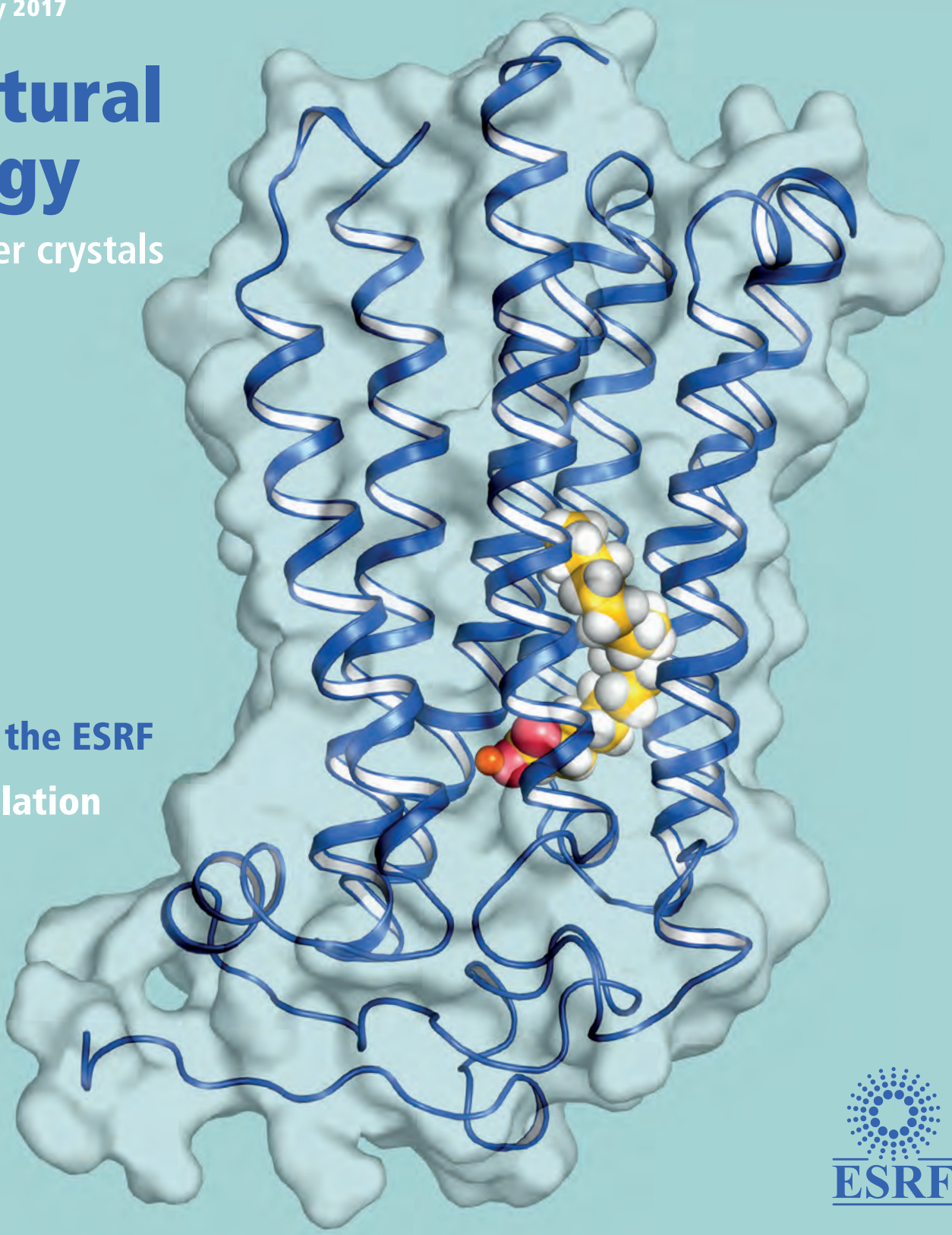
A Light for Science

ESRF news

Number 76 July 2017

Structural biology

Ever smaller crystals



India joins the ESRF

Heart regulation probed

ESRF

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SDD detectors for beam-line applications

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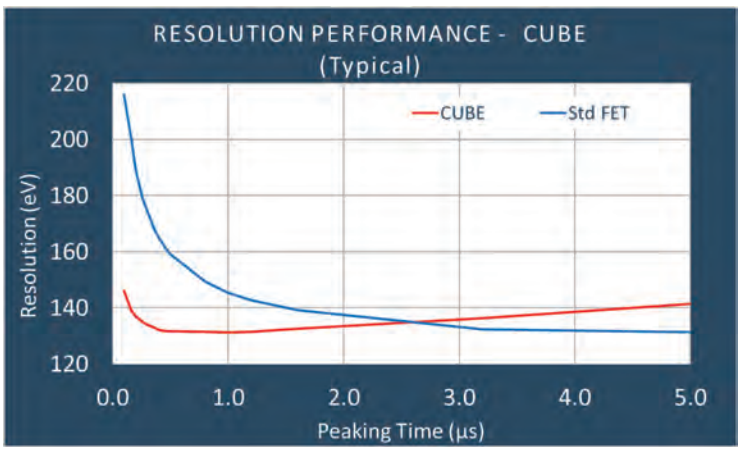

CUBE detectors offer improved resolution at shorter peaking times

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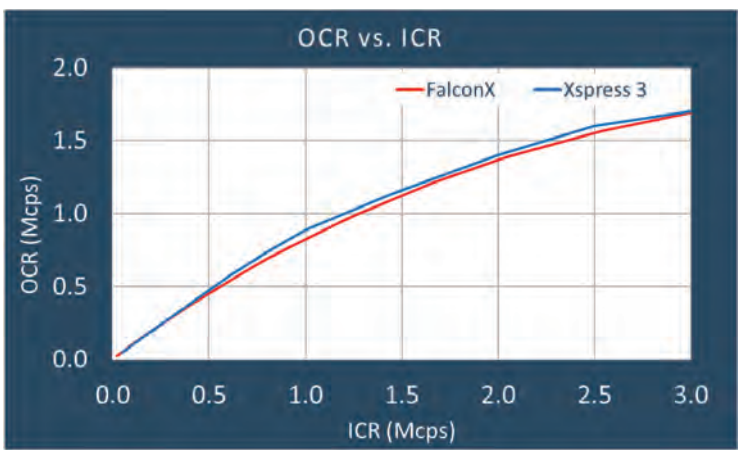
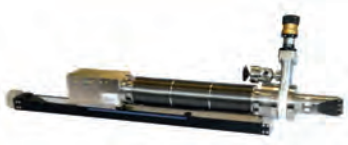


RaySpec SDD detectors - compatible with the latest Digital Pulse Processors from XIA and Quantum Detectors with input count rates >3Mcps

Single and Multi-Sensor SDD Detectors

Example of single sensor design



Example of multi-sensor design with UHV compatibility

Design Features

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Examples of Customised Designs

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4 Sensor Vertical Focused Array SDD

7 Sensor Circular Focused Array SDD

Windowless SDD design for UHV

Modular SDD Vacuum Compatible

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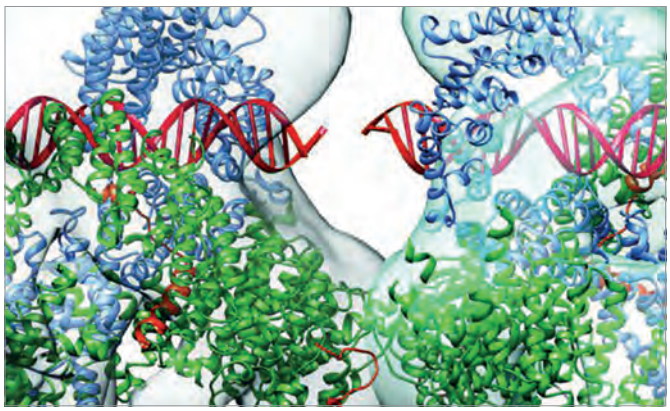
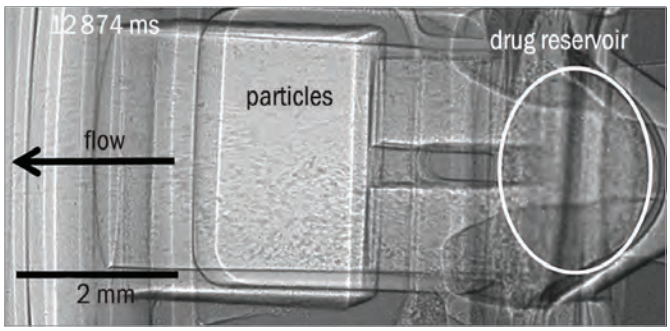
The European Synchrotron

Molecular-scale regulation of heart activity uncovered, p12.



Structural biology: an insight into DNA repair , p23.



Phase-contrast imaging films particles in asthma inhalers, p29.

I. VASILIAUSKAITĖ-BROOKS *ET AL.*/ *NATURE*

On the cover:
Crystal structure of AdipoR2, a protein that could be important in the onset of type-2 diabetes

ESRFnews Number 76 July 2017

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Veijo Honkimäki, Group Leader Structure of Materials, ESRF

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- *Room temperature operation*

synchrotron

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ESRFnews

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The first crystal structure of a protein was reported in 1958 and it was only in the 1980s that determining the crystal structures of biological macromolecules became relatively straightforward. A revolution, however, came in the late 1990s and early 2000s thanks to a combination of advances including the construction of highly brilliant, highly automated and user-friendly synchrotron beamlines for macromolecular crystallography (MX). Here, the ESRF – the world's first 3rd generation synchrotron source – helped lead the way with the commissioning of Europe's first undulator-based beamlines for MX and the world's first MX-dedicated micro-focus beamline (p16). These facilities helped precipitate an explosion in the determination of atomic resolution crystal structures of proteins, nucleic acids and their complexes. Indeed, the Protein Data Bank now contains more than 120,000 entries, offering insights into the mechanisms of action of almost all types of biological macromolecules and their complexes, including enzymes, membrane proteins, ribosomes and G-protein coupled receptors (p19), and providing the structural basis for the field of molecular medicine (p21 and p23).

"The ESRF has helped lead the way in structural biology"

New technology – including developments in X-ray detectors and in beamline-control hardware and software – mean that experimental sessions at MX beamlines now produce a deluge of raw and reduced data. Here, too, the ESRF has been at the forefront of efforts to find solutions; for example, in helping to develop experiment-tracking applications that allow users to decide, while an experimental session is in progress, which diffraction data will be most useful downstream (p25). But structural biology at synchrotron facilities is no longer limited to MX. High throughput small-angle X-ray scattering (SAXS) experiments on solutions of biological macromolecules (BioSAXS) at the ESRF's BM29 beamline (p15) are increasingly used to produce structural information complementary to that provided by MX. Moreover, this summer will see the installation, commissioning and first operation at the ESRF of a Titan Krios cryo-electron microscope dedicated to structural biology. For the ESRF's external user community, the microscope will be the focal point of a Partnership for Structural Biology platform for cryo-electron microscopy (cryo-EM) that will allow them both to exploit the recent "resolution revolution" in cryo-EM and to combine cryo-EM, MX, BioSAXS and other techniques in the search for the correct interpretation of the structural information they obtain.

The evolution of structural biology at the ESRF will continue with the Extremely Brilliant Source. This fast-approaching upgrade of the ESRF storage ring will provide unprecedented opportunities for structural biologists, with a suite of ultra-high brilliance beamlines that will deliver an improvement in flux density at the sample position of up to five orders of magnitude. This will enable studies of even smaller crystals and the further development of new techniques such as synchrotron serial crystallography (SSX). SSX should lead to a resurgence in room-temperature MX and time-resolved structural studies of biological macromolecules. Both of these areas will ensure that synchrotron radiation remains the most important tool for structural biology in the foreseeable future.

Jean Susini, *ESRF director of life sciences*
Gordon Leonard, *head of the ESRF structural biology group*

STEF CANDE

Synchrotron@ school welcomes new students

The ESRF's synchrotron@ school programme opened its doors to students from lycées professionnels (colleges) for the first time in April, to exhibit the diversity of jobs at the ESRF.

This year, the students came from a single lycée professionnel, Paul Béchet in Cluses, France, but organisers are planning to invite others from 2018 onwards. The new programme was run in addition to the existing synchrotron@school programme, which in total hosted 1500 students mainly from France and also Italy, Sweden, UK, Japan and Turkey. "It's a chance to show students what they can do with the diplomas they are studying towards," says ESRF volunteer Jacques Borrel.

SESAME opens

King Abdullah II of Jordan officially opened the SESAME light source in May, marking a new era of scientific co-operation in the Middle East and beyond. Three beamlines in the Jordan-based synchrotron will be operational this year, and a fourth is set to become operational in 2019. Early experiments are expected to focus on local pollution, new cancer drugs and cultural heritage. "In building SESAME, we had to overcome major financial, technological and political challenges," said SESAME's director, Khaled Toukan, adding: "Today we are at the end of the beginning."

The ESRF is co-ordinating an EU project to promote the best use of SESAME, by training staff, building up expertise in the region and raising awareness of the facility. "Long life to SESAME Synchrotron: a light for science, dialogue, peace for the Middle East and beyond," tweeted the ESRF director-general Francesco Sette. "It's an important day for Science Diplomacy."

India joins the ESRF

India has become the 22nd country to join the ESRF, following the signing of a three-year agreement between the Indian government and the synchrotron.

The agreement was signed by Sudhanshu Vrati, the executive director of the Regional Centre for Biotechnology (RDB) in Faridabad, and the ESRF director-general Francesco Sette, with the backing of both the Department of Bio-Technology of the Government of India and the ESRF Council. It will give scientists in India access to the synchrotron for non-proprietary research, in particular structural biology.

"I am confident that this new agreement will lead to exciting new discoveries and nucleate other scientific collaborations between India and Europe," said Vrati, upon signing the agreement.

Collaboration between the ESRF and India has been increasing steadily over recent years. In 2009, the ESRF and India's National Institute of Immunology signed a memorandum of understanding, enabling Indian scientists to share use of the ESRF macromolecular-crystallography beamline BM14 with the European Molecular Biology Laboratory. The new agreement gives Indian scientists full use of the synchrotron, at a critical time when the facility is preparing for the launch of an important upgrade, the Extremely Brilliant Source, in 2020.

"I am very pleased and honoured by the decision of India to join the ESRF," says Sette. "The ESRF community will greatly benefit from the collaboration with the vibrant Indian scientific community."

• An interview with Dinakar Salunke, who has nurtured the India–ESRF partnership, is on p27 of this issue.

