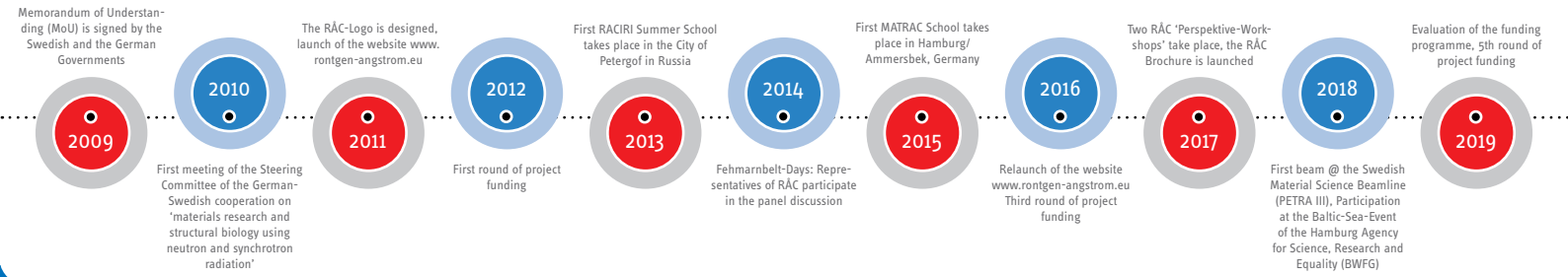
Röntgen Ångström Cluster

NEWSLETTER 17 | JUNE 2019



RÅC - MILESTONES

NEWS

Beatrix Vierkorn-Rudolph and Kurt Clausen new Chair and Vice Chair of ESS Council

Dr. Beatrix Vierkorn-Rudolph and Prof. Dr. Kurt Clausen are the elected new Chair and Vice Chair of the ESS Council, starting on the 1st of July 2019.

Beatrix Vierkorn-Rudolph has served as Vice Chair of the ESS Council since 2017, and prior to that she was one of the German delegates since the foundation of the European Spallation Source ERIC. She has a Ph.D. in Analytical and Atmospheric Chemistry from the Technical University of Darmstadt, and has a long record in management of scientific research infrastructures within the German Federal Ministry of Education and Research. She has served on many other panels, including as Chair for ESFRI (European Strategy Forum for Research Infrastructures) between 2010 and 2013.

Kurt Clausen has recently retired from a long career in scientific facilities, with a prominent role at the Paul Scherrer Institut in Switzerland, and is now Professor Emeritus at Danish Technological University. He has been continuously involved in the ESS project since 1993, participating in many of the early proposals for the facility and subsequently coordinating the Swiss participation in the ESS project in Lund. He has also chaired the ESS Technical Advisory Committee.

The current Chair of the ESS Council, Lars Börjesson, has now served the maximum of two terms, and will therefore step down on 30th June.

EDITORIAL

The year 2019 has so far been a very exciting one for science - and a historic one for Röntgen-Ångström Cluster (RÅC) as it is celebrating its 10 year anniversary. In April the mesmerizing first image of a black hole was released by an international team of researchers and it immediately made global headlines. This scientific milestone serves as prime example of what astonishing results international cooperation with large scale research infrastructures can deliver. This equally holds true for international partnerships with photon and neutron sources, which RÅC embodies.
When tackling fundamental questions in science, large scale facilities like the European Spallation Source, which will begin initial operations this year, are of ever growing importance. And in times of looming global uncertainties and a growing sensation of unilateralism in parts of the world, RÅC remains a prime example of research collaboration within Europe and beyond. Therefore, we wish the Röntgen-Ångström Cluster many more successful years as an international platform for scientific cooperation. As always, our newsletter will keep you informed about everything that's happening in the RÅC-cosmos. Enjoy the read.

The Editors

Beatrix Vierkorn-Rudolph and Kurt Clausen, Photo: ESS

NEWS

Sakura Pascarelli appointed scientific director at European XFEL

Sakura Pascarelli *© Chantal Argoud (ESRF)*

The Italian physicist Dr. Sakura Pascarelli will be responsible for scientific development of hard X-ray instruments.

She will join European XFEL on the 1st of September from the European Synchrotron Radiation Facility, ESRF in Grenoble, France. She succeeds Andreas Schwarz who retired at the end of 2018. As one of three scientific directors, Pascarelli will be responsible for the four short-waved hard X-ray instruments at European XFEL: FXE for studying extremely fast processes, SPB/SFX for investigating biomolecules and biological samples, HED for studying matter under extreme pressures and temperatures, and MID for investigating nanostructures or irregularly ordered materials such as glass, liquids and biological substances. In addition, Pascarelli will also be responsible for developing the scientific research program for these experiment stations.

