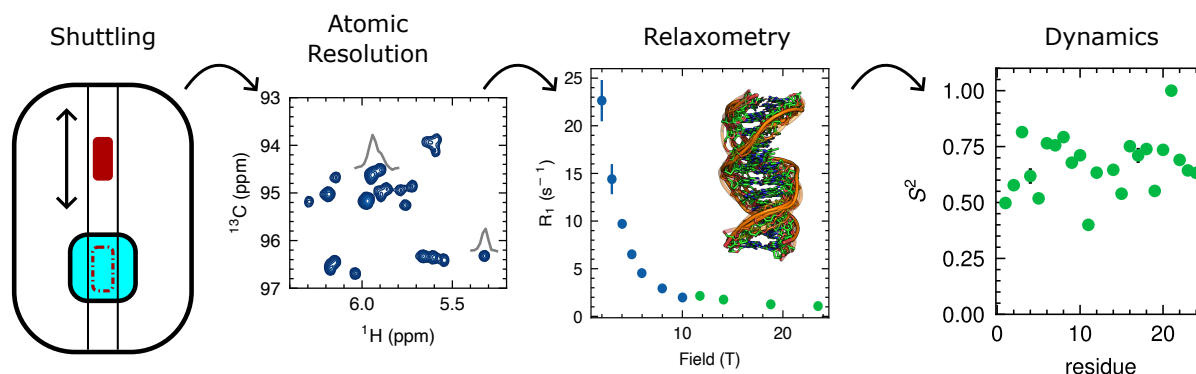


Fig.1. In (U)HRR experiments the sample is rapidly transferred to a point of the stray field, or a field cycling coil, to record low-field relaxation. Detection at the high field centre allows NMR dispersion profiles to be recorded with atomic resolution comparable to those obtained in high-field experiments. The NMRD profiles can then be interpreted to obtain parameters to describe internal motions.

A clear limitation of HRR lies in the ability to reach low fields fast. Here we introduce Ultrafast HRR, which combines fast shuttling (transfer times of 90 ms) with fast field cycling of an electromagnet. We measured longitudinal carbon-13 relaxation rates with atomic precision in methyl bearing side-chains in a 42 kDa MAPK kinase, p38 γ , over a range of fields from 100 μ T to 22.3 T to obtain the full NMR relaxation dispersion profile.

These studies illustrate the potential of high-resolution techniques to uncover detailed dynamics in biomolecules with atomic resolution, providing insights that are critical for understanding their biological roles and interactions.

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EFFECT OF TACKIFYING RESINS ON SBR DYNAMICS BY MEANS OF ¹H FIELD-CYCLING NMR RELAXOMETRY

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Polymers exhibit hierarchical dynamics, encompassing a wide range of motion time scales, from rapid local segmental motions to slow diffusive movements of the polymer chain's center of mass[1-3]. ¹H Field-Cycling (FC) NMR relaxometry has proven to be a very powerful technique for studying the dynamics of long polymers above the glass transition temperature, as it is capable of discerning and exploring different dynamic regimes (Figure 1), thanks to the possibility to measure ¹H T_1 over a wide range of Larmor frequencies[2]. This work employs ¹H FC NMR to investigate how the presence of tackifying resins affects the dynamics of styrene-butadiene rubber (SBR) in compounds of technological interest for the tire industry. We analyzed uncured and vulcanized samples containing different amounts, from 0 to 45 part per hundred of rubber, of either a petroleum-based resin or a resin of natural origin (rosin resin). The results provide insights into the effect of both the amount and type of resin on glass transition and polymer dynamics, which can be related to the resin-polymer interaction and miscibility. The results of our study are helpful to clarify the relationship between molecular dynamics and macroscopic properties, which is essential for designing new formulations with optimized performances.

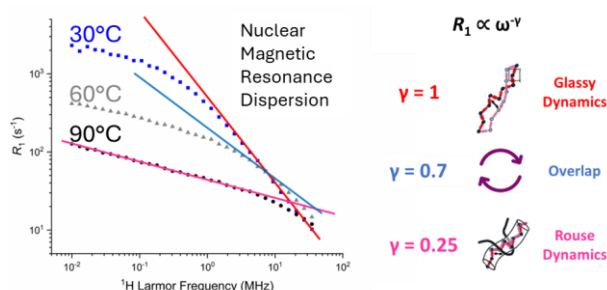


Fig. 1. Nuclear Magnetic Resonance Dispersion curves for pure SBR. It's possible to distinguish different dynamical regimes through the dependence of R_1 on ¹H Larmor frequency.

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MAXIMISING VALUE FROM FAST FIELD CYCLING NMR WITH THE 3TM SOFTWARE

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FFC NMR relaxometry is a powerful tool for obtaining nanoscale information from hydrated porous materials. The 3-Tau model (3TM) [1,2] is fit to NMR dispersion curves obtained from both soft and hard material and shown to yield physically-justifiable values for the surface, desorption and bulk dynamical correlation times (τ_ℓ , τ_d , τ_b), surface proton spin density (N_ℓ), solid paramagnetic (or solid proton) spin density (N_σ or N_H), and surface-to-volume ratio ($\chi = S\delta/V$, $\delta = 0.27\text{nm}$). The 3TM fitting software is available free to use and supported by the authors [3].

The surface-to-volume ratio χ can be transformed to a characteristic pore size parameter h . Pore sizes obtained from a hydrogel and a laminar biomaterial are found to agree remarkably well with neutron scattering [4] and X-ray measurements respectively. The change in h from NMRD curves of a curing cement paste provides a measure of reaction rate which is linked to final product strength [5]. High-quality fits to NMRD curves from Comte cheese are obtained with just two components: one capturing ^1H - ^1H interactions and one for ^1H - Fe^{3+} interactions. Fits are shown to reveal a reduction in h as the cheese matures, and pores reduce in size (Fig. 1).

The proton spin density at solid surfaces for soft material and biomaterial is shown to be typically 20-50% of the bulk water density. Examples of 3TM fits to healthy and tumorous murine tissue are presented. A fresh analysis of 32 dispersion curves from *in vivo* tumorous murine tissue [6] confirm the low-frequency relaxation rate R_1 as a tumour biomarker. We find that the reduction in R_1 with tumour fraction is due to the reduction of τ_b and χ explained by the increased size of the tumour cells due to ingress of water. The paramagnetic spin density N_ℓ is shown to be consistent with typical iron concentrations in mammals.

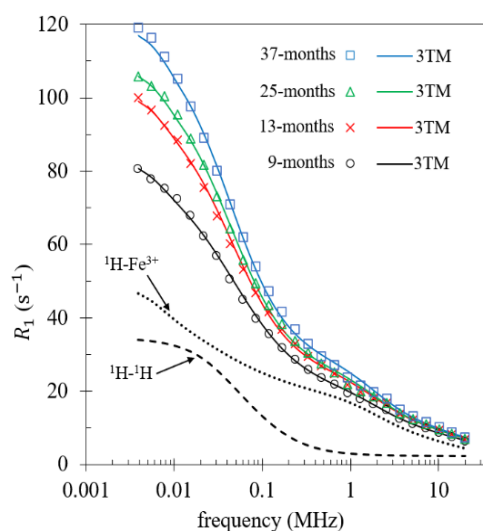


Fig. 1. Fits using 3TM for Comte cheese after 9-, 13-, 25- and 37-months maturation. Each 3TM fit is the sum of ^1H - ^1H and ^1H - Fe^{3+} contributions (shown for the 9-months sample).

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POSTER PRESENTATIONS



NMR relaxometry to monitor *in situ* the loading of ion exchange resins with Ni²⁺ and Cu²⁺ ions during a column experiment

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Water pollution by heavy metals is a major environmental problem [1]. To address this issue, the removal of heavy metals from wastewater often requires the use of ion exchange resins or adsorbents. However, current methods for assessing ion exchange/adsorption efficiency are often indirect and destructive. Some heavy metal ions, such as Cu²⁺ and Ni²⁺ exhibit paramagnetic properties that influence the NMR relaxation times T_1 and T_2 of water protons. Benchtop NMR relaxometry was thus already used to monitor the removal of paramagnetic heavy metals by sorbents (alumina and activated carbon) and ion exchange resins [2,3]. These studies paved the way for the use of NMR relaxometry directly on the sorbent/resin in a column experiment, with the aim to monitor *in situ* the gradual loading of the resin with the paramagnetic ions. The setting up of such an experiment is of course much more complicated than for batch experiments, as is the interpretation of the obtained curves. In this work, we followed by relaxometry the loading of two ion exchange resins beds (Amberlite IR120 and Dowex Marathon) with Ni²⁺ and Cu²⁺ in a column which was directly inserted into an NMR device (Fig. 1).

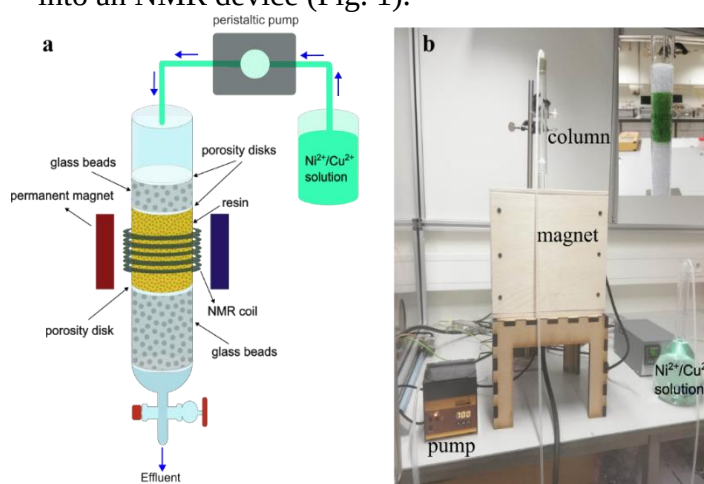


Fig. 1: (a) sketch of the experimental setup. (b) picture of the actual experiment, the inset shows a close-up of the column after saturation with Ni²⁺.

