# ESRF news

March 2019



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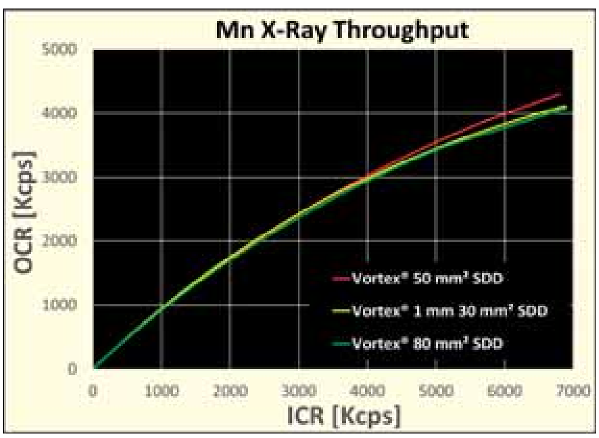


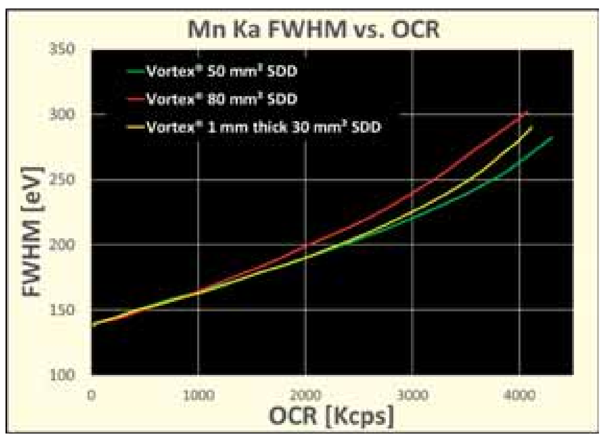


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# Making way for EBS photons

**Francesco Sette**
ESRF director-general

On 10 December last year, the ESRF's X-ray source was shut down for a 20-month upgrade to the new Extremely Brilliant Source (EBS). The activity has been very intensive for the ESRF teams, who have spent three months dismantling the original ESRF storage ring – the world's first third-generation light source, which has served the international scientific community for the past 25 years. More than 1720 tonnes of material has been removed from the tunnel, and, as this issue goes to press, the very first EBS girder is being installed. The teams now have just nine months to install and align each of the EBS's 128 assembled girders, to a precision of a few microns.


STEF CANDÉ

The EBS is definitely entering a new stage, the fruit of four years' hard work. Our imagination, engineering design, quality control and assembly, all guided by strict project management, have made it possible to start the swap in our tunnel between the original and the new storage ring, the first high-energy fourth-generation synchrotron. I wish to express to ESRF staff and our partner countries our profound gratitude, on behalf of all the scientific community using the ESRF.

## Modern outlook

As the ESRF enters a new era, so too does this magazine. On top of the fresh design, you will find more news, and the "Focus" section replaced by a longer feature article (this time on neurodegeneration, see p20). During the 20-month shutdown, an additional EBS section will offer you a snapshot of the upgrade activity underway at the ESRF (p14). As ever, *ESRFnews* looks forward to reporting on the breadth of the ESRF's research and technology, yet in a more modern and engaging manner. I wish you an enjoyable read and hope you like this new *ESRFnews*.

ESRF news

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ESRF/P JAYET

# User Meeting inspires new science

Its beam may be switched off, but the ESRF still welcomed 280 users to its annual User Meeting on 4–6 February. Following a busy year, in which there were a record number of experimental proposals and more than 1700 experiments performed, the users could listen to 26 presentations, view 80 posters, and reflect on the forthcoming opportunities of the ESRF's upgrade, the Extremely Brilliant Source (EBS).

Opening the keynote talks on the second day, Paul Shearing (pictured above) of University College London in the UK spoke about his long-term work on lithium-ion batteries. Ever more ubiquitous, powering our smartphones, laptops, cars and various other modern technology, batteries have been storing energy at higher and higher densities. But equally important, said Shearing, is their reliability. Batteries degrade over time, and can even fail catastrophically. "We take batteries for granted, [but as] we move towards more demanding applications, like electric vehicles, it's essential that we have an improved understanding of how these cells age, degrade and fail," he said. "The ESRF provides a unique toolbox for this, and the beamlines and people we work with at the ESRF are transforming our understanding."

*"The beamlines and people we work with at the ESRF are transforming our understanding"*

Shearing has been coming to the ESRF since 2012, at first to study fuel cells but more recently batteries of different types at different length scales. At a recent high-speed imaging experiment on the ID19 beamline, he and his colleagues learned how they could mitigate against catastrophic failure in novel types of lithium-ion cell (*J. Power Sources* **417** 29). Another recent study was their use of X-ray diffraction tomography at ID15 to reconcile the crystallography and morphology of particles in an operating battery for the first time (*Chem. Eng. Sci.* **196** 104).

### Long endeavour

Shearing believes that studying and improving batteries will keep him busy for many years to come. "But the insights that we gain from working at the ESRF really accelerate our understanding," he says. He is also looking forward to the EBS upgrade. "When [the ESRF–EBS] is back up and running, I understand that we should be able to do these experiments faster, and at higher resolution, which is very exciting."

The User Meeting is a big event, and has enough going on to attract users with all interests. The first day was devoted to tutorials, with topics ranging from sample-preservation strategies in structural biology to gender parity in research circles. "It's useful and totally new to me," said Anna Volkova of Moscow State University in Russia, a User Meeting first-timer who attended a tutorial on X-ray spectroscopy simulations using the software Crispy and Quanty. "The lecturer is friendly and helpful, and because the participants have varied backgrounds, the questions [the participants] raise make it easier to understand how to use the software."

On the second day there were three other keynote talks, other than Shearing's. Pierre Thibault, a developer of high-resolution imaging techniques at the University of Southampton in the UK, explained how ptychography and X-ray speckles can retrieve phase information of X-rays, helping scientists to image objects down to the nanoscale. Liu Hao Tjeng of the Max-Planck Institute for the Chemical Physics of Solids in Germany spoke about his development of the technique of non-resonant X-ray scattering at the PETRA III synchrotron in Hamburg, using analysers and a cryostat produced by the ESRF. Finally, Helena Käck from the pharmaceutical company AstraZeneca Sweden discussed the increasingly convenient use of synchrotrons for drug discovery (see p12).

Other highlights on the second day were the announcement of this year's Young Scientist Award (see below), and the reports from the ESRF directors. Francesco Sette, the ESRF director-general, presented some key statistics from last year, and explained the importance of this period for the ESRF, while Harald Reichert, the ESRF director of research in the physical sciences, gave an update of the EBS experimental programme

*"The EBS will allow us to do these experiments faster, and at higher resolution, which is very exciting"*

and the opportunities that will soon arise for users: four new flagship beamlines, refurbishments of existing beamlines, a high-power laser facility, an overhaul of instrumentation and a strong "data as a service" strategy.

The third and final day was given over to user-dedicated microsymposia, of which there were three: tunable past and time-resolved future on the ID29 beamline; recent applications, challenges and opportunities in X-ray microscopy for biology; and robust tools for imaging and dynamics with coherent X-rays.

Joanne McCarthy, head of the ESRF User Office, said that one of the key goals of the 2019 User Meeting was to keep close links with the user community during the shutdown period. "We want their ideas to bear fruit quickly with the capabilities of the new source," she said.

# Young Scientist 2019 revealed

A physicist-cum-chemist who studies the mechanisms inside commercial catalysts with X-ray spectroscopy has won this year's ESRF Young Scientist Award.

Elisa Borfecchia (right) of the University of Turin in Italy received the award during the plenary session of the 29th annual ESRF User Meeting. "I'm incredibly pleased and honoured, after a decade of amazing science," she said. Acknowledging the support of her team, including Kirill Lomachenko, the scientist in charge of chemistry and catalysis at the BM23 and ID24 beamlines, she added: "I've made many friends here and I hope that our collaboration will extend very far into the future."

Borfecchia trained as a physicist, and first became an ESRF user in 2008 during a master's degree. After a PhD and postdoc at Turin, she worked at the chemical company Haldor Topsøe in Denmark. A Marie Curie fellowship then took her to the catalysis group at the University of Oslo in Norway. Recently, she accepted a tenure-track position back at Turin.

