DOE/SC-0205

Biological Systems Science Division

Strategic Plan

April 2021

U.S. DEPARTMENT OF ENERGY | Office of Science

Office of Biological and Environmental Research

U.S. Department of Energy
Office of Science
Office of Biological and Environmental Research

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This report is available at genomicscience.energy.gov/2021bssdstrategicplan/.

Cover images: Microbes in thawing permafrost, Environmental Molecular Sciences Laboratory. Switchgrass field, Great Lakes Bioenergy Research Center; licensed under Creative Commons CC BY-NC-ND 2.0. Rhizosphere consortia, Lawrence Livermore National Laboratory.

Suggested citation for this report: U.S. DOE. 2021. *Biological Systems Science Division Strategic Plan*, DOE/SC-0205. U.S. Department of Energy Office of Science (genomicscience.energy.gov/2021bssdstrategicplan/).

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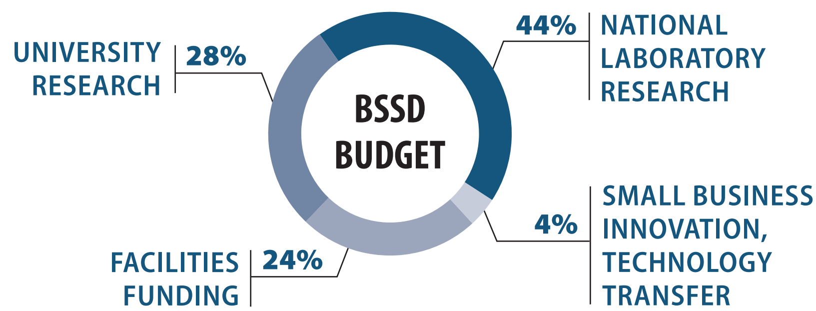
BIOLOGICAL SYSTEMS SCIENCE DIVISION | BY THE NUMBERS FY20

3 BSSD Primary Research Areas

- **BIOENERGY RESEARCH** *(Plant Genomics, Microbial Conversion, Sustainable Bioenergy)*
- **BIOSYSTEMS DESIGN** *(Secure Biosystems Design)*
- **ENVIRONMENTAL MICROBIOME RESEARCH**

$404.8 MILLION RESEARCH BUDGET



BSSD RESEARCH SPANS

11 DOE NATIONAL LABORATORIES

95 ACADEMIC, NONPROFIT, AND INDUSTRIAL INSTITUTIONS

31 STATES, WASHINGTON, D.C., AND PUERTO RICO

237 ACTIVE RESEARCH PROJECTS

- **165** LED BY ACADEMIC, NONPROFIT, AND INDUSTRIAL INSTITUTIONS
- **72** LED BY NATIONAL LABORATORIES

3,079 RESEARCHERS SUPPORTED

4 BIOENERGY RESEARCH CENTERS

- **3,756** PUBLICATIONS
- **781** INVENTION DISCLOSURES
- **558** PATENT APPLICATIONS
- **258** LICENSES/ OPTIONS
- **207** PATENTS
- **21** STARTUP COMPANIES

ENABLING CAPABILITIES AND COMMUNITY RESOURCES

COMPUTATIONAL BIOLOGY RESEARCH

22 PROJECTS LED BY UNIVERSITIES AND NATIONAL LABS

BIOIMAGING SCIENCE

- **9** NATIONAL LAB PROJECTS
- **19** UNIVERSITY PROJECTS *(10 QUANTUM PROJECTS)*

4 RESOURCES WITH >10,800 USERS A YEAR

DOE JOINT GENOME INSTITUTE SCIENTIFIC USER FACILITY

- **290,492** GIGABASES SEQUENCED
- **>2,000** CUMULATIVE PUBLICATIONS

STRUCTURAL BIOLOGY AND IMAGING RESOURCES

10 RESOURCES AT **6** DOE USER FACILITIES

KBASE

- **300** ANALYSIS TOOLS
- **34,564** USER NARRATIVES

NATIONAL MICROBIOME DATA COLLABORATIVE

17 TB OF OMICS DATA *(proteomes, metatranscriptomes, metagenomes, metabolomes, and more)*

Chapter 1

Fundamental Systems Biology Research for Accelerating a Burgeoning Bioeconomy

The United States currently holds an important innovative edge in the burgeoning and globally competitive bioeconomy market. This edge offers significant economic benefits to technological "first movers," but maintaining it will rely strongly on a vibrant basic science effort to understand the fundamental principles of genome biology. These principles, encoded in the genomes of plants and microbes, can advance breakthroughs in renewable biofuels and bioproducts development, biotechnology, and understanding of key interactions among microbiomes that shape our environment.

The Biological and Environmental Research (BER) program within the U.S. Department of Energy's (DOE) Office of Science has been at the forefront of genome biology research since its pioneering role in initiating the sequencing of the human genome. This effort was a milestone in genome biology that spurred an accelerating revolution in genome sequencing technology and other omics techniques that fuel today's biotechnology innovations. More recently, genomic science advances have stemmed from insights gained through the increasingly multidisciplinary collaborations of biologists, chemists, physicists, computer scientists, and engineers.

As a major supporter of basic genome-enabled research, BER's Biological Systems Science Division (BSSD) fosters scientific discovery by combining fundamental biological research across disciplines with enabling capabilities and world-class user facilities. This document outlines a high-level overview of BSSD's integrated science goals and strategies to understand, predict, manipulate, and design new biological processes for addressing DOE mission objectives in energy and the environment.

Strategic Foundation

The Division's strategy is rooted in broader planning efforts across DOE and seeks to align with DOE's strategic plan (U.S. DOE 2014) to enhance the nation's energy and environmental security and to promote basic research in the environmental and biological sciences in support of DOE's mission. Other inputs help further shape the Division's strategy (see Fig. 1.1, p. 2). BSSD receives stakeholder input through guidance from the Biological and Environmental Research Advisory Committee (BERAC), which publishes periodic reports on emerging research needs (BERAC 2017). BSSD also gathers feedback during workshops on mission-relevant topics. For example, recent workshops have sought to strengthen the Division's portfolio by exploring ways in which gene function may be better understood across diverse plant and microbial taxa (U.S. DOE 2019a) and examining how genomic information may aid in the synthesis and design of new biomaterials (U.S. DOE 2019b). The Division's strategy is further informed via a tight integration of program management activities with its research portfolio. In addition, BSSD leverages synergies across DOE and at other federal agencies to strengthen and enhance its strategic outlook, fill research gaps, and broaden the impact of its research community.

Overarching BSSD Goal

Provide the necessary fundamental science to understand, predict, manipulate, and design biological systems that underpin innovations for bioenergy and bioproduct production and enhance our understanding of natural, DOE-relevant environmental processes.

Research Portfolio

BSSD's overall research goal is to provide the necessary fundamental science to understand, predict, manipulate, and design biological systems that underpin innovations for bioenergy and bioproduct production and to enhance our understanding of natural,

Fig. 1.1. Multiple Mechanisms Shape BSSD's Strategy. BSSD relies on stakeholders and the research community to inform its vision, with these inputs all feeding back into each other in a dynamic interplay that helps to prioritize the research portfolio.

DOE-relevant environmental processes. At the core of this effort is BSSD's Genomic Science program, which supports basic research to answer fundamental biological questions including:

1. What information is encoded in a genome sequence, and how does this information direct the functional characteristics of cells, organisms, and whole biological systems?
2. How do interactions among cells regulate the functional behavior of living systems, and how can these interactions be understood dynamically and predictively?
3. How do plants, microbes, and communities of organisms adapt and respond to changing environmental conditions (e.g., temperature, water and nutrient availability, and ecological interactions), and how can their behavior be manipulated toward desired outcomes?
4. What organizing biological principles need to be understood to facilitate the design and engineering of new biological systems for beneficial purposes?

The Genomic Science program encompasses a broad range of research areas including bioenergy research, genome biology and sustainability of bioenergy crops, biosystems design or synthetic biology, environmental microbiomes, and computational biology and cyberinfrastructure for genomic science. These areas represent distinct pillars of the program, but each one is also tightly integrated with other portfolio elements, such as enabling capabilities and user facilities, through targeted, crosscutting funding opportunities

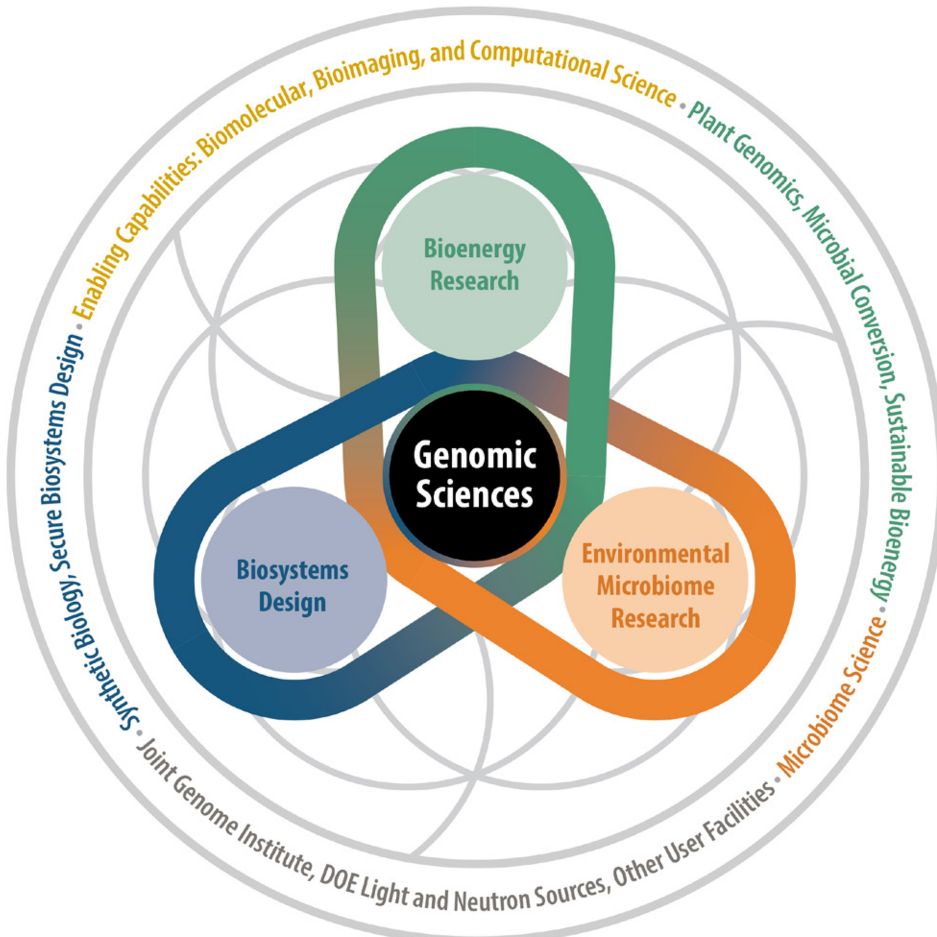


Fig. 1.2. Biological Systems Science Division Portfolio. BSSD's three primary research areas in genomic sciences—Bioenergy Research, Biosystems Design, and Environmental Microbiome Research—are supported by a suite of user facilities and enabling capabilities in computational biology and biomolecular characterization and imaging science.

and DOE national laboratory projects. Among these intersecting themes are three major components: Bioenergy Research, Biosystems Design, and Environmental Microbiome Research (see Fig. 1.2, this page).