PROJECTS

Studying collective motions within TT-SAS

The aim of the RÅC project "TT-SAS" between the Technische Hochschule Lübeck (THL) – with Manfred Rößle, Siawosch Schewa, Till Zickmantel - and European Molecular Biology Laboratory (EMBL) at DESY - with Dimitri Svergun and Martin Schroer - is to study collective motions within biological macromolecules excited by external THz radiation and probed by small angle X-ray scattering (SAXS). Biological macromolecules, like proteins, can show collective oscillations of their subdomains in order to perform their biological function. The frequencies of these conformational changes, which are of several Angstrom to a few nanometers, lie within a range from 0.3 to 6 THz. Therefore, these so-called normal oscillations are expected to be excited by THz radiation. The so-induced protein dynamics should be detectable by time-resolved SAXS measurements. As this non-equilibrium effect is, however, expected to be weak and highly dynamic, a number of developments in hardware, sample handling and software have been necessary for such experiments to be performed.

EMBL Part:
At the EMBL bioSAXS beamline P12 at the third generation synchrotron PETRA III, which is dedicated to SAXS on biological solutions, the experimental conditions to perform time-resolved SAXS measurements have been upgraded. A new multi-layer monochromator increases the flux of the already high X-ray brilliant beam by a factor of up to 80. Developing a fast chopper system in combination with a modern shutter system, a temporal resolution down to 10 µs can be achieved. With these improvements, it is possible to detect even weak structural changes, as possible induced by THz. In order to model experimental SAXS of proteins exhibiting conformation changes, the program SREFLEX, which is part of the ATSAS software package, has been developed. Using normal-mode analysis of the protein structure, the flexibility of high-resolution structures can be determined and used to describe the experimental SAXS data. With this approach, changes of the solution structure, such as likely induced by THz radiation, can be analyzed.

THL part:
In parallel, a new microfluidic sample environment has been developed at the TH Lübeck for combined THz-SAXS measurements. Because of the high absorption of THz radiation in aqueous solutions, only a thin layer (< 200 µm) of solution is actually excited. This limits the effective size of the sample volume and demanded the development of novel microfluidic cell. The challenge was to design a cell which is transparent for THz radiation, allows for SAXS data collection and in which small amounts of precious biological samples can be flowed through. First combined THz-SAXS experiments at P12 using the new cells indicated very weak changes in the SAXS curves of model proteins. In order to confirm our findings, new experiments are going to take place in summer 2019.

Scientists involved in the project: Till Zickmantel (l), Martin Schroer, Siawosch Schewa(r)

PROJECTS

Combined SANS/SAXS and model-independent simulations for structure determination of complex, therapeutically relevant lipid nanoparticles

PI: *University of Heidelberg, Germany*
CoPI: *Jan Swenson (S), Nadine Schwierz (G), Frederik Höök (S), Aurel Radulescu (G), Andrew Jackson (S), Ann Terry (S)*

Associated scientists: *Henrich Frielinghaus (MLZ-FRM2) Lennart Lindfors (Astra Zeneca), Adrian Rennie (Uppsala University), B. Nickel (LMU)*

Lipid nanoparticles (LNPs) represent a promising approach to deliver mRNA to living cells and to treat diseases by production of therapeutic proteins in vivo. However, the structure of LNPs, which are made of ionizable cationic lipid and helper lipids, as well as the mechanisms of uptake and release of molecular cargo are not well understood. The MediSoft project develops methods using combined SANS/SAXS measurements linked to state-of-the-art computational tools in order to elucidate structural transition of lipid based RNA nanoparticles. The structure determination is challenging due to the finite size of the soft nanoparticles, their multiple components, intrinsic disorder and hierarchical structure at different length scales. In addition, there is low lipid-RNA contrast and fast dynamics. Standard analysis using approximate analytical scattering functions fail to unravel functionally relevant details like phase separated surfaces domains, the structure of the interior bulk phase and the conformation of the encapsulated RNA macromolecules.