After the saturation, the slow fraction corresponds to the untreated solution (containing Ni²⁺ or Cu²⁺) flowing between the resin beads already saturated with paramagnetic ions. This interpretation is consistent with the time evolution of the T_2 distributions obtained by inverse Laplace transform. In actual systems, the metal concentration of the feeding solution will be smaller and the experiment longer, which will imply to adapt the measurement sequence and the interpretation of the results.

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Developing Copper(II) and Gadolinium(III) Coiled Coils as MRI Contrast Agent

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In diagnostic MRI, contrast agents are often used to help differentiate different tissue types. Traditionally, these agents, such as Dotarem, are based on small molecular complexes bound to Gd(III) or Mn(II) ions, which significantly reduce the T_1 relaxation time of surrounding water molecules. However, concerns about the safety of Gd(III) complexes in the body has prompted a shift towards exploring alternative metal ions with greater biological relevance.

Cu(II) has largely been overlooked as a viable metal ion for contrast agents because it has only one unpaired electron, compared to Gd(III)'s seven, which contribute to the high relaxivity of Gd(III) complexes. However, we recently demonstrated that, when coordinated to a coiled coil -a miniature protein scaffold made up of alpha helices- (see Figure A), Cu(II) complexes are capable of high relaxivity [1], giving rise to comparable r_1 and enhanced r_2 compared to its Gd(III) counterpart [2]-[4]. Herein, we present the design and development of novel Cu(II) and Gd(III) coordinated coiled coils. We report, for the first time, the use of relaxometry to help understand the mechanism by which these metallo-coiled coils achieve high relaxivity.

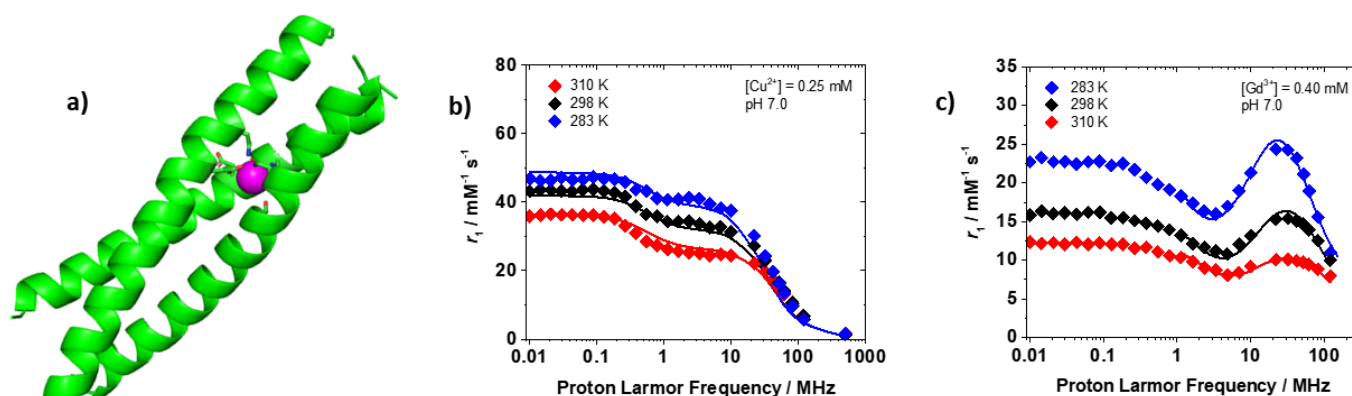


Fig. 1. Show a) Cartoon representation of a metalated coiled coil and ¹H NMRD profiles of a) Cu(MB1-2)₃ and b) Gd(MB1-2)₃ at different temperatures.

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FFC NMR RELAXOMETRY TO UNVEIL STRUCTURAL AND FUNCTIONAL FEATURES OF CERAMIC RAW MATERIALS FROM NORTH MOROCCO

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Clayey materials are the main raw materials used for manufacturing diverse ceramic products. Given the inherent complexity of the physical, chemical and mineralogical features of clayey materials, clays from different origins have unique properties as related to their genesis and diagenesis. Morocco has several deposits of clayey materials. However, only few studies have been carried out on the quality assessment of Moroccan natural clays. Following a previous study where the chemical and mineralogical compositions of Moroccan clays were determined [1], five clay samples derived from three North-West Moroccan regions (namely Berrechid, Tiflet, and Khemisset) were analysed by means of FFC NMR relaxometry. The FFC NMR relaxometry analysis was conducted as described by Conte et al., (2022) [2]. The regression analysis of the NMRD dispersion curves was performed by means of a model-free approach, that relies on the elaboration of the inverse integral transform of the NMRD curve with the BPP function [3], avoiding the introduction of discretion elements. The analysis was complemented by applying the Monte-Carlo approach, in order to calculate the indetermination of the regression parameters and to individuate possible artifacts. The obtained results highlighted the existence of three distinct dynamic domains. Each dynamic domain can be attributed to a specific water molecular motion occurring in clay samples. These directly depend on the nature of the ^1H - ^1H dipolar interactions between water molecules and clay surfaces that, in turn, are affected by the size and shape of the pores where water moves. The faster component (i.e., low τ_c) refers to the strongly retained water molecules and is due to the motion of intraparticle diffusion. The slower component (i.e., high τ_c) refers to weakly retained water molecules and is due to the motion of horizontal surface diffusion. Finally, the intermediate component can be attributed to the motion of interparticle diffusion. The absence of very slow components (i.e., $\tau_c < 0.001 \mu\text{s}$) indicated the absence of bulk water, in accordance with the microporous structure of clayey materials. The results of the study proved that the FFC NMR relaxometry coupled with the heuristic approach is a valuable tool to evaluate the structural and functional features of clay samples. The assessment of the main physical-chemical features of clays is a very important aspect for determining the technical performances of natural clayey materials.

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EXPLORING THE COMPETITIVE ADSORPTION OF WATER AND ETHANOL IN MESOPOROUS SILICAS WITH NMR RELAXOMETRY

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The relaxation behaviour of liquids confined within porous materials can be strongly influenced by co-imbibed species, allowing relaxation measurements to give important insights into the dynamics and structuring of liquid mixtures within the pore space [1]. In previous studies on alumina catalyst carriers [2] and Vycor glasses [3], it was shown that for binary liquid mixtures with large polarity differences the more polar species preferentially occupied the surface and forced the less polar species into the bulk pore space. In this work we have explored the competitive adsorption behaviour of water-ethanol liquid mixtures within silica supports, where both components are polar and have the potential to interact strongly with the surface. The silica supports had nominal pore sizes of 6, 10, 15, and 30 nm and surface hydroxyl densities, α_{OH} , in the range 1.3-5.2 nm⁻²; these materials are referred to as S6, S10, S15, and S30. T_1 - T_2 measurements at 43 MHz and fast field cycling NMR measurements were carried out as a function of composition for the four different silicas. For each liquid mixture, two distinct relaxation environments were observed, corresponding to the hydroxyl and alkyl functionalities. As seen from Figure 1, the relaxation measurements showed that the adsorption behaviour differed strongly between the silicas, with evidence of a microphase separation at the pore surface for the larger pore silicas (S15 and S30). The effects of pore size and surface hydroxyl characteristics of the silicas on adsorption and micro-phase behaviour were explored. These results are of particular interest with regard to how mesoporous silicas may be selected and optimised for use as catalyst supports or in molecular separation processes.

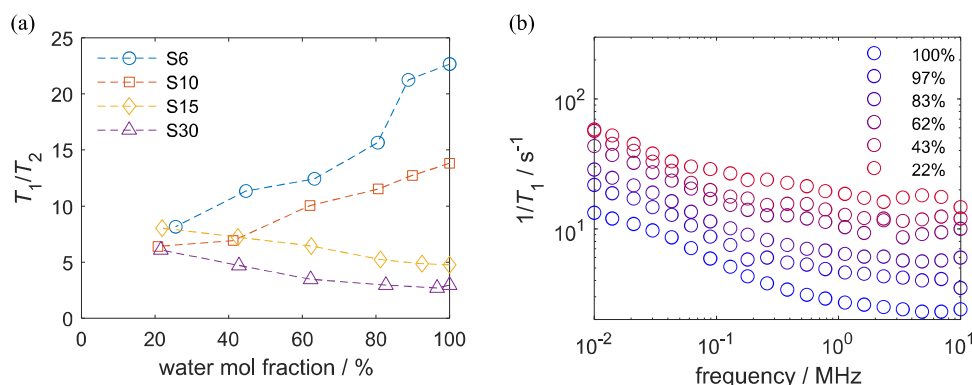


Figure 1 – The (a) T_1/T_2 ratio of the hydroxyl functionalities of water-ethanol binary liquid mixtures as a function of composition when imbibed within different silicas and (b) fast field cycling dispersion curves of the hydroxyl component imbibed within S30 silica. For each field cycling dispersion profile, the mole fraction of water in the liquid mixture is shown.

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Simulation of transverse nuclear magnetic relaxation induced by superparamagnetic nanoparticles with a semipermeable coating

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Superparamagnetic iron oxide nanoparticles (SPIONs) are characterized by a high magnetisation when submitted to a high external field, and no remnant magnetisation in zero field. Those properties make them suitable to be used as contrast agents in nuclear magnetic resonance imaging (MRI). Indeed, when present in a tissue, they change the relaxation time of the surrounding water. This in turn changes the MRI signal and therefore makes the area appear darker or clearer in contrast to the surrounding tissues.

