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Industrialization of Biology

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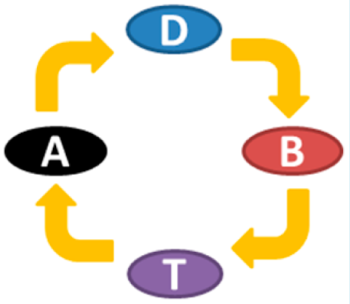
ABSTRACT: The advancement of synthetic biology over the past decade has contributed substantially to the growing bioeconomy. A recent report by the National Academies highlighted several areas of advancement that will be needed for further expansion of industrial biotechnology, including new focuses on design, feedstocks, processing, organism development, and tools for testing and measurement; more particularly, a focus on expanded chassis and end-to-end design in an effort to move beyond the use of *E. coli* and *S. cerivisiea* to organisms better suited to fermentation and production; second, continued efforts in systems biology and high-throughput screening with a focus on more rapid techniques that will provide the needed information for moving to larger scale; and finally, work to accelerate the building of a holacratic community with collaboration and engagement between the relevant government agencies, industry, academia, and the public.



The field of synthetic biology and its importance to the advancement of the bioeconomy and industrial biotechnology have grown substantially and rapidly over the past 10 years. According to an analysis by the Woodrow Wilson Center's Synthetic Biology Program, this rise has been concurrent with the investment of approximately $820 million dollars by the United States government[1] alone in the field. Noteworthy investments have included the establishment of the 10-year National Science Foundation (NSF)-funded Synthetic Biology Engineering Research Center (Synberc) ending in 2016, an increase in U.S. Department of Energy (DOE) investments starting in 2010, and the explosive rise of funding from the U.S. Department of Defense (led by DARPA).

At the same time as U.S. Government investments have risen, commercial interest has grown substantially with numerous biobased products starting to compete readily in the marketplace. In light of the changes occurring in the field, the enhancement in DOE interest and funding, and the sunset of NSF-funded Synberc, the National Academies of Sciences, Engineering, and Medicine were asked to develop a roadmap of necessary advances in science and engineering capabilities, and make relevant nontechnical insights, to help guide the funding agencies and the community in its next phase of development.

In March 2015, the Academies released the report *Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals.*[2] This 150-page report makes the case for additional focused attention on industrial biotechnology, and the bioeconomy, as an important and growing part of US economic development. While there is no official value reported by the US government, according to Rob Carlson of Biodesic, biobased products made up $350 billion dollar (or approximately 2%) of US GDP in 2012 and both the total value and its share of GDP are expected to grow substantially in the years to come.[3] Even with this impressive growth, there is still a lot of room for biological synthesis and engineering to contribute to chemical manufacturing. The Academies' report lays out a vision of the future as one where "biological synthesis and engineering and chemical synthesis and engineering are on par with one another for chemical manufacturing."

■ ROADMAP

The authoring committee identified the technical elements of the roadmap based on the core conclusion that "biomanufacturing of chemicals is already a significant element of the national economy and is poised for rapid growth during the next decade. Both the scale and scope of biomanufacturing of chemicals will expand and will involve both high-value and high-volume chemicals. Progress in the areas identified in [*Industrialization of Biology*] will play a major role in achieving the challenge of increasing the contribution of biotechnology to the national economy." The six technical areas outlined in the report are Feedstocks and Pre-Processing; Fermentation and Processing; Design Toolchain; Organism: Pathways; Organism: Chassis; and Test and Measurement. Figure 1 identifies the key elements identified for each technical area.

Within each of these categories, a series of roadmap goals are identified and can be found in the report and online at http://www.nap.edu/visualizations/industrialization-of-biology/. Overall these goals support the finding that synthetic biology will be at the center of chemical production in a growing bioeconomy. Broadly, the development of specialized organisms integrated with advanced production methods will in turn require advances in modeling and design techniques in metabolic engineering and process chemistry, advances in the underlying sciences for genome manipulations, and new and inexpensive high-throughput measurement techniques.

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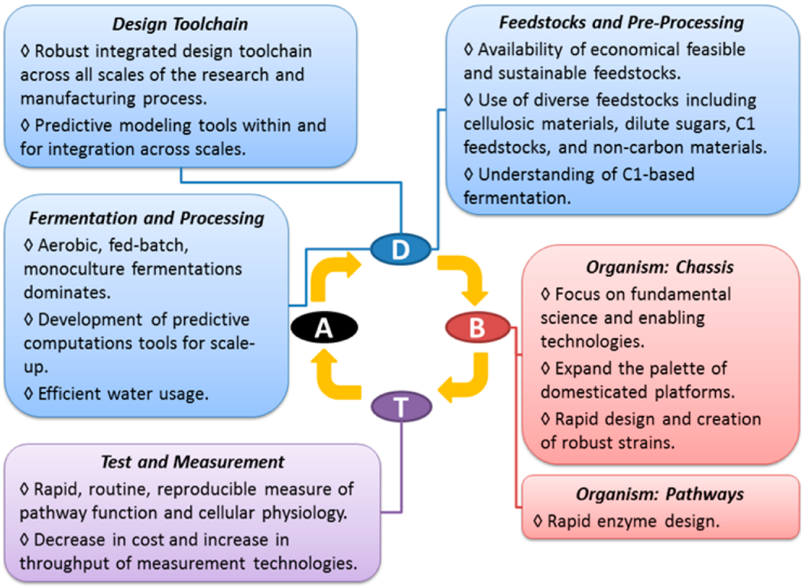

Figure 1. Key elements outlined in the Academies' report mapped to the **D**esign−**B**uild−**T**est−**An**alyze cycle.

