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Applications of New DOE National User Facilities in Biology

Workshop Report

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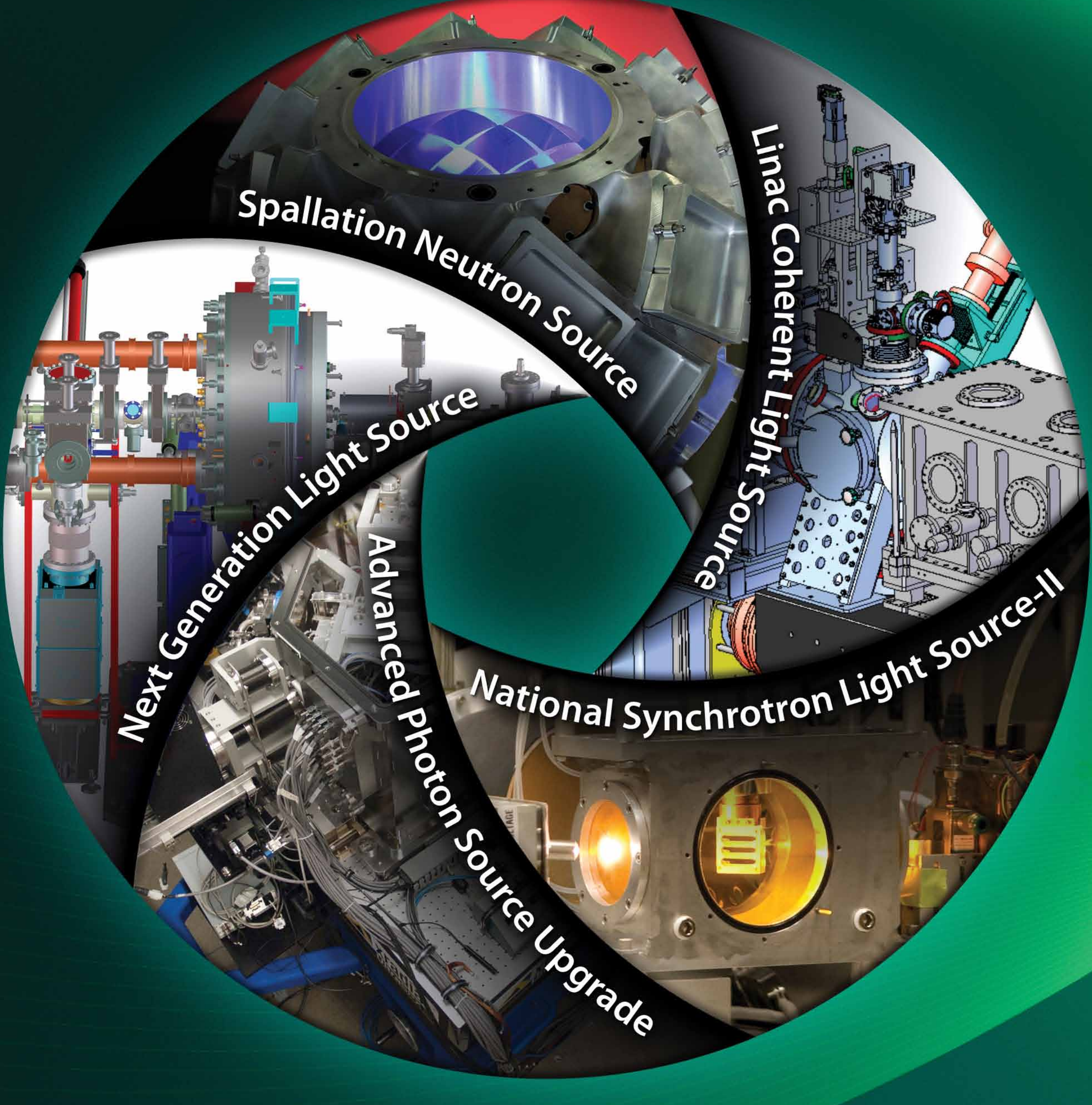

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Applications of New DOE National User Facilities in Biology Workshop

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About the Cover

Image credits clockwise from top:

- Detector array for the TOPAZ instrument, Spallation Neutron Source at Oak Ridge National Laboratory.
- Coherent x-ray imaging system, Linac Coherent Light Source at SLAC National Accelerator Laboratory.
- Bio x-ray absorption spectrometer, National Synchrotron Light Source at Brookhaven National Laboratory.
- BioNanoprobe prototype, Advanced Photon Source at Argonne National Laboratory.
- Advanced photoinjector and initial acceleration section, Next Generation Light Source at Lawrence Berkeley National Laboratory.

