Overview

EBRC Engineering Biology Research Consortium

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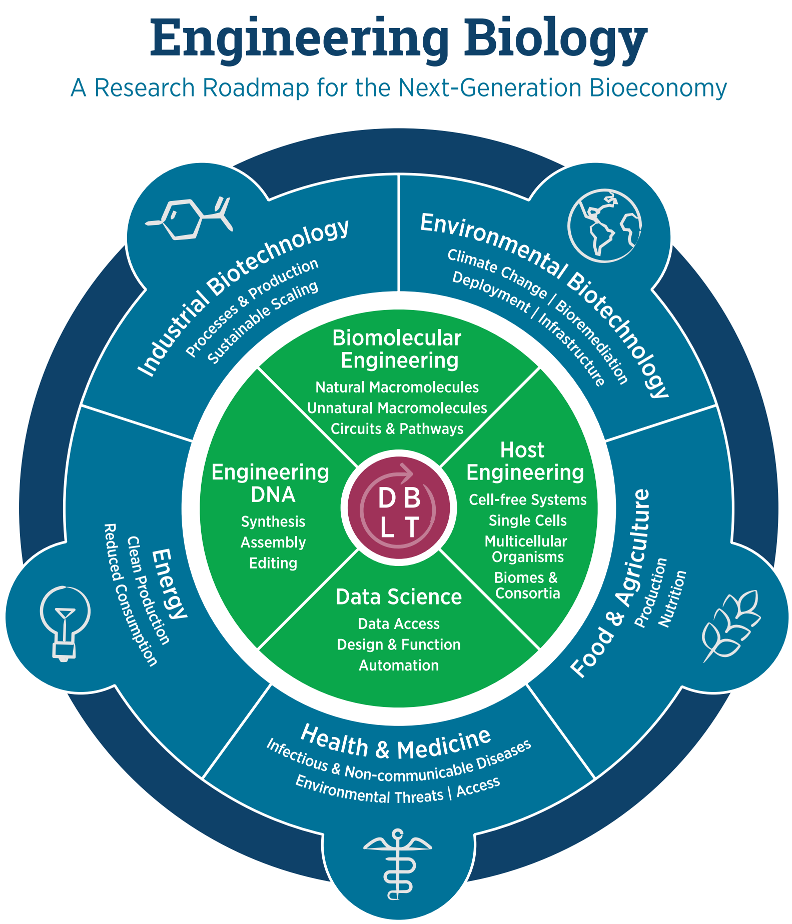
This material is based upon work supported by the National Science Foundation under Grant No. 1818248.

Introduction

The EBRC Roadmap is a critical assessment of the current status and potential of engineering biology. It is intended to provide researchers and other stakeholders (including government funders) with a compelling set of technical challenges and opportunities in the near and long term. Our ongoing roadmapping process was initiated in response to the recommendations put forth in the 2015 National Academies report, *Industrialization of Biology*, and at the request of the National Science Foundation and other US government stakeholders, including the National Science & Technology Council. With this inaugural release of the Roadmap, EBRC will provide a "go-to" resource for engineering/synthetic biology research and development.

Working with the broader EBRC community, the Technical Roadmapping Working Group led the development of the roadmap scope and content. Collective insight and substantive contributions were provided by more than 80 leading scientists and engineers, including academic, industry, and student members of EBRC and from the broader research community. Since mid-2018, the working group has held six workshops and countless teleconferences to develop the content and engage discussion around the roadmap. The result is a collaborative effort that represents the engineering biology research community's vision for the future of the field.



The Roadmap

The matrixed framework of the roadmap considers challenges, bottlenecks, and other limitations observed or predicted in the research, development, and application of advancements in engineering biology tools and technologies toward addressing broad societal challenges. The roadmap's four technical themes form the foundation of engineering biology research and technology and illustrate where our current abilities lie and what we might achieve in the next 20 years. Complementarily, the five roadmap application and impact sectors demonstrate the breadth and impact of technical advancements in real-world application areas and exemplify how engineering biology tools and products could be oriented towards some of the most complex problems we face as a society. The technical themes represent a "bottom-up" approach focusing on tool and technology innovations to move the field forward, while the five application and impact sectors are a "top-down" look at how engineering biology could contribute toward addressing and overcoming national and global challenges.

