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Editorial Introduction

Pawan K. Dhar* & Krishna Ravi Srinivas**

Synthetic Biology (SB) is an emerging technology that has been receiving much attention for the past decade and half. This Special Issue on SB is in line with this journal's objective of acting as a forum for debates and discussions on new technologies, trends and their impacts. While Genetic Engineering enabled manipulation through various tweaking methods, SB enables construction of biological components. In our view, "Synthetic biology is an engineering approach that involves rational design and construction of biological components and organisms." This potential to resign components and organisms brings enormous hope but is also the source for concern. Though genetic engineering methods have also led to redesign of organisms, we really never engineered genetics. Using traditional engineering approach, SB enables construction of biological systems much beyond traditional methods. We are talking of genome engineering not just genetic engineering. A valid question has been raised by some people : 'Are we playing God?'. In our view, that is an overstretch of imagination, as chemical synthesis of cellular components is not equal to creating a fundamental life force. Nevertheless, one must follow a responsible innovation approach to generate useful and safe innovations.

This Special Issue has seven articles, dealing with different aspects in SB, governance and regulation, its linkage with Access and Benefit Sharing (ABS), the international dimension and debates on SB and on Biofoundaries. We are aware that some topics have been left out in this issue, particularly the ones related to ethics, Intellectual Property and public perception and understanding of SB. These will be covered in future issues of the magazine.

SB is a discipline that is less than two decades old and is fast growing one, whether in terms of publications, patents, or funding. While much is said about its potential particularly for developing countries, SB is still in the early stages of adoption among most Asian countries. Global governance in SB is evolving but whether there will ever be a global regulatory regime

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for SB is doubtful. Another issue regarding SB is dual use and its linkages with bio-safety, bio-security and also with relevant international treaties/ agreements. The Do-It-Yourself SB (also understood as biohacking) has emerged as a major activity in SB, resulting in concerns over misuse and lack of regulation. These aspects make SB a unique and challenging one.

In this issue the articles discuss many important aspects of SB and read together they certainly provide an excellent overview of an emerging technology and challenges in harnessing it while ensuring that governance issues are addressed adequately.

To familiarize readers with SB, the first article by Mriganko Das and Pawan K. Dhar gives an introduction to SB, and, explains what is being done in SB. Tracing the origin of the concept, it describes SB, the components and policy issues besides elucidating the terminology.

Governance of SB has become a major issue, much more complex than regulating genetic engineering and as SB gathers pace and gets diffused and adopted, the challenges also undergo change. The governance of SB, thus, can while be based on some principles and norms, has to be dynamic on one hand, and, perhaps anticipatory on the other hand. National level governance is necessary but not sufficient given the global nature of SB. But a dilemma is on defining SB and differentiating it from Genetic Engineering and ensure that the risk assessment regime is appropriate for SB and concerns on biosafety and biosecurity are addressed. In 'Challenges in governance of Synthetic Biology: Biorisk assessment ' Prasanjeet Kaur and Archana Chugh, give an excellent analysis of the issues and how the challenges are being addressed, if not fully met by governments. Moreover they have given pertinent suggestions regarding SB in India. This comprehensive article should be enable the readers to understand and appreciate the intricacies and issues in Governance of SB.

If national governance of SB is a challenge, global governance is even more challenging and complex and is also evolving. While there is no specific treaty or agreement that is specifically meant for SB, negotiations under the auspices of Convention on Biological Diversity (CBD) are in progress. But given the wider ramifications, it is essential that national regulation is attuned to global developments. In 'Regulating risks in synthetic biology" Sachin Sathyarajan, Balakrishna Pisupati , Neeraj Verma,

and, Pawan K. Dhar, explore the global developments and identify the linkages and issues relevant for India and suggest that India should have an unambiguous policy on SB.

SB's interface with Access and Benefit Sharing has been addressed in the past. But emerging technological options question traditional understanding of what are 'genetic resources' and whether the current frameworks on ABS are robust enough to meet the emerging challenges. In DNA Data Storage and Access and Benefit-Sharing: Testing the Limits of the Term "Genetic Resources" for Synthetic Biology", Michelle Rourke, Fran Humpries and Charles Lawson take these issues and examine in detail the complex picture that is emerging. While SB opens up novel opportunities to use genetic resources and its components With the boundaries among material storage, information and matter/material resources, are becoming porous, novel questions are inevitable. Addressing them, they ask a pertinent question "As the technology moves from science fiction to reality, it is timely to debate whether it is even appropriate for the ABS concept to be used as a regulatory tool for DNA data storage and the technology's relevance for the conservation and sustainable use of biological diversity". This is a question which must be faced not just by developing countries but by all stakeholders.

Biofoundary is a hot topic in SB and is gaining much attention because biofoundaries enable mass production and industrial applications by using principles of SB. The OECD Science, Technology and Innovation Outlook 2021 has a chapter highlighting how biofoundaries can play an important role and the policy issues involved. As biofoundaries are emerging as key facilitators in this issue we have two articles on them, underscoring the need to understand them and why they are considered as important in harnessing advances in SB and how they can contribute to bioeconomy. India is one of the countries that has capacity in setting up biofoundaries and harness them. Shikha Thakur and Anu Raghunathan describe the idea of a biofoundary and how biofoundaries work highlighting their potential, including producing next generation vaccines. Biofoundaries can enable a leapfrogging in biomanufacturing and development of a new production paradigm. The examples given by them add credence to this. Stressing the potential of biofoundaries for India, Panda and Dhar point out what can

The final article in the issue calls for a SB policy for India highlighting the need for a policy and puts forth the view that a policy will go a long way in incentivizing SB besides resulting in clarity on governance. The recent call for comments by Department on Biotechnology on the Foresight Paper is a welcome sign and it is hoped that this will result in a policy on Synthetic Biology.

The book review by Sneha Sinha adds value to the issue.

Your comments and suggestions are welcome.

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What is synthetic biology?

Mriganko Das*, Pawan K Dhar**

Abstract: As a technology Synthetic Biology is hardly two decades old. It is considered as an application of engineering to biology to produce parts, modules and networks and also novel organisms. Whether it is an incremental advancement over genetic engineering or a new paradigm is a matter of debate. Although there is no consensus on a definition for synthetic biology, the key features are universally acknowledged and adopted. In terms of science thus there is a flexibility in defining and (de)limiting synthetic biology. But for policy and regulation we need a robust definition and best case scenarios and boundary condition so that these can be used and applied globally.

Keywords: genetic engineering, modularity, regulation, organisms, biological engineering

The origin of concept

More than two decades back, people asked if it was possible to bring 'construction approach' into biology and design systems from a standard inventory of DNA parts. The result was the demonstration of the proof-of-the-concept in early 2000s and Synthetic Biology meeting 1.0 at MIT with an announcement that a new field of synthetic biology had arrived.

The question is: How did this new thinking arrive? What were the principal components that determined a marked phase shift in doing science? Why has Synthetic biology become such a huge wave involving massive government and corporate funding, a large scientific community and policy makers?

This article attempts to explore these and many more questions with a hope of bringing clarity on the inclusion and exclusion criteria of synthetic biology, its best-case scenarios and boundary conditions.

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Broadly, there are two approaches of doing science: reductionism and Integration.

Reductionism is all about describing a system as a function of components. For example, to explain how a complex organism behaves, we open up organisms to study their internal composition with a hope to understand the higher-level functions. For example, in eukaryotes, the body is opened up to see the connectivity among organs. Further, technology is used to probe deeper to see the structure and function of every tissue. With the use of microscope and staining techniques we go deeper and probe into the structure of cells, organelles and molecules. This reductionist approach has been highly successful and has given birth to fields like gross anatomy, histology, cell biology, molecular biology, biochemistry and so on.

Due to immense success in probing deeper and uncovering information from low throughput to high throughput, a pressing need arose towards moving away from manual data management to computer assisted data storage, annotation, query, analysis, report, transfer, security and so on. The human genome project that generated a huge data and meta datasets, precipitated urgency in developing data handling protocols.

The availability of data collected through reductionist methods, accelerated efforts towards data integration giving rise to fields like computational biology, bioinformatics and systems biology. The goal was to develop tools for handling biological data (computational biology), solving biological problems through data analysis (bioinformatics) and generate virtual models of pathways and cells (systems biology) to perform biology in-silico.

Both reductionist approach and integrative approaches worked very well, giving rise to new knowledge, funding avenues and practical applications.

A third approach of doing science made inroads in the late 1990s when people discussed the possibility of bringing an engineering approach in biology. Though the term 'genetic engineering' was already in place, in reality molecular biologists were practicing 'probability'.

In a typical molecular biology setting one designs a vector, transfers the vector to the host cell and looks for its expression among millions of cells swimming out there in the culture dish. If things work well, one sees the

expression in a few cells, else one has to repeat the entire sequence from the beginning. Such an approach that is built purely on probability cannot be called engineering. An engineering approach would be precise, error free and fast. Due to this reason, the term 'genetic engineering' looks more like an intent than the actual practice.

Dr. Barbara Hobom was probably the first scientist to use the term 'synthetic biology' (Hobom 1980). However, the usage of the term remained largely dormant till 2004. One of the key foundational papers that hinted towards engineering approach to biology, was a three gene circuit called repressilator that was plugged into E.coli as a non-native applet and stably expressed (Elowitz and Leibler 2000). This paper accelerated the thought process that we now know as synthetic biology.

To give a certain kinetics and scale to the engineering approach in biology, the term "Synthetic Biology" was formally proposed in the first meeting of Synthetic Biology (June 2004) at MIT. The event received a massive press and triggered a new wave of thinking and excitement in the community. Though the term "synthetic biology" made significant media headlines, scientists questioned the very purpose of starting yet another field and also wondered if the term "synthetic" was appropriate.

The origin of engineering inspired approach stems from the fact that biology and engineering are similar in many aspects. For example, both exhibit multi-tasking, fault tolerance, linear and non-linear processes, analog and digital behavior and manage tasks in series and parallel.

However, there are also differences. In biology, introducing novel components into the circuit, modification of existing logic gates or overriding them completely to obtain desired results are non-trivial. These differences make it challenging to convert biology into an engineering discipline. Creating a circuit in isolation is one thing but expressing it in a living cell is a completely different scale of challenge. The take home message is: adopt an overall engineering approach but prepare for significant failures and the need to troubleshoot at every step.

The nomenclature variants

Initially, people felt that synthetic biology gave an impression of 'chemical biology' or probably something to do with 'synthesis'. However, the intended

meaning of 'synthetic biology' was engineering biological systems ground up. One could combine existing cellular parts to create new combinations or use novel parts to create a fresh design.

Thus, building non-natural parts, devices and circuits or making non-natural combinations of existing parts, devices and circuits was proposed early on. Somehow the term 'synthetic biology' didn't go well with some people and an alternative term "constructive biology" was proposed. However, the term "constructive biology" also did not resonate much and people wondered if the traditional approach should be called 'destructive'!

Further, terms like: biological technology, biomolecular engineering, biosystems engineering were also explored. Finally, it was felt that the term 'biological engineering' was closest to the intended meaning of "synthetic biology", as it encompassed engineering approach right from the level of parts (gene, RNA, protein), devices (e.g., operons) to pathways (metabolic, regulatory) and organisms.

Due to this reason, people use 'biological engineering' interchangeably with 'synthetic biology' to describe an approach towards construction of biological components as against reductionism and integration. Over the last decade and a half, the term 'synthetic biology' has been enriched with several flavors and practices from the scientific community.

A *chemical engineer* may consider synthetic biology as an approach to design novel controls on metabolic pathways for a more predictable output. A *metabolic engineer* may want to install novel metabolic pathways or transfer chunks from other organisms using the new 'synthetic biology' terminology. A *molecular biologist* may build biological standards, rules of composition, long DNA synthesis and genome editing technologies under 'synthetic biology'. For an *organic chemist*, it may be about synthesis of chemicals and biochemicals using microbial factories or creating a functional non-ATGC DNA. For a *systems biologist*, synthetic biology may be about finding how cells organize massively parallel and massively interactive processes and use the nature's designs to construct novel and stable networks.

The beauty of synthetic biology is that it leaves ample scope of innovation from parts to organisms. Unfortunately, in actual practice

things are that straightforward. The *de novo* design of complex biological systems may be computationally achieved with some trial and error but an experimental construction and stable maintenance of a circuit in changing intracellular / extracellular conditions, is challenging.

Experimentally designing 'apps' like translation, transcription, allosteric regulation, enzymatic reactions and so on the task is non-trivial as biological systems are based on non-linear and analog reactions that may be influenced by molecular crowding, emergence of unexpected biological behaviors and incomplete / inaccurate knowledge.

Definition from the policy perspective

It is important to have a crisp definition to ensure that people stay within the zone of responsible innovation. Given the diversity of perceptions and practices, there is a pressing need to develop an inclusion and exclusion criteria and keep original intent isolated from definition variants that may appear and dilute the primordial thought. Irrespective of supplementary flavors, 'engineering approach' may be the common minimum denominator of definition variants.

Synthetic Biology is NOT just another recombinant DNA technology that's largely based on permutation-combinations and a certain statistical probability. Synthetic Biology may import components of genome engineering, pathway engineering, tissue engineering and directed evolution but is based on the use of standards and construction rules towards precision engineering of cellular components to the multi-cellular consortia.

Individual perceptions may vary and but it's important to have a clear distinction between 'genetic manipulation' and 'genetic construction', identifying gaps and strengthening the regulatory frameworks. Terms like 'Unintended consequences' and 'Unpredicted events' may be avoided as they may lead to unrealistic imaginations and hinder good science.

As the policy framework evolves, the government may consider stringent regulations under environmental implications and moderate regulation in the health sector. The international Synthetic Biology community emphasizes sharing and open access, which may make the Access and Benefit Sharing difficult to implement. It is important for the regulations to be a bit easy on the implementation.

The Centre for Biodiversity lists several key definitions of synthetic biology in its 2015 report.

Synthetic biology aims to design and engineer biologically based parts, novel devices and systems – as well as redesigning existing, natural biological systems.'' (Kitney and Freemont 2012)

Synthetic biology … combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavors … rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics. (US Presidential Commission for the study of Bioethical issues 2010)

Synthetic biology attempts to bring a predictive engineering approach to genetic engineering using genetic 'parts' that are thought to be well characterized and whose behavior can be rationally predicted. (International Civil Society Working Group on Synthetic Biology 2011)

Synthetic biology aims to design and engineer biologically based parts, novel devices and Engineering systems as well as redesigning existing, natural biological systems. UK Royal Academy of Engineering, 2009

Synthetic Biology components

One often comes across engineering terminologies while reading synthetic biology papers. It may be useful to describe some of the key components to get an inside perspective.

Logic gates: A logic gate is a fundamental building block of an electronic circuit. The input and output may be represented as 0 (absence of signal) and 1 (presence of signal). Several examples of bio-logic gates exist e.g. lac operon (NOT gate), substrate-enzyme reaction (AND gate), activator-inducer mediated process (AND gate). Even though there are similarities at a higher level, it is important to note that the similarity between an electronic logic gate and bio-logic gate is only superficial, due to the reason that biologic systems are analog in nature, while electronic gates that are digital. Thus, even if we design and express logic gates in cells, it may be stable only within a narrow range of parameters values.

Truth table: A truth table is used to document simple input / output response of the system. In the standard truth table, both input and output values are in the form of 0 and 1. Compared to a Bio-Truth table is quantitative in nature e.g., given an inducer concentration what would be the corresponding protein concentration in a certain organism, in certain culture conditions? Unlike electronic truth table, the values in the bio-truth table are not portable, as these values are contextual i.e., they are dependent upon a given strain, metabolic state, culture conditions and so on.

Standard parts inventory: The concept of standard parts comes from engineering experience where a detailed data set for every part is used to assemble devices and complex systems from scratch. In the field of engineering the assembly line construction is so good that one can go from computer model to testing and manufacturing quickly e.g. engineers do not fly thousands of aircrafts to select good designs from the ones that crash! However, that's exactly what happens in biology.

Summary

Synthetic biology is a novel approach towards precision and predictive engineering of biological systems ranging from parts to modules to networks and multicellular consortia. Differences of opinion exist on whether synthetic biology is revolutionary or an incremental advancement of genetic engineering. However, rational design approach seems to be a common denominator among a range of thoughts expressed. While there is no internationally agreed definition of "synthetic biology", key features of synthetic biology include the "de novo" synthesis of genetic material and an engineering-based approach to develop components, organisms and products towards engineering applications. From the scientific perspective, one may be flexible in incorporating a diversity of thoughts. However, given its significant regulatory implications one needs to clear define the best case scenarios and boundary conditions that are easy to use and globally applicable.

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Navigating the technology landscape in Synthetic Biology

Neeraj Verma*, Pawan K. Dhar*

Abstract: Synthetic biology is the science of construction in biology. The construction comes in the form of building standards, rules of composition covering a range of parts, modules, pathways to multi-cell consortia. To scale up the efforts and make it sustainable, scientists, societies, governments and private stakeholders are working towards developing technologies that can accelerate innovations and generate useful applications. Here we examine some of the key advancements and enabling technologies in synthetic biology sector.

Keywords: DNA Synthesis, Genome Editing, standards, data storage

Introduction

Traditionally, reductionism was been used to generate a list of organs (gross anatomy), tissues (histology), organelles (cell biology) and molecules (biochemistry and molecular biology) to understand an organism in terms of its composition and function of sub-components. The reductionist approach was successful due to the development of enabling technologies like cell culture, microscopy, chromatography, electrophoresis, sequencers, microarrays, crystallography, NMR and so on When the data became large and manually unmanageable, computer programs were written to manage data (computational biology) and study biology from parts (bioinformatics) to pathways (systems biology). Both Bioinformatics and Systems Biology could be sustained due to rapid technological advancements in storage, analysis, transfer and display of data with high security. In early 2000, a third paradigm shift in biology happened. The new thinking (synthetic biology) was about design and construction in biology, ranging from genes to organisms.

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Synthetic biology uses engineering principles to develop standards and rules of composition. The construction may be as simple as an inventory of standard parts (e.g., genes, RNA, proteins) to a modules (e.g., operons) to circuits (e.g., metabolic and signalling networks) and multicellular consortia.

The biomolecular construction may involve rewiring of natural parts or using lab-made parts towards novel designs and installations[1]. The concept of engineering a living organism is typically based on "design, build, test, learn" (DBTL) cycle[2], a standard engineering approach that uses DNA as a building block to achieve higher-level functions. Due to the broad scope and novelty of the approach the ethical, legal and safety aspects have taken the centre stage in the synthetic biology policy discussions (NAS, 2018)[1].

Following are some of the key technological elements of synthetic biology:

Long DNA synthesis

The story began in the 1950s when a stretch of 17 base DNA was chemically synthesized (Agarwal *et al*, 1970). Dr. Hargobind Khorana synthesized several small DNA strings to understand genetic code. In the subsequent decades, significant improvements in accurate oligonucleotide synthesis and assembly resulted development of phosphoramidite method (Roy and Caruthers, 2013). This led to automation and commercialization of the DNA synthesis process. The technology of DNA synthesis has progressed rapidly, with the introduction of modern methods like enzymatic DNA synthesis and polymerase cycling assembly (PCA) [3]. PCA was originally used to synthesise the 303-bp HIV-2 Rev gene[2] and has subsequently developed into a commonly used generic technique for the synthesis of genes up to 1 kb in size[3].

The capability to create bigger assemblies from combinations of chemically synthesised or PCR amplified gene-size fragments has seen rapid advancements (Gibson, 2014). Many interesting assembly techniques for long DNA synthesis have been developed that do not leave behind scars at

1 https://www.genome.gov/aboutgenomics/ policy-issues/Synthetic-Biology

2 https://doi.org/10.17226/24890

3 Mandecki, W., Hayden, M. A., Shallcross, M. A. & Stotland, E. 1990. Gene 94 , 103-107. pmid:2227445

assembly junctions points. Some of the high throughput assembly methods include ligase cycling reaction (de Kok *et al*, 2014), Gibson assembly (Gibson *et al*, 2009), seamless ligation cloning extract (Zhang *et al*, 2012), yeast assembly (Gibson *et al*, 2008), circular polymerase extension cloning (Quan and Tian, 2009), sequence and ligation-independent cloning (Li and Elledge, 2007), Golden Gate (Weber at el, 2011) and others are routinely used in both academic and industrial settings.

The cost of DNA synthesis has seen a significant drop over the years. However, as the overall cost of long DNA sequences is dependent upon the cost of oligonucleotide synthesis, work is needed to reduce the cost at the building block level, increase the length of DNA synthesis, reduce errors and enable high throughput assembly. The DNA synthesis sector will see a huge transformation once the cost of DNA synthesis and DNA sequences match.

As long DNA synthesis continues to see technological advancements, it will have a transformational impact on a number of sectors, right from constructing a recombinant vector to designing organisms for useful applications.

Genome Editing

Genome editing is the science of performing targeted changes in the genome. The changes may be about adding or removing a piece of DNA from the chosen site. Techniques for genome editing have become more efficient for the last three decades and involve four types of "programmable" nucleases: meganucleases (MegNs), zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALEN) and Clustered regularly interspaced short palindromic repeat and CRISPR associated protein 9 (CRISPR/Cas-9) systems.

