Inside nmi3

Issue 4 - January 2013

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SEVENTH FRAMEWORK PROGRAMME

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Editorial

As announced in issue 3 of *Inside NMI3*, the changes in the composition and role of the Advisory Committee took effect with the start of the new project, NMI3-II, in February 2012; they hold until January 2016. The first formal change is to the name of the committee, which evolves from its original "Scientific Advisory Committee" (SAC) to the simpler "Advisory Committee" (AC). By simplifying the name, however, we broaden the remit of the Committee.

The newly-appointed AC met in Grenoble in March 2012, for the "Kick-off Meeting" of the NMI3-II project. The aim was to establish the tools and processes for working together, with the aim of providing the NMI3 Consortium with valuable feedback on its various activities.
In its first six months the AC's attention was focused on establishing a set of procedures for evaluating the European Neutron and Muon Schools (ENMS) supported by NMI3. We are now starting on the evaluation of the 2012 Schools and plan to produce a first evaluation report by April 2013 which will be presented in the Berlin meeting (June 20th).

The aim of the ENMS evaluation is set out in the objectives of the WP4 for NMI3-II:
"The objective of the ENMS is to integrate and support a distributed training facility for neutron and muon scattering in Europe based on existing periodic high-quality schools. Light but efficient governance will ensure an intensive exchange of experience and good practice between the individual schools that make up the ENMS."

The NMI3 Advisory Committee is responsible, in conjunction with the NMI3 coordination team, for evaluating each individual School. The evaluation is based on a short report and questionnaires to be completed by the students and School directors. The data thus collected will shed light on a number of parameters, including the quality of the teaching, teaching material available, students' satisfaction, synergies between the different schools, etc. The aim is to improve the existing initiatives and develop new ones, such as inter-School events for the students. We plan to establish a student database which will help to keep in touch with the young researchers' careers.

As we say in Italian, "A good day can be seen from the morning". We'll keep you posted on developments following these initial efforts by the new AC. Hopefully we're not too far off the mark; the day is young and there is an ambitious programme to come!

Romano Rinaldi
Chairman of the AC for NMI3-II

Activities

Focus on Joint Research Activities

In this issue of *Inside NMI3* we update you on the work carried out as part of the Deuteration Joint Research Activity.

The Deuteration JRA: capitalising on novel methods for sample production in biological systems

By Trevor Forsyth, Michael Haertlein, Michael Sattler, Luke Clifton, Christine Ebel and Hermann Heumann

This JRA has been developing protocols that are impacting strongly on the scope and quality of biological neutron scattering experiments carried out at central facilities throughout Europe. The need for this is very clear given the increasing trend towards interdisciplinary and integrated approaches for the study of biological systems. Neutron scattering has a unique and important role to play if the right types of sample can be made available. Deuteration is essential to this: the ability to label complex/interacting systems offers approaches that are simply not possible using other methods. This project is widening the access of neutron scattering methods to biologists throughout the European Union, both by extending the range of problems that can be tackled, and by reducing the cost impact of sample preparations. It exploits an obvious synergy with the nuclear magnetic resonance (NMR) community, which also has important needs for isotope labelling and within which there is increasing use of neutron scattering.

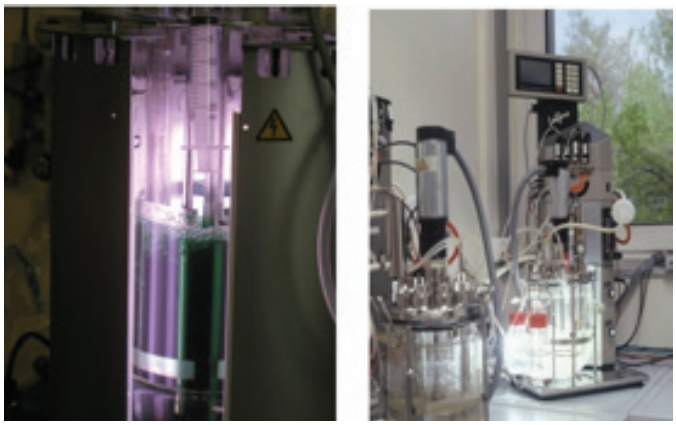
Optimisation of deuterated biomass production

A large number of biological neutron studies rely on the biosynthesis of deuterated biological macromolecules using deuterated carbon sources. The cost of these often limits experiments severely. In this task protocols have been developed for the optimisation of *E. coli* and algal biomass production. Since algae grow photosynthetically, relying only on D_2O medium, CO_2, and light, they are an ideal candidate for cheaper production of deuterated components. Major downstream applications in neutron scattering are obvious for these *in vivo* products: deuterated molecules can be purified and used as deuterated feedstock to bacteria such as *E. coli*.

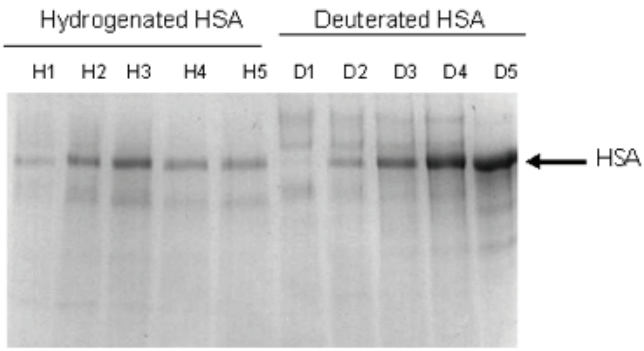
Production of labelled proteins in yeast

Most proteins used in neutron scattering studies are produced in bacteria such as *E. coli.* This type of protein production has had a huge impact on studies of biological systems using a wide variety of techniques. In many cases the use of *E. coli* is limited by folding/post translational modification problems. Some proteins have to be produced in lower eukaryotic expression systems. However there are difficulties in adapting such cells to growth in deuterated media.

Here we have developed methods whereby labelled proteins can be produced (intracellularly or exported) in yeast.



Deuterated biomass production from phototrophic (green algae) and heterotrophic (*E.coli* and *P.pastoris*) micro-organisms



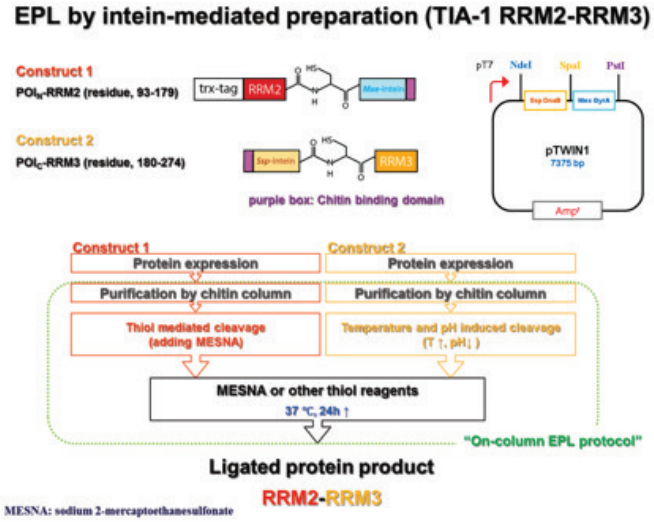
SDS–PAGE analysis showing expression of hydrogenated and perdeuterated HSA in *Pichia Pastoris* cell culture supernatants.

Segmental labelling

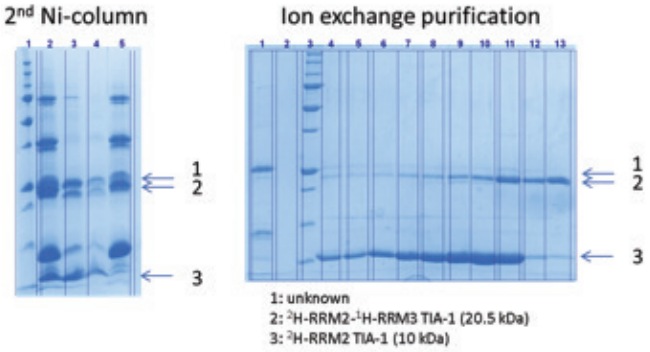
Over the course of the project we have established two model systems (U2AF65 and TIA-1) for implementing and optimizing protein ligation techniques and subsequently demonstrated the expression of fragments and the ligation using protein trans splicing techniques. The production of segmentally isotope-labeled proteins was first established using segmentally 15N-labeled proteins. The optimized protocol was then used for segmental deuteration of the protein TIA-1 RRM2-RRM3. The purified protein was used for SANS measurements with contrast variations at Institut Laue-Langevin (ILL) Grenoble to document the utility of segmental deuteration.

Based on the results obtained in this project a protocol for the production of segmentally deuterated proteins has been developed, which serves as a guideline and recommendation for the neutron community. The experimental protocols and optimisations of the production of segmentally deuterated proteins have been exchanged with the Life Sciences group at the ILL and will thus be available for the general scientific community of neutron researchers. The implementation of the protocol is being prepared for publication.

We have also started to explore the use of sortase-mediated protein ligation, which has been reported to yield better ligation efficiencies compared to intein-based methods. For the TIA-1 model



A segmental labelling protocol



Expression, ligation and purification of a segmentally labeled protein

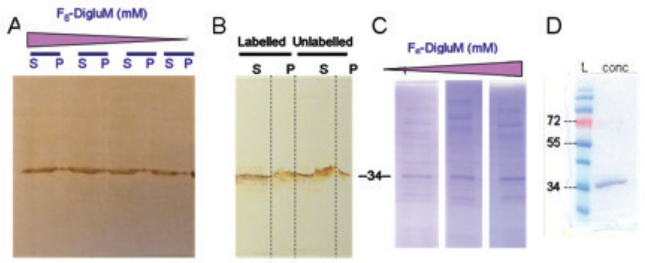
systems, this work is still in progress. However, for another multi-domain protein we have successfully implemented sortase-mediated protein ligation with very high yields.

Low cost D-glycerol production

The high cost of deuterated carbon sources for the expression of D-proteins in *E.coli* is still a stumbling block for the application of neutrons in biology. In this task, methods have been developed for the production of deuterated glycerol by algae under salinic stress. A novel protocol based on "milking" algae of the glycerol produced, dramatically reduces costs since the same biomass and D_2O can be used repeatedly. Approaches have been developed using *Dunaliella salina* and *Chlamydomonas reinhardtii* (a freshwater algae that could be competitive with *Dunaliella*). *Dunaliella* accumulates up to 6M glycerol in the cell and this task has focused on efficient release of glycerol into the media. Methods tested included high temperature treatment, cell immobilization and mild sonication.