Her career to date has focussed on the use of different synchrotron techniques to characterise nanomaterials, and in particular the use of X-ray absorption and emission spectroscopy to explore the properties and reactivity of metal sites in industrial, nanoporous catalysts. She is a regular user of the ESRF's BM23 and ID26 beamlines.

ESRF/C ARGOUD

Elisa Borfecchia of the University of Turin, who won the ESRF Young Scientist Award.

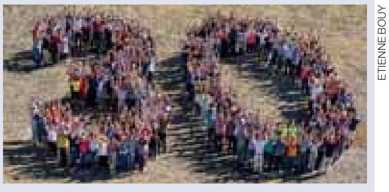
"The high-energy X-rays and the unique experimental set-ups and sample environments are huge advantages that make the ESRF my first choice for these experiments," she said. "What's more, the multi-disciplinary team here, whose vast range of skills meet all the needs for catalysis and spectroscopy, means that the ESRF offers conditions I can't find elsewhere."

Borfecchia's achievement arrived just a few days after the death of her friend and mentor Carlo Lamberti, professor of physical chemistry at the University of Turin. She dedicated her award to him.

## Users bag ERC grants

Two ESRF users have been backed by the European Research Council to the tune of nearly €3.5m. Marie-Ingrid Richard of Aix-Marseille University in France, a visiting scientist at the ID01 beamline, has €1.9m in a consolidator grant to develop coherent X-ray diffraction for the study of the nanostructures of catalysts and interfaces. Meanwhile, ID06 user Hugh Simons of the Technical University of Denmark has €1.5m in an early-career researcher starting grant to help his work on 3D piezoresponse X-ray microscopy, and to develop dark-field microscopy, which he hopes will be a standard technique on offer at fourth-generation synchrotrons such as the ESRF–EBS.

## Celebration day



ETIENNE BOUY

On 27 November last year, ESRF staff and representatives of its 22 partner countries celebrated the 30th anniversary of the world's first third-generation synchrotron light source. The December issue of *ESRFnews* was dedicated to its historical achievements.

## PaNOSC launches

A project coordinated by the ESRF under the EU's Horizon 2020 programme to promote open access to data officially launched in January. Photon and Neutron Open Science Cloud (PaNOSC) brings together six strategic European research infrastructures – the ESRF, the Central European Research Infrastructure Consortium, the Extreme Light Infrastructure, the European Spallation Source, the European X-ray Free Electron Laser and the Institut Laue-Langevin – to help construct the European Open Science Cloud, an ecosystem for universal and cross-disciplinary open access to data through a single access point.

## SESAME tomo in store

Led by the ESRF, nine institutes have joined forces to develop the scientific case for a tomography beamline at the SESAME synchrotron in Jordan. The Cyprus Institute, ALBA-CELLS in Spain, DESY in Germany, Elettra in Italy, INFN in Italy, PSI in Switzerland, SOLARIS in Poland and SESAME itself hope that the Beamline for Tomography at SESAME (BEATS) project within the EU's Horizon 2020 programme will boost the sustainability of SESAME's research infrastructure. The tomography beamline will be SESAME's fifth beamline, suited to the interest for cultural heritage and archaeology in the region.

## New lead on sleeping sickness

ESRF users from Germany have uncovered the way in which a certain inhibitor binds to a key protein in the African sleeping sickness parasite. Using X-ray crystallography at beamlines ID23 and ID29, as well as small-angle X-ray scattering at BM29, a team from the University of Mainz, the Goethe-University Frankfurt, the University of Würzburg and the University of Heidelberg, as well as the EMBL on the EPN campus, unexpectedly found that the inhibitor induces stable dimerisation of the protein tryparedoxin oxidoreductase (*Angew. Chem., Int. Ed.* doi:10.1002/anie.201810470). The findings could lead to new drugs for sleeping sickness.

## Cancer-attacker's secret exposed

ESRF users from France believe they have found out how a metal-organic molecule related to the widely prescribed drug tamoxifen attacks breast-cancer cells. The team – which includes scientists from the French National Institute of Health and Medical Research, the CNRS, Sorbonne University, PSL University, the University Grenoble Alpes and the ESRF – performed 3D cryo X-ray fluorescence microscopy at the ID16A beamline to see how the molecule enters the cells and attacks it in several places (*Angew. Chem., Int. Ed.* doi: 10.1002/anie.201812336). The molecule is considered a good candidate to treat the particularly tenacious "triple negative" type of breast cancer.

# Israel renews bond

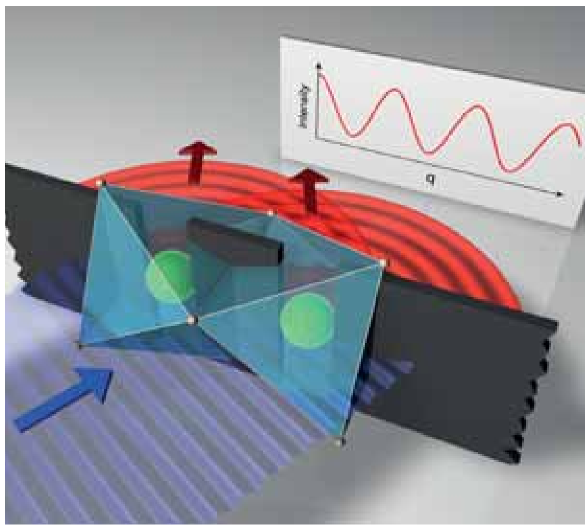
Israel has renewed its associate status with the ESRF, paving the way for its scientists to benefit from the Extremely Brilliant Source upgrade. Building on a 20 year relationship, the contract was signed at the ESRF by physicist Moshe Deutsch of Bar-Ilan University, the executive director of the Israel Academy of Sciences and Humanities, Galia Finzi, the chair of the ESRF Council, Miguel Ángel García Aranda, Israel's representative to the ESRF Council, Yuval Golan, and the ESRF director-general, Francesco Sette. "Thanks to the excellent work of Israeli researchers at the ESRF, such as that by the Nobel Laureate Ada Yonath, Israel's use of the facility has increased over the years," said Finzi. "The renewal of the agreement will allow Israeli researchers to continue their extensive activity at the ESRF."


# RIXS reboots classic experiment

An international team of physicists at the ESRF has performed a new take on the classic "double slit" experiment, using resonant inelastic X-ray scattering (RIXS).

In the original experiment, performed by the British physicist Thomas Young in around 1801, light from a point source is diffracted as it passes through a pair of slits in a wall; the resultant interference pattern of bright and dark patches on a screen demonstrates the light's wave – as opposed to particle – nature. As a matter of fact, 20th-century incarnations of the experiment showed that even single photons generate an interference pattern, but only if the slits are not monitored – a phenomenon that proves both wave-particle duality and the quantum-mechanical observer effect. In any case, the underlying process is elastic, because no energy is transferred between the light and the slits.

Developed over the past two decades, RIXS is an inelastic technique to probe electronic excitations by measuring the energy transfer as photons scatter off a material. Markus Grüninger at the University of Cologne in Germany and colleagues employed RIXS at the ESRF's ID20 beamline on a crystal of the iridium-oxide $Ba_3CeIr_2O_9$ containing dimers of iridium atoms.




MARKUS GRÜNINGER

X-rays (purple) excite core electrons on two iridium atoms (green), scattering inelastically and generating an interference pattern (red).

The interference pattern they recorded showed that the iridium dimers acted like pairs of slits – not only reasserting the wave-like nature of the photons, but also imparting new information about the crystal's excited states and their symmetry (*Sci. Adv.* **5** eaav4020).

The ESRF was one of only two synchrotrons worldwide that had the accuracy to perform such an experiment, says Grüninger. "This opens a new door for a whole series of further experiments that will allow us to gain a deeper understanding of the properties and functionalities of solids."

