



FC-RELAX Workshop on NMR relaxometry for biomedicine and advanced materials

Book of abstracts

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Welcome to the FC-RELAX Workshop on NMR relaxometry for biomedicine and advanced materials!

This workshop is the concluding scientific meeting organized within the framework of the MSCA-DN FC-RELAX activities. Designed to connect internationally recognized experts in field-cycling NMR relaxometry with doctoral candidates approaching the completion of their PhDs, the workshop represents a premier networking opportunity for driving scientific dialogue, sharing cutting-edge research, and fostering long-lasting professional connections.

Scientific Committee

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Angelo Galante – University of L'Aquila

Linda Cerofolini – CIRMMP, Florence

Organizing Committee

Linda Cerofolini, Francesca Morelli, Giacomo Parigi – University of Florence



The workshop takes place at the Grand Hotel Duomo in Pisa (Via Santa Maria, 94), Italy.

Invited speakers:

- Armin Afrough – Aarhus University
- Mauro Botta – University of Eastern Piedmont
- Sabine Bouguet-Bonnet – University of Lorraine
- Lucia Calucci – CNR, Pisa
- Pellegrino Conte – University of Palermo
- Valentina Domenici – University of Pisa
- Eliana Gianolio – University of Turin
- Anton Gradišek – Jožef Stefan Institute, Ljubljana
- Rémi Kogon – University of Surrey
- Zoltan Kovacs – University of Texas Southwestern Medical Center
- Giulia Licciardi – École Normale Supérieure, Paris
- Claudio Luchinat – University of Florence
- Thomas J. Meade – Northwestern University
- Carlos Platas Iglesias – University of A Coruña
- Anne-Laure Rollet – Sorbonne Université
- Jordan Ward-Williams – University of Cambridge

Doctoral candidates:

- Adam Kubrak (tutor: Giacomo Parigi) – University of Florence
- Kahinga Kamau (tutor: Danuta Kruk) – University of Warmia and Mazury
- Guru Kiran Kadanuru Rajashekar (tutor: Sophie Laurent) – University of Mons
- Muhammad Muntazir Mehdi (tutor: Pedro Sebastião) – Instituto Superior Técnico, Lisbon
- Angel Mary Chiramel Tony (tutor: Ralf Ludwig) – University of Rostock
- Rajka Pejanovic (tutor: Fabien Ferrage) – École Normale Supérieure, Paris
- Denis Burov (tutors: Gianni Ferrante and Angelo Galante) – Stelar
- Madalina Ranga (tutor: Zsolt Baranyai) – Bracco Imaging
- Valeriia Baranauskaite (tutor: Leonid Grunin) – Resonance Systems
- Mamoon Riffat (tutor: Erkki Lähderanta) – Lappeenranta-Lahti University of Technology

Short presentations:

- Jlenia Bindi – University of Florence
- Karolina Dydak – Adam Mickiewicz University, Poznań
- Lucas Siemons – École Normale Supérieure, Paris

Workshop schedule

	Sept. 8	Sept. 9	Sept. 10	Sept. 11
9.00-9.40		Kubrak	Kamau	Mehdi
9.40-10.10		Gianolio	Conte	Domenici
10.10-10.40		Meade	Rollet	Gradisek
10.40-11.10		coffee break		
11.10-11.50		Ranga	(Kiran) Kadanuru Rajashekar	Burov
11.50-12.20		Botta	Bouguet-Bonnet	Kogon
12.20-12.50		Kovács	Platas Iglesias	Bindi Closing
12.50-14.20		lunch		
14.20-15.00		Pejanovic	Riffat	
15.00-15.30		Luchinat	Licciardi	
15.30-15.45		Siemons	Dydak	
15.45-16.15		coffee break		
16.15-16.55		Chiramel	Barauskaite	
16.55-17.25		Calucci	Ward-Williams	
17.25-17.55		Afrough	Guided tour	
18.00-19.30	Arrivals and registration	FC-RELAX meeting		
20.00	dinner			

Program of the workshop

Tuesday September 8

18:00-19:30 Participant arrival and registration

20:00 *Dinner @ Osteria dei Cavalieri (via S. Frediano, 16)*

Wednesday 9

Chair: Giacomo Parigi

9:00-9:40 Adam Kubrak (University of Florence)

Field-cycling ^1H relaxometry of biomolecules and paramagnetic proteins

9:40-10:10 Eliana Gianolio (University of Turin)

Field-dependent relaxivity as a design criterion for next-generation GBCAs at 1.5-3 T

10:10-10:40 Thomas J. Meade (Northwestern University)

Seeing is believing: but just what are we really seeing?

10:40-11:10 *Coffee break*

Chair: Zsolt Baranyai

11:10-11:50 Madalina Ranga (Bracco Imaging)

Pure proton-exchange based relaxation agent for MRI applications

11:50-12:20 Mauro Botta (University of Eastern Piedmont)

Tuning molecular dynamics and hydration networks: the path to stable $q = 2$ gadolinium MRI contrast agents

12:20-12:50 Zoltan Kovacs (University of Texas Southwestern Medical Center)

The importance of long spin-lattice (T_1) relaxation times in hyperpolarized NMR/MRI

12:50-14:20 *Lunch*

Chair: Fabien Ferrage

14:20-15:00 Rajka Pejjanovic (École Normale Supérieure, Paris)

Deep-learning approach for the reconstruction of pure-shift (PS) high-resolution relaxometry (HRR) spectra

- 15:00-15:30 Claudio Luchinat (University of Florence)
Model-free analysis stimulates the search for reasonable physical models for complex dynamic processes
- 15:30-15:45 Lucas Siemons (École Normale Supérieure, Paris)
Deep-learning: suppression of vibration artefacts in high-resolution relaxometry experiments
- 15:45-16:15 Coffee break*
Chair: Ralf Ludwig
- 16:15-16:55 Angel Mary Chiramel Tony (University of Rostock)
A bottom-up approach: frequency-dependent relaxation rates from MD simulations
- 16:55-17:25 Lucia Calucci (CNR, Pisa)
Investigating elastomer dynamics in rubber using ^1H FC NMR relaxometry
- 17:25-17:55 Armin Afrough (Aarhus University)
Relaxation time distributions for multi-exponential analysis of decay and recovery signals: principles, pitfalls, and practice
- 18:00-19:00 *FC-RELAX Supervisory Board meeting*
- 19:00-19:30 *FC-RELAX Steering Board meeting*
- 20:00 Dinner @ Osteria in Domo (via Santa Maria, 129)*

Thursday 10

Chair: Linda Cerofolini

- 9:00-9:40 Kahinga Kamau (University of Warmia and Mazury)
Slow dynamics of biomolecular systems
- 9:40-10:10 Pellegrino Conte (University of Palermo)
Beyond the relaxogram: physically grounded indices of structural and functional connectivity from FFC-NMR dispersion profiles
- 10:10-10:40 Anne-Laure Rollet (Sorbonne Université)
 ^1H of water relaxation in the vicinity of aluminum oxyhydroxide particles
- 10:40-11:10 Coffee break*

Chair: Céline Henoumont

- 11:10-11:50 Guru Kiran Kadanuru Rajashekar (University of Mons)
Synthesis and relaxometric studies of Mn(II) complexes associated with silica nanoparticles as safer alternatives to gadolinium-based MRI contrast agents
- 11:50-12:20 Sabine Bouguet-Bonnet (University of Lorraine)
Unraveling supramolecular gels structuration via high-resolution and fast-field-cycling NMR
- 12:20-12:50 Carlos Platas Iglesias (University of A Coruña)
Critical evaluation of the potential of transition metal complexes as alternatives to gadolinium MRI contrast agents

12:50-14:20 Lunch

Chair: Erkki Lähderanta

- 14:20-15:00 Mamoon Riffat (Lappeenranta-Lahti University of Technology)
NMR-based investigation of wettability, stability, and interfacial dynamics in metal oxide nanoparticle systems
- 15:00-15:30 Giulia Licciardi (École Normale Supérieure, Paris)
Ultrafast high-resolution relaxometry for probing multi-timescale dynamics: application to imidazole glycerol phosphate synthase
- 15:30-15:45 Karolina Dydak (Adam Mickiewicz University, Poznań)
Molecular dynamics of GMO@DTPA-BSA-Gd nanoassemblies investigated by ^1H NMR relaxometry

15:45-16:15 Coffee break

Chair: Leonid Grunin

- 16:15-16:55 Valeriia Baranauskaite (Resonance Systems)
TD-NMR characterization of semicrystalline polymers: structure and dynamics
- 16:55-17:25 Jordan Ward-Williams (University of Cambridge)
Exploring the phase behaviour of water-ethanol mixtures within mesoporous silicas with NMR relaxometry

17:30-19:30 Excursion: guided tour of the Pisa Cathedral and the Leaning Tower

20:00 Dinner @ Grand Hotel Duomo

Friday 11

Chair: Pedro Sebastião

- 9:00-9:40 Muhammad Muntazir Mehdi (Instituto Superior Técnico, Lisbon)
Software-assisted FFC-NMR relaxometry: automated data processing and molecular dynamics of pyridinium ionic liquid crystals
- 9:40-10:10 Valentina Domenici (University of Pisa)
From ordering to dynamic properties in liquid crystals: an overview of NMR-based studies
- 10:10-10:40 Anton Gradišek (Jožef Stefan Institute, Ljubljana)
Fast field-cycling in liquid crystals: untangling the molecular dynamics in the beautiful state of matter

10:40-11:10 Coffee break

Chair: Angelo Galante and Gianni Ferrante

- 11:10-11:50 Denis Burov (Stelar)
Improved NMR detection system for fast-field-cycling relaxometry
- 11:50-12:20 Rémi Kogon (University of Surrey)
Field-cycling relaxometry for medical applications: the 3-tau model
- 12:20-12:35 Jlenia Bindi (University of Florence)
Probing molecular dynamics and interactions in human blood serum via ultrafast high-resolution relaxometry
- 12:35-12:50 Closing

12:50-14:20 Lunch

Field-Cycling ^1H Relaxometry of biomolecules and paramagnetic proteins

Adam Kubrak^a, Pedro Sebastiao^b, Giacomo Parigi^a

^a*Department of Chemistry and Magnetic Resonance Center (CERM), University of Florence, and CIRMMP, via Luigi Sacconi 6, 50019 Sesto Fiorentino, Italy*

^b*Center of Physics and Engineering of Advanced Materials, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisbon, Portugal*

Field-Cycling (FC) NMR relaxometry measures longitudinal relaxation rates (R_1) as a function of the magnetic field, yielding Nuclear Magnetic Relaxation Dispersion (NMRD) profiles. Fitting these profiles with suitable theoretical models provides insights into molecular dynamics across a wide timescale, both in diamagnetic and paramagnetic systems¹. In paramagnetic systems, the presence of unpaired electron(s) induces Paramagnetic Relaxation Enhancements (PRE)². This effect can be explored through FC relaxometry to dissect the multiple contributions to water-proton relaxation arising from first-, second-, and outer-sphere water molecules, as well as to determine key electronic parameters. Field-cycling relaxometry can be performed either by switching the applied magnetic field generated by an electromagnet or using high-resolution NMR spectrometers equipped with a shuttle system that mechanically moves the sample between different magnetic fields. This latter approach offers high resolution and enhanced sensitivity, enabling the detection of site-specific R_1 values for individual nuclei³.