Deuterated membrane proteins

Membrane proteins perform a wide range of essential cellular functions and play key role in (for example) transportation, energy management, signal transduction, photosynthesis. They are also implicated in a number of genetic diseases and have considerable therapeutic importance (70% of drug targets). This group has focused on the development of methods to optimise deuteration of membrane proteins. Model membrane proteins have been identified and bacterial expression systems in high cell density cultures used for deuteration. The deuterated membrane proteins will be used to



Screening experimental conditions for membrane protein synthesis: A. surfactant concentration in reaction mix. B. Deuterated versus hydrogenated amino-acids. C. Surfactant concentration in the feeding mix. D. Characterisation of the purified protein by SDS-PAGE.

reconstitute membrane systems with hydrogenated lipids for neutron studies and to test new classes of surfactants for their capacity to stabilize functional assemblies.

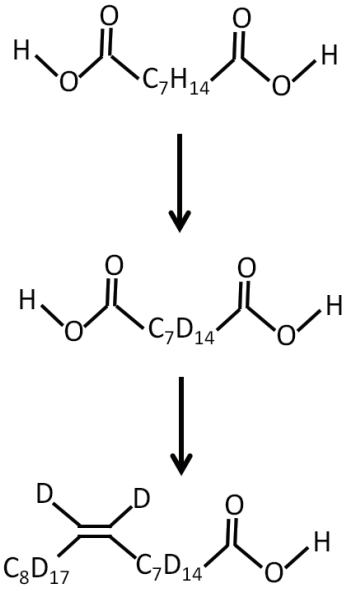
Deuterated lipids

One of the major limitations for the application of neutrons to the study of biological systems is the availability of deuterated lipids. Membrane biology is a particularly important area and a new range of powerful experiments could be carried out with the availability of selectively labelled lipids. The provision of unsaturated perdeuterated lipids with a range of head groups required the development of an optimised route for the production of oleic acid and conversion to the target lipids.

We have developed a methodology for the production of full and part deuterated oleic acid. Coupling of the acids to phosphocholine head group is straightforward chemistry that is accessible to a wide range of academic and commercial groups.

We plan to pass the material to a range of partners to both spread the load and develop a wider range of sources for the produced material. The phosphoglycerols (and phosphoserines) are synthetically accessible from the phosphocholines so these will be the main focus.

In conclusion, an optimised route for the production of fully and part deuterated oleic acid was developed. Stockpiling of this material should enable milligram quantities of deuterated unsaturated phospholipids for use in neutron scattering experiments to be made available at relatively low cost.



Main route to the production of deuterated oleic acid from azelaic acid to oleic acid.

Conclusions and future work

The tasks carried out as part of this JRA have provided new capabilities in the area of biological neutron scattering and this is having a significant impact in widening capabilities throughout this part of the user community. For the future there are a number of key areas where further method development will be focused. For example we believe that major progress is possible for the culture of mammalian cells, cell-free synthesis, and in a number of key scientific areas such as the study of intrinsically disordered proteins (IDPs).

In the case of mammalian cell systems, the drive is to allow the biosynthesis of deuterated macromolecules that cannot be obtained using bacteria, yeast, or algae. This is essentially unexplored territory, and will need careful development of adaptation processes. Success in this area will have an enormous impact on availability of molecules that cannot be obtained by other recombinant methods. A good example is cholesterol - currently impossible to obtain in perdeuterated form because chemical synthesis is too complex and biosynthesis is impossible in bacteria.

Cell-free systems are also of strong interest; these can be used for the production of recombinant

proteins, and have several advantages over traditional in vivo expression. For neutron scattering, a cell-free method developed and optimised for deuteration will allow amino acid labelling without isotope scrambling amongst the amino acids within the protein, and the production of toxic labelled proteins. The exploitation of the technique has been limited in the past by low yields. However the technology has changed and the approach is now feasible. A successful initiative in this area would also allow multiple selective amino acid labelling – where *in vivo* methods are very complex.

Deuterated intrinsically disordered proteins (IDPs) are also of central interest. IDPs are an important class of proteins that are either fully unfolded or contain significant contiguous regions that are devoid of secondary structural elements. IDPs play key roles in a vast range of physiological processes, and are also strongly implicated in important human diseases such as cancer and neurodegenerative diseases like Alzheimer's disease and prion-related diseases. The heterogeneity of these proteins means that crystallography is appropriate for their study. Selective deuteration will allow SANS and incoherent scattering studies in which there is a specific focus on a particular part of the protein. Method development will need to focus IDP systems where the component parts are expressed separately in *E.coli* together with intein sequences and then ligated in vitro – *i.e.* exploiting the types of segmental labelling that have been developed during the period of this JRA.

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Michael Sattler, Technische Universität München (TUM), Garching, Germany
Luke Clifton, SFTC Rutherford-Appleton Laboratory, Didcot, UK
Christine Ebel, Institut de Biologie Structurale (IBS), Grenoble, France
Hermann Heumann, Max Planck Institute (MPI), Martinsried, Germany

Relevant references:

Abla M. *et al.* (2012) *J. Fluorine Chem.*, 134, 63-71.
Blesneac I. *et al.* (2012) *Biochim. Biophys. Acta* 1818, 798-805.
Cuypers M. *et al.* (2012, in press) *Angew. Chem.*
Gallat F.-X. *et al.* (2012) *Biophys. J.*, 103, 129–136.
Grage S., *et al.* (2011) *Biophys. J.,* 100(5) 1252–1260.
Kennaway C. *et al.* (2012), *Gene Dev.*, 26, 92-104D.

Activities

Highlights from our Access Programme

NMI3-II continues to support access to neutron and muon facilities across Europe. In this issue of *Inside NMI3* we present to you highlights of research carried out thanks to our access programme.

Spins acting like real bar magnets in a new material

The dipolar force between magnetic moments is present in all magnetic systems. The lithium rare earth (RE) tetrafluorides, $LiREF_4$ are an excellent testing ground for the physics of dipolar-coupled systems because the spins in this material behave like real bar magnets.

Scientists from the École Polytechnique Fédérale de Lausanne (EPFL), the Paul Scherrer Institute (PSI), the Helmholtz-Zentrum Berlin (HZB), the University of Chicago, the University College of London, Oak Ridge National Laboratory and the University of Bern have focused their research on an antiferromagnetic member of the family $LiErF_4$ and addressed the magnetic order, the classical phase transition, and the transition and fluctuations about the quantum critical point.

Determining the magnetic structure

In order to determine the magnetic structure the team has performed neutron scattering, specific heat, and magnetic susceptibility studies. The HZB provided the ideal conditions required for the experiment. Temperatures down to 0.04 degrees Celsius above absolute zero were achieved using the dilution refrigerator at the E4 neutron diffractometer/ BERII, where they studied the ordered structure and its relevant critical exponents close to both classical and quantum phase transitions. Moreover, the Laboratory for magnetic measurements (LaMMB/HZB) performed very precise heat capacity measurements to characterize the thermal phase transition to the antiferromagnetic state. Complementary measurements were performed at the Swiss neutron source SINQ at PSI.

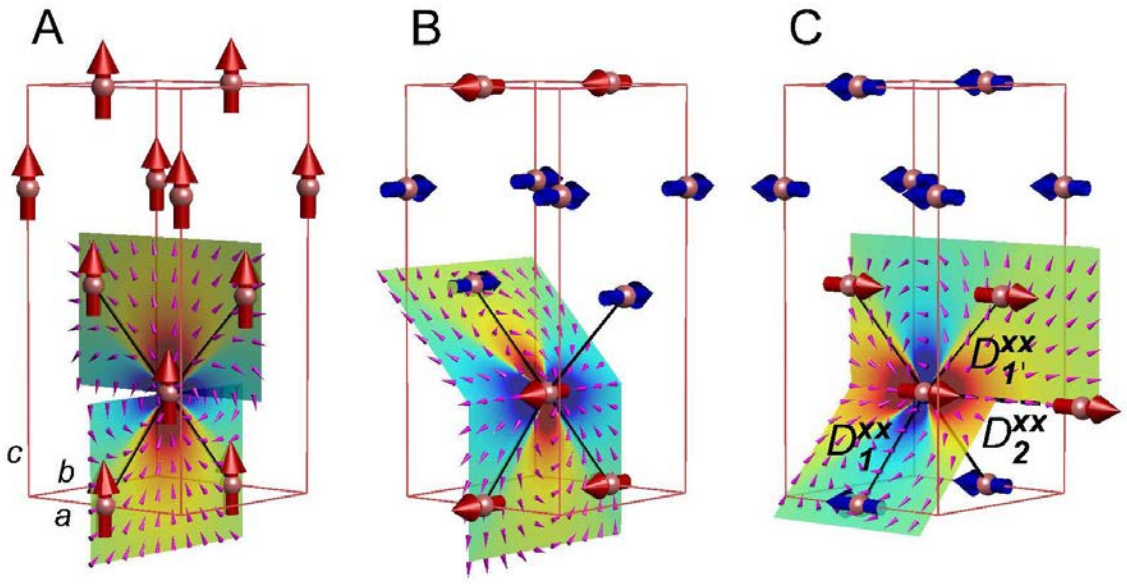


Fig. 1: Magnetic structures of $LiREF_4$

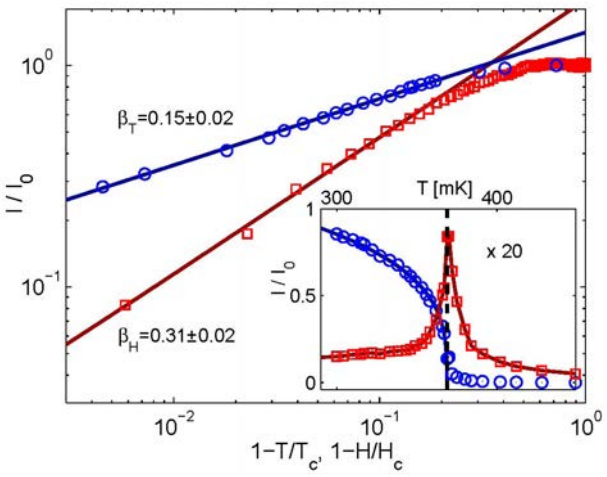


Fig. 2: Specific heat showing a pronounced ordering anomaly

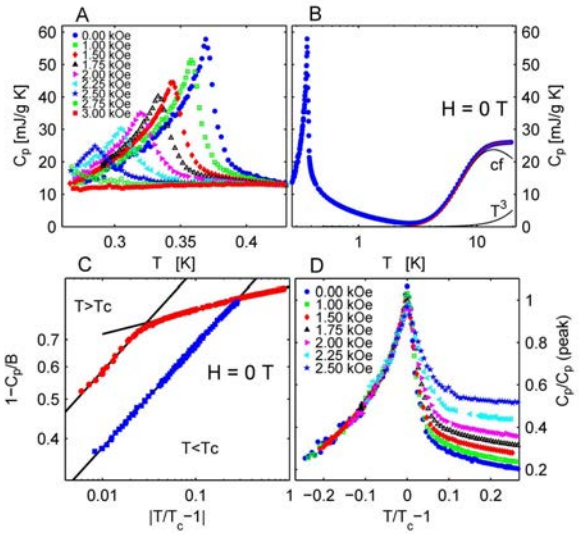


Fig. 3: Non-mean-field critical scaling for the classical phase transition at the antiferromagnetic transition temperature, consistent with the two-dimensional XY/h4 universality class.

