24 *hours* at the X-ray factory

Life in a synchrotron — a massive laboratory that runs day and night.

BY RICHARD VAN NOORDEN

The European Synchrotron Radiation Facility in Grenoble, France.

By half past four in the morning, PhD student Warren Stevenson has been awake for 22 hours. "I'm tired — but we work now or we don't work at all," he says, leaning back on his swivel chair and staring resolutely at two computer screens. "We plan to take a nap at 6 a.m. and wake up at 8. It'll be intense."

Stevenson's intensity is warranted: he has just a few precious hours to collect data crucial for his PhD about the structure of liquid crystals. And he is not the only scientist determined to defy sleep on this freezing November night. Nearby, in rooms positioned around a vast circular chamber, workers are simultaneously conducting 28 separate

ESRF

experiments. This is the European Synchrotron Radiation Facility (ESRF) in Grenoble, France — a giant science factory that, for 24 hours a day and as many days a year as its engineers can safely manage, pulses out the most intense high-energy X-ray beams in the world.

The teams who come here work in different fields: some study fossils, others batteries, still others proteins, minerals, artwork or archaeological treasures. But each visits for the same reason: to examine the structure of material by exposing it to light with the short wavelength that's needed to reveal details at the scale of atoms. Work hours are long: most of the current visitors arrived yesterday and have been granted only a few 8-hour shifts to collect their data. And competition to use the machine is so fierce — around 45% of requests are granted — that the facility operates around the clock to fit in as many as possible.

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Altogether, some 8,000 scientists visit here each year, conducting upwards of 2,000 experiments and producing the raw material for around 1,800 papers. In the past seven years, two Nobel prizes have been awarded for discoveries made at the synchrotron. It is a non-stop, international, interdisciplinary laboratory — which is why *Nature* spent 24 hours walking its tunnels to observe a slice of contemporary science as it unfolds (see 'The synchrotron that never sleeps').

"Our time here is precious. It will be months before our next visit — or it could be a year if we aren't lucky," says Xiangbing Zeng, Stevenson's PhD supervisor. Some visitors have teams large enough to rotate in shifts; many others will return home with dark circles under their eyes. But the scientists don't mind. They value the opportunity to bury themselves in data collection while escaping the rest of life. "For the week after, you feel jet-lagged," says biochemist Andrea Schmidt. "It doesn't get any easier. But it's always exciting to come here."

10:00 Schmidt is already looking harried. She and two colleagues flew in yesterday from the Charité medical university in Berlin, bringing with them 120 precious protein crystals frozen in a flask of liquid nitrogen. The German biochemists have just 24 hours to deduce the structure of their crystal — a bacterial protein that has been engineered to fluoresce when hit by red light and that is used to tag and study structures in living tissue. What's not clear is how such proteins work at the level of atoms and molecules. It would be an "important publication" if the team can explain it, says Schmidt.

Synchrotrons are the workhorses of structural biology. There are around 50 of them in the world, and the vast majority of the 6,000 or so atomic-resolution protein structures reported by scientists last year were solved at these facilities, by examining the diffraction patterns formed when high-power X-rays are fired at crystallized proteins. At the ESRF, working quarters consist of a small office opening onto a cramped experimental room called a hutch, which is where Schmidt and her colleagues will analyse their crystals — each less than a hair's width across, and trapped in frozen solvent in the centre of a half-millimetre loop of nylon.

As soon as Schmidt's team arrived this morning, the researchers began sticking tape over every visible light they could find. Light could cause molecules in the protein crystal to wiggle, making it impossible to capture an atomic-resolution picture. Schmidt flicks the light switch on and off, checking to see whether the rigged-up room is now completely dark. "It's MacGyver-like stuff," grins her PhD student Dennis Kwiatkowski.

10:23 Inside the 844-metre central ring of the synchrotron, electrons are circling at nearly the speed of light and spitting out X-rays like water flicking from a spinning car wheel. The X-rays are channelled through thin pipes to as many as 43 stations, called beamlines, around the ESRF ring, with a hutch and office attached to each.

Earlier this morning, specialist engineers injected fresh bunches of accelerated particles into the ring because the machine had been off for maintenance the day before. Each beamline has its own dedicated ESRF scientist who calibrates the X-ray beam for that day's experiment, and often sits with the team all day. "There are a lot of critical components and a lot of possible modes of failure," says David von Stetten, the support scientist for Schmidt's team. "It's important to check it every day."

10:46 Stevenson, Zeng and a third member of the team, PhD student Huanjun Lu, have started their day by preparing samples of the liquid crystals that they want to image. The group, from the University of Sheffield, UK, wants to work out how molecules are aligned inside the crystals, which are similar to those found inside LCD televisions. The work might one day lead to improved screens that can flicker on and off at higher rates.