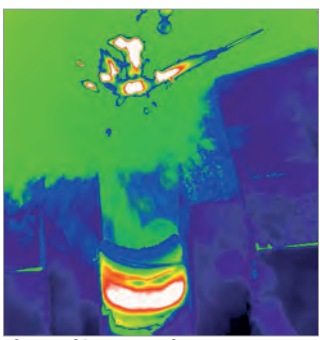
Batteries with less bang

Explosive batteries are a genuine user concern following reports last year that a Samsung smartphone model could cause fires. But now a study at the ESRF of how lithium-ion batteries behave in real time under short-circuit conditions could help improve safety and reliability.

Short circuiting is believed to be the cause of a number of high-profile battery failures, including that of Samsung's Galaxy Note 7. Previously, researchers have tracked the failure of lithium-ion batteries caused by extreme heat in real time, but never have they studied what happens when a short circuit is deliberately instigated at a specific location.

Chemical engineer Paul Shearing of University College London in the UK and colleagues have now done so at the ESRF beamline ID19, by inserting a special short-circuiting device into a commercial lithium-ion battery. Monitoring what happened via high-speed X-ray imaging, the researchers could witness the formation of gas pockets and temperatures swiftly rising to over 1000°C (*Energy Environ Sci*. doi:10.1039/C7EE00385D). "It's fascinating to see how quickly the process of thermal runaway can spread throughout these cells," says Shearing. "They went from being completely intact to being completely destroyed within around one second."

The results suggest that safety could be improved if failed cells could quickly be isolated within larger battery packs, although the researchers still have more work to do. "They already have beamtime lined up for the autumn," says co-author Alexander Rack of ID19. "We look forward to new exciting results – and exciting explosions as well!"



D P FINEGAN ET AL *ENERGY ENVIRON SCI*.

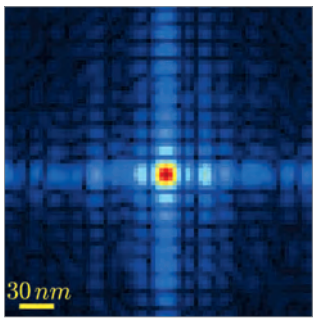
Thermal imagery shows runaway failure of a lithium-ion cell.

ID16A breaks resolution record

Scientists and engineers at the ESRF beamline ID16A have generated a high-energy beam with a spot size approaching 10 nm, a world first at energies greater than 20 keV. The focus of the beam, which verges on the diffraction limit, could have applications across the life, materials and environmental sciences where details of interest drop down to the nanometre.

"These nano-focusing results, close to 10 nm, at very high energy and with a very high flux, are really unique worldwide," says Peter Cloetens, the scientist in charge of ID16A. "This will create new opportunities in the fields of materials and life sciences."

Opened in 2014, ID16A is the ESRF's longest beamline with an end station 185 m from the source point. It is used to perform phase-contrast imaging, X-ray fluorescence imaging and ptychography, all combined with tomography to obtain three-dimensional imagery. ID16A already had precisely controlled temperature and stability. Key to the latest record, however, was the installation of a new Kirkpatrick-Baez mirror, which was figured and polished by JTEC Corporation in Japan before coming to the ESRF's Multilayer Laboratory for coating with 120 layers of tungsten and boron carbide. Such multilayers reduce the diffraction limit while maintaining a high photon flux.



J C DA SILVA ET AL / OPTICA

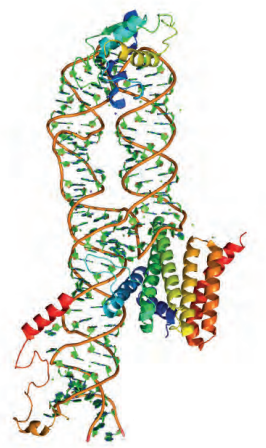
Smallest ever nanobeam.

Using ptychography, Cloetens and colleagues were able to characterise the size of the focal spot as less than 13 nm, at a flux of six billion photons per second (*Optica* **4** 492). Lead author Julio da Silva of ID16A believes the technique will only get better with the ESRF upgrade, the Extremely Brilliant Source (EBS). "In the future, the augmented coherence of the X-ray beams from the ESRF–EBS will further improve the performance of such a technique at high energies," he says.

ID29 hits 2000 mark

ID29 users have deposited their 2000th structure in the protein data bank (PDB) – the first ESRF beamline and only the second beamline in Europe to reach the milestone.

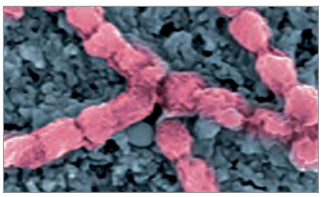
ID29 was designed to exploit anomalous scattering, tuneable over a wide energy range, for the determination of novel protein structures. Since its first commissioning in 2001, it has evolved with the crystallography field, being one of the first macromolecular crystallography beamlines to implement continuous scans with multiple motor movement. That allowed continuous helical oscillation and mesh scans, which are essential for the nascent field of protein microcrystallography. Such tools are among those that have made ID29 increasingly in demand for proprietary research, and depositions into the PDB have continually risen. "Congratulations to the ESRF users and the structural biology staff for this outstanding achievement," says Daniele de Sanctis, ID29 beamline responsible.



5M73: the 2000th structure.

EiroForum meets EU Commissioner

In May, the director-generals of the EIROforum met with the European Commissioner for Research, Carlos Moedas, and Director-General for Research and Innovation, Robert Jan-Smits, in Brussels to discuss the EC's current and future research programmes as well as the EC's plans to launch the European Open Science Cloud.

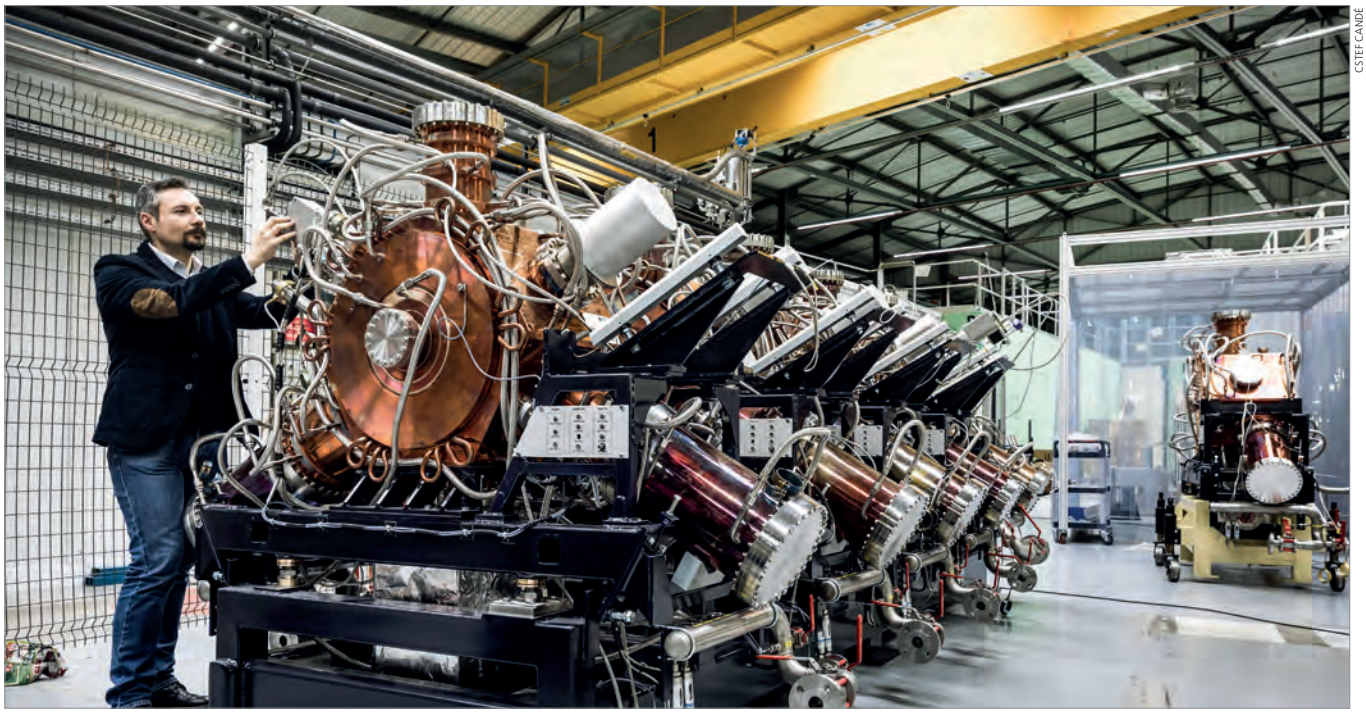


Sponge bacteria eat arsenic

A reddish sea sponge, *Theonella swinhoei*, is known to accumulate arsenic pollution. Now a team based in Israel and the US believes that the desirable ability in fact resides with a symbiotic bacterium, *Entotheonella*, which can mineralise arsenic and another toxic element, barium. Upon seeing initial electron-microscopy results, team member Boaz Pokroy at the Israel Institute of Technology in Haifa went to the ESRF beamline ID22 "within a week" for validation using X-ray powder diffraction, says lead author Ray Keren at Tel Aviv University. "There, he saw that barium is mineralised as barite and arsenic formed smaller peaks of an unknown mineral," which turned out to be calcium arsenate. The findings suggest a natural solution for detoxifying seawater, but the authors point out that they have to find a way to make the bacteria live without the sponge (*Nat. Commun.* doi:10.1038/ncomms14393).

Compressed matter workshop

Some 80 people came to the ESRF in March for the second workshop on studying dynamically compressed matter with X-rays. The aim of the workshop was to bring together future users of the high power laser facility at the ESRF, which is used to generate such matter states. The attendees talked about phase-transition dynamics in iron, what happens at the atomic scale during a shock compression, and what happens when you shock-compress a real rock sample, among other topics. Technical issues were discussed too, including the maximum pressures and temperatures that can be obtained at the ESRF's facility. "There were animated discussions," says the ESRF's Sakura Pascarelli, the scientist in charge of the ID24 beamline and one of the workshop's organisers.



CSTEFF CANDÉ

Alessandro D'Elia of the radio frequency group adjusts one of the new RF cavities. The smaller copper cylinders protruding in a star pattern from the main cylinder are the higher order mode dampers.

Main accelerator parts arrive

The ESRF saw 10 of the EBS's radio frequency (RF) cavities arrive by May, with the final two due to arrive as this issue went to press. The delivery puts engineers and technicians on track to begin attaching power couplers, tuning systems, field probes, water cooling hoses, instrumentation, temperature sensors, and other components.

The RF cavities are responsible for accelerating the electrons and maintaining their energy in a synchrotron. At every turn, an electron loses roughly one-twentieth of its energy to synchrotron radiation; to top up this energy in the EBS, the copper cavities will impose quickly alternating electric fields totalling more than six million volts. "We need to restore this energy to keep the electrons circulating, and emitting the radiation exploited by the users of the synchrotron," says Jörn Jacob, the head of the ESRF's radio frequency group.

RF cavities are electromagnetic resonators, and in addition to the fundamental resonance there are "higher order" resonances, or modes, which can destabilise the packets of electrons in the storage ring. As it is pushing the boundaries of synchrotron engineering, the EBS will be particularly susceptible to these higher order modes, and so its RF cavities contain special dampers to suppress their effect. There will be 14 RF cavities in the EBS: on top of the 12 delivered this year there are three existing prototypes, leaving one spare.

"The RF cavities in the EBS will deliver more than six million volts."

• A new video of the EBS is available to view online at www.youtube.com/user/LightforScience.

EBS seminar

The eighth EBS seminar, on 1 March, saw Riccardo Bartolini of Diamond Light Source give a presentation on the status of the UK light source's upgrade. The talk explored the design, installation and constraints of the Diamond II upgrade, which will strive to combine low emittance with a doubling of the number of straight sections. Diamond have successfully collaborated with the ESRF on their upgrade project, using the ESRF cell concept to modify their lattice design.

MAC pleased with contract progress

The fifth Machine Advisory Committee (MAC) meeting was held at the ESRF on 20 and 21 April.

Chaired by Richard Walker, the technical director of Diamond Light Source in the UK, the meeting brought together a panel of accelerator experts to discuss the progress of the ESRF–EBS project. Staff members gave presentations covering the progress of various aspects of the upgrade, including planning, procurement, assembly, dismantling and installation, as well as specific topics such as injection, magnets, vacuum and commissioning.

Attendees view mock-up cell.

The MAC had the opportunity to visit the Chartreuse Hall at the ESRF and the mock-up EBS cell, which consists of the girders and assembly table, a dipole–quadrupole and a dipole vacuum chamber. ESRF staff members provided explanations and insights into the different pieces of equipment. The MAC was pleased to hear that the contracts for the pre-series components had all been finalised and launched, and that all of the big contracts for deliverable items in the storage ring had already been launched. The EBS project leader, Pantaleo Raimondi, noted that a lot of work had been accomplished thanks to the strong support and motivation from all of the ESRF divisions.

Engineers begin vacuum tests

Tests have begun on prototypes of the EBS vacuum chambers and components, following their successful installation at the ID14 insertion-device section in March. The tests will establish whether outgassing and vacuum conditioning behave as predicted, and whether the components in control of so-called image currents are compatible with the ESRF's operation modes.

Vacuums are common to all synchrotrons, but the EBS pushes vacuum-engineering to its limit. The problem is actually one of the EBS's main design goals: a very low emittance, which means that the circulating electrons are tightly grouped together, and brighter as a result. Achieving a low emittance means placing strong magnets very close to the beam, but this leaves little space for a vacuum chamber. "There is hardly any space remaining," says Michael Hahn, the leader of the ESRF's vacuum group. Such confined geometries make it difficult to pump out molecules – hydrogen, nitrogen, water and others – that are naturally outgassed from the surface of the chambers.

C ARGOUD

Vacuum chambers are in place for testing.

Currently, the ESRF's vacuum chambers are made from stainless steel, a material that outgasses very little. To meet the EBS's complicated geometrical requirements, however, the ESRF has made several of the new chambers from aluminium, which is easier to machine. One of the tests performed at the ID14 test section was to check the levels of outgassing from one of these new chambers.

Another test dealt with the performance of a radio-frequency (RF) liner, which allows a current to flow through the chamber in a direction opposite to the electron beam. This backward or "image" current needs to exactly balance the forward current for proper synchrotron operation. Hahn's group tried deliberately misaligning the RF liner to observe the machine's response.