A variety of theoretical models allow to quantitatively predict the relaxation induced by SPIONs, depending on their physical properties (in particular, their size and saturation magnetisation). In those models, transverse relaxation at high magnetic field is caused by the progressive dephasing of the water protons magnetic moments. Dephasing is caused by diffusion of the water molecules in the magnetic inhomogeneities created by the nanoparticles. Indeed, as they diffuse, water molecules experience varying magnetic fields which will alter their precession frequency and cause a progressive dephasing [1]. Hence, relaxation times, and therefore contrast, are strongly linked to the diffusion coefficient of the water molecules.

However, due to their complexity, theoretical models are confined to modelling relaxation in a homogeneous medium, which can be a very approximative hypothesis. In particular, the environment directly surrounding the magnetic crystals is usually not homogeneous, as they are surrounded with a layer of coating. That coating is usually a polymer and is therefore semi-permeable to water, with a lower diffusion coefficient as compared to bulk solvent. This is believed to affect the measured relaxation times [2,3], especially as this zone of slow diffusion is also a zone of high magnetic inhomogeneities, being close to the surface of the nanoparticles.

This work aims at simulating the relaxation of water, as induced by SPIONs coated with a semi-permeable layer, with reduced diffusion coefficient. To that end, numerical simulations using Monte Carlo techniques, based on the random walk of water protons, and computation of the dephasing resulting from them, are developed. The goal of our work is to evaluate if, for three different nanoparticle sizes corresponding to three different relaxation regimes, slowed diffusion in the coating indeed impacts the relaxation of water protons.

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MONTE CARLO SIMULATIONS OF THE T₂ RELAXIVITY INDUCED BY CUBIC SHAPED SUPERPARAMAGNETIC NANOPARTICLES

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Nanoscale materials have garnered immense attention in the scientific community for the past few decades due to their wide range of applications [1] and their unique properties. At this scale, magnetite and maghemite particles exhibit superparamagnetic behavior at room temperature in addition to a high surface area-to-volume ratio. SuperParamagnetic Iron Oxide Nanoparticles (SPIONs) are predominantly used as T₂ and T₂^{*} contrast agents to detect tumors in Magnetic Resonance Imaging (MRI) [1]. When SPIONs are introduced inside a tumor by targeting methods, the associated T₂ is decreased which darkens the tumor on the MR images.

Usually, SPIONs particles are synthesized in a spherical shape. However, over this last decade, some studies synthesized exotic-shaped particles [2] and measured a decrease in T₂ by a factor 2 or even more compared to the usual spherical-shaped SPIONs. In our work, we propose to assess the impact of SPION's shape on T₂ using relaxation simulation and an analysis of the stray field of a cubic-shaped SPION.

NMR CPMG sequences were simulated using a well-known Monte Carlo method considering cubic and spherical SPIONs under a very high magnetic field B₀[3]. The magnetic stray field of a cubic particle is analytically derived from the demagnetization tensor field [4]. Proton diffusion is modeled by a random walk considering a water diffusion coefficient at 300°K. Each proton spin is represented by a vector in the plane perpendicular to B₀.

Our results indicate that there are no significant differences between cubic and spherical shaped SPIONs when their diameters are larger than 30 nm, corresponding to the Static Diffusing Regime (SDR) and over 200 nm in the Partial Refocusing Regime (PRR). However, in the Motional Average Regime (MAR), i.e. for particle sizes smaller than 30 nm, a 10 to 20% decrease in T₂ is observed for cubic SPIONs compared to spherical SPIONs. To quantitatively interpret these results, NMR relaxation models, which include an analysis of the field distribution, were applied to the two shapes [5] [6]. These models confirm our simulation results in the three regimes.

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Fast-field-cycling NMR Relaxometry and Biometric Analyses for the Evaluation of Hemp Inflorescences Traceability

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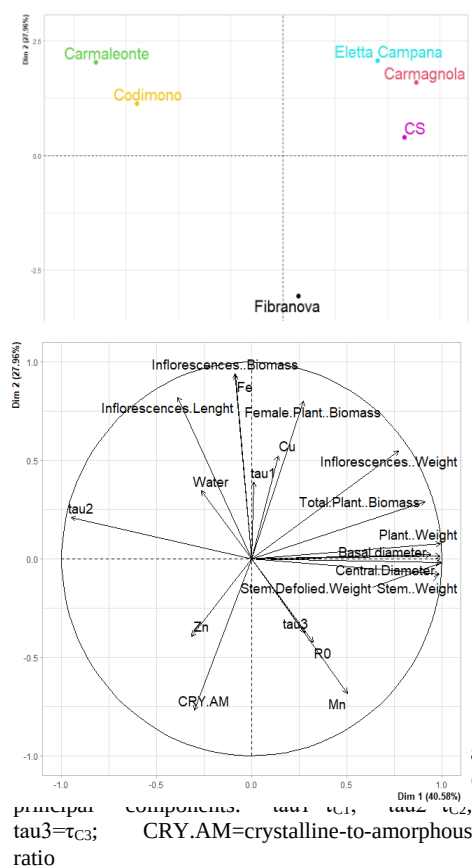
Hemp (*Cannabis sativa* L.), a versatile crop, offers numerous environmental advantages, including carbon sequestration, disease cycle disruption, soil erosion control, biodiversity support, reduced pesticide reliance, and alignment with the European Green Deal goals [1]. Industrial hemp varieties, adhering to the EU-mandated 0.2% Δ^9 -tetrahydrocannabinol (THC) limit, are freely cultivable. Beyond its conventional use as a source of stem-derived bast fibers, hemp finds applications in non-textile sectors. Notably, its inflorescences yield valuable essential oils (EO). However, EO composition and aroma profiles vary significantly across cultivars [2], necessitating raw material authentication. To address this, we employed various NMR techniques and biometric data to distinguish among seven hemp cultivars. High-resolution NMR spectroscopy and fast field cycling NMR relaxometry have proven effective in differentiating plant tissues based on origin [3]. NMR techniques offer advantages over other analytical methods due to their speed and non-destructive nature [4]. Furthermore, combining NMR data with biometric analyses through statistical methods enhances their potency [5].

During 2021, two monoecious (*Codimono* and *Carmaleonte*) and five dioecious hemp cultivars (*Carmagnola*, *Carmagnola Selected* (CS), *Eletta Campana*, *Fibrante* and *Fibranova*) were cultivated in an open field setting in Battipaglia, Italy. Biometric measurements and inflorescence sampling were conducted at the end of the crop cycle. Following a 65°C heat treatment, inflorescences underwent grinding in preparation for analysis. FFC NMR experiments were carried out at a constant 25°C using a Stelar Spinmaster FFC 2000 relaxometer, using a previously described experimental setup by Conte et al. [6]. Experimental data processing employed the ModelFreeFFC software developed at the University of Bologna (Bologna, Italy) to derive correlation time (τ_c) distributions. CPMAS ¹³C NMR experiments were conducted using a Bruker Avance 400 spectrometer operating at 100 MHz on the ¹³C nucleus with a rotor spin rate of 13 kHz. Cellulose crystallinity was determined by deconvolution of signals within the 95-80 ppm range, following the method described by Park et al. [7]. Total recoverable levels of Cu, Fe, Mn, and Zn in inflorescences were quantified using a Perkin Elmer AAnalyst 400 with flame atomization (Waltham, MA – USA) after nitric-perchloric acid digestion. Principal Component Analysis (PCA) was performed using the R software (v4.1.2) and the FactoMineR package.

The τ_c distributions derived from the FFC NMR study (not shown) revealed the presence of two or three bands across three distinct relaxation domains for all samples. Recognizing the complex molecular makeup of inflorescences, higher τ_c values can be attributed to components with low molecular mobility, such as polysaccharides, proteins, fibers, and adsorbed water. Conversely, intermediate and lower τ_c values likely represent more mobile components, including polyphenols, cannabinoids, terpenes, and others. Notably, the peak τ_c values



within each domain ($\tau_{C1} < \tau_{C2} < \tau_{C3}$) varied among cultivars, suggesting differences in inflorescence molecular composition.



In contrast, the CPMAS ^{13}C NMR spectra did not reveal inter-cultivar differences except within the 95–80 ppm interval. Variations in this region were attributed to differences in the amorphous and crystalline forms of cellulose. Significant differences among cultivars were also observed in biometric measurements and metal concentrations (data not shown).

To further investigate these distinctions, principal component analysis was performed using parameters derived from the NMR techniques, metal levels, and biometric measurements. Three distinct cultivar groups emerged from the PCA analysis. Along PC1, which accounted for 40.6% of the variability, Codimono and Carmaleonte were clearly distinguished from Eletta Campana, Carmagnola, and CS. This separation was driven by higher τ_{C2} values in Codimono and Carmaleonte, indicating a different composition of intermediate molecules, as well as by smaller stem dimensions.

Along PC2, explaining 24.8% of the variability, Fibranova and Fibrante were set apart by their higher crystalline-to-amorphous ratios and, to some extent, higher τ_{C3} values. Reduced inflorescence and female plant growth also contributed to the differentiation of these cultivars.

Conclusions

This study highlights the potential of combining FFC NMR relaxometry, CPMAS ^{13}C NMR, and biometric analyses as a comprehensive approach for differentiating among hemp cultivars. The distinct clustering of cultivars based on these parameters underscores the sensitivity of these techniques to variations in molecular composition, cellulose structure, and growth patterns. Future research

expanding upon these findings by correlating relaxometric characteristics with the biochemical composition of hemp inflorescences will further strengthen the value of this approach for cultivar identification and quality control in hemp production.