Bioenergy Research seeks to couple a basic understanding of plants and their associated microbial communities to advance the sustainable production of biofuels and bioproducts from plant biomass. Dedicated crops grown on marginal lands for conversion into renewable sources of fuels or valuable chemicals and bioproducts represent a key strategy to reduce the nation's reliance on fossil resources for the production of these critical materials. Because fossil resources are ultimately finite and subject to economic and geopolitical uncertainty, renewable sources for the fuels and products that support modern society are of keen interest to DOE, and they are a long-term strategic need for the nation and a strong bioeconomy (see sidebar, Maintaining U.S. Competitiveness in the Global Bioeconomy, p. 4).

BSSD's Biosystems Design efforts focus on understanding fundamental biological principles to enable the design and engineering of plants and microbes with new or enhanced traits beneficial for energy or environmental applications. Rapid advances in genome-enabled discovery, design, and engineering are leading to exciting new possibilities in biotechnology to create new biosynthetic processes by drawing from the gene diversity found in nature and accumulated

Maintaining U.S. Competitiveness in the Global Bioeconomy

Advances in fundamental biological research and enabling technologies have sped the creation of commercial opportunities in fields spanning from agriculture to pharmaceuticals to energy, producing major economic and societal benefits. *Safeguarding the Bioeconomy*, a report by the National Academies of Sciences, Engineering, and Medicine (2020), estimates the value of the U.S. bioeconomy at nearly $1 trillion, or 5.1% of gross domestic product. The report defines the bioeconomy as "economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences." Producing breakthrough scientific results that continue to fuel the bioeconomy hinges on sustained investment in basic science research and developing and attracting a skilled workforce, particularly in life science applications of computational and information science.

understanding of biological processes. This area of research is both fascinating in terms of its possibilities and challenging as the global pace of research is accelerating rapidly. The Division is committed to building on its established presence in the field of basic genome-enabled research and using newfound knowledge to explore possibilities in genome design.

BSSD's Environmental Microbiome Research seeks to understand how microbes and plants interact in their natural environment. Microorganisms and plants have evolved in the context of complex microbiomes and environmental change. Discovering how microbes interact within communities and adapt to environmental perturbations and long-term change is essential for understanding the many bioenergy and environmental processes relevant to DOE. Of particular interest is the ability to predict interactions among organisms based on the information encoded in their genomes, as well as the dynamic expression of their activities in association with one another and their environment. Gaining a predictive and functional understanding of microbiomes will enable better understanding of microbial ecology, plant-microbe interactions, and the cycling of elements in terrestrial environments.

These primary Genomic Science program elements are supported by BSSD's efforts to develop enabling capabilities. In particular, BSSD will build integrative, open-access computational platforms to combine datasets with analysis applications in a "virtual laboratory" concept to accelerate collaborative, multidisciplinary science. As demonstrated during the COVID-19 pandemic, the integrated, high-performance computing-based analysis of molecular, structural, imaging, multiomic, cellular, and multicellular datasets can efficiently guide researchers toward potential solutions to otherwise intractable problems (e.g., possible therapeutic solutions for COVID-19).

Going forward, BSSD will work to increasingly integrate data science techniques into its research approach to support DOE mission areas. Early efforts to create greater virtual integration of data and analytical capabilities are underway across the DOE Joint Genome Institute (JGI), Environmental Molecular Sciences Laboratory (EMSL), DOE Systems Biology Knowledgebase (KBase), and new National Microbiome Data Collaborative (NMDC). Re-envisioning the way that BER uses data to accelerate genome-enabled science could revolutionize how science is conducted. BSSD will pursue this virtual laboratory concept and seek partnerships within DOE and other agencies to realize this vision.

Outlined in the following sections are the current goals and objectives within the Division's major research efforts. These efforts are complemented by a suite of enabling capabilities and technologies available at DOE national scientific user facilities.

Chapter 2

Genomic Sciences: Primary Research Efforts

BSSD-supported research at universities and national laboratories is providing systems-level understanding of plants, microbes, and their communities. This multidisciplinary portfolio—broadly grouped under Bioenergy Research, Biosystems Design, and Environmental Microbiome Research—pursues innovative science underpinning advances in sustainable biofuels and bioproducts; the design, modification, and optimization of plants and microbes for beneficial purposes; and next-generation technologies for systems biology research.

Bioenergy Research

Goal: *Provide the basic science needed to convert renewable biomass to a range of fuels, chemicals, and other bioproducts in support of a burgeoning bioeconomy.*

Today's liquid fuels and many of the chemical products and materials that support modern society are primarily derived from petroleum and other fossil resources. Producing fuels, chemicals, and bioproducts (including materials) from renewable plant biomass could reduce our dependence on fossil resources and pave the way toward a more sustainable bioeconomy (see Fig. 2.1, this page).

BSSD Bioenergy Research efforts seek to provide the fundamental science needed to underpin the production, breakdown, conversion, and use of plant biomass as a renewable alternative to petroleum. The scope of this research includes gaining a basic understanding of plant and microbial genomics for dedicated crop development and conversion of plant biomass into products and pursuing fundamental insights into the sustainability of bioenergy crop production. Many of the

Fig. 2.1. Biofuel Feedstocks. Lowland switchgrass is ready for harvesting from a common garden in Overton, Texas. [Courtesy University of Texas–Austin]

Bioenergy Research Centers

genomicscience.energy.gov/centers/

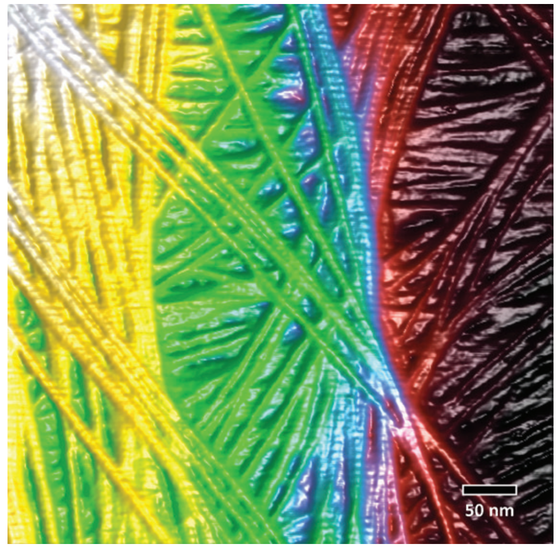
DOE's Bioenergy Research Centers take an integrated research approach that aims to improve and scale advanced biofuel and bioproduct production processes. Important goals are the sustainable production of feedstocks, their deconstruction and separation, and their conversion to next-generation biofuels and bioproducts.

Center for Advanced Bioenergy and Bioproducts Innovation (CABBI)
cabbi.bio
University of Illinois at Urbana-Champaign

Center for Bioenergy Innovation (CBI)
cbi.ornl.gov
Oak Ridge National Laboratory

Great Lakes Bioenergy Research Center (GLBRC)
glbrc.org
University of Wisconsin–Madison

Joint BioEnergy Institute (JBEI)
jbei.org
Lawrence Berkeley National Laboratory



Cellulose Microfibrils. The nanostructure of a native plant cell wall imaged using atomic force microscopy (AFM) shows layers of interwoven cellulose microfibrils. Scientists used AFM to study the dynamic structure of plant cell walls from fresh plant and lignocellulosic biomass during enzymatic deconstruction. [Courtesy Shi-You Ding, Michigan State University]

Division's recent efforts have been performed within the four DOE Bioenergy Research Centers (BRCs). These large, interdisciplinary BRC teams have provided key basic science insights needed to spur broader development of biofuels and bioproducts from lignocellulosic plant biomass (see sidebar, Bioenergy Research Centers, this page). Continued research within BSSD will seek to expand this body of knowledge to extend the range of biofuels and bioproducts that can be produced from biomass feedstocks.

The Division plans to maintain investments in the Bioenergy Research program's core strengths related to plant genomics and the development of dedicated bioenergy crops, deconstruction of plant biomass, microbial conversion of biomass to fuels and products, and the sustainability of bioenergy crop production. BSSD will support these efforts through awards to large, integrative teams such as the BRCs, smaller team research projects, and single investigators. Additionally, the Division will seek to encourage greater integration among the current BRCs toward common goals, objectives, and milestones that chart a path for the next decade of bioenergy research.

Plant Genomics

> ***Subgoal:*** *Gain a genome-level understanding of plant metabolism, physiology, and growth to develop new bioenergy feedstocks with traits tailored for bioenergy and bioproduct production.*

Realizing the potential of lignocellulosic biomass as a source of renewable energy and biobased products requires the development of high-yielding crops and trees or nonfood oil seed crops that efficiently use resources and minimally disrupt existing food and fiber markets. Additionally, bioenergy feedstock production needs to contend with changing climatic conditions and ensuing environmental impacts (e.g., drought,

Fig. 2.2. Plant Systems Biology. Rebecca Dewhirst, a postdoctoral researcher at Lawrence Berkeley National Laboratory (LBNL), studies the leaf water potential of poplar trees in response to an experimental drought. [Courtesy LBNL]

temperature extremes, and increased pathogen pressure), which may threaten the productivity of all agricultural crops (see Fig. 2.2, this page).

Plant research faces unique challenges in biological and genetic diversity, such as teasing out the frequent segmental and whole genome duplications that often result in large gene families and subfunctionalization of their member genes. These plant genome features add layers of complexity to the already intricate nature of eukaryotic gene expression and regulatory networks. While this complexity has increased plants' adaptability to diverse environments, it also poses challenges in identifying and characterizing the functional roles of genes responsible for plant phenotypes. Furthermore, researchers estimate that the function of about 40% of all genes in any sequenced plant genome remains unknown.

The Division recognizes that gene function determination has not kept pace with omics data acquisition and that this incongruence represents an ascending challenge for the research community. BSSD will therefore seek to support research into more efficient, higher-throughput, multidisciplinary methods for generating experimental evidence of gene function. This effort will involve integrating plant physiological experimentation with high-throughput phenotyping and novel computational approaches. Supported research will leverage the unique infrastructure offered by BER's user facilities (JGI and EMSL), as well as DOE's light and neutron sources, and research goals will tightly align with those of the computational biology portfolio. BSSD strives to achieve a better understanding of whole living systems by elucidating the properties of individual components within their molecular, cellular, and organismal contexts, thereby gaining the ability to predict bioenergy feedstock behavior under fluctuating and sometimes extreme conditions. A fuller picture of the role played by an organism's genetic background should allow researchers to accurately predict phenotype from genotype and enable more rapid scientific advancement.

In this context, current objectives for BSSD plant genomics research are to:

- Discover and functionally characterize key plant genes and alleles that influence yield and quality traits and/or confer adaptability or resilience to a range of environmental conditions and change in biomass crops (e.g., switchgrass, energy sorghum, poplar, and *Miscanthus* spp.) and nonfood oilseed crops (e.g., *Camelina* spp. and pennycress).
- Develop innovative approaches for understanding the distinct functions of genes, proteins, and metabolites of the multiple cell types found within plant organs.
- Comprehensively investigate genetic and epigenetic regulatory mechanisms and develop methods to discern regulatory differences among gene family members.