Many years ago, scientists were confronted with the task of genetically modify DNA sequences at predefined locations. As a result techniques like ZFNs (Urnov *et al*, 2010) and TALENs (Silva *et al*, 2011) were invented to incorporate DNA break at the desired genomic location. In zinc fingers, the DNA-binding domain and DNA-cleaving domain (Fok1 endonuclease) are combined to produce a highly specialised pair of "genomic scissors" (Bibikova *et al*, 2001). The TALEN system is similar to ZFNs and MegNs, because the proteins have to be rebuilt for each specific DNA sequence.

In principle, since the cleavage is more specific than the ZFN, any DNA sequence of any creature genome may be targeted for creating double strand breaks and knocking in/out sequences of interest[4]. The genome editing protocol has seen huge improvements in terms of the basic design and in reducing the off-target breaks[5].

Using CRISPR/Cas9 method, the genome can be edited or rewritten with ease. The enzyme Cas9 breaks DNA at a specific point, dictated by a supplementary RNA called guide RNA. The DNA breaks lead to the activation of the DNA damage repair pathway (nonhomologous end joining, NHEJ and homology-directed repair, HDR) and facilitate the introduction of site-specific genomic modifications. Several Cas-type enzymes with varying PAMs or activity have been developed improving the efficiency of the process further[6].

From the application perspective, TALENs have been used to produce hornless cows by the biotechnology company "Recombinetics" to rescue farmers from the problem of dehorning. CRISPR Cas9 technology has been used to repair disease-causing mutations, the only barrier being human immune responses to Cas9 (originating from Staphylococcus or Streptococcus bacteria). To tackle the issue, human in-vivo CRISPR-therapy studies have been initiated for treating hereditary blindness[7]. Despite the fact that ZFNs are more accurate and smaller in size than Cas9, they are not as widely employed as CRISPR-based techniques[8].

Building standards

Standards are the foundation of engineering. These are established guidelines or fixed quantities used reference in measurement, construction and so on e.g., weight, volume, distance, temperature standards and so on.

The earliest known attempt at developing standard for integrating biological parts was developed in 1996 called as Nucleic Acid Ordered Assembly with Directionality (NOMAD). The Biobrick initiative has been successful in generating awareness and community participation in building the Registry of Standard Biological Parts. Researchers are developing vectors that are compatible with BioBrick components e.g., ePathBrick vectors[9]. The BrickClip technology puts together component in a specific order and does not utilise restriction enzymes[10].

The development of standards has also accelerated progress in the automation of biological design, a computer-assisted approach of accelerating biological engineering. Combinatorial library design can generate a number of variants by bringing together genetic "components" in various possibilities e.g., a synthetic protein may be designed that are partially similar to existing proteins and incorporate a novel domain to enable novel interaction and function.

To overcome the limitation of standards in conventional molecular cloning methods the BioBrick assembly standards have been established supported by the Registry of Biological Standard Parts. All BioBricks are designed in a way to have a prefix and a suffix sequence at both the terminal. These sequences containing restriction sites can be utilised to join distinct BioBrick components to produce new parts that perform more complex functions. Based on restriction sites combinations there are five most prominent assembly standards have been introduced such as BioBrick Standard (RFC 10), BioBrick BB-2 (RFC 12), BglBricks (RFC 21), Silver Standard (RFC 23) and Freiburg Standard (RFC 25)[11]. Moreover, BioBrick assembly standards are expanded and the three most commonly used methods are developed such as antibiotics (3A) assembly methods[12], Amplified insert assembly[13], Gibson scarless assembly[14].

DNA data storage

The emergence of the internet era, and its related technologies, has resulted in an explosion in the volume of digital data generated. The need for data storage may surpass storage capacities[15]. To support world's information technology backbone and digital data storage system, novel and sustainable materials are needed. Given "DNA" as a nanometer scale device, can one use it store computer data?

In its natural setting, DNA serves as a repository of genetic information for living organisms. Not only DNA is available in abundance but, in theory, it has a much higher storage density than existing silicon-based storage devices. If one could use all of it, 1 kg of DNA has the capacity to store $2x10^{24}$ bits, whereas a silicon-based memory device would need more than 100 kg of silicon to store the same quantity of data[16]. Back of the envelope calculations indicate that, ~ 81 kg of DNA may be adequate to store the

entire world's data for thousands of years, as DNA from the dinosaur era has been found in a reasonably good shape.

Despite these benefits, DNA has still not seen widespread application in data storage. One of the key reason may the cost of DNA synthesis. In addition, one would probably need special read/ write heads for non destructively accessing DNA for data storage and retrieval. Researchers at the Wyss Institute have discovered novel enzyme-based method of DNA synthesis that is simpler and faster than standard chemical procedures[17]. New DNA synthesis techniques are likely to lower the cost of DNA drives while producing longer strands that are stable and do not come with mutations.

To store binary data into DNA, the bits 1 and 0 are transformed into the nucleotide alphabets A, T, G and C of DNA. The data is recovered by sequencing the DNA chain and decoding the order of nucleotides back into the digital one.

The proof of concept of DNA data storage was first demonstrated by Artist Joe Davis in 1988 in collaboration with Harvard scientists. David encoded a picture of a runic sign containing 35 bits of *E. coli* DNA[18]. Recently, researchers reported the storage of 16 GB of Wikipedia stored on synthetic DNA[19]. However, storage of data was done in vitro. Though *E. coli* is the most well suited prokaryote due to enormous information available, other microbes may also be utilised for DNA data storage in due course.

Till the experimental technology matures to the point where DNA data storage becomes a commonplace, one may use computationally use DNA sequence for data storage, including passwords[20]. The DNA sequence can be used for converting, storing the data in DNA coded form and retrieving data using pointer file approach. In this approach, the input data is converted into 4 base DNA sequence, called Nibble, mapped to the DNA sequence of an organism. The first position of each converted nibble is retrieved and stored in a pointer file. By mapping the positions of pointer file one the DNA sequence of the organism, the data can be retrieved.

Summary

The arrival of rational design approach in biology has given birth to interesting ideas, products and technologies. Some of the enabling

technologies that have accelerated making and testing of designs is long DNA synthesis. We are no longer talking of synthesizing primers. Technology has matured to the point of synthezing vectors and even microbes. As the cost of DNA synthesis drops and the length of synthesized DNA sequences increases, the community will see further acceleration of innovation. In future, hundreds and thousands of desgins will be tested in high throughput platforms at an affordable cost. The key would be speed, accuracy and affordability. Along with long DNA synthesis, genome editing tools will see huge transformation in terms of accuracy and negligible off target effects. Though DNA storage technology is at a very early stage, one expects to see commercially available biostorage technologies in 5-10 years from now. Given the pace of innovation, we are living in the most exciting times where innovation has a fair opportunity to meet the speed, scale and affordability. In future, we expect many more responsible innovations in synthetic biology connecting the science and the society.

Endnotes

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Challenges in governance of Synthetic Biology: Biorisk assessment

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Abstract: Synthetic biology is an emerging area of research representing one of the finest example of culmination of various engineering principles to biology resulting in multi-dimensional implications for humans. In other terms, as with any technology, synthetic biology presents plausible opportunities as well as potential risks. Commercialisation of synthetic biology- oriented products requires critical analysis to outweigh the probable risks. Synthetic biology based processes and products have been considered to be regulated under biotechnology regulatory framework due to existing overlap at various levels in the two fields. However, with ever widening scope and impact of synthetic biology, several nations have enacted various guidelines to regulate synthetic biology research. Outbreak of COVID-19 and various speculations about its origin has further attracted global attention to address bio risk concerns of synthetic biology. Therefore, the present study focuses on biosecurity, bioterrorism, and ethical aspects of synthetic biology, emphasising the urgent need for policymaking in this regard in India. In addition, role of various agencies in regulating synthetic biology has been reviewed. Furthermore, position of India in the synthetic biology race has been also assessed towards the end of the study..

Keywords: Synthetic biology, Biosecurity, Biosafety, Bioterrorism, Ethics, IPR

Introduction

Synthetic Biology: A new dimension to experimental biology

Amalgamation of engineering skills in biology has led to the emergence of an exciting field of synthetic biology. Remodelling existing biological systems or engineering a whole new system to serve the purpose is the core idea of this field. There is no unified definition accepted for synthetic biology to date due to the interdisciplinary nature of the field. However, interestingly, the practical implications have been already observed in bio-sensing (Del Valle et al., 2021), cancer-targeting (Cai et al., 2016), immunotherapy (Guo et al., 2016), bioremediation (Jaiswal & Shukla, 2020), vaccine development

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(Jain et al., 2012) and designer crops (Chugh et al., 2015). Several synthetic biology-based applications will involve exposure of a synthetic organism to the environment, raising social and ethical concerns (Saukshmya & Chugh, 2010a). At the same time, this creates a significant challenge in the engineering and designing process, questioning the predictability and robustness of the designed organism. Thus, unless all these criteria are met, proper caution should be taken into consideration by scientists and society. Interestingly, despite these dilemmas, the economic contribution from synthetic biology is expected to reach US$18.9 billion by 2024, at a compound annual growth rate (CAGR) of 28% (Mao et al., 2021).

From the bio risk perspective, the idea of converging infotech, biotech and nanotech may lead to radical changes in the lives of people and can raise myriads of biosafety, biosecurity and bioethical issues (European Commission, 2010). Sometimes the terms biosafety and biosecurity are used interchangeably without any agreed definition or scope. Regardless, the National Research Council has summarised the difference: "Biosafety is about protecting people from bad 'bugs'; biosecurity is about protecting 'bugs' from bad people". There are multiple accepted definitions for biosafety and biosecurity depending on the discipline involved and the nation in which it is used (Beeckman & Rüdelsheim, 2020).

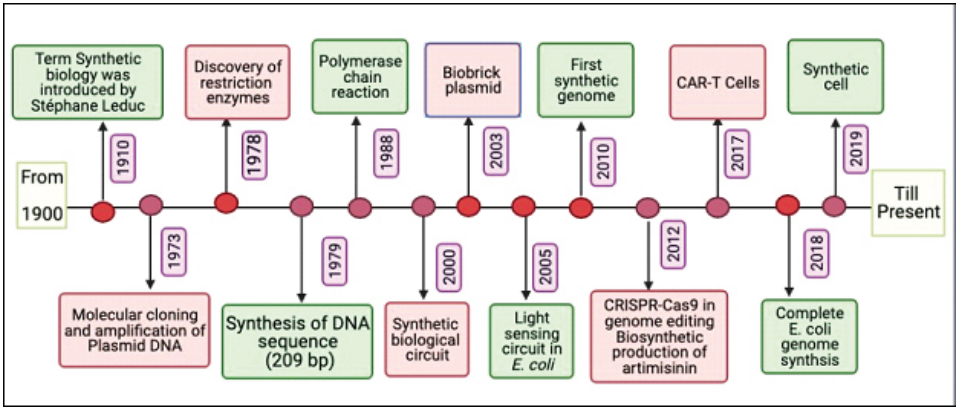
According to WHO, biosafety involves: "containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens or toxins, or their accidental release" (WHO, 2006: iii) whereas, biosecurity refers to: "the protection, control, and accountability for valuable biological materials within laboratories, in order to prevent their unauthorised access, loss, theft, misuse, diversion or intentional release" (WHO, 2006: iv).

Existing governance frameworks have focused on biosafety and biosecurity issues; however, bioethical issues are coming slowly to the forefront. This article seeks to address the concerns associated with synthetic biology, focusing on the preparedness of India to deal with biosafety, biosecurity and bioterrorism. Further, the role of various agencies involved in governing synthetic biology has been reviewed. Lastly, a detailed description of the status of synthetic biology in India has been discussed.

Trends in the field

The dawn of synthetic biology dates back to 1973 with the development of molecular cloning and plasmid DNA amplification. Later discovery of restriction enzymes and the invention of polymerase chain reaction (PCR) has accelerated the growth of the field. The development of synthetic circuits for light sensing in *E. coli*, invasion of tumour cells by bacteria, chemically synthesised DNA, and artificial chromosome arms are some of the follow-up innovations. Further revolutionary breakthroughs are expected in synthetic biology with the advent of CRISPR-Cas9 disruptive strategy for genome editing and beyond (Fig 1).

Fig. 1. A brief timeline of synthetic biology



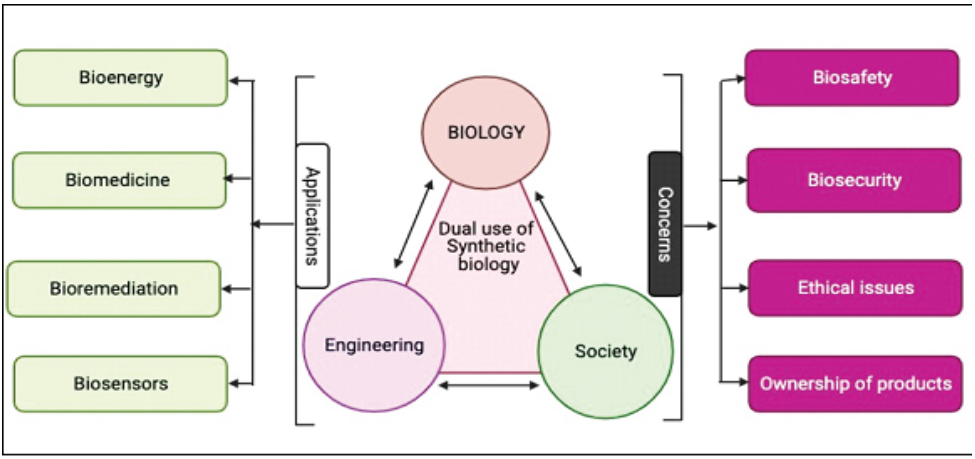
Source: Authors' compilation

Delineating potential applications and risks of Synthetic Biology – A field of dual use technologies

Technological innovations could be of dual-use, especially in the field of biology. Synthetic biology is also one of the controversial fields that can contribute in several areas of applied biology but simultaneously possesses the misuse attribute when considered a garage, do-it- yourself (DIY) or open biology platform. Due to rapid progress in the enabling technologies arising from synthetic biology, its scope is ever-broadening. Some of the areas in which the potential of synthetic biology is unleashed both for applications and concerns are shown in Fig. 2.

There were always some safety concerns associated with recombinant DNA technology, primarily dealt with experience and regulatory guidance.

Fig. 2. Dual aspects of synthetic biology. Concerns of Synthetic Biology



Source: Authors' compilation

Further, it is emergent that any new scientific field is also assessed for its success in terms of associated risks and responsibility of the various stakeholders. Risks associated with Synthetic biology are mainly discussed in the context of biosafety, biosecurity and bioterrorism. Moreover, it is essential to note that the workforce in synthetic biology may not be composed of core biologists but also amateurs with little understanding of associated risk and microbial safety (Kolodziejczyk, 2017). The budding culture of DIY biology and easy access to material and methods via the internet have further aggravated the concerns of the scientific community and the public. Therefore, proper dissemination of knowledge across all the associated fields of synthetic biology to promote responsible research is a prime requirement in the current scenario(Freemont et al., 2012).

Biosafety and Biosecurity

One of the primary concerns of synthetic biology is the accidental or deliberate release of modified organisms into the environment. As the behaviour of the organism in the natural environment and its interaction with other organisms is highly unpredictable, there is a requirement of necessary regulations to be in place regarding the containment of modified organisms. The United Nations (UN) and American and European biosafety associations (ABSA, EBSA) have biosecurity issues on their agendas. WHO has also

issued guidelines on "Biorisk Management - Laboratory Biosecurity guidance" and "Responsible life science research for global health security", focusing on DURC (dual-use research of concern) (WHO, 2006).

There has been scepticism about synthetic biology per se after the de novo synthesis of the poliovirus in 2001(Cello et al., 2002), which may jeopardise the long-term eradication of viral diseases. Further, intentional or unintentional spillovers can bring a storm of public indignation, shattering the entire scientific edifice. Therefore, possession of such high-risk infectious agents requires the vigilance of regulatory bodies and programmes such as the Federal Select Agents Program (FSAP, 2019), DURC and Coordinated Framework for Regulation of Biotechnology (United States Environment Protection Agency, 2017). Such inspective programs should be incorporated in every possible arena of research in synthetic biology.

Synthetic genomics offers a wide array of applications in vaccine development, codon repurposing, or as a bacterial chassis for metabolic engineering (Luo et al., 2018). The innovation in the field can resolve significant challenges in health, environment, energy and resources. However, the story on the other side of the table can turn malicious owing to either inadvertent or deliberate misuse of synthetic biology.

The year 2020 has delineated the dual aspect of synthetic biology. COVID-19 pandemic has left an indelible imprint for technological uncertainties, the culture of collaborations or the adoption of self-governance to guide innovation towards global interest. Although the origin of the pandemic remains obfuscated, the COVID-19 outbreak has set the stage for researchers, social scientists and policymakers to engage early in technology development and frame strategies to work upon emerging biosecurity concerns. The fleeting glimpse of the current Pandemic situation is sufficient to give due importance to the dire need for investment in biosafety and biosecurity at a global scale. On contrary, synthetic biology labs have geared up to find a solution for the COVID-19 pandemic. The DNA and mRNA-based vaccines and diagnostic kits in just a few months after the public release of the genetic code of the COVID-19 virus has revolutionized the idea of data sharing to foster beneficial outcomes. Therefore, the balance between risk aversion and opportunities for innovation is of utmost importance and an essential lesson from the present Pandemic times. There

are several incidences in the past, including the outbreak of the avian influenza virus, MERS coronavirus or Ebola virus, where data sharing, IPRs (Intellectual Property Rights) hampered access to medicines in developing nations (Bruynseels, 2020). A delicate balance between the monopolistic character of the IP regime and easy access to medicines at affordable prices is a pressing need in such Pandemic times. As an alternative, an incentive mechanism to reward inventors can be one of the viable strategies. In fact, such scenarios have led to the establishment of GISAID (a global initiative on sharing all influenza data), a platform to share viral sequences whose significance is discerned in current pursuits of the COVID-19 pandemic (Bruynseels, 2020).

Despite the swift response of synthetic biology in the current Pandemic situation, the concerns raised after the synthesis of poliovirus and horse pox virus cannot be ignored (Noyce & Evans, 2018). Thus, balancing of positive and negative perspectives of synthetic biology-based research is of critical significance.

Developing an effective biosecurity strategy would require forecasting the looming threats of emerging technologies. For instance, gene editing and related techniques such as CRISPR/Cas has opened the directions for improvement in health, agriculture and the environment, but nefarious use of such technology can cause harm at the same or even a larger scale than anticipated. The consequences might include the accidental release of gain of function variant in the environment, ecological disruption with engineered organisms or use of the technique to create bioweapons.

The gain of function studies of avian influenza virus, especially those involving efficient transmission, has received considerable attention during the present times. After careful consideration of the risk involved in the gain of function studies, the National Science Advisory Board for Biosecurity (NSABB) in the USA has proposed some guidelines to review the risk of gain of function experiments (LeDuc & Yuan, 2019). The efforts of NSABB serve as a guide for Institutional Biosafety Committees (IBCs) and other advisory committees to evolve and address the novel challenges of synthetic biology.

A substantial repository of literature on the stepwise protocol of genome editing or synthesis and the easy access to gene sequencing and other techniques may provide a platform to use such techniques against humanity.

The explicit governance strategies require a top-down approach for maintaining compliance at the international level and bottom-up approaches in which stakeholders directly involved in research look upon the proper application of technology.

Following are some of the key measures that can be considered for risk mitigation of Synthetic biology:

- Introduction of synthetic biology and its associated safety concerns as part of the coursework for every researcher.
- Ensuring the proper training of the staff working in the laboratory and formulation of laboratory-specific biosafety manual.
- Deployment of physical security and laboratory access to only trusted staff.
- Scrutinizing management and regulatory practices of the team members by a team leader.
- Formation of IBC to review and forecast the ongoing research regarding social and ethical backgrounds. In China and the US, these committees are rigorously involved in risk assessment of projects involving genomic manipulation of a pathogen. For receiving funding from the US National Institutes of Health, IBCs is the prerequisite. In Belgium, with the implementation of Directive 98/81/EC, biosafety officer (BSO) and biosafety committee appointment became compulsory. Several European countries such as Denmark, France, and the Netherlands have developed well organised legal biosecurity systems (Belgian Biosafety Server, 2021). Likewise, in Switzerland, the Swiss Expert Committee for Biosafety (SECB) is engaged in drafting laws, ordinances, guidelines and recommendations on safety measures for studies involving genetically modified, pathogenic or alien organisms (SECB, 2021).
- Investment in research associated with improvements in biosafety and biosecurity strategies. One such example is the Safe Genes, a DARPA (Defense Advanced Research Projects Agency) program that aims to develop tools to control and counteract the effects of genome editing (DARPA, 2016). Likewise, Open Philanthropy Project has raised funds for safety inclusion at the iGEM competition and the DIY Bio community (Open Philanthropy, 2020). Similar efforts are

required on a national and international level to ensure biosecurity.

