Synthetic Biology: Perspectives on Risk Analysis, Governance, Communication, and ELSI

Benjamin D. Trump, Christopher L. Cummings, S. E. Galaitsi, Jennifer Kuzma, and Igor Linkov

Synthetic biology is a technology with incredible promise yet equally galling uncertainty. The United Nations Convention on Biological Diversity defines synthetic biology as "biotechnology that combines science, technology, and engineering to facilitate and accelerate the understanding, design, redesign, manufacture, and/or modification of genetic materials, living organisms, and biological systems" (Convention of Biological Diversity). Synthetic biology can produce entirely new organisms, some of which may pose risks to naturally existing ecosystems. While humans have been selectively breeding plants and animals for millennia, synthetic biology and its enabling technologies allow combining genetic material from organisms that cannot procreate in nature and grant more deliberate and precise control over the selection of genetic processes.

Synthetic biology innovations might support disease prevention, large-scale food production, and sustainable energy, as well as more dubious applications like eugenics and invasive manufactured organisms. The difference between highly beneficial and highly hazardous outcomes depends upon the decisions of the people funding, producing, and regulating synthetic biology projects. The new and unique qualities of synthetic materials and their complex intersections with existing biological, ecological, and sociotechnical systems raise the specter of unpredictable outcomes (Linkov et al. 2018) and can complicate these decisions. For established

B. D. Trump (✉) · I. Linkov
US Army Engineer Research and Development Center, Vicksburg, MS, USA
e-mail: bdtrump@umich.edu

C. L. Cummings
Nanyang Technological University, Singapore, Singapore

S. E. Galaitsi
US Army Corps of Engineers, Washington, DC, USA

J. Kuzma
North Carolina State University, Raleigh, NC, USA

B. D. Trump et al. (eds.), *Synthetic Biology 2020: Frontiers in Risk Analysis and Governance*, Risk, Systems and Decisions, https://doi.org/10.1007/978-3-030-27264-7_1

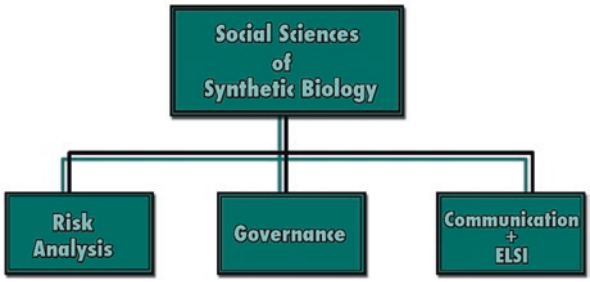

Fig. 1 Breakdown of disciplines within social science and implication-related research pertinent to synthetic biology

technologies, the current risk assessment and management paradigms are well-developed (Linkov et al. 2018), but there is uncertainty surrounding decisions in synthetic biology, including the scope of risks and the methods for monitoring them. This uncertainty should decrease as the field produces more data and stabilizes, which will require time, scholarship, and investment.

This book, *Synthetic Biology 2020: Frontiers in Risk Analysis and Governance,* examines the synthetic biology field after two decades of innovation. Within such a topic, the book includes perspectives of synthetic biology from the social sciences, such as risk assessment, governance, ethics, and communication (Fig. 1). Contributing authors in this volume represent diverse disciplines related to the development of synthetic biology's social sciences and consider different areas of risk analysis and governance that have developed over this time and the societal implications. The chapters of this volume note that while the first 20 years of synthetic biology development have focused strongly on technological innovation and product development, the next 20 must emphasize the synergy between developers, policymakers, and the public to generate the maximally beneficial, well-governed, and transparent technologies and products.

Making Sense of Synthetic Biology: Raw Opportunity and Uncertain Implications

The field is growing rapidly; estimates for 2020 equity funding forecast nearly $40 billion dollars to be directed to private synthetic biology companies (Polizzi et al. 2018), a 40-fold increase from funding in 2016. But the products of synthetic biology will not be demanded nor subsequently deployed if potential customers distrust their utility or safety. Fears of tragedies from synthetic biology applications are readily imaginable: privileged designer babies, bioterrorism, and disrupted ecosystems are all moral or physical calamities that could arise should synthetic biology development be inadequately regulated.

While there is usually risk in implementing new technologies, there is also risk in choosing to let existing hazards continue to control aspects of our environment. In that sense, unwarranted negative public perception of synthetic biology

innovations could hinder societal advancement (Palma-Oliveira et al. 2018). While industry, government, and private actors have different priorities and motivations in producing and using synthetic biology, concerns over the safety and protection of their communities and the natural world that supports them are universally shared. However, some end users may disproportionally bear potential risks of synthetic biology applications and thus rationally perceive safety differently. These perceptions can be captured and addressed through social science assessments to guide safe and socially acceptable development of synthetic biology. Anticipating both physical and social outcomes enables insights to be integrated into revisions of previous decisions and improves the value of iterative processes of experimentation and innovation.

Technological development and assessment have historically occurred as two distinct steps, often separated by a time period measurable in years. First, technological breakthroughs rise within the physical and natural sciences, which are subsequently discussed by social science regarding the technology's societal implications, risks, and regulatory needs. For example, the growth of mass transportation technologies in the early nineteenth century brought risks of mechanical accidents and toxic emissions (Cummings et al. 2013). When dichlorodiphenyltrichloroethane (DDT) use spread globally in the 1940s, its deleterious environmental and human health effects were unknown. It took until 1972 for the United States to ban it, followed by a worldwide ban under the Stockholm Convention in 2001 (Cummings et al. 2013).

Inferring policy needs and recommendations for developing technology is an uncertain business. A product's impacts on society are difficult to assess when the product is underdeveloped and does not yet resemble the version that will ultimately be adopted. Many products may prove infeasible and therefore inconsequential (see Fig. 2), and their assessments can squander precious resources. Yet, waiting for a relatively finalized product disadvantages social scientists because their inquiry will be in its earliest stages while the physical scientists are finalizing their own and potentially beginning to market a product. Jasanoff (2009) writes that the responsive and reflexive nature of social science inquiry causes it to lag behind physical science research. But if the reflexive nature of social science were incorporated within the innovation process, the societal infeasibility of some products could be identified earlier and used to guide physical scientists to create more universally beneficial products.