Acknowledgements

This work was supported by UNIHEMP research project “Use of iNdustrIal Hemp biomass for Energy and new biocheMicals Production” (ARS01_00668) funded by Fondo Europeo di Sviluppo Regionale (FESR) (within the PON R&I 2014-2020—Axis 2—Action II—OS 1.b), CUP: B76C18000520005.

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Impact of Simulated Fire on Soil Properties: A FFC-NMR Investigation

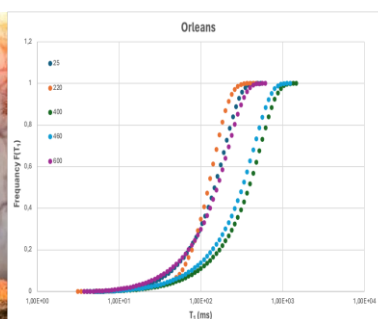
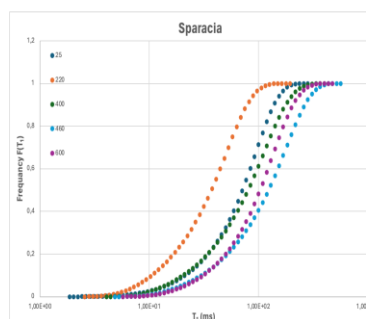
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Wildfires profoundly impact soil properties, influencing a lot of ecological processes. This study investigates the effects of simulated fire on two distinct soil types (Orleans, Sparacia) using Fast Field-Cycling Nuclear Magnetic Resonance relaxometry, which has been proven a powerful tool for investigating molecular dynamics in complex systems. We aim to elucidate how fire-induced alterations, simulated by controlled heating in muffle furnaces, impact the chemical and physical properties of soils. FFC-NMR measurements have been exploited to analyze changes in soil organic matter mobility and composition, as well as water dynamics, across varying degrees of simulated fire severity [1,2]. The technique sensitivity to pore size distribution and water dynamics enables the assessment of soil hydrological connectivity, a crucial aspect of soil functioning impacted by fire. To complement the FFC-NMR analysis, Scanning Electron Microscopy has been used to visualize changes in soil structure and morphology after simulated fire. Additionally, X-ray Diffraction will identify any changes in the mineralogical composition of the soil samples due to heating. This approach, combining FFC-NMR, SEM, and XRD, provides with a comprehensive understanding of the impact of fire on soil organic matter dynamics, overall soil quality, and mineralogical composition. Our findings may likely contribute to a better understanding of fire-affected ecosystems and inform post-fire management strategies.



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ACTIVATED CARBONS FROM CHERRY STONES: A GREEN STRATEGY FOR ORGANIC POLLUTANTS PHOTODEGRADATION .

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Activated carbons (ACs) stand out as a prominent class of materials known for their high porosity, high surface area, and readily tunable surface chemistry. Their ability to effectively sorb a wide range of substances makes them valuable in various industrial applications. Various precursors can be employed in the production of ACs, ranging from non-renewable sources (coal and petroleum coke) to renewable ones as agricultural biomasses. In particular, cherry stones have emerged as a particularly promising candidate due to their inherent composition and structure. The choice of activation method significantly affects the pore size distribution, surface area, and surface chemistry of the resulting AC, ultimately impacting its performance in specific applications [1]. Steam activation is a widely employed physical activation method, environment friendly and able to provide ACs with high surface areas and well-developed pore structures. By carefully controlling the steam concentration during the activation process, it is possible to finely tune the AC's characteristics to align with the specific requirements of targeted applications [2]. This study investigates the steam activated synthesis of ACs from cherry stones, employing a method with varying steam dosages, to elucidate the outcome of steam activation on the feature of the resulting ACs and correlate these changes with their performance in photodegradation experiments. Hence, we employed a multifaceted characterization approach. NMR relaxometry was utilized to provide detailed insights into the pore size distribution and surface characteristics of the ACs [3]. In addition, we studied the degradation of model dyes XY & YZ in presence of AC under halogen lamp to evaluate the photodegradation abilities of the synthesized ACs, with regard to emerging pollutants. By combining the insights derived from NMR relaxometry and photodegradation experiments, this study aims to provide a comprehensive understanding of how controlled steam activation can be exploited to tailor the properties of cherry stone-derived ACs for enhanced performance in photocatalytic applications.

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OXIDATIVE FUNCTIONALIZATION ASSESSMENT OF A POPLAR BIOCHAR

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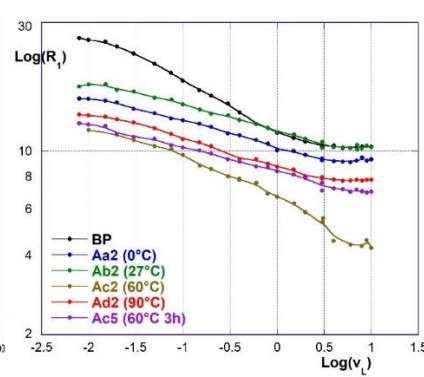
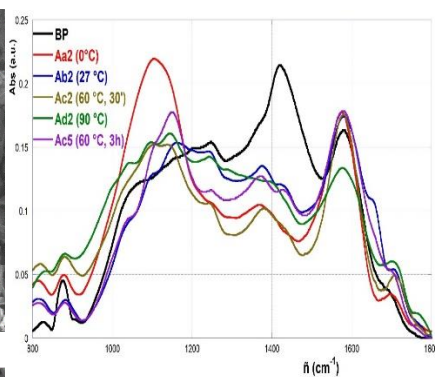
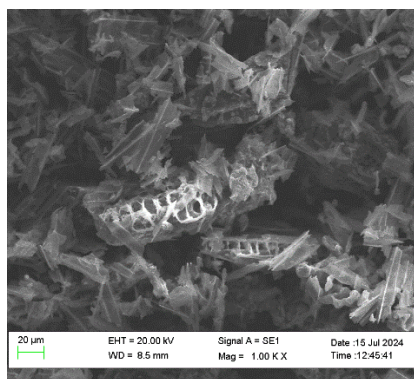
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Chemical functionalization of biochars is main route to the modulation of their physical and chemical properties. This, of course, requires a careful study of the outcome of the reaction method and conditions used (reactants, temperature, time, solvent, etc) on the features of the obtained product. This, in turn, is a mandatory requirement in order to set up an effective, and possibly sustainable, functionalization protocol. Hence, this study aims at exploring the functionalization of a poplar biochar obtained by high-temperature pyrolysis (1200 °C), under oxidative conditions typically used on Organic synthesis, such as the sulphonic mixture (i.e. conc. HNO₃/conc. H₂SO₄ 1:3 v/v) and the “piranha mixture”, applied for different reaction temperature and times. The obtained products were characterized by combined imaging (SEM), spectroscopic (ATR-FTIR) and FFC-NMR relaxometric techniques. In particular, relaxometric data, rationalized in terms of the Kohlrausch stretched exponential kinetic model [1], were analyzed by means of a recently proposed heuristic method [2,3]. The results obtained enabled us to rationalize the effect of the reaction conditions, and draw some hypotheses on the dynamics of water within the pore network of the materials.



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FFC-NMR STUDIES ON SICILIAN DIARY PRODUCTS

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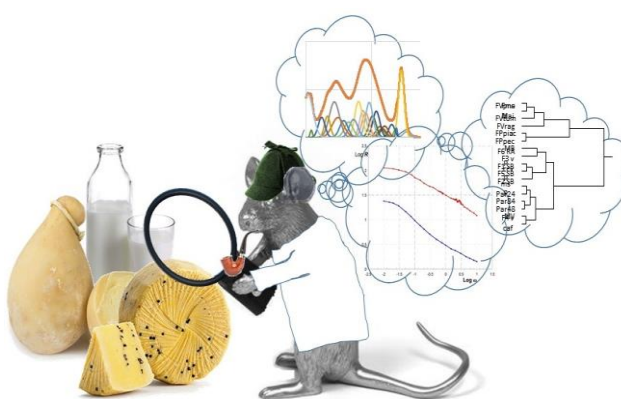
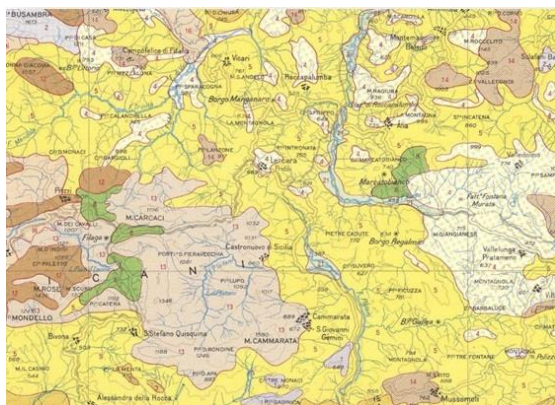
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Product traceability is of paramount importance for the quality assessment and the commercial valorization of dairy products, and for the valorization of the relevant production areas as well. As a part of a more comprehensive approach based on combined spectroscopic (FT-IR, NMR) and statistical multivariate analysis (HCA, PCA) techniques, here we present some preliminary results from a FFC-NMR relaxometric study on cheese samples mainly coming from the area of Sicani Mountains in central Sicily (Italy). Samples differ for their zoological origin (cow, sheep or mixed), and for animal feedstock in dependence of the pedological nature of the pasture soil (brown earths, regosols, vertisols). Relevant NMRD dispersion curves were analyzed by a combined approach, smartly exploiting a recent heuristic method [1,2] and a modified version of Kruk's equation [3]. Statistical data analysis seems to enable a fair discrimination between products of different origin.



