Project Title

Policy and Research Planning for Synthetic Biology

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Content

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Furthermore a detailed discussion on the foresight and policy matters was carried out with a larger group (Table 1) and observations were summarized.

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Synthetic Biology

Foresight Paper

Sachin Sathyarajan, Balakrishna Pisupati, Neeraj Verma and Pawan K Dhar

1. INTRODUCTION AND BACKGROUND

a. Building a conceptual foundation

More than ten years ago, on May 20, 2010, scientists in the J. Craig Venter Institute announced to the world that they have created the world's first self-replicating synthetic bacterial cell. [1] According to Venter, this was the first self-replicating species on the planet whose entire biological makeup was created with a computer.[2] This major breakthrough which brought large scale attention to the emerging field of synthetic biology happened a decade ago. In 2006, the Venter Institute had already identified the "minimum bacterial genome" – the smallest genome of any organism that can be grown in pure culture. [3]

Synthetic biology is an emerging field which combines the advancements in biotechnology, biochemical engineering, genomics, information technology and others. This leads to creation of new biological tools and techniques which can help tackle our biggest problems including renewable energy and synthetic vaccines. Since the revelation of DNA as a double- helix of nucleic acids in 1953, knowledge of molecular biology and methods for genetic manipulation has improved at an accelerating pace. This millennium saw humanity at a juncture, finally allowing the engineering and programming of living organisms and their genomes. Several new enabling technologies and ways of collaborative working have come together to both expand accelerate the possibilities of the sector.

The Nobel prize winning CRISPR technology was the biggest breakthrough for biosciences in this decade. The advent of CRISPR technology in 2011 meant that synthetic biologists had access to technology that can precisely alter DNA inside cells, particularly eukaryotic cells. Soon CRISPR was repurposed to invent the dCas9 as a

[1] Gibson, D. G. et al. Creation of a bacterial cell controlled by a chemically synthesized genome. Science 329, 52–56 (2010).

[2] Wade, Nicholas. "Researchers Say They Created a 'Synthetic Cell.'" The New York Times. 20 May 2010. www.nytimes.com/2010/05/21/ science/21cell.htm

[3] Hong Glass et al, Essential genes of a minimal bacterium PNAS January 10, 2006 103 (2) 425-430; https://doi.org/10.1073/pnas.0510013103

programmable binder of DNA to enable gene regulation.[4] The advent of next generation sequencing (NGS) technologies, gene synthesis has become much faster and there has been a steady decline in the costs. Using the current NGS technologies, the entire human genome can be sequenced within one day for a fraction of the amount spent on the decade long Human Genome Project.

Synthetic biology aims to build new organisms with functions that might not exist in nature.[5] Where previous genetic technology served as a tool of manipulating existing organisms, synthetic biology aims to create new life, sometimes from scratch. This has been possible through integration of computing technologies in the manipulation and design of biological components. Several scientists developed novel parts and design of genetic parts of the *E Coli*, which became an ideal test bed for its ease for manipulation.[6] In 2014, scientists were able to synthesize a functional designer eukaryotic organism - a modified yeast chromosome.[7]

The early efforts of storage and assembly issues was in the form of Registry of Standard Biological Parts[8] in a standardized BioBrick format and was followed by one step assembly methods such as Golden Gate and Gibson Assembly. [9] The translation of the registries into computing language such as Synthetic Biology Open Language (SYNTHETIC BIOLOGYOL) has given a standard software format to describe components. [10] In 2016, an end-to-end computer aided design system for logic circuit construction in E. coli called "Cello" was published. [11]

[4] Qi, L. S. et al. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. Cell 152, 1173–1183 (2013).
[5] Joachim Boldt and Oliver Muller "Newtons of the leaves of grass", Nature Biotechnology 387
[6] D Ewen Cameron, Caleb J Bashor and James J Collins, 'A Brief History of Synthetic Biology' (2014) 12 Nature Reviews Microbiology 381
[7] Annaluru et al , " Total synthesis of a functional designer eukaryotic chromosome" (20140 344 Science 55
[8] Knight, T. F. Jr Idempotent vector design for standard assembly of BioBricks. MIT Synthethic Biology Working Group Technical Reports [online], http://web. mit.edu/synbio/release/docs/biobricks.pdf (2003).
[9] Gibson, D. G. et al. Enzymatic assembly of DNA molecules up to several hundred kilobases. Nature Methods 6, 343–345 (2009
[10] Galdzicki, M., Rodriguez, C., Chandran, D., Sauro, H. M. & Gennari, J. H. Standard biological parts knowledgebase. PLoS ONE 6, e17005 (2011)
[11] Nielsen, A. A. K. et al. Genetic circuit design automation. Science 352, aac7341 (2016).