In the final test, Hahn and colleagues tested the gate valves that isolate the vacuum chambers in the event of failure. As this issue went to press, the engineers were beginning to dismount the components to check for signs of overheating and other possible damage.

Insight: permanent magnets

Are permanent magnets unusual in a synchrotron?
For the most part, yes. Synchrotrons such as the ESRF accelerate an electron beam via a circular lattice of magnets: dipoles for bending the beam, quadrupoles for focussing, and sextupoles and octupoles for the correction of aberrations.Historically these have all been electromagnets, which can be tuned after installation to provide exactly the right size and shape of field necessary to keep the electrons in check.

Permanent magnets are usually only used for the insertion devices, which stimulate the emission of synchrotron radiation at specific points in the storage ring. In the EBS, however, all 128 of the dipoles will be permanent magnets, each with a maximum field strength of 0.6 Tesla. The design is a radical step in accelerator engineering, made possible by ESRF expertise.

"The design is a radical step in accelerator engineering, made possible by ESRF expertise."

Why will the EBS use permanent magnets?
To have an extremely narrow and bright beam, a lot of the EBS's lattice magnets need to be very compact. Electromagnets are inherently bulky, due to electric coils, cables, water cooling and so on, whereas permanent magnets can be made much smaller. They have other advantages, too. They use no electricity, so are in that respect more environmentally friendly and pose no risk of electrical failure.

Does that mean they're the easy option?
Far from it. Although permanent magnets can be tuned in the lab – for example, by adding thin iron plates – once installed in the lattice their behaviour is essentially fixed. Some degree of beam adjustment in the storage ring will be provided by several corrector electromagnets, but there is little room for error, and ESRF–EBS engineers have had to make sure they get the permanent dipole behaviour absolutely right at the design stage. The engineers have also had to introduce passive mechanisms that correct for the fluctuation of a permanent magnet's field with temperature. Finally, there is the obvious fact that permanent magnets are always on, and liable to attract any metal object within arm's reach. "We have to be careful when we handle them," says Gael Le Bec of the ESRF's insertion device group.

At what stage is the installation now?
About one-third of the permanent dipoles have been built and tested. In the next stage, they will be installed on girders, ready for insertion into the lattice.

For more upgrade news, check out the EBS blog:
http://ebs.esrf.fr

News from the User Office

An impressive 1255 proposals were submitted for the last submission deadline on 1 March this year, requesting a total of over 17,700 shifts of beamtime. This is another all-time record for the ESRF, bringing the total number of proposals received for beam time this year to 2409. On 27 and 28 April, 117 external scientists met at the ESRF to evaluate these new proposals and provide recommendations for beamtime allocation, and we thank them for all their hard work with this important task.

The next deadline for standard proposal submission is 10 September this year for beam time during the period March to July 2018. Users are reminded that there are only two more calls for proposals remaining before the EBS upgrade shutdown.

Proposers are reminded by the Beam Time Allocation Panels of the importance of submitting experiment reports for all beam time allocations previously used, and of citing these in the relevant section of the proposal form. Resubmitted proposals should be clearly marked as such, and it is mandatory to clearly indicate what aspects of the proposal have been modified or improved. Continuation proposals must have an experiment report submitted for the original proposal.

Joanne McCarthy, Head of the User Office

News from the User Organisation Committee

The User Organisation would like to thank all participants of the User Meeting 2017 who completed our feedback survey, which acknowledged the high quality of the presentations, the event programme and the great organisational work carried out by ESRF staff. We are already working on next year's User Meeting, which will take place from 5–7 February 2018, and we invite users to propose topics for tutorials and for the user-dedicated microsymposia.

We are also happy to announce that the web page of the User Organisation is under renovation; its content is being updated and extended. It will include more information on the role and activities of the organisation, additional details on the eligibility conditions and selection process for the Young Scientist Award, as well as contacts of the major synchrotron user organisations in Europe.

Finally, we would like to remind all users who have questions, comments or ideas that they are welcome to contact the User Organisation directly at any time via e-mail. Representatives for each scientific community can be found at www.esrf.eu/UsersAndScience/users_org.

Paola Coan, chair of the User Organisation Committee

News from the beamlines

ID01 opens full-field diffraction X-ray microscope.

● The full-field diffraction X-ray microscope (FFDXM) at **ID01** is now open to user experiments. With its 200 nm resolution, the FFDXM offers a zoomed-in view for images acquired with X-ray diffraction topo- and tomography under Bragg diffraction conditions. Its fast acquisition time (~1 s) over a large surface area (Field of View ~200 × 200 μm^2) makes it ideal for *in situ* experiments. A future upgrade is focused on improving the spatial resolution (sub-50 nm) and the data acquisition speed (~10 ms).

● New mirrors have been installed in the **ID15A** double multilayer mirror monochromator, with an energy bandwidth of 0.35%, reflectivity 80% and energy spread along the mirror ≤0.1%.

● At the microtomography beamline **ID19**, the multi-modal monochromator has been equipped with the last missing items: two multilayer mirrors. Photon energies down to 10 keV can now be reached in a routine manner at a bandwidth of approximately 1%.

● **ID21** is starting its refurbishment, which includes an upgrade of the scanning X-ray microscope, targeting an extended energy range, smaller beam size, improved XRF detection, better sample preservation (*in cryo*), access to 3D information and better integration of complementary techniques (e.g. X-ray diffraction and ptychography). As a consequence, the beamline will be only partially operational in the coming three semesters. In addition, the infrared endstation will be definitively closed from October 2017 and the micro-diffraction activity will be temporarily stopped from December 2017.

● Following the EBS shutdown, only one of the two **Spanish CRG BM25** branches will continue operation at the ESRF. The activities of branch A (**BM25A**) will be transferred to the ALBA synchrotron, while branch B (**BM25B**) will continue its operation at the ESRF. Scientific proposals for BM25A will still be accepted for the ESRF proposal calls of September 2017 and March 2018; the BM25A activities will finish in the second semester of 2018. The BM25A activities X-ray absorption spectroscopy (XAS) and high-resolution powder diffraction (HRPD) will be moved to the ALBA synchrotron through a confluence to the "NOTOS" beamline, which should be built in the near future. On BM25B, dedicated to hard X-ray photoemission spectroscopy (HAXPES) and X-ray diffraction (GI-XRD, XRR, SRD, HRPD and XRD), work is going on to improve the technical and scientific capabilities of the beamline so that it may benefit from the EBS's qualitative improvements to the present X-ray source parameters, opening new opportunities for novel experiments.

● A specialised diffractometer has been built as a side station of the inelastic X-ray scattering (IXS) beamline **ID28** and can operate in parallel with it. The diffractometer is primarily aimed at the study of diffuse scattering in a large class of materials ranging from strongly correlated electron systems to nanoscale-modulated and low-dimensional systems, and will constitute a powerful tool in the study of lattice dynamics, complementing the inelastic X-ray scattering studies. Investigations of a large class of crystalline systems with correlated disorder will greatly benefit from the dedicated station, thanks to a flexible sample environment. The high brilliance of the X-ray source, coupled to state-of-the-art detection schemes using a hybrid pixel detector, PILATUS3 1M, will open the way for time-resolved studies and studies under extreme conditions. The combination of these two stations on ID28 is a unique worldwide capability, offering unprecedented access to lattice dynamics in condensed matter and the real structure of functional materials. The diffractometer operates in a wavelength range between 0.52 and 0.98 Å, providing photon flux up to 10^{12} s^{-1} and a focal spot down to 40 × 20 μm^2. The control system (Pylatus from SNBL) and reduction software (CrysAlis from Rigaku Oxford Diffraction) are familiar to the large user community.

● **XMaS** (**BM28**) is celebrating 20 years of operation. A special Users' Meeting, XMaS@20, will be organised at the ESRF on 20–21 September 2017 to mark this event. For more information and to register visit www.xmas.ac.uk/impact/meetings/xmas_20/.

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The heart of heart regulation

A molecular-level study of heart activity at the ESRF could help develop treatment for inherited cardiac diseases.

Hypertrophic cardiomyopathy – a thickened cardiac wall – is not something many of us would like to contend with. It is hard to detect, having few symptoms, yet it carries a lifelong risk of sudden death. Its most common cause is a mutated gene that leads, in turn, to a mutated protein in the heart's muscle cells.

Coming up with cures for hypertrophic cardiomyopathy requires a deeper understanding of how the heart performs its task at a molecular level. The heart has to pump blood through the body and through the lungs via two circulatory systems that are in series. This is a balancing act, as blood must not build up in one system at the expense of the other. For about a century, the Frank–Starling law – named after the German physiologist Otto Frank and the British physiologist Ernest Starling – has described this balance as a relationship between the force exerted by a ventricle during the contraction phase and the filling of that ventricle during the relaxation phase that preceded it. Simply put, the Frank–Starling law says: the more blood that fills a ventricle, the more the force supplied by that ventricle, and the more the blood that is pumped out again. Quite how this regulation manifests at a molecular level, however, has been another matter.

"We've changed the paradigm of the Frank–Starling law."

One clue came two years ago, in a collaboration between scientists at the University of Florence in Italy, King's College London in the UK and the ESRF. Using X-ray diffraction patterns recorded at the ESRF's ID02 beamline, the scientists were able to study the interaction between thin filaments (containing the track protein actin) and thick filaments (containing the motor protein myosin) in skeletal muscle cells, to find out how contraction is regulated. It was already known that calcium ions trigger muscle contraction by binding to a regulatory protein complex in the thin filament, allowing the myosin extending from the thick filament to bind to the thin filaments. However, the scientists found that a greater force on the thick filaments changes the arrangement of the myosin, freeing up more of the motors from their resting state (in which they are not consuming energy) in order to bind to actin and generate stronger muscular contraction. The results unmasked the muscular "gearbox" that, in skeletal muscle at least, increases the overall force of a muscle in response to load (*Nature* **528** 276).

Could such a gearbox be the molecular basis of the regulation of heart's contractility, too? In a new study, some of the same scientists have found that it does –with a surprising twist for how the regulatory mechanism at the basis of the Frank-Starling law should be interpreted. "Our results have changed the conventional paradigm of the Frank–Starling law," says Massimo Reconditi of the University of Florence.

Together with colleagues at the University of Florence in Italy and VU University Medical Center Amsterdam in the Netherlands, as well as Theyencheri Narayanan of ID02, Reconditi mounted tiny columns of cardiac muscle cells or "trabeculae" isolated from a rat's heart ventricle between force and length transducers in a physiological solution at ID02. Key to the experiment was the recent upgrade of the beamline that allowed the scientists to alter the distance between the detector and sample from 1.5 to 30 metres, enabling them to record the changes in structures from the nanometre protein scale up to the micrometre scale of the sarcomere, the 2 µm long structural and functional unit that repeats along the muscle cell. The set-up also allowed the scientists to impose different loading conditions during the contraction of the trabeculae starting from the same sarcomere length, while keeping the ends fixed or imposing length changes.

The results showed that, during muscular relaxation, myosin motors stayed in the off state. In addition, independent of the sarcomere length during the relaxation, the number of myosin motors turned on at the peak of the contraction was directly proportional to the force developed in the

cells. One of the implications of this was that, like skeletal muscle, the heart muscle has a gearbox to switch on more myosin motors, depending on the force during contraction (with the caveat that the contraction is sub-maximal, and varies under the control of several other intrinsic and extrinsic regulatory mechanisms). But another implication was that the traditional interpretation of the Frank–Starling mechanism – that the strength of contraction is determined in the relaxation phase by the filling of the ventricle and the sarcomere length – must be revised (PNAS doi:10.1073/pnas.1619484114.).

A molecular-level understanding of the

For about a century, the Frank–Starling law has described the balance of blood between the pulmonary and systemic circulatory systems, stating that the heart's contraction gets stronger the more the heart fills. According to Reconditi and colleagues, that law now needs to be reinterpreted.

heart is far from complete. Reconditi and colleagues now want to clarify the role of "accessory" proteins such as myosin binding protein-C and titin. In any case, the scientists believe that the current results bode well for studies into hypertrophic and other cardiomyopathies in which there is fault in the myosin regulatory mechanism. "The work establishes a new method to explore how cardiomyopathy-causing mutations impair the regulation of myosin motor activation, and to test specific small molecule effectors for new therapeutic interventions," says Reconditi.

Jon Cartwright

Wehinger at work on BM01.

Stretched to the full

The full elasticity tensor now comes from a single dataset.

Elasticity gives an important insight into the mechanical behaviour of crystalline materials. Measurements of it are used across the sciences, from understanding the propagation of seismic waves to defining quantum phase transitions in superconductors. It is encapsulated in the elasticity tensor, which is constructed from several elastic constants.

Determining these elastic constants isn't always easy. The two most common options are ultrasound measurements and Brillouin scattering, but the former struggles with small crystals and those placed in extreme conditions, while the latter is not always possible for opaque materials. Thanks to work by physicists at the University of Geneva and the ESRF, however, there is now a suitable alternative: thermal diffuse scattering.

Atomic vibrations

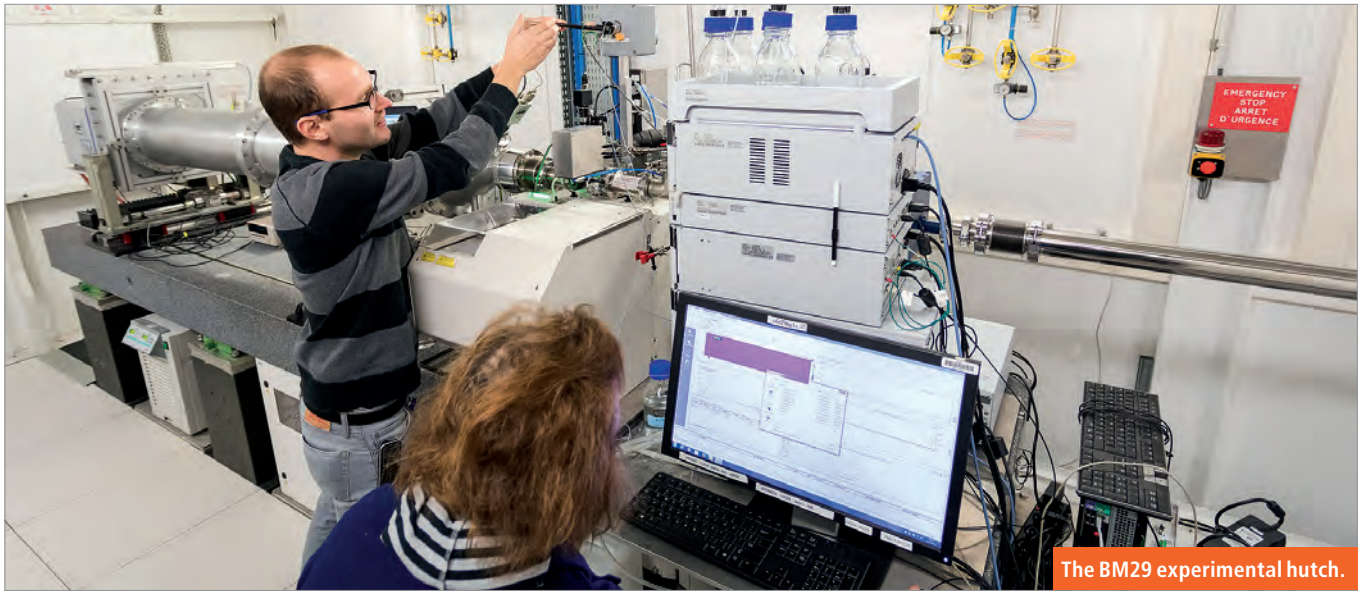
In basic terms, thermal diffuse scattering arises because elastic waves cause atoms within a crystal lattice to vibrate around their equilibrium positions. These vibrations cause the X-rays to scatter not only according to the Bragg condition, which is given by the crystal structure, but also at slightly different angles; the distribution is well defined and temperature dependent. Since the 1960s, physicists have known how to extract relative values of the elastic constants by measuring and analysing thermal diffuse scattering. Yet extracting the full elasticity tensor from a single experiment has proved challenging, because some of the elastic constants require very precise measurements of intensity at many different angles. The measurement of absolute values has been even harder.