Instrumentation

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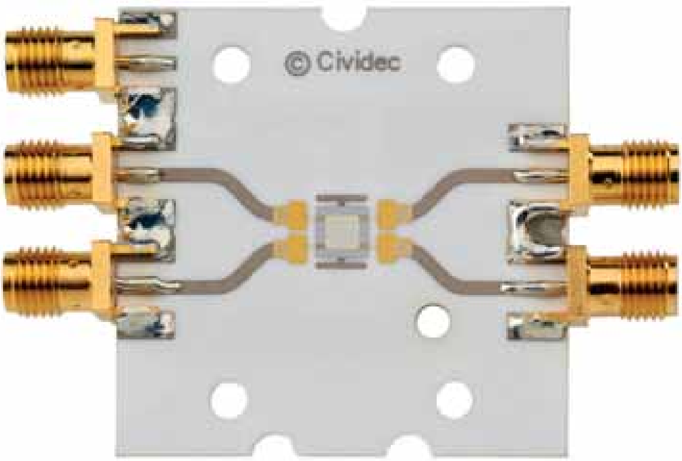


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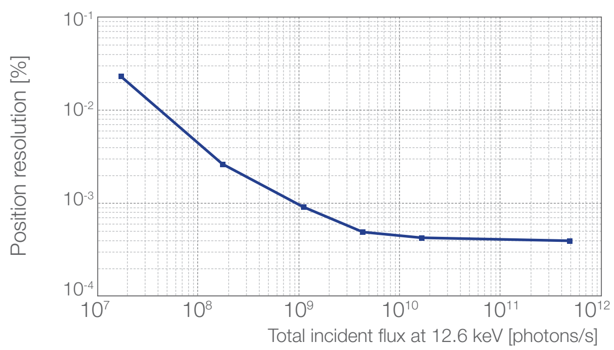


**Figure:** Measurements at Diamond Light Source Ltd., UK, show a position resolution better than $10^{-3}$ of the beamsize.

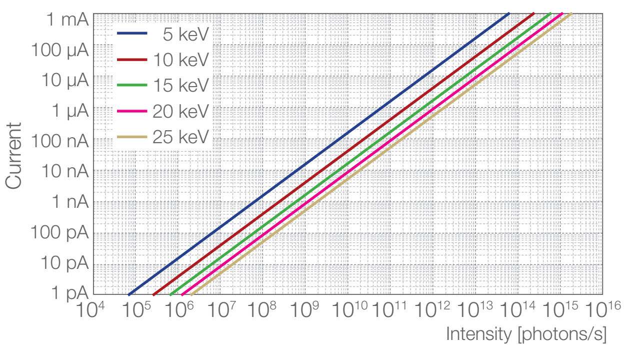


**Figure:** The detector response as a function of the photon energy and intensity.

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## Rembrandt's recipe found

Rembrandt was well-known for his impasto technique, in which paint is daubed thickly on a canvas to create a pronounced, light-reflecting texture. Now, thanks in part to high angular resolution X-ray diffraction and micro X-ray diffraction at the ESRF beamlines ID22 and ID13, researchers know his recipe. Having studied samples of several of Rembrandt's works, an interdisciplinary team at the Rijksmuseum and the Delft University of Technology in the Netherlands, as well as at the ESRF, identified the surprising presence of plumbonacrite, $Pb_5(CO_3)_3O(OH)_2$, a rare lead compound that suggests the Dutch artist mixed his paints in an alkaline binding medium, to help achieve the impasto effect (*Angew. Chem., Int. Ed.* doi: 10.1002/anie.201813105).

## X-rays spot $TiO_2$ origin

A combination of X-ray techniques can be used to distinguish anthropogenic – and potentially polluting – titanium-dioxide ($TiO_2$) nanoparticles in the environment from those that occur naturally. That is according to scientists from the University Grenoble Alpes, the Swiss Federal Institute of Aquatic Science and Technology, the University of Toulouse and the ESRF, who have employed a combination of X-ray fluorescence and X-ray absorption spectroscopy at the ESRF's ID21 and ID16B beamlines, as well as X-ray diffraction at BM25 and transmission electron microscopy, to study $TiO_2$ in both sewage and unadulterated soil. They found that the man-made $TiO_2$ particles in sewage were smooth and in aggregates dominated by organic matter, whereas in the soil they were rough and irregularly shaped and aggregated with organo-minerals (*Environ. Sci. Nano* **5** 2853).

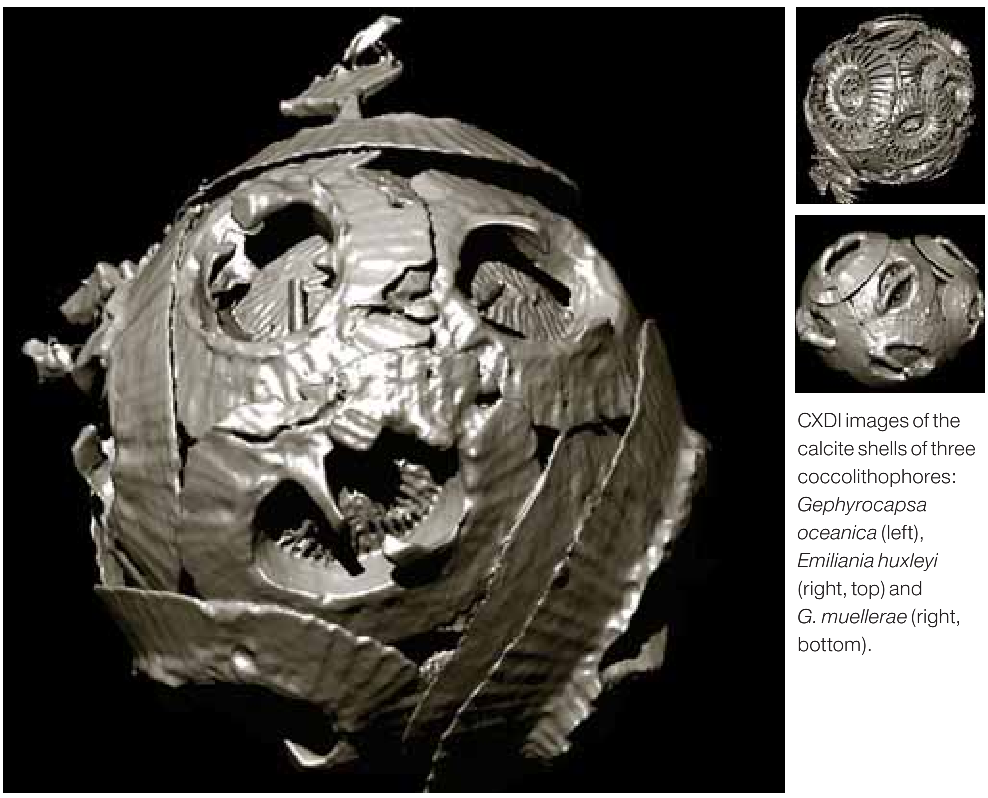
# A long time ago, in a habitat far, far away...

They may not actually be creatures from the *Star Wars* movie franchise, but coccolithophores have some fantastic traits: they evolved about 220 million years ago, and inhabit the largely unseen, microscopic world of ocean algae. Now, thanks to coherent X-ray diffraction imaging (CXDI) at the ESRF, researchers in France have been able to view them in 3D at resolutions verging on 30 nm. The images reveal for the first time what determines the mass of individual features, and support the possibility that the single-celled creatures could be used as yardsticks for ocean acidification.

Coccolithophores are at the bottom of the ocean food chain, eaten by small crustaceans, which in turn are eaten by fish. But they are also important in the carbon cycle: they absorb $CO_2$ as they photosynthesise, while on the other hand they emit $CO_2$ as they generate calcite by extracting bicarbonate from the water. This latter process is behind their unique shells, which are formed from individual features known as coccoliths. Scientists believe the calcification of coccolithophores is probably affected by the acidification of oceans under climate change, but to understand how, they need to chart their individual masses.

*"The single-celled creatures could be used as yardsticks for ocean acidification"*

Unlike polarised light microscopy, which has been used before to determine the mass of individual coccoliths, CXDI can image morphological features within single shells, and along any axis. Using CXDI data of seven species of coccolithophores taken at the ESRF's ID10 beamline, the team of scientists at the CNRS, the University of Le Mans, the University of Sorbonne, Aix-Marseille University and the ESRF discovered that the mass of individual coccoliths is proportional to the size of the cellular template around which they nucleate (*Nat. Commun.* **10** 751). Palaeontologist and team member Luc Beaufort of Aix-Marseille University thinks that is good for assessing the effects of ocean acidification. "It shows that the size and mass of coccoliths is customised very early inside the cell," he says. "The mass therefore makes a good marker, because it corresponds to a physiological response to the environment."