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FFC-NMR CHARACTERIZATION OF NANOSPONGE MATERIALS

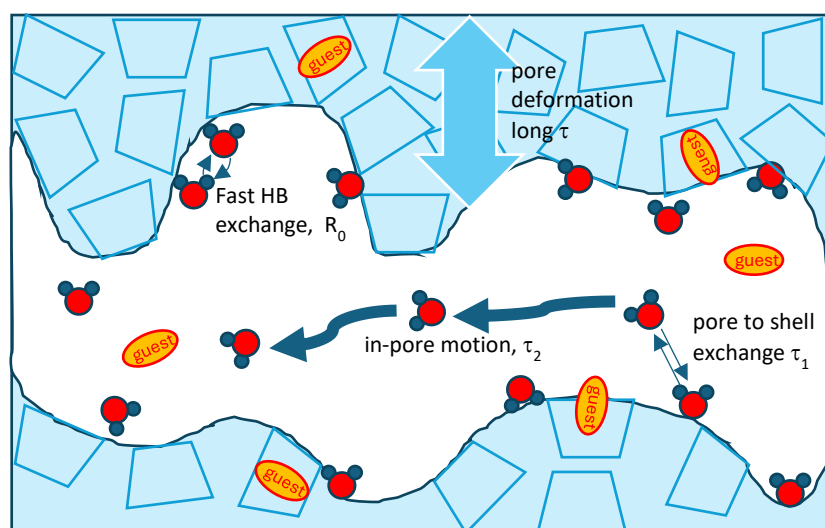
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Fast-Field-Cycling NMR relaxometric experiments were carried out on a set of diversely structured cyclodextrin-based nanosponges (NSs) [1-3], in order to clarify the microscopic and textural properties of these materials, and in particular the functional mobility of an aqueous medium within their pore network. Indeed, the features of NSs can be largely tuned by changing both the reactants nature and combination ratio, and even the synthetic protocol used. A recently proposed heuristic analysis of the NMRD dispersion curves [3,4] allowed to identify the characteristics dynamic of the system. The results obtained, in turn, were used for aiding the rationalization of a dataset pertaining to the adsorption and the controlled release kinetics of a suitable of *p*-nitroaniline, chosen as model guest. This led us to put forward a cute “bunny-hop-like” model to rationalize their release properties.



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The TRL scale and the development of FFC-NMR apparatus

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Developing a FFC-NMR from the scratch up to user ready stage is a mix of technical and design challenges. [1-2] Among other approaches to evaluate the technological impact of new solutions, the development of a desktop FFC home built equipment can be done taking advantage of the Technology Readiness Level (TRL) scale as represented in Fig. 1. [3]

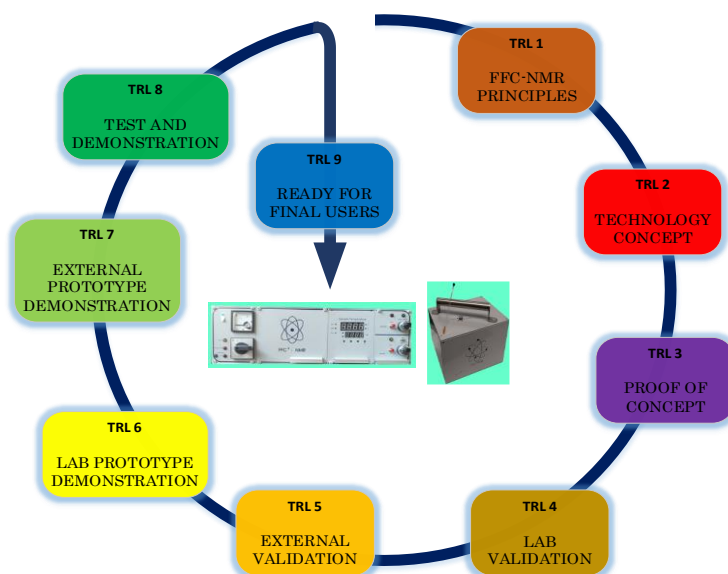


Fig. 1. TRL for FFC equipment (adapted from [3]).

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Optimized sulfamido-carborane-conjugated Gd complex as a theranostic probe for MRI-guided BNCT in mesothelioma therapy

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This study proposes the relaxometric characterization of a new multi-tasking agent, combining imaging and therapeutic properties, to enhance the efficacy of Boron Neutron Capture Therapy (BNCT) in cancer treatment. The agent Gd-CA-SF comprises a carborane unit (ten boron atoms for BNCT) linked to a sulfonamide group¹ on one side, designed to target and inhibit the enzyme carbonic anhydrase IX (CA IX), which is overexpressed in various aggressive tumors, including mesothelioma and breast cancer. On the other side, the agent features a Gd(III)DOTA monoamide complex as an MRI reporter for quantitative assessment of the B/Gd concentration.

The use of these theranostics offers two primary advantages: firstly, dual Gd/B compounds exhibit a higher NCT efficacy when compared to systems comprising boron alone. This is attributable to the pronounced thermal neutron cross-sections of the two stable Gd isotopes (¹⁵⁵Gd and ¹⁵⁷Gd), providing a remarkable 65-fold improvement over ¹⁰B in the case of ¹⁵⁷Gd. The longitudinal relaxivity of Gd-CA-SF measured at 0.5T and 25°C was 5.5 mM⁻¹s⁻¹, significantly exceeding the values of commercially available contrast agents (4.3-4.7 mM⁻¹s⁻¹). Interestingly, this is the first instance of a sulfonamide-carborane inhibitor moiety being conjugated to a hydrophilic Gd-complex. In vitro studies, evaluating the inhibition of esterase activity by the CAII and CAIX enzymes, confirmed the preservation of the inhibitory effect of the sulfonamide moiety even after its binding to the Gd-complex. Cell uptake studies conducted on mesothelioma cells revealed that the amount of boron internalized into tumor cells is sufficient for effective BNCT. Neutron irradiation was performed on mesothelioma cells and compared with the side effect observed on healthy cells. As the efficacy of the treatment is strongly correlated with the cell localization of the NCT agent, NMRD profiles of free complex were compared with those obtained on cell pellets after a 16h incubation with Gd-CA-SF. In conclusion, an accurate treatment planning is crucial for mesothelioma, a malignant neoplasm of mesothelial cells caused by asbestos exposure and currently without a definitive cure. NMRD profiles can be a useful tool to characterize Gd and boron containing agents and evaluate their binding with target enzymes and cells.

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INVERSE TEMPERATURE DEPENDENCE OF WATER RELAXATION IN INULIN AND KARRAGENAN MICROGELS: A CHEMICAL EXCHANGE DOMINATED REGIME

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Hydrogels are crosslinked polymeric networks, which can swell in water by absorbing it up to hundreds times larger of their dry mass. Water molecules confined in pores of gel matrix or interparticle spaces of microparticle agglomerates show different dynamics as compared to bulk water. In particular, one can mention about different fractions of water like free, bound or partially bound water, where the latter is especially characterized with slowed down diffusion due to the interaction with the gel surface. During such slow two-dimensional diffusion on the surface, water molecules also undergo subsequent adsorption and desorption cycles with the bound water so called as chemical exchange. Chemical exchange depends on pH, temperature, and composition of the surface i.e. number of hydroxyl groups. In this study, we investigate the water dynamics in Inulin and Karragennan hydrogel microparticles by performing FFC NMR measurements at different temperatures. ¹H NMRD profiles obtained on water swollen gels show unusual relaxation behavior i.e. proton relaxation rate increasing with temperature in low frequency region for Karragennan and in whole scanned frequency scale for Inulin. We explain such inverse temperature dependence with fast chemical exchange condition, where the relaxation rate is dominated by water exchange rate as often the case observed in hydrated proteins, tissues and biomacromolecules [1]. Theoretical analysis of relaxation data further showed that RMTD (Reorientation Mediated Translational Displacement) model is suitable to describe the molecular motion close to gel surface.

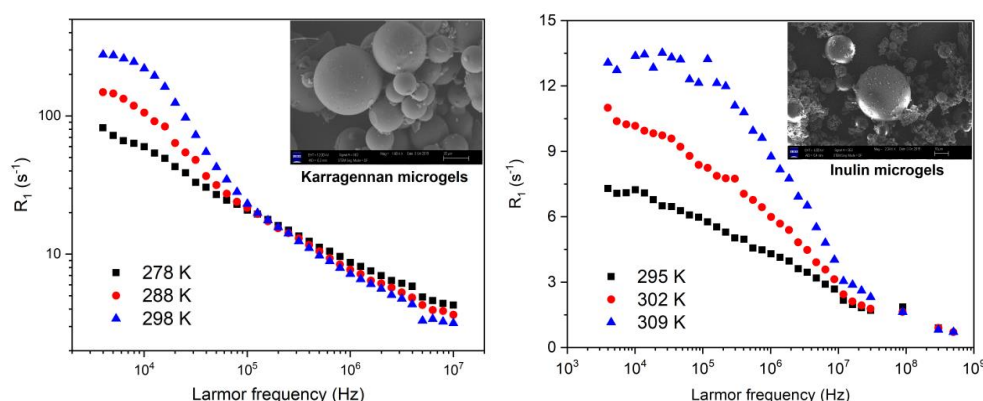


Fig. 1. NMRD profiles obtained on swollen state Karragennan and Inulin microgels

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FFC NMR RELAXOMETRY AS A TOOL FOR DETECTING THE QUALITY OF BIOTECHNOLOGICAL DRUGS