Alexeï Bosak, the scientist in charge of the ESRF's ID28 beamline, and colleagues, first suspected that technology had advanced enough to allow the extraction of the full elasticity tensor several years ago, when comparing experimental measurements with advanced model calculations. The calculations offered a perfect description, and so the researchers set about performing a quantitative analysis using magnesium oxide – a crystal with a simple, cubic structure and therefore only a few elastic constants – as a test case, with accurate data collected at the beamlines ID29 and BM01A at slightly different temperatures. That led to the development of a "powerful and flexible" data-analysis tool. "Significant technical progress on the signal detection thanks to the recent development of large-area, noise-free hybrid pixel detectors, and the possibility of advanced signal processing – a simultaneous fit of tens of millions of data points – allows the determination of the full elastic tensor to high precision," says principal investigator Björn Wehinger of the University of Geneva in Switzerland.

The researchers tested their new tool on calcite, which has lower symmetry than magnesium oxide and which therefore has a more complicated elasticity tensor. As they had hoped, it was possible to obtain the tensor from a single crystal diffraction experiment using monochromatic X-rays.

The main advantage of using thermal diffuse scattering is that it allows scientists to measure the complete elastic properties of even very small samples, regardless of their shape, optical properties or symmetry. Furthermore, it allows elasticity to be determined together with crystal structure in the same experiment – a great benefit when scientists want to be sure that elastic and structural properties were recorded in exactly the same experimental conditions. This issue is particularly important in high-pressure research, as it is often difficult to reproduce conditions from experiment to experiment.

Jon Cartwright

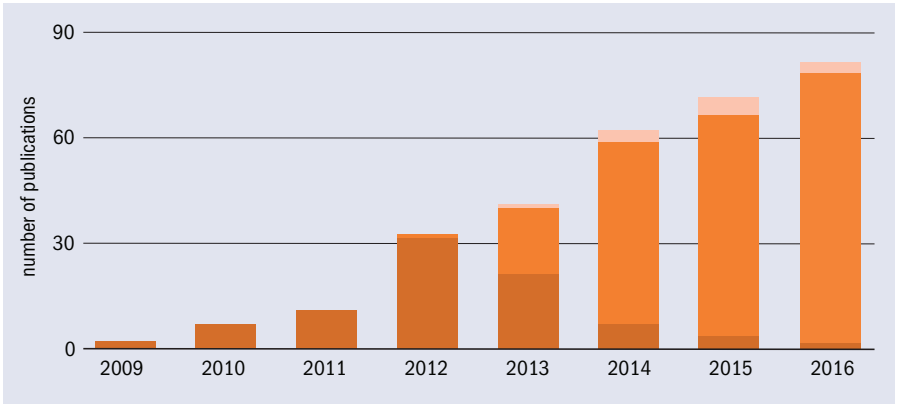


PETRA PERNOT/ESRF

The BM29 experimental hutch.

The rise of BioSAXS

Measuring X-ray scattering from solutions is becoming ever more popular, and for good reason.



The number of ESRF BioSAXS publications per year derived from ID14-3 (dark orange), BM29 (orange) and both ID14-3 and BM29 (light orange). A steady rise despite there being no BioSAXS facility at all during the first half of 2012, between the closure of ID14-3 to the opening of BM29.

Few techniques allow biologists to obtain structural information about biological molecules in their natural state. BioSAXS is one of those that can. While particles are in a solution, as they would be inside a living cell, the technique can obtain their interactions, their shape and their assembly, as well as variations of these for different solution conditions. Such validations and comparisons in solution are a must for any structural biologist who has already obtained a complete high-resolution structure by other means.

SAXS (small angle X-ray scattering) itself is not a new technique, with experiments dating back to the 1930s; its use on biological macromolecules in solution – BioSAXS – began around the same time. But in recent years, a combination of advances in sample handling, computer modelling and synchrotron sources have made BioSAXS more and more attractive. Whereas in the past, even experienced crystallographers complained that SAXS experiments required too much time and effort, now they consider it indispensable, despite its relatively low resolution (12 Å or less). The ESRF is leading the way, being the only synchrotron in the world to have a SAXS beamline dedicated to bio-solutions exclusively.

The first dedicated BioSAXS endstation at the ESRF was opened to user operation in 2008 at ID14-3. Then in 2012, as part of the ESRF Phase I upgrade programme, a new BioSAXS station was opened to users at BM29 within the structural biology "village" housing the macromolecular crystallography (MX) beamlines ID30 and ID29. The construction of BM29 has been crucial in the evolution of BioSAXS at the ESRF from a niche technique to one in which the annual number of publications has grown near-exponentially; that number is only now plateauing due to the oversubscription of beamtime (see figure above).

BioSAXS at BM29 is highly automated and offers two main experimental modes: BioSAXS with robotic sample changer (SC); or with online size-exclusion chromatography (SEC), which purifies samples just prior to X-ray exposure. In SC mode, up to a thousand measurements can be taken per day, with help from the dedicated beamline control, data-acquisition software, real-time data display and automatic data processing. Data collection parameters and results are logged and stored in ISPyBB, a BioSAXS version of the ISPyB database (see p25).

Last year, Marie Skepö of Lund University in Sweden and colleagues used the SC mode on BM29 to investigate the structure of the human salivary protein His5 in solution as a function of concentration. The experiment, which involved low quantities of a sample at very low concentration, would not have been possible without BM29's high flux and automation (*Protein Struct. Funct. Genet.* **84** 777). As the beamline continues to develop, other possibilities arise too. Adam Round at the EMBL and colleagues described the first implementation of ion-exchange chromatography for SAXS at the ESRF for the separation of similarly sized macromolecules prior to X-ray exposure (*Acta Cryst. D* **72** 1090). Sébastien Teychené of the University of Toulouse in France and colleagues integrated a microfluidics chip within BM29 to generate nanodroplets of a protein sample, allowing the study of, for example, the whole crystallisation process of proteins *in situ* (*Anal. Chem.* **89** 2282). Such examples of BM29 research underline the rise of BioSAXS – and long may it continue.

Petra Pernot, ESRF

Big prospects for tiny

The development of microcrystallography at the ESRF has led to groundbreaking discoveries in structural biology.

Since the first macromolecular structures were elucidated mid last century, macromolecular crystallography (MX) has contributed to stunning advances in our understanding of biology. From the beginning, however, growing big, well diffracting crystals has proved difficult, especially for large molecules or molecular complexes. Unfortunately, it is these large molecules that hold particular interest for structural biologists – G-protein coupled receptors (GPCRs), for example, which regulate the ways in which biological cells respond to external molecules (see p19).

The problem is that bigger molecules tend to have more heterogeneous structures, and it is all too easy for constituent proteins to "self-poison" the growth of a crystal by incorporating defects into the growing crystal in the wrong orientation. Frequently, molecules can only be induced to form very small crystals, on the order of just a few microns in one or more directions, and even then after only significant effort. A method that can take advantage of these smaller crystals is therefore of great interest to structural biologists.

This was the motivation for the development of MX microcrystallography, which opens the door to the study of small crystals through the delivery of tiny, brilliant X-ray beams, as well as tailored facilities for handling and analysis. The increased positional and spatial stability, and higher resolution sample visualisation, mean that MX microcrystallography differs markedly from classical crystallography. Before the pioneering work of the ESRF and the EMBL, however, there was uncertainty as to whether such experiments would even be possible.

Early work was performed on the ESRF's general purpose microfocus beamline ID13. While an extremely intense focused beam could be delivered to the sample position, the problem of the sample environment had to be tackled. This motivated the development of the first "microdiffractometer", which offered precise motorised movements for sample alignment, as well as beam visualisation and a high-quality on-axis microscope. Towards the end of the last century, these features, in combination with the beam properties of ID13, made microcrystallography experiments feasible for the first time, and showed that high-quality data could be obtained from microcrystals. As with traditional MX, MX microcrystallography complements other structural biology techniques such as BioSAXS (see p15) and, more recently, cryo-electron microscopy (see "Cool companion", below).

World first

In 2001, following these early successes on ID13, ESRF management began planning the construction of the world's first microfocus beamline fully dedicated to MX: ID23-2. Drawing on lessons learned from ID13, the new beamline placed a premium on beam stability and usability, with the goal of making microcrystallography accessible to structural biologists without specific microcrystallography expertise. In addition to the design and construction of the optics, the ESRF also introduced user-friendly software for data collection. Meanwhile, the EMBL contributed knowledge and microcrystallography expertise from the earlier ID13 experiments, the development of an automatic sample changer and a dedicated beamline scientist. Commissioning began in 2004, and since the start of user operation in 2005, ID23-2 has been critical for many projects.

One success story has been GPCRs, something of a holy grail in structural biology.

"The refurbished beamline will offer several key improvements."

They are involved in an enormous range of biological processes, and the elucidation of their atomic structures is of direct medical relevance. But they are also extremely complex molecules to work with, and in the early days of GPCR structural biology it was only ever possible to produce microcrystals. MX microcrystallography at ID13 and ID23-2 helped Brian Kobilka of Stanford University in the US and colleagues to explore the inner workings of a key family of GPCRs, a groundbreaking achievement for which Kobilka shared the 2012 Nobel Prize in Chemistry.

But a small X-ray beam in MX need not only be targeted at small crystals. Placed in such a beam, a larger crystal can be translated during data-collection, boosting the resolution in the final dataset. In 2015, Yuval Mazor and colleagues of Tel Aviv University in Israel used this technique to redetermine the structure of photosystem I, one of the reaction centres driving electron transport in photosynthesis. In doing so, they nearly doubled the resolution of the structure, from 4.4 Å to 2.8 Å (*eLife* doi:10.7554/eLife.07433).

This technique addresses radiation damage, a key challenge in MX microcrystallography. Because a crystal's lifetime is proportional

Cool companion

Electron microscopy (EM) has always complemented macromolecular crystallography (MX) thanks to its ability to provide structural data of large, complex molecules without the need for crystallisation. Its main drawback has been its lower resolution, but that is quickly changing with developments in cryo-EM – an EM variant in which the macromolecules under study are frozen-hydrated. Indeed, cryo-EM has approached atomic resolution, previously the domain of MX.

Like BioSAXS (see p15), cryo-EM portrays biological structures in conditions close to their native functional states. The fact that samples are frozen avoids the need for other sample preparations that could introduce artefacts, such as chemical fixation, staining or dehydration. The ice matrix has other benefits too: it mitigates the effects of radiation damage, such as mass loss, and it allows molecules to be viewed in a range of orientations.

To exploit these benefits, a new cryo-EM platform is due to begin commissioning at a user facility on the EPN campus, in the ESRF experimental hall. Continuing the existing EM activity at the IBS and the EMBL, the new Titan Krios equipped with a Quantum LS filter and phase plate will be open to users from October/November 2017, supported by scientists from the ESRF, the IBS and the EMBL.

