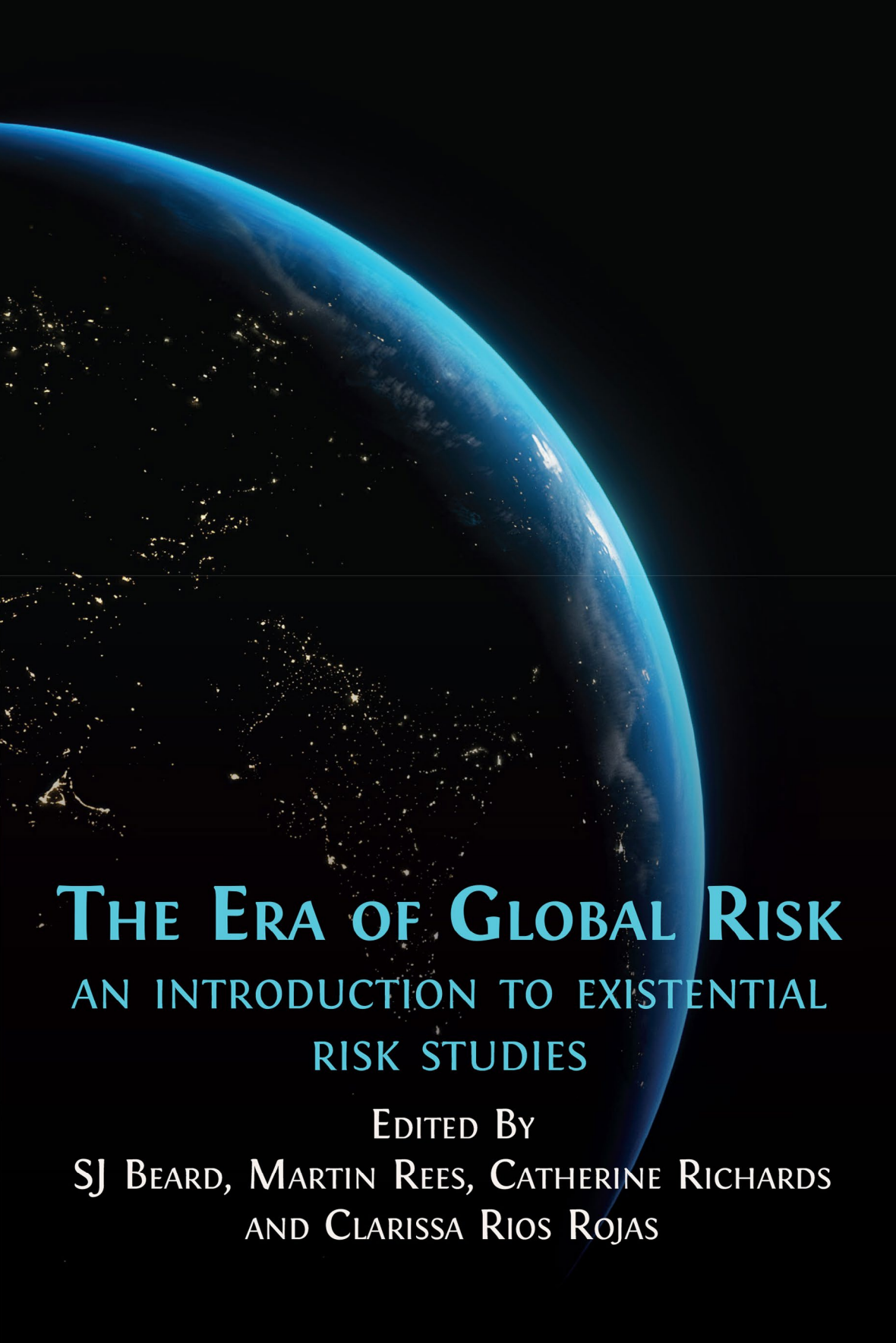

The Era of Global Risk

An Introduction to Existential Risk Studies

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8. Biosecurity, Biosafety, and Dual Use: Will Humanity Minimise Potential Harms in the Age of Biotechnology?

Kelsey Lane Warmbrod, Kobi Leins, and Nancy Connell

In the fall of 2001, a domestic attack[1] through the mail with a biological agent, *Bacillus anthracis* (more commonly known as anthrax) killed five and sickened 17 in the United States. The incident took place days after the unprecedented aeroplane attack on several sites in the United States, which permanently altered the global landscape. Similarly, the anthrax attacks created a convulsive and wide-ranging change in the global order with respect to infectious disease research and bioterrorism. Despite a strong and storied community[2] of experts in biological weapons development and use, the field was largely limited to historians, policymakers, and diplomatic circles associated with the Biological Toxins and Weapons Convention of 1972 (BTWC). The decade after 2001 ushered in fundamental changes in the broad perception of biological threats. The anthrax incident brought increased security and safety awareness to those working in the life sciences, accompanied by a sea-change in regulatory policy across several federal agencies. The field of microbial forensics developed following the recognition of 'biocrimes';[3] increased attention was paid by lawyers, policymakers, ethicists, and others to dual-use research of concern, or 'DURC'

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(discussed below). Biotechnology and life sciences research continued to advance with breathtaking speed, as heralded in Sir Martin Rees' *Our Final Century* musings on "Post-2000 Threats".