To address the need for easily accessible software tools for the analysis of the NMRD profiles, we present fiRelax (fitting interface for Relaxometry), a novel fitting platform equipped with a Graphical User-Interface (GUI), freely accessible as a web application at <https://firelax.cerm.unifi.it>. The platform is composed of a front-end that allows users to analyze experimental profiles and simulate theoretical relaxation curves with real-time result updates, eliminating the need for page reloads. The application's core is running in Java to ensure stability and longevity. fiRelax is designed to be accessible to users without in-depth knowledge of programming or advanced relaxation theory. On the back-end, all computations and minimization procedures are driven by the One-Fit-Engine⁴ (OFE), an open-source algorithm written in Raku and C, designed to serve as the fitting core for external programs. For paramagnetic systems, both the SBM and the Florence models⁵ have been implemented by adapting the Fortran code into OFE's C environment, resulting in a faster fitting process.

To show the versatility of the fiRelax platform, selected case studies are presented. These include paramagnetic systems exhibiting static Zero-Field-Splitting (ZFS), analyzed through the (modified) Florence model, as well as macromolecules in biofluids (e.g. human blood serum), where a model-free approach was applied to capture the underlying molecular dynamics.

¹A. Kubrak, R. Pejanovic, K. Kamau, D. Kruk, F. Ferrage, G. Parigi, *PCCP*, **2025**, 27, 1756–1771

²I. Bertini, C. Luchinat, G. Parigi, *Coord. Chem. Rev.*, **2011**, 255, 649

³J.A. Villanueva-Garibay et al., *Magn. Reson.*, **2025**, 6, 229–241

⁴github.com/fitteia/OneFit-Engine

⁵I. Bertini, J. Kowalewski, C. Luchinat, T. Nilsson, G. Parigi, *J. Chem. Phys.*, **1999**, 111, 5795

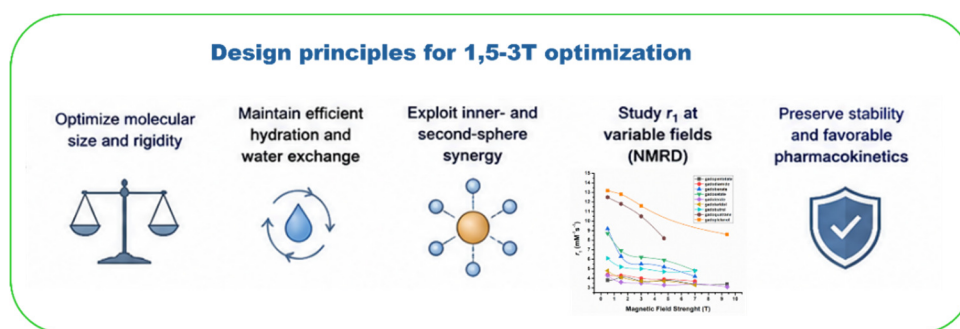
Field-dependent relaxivity as a design criterion for next-generation GBCAs at 1.5-3 T

Eliana Gianolio, Lorenzo Palagi, Silvio Aime

Department of Molecular Biotechnologies and Health Sciences, University of Turin, Turin, Italy

The development of next-generation gadolinium-based contrast agents (GBCAs) requires a shift from the pursuit of high relaxivity at a single magnetic field to the rational optimization of performance across the field strengths most relevant to clinical MRI. At 1.5-3 T, relaxivity is governed by a delicate balance among inner-sphere hydration, water exchange, electronic relaxation, second-sphere organization and, critically, the effective rotational correlation time of the paramagnetic unit. Systems optimized for low-field relaxometry by strong rotational slowing may lose efficiency at higher fields, whereas rigid low-to-medium molecular weight multimeric architectures can maintain high r_1 over a broader field window.

This lecture will discuss how variable-field relaxometry, especially ^1H nuclear magnetic relaxation dispersion (NMRD), provides a mechanistic map of these determinants and guides molecular design. Representative examples will include clinically translated and emerging high-relaxivity agents such as gadopiclesol and gadoquatane, together with medium-sized multimeric Gd systems in which controlled rigidity and limited local motion are exploited to approach the optimal dynamic regime for 1.5-3 T MRI. Attention will be devoted to digadoglutitol, a dinuclear macrocyclic GBCA derived from $[\text{Gd}(\text{HP-DO3A})]$, in which dimerization through a glucamine-based spacer combines increased molecular size with activated intramolecular catalysis of prototropic exchange and a sizeable second-sphere contribution. This design yields per-Gd relaxivities about two to three times higher than those of many current GBCAs while preserving an extracellular pharmacokinetic profile similar to approved macrocyclic agents. Finally, new Gd-tetramers from our laboratory will be presented. These compounds provide an instructive platform to assess how scaffold rigidity, linker dynamics, hydration and second-sphere water structuring cooperate, or compete, in defining field-dependent relaxivity. Overall, the comparison of molecular, dinuclear and tetrameric systems emphasizes that relaxivity measurements at variable magnetic field are not only a characterization tool, but a decisive design criterion for safer, lower-dose and field-optimized MRI contrast agents.^{1,2}



¹L. Palagi, D. L. Longo, E. Toth, C. C. Quattrocchi, A. J. van der Molen, S. Aime and E. Gianolio, *Eur. J. Med. Chem.*, **2025**, 292, 117668.

²S. Gazzetto, E. Gianolio, N. Guidolin, A. Fringuello Mingo, F. La Cava, S. Colombo Serra, L. Lattuada, N. Demitri, L. Palagi, S. Ghiani, S. Aime, L. Poggi and Z. Baranyai, *Chem Biomed Imaging*. **2025**,4:571-583.

Seeing is believing: but just what are we really seeing?

Thomas J. Meade

*Departments of Chemistry, Molecular Biosciences, Neurobiology and Radiology
Northwestern University
United States*

We have developed a new classes of enzyme-responsive magnetic resonance (MR) imaging probes that enable the non-invasive, real-time tracking of biological activity associated with gene therapy and cellular senescence. These small-molecule agents are activated by specific enzymatic processes, offering a chemical strategy for spatiotemporal imaging of otherwise silent molecular events.

Currently, there are no clinically available tools to directly assess the biodistribution or efficacy of gene therapies, particularly in tissues affected by senescence. This presents a major limitation in treatment development, as molecular responses often precede overt clinical improvement. Senescence, characterized by irreversible cell-cycle arrest and secretion of pro-inflammatory mediators, is a key driver of musculoskeletal (MSK) disorders such as osteoarthritis, where oxidative stress triggers dysfunction in synoviocytes, chondrocytes, and bone marrow cells.

To overcome this barrier, we synthesized bioresponsive Gd(III)-based MR probes that selectively respond to senescence-associated enzymes. These probes are capable of reporting activity within the central nervous system (CNS), peripheral nervous system (PNS), and MSK tissues. Their modular design enables tailored activation profiles and pharmacokinetics, opening new avenues for longitudinal imaging of therapeutic response and disease progression in vivo.

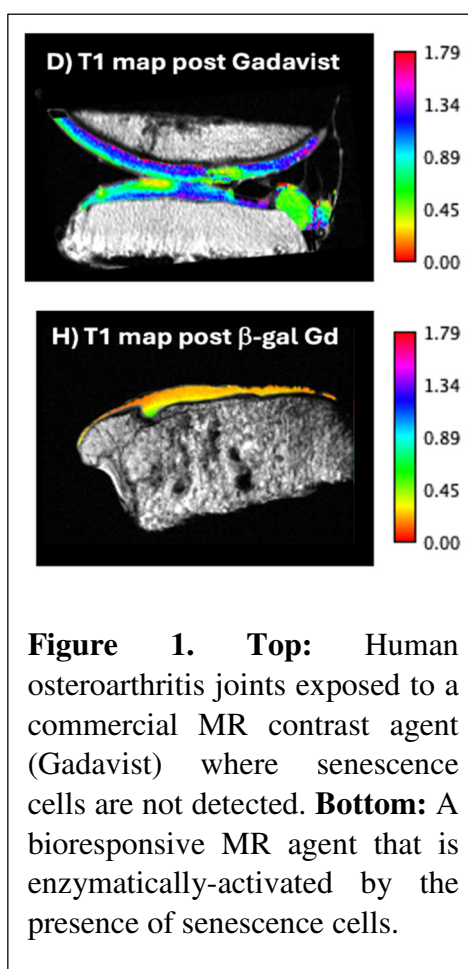


Figure 1. Top: Human osteoarthritis joints exposed to a commercial MR contrast agent (Gadavist) where senescence cells are not detected. **Bottom:** A bioresponsive MR agent that is enzymatically-activated by the presence of senescence cells.

