NEWSLETTER OF THE FP7-PEOPLE-2012-ITN "PNMR" PROJECT

Pushing the Envelope of Nuclear Magnetic Resonance Spectroscopy for Paramagnetic Systems

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pNMR news

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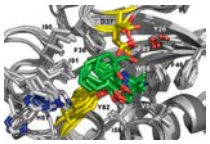
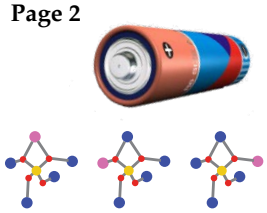




DRUG DISCOVERY AND PARAMAGNETISM: a new avenue for NMR into pharmaceutical research

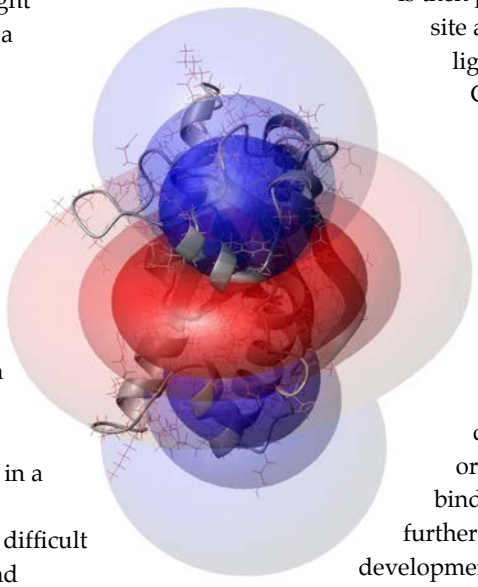
by MATHILDE LESCANNE

FINDING INHIBITORS of proteins involved in malignant tumor development is one of the main focuses in the fight against cancer. Finding small molecules that bind with a moderate/high affinity to the target protein is the first stage of drug discovery. For each target protein, thousands of compounds need to be screened before probing in more depth and further developing these 'hits'.

Classical NMR has been part of the drug discovery field for more than a decade as an alternative to Xray crystallography for studying molecular interaction with an atomic resolution.

Multidimensional NMR on proteins can provide a high resolution picture of the protein-ligand interaction but the experimental acquisition time and the required analysis are too laborious for screening ligand libraries in a reasonable time.

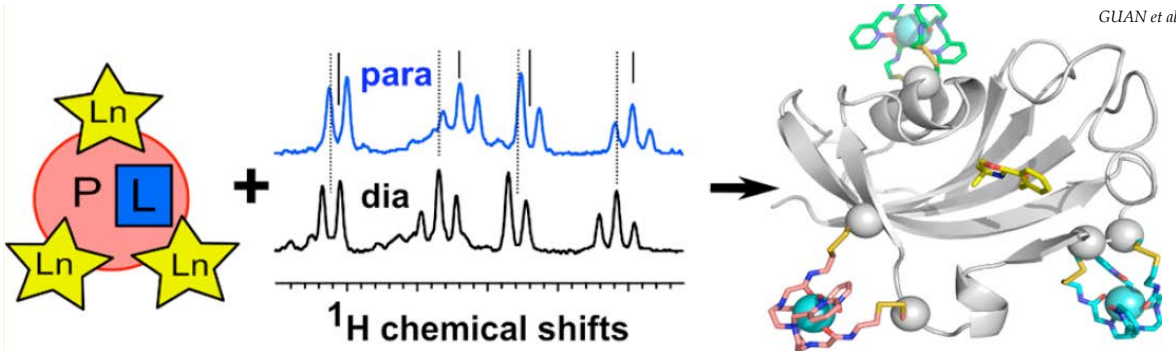
1D-NMR on proteins leads to crowded spectra that are difficult to analyze. However, solution 1D-^{1}H NMR on the ligand provides a clear spectrum. With a paramagnetic center on the protein, the ligand experiences paramagnetic effects in bound-protein state. Pseudo-contact shifts observed on the ligand protons depend on the relative positions between the ligand protons and the paramagnetic center. Knowing the paramagnetic susceptibility tensor and the protein structure, it is then possible to find the ligand binding site as well as the orientation of the ligand relative to the protein.



Combining several PCS datasets from different paramagnetic centers, ligand docking can be done using only ^{1}H data from the ligand.

A 1D NMR spectrum is recorded in a few seconds which makes ligands screening by 1D NMR realistic and efficient.

Paramagnetic NMR spectroscopy enables a quick and accurate determination of the location and orientation of small molecules that bind to proteins which can be used for a further hit validation during drug development.