- Develop comparative approaches to enhance knowledge of the structure, function, and organization of plant genomes and to identify reduced sets of candidate genes for detailed functional characterization across related species.
- Determine high-resolution molecular structures of proteins/enzymes and assemblies to identify and prioritize structural features affecting their function and specificity and integrate these structures with computational modeling to identify and prioritize structural features affecting their function and specificity.
- Dissect complex phenotypes (e.g., yield as well as water and nutrient use) into genetic components and use natural variants, mutants, gene editing, and transgenes to characterize and validate gene function to understand impact on phenotype.
- Develop and validate methods to map quantitative associations within clades using synteny, homology, cross-species co-expression networks, and other such analyses.
- Examine the complex interactions between bioenergy feedstock plants and their environment, as well as the influence of these interactions on plant growth and development, expression of bioenergy-relevant traits, and adaptation to changing environments.
- Develop new and fundamental knowledge of biomass deconstruction processes to convert a broader range of biomass types into a range of precursors that are readily convertible into biofuels and bioproducts.
- Increase degradability and expand usability of biomass components (e.g., hemicellulose and lignin monomers).

Microbial Conversion

> ***Subgoal:*** *Develop an understanding of microbial and fungal metabolism necessary to design new strains, communities, or enzymes capable of converting plant biomass components into fuels, chemicals, and bioproducts.*

Lignocellulosic biomass is an abundant and renewable natural resource. Converting it to fuels and bioproducts represents an important research frontier in the search for sustainable alternatives to nonrenewable fossil fuels. Importantly, lignocellulosic biomass crops do not necessarily compete against food crops for agricultural resources in the same way as first-generation biofuel production processes for ethanol. Moreover, not only is lignocellulosic biomass an abundant waste or byproduct of economic activity, its cultivation on marginal lands could have a positive economic impact on rural areas.

BSSD's research portfolio therefore targets a broad range of challenges affecting all points of the value chain for lignocellulose conversion, including biological solutions for biomass pretreatment and breakdown, conversion of biomass to fuels, and the development of other high-value chemicals and products (see Fig. 2.3, p. 9). Insights gained from this research are also applicable to the breakdown, conversion, and reuse of other manufactured products such as plastics and other polymers.

These research efforts span the breadth of BSSD's portfolio and include work at the Division's BRCs, DOE national laboratories, and academic laboratories. The Division emphasizes the deployment of genomic biology tools in the development of metabolic pathways, strains, or microbial consortia to achieve novel chemistries, reduce physiological barriers, and develop innovations that enhance the economic viability of biomass conversion. In addition, the emerging tools of synthetic biology, such as genome editing and *de novo* DNA synthesis, provide unprecedented opportunities for engineering both model and nonmodel organisms to achieve BSSD's mission.

In this context, the Division's objectives for microbial conversion research are to:

- Discover and develop new microorganisms with unusual or enhanced capabilities for converting plant biomass to next-generation biofuels, bioproducts, or biomaterials.
- Identify and characterize novel molecular structures, functional capabilities, and biosynthetic pathways that may help to increase the yield

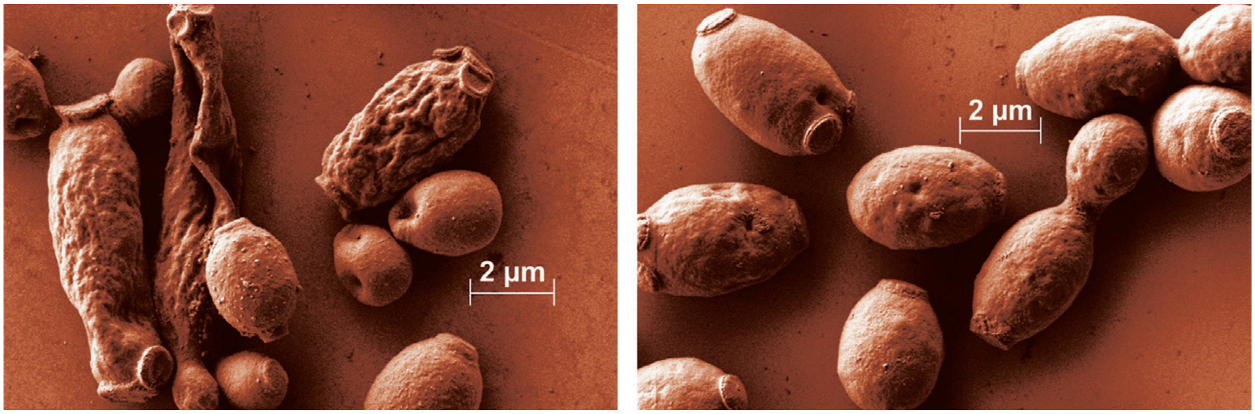


Fig. 2.3. Developing Robust Microbes. In breaking down plant cell walls, chemicals such as ionic liquids (ILs) are used, but ILs often keep microbes from growing. Scientists have learned how one strain of yeast, *Yarrowia lipolytica*, strengthens its membranes, enabling it to hold up better to ILs. These scanning electron micrograph images show **(left)** wild and **(right)** laboratory-evolved *Y. lipolytica* grown in a high IL concentration. The evolved strain's outer membrane displays much less disruption. These insights are important for developing robust microbes that can directly convert plant biomass treated with ILs into biofuels and biochemicals. [Courtesy University of Tennessee]

and/or synthesis of advanced biofuels, bioproducts, and biomaterials.

- Uncover the functional relationships within microbiomes and defined consortia that harbor the potential to produce biofuels, bioproducts, or biomaterials.
- Identify mechanisms for enhanced strain tolerance to physicochemical stresses associated with industrial-scale production (e.g., elevated temperature, altered pH levels, product toxicity, and toxin release).
- Develop the necessary high-throughput omics-based tools to design, build, and test microbial solutions and enhance their biofuel, bioproduct, and biomaterial production properties.

Sustainable Bioenergy

> ***Subgoal:*** *Understand the genomic properties of plants, microbes, and their interactions to enable the development of new approaches that improve the efficacy of bioenergy crop production on marginal lands with few or no agricultural inputs, while minimizing ecological impacts under changing environmental conditions.*

Sustainable cropping systems for bioenergy require a balance among improved biomass yield, inputs such as fertilizers, and efficient land use. Given the scale of production needed to contribute even a fraction of the nation's energy demand, the potential for negative ecological impacts is significant. The Division therefore maintains a continued focus on basic research related to domestically produced, sustainable lignocellulose biomass and its conversion to bioenergy and bioproducts. The aim is to leverage biological solutions to dramatically improve the sustainability and economic viability of biomass from marginal lands that do not compete with food production or further contribute to natural habitat degradation (see Fig. 2.4, p. 10).

BSSD supports research on diverse sustainability-related topics, including soil health, microbial processes and their interactions with bioenergy crops, improvements in the value chain for biomass conversion, and the biology of bioenergy plants. Opportunities to manipulate and engineer biological mechanisms for improved biomass production in plants may generate compounding returns when intersected with deeper knowledge of factors that control nutrient and water use efficiency by plants, fungi, and soil microorganisms. In this context, BSSD will closely cooperate with other DOE programs, such as the Advanced Research Projects Agency-Energy (ARPA-E) and Office of Energy Efficiency and Renewable Energy, as well as other

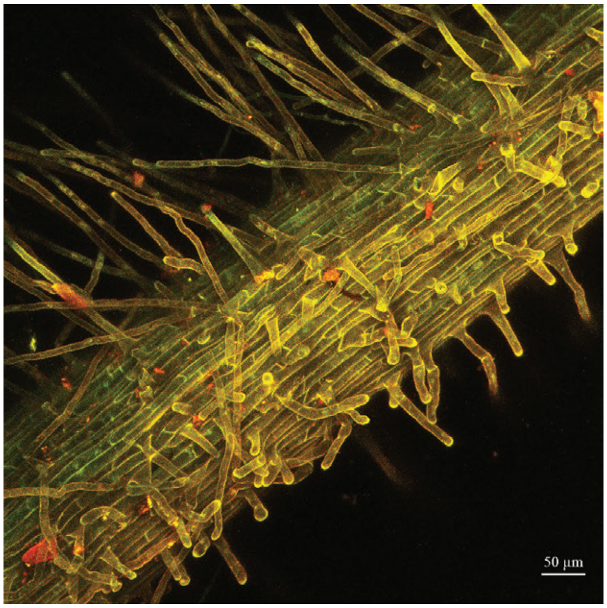


Fig. 2.4. Characterizing Plant-Microbe Interfaces. This confocal image shows the microbial isolate *Variovorax* CF313 (green) colonizing transgenic *Populus* PdKOR roots. Better understanding of the symbiotic relationships between organisms can help researchers engineer hardier bioenergy crops and more productive ecosystems. [Courtesy Oak Ridge National Laboratory]

federal agencies. To better understand spatial and temporal environmental impacts of energy crop growth and production, BSSD will also coordinate with BER's Earth and Environmental Systems Sciences Division (EESSD) on ecological modeling and leverage EESSD user facilities such as EMSL.

Important objectives for BSSD's sustainable bioenergy research are to:

- Develop high-throughput, nondestructive, and analytical techniques to measure plant and microbial phenotypes or functional processes in the environment.
- Expand understanding of genetic diversity and validate the functions of genes, genomic regulatory networks, and metabolites in plants and microbes, particularly those that enable crop adaptation to extreme conditions, changing environments, and episodic environmental events.
- Use biological data to model resource allocations and bottlenecks within bioenergy crop production systems to identify plant functional properties that can be modified to increase biomass degradability, increase yield, and enhance other desirable traits.
- Advance understanding of plant-microbe interactions and their influence on plant growth and stress responses and improve insights on how microbiome and plant diversity help deliver sustained ecological services in the environment.
- Understand microbially mediated soil biogeochemical processes (e.g., nitrogen cycling, greenhouse gas emissions, or carbon stabilization) and their impact on the sustainability of bioenergy cropping systems.
- Develop computational tools to process and use complex and large data architectures that include physiological, molecular, and spatial information such as above- and belowground plant architecture, soil chemistry, nutrient and water use efficiency, and multiomics data.
- Develop process-based, multiscale models to predict cropping and ecosystem behavior under changing environmental conditions.

Biosystems Design

Goal: *Advance fundamental understanding of genome biology and develop the genome-scale engineering technologies needed to design, build, and control plants and microbes for desired beneficial purposes.*

The field of synthetic biology continues to develop rapidly, amalgamating innovations in genome biology and data science with basic principles of engineering. Researchers are able to manipulate increasingly complex genomes and organisms using new technologies and techniques, such as introducing customizable synthetic genomes into eukaryotic organisms. New functions and metabolic pathways, which did not previously exist in nature, can now be designed and built into organisms using gene- and genome-editing technologies, and high-throughput engineering and testing approaches are being used to generate new microbial strains with recoded genomes. These technologies are also enabling the study and manipulation of microbial communities within their environments.

The ability to deliberately manipulate and design biological systems has large implications for BSSD-supported research, including the elucidation of gene function at the organismal level; production of novel, high-value fuels, chemicals, and materials; and manipulation of plant and microbial behavior and interactions for the development of sustainable biofuel and bioproduct production systems (see Fig. 2.5, this page). BSSD seeks to enable a future in which biological systems can be designed for specific purposes *in silico* and be built and tested using automated procedures, delivering new biosystems for deployment into the bioeconomy. Given the complexity and breadth of the requisite scientific challenges, this goal will require a broad, interdisciplinary, and cross-institutional approach. BSSD therefore recognizes that novel approaches to organizing scientific interactions and collaborations, such as virtual laboratories, may offer significant advantages (see Fig. 2.6, p. 12). The Division will also work to leverage the many synergies of current Biosystems Design developments with other BER program elements into a diverse research portfolio in biological engineering. As the promise of synthetic biology begins to bear fruit, the biotechnology industry is expected to play a growing role in the U.S. economy. BER is poised to contribute to growing opportunities in this area through its support of basic Biosystems Design research relevant to DOE's mission space.