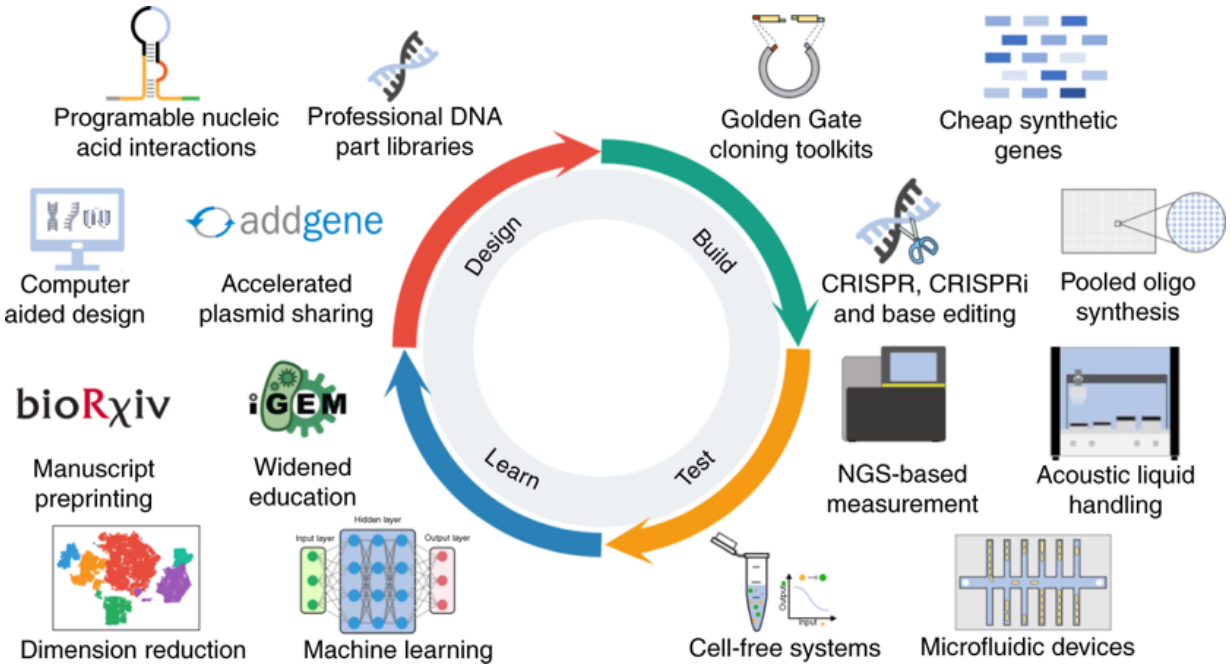

Image from https://www.nature.com/articles/s41467-020-19092-2#ref-CR2

In the mid 2000s, widespread recognition was brought to the field by the International Genetically Engineered Machine (iGEM) competitions, which attracted tremendous participation from universities, schools and general public.[12] In 2004, the first International conference for Synthetic Biology (S.B 1.0) was organized in Massachusetts Institute of Technology (MIT), US. The subsequent Conferences helped in globalizing the community and bringing attention to its various developments. [13]

A major success of the synthetic biology revolution is the increasing role of amateur innovators, substantially eliminating the barrier for non-specialists.[14] This is a departure from the days of conventional biotechnology, where innovation was the monopoly of well-funded corporations and academic laboratories. Advances in synthetic biology has democratized innovation in biotechnology with a plethora of Do-it- yourself (DIY) bio-hackerspaces. It is expected that significant contributions of DIY