Pure proton-exchange based relaxation agent for MRI applications

Madalina Ranga, Zsolt Baranyai

CRB Trieste, Bracco Imaging Spa, AREA Science Park, 34149 Basovizza (TS), Italy

Magnetic resonance imaging (MRI) is a widely used diagnostic tool that often relies on gadolinium(III)-based contrast agents (GBCAs) to enhance image quality in order to improve differentiation between healthy and diseased tissues. Although generally considered safe, the increase in signal intensity on non-contrasted T_1 -weighted MR images of patients that had undergone numerous exposures of GBCAs led a concern about the long term safety of these GBCAs.¹

Among the possible alternatives there is a growing interest for the CAs with labile protons which can generate the image contrast via Chemical Exchange Saturation Transfer (CEST).² In diamagnetic molecules (diaCEST), exchangeable -NH or -OH protons usually have small chemical shifts ($\Delta\omega=1-4$ ppm), overlapping with endogenous labile protons and the magnetization transfer (MT) background. Since this MT background diminishes beyond 10–12 ppm, agents with highly shifted exchangeable protons ($\Delta\omega>12$ ppm) provide superior selectivity and minimal MT interference.³ 1,8-bis(dialkylamino)naphthalenes (proton sponges) form a stable $N\cdots H^+\cdots N$ bond, giving an unusually downfield NMR signal ($\delta_H\sim 18$ ppm), but their proton exchange with bulk is too slow for CEST application. The proton exchange of the monoprotonated 1,8-diaminonaphthalene tetraacetic acid (HDANTA⁺, Figure 1A) is catalyzed by carboxylate groups without affecting the large chemical shift of the $N\cdots H^+\cdots N$ ($\Delta\omega=17.2$ ppm). The forward exchange rate with the bulk (k_{ex}) was found to be 208 and 492 s⁻¹ at 298 and 310 K, respectively. Phantom and *in vivo* imaging showed that HDANTA⁺ is about three times more effective than the gold-standard diaCEST agent, salicylate,⁴ at $B_1 = 3$ μ T, a saturation power compatible with human use.

High chemical shift of the exchangeable protons can be also achieved by the combination of paramagnetic Ln(III)-complexes with amide-NH, amino-NH or alcoholate-OH functions (paraCEST). Eu(III) analogue of the clinically used [Gd(HP-DO3A)] contrast agent (Prohance®) has been frequently used in ParaCEST investigations (Figure 1B). Variable pH and T ¹H NMR studies of [Eu(HP-DO3A)] with DANTE pulse train reveal that the exchange rate between the SAP and TSAP diastereomers of Eu(III) complex is pH-independent. However, the proton exchange between the -OH function in SAP and TSAP diastereomers and the solvent H₂O is pH-dependent process in general based catalyzed reaction. The protonation constant ($\log K_{EuLH-1}$) of the -OH function, the OH⁻ assisted exchange rate (k_{OH}) and the relaxation time (T_1) of the -OH proton in SAP and TSAP diastereomers of the [Eu(HP-DO3A)] differ considerably due to the different bond distance of the -OH group and the central Eu(III) ion in SAP and TSAP diastereomers of [Eu(HP-DO3A)] complexes.

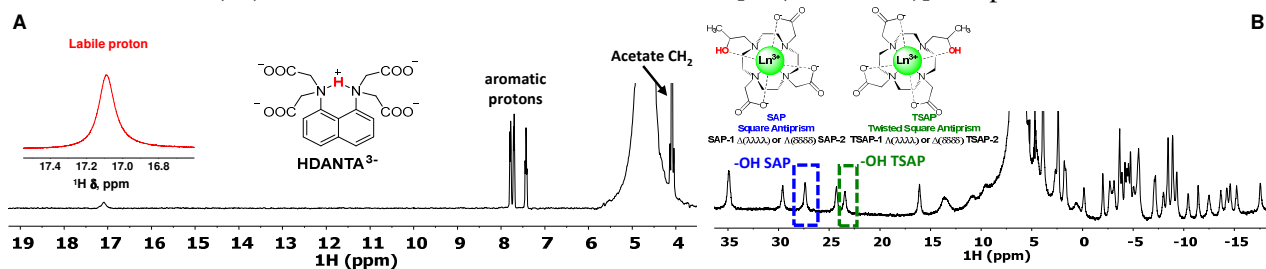


Figure 1 A: ¹H NMR spectrum of HDANTA⁺ in aqueous solution ([DANTA]=0.012 M, pH=7.07, 9.4 T, H₂O, 293 K, 0.15 M NaCl). **B:** The diastereomers of [Ln(HP-DO3A)] complexes and ¹H NMR spectra of [Eu(HP-DO3A)] ([EuL]=0.12 M, 9.4 T, pH=5.0, 1.0 M NaCl, H₂O, 293 K)

References: ¹ T. Kanda, et al., *Radiology*, **2014**, 270, 834–841. ² S. Viswanathan, et al., *Chem. Rev.* **2010**, 110, 2960-3018. ³ E. Vinogradov, et al., *J. Magn. Reson.* **2013**, 229, 155-172. ⁴ X. Yang, et al., *Angew Chem Int Ed* **2013**, 52, 8116–8119. ⁵ G. Ferrauto, et al., *Magn. Reson. Med.*, **2013**, 69, 1703-1711.

Tuning Molecular Dynamics and Hydration Networks: The Path to Stable $q = 2$ Gadolinium MRI Contrast Agents

Mauro Botta

Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale, Viale T. Michel 11, 15121 Alessandria - Italy

Clinical MRI contrast agents (CAs) were developed over a roughly 15-year period beginning in the mid-1980s, emerging directly from the foundational scaffold of GdDTPA (Magnevist).¹ In these traditional systems, the Gd(III) ion is encapsulated within an octadentate polyaminopolycarboxylate ligand cage. This arrangement leaves a single coordination site available for one bound water molecule ($q = 1$) that undergoes rapid exchange with the bulk solvent. Consequently, clinically approved gadolinium-based CAs (GBCAs) exhibit remarkably uniform physicochemical properties: low molecular weight, a single inner-sphere water molecule, and high thermodynamic stability.² However, they offer modest efficacy, characterized by relatively low longitudinal relaxivity (r_1) values. Upon administration, the CA accelerates the relaxation of nearby water molecules via three distinct mechanisms: inner-sphere (IS) water directly bound to the Gd(III) center; outer-sphere (OS) water diffusing near the complex; and occasionally, second-sphere (SS) water transiently interacting with the ligand via hydrogen bonding. For clinical GBCAs, the overall r_1 arises almost equally from the IS and OS mechanisms.³ Beyond clinical performance, the quest for higher relaxivity is increasingly driven by environmental sustainability. Developing agents with superior relaxivity allows for the same diagnostic quality at a significantly reduced dose, thereby improving patient safety and directly mitigating the accumulation of anthropogenic gadolinium in ecosystems. In this contribution, we discuss how r_1 can be optimized by precisely tuning the balance between molecular dynamics, hydration, and exchange kinetics. Recent research has focused on a three-pronged strategy: increasing the hydration number (q), slowing down the molecular tumbling rate (τ_R), and maximizing the second-sphere water contribution.

Finally, we present recent examples demonstrating how to amplify the SS contribution to relaxivity, and how to precisely evaluate the finer details of coordinated water exchange kinetics. Ultimately, we show how the synergistic combination of these design principles has culminated in the development of the first highly stable, clinically viable GBCA with a hydration state of $q = 2$.⁴

References

- ¹J. Lohrke, T. Frenzel *et al.*, *Adv. Ther.*, **2016**, 33, 1-28
- ²P. Caravan, J. Ellison, T. McMurry, R. Lauffer, *Chem. Rev.*, **1999**, 99, 2293–2352
- ³S. Aime, M. Botta, D. Esteban-Gómez and C. Platas-Iglesias, *Mol. Phys.*, **2019**, 117, 898–909
- ⁴R. Napolitano, N. Guidolin, M. Boccalon *et al.*, *Adv. Sci.*, **2025**, 12, No. e2415321

The Importance of Long Spin-Lattice (T_1) Relaxation Times in Hyperpolarized NMR/MRI

Zoltan Kovacs, Mai T. Huynh, Jae Mo Park, Eul Hyun Suh, Craig R. Malloy

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Solution state hyperpolarized (HP) NMR/MRI technology can increase the signal of NMR active nuclei by several orders of magnitude thereby making it feasible to observe low sensitivity nuclei in vivo.¹ The most commonly used HP-method is the microwave driven dynamic polarization (DNP).¹

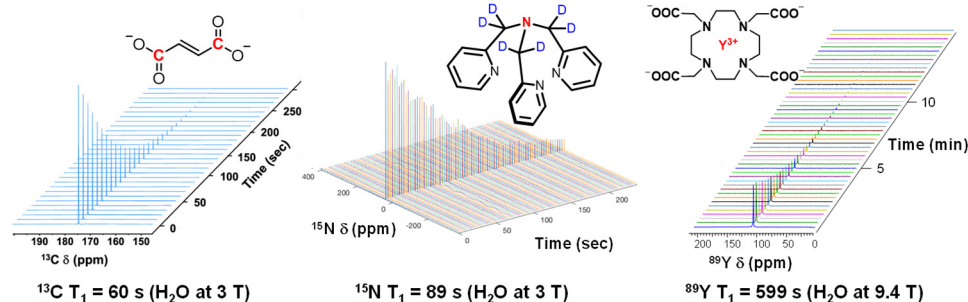


Figure 1. Examples of HP-agents with HP- ^{13}C , HP- ^{15}N and HP- ^{89}Y labels

The HP-magnetization is not persistent but returns to thermal equilibrium by spin-lattice (T_1) relaxation. This is a severe limitation and motivates the development of long T_1 -agents. Spin-lattice relaxation occurs by various mechanisms and the T_1 is determined primarily by the gyromagnetic ratio of the HP-nucleus, molecular structure, solvent and magnetic field strength.¹ Low gamma nuclei such as ^{15}N and ^{89}Y can exhibit exceptionally long T_1 (Figure 1).¹ For in vivo metabolic imaging with HP- ^{13}C -labeled substrates, longer T_1 translates into enhanced sensitivity. We recently demonstrated that in dissolution DNP of [1,4- $^{13}\text{C}_2$]fumarate, neutralization with meglumine instead of NaOH not only improved solubility but also prolonged the ^{13}C T_1 by nearly 20%, allowing the detection of previously unobservable intermediates of gluconeogenesis in healthy tissues (Figure 2).² In summary, long T_1 is advantageous because it extends the lifetime of the HP-signal, allowing sufficient time for agent delivery, metabolic conversion, and image acquisition before the enhanced magnetization decays.

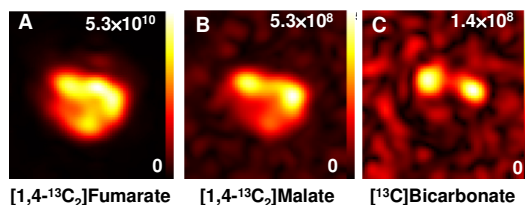


Figure 2. In vivo HP- ^{13}C metabolic imaging of gluconeogenesis in healthy rat kidneys with HP meglumine [1,4- $^{13}\text{C}_2$]fumarate.²

¹E.-H. Suh, Z. Kovacs, Editors, The Chemistry of Hyperpolarized Magnetic Resonance Probes. Academic Press, 2024 and references therein.

