Shorter, brighter, better

A laser technology with military roots looks set to make a big impact on biology. By creating short pulses of intense radiation, free-electron lasers will advance our understanding of biological molecules. Navroz Patel reports.

DESY

This German particle accelerator forms the basis for a new generation of high-intensity lasers.

It is a scene straight out of the movies — satellites, armed with high-powered lasers, blast incoming enemy missiles from the sky. But when President Ronald Reagan's controversial 'Star Wars' defence programme was phased out around a decade ago, this scene was relegated to the cutting-room floor.

Reagan's plans may be stalled, but the technology behind them is forging ahead. Free-electron lasers (FELs), which would have produced the intense beams needed to destroy missiles, are about to undertake a new mission — the transformation of structural biology.

In a few years' time, two new FELs could be producing X-ray laser pulses that are millions of times more intense than those from existing sources. Based at DESY, Germany's high-energy physics research centre in Hamburg, and the Stanford Linear Accelerator Center (SLAC) in Menlo Park, California, these devices have the potential to reveal the secrets of biological molecules that have so far resisted structural analysis.

The concept behind FELs dates back to the early 1970s, when it was proposed by John Madey, then a low-temperature physics PhD student at Stanford University in California (J. M. J. Madey *J. Appl. Phys.* **42,** 1906–1913; 1971). Many infrared FELs have been built in the intervening years, but until now interest in the technology has mainly been limited to the physics community.

FELs, like synchrotron X-ray sources, exploit the radiation emitted by fast-moving electrons as they change direction. Large FELs, such as those planned at DESY and SLAC, use particle accelerators to boost bunches of electrons to close to the speed of light. The bunches pass through an undulating magnetic field which forces the electrons to follow a sine-wave path.

This wiggling path causes the electrons to emit electromagnetic radiation, which quickly catches up, and interacts with, other electrons in the bunch. The effect of this interaction depends on the position of each electron and the phase of the wave that catches it up: some electrons are accelerated, whereas others are slowed down. The overall effect is to force the electrons into a series of smaller, more compressed bunches. The radiation emitted by these 'micro-bunches' is more intense, and helps to create more micro-bunches. The pulse that finally emerges from the FEL is a series of high intensity bursts from several thousand micro-bunches given off as they leave the magnetic field.

Racing pulses

One of the biggest selling points of the new FELs is the intensity of radiation this process produces. "The X-ray FELs will offer 10 orders of magnitude more photons per pulse than the most intense synchrotrons currently available," says Janos Hajdu, a biochemist at Uppsala University in Sweden, who has worked on the plans for both new FELs.

Operations at DESY will halt in the next few months to allow for the upgrade, which should be finished in 2004. Keith Hodgson, director of synchrotron research at SLAC, says Stanford's FEL should be ready in late 2006.

The two new devices will initially produce X-ray pulses with wavelengths of around 10 nanometres but should eventually operate in the 0.1-nanometre range. Last September, researchers at DESY took a step towards this goal when they coaxed ultraviolet radiation out of their existing device. At 80 nanometres, the light's wavelength was the shortest ever produced by a FEL.

Both facilities will appeal to researchers from many disciplines. Physicists are keen to use the new FELs, as the beams will let them study little-understood states of matter. Warm dense matter (WDM), a state somewhere between a solid and a plasma, is one example. WDM is found in the cores of large planets, but can be created in the laboratory by focusing the high-intensity radiation produced by FELs on metal targets. The character of the WDM can then be probed by observing the way it scatters laser light.

But it is in biology that the X-ray FELs will have the biggest impact. Unlike radiation of

longer wavelengths, X-ray pulses are diffracted by the gaps between atoms in molecules. By studying the patterns made by these diffracted rays, biologists can deduce the structure of the molecule under analysis.

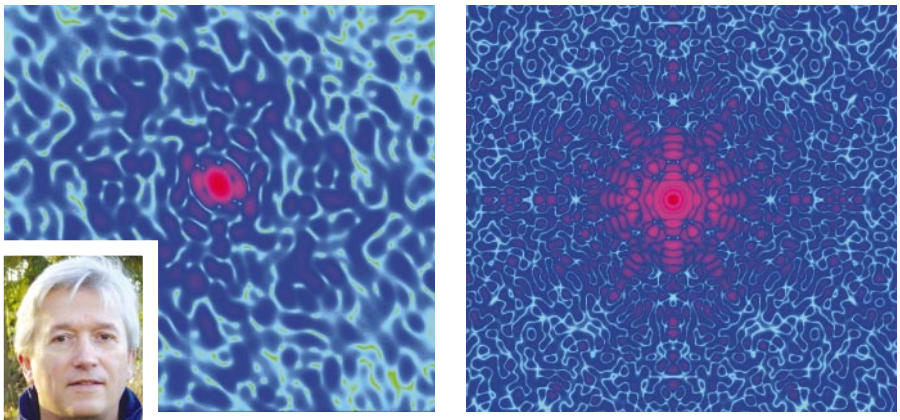
X-rays produced by conventional lasers and synchrotrons are already used to probe the structure of biological molecules, but both systems are limited by the intensity and pulse length of their radiation. The short, high-intensity pulses from the new FELs should allow researchers to overcome both of these stumbling blocks.