[12] Smolke, C. D. Building outside of the box: iGEM and the BioBricks Foundation. Nature Biotech. 27, 1099–1102 (2009).
[13] D Ewen Cameron, Caleb J Bashor and James J Collins, 'A Brief History of Synthetic Biology' (2014) 12 Nature Reviews Microbiology 381 <http://dx.doi.org/10.1038/nrmicro3239> .
[14] Drew Endy, "Foundations for Engineering Biology," 2005, 438 Nature 449, 450

synthetic biologists will arise in the context of collaboration and open source, similar to the role played by hackers and open innovation in software development.[15]

The iGEM is a brilliant reflection of how amateurs are thriving on the innovation platform. In 2011, iGEM was expanded to include not only collegiate teams, but also teams comprising high school students.[16] Much like mobile applications, the tools developed by synthetic biology can cater to a wide range of human needs from entertainment and aesthetics to health and climate change mitigation.

In the San Francisco Bay area, an organization called "BioCurious" has opened a community biotechnology laboratory where interested amateurs can learn the techniques and use them to create their own products.[17] A similar community bio-lab called Genspace was opened in New York in 2010 organizing classes and events for the inquisitive minds.[18]A communal synthetic biology project called the "Glowing Plant," showed great promise for urban sustainability by engineering bioluminescent plants.[19]

b. *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, focusing on why, how and when a technology be developed and/or deployed . International law requires state parties to the respective treaty regimes to take measure, 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.[20] Laws and regulations can be as consequence

[15]Nathaniel Johnson, "Steal This Genome", March 2005, East Bay Express http://www.eastbayexpress.com/ebx/steal-this-genome/Content?oid=1077148.
[16] iGEM results at http://2017.igem.org/Competition/Results
[17] BioCurious, "The World's First Hackerspace for Biotech, Located in Silicon Valley" at http://biocurious.org/
[18] Genspace at http://genspace.org/page/About
[19] Growing Plant "Natural Lighting Without Electricity" at http://glowingplant.com/
[20] https://www.who.int/heli/tools/legis_regul/en/

of insightful policy-making, but their manner and effectiveness of implementation can lead to a process of further policy development.[21]

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. A major reason for the polarization is the large degree of scientific uncertainty that surrounds any emerging technology. The policy considerations for synthetic biology should take into account promises of radical benefits, and also possible risks

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 had set up a Task Force on systems biology and synthetic biology research in 2011.[22] India has informed international bodies that the technology is still at its infancy in the country and private sector involvement is limited to few companies.[23]

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.[24]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.[25] Initiatives include the Indian Biological Engineering Competition [26] and the DBT training program.

The report had emphasized that India has the opportunity to be a world leader as a protector and supporter of "open source biological platforms". [27] This requires a

[21] UNEP/IUCN Joint Environmental Law Database (http://www.ecolex.org)

[22] https://dst.gov.in/sites/default/files/3-tf_ssynthetic biologyrn.pdf
[23] India's submission on synthetic biology in response to CBD Notification No. 86375 dated 16 March, 2017
[24] Report Of The Planning Commission Constituted Task Force On Synthetic And Systems Biology Resource Network, 2011
https://dst.gov.in/yearsplan/synthetic-and-system-biology-resource-network-ssynthetic biologyrn
[25] http://www.syntheticbiology.in/
[26] As a precursor event to the iGEM competition https://syntheticbioindia.weebly.com/ibec-2016-description.html
[27] 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

supportive legal and regulatory environment in which small biotechnology players can participate.

This document discusses various international developments and discussions and related treaty framework which is directly applicable to designing a synthetic biology policy framework for India. Besides, it will outline the well-established principles of international law that can serve as a guiding tool for imagining a policy framework that addresses the political, social, economic, environmental and human rights concerns of the technology.

c. *Regulatory Aspects*

Regulation refers to interventions that are put in place by relevant agencies "*to control and channel conduct in the desired way*." [28] 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.

As synthetic biology is seen as one of the top ten breakthrough technologies as part of the "new industrial revolution "that are most likely to change the world", the regulation of both the benefits and risks become important for the international community.[29] The accelerating pace of scientific research and research irregularities about the specific benefits of synthetic biology create complex challenges for national regulation. On the other end it can also pose risks such as bioterrorism, loss of trade opportunities, environmental damage, tranboundary harm and the related.