²M. T. Huynh, Z. Erfani, S. Al Nemri, S. Chirayil, Z. Kovacs, J. M. Park, *ACS Appl. Mater. Interfaces* 2024, 16 (29), 37435-37444.

Deep-learning approach for the reconstruction of pure-shift (PS) high-resolution relaxometry (HRR) spectra

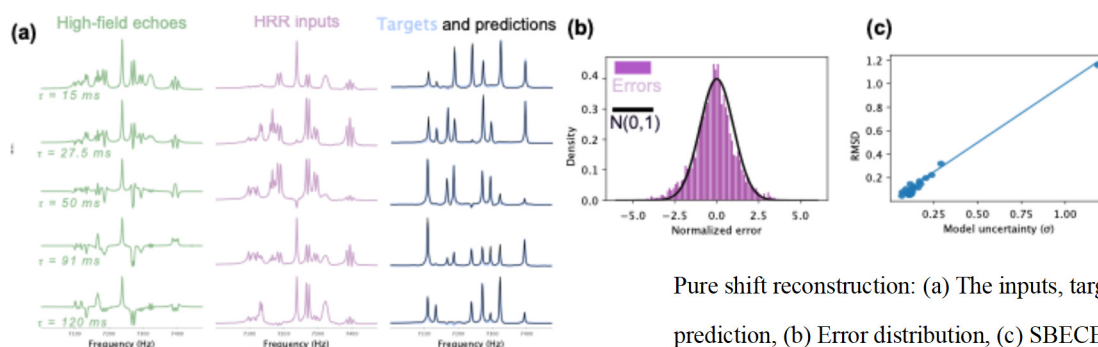
Rajka Pejanovic,¹ Lucas Siemons,¹ Alessandro Ruda,¹ Jorge Garibay,² Philippe Pelupessy,¹
Guillaume Bouvignies,¹ Fabien Ferrage¹

¹CPCV, Département de chimie, École Normale Supérieure, PSL University, Sorbonne Université, CNRS, Paris, France, ²Bruker BioSpin GmbH, Ettlingen, Germany

High-resolution relaxometry (HRR) extends NMR relaxation measurements to fields far below those available with cryogenic magnets while preserving the spectral resolution and sensitivity of high-field detection[1,2]. Proton HRR enables characterization of transient interactions between small molecules and macromolecules in complex mixtures through relaxation-dispersion analysis[3]. However, quantitative interpretation is often hindered by spectral crowding, as proton resonances appear as multiplets from homonuclear scalar couplings [4]. PS NMR experiments collapse multiplets into singlets and improve resolution, but their implementation often suffer from reduced sensitivity [5]. We present a deep-learning framework for reconstructing pure-shift HRR spectra from conventional HRR measurements. The approach uses a modified JTF-WaveNet architecture with five parallel output heads that process FIDs acquired at multiple relaxation delays simultaneously.

The network takes ten FIDs as input: five high-field reference FIDs recorded with a series of echo times and five HRR FIDs acquired at the shortest echo time but with five different relaxation delays at a given low field. High-field spectra encode multiplet structure, while HRR spectra provide relaxation-dependent amplitudes. By combining high-field experiments with low-field experiments, we aim to perform the pure-shift transform on an entire HRR dataset (typically 5 relaxation delays for 40-50 fields, so 200+ spectra) by acquiring only five additional FIDs at high field.

Preliminary results on synthetic and experimental datasets demonstrate accurate reconstruction of pure-shift HRR spectra. The architecture predicts five spectra simultaneously and provides point-wise uncertainty estimates for each spectral point, enabling quantitative assessment of prediction confidence.



Pure shift reconstruction: (a) The inputs, target and the model prediction, (b) Error distribution, (c) SBECE calibration plot

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Model-free analysis stimulates the search for reasonable physical models for complex dynamic processes

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Forty-four years ago, Lipari and Szabo published a paper¹ that did not contain anything new, but at the same time provided a mental breakthrough for many working in the field of magnetic resonance. It was then clear that complicated dynamics that were at the origin of nuclear relaxation data could be tackled without knowledge of the detailed underlying physical processes. This “model-free” approach became popular and, since then, many researchers took advantage of the simplicity of this model-free treatment. Of course, being model-free, the treatment does not provide physical insight. Yet, if the data can be successfully analyzed in a model-free way, then they show that two- or even multi-timescale dynamic processes are present, and then appropriate models should be formulated and tested. Fast field cycling relaxometry is an ideal tool to reveal multi-timescale dynamics and, together with the recent introduction of high-field, high-resolution relaxometry, provides the possibility of measuring relaxation rates as a function of magnetic fields over ca. five orders of magnitude.

I will provide examples of multi-scale dynamics in very diverse systems such as proteins, olive oil, and water solutions of contrast agents. Starting with model-free analysis one can then look for reasonable dynamical models, which in some cases provide interesting and unexpected results.

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Deep-Learning: suppression of vibration artefacts in High Resolution Relaxometry experiments

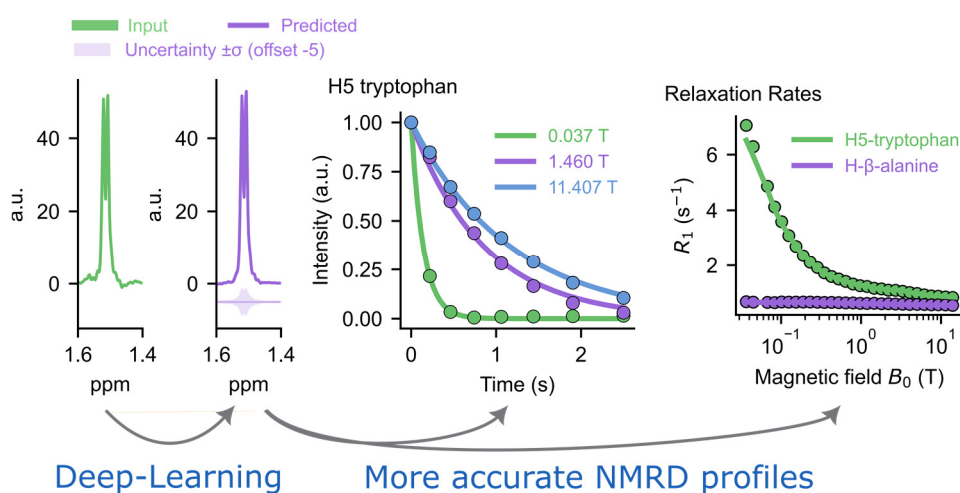
Lucas Siemons¹, Rajka Pejanovic¹, Alessandro Ruda¹, Vineeth Francis Thalakkottor Jose Chacko¹, Guillaume Bouvignies¹, Philippe Pelulessy¹, Jorge A. Villanueva-Garibay², D. Flemming Hansen^{3,4}, Fabien Ferrage¹

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High-Resolution Relaxometry couples low-field relaxation with polarisation and detection in a homogeneous high-field magnet by rapidly moving (~60 ms transfer times) the sample to the stray field of the superconducting magnet. Combining high-field polarisation and detection with low-field relaxation.

In these experiments, fast transfer times are critical to prevent polarisation loss during transfers. In mechanical shuttle systems, motor vibrations propagate through the spectrometer and modulate the impedance in the detection coils, leading to modulations of the free induction decay, producing vibration artefacts in the recorded spectra. These peak distortions make quantifying intensities and relaxation rates challenging.

We developed the Joint Time-Frequency WaveNet (JTF-WaveNet) model to (1) efficiently remove the vibration artefacts while maintaining the correct line widths (2) produce well calibrated errors for the transformed spectra. This model was trained with on-the-fly data generation where simulated spectra were modulated by a point spread function yielding anti-phase artefacts. The performance of the model was evaluated on experiments recorded on a mixture of amino acids in solution with human serum albumin. Quantifying the uncertainty for low-field longitudinal relaxation rates determined from experiments using traditional processing methods and our deep-learning approach, shows that we are able to reduce the standard error of our low-field relaxation measurements by a factor ~2.5x. This work highlights the significant potential of deep learning for processing high-resolution relaxometry experiments and aiding in the extraction of information from complex spectra.



A Bottom Up Approach: Frequency Dependent Relaxation Rates From MD Simulations

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Interpreting FFC-NMR data often requires motional models that are specific to certain systems and assume often simplified analytical forms of the relevant time correlation functions. Here we propose a novel approach for computing the inter- and intramolecular contribution to the magnetic dipolar relaxation from molecular dynamics (MD) simulations, enabling us to predict NMR relaxation rates addressing the full FFC frequency range, covering many orders of magnitude. We also apply a correction factor avoiding influences due to limitations in system size and the accessible time interval. We compute the inter- and intra-molecular NMR relaxation of $\frac{1}{2}$ spin nuclei like ^{19}F in the ionic liquid n-pentyl- pyridinium bis-(trifluoromethyl-sulfonyl)imide with deuteration to avoid heteronuclear contributions. We also address the structure and dynamics of more complex Water-in-Salt(WiS) Electrolytes [1] based on mixtures of Li-bis(trifluoromethanesulfonyl)imide with either H₂O or D₂O in 1:3, 1:4 and 1:5 mixing ratios. We complement this experimental study with molecular dynamics (MD) simulations employing the computational framework [2-4]. We make excellent predictions describing the translational and rotational dynamics with the NMR active nuclei ^1H and ^{19}F on water molecules and anions respectively.

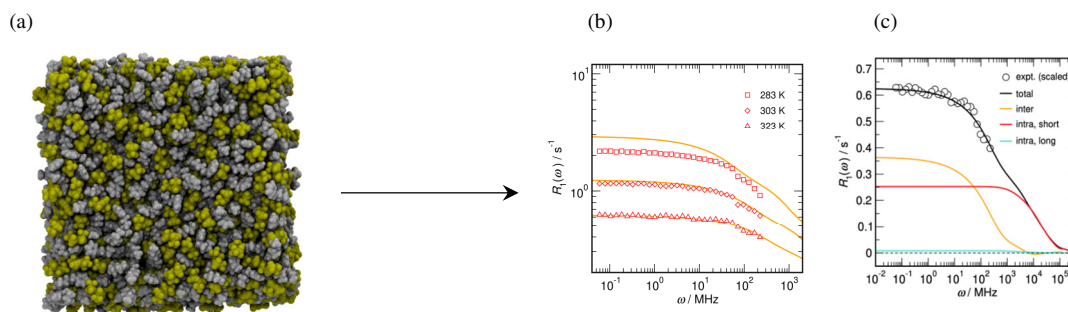


FIGURE 1. (a) MD simulation Snapshot of system containing 1000 ion pairs of $[\text{C}_5\text{Py}] [\text{NTf}_2]$. (b) Experimental and computed ^{19}F NMR relaxation rates of fully deuterated $[\text{C}_5\text{Py-D16}][\text{NTf}_2]$ as a function of temperature. The red open circles represent experimental FFC NMR relaxation data. The solid golden lines represent relaxation data obtained from MD simulations. (c) Intramolecular and intermolecular contributions to the ^{19}F NMR relaxation rate as well as their sum of fully deuterated $[\text{C}_5\text{Py-D16}][\text{NTf}_2]$ at 323 K.