By using neutron spectroscopy on a single crystal the team has determined the crystal field, which provided the position of the energy levels and the matrix elements of the angular momentum operators, which completed the team's powder neutron diffraction studies. The obtained magnetic Bragg peaks proved that the arrangement of the spins was antiferromagnetic and their intensities were consistent with the bilayered antiferromagnetic structure depicted in figure 1, also verified by powder diffraction. The specific heat showed a pronounced ordering anomaly (fig. 2), which was in good accordance with the phase diagram established by neutrons.

The properties of $LiErF_4$

This research established $LiErF_4$ as a model dipolar-coupled antiferromagnet with XY spin-anisotropy and a quantum phase transition in applied field HC|| = 4.0 ± 0.1 kilo-oersteds. The researchers have discovered non-mean-field critical scaling for the classical phase transition at the antiferromagnetic transition temperature, which is consistent with the two-dimensional XY/h4 universality class (fig. 3). In line with this, the quantum phase transition at Hc exhibits three-dimensional classical behaviour. The team believes that the effective dimensional reduction may be a consequence of the intrinsic frustrated nature of the dipolar interaction, which strengthens the role of fluctuations.

Future implications

$LiErF_4$ has the advantage of a simple, well-characterized Hamiltonian and of being available in large, high-quality single crystals. With the discovery of its properties, researchers now have a material that provides a perfect test bed for getting insights into the fundamental science of quantum dipolar antiferromagnetism.

Inside NMI3 thanks Neda Nikseresht and Henrik Rønnow from the Laboratory of Quantum Magnetism, Switzerland, for reviewing this article.

Published results:

Kraemer C., Nikseresht N., Piatek J.O., Tsyrulin N., Piazza B., Kiefer K., Klemke B., Rosenbaum T.F., Aeppli G., Gannarelli C., Prokes K., Podlesnyak A., Strässle T., Keller T., Zaharko O., Krämer K.W., Rønnow H.M. (2012) Dipolar Antiferromagnetism and Quantum Criticality in $LiErF_4$. *Science*, 336 (6087), 1416-1419.

The rht net: an ideal blueprint for the construction of a metal–organic framework platform

The need for tunable functional solid-state materials is increasing because of the growing demand to address persisting challenges in global energy issues, environmental sustainability, and others. It is practical and preferable for such materials to be pre-designed and constructed to exhibit the desired properties and specific functionalities for a given targeted application.

Metal–organic frameworks

Metal-organic frameworks (MOFs) have emerged as a unique class of solid-state materials. Given that it is possible to introduce a desired functionality pre- and/or post-synthesis, these materials have the required attributes and thereby offer great promise to unveil superior materials for many lasting challenges.

A remarkable feature of MOFs is the ability to build periodic structures with built-in functional properties using the molecular building block (MBB) approach. This approach utilizes pre-selected organic and inorganic MBBs with a desired function, which are carefully chosen to possess the proper geometry, shape, and directionality required to target given underlying nets for assembly.

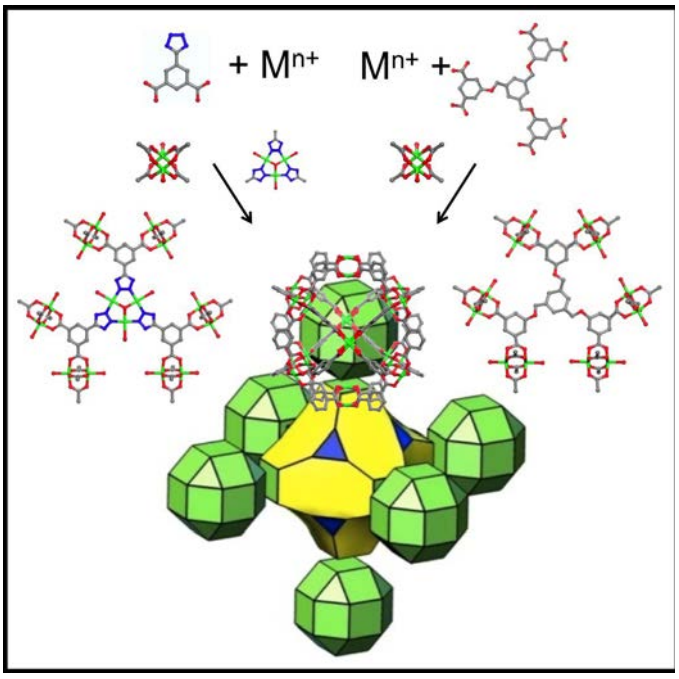


Fig. 1. Relationship between the Cu-paddlewheel MBB, the SBB, and their corresponding building units in the design strategy for the construction of rht-MOF-1.

Properties of an ideal blueprint

An ideal blueprint starts with a net that is singular, exclusive for the assembly of given building units, preferably encloses polyhedral cavities with 3D interconnecting channels; and is not susceptible to self-interpenetration upon net expansion and/or decoration. It is quite rare to find a material that combines all these properties.

The rht net

Edge-transitive nets (*i.e.* one kind of edge) are suitable targets in crystal chemistry and therefore are a prime source for obtaining singular nets for the rational construction of MOFs. The analysis of edge-transitive nets revealed an exceptional net – rht - which met all requisite criteria.

The rht net is singular for the assembly of 24-connected vertices (rhombicuboctahedral (rco) vertex figure) and 3-connected vertices (triangular vertex figure). This study has employed the supermolecular building block (SBB) approach, utilising externally functionalised metal–organic polyhedra (MOPs) as SBBs, to access the high connectivity rco necessary for constructing rht-MOFs as the original rht-MOF-1 (Fig. 1). The ability to target a single MOF from particular MBBs and SBBs favours platform design and facile tuning. The rht-MOF platform can readily be tuned via four basic pathways: 1) expansion of the SBB; 2) spacing of the distance between SBB and triangular MBB; 3) substitution of the triangular MBB; and 4) functionalisation.

Researchers have found that the exceptional nature of the rht-MOF allows expansion without concern for interpenetration as well as building block substitution/decoration and functionalisation (*i.e.* isoreticular chemistry). The construction of two such expanded-SBB novel rht-MOFs, as well as a series of predicted isoreticular rht-MOFs with extra-large cavities are described here using this effective SBB approach to meet the objectives.

Gas storage or separation is one of the important potential applications of these materials, and these properties depend primarily on the way gas molecules bind to the framework of the host material. These researchers inferred some atomic-level details on the types of binding sites

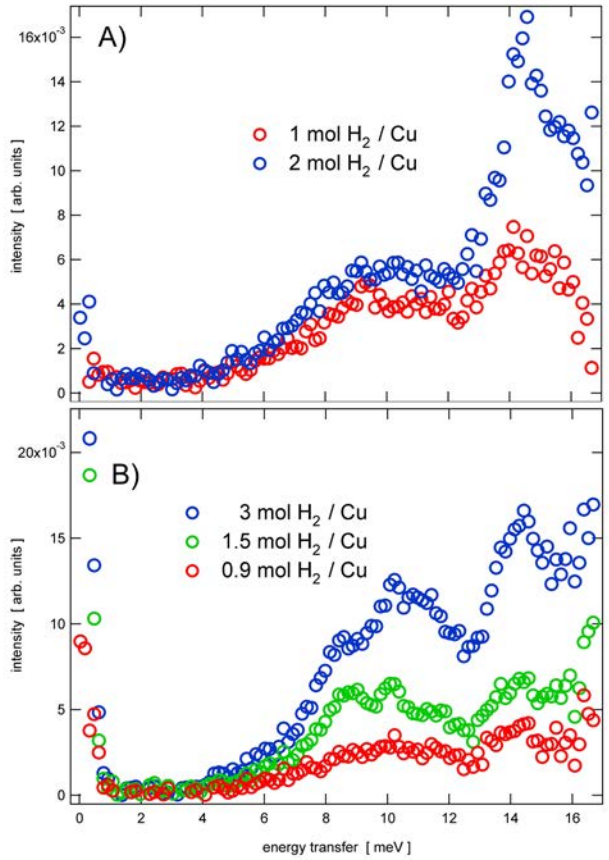


Fig. 2. A) Inelastic neutron scattering results for rht-MOF-1 with 1 and 2 moles of H_2 per Cu. B) Inelastic neutron scattering results for rht-MOF-4a with 0.9, 1.5 and 3 moles of H_2 per Cu.

for hydrogen in rht-MOF-1 and rht-MOF-4a from inelastic neutron scattering studies carried out on the FOCUS spectrometer at SINQ. The researchers chose to compare the rotational spectra of H_2 adsorbed in rht-MOF-1 and rht-MOF-4a to study the effect of core substitution (*i.e.*, $Cu_3O(N_4R)_3$ trigonal core vs. tri-methoxy benzene trigonal core) (Fig. 2) on the isoreticular structures while keeping all other compositional elements consistent (i.e., Cu paddlewheel and 5-R-isophthalate moieties). Detailed inspection and analysis of the spectra for various loadings of H_2 in the two rht frameworks made it possible to differentiate the two Cu binding sites present in rht-1 (but not rht-4a) and understand the higher heats of adsorption determined for rht-4a by the identification of stronger binding sites in the latter compound from the respective rotational spectra.

Conclusion

The exceptional nature of the rht-MOF platform, based on a singular edge-transitive net (the only net for the combination of 3- and 24-connected nodes), makes it an ideal target in crystal chemistry. The high level of control indicates an unparalleled blueprint for isoreticular functional materials (without concern for interpenetration) for targeted applications, some of which were investigated in more detail by inelastic neutron scattering studies.

Published results:

Eubank J., Nouar F., Luebke R., Cairns A., Wojtas L., Alkordi M., Bousquet T., Hight, M., Eckert J., Embs J., Georgiev P., Eddaoudi M. (2012) On Demand: The Singular rht Net, an Ideal Blueprint for the Construction of a Metal–Organic Framework (MOF) Platform. *Angew. Chem. Int. Ed.*, 51(40) 10099–10103

Inside NMI3 thanks Jan Peter Embs for reviewing this article. He is the responsible scientist for the cold-neutron time-of-flight spectrometer FOCUS at Paul Scherrer Institute (PSI), Villigen, Switzerland.

