How Light and Neutron Facilities Can Enable Biological Systems Science Relevant to DOE's Biological and Environmental Research Mission

Report from the Workshop

Convened at SLAC National Accelerator Laboratory
Menlo Park, California
August 25, 2016

Rationale for Workshop

The Genomic Science Program (GSP) of the U.S. Department of Energy's (DOE) Office of Biological and Environmental Research (BER) supports systems and synthetic biology research aimed at identifying the central principles driving the biological systems of microbes, plants, and multispecies communities. GSP research focuses on developing a fundamental understanding of genome biology. This knowledge is needed to design, modify, and optimize plants, microbes, and biomes for beneficial purposes relevant to DOE missions in energy and the environment.

Across the DOE complex is a portfolio of research technologies, methodologies, and instruments currently available, or to be developed, especially using DOE synchrotron and neutron national user facilities. These resources can enable critical experiments needed to understand processes of importance to BER GSP–funded investigators and centers. The spatial and temporal resolutions available from neutron and photon beams enable unprecedented characterization and imaging of interactions among plants, microbes, and the environment. The scales studied range from subnanometer to millimeter length and over time dimensions from femtoseconds to seconds. The capabilities to provide molecular fingerprints and mechanistic and dynamic understanding of *in situ* ecosystem processes impact various BER science focus areas (SFAs). See Fig. 1, p. 2, for a graphic perspective of this research space. (Image from the 2015 BER Molecular Science Challenges Workshop Report).

Goals and Objectives

The purpose of this workshop was to develop a strategy to promote and expand collaborations between BER-supported user facilities and the BER research community. These interactions will enable and facilitate the necessary fundamental science to understand, predict, manipulate and design biological processes that underpin innovations in DOE energy and environmental missions. BER sees a unique opportunity afforded by photon and neutron sources to innovate and develop new tools for

understanding the interface of biology with the physical sciences in BER mission areas. Specific aims discussed at the workshop included:

- Build upon the existing investments and align light and neutron source capabilities to the mission needs of DOE BER.
- Foster a spirit of collaboration to enable integrative capabilities within and among DOE user facilities to foster a fully interdisciplinary approach to BER-relevant science.
- Reach out to those in the existing BER research community to evaluate their needs and train them in new experimental approaches, thus propagating the knowledge and broadening the community to generate high-impact scientific results.
- Develop innovative, enabling technologies, through the construction of state-of-the-art instruments that exploit the world-leading characteristics of each source. These instruments will boost capabilities for basic scientific biological knowledge, thereby providing DOE and the nation with leading-edge biological science. This new instrumentation will enable multimodal imaging capabilities over length scales from subnanometer to millimeter.

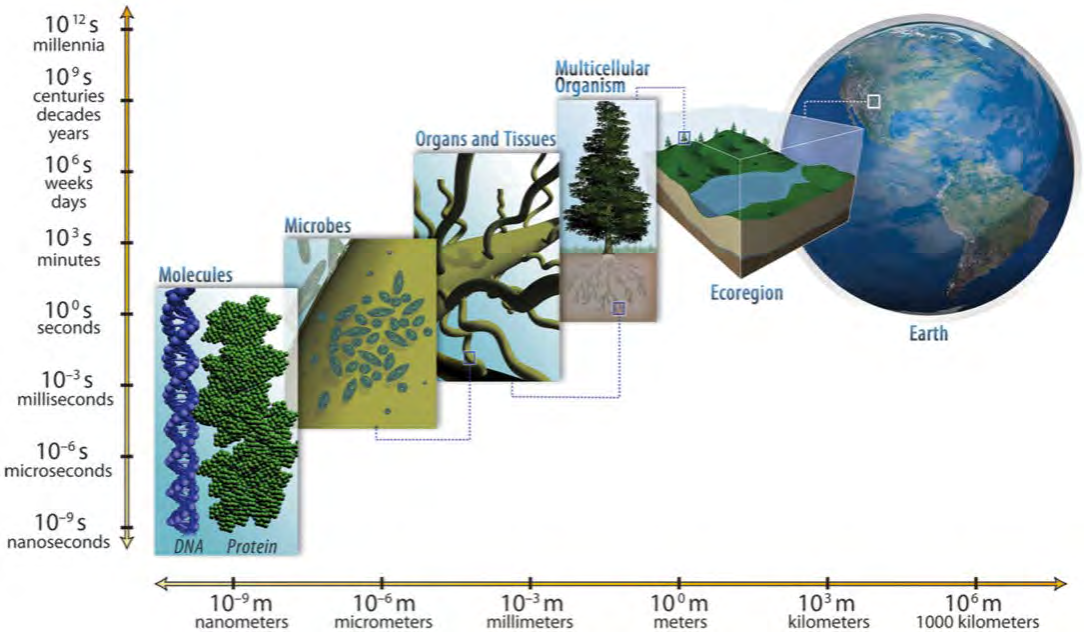

Fig. 1. Graphic perspective of biological and environmental interactions across scales. (Figure from U.S. DOE. 2015. *Office of Biological and Environmental Research Molecular Science Challenges; Workshop Report*, DOE/SC-0172. U.S. Department of Energy Office of Science (genomicscience.energy.gov/molecularscience/).