The team is one scientist down: a Chinese national couldn't get his visa in time, so it's impossible for the rest to pair up in shifts as they had planned. There won't be any chance to leave the building, says Stevenson, but he shrugs. "It's just the work ethic. We never see Grenoble when we come here."

12:15 In a hutch 200 metres away, PhD student Annalisa Chieli is using a microtome to painstakingly cut ultra-thin slivers of dry paint from a block. It is her first time at the synchrotron. Yesterday, at home with her parents in Perugia, Italy, she watched a YouTube video about it. Now she is here, she says, "you can feel the research in the air".

Chieli, from the University of Perugia, is preparing to shine X-rays at samples taken from one of the four versions of *The Scream*, a painting by the famously melancholic Norwegian artist Edvard Munch, as well as samples from Jackson Pollock's *Alchemy*. Yellowish hues in both artworks have faded over time, and museum curators are not sure why. The synchrotron work could help to explain it, and perhaps protect the art.

Today is prep work, explains team leader Letizia Monico, from the Institute of Molecular Science and Technology of Perugia: they are scanning various samples of yellow paint to build up a reference library showing how pigments of different elemental composition absorb X-ray light and how that changes with age. Tomorrow, precious flakes from the real paintings will be scanned and compared with this gallery to decipher how the compounds in them have changed with time.

Like most of the researchers here, Monico and Chieli need pay nothing to visit. Twenty-one countries have signed up as partners of the synchrotron, contributing a combined €110 million (US$124 million) to operate it each year. The cash covers all the food and accommodation expenses for three members of each team visiting from a partner nation.

13:17 Because the clientele is international, the two canteens have to be, too. The larger one is buzzing as visitors and staff scientists tuck into a selection of meat, fish, pizza, pasta, desserts, cheese, yogurt — and a choice of wines (often French). Altogether, the canteen doles out some 1,000 meals a day. The working language of the ESRF is English, but here the multilingual chatter is like a session at the United Nations.

Monico's team picks the quieter, upper canteen. "For me, salad, and lots of vegetables," says Monico, a small, brown-haired Italian who gesticulates animatedly as she explains the chemistry of the cadmium sulfide yellow pigment that she expects to find in Munch's work. "Art is my passion," she says. The third member of the group, Frederik Vanmeert, of the University of Antwerp in Belgium, says his passions lie elsewhere. "I'm interested in the techniques," he says.

14:00 Back at her hutch, Schmidt's expression grows — if possible — slightly more anxious. The team is behind schedule: half the day has been spent setting up everything for the experiment on the light-sensitive protein. "If you don't have a good method to overcome frustration, then you are in the wrong field," she says, staring at a magnified computer-screen image of her frozen sample.

Schmidt and her group leader, Patrick Scheerer, want to get a picture with better than 2.8-ångström resolution to distinguish the separate amino-acid side chains of the protein. But Schmidt is on the 9th sample out of 100, and hasn't seen a discernible image yet. "Ninety per cent of the experiments go wrong," she says, as she moves her mouse to decide where to aim the X-ray beam next.

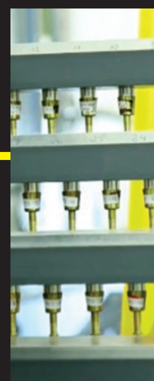
She clicks the mouse button — and throws up her hands in frustration. "Aah, 4.85 ångströms. You can only see a sheet or a helix, nothing else. Patrick will kill me if I don't collect the data."

Schmidt knows she could be in for a slog.

THE SYNCHROTRON THAT NEVER SLEEPS

Because of high demand, the European Synchrotron Radiation Facility runs day and night, pulsing out high-energy X-ray beams to 43 experimental stations to explore the atomic structure of samples ranging from proteins to portraits.

For a video of 24 hours in the synchrotron, see go.nature.com/2frnxg



ESRF (LEFT IMAGE); NATURE

When US structural biologist Brian Kobilka used the ESRF's tightly focused beamline in 2007 to take the first picture of a G-protein-coupled receptor — a structure that would win him the 2012 Nobel Prize in Chemistry — his team worked through 1,043 crystals before it hit the jackpot.

16:00 Next door, Matthew Bowler is looking relaxed. He has already scanned 80 crystal samples, couriered in from Helsinki the day before, and has successfully determined 3 protein structures without breaking a sweat.

Bowler hasn't done this all by himself. Rather, he works on one of the world's only automated X-ray crystallography beamlines. The robot, which Bowler built with other ESRF staff scientists, loads up crystal samples, scans each frozen blob, decides where to fire the X-rays for best results, collects data sets and then moves on to the next one. "It does this 24 hours a day, and it doesn't get tired," Bowler says with pride. The robot has processed 15,000 crystals over the past year. (Unfortunately for Schmidt, the specialized light conditions required by her protein make it impossible for the robot to handle.)