The consideration of organism as the means of production is first and foremost. Many of the demonstrations in synthetic biology have been divorced from practical applications, especially in metabolic engineering and process chemistry. As the field moved forward synthetic biology advances needed to be more closely integrated with a general framework for how biological materials could be produced. To this end, greater research is needed into the biological "chassis" that are utilized in synthetic biology. We need to move from research that is *E. coli*- or *S. cerivisiae*-centric to work that utilizes single celled organisms more suitable to fermentation and production. Just as there are obvious benefits to increasing target availability, so too are there benefits to increasing the possible feedstocks available for large scale conversion. Expansion beyond the use of simple sugar feedstocks to a more direct use of recalcitrant lignocellulosic biomass would open the door to competing with the extant chemical industry. These directions are however complicated by the fact that the diversity of metabolic and physiological requirements for using a given feedstock and making a given product will inherently require a range of chassis. This is where one of the underlying ideals of synthetic biology, that it is all just DNA, no matter what organism it comes from or goes into, advances from being wishful thinking to practically enabling. To make good the promise of chassis agnostic engineering, an array of tools for genomic editing in any organism will be required. The Cas9 revolution is a good start, but only a start.

Beyond the wherewithal to work in new organisms, new modeling methods that take into account issues that scale from feedstock to reaction to pathway to metabolism to physiology to reactor should enable DNA to be written to spec for new production species. The expansion of systems biology that is occurring apace with synthetic biology will continue to provide much of the data for modeling, although targeting industrial strains should become a priority. However, systems biology efforts will not necessarily provide the information necessary for initiating and scaling production. As useful pathways are cobbled together from a complex array of reactions from across phylogeny, an overwhelming number of molecular, metabolic, and physiological parameters will need to be measured in parallel to ensure that pathways are working in what will quickly become wholly chimeric metabolisms and physiologies. In particular, current techniques in metabolomics are too slow and require optimization on a case-by-case basis to provide useful information. New analytical methods that work between multiple sensor modalities and in a high-throughput mode will be enabling, as will continuing attempts to scale virtually all aspects of biochemical analysis via NextGen sequencing (for example, can we do metabolomics via NextGen?). The data glut that is emerging requires new informatics tools that can directly pipe both into improved systems biology understanding and into end-to-end pathway and production modeling.

Finally, while considering the scientific and technical advances that are required to push the field forward, a continued focus on public policy, training and engagement, and societal concerns will become increasingly important. A quantitative and authoritative measure of the bioeconomy is required before industrial biotechnology can be valued as a key player in US manufacturing. To that end, the report recommends that the US Government should report a "regular quantitative measure of the contribution of bio-based production" to assess the economic impact of the field. Likewise, a recommendation for a continuing assessment of the adequacy of existing governance, including regulation, was outlined and in July the White House issued a memorandum[4,5] laying out a broad review of the regulatory framework for the products of biotechnology. To take the necessary, all-inclusive approach, the report went on to encourage science funding agencies to take part in the discussion of responsible innovation and ensure their policy offices focus outreach efforts in this area. As major industrial biotechnology firms rapidly grow their manufacturing capabilities, "strong partnerships with all levels of academia, from community colleges, undergraduate, and graduate institutions" will be needed to fill the jobs available in the future bioeconomy. To that end, the report recommends that student trainees be exposed to paradigms relevant to industrial biotechnology, at both small and large scale which should be supported by collaboration among U.S. Government agencies, academia, and industry.

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MOVING FORWARD

The opportunities and challenges inherent in industrialization of the bioeconomy will task scientists, regulators, and policy makers in a way that has not frequently been taken up across a multibillion dollar sector in the United States: to think strategically at all levels. That said, the goals outlined by the Academies' report, and reiterated in our own context here, will only be realized by strong community engagement in the broadest sense. The authoring committee "recommends that the relevant government agencies consider establishment of an on-going road-mapping mechanism to provide direction to technology development, translation, and commercialization at scale." A true partnership between relevant government agencies, industry, academia, and the public has the potential to increase the momentum going forward and is what is needed now. The practice of biology is no longer limited to those with access to large laboratories and years of advanced training. New startups are leading the way, just as was the case during the Internet revolution. Gated communities, stovepipes, and entrenched (and tenured) interests will have to get out of the way and give way to a feeling of participation that is neither top-down nor bottom-up.

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Notes

The views expressed herein do not necessarily represent the views of the National Academies of Sciences, Engineering, or Medicine or its Board on Chemical Sciences and Technology.

The authors declare no competing financial interest.

REFERENCES

(1) The Wilson Center. *U.S. Trends in Synthetic Biology Research Funding*, 2015; http://www.synbioproject.org/site/assets/files/1386/final_web_print_sept2015.pdf (accessed Oct 1, 2015).

(2) National Research Council. *Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals*; The National Academies Press: Washington, DC, 2015.

(3) Carlson, R. *The U.S. Bioeconomy in 2012 reached $350 billion in revenues, or about 2.5% of GDP*, 2014; http://www.synthesis.cc/2014/01/the-us-bioeconomy-in-2012.html (accessed Oct 1, 2015).

(4) Holdren, J. P., Shelanski, H., Vetter, D., and Goldfuss, C. *Improving Transparency and Ensuring Continued Safety in Biotechnology*, 2015; https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology (accessed Oct 1, 2015).

(5) Holdren, J. P., Shelanski, H., Vetter, D., and Goldfuss, C. *Memorandum: Modernizing the Regulatory System for Biotechnology Products*; The White House: Washington, DC, 2015.

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