Ideally, including social science in the innovation process can provide transparency that may reassure members of the public that the benefits of a new technology outweigh the risks. Such social science scrutiny promotes developing governance initiatives that can be operated in tandem with broader technological dissemination. However, the same critical inquiry of developing technologies may stoke fears of the new, uncertain, and unknown. Ideas can be presented out of context in ways that emphasize their risks without communicating their safeguards and may provoke public criticism and opposition. Too much opposition can hamper or even halt innovations before scientists can incorporate or address criticism in their products. A two-step process that separates innovation from evaluation precludes this type of

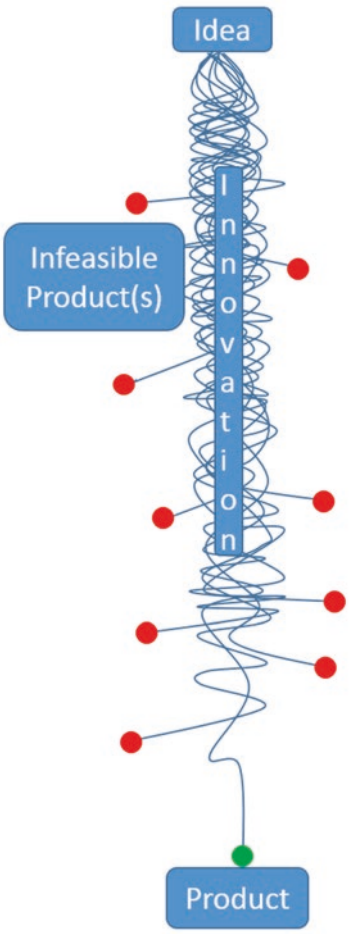

Fig. 2 Illustrating path dependency or the winding road and various choices that transform a scientific idea into a commercial product

project derailment – but also can bring products to market without adequate safeties in place.

The social convulsions associated with emerging technologies could be less dramatic or harmful when better anticipated. Consider the automobile: delayed full-privileged licensure for teenage drivers, in combination with other factors, reduces crash rates for new drivers (Ferguson et al. 1996; Williams 2009). This information would have been useful in the 1940s when most US states picked the age 16 as the minimum driving age. States partially addressed the issue later by implementing graduated licensing laws, but the minimum driving age is now ingrained in the United States' car-dependent culture and is unlikely to change despite its recognized risks.

In recent decades, the time lag between physical science innovation and social science assessment and governmental mobilization has narrowed. Lessons learned from previous mistakes have prompted greater scrutiny and evaluation of technological impacts prior to their immersion in society. Synthetic biology in particular has not been insulated from social science inquiry during the innovation process. The physical and social science publications examining synthetic biology show nearly parallel trends in growth, indicating that social scientists have the ability to directly comment on emerging research (Trump et al. 2019). Torgersen and Schmidt (2013) and Shapira et al. (2015) attribute the contemporaneous, rather than lagged, growth of social science discourse of synthetic biology to the foundations laid by social science research on genetically modified organisms (GMOs), which had a controversial reception in the public sphere.

The simultaneous inquiry by both physical and social scientists augurs a process that will be fundamentally different than for previous innovations that developed outside of the public eye. Synthetic biology offers powerful remedies for some of the world's most intractable problems, but these solutions may not be developed or applied if the public perceives them to accompany unacceptable risks. Already a small but notable population exists that favors banning the field outright until the risks are better understood (Pauwels 2009; Pauwels 2013; Marris 2015). Such public mistrust and suspicion can be fueled by interest groups or misguided individuals (Linkov et al. 2018) who enjoy the public's attention. Calvert and Martin (2009) argue that the social concerns surrounding synthetic biology research through 2009 might have been addressed by "institutionaliz[ing]" social scientists' involvement in the field. A proactive and adaptive approach to risk management and governance can aid risk assessment in circumstances of limited experimental data (Oye 2012; Trump 2017), and social science inquiry can play a key role (Trump et al. 2018).

Since social science research of synthetic biology is already underway, physical and natural scientists have the opportunity to actively engage social scientists to evaluate innovations and help develop feasible products. In our modern era, physical scientists must understand that public perception matters and is a determinant in how applications of synthetic biology are ultimately funded, used, and governed. Because synthetic biology has the attention of social sciences so early in its innovation process, it has an opportunity to demonstrate the value of transdisciplinary collaboration in technological innovation as a way of providing secure benefits and a safe and socially acceptable forum for further exploration and development. Myriad perspectives around synthetic biology represent distinct motives and can directly address public wariness to adopt new technologies (Linkov et al. 2018). These steps may prevent a world of draconian policies based on insufficient understanding and widespread fear. Collaboration between physical scientists and social scientists during the innovation process should provide valuable opportunities to question potential broader impacts and ensure that products are acceptably safe.

Twenty Years of Synthetic Biology Development

Here, we present a short history of synthetic biology's development followed by brief descriptions of the chapters in this volume. As editors, we hope to provide a valuable and compelling resource that motivates the next generation of stakeholder collaborations to be resolute in envisioning a future that maximizes the potentials of synthetic biology while anticipating and respecting the needs and values of a diverse global citizenry.

Starting in the late 1970s, genetic engineers could blindly launch a novel gene into a host cell, hoping it landed in a good spot and worked in the new environment. After decades of incremental improvements in biochemical and genomic science, modern synthetic biology began to take root in the 1990s and early 2000s through engagement in more complex system engineering of viruses and bacteria. During the 1990s, "automated DNA sequencing and improved computational tools enabled complete microbial genomes to be sequenced, and high-throughput techniques for measuring RNA, protein, lipids and metabolites enabled scientists to generate a vast catalogue of cellular components and their interactions" (Cameron et al. 2014). This, coupled with a system engineering approach to biology, served as the core principles that made modern synthetic biology possible (Porcar and Peretó 2014; Cameron et al. 2014). In other words, genetic engineering around this time began to consider whether complex cellular networks could be viewed as engineered systems where biological engineering of a cell's DNA could yield complex changes to how those systems operate.