Proteins perform without water

The thin film of water around proteins, their hydration water, is vital to the macromolecule's biological activity. It was believed that without hydration water, proteins would not only be incorrectly folded but also lack the conformational flexibility that animates their 3D structures and brings them to life. However, a team of scientists from the Institut de Biologie Structurale (IBS), the University of Bristol, the Australian National University, the Jülich Centre for Neutron Scattering (JCNS) at FRM II and the Institut Laue-Langevin (ILL) found out otherwise. They investigated novel nano-materials that are hybrids of proteins surrounded by a 'corona' of polymer surfactant molecules (see figure) that contain no water, nor any other solvent for that matter. Yet, surprisingly, these nano-hybrids are biologically active. Furthermore, researchers from the IBS, the University of California, the Australian Institute of Science and Technology Organisation and the JCNS have applied neutron scattering techniques to an intrinsically unfolded protein called tau and found out that protein and hydration water motions mutually affect and shape each other.

Myoglobin behaviour without water

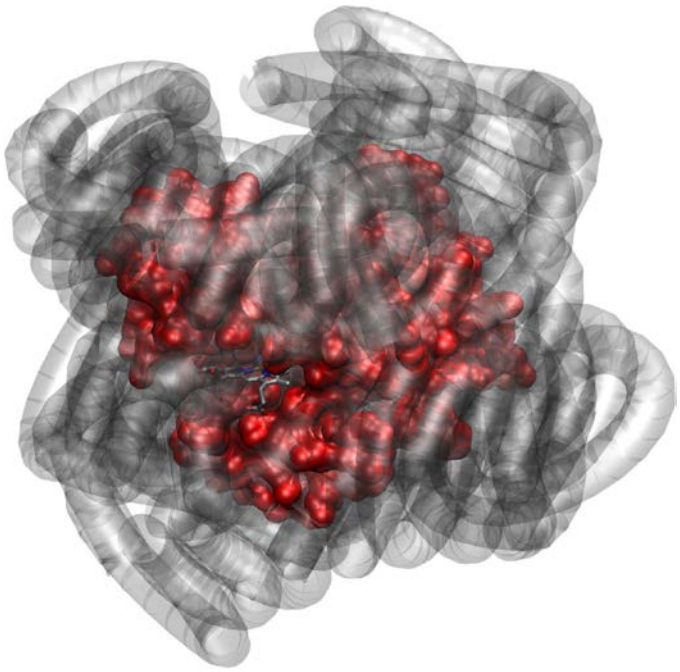
Myoglobin is common to almost all mammals and responsible for the red colour of raw meat. Observing biological activity in solvent-free protein polymer hybrids means that existing theories about aqueous and non-aqueous solvents being unique promoters of protein dynamics linked to function might have to be reconsidered.

As a first step of their research, these scientists wanted to assess whether the structure of myoglobin could still move and continue to bind oxygen if all the water was completely removed and replaced by synthetic molecules. The team analysed three samples: a wet sample (the protein in water), a dry sample (the dehydrated protein) and a dry protein-polymer hybrid sample where the water molecules had been replaced by synthetically crafted polyethylene glycol-based polymer surfactant molecules. By using incoherent neutron scattering at IN16 at the ILL and SPHERES at the JCNS, the team was able to monitor the motions in the protein and in the polymer surfactant separately. This separation has been made possible by specific labelling, carried out in a dedicated deuteration laboratory, by which either polymer or protein motions are masked by replacing hydrogen with its heavier isotope, deuterium.

What they found was that the myoglobin molecules surrounded by polymer moved just as well as the wet sample, and that the dry sample had very little mobility. These observations lead to the conclusion that the polymer surfactant coating plasticises protein structures in a similar way to hydration water.

Knowing that proteins can function outside of water opens them up to use in real life applications because it shows that there are other alternatives if water is unavailable. Examples of where they could be used include biochemical gas sensors, as myoglobin can bind carbon monoxide molecules. Another potential application is in the development of new wound dressings, where the liquid protein could be applied to the wound to reduce healing time by supplying oxygen or other essential chemicals to the damaged tissue.

Adam Perriman of the University of Bristol said: "These discoveries have increased our fundamental understanding of proteins and how they behave, which could create many new opportunities for



Myoglobin (red) exhibits biologically relevant dynamics, even when its hydration sphere is replaced by a polymer surfactant corona (grey).

their application in industrial processing and in medical technologies. The fact that our proteins can happily perform their function outside of water, a substance generally thought to be vital for life, really drives home just how robust these biological nanomachines are. ”

Martin Weik of the IBS explained: “Neutron scattering techniques are excellent for studying the dynamics of proteins and of their environment. The world class neutron scattering facilities at the ILL and the FRM II allow us to analyse how proteins move, thus complementing the single snapshots of their structures provided by crystallography.”

Intrinsically disordered proteins – the tau protein

These researchers have extended their studies to a third class of proteins, *i.e.* intrinsically disordered proteins (IDP) that do not have a well defined 3D structure and fold only upon interaction with a target ligand. Most proteins can only fulfil their intended function when the chains of amino acids that constitute them are folded into a convoluted cluster in the right way for the individual protein. However, the tau protein, which stabilizes transport paths in biological cells, is only partially folded. Disordered tau proteins tend to build up as deposits and destroy cells. Such deposits are found in the brains of those suffering from dementia, for example, Alzheimer patients.

Very little is known about the functionality of disordered proteins. Now, for the first time, the team has investigated the motions of the tau protein and its hydration shell as representative of disordered proteins. They wanted to understand how its flexibility and its interactions with water differ from ordered proteins from cell plasma and the cell membrane. Combining neutron scattering and protein perdeuteration, they found that the coupling of the disordered tau protein with water motions was much tighter than for folded proteins. They also revealed a greater motional flexibility and more restricted water motions on the IDP surface, as compared to folded proteins. The results provide evidence that protein and hydration-water motions mutually affect and shape each other, and that there is a gradient of coupling across different protein classes that may play a functional role in macromolecular activity in a cellular context.
IDPs are of significant interest in a medical context because they can aggregate and cluster together to create the amyloid fibrils behind neuro-degenerative diseases such as Parkinson’s and Alzheimer’s. Whilst the ordered structure of folded proteins makes it possible to develop drugs that fit into the protein like a key in a lock, the conformational variability of an intrinsically disordered protein like tau makes it more difficult. A more in-depth understanding of their dynamics is required and the discovery of tight coupling with water motions is a significant step forward.

This article has been prepared from materials from the JCNS, ILL and PSB.
Inside NMI3 thanks Martin Weik from the Institut de Biologie Structurale for reviewing it.

Original publications

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Towards a new tumour-specific contrast agent for MRI applications

By Luigi Paduano

Nowadays, it is estimated that cancer is responsible for about 25% of all deaths in industrialised countries, 8 million people worldwide. Scientific research is currently studying novel strategies (including drugs, therapies and devices) able to be successfully used in medicine, if early diagnosis and/or techniques like radiation therapy, immunotherapy, chemotherapy, etc. have proved to be ineffective.

Potentiating cancer detection at early stages

With the aim of developing both diagnostic and therapeutic devices, research groups from the "Università degli Studi di Napoli Federico II" have investigated about supramolecular aggregates formed by peptides as well as a new set of Gadolinium-based contrast agents for Magnetic Resonance Imaging (MRI), namely a non-invasive medical diagnostic procedure capable of giving high-quality images of the inside of the human body. Supramolecular aggregates allow cancer detection at early stages, through the recognition by the peptide that leads to a selective accumulation in some cancer tissues. The physico-chemical characterisation of the obtained nanodevices has been carried out through several techniques (dynamic light scattering, electron miscroscopy), including small-angle neutron scattering (SANS) with the instruments KWS1 and KWS2 of the Jülich Centre for Neutron Science (JCNS) at the FRM II, under the NMI3 access activities. In particular, SANS has allowed getting structural information on both size and shape of aggregates.

Series of synthesised molecules

All the synthesised molecules series are reported in Fig. 1 and have a single or double non-polar alkylic chain able to promote the formation of micelles and liposomes, respectively. Molecules a) and c) contain a moiety (DTPAGlu) able to bind Gd^{3+} ions to carry on the contrast agent task. Molecules b) and d) contain the C-terminal peptide-sequence of the cholecystokinin hormone (CCK8) able to bind to a number of cholecystokinin receptors. These receptors are overexpressed in certain human tumours, i.e. for some tumours, ill cells have on their outer membrane a higher number density of these receptors if compared to healthy cells. Finally, molecule e) contains both moieties. Mixed micelles or mixed vesicles, contained both the chelating agent and the CCK8 moiety (e.g. a) + b), as well as c) + d) or e) by itself).

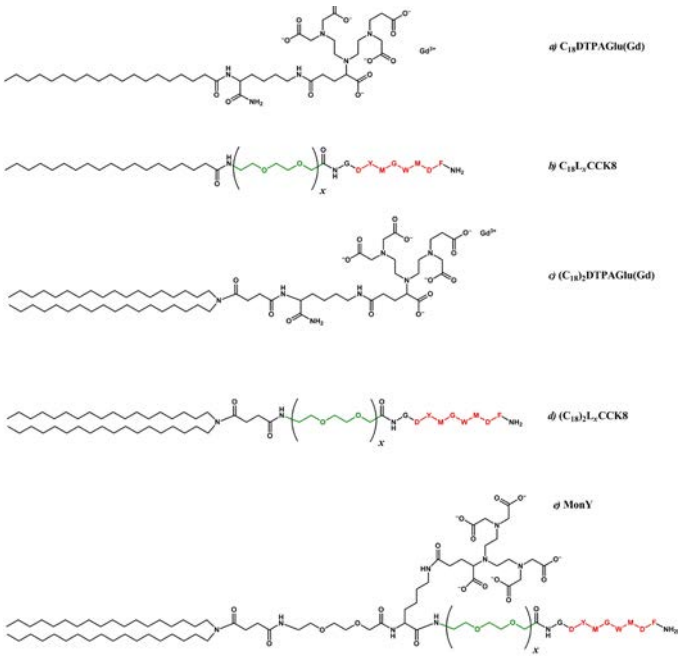


Fig. 1 – Structures of molecule series synthesized.

Results and conclusions

Analysis of the scattering data have shown that while mono-tailed molecules form spherical micelles, bi-tailed molecules can arrange in worm-like micellar aggregates and/or liposomes, depending on the pH of their environment (Fig. 2).