Workshop Format and Agenda

The workshop was organized to foster discussions between BER user facility scientists with investigators whose research portfolios involved BER mission science areas. The workshop agenda is appended at the end of this report. The first facilities presentation provided an overview of the resources available at the light and neutron sources and how they can be used to address a broad range of biological questions. This overview was followed by four science presentations from BER-funded researchers in biology. In all cases, there was clear synergy between the complex and multiscale nature of the research questions posed by the BER-funded investigators about the capabilities of the light and neutron sources. A second facilities presentation by the DOE Joint Genome Institute (JGI) outlined its capabilities in genome sequencing and synthetic biology and how JGI's efforts relate to downstream "omics" technologies available at DOE's Environmental Molecular Sciences Laboratory (EMSL). There was extensive discussion and planning for steps to follow the workshop. A summary of these discussions and workshop outcomes follows.

Discussion Summary and Conclusions

DOE noted to participants that there are major DOE investments in the construction and operation of the light and neutron sources. The research capabilities offered by these state-of-the-art national user facilities impact many areas of science and technology, including the biological sciences. In addition, there have been long-term, coordinated investments by BER and the National Institutes of Health (NIH) in the construction and operation of light and neutron source beam lines and instruments for biology applications. This collaborative support has led to significant growth in scientific discoveries, publications, and resource users in broad areas of the biosciences, perhaps most dramatically in the biomedical area. This is an opportune time and excellent opportunity to build on the existing investments and align light, neutron, and, possibly in the future, electron source capabilities with other DOE-funded resources to advance BER mission needs. Such a focused initiative involving the light and neutron sources could be achieved in a coordinated manner, targeting specific BER-relevant scientific problems and needs. This approach would enrich and expand BER-funded programs already supported at the facilities and open up new science opportunities relevant to the DOE BER mission. The discussions focused around the topics described below.

Outreach. Fostering a spirit of collaboration will be important to enable integrative capabilities for nurturing a fully interdisciplinary approach to BER-relevant science. One key aspect would be effective dissemination of information about the light and neutron source capabilities and methodologies. A key to achieving these objectives is to make available

coordinated information across the user facilities through a common access web portal. In addition to capabilities and user access information, the website could feature recent science highlights and information in video clips.

There also was discussion about reaching out to those in the existing BER research community to evaluate their needs and train them in the new experimental approaches. This would be the most rapid way to lead to high-impact scientific results. One means of achieving this would be through workshops and hands-on training, for example, in conjunction with BER genomic science principal investigator (PI) meetings, facility user meetings with BER-specific workshops, and symposia. In addition, a coordinated effort will be needed to target relevant national meetings focusing on biological problems rather than on technology.

***Training*.** Also important will be nurturing collaborations and interdisciplinary research, especially because some investigators may be more accustomed to working as individual PIs and do not possess the necessary expertise in x-ray and neutron techniques in their own laboratories. Means should be sought to find better ways of outreach to biology laboratories and new training methods. The BER SFAs offer a good starting point to develop an effective model for interaction. There also are significant opportunities to take advantage of recent developments in remote access and automation for training purposes. Two other strategies would be to engage DOE BER young investigator awardees and seek to use the DOE Office of Science Graduate Fellowship (SCGF) program. An objective should be to facilitate cross-technique and cross-facility training. This process eventually could be expanded to give available funding to postdoctoral and visiting fellow programs. In this regard, a helpful mechanism for BER to consider would be supplementary funding for BER investigators that would enable them to employ these unique resources and to develop expertise for use in their own laboratories. This approach would create a self-sustaining community in BER-related biophysical research.

***Access Mechanisms*.** Clearly, the diversity of science questions being addressed by BER investigators demonstrates that a combination of multiple capabilities will be used to solve the most challenging and complex biological problems and will lead to the most impactful discoveries. To achieve these objectives, a mechanism is needed that allows investigators to submit a single proposal for access to all relevant capabilities at BER-funded facilities. Appropriate facilities could coordinate proposal reviews and, ultimately, create a common “gateway” for user access. This could be accomplished by expanding ongoing collaborative science initiatives (e.g., the Spallation Neutron Source–High Flux Isotope Reactor / National Synchrotron Light Source II and the DOE JGI / EMSL / Argonne National Laboratory (ANL) pilot partnerships) to deliver innovative science while

expanding the reach and impact of the user facilities. Another idea would be to rapidly establish an inter-facility pilot program that integrates JGI / EMSL / light and neutron sources (or that integrates with the Facilities Integrating Collaborations for User Science (FICUS) effort between DOE JGI and EMSL.

