GENETICS, BIOSECURITY AND THE BIOECONOMY: LOOKING TO THE TWENTY-FIRST CENTURY AND THE AGE OF BIOLOGY

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Abstract
As the "Century of Biology" advances, multiple technologies are converging in the development of creative new approaches to sustainability in manufacturing. Genetics, artificial intelligence, engineering, and chemistry are combining to solve many of the world's pressing problems in agriculture, food, medicine, and the environment. Here we summarize some of these developments to illustrate the kind of advances in bio-manufacturing that exemplify new approaches to sustainable manufacturing. Accompanying these developments are concerns with the possible dual-use aspects of some of these technologies. We discuss some of the approaches within the biotechnology field to allay such concerns.

Keywords: genetics, biosecurity, bioeconomy, dual-use

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INTRODUCTION

The bioeconomy commonly refers to the phasing out of non-renewable, polluting resources and replacing them with biological, renewable alternatives (1). Simply, the bioeconomy is an economy based on biologically-sourced goods and services, also known as bioresources. The bioeconomy encompasses the sustainable production and conversion of biological materials, such as crops, forests, marine resources, and microorganisms into a wide range of products like food, feed, biofuels, chemicals, pharmaceuticals, and more. Nearly 60% of the physical inputs to the global economy could, in principle, be produced biologically. The bioeconomy emphasizes sustainability and minimization of environmental impact, to promote long-term availability of resources. A primary goal is to reduce reliance on fossil fuels. It encourages research and innovation in biotechnology, as detailed below. The bioeconomy aligns with the concept of "circular economy", whereby waste and by-products are minimized, and materials are reused or recycled whenever possible. Finally, the global bioeconomy plays a role in addressing global challenges including food security and climate change facilitating a transition to more sustainable industrial practices. The global bioeconomy is estimated to process up to $4 trillion US dollars per year globally over the next 10 years.

Role of biotechnology

Biotechnology plays a central and transformative role in the emerging bioeconomy, serving as a key driver in innovation and sustainability. Bioprocessing and biomanufacturing rely heavily on biotechnological innovation. In agriculture and crop improvement, biotechnology is employed to create high-yield and/or pest-resistant crops. Biotechnology is instrumental in drug discovery, vaccine development, and personalized medicine. Remediation and waste conversion methods offer solutions to environmental problems and rely on biotechnological tools and techniques. Finally, synthetic biology enables the design of biological systems and organisms for specific applications. Here, we describe several examples of the use of synthetic biology, to solve a range of problems in industrial manufacturing, agriculture, medicine, and environmental protection.

Synthetic Biology (SynBio)

Remarkable advances in genetics over the last decade have led to the ability to read, write, and modify DNA inexpensively and with great precision. These developments opened the door to SynBio, a multidisciplinary field of science that focuses on living systems and organisms, and it applies engineering principles to develop new biological parts, devices, and systems. SynBio relies on the rapid advances in multiple fields, including chemistry, microbiology, genetics, engineering, mathematics, physics, social sciences, computer science, and bioinformatics. The approach is based on the iterative and circular engineering principles of "Design-Build-Test-Redesign"(2). A simplified description of the process has the following steps:

1. Design: Scientists start by identifying a biological function they want to create or modify. This could involve designing a new protein, pathway, or even an entire organism.
2. DNA Manipulation: The genetic information needed to implement the desired function is encoded in DNA. Researchers can manipulate DNA through techniques like gene synthesis, polymerase chain reaction (PCR), or gene editing using a variety of tools such as CRISPR-Cas9.
3. Assembly: The modified DNA sequences are then assembled into a plasmid, which is a small, circular piece of DNA that can be inserted into a host organism such as a bacterium, yeast, or mammalian cells.

   These "host" organisms serve as "factories" to produce the desired biological product.
4. Testing and Iteration: The engineered organism is tested to see if it exhibits the desired function. If the test fails, the system can be further modified, and the process is repeated until the desired result is achieved.

Applications

The final engineered organism or system can be applied in various fields, such as medicine, agriculture, energy production, and environmental remediation. The applications of synthetic biology range from creating new biofuels and pharmaceuticals to novel organisms that clean up pollution or produce sustainable/biodegradable materials. The promise and opportunity of SynBio are best described with specific examples such as those below.

Microbial production of biofuels:

Scientists at LanzaTech in Illinois (https://lanzatech.com/) identified an organism that can synthesize ethanol from industrial waste gases. The bacterium was further refined with additional genes to maximize efficiency and expand its repertoire; LanzaTech's first commercial plant in China has produced millions of gallons of ethanol from steel mill emissions. The ethanol can be converted into jet fuel and other products (3).