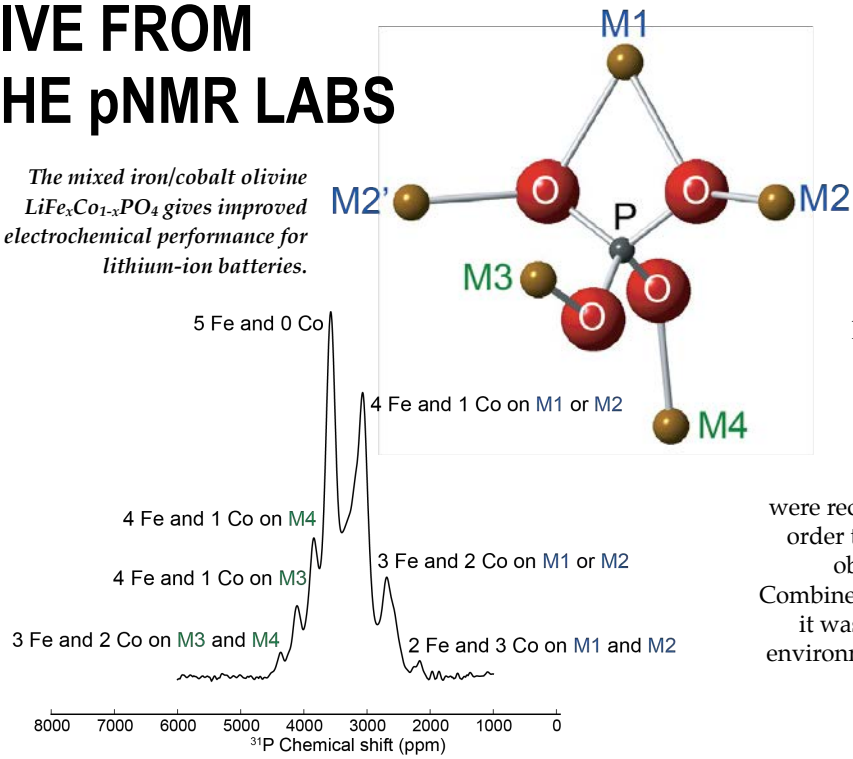


GUAN et al. J. AM. CHEM. SOC. 2013, 135, 5859-5868.

Interaction between a target protein and a ligand. The three different Lanthanides (carried by the molecule CLaNP-5) attached one by one to the protein give three PCS datasets used for the ligand docking.

LIVE FROM THE pNMR LABS

The mixed iron/cobalt olivine $LiFe_xCo_{1-x}PO_4$ gives improved electrochemical performance for lithium-ion batteries.



$LiFe_xCo_{1-x}PO_4$ STRUCTURE : Building batteries with enhanced energy storage capacity

THE $LiFePO_4$ olivine materials have been of much interest to the scientific and industrial communities, as a class of high-energy-density cathode materials for lithium-ion batteries. Partial substitution of cobalt for iron, giving $LiFe_xCo_{1-x}PO_4$, has been shown to improve the electrochemistry. In a collaboration between the Cambridge and Lyon laboratories ^{31}P solid-state NMR was performed to gain a better understanding of the local structure, which is crucial for understanding the electrochemistry. State-of-the-art experiments that were recently developed by the same groups were applied in order to give the high resolution that is required in order to observe the different phosphorus sites that are present. Combined with hybrid density functional theory calculations, it was possible to assign and rationalize all 32 phosphorus environments, thus giving a complete description of the local structure of these materials.

STROBRIDGE et al. J. MAT. CHEM. A. 2014, in press.

pNMR FELLOWS ON THE MOVE

pNMR Early Stage and Experienced Researchers (ESRs and ERs) have started their Secondments programme, which is a period during which fellows spend time working on a research project at another partner's premises. It aims at fostering high level training as well as collaborations and cooperation between project partners, and will help fellows constitute their own network by expanding their research contacts.

An interesting aspect of these mutual visits is the intercultural comprehension ESRs and ERs will have to develop. The amount of interactions, collaborations and cross-fertilization between the 13 nodes of the network in 2014 can be seen in the map next.