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Executive Summary

Biology has benefited greatly from resources enabling atomic-level investigations of matter. Biological questions that can only be addressed using high-intensity photon and neutron beams are now being explored. Particle accelerators developed over decades of research in high-energy physics have led to synchrotron light sources that offer very intense beams with tunable energies. Important contributions to the current understanding of a cell's biological infrastructure and the chemistry underpinning cellular function are based on results from experiments conducted at these synchrotrons.

An estimated 30% to 40% of light source users are from the biological sciences, and Nobel Prizes awarded in 1997, 2003, 2006, and 2009 recognized biochemical discoveries enabled by light sources. In fact, the biology community probably represents the largest single user group, even though synchrotron facilities in the United States generally were developed to support research in a variety of other fields, particularly materials science, geoscience, chemistry, and nanoscience.

In the United States, large scientific user facilities relevant to biological science are supported by many federal and state agencies. This report concerns facilities funded by the Department of Energy's (DOE) Office of Science, which develops and operates the largest base of national user facilities in the country. Within the Office of Science, the Office of Advanced Scientific Computing Research supports several of the world's fastest leadership computing facilities, with significant applications in biological science. The Office of Basic Energy Sciences (BES) maintains 17 user facilities including synchrotron radiation light sources, high-flux neutron sources, electron beam microcharacterization centers, and nanoscale science research centers. BES facilities enable progress in many scientific and technological disciplines and are used by more than 14,000 researchers annually. The Office of Biological and Environmental Research (BER) operates three major user facilities (the Atmospheric Radiation Measurement Climate Research Facility, the Environmental Molecular Sciences Laboratory, and the DOE Joint Genome Institute) that serve more than 3,000 users annually. The Offices of Fusion Energy Sciences, High Energy Physics, and Nuclear Physics also operate key facilities for research in physics that, in some cases, also have applications in the life sciences (for example, experiments for development of particle beam therapies).

BER has played a major role in enabling new capabilities for biological research at existing Office of Science facilities. The primary focus of BER's Structural Biology activity is to support specialized instrumentation for biology at synchrotron light sources and neutron facilities. The light sources produce intense beams of x-rays and other wavelengths extending into the infrared to terahertz region, while particle accelerators and nuclear reactors produce neutron beams. These beams are directed into experimental stations housing instruments configured for specific biological investigations. This infrastructure provides user access to beamline instrumentation for studies of biological organisms and molecules in all areas of life science research. BER has supported development and operation of many of the instruments at the facilities, in close coordination with counterpart programs at other agencies and in the private sector.

These research facilities enable scientific studies aimed at understanding the structure and properties of matter at the atomic, molecular, and cellular levels, experiments not possible with instrumentation available in university, institute, or industrial laboratories. Several major techniques play a dominant role in structural biology: macromolecular crystallography, scattering from noncrystalline and semicrystalline materials, x-ray spectroscopy, and imaging using x-rays or other parts of the spectrum. Each of the five facilities described in this report will offer advanced capabilities for these techniques. Experimental results from such facilities have become critical parts of many investigations into the properties of biological systems from the molecular to cellular level. Facility use has become so important and widespread in biology that support staff have been specifically designated to assist novice users in accessing these resources.

Facility capabilities are essential for studies at the frontiers of science as well as for industrial research and development. Transfer of the knowledge gained from basic biological research at these facilities often leads to advances in industry and commerce. For example, the pharmaceutical industry has benefitted from these facilities in developing cancer treatments (including a recent therapy for melanomas) and new drugs for combating infections such as HIV. Collaboration between facilities and scientific users ultimately benefits both. Continued involvement of academic scientists working at DOE national user facilities ensures development of advanced methods, and ongoing facility access allows new scientists to be trained in the design and building of new instrumentation. In fact, the training of new scientists familiar with the potential of these facilities is essential for future cutting-edge science in biology and all other fields.

New Capabilities for Biological Research

With recent advances in synchrotron physics and advanced laboratory automation, national user facilities can now be upgraded to investigate new frontiers of biology. Planning for such enhancements thus is timely. Indeed, recent upgrades to European and Japanese synchrotrons are attracting some American investigators to compete for time on these remote facilities to perform advanced experiments not yet possible in the United States.