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Biotechnological drugs are mostly composed of proteins or peptides. Therefore, any change in ambient conditions during storage and administration to patients can lead to structural modifications, lowering the quality and effectiveness of these drugs. Among the different drug quality issues that hamper drug stability and pharmacokinetics, aggregation, and glycation are the most commonly observed. Aggregation is the clustering of adjacent proteins via intermolecular interactions (i.e., Van der Waals, hydrophobic interactions), which are already responsible for protein folding that is crucial for pharmaceutical activity. On the other hand, glycation stems from the reaction between a protein and a sugar, which results from the hydrolyzation of lactose or sucrose that are commonly included in drugs. Both processes involve changes at the molecular level that can be indeed probed by field cycling NMR relaxometry as an alternative to traditional techniques (i.e., HPLC, Mass Spectroscopy, High Resolution NMR) used in detecting drug quality issues. In this study, as a forthcoming problem in diabetes pharmaceuticals, aggregation effects on a commercially available insulin drug (Humulin-R) and glucose-mediated glycation of Bovine Serum Albumin - BSA (as a model serum protein for in vitro tests) were investigated by means of FFC NMR Relaxometry experiments. NMRD profiles obtained on insulin samples treated under three different stress conditions show that for sample agitated at high temperature ($T=50\text{ }^{\circ}\text{C}$), one observes a significant low frequency dispersion that can be associated with rotational / reorientational motion of clusters formed under this condition. Regarding the glycation experiments on BSA solutions, the low frequency proton relaxation rate R_1 , increases with the surrounding temperature and glycation time. This is not surprising because FFC NMR is sensitive to the surface proton arrangement and during the glycation process; the reaction of primary amine molecule with glucose causes the formation of Advanced Glycation End products (AGEs) on the surface of BSA, accordingly changes the proton arrangements of molecules. Overall, as a quality control method for biotechnological drugs, FFC NMR Relaxometry is a promising non-invasive and relatively low-cost technique that does not involve any additional sample preparation procedures or the usage of chemicals.

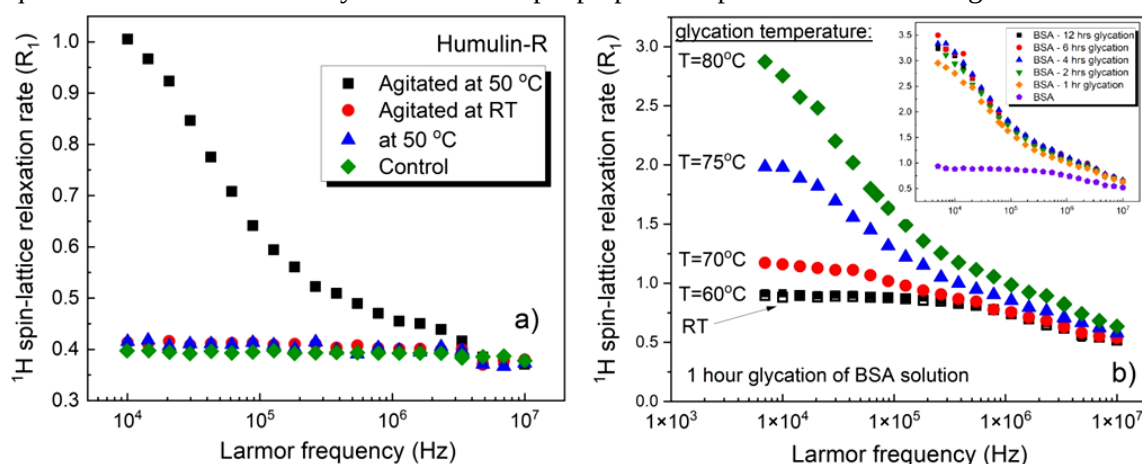


Fig.1 Room temperature NMRD profiles of a) Humulin-R under different stress conditions and b) BSA solution glycated at different temperatures and glycation time (inset figure).



LATEST ACHIEVEMENTS OF THE DNP FFC TECHNIQUE TO STUDY COMPLEX SYSTEMS

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Since the last decade, a combination of DNP-FFC [1, 2] has been developed into an effective technique for studying dynamics in a variety of systems, such as porous media, polymer systems, petroleum materials, ionic liquids, etc. [2, 3]. The last achievements include studying dynamics and features of polarization transfer in the presence of modified silica surface [4], new DNP effects combinations in ionic liquids [5], and demixing liquids in porous media. In the current contribution, we present and discuss the latest results in the field of study dynamics and hyperpolarization of adsorbed liquids in porous systems.

The combined DNP-FFC measurements of water and alkanes adsorbed on fumed silica 7 nm particles as well as in porous glass Vycor with 4 nm pore size were carried out using recently built X- and S-band resonators with ZrO₂ ceramic dielectric inserts, both working in TM₁₁₀ mode at 9.8 GHz and 2.3 GHz, respectively (see Figure 1a). New probes were tested with set of calibration samples as well as with samples of Vycor porous glass with mixtures of liquids such as water-acetone, THF-cyclohexane, etc. (see Figure 1b).

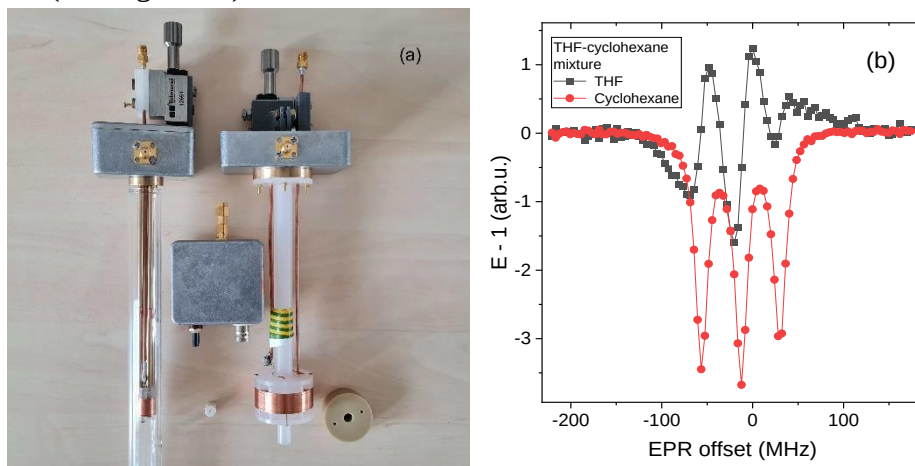


Fig. 1. (a) X- and S-band resonators with ZrO₂ inserts and (b) experimental DNP spectra of a mixture of THF and cyclohexane with 10 mM TEMPO in Vycor porous glass

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FFC-NMR Relaxometry of Perfluorosulfonic Acid Ionomers and Their Perfluorosulfonyl Fluoride Precursors Membranes

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The spin-lattice relaxation rates (R_1) of fluorine nuclei in perfluorosulfonic acid (PFSA) ionomer membranes and their precursor solid perfluorosulfonyl fluoride (PFSF) were measured by FFC-NMR relaxometry [1]. The XRD profiles of PFSA and PFSF are similar and show a characteristic peak, indicating the alignment of main chains. While the SAXS profiles of the PFSA membranes show two peaks, those of the solid PFSF lack the ionomer peak which is characteristic of hydrophilic side chains in the PFSA ionomer membranes. The Larmor frequency dependence of R_1 obeys power law and the indices are dependent on the sample and temperature. The indices of the PFSA membranes change from $-1/2$ to -1 along with the Larmor frequency and temperature dependence decrease, which is consistent with the generalized defect diffusion model [2]. Estimated activation energies are in good agreement with those obtained from dynamical mechanical analysis and dielectric spectroscopy, indicating the segmental motion of the backbones as the common origin of these observations. On the other hand, the index changes to $-3/4$ in the case of the PFSFs, which has been predicted by the reptation model [3].

This work is based on results obtained from a project, JPNP20003, commissioned by the New Energy and Industrial Technology Development Organization (NEDO).

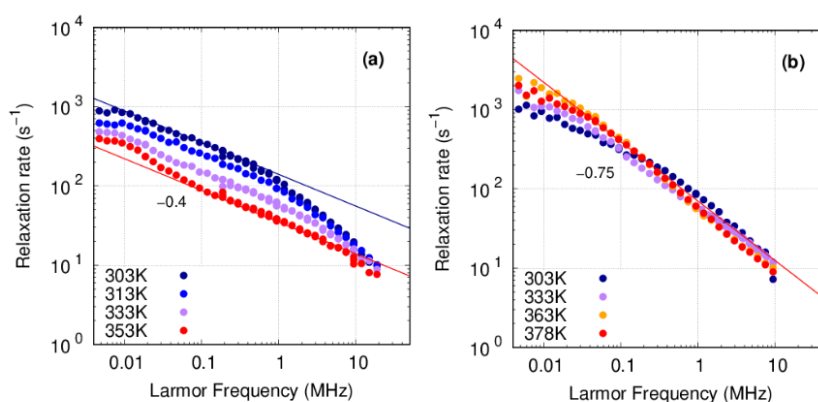


Fig. 1. Spin-lattice relaxation rate profiles of PFSA and PFSF membranes (a) E98-05S (b) P98-SO2F.