It is important to understand that the technology cannot advance without some freedom in research and development. The regulatory challenge is how 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.

[28] Brownswood, Rights, Regulation and the Technology Revolution" (2008) 27
[29] Church and Ed Regis "Regenesis: How synthetic biology will reinvent nature and ourselves " 2013

The key point of difference is that the synthetic biology organisms are able to self-replicate and spread rapidly and evolve on their own. Since we have not yet realized the full potential of the technology, we cannot be sure of how it will play out in the future. We have to develop a framework for anticipatory governance - providing a set of procedural principles about how to collectively imagine, deliberate, influence and design its development. [30]

Though industrial self-regulation and non-governmental interventions are discussed in the report, they do not substitute the governmental regulatory oversight that is necessary to protect the public confidence in the technology. 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 regulatory framework.

2. A DEEPER UNDERSTANDING OF SYNTHETIC BIOLOGY

a. Defining synthetic biology

The term 'synthetic biology' was first used by Barbara Hobomin in 1980, to describe bacteria that had been genetically engineered using recombinant DNA technology.[31] Synthetic biology was initially synonymous with 'bioengineering'.

In 2000, the term 'synthetic biology' was again introduced by Eric Kool and other speakers at the annual meeting of the American Chemical Society in San Francisco.[32] In this context, the term was used to describe the synthesis of unnatural organic molecules that function in living systems. More broadly in this sense, the term has been used with reference to efforts to 'redesign life'.

[30] Arnim Wiek and others, 'Sustainability and Anticipatory Governance in Synthetic Biology' (2012) 3 International Journal of Social Ecology and Sustainable Development 25.
[31] Hobom B. Surgery of genes. At the doorstep of synthetic biology. Medizin. Klinik.
[32] Steven A. Benner and A. Michael Sismour " Synthetic biology"

However the complexity and interdisciplinarity of the field makes a single definition which is commonly accepted difficult. Synthetic biology has enabled scientists to design and synthesise new sequences of DNA from scratch. This in turn supports the design of cells and organisms that can be applied for useful industrial processes such as produce biofuel or act as biosensors.

The ability to convert and represent DNA base pairs, genes and regulatory elements in a digital form has been the biggest driver of this technology.[33] This information, also titled Digital Sequence Information (DSI), enables researchers to understand the genetic blueprints of an organism in a computational environment.

This in-turn opens the door to designing, editing and modelling biological components prior to physically producing and inserting them into a cell or organism. This means increasing access to digital sequence information and computer automation has dramatically impacted the time and difficulty in designing these synthetic biology components.

Synthetic biology is embodied in a broad set of tools, processes and disciplines.

- The tools that facilitates synthetic biology includes (i) CRISPR-Cas9 reagents (that are used to cut and splice DNA), as well as (ii) DNA sequencers and (iii) DNA design software packages.

- Significant synthetic biology processes include (i) genome editing, (ii) whole genome sequencing and (iii) functional screening.

- The disciplines associated with synthetic biology include (i) systems biology, (ii) bioinformatics, (iii) molecular biology, (iv) microbial ecology and (v) plant virology.

[33] National Academies of Sciences, Engineering, and Medicine, 2017

This diversity of processes and discipline, and the borrowing of tools from other domains, makes a uniform definition of synthetic biology challenging.[34] Specific tools or processes can are not exclusively associated with synthetic biology. For instance, CRISPR-Cas9 may be employed in various non-synthetic biology contexts.

There is vast scope for synthetic biology to evolve further considering interactions between nanotechnology, artificial intelligence, robotics and a plethora of biological innovations breakthroughs in medical technologies, smart materials, energy production, etc. The World Economic Forum had predicted constant and potentially extremely broad interaction and innovation frontier between this "Fourth Industrial Revolution" and biodiversity.[35]

While synthetic biology is evolving so rapidly that no commonly accepted definitions exist, underlying all definitions is the concept that synthetic biology is the application of engineering principles to the fundamental components of biology. [36] It is radically altering the meaning of biology and what is it be "Alive.[37]"

The operational definition considered by the Convention on Biological Diversity Ad Hoc Technical Expert Groups on Synthetic Biology (CBD AHTEG) as a useful starting point for discussions about synthetic biology is as follows:

"*a further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems*" (UN CBD, 2017).

