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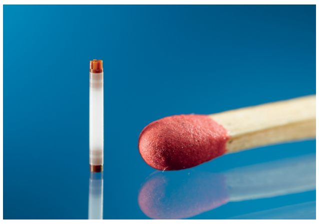
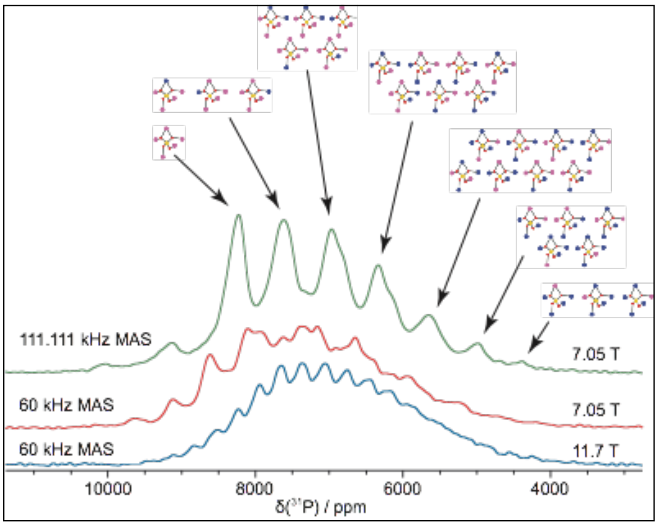


Solid-State NMR of Paramagnetic Inorganic Materials using >100 kHz Magic-Angle Spinning

By Kevin Sanders, CNRS Lyon

The interactions between NMR-active nuclei and the unpaired electrons of paramagnetic metals potentially yield important information about systems of interest in catalysis, energy conversion and storage, and biochemistry. However, these same interactions cause challenging problems when attempting to acquire NMR spectra of paramagnetic samples, notably large shifts and shift anisotropies which lead to inefficient excitation using conventional pulses, large paramagnetic relaxation enhancements which cause coherences to decay rapidly after excitation, and large anisotropic bulk magnetic susceptibilities, which in-homogeneously broaden the lines. This commonly leads to the failure of conventional experiments to yield any data, and even if data has been successfully recorded the low sensitivity and poor resolution may hinder interpretation.



The recent development of probes where the sample is rotated at the so-called magic-angle (54.7º) at very fast rates has revolutionised the field of paramagnetic solid-state NMR. In collaboration with Bruker BioSpin, we have investigated the advantages offered by a new probe capable of magic-angle spinning (MAS) rates higher than 100 kHz using a 0.7 mm rotor for the study of paramagnetic materials. Important benefits of this spinning regime include (i) an improved averaging of dipolar couplings and the separation of sidebands, with a notable increase of resolution, sensitivity and coherence lifetimes compared to previously available MAS rates; (ii) the possibility of reaching very large RF fields with very small amplifier powers, with a significant improvement in excitation bandwidth and pulse efficiency; (iii) the completely new possibility of applying broadband irradiation schemes which are based on low-power RF elements.

These benefits are illustrated here by a highly paramagnetic inorganic complex, $LiFe_{0.25}Mn_{0.75}PO_4$, a promising paramagnetic battery cathode material. This mixed phase adopts the olivine structure, and the disordered occurrence of Mg and Mn ions results in many different ^{7}Li and ^{31}P environments, with shift anisotropies close to 1000 ppm, coherence lifetimes shorter than 1 ms, and a isotropic chemical shift dispersion that for ^{31}P spans about 4000 ppm.

The ^{31}P spectra of $LiFe_{0.25}Mn_{0.75}PO_4$ (Figure) were acquired on Bruker Avance III spectrometers operating at 500.195 MHz (11.7 T) and at 121.95 MHz (7 T). An impressive increase in sensitivity and resolution is observed because of efficient separation of sidebands and increased pulse efficiency. By spinning at 111 kHz, site resolution is observed whereas 1D experiments utilizing 60 kHz MAS yielded a spectrum with almost no resolution on the paramagnetic resonances.

We anticipate that the possibilities offered by this new spinning regime could revolutionize the study of paramagnetic samples which are central in many areas of modern chemistry, biochemistry, and materials science.

PNMR NETWORK TRAINING

Leiden

In **2014** the pNMR network has been at the forefront in the organization of 7 applied trainings, schools, and workshops, all for the sake of NMR and opened to external PIs and students.