Bowler supervises the machinery and loads crystals into a sample-changer at the beginning of the day, but doesn't need to intervene regularly: researchers who send in samples to be analysed are informed of results by automated e-mails. The best part? It keeps Bowler's hours regular: he works from 8 a.m. until 6 p.m. each day. "I'm going to pick up my daughter from a piano lesson, then I'm done for the day," he says.

18:50 Nearby, Alexey Nikulin and Natalia Lekontseva are filling up a vacuum flask at a liquid-nitrogen dispenser. They flew in from the Institute of Protein Research in Pushchino, near Moscow, on Monday, and depart at the end of the week. "Hamburg's synchrotron doesn't work at the moment, and Berlin's is full up," says Nikulin, as the two trundle the full, heavy vessel back to their hutch. The liquid nitrogen will be used to keep their crystals, of an RNA-binding protein, frozen until they are ready for use.

19:10 Out in the corridor, Magnus Larsson walks past, on his way home for the day. He's easily identifiable as a non-researcher from his suit. Larsson is an industrial liaison officer who is visiting from the MAX IV synchrotron in Lund, Sweden, the world's first 'fourth-generation' machine, which promises to produce tighter, brighter beams of X-rays when it opens in June. He has been visiting to get tips on how the ESRF works with industry researchers, who pay their own way but are allowed no more than 10% of the synchrotron's beamtime.

After he's gone, the synchrotron's grey corridors are empty. The air conditioning clanks and hums. Although each group works just a minute or two's walk away from its neighbours, the teams rarely interact.

As darkness falls outside, researchers begin drifting back towards the synchrotron's canteen for dinner. The superior intensity of the X-rays generated by modern machines — which collect data in minutes, where older ones took hours — means that scientists who come to synchrotrons now have less time away from their hutches, says Joanne McCarthy, who's in charge of the ESRF's user programme. "In the olden days, you prepared your samples for measurement and went off to have dinner in town," she says.

21:00 The synchrotron's electrons are tiring out. The lead-lined pipe is not a perfect vacuum, and occasional collisions with air molecules make the tightly focused bunches of electrons spread out slightly and lose energy, causing the flux of each X-ray beam to drop. Engineers pump replacements into the synchrotron's storage ring to maintain the beams through the night.

21:36 In hutch ID22, the computer emits a gong sound — an alert signifying that the most recent measurement has ended. The team of five scientists, led by Boaz Pokroy from the Technion in Haifa, Israel, applied for time here eight months ago. It was worth the wait, Pokroy says: "The ESRF is, no question, the best synchrotron on this Earth."

The researchers are here in the name of materials science: they are examining the crystals that form when biological molecules, such as amino acids, are mixed with inorganic minerals such as copper oxide, so that the two crystallize together in a composite. The team is exploring whether this changes the electronic properties of the minerals in predictable ways, Pokroy says, perhaps leading to semiconductors with new properties.

Carlotta Giacobbe, their Italian staff-support scientist, points to a closed-circuit-television picture on the computer monitor, which shows a tall yellow robotic arm dipping to remove some tubes of powdered crystalline samples from the X-ray beam. "There are a lot of sounds," Giacobbe says: "there's a train whistle when the measurement starts, a gong when it stops and a scream if there's a problem with data backup." (There's also a donkey bray and the sound of laughter, which play when the scientists make mistakes.)

22:19 The researchers in Monico's team are finishing their paint analyses and are about to retire to the ESRF's guesthouse, which has 173 rooms and is full up tonight. Vanmeert is entering code on the computer, instructing a robot to move a sample of pigments slowly through the X-ray beam while they're gone.

"If you make a single error, you lose the night," warns ESRF beamline scientist Marine Cotte. Vanmeert is careful, but he is also looking forward to bed. "I will read a book and dream about beamlines," he says.

23:00 At Pokroy's beamline, things aren't going so well. The gong sounds, and Giacobbe looks at the camera, expecting the yellow arm to move towards a fresh array of samples. Nothing.

"No ... shit. Wait, it didn't work," she sighs. "OK. This means that the night will be longer than expected."

Pokroy leans over. "The robot is shy? Why didn't it change?"

"I don't know," Giacobbe says, rapidly typing in commands.

She and Pokroy go inside the hutch and fish around at cables, while the rest of the team looks concerned. Pokroy finds a possible culprit — a red cable that appears to have been cut. But no-one is sure of the problem, and it is too late to call in a technician, so data collection will stop. "We will lose a night," Giacobbe says, looking downcast. The six scientists put on their coats, pick up their bags, and leave for the guesthouse. Behind them, the robot is still.