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Investigating elastomer dynamics in rubber using ^1H FC NMR relaxometry

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^1H field-cycling (FC) NMR relaxometry is an ideal technique for investigating multiscale polymer dynamics, spanning from the fast scale of local segmental dynamics and internal motions (10^7 – 10^{12} Hz) to the very slow scale of diffusive motions of the centre of mass (1 – 10^3 Hz). Indeed, it provides access to longitudinal relaxation rates ($R_1(\omega)$) across a broad Larmor frequency range (10^3 – 10^9 Hz), which can be further extended by applying the frequency–temperature superposition principle. Since the pioneering work by Kimmich and Fatkullin,¹ FC NMR relaxometry has been established as a powerful tool to study the temperature-dependent dynamics of linear polymers melts, both below and above the entanglement limit, with the aim of validating theoretical models of polymer dynamics through the predicted frequency dependence of R_1 on Larmor frequency ($R_1(\omega) \propto \omega^{-\gamma}$). This investigation has been extended to the dynamics of elastomers and rubbers of interest to the tire industry.²

In this lecture, I will present recent examples from our research group on using ^1H FC NMR relaxometry to study how cross-linking and curing parameters (i.e., temperature, sulphur content, and sulphur/accelerator ratio), as well as addition of fillers and additives, affect both segmental and polymer dynamics in various elastomers (including cis-1,4-polyisoprene, cis-1,4-polybutadiene, and co-poly[styrene-butadiene]). Segmental dynamics was thoroughly characterized by determining the temperature dependence of motional correlation times. In vulcanized elastomer compounds, correlation times were found to depend on rubber properties (such as cross-link density and sulphur bridge structure)^{3,4} and composition (including the presence of fillers or tackifying resins).^{5,6,7} Polymer dynamics in the entangled regime, which occur at very low frequencies, could only be observed at high temperature for elastomer melts and lowly cross-linked networks. The effects of fillers on dynamics in this regime were highlighted.⁵ Advantages and limitations of ^1H FC NMR relaxometry will be presented and discussed.

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Relaxation Time Distributions for Multi-Exponential Analysis of Decay and Recovery Signals: Principles, Pitfalls, and Practice

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Multi-exponential decay and recovery signals are ubiquitous in magnetic resonance relaxation. Inversion of such signals to continuous lifetime distributions can provide insight into the dynamics of chemical species, health and disease in biological tissue, and pore size distribution in technological materials. Despite opportunities such inversions offer, the magnetic resonance community has remained hesitant to adopt continuous lifetime distributions widely. This hesitancy comes from concerns that (1) the inversion is sensitive to noise, (2) recovered distributions depend on regularization and are not unique, (3) typical magnetic resonance data are not acquired with sufficient quality for reliable inversion, and (4) the assignment of distribution components is difficult. Here, we argue that concerns (1)-(3) are often overstated. We show that careful experimentation, quality control, and signal inversion enables recovering reliable lifetime distributions from noisy magnetic resonance signals^{1,2}. First, we demonstrate successful inversion of multi-exponential signals containing up to five components spanning four orders of magnitude in lifetime at SNRs between 10 to 1000². Second, we show that current open-access tools can correctly determine optimal smoothing for relaxation time distributions³. Third, we provide practical guidelines for acquisition and quality control of time-domain magnetic resonance data intended for such inversions. We acknowledge that component assignment, concern (4), remains an open problem for the community. Nevertheless, a selection of benchmark problems show satisfactory inversion quality and illustrative applications are presented from NMR relaxation of food, T_1 - T_2 relaxation correlation of rocks, and analysis of DNP build-up curves.

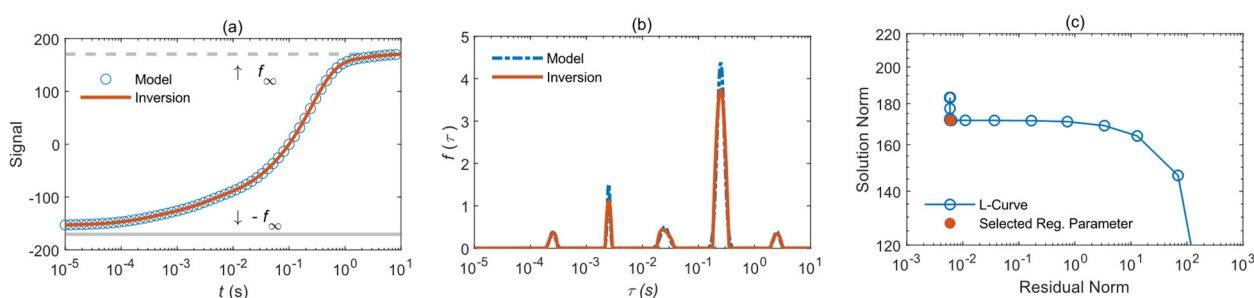


Figure – Transformation of (a) inversion recovery model data with 64 time-domain points to (b) its relaxation time distribution with optimal smoothing guided by (c) the L-curve.

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Slow Dynamics of Biomolecular Systems

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The slow molecular dynamics of biomolecular systems were investigated using ¹H spin-lattice and spin-spin relaxation experiments. Exploiting Fast Field Cycling NMR (FFC-NMR) relaxometry (STELAR s.r.l. relaxometer, Mede, Italy) ¹H spin-lattice relaxation experiments have been performed in the frequency range from 10kHz to 20MHz versus temperature. The studies have been complemented with spin-lattice and spin-spin relaxation experiments performed in time domain – referred to as TD-NMR (Resonance Systems GmbH, Kirchheim unter Teck, Germany) at the frequency of 18.5 MHz (matching the high frequency limit of FFC-NMR).

There are several models linking the relaxation features with dynamical properties of the systems. Relaxation studies covering a broad range of resonance frequencies make it possible to probe dynamical processes occurring on much different time scales. This implies, that ¹H spin-lattice relaxation data for protein systems can be reproduced in terms of relaxation contributions expressed in terms of Lorentzian spectral densities with different correlation times. This approach has been applied to protein solutions of high and low concentrations [1,2] as well as solid proteins [3]. In these studies, the relaxation contributions are attributed to water molecules interacting with different binding sites of the proteins (this relaxation scenario can be mediated by exchange dynamics between the interaction sites). As the observed relaxation processes stem from water molecules, concepts involving specific diffusion models (3D and 2D diffusion) have been exploited as well [4].

This approach provided insight into how biomolecular systems in solvent environment and structural complexity govern different molecular motions. The results demonstrated that NMR relaxometry is particularly suitable for revealing heterogeneous dynamical features in different biological systems.

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Beyond the Relaxogram: Physically Grounded Indices of Structural and Functional Connectivity from FFC-NMR Dispersion Profiles

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Fast-field-cycling NMR relaxometry provides direct access to the distribution of molecular correlation times, $\rho(\tau_c)$, through model-free inversion of the full NMRD profile. Despite the rich dynamic information encoded in this distribution, its analytical potential has largely been reduced to qualitative interpretation or single-field snapshots. This contribution presents a framework for extracting two scalar indices – the Structural Connectivity Index (SCI) and the Functional Connectivity Index (FCI) – directly from $\rho(\tau_c)$, without imposing thresholds, breakpoints, or user-defined partitions.

SCI is defined as the normalized Shannon entropy of the log-correlation-time distribution and quantifies the degree of motional heterogeneity across dynamic environments. FCI is defined as the normalized first moment of the same distribution and describes the average position of the system along the fast-to-slow motional axis. Both indices are dimensionless, range between 0 and 1, and are applicable to unimodal, broad, and multimodal distributions alike.

The framework is validated across systems of increasing complexity: reference minerals with well-defined pore morphologies (zeolite, montmorillonite, kaolinite), natural clay soils subject to erosion and sediment redistribution, soil–biochar mixtures spanning a controlled compositional gradient, and a clay soil measured over the temperature range 25–50 °C. In all cases, SCI and FCI provide complementary and non-redundant information, as demonstrated most directly by their opposite responses to temperature: SCI decreases while FCI increases, confirming that the two indices capture physically independent properties of the same motional distribution.

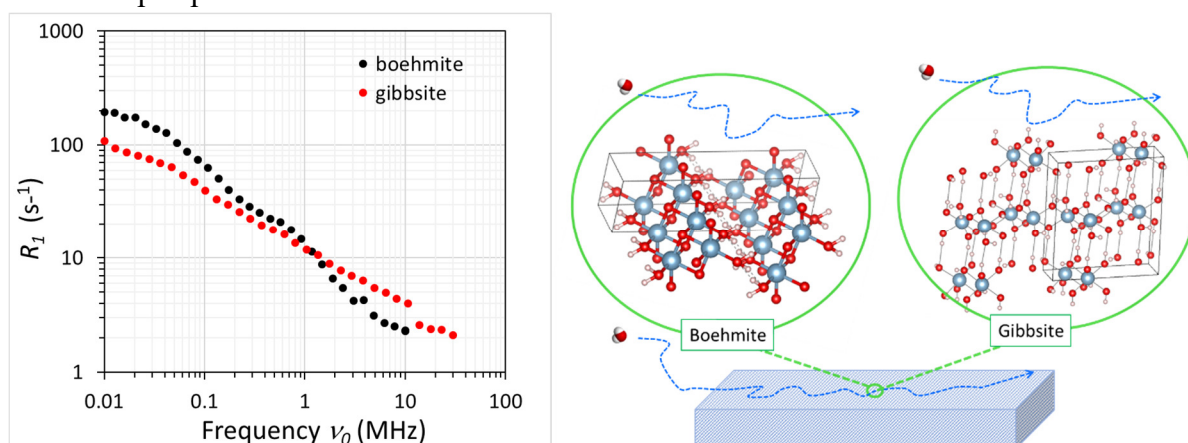
Because the approach operates entirely in correlation-time space and requires no system-specific assumptions, it is transferable to any porous or heterogeneous system amenable to FFC-NMR characterization.

