

Using *in vivo* crystallized proteins for drug discovery

Drug discovery is driven by the precise characterization of targeted proteins. However, extracting, purifying and crystallizing proteins for study typically take them far away from their natural environment, with unknown effects on their structure. *In vivo* crystallization – the process by which organisms grow small, high-quality protein crystals within their cells – can provide specimens with nearly unaltered structures.

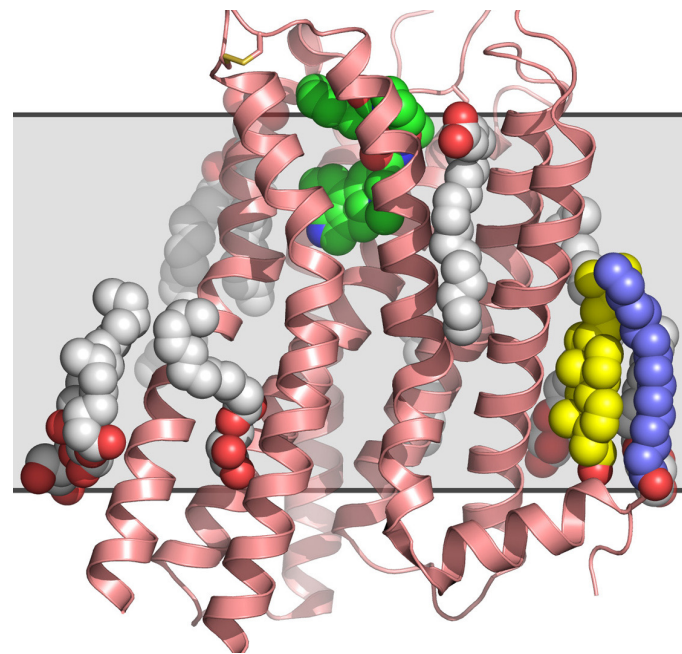
How LCLS Can Help

The molecular structure of *in vivo* crystallized proteins can be reconstructed by collecting a series of X-ray diffraction patterns using the ultrabright X-ray pulses of LCLS. Already, LCLS has revealed the detailed structure of an enzyme associated with transmission of African sleeping sickness.

Citation: Redecke, et al., *Science*, 339, 6116 (2013).



Advancements in structural biology with LCLS can aid the development of new drugs. (iStockphoto.com/Getty Images)



This rendering shows the structure of the human serotonin receptor bound to ergotamine (green), an anti-migraine drug. (The Scripps Research Institute)

Studying G protein-coupled receptors

G protein-coupled receptors (GPCRs) are targets for the majority of drugs today. GPCRs have a uniquely important role in human physiology by mediating communication between the inside and outside of cells. Large, high-quality GPCR crystals can require years of effort to grow, hindering the progress of drug development.

How LCLS Can Help

Small GPCR crystals can be used to determine structure when probed by LCLS. Samples can be delivered slowly into the interaction region, thus requiring only small quantities of sample to obtain complete structural information.

Citation: Liu, et al., *Science*, 342, 1521 (2013).

For more information

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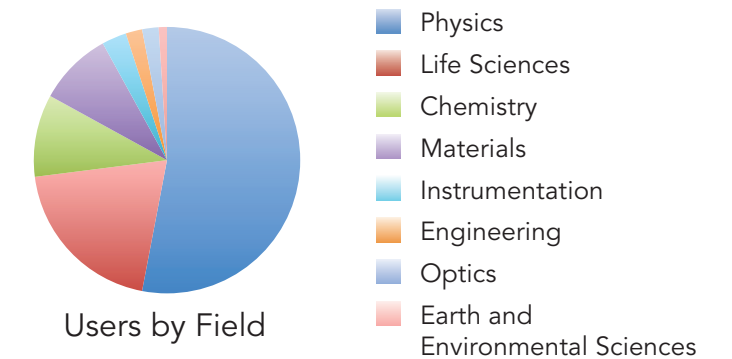
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The Linac Coherent Light Source (LCLS) A Powerful Tool for Materials Research and Life Sciences

The LCLS produces the world's brightest X-ray pulses. Like a high-speed camera with an incredibly bright flash, it takes X-ray snapshots of atoms and molecules at work, revealing fundamental processes in materials, technology and living things.