Drought resistance:

Cytokinin is a plant hormone that under dry conditions signals to the plant to close pores to retain water and slow growth. Synthesis of the hormone is expensive. To circumvent using the hormone to induce pore closure, scientists developed tomato plants with novel receptors that respond to fungicide instead of cytokinin, making the plants more resilient under drought conditions. In related work, scientists at the Salk Institute have identified the genetic pathways that promote deep root growth in a plant's root system. These genes can prompt the development of deeper roots, enabling crops to resist stress, sequester more carbon, and enrich the soil. These are two examples of SynBio holding great promise in increasing agricultural yields (4).

Built-in fertilizer:

Most plants must acquire nitrogen from the soil or from chemical fertilizers to synthesize proteins and other components. Legumes have microbes associated with their roots that can remove nitrogen from the atmosphere and "fix" it into a form that can then be taken up by plants to make cell components. Fertilizer is produced mainly from fossil fuels and contribute to both greenhouse gas emissions and eutrophication. Pivot Bio, a California company (https://www.pivotbio.com/), engineered a microbe that lives on the roots of corn, wheat, and rice plants with genes from the nitrogen-fixing bacteria, to enable the crops' microbes to extract nitrogen from the atmosphere and supply it to the plant. In field tests, its nitrogen-producing microbe for corn yielded 7.7 bushels per acre more than chemically fertilized fields (5).

Sustainable foods:

Impossible Foods' plant-based burger (https://impossiblefoods.com/) contains synthesized heme protein, the iron-containing molecule found in animals and plants. Scientists added the plant gene encoding heme to yeast, which, after fermentation, produced large quantities of the heme protein. Impossible Burger uses 75 percent less water and 95 percent less land than a regular beef burger and produces 87 percent fewer greenhouse gas emissions (6).

As the demand for seafood grows globally (fishing stocks are already 90 percent overfished), so does the need for fishmeal, the protein pellets made of ground-up small fish and grain that feed farmed fish and livestock. California-based NovoNutrients (https://www.novonutrients.com/) uses CO_2 from industrial emissions to provide carbon to engineered bacteria, which then produce protein similar to the amino acids fish get by eating smaller fish and fishmeal. The bacteria replace the fishmeal, providing the fish with protein and other nutrients (7).

Cement/concrete:

Traditional cement production accounts for 8% of global carbon dioxide emissions. Global demand continues to grow with enormous environmental impact. If the cement industry were a country, it would be the third largest carbon dioxide emitter in the world with up to 2.8 bn tons, surpassed only by China and the US. Companies such as Biomason (https://biomason.com/) have developed a system to create new building materials by placing sand in molds and injecting them with bacteria. Calcium ions are used by the bacteria to produce a calcium carbonate shell with the bacteria's cell walls, causing the particles to stick together. A brick grows in three to five days (8). These cement bricks can be used in construction and landscaping.

Textiles and dyes:

DNA synthesis is used to create genes that encode enzymes tailored to produce different pigments. No petroleum products or chemicals are used and only one-fifth of the water of regular dyes is required. Spider silk is one of nature's strongest materials as it is elastic, durable, and soft (9). Companies such as Bolt Threads (https://boltthreads.com) are using engineered genes from spider DNA and expressing them in yeast. Then the yeast cells are grown in large fermentation tanks to produce large quantities of liquid silk proteins. The silk protein is then spun into fibers, which can be made into renewable Microsilk.

Risks and benefits: Dual-use

It is possible to imagine malicious uses that could lead to events that might threaten the health and safety of citizens, destabilize governments, disrupt social enterprises, destroy agriculture and the global economy, and imperil the very survival of the planet. The risk of malevolent use of technology is often referred to as the "dual use conundrum":

> "Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, crops and other plants, animals, the environment, or material."

-National Science Advisory Board for Biosecurity (10)

Essential to the oversight of potentially dangerous research are the processes of biosafety and biosecurity, and the terms are interrelated. The National Institute of Standards and Technology (NIST) published a bioeconomy lexicon (https://www.nist.gov/bioscience/nist-bioeconomy-lexicon) that defines biosafety as "practices, controls, and containment infrastructure that reduce the risk of unintentional exposure to, contamination with, release of, or harm from pathogens, toxins, and biological materials," and biosecurity as "security measures designed to prevent the loss, theft, misuse, diversion, unauthorized possession or material introduction, or intentional release of pathogens, toxins, biological materials, and related information and/or technology." In the context of biomanufacturing and the potential creation of entirely new organisms, it is clear that these terms will need to be expanded in their reach to think about biosecurity broadly, to include any kind of action with intent to cause harm that uses biological systems or data. The recognition of the potential risks of applications of advanced genetic and other technologies has led to a resurgence of interest in applied biosafety research. For the most part, this resurgence has focused on laboratory containment techniques, specifically with human or zoonotic pathogens.