¹H of water relaxation in the vicinity of aluminum oxyhydroxide particles

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Alumina (Al₂O₃), a widely support catalyst, derived from the topotactic calcination of pastes of aluminum oxyhydroxide particles, in particular boehmite (γ-AlOOH) and gibbsite (α-Al(OH)₃). This topotactic transformation makes it very interesting to study the dynamics of mobile molecules in boehmite and gibbsite confined system, at different water content. The hierarchical multi-scale structure of such materials imposes a multiscale approach. In this regard, FFC NMR relaxometry provides a crucial insight into the intermediate timescale (ns-μs). The challenge is then to analyse the ¹H NMR dispersion profiles that are quite smooth (see figure) and reach the uniqueness of the model. The combination of complementary techniques appears mandatory, from both a dynamic and a structural perspective.



A first step was to attribute the origin of the bump around 0.7 MHz before modelling the global shape of the NMRD profile. Indeed, Ward-Williams et al.¹ and Belorizky and Fries et al.² attributed this specific feature to different origins. Evolution in temperature of the NMRD profiles helps us to confirm the quadrupolar relaxation enhancement (²⁷Al) origin of the bump.³

The second step is to identify the origin of the magnetic fluctuation experienced by the ¹H. The analysis showed the predominant role of the surface curvature and of the surface diffusion coefficient.⁴

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Synthesis and Relaxometric Studies of Mn (II) Complexes Associated with Silica Nanoparticles as Safer Alternatives to Gadolinium-Based MRI Contrast Agents

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Mn (II) complexes have emerged as promising gadolinium-free alternatives: The main challenge lies in designing ligands that combine high thermodynamic and kinetic stability with optimal water-coordination properties. The present work focuses on the development of high-performance Mn (II) complexes based on the pycnen-derived PC2A scaffold, used both as discrete molecular contrast agents and in association with silica nanoparticles to further enhance their relaxometric performance. A library of structurally diversified ligands (fig.1) was synthesized to fine-tune relaxivity of the corresponding Mn²⁺ complexes, as well as their kinetic stability. The Mn²⁺ complexes were prepared and fully characterized, and their relaxometric properties were investigated by combined ¹H NMRD profile analysis, variable-temperature ¹⁷O NMR, and multifield T₁/T₂ measurements. Their kinetic stability was also investigated through transmetallation measurements with the zinc ion. These studies revealed how fluorination, hydroxylation, and carboxylate arms tune relaxivity, hydration number (q), water residence lifetime (τ_m), and complex stability.

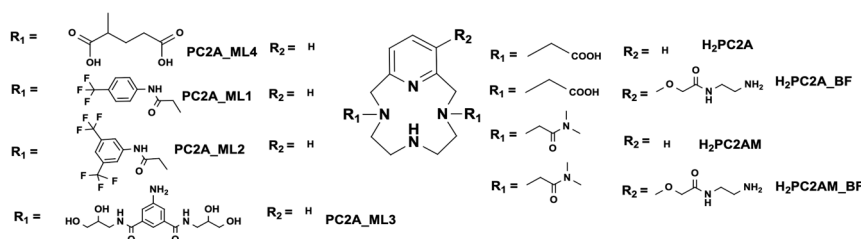


Fig.1. Chemical structures of the synthesized PC2A-based ligands.

In a second step, two complementary nanostructured strategies were explored to amplify the relaxivity per Mn²⁺ ion. First, the Mn-PC2A complex was encapsulated within silica nanoparticles¹, taking advantage of confinement effects and a high local payload of paramagnetic centers. Next, the Mn-PC2A-BF derivative was covalently grafted onto the silica surface through water in-oil microemulsion synthesis strategy² to study the effect on the surface grafting. Both constructs were characterized and their relaxometric behavior was compared with that of the parent molecular complexes in solution. In both cases, a marked enhancement of longitudinal relaxivity was observed and rationalized in terms of the higher rotational correlation time (τ_R) imposed by the nanoparticulate carrier together with the high local density of Mn²⁺ centers. Altogether, these results highlight the versatility of the PC2A platform for the design of stable, high-relaxivity Mn (II)-based contrast agents and demonstrate that combining ligand-level molecular engineering with silica-based nanoplateforms is a powerful strategy toward safer, gadolinium-free MRI probes.

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Unraveling supramolecular gels structuration via High-Resolution and Fast-Field-Cycling NMR

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Supramolecular gels consist of molecular assemblies interconnected through non-covalent interactions, enabling them to immobilize solvent molecules within a three-dimensional network. The organogelation process strongly depends on the nature of the gelator-solvent pair, while intermolecular forces such as hydrogen bonding, π - π stacking, and electrostatic interactions determine the architecture of these physical gels. Nuclear Magnetic Resonance (NMR) spectroscopy is particularly well suited for probing solvent dynamics in such systems.

This work presents studies on two distinct supramolecular gel systems. The first is a low-molecular-weight organogel formed from a modified phenylalanine derivative bearing a naphthalimide moiety in toluene, while the second is a nucleopeptide-based hydrogel.

Below the liquid-to-gel transition temperature, high-resolution NMR spectra reveal not only solvent signals but also signals from mobile gelator molecules. These species constitute the so-called isotropic phase, in which gelator molecules retain liquid-like behavior and may rapidly exchange with molecules incorporated into the gel network. Temperature-dependent variations in signal intensities provide valuable insights into these processes, and diffusion measurements using the pulsed-gradient spin-echo (PGSE) technique can further characterize molecular mobility. In addition, Fast Field-Cycling (FFC) relaxometry offers access to much slower solvent dynamics, yielding information on the system both during gelation and after the gel network has formed.

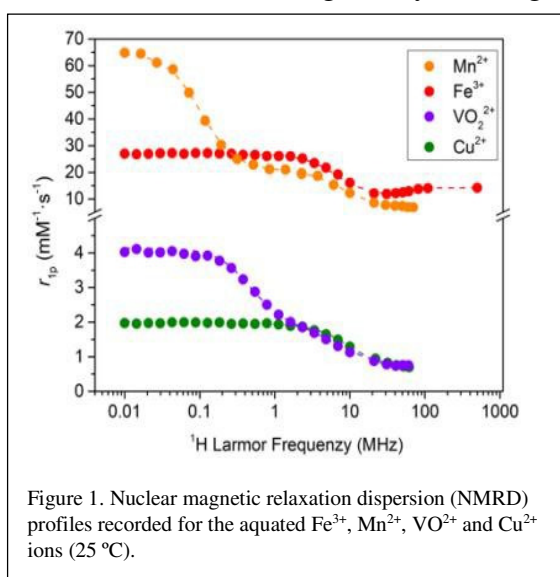
Overall, these complementary NMR approaches provide a comprehensive picture of molecular mobility and exchange processes in supramolecular gels, contributing to a deeper understanding of their structure-dynamics relationships.

Critical evaluation of the potential of transition metal complexes as alternatives to gadolinium MRI contrast agents

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Contrast agents for magnetic resonance imaging (MRI) are small gadolinium(III) complexes used in clinical practice to facilitate the diagnosis of various pathologies.¹ These complexes contain one or more water molecules coordinated to the paramagnetic metal ion, which are involved in water exchange with the surroundings, enhancing the relaxation of water molecules in their vicinity. Despite the routine use of these agents by radiologists, some toxicity concerns have been raised over the past



decade, related to the discovery of gadolinium deposits in the brain and other organs of patients after gadolinium-enhanced MRI.² This triggered a renewed interest in finding Gd-free alternatives based on transition metal ions such as Mn(II) and Fe(III).^{3,4} In this contribution, the relaxation properties of Gd(III), Mn(II) and other transition metals will be analyzed using the classical relaxation theory of paramagnetic relaxation and specific examples (Fig. 1). This overview of the relaxation properties of transition metal complexes will highlight the opportunities and also the challenges that need to be addressed for the development of the next generation of contrast agents for MRI.

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NMR-Based Investigation of Wettability, Stability, and Interfacial Dynamics in Metal Oxide Nanoparticle Systems

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Understanding wettability, colloidal stability, and interfacial molecular dynamics in metal oxide nanoparticle systems is important for applications in catalysis, adsorption, and functional colloidal materials[1][2][3]. In this study, Time-Domain Nuclear Magnetic Resonance using Spin Mate NMR Analyzer (Resonance System, Germany) was employed as a non-destructive technique to investigate the wettability behavior of TiO₂, ZnO, three different categories of silica, and γ -Al₂O₃ nanoparticle suspensions prepared at various mass concentrations. Relaxation parameters obtained from TD-NMR measurements were used to evaluate the relative wettability of the oxide systems. For ZnO and γ -Al₂O₃ suspensions, sodium dodecyl sulfate (SDS) and polyvinylpyrrolidone (PVP) surfactants were additionally introduced to investigate their influence on colloidal stability and wettability behavior. The observed relaxation trends were compared with the enthalpy of immersion and contact angle measurements reported in the literature.

To obtain deeper insight into interfacial molecular dynamics, γ -Al₂O₃ nanoparticle suspensions and their corresponding SDS- and PVP-modified systems were further analyzed using Fast Field-Cycling (FFC) relaxometry and high-resolution relaxometry with a Fast Shuttle system (Paris, ENS). Proton spin-lattice relaxation measurements were performed over a broad magnetic field range to investigate concentration-dependent molecular mobility and surface-induced relaxation behavior. The resulting Nuclear Magnetic Relaxation Dispersion (NMRD) profiles revealed frequency-dependent relaxation mechanisms associated with restricted molecular motion, surfactant-assisted stabilization details, and interfacial interactions near the γ -Al₂O₃ surface.

The combined TD-NMR, FFC relaxometry, and Fast Shuttle System, high-resolution relaxometry demonstrates the potential of NMR techniques as sensitive and non-invasive tools for evaluating wettability, colloidal stability, and nanoscale interfacial dynamics in oxide nanoparticle systems. The findings further highlight the role of surfactant-modified interfaces in controlling molecular mobility and liquid-solid interactions in nanoparticle suspensions.