- Engagement of industries and service providers in the screening process. Most of the DNA synthesis companies that are members of the International Gene Synthesis Consortium (IGSC); have taken a commendable step to screen their customers for security reasons (Trump et al., 2020). As the commercial sector of synthetic biology expands globally, the increase in demand and reduction in cost can result in a capricious screening of requests. As a result, a common mechanism for DNA sequence screening accessible at low cost and easy to use by all providers of DNA is proposed by the working group of Nuclear Threat Initiative (NTI) and the World Economic Forum in 2019 (NTI, 2019).
- International cooperation is required to prevent and control bio-risks. The John Hopkins Center for Health and Safety, US and Center for Biological Safety Strategic Research, China co-sponsored the "Track II dialogue" on "The Challenges Facing China and the United States in the Era of Synthetic Biology". Experts from different fields discussed the strategies for dealing with biosafety and biosecurity risks (Li et al., 2021).

Synthetic Biology Research Centre (SBRC)-Nottingham has initiated a Responsible Research and Innovation (RRI) program to address synthetic biology-related concerns. According to Research Councils in the UK, it is "the process that helps researchers understand the benefits and risks of emerging technologies early on in the innovation process." It includes public engagement, risk management, life cycle analysis, ethical approval and regulation.

The critical dimensions of its programme are, Anticipate, Reflect, Engage, and Act (AREA), extending further to product commercialisation and innovations. Such attempts are required globally to attain minimum biosecurity standards as the contemplation of the established measures is based on the particular -nation's risk tolerance, thereby neglecting the risk-prone nations. (SBRC, 2018)

Engineering the evolutionary potential of biological systems is one of the most challenging dimensions of synthetic biology. There exists a possibility for the synthesised structure either mutating into the worst form or vanishing,

raising ethical issues in both cases. The behaviour of synthetic biology-based organism should be predicted before synthesising for biosafety over a longer timescale. Nevertheless, prediction or risk assessment remains the most challenging task in synthetic biology. However, genetic manipulation has become the most straightforward task for a synthetic biologist with the advent of newer technologies, but this has also increased the chances of failure to control the release of such modified entities from the lab unless proper guidelines on biosafety are in place at a global level. The new organisms should be released into the environment after assessing their potential risk to the other organisms and the environment. Computational modelling can assist in predicting the pathogenic behaviour of multiple proteins, the impact of mutations on virulence and environmental effect on the pathogenicity. Further, to predict the unknown functions in poorly annotated sequences, machine learning can assist (Leo Elworth et al., 2020). All such factors that could reduce the risk should be well known before release (Anderson et al., 2012).

Bioterrorism

The draft Model State Emergency Health Powers Act (MSEHPA) of 2001 has defined bioterrorism as "the intentional use of any microorganism, virus, infectious substance, or biological product that may be engineered as a result of biotechnology, or any naturally occurring or bioengineered component of any such microorganism, virus, infectious substance, or biological product, to cause death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism in order to influence the conduct of government or to intimidate or coerce a civilian population" (Gostin et al., 2002). Technological advancement has made genetic manipulation an easy and cost-effective process. The development of high- throughput technologies has accelerated the research by creating large gene cassettes to produce biofuels, therapeutics, and novel gene networks (Singh et al., 2015). Such molecular biology tools are a boon for biologists working in different fields; however, it also raises significant concerns for easy access to non-professionals to manipulate the genome that may create bioweapons.

The concerns for biological weapons, predates the advent of synthetic biology. The historical record of events involving infectious agents in conflicts is well known (Frischknecht, 2003). Several nations have included

biological weapons in their defence system. In 1975, the Biological and Toxin Weapon Convention (BTWC) came into force, and more than 100 nations, including India, have ratified this Convention (NTI, 2021). The Convention aims to end the development and production of biological weapons, but the threat from terrorists and nations not committed to this Convention persists.

The expert opinions on the conceivability of a biological attack have various perspectives. In short terms, it is implausible that non-state actors would employ technological pathways to create bioweapons. Nevertheless, in the long term, if the potential of synthetic biology is realised to make biotechnology cheaper and more accessible, bioterrorism can become a reality in future. Regardless of the probability of attack, the strategic plan of action should always be ready to counteract such warfare in future. The International Committee should strengthen its norms against bioweapons development and complements its traditional approaches to tackle negative implications with innovative initiatives. The focus should be to reinforce safety and security by devising a shared responsibility in science, industry, politics and society (UNICRI, 2012).

While bioterrorism issues are being raised nationally or internationally, there is no mention of marine bioterrorism on how and who would regulate the activities in marine areas outside the national jurisdiction. Nearly two-thirds of the ocean lies in areas beyond national jurisdiction (ABNJ), rich in unique species and ecosystems. Some negotiations are underway to close the existing gap in ABNJ governance under the UN Convention on the Law. These negotiations can provide a global framework to assess harmful activities, facilitate scientific research with equitable sharing of benefits from marine genetic resources (UNEP-WCMC, 2017).

Finally, it is essential to ensure that regulatory measures go hand in hand with scientific innovations. The development in the field can be a game-changer in both perspectives; therefore, positive implications should overpower the potential misuse.

How prepared India is

India began to train its personnel for bioterror attacks back in 1998. Additionally, the Defense Research and Development Organisation (DRDO) has been working on counteracting nuclear, biological, and chemical warfare

(Krishan et al., 2021). India has been fortunate that it did not have to experience bioterrorism, but back in 2001, after anthrax attacks in the US (Das et al., 2001), India also faced similar events, later declared a copycat hoax. Following the anthrax attack, the US has been funding the Centers for Disease Control and Prevention, Department of Health and Human Services, and the Environmental Protection Agency for prevention, surveillance, and preparation for bioterrorism attacks (Grundmann, 2014). However, in India, such initiatives are still lacking. It is worth noting that 21st century is an era of advancemens in biology, including synthetic biology, with many novel technological inventions that carry the potential to be exploited to create unprecedented incidences of bioterrorism. Furthermore, the weaknesses and lack of preparedness to deal with biological threats have placed India on the biological time bomb.

Following are some of the Recommendations that can equip India efficiently to deal with such emerging concerns of bioterrorism

- Investment in scientific research and incentives for researchers involved in scientific innovation.
- Improving the medical infrastructure and formulating SOPs at all levels of health care.
- Encouraging novel vaccine development platforms and developing robust mass level immunization strategies and programmes to protect people at risk.
- Good disease surveillance network and coordination among ministeries to deal with the situation conclusively.
- Formulation of dedicated policy to deal with bioterrorism and involvement of experts from outside the government in decision making.
- Preparation of institutional specific response plans in collaboration with local and state health departments. The plan should be practical and realistic to deal with any actual or suspected bioterrorism attack.
- Mass scale events to spread awareness and encourage citizens to participate in the disaster management committee.
- Providing a platform and motivating citizens to actively participate in synthetic biology talks to express their views and suggestions on innovative, biosafety and biosecurity aspects.

Ethical issues

In the ethical debates, synthetic biology is criticised as "playing god," evoking the religious sentiments of people. The developments in the field were being misled by this perception (Dabrock, 2009). Besides, the proposal on entire genome synthesis raises concerns about the potential misuse of the technology. The ENERI (European Network of Research Ethics and Integrity) project has collected the code of conduct established at the national or international level to promote research ethics and research integrity between experts (ENERI). In addition, Conduct for Biosecurity has been implemented in Italy in 2010 (Bielecka & Mohammadi, 2014).

Further, using machine metaphors such as nuts and bolts to represent genes and proteins gives a misguided image of research to the public and raises ethical concerns. The global standard for ethics is required to resolve ethical issues and gain public trust without raising Frankensteinian fears. As synthetic biology is still in its developmental stage, some unexpected ethical issues may also raise novel challenges in the future; therefore, related research in the field of socio-ethics and law should be carried out if possible, simultaneously with technological research (Zhao, 2021).

Ownership of products

IPRs protect the new creations (inventions) and are trade currency for commercialising the product/process. Synthetic biology amalgamates multiple fields and techniques, making it challenging to frame IP rights fairly and responsibly (Lentzos et al., 2012). For rapid advancement in the field, openness in research results and tools is required, but with the falling cost of DNA synthesis, the risk of bioterrorism also increases. However, to unleash the full potential of synthetic biology, optimization and governance of the patent regime is required. Both open-source and IP approaches have played an essential role in the development of synthetic biology (Saukshmya & Chugh, 2010b) till now, and at this stage of the innovation race, it is difficult to predict which culture will prevail in future for synthetic biology. However, the most comprehensive agreement on IPR to date is the WTO (World Trade Organization) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). According to its Article 7, the enforcement of IP rights should promote technological innovation,

and the dissemination of the technology should benefit both producers and users of technology (WTO, 1995).

Furthermore, the waiver of certain IP rights to combat global crisis, such as the COVID-19 pandemic, is also included in the agreement (Balfour, 2021). As in the current scenario, the vaccine development being confined to only a few pharmaceutical giants involving Moderna, Novavax, Johnson & Johnson, and Astrazeneca has created a vast disparity in COVID-19 vaccination (Forni et al., 2021). As a result, India and South Africa have argued upon the rapid access to affordable diagnostic kits and proposed patent waiver on vaccines which is being opposed by various western countries (Lindsey, 2021). According to Western nations, the central idea behind the protection of IP rights is to encourage research and innovation as well as maintain quality and safety (Balfour, 2021). However, this will lead to immense loss of lives due to delayed actions and such restrictions in emergencies in several developing countries. Therefore, these loopholes of IP rights which also exist in synthetic biology-based processes and products should be identified, analysed and resolved to avoid disputes in times of emergency. Different stakeholders should involve in finding a middle ground where risk reduction does not hamper innovation. Furthermore, discussions on finding a solution for easy access to patented technology should also be conducted. Although patents will remain one of the crucial aspects of synthetic biology, the consideration of other IPRs such as trademarks, copyrights and trade secrets should not be undermined.

To discuss the emerging challenges and opportunities at the interface of synthetic biology and IPRs, European Research Area Network in Synthetic Biology (ERASynBio) sponsored the Danish Agency for Science, Technology and Innovation. The recommendations proposed in the meeting include Empirical evidence and open-source software tools, use of public domain tools, patent quality and transparency, best licensing practices, private ordering mechanisms, legislative and regulatory changes (Minssen et al., 2015). Such meetings should be organised globally to discuss the IPRs and future challenges involving biosafety and biosecurity concerns associated with the advancement in the field.

Agencies involved in regulating synthetic biology

The first conference to assess and evaluate the concerns regarding the then ongoing research in biotechnology was the Asilomar Conference on Recombinant Molecules held in 1975. This conference was the result of the self-governance of scientists, discussing potential risks in their fields. As synthetic biology is associated with genetic manipulation and much more, governance measures are required, and scientists have effectively applied self-governance to date. The concept of gene drive was well speculated by the scientists for the safety of techniques outside the laboratory. Similarly, various discussions were held related to germ-line editing amongst humans, and the idea was discouraged. The National Academies of Science, USA (Gronvall, 2015) proposed guidelines for gene-editing research.

Although self-governance has been extensively followed but is not reliable internationally, various other governance mechanisms are observed parallel to self-governance. The United Nations Convention on Biological Diversity (CBD) is one such group of a Conference of Parties (COP), including 196 countries. The first subsidiary agreement of CBD, termed Cartagena Protocol on Biosafety (CPB), has set some regulatory measures to use living modified organisms (LMOs) safely. CPB considers characteristics of an organism, intended use and the environment exposed to the organism for risk assessment. The current risk assessment methodologies are similar for LMOs and the organisms produced through synthetic biology. As synthetic biology is a more advanced field, specific considerations must be identified and address the gaps in the risk assessment methodologies (Keiper et al., 2020).

For access and benefit-sharing (ABS) to the CBD, Nagoya Protocol was introduced. It includes appropriate funding and sustainable use and transfer of technologies, including all rights over the resources. Under this protocol, any company or research organisation seeking access to genetic resources should apply for consent to the concerned authority and agree to share benefits from resource utilisation. For effective enforcement, each party has to adopt provider measures and user measures, which will ensure that access to resources is on mutual terms.

The current Nagoya-Kuala Lumpur protocol provides rules and procedures to redress LMOs (Keiper et al., 2020). CBD and Nagoya Protocol

regulate the physical transfer of genetic material. Still, with the emergence of genome sequencing, the paradigm shifts towards the digital transfer of information, thereby requiring clarification of ABS requirements under such scenarios. Although the matter is not resolved at an international level, some nations have adopted unilateral ABS efforts to regulate access and information from their genetic resources (Manheim, 2016).

The evolution of synthetic biology goes hand in hand with advancements in technology and scientific knowledge, challenging the identification and distinction of genuinely new that is not within the scope of existing regulatory mechanisms. In order to tackle this gap, regulatory measures need to be modified accordingly. USA is the world leader in investment in research and development (Si, T. & Zhao, H., 2016); the first policy discussion regarding synthetic biology took place in the USA. The governing body includes executive, legislative and judicial branches of the Federal government with multiple veto players, making the decision process a politically intensive one that can take years to achieve. Further, the role of courts to resolve disputes complicates the governance process (Trump et al., 2017). Various other guidelines for the regulation of synthetic biology include:

Federal regulations of United States of America

Regulation for recombinant technology: NIH (National Institute of Health) has laid down the guidelines for experiments concerning recombinant nucleic molecules' safety and containment aspect (Yam et al, 2012). NIH guidelines have classified experiments related to recombinant DNA technology into six categories depending upon the experiment type and the action required by regulatory agencies IBC (Institutional Biosafety committee), RAC (Recombinant DNA Advisory Committee) review, and NIH director approval

Regulations for GMOs: There are various agencies like EPA (Environment Protection Agency), USDA (US Department of Agriculture)-APHIS (Animal and Plant Health Inspection), and FDA (Food and Drug Administration) that have imposed restrictions on using genetically modified organisms and their products for commercial purposes.

EPA regulates the production of new microbes by recombinant genetics under the TSCA (Toxic Substances and Control Act) and genetically

engineered pesticides under the FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act). The exploitation of microbes for a commercial purpose requires filing either MCAN (Microbial Commercial Activity Notice) or TERA (TSCA Experimental Release Application).

USDA-APHIS regulates the commercialization of genetically engineered plants, insects, or microbes that may risk animals and plants health.

In addition to regulating the commercial use of various foods and drugs, FDA also regulates the food derived from genetically altered plants that significantly differ in one or more components than their natural counterparts. FDA and EPA collectively hold in specific scenarios.

Regulations for export of genetic elements (mainly associated with pathogenicity): The Department of Commerce, Bureau of Standards and Security, is an authority that issues a license in the export of synthetic genes related to either pathogenicity or synthesis of toxins.

European Union directives and regulations

The European Union follows a more decentralised and co-operational approach in development and legalism, respectively. There are specific directives attributed to GMOs and emerging biotechnologies.

The European Union has also framed laws related to the process and products of synthetic biology. The various directives and regulations were laid covering genetically modified organisms and food. The multiple directives of the EU related to synthetic biology are:

1. Directive 90/219/EEC on Contained Use of Genetically Modified Micro-organisms
2. Directive 2001/18/E.C. on Deliberate Release into the Environment of GMMs
3. Regulation 1829/2003 on Genetically Modified Food and Feed
4. Regulation 1830/2003 Concerning Traceability and Labeling of GMOs and the food and feed products produced by GMOs
5. Regulation 428/2009 on Export Controls of Dual-Use Goods
6. European Agreement Concerning International Carriage of Dangerous Goods by Road

7. EU Legal Framework Concerning the Prevention of Bio-Terrorist Acts
8. Directive2004/35/E.C. on Environmental Liability

UN Bioweapons Convention (BWC)

UN Bioweapons Convention (BWC) deals with the Prohibition of the Development, Production, and Stockpiling of Bacteriological or other microbial (Biological) and Toxin Weapons during warfare. The rapid advancement in the dual-use dimensions of life sciences has pushed back BWC. The greatest challenge is to keep pace with the advancements and to ensure the use of BWC norms. The state parties are given the authority to complain about other member states if found violating the Convention to UN Security Council (UNSC).

The Australia Group Guidelines

This group has been formed to prevent the use of chemical weapons by Iraq in the war, thus controlling chemical and biological weapons development. After that, its regulatory scope has been widened to include synthetic biology-related advisory imposing various guidelines.

Asian countries in the race of synthetic biology

The advancement of synthetic biology in China results from aggressive science and technology policies and the emphasis of Chinese leaders on science and education for economic development. The role of organisations such as the Chinese Academy of Sciences (CAS), the Chinese Academy of Engineering, China Academy of Machinery Science and Technology and medical universities in synthetic biology is well known. Besides, multiple funding agencies promote research, such as the National Natural Science Foundation of China, state-level labs, and the CAS Knowledge Innovation Programme (National Academy of Engineering and National Research Council, 2013). The strategic roadmap specifying the timeframe for desired achievements has been drafted. Addressing legal, ethical and security issues and protecting the health and safety of human resources is equally prioritized (National Academy of Engineering and National Research Council, 2013).

China has also formulated laws and regulations for laboratory practices considering biosafety and biosecurity concerns.

The US, China and Europe being the leading nations in synthetic biology development, conducted the workshop to bring technical and policy experts from these nations under one umbrella to promote global biosafety and biosecurity issues (Inglesby et al., 2019). Considering the lack of any international governing regulations, the participants looked upon China and the US to formulate norms for responsible conduct of synthetic biology by collaborating with worldwide experts and policymakers.

Synthetic Biology and India

The Department of Biotechnology was established in India during the late 1980s to harness the potential of science and technology in the nation's economic development. It is a significant driver to target USD 5 trillion economy target by 2024 (India Bioeconomy Report, 2020). Likewise, synthetic biology can also play a significant role in building the bioeconomy. However, there is a lack of consensus and clarity among scientists, industry and policymakers on synthetic biology; India needs to define synthetic biology and the research in this field. Initiatives like Global Bio-India-2021 showcasing the strength and opportunities of the biotechnology sector at the national and international level are needed separately for synthetic biology (DBT, 2021).

In India, the research on synthetic biology is in its infancy and confined to only a few institutes and groups, thereby limiting the transfer to industry. The involvement of the private sector is minimal, and the firms working in this arena are involved only in R&D. In terms of industrial applications, not much is happening, but India may witness the resurgence of small enterprises working in niche areas in synthetic biology. However, to promote the growth, a task force on the system and synthetic biology were set up under the twelfth five-year plan. (12th five year plan, 2012). The overview, status, and regulatory issues associated with synthetic biology have been discussed in this plan. The emphasis is on the development of proper infrastructure and engineering curriculum with exposure to biological aspects.

Moreover, creating training centres, building international linkages, generating fellowship, and developing translational capabilities were

recommendations to boost the research in synthetic biology. It took into consideration the global scenario and the status of research in India. The emphasis on critical aspects such as infrastructure and research expertise was laid down based on the analysis. Besides, it gives equal weightage to the transparency, public acceptance, and biosafety issues in line with technological development. Regarding regulatory guidelines on ethical, social, and legal issues, each agency and department must address their own as there is no description of coherent authority in the plan (Synthetic and System Biology Resource Network (SSBRN, 2012).

Where we stand today

Despite the biotechnological potential, the growth of synthetic biology in India is minimal. After the dissolution of five-year plans, no new guidelines to address synthetic biology's current issues and progress have been reported. Moreover, the absence of a separate program on synthetic biology, integrating different projects being carried out, makes it challenging to get exact information on ongoing activities in the field. The lack of specialised human resources and interdisciplinary approaches in institutions further impede development.

India is an agro-based economy; the emphasis should be on utilising synthetic biology in the agriculture sector to increase crop productivity. At this stage, India needs a foresight assessment of technology in terms of development, societal impact, and policymaking. Although the experts in the field have to play a central role in policy development, participants from other areas and governing bodies are required to participate actively. It is about responsibly sharing the benefits of science and promoting its expansions while looking at its potential long-term impact on the environment and society.

India also possesses vast potential in marine synthetic biology. Oceans consists of immense biodiversity which has been insufficiently exploited yet. Thus, sustainable bioprospecting can boost the economy of India (Demunshi & Chugh, 2009). Even though the future of marine synthetic biology is bright, it will, however, raise questions on the regulatory guidelines and fair and equitable sharing of any commercial profiteering (Bhatia & Chugh, 2014). The exploitation of marine-based gene pool for synthetic biology

should be made considering various rights, including industrial property law, maritime law, United Nations Convention on the Law of the Sea (UNCLOS), and the CBD. UNCLOS defines the rights and responsibilities of nations to use the world's oceans and establish guidelines for the management of marine natural resources (Bloch & Tardieu-Guigues, 2014). CBD focuses on the preservation and sustainable use of biodiversity. The role of CBD in regulating synthetic biology has already been discussed. Apart from all these international organisations, India should set up access and regulatory guidelines for the use of its marine resources. The enforcement of such guidelines will ensure the act of bio-piracy in case of non-compliant practices. The incorporation of clauses for addressing marine synthetic biology or synthetic biology per se issues of patent infringement or biopiracy should be dealt with in the Indian judiciary system. A separate committee of experts should be formulated to look upon such issues. Furthermore, the random use of marine synthetic biology should have concrete regulations in place keeping in sight the unique challenges that may emerge under marine environments, especially the use of synthetic biology in the areas beyond national jurisdictions. A proactive approach is required on guidelines regarding use of biosafe practices, biosecurity and harmonization in dealing with bioterrorism through national and beyond national jurisdictions.