The 20th century had seen its share of biological hazards. Rees discusses the extensive biological weapons programs carried out in the 1940–60s in the US, the UK, the former USSR, and Japan; the signing and ratification of the BTWC by those countries and most of the world put an end to openly offensive activities. But the treaty was fashioned half a century ago and was designed for control of natural biological threats: viruses, bacteria, and toxins found in nature. At the turn of the millennium, the ability to read DNA—DNA sequencing—was a slow and expensive proposition; gene synthesis technologies were in their infancy and genomic editing was very difficult; now, the reading, writing, and editing of DNA[4] has become commonplace, inexpensive, and ubiquitous across the world. Monitoring the expression of genes or the proteins they encode was laborious: now, the complex interplay of patterns of small molecule expression at the organism level all the way down to interactions in a single cell can be measured and analysed using multifaceted algorithms. The intersection of big data and artificial intelligence has unmasked deeper complexities than we ever imagined. Knowledge of neuroscience, immunology, and genetics is converging[5] with AI, nanotechnology, and synthetic biology, and quantum biology is on the horizon; the 21st century is the Century of Biology. Here, we survey several advancing biotechnologies and their progress since 2000, warn against their potential misuse, and call for safe and equitable implementation. Indeed, the 21st century is also the Century of Biosecurity.

Dual-use research and its governance

Many biosecurity discussions centre on the concept of dual-use technologies.[6] Legal scholars use the 'civilian use' versus 'military use' definition. The life sciences use a different definition: research with legitimate scientific purpose, the results of which may be misused to pose a threat to the public and/or national security.[7] Dual-use remains an ongoing concern for regulation of military use of science. The World Health Organization (WHO) states that "[d]ual use research of concern

(DURC) is life sciences research that is intended for benefit, but which might easily be misapplied to do harm".[8] Some types of research and technologies have long been labelled as 'dual use' and been priorities for governance,[9] such as DNA synthesis or synthetic reconstruction of pathogens. Multiple technologies in the life sciences may be labelled as dual use: pathogens, nanomaterials, DNA, just to name a few.

In early 2004, the National Science Advisory Board for Biosecurity[10] (NSABB) was formed in the US to provide guidance on education, regulation, and strategies for 'dual-use' research. Its agenda included the provision of tools to identify and evaluate the risks and benefits of particular kinds of science. In 2007, NSABB completed a report called *Proposed Framework for the Oversight of Dual-Use Life Sciences Research*, which defined dual research as:

> [A] term to refer in general to legitimate life sciences research that has the potential to yield information that could be misused to threaten public health and safety and other aspects of national security such as agriculture, plants, animals, the environment, and material.[11]

Given that almost all scientific research could fall within this definition, NSABB offered another category of 'dual-use research of concern', which was defined as:

> [R]esearch that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or material.[12]

Despite the inevitability of the dual-purpose nature of research, including a multi-billion-dollar increase in biodefence research funding in the United States after 2001, "much of it supporting civilian research",[13] surprisingly little research is censored or held to be a risk.[14]

Particularly in the case of nanomaterials used for advances in neuroscience, the risks of dual use need to be managed very carefully. The CWC incorporates lists of materials that are dual use and limits the quantities in which they can be purchased, sold, or transferred across national boundaries. A challenge not particular to—but especially a feature of—nanomaterials is that, given the literally invisible nature of potentially toxic materials, similar control measures will not be effective

for nanomaterials. One such example is virus-like nanoparticles, currently being researched for targeting cancer, but again, with potential dual use.[15] Garage biology or DIY ('Do It Yourself'—a term used to refer to individuals conducting experiments on their own) biology also poses a security threat, with its decreasing costs and automation.[16] The extent to which these types of threats remain a risk is considered within the DURC framework mentioned earlier, one in which "the overall approach is to treat the use of biological weapons as a low probability high impact risk".[17] Similar frameworks must be developed for other new DURC developments.