In 2000, *Nature* published two articles that discussed the deliberate creation of biological circuit devices (where biological parts inside a cell are designed to perform logical functions mimicking those observed in electronic circuits) by combining genes within *E. coli* cells. Gardner et al. (2000) constructed a genetic toggle switch to influence the expression of mutually inhibitory transcriptional repressors. Elowitz and Leibler (2000) engineered an oscillatory circuit that, when activated, produced the ordered and periodic oscillation of repressor protein expression. These publications encouraged the further development of research centered on circuit engineering and synthetic circuit construction to influence a cell's network design, including cell-to-cell communication and interactions (Weiss and Knight 2001).

During this time, the field of systems biology also emerged as a mature and independent field of inquiry pertaining to the computational and mathematical modeling of complex biological systems (Kitano 2002; Ideker et al. 2001). The field seeks to better understand the various properties of cells, tissues, and the systemic infrastructure that comprises living organisms (Hucka et al. 2004; Hood et al. 2004). This generally entails researching cell signaling networks or the signals and stimuli that govern and control cellular actions (Ingber 2003; Kitano 2002). For example, Park et al. (2003) published their work on posttranslational regulation using protein–protein interaction domains and scaffold proteins using *S. cerevisiae*. Coupled with earlier principles of genetic engineering, the technological and scientific

advancements derived within systems biology serve as some of the driving forces behind the development of synthetic biology research (Andrianantoandro et al. 2006; Khalil and Collins 2010).

By 2004, synthetic biology had clearly evolved from a small number of biologists and engineers into a growing and unique field of emerging technology research in its own right. The Massachusetts Institute of Technology hosted "Synthetic Biology 1.0" in June 2004 as the first international conference explicitly dedicated to synthetic biology research (Ball 2004). At this meeting, an interdisciplinary collection of professionals encompassing the field of biology, chemistry, computer science, and others discussed the desire to design, build, and characterize biological systems and interactions (Ferber 2004). This conference spurred further international meetings known colloquially as the SBx.0, with the latest iteration as of this writing held in Imperial College London in 2013 (SB 6.0). This conference series advanced discussion around blending elements of engineering with molecular biology to determine whether synthetic biology could develop as an engineering field like electrical engineering or materials science (Cameron et al. 2014). Specifically, Endy et al. (2005) and Cameron et al. (2014) describe these early efforts as an attempt to produce a collection of modular parts and improve design pathways for engineered cells with the idea that modifying specific cell circuit designs could deliberately change the behavior or interactions of that cell with its local environment.

Between 2004 and 2010, "the second wave of synthetic biology" produced circuit design and metabolic engineering (Purnick and Weiss 2009; Isaacs et al. 2004). The former included attempts to expand RNA-derived cellular systems of biological circuit engineering from "transcriptional control" into posttranscriptional control vehicles and capabilities (Bayer and Smolke 2005). Generally accomplished using *E. coli*, various scientists sought to expand circuit and part designs, with one such circuit dedicated to the conversion of light into gene expression for a collection of *E. coli* cells (Levskaya et al. 2005).

For the developments in metabolic engineering, a group of scientists at the University of California, Berkeley, studied isoprenoid biosynthesis which produces artemisinic acid, or the component precursor to the wormwood *Artemisia annua* (Ro et al. 2006). Using a collection of organisms including *Saccharomyces cerevisiae* and *E. coli,* scientists under the leadership of Dr. Jay Keasling produced artemisinic acid using fermented yeast cells in controlled and pre-planned settings (Ro et al. 2006; Hale et al. 2007). The World Health Organization uses artemisinin combination therapies as the primary initial treatment for *P. falciparum* malaria. The drug destroys the majority of parasites in a patient's blood upon the drug's ingestion (Nosten and White 2007; Van Agtmael et al. 1999). However, the plant's erratic price points (ranging from $120 to $1200 USD per kilogram between 2005 and 2008) and fluctuating production levels have hindered naturally produced artemisinin antimalarial drug distribution in Africa and Southeast Asia (Mutabingwa 2005; White 2008; Kindermans et al. 2007). Natural artemisinin-based treatments may require subsidies and controlled crop development to ensure accessibility (Mutabingwa 2005; White 2008). However, synthetic production of artemisinic components provides a faster timeline and more efficient resource use and can

obviate the reliance upon natural crop cycles for artemisinin plants. By 2013, the World Health Organization prequalified the use of semisynthetic artemisinin, allowing the pharmaceutical company Sanofi to begin its distribution with an initial shipment of 1.7 million artemisinin treatments in August 2014 (Singh and Vaidya 2015). This advancement in synthetic biology research demonstrated the technology's ability to yield therapeutic benefits for human health and commercial products (Hale et al. 2007; Westfall et al. 2012; Kong and Tan 2015).

Contemporary to these developments, since 2003, the nonprofit foundation International Genetically Engineered Machine (iGEM) has hosted annual competitions for teams of high school students, undergraduate students, graduate students, and entrepreneurs to build synthetic biological systems using pre-defined parts (Kelwick et al. 2015). Teams receive a kit of biological components from which to build biological systems and operate them in living cells (Kelwick et al. 2015; Mercer 2015; Stemerding 2015). Each fall, teams gather to demonstrate their creations and operate the pre-defined parts alongside biological parts they fostered for the competition (Kelwick et al. 2015; Stemerding 2015). The competition's membership grew to 130 teams worldwide by 2010 and 341 teams by 2019, with at least one team from every habitable continent on Earth (iGEM 2019). However, Tocchetti and Aguiton (2015) and Gronvall (2018) note that such "do-it-yourself" research raises concerns about biosafety and biosecurity risk. Though iGEM participants are screened and reviewed by multiple judges for safety concerns, some stakeholders in government and the lay public remain uneasy about the potential for risks, making the competition's biosafety and biosecurity practices a point of discussion for the synthetic biology community (Guan et al. 2013).

Following the rise in circuit design and eventual characterization alongside the growth and development of the synthetic biology research community, by 2008, synthetic biology's development had accelerated to creating more complex biological circuits and better controlling systemic biological behavior within cells. In this timeframe, the declining cost of gene synthesis alongside the development of high-throughput DNA assembly approaches advanced circuit engineering capabilities (Engler et al. 2008; Gibson et al. 2009; Cameron et al. 2014). This enabled greater control of genetic systems and novel gene expression such as light-sensing circuits within bacteria (Tabor et al. 2009) and faster and more complex pattern formation in *E. coli* swarms (Liu et al. 2011). Overall, this period drove greater connections between synthetic biologists and network engineers to improve controlling and altering the form and function of cellular networks on a system level (Cameron et al. 2014).