How synthetic biology can benefit India

It is an emergent need for India to address public health, nutrition, resources and promotion in science and technology. The rich biological diversity and traditional knowledge of India (Demunshi & Chugh, 2010) can provide a perfect platform for synthetic biology-based innovations to resolve these concerns. Other than this, the issues that require immediate attention include investment in R&D, transparency in research and policy development, capacity building, biosecurity, biosafety and IPRs. As a developing nation, synthetic biology can also play a significant role in bio-economy enhancement. India has formulated its bio-economy strategy to measure and monitor the growth and performance over time and make India a $100 billion bio-economy by 2025. For accelerating the research in biopharmaceuticals, an industry-academia collaborative mission, "Innovate in India", is initiated by DBT and implemented by BIRAC (Biotechnology Industry Research Assistance Council) (DBT, 2012). However, as India

progresses in synthetic biology-based processes and products, bringing various benefits for human welfare, it is important to keep in sight the dual use synthetic biology and develop a robust governance regime that is well equipped to deal with described concerns of synthetic biology. The role of the judiciary at the national level and, also of the international court of justice will become important in the coming years for transnational cases of biosecurity and bioterrorism.

The following sections make an attempt to provide an understanding of the dual use of synthetic biology.

Promoting and regulating DIY synthetic biology

It is a rapidly evolving social biotechnology movement undertaken by experienced individuals to mentor novice DIY biologists. The term is often linked with biohacking and wetware hacking, which refers to exploiting genetic material for varied purposes. In recent years many DIY labs have emerged globally in non-academic settings to bring biotechnology closer to the lay public (Kolodziejczyk & Kagansky, 2017). The features that characterise DIY are interdisciplinarity, not-for-profit endeavour, cost-effective equipment, focus on open science innovation and self-empowerment (Gómez-Tatay & Hernández-Andreu, 2019).

The safety risk associated with DIY biology is also high as individuals involved have no formal training in safety and ethics. Therefore, equal importance should be given to formulating strategies to minimise risk, as, in Singapore, licensing is mandatory for biohackers to pass ethics and safety tests (Kolodziejczyk, 2017).

Governance regimes

The fast-paced field of synthetic biology outpaces the established biosecurity and biosafety measures. The same old policies are being implied on the new technology, raising the debates among the concerned authorities. The formulation of effective strategies to mitigate risk requires proper understanding and foreseeing the novel threats that can arise with advancement. Although the debate on regulatory measures is still open, several biosafety measures that have been proposed for biocontainment are described in table 1 (Gómez-Tatay & Hernández- Andreu, 2019).

Table 1: Different biocontainment measures

Biocontainment measures	Features	Drawbacks
Inducible systems	Specific inducers of gene expression are not common in the environment	Do not address the risk of horizontal gene transfer
Auxotrophy	Requires a particular vital compound in the media.	Cannot prevent horizontal gene transfer
Safety circuits	Includes kill switches leading to cell death when activated.	Cannot achieve desired escape rates
Xenobiology	Use of xenobiotic nucleic acid	Can contribute to the creation of new pathogen
Toxin-antitoxin pairing	Combination of stable toxin and unstable antitoxin	Only applicable to mobile DNA elements
Genetic barcodes	It makes synthetic genes easily traceable	More likely to be lost during recombination

Source: Authors' compilation

However, some limitations are associated with the strategies mentioned above, for which several complement methods are being explored. Other biosafety measures that three European Scientific Committees (SCENIHR, SCHER, and SCCS) proposed include:

- Development of computational tools to predict the properties of synthetic organisms.
- Adopting a standard method for data submission related to genetic modification to risk assessors.
- Approval of the GMOs with proven safety records.
- Framing the regulatory guidelines in parallel with technological advancement (SCENIHR, SCHER, and SCCS, 2015).

Table 2: Agencies dealing with the approval of GMOs in India.

Committees	Constituted by	Role	Regulatory approvals
RDAC	DBT	Submits recommendations on safety regulations of GMOs	It is an advisory committee.
RCGM	DBT	Looks after safety aspects of genetically engineered organisms	Group II, III- Plants Group I, II, III- Animals
IBSC	Research organisation	Handle on-site emergency plans and ensures the safety aspects in addition to progress in research	Group I- Plants Group I, II, III – Animals/human stem cells
GEAC	Ministry of environment and forest	Involve in approval of large scale use of GMOs in research, industrial production and application	Group II, III- Plants Group I, II, III- Animals/human stem cells
SBCSS	State level- headed by the chief secretary of state	Inspect, investigate and take punitive action in case of violation of statutory provisions	Involved in monitoring
DLC	District level- headed by the district collector	Monitor the safety regulations in installations for the use of GMOs in research and application.	Involved in monitoring

Source: Authors' compilation

Governing agencies in India

The regulatory consideration for genome-edited organisms in India depends on the extent of modification introduced and the risk associated with the resultant product. Three risk categories are recognised based on risk assessment (Barse and Yazdani, 2020):

Group I: Single or few base pairs edited, leading to low complexity.
Group II: Several base-pair edited leading to complex genotype.
Group III: Insertion of foreign gene sequence leading to highly complex genotype.

For regulatory approvals regarding the research dealing with GMOs, six competent committees are currently working in India: 1. The Recombinant DNA Advisory Committee (RDAC), 2. The Review Committee on Genetic Manipulation (RCGM) 3. Institutional Biosafety Committee (IBSC) 4. Genetic Engineering Approval Committee (GEAC) 5. State Biotechnology Coordination Committee (SBCC) 6. District Level Committee (DLC). Their role and regulatory framework are described in Table 2. The granting of approvals by the committees mentioned above are based on the purpose of approval, the extent of modification introduced, and the risk level of the resulting product (Chimata & Bharti, 2019).

Besides the national level regulatory agencies, India is a member of CBD and a signatory to CPB and Nagoya Protocol. As a member of CBD, India is committed to taking necessary steps to regulate GMOs as and when required (Ahuja, 2018).

Apart from these measures, what India needs to adopt is:

- Establishment of an independent authority for decision making with all the stakeholders involved in the decision-making process to avoid biases.
- Framing regulatory guidelines and funding policies to promote security. The guidelines should also incorporate measures such as raising awareness, education and training.
- Censorship of the content that can be potentially misused.
- Proper control and record of the synthesis and distribution of genetic sequences.
- Pre-preparation to deal with adverse outcomes.

Conclusion and Recommendations

Synthetic biology is a two-edged sword that has the immense potential to do great good or great harm. It is an emerging interdisciplinary field aiming to address health, energy or environmental issues. However, the breakthroughs

in the field have raised various biosafety, biosecurity, bioterrorism and bioethical issues. Further, the current pandemic situation has also placed synthetic biology in the dock of public concerns. Although synthetic biology is a new field, the regulatory framework of recombinant DNA technology can be useful in certain instances of synthetic biology to begin with. The primary international forum contemplating synthetic biology is the CBD, with its associated agreements. Other agencies regulating synthetic biology include United States federal regulations, EU directives and regulations, BWC and the Australian group guidelines.

India harbours considerable potential in both terrestrial and marine synthetic biology owing to its rich biodiversity and extensive coastline. On current trends, India needs to boost its synthetic biology sector and invest equally in biosafety and biosecurity aspects to maintain balance in the development process of the field of synthetic biology.

- The government organisations such as DST, DBT, ICMR should take the initiative to define synthetic biology and track the status of research vis-à-vis advancements, bottlenecks and potential risks and challenges.
- The government should develop policies to promote commercialisation of synthetic biology-based products and address public concerns regarding the safety of the products.
- Workshops and conferences by stakeholders from academia, industry and government should discuss strategies and regulations for biosecurity surveillance and risk management.

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DNA Data Storage and Access and Benefit-Sharing: Testing the Limits of the Term "Genetic Resources" for Synthetic Biology

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Abstract: With the increased rate of data collection, there are growing problems with how to efficiently and economically store that data. DNA data storage is an option that seemed untenable until recent improvements in the ability to read, write and store data in synthetic DNA molecules. There is growing interest as to how the international access and benefit-sharing (ABS) regime created under the United Nations' Convention on Biological Diversity (CBD) and its associated Nagoya Protocol will apply to synthetic biology, but the discussions have so far only dealt with artificially modified genetic resources that have a natural precursor from the environment. This is the first exploration as to whether ABS policies can be applied, or are likely to be applied, to purely synthetic DNA molecules that have been synthesised with the sole purpose of storing non-biological data.

Keywords: DNA Data Storage; Synthetic Biology; Access and Benefit-Sharing; Convention Biological Diversity; Nagoya Protocol; Biological Diversity Act, 2002 (India)

Introduction

The *Convention on Biological Diversity* (CBD) was one of three international environmental agreements to come out of the United Nations Rio Earth Summit in 1992 (Secretariat CBD 2005). The CBD was originally designed, in part, to regulate bioprospecting activities. Contracting Parties were obliged to implement legislative, administrative and policy measures for collecting and using genetic resources from the environment and to share the benefits associated with the use of those genetic resources with the country of origin (Humphries *et al*. 2021). This is a policy known as access and benefit-sharing (ABS), designed as a financial mechanism to generate benefits (monetary and non-monetary) to be channelled into environmental

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conservation efforts and sustainable development (the "grand bargain": Wynberg & Laird, 2009). ABS applies to genetic resources – the "functional units of heredity" (CBD, Article 2) to facilitate access to those resources in exchange for sharing the benefits (CBD, Article 15) – used specifically for their genetic componentry in scientific research and development. In this context "genetic resources" are essentially biological materials with genetic components like genes, proteins and cells, but the term does not apply to natural resources when used as bulk products or food stuffs (Ad Hoc Open-Ended Working Group on Access and Benefit Sharing, 2010). In 2010, the Conference of the Parties to the CBD adopted the *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation* (Nagoya Protocol) that provides further details about the ABS policy process and guidance for Contracting Parties to implement in their domestic ABS legislative, administrative and policy measures.

The CBD and Nagoya Protocol were originally negotiated with physical genetic resources in mind (see Lawson *et al*., 2020). There are currently negotiations at the CBD and other international forums that deal with ABS (including the Food and Agriculture Organization of the United Nations' *International Treaty on Plant Genetic Resources for Food and Agriculture* and the World Health Organization's *Pandemic Influenza Preparedness Framework* (PIP Framework)), about the applicability of ABS to digital sequence information (DSI) derived from physical genetic resources (Laird & Wynberg, 2018; Lawson *et al*., 2020). ABS policies are shifting their focus on tangible (physical) genetic resources to the intangible (informational) aspects of genetic resources at the same time the biological sciences are growing more reliant on advances in big data, information technology and computing power. As benefit-sharing obligations are now attached to research and development activities far removed from the sorts of bioprospecting activities that the negotiators of the CBD originally envisaged (see Laird *et al*., 2020), it is important to consider if and how ABS policies apply to synthetic genetic resources. In technological fields, like synthetic biology, "the uncertain zone of words and criteria used as triggers for [benefit-sharing] obligations will tend to be greyer and greater" (Tvedt, 2021: 88). The limits of ABS policies are undefined, making navigating those policies difficult for synthetic biologists.[1] The purpose of this article

is to determine whether the international ABS regime as provided for by the CBD and its Nagoya Protocol applies to the branch of synthetic biology that focuses on storing non-biological data in DNA molecules: DNA data storage. This is important as the increased rate of data collection raises the growing problem of how to economically and efficiently store that data. DNA data storage is an option that seemed untenable until recently. Synthetic biology, however, delivering improvements in the ability to read, write and store data in synthetic DNA makes the DNA molecule as a data storage medium feasible.

For the purposes of this article, it is conceptually useful to think of genetic resources as existing on a spectrum from "natural" at one end to "synthetic" on the other. We can consider that wild-type genetic resources collected directly from the environment sit at the natural end of the spectrum. Those same genetic resources taken from the environment and later artificially modified in the laboratory at one or two nucleotide sites can be considered to exist somewhere further along that spectrum, moving towards the synthetic end. If we were to move further towards the far synthetic end of the spectrum, we might start to see innovations such as synthetic cells where the degree of human intervention to make the novel lifeform is high. The existing literature on the applicability of ABS to synthetic biology has focused on these types of resources: genetic resources where, even with artificial genetic modification, the modified product can still be traced back to one or more wild-type genetic resources once taken from the environment (see, e.g., Rourke, 2021). There has been little discussion as to whether ABS obligations could exist for purely synthetic constructs that do not have a precursor genetic resource found in nature. This is an important question for synthetic biologists because it provides insights as to the level of modification required before ABS obligations no longer apply. Where on the spectrum from natural to synthetic can ABS policies reach? On our theoretical spectrum of genetic resources, the DNA molecules synthesised for the purposes of storing data would sit at the very far synthetic end of our natural to synthetic genetic resources spectrum. The applicability of the international ABS regime to DNA data storage has been hinted at by Bond and Scott (2020: 30), but has not yet been investigated. In trying to determine the theoretical limits of the applicability of ABS regulations to synthetic biology, it is worth examining whether its reach extends to DNA

data storage, at the extreme synthetic end of the spectrum.

This article explores whether ABS policies and regulations can be applied, or are likely to be applied, to purely synthetic DNA molecules that have been synthesised with the sole purpose of storing non-biological data (such as an algorithmically coded music file or a text file). It will first explain what DNA data storage is and briefly outline the developments in this fast-growing branch of synthetic biology. We will then outline the objectives of the CBD and analyse whether the definition of "genetic resources" under the CBD (and adopted by the Nagoya Protocol) could be interpreted to include purely synthetic DNA constructs designed for the sole purpose of storing non-biological data, and whether the term "utilisation" could cover the use of such constructs. The article concludes with an examination of Indian ABS legislation to see what this can tell us about the theoretical regulation of DNA data storage technologies in India. Subject to further clarification from the Indian government, it may be argued that purely synthetic DNA storage molecules fall within the scope of "biological resources" under the *Biological Diversity Act, 2002*, under certain circumstances. This case study shows that while ABS laws *can* be applied to synthetic DNA constructs used to store data, it is not necessarily an appropriate regime to manage this emerging technology or its products.

DNA Data Storage

The growing demand for data storage will eventually exceed the capacity of traditional digital information storage media (Dong *et al*., 2020 and Panda *et al*., 2018). The mining of silicon used in computer chips has negative environmental impacts and the magnetic tapes currently used for data archiving have a limited shelf life (Panda *et al.*, 2018). Furthermore, both silicon chips and magnetic tape have capacity (or storage density) limits. Other forms of data storage, such as paper, while extremely successful lack an efficient recovery mechanism and involve high maintenance costs.

One possible solution for addressing data capacity shortages in the future is DNA data storage. Deoxyribonucleic acid (DNA) is the organic molecule that has stored the genetic code of biological (living) organisms for billions of years. Scientists have been able to sequence DNA molecules that are hundreds of thousands of years old, demonstrating how robust this form

of information storage can be, even in imperfect preservation conditions (Panda *et al*., 2018). In terms of storage density, it is estimated that "all the information ever produced by [hu]mankind" could be stored in "just a few grams of DNA" (Panda *et al*., 2018: 8). It is also extremely energy efficient compared with modern storage media (Lee *et al*., 2020). With the formation of the *DNA Data Storage Alliance* (DDSA) in November 2020, "a coalition of computing and biotech firms including Microsoft, Twist Bioscience, Illumina and Western Digital" (Vitak, 2021), it is clear that industry is starting to see the commercial potential of DNA as a data storage medium.

The "information" stored in DNA is gleaned from the way that the A, G, T and C nucleic acid bases (nucleobases) are arranged within the DNA molecule. This is the genetic code required for a cell to transcribe the specific stretch of DNA into RNA, and then translate that RNA into a protein (the "sequence hypothesis" of biology) (Crick, 1970). The arrangement of these nucleobases is unique to each organism and the complement of this information (genome) is required, together with other environmental information, for organisms to grow and recreate themselves. Since the 1970s, the ways scientists have learned to isolate, read, amplify, modify, and synthesise stretches of DNA have become more efficient. It is now possible to read the sequence of nucleotides in a DNA molecule relatively quickly and cheaply, and to turn digital sequences of As, Gs, Ts, and Cs on the computer back into physical DNA molecules (Carmean *et al.*, 2019). This can be expected to become increasingly easier and more efficient. Thus, we have the basic tools required to store information as a physical DNA molecule and access and read that information out again as required (Carmean et al., 2019).

To store information in DNA, text, images, sound or video files for example, the information is first turned into binary (or other types of) code. That data can be compressed using compression algorithms which increases the amount of data that can be stored in a given stretch of DNA. Binary data could be coded in DNA with each of the 4 nucleobases representing 2 bits of binary data (e.g., G = 11, T = 00, A = 10, and C = 01), although other coding schemes can be used to turn various data into certain arrangements of bases (Dong *et al*., 2020). There are strengths and weakness for each coding scheme, and each will produce DNA molecules with different physical characteristics (see e.g., Dong *et al*. 2020: 1099). The DNA strands

with the desired sequence of As, Gs, Ts and Cs are synthesised as a chain of nucleobases (oligonucleotides) and can be stitched together using molecular assembly techniques to make longer strands of DNA. These DNA molecules can later be read using high-throughput genetic sequencing (Lee *et al*., 2020) and algorithmically decoded to retrieve the information contained therein.

Storing the same data on multiple DNA molecules creates physical redundancy, ensuring that if there are any errors, such as insertions, deletions or base pair mismatches, it is possible to detect errors upon data retrieval (Carmean *et al.,* 2019). An index is included on the DNA molecule, providing the location details as to where certain information is stored. The DNA can be stored *in vivo* or *in vitro*. An example of *in vivo* storage is where the DNA molecule incorporated into the genomes of living bacterial cells which have a "surprisingly large tolerance" for the insertion of foreign DNA (Dong *et al*., 2020: 1103). An example of *in vitro* storage is having the DNA molecule encapsulated in silica (Grass *et al.*, 2015), which, if kept at low temperatures is estimated to keep the DNA molecule viable for millions of years. The immense storage density of DNA means that the stored DNA takes little physical space and optimal environmental conditions are therefore easy to maintain.

DNA data storage has some shortcomings. At this stage, the process of storing and retrieving data is not remotely user-friendly. It is time consuming and requires a high degree of training and technical know-how. These problems are not likely to change in the near future. The other problems of DNA data storage are high error rates and high costs (Tabatabaei *et al*., 2020). As the technology improves, both of these problems are likely to be mitigated, making DNA data storage a viable solution for single use (non-modifiable), long-term data storage that does not require frequent access, such as archival records.

The field of synthetic biology is at an early but growing phase in India, with multiple government initiatives supporting relevant training and providing funding for synthetic biology projects across a range of industries, in both public and private arenas (Barse & Yazdani, 2020; 569-570). While India is not presently known as a leading country in DNA data storage, it certainly has the capacity to conduct all the steps required to store and retrieve data in DNA molecules (Rerimassie, *et al.*, 2015). As it moves from the realm of science fiction to reality (Vitak, 2021), DNA data storage

technology could test the limits of what the CBD and Nagoya Protocol, as well as what their domestic implementing legislation can apply to. That is, whether countries claim sovereign authority over a genetic resource that is entirely synthetic, and regulate it in accordance with its national and subnational ABS legislative, administrative or policy measures? The following section examines the definitions of "genetic resources" and "utilisation" in the CBD and Nagoya Protocol to determine if DNA data storage can be regulated under the international regime on ABS. We then examine Indian ABS legislation as a case study of how domestic ABS laws may be applied to the molecular product formed through the process of DNA data storage within national territories. India ratified the CBD in 1994 and established its National Biodiversity Authority under the Ministry of Environment and Forests in 2003 "to facilitate, regulate, and advise the government on conservation, the sustainable use of biological resources, and fair and equitable sharing of benefits arising out of the use of those resources" (Barse & Yazdani, 2020; 274). It is a useful case study for DNA data storage because of the range of biological resources, associated information and activities that fall within scope of its ABS obligations.

Are data stored in DNA "genetic resources" for the purposes of ABS?