Small angle scattering with either neutrons (SANS) or X-rays (SAXS) probe length scales from 1 nm to 1 m. Since X-rays interact with electrons while neutrons see the nuclei, the combination of SAXS and SANS offers a unique way for an unambiguous characterization of complex multi-domain or multicomponent biological systems, such as drug delivery carriers. In addition, contrast variation exploits the difference in the neutron scattering length density of hydrogen and deuterium and contrast matching allows for probing selected components in the presence of other contrast matched components in a multicomponent system. Typically, several SANS data sets are obtained for a series of different H/D ratio. The data analysis of SANS contrast series combined with SAXS data is challenging and only possible if appropriate analytical models exist. However, the combined use of multiple SAXS/SANS sets of experimental data to infer unknown structural details with the help of computational simulations is promising as computer capacity is growing. With the recent developments in coarse grained simulations and the planned efforts to install the next-generation of neutron source, ESS, at Lund, there is a timely opportunity to develop the methods and infrastructure that allows for combined SANS/SAXS measurements linked to state-of-the-art computational tools for multi-experiment structure determination.

In the first phase of the project, the group of Nadine Schwierz at the MPI for biophysics in Frankfurt developed algorithms to determine the secondary structure of RNA in bulk and at solid surfaces. For RNA modeling both full atomistic as well as coarse-grained models are used. In the case of lipid membranes a coarse-grained model using the established „Martini“ force field was used. Fig.1 shows an image of a binary lipid membrane composed of neutral lipid (DOPC) and cationic lipid (DOTAP). First simulations showing how RNA adsorbs to cationic membranes were carried out. The group of Lennart Lindfors (Astra Zeneca) together with Aurel Radulescu (FRM-2) performed SAXS and SANS structural studies of lipid mixtures already evaluated in clinical trials (Arteta, et al. “Successful Reprogramming of Cellular Protein Production Through mRNA Delivered by Functionalized Lipid Nanoparticles.” Proceedings of the National Academy of Sciences 115, no. 15, 2018). In continuation, the group of Joachim Rädler at the LMU Munich studied the structure of the bulk phase of three different LNP formulation in comparison using SAXS. The lipid mixtures differed in the type of ionizable lipids (DLin, DLin-KC2-DMA, DLinMC3-DMA), which slightly vary in their ionizable head group, but differ order of magnitude in efficiency. In the study the structural changes observed in the bulk phases of the lipids will be related to the efficiency and delivery timing of the respective LNPs. To this end a single cell in-vitro transfection assay was developed in the Rädler group, which allows to assess the delivery time and single cell gene expression trajectories after RNA transfer with high precision. Bulk and surface structure of dispersed lipid based nanosystems are determinants of packing and delivery efficiency. The project is expected to have fundamental significance for the development of mRNA therapies, a field which is still limited by the development of an efficient and safe delivery system of the modified mRNA molecules. Lipid nanoparticles are considered the most promising delivery system in this area. However, beside the proof of in-vivo efficiency basic understanding of the biophysical mechanisms is essential in order to improve the delivery for clinical applications.

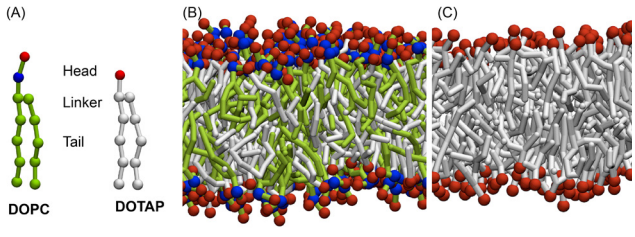


Fig.1: Coarse grained simulation of a lipid membrane: (A) Representation of DOPC and DOTAP lipids. Lipids are composed of a hydrophilic head, a linker and a hydrophobic tail. Snap-shot of a simulation: (B) Binary mixture of zwitterionic DOPC and cationic DOTAP lipids (C) Cationic membrane of charged DOTAP lipids.

SCHOOLS

group picture, Photo: Schürmann/TUM

MATRAC 2: Application of Neutrons and Synchrotron Radiation in Materials Science with Special Focus on Fundamental Aspects of Materials

40 students and young scientists from Germany, Sweden, and six other European and EU associated countries met in Herrsching/ Ammersee near Munich from 31.03.2019 to 05.04.2019 to participate in the MATRAC 2 School. Organisers of the school were HZG, CAU Kiel, Linköping University (Sweden), Chalmers University of Technology (Sweden), University of Göttingen and University of Bremen, with financial support of the Federal Ministry of Education and Research (BMBF) and the Swedish Research Council (VR), the EU programme SINE2020 and the German Länder Hamburg, Bremen, Mecklenburg-Vorpommern, Niedersachsen and Schleswig-Holstein. The school started with a get together on Sunday night and included a three-day theoretical course and two days of practical training.

The lectures given by 15 experts from Swedish and German universities, research centres and the Heinz Maier-Leibnitz Zentrum (MLZ) in Garching ranged from the fundamentals of elastic and inelastic scattering of neutrons and X-rays to details of experimental techniques to modern functional materials and biomaterials. The school provided a systematic overview of the application of neutrons and synchrotron radiation for the structural and dynamical analysis of materials and focused on neutron scattering and imaging experiments.