CXDI images of the calcite shells of three coccolithophores: *Gephyrocapsa oceanica* (left), *Emiliania huxleyi* (right, top) and *G. muellerae* (right, bottom).

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# AZ Sweden goes synchrotron-only

The long relationship between AZ and the ESRF continues to evolve.


ASTRAZENECA

Linda Öster prepares samples for shipment.

It is like a love story with the happiest of endings. Having started using the ESRF 20 years ago, AstraZeneca (AZ) Sweden has decided not to replace their aging in-house X-ray system and use synchrotron sources for all their research.

"The high-energy brilliance beam produced from synchrotrons is instrumental for structural biology," says Linda Öster, a scientist at the pharmaceutical company's protein structure group. "With the recent advancement of super-fast and sensitive detectors, together with automation, the way to use synchrotrons has shifted, and today we can collect datasets in an extremely fast and easy way."

AZ Sweden started coming to the ESRF in the early days of the facility, in 1999. Having in-house X-ray systems with robotics, its researchers screened all their crystals before sending them to the synchrotron for more detailed analysis; equally, they collected many datasets in-house if the quality of the crystals allowed. For those samples that required synchrotron radiation, the researchers had eight hours of synchrotron time roughly every three weeks. The access mode to the ESRF was remote, which means that a scientist at the ESRF would load the samples in the sample changer while the AZ researchers would collect the data back in their dedicated workstation in Sweden. This is a system that has been used at the ESRF for many years and it has proved very successful with industrial users.

Today, the AZ Sweden team consists of 11 employees and several students and post-doctoral researchers. The AZ Sweden site is one of two with a protein structure group in Europe. The decision to move to a synchrotron-only model was triggered by several factors. For starters, the in-house system was getting old and required an increasing amount of maintenance, as well as longer shutdown periods. "It was either investing on a new machine in-house, with all the maintenance that goes with it, or go for a synchrotron-only model, like our counterparts in the UK had already done," says Öster. According to Helena Käck, scientist at AZ, the synchrotron-only approach also means getting the best possible data directly. "This is very beneficial for systems that require synchrotron radiation," she says. "We also need fewer crystals overall, and we don't have to prescreen them before sending them out." The drawback is not being able to immediately test crystals when establishing new protocols.

### Ready to go

AZ Sweden decided to try the synchrotron-only model in January last year, so the mechanism is in place already. "To prepare for the change, we booked six-hour shifts at the ESRF every week," Öster explains. "In each shift, we can usually have data collected from around 80 crystals. We now have a working model where we preferably have a collection shift at the end of the week, Fridays or Thursdays, and the dewar is sent two days before the actual data collection – on a Wednesday morning for a Friday data collection. We then have a rotating schedule to determine the person responsible for organising each trip and to do the actual data collection."

According to Käck, the experience of the synchrotron-only model so far has been successful. "Overall, we are happy with our first year using only synchrotron sources," she says. "Coming to the ESRF for remote access has always been very straightforward, without needing more paperwork than necessary. There is a very good communication between us and the industrial liaison and that translates to a very efficient way of working." The catch is that, being dependent all year round on synchrotron radiation, which have inevitable shutdowns, Käck and her colleagues need to work with several light sources. That means more administration and adjustments to the setups of the different synchrotrons, she says.

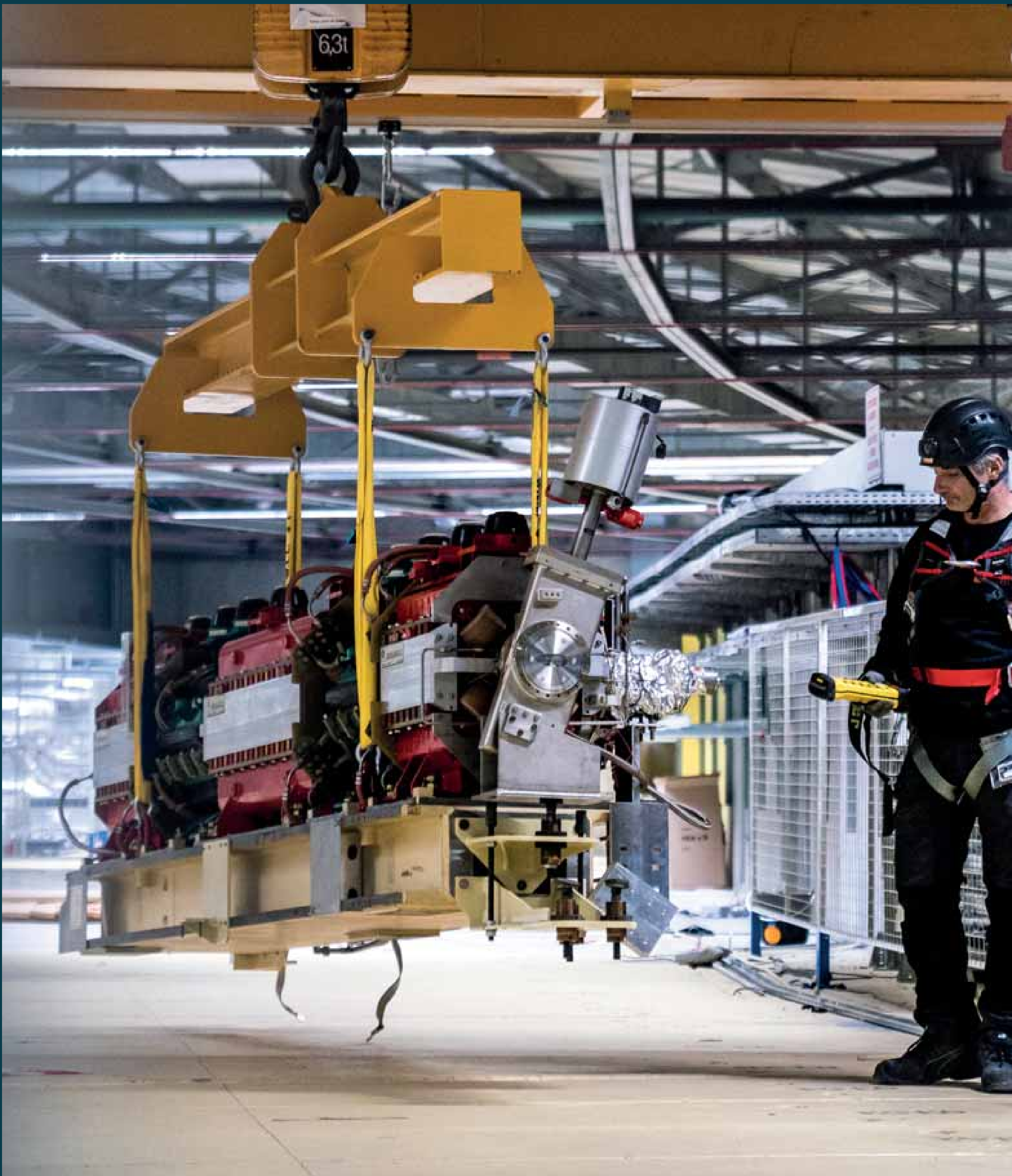
The ESRF's Extremely Brilliant Source upgrade could offer a panoply of new opportunities for AZ Sweden, even if the core of its work at the ESRF is routine scans. "We still haven't studied the benefits of the serial crystallography beamline, for example," says Käck. "That might be interesting not so much for our routine work, but for more exploratory routes." ■

### Further reading from the group

• G Gangadhara *et al* (2019) *Nat. Chem. Biol.*
• F Narjes *et al* (2018) *J. Med. Chem.*
• L Öster *et al* (2015) *Drug Discov. Today.*

**Montserrat Capellas Espuny**

STEF CANDÉ



# Raising the game

A crane operator removes the first girder in the dismantling of the ESRF's original storage ring. Making way for the new Extremely Brilliant Source (EBS), the dismantling phase has seen 160 girders full of equipment removed from the 844 m-circumference ring in less than three months.