The three objectives of the CBD "are [1] the conservation of biological diversity, [2] the sustainable use of its components and [3] the fair and equitable sharing of the benefits arising out of the utilisation of genetic resources" (Art 1). Access to genetic resources and the fair and equitable sharing of benefits associated with their use (termed ABS) is the policy that comes out of the third objective of the CBD and is linked to the first two. Its parameters come from Article 15 of the CBD, which states (in summary) that countries have sovereign authority to determine access to their genetic resources, subject to national legislation (Art 15.1). Parties wishing to access sovereign genetic resources must do so with the prior informed consent of the country of origin (Art 15.5) (or other authorised provider, Art 15.3) unless otherwise determined by the provider country, and come to mutually agreed terms (Art 15.4) about the sharing of benefits associated with the use of those genetic resource (Art 15.7). ABS was designed as a transactional mechanism to generate benefits from the use of genetic resources in order

to channel those benefits into conservation and sustainable use measures and ensure that those same genetic resources would be available to future generations for access and use. The CBD provided scant details about how to implement ABS measures within domestic legislation. To address this, at least in part, the Nagoya Protocol provides more details of the ABS mechanisms for contracting parties, including National Focal Points and National Competent Authorities to set standards and settle processes (Art 13), more formalised compliance measures (Arts 15 and 16) and monitor uses (Art 17). The Nagoya Protocol's scope for genetic resources is taken from Article 15 of the CBD (Nagoya Protocol, Art 3) and provides further relevant details including clarifying that "utilisation" of genetic resources "means to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology" (Nagoya Protocol, Art 2).

The CBD defines "genetic resources" as "genetic material of actual or potential value" (Art 2). "Genetic material" is further defined as "any material of plant, animal, microbial or other origin containing functional units of heredity" (Art 2). The Nagoya Protocol takes its relevant definitions from the CBD, but also defines a new term "derivative" to mean "naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity" (Nagoya Protocol, Art 2). The focus of the text in both the CBD and Nagoya Protocol is the physical material of genetic resources and genetic material and this is at the heart of the current debate on DSI at the CBD and other forums (see, e.g., Lawson *et al*., 2020). Our focus in this article is not about the informational dimensions of genetic resources (and the DSI debates), but instead, whether the synthetically produced physical DNA molecules used to store non-biological information can also be considered genetic resources under the CBD and Nagoya Protocol for the purposes of ABS. In this sense it is the physical DNA molecules and not the stored non-biological information that is our focus.

At first glance, it may seem that the environmental conservation and sustainable use objectives of the CBD would mean that it cannot apply to synthetic DNA created for the purposes of data storage. It could be argued that the purpose of ABS is to contribute to the attainment of the other two objectives of the CBD (conservation and sustainable use) and that DNA

data storage molecules are not the sort of genetic resource that the CBD and Nagoya Protocol sought to protect. However, this argument arose in 2007 when the CBD was applied to samples of human pathogens (Sedyaningsih *et al*., 2008). Critics of this stance stated that pathogens "are not the kind of biological and genetic resources that CBD sought to protect and regulate through the principles of sovereignty, prior informed consent, and mutual benefits from access and exploitation" (Fidler, 2008: 90). This argument did not convince Member States of the World Health Organization, with the World Health Assembly passing a resolution in 2011 implementing a multilateral agreement for accessing pandemic influenza virus samples and sharing the benefits associated with their use, such as vaccines and antivirals (PIP Framework, 2011). The PIP Framework "recognize[d] the sovereign right of States over their biological resources" and regulated human pandemic influenza viruses accordingly (PIP Framework, 2011; Art 1.11). Multiple parties to the CBD have included pathogens in their domestic ABS measures,[2] indicating that conservation and sustainable use are not necessary requirements for the regulation of genetic resource through ABS policies (most would prefer to eradicate disease rather than conserve it). Additionally, analysis of the negotiation process of the Nagoya Protocol has shown that conservation and sustainable use was a 'nice to have', but not a necessary requirement for the implementation of domestic ABS measures (Sirakaya, 2021).

Therefore, for our purposes, the notion of whether synthetic physical DNA molecules for data storage is included within the global regime on ABS hinges on the definition of the term "genetic material", and the text that includes the phrase "other origin". Gerd Winter has posed the question "is any new genetic resource the 'property' of the state?" (Winter, 2016: 206). His conclusion is that because of the presence of the term "other origin" in the definition of "genetic material", the state *does have* sovereign rights over "new creations" (Winter, 2016: 206). Indeed, the term "other origin" could certainly be interpreted to include a laboratory origin. However, in his discussion, it is clear that his conception of "new creations" is still the artificial modification of existing genetic resources.[3] In her discussion about DNA componentry used in synthetic biology to assemble synthetic biological devices and machines, Michelle Rourke (2021) showed

that even when natural genetic resources are fragmented "into their smallest functional units to create standardized, interchangeable 'bioparts', the building blocks for assembling synthetic biological devices", they can still be considered genetic resources for the purposes of ABS (Rourke, 2021: 1). The current negotiations about DSI have shown that the term "genetic resources" can be, and has been, applied to genetic sequence data (Lawson and Rourke, 2020). Perhaps this analysis overlooks the important temporal element. All genetic resources were new at some time, and drawing a distinction between *old* new creations and *new* new creations seems artificial and abstracted. Again, though, we are still discussing the applicability of ABS regimes over objects that can be traced back to a natural origin, whether that is a biopart such as a promotor, terminator, protein coding sequence, and so on, that is a modified version of a natural analogue, or whether it is a genetic sequence derived from a physical genetic resource. These have a link to the natural world with varying degrees of affinity. Our question is whether the state can claim sovereignty over a completely new construct, not just an artificially modified genetic resource that can ultimately be traced back to a physical (old) genetic resource sourced from nature. Would a purely synthetic strand of DNA, made using the sequence of nucleobases algorithmically determined to store certain non-biological data, be considered a genetic resource in accordance with the CBD's definition, and therefore subject to the ABS legislative, administrative and policy measures? Yes and no depending on temporal ideas about old and new genetic resources and whether the nation state of origin (or fabrication) decides to include such material within its definitions.

Then we are left to deal with the final qualifier contained in the definition of genetic material: "containing functional units of heredity" (Art 2). At the time of the CBD's writing, this term was inferred to mean genes in the sense of a linear coding region with a regulatory sequence (Tvedt & Schei, 2013). However, since the late 1980s and early 1990s when the CBD was negotiated, it has become clear that the functional regions of genomes are not limited to the open reading frames for RNAs and proteins. Benefit-sharing obligations can certainly apply to genetic material that does not, in the

strictest sense, contain a gene. The inclusion of the term "derivative" in the Nagoya Protocol clarified that the international regime on ABS could indeed apply to compounds "even if it does not contain functional units of heredity" (Nagoya Protocol, Art 2). DNA data storage molecules are functional in the sense that they have a use. Data stored in a DNA molecule is also capable of being amplified (replicated) by human intervention (PCR), and if stored *in vivo,* in bacterial genomes for example, it is also capable of being replicated organically. The data stored in the DNA exists then as both the template and the copy, the replicant and the replicated; and the data stored is heritable. Therefore, we can see that it is possible to interpret the term "containing functional units of heredity" as being applicable to DNA molecules that are synthesised for the purposes of storing non-biological data. Thus, all the criteria are met for qualifying DNA data storage molecules as "genetic resources" for the purposes of ABS.

This is an interesting exercise, but all of the discussion about definitions is possibly a moot point. The ABS provisions of the CBD and Nagoya Protocol provide "only floors – minimum obligations – and not ceilings" (Bagley, 2015: 8), meaning countries have "the sovereign right to exploit their own resources pursuant to their own environmental policies" (CBD, Art 3). Countries can claim sovereignty over and regulate the use of whatever genetic resources (and whatever they determine to be genetic resources) they want, whether they are wild-type natural genetic resources sourced directly from their jurisdiction, or purely synthetic DNA molecules that store data, synthesised within their jurisdiction, even if these DNA molecules have no discernible link to the (past) natural world.

The question then becomes whether or not states *should* exercise their sovereignty through the application of ABS regulations. In his discussion about artificially modified genetic resources, and the hypothetical "if a German researcher applying synthetic biology methods constructs a new microorganism in a Brazilian laboratory, has Brazil sovereign rights to regulate the access and utilisation of this organism", Winter states that it would be unwise for countries to claim sovereignty and apply ABS regulations to new creations (Winter, 2016: 206). He accepts that states can assert sovereignty

("state has indeed sovereign rights over those new creations") and does not then provide reasons why he does not consider states should assert sovereignty (Winter, 2016: 206). The regulation of artificially modified genetic resources that can be traced back to natural resources through ABS policies have a tenuous link to the objectives of the CBD. This is an issue that is currently being explored in the negotiations over DSI, where natural genetic resources have been transformed into "widely accessible virtual resources that are practically de-linked from their origins" (Oguamanam, 2019: 196), potentially undermining the ABS policies that have largely focused on the regulation of physical genetic resources found in nature. However, it is much harder to see how data stored in DNA might be useful to the CBD's first two objectives: the conservation of biological diversity and the sustainable use of its components. The third objective, the fair and equitable sharing of benefits associated with the use of genetic resources is indeed connected and important.

There are other reasons why a country may wish to regulate artificial genetic constructs created for the purposes of DNA data storage. Benefit-sharing obligations attached to the use of such DNA molecules may create opportunities for capacity building and technology transfer, however, the sorts of countries that will be leading the charge on DNA data storage are the countries that already have the technology and know-how. There would be little need to seek capacity building through ABS. Requiring benefit-sharing for the use of data stored in DNA may help with the costs of maintaining DNA storage libraries and accessing data from stored DNA molecules. Though this would likely be conducted as a commercial transaction, as opposed to an ABS agreement between the country of origin and the user party, as envisaged by the CBD and Nagoya Protocol. It is worth keeping in mind that the data stored in DNA may be subject to other laws and policies, such as personal privacy, national security, and intellectual property laws. The growing movement for data sovereignty (see e.g. Oguamanam, 2019) means that there are other ways for countries to claim sovereignty over the data stored within a synthetic DNA molecule (as opposed to exercising sovereignty over the molecule itself). Furthermore, if the information being stored is

about a biological resource, that information may itself fall within the scope of the term "genetic resource" under ABS rules.

Indian ABS legislation and DNA data storage

Processes and products derived from synthetic biology techniques are subject to a range of regulatory frameworks in India, including biosafety, food safety and weapons legislation.[4] After ratification of the CBD in 1994, India's central government developed a comprehensive ABS framework under the *Biological Diversity Act, 2002* (BD Act), which provides for the conservation of biodiversity, sustainable use of its components and fair and equitable sharing of the benefits arising from the use of "biological resources, knowledge and for matters connected therewith or incidental thereto" (BD Act, Preamble). Two years later, India's central government passed the *Biological Diversity Rules 2004* (BD Rules), which prescribed more specific procedures for approvals and criteria for equitable benefit sharing, among other things. Following India's ratification of the Nagoya Protocol in 2012, the central government passed the *Guidelines on Access to Biological Resources and Associated Knowledge and Benefits Sharing Regulations* 2014 (BD Regulations) to bring the ABS framework into line with its international obligations. Indian States have implemented State Rules which prescribe rules for notification requirements and management of the Local Biodiversity Fund among other things.[5] The ABS framework is implemented by three tiers of government – the National Biodiversity Authority (national level), State Biodiversity Boards (State level) and Biodiversity Management Committees (local level) (Indian Government, 2017).

The Indian ABS framework applies broadly to "biological resources". These are defined as "plants, animals and micro-organisms or parts thereof, their genetic material and by-products (excluding value added products) with actual or potential use or value, but does not include human genetic material" (BD Act, s 2(c)). The framework does not include a definition of genetic material, although "value added products" means "products which may contain portions or extracts of plant and animals in unrecognisable and physically inseparable form" (BD Act, s 2(p)). The National Biodiversity Authority has provided little clarity about the meaning and examples of "value added products", other than to repeat the definition.[6] However, the

definitions of "biological resources" and "value added products" appear to imply a distinction between products created through human intervention, which may be unrecognisable from the original biological form and do not fall within scope, and by-products that may or may not be created through human intervention but which are derived entirely from natural processes. Subject to further clarification from the Indian government, it may be argued that purely synthetic DNA storage molecules are outside scope of "biological resources" and the BD Act's ABS obligations, unless they have recognisable biological origin. One may argue, however, that the starting point of a "value added product" is a plant or animal, which is not the case for purely synthetic DNA molecules storing non-biological data.

The Indian ABS framework is prescriptive about the types of use and activities that attract ABS obligations, depending on whether the activity is undertaken by Indian citizens/organisations or those that are not (non-Indians). In addition to the transfer of research results (BD Act, s 4) and applying for intellectual property (BD Act, s 6), activities captured by ABS obligations include:

Research, which means "study or systematic investigation of any biological resource or technological application that uses biological systems, living organisms or derivatives thereof to make or modify products or processes for any use" (BD Act, s 2(m)).

Commercial utilisation, which means "end uses of biological resources for commercial utilisation such as drugs industrial enzymes, food flavours, fragrance, cosmetics, emulsifiers, oleoresins, colours, extracts and genes used for improving crops and livestock through genetic intervention, but does not include conventional breeding or traditional practices in use in any agriculture, horticulture, poultry, dairy farming, animal husbandry or bee keeping" (BD Act, s 2(f)).

Bio-survey and bio-utilisation, which means "survey or collection of species, sub-species, genes, components and extracts of biological resource for any purpose and includes characterisation, inventorisation and bioassay" (BD Act, s 2(d)).

Arguably "research" may capture the process of storing data in a DNA molecule or of retrieving and using data stored in a DNA molecule, if that DNA molecule is classified as a "biological resource" or "derivative

thereof". "Bio-survey and bio-utilisation" could include a range of testing and monitoring activities relating to data stored in DNA molecules. DNA molecules as a commercial product might fall within the definition of "commercial utilisation", which has a non-exclusive list of end uses. Again, these uses would depend on the classification of synthetic DNA molecules as a "biological resource", "derivative thereof" or a "value added product".

Non-Indian persons and entities must obtain prior approval of the National Biodiversity Authority to "obtain any biological resource occurring in India or knowledge associated thereto for" the commercial and non-commercial activities above (BD Act, s 3). On the other hand, Indians (persons and organisations) must only give "prior intimation" to the State Biodiversity Board "to obtain any biological resource for commercial utilisation, or bio-survey and bio-utilisation for commercial utilisation" (BD Act, s 7). In other words, prior intimation is not required for research activities and non-commercial uses by Indian people and entities.

The different rules for authorisation between Indians and non-Indians could be significant for synthetic biology research and development. While the rules relating to Indians outlined above only relate to "biological resources", those relating to non-Indians relate to "biological resources *or knowledge associated thereto*" for the relevant activities (emphasis added). In *India's submission on Digital Sequence Information on Genetic Resources in response to CBD notification 2019-012 dated 5 February 2019 pursuant to decisions 14/20 and NP-3/12*, the government clarified that while India's ABS legislation:

do not include explicit reference to DSI or any such terminology, the relevant provisions in the Act can cover in their scope the utilization of DSI. For example, the term research as defined in Section 2 would cover DSI. Similarly, the requirement prescribed in Section 6 which refers to 'information on biological resource' would cover DSI ("Indian Government 2019: 3").

Subject to clarification from the government, this might mean that Indians would not be subject to access authorisations for research relating to DNA data storage (because they do not require authorisation for "research"). However, if an Indian person or organisation wishes to apply for intellectual property for an invention based on "research or information

on a biological resource obtained from India", then they must obtain the prior approval of the National Biodiversity Authority before making an application (BD Act, s 6). On the other hand, arguably any research, development and commercialisation activity in India relating to DNA data storage that meets the subject matter and activity definitions by a non-Indian person or organisation could be subject to ABS obligations. The complexity and uncertainty of whether or not DNA data storage might be captured, demonstrates the challenges that potential developers and users of these technologies have about understanding their obligations. In the end, it will be up to governments to advise in a given case whether or not their legislative and policy frameworks apply.

Discussion

The analysis, so far, shows that the definitions of genetic resources in both CBD and Nagoya Protocol can include physical DNA molecules holding data because synthetic DNA could be both a "genetic material" of "other origin" and "contain[] functional units of heredity" (Art 2). As such, and as states have sovereignty over their genetic resources, it is a matter for the state to determine whether their ABS legislative, administrative and policy measures can and should apply to any newly created DNA molecules storing data. The analysis of India's BD Act reveals first that DNA data storage is not an obvious fit with the current framework because the term "biological resources" (BD Act, s 2(c)) requires a tortured interpretation to include data storage DNA. Secondly, if a specific circumstance of DNA data storage were to fall within scope, different rules for authorisation for Indians and non-Indians may apply depending on what activities are being conducted. This brief analysis clearly shows that if states were to embrace synthetic DNA molecules in their ABS legislative, administrative and policy measures then they will probably require, like India under the BD Act, a reconsideration of how the ABS measures should apply. This perhaps addresses a broader question about ABS and whether the CBD and Nagoya Protocol are the appropriate regulatory regime for synthetic DNA constructs and perhaps synthetic biology more broadly. This involves addressing some more fundamental policy questions.

What is the purpose of ABS? While it is possible for nations to claim sovereignty over whatever genetic resources they like, whether natural

or purely artificial, the application of ABS regulations to purely artificial constructs do not apparently contribute to any of the objectives of the CBD. Recall the policy objectives of the CBD and Nagoya Protocol are both conservation *and* sustainable development (CBD, Art 1; Nagoya Protocol, Art 1). While conservation has not been the main focus of ABS to date (Lawson and Pickering, 2021), the ideals of sustainable development are increasingly important and a significant mandate for many states negotiating and adopting the CBD as environmental regulation attempting to balance their "ecology" and "economy" (see Brand *et al.*, 2008: 54). The current United Nations *Sustainable Development Goals* (SDGs) embracing the diverse and current social and environmental concerns seek to balance economic, social and environmental dimensions including ending poverty and hunger, protecting the planet from degradation, harmonizing economic, social and technological progress with nature, and addressing the needs of the poorest and most vulnerable (UNGA, 2015). This means "[d]evelopment that meets the needs of the present without compromising the ability of future generations to meet their own needs" (World Commission on Environment and Development, 1987: 37) through maximising environmental, economic and social systems (see Barbier, 1987). There appears here a clear link between the CBD (and Nagoya Protocol) aspiring to sustainable development and embracing developments that engage genetic resources. Recall that CBD expressly defined "biotechnology" to mean "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" (Art 2), and that this was, in part, necessary to "make use of genetic resources" (Art 16.1). As such, the purpose of ABS is both conservation and sustainable development. And in that context the embrace of newly created DNA molecules as data storage might be framed as genetic resources and included within a state's ABS legislative, administrative and policy measures, particularly if the data stored is related to biological resources or the conservation of biological diversity. If this is accepted, then including purely synthetic DNA molecules storing non-biological data may be desirable.

Perhaps a more important policy question for our purposes is whether ABS is an appropriate way to regulate DNA data storage or some other aspects of synthetic biology? While a state's ABS legislative, administrative and policy measures might be appropriate, there are other regulatory

frameworks that will apply. These include the regulation of genetic manipulation laws and intellectual property. Presumably because synthetic DNA molecules holding data will involve some kind of making, storing and later reading, then the DNA molecules will be subject to laws addressing both the application of the relevant DNA manipulation techniques and the places where those activities might be carried out. In India the *Environment (Protection) Act, 1986* provides for certain rules (ss 6, 8 and 25). Under this power the "Rules for the manufacture, use, import, export and storage of hazardous microorganisms, genetically engineered organisms or cells, 1989" have been notified and these establish a framework for the places and products of biotechnology including "the application of the gene technique called genetic engineering" (s 3). Again, like the BD Act, these rules may require modification to properly and specifically address making and using synthetic DNA molecules holding data. The framework does, however, reveal that these kinds of activities are subject to forms of regulation, and where this includes placing these molecules into organisms then there is a complex form of regulation about their import, export, transport, manufacture, process, use and sale (s 7), and a further series of guidelines addressing contained research, biologics, confined field trials, food safety assessment, environmental risk assessment, and so on. Depending on the ways these laws are applied there is the potential to permit and promote particular kinds of activity within an economy.

Under India's intellectual property laws, DNA molecules holding data will potentially be subject to copyright under the *Copyright Act, 1957* (Copyright Act) and intention under the *Patents Act, 1970* (Patents Act). Under the Copyright Act, for example, a DNA molecule might be characterised as a "literary work" that will include "computer programmes, tables and compilations including computer databases" (s 2) or a "computer programme" means "a set of instructions expressed in words, codes, schemes or in any other form, including a machine readable medium, capable of causing a computer to perform a particular task or achieve a particular result" where "computer" means "any electronic or similar device having information processing capabilities" (s 2). As such, copyright will automatically subsist in the literary work (s 13(1)) and will be subject to the exclusive rights that include copy, make, translate, adapt, and so on (s 14). Under the Patents Act the issues are less certain for DNA where natural

DNA sequences appear to be limited (see s 3(c)), while synthetic sequences are certainly patentable as an "invention" being "a new product or process involving an inventive step and capable of industrial application" (s 3(j)). After a grant for such an invention of a new DNA molecule (with a unique arrangements of nucleotides) (s 47), the exclusive rights are to making, using, offer for sale, selling or importing of the molecule (s 48). As this brief survey illustrates, the ways these laws are applied has the potential to permit and promote particular kinds of activity within an economy and promote commercial exploitation and advantages.