The Office of Science has a long-term plan for development of new or upgraded national user facilities with capabilities beyond those currently delivered. Two such facilities with important implications for biological science recently began full operation, and three others are in various stages of construction or planning:

- **Advanced Photon Source Upgrade (APS-U)** at Argonne National Laboratory — planning stage.
- **Linac Coherent Light Source (LCLS)** at SLAC National Accelerator Laboratory — operating.
- **National Synchrotron Light Source-II (NSLS-II)** at Brookhaven National Laboratory — under construction, with full operations expected to begin in 2015.
- **Next Generation Light Source (NGLS)** at Lawrence Berkeley National Laboratory — planning stage.
- **Spallation Neutron Source (SNS)** at Oak Ridge National Laboratory — operating.

To identify the new experimental capabilities that these facilities will provide and assess their potential impact on biological research, BER convened the *Applications of New DOE National User Facilities in Biology* community workshop from May 9–11, 2011, in Rockville, Maryland. The workshop was co-chaired by David Eisenberg (University of California, Los Angeles) and Dagmar Ringe (Brandeis University) and included a panel of experts in biological research enabled by synchrotron light sources, neutron facilities, and free-electron lasers, as well as in other types of key instrumentation used in biological research (see Appendix F for the workshop agenda and a list of participants). Scientists from each of the national laboratories prepared preworkshop papers about the new facilities (see Appendices A–E) and made presentations and engaged in discussions with panel members during the meeting. The panel then wrote chapters describing each facility and its potential for supporting high-impact biology. The following brief summaries capture the key points in the five chapters.

Advanced Photon Source Upgrade

APS, the largest synchrotron facility in the United States, runs an extremely successful user program, especially for structural biology. It is the only U.S. light source that can provide high-energy x-ray undulator radiation now and in the near future. APS has been in operation for more than 10 years, and the timely upgrade will allow major advances in synchrotron technology to be integrated into existing or new beamlines. The upgraded facility will provide x-rays with the highest flux and brightness at energies above about 10 and 20 kiloelectron volts (keV), respectively. Such capabilities will be achieved through long, straight sections; revolver and superconducting undulators; higher electron current; and improved beam stability. Novel "crab cavities" will enable 1 picosecond pulses in time-resolved experiments. Complementing the machine upgrade is a forefront instrumentation and beamline development program for ultrafast, high-energy imaging, and *in situ* studies. The proposed beamline and instrument upgrades build on world-leading programs and fully exploit unique APS properties. Importantly, in view of APS's pivotal role in academic and industrial structural biology, machines will be upgraded with minimal loss of operating hours for ongoing programs. Two infrastructure projects—an automated crystallization facility and the Cryo Sample Preparation Facility—will meet the increasingly important need for onsite sample preparation in biological research. In summary, the proposed upgrade program is essential for restoring APS as a leading synchrotron source among new and recently upgraded facilities with significant impacts in biology.

Linac Coherent Light Source

LCLS is the world's first x-ray free-electron laser (XFEL) user facility. The machine produces extremely bright x-ray pulses as short as 10 femtoseconds over the energy range of ~500 to 10,000 eV with ~10^{12} photons per pulse. LCLS is capable of producing x-ray pulses of the highest energy of any XFEL worldwide. Five of the six planned multidisciplinary experimental stations are open to the user community and have produced exciting results; the sixth (Matter in Extreme Conditions) is in commissioning and will begin serving users in May 2012. The initial success of experiments on femtosecond nanocrystallography at LCLS has generated great excitement among structural biologists. Structure determination is based on collection of thousands of femtosecond x-ray diffraction snapshots collected on a stream of nanocrystals by femtosecond pulses. As diffraction is recorded in femtoseconds before the sample is destroyed, this method (1) overcomes the radiation damage problem in x-ray crystallography, (2) enables data collection on crystals that contain less than 1,000 unit cells, (3) allows data collection at room temperature, and (4) may open the way for a new era of x-ray crystallography from nanocrystals. The first time-resolved femtosecond crystallography experiments indicate that LCLS will enable the determination of time-resolved x-ray data that could lead to molecular movies of biomolecules at work on a subpicosecond time scale. Early results from coherent x-ray imaging of single virus particles indicate that single particles can be imaged at LCLS and that the higher peak brilliance of the facility's planned expansion (LCLS-II) may extend single-particle analysis to atomic resolution. Plans for LCLS-II, to be completed in 2018, include increasing the peak brilliance of x-ray pulses, extending the energies accessible to a range from 200 eV to 20 keV, and supporting up to six simultaneous experiments. LCLS holds great potential for enabling researchers to obtain high-resolution structural data from biological samples free of radiation damage. Realizing this exciting promise will require further development of new detectors, rapid and low-consumption sample delivery techniques, and improved data analysis methods.