Petra Pernot, ESRF

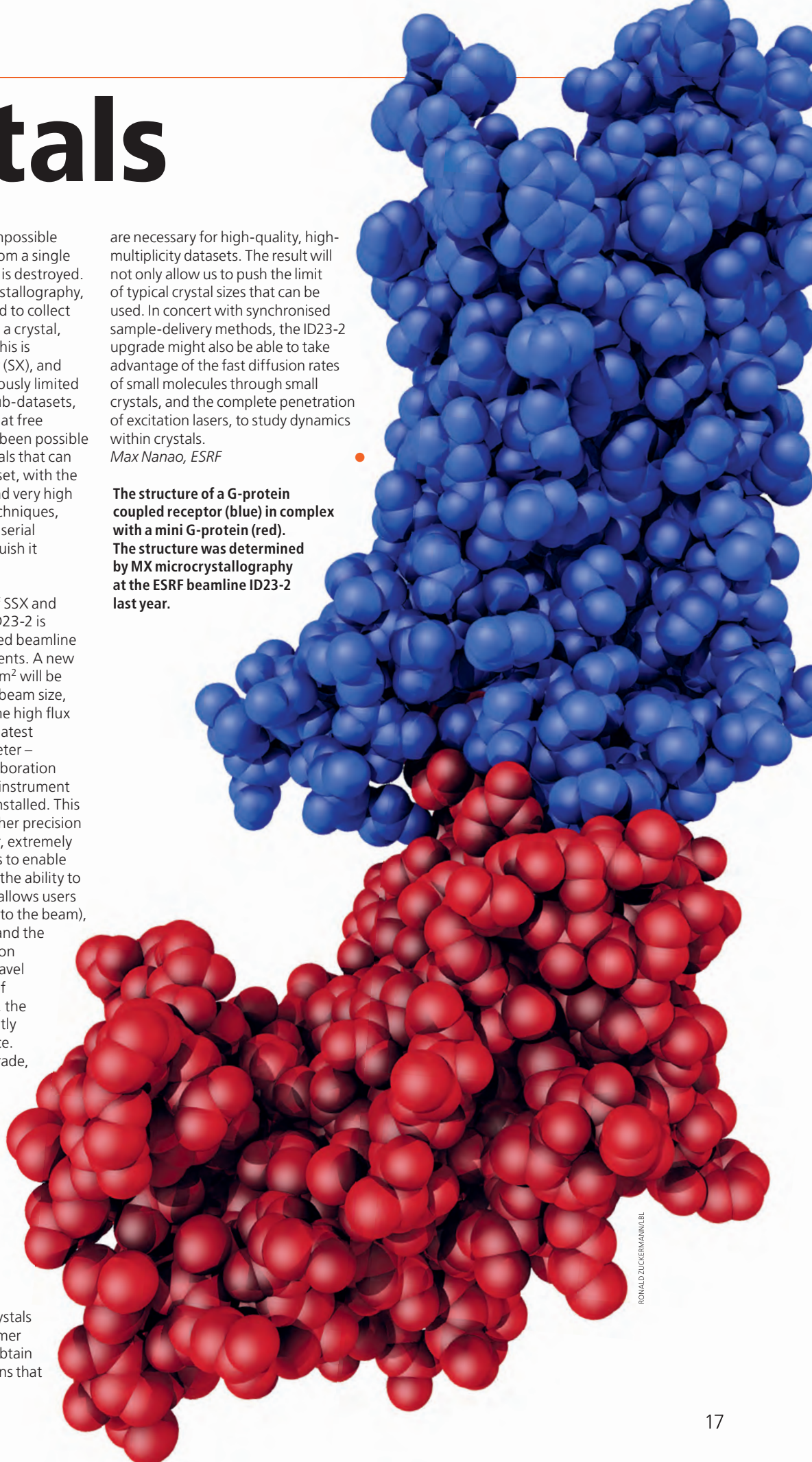
y crystals

to its mass, it is difficult if not impossible to collect a complete dataset from a single microcrystal before that crystal is destroyed. Since the early days of microcrystallography, researchers have sometimes had to collect data from multiple positions on a crystal, and/or from multiple crystals. This is known as serial crystallography (SX), and practical constraints have previously limited synchrotrons to a few tens of sub-datasets, at best. Based on the successes at free electron lasers, however, it has been possible to increase the number of crystals that can be used to produce a final dataset, with the use of new analysis methods and very high throughput sample-delivery techniques, commonly termed synchrotron serial crystallography (SSX) to distinguish it from X-FEL serial femtosecond crystallography (SFX).

In order to take advantage of SSX and analyse even smaller crystals, ID23-2 is being upgraded. This refurbished beamline will offer several key improvements. A new beam size of roughly $1.5 \times 1.5\ \mu m^2$ will be added to the existing $7 \times 5\ \mu m^2$ beam size, but with approximately the same high flux as the original. In addition, the latest generation of microdiffractometer – unique in the world, and a collaboration between EMBL and the French instrument manufacturer Arinax – will be installed. This diffractometer offers much higher precision than the current diffractometer, extremely fast and repeatable movements to enable rapid scanning across samples, the ability to use a kappa movement (which allows users to re-orient the sample relative to the beam), improved sample visualisation and the ability to work with crystallisation plates. Finally, a large vertical travel will accommodate the testing of other sample delivery methods, the development of which is currently proceeding at a remarkable pace.

The design of the ID23-2 upgrade, which is expected to be in user mode this month, has since its inception been planned in the context of the EBS. As such, the function of the beamline will be essentially unchanged between the current and the EBS lattice, although the latter will bring benefits – notably a four-fold increase in flux at both beam sizes to allow for higher rates of sample processing, as well as a moderate reduction in beam sizes to analyse smaller crystals or positions on crystals. This former improvement will be critical to obtain the numerous diffraction patterns that are necessary for high-quality, high-multiplicity datasets. The result will not only allow us to push the limit of typical crystal sizes that can be used. In concert with synchronised sample-delivery methods, the ID23-2 upgrade might also be able to take advantage of the fast diffusion rates of small molecules through small crystals, and the complete penetration of excitation lasers, to study dynamics within crystals.

Max Nanao, ESRF



The structure of a G-protein coupled receptor (blue) in complex with a mini G-protein (red). The structure was determined by MX microcrystallography at the ESRF beamline ID23-2 last year.

RONALD ZUCKERMANN/LBL

How to suppress diabetes

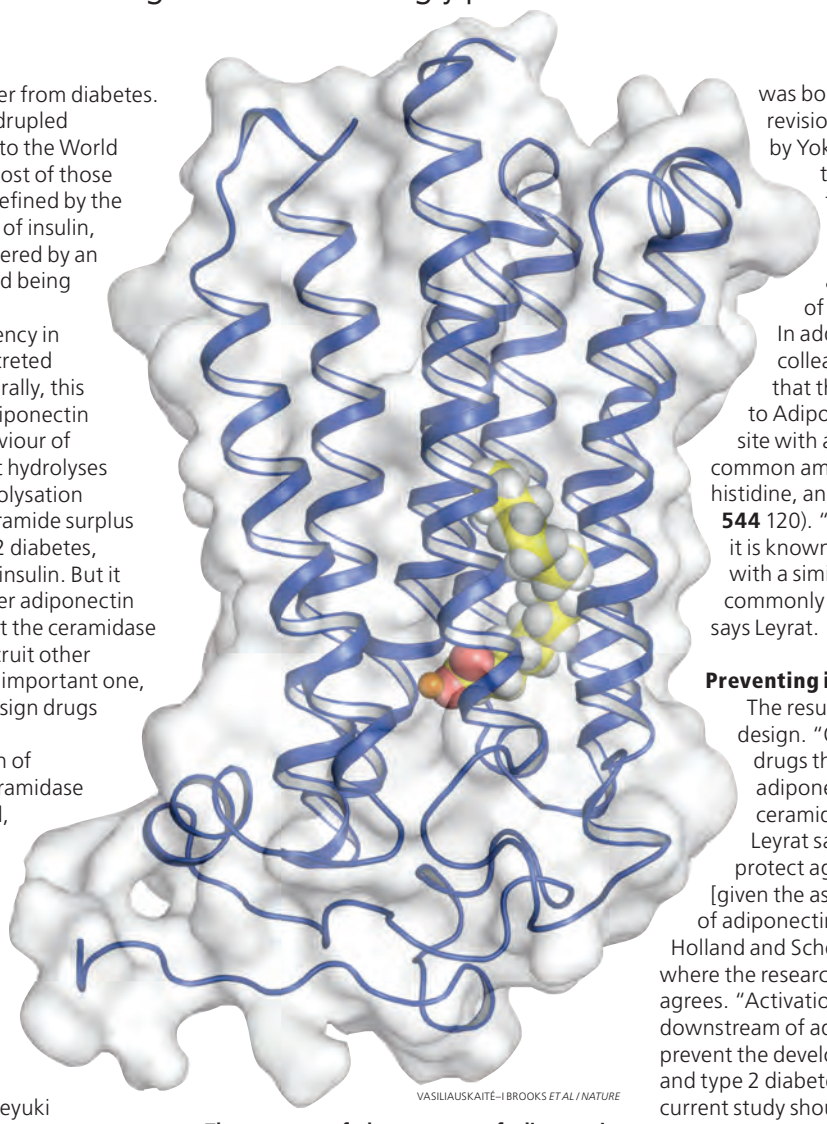
A study of a fat-derived hormone at the ESRF could help design drugs for an increasingly prevalent disease.

More and more people suffer from diabetes. The number has nearly quadrupled since the 1980s, according to the World Health Organization, and most of those are suffering from type 2. Defined by the body's inability to make use of insulin, type 2 diabetes can be triggered by an unhealthy diet, inactivity and being overweight.

It is also linked to a deficiency in adiponectin, a hormone secreted by adipose – body fat. Generally, this is thought to be because adiponectin receptors mediate the behaviour of ceramidase, an enzyme that hydrolyses ceramide, a lipid. Such hydrolysation forestalls that effect of a ceramide surplus which is a hallmark of type 2 diabetes, namely a desensitisation to insulin. But it has never been clear whether adiponectin receptors themselves exhibit the ceramidase activity, or whether they recruit other proteins. The question is an important one, as it might be possible to design drugs that replicate the function.

In 2011, when the relation of adiponectin receptors to ceramidase activity was first established, William Holland and Philipp Scherer at the University of Texas Southwestern Medical Center in Dallas, US, and colleagues believed that proteins were recruited, although at that time the structures of the adiponectin receptors were not known. That changed in 2015 when Shigeyuki Yokoyama at the RIKEN Systems and Structural Biology Center in Yokohama, Japan, and colleagues managed to produce crystals of the receptors. According to Cédric Leyrat of the University of Montpellier in France, however, Yokoyama's group misinterpreted the crystallographic data, and also missed the possibility that enzymatic activity was lurking in the receptors' zinc binding sites.

This is exactly where Leyrat and colleagues, led by Sébastien Granier of the University of Montpellier, have now found evidence for such activity. Using macromolecular microcrystallography (see p16) data collected at the ESRF beamline ID30B, the researchers solved the structure of one of the two adiponectin receptors, AdipoR2, and discovered that the receptor was bound to a fatty acid; their revision of the structure solved by Yokoyama's group showed the same. The presence of a fatty acid trapped within a protein suggests catalytic activity, because a fatty acid is one of the products of the ceramidase reaction. In addition, Granier, Leyrat and colleagues' structure showed that the fatty acid was bound to AdipoR2 close to a zinc binding site with a particular composition of common amino acids: three residues of histidine, and one of aspartate (*Nature* **544** 120). "Based on the literature, it is known that zinc binding sites with a similar composition are most commonly found in enzymes," says Leyrat.



VASILIAUSKAITĖ–I BROOKS *ET AL* / *NATURE*

The structure of a key receptor of adiponectin, AdipoR2, reveals the presence of a bound fatty acid (spheres, centre) at a zinc binding site, a signature of enzymatic activity. The lack of such activity, which influences the onset of type-2 diabetes, could be targeted by new drugs.

"The ESRF's mesh and collect method allowed us to detect the fatty acids."

Preventing insulin resistance

The results are good news for drug design. "One can imagine designing drugs that mimic the function of adiponectin, by activating the ceramidase activity of AdipoRs," Leyrat says. "Such drugs might protect against type 2 diabetes, [given the association] with low levels of adiponectin." An opinion piece by Holland and Scherer in the journal *Nature*, where the researchers' study was published, agrees. "Activation of signalling pathways downstream of adiponectin might help to prevent the development of insulin resistance and type 2 diabetes," they write. "The current study should greatly aid the quest to design drugs that promote AdipoR activity."

Yet the results also show off the capabilities of microcrystallography, and in particular the "mesh and collect" method in which many small crystals can be harvested directly from crystallisation drops with a mesh sample holder. In the next step, a two-dimensional scan with a low-intensity X-ray beam at cryogenic temperatures establishes the positions of individual crystals. Partial diffraction datasets of each of these crystals can then be recorded, and finally merged into a complete dataset for structure-solving. "The mesh and collect method at the ESRF has allowed us to detect [the] fatty acids," says Granier. "We couldn't have done it without this method, as our crystals were too small."

Jon Cartwright

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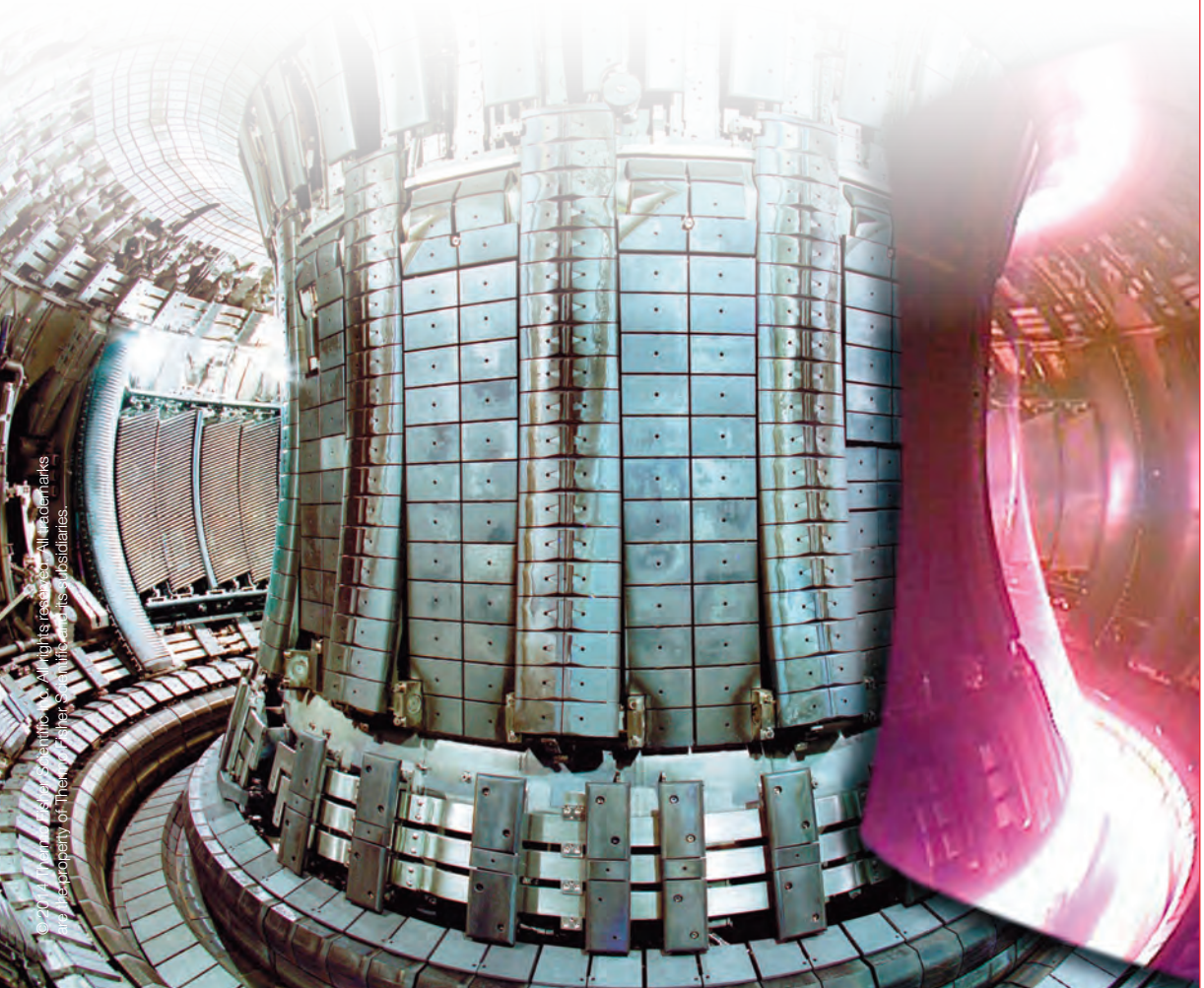

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Riding the protein pipeline

Thanks to a new EMBL–ESRF service, industrial clients can now send a protein solution and expect diffraction data in return.