X-ray diffraction works well with biological molecules in crystalline form, as the rays are reflected between the crystal's layers and combine to produce a measurable diffraction pattern. This means relatively low-intensity X-ray sources can be used to create diffraction patterns. But for single molecules, low-intensity X-rays are of little use, as the signal produced is too weak and noisy to interpret.

The new FELs will allow analysis of samples of just tens of molecules, and perhaps even single molecules, which should remove a host of limitations. The shapes of proteins in a crystal, for example, are constrained by the surrounding molecules, so current diffraction studies can probe only a limited range of the shapes that the molecules are thought to assume. And because the shapes of proteins in a crystal vary, X-ray diffraction actually records an average of a range of different structures. It is also often impossible to study a protein's interactions with other biological molecules when it is frozen in crystalline form.

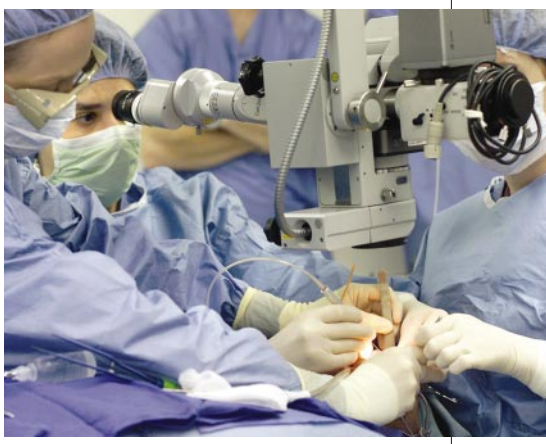
At the moment, structural biologists use nuclear magnetic resonance spectroscopy to overcome these obstacles. This can reveal the structures of proteins in solution, but it has not yet been made to work for large proteins. Hajdu believes this obstacle will be removed once the X-ray FELs are up and running. "The new FELs could get rid of the 'crystal' in 'crystallography' altogether," he says. In addition, the frequency of FEL radiation can be adjusted, allowing researchers to tailor the pulse to suit the molecule being studied.

Hajdu has already used computer simulations to reveal what the X-ray pattern created by both a single enzyme and an individual virus will look like (R. Neutze, R. Wouts, D. van der Spoel, E. Weckert & J. Hajdu *Nature* **406,** 752–757; 2000). Once available, he intends to use the new FELs to test these predictions out.



E. WECKERT/DESY

Singled out: Janos Hajdu has modelled X-ray diffraction of an individual molecule of the enzyme lysozyme (left) and a virus that affects tomatoes (right).



D. JOHNSON/VANDERBILT UNIV.

Clear cut: the high-intensity beams from free-electron lasers have been used in eye operations.

Keith Hodgson hopes to have Stanford's X-ray free-electron laser up and running by 2006.

Beamline bonanza

Other researchers plan to use the FELs to study the proteins that crystal-based methods have missed altogether. Proteins linked to lipids and embedded in cell membranes, for instance, are very difficult to crystallize. At present, says Carol Robinson, a chemist at the University of Cambridge, there is relatively little good structural data on membrane proteins. These proteins are important, she says, because they regulate traffic into and out of cells.

Another advantage offered by FELs is their short pulse length. Synchrotrons emit pulses that are typically a few tens of picoseconds (10^{-12} seconds) long. But vibrating molecules can change shape in a few femtoseconds (10^{-15} seconds). The femtosecond pulses produced by FELs should open up these vibrations for study. Indeed, among the other FELs under development, one will soon be using short infrared pulses to study the vibrations of DNA.

Researchers at the University of Maryland in College Park are building a 'compact' FEL — a smaller device that uses lower-speed electrons and so does not need a large particle accelerator. Compact FELs produce pulses that have longer wavelengths and a lower intensity than those from X-ray FELs.

The Maryland FEL, which should be ready this year, will be used to study how changes in the shape of DNA affect the way it interacts with other molecules. The vibrations within DNA and the larger changes in the shape of the molecule itself are thought to play a fundamental role in the synthesis of other biological molecules. A clear-cut experimental analysis of this role has so far eluded researchers — but the Maryland FEL should help to redress the balance.

With a wavelength of between 3 and 30 micrometres, the FEL's radiation is the right frequency to make DNA vibrate by interacting with the concentrations of charge found along DNA's double helix. Researchers can then follow interactions between the vibrating DNA and other molecules by studying the way additional FEL pulses are scattered.

Compact FELs also have medical uses. Eye surgeons at Vanderbilt University in Nashville have used short, intense FEL pulses to operate on the back of the eye.

Given that FELs offer a range of advantages over other light sources, why are they not more widely used? Conventional lasers, by contrast, are found everywhere from industrial manufacturing to domestic compact disc players.

Madey, now at the University of Hawaii in Manoa, suggests the problem is that FELs have largely been the preserve of accelerator physicists, who are less in tune with potential applications. "They have worked without the scientific insights needed to adapt the technology for use in near-term research and manufacturing applications," he says.

But as excitement about the new facilities grows, the profile of FELs is set to get a much-needed boost. Star Wars, it seems, may have a surprisingly useful legacy. ■

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DESY ▸ **tesla.desy.de**

SLAC ▸ **www-ssrl.slac.stanford.edu/lcls**