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Ultrafast High Resolution Relaxometry for probing multi-timescale dynamics: application to imidazole glycerol phosphate synthase

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While high-field NMR spectroscopy offers atomic-level resolution information on structure and fast motions, accessing slower or field-dependent processes remains a challenge. Here, we present Ultrafast High-Resolution Relaxometry (UHRR), a new methodology that bridges this gap and overcomes the limitations of field cycling relaxometry (FFC), by combining high-field resolution with low-field sensitivity to spin dynamics. The newly developed Fast Shuttle System (FSS) features a high-speed hybrid pneumatic/mechanical shuttle transferring samples at velocities up to $\sim 27 \text{ m}\cdot\text{s}^{-1}$ between high (up to 16.4 T) and low magnetic fields, where a field cycling coil allows for reaching magnetic fields down to 100 μT in less than 2 ms. The device is compatible with standard NMR probes and hardware, without compromising spectral quality or experimental throughput [1].

We applied UHRR to study the dynamics of imidazole glycerol phosphate synthase (IGPS), a heterodimeric enzyme composed of two subunits, HisH and HisF. IGPS is a model allosteric system in which binding of PRFAR in HisF enhances glutamine hydrolysis in the HisH active site by ~ 5000 -fold despite a separation of $\sim 30 \text{ \AA}$ [2,3]. Using selectively labeled isoleucine, leucine, and valine methyl groups ($^{13}\text{CHD}_2$ isotopomers), we recorded residue-specific nuclear magnetic relaxation dispersion profiles over more than 30 magnetic fields spanning five orders of magnitude. The data were analyzed with the in-house software MINOTAUR using model-free approaches [4], and compared with molecular dynamics simulations. To probe slower millisecond motions, we also acquired multiple-quantum CPMG relaxation dispersion experiments [5]. Our integrative approach aims at enabling the decomposition of motions probed by methyl groups into contributions from methyl rotation, side-chain motions, global tumbling, and slower conformational transitions, providing a comprehensive description of IGPS dynamics from picoseconds to milliseconds and their role in allostery.

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Molecular Dynamics of GMO@DTPA-BSA-Gd Nanoassemblies

Investigated by ^1H NMR Relaxometry

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Embedding amphiphilic Gd-chelates into lipid nanoassemblies increases the effective molecular size of the formed contrast agent relative to low molecular weight contrast agents, slowing rotational tumbling and extending the rotational correlation time τ_R - a key determinant of longitudinal relaxivity r_1 at clinically used magnetic fields. However, the molecular dynamics parameters governing the relaxometric performance of such lipid GMO-based nanoparticles with Gd-chelating lipids have not been reported. Characterization of the underlying molecular dynamics parameters is therefore essential for a comprehensive understanding of these complex systems and their final performance. Nanoassemblies, formulated with 2% w/w glyceryl monooleate (GMO), DTPA-bis(stearylamide) gadolinium salt (DTPA-BSA-Gd) at 20% w/w, and Pluronic F127 at 25% w/w, all relative to GMO weight (2GMO-20DTPA-25F127), exhibited sufficient colloidal and chemical stability across physiologically relevant media, with limited Gd^{3+} release ($\leq 4.0\%$). ^1H NMRD profiles obtained at temperatures 298 K and 310 K (0.01 - 300 MHz) were fitted with a modified two-population SBM model, incorporating two effective rotational correlation times.

Values of $\tau_{R1} = 2.09 \times 10^{-9}$ s and $\tau_{R2} = 0.22 \times 10^{-9}$ s were obtained from the fitted function at 298 K from the ^1H NMRD profile of a single unfractionated sample. The two-component rotational dynamics is consistent with the autocorrelation function (measured by Dynamic Light Scattering), requiring a bi-exponential model, and is interpreted as reflecting two distinct local motional regimes of the Gd^{3+} coordination sphere within the two nanoassembly size-related populations. The water residence time τ_M decreases from 756 ns at 298 K to 141 ns at 310 K, confirming a water exchange-limited regime and accounting for the increase in r_1 from 9.9 to 14.1 $\text{mM}^{-1}\text{s}^{-1}$ at 23 MHz, exceeding the 3.0 - 4.2 $\text{mM}^{-1}\text{s}^{-1}$ range reported for clinically approved low molecular weight GBCAs at comparable field strengths^{1,2}.

The research provides a detailed analysis of the molecular dynamics parameters that govern relaxometric performance in 2GMO-20DTPA-25F127 nanoassemblies, advancing understanding of this class of lipid-based MRI contrast agents.

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TD-NMR characterization of semicrystalline polymers: structure and dynamics

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Time-Domain NMR (TD-NMR) is often used to characterize phase composition, molecular mobility, and morphology in semicrystalline solids. Their heterogeneous structure, consisting of rigid crystalline domains embedded in amorphous phases, leads to variations in mobility, dipolar interactions, and relaxation behavior. TD-NMR is well suited for investigation of these features and provides both qualitative and quantitative information on crystallinity, molecular dynamics, and phase transitions¹.

In this work the commodity polymers, namely polyethylene, polypropylene, and polystyrene, with varying crystallinity and molecular weight were investigated. Experiments with Free Induction Decay (FID) and alternative sequences were performed in a wide temperature range (−40 to 120 °C). Relaxation data were used to determine apparent transverse relaxation times (T_2^*), reconstruct FID signals, analyze melting behavior, and estimate activation energies associated with molecular motions. Distinct behavior in temperature regions linked to changes in local and segmental dynamics was identified through combined analysis of relaxation and spectral parameters². Longitudinal relaxation analysis showed characteristic extrema associated with different thermally activated molecular motions, ranging from localized side-group reorientations to larger-scale segmental chain dynamics³.

Double-quantum and multiple-quantum NMR experiments were used to estimate the distributions of residual dipolar couplings, that are connected to motional constraints and structural heterogeneity⁴. A novel method for reconstruction of overall MQ relaxation curve from DQ build-up data was tested for the wide range of polymers under study. To estimate the morphology of the rigid and amorphous domains, spin-diffusion experiments (Goldman–Shen and DQ spin-diffusion filtering) were performed, allowing determination of domain sizes without spectral deconvolution.

The combination of various TD-NMR techniques with analysis based on the second-moment approximation, gives a comprehensive framework for characterizing polymer crystallinity, molecular mobility, and phase behavior. Overall, the results demonstrate that low-field TD-NMR can deliver detailed, model-free structural and dynamic information across a broad range of polymer materials.

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Exploring the phase behaviour of water-ethanol mixtures within 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. In previous studies on alumina catalyst carriers¹ and Vycor glasses,² 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 influence of pore size, surface hydroxyl density, and mixture composition on the liquid structuring within the pore space was investigated. Fast field cycling NMR and T_1 - T_2 measurements at 43 MHz were carried out as a function of composition for mixtures imbibed within four different mesoporous silicas. For each liquid mixture, two distinct relaxation environments were observed, corresponding to the hydroxyl and alkyl functionalities. Figure 1 shows that the adsorption behaviour of the liquid mixtures differed strongly between the silicas, with the hydroxyl density being the dominant factor in determining the extent of microphase separation that occurred within the porous silicas studied. 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.

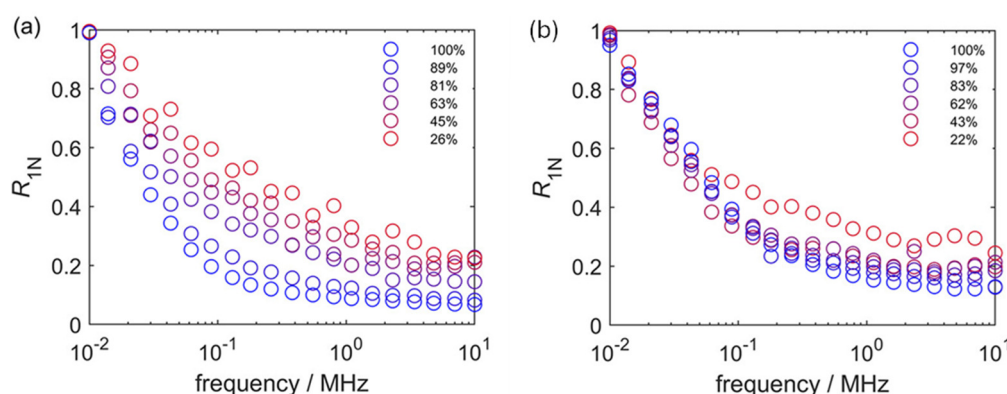


Figure 1 – The normalized NMRD profiles of the hydroxyl functionalities of water-ethanol binary liquid mixtures as a function of composition when imbibed within (a) Q6 silica (5 nm pores) and (b) Q30 silica (27 nm pores). For each NMRD profile, the mole fraction of water in the liquid mixture is shown.

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Software-Assisted FFC-NMR Relaxometry: Automated Data Processing and Molecular Dynamics of Pyridinium Ionic Liquid Crystals

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NMR relaxometry is widely applied to soft matter systems, including ionic liquids, liquid crystals, and lyotropic mesophases.¹ Relaxation dispersion profiles encode molecular and collective dynamics, including rotations, reorientations, diffusion, director fluctuations, and layer undulations, which govern low-frequency relaxation and require systematic model fitting for accurate interpretation.² This work combines FFC-NMR relaxometry and conventional NMR covering a frequency range from 10 kHz to 300 MHz to study molecular and collective dynamics of four pyridinium-based ionic liquid crystals: ([C12-pyr][Br]), 1-hexadecylpyridinium bromide ([C16-pyr][Br]), 1-dodecyl-2-methylpyridinium bromide ([C12-2-Pic][Br]), and 1-hexadecyl-2-methylpyridinium bromide ([C16-2-Pic][Br]).³⁻⁵ Pure thermotropic compounds were investigated at 90°C, 110°C, and 130°C across their smectic and isotropic phases. The two 2-methylpyridinium systems were additionally studied as 60 wt% aqueous mixtures at 30°C, 40°C, and 50°C, accessing lyotropic smectic phases stabilised by hydration while remaining well below boiling point to ensure sample integrity.^{3,4}

Dispersion profiles reveal systematic differences associated with headgroup substitution and alkyl chain length. The hydrated systems additionally require bi-exponential analysis: two distinct relaxation components with temperature-dependent relative contributions reflect the dynamically heterogeneous nature of the lyotropic mesophase.³ A persistent challenge in FFC-NMR is the lack of standardised, instrument-independent tools for multi-component relaxation analysis. This work therefore also presents a modular Python framework integrating the PyOFE-API fitting interface with STELAR HDF5 and SDF data import filters, enabling automated extraction, normalisation, and bi-exponential fitting of relaxation datasets, with careful attention to recovery delay selection for accurate multi-component analysis and improved cross-laboratory reproducibility.¹⁻⁵