It has been a labour-intensive process, yet just one part of the €150 m EBS project, which will replace the previous storage ring with a new "fourth-generation" lattice, designed to increase the brilliance and coherence of the generated X-ray beams by a factor of 100.

Each section of five girders – that is, one cell of the storage ring – has taken around two weeks to fully remove. ESRF staff and external contractors have worked hard to keep to the tight schedule, which has involved removing cables and piping, lifting the girders through the roof with cranes, and cleaning and painting the tunnel ready for the new source.

The new girders, which have already been pre-assembled with innovative new magnets, compact vacuum chambers and associated instrumentation, are just beginning to be installed in the tunnel. ■

**Anya Joly**

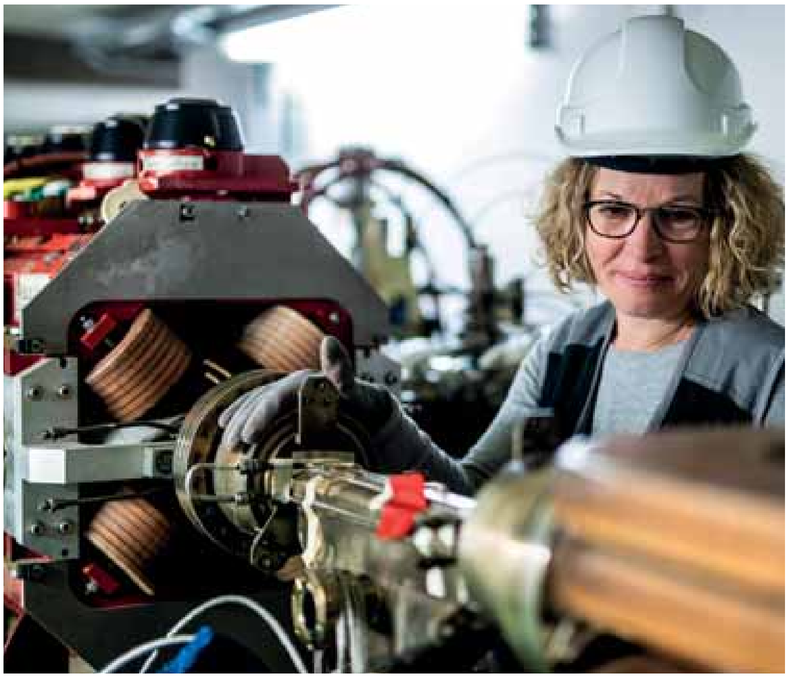
# Entering a new era

As excitement builds for the EBS installation, ESRF staff bid farewell to the original third-generation storage ring.

Sometimes, beginnings can look like endings. That is certainly what it looked like in the ESRF's storage ring tunnel on 6 January, when the first of 160 girders, stacked high with the magnets, vacuum chambers and instrumentation that have helped produce the ESRF's record-breaking X-rays for the past 30 years, was lifted out through the tunnel roof.

Isabelle Leconte, one of the coordinators of the dismantling process, was watching the machine she has worked on for more than 20 years – first in the vacuum group, later as shutdown coordinator – being taken apart. "I spent 21 years of my career safeguarding against the tiniest air leak in this ring, so this goes against all nature for me," she said. "But it's for a good cause – the EBS!"

There was little time for reflection, however, as the tunnel bustled with safety-booted engineers, hard-hatted handling operators, plumbers and electricians, all working swiftly to keep to the demanding schedule. "We have just 11 weeks to remove around 1720 tonnes of material," said another dismantling coordinator, Pascal Renaud. Speed was definitely of the essence here – the dismantling was carried out in three zones around the ring simultaneously, each front line advancing cautiously but quickly. The original storage ring was removed in sections, or cells, each one taking around two weeks.



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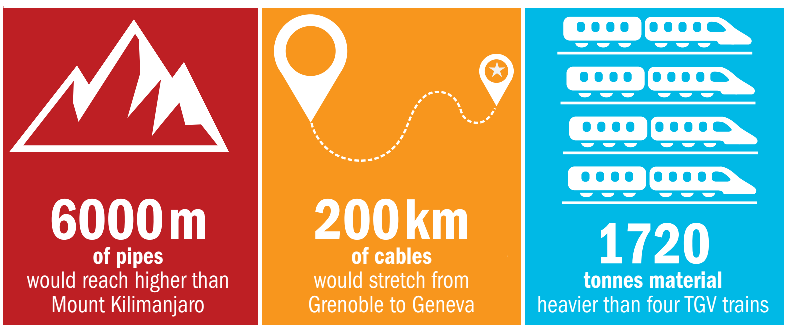


### Swift progress

In one cell, a team of four were busy cutting cables, hauling them out of the tunnel in great serpentine armfuls. In another cell, Leconte oversaw the attachment of a girder to a crane, ready to be winched out of the tunnel through the roof. On the other side of the tunnel wall, a trolley operator waited patiently to receive the girder before whisking it off to storage buildings, where each individual piece – down to the last screw – could be dismantled and tested. "It's an extraordinary experience and an unforgettable challenge," said Leconte. "The variety of the technical tasks and the numerous different kinds of expertise represented by the teams involved is a real source of motivation – there's a great energy and atmosphere down here in the tunnels."

The EBS may indeed have its challenges: the sheer scale of the tasks and the ambitious schedule, not to mention heavy reliance on the three cranes around the ring, which have been serviced weekly to ensure they can withstand the 16-hour working days. But above all, it is an adventure, not only for ESRF staff but for synchrotrons all over the world, looking to the ESRF for inspiration for their own upgrades.

"There's great energy down here in the tunnels"

Another person looking forward to the new EBS storage ring is Laurent Hardy, the ESRF's operation manager for the past 25 years. "We've learned a lot of lessons from this machine," he said. "It has been a great precursor for the EBS, which will allow us to reach the limits of current accelerator technology. Nothing on this scale has been done before." The real adventure for him? "Turning on this new machine and seeing what it can do."

As this issue went to press, the dismantling phase was completed, and the first EBS girder was being installed. A new beginning, and indeed a new challenge, was in sight. ■

**Anya Joly**

# In search of synchrony

The ESRF's upcoming Extremely Brilliant Source (EBS) will have almost 100% coherence, delivering a raft of new experimental possibilities.

**What is a coherent light source?**
Individual waves are coherent if they share the same frequency, phase and amplitude – in other words, if they retain perfect synchrony along their path of propagation. Coherent X-ray beams are a pure and, for experimentalists, highly valuable type of radiation, but they are also very hard to achieve in a synchrotron light source.

**Why are they so hard to achieve?**
The amount of coherent light generated by a synchrotron depends on a parameter known as emittance: how loosely packed the electrons are as they orbit the storage ring. The smaller the emittance, the greater the coherence of the X-ray beam. Even if the emittance of the electrons were zero, there would still be some effective emittance in the generated X-ray photons because of an optical phenomenon known as the diffraction limit – the smallest spot over which any radiation can be focussed. For that reason, a 100% coherent X-ray beam only requires that the electron emittance verges on this lowest effective photon emittance – still a very tall order, equating to a minuscule 5 picometre milliradians (pmrad) for photons of energy 10 keV. Nevertheless, in recent years the ESRF achieved this feat in the vertical direction for the electrons in its original storage ring.

**What was the motivation?**
When the ESRF switched on in 1994, X-ray coherence – and by extension, electron-beam emittance – was not a priority for synchrotron users. Even though the ESRF was a revolutionary light source, with X-rays far outshining those available anywhere else, its emittance was still about 6200 and 620 pmrad in the horizontal and vertical directions, respectively. But in the late 2000s, with the lust for even more innovative science, as well as the construction elsewhere of highly coherent free-electron X-ray lasers, priorities changed. Fortunately, the ESRF's original storage ring proved adaptable: it could reduce emittance in the horizontal direction roughly two-fold, and in the vertical direction 124-fold, through improvements in magnet alignment and the installation of beam correctors. The result has been a flurry of new or improved X-ray techniques.