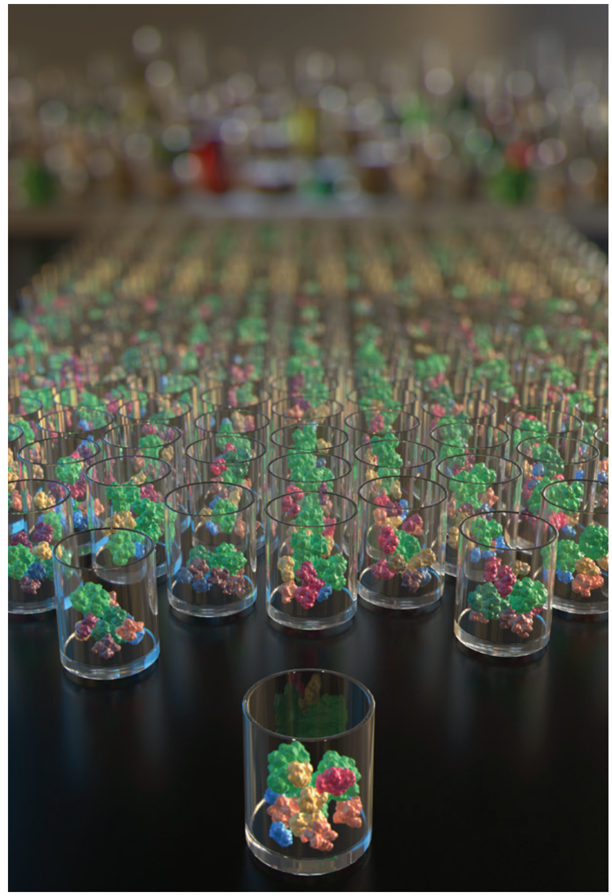


Fig. 2.5. Metabolic Mixology. Cell-free prototyping offers a metabolic mixology approach for accelerating the design of biosynthetic pathways for sustainable manufacturing. [Reprinted by permission from Springer Nature from Karim, A. S., et al. 2020. "*In Vitro* Prototyping and Rapid Optimization of Biosynthetic Enzymes for Cell Design," *Nature Chemical Biology* **16**(8), 912–19. Copyright 2020.]

Broadly, BSSD's Biosystems Design research objectives seek to:

- Discover and develop novel platform organisms across a range of physiologies as chassis for synthetic biology.
- Develop innovative genome-engineering tools, including large-scale DNA synthesis and intracellular delivery, recoded and minimal genomes, orthogonal pathways, and cell-free systems.
- Develop high-throughput genome editing, automated screening, characterization, phenotyping, and testing of engineered organisms.
- Elucidate gene function at the genome scale to develop generalized approaches for biological engineering.
- Provide computer-aided design tools, including artificial intelligence and machine-learning techniques, in an integrated, open-access platform for plants and microbes as part of an *in silico* or virtual laboratory capability.
- Develop analytical and characterization tools to understand processes of organic and inorganic synthesis and degradation in engineered organisms.

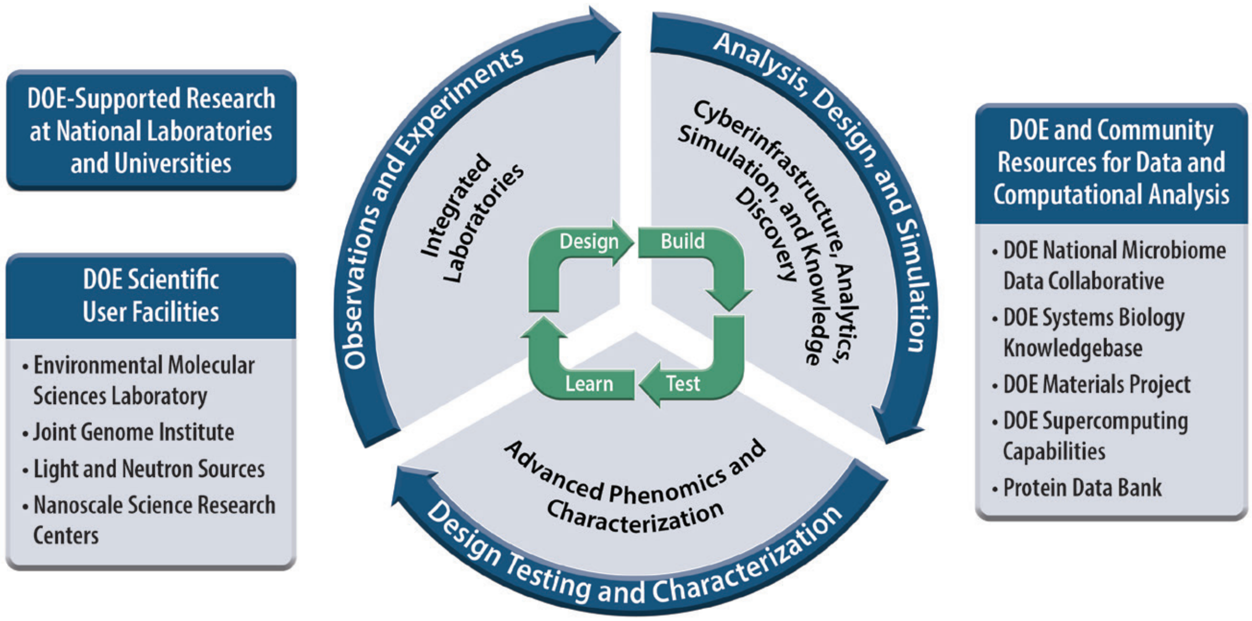


Fig. 2.6. Framework for Accelerating Biological System Understanding. Virtual laboratories represent a tool for integrating research results from the scientific community, resources for data and computational analysis, and DOE user facility capabilities to drive collaboration and new scientific insights.

- Elucidate mechanisms for the acquisition, storage, transport, and chemical transformation of substrates in engineered organisms.
- Support research to build new genetic, regulatory, and biosynthetic networks to biologically produce useful molecules and materials that may or may not exist in nature.
- Develop new approaches for novel macromolecular design, characterization, and testing.
- Expand the "design-build-test-learn" cycle to organismal consortia.

Secure Biosystems Design

> ***Subgoal:*** *Build on advances in genome science and synthetic biology to design and engineer DOE-relevant biological systems with built-in biocontainment measures and develop strategies to address risks of unintended consequences, while enabling a sustainable bioeconomy.*

The ability to redesign biological systems and engineer completely new organisms offers great opportunities in biotechnology. However, engineered organisms also pose significant potential risks, so safeguards must ensure that their deployment does not cause unintended, negative environmental and social impacts. In this context, BSSD intends to build risk awareness through analysis and research efforts. The Division's basic research endeavors will also underpin efforts to characterize, forecast, and assess accidental or natural biological threats related to engineered organisms, as well as predict, prevent, detect, respond to, and recover from biological escapes. These efforts include implementing standard risk mitigation and biocontainment approaches as inherent features of designed biological systems. BSSD will also integrate advanced computational modeling and genome engineering with the environmental microbiome and sustainability program elements (see Fig. 2.7, p. 13).

Some aims the Division will support in secure biosystems design include:

- Develop approaches to understand and enhance stability, resilience, and controlled performance

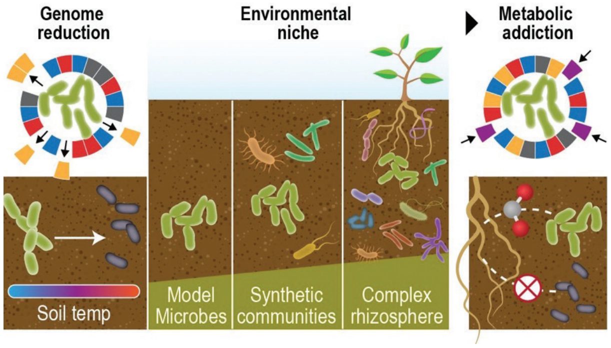


Fig. 2.7. Persistence Control of Engineered Functions in Complex Soil Microbiomes. Led by Pacific Northwest National Laboratory (PNNL), the Persistence Control project uses the mechanisms of genome reduction and metabolic addiction to drive secure rhizosphere community design for robust biomass crops. This is one of several new national laboratory projects in secure biosystems design supported by BSSD. [Courtesy PNNL]

of DOE-relevant plant and microbial systems in their natural environments.

- Research novel biocontainment strategies such as gene drives, non-natural metabolite dependency, and genetic isolation, as well as prevention of evolution and horizontal gene transfer.
- Develop computational and experimental strategies to detect, predict, and ameliorate the effects of engineered organisms in different environments.
- Explore the potential for engineering plants, microbes, and microbiomes to detect or control other engineered organisms released into the environment.

Environmental Microbiome Research

> **Goal:** *Develop a process-level understanding of microbiome function and be able to predict ecosystem impacts on the cycling of materials (carbon, nutrients, and contaminants) in the environment.*

An important driver of BER's overall research focus is the need to reconcile the demand for resources with the limitations imposed by scarcity and environmental degradation. Human activities, such as agriculture or the burning of fossil fuels, leave large and long-lasting impacts on natural ecosystems, with the potential for permanent degradation of the nation's natural resources, broadly including soil and cropland productivity, water quality, and ecosystem services. BSSD's contribution within BER therefore seeks to support leading research that enables a better understanding of biological processes in the environment—including the fate, transformation, and transport of elements—particularly as they relate to the sustainability of current and future energy-related activities (see Fig. 2.8, p. 14).

A key part of this understanding are microbial populations, which profoundly impact the world around us. They shape large-scale environmental processes (e.g., carbon, nitrogen, iron, phosphorus, and sulfur cycling), affect public health, and play an important role in industrial and biotechnology applications. Advances in the ability to measure, analyze, and manipulate microbiomes continue to provide exciting opportunities for scientific discovery. BSSD has long been a vanguard of microbiome science by supporting transformational environmental research and investing in the development of cutting-edge technologies. The Division will continue to build on this legacy by supporting omics-enabled basic research that tackles fundamental scientific and methodological challenges in microbiome science while maintaining an emphasis on the bioenergy, sustainability, and biogeochemical cycling elements of its research portfolio.

Significantly, the breadth and complexity of biotic interactions that occur within and across microbiomes are not sufficiently captured by the current state of knowledge. Moreover, a persistent challenge in microbiome science is the ability to quantitatively model or temporally predict microbiome structure and behavior. BSSD thus supports experimental and computational research that aims to understand microbial community interactions and biogeochemical cycling across broad time and space scales. In this context, the Division supports studies that interrogate the vast, uncharacterized genomic diversity of environmental microbes, which represents an important bottleneck of discovery. Relevant efforts are closely tied to developing a better understanding of microbial impacts on sustainable bioenergy crop growth and yield. Finally,

Fig. 2.8. Soil Carbon Dynamics. Researchers Kristen DeAngelis and Alex Bales sample soils from the Harvard Forest long-term warming experiment to understand how climate change affects microbial growth efficiency and soil carbon stocks, as well as feedbacks to the climate system. [Courtesy University of Massachusetts–Amherst]

BSSD also seeks to leverage emerging opportunities in synthetic and computational biology by exploring the potential of synthetic microbiome science to advance predictive capabilities and to understand gene function across microbial taxa and ecosystems.