One approach to dual-use governance is to recognise that all life sciences research and technology has the potential to be misused, and that dual-use concerns lie along a spectrum of potential hazards.[18] Some research, technologies, or information in the life sciences may have very low risk of causing harm either accidentally or deliberately, while others may have a high risk of potential harm. We are not well equipped to understand where on the spectrum of dual-use risk something may fall, because it is hard to accurately predict the trajectory of advancement. For example, metallurgy was the foundation needed to develop nuclear weapons, but it is unlikely that the scientists researching metallurgy suspected that their research would lead to the development of nuclear weapons. Additionally, a technology or area of research's position on the spectrum is not static. Potential to cause harm will change as governance mechanisms change, novel ideas emerge, new information is gathered, and technologies from different areas are combined in new ways. This is especially true as we see increasing convergence among the life sciences and other fields, such as artificial intelligence, microfluidics, and nanotechnology. There is great potential for fields in the life sciences such as neurobiology, immunology, ecology, genetics, and developmental biology to blend with other disciplines to solve some of the biggest challenges we face today, such as food insecurity, climate change, or disease. There are legitimate purposes and potentially great benefits from such work. However, there are also great risks associated with such convergences. As a society, we must decide how to weigh the benefits and risks of these technologies, and engage with a diverse and broad audience to decide what work should or should not move forward. Especially important is ensuring that those most likely to be

disproportionally impacted are represented in these conversations. Qualitative frameworks[19] can assist in the assessment of risk and benefits of individual applications of biotechnology, and allow continuous monitoring of their ethical impacts on society, as well as expanding existing controls, such as the Chemical Weapons Convention's lists of dual-use materials, as knowledge of their toxicity becomes available.

All of the technologies in the life sciences have the potential to be dual-use technologies. Each has the potential to make substantial improvements in or lead to possible harm to human, animal, plant, and environmental health. Existing 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. Among the models under discussion is network-based governance: a transnational mix of government, sub-government, and stakeholders who work together to solve collective problems.[20] Qualitative framework analysis can bring clarity to the assessment of new uses of technology; they can "provide the basis to structure... discussions about potential risks and benefits, reveal areas of agreement and disagreement, and provide a basis for continuing dialogue".[21] Others have "advocate[d] flexibility to adapt current practices—and develop others anew—to remain apace with the capabilities, concerns, risks and threats of ongoing developments in both synthetic biology and its possible uses on the global stage".[22] Finally, as new models for oversight emerge, some scientists call for systematic analysis of new governance structures, applying evaluative tools and allowing iterative development of new approaches.[23]

Genomic technologies

Biotechnology is continuously improving and expanding our capabilities in genetics as the old 'rules' of biology are challenged, broken, and refashioned. New technology allows us to collect and analyse more information, faster and at a higher resolution. Critically, we are expanding multidisciplinary approaches, enabling new solutions to old problems. For example, sequencing technology has drastically improved in the last ten years to enable multiomics studies

that generate millions of data points. Sequencing protocols combining[24] traditional methodology with microfluidics have been developed for analysing genomic, transcriptomic, and epigenomic data within a single cell. Single cell resolution[25] of genomic, transcriptomic, and epigenomic information has been invaluable for understanding disease mechanisms, pharmacogenetics, and cell development, as well as enabling spatial analysis. While our capabilities rapidly grow, we must continue to assess the context in which the technologies might be used and examine what governance mechanisms are needed to ensure the risks of such technologies are mitigated equitably.

As biotechnological capability expands, there is expanding knowledge of genetics of multiple species. Deeper understanding of human, microbial, animal, and plant genetics are all critical for human health; indeed, the emerging multidisciplinary field of One Health[26] recognises the interrelatedness of plant, animal, and human health. Discoveries in these areas are enabling improved disease management, drug choice, crop yields, and understanding of the environment. While there are extensive benefits from this work, there are also growing opportunities for misuse or inequitable application of the information or the technology. For example, the same information that allows us to determine the ideal dosage of a drug for a given individual can also be used to determine a lethal dosage. Identifying protective alleles for one disease in one population could also reveal increased susceptibilities in another population. As the body of knowledge increases, all stakeholders in the life sciences must be engaged and empowered to recognise the risks, implement mitigation measures, and ensure equitable distribution of both benefits and risks.

Our understanding of disease (both infectious and non-infectious), human evolution, and history is greatly expanded by human genetics. However, long before clarification of the molecular mechanisms of transcription and translation, genetics has been used as a justification for racist, ableist, sexist, transphobic, and xenophobic policies and practices.[27] Forcible sterilisation, involuntary commitments to mental institutions, and genocide are just some of the acts that have been—or in some cases continue to be—committed, with genetics-based justification.