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MYOGLOBIN IN MOTION: ¹H RELAXATION TECHNIQUES UNVEILED

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We explore the dynamics of myoglobin, an essential protein for oxygen storage and transport in muscle tissues, using an advanced integrative approach combining ¹H spin-lattice and spin-spin relaxation techniques. Our study employs Fast Field Cycling NMR (FFC-NMR) relaxometry, covering a frequency range of 10 kHz to 20 MHz, alongside time-domain NMR (TD-NMR) at 18.5 MHz, to probe the relaxation behavior of myoglobin in both H₂O and D₂O solutions, with myoglobin. The comprehensive relaxation data obtained across these varied frequencies enable us to investigate dynamical processes spanning multiple time scales. This approach facilitates the characterization of relaxation contributions through Lorentzian spectral densities with distinct correlation times. Previous applications of this methodology to both dilute and solid protein systems [1] have linked relaxation features to interactions between water molecules and protein binding sites, as well as diffusion dynamics [2,3].

Our findings highlight the complexity of interpreting relaxation data and the necessity for robust theoretical models. We aim to provide a coherent analysis of ¹H spin-lattice and spin-spin relaxation data, noting the bi-exponential behavior observed, and elucidate the impact of isotope substitution on understanding individual relaxation contributions. This insight is crucial for deciphering the interplay between water and protein dynamics, enhancing our knowledge of myoglobin's structural and functional properties

Acknowledgments/Funding

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Non-invasive Characterization of Cholesterol Solid; T_1 Relaxation, Solid Content, and Phase Transition Using TD-NMR

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Abstract:

Non-invasive characterization of cholesterol solid is essential for optimizing its application in various industrial products including cosmetics as a skin care creams and moistures, pharmaceuticals as an excipient in drug formulations, and in some dietary supplements[1, 2]. This study employs the Time Domain Nuclear Magnetic Resonance (TD-NMR) to investigate the spin lattice relaxation time (T_1), phase transitions and solid content of cholesterol over a temperature range of 20 °C to 150 °C. Initially, T_1 measurements revealed temperature dependent relaxation behaviors indicative of molecular dynamics within the cholesterol matrix. Simultaneously, we have also exploited TD NMR by employing infamous Solid Echo Sequence, aims to measure the melting curves of cholesterol sample to investigate the phase transition from crystalline to amorphous state. This transition was quantitatively modeled using a sigmoidal function, yielding a melting curve that pinpointed the melting temperature of cholesterol at 112 °C.

To comprehensively investigate the thermal history effects and stability in real applications, an additional study was conducted. Cholesterol solid samples were heated at 112 °C to erase the thermal history, then analyzed at room temperature (25 °C), refrigerator temperature (8 °C), and at (-4 °C) over three consecutive days and after a three-day interval. Initial observations indicated higher solid content at lower temperature on the first day. Then over subsequent days, the solid content plateaued at lower temperatures, while at room temperature it took more time to achieve the plateau. This study provides the critical insights into the thermodynamic behavior of cholesterol, demonstrating how temperature variations influence the crystalline stability and phase kinetics of cholesterol sample.

Acknowledgments/Funding

This research has received funding from the European Union's Horizon Europe research and innovation program under grant agreement No 101072758 (project "FC-RELAX").

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EVALUATION OF RADICAL-EFFECTS IN PROTON NMR RELAXOMETRY OF DEGRADED LUBRICANT OILS

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Internal combustion engine lubricants have been successfully characterized using fast field-cycling (FFC) NMR relaxometry [1]. These fluids are complex mixtures of hydrocarbons composed of base oil and additives [2]. The degradation of motor oils can be associated to different processes that may severely affect their performance. Laboratory controlled thermal degradation of lubricants has been recently analyzed using NMR relaxometry and spectroscopy [3,4]. Radicals are formed as a product of the thermal degradation, which can be clearly observed using paramagnetic resonance spectroscopy or EPR. In this work, we analyze the effects of these radicals on the proton relaxation of base oil using FFC NMR relaxometry and EPR quantitative measurements. The inclusion of a correction term in our previous model [1,3,4] was considered. We analyze these new results in terms of the evolution of the magnetization in field-dependent proton-relaxation experiments, and in contrast to previous experiments in similar situations were FFC-DNP experiments have been described [5].

EME, CCF and LJG have equally contributed to this work.

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DYNAMICAL PROPERTIES OF BIOMATERIALS - INSIGHT FROM ¹H FFC-NMR AND TD-NMR RELAXATION

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In this work, the dynamical properties of biomaterials used in regenerative medicine to promote tissue healing have been studied by combined FFC-NMR and TD-NMR relaxation methods. For tissue regeneration, it is essential to increase the number of cells that make up the tissue and to reconstruct the extracellular matrix structure, which is composed of water, fibrous structural proteins such as collagen, elastin, fibronectin, vitronectin, and polysaccharides. There are several clinically available decellularized extracellular matrix grafts that differ in their source tissue (such as human, porcine, bovine, or equine) and the methods used to decellularize the tissue. Ovine forestomach matrix is a decellularized extracellular matrix bio-scaffold, available in both sheet and particulate forms, used as a dermal matrix in various soft tissue reconstruction procedures. It contains both structural and functional proteins such as collagen I, II and IV, elastin and glycosaminoglycans.

The dynamical properties have been investigated in both solid and hydrated forms at room and body temperatures. The ¹H spin-lattice relaxation experiments have been performed using FFC-NMR (Fast Field Cycling NMR relaxometry) in the frequency range from 10 kHz to 10 MHz (STELAR s.r.l., Mede, Italy). Similarly, time domain, TD-NMR equipment (Resonance Systems GmbH, Kirchheim unter Teck, Germany) has been used to obtain the spin-lattice and spin-spin relaxation rates at 18.5MHz.

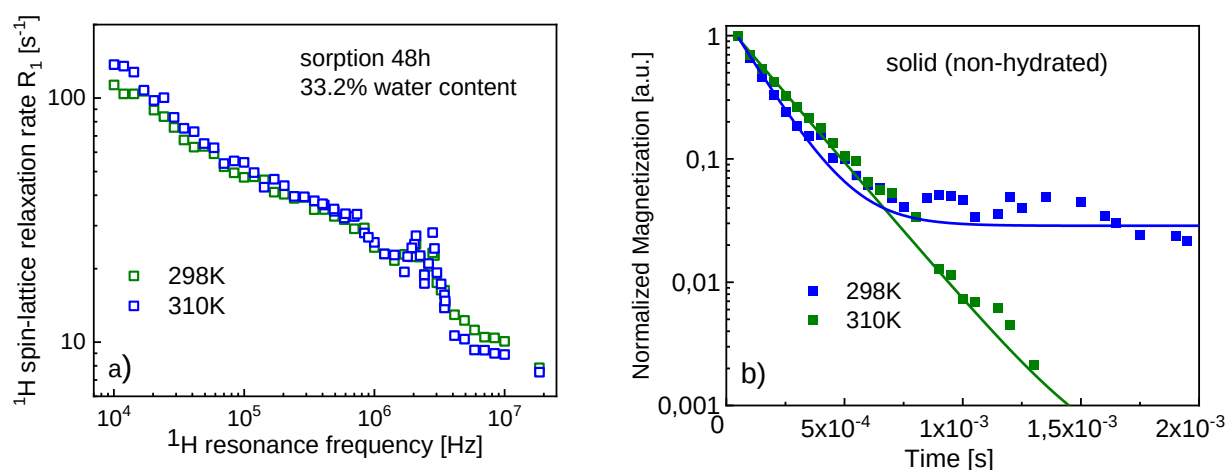


Fig. 1. a) ¹H spin-lattice relaxation data (FFC -NMR) for the hydrated biomaterial, b) ¹H spin-lattice and spin-spin relaxation data (TD – NMR) for the non-hydrated biomaterial.

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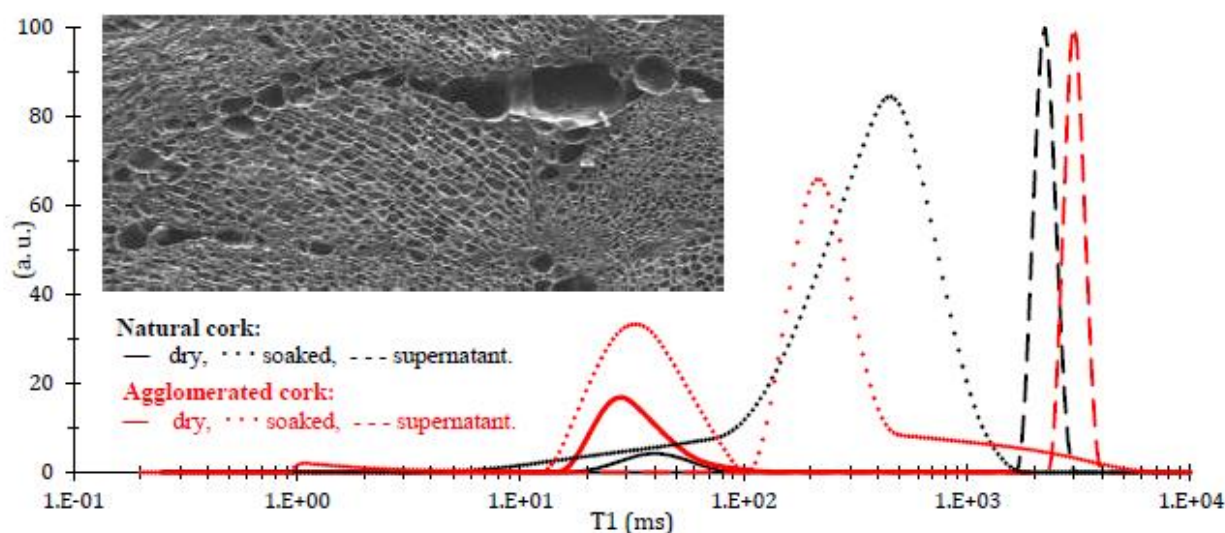
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Comparison of Natural and Agglomerated Cork Stoppers in Dry and Soaked States

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Natural and agglomerated cork stoppers were cut in half at mid-height. One half was submerged in water at 25 °C for one year, while the other half was stored in air at 45% relative humidity and 25 °C. Proton longitudinal relaxation times were recorded and analyzed using UPEN. The distribution of relaxation times reveals distinct signals from cork and glue, highlighting the different behaviors of cork cells upon soaking, depending on whether the stopper is made of natural or agglomerated cork. The effects of supercritical CO₂ extraction are also observable in the supernatant.