Major BSSD science and technology objectives in Environmental Microbiome Research are to:

- Support the development of environmental omics approaches (e.g., metagenomics, metatranscriptomics, metaproteomics, and community-scale metabolomics) and associated data integration tools to investigate *in situ* microbial community functional activities controlling key environmental processes.
- Facilitate realistic recapitulations of microbial ecosystems that move beyond the simple characterization of microbial diversity in the environment.
- Consider complex interkingdom biological dependencies among soil microbial community members (e.g., bacteria, fungi, archaea, viruses, and protists) and the spheres they inhabit (e.g., phycosphere and rhizosphere).

- Provide a framework for predictive modeling to understand microbial community function and dynamics by using omics data.
- Leverage omics and modeling approaches to understand the rate and magnitude of microbially mediated biogeochemical cycles (e.g., carbon, nitrogen, phosphorus, sulfur, and other elements) in the environment and to understand feedbacks with and responses to global change.
- Develop tools and techniques to manipulate microbiomes for beneficial purposes, such as enhanced sustainability, bioenergy crop productivity, and soil carbon storage.
- Facilitate novel and innovative approaches to functional gene characterization, including the use of data science tools (e.g., artificial intelligence and machine learning) and close integration with computational biology and infrastructure elements of BSSD's portfolio (e.g., KBase, JGI, and NMDC).
- Develop omics-enabled techniques for imaging microbial community structure and function in terrestrial environments, with an emphasis on technically challenging settings such as soils, sediments, and key interfacial environments (e.g., decaying organic material, mineral aggregates, and plant roots), potentially by integrating these activities with BSSD's biomolecular characterization and imaging science portfolio.
- Combine omics with *in situ* technologies that enable nondestructive, high-throughput sampling or measurements of microbial communities to understand process-level interactions.
- Seek a mechanistic understanding of cell-to-cell interactions, signaling, resource sharing, and communication at molecular, cellular, and community scales.

Chapter 3

Enabling Capabilities

Goal: *Support the development of computational and instrumental platforms to enable broader integration and analysis of large-scale complex data within BER's multidisciplinary research efforts.*

BSSD's programs are increasingly multidisciplinary, quantitative, and data-centric. As the Division progresses toward gaining a predictive understanding of biology for a host of DOE mission objectives, a continuing and growing challenge is how to make effective use of the large, multidisciplinary datasets generated within BSSD programs to spur scientific discovery and design. Nowhere is this challenge more evident than in the sheer volume of genomic and other omics data produced every year within the portfolio and the larger biological research community. New breakthroughs in imaging and analytical technologies also add to an overwhelming flood of data potentially available to the scientific community (see Fig. 3.1, this page). The Division will thus seek to create computational platforms that facilitate accessing, integrating, analyzing, and sharing results from large-scale, integrated omics, instrumental, and imaging datasets.

The following two sections further outline BSSD's efforts to develop enabling capabilities in computational biology and biomolecular characterization and imaging science.

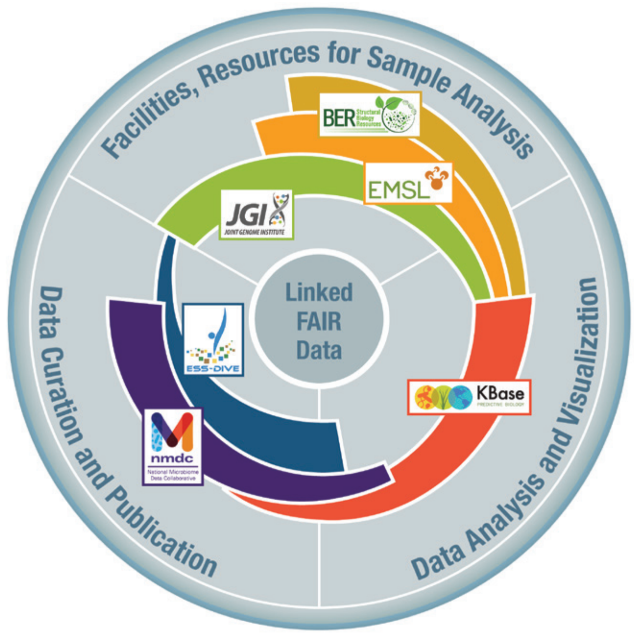


Fig. 3.1. Data and Analysis Ecosystem. BER researchers and facilities produce a wealth of data for predictively understanding complex biological systems. To fully leverage this data, BSSD is supporting integrative computational and data science platforms to facilitate community access, analysis, and sharing of omics, imaging, and other data types. [Courtesy Lawrence Berkeley National Laboratory]

Computational Biology: Integrated Computational Platforms

Subgoal: *Create open-access and integrated computational capabilities tailored to large-scale data science investigations for molecular, structural, genomic, and omics-enabled research on plants and microorganisms for a range of DOE mission goals.*

Historically, systems biology computational infrastructure and software have been highly fragmented and lacked clear software development standards. Information streams are highly diverse, produced by many labs in a noncentralized manner, and are composed of vast quantities of data. To strengthen computational capabilities that broadly enable BSSD's research community, the Division has been making a sustained investment in developing frameworks for open-access cyberinfrastructure for systems biology research through the KBase project. Additionally, BSSD is supporting efforts to make data objects FAIR (findable, accessible, interoperable, and reusable) through the NMDC and JGI data portals (see sidebar, BSSD Open-Access Cyberinfrastructure, p. 18).

Looking into the future, BSSD will invest in and partner with other DOE Office of Science programs to provide access to enhanced mid-range and high-performance computing (HPC) facilities and cloud-based resources tailored to large-scale, integrative data science. As demonstrated during the COVID-19 pandemic, HPC-based analyses of integrated molecular, structural, genomic, and omics-enabled data can provide key insights into disease etiology and efficiently guide research toward potential treatment options out of myriad possibilities. This kind of powerful scientific inference, obtained from analyses of vast integrated datasets, needs to become a mainstay of BSSD endeavors in Bioenergy Research, Biosystems Design, and Environmental Microbiome Research (see Fig. 3.2, p. 19). The Division will therefore seek to build these capabilities into its portfolio, integrating them when practical and combining capabilities when necessary.

The availability of high-throughput, multiomics techniques is revolutionizing biological research, producing rich data layers of genomes, transcriptomes, proteomes, metabolomes, and other relevant data types. These data increasingly provide unparalleled insight into cellular processes, opening the door to significant advances in biological research (e.g., genome-scale engineering). However, the analysis of vast quantities of disparate data types is daunting, requiring new approaches for biological science.

DOE supports some of the most powerful computational systems and data transfer networks in the world, but these systems are not necessarily optimized for large-scale biological data science. Conducting next-generation biological research involves the use of big data, and BSSD's ability to work efficiently and meaningfully with large datasets is increasingly important. Countries that develop the basic science infrastructure to work easily with large, complex datasets, particularly in the biosciences, will lead the world in bioenergy, biotechnology, synthetic biology, and microbiome science with enormous implications for human, economic, and environmental health.

BSSD will seek to develop online, open-access computational platforms for systems biology research. Integrative efforts within KBase and NMDC and

BSSD Open-Access Cyberinfrastructure

Systems Biology Knowledgebase (KBase)

kbase.us

KBase is a BSSD cyberinfrastructure effort that aims to enable researchers to predict and design biological processes in plants and microbes via persistent, citable, executable, and reusable electronic narratives that allow scientists to build on the work of others.

National Microbiome Data Collaborative (NMDC)

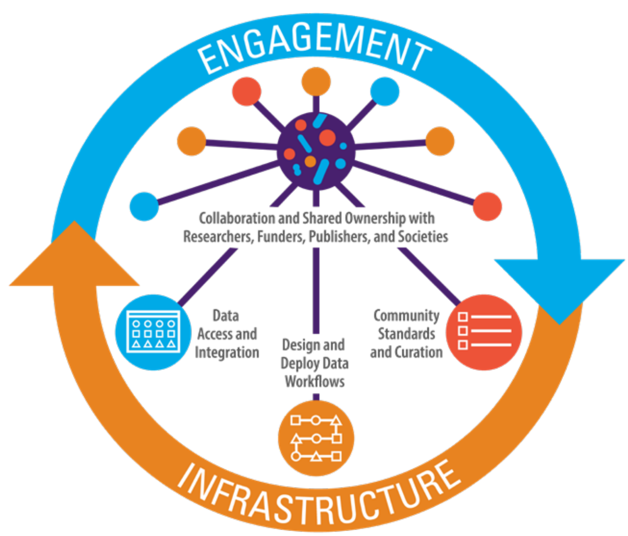
microbiomedata.org

NMDC is a BSSD-supported initiative to empower the research community to harness microbiome data by exploration and discovery through a collaborative, integrative data science ecosystem.

DOE Joint Genome Institute (JGI)

jgi.doe.gov

JGI is the global leader in generating genome sequences of plants, fungi, microbes, and microbiomes. JGI has developed a suite of bioinformatics tools, based on computational biology methods, for analyzing this sequence data.



Data Discovery Platform. NMDC's data discovery platform promotes open science and shared ownership across a broad, diverse community of collaborators through an integrated, open-source microbiome data ecosystem. This platform leverages existing resources and enables comprehensive access to multidisciplinary microbiome data and standardized, reproducible data products. [Courtesy NMDC]