Thirty years ago, it was common practice for industry researchers to grow their protein crystals at home then take them to a synchrotron source and carry out experiments in person. At the turn of the century, the process became more cost-effective, as industry cut out the human escort and began mailing crystals to synchrotrons for use in remote-access data-collection sessions.

Now, thanks to an automated "pipeline" service being pioneered by the EMBL and the ESRF, the process is set to become even more streamlined. A connection of the EMBL's CrystalDirect and the ESRF's MX beamlines supported by the in-house expertise of both institutions, will give industrial clients worldwide the option to send clean proteins to Grenoble in return for diffraction data. The CrystalDirect-MX beamline pipeline will link crystal generation and automatic crystal harvesting with intelligent diffraction data collection; all the client has to worry about is dropping the proteins in the mail, watching the results being generated and, finally, downloading them for use in downstream structure solution and refinement processes. Indeed, the client can remotely control and monitor the whole process via the Crystallisation Information Management System (CRIMS) and ISPyB experiment-tracking software. "There is no more convenient way to obtain high-quality, high-throughput crystallography data," says José Marquez, head of the EMBL high throughput crystallisation (HTX) facility.

Though the assembly of the pipeline is ongoing, all its individual elements are already in place. On the EPN campus in Grenoble, the EMBL has been able to crystallise proteins robotically with its HTX facility for about a decade; in the past two years, it has introduced the automated laser-based technology for crystal harvesting and cryo-cooling, too. Meanwhile, the ESRF has for several years been able to offer fast-turnaround screening, analysis and data-collection via its automated macromolecular-crystallography beamlines, MASSIF-1 and MASSIF-3; recently, that automation has spread to the remainder of the MX beamlines.

Complete security

In principle, combining the EMBL's and the ESRF's capabilities into a new industry service will be straightforward. But as Ed Mitchell, head of business development at the ESRF, explains, there are pragmatic issues that need to be overcome – making the commercial offer between the two institutions clear and simple, for example, and working out how to make the pipeline function on large-scale projects. He and his colleagues are also well aware that the service will require something of a cultural change for pharma and biotech, as they will need to feel that their prized samples will be taken care of. "We need to reassure them there's security and confidentiality as well as the production of the best quality diffraction data," Mitchell says.

Currently, the EMBL and the ESRF are piloting the pipeline with the German pharmaceutical company Merck–Serono, which has helped to validate and adapt the pipeline to the specific needs of industry. "EMBL did a number of feasibility studies for industrial partners, all of which want to come back for larger projects," says Jürgen Bauer from EMBLEM, EMBL's technology transfer arm. "There's also interest from several other companies." An equivalent service for academic users is already available through iNEXT, a system funded by the European Commission.

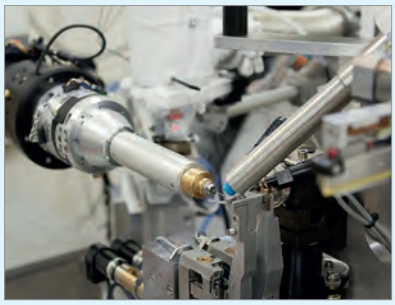
"The pipeline democratises access to Structural Biology," Mitchell explains. "You no longer need to be a skilled crystal grower and harvester or be experienced in diffraction data collection; you can now get others to carry out these steps for you and use that time for other, more valuable things. We hope the pipeline will open up drug discovery and fragment screening not just to big companies but also to smaller companies that don't currently have the internal resources. We want to provide a global service for all our potential clients."

Jon Cartwright

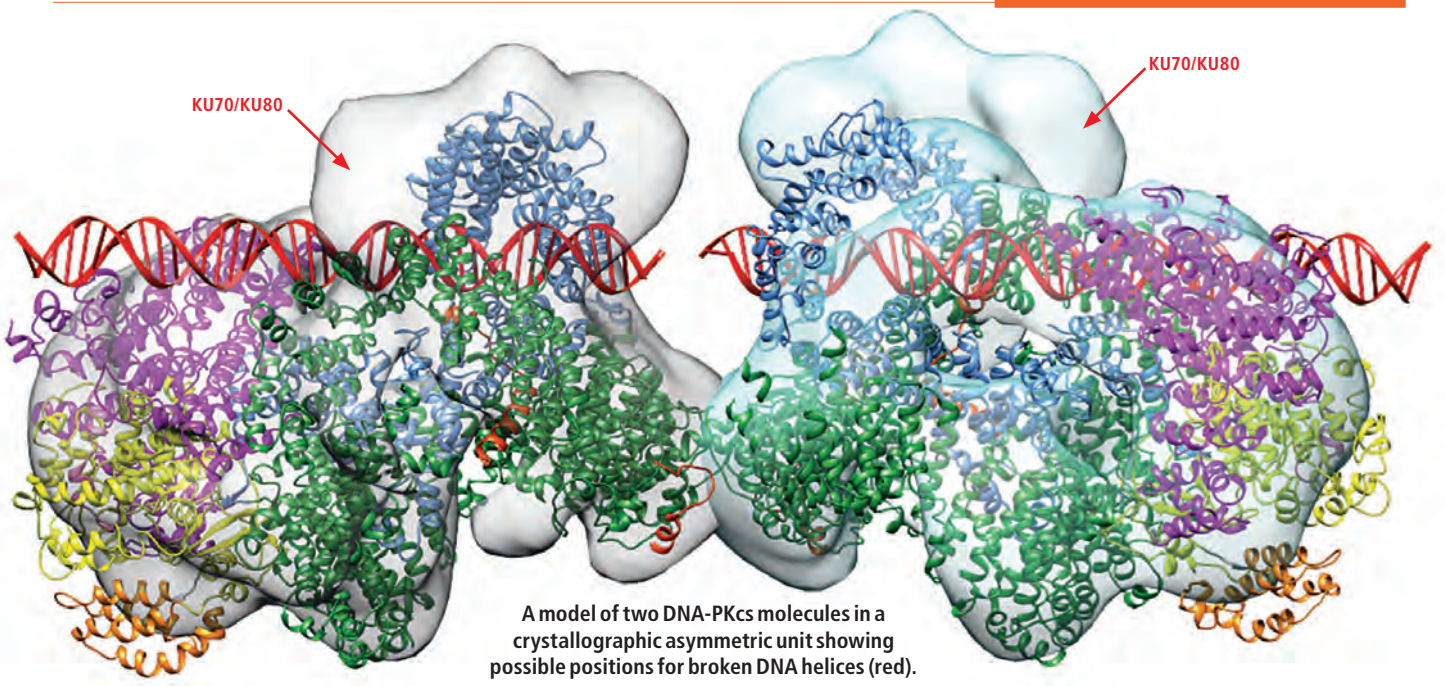
1 **A company sends a purified, concentrated protein sample to the EPN campus in Grenoble.**

2 **Expert technicians at the EMBL's HTX facility generate crystals of the protein, which are then harvested robotically.**

3 **The ESRF's automated MX beamlines are used to screen and analyse crystals before intelligently collecting full diffraction data.**



4 **The diffraction data can be downloaded by the client using ISPyB.**



A model of two DNA-PKcs molecules in a crystallographic asymmetric unit showing possible positions for broken DNA helices (red).

Tying up loose ends

An X-ray study of how DNA is repaired could help develop drugs for cancer.

DNA takes quite a beating. Every day, sunlight, chemicals and even mechanical stress cause thousands of breaks within the chromosomes inside our cells. Left alone, such breaks prevent the genes from being read correctly, leading to mutations in newly produced cells and, in the worst case, cancer.

Fortunately, our bodies are well equipped to handle DNA breakages. Every cell contains enzymes and proteins that maintain chromosomes by repairing DNA or, failing that, initiating a self-destruct process that prevents severely damaged genes from being passed on to new cells. For clean, double-strand breaks in DNA, there are two principal repair mechanisms known. The first requires the presence of an undamaged sister chromosome-fragment or "chromatid", which, via a process known as homologous recombination, acts as a template to reconstruct the gene sequence. Should that chomatid be absent, the second option comes into play. Known as non-homologous end joining, this mechanism involves the broken ends of DNA being joined together directly.

Understanding non-homologous end joining could be crucial for the development of drugs that tackle runaway, cancerous instances of the mechanism. That was the goal of a recent ESRF study by biochemists Tom Blundell, Lynn Sibanda and Dima Chirgadze of the University of Cambridge in the UK, as well as David Ascher, who is now based at the University of Melbourne in Australia. To the beamlines ID23-1 and ID29, they brought crystals of a protein known as Ku, which assembles on broken DNA ends and mediates the process of non-homologous end-joining, in complex with an enzyme known as DNA-PKcs, which among other things acts as a platform for repair. "We wish to understand this complex series of events, which are important for keeping human cells alive," says Blundell. "Breaks are occurring regularly, [and] they occur more often in cancer, where much of the individual cell activity is lost."

Largest protein structure

Obtaining the structure wasn't easy. DNA-PKcs in particular is a huge enzyme containing some 4000 amino acids; in complex with Ku it ranks, Blundell says, as the longest structure of a single-chain globular protein defined by X-ray crystallography. "The crystals were rather weakly diffracting to X-rays and we needed the ESRF's help to get good diffraction patterns, in order to solve the structure," he adds.

DNA-PKcs has a kinase or head region – a part that catalyses the transfer of a phosphate group from the compound ATP – and like other kinases its active site contains an activation as well as a catalytic loop. Access to the active site, however, appears to require substantial conformational changes that are instigated when the Ku protein binds to a different part of the protein, the scientists say. This binding site is close to a binding site for another protein, BRCA1, which the scientists think influences the Ku binding in order to activate the alternative, template-based repair of homologous recombination.

"We needed the ESRF to solve the structure."

Putting it all together, Blundell and colleagues believe that they now have a much clearer picture of non-homologous end joining. First, a Ku protein binds to the broken double ends of a strand of DNA and recruits the DNA-PKcs enzyme, in doing so opening up the latter's active site. The DNA-PKcs enzyme then goes through a well established process known as phosphorylation, which raises a flag to signal the damage to other enzymes. In the next step, there is a competition between BRCA1 and Ku to determine which of the two repair pathways is to be used for DNA. Finally, other enzymes take their turns to administer the repair, before the Ku and DNA-PKcs is released (*Science* **355** 520).

Blundell and colleagues now want to investigate the structure of DNA-PKcs in complex with some of these other components, to understand the repair process fully and, they hope, discover medical benefits. "We will use the structure to guide targeting of this system with new drugs," Blundell says.

Gary Admans and Jon Cartwright

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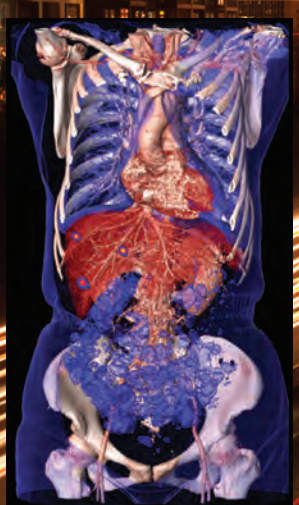

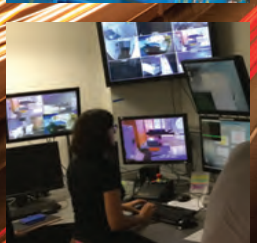

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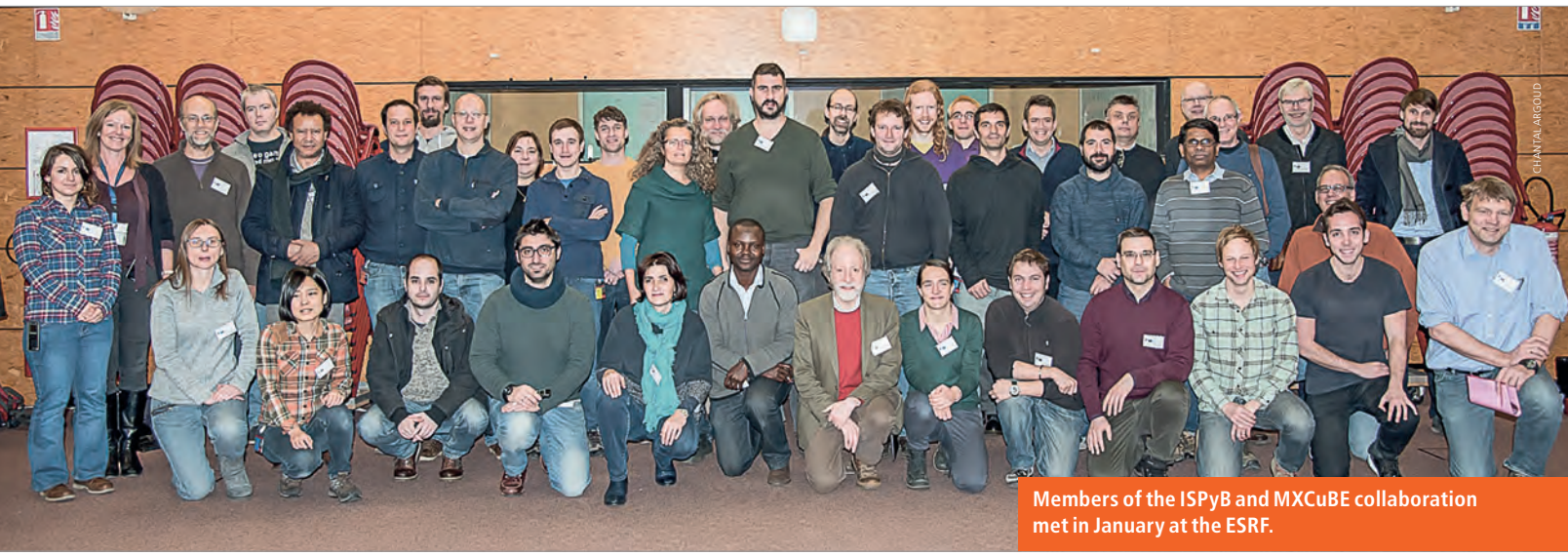

Members of the ISPyB and MXCuBE collaboration met in January at the ESRF.

The management system ISPyB plans to offer even more support for structural biologists.