In early 2022, the first DNA sequence of the full human genome without any gaps was published.[28] This gap-less sequence is an

important improvement over previous work because it includes discoveries such as duplicated regions and centromeric sequences; the new information enables better assembly for sequencing fragments going forward. Notably, this new human reference assembly was created from genomes of multiple individuals.[29] It has long been recognised that human genetic studies have been insufficiently diverse, with people of European ancestry often overrepresented compared to all other races and ethnicities, which has caused results from studies to be less applicable to Black, Asian, Oceanic, Indigenous, Latinx, and Middle Eastern populations. Estimates of risk or disease burden and effectiveness of interventions have repeatedly been shown to be inaccurate for these populations when based on studies in which European descent populations are overrepresented.[30] Such outcomes exacerbate existing inequalities in healthcare and access to effective treatment. Several studies and consortia have sought to diversify the pool of sequences, such as the EU Health Data Space[31] and All of Us[32] study of the US National Institutes of Health. However, such endeavours must be approached with buy-in from all communities to avoid exploitation or further harm. For example, researchers have in the past collected DNA from Native American tribal members and used the sequencing information for purposes other than what the tribe approved.[33]

As knowledge of human genetics and our ability to edit DNA expands, the spectre of human genetic engineering grows larger. The 'CRISPR babies'[34] created in 2018 were the first reported cases of germline genetic engineering in humans. The researcher responsible for the genetic engineering in these cases claimed that the changes were intended to reduce the risk of the children being infected with HIV in the future. However, the modifications made in order to decrease risk of AIDS may have increased risk of other diseases.[35] Additionally, there are serious ethical questions concerning intergenerational justice and consent for such germline modifications. While the 2018 'CRISPR babies' case is centred on lowering risk for an infectious disease, there is also concern that in the future, germline genetic engineering may be used for human enhancement.[36] The 'super soldier' example is often cited as a possible misuse of germline genetic engineering, where a nation with sufficient resources may utilise the technology to create faster, stronger, smarter soldiers that have multiple advantages over soldiers from countries

without access to the technology. In another example of convergence of fields, the risk of creating unnatural advantages between people is higher when implantable devices are included (either in addition to genetic engineering or alone). Devices that can be implanted within the brain have been created to aid people with neurodegenerative disorders or limited mobility. Implantables for enhancing cognition or providing extra capabilities are already being tested.[37]

Another area where human genetics has enjoyed significant advances is in gene therapy, whereby a genetic disease is treated or prevented by altering the individual's genetics. In some cases, a new gene or gene copy may be introduced into the cells of a patient. In other cases, gene-editing constructs are introduced to the cells to modify, turn on, or turn off a gene in the patient. Gene therapy is being used to treat several disorders, such as eye,[38] muscular[39] system, and neurological disorders.[40] However, multiple scholars have pointed out inequitable[41] access to this expensive treatment type. Additionally, as more information is gained while researching how to make gene therapies more targetable or effective, information for how to create more targetable and effective *delivery* systems of biological agents is also gained. The same systems that may modify a gene to cure a disease could modify a gene to be lethal, with efficient delivery systems as well.

The development of microbial genetics is on a similarly rapid trajectory.[42] Research into the microbiome, pathogens, and molecular epidemiology has enhanced our ability to detect, identify, track, and protect against bacteria and viruses. We have greater understanding of microbial evolution, population dynamics, function, and diversity, all of which are critical for creating more effective therapeutics and understanding the role of different microbial species in the environment. As we gain more knowledge about the genetics and biochemistry of microbes that have been engineered by nature, we also learn valuable information about how we can create a desired change through our own engineering.

Advances in microbial genetics are critical for enabling the growth of the bioeconomy. Utilising genetic engineering in microbial species allows the creating of high-value compounds, drugs, meat, textiles, and many other items using bacteria rather than traditional manufacturing processes. These bio-based strategies for manufacturing are considered more sustainable than previous mechanisms and may enable more

distributed manufacturing. Critical for the success of the bioeconomy is our ability to create specific, targeted mutations in microbial species. The ability to predict what a specific change may create—and how to create that change—is vital for being able to effectively create a desired engineered microbe. Foundational knowledge and gene-editing tools, especially tools that work at scale, enable the growth of the bioeconomy.

Methods for analysing microbial genetics are also in a period of rapid development. Approaches to analysing evolution and genetic epidemiology of viruses and bacteria allow us to better detect and track the spread of infectious diseases. During the COVID-19 pandemic, sequences of SARS-CoV-2 were and are rapidly shared and analysed to track the movement of COVID-19 within and across countries, supplement contact tracing efforts, and inform policies for response to the pandemic.[43] New uses of these analyses are continuing to be identified as the pandemic continues. However, potential misuses or harms from the system have also been identified. For example, wastewater monitoring for pathogens has been very helpful for monitoring the incidence of a pathogen in a community when there is a lack of diagnostic testing.[44] However, there are also concerns about misuse of those samples by law enforcement.[45] Many samples collected for wastewater surveillance will contain the genetic information for humans as well as the pathogen, and unless there are measures in place to prevent the human genetic information from being sequenced or shared, there is potential for misuse or invasion of privacy. Such information may be used by law enforcement to identify suspects or collect information without directly approaching a suspect.