It seems unlikely that even if countries determine that they have sovereignty over these resources, that they would then choose to regulate purely synthetic DNA molecules storing data and the associated information under an ABS scheme. It could happen, but it is unlikely because these molecules, even if they meet the definition of genetic resources and/or genetic material in accordance with the CBD (and therefore the Nagoya Protocol), probably fit better within other data schemes. ABS is essentially a scheme that applies to downstream uses of a genetic resource and might usefully apply to users of DNA molecules rather than the makers – users under ABS schemes generally want the DNA molecules so as to reveal what unknown information is in the DNA molecules held by someone else, while DNA storage addresses information coded in the DNA molecule where the user already knows the information and the molecule is about storing the information. A more likely and suitable scheme would be directed to the owners of the information (those with a lawful claim to use the information) that will be coded in the DNA molecule and they will probably want to have control over the DNA molecule *and* the information probably including the kinds of exclusive rights available under copyright laws (such as copy, make, translate, adapt, and so on). As India has demonstrated with its *Protection of Plant Varieties and Farmers Rights Act, 2001* there is the potential to develop *sui generis* intellectual property laws suited to particular domestic intellectual property requirements, such as farmers variety rights that protected specific varieties of plants with tailored exclusivity (see Trustum-Behan and Lawson, 2016). Applying the same reasoning and an acute awareness of the specific state circumstances, then developing new laws might be better than retrofitting existing schemes, which the analysis here shows would be likely necessary. There is still, however, a great deal

of work to be done by policy-makers and legal scholars to work out where DNA data storage fits within the existing legal regimes.

Conclusion

New developments in synthetic biology continue to test the limits of the term "genetic resources" which attach ABS obligations to certain research, development and commercialisation activities. Using DNA molecules as a data storage medium was not feasible until recent improvements in the ability to read, write and store data in synthetic DNA constructs. A liberal interpretation of the CBD and Nagoya Protocol ABS framework indicates that DNA data storage as a purely synthetic human-made molecular construct unconnected with a known biological origin could still fall within the definition of a "genetic resource". The DNA molecule as the data storage medium is capable of being amplified (replicated) through human intervention and organically and so arguably contains "functional units of heredity".

As with the debate on whether and how to capture DSI in the ABS transaction, a similar debate may arise about how related that DSI must be to an originating genetic resource (taken from nature) in order fall within the scope of a range of international ABS agreements including the CBD, Nagoya Protocol, Plant Treaty and the Pandemic Influenza Preparedness (PIP) Framework (see Lawson *et al.,* 2020). However, while this debate may occupy analysts, states will continue to assert their sovereign rights to determine what they consider to be "genetic resources" under their regimes to suit their national interests. India is an interesting case study for demonstrating the ambiguity about whether national laws regulate DNA data storage technologies. The BD Act's definitions of "value added products" and "biological resources" create ambiguity about their applicability to physical DNA data storage molecules, but it is conceivable that they could be interpreted liberally to include this technology and its products within scope. Assuming this threshold test is passed, there may be a range of regulatory outcomes depending on the type of activity that is undertaken with the technology, the extent to which materials and information are used in the activity, and whether it is used by an Indian or non-Indian person or entity. Ultimately, it is up to governments to clarify whether they intend DNA data storage technologies to be the subject of an ABS transaction in a particular situation.

The creation and use of DNA data storage raises a host of complex legal and philosophical questions for a much broader range of national policies and laws that regulate purely synthetic constructs, including intellectual property and gene technology frameworks. These questions include: whether it is in fact artificial to make a distinction between purely synthetic DNA constructs and DNA in the natural world; and the extent to which DNA data storage uses information "associated with genetic resources". As the technology moves from science fiction to reality, it is timely to debate whether it is even appropriate for the ABS concept to be used as a regulatory tool for DNA data storage and the technology's relevance for the conservation and sustainable use of biological diversity.

Endnotes

[1] It is a question of whether the laws are both "efficient", in terms of "minimizing compliance and other costs imposed on the community" and "effective" in "addressing an identified problem": Productivity Commission, Regulation and Its Review 2002-03, Annual Report Series (Productivity Commission, 2003) p 1.

[2] The WHO are currently undertaking research to determine the extent of existing domestic implementing ABS legislation that relates to the sharing of pathogen samples (see 72nd World Health Assembly, Decision WHA72(13) The Public Health Implications of the Implementation of the Nagoya Protocol: https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72(13)-en.pdf).

[3] The quote in full: "The second question is whether not only natural but also artificially modified genetic resources should be subject to the sovereign rights of states. For instance, if a German researcher applying synthetic biology methods constructs a new microorganism in a Brazilian laboratory, has Brazil sovereign rights to regulate the access and utilization of this organism, allowing the state, for instance, to ask for prior consent? In more general words, is any new genetic resource the 'property' of the state? Once more, the question is hard to answer and has hardly even been discussed. My suggestion is this: The state has indeed sovereign rights over those new creations. This follows from the definition of genetic resources which covers genetic material not only of plant, animal and microbial origin, but also of 'other origin'" (Winter, 2016: 206).

[4] The primary framework of relevance to DNA storage would be the biosafety regulatory framework established under "Manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or cells, Rules 1989 (Rules 1989) under Environment (Protection) Act (EPA), 1986", which relates to "the research, manufacture, import and storage of micro-organisms and Gene-Technological products" (India Government 2020: 8). The question of whether 'storage of microorganisms' includes 'microorganisms as storage devices' is beyond the scope of this paper. However, it highlights the point that using the products of synthetic biology in ways not previously envisaged by regulators can raise interesting legal questions of scope. Other applicable regulatory frameworks include Drugs and Cosmetic Act, 1940; Seed Act, 1966; Protection of Plant Varieties and Farmers Rights, 2001; Food Safety and Standards Act, 2006; Plant Quarantine Order, 2003; Unlawful Activities (Prevention) Act, 1967; Disaster Management Act, 2005; Weapons of Mass Destruction and Their Delivery System (Prohibition of Unlawful Activities) Act, 2005 (India Government 2020: 9).

[5] http://nbaindia.org/content/18/21/1/notifications.html

[6] http://nbaindia.org/content/19/16/1/faq.html

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Biofoundries: The Next Frontier In Cell Factory Design And Manufacturing

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Abstract: The Biofoundry model is at the helm of next generation cell factories and biomanufacturing. The goal for synthetic or engineering biology is in alignment with the design-build-test-learn cycle (DBTL) to enable rapid commercialisation. The hierarchy and modularity that exists in biological systems can be harnessed using the DBTL paradigm to make genetic circuits that make molecules of interest and value added products. This paradigm is critical to achieve a sustainable circular bioeconomy. A biofoundry can be established through six modular steps organized to be iterative in nature that result in a fully integrated industrial bioprocess. The biofoundry model essentially supports the development of a holistic integrated technology platform that encompasses rational strain design creation and construction through genetic toolboxes, quantitative-small scale screening, prototyping through high-throughput micro-cultivation platforms and testing, OMICS data collection and modelling strategies, scale up and fermentation. All of these are intimately linked and critical to the biorefinery and biomanufacturing process. We foresee the need for such biofoundry stacks distributed globally across nations and continents in institutions of eminence for globally standardised, informed and coordinated operation. This review discusses an outlook on such a biofoundry model.

Keywords: Biofoundry, Synthetic Biology, design-build-test-learn cycle, High throughput fermentation, bio-based products

Introduction

A sustainable circular biobased economy lies at the intersection of biorefinery and synthetic biology. Synthetic biology or engineering biology focuses on deploying biological systems microbes/organisms as next generation cellular factories to produce molecules of interest in the wake of the depleting natural resources and growing environmental concerns. The

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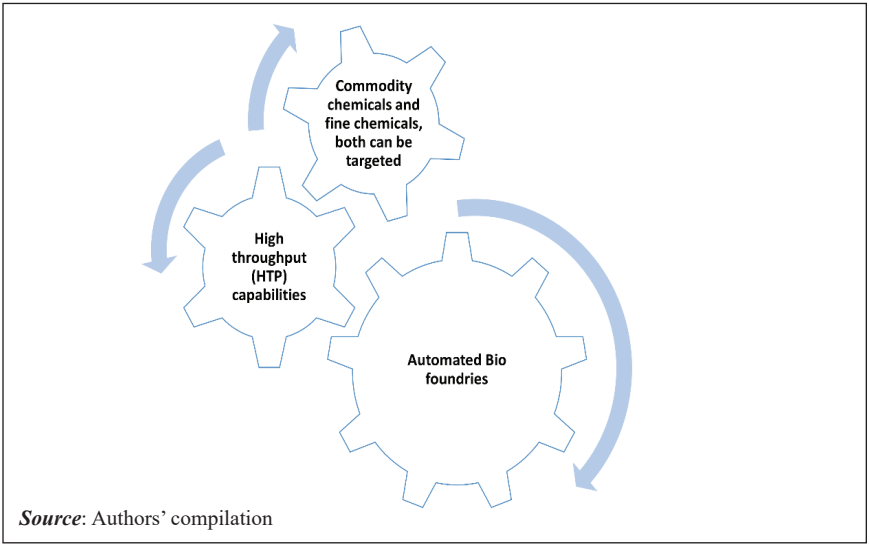
COVID-19 pandemic has further underscored the importance of engineering biology with the delivery of multiple vaccines equitably exerting a tangible economic and social impact on health (OECD, 2021). Biomimicry and its translation to engineering biology brings design to the space of living natural matter to harness their production capabilities at scale. From liquid fuels and commodity chemicals all the way to polymeric materials like spider silk and live cell therapeutics these models can chart the path of the current biorevolution creating innovative global roadmaps for engineering biology. The Biofoundry - a new technology platform for next generation cell factories steering a novel biofabrication and manufacturing model can thus leverage the entire process of engineering biology (Cameron et. al., 2014).

THE CONCEPT OF THE BIOFOUNDRY MODEL

Biofoundry is an emerging model in the biorefinery space at the cross-roads of design, biology and engineering. The grand appeal of this model in contrast to the incumbent fossil economy is driven by the fact that bioprocesses depend on renewable resources, ambient temperature and pressure along with low energy requirements. The underlying idea behind building biofoundries is optimizing and controlling biological systems for industrial scale production. Implicit in this concept is the idea that one can separate design (bio-design) from manufacturing (bio-refinery) (Opgenorth et. al., 2019). Hence the biofoundry model can essentially dovetail the design and development of a cell factory across the globe (bio-designs can be shared digitally) to distinct manufacturing sites (local manufacture based on demand) and elegantly promote next generation bioprocess industries. The vision of applying engineering to make biology faster, cheaper and more reliable can, thus, become a reality. The biofoundry model thus gives an advantage of offering high throughput (HTP) capabilities and being automated, in targeting a range of commodity chemicals, fine, speciality chemicals, biopharmaceuticals and even cell based therapeutics (Panda et. al., 2021) (Fig. 1). The overall goal of the biofoundry model is to enable biorefineries to achieve a reduction (at least 50%) in the time it takes them to develop bioprocess and productionise synthetic biology. One of the reasons we need to move away from the native producers and engineer host cells for metabolic engineering are: (i) to simplify the process of synthesis

Figure. 1: Features of the Biofoundry Model. The biofoundry model offers a) automation b) high throughput and c)diversity of target molecules



Source: Authors' compilation

(ii) to optimize the yield of a natural compound or its intermediate and (iii) to address the problem of insufficient supply versus market demand. A successful development of chassis organisms representing new and established industrial hosts would also increase diversity of bioprocesses. The potential outcomes of the biofoundry to develop and deploy technologies that enable commercially relevant biomanufacturing for a wide range of bioproducts would increase global competitiveness and opportunities in the private sector (Chao et. al., 2017; Fink et. al., 2021).

Rationale for the Biofoundry Model

Biofoundries facilitate development of economically important products and organisms in an accelerated way. Such an approach towards research and application in synthetic biology is a significant strategic and economic driver. The need to establish biofoundries is implicit in its structure and function through state of the art infrastructure and standardised protocols, that promote both fundamental research in understanding biological systems and translation to industry. The infrastructure enables rapid design, construction, and testing of the genetically reprogrammed and repurposed

organisms for large scale industrial application and research.

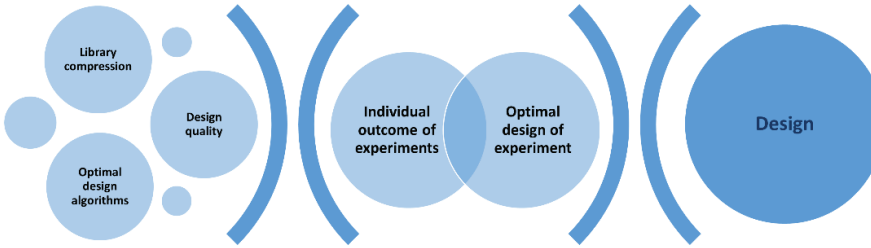
The Global Biofoundry Alliance (GBA) is an alliance between the 15 non-commercial biofoundries from four-continents (namely, North America, Europe, Asia, Australia). The alliance will help in coordinating the global efforts to connect Biofoundries world over. GBA would provide a platform to work in coordination and also collectively share the experiences and resources of the members and users, to resolve the unmet scientific and engineering needs (Hillson et. al., 2020). Globally, 40 countries have national strategies relating to the 'bioeconomy' (the economic potential of bioscience) and/or synthetic biology, including the USA, the UK and the Australian Council of Learned Academies (ACOLA) (Holowko et. al., 2021).

Synthetic Biology as a Paradigm for Biofoundries

The synthetic biology paradigm of the Design-Build-Test-Learn (DBTL) cycle (Figure 2) is central to the establishment of a Biofoundry. This cycle essentially involves computational design of genetic parts, their physical assembly, prototyping and testing performance of designs in living cells. This is generally augmented with modelling and computational learning tools to iteratively re-design processes to optimality. The biofoundry concept allows one to develop an organisational structure between academia and industry, coupling public investment in biomanufacturing infrastructure to private investment in product development, scaling it up and tailoring it to unique products and pathways.

Synthetic Biology continues to move forward at speed, enabled by the iterative cycle of 'Design-Build-Test-Learn' (DBTL) for DNA and strain engineering (Cameron et. al., 2014). The typical life cycle of a biofoundry (Figure 1) showcases tools, methods, and processes driving the iterations of the DBTL cycle. The purpose of the biofoundry is to accelerate development in bioengineering and reducing time from bench to market. The advantages offered by a biofoundry in addition to the high throughput (HTP) methods are simultaneous exploration of larger number of designs through miniaturisation of reactions and scale of resources being used (volume of reagents). This results in exploration of unique hypothesis and reduction of time to successfully identify candidate strains. Roadblocks to HTP project

Figure. 2: The DBTL cycle forms the core of a Biofoundry. Numerous iterations of the DBTL cycle lead to designs that suit the needs and technical specifications of the desired bioprocess



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implementation include equipment access, price, expertise and IP. Important to many industries are throughput, turnaround time, price, expertise or scientific support, services. Microbioreactors and microcultivation systems with real time online multiparametric monitoring and automated control are critical to biofoundries globally. They facilitate cultivation and screening of multiple synthetic biology designs to narrow down on a prototype in a high-throughput manner with real-time monitoring of important fermentation parameters like pH and dissolved oxygen. Thus a portfolio of experiments ranging from clone selection, physiological monitoring to substrate feeding strategies can be designed and performed in within a short period compared to traditional approaches to accelerate bioprocess development. The emphasis on HTP methods requires concomitant attention to software, protocols and the integration of physical and digital infrastructures to efficiently prepare and track samples. A biofoundry may be considered as a bioengineering service facility that takes the bio designs for HTP assembly and transformation into hosts, phenotype them and analyse the data. Biofoundries are thus at the forefront of a paradigm

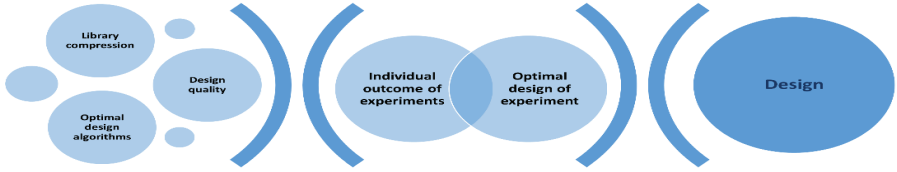
shift in biological engineering toward a more automated, design-focused venture. Despite all the challenges, biofoundries are our most promising hope to survive the demands of a potential circular bioeconomy (Chao et. al., 2017, Fink et. al., 20210.

The DBTL Paradigm

The DESIGN Aspect

The DBTL cycle elaborated begins with the DNA Design phase which essentially includes gene sequence optimization, batch design of DNA constructs, plasmids, vectors, cloning strategies based host organisms. The robustness can be built into it through a standardised parts registry, similar to the bio bricks repository. Design aspect also focuses on host selection, pathway selection for host modification. Decisions are taken through multiple *in silico* computational approaches for pathway analysis to understand redundancy and pleiotropy in the cellular system for the molecule of choice (Opgenorth et. al., 2019) (Fig. 3).

Figure.3: Design aspect of the DBTL cycle incorporates optimal design of DNA circuits, experiments, selection of the pathways and hosts for manipulation



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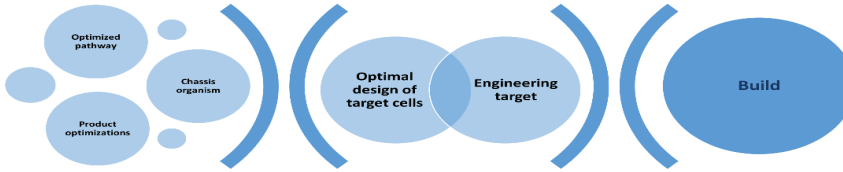
The BUILD Aspect

In the Build phase the biofoundry typically offers DNA assembly, organism transformation, isolation and clone selection followed by nucleic acid or protein extraction. Gene synthesis, gene assembly make for important steps in this phase of the DBTL cycle (Fig. 4). The genes, synthesised, may be assembled in part, or they can be assembled within the chassis organism in a combinatorial fashion. After the gene assembly, screening and selection of the clones, testing and analysis would be required to narrow down prototypes for further scale up (Jessop et. al., 2019; Kitney et. al., 2019).

Figure. 4: Build aspect of the DBTL cycle incorporates assembly of the parts and pathways that are developed, individually or in combination within the chassis organism to develop prototype strains



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The TEST Aspect

The test cycle offers cell phenotyping, OMICs data acquisition, Microbioreactor culture, and process optimisation. During the test phase of the DBTL cycle screening of the various biodesigns developed in the design and build steps, is carried out (Fig. 5). Testing and analysis of the numerous variants is eased by use of HTP platforms like microbioreator systems discussed earlier. Understanding underlying physiology and impact of genetic modifications is critical to the success of synthetic biology based strain designs. Delineating the genotype-phenotype relationship through HTP OMICS profiling (transcriptomics, proteomics , metabolomics, fluxomics and phenomics) would facilitate understanding specific molecular phenotypes holistically within the cell that would have an integrated impact on cell function.

Figure. 5: Test aspect of the DBTL cycle focuses on high throughput quantitative and qualitative screening and analysis of the built designs using OMICS data acquisition, Software and data management systems

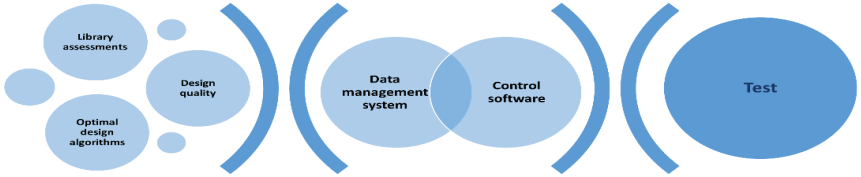

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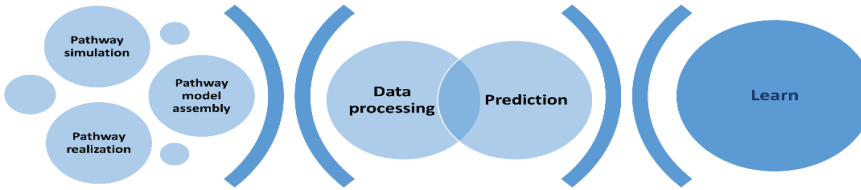
Figure. 6: Learn Aspect of the DBTL iterative cycle can be used to improve upon the experimental design using AI, ML algorithms, mathematical modelling and predictions



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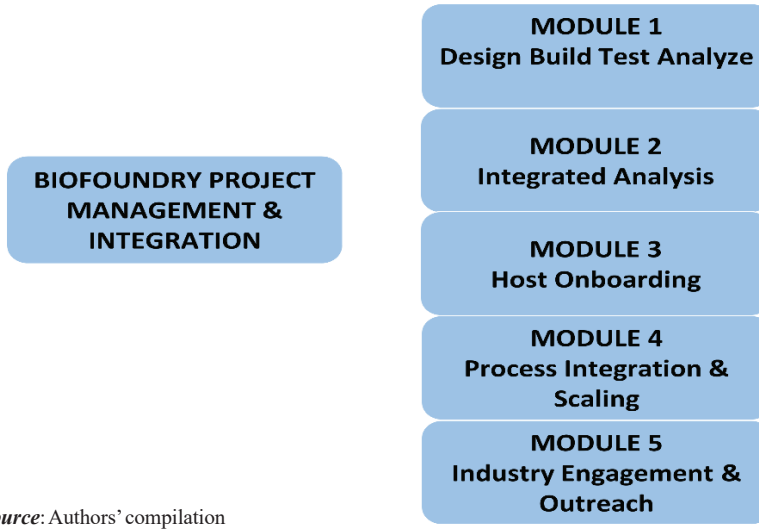
The LEARN Aspect

Finally, in the learn phase of the DBTL cycle, data clean up and analysis using artificial intelligence and machine learning (AI-ML) tools is critical (Fig. 6). AI-ML aid in understanding the strain performance and prediction of efficiency under different environmental (substrates and media) conditions. Biological systems are complex and more than the sum of their individual parts. There is a need to understand emergent properties in cellular systems in order to manipulate pathways of interest. *In silico* approaches like constraints based modelling, metabolic modelling, kinetic modelling, graph theory etc. allow one to understand the interplay and cross talk between various molecular components in the cell that determine cell phenotypes (Coley et. al., 2019, EMBO report, 2008).