Structural biology has always been a data-intensive science. These days, however, individual research groups are analysing several thousand samples at synchrotrons every year. The resultant deluge of data can be hard to keep track of – especially during an experiment, when researchers want to be confident that they are getting the data they need in order to answer the biological questions they are asking.

The Information System for Protein crystallography Beamlines (ISPyB), which has existed for almost two decades, efficiently manages and stores structural-biology data – initially from macromolecular crystallography (MX) experiments, but more recently from BioSAXS, cryo-EM and other techniques that have similar workflows to MX. A web-based system, ISPyB, in conjunction with a graphical user interface for beamline control, MxCUBE, aims to help users to make sure that the best possible experiments are performed and that the best possible data are fed downstream for structure determination and analysis. ISPyB has continually evolved since its launch, and several synchrotron sites have recently joined the ESRF and Diamond Light Source (DLS) in the development of common data models that will make the data management easier and more streamlined.

Data management for MX experiments at the ESRF started in 2001 with the development of a prototype, PXWeb, which had a rather limited scope and functionality. ISPyB was born in 2005 as the result of collaborations initially between the ESRF and e-HTPX (a UK-based e-science project), then between the ESRF and DLS. These collaborations improved the sample management, using barcodes to track the location of samples from the user lab to the synchrotron, to the beamline sample-changing robots, and back to the user lab. The collaborations also enhanced the recording and storage of metadata pertaining to individual experiments, to include all relevant experimental parameters, snapshots of the sample as mounted on the goniometer and diffraction image thumbnails. This information allows researchers to better understand their results and, should the need arise, reproduce the conditions under which an experiment was carried out. Perhaps most impressively, ISPyB can also display the results of online data processing pipelines occurring during an experiment, allowing a user to quickly assess the quality of measurements in a dataset and, in so doing, make decisions on what measurements to take next.

In the past few years, several other European synchrotron sources (SOLEIL in France, EMBL-HH in Germany and MAX-Lab in Sweden) have installed the ISPyB software, and other facilities have expressed a wish to join them. Structural biologists rarely carry out all their experiments at a single synchrotron site and having similar tools at different sites makes life much easier. Moreover, joining expertise from different synchrotrons rather than reinventing the wheel at each site is clearly of benefit to both users and synchrotron sites.

“Joining expertise is clearly of benefit to both users and synchrotron sites.”

Common model

At the beginning of 2017, eight parties – CELLS in Spain, HZB in Germany, Global Phasing in the UK, MAX-IV in Sweden, the ESRF, DLS, SOLEIL and the EMBL – signed an agreement to collaborate on the development of a common data model for ISPyB. Although each site currently stores its users’ metadata locally, the idea is to allow users to log in to any database from any site, in order to browse all experimental data related to a project, including those from techniques complementary to MX. One can also imagine, thanks to ISPyB, that partial datasets collected at various sites could be combined to produce a final dataset for structure solution.

The life of the ISPyB project has reached a phase where the ESRF and DLS are no longer isolated and developing the system at their own pace. The six new sites that have recently joined the project are now actively participating by proposing solutions and contributing blocks of code. Meanwhile, tools such as a software-development platform on Github have already been put in place to help the common development of the database. The sharing of resources resulting from this new collaboration forms a very sound basis for the further enrichment of ISPyB and will be of clear benefit to researchers in structural biology throughout Europe.

Stéphanie Monaco, ESRF

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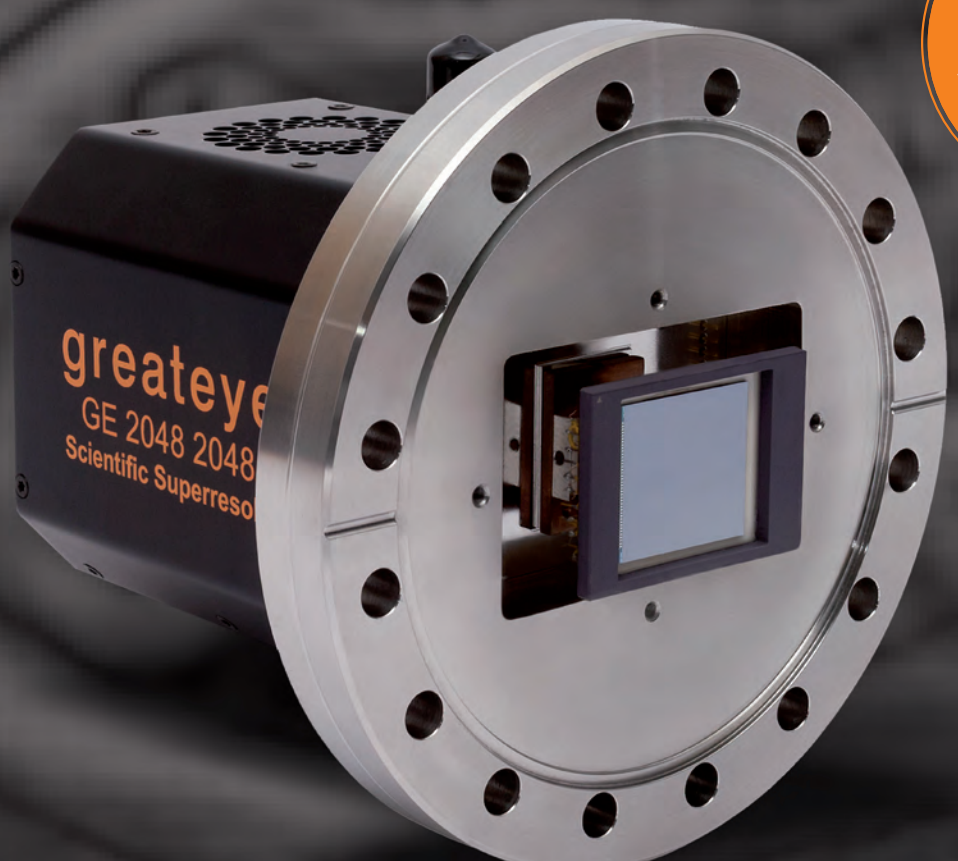

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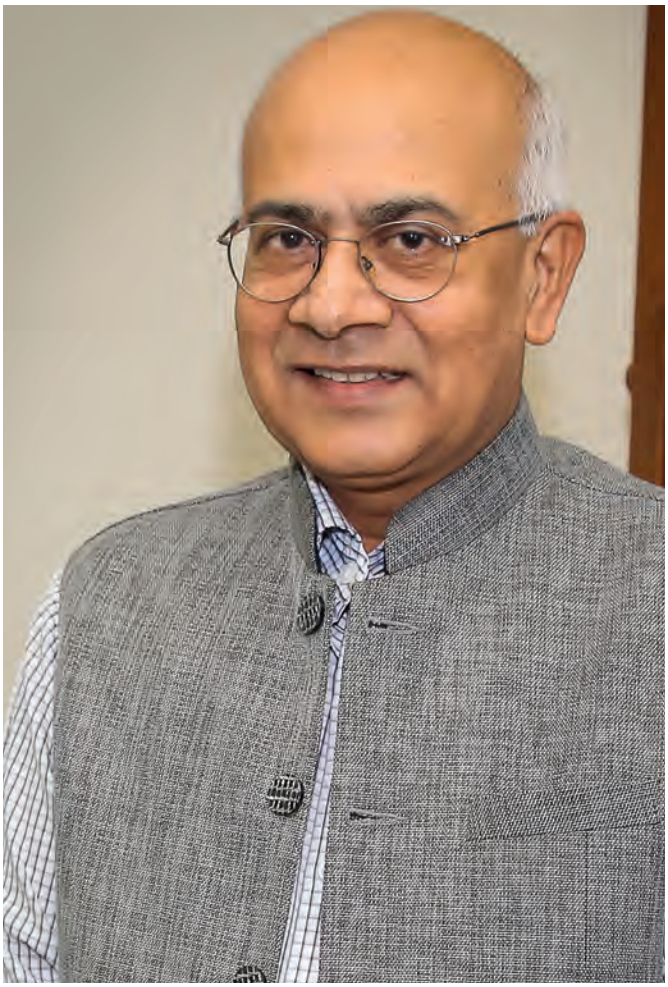
A boost for India

As a promoter of the India–ESRF partnership, **Dinakar Salunke** has witnessed the benefits of the synchrotron for Indian structural biology.

In the 2000s, says Dinakar Salunke, structural biology in India was effectively stagnating. After many delays, the country finally had its own synchrotron, Indus-1, but it operated at relatively low intensity; meanwhile, scientists found it difficult to travel abroad to collect diffraction data. So it came as a welcome surprise when, in 2009, the country was offered the joint use with the EMBL of an ESRF beamline, BM14, after the departure of the previous partner, the MRC Laboratory of Molecular Biology in Cambridge, UK. The stagnation of India's structural-biology research was over, says Salunke, and "the ESRF partnership opened the gates to more challenging problems to be addressed".

Salunke was chosen to work towards the nascent ESRF–India partnership. As it turned out, however, BM14 wasn't quite enough for the country's scientists. True, the annual number of protein structures uploaded to the Protein Data Bank nearly doubled, from about 125 to 250. But there uploads began to plateau. The reason, says Salunke, is that BM14 is not as bright as some of the other beamlines, and is less able to tackle very small crystals and membrane proteins, which were of growing interest. Given the "very comfortable" relationship experienced with the ESRF so far, he says, the Indian science ministry therefore sought membership with the synchrotron, so that its scientists would be able to use all the beamlines (see In Brief, p6).

ESRF membership is part of a broader strategy within the Indian science ministry to better integrate Indian scientists with scientific communities abroad; the country has also recently become a member of the European Molecular Biology Organization, for example. The move has been received well among Indian structural biologists, who have been "very excited" about their new freedom to use the ESRF, and in particular the forthcoming cutting-edge cryo-EM facility, says Salunke. "There is a lot of excitement. We are already familiar with the ESRF, so we're looking forward to the expanded scope."



DIRECTOR SECRETARIAT, ICGEB, NEW DELHI

Dinakar Salunke in brief

Born: 1955, Belgaum, Karnataka, India.

Education: BSc physics, mathematics and statistics (1976), MSc physics (1978), Karnataka University, Dharwad; PhD molecular biophysics, Indian Institute of Science, Bangalore (1983).

Career: Postdoc, Brandeis University, Massachusetts, US (1985); staff scientist, NII (1988); Deputy Director, NII (2008–2010); Executive Director, RCB (2010–2015); Director, ICGEB, New Delhi (2015–).

"We're looking forward to the expanded scope at the ESRF."

For most of his career in his home country, Salunke has been a leader as much as a scientist. For nearly two years he has headed the International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi. Before that, as the founding executive director he helped establish the Regional Centre for Biotechnology (RCB) – an education, training and research institution of the Indian government, under the auspices of UNESCO and the larger biotechnology campus in Faridabad, which also includes the Translational Health Science and Technology Institute (THSTI).

As is common among scientist-turned-leaders, Salunke has at times felt the loss of time he can devote to research. "I recognise that, having taken up these leadership roles, my engagement in science is reduced to some extent," he says. To counter the problem, and to ensure he "leads from the front" in recruiting young scientists to the field, he has made sure that he has always had an actively running lab at the ICGEB and the RCB.

While his interests in structural biology are varied, his major focus has been in immunology since the start of his independent career, an area that came about largely by accident. A physicist by training, he was inspired to cross over into biology by the work of one of the earliest and greatest biophysicists, G N Ramachandran; after his postdoc, a position came up as a staff scientist at the National Institute of Immunology (NII) in Delhi. "To be honest, I was looking at all possible options," he says, "because I realised that it doesn't matter what problem you approach, you can address it and find out interesting things."

Jon Cartwright

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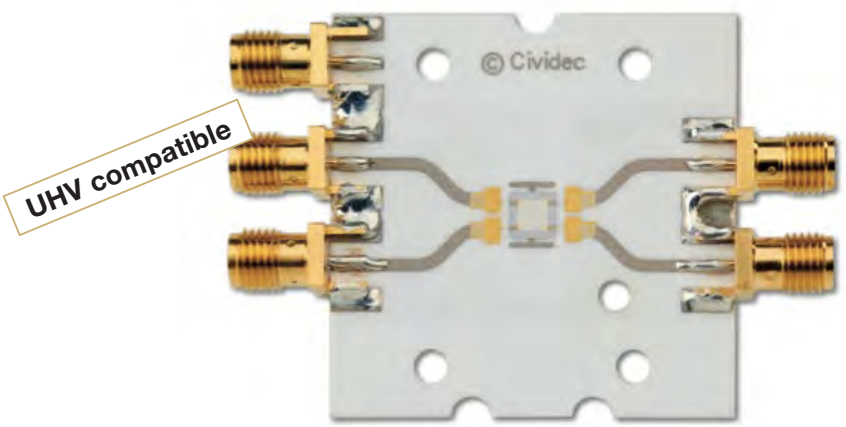

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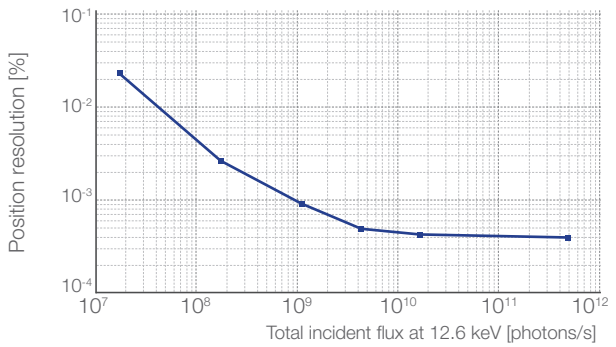

Figure: Measurements at Diamond Light Source Ltd., UK, show the measured position resolution at 1 kHz bandwidth for various beam intensities of the 12.6 keV photons. A position resolution of better than 0.1% of beamsize is obtained even for an incident flux as low as 10^9 photons/s.

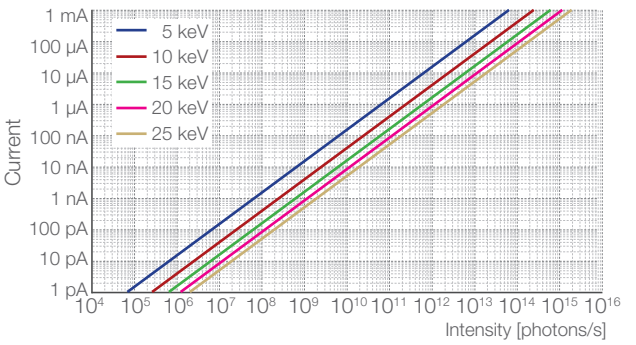

Figure: The detector response as a function of the photon energy and intensity demonstrates the wide dynamic range of the XBPM System in combination with the C8 Electrometer Amplifiers.