Microbial forensics and environmental surveillance are two overlapping fields experiencing significant advancement. Collecting, analysing, and monitoring microbial populations in the environment allows better understanding of microbial population dynamics in the environment and identification of signatures that may be unique to a given location or environmental characteristic. Such information can be useful for assessing zoonotic pathogens, like coronaviruses in bats,[46] to understand what viruses may be circulating in animals that could 'jump' into humans, and/or to assess the 'sequence space' (range of potential mutations that can be acquired) available to viruses.[47] Such knowledge can provide situational awareness of what may occur in the future and help guide medical countermeasure development or

resource allocation before an event occurs. There are biosafety concerns associated with field collection of these samples; if a researcher is accidentally infected with a pathogen while collecting samples in the field, it could become a public health threat if the agent is communicable in humans. Additionally, such information may be useful for tracking movement of an entity or determining if two entities were in contact with each other in the past. There is ongoing work exploring the use of barcodes in microbial species to track movements,[48] which could be used as evidence in cases of theft or trafficking. However, there are also privacy and consent concerns surrounding the use of such methods.[49]

While many of the risks presented in this section do not rise to the level generally attributed to global catastrophic risk, the technologies could be misused to pose significant risk to public health, or implemented or used in such a way that it exacerbates inequities within the area of public health. Potential harms will likely be amplified in a crisis situation and could impede efforts to respond to the situation, as we have seen in the global response to the COVID-19 pandemic.[50]

'Gain of function'

As briefly discussed above, advances in microbial genetics have greatly increased our knowledge of how microbes function and how one might modify those functions. An area of specific concern for many in the life sciences is the risk(s) associated with modifying microbes to be more transmissible, pathogenic, virulent, or otherwise dangerous from what nature has already created. In genetics, the term 'gain of function' refers to a type of mutation that results in a gene product with enhanced and/or additional function.[51] Theoretically, 'gain of function' in the context of experiments with pathogens would lead to the pathogens acquiring an additional function over the course of experimentation. More recently, the term 'gain of function' has been used to describe work conducted by humans that could reasonably be expected to generate a version of a pathogen that is a greater risk to human health than what has been identified in nature. There exists no clear, standard definition of 'gain of function' shared amongst the community. Influenza viruses[52] and coronaviruses[53] have been at the centre of global controversies about the value of such experimentation. Stakeholders have debated for years about how 'gain of function' experiments should be governed.[54] Some

have called for complete moratorium of 'gain of function' research; others have proposed that only some 'gain of function' research should not be conducted, and still others have stated that most 'gain of function' work can and should be done if sufficient biosafety measures are in place. The continuing debate on 'gain of function' work has not advanced, in part due to a lack of nuance and understanding of the issue.

Despite the knowledge amassed concerning microbial genetics and evolution, we are still not able to predict how a given mutation will change function—i.e. predict evolution—without either prior knowledge or a comparator. Indeed, the misconception that pathogens evolve to become less virulent is nearly universal.[55] A scientist can make a specific, directed change to a pathogen's genome, but prediction of the new phenotype that will result from the change is not guaranteed and will usually require further experimentation. Furthermore, a directed mutation is not required to create a pathogen with a new phenotype; serial passaging is a common laboratory method for creating new mutations in microbes, and is often used for the purpose of 'creating' new phenotypes. Each passage is an opportunity for the pathogen population to evolve, potentially gaining a new function; this new function can be 'directed' by providing specific conditions during the serial passage.[56] In either the directed mutation or passage situation, the resulting organism may have gained new functions, lost functions, have greater or lesser ability to transmit, infect, or cause disease, or have no measurable change from the starting agent. In other words, the complexity of interactions of the products of gene mutations is immense. There may be an enhancement of one characteristic but attenuation with respect to another characteristic. Selection experiments with a microbial agent could result in creating an agent with a completely unanticipated phenotype; indeed, it is often the case that the characterisation of a selected mutant reveals what the actual selection conditions were (i.e. you get what you select for). The complexity of genetic interactions in any organism precludes precise prediction of the outcome. These observations directly reflect what takes place in nature as infectious microbes multiply in their hosts. For example, there is growing evidence of the importance of cooperative functions within a microbial population—not just individual functions, as is seen with viral quasispecies.[57] Characterisation of phenotype is often performed at the level of the individual rather than at population

level: a more nuanced assessment and consideration of populations is needed to understand impactful and meaningful changes.[58]