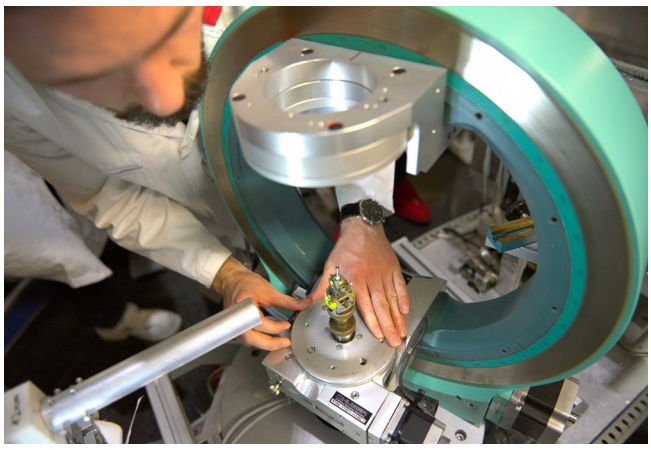
This focus was enhanced by the two-day practical course with hands-on experiments at the FRM II in Garching where the students were introduced to the MLZ instruments and every participant had the possibility to perform two experiments - a short and a long one, the latter with an extensive evaluation on the second day.

The school location in the village of Herrsching fostered many scientific discussions, especially during two poster sessions on Monday and Tuesday night, when most of the participants presented their work, and also after dinner. One of the dinners was taken at a country inn with fine local specialties in a neighbouring village of Herrsching.

On the last day of the school, the theoretical course was wrapped-up by the two talks “Data Treatment and Modelling” and “Examples of Research with Neutrons: Ionics and Protonics studied with INS and QENS”, followed by a students’ presentation session, in which the students outlined and explained the results of their long experiments during the practicals.

The students‘ feedback on the MATRAC 2 School, obtained through a questionnaire and a feedback session, was very positive. In particular, the practicals were highly appreciated and the commitment of the scientists of the MLZ instruments was highlighted.

The next MATRAC 2 School in Herrsching and at FRM II will take place in the spring of 2021. The next MATRAC 1 School in Lauenburg and at DESY in Hamburg is scheduled for September 2020.



hands-on experiment, Photo: Schürmann/TUM

ANNOUNCEMENT

A new call within the framework of the Swedish-German collaboration in materials science and structural biology using neutrons and synchrotron radiation is open.
Please check www.rontgen-angstrom.eu for further information.

RACIRI in 2019

The next RACIRI School will take place from August 4th to 11th, 2019 in Svetlogorsk, Russia. This year's theme is the "Structure, Real-time Dynamics and Processes in Complex Systems". For more information visit us at www.rontgen-angstrom.eu or see www.raciri.org.

MATRAC in 2020 and 2021

The next MATRAC 1 School in Lauenburg and at DESY in Hamburg is scheduled for September 2020.

The next MATRAC 2 School in Herrsching and at FRM II will take place in the spring of 2021.

Further information about MATRAC Schools can be found at www.rontgen-angstrom.eu

THE OTHER NEWS

Everything okay?

The term "Okay" / "OK" / "O.K." is considered the most widely spoken word in the world in a multitude of different languages - including German and Swedish. Its meaning is close to identical in all languages, signaling general consent.

How often do you say, see, hear – or click – Okay in just one day? The origin of the term has been subject to a long history of research and debate among academics. In a series of articles published in the journal of American Speech between 1963 – 1964, the American etymologist Allen Walker Read was able to provide solid evidence that the origin of the word is based on a joke: a deliberate spelling or more phonemic spelling „oll correct" as an abbreviation for „all correct", in which actually nothing is correct. However, to this day there is a large number of folk etymologies surrounding "Okay." Among them there are theories which place the origins of the term with the US-military, on the African continent or within the context of monarchy: Rooted within the United States Army, one theory claims that OK is an abbreviation for "Order Known", the routine confirmation of a given command. Another popular answer to the question of the origin of Okay lies in West Africa: Some believe slaves brought the expression to America. This assumption goes back to a claim by the Africa linguist David Dalby, who found the word "woukay"in the West African language of Wolof which means something like „in order". Lastly, some people place the origin in an aristocratic or royal context. According to proponents of this theory, the word Okay is simply an abbreviation for "by Order of the King".

Whatever the origin of Okay may be, it is safe to say that we are very thankful for the existence of this verbal equivalent to the Swiss army knife.

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