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How to breathe easy

With the ESRF's intense X-rays, Prior PLM Medical creates internal videos of asthma inhalers.

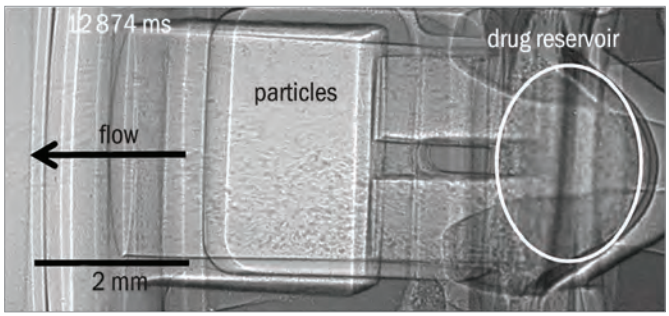
If you don't have asthma, the chances are that you know someone who has. According to the World Health Organization, more than 300 million people worldwide suffer from it and other respiratory diseases, such as chronic obstructive pulmonary disorder. Yet these diseases are surprisingly hard to treat directly, as common inhalers – either pressurised metered dose inhalers (PMDIs) or dry powder inhalers (DPIs) – often only deliver 10–20% of released medicine to the lungs.

This lack of efficacy is thought to be due at least partly to the behaviour of the plume of medicine before it exits an inhaler, which is hard to study. While X-rays are well-suited to look inside an inhaler's enclosure, industrial computed-tomography scans are too slow for the speed of medicine release. For that reason, Ireland-based medical-technology company Prior PLM Medical have come to the ESRF, where beamlines have the intensity to give sufficient temporal resolution.

Prior physicist Alan McKiernan brought PMDIs with a range of canisters, propellants and valve types to the ESRF beamline ID19, along with a custom-built Prior fixture to shake and activate them. He and his colleagues performed phase-contrast imaging to construct a video of a dose release from each inhaler combination, revealing the behaviour of the propellant mixture, as well as mechanical interactions, inside the canister and actuator. Despite the low density of the polymers, propellants and drugs involved, the technique gave "excellent" contrast, McKiernan says.

"Our work at the ESRF has allowed us to see what's happening inside both developmental-stage and off-the-shelf commercial inhaler devices, to enable our clients to make informed design decisions," he adds. "We also use the facility for our own internal R&D programmes, and are very excited by the prospect of the ESRF upgrade, the Extremely Brilliant Source."

Jon Cartwright



PRIOR PLM MEDICAL

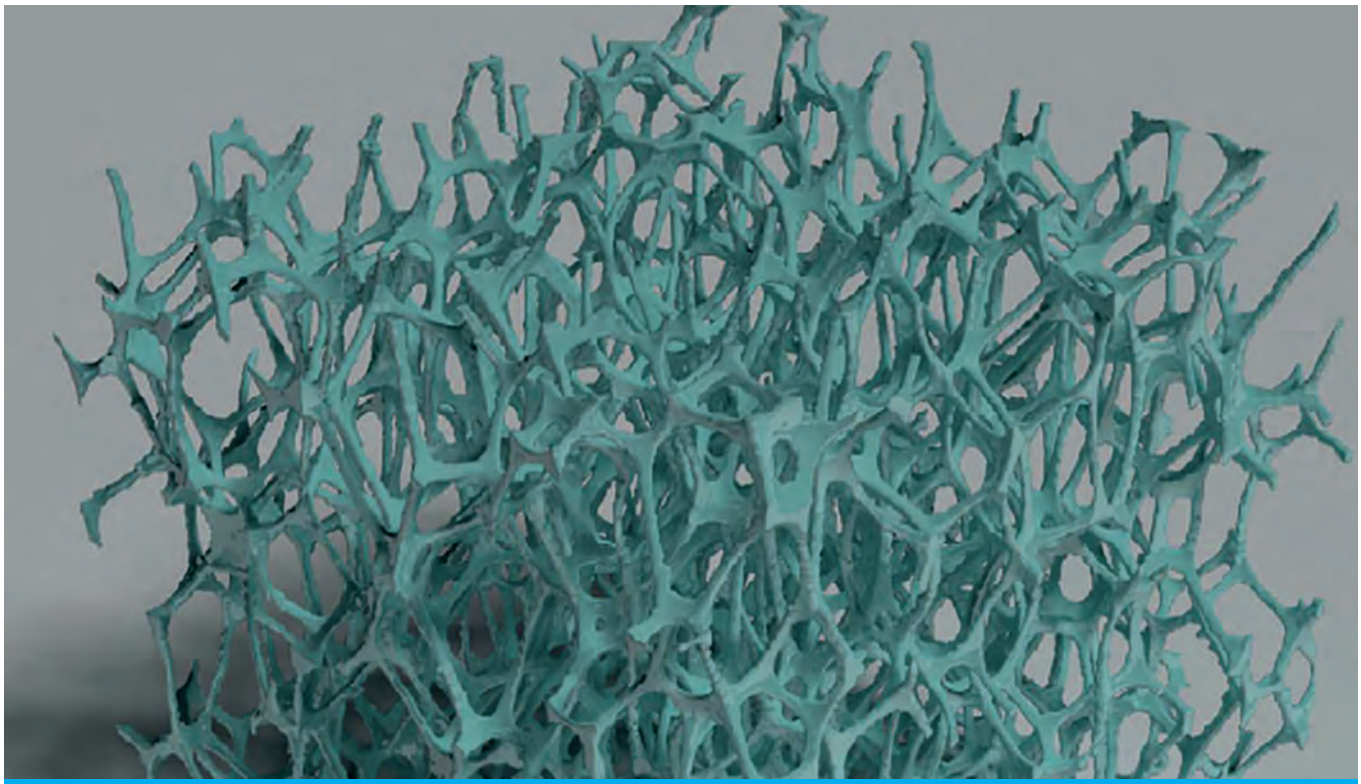
High-speed phase-contrast X-ray imaging of a dry-powder inhaler releasing a dose.

Asthma inhalers only manage to deliver a small fraction of drugs to the lungs. Understanding the behaviour of the drugs as they are released could improve designs.

Movers and shakers

Nina Rohringer and **Melanie Schnell** were named in April as two new leading scientists in the photon science department at the German Electron Synchrotron (DESY). An expert in ultrafast, non-linear X-ray physics, Rohringer (top) recently became a professor at the University of Hamburg in Germany, a position she will continue to hold. At DESY she hopes to carry out new types of experiments at X-ray free electron lasers, as well as quantum-mechanical processes at high temporal resolutions using X-ray spectroscopy. Meanwhile, Schnell (bottom) will retain her recent appointment as professor at the Christian Albrechts University of Kiel in Germany, and will use her expertise in the structure and dynamics of molecules to develop new methods in the field of rotational spectroscopy. She also plans to investigate which chemical processes can take place in the harsh environment of interstellar space. Both Schnell and Rohringer headed research groups at the Max Planck Institute for the Structure and Dynamics of Matter on DESY's Hamburg campus before their latest appointments.

Bernd Rechr was appointed the provisional scientific director of Helmholtz-Zentrum Berlin (HZB) in Germany, which oversees facilities such as the BESSY synchrotron, in May. A physicist by training, Rechr has spent his entire career working on renewable energy, and in particular solar cells; he holds more than 10 patents and has published more than 300 articles in peer-reviewed journals. Since 2006 he has headed the Institute for Silicon Photovoltaics at HZB, and he has previously held positions at the Jülich Research Centre and the Technical University of Berlin in Germany, as well as the University of Ljubljana in Slovenia. His predecessor at HZB, Anke Kaysser-Pyzalla, has taken up the presidency of the Technical University of Braunschweig in Germany, where she becomes the first woman to head one of Germany's nine leading technical universities.



JOACHIM OHSER/H_DA

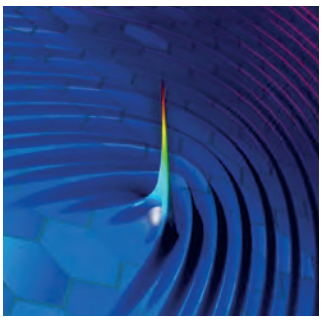
Life-saving sponge?: An open-celled material like this, imaged using time-resolved microtomography at the ESRF beamline ID19, has the potential to treat those suffering from leukaemia by filtering cancerous cells from the blood. Normally cancerous cells are separated by centrifuging the blood, or sorting cells via fluorescence techniques, but "chromotographic" filtering with microscopic sponges could be faster and more effective. A team of researchers from the University of Applied Sciences in Darmstadt, Germany, the University of Lorraine in France and the pharmaceutical corporation MERCK have been studying what happens inside the sponges during their operation, to try to find out what types of pore and coating produce the best results. They found that the shape of the inner surface of the sponge plays a key role in the trajectory of blood particles.

In the corridors

Hat-trick for industry

Johnson Matthey has long enjoyed the ESRF's facilities, and now more so than ever. On 21 April, the British chemicals and sustainable-technologies company was working on three ESRF beamlines at once: one proprietary study at ID21 on sulphur speciation on poisoned catalysts; one peer-reviewed project at BM26A on high-temperature water gas shift catalysts; and a further peer-reviewed project at ID15 on methane dehydroaromatisation. Such a hat-trick is thought to be an industrial first for the synchrotron. *ESRFnews* will explore Johnson Matthey's industrial work in a forthcoming issue.

X-rays could be handheld



Engineers at the Singapore Institute of Manufacturing Technology (SIMTech) and the Massachusetts Institute of Technology in the US claim that the wonder material graphene could one day become a handheld, directional source of X-rays. According to the numerical simulations performed by SIMTech's Liang Jie Wong and colleagues, electrons incident on a sheet of graphene that has been deposited on an insulator will interact with the graphene's surface "plasmons". The result is a "wiggling" of the electron motion, which generates X-rays at a frequency of the engineers' choosing. "Developing an intense X-ray source that can fit on a table or be held in one's hand would potentially revolutionise many areas of science and technology," says Wong. Small X-ray sources already exist, particularly in medical diagnostics, but they are wasteful in that they emit X-rays in all directions; also, they are not tuneable.

ESRF marches for science

The directors of the ESRF have joined scientists from over the world by supporting the "March for Science", a campaign to highlight the role of science in policymaking. The march itself was on 22 April in Washington DC, US, where attendees highlighted the universal principles of science, scientific investigation and discovery as processes for the advancement of humanity. The ESRF directors chose to support the movement because they believe its motivation tallies with the core mission of the European synchrotron, which includes attracting the best minds to address the most challenging problems. "For almost 30 years, the ESRF has been contributing to scientific advancement thanks to the research of its users," the directors' statement read. They added that they support the march "as an opportunity to promote Science for a peaceful growth of society worldwide."

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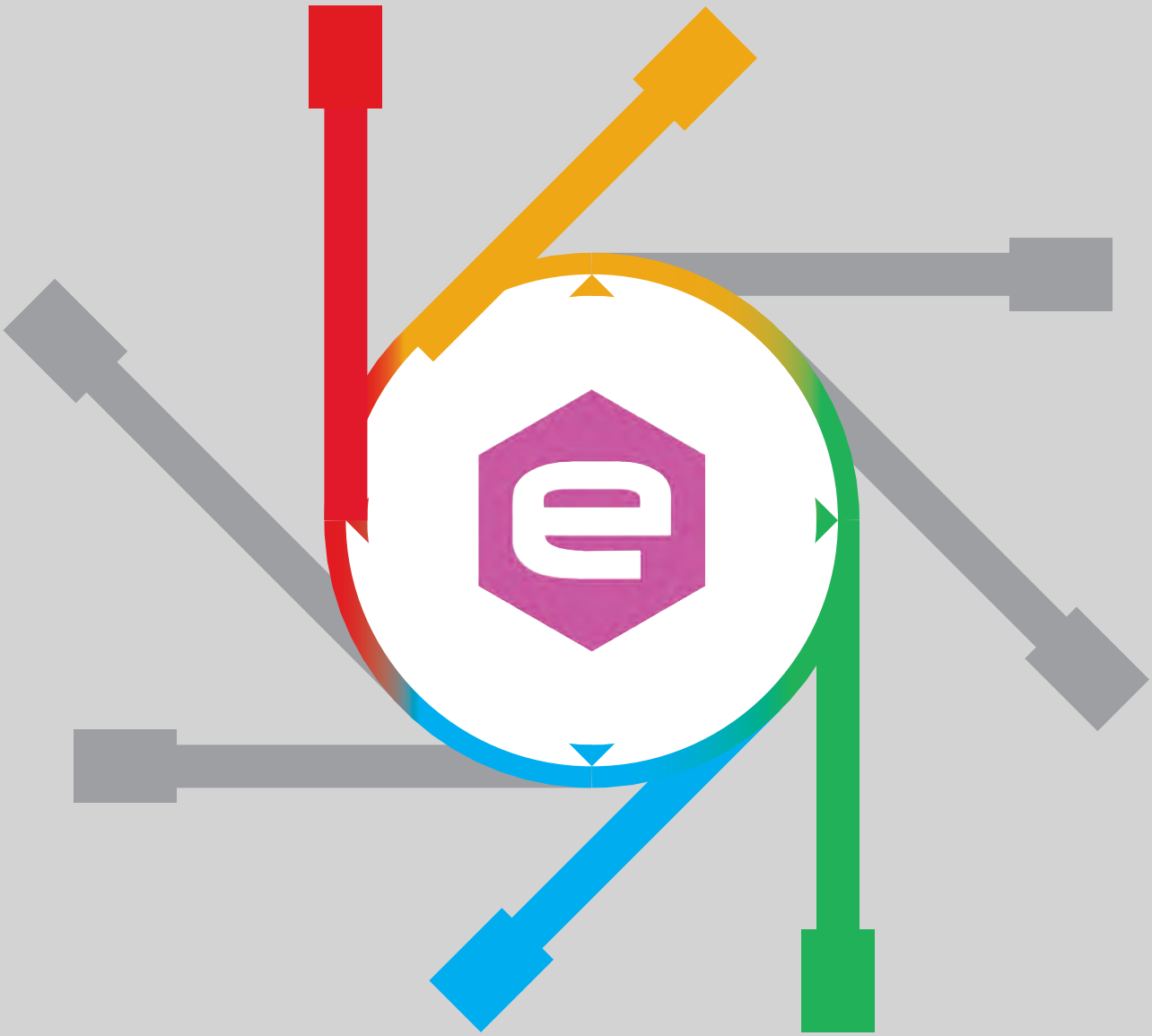

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