Being able to determine likely outcomes of a genetic experiment is highly dependent on prior knowledge or availability of a comparator. An obvious area of concern is the growing possibility to intentionally and directly create something more dangerous to human or animal health. As protein structure prediction software matures,[59] as well as our foundational knowledge of sequence space and protein function, there is increased potential for the deliberate creation of an entity with an enhanced characteristic(s). This kind of basic knowledge will decrease the barriers around our (currently limited) ability to predict evolution.[60]

Considering the diversity in potential outcomes and types of experiments that have the potential to generate a pathogen with increased transmissibility, infectivity, pathogenicity, or virulence, we argue that it is not useful to suggest banning all experiments defined as 'gain of function'. To do so would be to shut down a large swath of microbiology research that is critical for understanding pathogenesis and disease, and creating novel therapeutics. Rather, we should focus on creating and conducting robust risk assessment methodology and implementing appropriate biosafety measures, discussed below. Additionally, governance measures for technologies that will further lower the barriers that enable directed evolution are appropriate.[61]

Gene drives

Gene drives are a technology that allows scientists to push and distribute a desired gene into a population at higher rates than would be expected under normal conditions of replication and inheritance. The most cited example of gene drive application is the creation of gene drives in mosquitoes to limit the transmission of mosquito-borne diseases.[62] In one use case, the drive would spread a gene that would prevent transmission of the malaria parasite throughout a mosquito population within a few generations; other uses would exploit a gene called 'doublesex' to suppress the reproductive capability of an entire population.[63] Gene drives provide a benefit over conventional genetically modified organisms (GMOs) in the genetic control of an insect population: less human intervention is needed to reach sufficient

levels of a wild population. In other words, whereas a conventional GMO might require thousands of modified organisms to be released in order to fix the gene of interest in the population, a gene drive may be able to get to the same end point with a fraction of the number of initial modified organisms.[64] Significant funding continues to flow in many directions of gene-drive research. In addition to the mosquito-borne disease case described above, there is interest, for example, in creating a gene drive in bats[65] that could limit their susceptibility to coronaviruses or a gene drive to eliminate invasive species, like rodents.[66]

One of the reasons gene-drive technologies have the potential to be so powerful, requiring less human intervention, is the ability of the gene drive to self-propagate. While this decreased reliance on resources is hugely beneficial for settings with limited resources, it also creates new risks. We would have less control over a gene drive if one were to be released compared to traditional GMOs. To stop the gene drive, if there is no built-in mechanism;[67] we would have to remove all individuals carrying the drive from the population or release another gene drive to reverse the first drive, unlike with a conventional GMO. The potential for unintended consequences is higher with this technology than with others due to the potential ecological consequences combined with our limited control and recall measures. For the gene drives seriously being considered for deployment, significant research is being done to assess the ecology, species interactions, food chains, population structures, molecular mechanisms, potential environmental impact, and many other aspects of what could happen if the gene drive were to be deployed. However, the complexity of these environmental and ecological interactions is enormous.[68]

Due to the broad and potentially substantial risks associated with gene drives, there are robust international efforts focused on implementing strong safety and security measures for the technology.[69] Gene drives, like infectious diseases, will not stop at national borders, so international cooperation and collaboration is vital. The Cartagena Protocol on Biosafety of the Convention on Biological Diversity is one of the key international treaties that covers gene-drive technologies. However, gaps remain in gene-drive governance, especially since not all countries (including the United States, the location of much of the relevant research) are signatories of the Convention or its protocol. Another key concern is consent by

communities. Because gene drives can easily cross borders without people being aware, the question of how and from whom consent is needed is not clear. This is particularly true with Indigenous populations, many of which have historically been stewards of their environment but have since been barred from making decisions regarding their land. Indigenous populations are one of the most disenfranchised, but not the only populations who are historically blocked from power that should have a say in whether or not a gene drive is released.[70] As the technology races towards maturity, there remains a wide range of moral stances on gene-drive technologies, including the very basic notion of whether the technology is "compatible with humans' role in nature (interference stance) or not (non-interference stance)".[71]

Synthetic biology

Synthetic biology (SynBio) is a multidisciplinary field comprising the convergence of engineering with biotechnology and genetics. The US National Academies of Science, Engineering and Medicine define synthetic biology as "concepts, approaches, and tools that enable the modification or creation of biological organisms", further stating that "while the goals of synthetic biology are beneficial, these capabilities also could be used to cause harm".[72] SynBio is a subset of the broader field of "engineering biology", collectively projected to transform the entire world within the next two decades, with an estimated value of $4–30 trillion.[73] The novelty of engineering biology derives from the application of engineering principles to the design of genetically engineered organisms. The ability to synthesise DNA efficiently or modify existing DNA sequences quickly and with great precision allows the creation of genetic components ('bricks')—discreet functional short pieces of DNA. Catalogues of components have been assembled, providing great diversity in manufactured constituents. These components are combined to create new genomes or modify those of existing organisms (usually bacteria) so these recombinants can carry out specified services, such as synthesising small molecule drugs and other pharmaceuticals, chemicals, food ingredients, novel energy sources, etc. Synthetic biology adopts the 'design, build, test' model of engineered design, introducing both precision and convenience in the design of new organisms.[74]