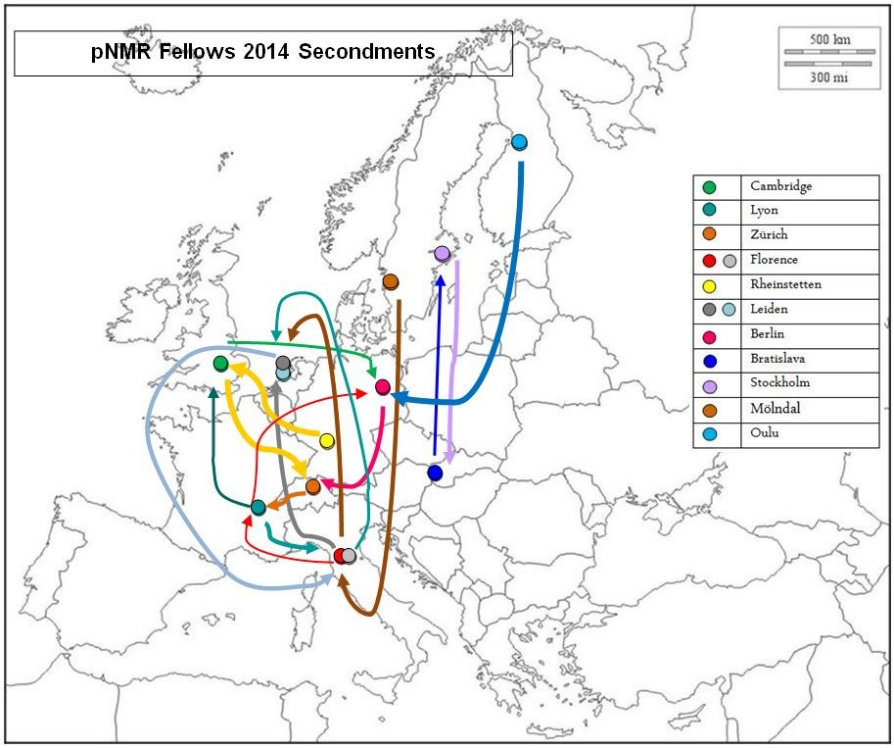
FELLOWS SECONDMENTS : cross-fertilisation among pNMR labs

Secondments are a key element of the project. Each network partner will send his/her fellow to at least another partner's premises, where s/he will have the opportunity to benefit from the expertise in a particular area of pNMR of another group of the network, thus extending their understanding of these phenomena.

All ESRs will have secondments at industrial partners of the network. During their stay at BBIO, Giotto, ZoBio, and AstraZeneca, fellows will have the opportunity to be exposed to the challenging environment of industrial R&D.

The 3 ERs associated with the 3 full private partners will be essential in providing an efficient bridge between the developments targeted in the private nodes and research carried out in the academic labs.

The 2014 Secondments session started with Arobendo Mondal ESR2 spending 3 months at ETH Zürich. Tobias Schubeis ER2, as well as Florian Allouche ESR9, are currently working in our premises in Lyon for a respective duration of 3 and 1 months. Most pNMR Fellows will go on secondment over the summer, with a couple of them meeting at the same premises, such as David Benett ER1 and Kevin Sanders ESR1 at the University of Cambridge, or Syed Awais Rouf ESR3 and Roberta Pigliapochi ESR4 at the Technische Universität Berlin.



Student profiles

Arobendo MONDAL
Technische Universität Berlin (Germany)
Peter Cherry
Institute of Inorganic Chemistry, Slovak Academy of Sciences (Slovakia)

What is it about the Marie Curie funded ITN projects which appealed to you and motivated your application ?

Peter: Asides from my interest in the subject, the main thing which makes the ITN project stand out is the guarantee that I will travel and work in multiple different groups over the course of my PhD. Working in a variety of different groups will not only be an exciting experience on a personal level, but will encourage me to see problems from a different angles, and hopefully enable me to produce more original work.
Arobendo: As Peter pointed out, the most fascinating aspect of MCA ITN funded projects, is the opportunity for fellows to visit partners' labs . This not only leads to enrichment of knowledge, but also helps PhD students to establish their own network by virtue of their interactions with prominent scientists in the network. As aunique feature of MCA ITN funded projects, it made it stand out from other PhD programs, and definitely motivated my application.

How has working in a foreign country compared with your expectations?

Arobendo: During my prior experience of an internship in a foreign country, I admired the work environment as well as work ethics being practiced there. I had therefore, similar expectations about my new lab, and I am happy to say that it exceeded them. To me it is such an enriching as well as satisfying experience to be in Germany, and even more in Berlin !
Peter: Unlike Arobendo, I had never worked abroad before, so I didn't really know what to expect. So far I've been very pleasantly surprised with how welcoming everyone is and how easy it has been to adapt to working in a new place. Perhaps the most striking thing is how little difference there is.

Are there any collaborations/secondments to which you are particularly looking forward?

Peter: I am particularly looking forward to going to Florence and working with GIOTTO Biotech. This will be a real change and challenge for me, as my background is much more on the theoretical end of physics, so I shall be excited to try and work in a more practical setting.

Peter Cherry PhD research project deals with Fully relativistic pNMR theory: development, interpretation and applications. He works under the direction of Pr. Malkin.

Arobendo: I am not actually looking forward to any particular collaboration : to me, each one of them is a learning opportunity. Therefore, irrespective of which collaboration or secondment I will be involved in, it will always help me learning something new, and enable me to work with an eminent scientist in the field of pNMR.

Is there anything in particular you hope to accomplish during your PhD?

Arobendo is working on a PhD research project is about Periodic solid-state calculations of paramagnetic NMR shift tensors using advanced DFT methods, under the direction of Pr. Kaupp.