Governance – what are we doing, what can be done, and what should we do?

Accompanying the need for biosafety and biosecurity processes to keep pace with the rapid pace of biotech development is the need for governance and oversight. Different governance tools and mechanisms are needed to achieve diverse goals and engage different stakeholders (11). They include laws and regulations, standards, guidelines, best practices, codes of ethics, research review processes, awareness-raising activities, training, and education (12).

The collective process of creating an international governance mechanism for research and applications with the potential for harmful application requires the standardization of language and concepts. Frameworks – decision models - help clarify and standardize the approach being used. Frameworks can ensure that estimates include all the components that the collaborating decision makers believe are important, and second, they enable comparisons across multiple estimates. Developing shared frameworks increases the usefulness of estimates of risk and allows comparison across national and conceptual boundaries. Several frameworks, or decision trees, have been elaborated for analysis of the risks and benefits of research with dual-use potential (13). Qualitative frameworks serve as a tool to evaluate risks and benefits and determine how to address them both. The process of using the frameworks to discuss scientific and technological capabilities organizes information in ways that illuminate unstated assumptions, clarify areas of agreement and disagreement, bring forward questions, and facilitate productive discussions. In this way, the frameworks enable potential security risks to be assessed in a systematic way to inform policymakers and support the goal of evidence-informed policy.

A compelling example of an international body contributing to dual-use governance is *The International Genetic Engineering Machine Competition* (iGEM) (14). iGEM was started twenty years ago in the USA and now has yearly participants from 66 countries and regions with 6,000 students competing each year in 400+ teams. Multidisciplinary students work together in teams to identify problems to be solved, designing solutions using synthetic biology and engaging in self-organization to address societal problems safely and securely. Intrinsic to the iGEM process of project development is a dedicated biosafety and biosecurity program (15). The iGEM Safety and Security Committee comprises a team of specialists from a range of fields with expertise in biosafety, biosecurity, and risk assessment. Its members represent multiple sectors of industry, academia, and government. The committee oversees iGEM's safety and security programs, offering guidance on potential safety and security concerns and systematically reviewing each of the proposals. The competition has a number of checks for dual use along the life cycle of the projects: the parameters for evaluation also include human practices and rules for communication and transfers of microorganisms. Thus, students who compete in iGEM have early career exposure to the basics of responsible science. Over 40,000 students, instructors, and judges have passed through the iGEM system since 2004 and spread across the field of biotechnology.

CONCLUSION

Global biomanufacturing is at the beginning of a true revolution. Multiple problems facing humanity can likely be solved using genetic technologies such as those described in this article. Sustainable and circular approaches to the generation of goods and products are necessary to protect the natural resources of the planet, under severe threat from overuse and climate crisis. However, any technologies in the life sciences have the potential for dual-use applications. Each has the potential to make substantial improvements in or lead to possible harm to human, animal, plant, and environmental health. The risks that accompany many of these technologies must be addressed by biosafety and biosecurity governance mechanisms that represent a moving target. Applied research into biosafety and biosecurity practices can be used to standardize across regions as appropriate. Existing and future governance structures will need to be adapted to be relevant to changing environments, advances in technology, and novel applications, and in some cases, where existing governance structures are inadequate, new structures and ways of limiting harm are urgently needed.

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S A Ž E T A K

GENETIKA, BIOSIGURNOST I BIOEKONOMIJA: GLEDAJUĆI PREMA DVADESET PRVOM STOLJEĆU I DOBU BIOLOGIJE

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Sažetak
Kako „Stoljeće biologije“ napreduje, više se tehnologija istovremeno razvija i međusobno povezuje u stvaranju kreativnih novih pristupa održivoj proizvodnji. Genetika, umjetna inteligencija, inženjerstvo i kemija udružuju se kako bi riješile mnoge od gorućih svjetskih problema u poljoprivredi, prehrani, medicini i zaštiti okoliša. U ovom radu sažimamo neka od tih dostignuća kako bismo ilustrirali napredak u bio-proizvodnji koji predstavlja nove pristupe održivoj proizvodnji. Uz ove razvojne procese javljaju se i zabrinutosti zbog moguće dvostruke namjene nekih od tih tehnologija. Raspravljamo o nekim pristupima unutar biotehnološkog sektora koji nastoje umanjiti te zabrinutosti.

Ključne riječi: genetika, biosigurnost, bioekonomija, dvostruka namjena

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