A widely publicized development within the second wave of synthetic biology occurred at the James Craig Venter Institute (Gibson et al. 2010; Ellis et al. 2011; Elowitz and Lim 2010; Cameron et al. 2014). In 2010, the Institute announced the creation of the first synthetic cell (Gibson et al. 2010). Using a modified *Mycoplasma mycoides* genome, Venter's team demonstrated that genome design may be "constructed on a computer, chemically made in the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome" (JCVI 2010). In their experiment, Venter's team synthesized a

version of the *M. mycoides* genome and transplanted it into an empty *Mycoplasma capricolum* bacterial shell (JCVI 2010; Cameron et al. 2014; Gibson et al. 2010; Ellis et al. 2011). This process fostered a self-replicating bacteria cell containing only the Institute's synthesized genome through transplantation of digitally synthesized genetic base pairs (Gibson et al. 2010). Within a year, a research team led by Jef Boeke at Johns Hopkins University performed a similar synthesis of *S. cerevisiae* in yeast (Dymond et al. 2011).

The Venter team's breakthrough proved the viability of constructing and editing a computerized genome for physical transplantation of a fully synthetic genome in a bacterial cell in controlled settings (JCVI 2010; Gibson et al. 2010). New developments enable scientists to cut and delete particular spots of DNA, replace portions of genes, or add entirely new genes in specific places. These techniques, collectively called "gene editing," are akin to our abilities to take pen to paper to correct typos, delete words or phrases, rearrange sentences, or add new ones. Current developments of synthetic biology applications are increasingly globalized and bring ever-expanding opportunities but more uncertainty around risk.

A team led by George Church developed the multiplex automated genome engineering (MAGE) platform to rapidly alter multiple loci in the *E. coli* genome (Wang et al. 2009; Cameron et al. 2014). This platform enabled the "proof-of-principle replacement of all TAG stop codons with the synonymous TAA codon" (Isaacs et al. 2011; Cameron et al. 2014; Wang et al. 2009). Jiang et al. (2013) and DiCarlo et al. (2013) used the clustered regularly interspaced short palindromic repeats-associated system (or CRISPR-Cas, for short) as a tool for genome editing that helped to generate genomic mutations within a cell. This increased the ability of geneticists to alter genetic structures in bacteria and yeast (Jiang et al. 2013; DiCarlo et al. 2013). CRISPR-Cas9 allows genetic engineers to mutate, swap, or add multiple genes at one time. Researchers used this approach to efficiently edit a set of 62 pig genes to produce porcine organs that harbor fewer viruses and so are safer for human transplantation (Servick 2017). Another gene-editing technique, zinc fingers, is particularly useful for engineering proteins that target specific genes (Klug 2010), allowing scientists to selectively switch specific genes on and off (Heinemann and Panke 2006; Klug 2010), and enabling more complex genetic manipulation of larger eukaryotic organisms (Khalil et al. 2012).

Animal and crop genetic engineering are heading quickly toward gene editing, not just because of its speed and creative power but also because developers recognize loopholes in oversight in the United States. Some of the new gene-editing techniques fall outside of current regulatory definitions, which are based on early genetic engineering applications. As a result, several edited crops have evaded US regulation (Kuzma 2016).

Synthetic biologists became increasingly able to alter cell DNA and produce systemic-level change to the cell's genome and behavior. However, significant challenges remain to synthetic biology, such as with the high variability of cellular part and circuit performance to overall cellular circuit construction (Nandagopal and Elowitz 2011). Smith et al. (2014) and Baltes and Voytas (2015) further note

that variability within a complex intracellular environment is inherent and, at least currently, seemingly improbable to prevent or avoid.

Purnick and Weiss (2009), Andrianantoandro et al. (2006), Ellis et al. (2009), and Cheng and Lu (2012) sought to work around this problem by constructing libraries of synthesized cellular parts and rigorously quantifying the behavior and activity of these parts under certain conditions. Such libraries support assembling cellular circuits from thoroughly researched collections of parts, which would then be screened and improved as necessary for a particular function or project. The International Open Facility Advancing Biotechnology (BIOFAB) aims to construct and characterize libraries of bacterial promoters and transcription terminators (Mutalik et al. 2013; Cambray et al. 2013). Specific to this aim, BIOFAB seeks to foster a reliability score for individual cellular parts, which characterizes the potential flaws that each part may express, which can assist debugging efforts within circuit engineering exercises (Mutalik et al. 2013).

Most genetically engineered organisms (GEOs) approved for release into natural or agricultural environments are not expected to survive on their own for multiple generations because they are either less fit than the wild type or designed for human-managed systems. Confinement of the GEO and the introduced genes has been desirable for current applications of GEOs such as GE plants in agriculture or GE microorganisms for environmental pollution remediation. However, a recent advancement in gene editing enables spreading altered genes through entire populations in either a self-limited or unlimited way.

Most genes in sexually reproducing species follow the laws of Mendelian inheritance: an introduced gene is carried on one of a pair of chromosomes and is thus inherited by about half of the offspring in the first generation. If there is no selective advantage to the gene, it will dilute in the population over time. However, diverse genetic mechanisms can enable genes to occur more frequently than the expected 50% of first-generation offspring. Evolutionary biologists have been studying these naturally occurring "selfish genetic elements" for over 80 years, but only in the past decade have researchers synthesized genetic elements with these properties. Experimental new "gene drive" systems allow an edited gene on one chromosome to copy itself into its partner chromosome to ensure that nearly all offspring will inherit the engineered gene. Thus, even if just a few organisms with gene drives are released into the wild, species with short generation times and random mating could spread an engineered gene through a large population within just a season. Synthetic "gene drive" systems took a leap forward with CRISPR-Cas9 technology, which greatly increases the ease and pace at which engineered organisms with drive mechanisms can be produced (Esvelt et al. 2014, Mali et al. 2013).

Gene drives have not yet been released into the wild, but they have been demonstrated in laboratory-cage experiments with fruit flies and mosquitos. In the wild, the drives could spread killer genes to destroy unwanted pest populations, invasive species, or disease-carrying organisms. Releasing a few individuals with killer-drive systems could theoretically eradicate a whole population, like mosquitos carrying dengue, malaria, or Zika virus. Gene drives could also add beneficial genes to populations to immunize endangered species against disease or protect them from the

effects of climate change. In some cases, gene drives might be the only option to save an endangered species or to protect humans from great harm.