In addition to bioproduction, synthetic biology has entered the field of biosensing, allowing organisms to perform detections in disease diagnosis, hazard detection, food/water safety, physiological state, etc. Biosensing is among the most extensively developed applications in the biotechnology arena and will be a key player in the advance to the 'Internet of Living Things'—the network of objects in which data is collected and used to carry out tasks in real time. A particularly interesting use of biosensing is in space exploration (synthetic geomicrobiology[75]) and metal mining in space.[76] In health, closed-loop therapeutic delivery systems[77] provide a sensor to continuously monitor a small molecule, an algorithm to determine the need for treatment, and an actuator to release or express the needed therapeutic.

The impressive breadth of applications of engineering biology will require an informed and aware workforce from the converging fields of biology, chemistry, and engineering. Education and awareness are key components of the 'Web of Prevention' by which effective biosafety and biosecurity can be maintained going forward in the 21st century.[78] Many students around the world are exposed to these ethical issues in the annual worldwide Genetically Engineered Machine (iGEM) competition,[79] which has had a transformative impact on synthetic biology training in multiple nations. Intrinsic to the process of engaging in the competition is analysis of the social impact, biosafety, and biosecurity implications of the students' projects; these aspects are evaluated with the same rigour applied to the scientific components of the work. Beginning in 2004 with 31 students and five teams, the competition has expanded to over 7,000 students in 350 teams in 2021; a total of 50,000 young scientists have been involved in iGEM projects and have gone out to seed the scientific world. As stated on iGEM's webpage: "We foster a community that is mindful and responsible about the development, application, and impact of their work, both inside and outside the lab".[80]

AI and big data in the life sciences

Biology has benefited immensely from advances in other fields, including from data science and computing. Not least among the trend of convergence of scientific and technical fields is the impact of artificial intelligence (AI) on the life sciences. Artificial intelligence technologies (AIs) are already contributing to many aspects of healthcare and

medicine, including in diagnosis, clinical care, management, and medical research. We have seen rapid expansion of the use of AIs during the pandemic in many areas of public health—in disease surveillance and response, but also the (failed) use of apps to limit the spread of COVID-19,[81] and use of Facebook and other social media site data to understand how and why people were physically moving and potentially spreading COVID-19.[82]

AI technologies, however, are not neutral. The fundamental questions about the use of these technologies are based on the issue of power.[83] When and by whom are AIs used? What datasets are used and how are they labelled? How are algorithms validated? Was the data obtained with consent? When operating at speed and scale, and with interoperable systems, or immutable biometric data (such as DNA), these questions become even more urgent.

Any collection of data and classification contains embedded values. Fairness, accountability, transparency and explainability are raised as issues to be contemplated, yet each of these terms has different definitions in different communities. International legal human rights and ethical frameworks are increasingly used to frame the risks. International standards are being negotiated to ensure safety and to minimise and assign risk within corporations as this is being written. International treaties are being called for. Each of these conversations has implications for advances in the biological sciences, and researchers in the biological sciences need to follow these rapidly moving discussions to understand where the risks and issues in use of these tools lie in order not to promote further problematic approaches and issues embedded at speed and at scale.

These tools often carry embedded biases and are characterised by lack of transparency; the harm that can be done to human rights is hotly debated across the technological world. AI comprises many tools, such as machine/deep learning, natural language processing, robotics, etc., that solve different kinds of problems by recognising patterns in data. The power that AI tools will have in the life sciences going forward is undeniable. Here, we discuss several applications of AIs to life sciences research and explore the complexity of the ethical convergences.

AI tools are used in multiple scientific areas other than healthcare. For example, AlphaFold[84] (the product of the company DeepMind) is

a system by which the three-dimensional structure of proteins can be predicted by examining the sequence of their amino acids' chains—the building blocks of which proteins are composed. Structural predictions from linear sequencing have been an intractable problem in biochemistry for decades. AlphaFold was developed using machine learning, by studying the structure of a hundred thousand proteins whose exact 3D structures are known relative to their amino-acid sequence. The repertoire of the tool has expanded to hundreds of thousands of additional structures; the source code—how the tool works—has been released for open access. While the functional impact of this new tool in medicine and science will be gradually be revealed, it has great potential, since understanding how a protein is structured can lead to understanding how it functions. This knowledge in turn might lead to novel therapies.