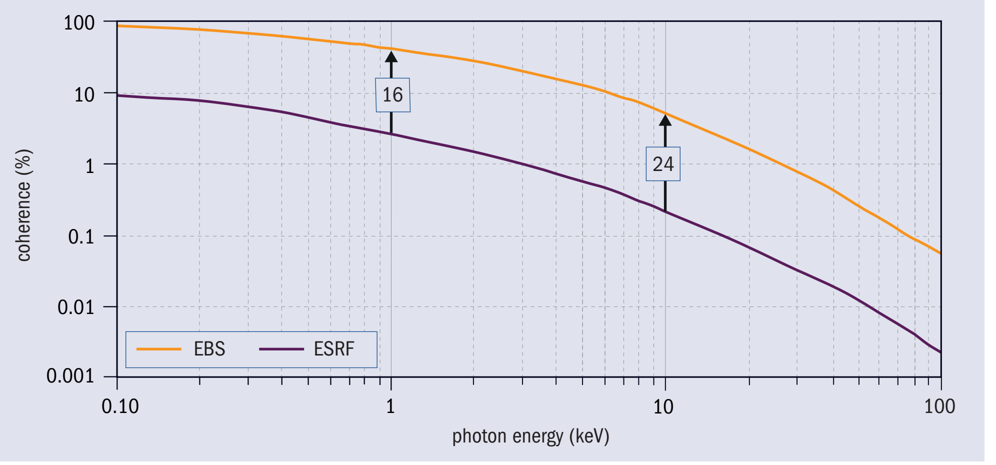


**Figure 1** The EBS boosts the ESRF's transverse coherence, making it laser-like at low photon energies and still profitable at energies up to 30 keV.

**What sort of techniques?**
If an X-ray beam starts off coherent, then an experimentalist can measure how its wavefield interferes with itself as it is scattered by an object. One of the first applications of coherent X-rays at the ESRF was phase-contrast imaging, in which the phase shift experienced by a beam as it propagates through an object provides very high-contrast 3D images of samples at low radiation doses. The ESRF now also provides coherent X-ray diffraction imaging (CXDI), which reconstructs far-field diffraction data to generate high-resolution images, and ptychography, in which various overlapping diffraction measurements are melded together to focus nanobeams down to 13 nm. The method that perhaps benefits the most from coherence, however, is X-ray photon-correlation spectroscopy (XPCS), in which the evolution of interference data allows scientists track the dynamics of slowly changing phenomena at the atomic scale.

*"The smallest timescale of XPCS could be boosted 10,000-fold"*

**How will the Extremely Brilliant Source (EBS) benefit these?**
Broadly speaking, emittance is reduced by increasing the number of bends in a storage ring, to improve the smoothness in the electron trajectories. Thanks to the EBS's hybrid multi-bend achromat lattice, which more than triples the number of bends over the original storage ring, the horizontal emittance will be reduced to 110 pmrad. The result will be an almost 100% transverse-coherent beam at lower energies, and much improved transverse coherence at higher energies (see fig. 1). CXDI and ptychography will deliver resolutions three to five times greater than before, while XPCS could have its smallest accessible timescale boosted 10,000-fold.

**What sort of new science will result?**
Anything that benefits from higher resolution and speed – for example, following catalytic reactions in operational conditions; exploring microsecond fluctuations in biological systems; studying the behaviour of nanomechanical systems under stress and vibrations; peering into complex bio-materials in untold detail; and capturing real-time movies of structural dynamics over multiple length scales. The list will be as long as ESRF users' imaginations. ■

PIERRE JAYET

# MIND READERS

Neurodegeneration is one of the biggest, and scientifically most elusive, problems of our societies today. ESRF users are investigating various possible causes, including toxic metals.

AGE steals away all things, even the mind. So wrote Virgil, and on good authority, relatively speaking. In his time, the ancient Roman poet would have been considered exceptionally old when he died at 50.

Today, what constitutes being old has changed dramatically. In the past century or so, life expectancy has risen meteorically, to the extent that in Europe, one-quarter of the population is expected to be over the age of 65 by 2030. The downside: a related upsurge in the prevalence of age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's. One 2016 study by researchers at the University of Hradec Kralove in the Czech Republic predicted that by the middle of this century, the cost burden of these two conditions alone in Europe will be more than €350 billion. It seems that Virgil's maxim is hard to avoid.

For sufferers of Alzheimer's or Parkinson's, medical progress has been frustratingly slow. Both diseases are known to involve the death of neurons in the brain and the build up of protein aggregates in or around neurons. But differentiating cause from consequence has proved elusive, and the conditions themselves are not sharply defined. Parkinson's disease, for example, is just one of several conditions that exhibit tremors, rigidity and unstable movement symptomatic of a broader "parkinsonism" syndrome.

Given this murky state of affairs, it is welcome that the ESRF has enough techniques on offer to study neurodegeneration from almost every conceivable angle (see "Neurodegeneration at the ESRF", overleaf). Led by Richard Ortega at the CNRS and the University of Bordeaux in France, one of the longest running projects concerns the increasingly recognised role of metals such as iron. Thanks to the steadily improving resolution of the ESRF's microfocus instrumentation with Kirkpatrick–Baez optics – lately at the ID16A beamline – Ortega's group has been able to study the distribution and species of metals inside single cells. "That wasn't possible before," says Ortega. "To do it we needed high sensitivity and high resolution – and that was developed at the ESRF."

Parkinson's affects a mid region of the brain known as the substantia nigra, which controls bodily movement via special neurons emitting a chemical known as dopamine. It has long been known that the concentration of iron is greater in the substantia nigra for Parkinson's sufferers, but before Ortega and colleagues' work no-one knew where in cells the iron amassed. Back in 2007, the researchers performed X-ray fluorescence at resolutions down to 90 nm on model dopamine neurons exposed to excess iron, and discovered the metal lurking in dopamine vesicles (*PLoS One* **2** e925). Because iron can interact with dopamine to induce oxidative stress, the result suggested a possible way in which dopamine cells could be lost.

> "Few places have people working on the same topic with so many different approaches"

The release of dopamine itself is regulated by a protein called alpha-synuclein. In a more recent study carried out in 2016, Ortega and colleagues found that when model neurons over-expressing alpha-synuclein were over-exposed to iron, the metal became concentrated in alpha-synuclein aggregates (*Mol. Neurobiol.* **53** 1925). The result implicated excess iron in another possible neuron-death mechanism: a toxic partnership with high levels of alpha-synuclein. But it could not explain why the iron is more abundant in the first place, nor how the mechanism could be linked with their earlier result showing iron in dopamine vesicles.

Perhaps a bigger question is how Parkinson's is linked ▸

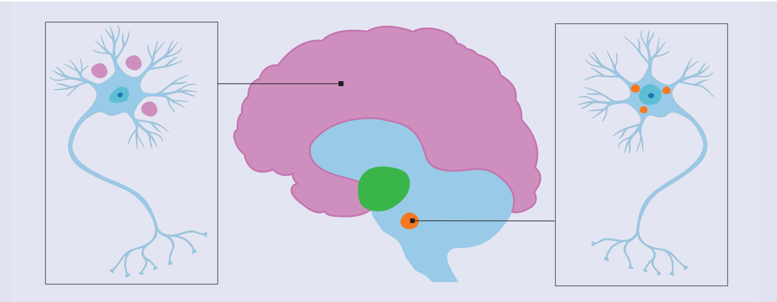

**Figure 1** Parkinson's disease leads to the build up of Lewy bodies inside neurons in the brain's substantia nigra (orange). Manganism, a variant of parkinsonism caused by environmental exposure to manganese, affects the globus pallidus (green), without any Lewy bodies. Alzheimer's disease leads to the build of amyloid plaques around neurons in the cortex (pink).