The ecological and health risks and benefits of synthetic biology will depend on the species engineered, the type of alteration carried, the place where it is released, the strategy for release and monitoring, and the properties of the genetic alterations. Some questions for thinking about these risks of synthetic biology include the following: How might a genetic construct(s) spread to a natural population, both intentionally or not? Does the construct(s) alter the characteristics of individuals in the population (ability to transmit pathogens), decrease population size, or both? Could the construct(s) cause extinction of the population or even the species, and is that desirable? Will the construct(s) remain in a wild population or be lost with time? Is there a means for "recalling" (or eliminating) the initially released construct(s) by releasing other variants of the target species? How would changes in the target population affect the overall ecosystem? Could other more harmful species fill the ecological niches of the eradicated organisms, perhaps ones spreading even more detrimental human or ecological disease?

These are scientific questions with potentially broad social science implications. Many chapters in this volume provide new data and approaches that demonstrate the feasibility for multi-stakeholder efforts involving policymakers, regulators, industrial developers, workers, experts, and societal representatives that can together create effective and acceptable governance in the face of uncertain risk probabilities. Such participation bestows responsibility and is a partial remedy for ignorance and may provide a pathway for humanity to maximize its benefits from synthetic biology while minimizing risks.

A Brief Introduction to *Synthetic Biology 2020's* Chapters

The chapters in this book provide perspectives of historical synthetic biology developments and implications for the technology's applications in the future. Topically, they range from general background, to differing perspectives on risk assessment and management, to governance, to risk communication and ethical decision-making.

In chapter "Synthetic Biology: Research Needs for Assessing Environmental Impacts," the team of Warner, Carter, Lance, Crocker, Meeks, Adams, Magnuson, Rycroft, Pokrzywinski, and Perkins reviews multiple platforms of synthetic biology research to better understand their potential environmental implications. Such a comprehensive review of technological use scenarios as well as their hazards and exposure considerations helps to structure the research environment and identify areas where potential threats or safety challenges may be likely or unacceptable.

Chapter "Transfish: The Multiple Origins of Transgenic Salmon" documents the development of transgenic salmon and the various mechanisms that render such an innovation "safe" in the eyes of US consumers. It describes consumer suspicions

and misunderstandings of synthetic biology products (will fish antifreeze make ice cream taste fishy?) and the approval process in the United States.

In chapter "The State of Synthetic Biology Scholarship: A Case Study of Comparative Metrics and Citation Analysis," Cegan applies a network/connectivity analysis to synthetic biology publications to better understand the different disciplines and actors evaluating synthetic biology and where they are headed. Using network and citation analysis, this chapter demonstrates how more advanced analytical tools can help make sense of a rapidly growing body of literature such as the physical/natural and social sciences of synthetic biology.

In chapter "Synthetic Biology, GMO, and Risk: What Is New, and What Is Different?," Trump offers a background of synthetic biology's various threats, including those related to biosafety and biosecurity. This chapter examines what types of risk may be unusual, novel, or particularly difficult for a stakeholder to assess and thereby contribute to governance challenges where no clear best practice or operating procedure has yet been identified.

Chapter "Estimating and Predicting Exposure to Products from Emerging Technologies" (Vallero) describes the risk assessment and management paradigm applied by environmental agencies in the United States and methodologies for estimating human exposures to contaminants. Vallero asserts that better understanding exposures and subsequent risks will support informed decisions involving synthetic biology and emerging technologies.

In chapter "Mosquitoes Bite: A Zika Story of Vector Management and Gene Drives," Berube examines the trade-offs of continued disease infection and disease reduction enabled by releasing varieties of engineered mosquitos, and the public reception of those options. Berube writes, "What stands between us and addressing one of the biggest public health issues in the world is not science. It's how we talk about science."

In chapter "Synthetic Biology Industry: Biosafety Risks to Workers," Murashov, Howard, and Schulte consider the risks of synthetic biology to the workers in the biotech industry. The authors describe the safety measures that can be implemented to mitigate worker risk from exposure to hazardous materials. Demonstrated containment and control of synthetic biology will support the safety of innovation processes.

Finkel (chapter "Designing a "Solution-Focused" Governance Paradigm for Synthetic Biology: Toward Improved Risk Assessment and Creative Regulatory Design") reviews challenges associated with quantitative risk assessment relative to synthetic biology and describes how a complementary approach, known as "solution-focused risk assessment," can better inform the trade-offs and implications of synthetic biology applications in areas of considerable uncertainty. As new technologies empower humans, new inventions must examine the full spectrum of trade-offs, including risks, their associated uncertainties, and their variation across different populations. Finkel advocates for transparency in hidden influential value judgments as part of risk communication.

Chapter "A Solution-Focused Comparative Risk Assessment of Conventional and Emerging Synthetic Biology Technologies for Fuel Ethanol" (Wells, Trump,

Finkel, and Linkov) compares conventional options for energy production from corn and sugarcane feedstock to biofuel produced from engineered algae. Wells et al. utilize one permutation of Finkel's proposed solution-focused risk assessment to identify areas of novel risk to weigh against the benefits of algal biofuels and incorporate the uncertainty of synthetically engineered biofuel impacts. This holistic process could be a tool for assuaging public concerns surrounding synthetic biology for fuel production.

Chapter "An Initial Framework for the Environmental Risk Assessment of Synthetic Biology-Derived Organisms with a Focus on Gene Drives" (Landis, Brown, and Eikenbary) uses a more advanced analytical approach to demonstrate how the environmental impacts of synthetic biology-derived organisms can be assessed for environmental risk implications. Whereas a major concern of the potential use of gene drives is the irreversibility and disruption posed by engineered organisms upon the natural environment, Landis et al.'s approach is one that can help inform developers and policymakers alike of the safe use requirements and best practices that synthetic biology research should incorporate.

Kuiken (chapter "Biology without Borders: Need for Collective Governance?") begins by using the competition iGEM and its Safety and Security Committee as a study of governance for synthetic biology. Kuiken expands on ideas of equity and safety as he profiles the synthetic biology community that emerged from independent informal laboratories around the United States and the world. He shares a model for collective governance that can reconcile international laws and provide a means for overseeing synthetic biology as it evolves.