Approach to Establish a Biofoundry

Establishing a biofoundry requires significant and continuous investment and is more than simply setting up a well-equipped physical space. Private enterprises can interact with public-facilities in order to advance their research and development capabilities. Such an interaction between the private and public enterprises makes for the true public-private biofoundries alliances. Market demand of bio-based products, the scale of investment, scientific expertise and nature of experiments to be carried out are key points that determine the business angle of the biofoundry model. The exact set-up, its maintenance and up-keep would depend essentially on the anticipated throughput. In contrast to genetically modified crops or organisms, handling biofoundry commodity molecules are easier to handle as microbes are merely production hosts (Hayden, 2014).

Figure. 7: The modular structure of a biofoundry. The integrated function of the different modules leads to bio-based product and process development from ideation to DBTL cycle iteration, and final portfolio of digital bio designs



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The many tasks that comprise running a biofoundry to deliver a product of interest can be organized in a modular fashion and include the following 6 Modules (Holowko et. al., 2021) (Fig. 7).

Achieving Modular Structure of a Biofoundry

MODULE 1: Design-Build-Test-Learn

The main goal of this module is to demonstrate the use of the DBTL cycle and establish routes in microbial hosts to bridgehead/nodal molecules of high strategic interest. This would include development of library of standardised genetic parts including promoters, ribosome binding sites, vectors, markers and tags will be established to be used to build DNA constructs, switches and circuits. This would be followed by sequence confirmation followed by benchmarking designs through testing and validation protocols.

MODULE 2: Integrated Analysis

The goal of this module will be to analyse proposed target and bridgehead molecules of interest with Techno Economic Analysis (TEA) and Life Cycle Assesment (LCA) methodologies. Techno economic analysis (TEA) evaluates the technical performance and economic feasibility of a technology. Life cycle assessment (LCA) evaluates the potential environmental impacts associated with a product system throughout its life cycle from raw material extraction to disposal.

MODULE 3: Host Onboarding and Development

The goal of this module is to develop methodologies and toolboxes to work with a wide variety of organisms as hosts for production. This includes not only genetic tool development and gene/genome editing tools like CRISPR for diverse organisms but also collection of physiological data for them. This process will facilitate onboarding host organisms apart from the traditional microbial hosts like *E. coli* and Yeast.

MODULE 4: Process Integration and Scale up

The goal of this module is to optimize process parameters for fermentation and to use industrial raw materials with C5/C6 streams from starch or cellulosic hydrolysates. The process will be scaled up for fermentation in bioreactors and tested for Titre, Yield and Rates.

MODULE 5: Industry Engagement and Public Outreach

The goal of this module is to establish metrics to assess impact of the biofoundry on industry, and identify barriers if any to industry adoption.

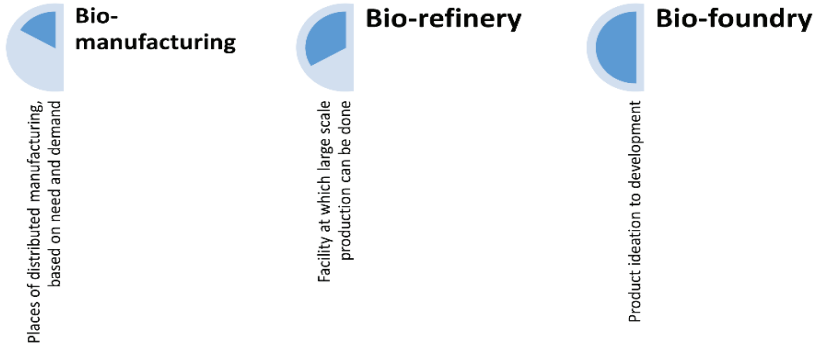
MODULE 6: Outcome Management

The goal of this module is to manage outcomes of the other modules of the biofoundry and identify technologies ready to license off the shelf and to determine success metrics.

Outcomes of the Biofoundry Model

Biofoundry infrastructure would thus provide integrated facilities for high-throughput iterative prototyping of biodesigns, prior to any scale-up such

Figure. 8: Journey of a bio-based product from its conception at a biofoundry to it being bio-manufactured at a site where its production, manufacturing and market supply is desirable



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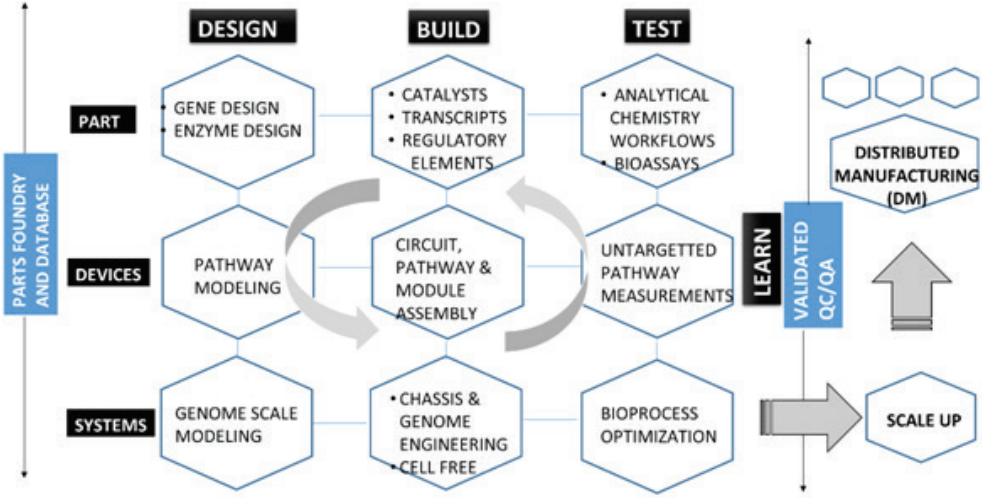
as a pilot-scale fermentation or biomanufacturing. The ability to parallelize, automate and miniaturize the steps in the synthetic biology design-build-test cycles and autonomously learn about the design and construction of biosystems through AI-ML approaches to narrow synthetic biology's potential design solutions to a number that can be efficiently generated and tested at scale (Opgenorth, 2019).

Such a conceptualisation of a modular biofoundry, with automated high throughput laboratory with equipment, standardised protocols and workflows that are semi or fully automated are currently being prototyped across various locations around the world targeting experimental fabrication methods all the way to mass production and maturation (Fig. 8).

Distributed Manufacturing Coupled to Biofoundries

Implicit in the concept of the Biofoundry is also the idea of distributed manufacturing (Fig. 8). Distributed manufacturing is specifically useful for products like vaccines or for cellular therapeutics. This would eliminate difficulties associated with cold-chain-dependence or regulated transport conditions wherever needed. With this option, right after the design phase, the digital code for vaccines for example can be transferred to a small-scale manufacturing facility close to the point of care or need. The biofoundry ensures reliability and reproducibility of such a process.

Figure. 9: The DBTL Paradigm and its components for large scale-manufacture of desirable commodities



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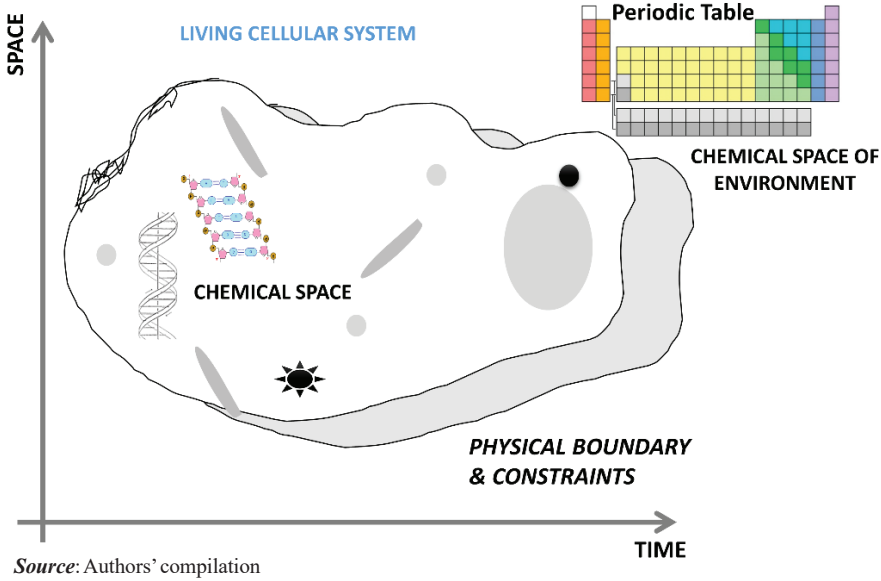
Biofoundries that essentially reduce the time from idea to product, and improve the reliability and reproducibility in biotechnology and biomedicine can be developed through either public enterprises, private enterprises, or they can be public-private partnerships (Fig. 9). Thus important things to be considered while setting up one include but are not limited to Institutional and Funding Model, Development Strategies and Client Engagement, Site considerations, Personnel, Automation and integration strategy, Data access, Biosafety and Biosecurity, Materials (DNA, Cells, Mol Biology Kits), Hardware (Automation, new equipment), Software (AI/ML), Application (Academia/Industry) (Farzaneh et. al., 2021).

Metabolic Pathways as a Transit Map

One of the over-arching goals of a Biofoundry are to deliver innovation in bio-based chemicals production through efficient, reliable, predictable, and safe bio-factories for fine chemicals and pharmaceuticals for biotechnology industry.

Bio-based products, that are basically made by way of redesigning life, taking inspiration from nature, can be easily brought into being by use of biofoundries (Fig. 10).

Figure. 10: Redesigning life through biomimicry. The assembly of a cell factory and its eventual growth in the actual physical space requires chemical/material space for function



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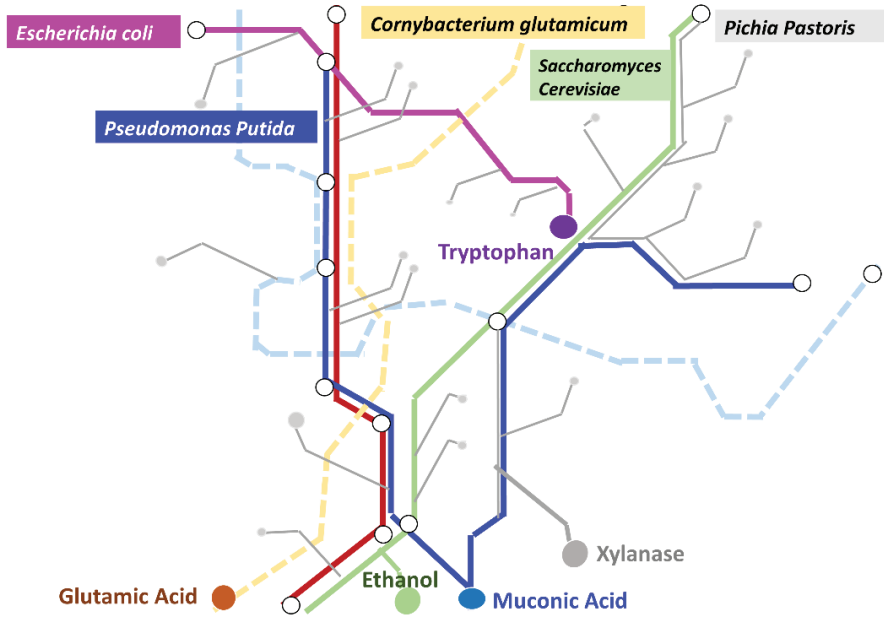
The main workflow of a biofoundry starts with identification of specific target molecules followed by multiple cycles of DBTL to achieve target metrics including reduction of time and cost to scale up and commercialisation. Molecules of interest can be identified through cell pathway maps. The cell pathways can be considered as analogous to a transit map of a city with the stations or stops compared to the strategic intermediate molecules, nodal points or bridge molecules that can be converted into multiple biological products (Fig. 11). Targets are molecules to be produced determined mainly through commercial objectives. Akin to the concept of multiple metro railway lines on the transit map are different industrially relevant host organisms that are in use or new hosts that can be onboarded with the sole purpose of producing newer or different molecules of interest.

These can be easily explained with the help of a metabolic pathway maps where in central metabolism space, intermediate metabolites like pyruvate, citrate, aspartate, glutamate, malonate, chorismite are obvious bridge nodal molecules that can be converted into specific target molecules of interest. Some other intermediates in the mevalonate pathway can be converted into carotenoids, terpenoids or lipid targets.

Figure. 11: Cellular pathways as transit pathways. Each organism represents a coloured metro line with station stops representing bridgehead, nodal and final destinations representing target molecules. The metro map here is adapted from the Mumbai Metro Rail, India.



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Pseudomonas putida for example, can be used to make protocatechuate bridge molecules that can be eventually converted to muconic acid target by industry (Bentley et. al., 2020). Another goal is to identify potential new molecules that can be developed based on pathway fluxes and flows, greenhouse emission and techno economic analysis and lifecycle assessments (Banerjee et. al., 2019). Where do you develop the best opportunities in bridge head molecules that give a bio-advantage. Development of hosts in bacterial and fungal space can be divided into multiple tiers so there is fundamental knowledge and advanced information about the physiology and cell biology of these organisms in addition to genetic tools for manipulation for rapid and robust DBTL cycles. Development of strains for production of target associated with beachhead will allow production of related product. Specific destination product development can be funded by private

partnerships. Bridgehead molecules associated with those can be funded by public investments. Thus, providing a good model for public private partnership and industry-academia collaboration (IBISBA Report, 2021).

Application Examples

The biofoundry model lends itself as a paradigm to the production of value added products like commodity and fine chemicals, next generation energy sources and vaccines, diagnostics, devices, sensors, biopharmaceuticals and cell based therapies. Some examples are discussed in the following sections.

Commodity Chemicals

Adipic acid , a widely used aliphatic dicarboxylic acid is a high value market chemical with a volume of 2.6 tonnes/year with industrial applications ranging from production of Nylon66, polyurethanes to PETs. The bridgehead intermediate is protocatechuate through central metabolism that can be converted to muconic acid and finally adipic acid catalytically. The greenhouse gas (GHG) emissions calculated as kg CO2 /Kg adipic acid are around 10.2 with the market price being 1.89$/kg

Another chemical metabolite that has been created using the DBTL cycle (Figure 11) is Isobutyrate. Lygos™ and the Agile BioFoundry™ have generated one of the largest multi-Omics datasets to accelerate machine learning capabilities for engineering strains for producing organic acids like Isobutyric acid.

Fine chemicals

Fine chemicals, as opposed to the commodity chemicals, offer a wider market, owing to the low volume and high value of the products involved. There is an urgent need for alternate methodologies to make foods and fragrances and fast moving consumer goods (FMCG) using. Evolva™, a synthetic-biology company, based in Switzerland, has shifted its research/ market focus from biofuels and rubber to foods and fragrances like vanilla (vanillin). Vanillin is the most important taste component present in vanilla, extracted naturally from the seed pods of vanilla orchid. A modified strain of yeast capable of converting sugars to vanillin via fermentation was developed. This has now become a cost-effective process offering a stable supply chain. This also marks a shift in gears for an industry that typically

tends to focus on synthesising drugs, biofuels, bioplastics to more esoteric flavours and fragrances. These products tend to be more cost effective, and offer higher returns, compared to the commodity chemicals (Hayden, 2014). Likewise, other fine chemicals making part of the FMCG supply chain can be bio-designed, scaled up, be manufactured and sold in large volumes for profit.

Next generation energy sources

The next frontier of alternate energy sources like Hydrogen could be hydrogen forming microbes capable of carrying out industrial photosynthesis. Till date, unicellular microbes have been engineered to assimilate one carbon source, through gas phase fermentation and produce commercially relevant products. Clostridium species have been engineered to ferment carbon dioxide and carbon monoxide and efficiently co-produce isopropanol, 3-hydroxybutyrate and ethanol. Reiterations of such designs coupled with optimizations on a bio-design prototype can be taken to the biorefineries and biomanufacturing for large scale production and usage (Dechen et. al., 2021).

Next generation Vaccines

The standard vaccine production process typically starts with the generation of the antigen for viruses like influenza by growing them in primary cells in chicken eggs, while hepatitis A can be continuously cultured in human cell lines. In the case of bacterial pathogens like Haemophilus influenzae Type B, they are typically grown in bioreactors. The vaccine production model that is long, complex and needs a large facility handling infectious virus particles needs a major overhaul. The power of DBTL cycle is evident in the equitable access of the next generation nucleic acid (mRNA or DNA) vaccine for SARS CoV2 developed by focussing on the Spike protein involved in the entry into the human host (OECD, 2021).

Cold chain elimination in vaccine distribution

The long distribution chains of centralised vaccine production can be patchy resulting in incomplete geographical coverage. The concept of distributed manufacturing as the name suggests distributes small-scale manufacturing to

many geographical locations in contrast to the centralised mass production paradigm. Next generation nucleic acid vaccine platforms are generally less stable and would benefit from production close to the end user. After the design phase of the vaccine, the digital code can ideally be transferred to a small-scale manufacturing facility close to the point of care. This would eliminate the physical transfer of the cold-chain-dependent vaccine. Thus, the concept of a Biofoundry coupled to distributed manufacturing model would potentially break the economies-of-scale model for vaccine manufacturing and lend itself elegantly to mitigate the complexity of the distribution process with high scalability (Crone et. al., 2020).

Biopharmaceuticals

A target of the biopharmaceutical sector is to replace or improve the function of a protein or enzyme with biological drugs or biosimilars. 'Biobetters' provide molecular or chemical modification to original biological or biopharmaceutical molecule constituting an improvement over the originator drug and its biosimilar competitors. The DBTL cycle can thus potentially help improve the half-life, efficacy, aggregation problems or adverse effects of the original biological. Gene editing through CRISPR-Cas9 methodologies, protein and enzyme engineering can modify ligand binding or catalytic activity. Trastuzumab biobetter or Filgristin biobetters that have improved efficacy and dosing frequency have now gained FDA approvals (Burchiel et. al., 2019).

Cell-based Therapeutics

Manufacturing Chimeric Antigen Receptor T (CAR-T) cells for cancer patients could be next generation cell therapeutics by coupling the concept of distributed manufacturing and with biofoundry model. The DBTL cycle can help developing methods for reliably and reproducibly growing and expansion of Human T cells with and without introduction of CAR sort of akin to cell line development with standard operating procedures and QC/QA measures (Zhang et. al., 2017).

Conclusion

The Biofoundry model aims to provide a complete synthetic biology technology stack to deliver complex bio-design projects that are vertically integrated and reproducible that enable the quantitative precision required for modern biomanufacturing (Holowko et. al., 2021). Research biofoundries with chemically aware control loops may become potential testbeds for soft robotics and autonomous bioreactors to build more robust systems and bioengineering designs (Dixon et. al.,2021). It is thus imminent to identify key technical, regulatory and societal challenges in order to enable the development and adoption of such approaches by the biofoundry and industrial stakeholders. We foresee within the biofoundry model, a seamless interface between genetic engineered organism designs, biofabrication prototypes, cloud-based upstream prototyping activities and downstream industrial biomanufacturing for a future in sustainable circular bioeconomy.

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Regulating Risks in Synthetic Biology

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Abstract: Synthetic Biology is considered as a key emerging technology. Globally regulating risks in Synthetic Biology is a contentious issue. Discussions on regulating Synthetic Biology and it's relevance for various treaties, conventions and protocols are on going in many fora, convened under, inter alia, Convention on Biological Diversity. Given it's ramifications, such discussions are inevitable. Regulating biosafety and biosecurity, and, liability for harm are key themes on which discussions are being held. This article describes these developments and their importance. In India the XII th Five Year Plan considered harnessing synthetic biology for national development and regulating it. India has a biotechnology regulatory regime. But develop a robust policy for synthetic biology, foresight and analysis are needed. The global developments on regulating synthetic biology are relevant for development and regulation of synthetic biology in India.