LCLS Facts

- 594 scientists conducted experiments in 2013
- 4,580 operating hours in 2013
- 277 publications since LCLS began in 2009
- 15 collaborators, on average, per experiment proposal
- 6 experimental stations



Materials Research Highlights

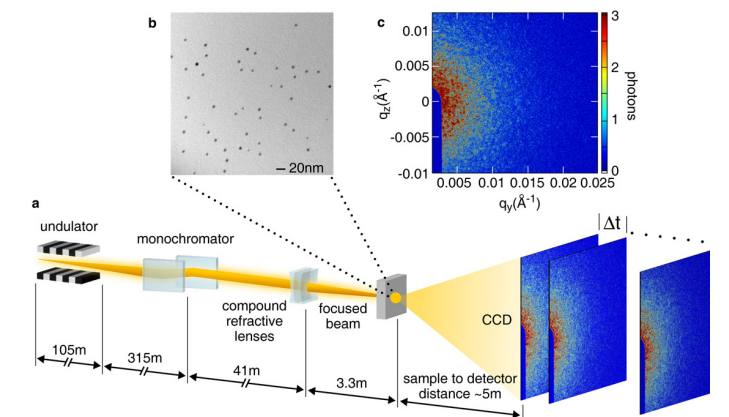
Probing slow dynamics in complex systems

Industrial compounds often consist of complex soft-matter systems such as liquids, colloids, liquid crystals, polymers, foams, gels and granular materials. Although these complex materials are widely used, their macroscopic properties are still poorly understood. Elucidating their properties will ultimately allow us to control and engineer these materials, leading to significant advances in industrial products.

How LCLS Can Help

LCLS can be used to record the motion of flexible long-chain molecules such as polymers as they are cooled from a molten state to a more solid form. X-ray images can be taken in sequence with a time delay of seconds to minutes, allowing scientists to see the evolution of the material over a much longer timescale than previously possible.

Citation: Carnis, et al., *Scientific Reports*, 11 Aug. 2014 (10.1038/srep06017).



The setup for an X-ray photon correlation spectroscopy experiment studying polymer samples. Nanoscale gold spheres embedded in a molten polymer helped study its motion. A speckle pattern was produced as X-rays struck the polymer sample at different time steps.

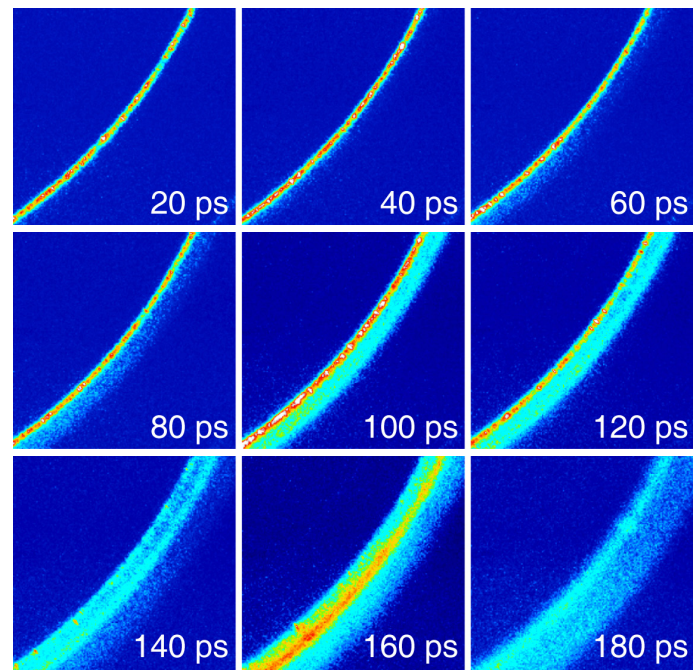
Observing ultrafast deformation mechanisms in metals

A metal's response to stress depends on its mechanical properties. One way to understand those properties is to simulate the behavior of many millions of atoms within a tiny metal sample. Experiments that test the validity of such simulations are very challenging because of the small sample sizes and short timescales involved.