Trump, Siharulidze, and Cummings (chapter "Synthetic Biology and Risk Regulation: The Case of Singapore") differ from other governance chapters by reviewing the hard and soft law activities within Singapore. As a growing developer of synthetic biology and its enabling technologies, Singaporean governance of synthetic biology differs from their Western counterparts due to its inherently diverging political and institutional frameworks and can cause it to address and govern the risks posed by such technologies in an equally divergent manner.

Novossiolova, Bakanidze, and Perkins (chapter "Effective and Comprehensive Governance of Biological Risks: A Network of Networks Approach for Sustainable Capacity Building") document the various factors spurring innovation in synthetic biology and emphasize that regulations must manage risk without stymieing innovation. Lela examines various governance structures and asserts that biological security will benefit from both top-down actions, such as regulations and inspections, and bottom-up approaches, including education and standardized procedures.

Ndoh, Cummings, and Kuzma (chapter "The Role of Expert Disciplinary Cultures in Assessing Risks and Benefits of Synthetic Biology") review not only how different expectations, norms, values, and operating requirements within various disciplinary domains shape their perception of synthetic biology and its products, but also how risk analysis, policy, and governance are crafted and executed to capture the technology. Their notion of "expert culture" is one that demonstrates the usefulness of a collaborative and mixed-method approach toward

synthetic biology governance moving forward, including the combined views of natural and social scientists.

Howell et al. (chapter "Scientists' and the Publics' Views of Synthetic Biology") analyze surveys of scientific experts and members of the American public to examine their respective risk perceptions of synthetic biology. Howell recognizes the polarization that has grown around issues like genetically modified crops or stem cell research, and the path forward for synthetic biology appears to be through public engagement in decision-making.

In chapter "Dignity as a Faith-based Consideration in the Ethics of Human Genome Editing," Austriaco explores the notion of human dignity to explain divergent views on synthetic biology between religious and lay communities. The confluence of values like dignity, free will, and agency supports understanding the emotional connotations that communities voice around issues like gene editing for human babies.

In chapter "Highlights on the Risk Governance for Key Enabling Technologies: From Risk Denial to Ethics," Merad explores the confusion between science and counter science and the denial of scientific fact. This can help frame how scientific information is developed, disseminated, and consumed and the trade-offs are considered by different actors in that process.

Ultimately, synthetic biology can provide valuable benefits to humanity that likely cannot be achieved by alternate means. Such innovations will certainly also enrich the teams that create them. The incentives are prodigious and obvious, and the public deserves assurances that all potential downsides are understood and minimized accordingly. Social science may impose additional constraints on the innovation process, but its simultaneous support in improving end product acceptability to society at large is a worthy trade-off.

References

Agtmael, V., Michiel, A., Eggelte, T. A., & van Boxtel, C. J. (1999). Artemisinin drugs in the treatment of malaria: From medicinal herb to registered medication. *Trends in Pharmacological Sciences, 20*(5), 199–205.

Andrianantoandro, E., Basu, S., Karig, D. K., & Weiss, R. (2006). Synthetic biology: New engineering rules for an emerging discipline. *Molecular Systems Biology, 2*(1), 2006–0028.

Ball, P. (2004). Synthetic biology: starting from scratch. *Nature – London*, (7009), 624.

Baltes, N. J., & Voytas, D. F. (2015). Enabling plant synthetic biology through genome engineering. *Trends in Biotechnology, 33*(2), 120–131.

Bayer, T. S., & Smolke, C. D. (2005). Programmable ligand-controlled riboregulators of eukaryotic gene expression. *Nature Biotechnology, 23*(3), 337–343.

Calvert, J., & Martin, P. (2009). The role of social scientists in synthetic biology. *EMBO Reports, 10*(3), 201–204.

Cambray, G., Guimaraes, J. C., Mutalik, V. K., Lam, C., Mai, Q.-A., Thimmaiah, T., Carothers, J. M., Arkin, A. P., & Endy, D. (2013). Measurement and modeling of intrinsic transcription terminators. *Nucleic Acids Research, 41*(9), 5139–5148.

Cameron, D. E., Bashor, C. J., & Collins, J. J. (2014). A brief history of synthetic biology. *Nature Reviews Microbiology, 12*(5), 381.

Cheng, A. A., & Lu, T. K. (2012). Synthetic biology: An emerging engineering discipline. *Annual Review of Biomedical Engineering, 14*, 155–178.

Cummings, C., Frith, J., & Berube, D. (2013). Unexpected appropriations of technology and life cycle analysis: Reframing cradle to grave approaches. In N. Savage, M. E. Gorman, & A. Street (Eds.), *Emerging technologies: Socio-behavioral life cycle approaches* (pp. 251–271). CRC Press, Boca Raton, FL.

DiCarlo, J. E., Norville, J. E., Mali, P., Rios, X., Aach, J., & Church, G. M. (2013). Genome engineering in Saccharomyces cerevisiae using CRISPR-Cas systems. *Nucleic Acids Research, 41*(7), 4336–4343.

Dymond, J. S., Richardson, S. M., Coombes, C. E., Babatz, T., Muller, H., Annaluru, N., Blake, W. J., et al. (2011). Synthetic chromosome arms function in yeast and generate phenotypic diversity by design. *Nature, 477*(7365), 471.

Ellis, T., Wang, X., & Collins, J. J. (2009). Diversity-based, model-guided construction of synthetic gene networks with predicted functions. *Nature Biotechnology, 27*(5), 465.

Ellis, T., Adie, T., & Baldwin, G. S. (2011). DNA assembly for synthetic biology: From parts to pathways and beyond. *Integrative Biology, 3*(2), 109–118.

Elowitz, M. B., & Leibler, S. (2000). A synthetic oscillatory network of transcriptional regulators. *Nature, 403*(6767), 335.

Elowitz, M., & Lim, W. A. (2010). Build life to understand it. *Nature, 468*(7326), 889.

Endy, D., Deese, I., & Wadey, C. (2005). Adventures in synthetic biology. *Nature, 438*(7067), 449–453.