The series of activities started in Mariapfarr, amongst the snowy Austrian Alps in February with an ***'electronic and nuclear relaxation, and structure calculation'*** school organised by the Institute of Inorganic Chemistry in Bratislava, in collaboration with TU Berlin and ahead of the 7th annual workshop on Modern Methods in Quantum Chemistry. The peaceful scenery helped the 38 participants coming from all Europe to discuss the physical and quantum chemical background of NMR shifts of paramagnetic compounds.

Mariapfarr

Florence

In July, 33 participants from the EU, South Africa, Russia, Saudi Arabia, Japan, Israel, the USA, and Australia attended a ***'liquid and solid-state NMR of paramagnetic proteins'*** training organised by CIRMMP (upgraded into a larger EMBO workshop) in Florence, Italy. Theoretical and practical insights were provided for an optimal use of the protocols in order to study the molecular structure and dynamics through solution and solid state NMR. pNMR fellows then had the opportunity to deepen their knowledge in ***'NMR Relaxation theory'*** thanks to a training organised by Stockholm University in the nice Florentine area.

Leiden

Florence

The Summer trainings ended in Leiden, the Netherlands, where 10 participants learned through hands-on experiments how to modify a protein with a lanthanide tag, acquire NMR spectra, and analyse paramagnetic effects, with a particular focus on the application of protein-ligand complexes in drug discovery during the ***'paramagnetic protein tagging, and NMR in drug discovery'*** training organised by Leiden University and ZoBio, our associated partner.

Cambridge

September was full of activities organised by the University of Cambridge. 67 people attended a training on the application of pNMR on ***'Inorganic materials'*** and in particular to battery and fuel cell materials, which was followed by 2nd Annual Workshop of the pNMR project, this year focusing on ***'new developments in experimental and theoretical techniques for the study of paramagnetic inorganic materials'.***

A hundred people from all over the world participated in this event over 3 days, during which a wine and cheese tasting was organised, as well as a diner in a Harry Potter style dining hall.

Cambridge

The event was even opened to high-school students from the Cambridge area, who, after an active lab tour and an explanation on battery research and the use of NMR, attended the 'industrial applications of pNMR' session of the workshop.

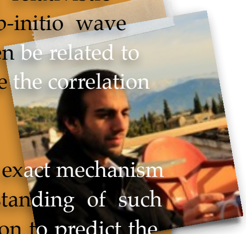
Finally, pNMR fellows and others could attend a training on ***'how to write, edit a scientific paper, and get it published'*** given by the RSC.

Today a third of clinical MRI scans are performed with the aid of paramagnetic molecules, representing a billion dollar market worldwide. The development of these compounds is a direct result of fundamental paramagnetic NMR studies characterizing the relaxometric properties of such molecules.

Some time ago, things looked pretty simple: we had a natural picture of relaxation and some well-defined equations, described by the Solomon-Bloembergen-Morgan theory, that could explain the process. All then that was required was an understanding of the correlation time of the molecular tumbling, the chemical exchange and a few other parameters that are either constants or can be fixed in the laboratory.

However, in multi-electron paramagnetic systems, the hyperfine interaction between unpaired electrons and nuclear spins increase the longitudinal nuclear relaxation rates in a more complex fashion. For example, the electron spin relaxation for high-spin Gadolinium(III)(S = 7/2) systems(which are the types of molecules which are most used in MRI) is caused mainly by the second-order spin-orbit coupling term. This is due to the highly symmetrical electronic structure of the seven parallel 4f electrons in the 8S state: the first order contribution will vanish for the S state. The spin-orbit coupling results in breaking the degeneracy of the Kramer doublets of the electronic ground state, the phenomenon known as Zero-Field Splitting in the spin Hamiltonian formalism.

The research at Stockholm University is primarily concerned with understanding the role that these 'higher-order' terms play in influencing the relaxation process of clinically relevant complexes. It aims at employing state-of-the-art methods for studying solution dynamics of complexes of heavy atoms, including relativistic descriptions of the Zero-Field Splitting, based on ab-initio wave function and density functional methods. These can then be related to relaxation parameters by using spin dynamic theories to compute the correlation times of various parameters of interest.



The consequence of such research is a better deconstruction of the exact mechanism that determines the relaxation rate. If a full coherent understanding of such processes is eventually achieved, one would be in a better position to predict the indicators that enhance the resolution of MRI scans, since the signal intensities depend upon the density and relaxation rates. The advantages of such manipulations are unforeseeable, and even more so for the theoretical and computational scientist like myself, is the sheer excitement of understanding the electronic structure of yet unexplored molecules and extending existing theories for more complex cases.