Machine learning (ML) has been used to assist in the process of drug discovery. For example, understanding how specific chemical structures are associated with drug efficacy leads to those structures' utility in the design of new drugs, like antibiotics or receptor inhibitors. As large numbers of structures are screened by the AI, choices are rewarded if the algorithm detects a positive result. Recently, this methodology was turned on its head by a group of researchers comprising both chemists and a social scientist who performed a computational experiment[85] to test whether ML could be used to design chemical weapons. This study used similar algorithms yet reversed the calls and rewarded toxicity. Within just a few hours, thousands of molecules toxic to humans were identified or designed, and one of these was a known neuro-agent. The published paper examined the reasons for both performing the computational exercise and publishing the results; the authors posed a number of recommendations, including raising awareness amongst students and the drug discovery community, and an "Application Programme Interface"[86] that would restrict access to the code to begin to control how discovery models are used and published.

The ease with which these tools can be used to drive discoveries is described below in an entirely different kind of study. Xenobots are synthetic lifeforms—multicellular assemblies—built from combinations of different biological tissue and/or cells. They are designed to perform specific functions. For example, frog cells—when dissociated from the

parent organism—form assemblies that can be instructed by AIs to perform specific tasks. In one case, the task assigned to the xenobot was to go out across its petri dish and find more cells and use them in a sort of swarming activity to replicate itself.[87] AI was used to design the first parent in a shape that most promoted this form of replication, called kinematic self-replication. While self-replicating robots have been imagined since 1948 by Jon von Neuman,[88] and molecules have long been known to self-assemble and replicate, this work is the first to demonstrate replication of a synthetic lifeform. The designers of these quasi-organisms promote their use in medicine for delivery of treatment, as the xenobots could be derived from the cells of the patient. Indeed, the xenobots are envisioned to assist in such tasks as therapeutic delivery and environmental remediation.[89]

It has been noted that early ethical analyses[90] did not include the possibility of xenobot replication, as it was deemed unlikely. The ethical concerns included (1) dual-use implications—the development of xenobot weapons, for example; (2) the possibility of the organisms becoming sentient; and (3) creators of xenobots are 'playing god'—the argument here is that life is then devalued.[91] Since we can add to this mix the complication of self-replication, we will need to revisit these issues as the technology continues to mature. Yet the impact of AI on life sciences research is not just about the individual systems that benefit; the tools of AI have been used to create multiple systems that interact and are interdependent. Questions remain about how to interrogate systems that operate at speed and scale and affect each other, and biological advances that affect medicine and public health—particularly when involving datasets that are largely incomplete or preferencing particular groups, furthering those power imbalances in their use in AI or other algorithmic applications.

We note that this review has not touched on recent generative AI technologies such as DALL-E and ChatGPT. The release of these tools to the public has jettisoned both interest and concern in artificial general intelligence to the headlines. Extractive systems such as ChatGPT3 that produce seemingly coherent academic papers may undermine and devalue actual scientific work, with the increasing perception that real science can be fully automated and the risk that knowledge and critical thinking in areas will be increasingly devalued, at a serious

cost and broadening risk. Accompanied by the spectacle of human-like creativity is increased awareness of the human toll extracted by these developments: the massive amounts of data and energy required to build these technologies are collected and mined by poorly paid and unsupported global workers on multiple continents. These vast hidden costs, although outside the scope of this discussion, must be factored into risk/benefit analyses of AI technologies as we hurtle forward into the AI age.

Conclusion

This chapter has discussed several advances in the life sciences, their necessary convergence with multiple disciplines, and the harms that might be caused by their misuse, whether accidentally or intentionally. We have threaded throughout the chapter calls to action for researchers and practitioners to address the challenges we currently face as biology marches towards a global bioeconomy. As argued by Sundaram in this volume, new models for governance and oversight must override the current polarised stance between 'top-down' structures vs those derived within practicing institutions; science can be governed by "shaping and steering technologies as they develop". Calls for action are not new; many were being sought two decades ago when Rees wrote:

> When a potentially calamitous downside is conceivable—not just in accelerator experiments, but in genetics, robotics, and nanotechnology—can scientists provide the ultraconfident assurance that the public may demand? What should be the guidelines for such experiments, and who should formulate them? Above all, even if guidelines are agreed upon, how can they be enforced? As the power of science grows, such risks will, I believe, become more varied and widely diffused. Even if each risk is small, they could mount up to a substantial cumulative danger.[92]

Clearly, a Doomsday Clock applied to the risk of biological disaster would be poised just before midnight, as microscopic events rush headlong to unveil the massive power and risk of biological technologies.

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