Engler, C., Kandzia, R., & Marillonnet, S. (2008). A one pot, one step, precision cloning method with high throughput capability. *PLoS One, 3*, e3647.

Esvelt, K. M., Smidler, A. L., Catteruccia, F., & Church, G. M. (2014). Emerging technology: Concerning RNA-guided gene drives for the alteration of wild populations. *Elife3, 3*, e03401.

Ferber, D. (2004). Time for a synthetic biology Asilomar? *Science, 303*, 159.

Ferguson, S. A., Leaf, W. A., Williams, A. F., & Preusser, D. F. (1996). Differences in young driver crash involvement in states with varying licensure practices. *Accident Analysis & Prevention, 28*(2), 171–180.

Gardner, T. S., Cantor, C. R., & Collins, J. J. (2000). Construction of a genetic toggle switch in Escherichia coli. *Nature, 403*(6767), 339.

Gibson, D. G., Young, L., Chuang, R.-Y., Craig Venter, J., Hutchison, C. A., III, & Smith, H. O. (2009). Enzymatic assembly of DNA molecules up to several hundred kilobases. *Nature Methods, 6*(5), 343.

Gibson, D. G., Glass, J. I., Lartigue, C., Noskov, V. N., Chuang, R.-Y., Algire, M. A., Benders, G. A., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science, 329*(5987), 52–56.

Gronvall, G. K. (2018). Safety, security, and serving the public interest in synthetic biology. *Journal of Industrial Microbiology & Biotechnology, 45*(7), 463–466.

Guan, Z.-J., Schmidt, M., Pei, L., Wei, W., & Ma, K.-P. (2013). Biosafety considerations of synthetic biology in the international genetically engineered machine (iGEM) competition. *Bioscience, 63*(1), 25–34.

Hale, V., Keasling, J. D., Renninger, N., & Diagana, T. T. (2007). Microbially derived artemisinin: A biotechnology solution to the global problem of access to affordable antimalarial drugs. *The American Journal of Tropical Medicine and Hygiene, 77*(6_Suppl), 198–202.

Heinemann, M., & Panke, S. (2006). Synthetic biology—Putting engineering into biology. *Bioinformatics, 22*(22), 2790–2799.

Hood, L., Heath, J. R., Phelps, M. E., & Lin, B. (2004). Systems biology and new technologies enable predictive and preventative medicine. *Science, 306*(5696), 640–643.

Hucka, M., Finney, A. B. B. J., Bornstein, B. J., Keating, S. M., Shapiro, B. E., Matthews, J., Kovitz, B. L., et al. (2004). Evolving a lingua franca and associated software infrastructure

for computational systems biology: The Systems Biology Markup Language (SBML) project. *Systems Biology, 1*(1), 41–53.
Ideker, T., Galitski, T., & Hood, L. (2001). A new approach to decoding life: Systems biology. *Annual Review of Genomics and Human Genetics, 2*(1), 343–372.
iGEM. Team list for iGEM 2019 Championship. https://igem.org/Team_List. Last accessed 3 Apr 2019.
Ingber, D. E. (2003). Tensegrity I. Cell structure and hierarchical systems biology. *Journal of Cell Science, 116*(7), 1157–1173.
Isaacs, F. J., et al. (2004). Engineered riboregulators enable post-transcriptional control of gene expression. *Nature Biotechnology, 22*, 841–847.
Isaacs, F. J., Carr, P. A., Wang, H. H., Lajoie, M. J., Sterling, B., Kraal, L., Tolonen, A. C., et al. (2011). Precise manipulation of chromosomes in vivo enables genome-wide codon replacement. *Science, 333*(6040), 348–353.
Jasanoff, S. (2009). *The fifth branch: Science advisers as policymakers*. Cambridge: Harvard University Press.
JCVI. (2010). First self-replicating, synthetic bacterial cell constructed by J. Craig Venter Institute Researchers [Press Release]. Retrieved from https://www.jcvi.org/first-self-replicating-synthetic-bacterial-cell-constructed-j%C2%A0craig-venter-institute-researchers
Jiang, W., Bikard, D., Cox, D., Zhang, F., & Marraffini, L. A. (2013). RNA-guided editing of bacterial genomes using CRISPR-Cas systems. *Nature Biotechnology, 31*(3), 233.
Kelwick, R., Bowater, L., Yeoman, K. H., & Bowater, R. P. (2015). Promoting microbiology education through the iGEM synthetic biology competition. *FEMS Microbiology Letters, 362*(16), fnv129.
Khalil, A. S., & Collins, J. J. (2010). Synthetic biology: Applications come of age. *Nature Reviews Genetics, 11*(5), 367.
Khalil, A. S., Lu, T. K., Bashor, C. J., Ramirez, C. L., Pyenson, N. C., Joung, J. K., & Collins, J. J. (2012). A synthetic biology framework for programming eukaryotic transcription functions. *Cell, 150*(3), 647–658.
Kindermans, J.-M., Pilloy, J., Olliaro, P., & Gomes, M. (2007). Ensuring sustained ACT production and reliable artemisinin supply. *Malaria Journal, 6*(1), 125.
Kitano, H. (2002). Systems biology: A brief overview. *Science, 295*(5560), 1662–1664.
Klug, A. (2010). The discovery of zinc fingers and their applications in gene regulation and genome manipulation. *Annual Review of Biochemistry, 79*, 213–231.
Kong, L. Y., & Tan, R. X. (2015). Artemisinin, a miracle of traditional Chinese medicine. *Natural Product Reports, 32*(12), 1617–1621.
Kuzma, J. (2016). Policy: Reboot the debate on genetic engineering. *Nature, 531*, 165–167.
Levskaya, A., Chevalier, A. A., Tabor, J. J., Simpson, Z. B., Lavery, L. A., Levy, M., Davidson, E. A., et al. (2005). Synthetic biology: Engineering Escherichia coli to see light. *Nature, 438*(7067), 441.
Linkov, I., et al. (2018). Comparative, collaborative, and integrative risk governance for emerging technologies. *Environment Systems and Decisions, 38*(2), 170–176.
Liu, C., Fu, X., Liu, L., Ren, X., Chau, C. K., Li, S., et al. (2011). Sequential establishment of stripe patterns in an expanding cell population. *Science, 334*(6053), 238–241.
Mali, P., Esvelt, K. M., & Church, G. M. (2013). Cas9 as a versatile tool for engineering biology. *Nature Methods, 10*(10), 957.
Marris, C. (2015). The construction of imaginaries of the public as a threat to synthetic biology. *Science as Culture, 24*(1), 83–98.
Mercer, D. (2015). iDentity and governance in synthetic biology: Norms and counter norms in the international genetically engineered machine (iGEM) competition. *Macquarie Law Journal, 15*, 83.
Mutabingwa, T. K. (2005). Artemisinin-based combination therapies (ACTs): Best hope for malaria treatment but inaccessible to the needy! *Acta Tropica, 95*(3), 305–315.