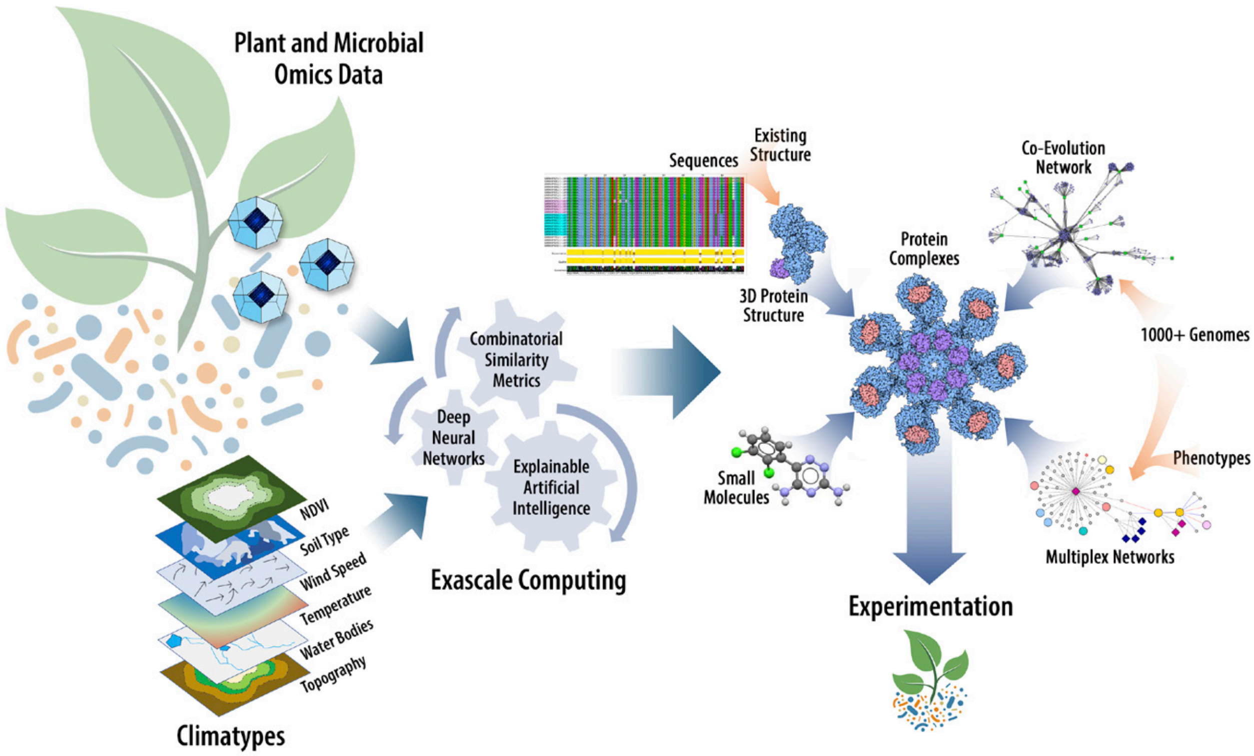


Fig. 3.2. Integrated Systems Biology and High-Performance Computing Research Approach. Relationships within and across omics, phenomics, and environmental layers of data are captured with data-analytic and explainable artificial intelligence algorithms running on supercomputers and modeled as multiplex networks. Network-mining algorithms are then used to extract functional subnetworks of interest for mechanistic understanding of complex phenomena. Interactions among proteins and small molecules in these networks can be further modeled and explored in three dimensions. [Courtesy Oak Ridge National Laboratory, with portions reprinted with permission from Elsevier from Streich, J., et al. 2020. "Can Exascale Computing and Explainable Artificial Intelligence Applied to Plant Biology Deliver on the United Nations Sustainable Development Goals?" *Current Opinion in Biotechnology* **61**, 217–25. DOI:10.1016/j.copbio.2020.01.010. © 2020.]

the bioinformatics capabilities within JGI will continue to progress toward a common computational environment as BSSD seeks to incorporate data connections across DOE, its user facilities, and the larger research community to stand up a virtual laboratory for systems biology research (see Fig. 2.6, p. 12). This virtual laboratory will provide access for researchers to easily and collaboratively work with large-scale, disparate data. To realize this vision, the Division will seek investments in computational hardware and data storage and transfer capabilities either alone or in partnerships.

Other computational biology objectives are to:

- Assemble capabilities for processing large, complex, and heterogeneous systems biology data into open-access analysis platforms addressing DOE missions.
- Create the next-generation data systems and algorithms needed for large-scale systems biology data science that connects observations across scales and integrates molecular, structural, genomic, and other omics data with cellular and multicellular processes.
- Develop explainable artificial intelligence algorithms to identify relationships among different parts of genomes and build integrated biological models that capture higher-order complexity of the interactions among cellular components that lead to phenotypic differences.
- Generate advanced algorithms and data-handling techniques to process and integrate imaging and structural biology data with simulations and other biological measurements.

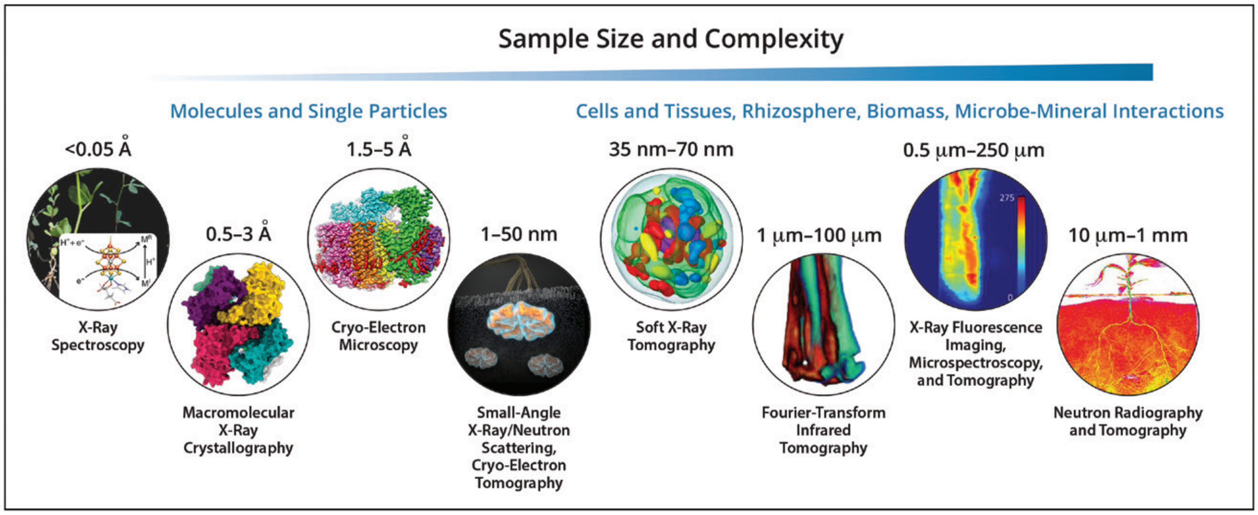


Fig. 3.3. Structural Biology Techniques and Length Scales. Critical structures and functions in biology occur across a wide range of distances (subnanometer to centimeter) and times (subpicosecond to minutes). Today, advanced imaging and characterization techniques enable researchers to image molecules, complex biological machines, native cellular structures, and tissue architectures at or near atomic-level resolution and with high temporal resolution. Such techniques are available to the research community through BSSD-supported structural biology resources at DOE user facilities across the country. [Courtesy Stanford Synchrotron Radiation Lightsource at SLAC National Accelerator Laboratory. See Appendix, p. 31, for image credits.]

- Develop advanced simulation capabilities to model key processes at varying scales occurring within or among cells building toward whole-cell simulation.
- Assemble an integrated systems biology virtual laboratory to accelerate *in silico* ideation and collaboration within the research community.

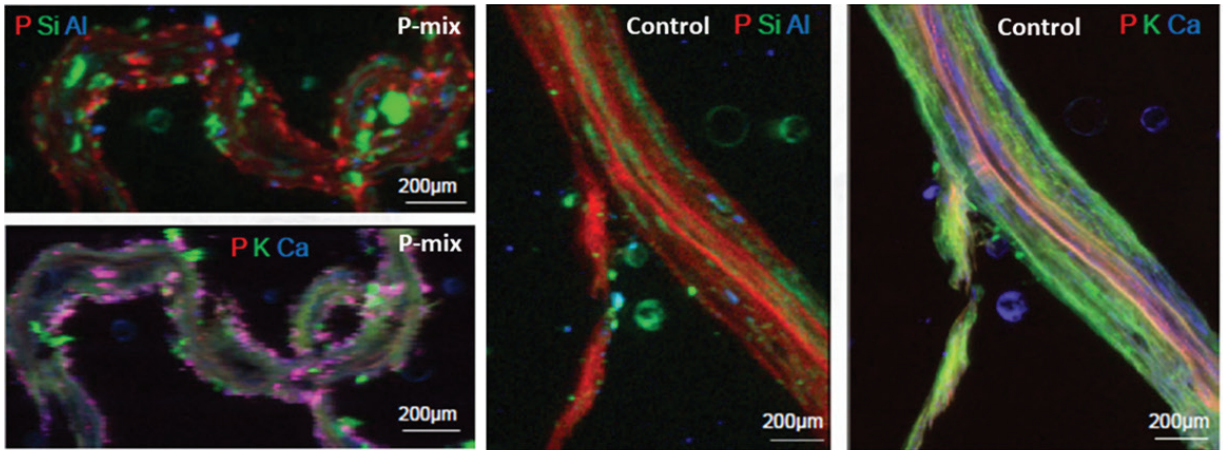
Research in these areas will address significant lingering challenges facing the Division, such as integrating datasets across varying spatial and temporal scales; extracting meaning from large, heterogeneous datasets; and linking three-dimensional structural protein data with network interaction models to predict protein interactions and small-molecule docking. Finding ways to efficiently solve current and future data challenges is a critical need for advancing BER science and will require close coordination with DOE's Office of Advanced Scientific Computing Research and potentially other federal agencies. BSSD computational efforts will leverage DOE's HPC backbone, as future computing needs are anticipated to grow significantly.

Biomolecular Characterization and Imaging Science

Subgoal: *Improve or develop new multifunctional, multiscale imaging and measurement technologies that enable visualization of the spatiotemporal and functional relationships among biomolecules, cellular compartments, and higher-order organization of biological systems.*

Insights into the properties, behavior, and functions of biological systems are greatly enabled by the availability of spatial, structural, and dynamic information at varying scales. Knowing how cellular components, whole cells, or populations can assemble, interact, and physically behave in time and space can provide unique clues about function and reveal opportunities for experimental manipulation. To address BSSD's biomolecular characterization and imaging science goals, the Division will support the development of bioimaging tools, methods, and technologies and invest in related infrastructure and resources. This support includes developing technologies for structural biology and biological imaging at subnanometer to micrometer resolution, as well as approaches for real-time, nondestructive visualization of living systems (see Fig. 3.3, this page). In addition, the Division seeks to satisfy

Structural Biology and Imaging Resources



Micro-X-Ray Fluorescence (μXRF) Maps of Longitudinal Root Sections. The μXRF maps show evidence of phosphorus uptake in a plant that has the endophytic bacterial strains WP5 and WP42 ("P-mix"). The P-mix sample exhibits phosphorus hot spots, while the control displays a more homogeneous phosphorus distribution. Phosphorus appears pink in the bottom left and far right images due to phosphorus and calcium overlapping. [Reprinted under a Creative Commons Attribution License (CC BY 4.0) from Varga, T., et al. 2020. "Endophyte-Promoted Phosphorus Solubilization in *Populus*," *Frontiers in Plant Science* **11**, 567918.]

Structural Biology Portal and Cryo-EM

berstructuralbioportal.org

BER supports structural biology and imaging research via unique crystallography, scattering, spectroscopy, imaging, and cryogenic electron microscopy (cryo-EM) and tomography capabilities available at national neutron and light source user facilities operated by DOE's Office of Basic Energy Sciences. Cryo-EM is a novel technique that enables characterization of cellular structures and proteins without the need for crystallization.

Bio- and Quantum Imaging

science.osti.gov/ber/bioimaging-research

BSSD supports research on multifunctional technologies to image, measure, and model key metabolic processes within and among microbial cells and multicellular plant tissues. This research includes new efforts to leverage quantum-based phenomena to develop novel imaging modalities.

unmet needs across all BSSD portfolio elements by aligning imaging and structural biology with genomic science capabilities and by leveraging DOE's unique beamline and computational infrastructure. In light of these priorities, BSSD supports programs that leverage both the spatial and temporal resolutions available from neutron, photon, and electron beams, as well as the advantages offered by the direct, *in situ* visualization of living tissues through light, electron, and quantum science–enabled microscopy.