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From ordering to dynamic properties in liquid crystals: an overview of NMR-based studies

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Since their discovery in 1888, liquid crystals have been characterized thanks to the presence of the unusual fluidity, typical of liquids, and the partial ordering properties, typical of crystalline solids.¹ Within few decades, several types of supramolecular aggregations having liquid crystalline properties were discovered, with a clear distinction between mesophases formed by achiral molecules (i.e. nematic and smectic phases) and those appearing in the presence of chiral molecules, such as the cholesteric phase.² The first study of liquid crystals based on NMR spectroscopy was performed in 1963 by Saupe and Englert³ with a nematic phase used to orient small molecules, while the first observation of the orientational order in a nematic phase oriented in a relatively strong magnetic field was carried out by Lohman and MacLean only in 1978.⁴ Later on, NMR spectroscopy has been intensively used to study the orientational order, the conformational properties of mesogens in different liquid crystalline environments and the molecular and collective motions.⁵⁻⁷ For instance, ¹H spin-lattice relaxation studies played a crucial role in the late 1960s in identifying collective motions, called order director fluctuations (ODF) in liquid crystals.⁸

In this talk, following an historical / educational approach, several crucial NMR studies of liquid crystals, with a focus on their dynamic properties, will be presented and discussed to underline the complexity which arises from the interplay between ordering and dynamic properties in these particular states of matter.^{9,10}

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Fast field-cycling in liquid crystals: untangling the molecular dynamics in the beautiful state of matter

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As kids, we learn that there are three phases of matter – solid, liquid, and gas. Later, we maybe also mention plasma, and perhaps more exotic states, such as the Bose-Einstein condensate. But one particular state of matter can be called beautiful. These are liquid crystals that form picturesque textures when observed under a polarized microscope.

Liquid crystals are made of long molecules, as well as sometimes disks or ionic liquids. When the interactions between the molecules become strong enough, the molecules self-order and form different phases. The best known is the nematic phase where all molecules are pointing roughly in the same direction. Next group are the smectic phases where molecules stack in layers. And it gets even more complex, with elaborate 3D structures of blue and twisted grain boundary phases.

Apart from being beautiful, liquid crystals are also highly useful in various applications, from the well-known displays to novel sensors. To get a better understanding of what is taking place on the molecular scale, fast field-cycling is a powerful technique that provides insight both on the level of motions of individual molecules as well as of the collective dynamics in the oriented phases. In the talk, I will present some of our work in the framework of the ongoing collaborations.

Improved NMR Detection System for Fast-Field-Cycling Relaxometry

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Fast-field-cycling (FFC) NMR relaxometry probes inter- and intramolecular dynamics across a wide range of magnetic fields without any moving parts, yet its sensitivity is ultimately set by the radio-frequency (RF) detection chain. This thesis deals with improvement of that chain—raising the signal-to-noise ratio (SNR), shortening signal-acquisition delays, and producing more homogeneous and more manufacturable RF coils—and is organized around two contributions: design of improved RF coils, testing of a ringing-compensation pulse sequence. This activity was complemented by the design and realization of surface and volume RF coils for MR Imaging.

Starting from the current STELAR design for saddle coils, new coils for the one-inch wide-bore systems were designed. The approach followed was to generalize the single turn saddle optimum of Bonetto *et al.* to the multi-turn case to achieve better Signal to Noise Ratio. This approach was successful in improving SNR for large samples but suppressed the signal from small, centrally placed samples more than expected by simple filling factor considerations, because of an M-shaped radial B_1 profile. This result was identified as a limitation for users with a small available sample volume but a large bore FFC system. To address it an improved approach to RF coil design was adopted, based on the static target-field method. The continuous stream-function was obtained by solving the inverse quasi-magnetostatic problem in discretized space, using a single harmonic of a Tikhonov-regularized surface-current expansion. The approach not only restored a flat profile but also resulted in a slightly improved quality factor (Q 62 vs. 55 as from full wave simulations). In the first experimental realization, the brittleness of the used flat flexible PCB substrate resulted in fractured tracks during bending inside the cylindrical bore. A special bending tool was developed to perform bending more robustly and safely. A similar algorithm was also used for the small-bore 3T STELAR system. In this case the proposed design retains multiple odd-cosine harmonics in the stream-function expansion, solved against a Biot–Savart forward model, to achieve high B_1 homogeneity with optimized RF efficiency. Within the RF coil improvement, the SNR optimal Q factor was derived for each sample's T_2^* , useful to define a “ Q -matching” approach to signal detection.

The second part considered all possible temporal delays for the signal detection windows along the RF chain. Once the ring-down of the coil was identified as the dominant contributor (at least for Q equal or larger than 40) a composite excitation pulse was designed to reduce it. The standard excitation pulse is followed by a shorter and weaker phase-shifted second lobe which forces destructive interference in the coil with negligible effect on the spin dynamics. The approach was experimentally verified both in the UNIVAQ RF laboratory and on Stelar hardware, giving a reproducible dead-time reduction of several microseconds. This allows to recover otherwise-lost FID signal from short-lived macromolecules, improving SNR.

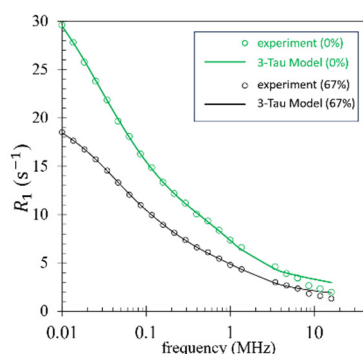
The work with MRI coils included the study of a new decoupling mechanism for transverse surface Figure-of-Eight coils and the behavior of an RF Helmholtz volume coil at 3 T.

Field-cycling relaxometry for medical applications: the 3-tau model

Rémi Kogon, David Faux

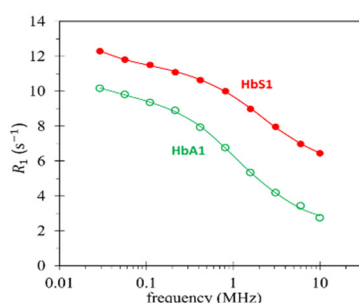
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The 3-Tau Model¹ (3TM) is used to interpret FFC NMR dispersion (NMRD) profiles from water-bearing soft or hard materials with or without paramagnetic ions. We review recent applications to systems of medical interest yielding fresh insight and the prospect of new applications in healthcare.



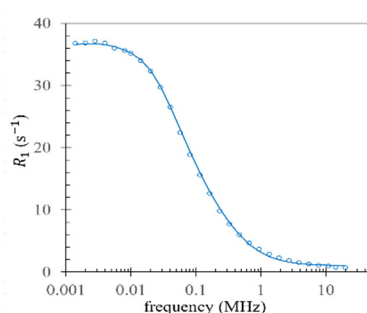
Tumorous tissue²: Excellent 3TM fits to 32 NMRD profiles for 0%–83% tumour fractions are obtained (Fig. 1). Statistical analysis of parameter variability with tumour fraction found that two parameters acted as biomarkers. The origin of the biomarkers is consistent with changes in cell surfaces leading to the ingress of extracellular water to the intracellular volume for tumour cells, thereby explaining the low-field dependence of R_1 to tumour fraction.

Fig. 1. 3TM fits (solid lines) to NMRD profiles from healthy murine tissue (top) and 67% tumour (bottom)



Hemoglobin³: Sick cell disease (SCD) is a serious blood disorder that can lead to organ damage. Hemoglobin S (HbS) is the primary protein within red blood cells of patients with SCD. Two 3TM dynamic time parameters for HbS were approximately half those for HbA allowing HbA and HbS samples to be clearly distinguished (Fig. 2). FFC NMR with 3TM analysis shows promise both as a diagnostic technique for SCD and conditions that lead to thickening of blood.

Fig. 2. 3TM fits to healthy hemoglobin (bottom) and SCD hemoglobin (top)



Hydrogel⁴⁻⁶: Hydrogels are 3D hydrophilic, polymeric networks used as slow-release drug delivery systems. The rate of release depends critically on mesh size. Small-angle neutron scattering (SANS) was applied to a hydrogel sample finding a mesh size $h = 7.5\text{nm}$.^{4,5} The 3TM analysis found $h = 6.6\text{nm}$. FFC NMR with 3TM analysis therefore allows a non-destructive, rapid and inexpensive laboratory alternative to SANS for determining mesh size in hydrogels.

Fig. 3. Example of a 3TM fit (solid line) to a hydrogel

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Probing Molecular Dynamics and Interactions in Human Blood Serum via Ultrafast High-Resolution Relaxometry

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Nuclear Magnetic Relaxation Dispersion (NMRD) profiles carry information on the molecular dynamics across a broad range of timescales, but exploiting this in a complex biological matrix has long been limited by sensitivity and resolution. Ultrafast High-Resolution Relaxometry (UHRR) overcomes these limitations by combining high-field NMR detection with a Fast-Shuttle-System (FSS) and a prototype Field-Cycling-Coil (FCC), enabling site-specific ¹H relaxation rate measurements from 0.1 mT to 11 T on a 600 MHz spectrometer.

Here we applied UHRR to intact Human Blood Serum (HBS), without any pre-treatment or purification, as a proof of concept for the characterization of molecular dynamics and metabolite-macromolecule interactions in native biofluids. NMRD profiles were acquired for both macromolecular components and small metabolites. All UHRR measurements were analysed using TrAGICo, a Python-based software package designed for extracting and evaluating data from 1D and pseudo-2D Bruker NMR spectra¹.

Our results demonstrate that lipoproteins, glycoproteins, albumin lysyl groups and phospholipids, all exhibit characteristic dispersions described by distribution of correlation times spanning nanoseconds to microseconds. For most small metabolites (e.g. lactate, creatinine, 3-hydroxybutyrate, valine, alanine), the NMRD profiles show modest or absent field dependence, preventing a clear detection of binding interactions under the experimental conditions. A notable exception is phenylalanine, whose aromatic protons display a well-defined dispersion, suggestive of a transient interaction with a serum macromolecule. The sensitivity of UHRR toward protein–ligand interactions was further validated by spiking HBS with Y-DOTA(BOM)₃, an albumin-targeted complex. Its NMRD profile in serum displays a clear dispersion with $\tau_c \approx 30\text{--}32$ ns, consistent with albumin tumbling and in excellent agreement with previous results².

Taken together, these results establish UHRR as a powerful tool for the in situ dynamic fingerprinting of biofluids, with direct implications for biomarker discovery and the characterization of metabolite–protein interactions in their native biological context.

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