Keywords: Convention on Biological Diversity, Biosafety, Harm and Liability, risk assessment

Brief Introduction

Synthetic biology is one of the top ten breakthrough technologies as part of the "forth industrial revolution" that are "most likely to change the world" (Brownsword, 2008). Synthetic biology aims to build new organisms with functions that might not exist in nature (Boldt and Müller, 2008). Where previous genetic technology served as a tool of manipulating existing organisms, synthetic biology aims to create new life, sometimes from scratch.

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It is important to understand that any technology cannot advance without some freedom in research and development. The objective for a national legal framework is to leverage its anticipated benefits while guarding against its potential risks. The laws and regulations framework governing traditional tools and products of biotechnology can be applicable to this relatively nascent field in some ways, but most often it fails to fully adapt to the evolving possibilities of synthetic biology.

Synthetic biology organisms are able to self-replicate and spread rapidly and evolve on their own. We cannot be sure of how it will play out in the future, so all countries including India has to develop a framework for anticipatory governance. There are key areas of national interest pertaining to biosecurity, biosafety, liability, intellectual property, trade and ownership which warrants great attention in designing an effective governmental policy and regulatory framework (Wiek *et al*. 2012).

Initiatives from India

There are complex challenges for a country like India which has a rich biodiversity and is increasingly adopting the technology. As part of the 12th five year plan, India has set up a Task Force on systems biology and synthetic biology research in 2011[1]. The country has informed international bodies that the technology is still at its infancy in the country.

The Task Force came up with a report and has acknowledged the potential with regards to key applications in biofuels, bioremediation, biosensors, food and health. The Task Force had made a strong case for a push for the technology, and few initiatives have been launched by departments such as Department of Biotechnology and Department of Scientific and Industrial Research[2]. Initiatives include the Indian Biological Engineering Competition and the DBT training program[3].

The report had emphasized that India has the opportunity to be a world leader as a protector and supporter of "open-source biological platforms"[4]. This requires a supportive legal and regulatory environment in which small biotechnology players can also participate. Recently, the DBT funded policy and research planning for synthetic biology (JNU and FLEDGE collaborative program) and recommendations were submitted.

Policy Aspects

A policy framework related to technology lays down the objective, the scope of legislation on a particular subject and its relationship to existing international and national frameworks. The policy framework focuses on why, how and when a technology is developed and deployed. International law requires state parties to the respective treaty regimes to take measures at the national level, to achieve common stated objectives in the manner it has been collectively agreed.

Subsequent laws and regulations provide tools for effective national policy implementation, backed by enforcement, as well as detailed procedures for the redress of damages[5]. Section 4 discusses the various international developments and related treaty frameworks which is directly applicable to designing a synthetic biology policy framework for India.

Global Policy Initiatives

Synthetic biology is impacted by discussions at international, regional and private-sector driven positions and interests. Various international treaties and organisations are currently examining the impacts of synthetic biology and engineered gene drive systems on their respective agreements. India is a party to all the international governance bodies discussed below

i. Convention on Biological Diversity (CBD)

The Convention on Biological Diversity (CBD) has been ratified by 196 states. The United States of America (US) is a non-party to the convention. Synthetic biology is a new and emerging issue in the context of realizing the objectives of convention.

The twelfth Conference of the Parties (COP12) and COP13 produced decisions seeking a more robust assessment of synthetic biology against the Convention's new and emerging criteria[6]. The Parties decided to establish an Ad Hoc Technical Expert Group (AHTEG) and convened a moderated online forum[7].

The AHTEG has produced multiple reports and recommendations but is yet to come up with a robust assessment against the new and emerging criteria as mandated by the COP[8]. At the COP 14, Parties agreed on a need for regular horizon-scanning of the most recent technological developments

for reviewing new information regarding potential impacts of synthetic biology[9].

a. The Cartagena Protocol on Biosafety

The CBD COP extended the AHTEG on synthetic biology, taking into account the work under risk assessment under the Cartagena protocol on Biosafety[13]. Current deliberations are also considering whether any living organism developed thus far through new developments in synthetic biology fell or could potentially fall outside the definition of a living modified organism (LMO) and thus be subject to the risk assessment requirements of the Cartagena Protocol on Biosafety[10].

b. The Nagoya Protocol on Access and Benefit Sharing

In 2017, the Secretariat of the CBD commissioned a report examining the impacts of digital sequence information (DSI) as it relates to the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation (ABS) to the Convention on Biological Diversity (Wynberg and Laird, 2018). An Ad Hoc Technical Expert Group (AHTEG) was also established to provide recommendations for member states on those impacts and a draft decision was submitted with vast disagreements[11].

ii. Food and Agricultural(FAO)

The FAO International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) report commissioned in 2017 examined the impacts of synthetic biology and digital sequence information (DSI) on the Plant Treaty (Welch *et al*, 2017). The report addresses the phenomenon of "dematerialisation", which suggests that "the information and knowledge content of genetic material extracted, processed and exchanged in its own right, detached from the physical exchange of the plant genetic material". It included the scientific and technological changes affecting the Treaty and the broader legal considerations and opportunities for benefit sharing within the ITPGRFA framework[12].

iii. Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)

CITES has been engaged in discussion on the question of synthetic products that are indistinguishable from products from listed specimens and the status of modified organisms and products under the Convention[13]. Seventieth meeting of the CITES Standing Committee in October 2018 adopted a report on the "Specimens Produced from Synthetic and Cultured DNA"[14]. The study notes that regulation under the treaty becomes challenging since synthetic biology specimens may be extremely difficult to differentiate from that of wild specimens by visual or analytical means.

iv. International Union for the Conservation of Nature (IUCN)

IUCN Members adopted Resolution titled "Development of IUCN policy on biodiversity conservation and synthetic biology" to map the impacts on conservation and sustainable use of biodiversity[15]. In early 2018, an IUCN Synthetic Biology and Biodiversity Conservation Task Force, was created to oversee the implementation of the Resolution and to develop policy recommendations before the 2020 World Conservation Congress.

v. Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS)

The focus under TRIPS, on issues related to synthetic biology, pertains to the intellectual property rights issues. The results of current synthetic biology research that is focused on modifying existing "natural" genomes could qualify for the "breeder's right" under the International Union for the Protection of New Varieties of Plants (UPOV Convention) If in the future, there are new plant varieties developed as a result of the production of entirely novel genomes, protection under breeder's rights is being discussed.

vi. UN Convention on the Law of the Sea (UNCLOS)

UNCLOS includes activities and resources beyond national jurisdiction. In relation to a new treaty under negotiation that includes marine genetic resources in areas beyond national jurisdiction (ABNJ), including sharing of benefits synthetic biology and its impact on ocean governance is being discussed.

Regulatory Aspects

Regulation refers to interventions that are put in place by relevant agencies "*to control and channel conduct in the desired way*" (Brownsword, 2010). Regulation is designed to implement the specifics of a policy or legislation. Regulations are to be authorized by the governmental agencies that hold the designated authority. Synthetic biology is not insulated from the highly polarized debates that are surrounding the use and management of the new wave of fourth industrial revolution technologies.

The rapid pace of scientific research and irregularities about the specific benefits of synthetic biology create complex challenges for national regulation. Synthetic biology can also pose risks such as bioterrorism, loss of trade opportunities, environmental damage, and transboundary harm.

Considering the multifarious applications of synthetic biology like energy, agriculture and biofuels, there is always a perceived threat of components releasing into the open environment. Risk and uncertainty give rise to synthetic biology's major governance challenges. On a spectrum we are looking at an intentional bioterrorist attack on one hand to accidental damage to the environment on the other. There is a difference between risk and uncertainty. Risk refers to an event that can be estimated using theory or experience or both but uncertainty cannot be estimated by either methods.

Biosafety addresses the "inherent risks of a biological agent or material to cause unintentional harm to human health and the environment".[16] In contrast, **biosecurity** concerns itself with the intentional uses of a biologic agent or material through loss, theft, diversion, release, or inadvertent research results that have security implications.[17] Intention is the key difference between both the two concepts and biosafety mostly refers to accidental events. National biosafety regulations like that of India[18] may provide that certain activities require prior authorisation or notification, containment procedures or other forms of administrative oversight.

Risk Assessment- Biosafety and Biosecurity

The World Trade Organization's 1995 Agreement on the Application of Sanitary and Phytosanitary Measures (SPS) and the 2000 Convention on Biological Diversity's Cartagena Biosafety Protocol seem inadequate to deal with biosafety issues posed by synthetic biology. The WTO's SPS measures

limit the space for member states to introduce trade restrictions based on considerations of food safety, and plant and animal health.

The Cartagena Protocol deals with import and export (transboundary movement) of LMOs, including illegal and unintentional transboundary movements. It enables import of certain living modified organisms subject to an Advanced Informed Agreement procedure.[19] The traditional biosafety framework was created in response to the issues raised by the recombinant DNA technology. Agricultural biotechnology can cause GM crops outperforming non-modified species and create undesired gene transfer. There are additional questions of safety of GM food for consumption.

The CBD Cartagena Protocol applies to all "Living modified organism" (LMO) which are "living organisms that possesses a novel combination of genetic material obtained through the use of modern biotechnology".[20] The scope can extend to animals, plants, food, pharmaceuticals and insects. Most countries have designed national regulatory frameworks for risk assessment and management in relation to LMOs.

The Cartagena Protocol[21] requires Parties to "establish and maintain appropriate mechanisms, measures and strategies to regulate, manage and control risks" connected with the use, handling and transboundary movement of living modified organisms (LMOs) This includes "possible adverse effects of LMOs on the conservation and sustainable use of biological diversity" The terminology "modern biotechnology" according to the Protocol drafted in 2000 does not include techniques like genome editing.[22] The Protocol does not concern itself with constituent parts like DNA under Article of the Protocol.

The 1972 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (usually referred to as the Biological Weapons Convention) was the first multilateral undertaking prohibiting the development or acquiring of biological agents or weapons for hostile purposes or armed conflict. The scenario is not adapted for the conduct of non-state actors apart from governments becoming biosecurity threats.[23]

The increased securitisation of public health is bringing increased focus on both intentional and unintentional release of biohazardous organisms. The World Health Organization revised International Health Regulations (IHRs)

in 2005 to ensure States notify the organisation in case of an unexpected or unusual public health event within its territory.[24] Proposals for screening customers who are ordering material which could be weaponised are made to commercial providers of synthetic DNA.

National Biosafety Regulations

The Cartagena Protocol currently ratified by 171 Parties, but is yet to be ratified by several countries active in the application of biotechnology. Major biotechnology players such as the US, Canada and Argentina are not Parties to the Protocol. Many countries have biosafety regimes in place that fully or partially follows the risk assessment framework outlined in the Protocol.[25]

The 1989 Rules for manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or cells is jointly implemented by the Ministry of Environment and Forests (MoEF) and the Department of Biotechnology in India. The 1989 Rules regulate research, development and large-scale commercialisation of GM crops as well as post- approval monitoring and compliance in accordance with the treaty obligations of India.[26]

The scope of applicability of the Cartagena Protocol to synthetic biology is a contested topic. CBD Parties during the Mexico COP13 in 2016 noted that it is not clear whether SYNTHETIC BIOLOGY organisms would fall under the definition of LMO[27]. In 2017, the CBD AHTEG concluded that most living organisms developed through techniques of synthetic biology, including organisms containing engineered gene drives, fell within the definition for LMOs.[28] In November 2018, CBD COP14 emphasised the need for case-by-case risk assessments and specific guidance on such risk assessment could be useful.[29]

Regulatory Stages and Requirements

Biotechnology applications are subject to step-by-step regulation and monitoring at various levels in different jurisdictions. Most countries require some sort of authorisation system depending on the risk associated. In Canada, the release of GM plants with "novel traits" has to pass through various stages including import, contained use in a laboratory or greenhouse, unconfined release and commercialisation.

The proposed Biotechnology Regulatory Authority of India Bill is pending approval in the Parliament since 2013.[30] Various stages of regulatory approval include the manufacture, use, sale, import, export and storage of GMOs.[31] The Indian regulatory system also comprises of other legal instruments including the Drugs and Cosmetics Rules – 1988, Protection of Plant Varieties and Farmers' Rights Act, 2001, Biological Diversity Act, 2002.[32]

There is a three-tier system of approval for GMOs as well as their products under Rules 1989. The initial assessment of applications begins at the institutional level itself by the IBSCs, where the proposals are evaluated and recommended to the RCGM (Choudhary *et al*, 2014). After an in-depth evaluation of the forwarded proposals, the RCGM sends its recommendations to the GEAC.

In 2014, a ten-year moratorium was imposed on commercialisation and release of BT Brinjal. Several State governments like Andhra Pradesh, Maharashtra and Karnataka have approved field trials for few crops including food crops. Within the EU, member states have powers to "opt-out" and close areas and even the state borders to release GM plants.[33]

Liability for International Harm

The international legal principle of state responsibility for international harm provides for liability for possible damages attributable to synthetic biology. The Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress [Supplementary Protocol] to the Cartagena Protocol provides for states to establish national frameworks for liability in cases of environmental harm.

The Supplementary Protocol has 42 parties to date and there are no binding obligations for establishing civil liability. The national frameworks can provide for rules and procedures that address damage, including civil liability, but they do not have a binding obligation for the operator to take appropriate action. Some states have adopted a non- state liability approach while others opt for a fault based liability.

EU legal instruments apply a principle of strict liability, or no-fault liability, for any damage to the environment resulting from dangerous activities.[34] The European Convention on Civil Liability for Damage

Resulting from Activities Dangerous to the Environment (The Lugano Convention) covers the production, storage, use disposal or release of GMOs.

Fault-based liability may be difficult to prove in the context of synthetic biology. There may not be a sufficiently close causal link between the activity and the damage to show liability. Strict liability is typically reserved for acutely dangerous activities or activities delineated in national legislation.[35]

Conclusion

This compilation is intended to provide a foresight for further developing a national policy framework for India. it is important to consider the international developments and global initiatives while developing the national policy for India, especially since the science and regulatory framework related to use of the science is driven by global considerations. It is time for India to consolidate its stand on the science of synthetic biology and communicate its interests and aspirations in relevant international fora with clarity and should avoid conflicting stands on science on one hand and regulation on the other.

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2 Report Of The Planning Commission Constituted Task Force On Synthetic And Systems Biology Resource Network https://dst.gov.in/yearsplan/synthetic-and-system-biology-resource-network-ssynthetic biologyrn

3 As a precursor event to the iGEM competition https://syntheticbioindia.weebly.com/ibec-2016-description.html

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9 CBD COP decision 14/19

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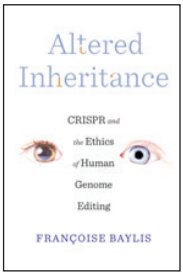
Book Review

Altered Inheritance: CRISPR and the Ethics of Human Genome Editing



Author: Françoise Baylis

Publisher: Harvard University Press

Year: 2019

ISBN: 978-0674976719

Pages: 304; Price: INR 1548.00

The book analyses scientific, ethical, societal and political aspects of the early history of the human genome editing. Not limiting the discussions about the future use of technology within the "scientific, medical, political, corporate, or other elites", author firmly puts forth the need for societal consensus in shaping the way forward for best harnessing the potential of genome editing for humankind. Thus, bringing together "all of us" in deciding if human genome editing is a boon or a threat. The author, Françoise Baylis has worked extensively on heritable human genome modification, bioethics, assisted human reproduction, women and public health, polices and ethics. She is Professor at Dalhousie University, Canada and was a member of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.

For this book, Françoise received the PROSE Award in Clinical Medicine in 2020. During the same year, Emmanuelle Charpentier and Jennifer Doudna were awarded the Nobel Prize in Chemistry for the development of the revolutionary gene manipulating technology 'Clustered Regularly Interspaced Short Palindromic Repeats' in association with the Cas9 DNA-cutting enzyme (CRISPR/Cas9 genetic scissors). Often seen as a 'double edged sword', scientists have raised numerous scientific, societal, governance and ethical issues associated with CRISPR. In September 2020, detailed 'consensus' study report on the Heritable Human Genome Editing (HHGE) came up with several recommendations, including extensive

societal dialogue before pre-clinical use of HHGE in any country. Françoise was invited to share her reactions on the report. While acknowledging report's emphasis on the need to involve society in discussion around HHGE's (im)permissibility, she pointed that there was no mention of societal consensus (which is also the fulcrum of her book).

The book is lucidly written, comprehendible and aims to empower discussion on governance and ethics of HHGE. She presents useful timelines on science and social relations of human genetics during 1880 and 2018 and science policies of human genome editing during 2015-2018. The proponents put forth the compelling medical need and benefits of somatic cell gene editing in correcting faulty genes and curing Huntington's disease, and preventing genetic diseases in future generations. However, germline editing could cause heritable permanent changes and expose genetically modified babies to long-term untold harms. The potential harms, concerns of accessibility and shift from "health-related to non-health-related genetic modifications" were discussed, along with simpler and safer alternatives to HHGE. It is important to discuss and deliberate responsibly to forsee "potential biological, societal, and cultural consequences". The book delves into various ethical debates around complicated design projects of "better babies". With greater use and normalization of genetic and reproductive technologies there are risks of exposure to harmful and "oppressive acts of discrimination, stigmatization, and marginalization".

The author neither firmly advocates nor strongly opposes HHGE, giving a well-balanced assessment and evaluation of potential benefits and harms, ethical and societal risks and challenges of these HHGE developments. She underlines that some "underscore the importance of public dialogue and seek to position themselves as knowledgeable contributors to this dialogue." The book argues for a "broad societal consensus" which according to her "is a process that involves seeding global dialogue, engaging in a respectful exchange of divergent views and values, building trust, and exploiting collective intelligence on how best to use science and technology to create a better world."

The author emphasizes on adopting "slow science" that advocates scientists to slow down, take time and think how their work could help achieve societal goals. In contrast with the present culture of "fast science"

that is largely fueled by personal and commercial interests, often directed by market forces and profits. She underlines that it is the social responsibility of science and scientists to contribute to public policy for common good. An important aspect of this is making scientific accessible to policy makers, public as well as science diplomats. At this stage, she asserts that repeated calls by scientists, professional science organizations, national ethics and transnational governance for time-bound prohibitions is crucial and will provide scope for science diplomats to work with civil societies and ethicists to deliberate on policy choices to promote "common good for the commonweal". She underlines critical 'roles' played by bioethicists in the HHGE debates to situate science in the larger socio-cultural context and ensure wider representation of values, interests and beliefs, towards - "all of us" shaping the way forward for "us all".

Calling for action towards an equitable and just world, the book focuses on maximum participation towards collective informed decision making for "our biological and social future." The author has very well placed all aspects of the HHGE developments, potential benefits and risks, including "designer babies". The book caters to a wide range of audience, and very strongly puts forth the need for "broad social consensus" which is a very timely, significant and thought-provoking intervention into the ongoing debates around HHGE, which will shape our informed actions to understand what are the gains and loss for the future. The book adequately explores and identifies various 'participants' of the multi-stakeholder discussions and deliberations. Thus, paving the way forward for evaluating/assessing/weighing the technology's potentialities and harms, which will be very useful in developing both national and international regulatory frameworks.

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3. Use 's' in '-ise' '-isation' words; e.g., 'civilise', 'organisation'. Use British spellings rather than American spellings. Thus, 'labour' not 'labor'.
4. Use figures (rather than word) for quantities and exact measurements including percentages (2 per cent, 3 km, 36 years old, etc.). In general descriptions, numbers below 10 should be spelt out in words. Use thousands, millions, billions, not lakhs and crores. Use fuller forms for numbers and dates— for example 1980-88, pp. 200-202 and pp. 178-84.
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All references should be embedded in the text in the anthropological style–for example '(Hirschman 1961)' or '(Lakshman 1989:125)' (Note: Page numbers in the text are necessary only if the cited portion is a direct quote).

Citation should be first alphabetical and then chronological–for example 'Rao 1999a, 1999b'.

More than one reference of the same date for one author should be cited as 'Shand 1999a, 1999b'.

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(a) Books:

Hirschman, A. O. 1961. *Strategy of Economic Development*. New Haven: Yale University Press.

(b) Edited volumes:

Shand, Ric (ed.). 1999. *Economic Liberalisation in South Asia.* Delhi: Macmillan.

(c) Articles from edited volumes:

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(d) Articles from Journals:

Rao, M.G., K. P. Kalirajan and R. T. Shand. 1999. "Convergence of Income across Indian States: A Divergent View". *Economic and Political Weekly,* 34(13): pp. 769-78.

(e) Unpublished Work:

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Synthetic Biology (SB) is an emerging technology that has much potential and there are concerns about risk and governance in SB. In this special issue on SB there are seven articles that deal with different aspects of synthetic biology ranging from introducing SB to relevance of biofoundries for a developing country like India. Given the international dimension of risk and regulation in SB, two articles discuss them in detail giving an international perspective and describing the regulation in India. Similarly Access and Benefit Sharing (ABS) and SB is explored in an article in the context of genetic resources. This special issue is part of RIS's research and publications on SB, which is a component of RIS's work on emerging technologies.

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