With respect to structural biology portfolio elements, a suite of experimental structural biology research technologies, methodologies, and instruments are supported at the DOE synchrotron and neutron user facilities. Important recent additions to these capabilities are cryogenic electron microscopy and tomography, technologies that offer important complementary high-resolution and three-dimensional options for imaging and structural characterization of biological samples (see sidebar, Structural Biology and Imaging Resources, this page). In

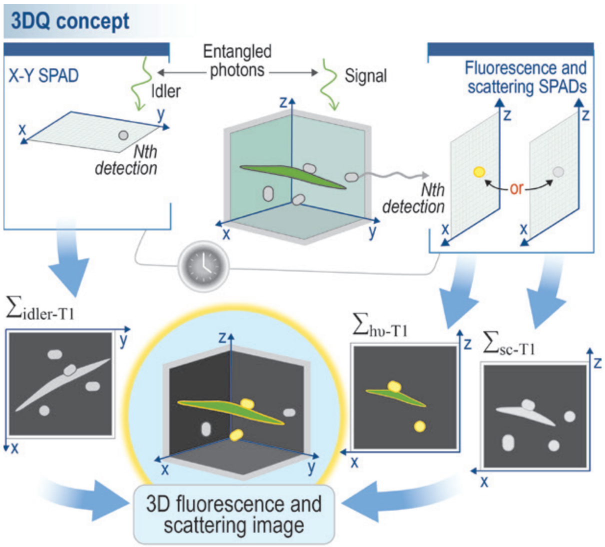


Fig. 3.4. Quantum-Enabled Techniques. BSSD researchers are developing quantum imaging modalities, such as the three-dimensional quantum microscope illustrated here, which will use entangled photon pairs to obtain information beyond standard fluorescence or scattering measurements. [Courtesy Lawrence Livermore National Laboratory]

addition to these capabilities, BSSD also supports expertise at these facilities to aid BER scientists in using these tools to advance their research.

Characterizing complex systems at a range of spatial and temporal scales often requires multiple methods. Integrating methodologies to connect molecular properties to system-level functions is therefore a priority. Examples of targeted research areas include understanding how macromolecules and complexes are structured, how interactions at the macromolecular level confer function (i.e., the workings of "molecular machines"), how molecular assemblies are organized and networked in the cellular environment, and, ultimately, how their pathways are regulated to achieve functional characteristics. Integrating experimental capabilities via computational resources is critically needed to synthesize requisite measurements across multiple scales of length and time. Modern imaging technology creates enormous amounts of data that require computationally intensive processing and interpretation. These capabilities, along with the need to integrate image data with other biological characterization data, represent challenges requiring new mathematical and computational approaches. The Division will therefore seek synergy with its computational biology portfolio elements and support research that meets relevant data integration challenges across BER.

BSSD will also continue to support fundamental research to enable novel bioimaging and characterization technologies for nondestructive, *in situ*, real-time measurements and their integration with omics measurements. Observing cellular components *in vivo* and in real time provides an indispensable perspective of biological systems in their living context. Advances in both computational and optical techniques can thus offer new insights into questions relevant to BER researchers. New technologies may, for example, enable measurements of enzyme function within cells, tracking of metabolic intermediates *in vivo*, monitoring of substrate and bioproduct transport within cells or across cellular membranes, and understanding of signaling processes among cells within plant-microbe and microbe-microbe interactions.

In addition to traditional optical imaging, an important future priority for BSSD will be quantum-enabled techniques (see Fig. 3.4, this page). Multiphoton microscopy has enabled higher-resolution and deep-section imaging of thick biological samples, but classical light absorption requires high laser fluence that can be damaging and cause significant perturbation for *in vivo* imaging. By contrast, entangled photon absorption uses much lower photon fluxes, thereby enabling new imaging modalities. Moreover, quantum-entangled imaging can be combined with quantum probes with high multiphoton cross-sections, multiple chemical functionalization and molecular tracking, spectrally tunable emission, and quantized absorption and emission states to enable high absorption of multiple entangled photons. Single-quantum emitter probes coupled with quantum-entangled photon imaging can thereby enable subdiffraction-limited imaging *in vivo.* Potential quantum-enabled imaging approaches may thus dramatically enhance the ability to measure biological processes in and among living cells and enable dynamic localization and imaging of cellular processes.

The overall objectives of BSSD's biomolecular characterization and imaging science portfolio are to:

- Enhance the accessibility of bioimaging and structural biology infrastructure within the research community and at DOE user facilities.
- Develop and enhance tools for sample handling and transfer, optimizing the samples for multiple imaging modalities and approaches.
- Develop fast and sensitive detectors with extremely high rates of data collection and the necessary computational tools to handle large, real-time, noisy, multimodal, and multiscale data.
- Develop multifunctional, *in situ*, and nondestructive observation technologies for repetitive sample analyses for systems biology research.
- Visualize the spatial and temporal dynamics of expressed biomolecules within or between living plant or microbial cells and their communities.
- Explore quantum science concepts for optical imaging and sensing of cellular processes.
- Incorporate newly developed technologies into DOE user facilities or provide opportunities for commercial development through DOE programs for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR).

Chapter 4

User Facility Integration

Goal: *Build unique, best-in-class capabilities within Office of Science user facilities (including JGI, EMSL, and DOE's light and neutron sources) to enhance the multidisciplinary Bioenergy Research, Biosystems Design, and Environmental Microbiome Research supported by the Division.*

Nowhere is the need for integrated research more apparent than in today's biological sciences. Whether the aim is to increase a bioenergy crop's yield, understand microbial processes in the environment, or design whole genomic architectures *de novo*, biology usually cannot be understood without taking a holistic, broad, and multidisciplinary perspective. DOE maintains a range of state-of-the-art facilities that could greatly accelerate this necessary integration by re-imagining access to some of the world's leading capabilities to study living systems (see Fig. 4.1, this page). BER strongly encourages collaboration among its user facilities and will continue to engage in crosscutting research efforts that use multiple DOE resources (see sidebar, BER-Supported User Facilities, p. 26). For example, JGI and EMSL annually issue joint solicitations specifically tailored to research projects that leverage capabilities at both user facilities. These calls are issued through the Facilities Integrating Collaborations for User Science (FICUS)

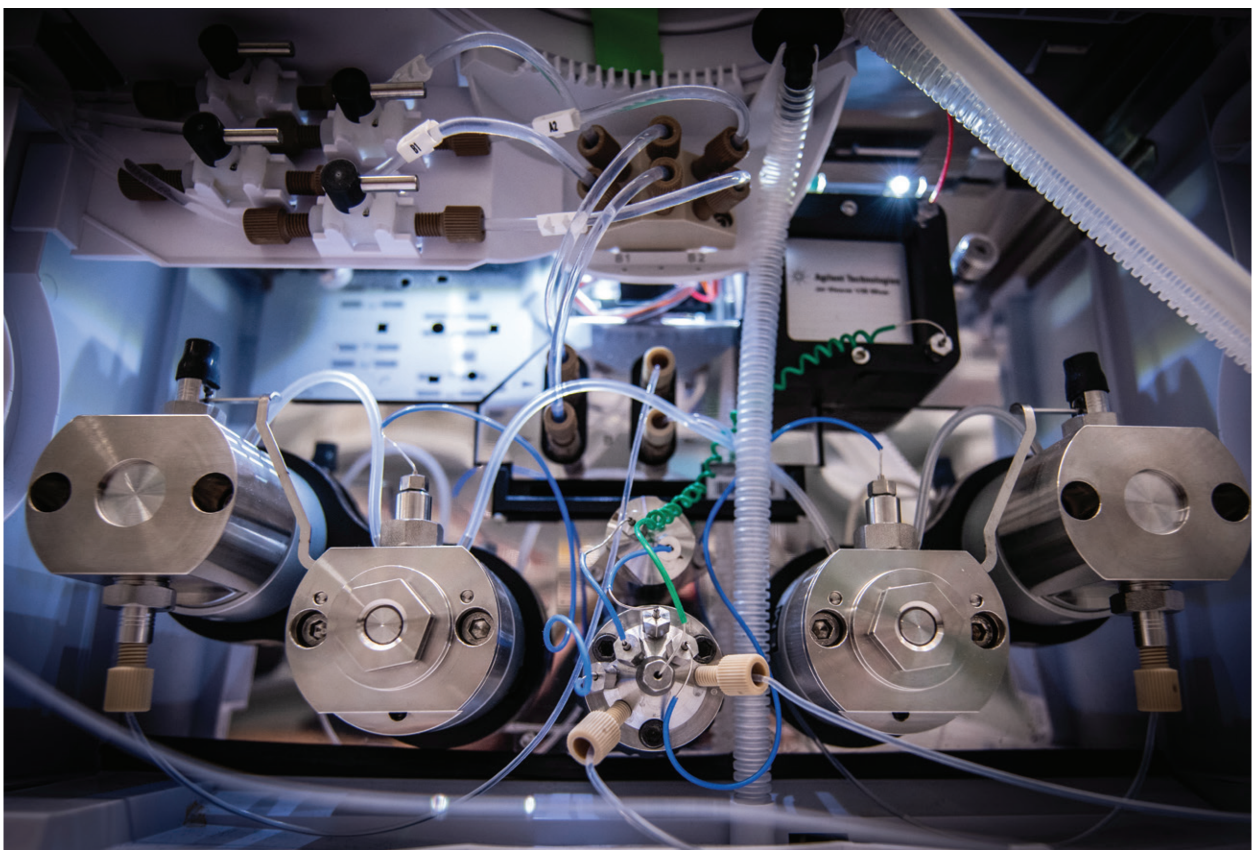


Fig. 4.1. Inside the DOE Joint Genome Institute's Integrative Genomics Building. Closeup view of an Agilent Technologies metabolite analysis instrument. Mass spectrometry enables the analysis of complex samples for semi-quantitative and quantitative measurements and detection of novel secondary metabolites. [Courtesy DOE JGI]

program, which enables the research community to more easily take advantage of the expertise and capabilities of multiple DOE user facilities. BSSD will continue this effort and seek additional linkages across the DOE complex and other federal agencies to bring new resources and capabilities together for multidisciplinary science. Investments in DNA synthesis capacity, cryogenic electron microscopy, computational platform development, and enhanced alignment with structural biology and imaging capabilities will likely be important drivers for advancing the next generation of biological sciences.

Overall, the Division will seek to:

- Establish scientific connections among multiple DOE user facilities to enable multidisciplinary users engaged in BSSD research.
- Align and create joint collaborative efforts among user facilities whose capabilities complement current research efforts within the Division.
- Create new capabilities at existing BER user facilities and among existing collaborative BSSD research efforts.
- Develop capabilities for integrating data within and among user facilities and capabilities for BER science.
- Provide platforms to enable integrated analysis of data generated across BER user facilities and capabilities.

BER-Supported User Facilities

DOE Joint Genome Institute (JGI)

jgi.doe.gov
jgi.doe.gov/user-programs/program-info

JGI is BSSD's flagship user facility, providing genomic science user support for bioenergy research and other DOE mission-relevant topics such as biosystems design and environmental systems biology. Capabilities including genomic sequencing, DNA synthesis, and metabolomics are made available through regular community proposal solicitations and joint funding with the Environmental Molecular Sciences Laboratory via the FICUS program.

Environmental Molecular Sciences Laboratory (EMSL)

emsl.pnnl.gov

EMSL is supported though BER's Earth and Environmental Systems Sciences Division (EESSD) and works in close collaboration with JGI. EMSL provides BSSD principal investigators with cutting-edge scientific and analytical support to enhance a mechanistic understanding of physical, chemical, and intra- and intercellular processes and interactions.

Other Office of Science–Supported User Facilities

energy.gov/science/science-innovation/office-science-user-facilities

In addition to JGI and EMSL, BSSD-supported researchers leverage the full ecosystem of Office of Science–supported user facilities. In many cases, these facilities bring significant added value to BSSD's research program and portfolio.