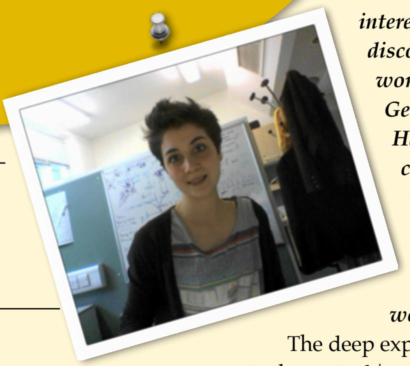
Shehryar Khan, Stockholm University

LIVE FROM THE pNMR LABS

Student profile

Roberta Pigliapochi

University of Cambridge (UK)



Where are you from and where are you currently enrolled ?

I come from Italy, originally from Jesi (AN) and later moved to Bologna for my Undergrads and Masters, with some periods abroad. Since January 2014 I am a PhD student at the University of Cambridge.

Where did you go, and/or will you go during your PhD ?

I have so far been at the Technische Universität Berlin for a first 3-month secondment, where I will go back for as much time again; my other secondment will be at the BBIO Bruker facility in Rheinstetten, Germany.

Did anything strike your attention when you arrived at the University of Cambridge to start your PhD? What about at Technische Universität Berlin ?

The warmth and enthusiasm with which both groups welcomed me amazed me. Since the very first day I joint the group in Cambridge I immediately felt part of it: the importance given to discussion and cooperation makes everyone contribute actively, and being surrounded by such a passionate environment has always made me feel supported.

The Berlin group involved me in all the activities and discussions as if I was part of it, and the mutual interest in our research made the time spent there very fruitful and enriching.

What is the most interesting thing you discovered while working in Germany ? Has your stay there changed anything in your intercultural comprehension of the workplace ?

The deep expertise of Kaupp's group in theoretical/computational research taught me a lot and made me think about my study and about the overall picture from a different and wider perspective. Besides, that was my first experience in Germany other than for mere holiday, and even if my big fault was not to put enough effort in trying to learn the language beforehand - which is an aspect I am committed to improve before my next secondment - I was amazed to find such an international and multicultural scene, both within the University and in every other aspect of everyday life.

Do you think secondments stimulate your research projects ? What about secondments at industrial partners premises ?

Secondments absolutely give a boost to the project and help the student grow as a researcher: the wish of sharing the own expertise and at the same time of taking the most out of the period abroad certainly motivates. I haven't been on secondment at an industrial partner yet but I am sure it will be enriching alike, broadening the research perspective and teaching me different aspects I wouldn't have come across otherwise.

What could you say about your experience of multi-sites training and international cooperation with the pNMR project so far?

The cooperation within the pNMR network is a very important support to always rely on. It stimulates discussions and collaborations between not only the singular fellows but their entire groups as well.

What about fellows coming on secondments in your home institution ?

Having fellows working with us for some time has always been very interesting and fruitful, and it has always been considered as a source of enrichment by the entire group.

Would you say the project is going to improve your contact network, and/or experience in foreign languages ?

I couldn't expect so much cooperation before I started this experience and my contact network has already enlarged hugely. Also, after my first experience in Berlin I am even more motivated to challenge myself to learn a new language, taking the secondment as an opportunity to prove and practice it!

What will you remember about being part of a Marie Curie ITN project ?

Oh well such a dynamic 3-year project with so many different experiences and connection has increased my professional and cultural knowledge so deeply that it will not only be remembered but it will constitute an important baggage in my future as well.