23:13 The guesthouse is so full that some scientists couldn't get rooms. Georgios Kalantzopoulos and Erik Glesne, two materials scientists from the University of Oslo, set out to walk the 40 minutes into Grenoble for a hotel they have booked there instead. It's raining, and by the time they arrive, they are drenched.

00:00 At last, a breakthrough. By slogging through dozens of crystals, Schmidt's team has managed to get a 2.5-ångström-resolution picture of the light-sensitive protein — enough for the core of a research paper, although they won't know the protein's full shape until the researchers can analyse the data later on.

"If we have exciting results like these, we don't need any coffee to stay up," says Schmidt's colleague, Bilal Qureshi. Qureshi says he likes the single-minded focus the team can achieve on a synchrotron visit. "We generate a lot of ideas, and we don't think about much else."

2:00 The synchrotron is emptying — but where samples can't be changed by robot or need careful supervision, dozens of experimenters remain in their hutches. One of them is Stefan Mebs, a cheery German chemist from the Free University in Berlin; he and his colleague Peer Schrapers have elected to do night shifts for the next two weeks, because their samples must be changed every half-hour by hand. "On the day shift, you can sleep at normal times — but the experiments are more stressful," says Mebs. "At night, it's more relaxed. It's quite calm."

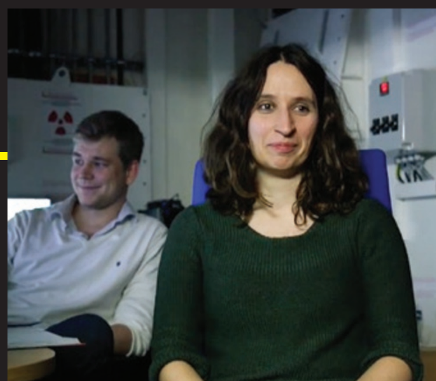
This group is blasting X-ray pulses at haemoglobin — the oxygen-carrying protein in red blood cells — in the hope of working out exactly how oxygen molecules bind to its iron-atom core. The team wants to examine this at room temperature as well as the sub-zero conditions that are usual for working with crystals, to see whether the binding is different at each, says Mebs.

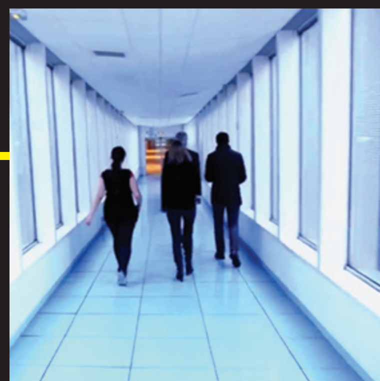
3:00 On the far side of the synchrotron, three scientists are still up — although they have installed a sofa in their office in case they have time to catch a nap, says Julie Villanova, the ESRF staffer on the beamline. "When people come here, they are really motivated, and they push us all," she says. Her two users for the day — Peter Joergenesen and Salvatore De Angelis of the Technical University of Denmark in Kongens Lyngby — are taking pictures of tiny pits in electrodes from different samples of solid oxide fuel cells to see how they have degraded over time.

Villanova makes an espresso in a kitchen nearby, although she does not drink it herself — something that impresses the Danish visitors, who can't imagine how else one would stay up. "Sometimes people jog around the inside of the tunnel," Villanova says. "Though there's a nice river not far away."

5:00 Despite their earlier success, Schmidt and her team have come unstuck because of a broken sample holder. After half an hour trying to fix it, they give up for the night. With 30 crystals not yet analysed, they creep wearily back to the guesthouse for 5 hours' sleep before they fly back to Germany. Schmidt will be back in two weeks to do it all again.

6:45 Stevenson and Zeng have been up for well over 24 hours, but they have managed to obtain results on two liquid crystal samples. "I'm as pleased as I can be in the present circumstances," Stevenson says. "I think I'll just pass out, eventually."





8:00 With the night shift ending, cleaners mop and vacuum the tunnels before a new tide of scientists pours into the synchrotron. Giacobbe returns early with two colleagues to try to sort out last night's problem. "We thought it was the wires, but it was actually a software fault," she says. "I feel relieved. It's nice when you discover what the problem is and fix it."

The gong sounds, and then the train whistle, and in the hutch beyond, a robotic arm whisks around to pick up a sample. Giacobbe smiles. "It's OK to lose one shift. They can recover the time."

9:00 Two fresh-faced researchers walk into the office just vacated by Schmidt's group and put down their bags. Theodoras Goulas and Mariana Castrillo Bricenyo have just arrived from the Institute of Molecular Biology in Barcelona, Spain — and now, like their predecessors, they have 24 hours in the hutch. Goulas is looking forward to the long day ahead. "I'm pretty sure we'll get something," he says. ■

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