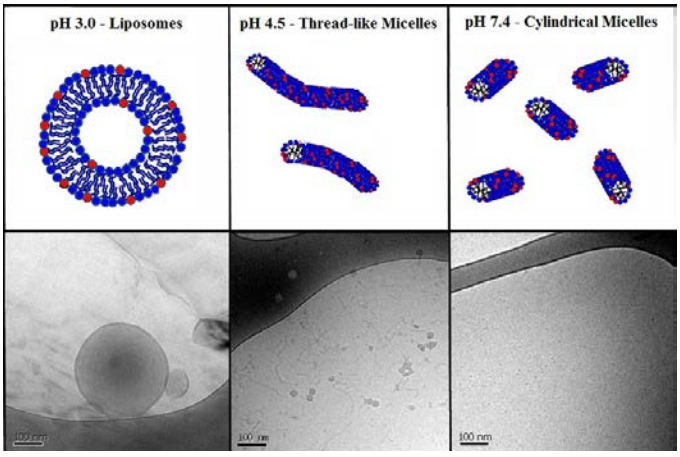


Fig. 2 – Cryo-TEM image for systems composed by molecules b) + c).

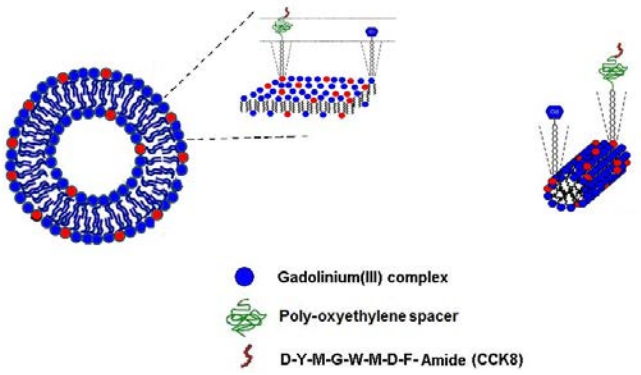
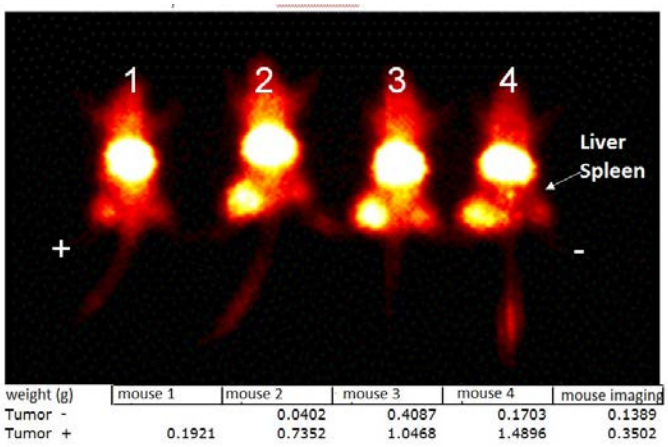


Fig. 3 – CCK8 peptide sequence completely exposed beyond the surface of aggregates (both micelles and liposomes).

SANS data has also allowed determining the dimension of the aggregates, which is fundamental to check for a correct and optimal recognition of the cellular receptors (Fig. 3).

In fact, for this purpose, the bioactive fragment CCK8 must be completely exposed beyond the micelle surface. Finally, in order to verify the effective specificity of the aggregates obtained and characterised through SANS, in vitro and in vivo tests have been performed for a number of systems. These tests assured a sufficient exposure of the bioactive CCK8 sequence and a good selectivity for CCK8 receptors overexpressed in tumour affected tissues (Fig.4).



weight (g)	mouse 1	mouse 2	mouse 3	mouse 4	mouse imaging
Tumor -		0.0402	0.4087	0.1703	0.1389
Tumor +	0.1921	0.7352	1.0468	1.4896	0.3502

Fig. 4 – *In vivo* biodistribution - receptor positive (CCK2-R+) and receptor negative (CONTROL) xenografts with mice 16h after injection.

The overall results of the investigations have shown the ability of the aggregates to recognise specific cells that overexpress cholecystokinin receptors and behave differently depending on the pH. This scenario opens new opportunities for the development of diagnostic and/or therapeutic systems for the treatment of cancer pathologies.

Luigi Paduano is a Full Professor of Physical Chemistry at the Department of Chemical Sciences of the University of Naples Federico II. This research was carried out together with Gaetano Mangiapia, Gerardino D'Errico, the group of Prof. Morelli from the University of Naples and Dr. Luigi Aloij of the Fondazione Pascale, Italy

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News from the facilities

Robert McGreevy appointed Director of ISIS

Robert McGreevy, the first coordinator of NMI3, returned to the Rutherford Appleton Laboratory in September 2012, as Director of the ISIS facility. His return to England follows roughly a year spent as Deputy Associate Laboratory Director at the Oak Ridge Spallation Neutron Source (SNS).
Robert McGreevy was Head of the Diffraction Division at ISIS back in 2002, when he took on the challenge of launching the European project NMI3. Before that, he was Director of the Studsvik Neutron Research Laboratory at Uppsala University, Sweden. *Inside NMI3* wishes him all the best for his new position!

European Commission representative visits NMI3 coordinator

Ana Arana Antelo, Head of the Research Infrastructures Unit of the European Commission, visited the NMI3 coordinator at the Institut Laue-Langevin (ILL) in Grenoble on the 21st of November 2012. Her visit to the ILL was part of a visit to several research infrastructures in Grenoble.

Prof. Dr. Helmut Schober, ILL's Science Director, received Ms. Antelo, not only on behalf of the ILL but also as Coordinator of NMI3. After a short presentation on the history of the ILL as a European facility Ms. Antelo was offered a tour of the reactor and instrumentation hall. She was particularly impressed by the ILL's instrumentation, its partnerships with other institutions, and the international culture at the Institute.

Ana Arana Antelo with NMI3 team

GEMS: neutrons and X-rays for material science

As of 2011, the scientific use of FRM II is being jointly organised by the Technical University of Munich (TUM) and the Helmholtz Association, with significant additional funding provided by the German federal government.
The Helmholtz Association, which brings together the Forschungszentrum Jülich (FZJ), the Helmholtz Zentrum Geesthacht (HZG) and the Helmholtz Zentrum Berlin (HZB), contributes almost half of the instruments operating at FRM II. Within this collaboration, the HZG focuses on materials research. It operates the German Engineering Materials Science Centre (GEMS), a platform providing infrastructure unique in the world for

Flags of the collaborating centres at the entrance of the FRM II

complementary research with neutrons (HZG outstation at FRM II) and photons (HZG outstation at DESY). A new proposal system was installed in 2012 enabling users to exploit the complementarity of the two probes by applying for beamtime on GEMS instruments at FRM II and DESY via a single proposal. Users can also access additional support facilities for the preparation and analysis of samples not far from the GEMS instruments. At FRM II, a materials science lab is operated for this purpose, with close cooperation between GEMS and TUM.
The GEMS instruments at FRM II include GISANS and the reflectometry machine REFSANS, the new small-angle scattering machine SANS-1, and the stress and texture diffractometer STRESS-SPEC, which are partially operated together with TUM. The biggest investment made was on the new SANS-1 instrument, which was built together with TUM. SANS-1 should become one of the world's leading SANS machines. GEMS is currently extending its portfolio at FRM II towards neutron imaging, which complements the strong imaging activities of GEMS at DESY.

There have been a number of scientific publications from this collaboration. They record research on texture analysis, for instance, conducted with the neutron diffractometer STRESS-SPEC, demonstrating the broad range of texture applications offered by the instrument[1,2]. Other STRESS-SPEC publications cover research by materials engineers, with investigations into batteries[3], stress relaxation[4,5,6,7] and new high-temperature alloys for gas turbine applications. One such example is the analysis of stress relaxation through ageing heat treatment, with results suggesting that creep may be the means by which stress relaxation takes place in polycrystalline Ni-base superalloys (present in gas turbine engines) during ageing[8]. GEMS' REFSANS reflectometer is used to investigate a variety of polymer films[9,10] or explore the potential for innovative solar cell techniques[11]. As for SANS-1, it has just started operation and is sure to make its contribution in many fields, including the development of alloys for new forms of steel or high-temperature materials.

For more news and information on this collaboration, instruments and research, see the GEMS website: http://gems.hzg.de

This article was prepared in collaboration with Andreas Schreyer, Director, Institute of Materials Research, HZG.

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Schools

The European Neutron and Muon Schools in 2012

In 2012, NMI3 launched a new funding programme for the European Neutron and Muon School (ENMS). The schools provide training to researchers with a variety of needs and scientific interests. They take place all over Europe, on an annual or bi-annual basis.

The 2012 schools were very successful, as can be seen in the short articles below. *Inside NMI3* presents an account of the schools held this year.

Advanced Seminar on "Perspectives for Neutron Science in Novel & Extreme conditions"

Zaragoza, Spain
May 27-31
next dates: t.b.d.
http://www.unizar.es/setn/eventos/perspectives/index.php

Sixty-four participants attended this Zaragoza seminar last May, including 25 invited speakers. The Advanced Seminar on "Perspectives for Neutron Science in Novel and Extreme Conditions" addressed a wide scientific community with the aim of identifying the real scientific drivers requiring novel and extreme conditions and the contribution to be made by the neutron scattering community. The seminar speakers provided an excellent overview of the state of the art in high pressure, high magnetic and electric fields, soft matter equipment, low temperature and high temperature.

The subsequent discussions enabled the participating scientists, who were not all from the neutron scattering community, to explain the requirements of their research and question the instrument specialists and engineers present. The novel and extreme conditions technology being prepared will clearly open up new areas of science for neutron scatterers.

The initial feedback on the event from the participants was extremely positive. This Advanced Seminar was an excellent opportunity for the participants to network with experts in the field of neutron scattering techniques.

Participants at the 2012 Advanced Seminar on "Perspectives for Neutron Science in Novel & Extreme conditions"

Baltic School on Application of Neutron and Synchrotron Radiation in Solid State Physics and Material Science (BSANS-2012)

Riga, Latvia
October 1-4
next dates: t.b.d.
http://www1.cfi.lu.lv/teor/BSANS/

The first Baltic School on the Application of Neutron and Synchrotron Radiation in Solid State Physics and Materials Science was held in Riga, Latvia, on October 4, 2012. The participants included graduate students, post-doctoral fellows and scientists new to the field of neutron and X-ray research.

This school was structured around a series of lectures by leading European scientists on topics such as neutron sources and instrumentation, diffraction, spectroscopy, reflectometry, small-angle scattering, neutron engineering and practical applications. It provided a precious opportunity for young scientists to participate in four days of scientific discussion with experienced users. The participants presented posters of their research projects and were able to gather valuable feedback from other researchers.

The school organised a visit on the final day to the Institute of Solid Physics, during which participants were able to obtain a good overview of the research carried out in Riga.