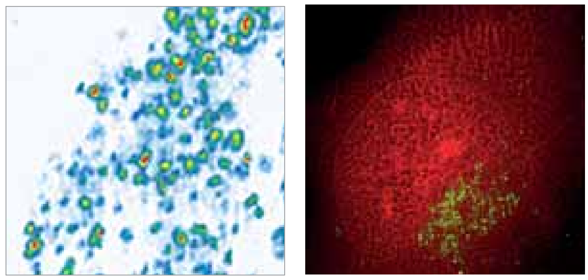

**Figure 2** Left: X-ray fluorescence imaging at ID16A reveals the distribution, down to 50 nm, of manganese in a cell expressing a mutation linked to parkinsonism. Right: combined with a potassium distribution (red), the manganese (green) can be located to the cell's Golgi transport vesicles, which may be where the metal stifles neurotransmission.

with Alzheimer's. The characteristic loss in Parkinson's is motor function, whereas in Alzheimer's it is memory and intellect. But superficially, the two diseases have a lot in common, as both involve the aggregation of proteins, only in different places: in Parkinson's they form "Lewy bodies" inside neurons in the substantia nigra, while in Alzheimer's they form "amyloid plaques" around neurons in the cortex (see fig. 1, above). Many scientists suspect a deep relationship between the two diseases, including the ESRF's Montserrat Soler-Lopez, whose own research aims to tackle their molecular basis in a protein complex involved in cell respiration (see "Root cause?", right). Meanwhile, preliminary infrared and X-ray microscopy results from Núria Benseny at the ALBA synchrotron, Josep Cladera at the Universitat Autònoma de Barcelona in Spain and others using the ESRF's ID21 and ID16B beamlines are indicating raised levels of metals in the amyloid plaques of Alzheimer's – as in the neurons of Parkinson's – albeit in this case iron and copper.

Improved medical treatment is a major driver for research. Ortega believes that his group's results could boost the prospects of a proposed Parkinson's treatment known as iron chelation therapy, by directing it only towards regions of problematic – and not healthy – iron build-up. But according to Asunción Carmona, a member of his group, the best route to new treatments is learning why the disease occurs in the first place. Driven by this question, "every time I visit the ESRF, I feel happy, and nervously excited", she says. Indeed, focussing on the "why" can open surprising new avenues of enquiry. In analysing the iron data for their 2007 paper, Ortega, Carmona and colleagues discovered another metal, manganese, in unusual concentrations around the cell's nucleus. Three years later, they pinpointed the metal's location as the "Golgi", a cellular post office that packages and sends proteins and neurotransmitters such as dopamine to where they are needed. The researchers speculated that the manganese interacts with those proteins, clogging up the Golgi and stifling the neuron's function (*ACS Chem. Neurosci.* **1** 194).

Unlike iron's, manganese's link to Parkinson's disease is subject to much debate. Scientists know that acute exposure to the metal – through occupations such as mining, smelting and welding – leads to a form of parkinsonism known as manganism, but this affects the region of the brain known as the globus pallidus, not the substantia nigra as in Parkinson's. Much less established is whether lower, chronic exposure to manganese in the environment can also trigger manganism or Parkinson's – and if so, which manganese compounds pose the greatest risk.

Although synchrotron fluorescence imaging depicts metal distributions at high resolution, it cannot detect the species of metal ions to indicate their parent compounds. For this goal, therefore, Ortega's group combined synchrotron fluorescence with X-ray absorption near-edge structure (XANES) spectroscopy, which can differentiate between chemical species. In 2014, the researchers

## NEURODEGENERATION AT THE ESRF

- Richard Ortega at the CNRS and the University of Bordeaux and others have employed nano X-ray fluorescence and XANES at **ID16A** and **ID21** to study the role of metals in Parkinson's and parkinsonism (see main text).
- Montserrat Soler-Lopez at the ESRF has employed SAXS at **BM29**, cryo-EM at **CM01** and crystallography at the **MX beamlines** to seek a possible molecular basis for Alzheimer's in mitochondrial complex I.
- Paola Coan and others at Ludwig Maximilians University in Germany have employed X-ray phase-contrast tomography at **ID17** to virtually "slice up" a brain to study how amyloid plaques develop and respond to treatment.
- Angelo Accardo at the Laboratory of Analysis and Architecture of Systems in Toulouse in France and others use infrared spectroscopy at **ID13** and **ID21** on microfluidic surfaces to monitor the protein make-up of amyloid plaques.
- Meytal Landau and others at the Technion – Israel Institute of Technology have employed X-ray diffraction at **ID23-2** and **MASSIF-3** to study the similarities between bacterial and human amyloids, in case microbes play a role in neurodegeneration.

employed this two-pronged approach at the ESRF to study the toxicity towards dopamine neurons of various manganese compounds, including inorganic compounds found in food and airborne pollution, and organometallic compounds found in fungicides and petrol additives. They found that, so long as the compound was soluble, its manganese ended up in the Golgi in the +2 oxidation state, and had exactly the same toxic effect (*Metallomics* **6** 822). "You might have thought that one would be more or less toxic," says Ortega. "But we found that in the end, it just comes down to the compound's solubility."

### Unwelcome inheritance

For Ortega, the question of manganese's potential role in manganism or Parkinson's at low, chronic levels of environmental exposure is very important for newborns and children, whose brains are especially susceptible to pollutants. For that reason, he is looking into the neurological effects of manganese in infant formulae. But the environment is not the only cause of manganese-based parkinsonism. The syndrome can also be inherited, and this type has been linked to mutations of the gene Slc30a10, whose protein helps to rid cells of manganese.

Until recently, no-one knew how manganese becomes toxic in the presence of such mutations. Towards the end of last year, however, Ortega, Carmona and colleagues performed micro X-ray fluorescence imaging at the DESY synchrotron in Hamburg, Germany, on cells at room temperature containing mutated and non-mutated Slc30a10. As in their work on environmental exposure, the researchers found that the manganese lit up particularly in the Golgi region of the mutated cells. Then they brought frozen samples to the ESRF's ID16A beamline, which could deliver resolutions down to 50 nm. It turned out that, in the mutated samples, the metal was inside transport vesicles of the Golgi (see fig. 2, left), suggesting a disruption of protein transport (*ACS Chem. Neurosci.* **10** 599). "The ESRF is the only place where we could have spotted such small amounts of manganese," says Carmona.

Miki Aschner, a neurobiologist and expert on metal neurotoxicity, is impressed by the observations made possible by the instrumentation at ID16A, and in particular the link between genetics and environmental exposure. "These results corroborate interactions between manganese and the vesicular trafficking machinery, which has implications not only for exposure to manganese, but also for diseases with analogous etiology, such as Parkinson's," he says.

Does all this mean that metals are the cause of Parkinson's, parkinsonism and Alzheimer's? Or are the metals merely a consequence of a deeper mechanism? It is too early to tell, but Ortega does have grounds for optimism. "For some questions we had 15 years ago, we now have the answers," he says. And then there is the sheer breadth of neuroscience that can be performed at somewhere like the ESRF. "There are not many places where we have people working on the same topic with so many different approaches, over so many different length scales." ■

**Jon Cartwright**

ESRF/ETIENNE BOUY

## ROOT CAUSE?

Among several neurological traits common to both Parkinson's and Alzheimer's is a decline in cell respiration, for which five protein mega-complexes – known collectively as the mitochondrial respiratory chain – are responsible. In the presence of amyloid plaques in Alzheimer's sufferers, the activity of the first of these protein mega-complexes (CI) is just 40% of what it should be. "Somehow, the amyloids are perturbing the assembly of 45 individual proteins into the functional CI. We want to figure out why," says Montserrat Soler-Lopez (above), a scientist in the ESRF's structural biology group, who adds that a similar assembly disruption could be taking place among the Lewy bodies symptomatic of Parkinson's.

Soler-Lopez identified one of several possible CI assembly factors, known as ECSIT, involved in Alzheimer's while she was a lab director at the Barcelona Institute for Research in Biomedicine in Spain, and joined the ESRF four years ago in order to study it with X-ray structure techniques. Since then, she has been using small-angle X-ray scattering, crystallography and cryogenic electron-microscopy to uncover how it and other assembly factors interact in order to generate a mitochondrial CI assembly (MCIA) complex, to allow CI to function (*Front. Mol. Biosci.* **3** 43). "If we know how those proteins assemble, we know how they function," she says. "That's the beauty of structure." Meanwhile, she is using cell-biology techniques such as immunofluorescence to understand how the function of MCIA factors affect – or are affected by – amyloid plaques.

As advances in neurodegenerative research have been slow, such new approaches should be welcome, says Soler-Lopez. "We have to look at things differently. Our aim is to find the root cause – and now, four years later, we are getting some good results."