How LCLS Can Help

LCLS's ultrashort pulses enable this type of experiment. One such demonstration at LCLS revealed an elastic-to-plastic transition in a 1-micron-thick shocked copper sample. Although the transition happens within a few tens of picoseconds, LCLS was able to capture images showing movement of atoms in the copper sample. The time and distance scales were comparable to those of theoretical simulations, allowing a direct comparison.

Citation: D. Milathianaki, et al., Science, 11 Oct 2013 (10.1126/science.1239566).



A sequence of X-ray diffraction images from a 1-micron-thick shocked copper sample undergoing elastic-to-plastic transition shows changes over time (in picoseconds).

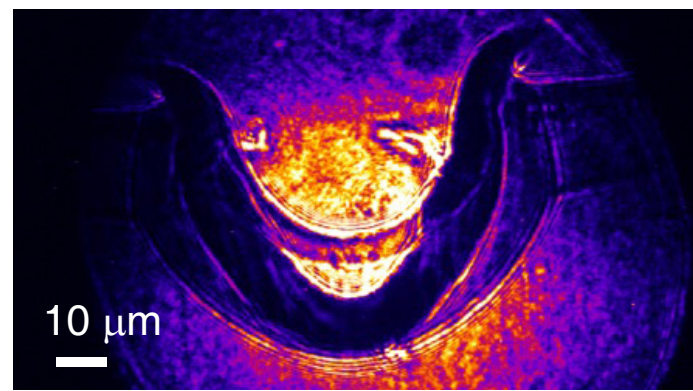
High-resolution imaging of materials at high pressure

Industrial materials, such as concrete, experience high stresses during processing, potentially resulting in permanent structural changes. Similarly, aircraft engine fan blades and automotive parts undergo surface treatments that induce compressive stresses to inhibit growth of cracks. Precise evaluation of the material's behavior during these processes requires characterization techniques that offer high spatial and temporal resolution.

How LCLS Can Help

By combining the LCLS X-ray beam with high-power optical laser beams, it is possible to induce and characterize phase transitions, formation and growth of defects, and other effects of industrial materials processing at very fast timescales. High-resolution X-ray imaging performed at LCLS can identify changes in materials at sub-micron scales.

Citation: Schropp, et al., Scientific Reports, 09 April 2013 (10.1038/srep01633).



(Top) The Materials in Extreme Conditions (MEC) chamber with its suite of X-ray diagnostics. (Bottom) A phase-contrast image of a laser-generated shock wave as it propagates in silicon. The stress front was resolved with sub-micron resolution. (B. Nagler, et al., publication in preparation, MEC, LCLS)

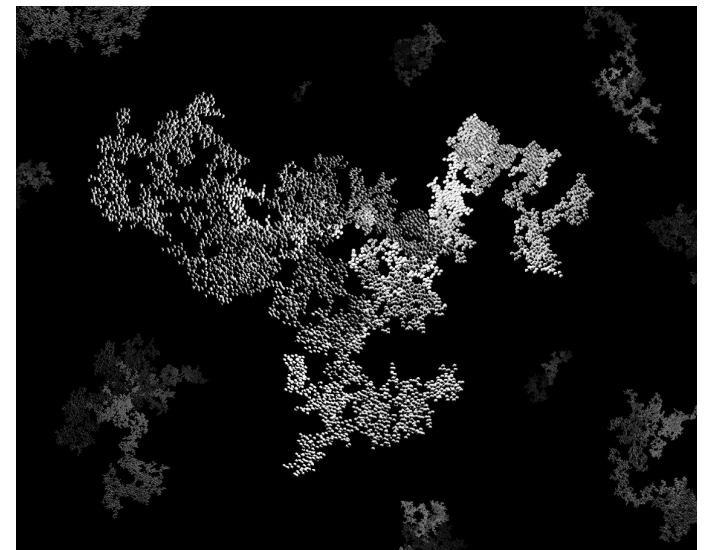
Imaging microscopic components of air pollution