Berlin School on Neutron Scattering

Berlin, Germany
March 5-16
next dates: February 28 – March 8, 2013
http://www.helmholtz-berlin.de/events/neutronschool/

Twenty seven students from 10 different countries attended the 32nd Berlin Neutron School. The vast majority were PhD candidates, but diploma and master students, post-doctoral and senior researchers also attended. The students came from a wide range of scientific backgrounds: biology, chemistry, engineering, materials science and physics.
The school provided an introduction to neutron scattering with an emphasis on hands-on, practical experience on the instruments at the BERII reactor. The first 3 days were dedicated to a series of lectures and tours of the beam halls, an introduction to neutron user services and a discussion on future facilities. The next 3 and a half days were devoted to practical experimentation. The students were divided into small groups by subject area and performed a total of seven 3-hour experiments (triple-axis spectroscopy, powder diffraction, small-angle scattering, reflectometry, time-of-

flight diffraction, tomography and residual stress diffraction).
The last morning of the school consisted of lectures on how to use neutron scattering as a tool for research in the areas of biology, engineering and physics. The students also attended a lecture on future neutron sources in Europe given by Michael Steiner, Chairman of the European Neutron Scattering Association (ENSA); there was also a session on how to apply for beamtime.

For the next school, participants will have access to two more instruments, providing experience of experiments on powder diffraction and small-angle neutron scattering.

Students at the HZB Neutron School 2012. Picture courtesy of the organisers.

Central European Training School on Neutron Scattering (CETS)

Budapest, Hungary
May 14-19
next dates: 2014
http://www.kfki.hu/~cets/

In May 2012, 15 students from 10 different countries attended the 6th Central European Training School on Neutron Scattering (CETS). The main scope of this course was to provide insight into neutron scattering techniques and their application for studies on the structure and dynamics of condensed matter.
After the lectures the students were split into groups for the practical sessions. With each group performing two neutron scattering experiments per day, every student was able to experience work on 6 different instruments during the week (powder diffractometer, a small-angle neutron scattering instrument, polarised neutron reflectometer, three-axis spectrometer, time-of-flight spectrometer, prompt-gamma activation analysis). The staff scientists at the Neutron Spectroscopy Department of the Budapest Neutron Centre (BNC) led the students through procedures for sample preparation, planning and running experiments, data processing and the interpretation of results.
The school was also able to take advantage of the presence of Professor George Grüner (University of California, Los Angeles) in Budapest, a renowned expert in nanotechnologies and a successful businessman in this field, a lecture on the "Business of Academic Research" opened up a lively discussion on the opportunities for business with table-top science or the large scale facilities. CETS was also an opportunity for the young scientists to present and discuss their own research over half a day. Whereas the poster session provided the space for detailed explanations, the students' flash oral presentations were, as in previous years, an exciting and cheerful highlight of the school.
According to the lecturers and instrument scientists, the attendees were actively engaged throughout the week during both the lectures and experimental work. All in all, CETS 2012 was a very successful event for the neutron community.

Students at CETS 2012. Picture courtesy of the organisers.

European Summer School on Scattering Methods Applied to Soft Condensed Matter

Carcans-Maubuisson, France;
June 7-14
next dates: 2014
http://www.ill.eu/bombannes

The Bombannes Summer School covers the fundamentals of current methodology in static and dynamic scattering techniques and their application to soft matter systems. 39 students of 17 different nationalities have attended this school's 11th edition.

The students attended 20 general lectures divided in two parts: the first half of the week was an introductory session providing a general introduction to scattering experiments, basic concepts of data treatment, the notion of contrast, general theorems, instrumentation and resolution effects. During the second half of the week, presentations focused on the use of static and dynamic scattering techniques to investigate typical soft matter systems such as colloidal suspensions, microemulsions, micelles and surfactant solutions, polymers, biological systems and turbid suspensions. A particularly successful feature of the Bombannes School is the combination of general lectures with the compulsory oral contributions by the students during the evening after-dinner sessions. These contributions train the students to present their specific fields of research and provides a forum for discussion and exchange of experience when using complementary experimental methods. Additionally, students had the opportunity to discuss the status of the future European Spallation Source (ESS) with members of the ESS Scientific Advisory Committee.

Students and lecturers at Bombannes 2012. Picture courtesy of the organisers.

Giornate Didattiche della Societá Italiana di Scattering di Neutroni (SISN)

San Giovanni in Valle Aurina, Italy and Grenoble, France
June 24 – July 2
next dates: June/July 2013
http://www.sisn.it/

Last summer, 25 mainly Italian undergraduate students, master students, PhD and young researchers attended the Giornate Didattiche della SISN for an introduction to the different neutron scattering techniques.

The first part of the school took place in S. Giovanni in Valle Aurina, Italy, and provided a theoretical introduction to neutron scattering. The students were divided into small groups led by a tutor to facilitate active participation during the exercises.

For the second part of the school, the group travelled to the Institut Laue-Langevin (ILL) in Grenoble, France. The students, again in small groups, could become involved in the experiments performed on the Italian Collaborative Research

Group instruments BRISP and IN13, as well as the ILL diffractometer D4. At the end of the school, the students reported their experimental results in a clip session.

Participants at the Giornate Didattiche 2012. Picture courtesy of the organisers.

HERCULES - Neutrons and Synchrotron Radiation for Science

Grenoble, France (and other locations)
March 4–April 4
next dates: February 24 to March 27, 2013
http://hercules-school.eu

From March to April 2012, 82 participants from several countries attended the HERCULES school on Neutron and Synchrotron Radiation for Science. HERCULES 2012 included lectures and tutorials, practicals (about 40% of the time), visits to laboratories and a poster session.

During the first week and a half the participants followed a trunk module for a multidisciplinary audience. The lectures covered the various properties of neutrons and synchrotron radiation beams, and presented the most appropriate methods and instruments for the young scientists' future needs, *i.e.* basic notions on sources, detectors, optics, interaction of neutrons and X-rays with matter, powder and single crystal diffraction, small-angle and diffuse scattering, inelastic scattering, absorption spectroscopy and imaging techniques. The complementary nature of X-ray and neutron techniques was particularly highlighed. During the following three and a half weeks, the students were divided into small groups to carry out experiments and data analysis. There were two different sessions: A) the application of physics and chemistry to condensed matter and B) biomolecular structure and dynamics. During these weeks, the participants were able to train with the beam open on state-of-the-art instruments. The whole set of PSI/SLS beamlines were available.
The practical part of the course took place in three different locations: 1) 3 days at the Swiss Light Source, Paul Scherrer Institute, Villigen for 72 participants; 2) a week at the Laboratoire Léon Brillouin, Saclay, for 16 participants, for a reinforced neutron experimental programme; 3) a week at the SOLEIL Synchrotron, St. Aubin, for 56 participants, for a course on the application of soft X-rays, ultraviolet and infrared radiation

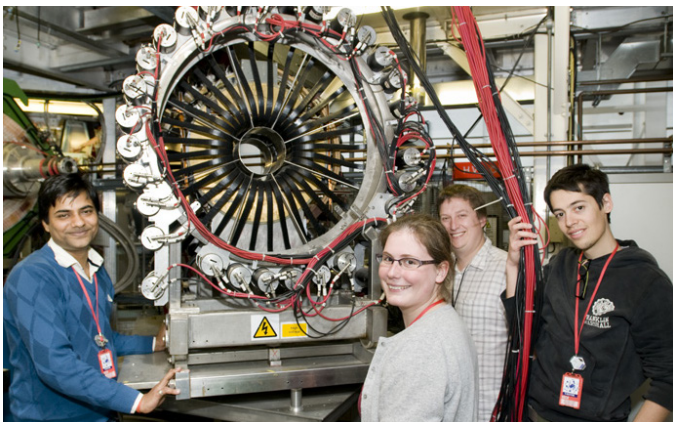
An important bonus with this intensive course is that it contributes to the construction of a European network of young researchers using Neutron and Synchrotron Radiation for condensed matter studies and has greatly contributed to consolidate the communities of these two complementary probes. The HERCULES participants' interactive network on the web has helped create links among the participants of the 2012 course as well as between participants from previous and future sessions. The HERCULES school will continue supporting young researchers in 2013!

Students at the HERCULES 2112 school

ISIS Muon Training School 2012

Didcot, UK
March 19-23
next dates: 2014
http://www.isis.stfc.ac.uk/groups/muons/muon-training-school/muon-spectroscopy-training-school7869.html

In March 2012 a group of 17 PhD students and post-doctoral researchers attended the ISIS Muon Spectroscopy Training School. The school provided practical training on the use of muons in condensed matter research. It included a variety of lectures and workshops on the muon technique given by experienced researchers, and also the chance to perform muon experiments.
The school ran for five days and consisted of lectures about the muon technique to complement experiments using the four muon spectrometers at ISIS. Each participant had the opportunity to perform two different experiments. They were run by ISIS Muon Facility staff together with external researchers, experts in their fields of condensed matter.
The ISIS Pulsed Source, at STFC's Rutherford Appleton Laboratory (RAL), is home to the world's most intense beam of pulsed muons for condensed matter investigations. The topics covered enabled participants to gain the maximum benefit from future beamtime, provided valuable experience of working at a large, international facility and improved their knowledge in related fields such as computing and cryogenics!



Students at the ISIS Muon trainig school 2012. Picture: Stephen Kill, ISIS

JCNS Laboratory Course on Neutron Scattering

Jülich and Garching, Germany,
September 3-14
next dates: September 2-13, 2013
www.neutronlab.de

In September 2012, 59 participants from 14 different countries attended the JCNS Laboratory Course on Neutron Scattering. For the first time in the history of the course the majority of the students had a chemistry background (28), followed by physics (24) and material sciences (7).
The aims of the school were to provide realistic insight into the experimental techniques of neutron scattering and its scientific power. The laboratory course consisted of one week of lectures held at the Forschungszentrum Jülich followed by one week of neutron scattering experiments at the FRM II research reactor in Garching. The lectures introduced neutron sources, scattering theory, instrumentation and selected topics of condensed matter science. The lectures were accompanied directly by practical exercises. This new concept was introduced last year and proved successful again.

In the second week, the students worked in small groups at Garching to perform neutron scattering experiments on eleven of the FRM II instruments, including the neutron spin-echo spectrometer J-NSE, the backscattering spectrometer SPHERES and the small-angle scattering instruments KWS-1 and KWS-2.

Students and instrument scientist at the JCNS LabCourse 2012. Picture: Wenzel Schürmann, TU München.

PSI summer school on condensed matter research

Villigen, Switzerland
August 11-19
next dates: August 17 – 23, 2013
http://indico.psi.ch/conferenceDisplay.py?confId=1386

The 11th PSI summer school was dedicated to the fascinating and growing field of imaging experiments at large scale facilities. The participants included 81 PhD students and postdoctoral scientists from 15 different countries with no prior knowledge of neutron, muon and X-ray techniques but with an interest in learning how these techniques can be used in their research fields.