Technical Themes

The technical themes of the roadmap focus on four key areas of engineering biology research and development: 1) Gene editing, synthesis, and assembly; 2) Biomolecule, pathway, and circuit engineering; 3) Host and consortia engineering; and 4) Data Integration, Modeling, and Automation. Each technical theme has a series of transformative tools and technologies - platform technical areas in which advancement is both necessary and will have a significant impact on revolutionizing the field - and aspirational goals that drive the progression of research and development. Construction of the technical roadmap is accomplished through delineation of milestones at 2, 5, 10, and 20 years and each milestone is elaborated by anticipated or imagined bottlenecks and creative potential solutions. The 2-year and 5-year milestones are intended to signify objectives that can be reached with current or recently implemented funding programs, as well as existing infrastructure and facilities resources. The 10-year and 20-year milestones are expected to be more ambitious achievements that may require (and thus, result in) significant technical advancements and/or increased funding and resources and new and improved infrastructure. The goals and breakthrough capabilities therefore represent the visionary 20+ year aspirations for the technical themes.

In the case of *Gene editing, synthesis, and assembly*, the future holds the potential for rapid, *de novo* synthesis of entire genomes, which is reflected in goals focused on the manufacture of high-fidelity oligonucleotides at 10,000-oligomer length, design and assembly of megabase clonal DNA fragments, and highly advanced precision gene editing without off-target effects. *Biomolecule, pathway, and circuit engineering* focuses on the activity and assembly of individual biomolecules into networks to carry out larger functions of the cell, and how we might design, create, and evolve these macromolecules from both natural and non-natural building blocks, with the end goal of achieving integrated, controlled circuits and pathways. Envisioned is the ability to routinely design and predict the structure and function of macromolecules, biosynthesis of unnatural amino acids and other building blocks, and controlled expression of transcription factors determining cell state. This blends and transitions into the larger and more complex functions of individual cells, whole organisms, and biomes described in *Host and consortia engineering*, where we detail necessary advancements to achieve customized cell-free systems and synthetic cells, on-demand production and control of single cells and multicellular organisms with highly-defined functions, and finally the engineering of multi-genome systems and biomes. While, classically, engineering biology has focused on microorganisms as tools for production, we aim to expand this vision to include cells as the products themselves, and provide an outlook for enabling complex engineering of plants, animals, and multi-organism systems. Cornerstone to enabling engineering and production of designed genomes, non-natural biomolecular circuits, and customized cells and organisms, is the integration of advanced data analysis, design, and data modeling. *Data Integration, Modeling, and Automation* highlights the transformative potential of integrated biological data models, design frameworks for biomolecules, hosts, and organismal communities, and the promise of automating the design-build-test-learn process. Together these four technical areas establish the foundation from which we can enable the rapid progression and expansion of engineering biology into industry and application.

Application and Impact Sectors

The roadmap also illustrates many potential applications of engineering biology, and demonstrates the possible use and impact of these tools and technologies to address and overcome societal challenges, through a focus on five sectors: 1) Industrial Biotechnology; 2) Health & Medicine; 3) Food & Agriculture; 4) Environmental Biotechnology; and 5) Energy. We frame these possibilities through the lens of solving pervasive societal challenges, including enabling and establishing a cleaner environment, supporting the health and well-being of growing populations, and accelerating innovation and economic viability of industry. From each framing societal challenge, we consider the science and engineering aims and objectives for engineering biology that may be necessary or instrumental to overcoming the challenge and we identify potential discrete technical achievements towards the objective. These technical achievements in each sector reflect our four technical themes, allowing for future mapping of the technical milestones to the engineering biology sector objectives.

The roadmap details many potential applications of engineering biology toward establishing the U.S. as a global leader in the bio-based economy is the basis from which *Industrial Biotechnology* looks at sustainable manufacturing, novel product discovery and development, and integrated workflows and pipelines for biology-based products and materials. *Health & Medicine* focuses not only on developing and advancing tools for fighting disease, but also improving wellbeing through bio-integrated lifestyle technologies, offering new options to people with disabilities through engineered cell systems, and addressing the damage of environmental threats to health. Producing more food that is healthier and increasingly nutrient-dense is the focus of *Food & Agriculture*, including advancing the production of food and nutrients from atypical and under-utilized sources, such as microorganisms, insects, alternative plant species, and “clean meats”. Engineering biology achievements in *Environmental Biotechnology* will enable advancements in bioremediation, resource-recovery, the deployment of engineered organisms, and bio-enabled and bio-built infrastructure, contributing to cleaner lands, waters, and air. And finally, *Energy* focuses on the production of energy-dense and carbon-neutral biofuels, and tools and products to reduce energy use and consumption. Combined, the Roadmap sectors suggest the potential breadth and utility of engineering biology tools and technologies in creating a better world.