Arobendo: pNMR is a developing field and there are many researchers contributing towards it both theoretically and experimentally. During my PhD, I would like to try to gather a better understanding of the field, which would enable me to contribute significantly towards it. Additionally, I would like to make my input to method development which would be implemented in computational packages and ultimately applied. Basically, I am so looking forward to it!
Peter: It might sound simple, but my main aim is just to understand what I am working on, and hopefully contribute to other people's understanding as well. Ideally, I would successfully extend and implement the current theoretical models for calculating g-tensors, and then get to see this new theory validated by experiment.

How do you think it will prepare you for your future career?

Peter: The chance to collaborate closely with a much larger number of leading scientists than is usually possible over the course of a PhD will be very helpful in preparing me for the future. Asides from the sheer intellectual benefit, this experience will also help me become a better collaborator, one who is more receptive to the ideas of others.

Arobendo: Thanks to the work I will do during my PhD, I will be armed to handle more complex problems in the field of pNMR, that will be helpful for my future career, as will it enable me to play a significant role in expanding the repertoire of knowledge in this field. Additionally, as Peter said, the unique nature of this MCA ITN project will definitely help me to become an efficient collaborator, able to exchange ideas leading to innovative work .

PNMR NETWORK TRAINING

INTEGRAL TO the research-based training programme is the series of workshops, practical training courses, international conferences, and outreach actions, located at the different sites. These will i) train the young researchers of the network in the basics of pNMR and ii) disseminate the results of the network to the larger NMR community and to the general public.

Electronic and Nuclear Relaxation, and Electronic Structure Calculation

Mariapfarr, Austria - February 22-24 2014

By Peter Cherry, ESR 5, and Arobendo Mondal ESR2.

The village of Mariapfarr has hosted the European electronic structure Workshop for the past seven years. It is not hard to see why : as well as possessing the kind of peaceful atmosphere well suited to scientific thought and discussion, it also possesses numerous ski resorts, guaranteeing a conference which is both mentally and physically invigorating.

A key goal of the pNMR project is to foster collaboration between experimentalists and theoreticians. The first speaker of the training school, Prof. Giacomo Parigi of CERM, is a great example of this interdisciplinary approach. His talk focused on relating the fundamental theoretical concepts which underpin pNMR to experimental results. The second speaker was Prof. Kowalewski from Stockholm University, who spoke about the challenges of modeling spin relaxation, and how acquiring a better understanding of this complex phenomenon can help with both interpretation and design of experiments. The poster session held afterwards was very fruitful as it allowed participants to gather knowledge about research work being done as well as interact with each other.

The second day of the conference began with two speakers from Berlin: Prof. Martin Kaupp and Dr. Ladislav Bender, who elaborated on the technicalities of different computational methods, and the systems to which these methods are most appropriately applied. Then, Prof. Juha Vaara, Dr. Jiri Mares and Jyrki Rantaharju, from Oulu University, elaborated on some of the more advanced and specialized parts of the theory, such as the methods of calculating zero field splitting and spin relaxation, whilst also discussing the practical relevance of these techniques in fields such as protein structure determination.

The round table discussion was quite intense and conclusive. Starting with discussion on Co (II) excited state complexes, which are very interesting from the viewpoints of experiments and theory, participants wondered how to form a bridge between experiments and theory. All Participants agreed they should come up with good model systems working for both theoretical and experimentalists groups, therefore allowing researchers to see the same problem from different dimensions.

The last day of the event focused more heavily on relativistic effects. It began with a talk by Dr. Vladimir Malkin on importance of relativistic effects, and on recent progress in modeling, followed by a heavily theoretical discussion by Dr. Komorovsky, who detailed density functional theory-based four-component relativistic methods, how these differ from two component methods, and the areas of study to which they are most suited. Dr. Helene Bolvin addressed afterwards ab-initio methods, and how application of these methods, combined with extensive theoretical investigation, can provide insight into the physical meaning of the g-tensor and consequences arising from zero field splitting. The final talk of the training school was given by Prof. Alessandro Bagno, who discussed the value of using non-empirically based computational techniques in the interpretation of spectra. *Photos : Arobendo Mondal*

UPCOMING EVENTS

For more details and registration visit www.pnmr.eu

Applied Training Courses Florence, Italy

13-20 July 2014

Solution and solid-state NMR of Paramagnetic Molecules

cosponsored by EMBO, and

NMR Relaxation Theory

Students Applied Training Course Leiden, Netherlands

8th-22nd August 2014

Paramagnetic tagging for drug research

Second Annual Scientific Conference

New Developments in Experimental and Theoretical Techniques for the Study of Paramagnetic Inorganic Materials

Corpus Christi College
Cambridge University, UK
16th-18th September 2014