New Methods, Complementary Technologies and Instruments. At the frontier are new instruments (or integration of existing ones) that will enable multimodal imaging capabilities over length scales from subnanometers to millimeters. Participants recognized that there are opportunities to take further advantage of the new x-ray free electron laser (XFEL) sources and optimize their use by developing coupling technology at light sources that feeds into XFEL sources and *vice versa*.

The integration of complementary techniques is another area of opportunity. The need for R&D and capital investment in cryo-electron microscopy and tomography (cryo-EM/ET) and single-particle characterization capabilities also was discussed. These techniques potentially could revolutionize future protein structural biology and cellular imaging but require significant capital and human investment that is now out of reach for many research institutions. Co-locating cryo-EM/ET facilities at neutron and light sources would be practical, capitalizing on established open access user programs and the expertise in operating advanced instrumentation. Currently, this approach is under way at the Diamond Light Source in the United Kingdom. Another key component is high-performance computational methods development (e.g., three-dimensional models, disordered systems, spectroscopic characterization, and dynamics). As the complexity of the systems under investigation by BER researchers increases, the need becomes critical to develop computational tools that allow analysis of data sets from disparate sources over multiple length and time scales. National laboratory resources provide opportunities for scientists to use existing cutting-edge computing capabilities for advanced data analysis and modeling, and this access could have an important role in developing next-generation capabilities. In all these areas, the cross-fertilization between different facilities and techniques is essential to offer another area of opportunity for effective national stewardship through DOE BER and NIH coordination.

Key to future impact and innovation is the continued development of enabling technologies, through the construction of state-of-the-art instruments exploiting the world-leading characteristics of each of the light and neutron sources. These instruments will boost capability for basic biological scientific knowledge, thereby providing leading-edge science for DOE in this area.

Actions. Workshop participants proposed establishment of a core steering committee to coordinate efforts. Suggestions for the steering group's

charge and configuration include (1) communicating frequently, at least monthly, via telecom; having one formal representative from each facility; and identifying additional scientists to act as “points of contact” for each technique. A BER science user group should be named to provide advice, which should flow up through the steering committee.

Further, a one-page summary of workshop outcomes should be prepared, along with a more in-depth report. Slides were prepared in anticipation of an opportunity for presentation at the September BER workshop, Technologies for Characterizing Molecular and Cellular Systems Relevant to Bioenergy. A science slide from each of the four workshop speakers also was produced to illustrate the impact and opportunities from using the light and neutron sources. Coordination of these efforts with FICUS and BER program staff should continue. In addition, an outreach process should connect with major BER programs such as new Bioenergy Research Centers and SFAs. Plans should be made for outreach and information exchange at the 2016 DOE Genomic Science Program Annual PI Meeting in February 2017. Formulation of steps should be taken for developing a web portal to provide information on BER user facility capabilities and access to them.

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Agenda

8:20	Registration
8:50	**Amy Swain**, DOE BER: Introduction and BER perspective
9:00	**Keith Hodgson**, SLAC National Accelerator Laboratory (SLAC): U.S. light and neutron source capabilities
9:40	**Paul Gilna**, Oak Ridge National Laboratory (ORNL)
10:20	**Kirsten Hofmockel**, DOE Environmental Molecular Sciences Laboratory (EMSL)
11:00	Coffee break
11:20	**Sabeeha Merchant**, University of California, Los Angeles (UCLA)
12:00	**Michelle O'Malley**, UC, Santa Barbara (UCSB)
12:40	Working lunch
13:40	**Yasuo Yoshikuni**, DOE Joint Genome Institute (JGI)
14:20	**Soichi Wakatsuki** and **Britt Hedman**, SLAC: Session 1 discussion leader
15:20	Coffee break
15:40	**Paul Adams**, Lawrence Berkeley National Laboratory (LBNL), and **Sean McSweene**y, National Synchrotron Light Source II (NSLS-II): Session 2 discussion leaders
16:40	**Andrzej Joachimiak**, Argonne National Laboratory (ANL), and **Hugh O'Neill**, ORNL: Plan of action, closing remarks

Workshop Attendees

Paul Adams, LBNL
Wah Chiu, Baylor Medical College
Britt Hedman, SLAC
Keith Hodgson, SLAC
Paul Gilna, ORNL
Kirsten Hofmockel, EMSL
Andrzej Joachimiak, ANL
Sean McSweeney, NSLS-II
Sabeeha Merchant, UCLA
Michelle O'Malley, UCSB
Hugh O'Neill, ORNL
Amy Swain, DOE BER
Soichi Wakatsuki, SLAC