The Way Ahead

As our roadmapping efforts progress, there is opportunity to expand each technical theme, to better capture the considerable breadth of engineering biology research, especially in related fields, such as bioinformatics, biomedical engineering, physics, and microscopy, to spur greater integration. A further focus on pipeline technologies, such as advanced robotics and machine learning, bio-integrated electronics, precision microfluidics and high-throughput screening, DNA barcoding, and novel biosensors, may elaborate near-term technical milestones and provide incentive for additional investment into emerging technologies. The greater roadmap framework and organization has been designed such that there is nearly-unlimited space to investigate the overlap between advancements in engineering biology tools and technologies and the impact and utility of these tools and technologies toward solving economic, industrial, and environmental problems; to this end, future EBRC roadmapping efforts are likely to include additional, intricate integration of the technical themes and application sectors. Similarly, our roadmapping efforts aim to be an evergreen process through consideration and assessment of the identified milestones to track attainment, and updates to acknowledge and explore new avenues and technical landscapes.

With this technical roadmap, EBRC hopes to establish a resource for the research and research-support community, including educators, policymakers, and funding bodies, that portrays the importance and impact of engineering biology tools and technologies and highlights community-identified areas for innovation and advancement.

Linking to Societal Considerations and Integrating Public Values

The current roadmap highlights a suite of technical ambitions and potential pathways for advancing the engineering of biology. It represents the initial outcome of a broad consultation of the scientific and engineering community to identify goals for the field and offers a vision of the technical possibilities and challenges of engineering biology in the service of broad social, ecological, and economic priorities. However, the current material does not explicitly address the policy and social environments that new technologies and tools must navigate if they are to make a difference in the real world.

The roadmap exists on a yet-unspecified landscape of social priorities, cultural preferences, ethical minefields, political traditions, and economic realities. Interdisciplinary scholarship in fields complementary to science and engineering can be engaged in critically evaluating and framing the goals and aims of this technical roadmap. As the roadmap evolves, it will be important to question how engineering biology is utilized to address these global problems, and ways that novel technologies might create new problems or exacerbate existing social and political inequalities. To maximize the possibility of positive outcomes, technological pursuits will need to be coupled with ongoing study and negotiation of the social, cultural, political, and economic landscapes for which they are being designed. Doing this will require leveraging expertise in disciplines beyond science and engineering, including the arts, humanities, and social and behavioral sciences.

With this technical roadmap as a first step, EBRC hopes to establish a resource for the research and research-support community, including educators, policymakers, and funding bodies, that portrays the importance and impact of engineering biology tools and technologies and highlights community-identified areas for innovation and advancement. This will include outlining areas of research and forms of stakeholder engagement needed to steer the field towards desirable societal outcomes. We can expect, over time, for the goals and priorities of this roadmap to change. We emphasize that broad interdisciplinary and ongoing engagement with a wide range of partners will be essential to guiding research trajectories in the most meaningful directions. EBRC will engage current and future supporters of this roadmap to prioritize such integrative and interdisciplinary considerations as part of its ongoing development.

Security: Managing Risk through Engagement

The development of synthetic biology technologies and their applications alters the overall biological security landscape. In order to best assess the opportunities for science and technology advancement, it is important to frame the advances in terms of their impacts on national and global security. This is especially relevant given that we encourage the further advance of technologies that can improve our economic security, while not challenging our physical security. While no technology is risk-free, by being able to carry out rational assessments of integrated risk it should be possible for policy makers and others to better assess whether investments are likely to enhance prosperity and security.

The roadmap has been written in a manner that implicitly considers security and has been, and continues to be, reviewed to identify any potential for misuse of the engineering biology tools, technologies, and applications outlined in the roadmap. The proposed roadmap elements are written at a level of detail that are not expected to directly enable malicious misuse; however, potential security concerns that could arise as the field achieves the technical goals put forth in the roadmap have been identified. Ongoing efforts will provide necessary description and context for these concerns, to be integrated with the current roadmap and/or published separately, as well as consideration of security issues independent of the present material. The goal of such current and ongoing security assessments are first and foremost to ensure that we do not enable malicious actors or activities through our work. Furthermore, it is incumbent on us to engage directly with the security community, policymakers, and other stakeholders about concerns we anticipate may emerge and how the EBRC community, through the Security Working Group, is engaging and collaborating with others to mitigate these concerns. Ongoing stakeholder engagement in the social and political context in which these technologies are developed is essential to ensuring that this roadmap does not introduce new vulnerabilities, and EBRC and its partners are committed to strengthening that engagement.

In concert with strategies to mitigate potential misuse, an overarching goal of this roadmap is to develop pathways for technology developments that has potential to enhance both economic and national security. These include strategies to incorporate security design into technologies from the outset, enable improved regulatory science, and protect human health, the environment and the economy. We remain strong advocates for diligent consideration of potential security considerations, by all stakeholders, in their pursuit to advance engineering biology.