The participants were introduced to real space imaging from the life and materials sciences, covering not only methods like tomography, phase contrast imaging or image processing, but also diffractive and spectroscopic imaging and reflectometry. The evening lectures highlighted the use of imaging techniques in further high impact fields of science like palaeontology and cultural heritage.
Following the school, 24 of the participants received practical training at PSI's large-scale facilities, the Swiss Light Source (SLS), spallation neutron source (SINQ) and Muon Source (SμS). The school offered sessions on X-Ray Coherent Diffractive Imaging; MicroXRF/XAS studies on the chemical speciation of nano-particles within planctonic invertebrate species; scanning soft X-ray microscopy; grating interferometry for imaging and metrology; mapping magnetic profiles on a nanometre scale. The participants had the opportunity to use real-time neutron imaging, neutron tomography and material characterization using selected neutron energies; they were given access to the new electronic moisture sensor developed at EMPA and investigated the similarity of an eraser and an aluminium component.

Registration for the 2013 school is open!

Students and lecturers at the 2012 PSI summer school. Picture courtesy of the organisers.

Forthcoming schools

ENMS will continue providing young researchers with valuable know-how and practical training. To learn more about the schools supported by NMI3 please consult the Schools brochure on our website.

The following schools are already scheduled for 2013:

Berlin Neutron School
February 28 – March 8, 2013 at Berlin, Germany

HERCULES school
February 24 – March 27, 2013 at Grenoble, France (and other locations)

12th PSI summer school on condensed matter physics
August 17 – 23, 2013 at Zuoz, Switzerland

16th JCNS Laboratory Course on Neutron Scattering
September 2-13, 2013 at Jülich and Garching, Germany

13th Oxford School
September 2 – 13, 2013, Oxford, UK

Other schools with 2013 dates to be confirmed are the following:

Giornate Didattiche della SISN
Early summer 2013, Italy

HZB summer school
Lauenburg near Hamburg, Germany

6th FullProf school
End of September 2013, Grenoble, France

Fan du LLB
November/Devember 2013, France

Please note that even though NMI3 also funded the "Fan du LLB" school, by the time this newsletter was written, the school hadn't taken place yet.

From Bragg's law to neutron diffraction

On the occasion of the 150th anniversary of the birth of W. H. Bragg and the 100th anniversary of Bragg's law, Inês Crespo reviews the reasoning that led W. L. Bragg to his famous equation, setting the foundations for the deployment of neutron diffraction to spur development in fields as varied as computer memory chips, aircraft turbine engines and energy storage devices.

"Bragg and son"

Last July marked the 150th year since the birth of Sir William Henry Bragg, who, in collaboration with his son William Lawrence Bragg, was to found a new branch of science, the analysis of crystal structures using X-rays. The two men were awarded the Nobel Prize in Physics in 1915 for their work, with Lawrence Bragg the youngest-ever Nobel laureate, at the very early age of 25.

Bragg's law

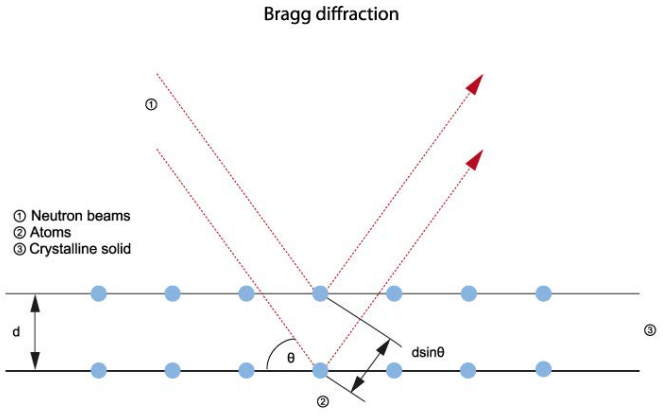
William and Lawrence Bragg were inspired by the work of Max von Laue, who had received the Nobel Prize for Physics for his discovery of X-ray diffraction by crystals. Max von Laue had detected that when the X-ray beam passed through a crystal there was a selection of the angle of diffraction. He suggested that this happened due to certain wavelengths in the X-rays. In studying his work, it occurred to Lawrence Bragg that it would be interesting to tackle the problem from a different perspective, focusing on the crystal structure rather than on the constitution of the X-ray beam. He therefore investigated what would happen if a series of irregular pulses fell on diffracting points arranged on a regular space lattice. A century ago, this work led him to formulate "Bragg's law", which is still widely used today. In his Nobel lecture, he explained the reasoning that brought him to formulate the equation:

"The points of a space lattice may be arranged in series of planes, parallel and equidistant from each other. As a pulse passes over each diffracting point, it scatters a wave, and if a number of points are arranged on a plane the diffracted wavelets will combine together to form a reflected wave front, according to the well-known Huygens construction. The pulses reflected by successive planes build up a wave train, which analysis shows to be composed of the wavelengths given by the formula:

$$n\lambda = 2d\sin\theta$$

In this expression, n is an integer, λ is the wavelength of the X-rays, d the spacing of the planes, and θ the glancing angle at which the X-rays are reflected."

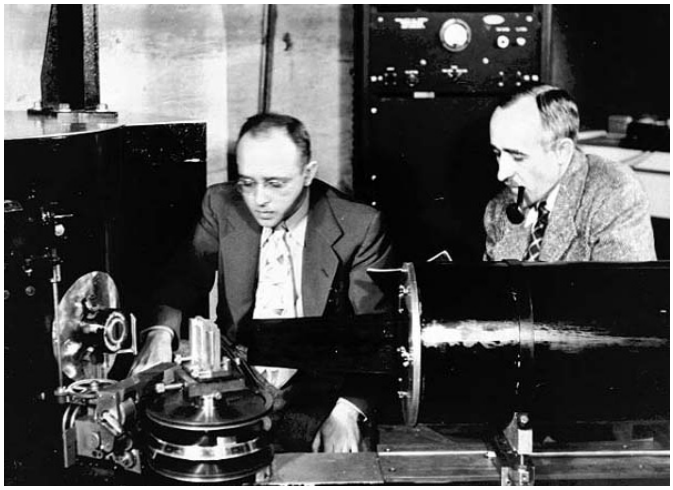
The work of William and Lawrence Bragg provided the basis for current research on neutron diffraction. In fact, the measurement principle of neutron diffraction is based on the Bragg equation.



Bragg diffraction scheme

It was only in 1932, over 10 years after the Braggs' work on the analysis of crystal structures using X-rays, that James Chadwick proved the existence of neutrons. The advantage of these elementary particles is that they do not need to overcome an electric barrier and are capable of penetrating and splitting the nuclei of even the heaviest elements. However, as Clifford G. Shull explained in his Nobel lecture in 1936, "it seemed unlikely that neutron diffraction would develop as a useful tool because of very low source intensity." This limitation changed dramatically in 1939-1943 with the discovery of nuclear fission by Otto Hahn and Lise Meitner and Enrico Fermi's subsequent demonstration of a self-sustaining, neutron chain-reacting assembly.

A few years later, in 1946, Shull and Ernest Wollan performed the first neutron diffraction experiments.



Wollan and Shull using a diffractometer at the Graphite Reactor in 1950. Courtesy of the Oak Ridge National Laboratory, managed for the U.S. Dept. of Energy by UT-Battelle, LLC

Neutron diffraction – the technique

Neutron diffraction or elastic neutron scattering is the use of neutron scattering to determine the atomic and/or magnetic structure of a material. The sample is placed within a neutron beam and the angles at which the neutrons are deflected or scattered by the material are recorded to generate a "diffraction pattern" from which structural information can be extracted.

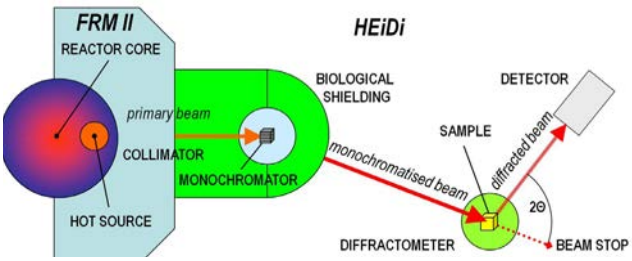
Neutron diffraction is similar to X-ray diffraction, but it provides complementary information and has a number of advantages. For instance, unlike X-rays, due to their weak interaction with matter, neutrons penetrate well beyond the surface of the sample, providing information on the interior of the sample being investigated. However, due to this weak interaction with matter, larger amounts of sample material are necessary.

Neutron diffraction is not limited to studies on the atomic position of light elements, neighbouring elements in the periodic table, and isotopes. Due to their magnetic moment, neutrons can also be used for the determination of the magnetic structure of the sample. Their diffraction can also provide precise data on the mean square displacements of atoms around their average positions, informing on possible static or dynamic disorder.

Given that a strong neutron flux is necessary for neutron diffraction, the technique is available only at large-scale facilities. The European research centres with neutron diffraction facilities are the Institut Laue-Langevin (ILL) and the Laboratoire Léon Brillouin (LLB) in France, the ISIS Pulsed Neutron Facility in the UK, the Forschungs-Neutronenquelle Heinz Maier-Leibnitz (FRM II) and the Helmholtz-Zentrum Berlin (HBZ) in Germany, the Frank Laboratory of Neutron Physics and Petersburg Nuclear Physics Institute in Russia, the Nuclear Physics Institute (NPI) in the Czech Republic, the Paul Scherrer Institute (PSI) in Switzerland, the Institute for Energy Technology (IFE) in Norway and the Budapest Neutron Centre (BNC) in Hungary.
Across the world, neutron diffraction is supporting research at, for instance, the Oak Ridge National Laboratory (Spallation Neutron Source (SNS) and the High Flux Isotope Reactor (HFIR)), the NIST Center for Neutron Research and Los Alamos Neutron Science Center (LANSCE) in the USA, the Brockhouse Institute for Material Research in Canada, the Australian Nuclear Science and Technology Organisation (ANSTO) and, in China, the Advanced Research Reactor (CARR).

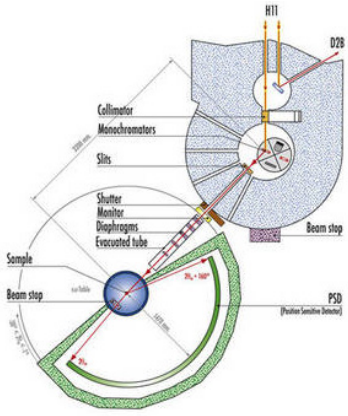
Neutron diffraction, science and society

Neutron diffraction has a myriad of applications. For instance, this technique enables the prediction of properties and behaviours of nanomaterials, offering new insights for the development of devices such as ever smaller computer memory chips; it is widely used in engineering for examining the mechanical behaviour of materials or mapping internal stress, contributing thus to the characterisation of the magnetic properties of advanced materials and the engineering of aircraft turbines.