"These results have implications not only for manganese exposure, but also for diseases such as Parkinson's"

# A new dawn

In the era of digital biology, the new director-general of EMBL, **Edith Heard**, seeks ever greater collaboration.

In the early 19th century, the French physicist Pierre-Simon Laplace envisaged an omniscient intellect who, by knowing the positions and momenta of all fundamental particles, could recall the past and predict the future with total accuracy. In time, thermodynamics and quantum mechanics seemed to rule out such certainty in the atomic domain. But according to Edith Heard, something resembling Laplace's vision is actually dawning in the life sciences – a "digital biology" in which information from multiple scales is processed to make predictions at the organism or even population level. "I really think in the next 10 years we're going to make some major discoveries that will truly make sense of life," she says.

Biology's world is expanding rapidly, and so is Heard's. From January this year, she is the new director general of the European Molecular Biology Laboratory (EMBL), Europe's flagship research institution for the life sciences with six sites spread across Germany, France, the UK, Italy and Spain – the French site being in Grenoble on the EPN campus, next to the ESRF. Like the ESRF, EMBL is already a highly collaborative institution, yet Heard wants to go further, encouraging interactions between scientists studying organisms at different scales. She also wants to invite those from other disciplines, such as physics and mathematics, to advance digital biology by bringing different datasets together with advanced computer models – indeed, EMBL's current five-year programme, initiated in 2017 by the previous director general of EMBL, Iain Mattaj, is actually called Digital Biology. Earlier this year, Heard discussed future plans with Stephen Cusack, head of EMBL's Grenoble site, and Francesco Sette, the director-general of the ESRF, during her first visit to the EPN campus. "It was inspiring to talk with them," she says. "We're all converging on this view that in order to address the most pressing questions in biology, you need to go towards these modelling approaches. There's huge potential on the EPN campus."

Heard herself knows how to traverse disciplines. As a student at the University of Cambridge in the 1980s she specialised first in physics, but quickly picked up on the rapid advances in biology, helped in no small part by her tutors Michael Ashburner, who later co-founded another of EMBL's sites, EMBL-EBI, and John Gurdon, who would win the 2012 Nobel Prize in Physiology or Medicine for his work on stem cells. She became a geneticist, and during her PhD attempted to understand how parts of the genome can be amplified in cancers. Thanks to this work she realised that in cancer, it was not just DNA sequences that were changing, but the way those sequences were used. Thus she turned to the emerging field of epigenetics, and to the paradigm of X-chromosome inactivation, when one of the two X chromosomes present in all of the cells in a woman's body is silenced during development. Her work has been recognized with many prizes, most recently the 2017 European Society for Human Genetics Award. Since 2013, she has been a Fellow of the Royal Society.

The future of digital biology and the EMBL is closely linked to the ESRF thanks to a long-standing memorandum of understanding between the two facilities – a recent example being the joint installation (together with the Institut de Biologie Structurale and the Institut Laue-Langevin) of the cryo-electron microscopy facility, CM01. "That's a fine example of how EPN campus institutes working together can be greater than the sum of their parts," she says. ■

**Jon Cartwright**

EMMA STEER/EMBL

**BORN:** 1965, London, UK.
**EDUCATION:** BA Natural Science (genetics), University of Cambridge, UK (1986); PhD biochemistry, Imperial Cancer Research Fund, UK (1990).
**CAREER:** Postdoc, then CNRS research scientist, Pasteur Institute, France (1990–2000); group leader (2001–2018) and director of genetics and developmental biology unit (2010–2018), Institut Curie, France; Chair of epigenetics and cellular memory, Collège de France (2012–); director-general, EMBL (2019–).

"The cryo-EM facility is a fine example of EPN campus institutions being greater than the sum of their parts"

# EVENTS

### EBS workshop on X-ray Raman scattering spectroscopy for hard X-ray probing of low-Z elements

**3–5 April 2019**

ID20 hosts a worldwide unique spectrometer to study low energy absorption edges using hard X-rays. The workshop aims to bring together experts and novices in the field to collectively assess and discuss the current status, potential, and future prospects for this emerging inelastic X-ray scattering technique in the frame of the ESRF–EBS project. It wishes to strengthen the current user community, define future research directions, and guide the worldwide efforts to build new dedicated end-stations. With 17 speakers currently confirmed, topics include: instrumentation; low-Z elements under extreme conditions; soft condensed matter; statistical systems; correlated electron systems; direct tomography imaging; and theoretical approaches.

### Cryo-EM Workshop

**21–23 May 2019**

This 2.5-day practical workshop on sample preparation for single particle cryo electron-microscopy (cryo-EM) will be held at the IBS and the ESRF. Jointly organised by the ESRF, EMBL Grenoble and the IBS, it will be the second in a series of hands-on workshops, and is aimed at doctoral students, post docs and young scientists new to the field of single particle cryo-EM. During the course, participants will learn theoretical and practical aspects of sample preparation for single-particle cryo-EM including prior quality control by negative staining. The ESRF's cryo-EM facility, CM01, remains open for the duration of the 20-month shutdown for the EBS upgrade.

### Hands on! High-pressure techniques at the ESRF–EBS

**17–21 June 2019**

The EBS, together with beamline upgrades and technical advancements in high-pressure instrumentation, will offer new and unique research opportunities for studies at extreme conditions. This school will give an introduction to high-pressure research at synchrotron radiation facilities and will present the unique opportunities that will come in this field with the ESRF upgrade. It comprises lectures covering the basic principles of synchrotron-radiation techniques used to explore matter at extreme conditions. The new capabilities of the EBS machine and the upgraded beamlines will be also presented in detail. Lectures will be completed with hands-on, step-by-step practicals. It hopes to promote a lively exchange between experts in the field and the future user community on instrumental developments to exploit the EBS upgrade.

### 21st International Magnetic Measurement Workshop

**24–28 June 2019**

The ESRF will host the 21st International Magnetic Measurement Workshop (IMMW21). A week-long event, IMMW21 is a forum for presentations and open discussions on the equipment and techniques used to measure, characterise, and fiducialise magnetic fields – typically those of accelerator magnets and insertion devices. Topics covered over the four days of talks will include an overview of magnetic measurements; sensors; measurement reports; instruments; methods; and fiducialisation and alignment.

# MOVERS & SHAKERS

**Bernard Bigot** has been given a second five-year term as director-general of the international ITER nuclear fusion experiment. The ITER council reappointed Bigot due to his strong leadership and to provide stability as the project enters a complex assembly and installation phase. Bigot has been credited with turning around ITER via organisational reform after a critical internal assessment report in 2013 by the management, which warned of the project's failure. In November last year, the project was judged to be 60% on its way to "first plasma" by 2025, a crucial milestone.

**Wim Leemans** has been made the new director of the accelerator division at the German accelerator centre DESY. Currently in charge of accelerator technology and applied physics, as well as the laser accelerator centre BELLA at Berkeley Lab in California, US, he is recognised as a leader in accelerator research, in particular laser plasma acceleration. His team was first to accelerate electrons to giga-electronvolt (GeV) energies in a laser plasma accelerator. He succeeds Reinhard Brinkmann, who has opted to return to being a lead scientist in DESY's accelerator research unit.

**Michael Krisch,** who has led the ESRF's Instrumentation Services and Development Division (ISDD) since 2015, has been appointed as beamline responsible for ID17 in the complex systems and biomedical sciences group. His new position will come into effect on 30 April. "This appointment will help to address the scientific and instrumentation challenges in this particular area," says Francesco Sette, the ESRF director-general. "We would like to thank Michael for his excellent leadership of ISDD, and for his outstanding dedication to the ESRF."

**Marine Cotte,** an analytical chemist at the CNRS and scientist responsible for the ESRF's ID21 beamline, has won the 2018 Descartes-Huygens Prize. Established by the French and Dutch governments in 1995, the prize recognises a researcher's "outstanding work and their contribution to French-Dutch relations", and has a value of €23,000 to cover the cost of a research residence in both the Netherlands and France. Cotte's research "is of enormous value to society because it provides the basis for managing and protecting important examples of cultural heritage," the prize jury said.