Chapter 5

Other Opportunities and Impact Multipliers

Within the larger DOE Office of Science, additional programs offer opportunities for enhancing BSSD science. These programs target students, early career scientists, and technology transfer opportunities. The Division will continue to participate in these programs and align topics to complement current and existing research priorities and technology needs.

Office of Science Graduate Student Research Program

The foundation of a vibrant science and technology research enterprise is a persistent and focused commitment to professional training. A highly trained technical workforce is necessary to sustain U.S. scientific leadership and to find scientific and technical solutions to important, BER-relevant challenges. BSSD will seek to make a sustained commitment supporting the Office of Science Graduate Student Research (SCGSR) Program, which enables U.S. graduate students to conduct a portion of their research at a DOE national laboratory or facility. These graduate research awards are a key conduit for professional development and recruitment into the community of DOE-supported researchers. To grow expertise in BER's mission space, annual SCGSR award topics will mirror BSSD's primary basic research efforts.

Fig. 5.1. Emerging Leaders. Early career scientist Joanne Emerson, right, collects sediment samples from a brackish wetland in Bodega Bay, California, with Ph.D. student Sara Geonczy for viral ecological analyses. [Courtesy Christian Santos-Medellin, University of California–Davis]

Early Career Research Program

Similarly, the Division will continue to participate in DOE's Office of Science Early Career Research Program that supports exceptional young scientists and emerging thought leaders (see Fig. 5.1, this page). BSSD topics within funding opportunity announcements (FOAs) for the Early Career Research Program will be tailored to reinforce existing portfolio elements and will aim to support researchers with crosscutting, mission-relevant, and budding research programs. An adaptive emphasis will be placed on topics with recent Genomic Science FOAs in plant, microbial, biosystems design, and environmental microbiome sciences with the expressed intent to pair early career scientists with existing cohorts of researchers in ongoing BER-relevant topical research.

Small Business Innovation Research and Small Business Technology Transfer

Complementary to its main basic science efforts, BSSD will provide opportunities for the small business commercial sector to pursue parallel research objectives through the SBIR/STTR Program. DOE's

Office of Science participates in the SBIR/STTR process through its program offices to enable small business research, technology development, and commercialization across several topical areas that align with BSSD objectives. For example, plant and microbial genome engineering, synthetic biology and associated biotechnology, imaging science, and computational science are advancing at a rapid pace and can be addressed through SBIR/STTR projects. The Division will therefore support existing and new topics and technologies that have significant potential for transforming aspects of BER-relevant environmental science, bioenergy production, biomanufacturing, and the bioeconomy at large.

In addition to the series of annual topics offered under the SBIR/STTR FOA, BSSD will support technology transfer opportunities to leverage tools and capabilities produced within the DOE laboratories, as well as seek opportunities within other DOE programs such as the Office of Technology Transitions via the Lab Partnering Service (LPS), Lab-Embedded Entrepreneurship Program (LEEP), and Energy Innovation Corps (Energy I-Corps). LPS is a portal that enables the searchability of licensable technology, development opportunities, and connections to expertise at the DOE national laboratories to rapidly cultivate external handoffs for technology commercialization. LEEP offers private entrepreneurs a chance to bring their technologies to DOE laboratories to leverage the available capabilities and expertise. In the biomanufacturing and biotechnology commercial sectors, BER user facilities and national laboratory expertise could be an excellent bridge for small businesses and startups to rapidly advance their technologies. Finally, the Energy I-Corps provides laboratory principal investigators with a mechanism for investigating market opportunities for commercializing technologies, as well as exploring the fundamentals of building a product that could become a business spinoff from the laboratory. These opportunities may assist SBIR awardees with additional avenues for commercializing technologies that will advance DOE science and research and serve the American people.

Chapter 6

Summary

The biological sciences continue to advance at a breathtaking pace. With roots in natural history and plant science, the impacts of biological research are pervasive in our modern lives, providing significant benefits in a range of economic sectors including agriculture, medicine, and energy. A recent confluence of technological advances promises to dramatically accelerate the ability to manipulate biological processes for productive uses. These transformative advances include genome editing and high-throughput DNA synthesis technologies that enable reconfiguration of genomic content, vastly improved computational capabilities, increased availability of immense amounts of omics-derived data, and the development of novel analytical solutions (e.g., artificial intelligence and machine learning). With these tools, the biobased economy holds promise for transforming our lives in remarkable ways.

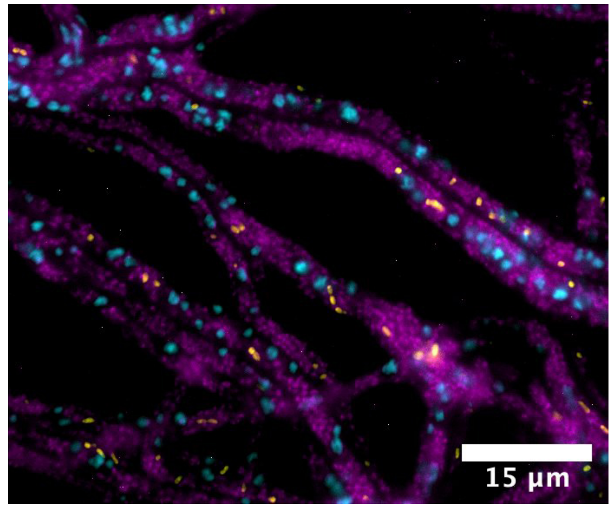


Fig. 6.1. Symbiotic Interactions. Fluorescence *in situ* hybridization image of the endobacteria *Mycoavidus* sp. in the fungus *Mortierella elongata*. Cyan: *M. elongata* nuclei; magenta: *M. elongata* mitochondria 16S rRNA; yellow: *Mycoavidus* sp. 16S rRNA. Scientists use such bioimaging techniques to understand the mechanisms driving the interactions and functions of soil bacteria and fungi. [Courtesy Los Alamos National Laboratory]

BSSD-supported research is at the nexus of many of the defining frontiers of plant science, agricultural sustainability, synthetic biology, biobased materials, and environmental microbiome science (see Fig. 6.1, this page). In addition, the Division tightly integrates this portfolio of scientific research projects at national laboratories and universities with support for world-leading user facilities, computational community resources, and research centers. Consequently, BSSD is well positioned to tackle exciting, emerging challenges and develop next-generation technological solutions that will unlock the promise of an innovative, resilient, and sustainable U.S. bioeconomy (see sidebar, BSSD Research Goals, p. 30).

BSSD Research Goals

BSSD seeks to provide the necessary fundamental science to understand, predict, manipulate, and design biological systems that underpin innovations for bioenergy and bioproduct production and enhance our understanding of natural, DOE-relevant environmental processes.

Bioenergy Research

Goal: Provide the basic science needed to convert renewable biomass to a range of fuels, chemicals, and other bioproducts in support of a burgeoning bioeconomy.

- ***Plant Genomics***
  Subgoal: *Gain a genome-level understanding of plant metabolism, physiology, and growth to develop new bioenergy feedstocks with traits tailored for bioenergy and bioproduct production.*
- ***Microbial Conversion***
  Subgoal: *Develop an understanding of microbial and fungal metabolism necessary to design new strains, communities, or enzymes capable of converting plant biomass components into fuels, chemicals, and bioproducts.*
- ***Sustainable Bioenergy***
  Subgoal: *Understand the genomic properties of plants, microbes, and their interactions to enable the development of new approaches that improve the efficacy of bioenergy crop production on marginal lands with few or no agricultural inputs, while minimizing ecological impacts under changing environmental conditions.*

Biosystems Design

Goal: Advance fundamental understanding of genome biology and develop the genome-scale engineering technologies needed to design, build, and control plants and microbes for desired beneficial purposes.

- ***Secure Biosystems Design***
  Subgoal: *Build on advances in genome science and synthetic biology to design and engineer DOE-relevant biological systems with built-in biocontainment measures and develop strategies to address risks of unintended consequences, while enabling a sustainable bioeconomy.*

Environmental Microbiome Research

Goal: Develop a process-level understanding of microbiome function and be able to predict ecosystem impacts on the cycling of materials (carbon, nutrients, and contaminants) in the environment.

Enabling Capabilities

Goal: Support the development of computational and instrumental platforms to enable broader integration and analysis of large-scale complex data within BER's multidisciplinary research efforts.

- ***Computational Biology: Integrated Computational Platforms***
  Subgoal: *Create open-access and integrated computational capabilities tailored to large-scale data science investigations for molecular, structural, genomic, and omics-enabled research on plants and microorganisms for a range of DOE mission goals.*
- ***Biomolecular Characterization and Imaging Science***
  Subgoal: *Improve or develop new multifunctional, multiscale imaging and measurement technologies that enable visualization of the spatiotemporal and functional relationships among biomolecules, cellular compartments, and higher-order organization of biological systems.*

User Facility Integration

Goal: Build unique, best-in-class capabilities within Office of Science user facilities (including JGI, EMSL, and DOE's light and neutron sources) to enhance the multidisciplinary Bioenergy Research, Biosystems Design, and Environmental Microbiome Research supported by the Division.

Appendix

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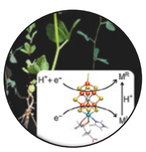
Image Credits Fig. 3.3



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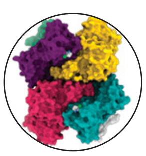

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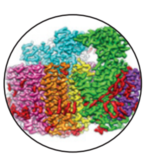

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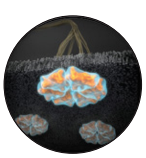

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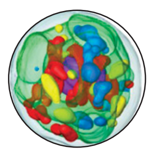

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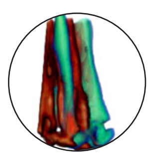

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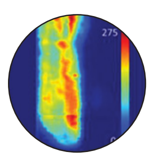

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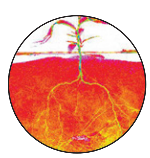

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Acronyms and Abbreviations

AFM	atomic force microscopy
ARPA-E	Advanced Research Projects Agency-Energy
BER	DOE Office of Biological and Environmental Research
BERAC	Biological and Environmental Research Advisory Committee
BRC	DOE Bioenergy Research Center
BSSD	BER Biological Systems Science Division
CABBI	Center for Advanced Bioenergy and Bioproducts Innovation
CBI	Center for Bioenergy Innovation
Cryo-EM	cryogenic electron microscopy
DOE	U.S. Department of Energy
EESSD	BER Earth and Environmental Systems Sciences Division
EMSL	DOE Environmental Molecular Sciences Laboratory
Energy I-Corps	Energy Innovation Corps
FAIR	findable, accessible, interoperable, and reusable
FICUS	Facilities Integrating Collaborations for User Science program
FOA	funding opportunity announcement
GLBRC	Great Lakes Bioenergy Research Center
HPC	high-performance computing
IL	ionic liquid
JBEI	Joint BioEnergy Institute
JGI	DOE Joint Genome Institute
KBase	DOE Systems Biology Knowledgebase
LEEP	Lab-Embedded Entrepreneurship Program
LPS	Lab Partnering Service
µXRF	micro-X-ray fluorescence
NMDC	DOE National Microbiome Data Collaborative
SBIR	Small Business Innovation Research
SCGSR	DOE Office of Science Graduate Student Research Program
STTR	Small Business Technology Transfer