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TOWARDS FFC PROBING SAMPLES AT SHORTER ECHO AND FID TIMES

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Most NMR relaxometers use either solenoidal or Helmholtz-like coils, depending on the main magnetic field orientation. A Helmholtz-type coil, consists of two identical multiturn flat coils in a saddle configuration, mounted 180 degrees apart on a cylindrical surface [1]. For certain geometrical ratios, this setup can produce a homogeneous magnetic field at the isocenter. In practice, these coils are quite small and are often printed on a flexible dielectric substrate. The multiturn configuration deviates from the classic single-turn Helmholtz pair, resulting in a less homogeneous B₁ field but with higher amplitude. These coils typically function as transceive coils, meaning they both emit and receive signals. A key physical limitation of these coils arises from their operational principle, particularly the phenomenon known as ringing. Ringing occurs after a signal is transmitted in a coil with a high Q-factor, which is even more pronounced at lower frequencies. While higher Q-factors are desirable for achieving stronger signals, they also promote these unwanted oscillations. During the ringing period, the preamplifier becomes saturated and inoperable, resulting in what is known as “dead time”—the interval from the start of the pulse to when the preamplifier recovers and becomes active again [2]. This “dead time” can last from dozens to hundreds of microseconds, during which a significant portion of data is lost because the receive coil cannot read it. Although there are algorithms for extrapolating and reconstructing this missing initial frequency induction decay (FID) data, the issue fundamentally resides in the hardware. The issue becomes even more problematic for relaxometric measurements of solids, which have very short T₂^{*} times and thus, shorter FID. The truncation of their FID signals compromises the accuracy of the nuclear magnetic resonance dispersion (NMRD) profile, a resultant data obtained through the fast field cycling (FFC) method.

To mitigate the limitations of the transceive approach, we propose using separate Tx and Rx coils. Specifically, we considered two identical multiturn Helmholtz-like coil pairs oriented 90 degrees relative to each other to minimize mutual coupling. One coil is connected to the Tx channel and the other to the Rx channel. Preliminary full-wave modeling of this structure indicates that the orthogonal placement of the two Helmholtz-like coils reduces coupling to negligible levels (approximately -40 dB) while achieving optimal matching conditions at 7.5 MHz with two capacitors per channel (each with several dozen pF capacitance, depending on the load).

With this low Tx/Rx coupling, only a minimal portion of the excitation signal reaches the receive channel, preventing preamplifier from saturation. This configuration allows for measurements with shorter echo times and preserves the initial part of the data, thereby enhancing the accuracy of the NMRD profile, especially in relaxometric measurements of solids.



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¹H RELAXATION FEATURES OF ENDOMETRIUM TISSUES

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The potential of NMR relaxation studies over a wide range of magnetic fields (resonance frequencies) has been widely exploited to study the dynamical and structural properties of molecular and ionic systems of varying complexity, from bulk liquids to complex multicomponent macromolecular systems. In this context, surprisingly few examples of NMR relaxometry studies have been performed on tissues, despite the encouraging results [1-4].

The aim of this work is to reveal relaxation features characteristic of human endometrium tissues by combining Fast Field Cycling (FFC) and Time Domain (TD) NMR relaxation experiments. The tissue samples were obtained during routine surgery with the need to remove uterine tissues due to endometrial cancer. The FFC-NMR studies have resulted in a series of ¹H spin lattice relaxation data collected in the frequency range from 10kHz to 10MHz. It has been demonstrated that although the values of the ¹H spin-lattice relaxation rates differ between the patients, the shape of their frequency dependencies can be reproduced in terms of a power law: $R_1(\omega) \sim \omega^{-\alpha}$, with similar values of α (about 0.35). The exponentiality of the ¹H spin-lattice relaxation process has been analyzed in detail - it has been found that the relaxation is single - exponential in the whole frequency range for all cases. This finding is in agreement with the results of the ¹H spin-lattice TD-NMR studies performed at the frequency of 18.5 MHz - the TD-NMR experiments also showed single-exponential spin-lattice relaxation. In contrast, the TD-NMR spin-spin relaxation studies have shown that the spin-spin relaxation is bi-exponential in all cases. The averaged relaxation rate associated with the slower component of the spin-spin relaxation processes is about 5s⁻¹, while the relaxation rate corresponding to the faster component is about 20s⁻¹. The averaged ratio between the amplitudes of these relaxation contributions is about 0.4, although it varies significantly for individual cases.

The combined FFC-NMR and TD-NMR studies are a step toward revealing characteristic relaxation features of tissues with the goal of relating them to the state of the tissue.

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MOLECULAR INSIGHTS INTO MILK COMPOSITION USING NUCLEAR MAGNETIC RESONANCE RELAXOMETRY

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This study investigates the composition of various milk types from the Kenyan and Polish markets. By employing an integrated approach that combines ¹H spin-lattice and spin-spin relaxation experiments, we explored the molecular dynamics of these milk samples.

Using Fast Field Cycling NMR (FFC-NMR), we conducted ¹H spin-lattice relaxation measurements over a frequency range of 10 kHz to 10 MHz at different temperatures of 298K and 310K. These experiments were supplemented by time-domain spin-lattice and spin-spin relaxation measurements (TD-NMR) at 18.5 MHz. Several models were developed to correlate the relaxation properties with the molecular dynamics of the milk samples. The ¹H spin-lattice relaxation data for these milk samples were interpreted using relaxation contributions expressed through Lorentzian spectral densities with varying correlation times [1, 2]. This approach allowed us to analyze low-fat, high-fat and lactose-free milk [3, 4].

The combined application of FFC-NMR and TD-NMR provided a comprehensive understanding of the molecular dynamics and structural stability of milk from Kenya and Poland. The findings offer initial insights into how FFC-NMR and TD-NMR can be used to determine the differences in milk composition, paving the way for future studies on the impact of geographic and environmental factors as well as adulterants on milk composition and quality.

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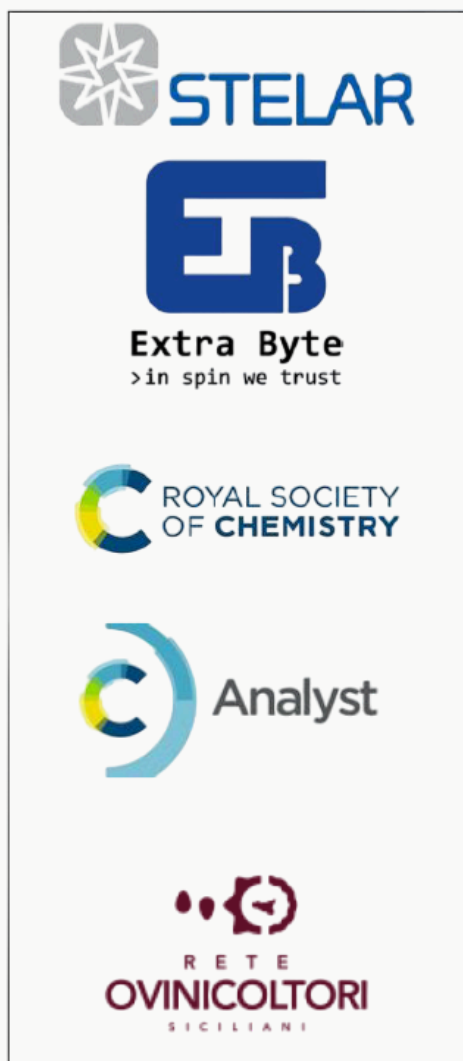
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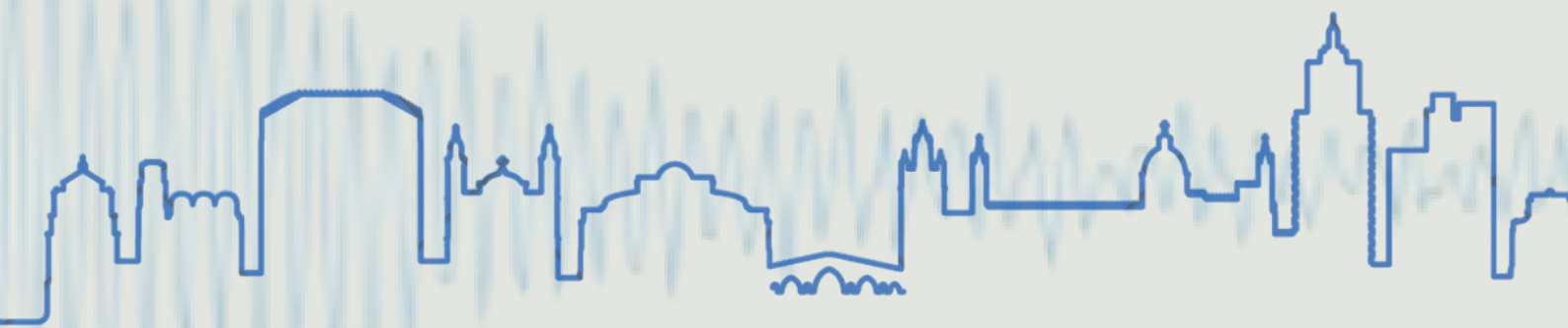
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