Scheme of the hot single crystal diffractometer HeiDi at FRM II. Courtesy of FRM II

Gabriel Cuello from the ILL told *Inside NMI3* that this technique is helping him determine the structure of liquids and amorphous systems, investigating the kind of atoms that can be found around these systems (e.g. [1]). This information is valuable for defining methods for decontaminating water supplies, for instance.



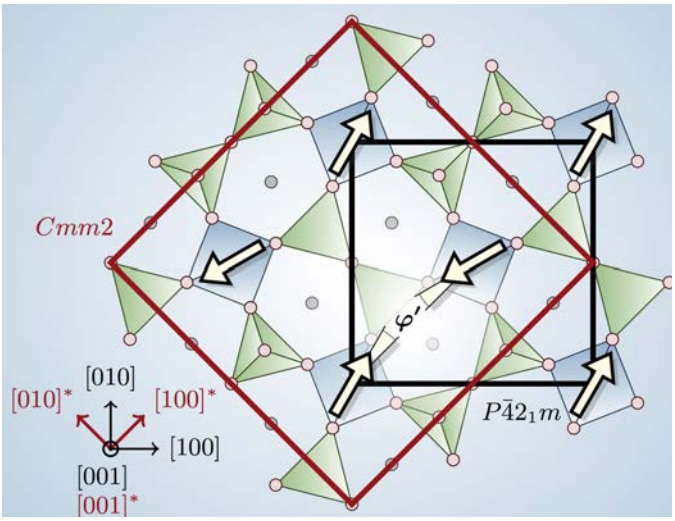
Gabriel Cuello next to the high-intensity two-axis D20 diffractometer at ILL and D20 scheme. Picture: *Inside NMI3*. Scheme: Courtesy of ILL

Martin Meven, who is responsible for the hot single crystal diffractometer HEIDI at FRM II, told Inside NMI3 that neutron diffraction on this instrument is used to determine hydrogen bonds in crystalline structures [2], light elements in ionic conductors as potential storage compounds [3] and structural and magnetic phase transitions, e.g. in multiferroics [4] and high-Tc-superconductors [5].

As you can see in our "Activities" section, neutron diffraction at the HZB has allowed researchers to identify a material providing an excellent testing ground for the physics of dipolar-coupled systems; in fact the spins in this material behave like real bar magnets [6].

At ANSTO in Australia, researchers are using neutron diffraction to examine the potential to improve the shelf life of Li-ion batteries [7]. Lithium battery technology could provide a more durable power source for our electronic devices and for the electric cars of the future.

Superconductors are capable of losslessly transporting large amounts of electric current and could therefore play a key role in power transmission. Neutron diffraction is improving our understanding of superconducting materials and revealing opportunities for improved energy efficiency, a crucial factor in the production of green energy. Experiments carried out at the Swiss Spallation Neutron Source (SINQ) at PSI indicated that superconductors use electron pairing to transport electrical current without resistance [8].
Neutron diffraction also has valuable information to offer to those working on the development of materials for hydrogen storage. Hydrogen is seen as a major mobile energy carrier of the future, for the production of low-carbon-emission vehicles. There are difficult challenges to be met however, to ensure the safe and efficient storage of hydrogen in the carrier device. Research teams at ILL [9,10] and ISIS [11] are tackling this issue by monitoring hydrogenation/dehydrogenation reactions in potential hydrogen storage materials.



Magnetic structure of $Ba_2CoGe_2O_7$ at 2.2 K. [4]

What future for neutron diffraction?

Neutron diffraction is now a tried-and tested technique in strong demand by researchers investigating the structure of materials. As Martin Meven points out, "Neutron diffraction is making valuable contributions to several of today's hot topics, such as the search for new materials to be used for data or energy storage". The demand for the technique will continue to increase. A new diffractometer is currently being built at the Delft Reactor Institute in the Netherlands to support the Dutch user community "with an easy-access, versatile and competitive neutron diffractometer".

In Japan, a new neutron diffraction device was completed last September: ¨SPICA¨ will be used to analyse atomic structures and the behaviour of batteries during their charge cycle.

Neutron diffraction is also being used to develop technologies for electrical energy storage: researchers are investigating the light elements present in compounds suitable for ion exchange systems.
As the technique advances and wider ranges of temperature and pressure are incorporated, the research conditions will improve, opening the doors for new investigations. Researchers need to investigate smaller samples and therefore one of the biggest challenges for the world's future spallation sources is to increase the neutron flux.

Further reading

Furrer A., Mesot J., Strässle T. (2009) Neutron Scattering in Condensed Matter Physics (World Scientific)

NMI3 webpages:
http://nmi3.eu/neutron-research/techniques-for-/structural-research.html

Inside NMI3 thanks Gabriel Cuello and Martin Meven for their valuable contribution and advice.

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News from around the World

New nuclear reactor planned in Argentina

In 2011 it has been decided that a new nuclear reactor will be constructed in Argentina. It will become the 10th nuclear reactor in the country and the Atomic Energy National Commission (Comisión Nacional de Energía Atómica, CNEA), which is the main responsible for the project, plans that this OPAL-like reactor will start operating by 2018 in a location to be defined. This project has three aims: 1) producing isotopes for medicine because Argentina is one of the main providers of isotopes in Latin-America; 2) irradiation of fuel elements for the development of nuclear reactors built and sold by Argentina; 3) producing neutron beams for research. A number of nuclear centres are participating in the project, the Centro Atómico Bariloche (CAB) being the main supporter.

Bariloche is one of the most prestigious research centres in Argentina. Starting only as a physics school in the 1950's, it gradually developed to became the Instituto Balseiro and CAB, first by adding a nuclear engineering school for elite students and then a mechanical engineering school. Currently the majority of scientists involved in building nuclear reactors in Argentina come from these schools.

The construction of a new reactor in Argentina was actually planned in the 1980's but the project did not go ahead due to lack of funds. However, that project was the motivation that led Gabriel Cuello Institut Laue-Langevin (ILL) to work on neutron physics in the 80's. After his PhD and post-doc in Bariloche, work in the Institute for Structure Matter in Madrid and finally at the ILL, he is now supporting decision-making regarding the source and instruments to be used in the new reactor. He has told *Inside NMI3* that he is gathering efforts to create a community of Argentinean users. He believes that it would be valuable to reach an agreement between the ILL and the Argentinean Research Ministry so that future users of the Argentinean new reactor could receive training at the ILL during the years prior to the start of operation.

CAB in 1958 (courtesy of CAB)

Reactor RA6 in CAB in 2012 (courtesy of CAB)

Coordination and Management

New NMI3 Information Manager

The NMI3 has a new information manager. Inês Crespo started last September, taking over from Juliette Savin. She is responsible for updating the NMI3 website and for communicating through various channels on NMI3 activities, events and achievements to the scientific community and the broader public.

Inês studied environmental engineering. Previous to her position with NMI3 she worked for 4 years at the European Commission Joint Research Centre carrying out research on science communication and public reception of the media.

“It is fundamental to communicate science in order to reach out to the scientific community and the public. I like the challenge of bridging the gap between scientists and society. Through our website and newsletter every researcher has the opportunity to make his/her science visible to others and to learn about other scientific developments. I am counting on you to send me news of your research achievements!”

email addresses: **info@nmi3.eu**
ines.crespo@frm2.tum.de

The schools’ coordinators

NMI3 supports a selected group of 14 schools, some taking place once a year, others once every two years. This short article introduces Laurence Tellier and Ross Stewart. They are the coordinators responsible for smoothing the functioning of the European Neutron and Muon School (ENMS).

Laurence Tellier started getting involved in NMI3 during the FP6 proposal in 2004. At the time, Helmut Schober was the networking coordinator and Laurence his personal assistant. She managed the proposal rounds for the schools and workshops, reduced to schools only during the first FP7, and have become part of the grant agreement in NMI3-II (FP7) when the schools to be receive NMI3 funds were preselected. Laurence manages the funding letters upfront and the collection of the school reports once the schools have taken place. Once the reports are complete she makes the payments. At the end of each year, she also organises the evaluation of the schools by the Advisory Committee. Besides supporting the ENMS, she is the secretary and event manager for two instrument groups at the Institut Laue-Langevin in Grenoble: the Three-axis spectrometers (TAS) and Time-of-flight and high-resolution (TOF/HR) groups.

Ross Stewart took on the role of ENMS coordinator about a year ago. He will ensure that the NMI3 supported schools operate in a coherent manner,

Coordination and Management

with each school being funded appropriately given its size and scope. Together with Juliette Savin, our former information manager, Ross has edited the ENMS brochure, promoting NMI3's role in supporting the schools. Apart from the ENMS, Ross is the leader of the Excitations Instrument group at the ISIS Pulsed Neutron and Muon Source, which runs the MAPS, MERLIN, LET, MARI and ALF instruments.

Laurence Tellier

Ross Stewart

The 3rd Neutron & Muon PR network meeting in Grenoble

On October 15 in Grenoble, press officers from various neutron and muon European institutions met for the third time. The meeting focused on the development of the future web platform 'neutronsources.org'. The aim of this platform is to increase the visibility of worldwide neutron research on the internet, as well as to provide access to reliable and up-to-date information on neutron research.

Each of the press officers at the meeting gave valuable input on their views for the outline of the website, which is to be launched during the first months of 2013. The press officers' network and an editorial group, made up ideally of representatives from neutron institutions, will support the NMI3 information manager in maintaining and enhancing the website content. Worldwide institutions are getting involved and are being kept up-to-date on the decisions taken, so that everyone can take part of this initiative! If you would like to get involved, please contact info@neutronsources.org.

Press officer network meeting in Oct. 2012 at ILL

Calendar

NMI3-II General Assembly
June 20-21, 2013 in Berlin-Brandenburgische Akademie der Wissenschaften

International Conf. Neutron Scattering - ICNS
July 8-12, 2013 at Edinburgh International Conference Centre

Industry Workshop
July 9, 2013 (afternoon), NMI3 Industry satellite workshop at ICNS

Winners of the third *Illustrating NMI3* picture competition

We are pleased to announce the winners of the third ´Illustrating NMI3´ picture competition.

The first prize goes to Henrich Frielinghaus, group leader of the SANS group of the Jülich Centre for Neutron Science in Germany, for his picture of the rheometer installed at the SANS instrument KWS-1 in Garching, Germany.

1st prize - The rheometer installed at the SANS instrument KWS-1 for characterizing hexagonal microemulsions. The sample consisted of D_2O, n-decane, the surfactant $C_{10}E_4$ and the polymer PEP_5-PEO_{15}.

The second prize goes to Frederik Lipfert from the Jülich Centre for Neutron Science for his picture of Dr. Henrich Frielinghaus conducting Rheo-SANS experiments at the instrument KWS-1 at the FRM II, in Garching.

2nd prize - Henrich Frielinghaus conducting Rheo-SANS experiments at the instrument KWS-1 at the FRM-2, Garching.

Editors

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