National Synchrotron Light Source-II

Currently under construction, NSLS-II is set to begin operations in 2014. This synchrotron radiation source, located near the original NSLS, will accommodate at least 58 beamlines covering a wide range of disciplines, including the life sciences. Completely new, NSLS-II will deliver an extremely bright beam from the far infrared to the very hard x-ray region. By providing the world's brightest light source x-ray beams ranging from 2 to 10 keV, NSLS-II will be uniquely positioned to provide capabilities in this energy range, such as bright coherent beams for imaging and spectroscopy. For higher-energy x-rays, NSLS-II will be comparable to the best light sources. This facility will open new frontiers in photon sciences and engender development of new instruments and techniques to exploit fully its beam characteristics with cutting-edge projects such as a 1 nm hard x-ray nanoprobe. Planned biological beamlines at NSLS-II encompass macromolecular crystallography, scattering, spectroscopy, and imaging, ensuring that NSLS-II will play a major role in future biological research. In addition, the NSLS-II design includes a Biology Village or community of highly integrated groups working in different but related areas of the life sciences. This Village will provide a unified and synergistic environment for life science experiments and change the way researchers interact and work at a synchrotron radiation user facility. NSLS-II promises to be an outstanding source for many new types of experiments in various disciplines and will help the U.S. maintain a strong leadership position in synchrotron-based biological research.

Next Generation Light Source

NGLS is a new facility in the early stages of planning (anticipated first light is in 2022). With an array of 10 independently configurable XFELs powered by a superconducting linear accelerator, NGLS will be capable of delivering ultrafast, high-brightness, and high-resolution pulses of low-energy x-rays at high repetition rates. Each of these features distinguishes NGLS from any existing synchrotron or XFEL and contributes to its currently envisaged suite of transformative scientific capabilities for biology. For example, macromolecules, molecular assemblies, organelles, and cells will be imaged in real time and in real biological contexts. Individual biological objects will be imaged, rather than averaged over a large sample, to enable new understanding of the role of biological heterogeneity. Selective enhancement of scattering from specific chemical groups will permit simultaneous investigations of the structure and chemistry of molecular systems in solution. Additional powerful applications undoubtedly will emerge once this unique light source comes online.

Spallation Neutron Source

SNS approached its designed operational capability about a year ago, becoming one of the world's two most powerful sources for investigating the structure and dynamics of biomolecular systems by elastic and inelastic neutron scattering. Isotopic substitution, specifically deuterium for hydrogen in the case of biological systems, coupled with contrast matching of selected components, provides a distinct advantage for these neutron-scattering techniques. This method can reveal key aspects of structure and dynamics over a wide range of length and time scales within complex macromolecular systems. Although important for studying biological macromolecules in single crystals, these techniques are essential for investigating more complex, noncrystalline systems, including multicomponent macromolecular assemblies in solution and liquid-crystalline membranes. Two important upgrades have been proposed and built into the SNS design. One would expand the proton accelerator's power, increasing by two to three times the flux of spallation-produced neutrons. This increase is highly significant because most neutron-scattering experiments are "flux-starved" (i.e., limited only by the available neutron flux). The other upgrade would add a second target station optimized for producing longer-wavelength "cold" neutrons important for structural studies of large macromolecular systems at longer length scales. This upgrade also will provide much needed additional capacity, including instruments optimized for studying biological systems.

The Path Forward

This workshop report describes in detail these five major national user facilities and identifies their potential for significant impacts on biological research. The facilities—which have begun initial operations or are expected to move from planning to upgraded or new construction in the coming decade—will support a wide range of biological experiments. Such experiments include those that can be planned now and others that can be planned only after capabilities of the new facilities emerge. These facilities are expected to offer new technologies that will advance not only biology, but also many other disciplines such as chemistry, geology, physics, and materials science.

For optimal service to the scientific community, the facilities also must consider the collateral needs of users. Of paramount importance will be development of a new generation of detectors, as well as advanced approaches for specimen mounting, preservation, and changing, including robotic devices for high-throughput applications. These capabilities will maximize the output of the experimental stations at the facilities. Advances in technology and methods for data processing and storage will be critical, and adequate plans to recruit, house, and train new users are essential.

By focusing on the present and potential future capabilities of the five facilities, this report seeks to increase awareness of them among scientists in all areas of biology and related disciplines. Informing researchers about such capabilities and how they can be used to advance individual research is a challenge for each facility.