Airborne soot particles are a key contributor to global warming and are also a health hazard. A better understanding of the complex structures of these particles could help scientists understand atmospheric processes related to climate change and help engineers design cleaner fuel sources and car engines.

How LCLS Can Help

LCLS can capture ultrafast images of airborne particles, such as soot emitted from diesel engines. The resulting high-resolution images reveal complex structures on a nanometer scale. This method allows scientists to investigate a broad range of individual particles and examine both their structures and particle dynamics.

Citation: Loh, et al., Nature, 486, 28 June 2012 (10.1038/nature11222).



These simulated particles, based on previous research models, illustrate the expected structure of soot particles in the air.

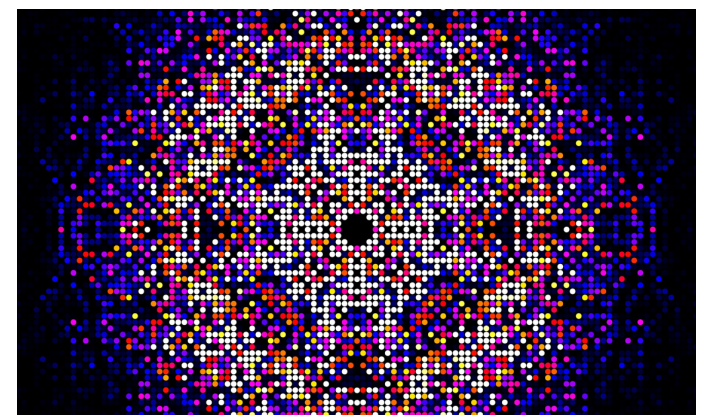
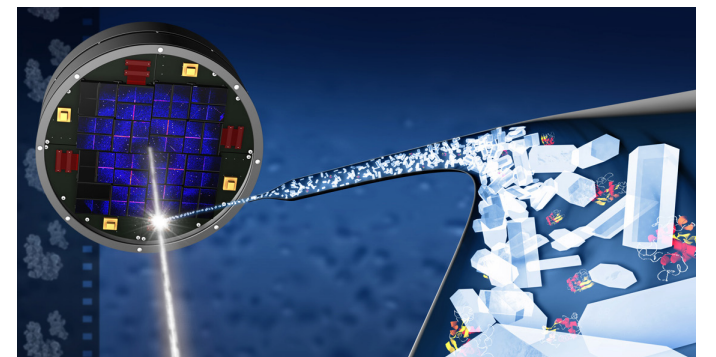
Life Sciences Highlights

Mapping protein structures with tiny crystals

It can be difficult to determine the atomic structure of proteins and organic compounds because of the challenges in developing large, high-quality crystallized samples that can be explored with X-rays. Academic institutions and industry have sometimes dedicated years to making suitable crystals of a single target molecule.

How LCLS Can Help

LCLS's extremely intense, highly focused X-rays allow collection of data from much smaller crystals that can be easier to prepare. The short-duration pulses, measured in femtoseconds, gather the necessary data in the instant before radiation damage sets in. In addition, protein structures can be determined at room temperature under close to physiological conditions, revealing the true structure of the molecules unaltered by cryogenic freezing.



(Top) In this illustration tiny crystallized protein samples are streamed across X-ray laser pulses. (Bottom) Hundreds of thousands of X-ray images are merged to obtain the pattern shown. (Karol Nass/CFEL)