Mutalik, V. K., Guimaraes, J. C., Cambray, G., Lam, C., Christoffersen, M. J., Mai, Q.-A., Tran, A. B., et al. (2013). Precise and reliable gene expression via standard transcription and translation initiation elements. *Nature Methods, 10*(4), 354.

Nandagopal, N., & Elowitz, M. B. (2011). Synthetic biology: Integrated gene circuits. *Science, 333*(6047), 1244–1248.

Nosten, F., & White, N. J. (2007). Artemisinin-based combination treatment of falciparum malaria. *The American Journal of Tropical Medicine and Hygiene, 77*(6_Suppl), 181–192.

Oye, K. A. (2012). *Proactive and adaptive governance of emerging risks: The case of DNA synthesis and synthetic biology*. International Risk Governance Council.

Palma-Oliveira, J. M., Trump, B. D., Wood, M. D., & Linkov, I. (2018). Community-driven hypothesis testing: A solution for the tragedy of the anticommons. *Risk Analysis, 38*(3), 620–634.

Park, S. H., Zarrinpar, A., & Lim, W. A. (2003). Rewiring MAP kinase pathways using alternative scaffold assembly mechanisms. *Science, 299*, 1061–1064.

Pauwels, E. (2009). Review of quantitative and qualitative studies on U.S. public perceptions of synthetic biology. *Systems and Synthetic Biology, 3*(1–4), 37–46.

Pauwels, E. (2013). Public understanding of synthetic biology. *Bioscience, 63*(2), 79–89.

Polizzi, K. M., Stanbrough, L., & Heap, J. T. (2018). A new lease of life: Understanding the risks of synthetic biology. An emerging risks report published by Lloyd's of London. https://www.lloyds.com/news-and-risk-insight/news/lloyds-news/2018/07/a-new-lease-of-life. Accessed 4 Sept 2018.

Porcar, M., & Peretó, J. (2014). Synthetic biology in action. In *Synthetic biology* (pp. 45–53). Dordrecht: Springer.

Purnick, P. E. M., & Weiss, R. (2009). The second wave of synthetic biology: From modules to systems. *Nature Reviews Molecular Cell Biology, 10*(6), 410.

Ro, D.-K., Paradise, E. M., Ouellet, M., Fisher, K. J., Newman, K. L., Ndungu, J. M., Ho, K. A., et al. (2006). Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature, 440*(7086), 940.

Servick, K.. (2017). CRISPR slices virus genes out of pigs, but will it make organ transplants to humans safer? Science Magazine. Available https://www.sciencemag.org/news/2017/08/crispr-slices-virus-genes-out-pigs-will-it-make-organ-transplants-humans-safer

Shapira, P., Youtie, J., & Li, Y. (2015). Social science contributions compared in synthetic biology and nanotechnology. *Journal of Responsible Innovation, 2*(1), 143–148.

Singh, M., & Vaidya, A. (2015). Translational synthetic biology. *Systems and Synthetic Biology, 9*(4), 191–195.

Smith, M. T., Wilding, K. M., Hunt, J. M., Bennett, A. M., & Bundy, B. C. (2014). The emerging age of cell-free synthetic biology. *FEBS Letters, 588*(17), 2755–2761.

Stemerding, D. (2015). iGEM as laboratory in responsible research and innovation. *Journal of Responsible Innovation, 2*(1), 140–142.

Tabor, J. J., Salis, H. M., Simpson, Z. B., Chevalier, A. A., Levskaya, A., Marcotte, E. M., Voigt, C. A., & Ellington, A. D. (2009). A synthetic genetic edge detection program. *Cell, 137*(7), 1272–1281.

Tocchetti, S., & Aguiton, S. A. (2015). Is an FBI agent a DIY biologist like any other? A cultural analysis of a biosecurity risk. *Science, Technology, & Human Values, 40*(5), 825–853.

Torgersen, H., & Schmidt, M. (2013). Frames and comparators: How might a debate on synthetic biology evolve? *Futures, 48*, 44–54.

Trump, B. D. (2017). Synthetic biology regulation and governance: Lessons from TAPIC for the United States, European Union, and Singapore. *Health Policy, 121*(11), 1139–1146.

Trump, B., Cummings, C., Kuzma, J., & Linkov, I. (2018). A decision analytic model to guide early-stage government regulatory action: Applications for synthetic biology. *Regulation & Governance, 12*(1), 88–100.

Trump, B. D., Cegan, J., Wells, E., Poinsatte-Jones, K., Rycroft, T., Warner, C., et al. (2019). Co-evolution of physical and social sciences in synthetic biology. *Critical Reviews in Biotechnology, 39*(3), 351–365.

Wang, H. H., Isaacs, F. J., Carr, P. A., Sun, Z. Z., Xu, G., Forest, C. R., & Church, G. M. (2009). Programming cells by multiplex genome engineering and accelerated evolution. *Nature, 460*(7257), 894.

Weiss, R., & Knight Jr, T. (2001). Engineered communications for microbial robotics. In lncs 2054.

Westfall, P. J., Pitera, D. J., Lenihan, J. R., Eng, D., Woolard, F. X., Regentin, R., Horning, T., et al. (2012). Production of amorphadiene in yeast, and its conversion to dihydroartemisinic acid, precursor to the antimalarial agent artemisinin. *Proceedings of the National Academy of Sciences, 109*(3), E111–E118.

White, N. J. (2008). The role of anti-malarial drugs in eliminating malaria. *Malaria Journal, 7*(1), S8.

Williams, A. F. (2009). Licensing age and teenage driver crashes: A review of the evidence. *Traffic Injury Prevention, 10*(1), 9–15.