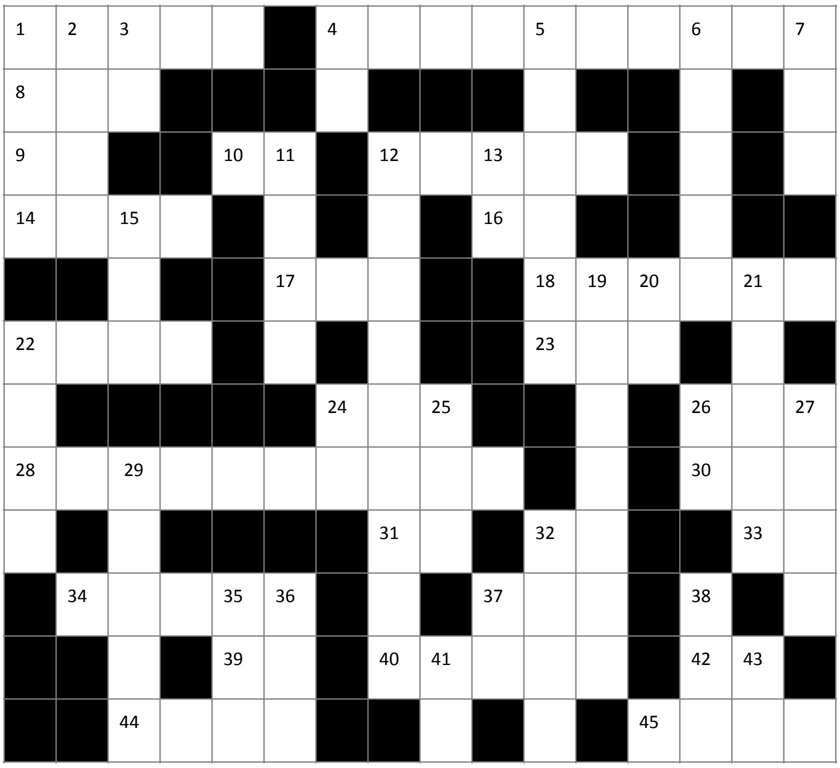
Have your career objectives shifted since you started your PhD a year ago ?

I think that a PhD project is an ever-growing experience and in my case it didn't really start off with definite objectives but rather with desire to do and learn. I have still a long way to go and my career will evolve and grow with time, open to new ideas and chances.

FOOD FOR THOUGHTS

(if pNMR leaves you any time to think)

By Andrea Bertarello, CNRS Lyon



Across

1. Transferred echo double resonance
4. American physicist, most known for his work on spin polarization transfer
8. Pseudocontact shift
9. Its values depend on the acidity of a solution
10. Chemical element discovered by Wollastone (symbol)
12. A dancing decoupling sequence
14. Iodine for French people
16. Before Christ
17. The basic unit of information in computing and digital communications
18. The difference between the rotating frame frequency and the Larmor frequency
22. A 2D homonuclear correlation experiment
23. Rotating frame Overhauser effect
24. A magnetic resonance technique widely used in medicine
26. One of the fundamental techniques in solid state NMR
28. Its value is 54.7 °
30. Electron spray ionization
31. He developed the general theory of relativity (initials)
32. You have to type it in Topspin if you need to reboot a console
33. It is a type of junction in semiconductors
34. A Disney character but also a family of decoupling sequences
37. ^{14}N nuclear spin number value
39. Actinium
40. An EPR technique used to probe the environment surrounding paramagnetic centers
42. Increment
44. X-ray technique often used to refine protein structures
45. Without it we would not be paid

Down

1. An acquisition technique for phase sensitive multidimensional NMR experiments
2. She was a nymph in Greek mythology but it is also used in NMR experiments
3. Dummy scans
4. Osmium
5. A heteronuclear correlation experiment
6. They are two in an AX system
7. NMR for French people
11. NMR experiment that gives correlations between carbons and protons that are separated by more than one bond.
12. A technique to suppress the water signal
13. A growth medium for bacteria
15. Disk Operating System
19. The French mathematician who transformed NMR...
20. Iron
21. A command line you type in Topspin to edit acquisition spectrometer parameters
22. It uses a train of π pulses to refocus inhomogeneous broadening of the nuclear spins
24. Manganese
25. Isoleucine
26. Methyl group (abbreviation)
27. A window function for apodization
29. The cgs unit of measurement of the magnetic field
32. A type of steel particularly resistant to corrosion
35. One of the pioneers in protein NMR
36. Carbonyl sulfide (formula)
37. You monitor its value at 600 nm when you are growing bacterial cultures
38. You have to type it when you turn on your mobile phone
41. North – East
43. Nanomolar

Answers will be available online this summer at www.pnmr15.eu.

UPCOMING EVENTS

For more details and registration visit www.pnmr.eu

Applied training course

Introduction to practical pNMR shift calculations

29th-30th June 2015

TU Berlin, Germany

Applied Training Courses

Florence, Italy

Liquid State NMR
&
Protein Expression and Purification

9th-11th September 2015