[34] Shapira, P., Kwon, S. and Youtie, J. (2017). 'Tracking the emergence of synthetic biology'. Scientometrics. Springer, 112(3), at. https://doi.org/10.1007/s11192-017-2452-5

[35] World Economic Forum's System Initiative on Shaping the Future of Environment and Natural Resource Security, 2018

[36] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane and Jonathan S. Adams "IUCN Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation" (2019)

[37] Torrance (n 1).

Some of the alternative definitions that are also being used include:

- *The application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms* (SCENIHR, SCCS, 2014).

- *The design and construction of novel artificial biological pathways, organisms and devices or the redesign of existing natural biological systems (The Royal Synthetic Biology Society*, (2017).

- *A new field of research in biotechnology that draws on engineering principles to manipulate DNA in organisms. It allows for the design and construction of new biological parts and the re-design of natural biological systems for useful purposes*. (OECD, 2016).[38]

b. The Building Block for synthetic biology - Digital Sequence Information

Next generation sequencing (NGS) or deep sequencing describes a DNA sequencing technology which is an important tool for synthetic biology.[39]. NGS platforms produce massive amounts of sequencing data because millions of DNA fragments can be sequenced in parallel and simultaneously. The cost of DNA synthesis is progressively decreasing and the ease of making genetic modifications with tools such as CRISPR/Cas9 is increasing rapidly.

There is an explosion of knowledge where we are creating digital databases that contains the collective biological intelligence of billions of years of evolutionary history.

[38] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane and Jonathan S. Adams "IUCN Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation" (2019)

[39] Sam Behjati and Patrick S Tarpey, "What is next generation sequencing?" available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3841808/

This information may characterize genetic material found in nature, that is designed, mutated, or degenerated, or that is purely hypothetical.[40]

The term "digital sequence information" (DSI) was introduced in decisions CBD XIII/16 and Nagoya Protocol NP-2/14.[41]Terms more commonly employed by the scientific community and databases include genetic sequence data, nucleotide sequence data, nucleotide sequence information, and genetic sequences. The 2018 the CBD scoping study on SYNTHETIC BIOLOGY has noted that differences in terminology in scientific circles reflect differences in the material referred to, as well as the speed and transformative nature of technological change today. [42]

The terminology used also varies between international policy processes. The term "sequence data" is used in the scoping study on synthetic biology recently commissioned by the Secretariat of the International Treaty on Plant Genetic Resources (ITPGRFA).[43] The Commission on Genetic Resources for Food and Agriculture (CGRFA) however uses the term "digital sequence information" on genetic resources for food and agriculture in its exploratory fact-finding scoping study, in line with the CBD COP decision XIII/16. [44]

In the context of the discussions of the Preparatory Committee established by resolution 69/292 "Development of an international legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction", the terms "*resources in silico*" and "*digital sequence data*" have been used by different delegations.[45]

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[40] IUCN available at https://www.iucn.org/theme/science-and-economics/our-work/culture-science-and-knowledge/synthetic-biology-and-biodiversity-conservation/synthetic-biology-and-convention-biological-diversity

[41] Convention on Biological Diversity (2018) , Fact-Finding And Scoping Study On Digital Sequence Information On Genetic Resources In The Context Of The Convention On Biological Diversity And The Nagoya Protocol

[42] Convention on Biological Diversity (2018), Fact-Finding And Scoping Study On Digital Sequence Information On Genetic Resources In The Context Of The Convention On Biological Diversity And The Nagoya Protocol

[43] Potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or 'Treaty') October 2017

[44] Commission on Genetic Resources for Food and Agriculture at http://www.fao.org/3/my588en/my588en.pdf

[45] United Nations Convention on the Law of the Sea resolution 69/292

The World Health Organization Pandemic Influenza Preparedness (WHO PIP) Framework uses the term genetic sequence data, and defines genetic sequences as: "*The order of nucleotides found in a molecule of DNA or RNA... containing the genetic information that determines the biological characteristics of an organism or a virus*".[46]

3. RESEARCH AND DEVELOPMENT IN SYNTHETIC BIOLOGY

Ever since Synthetic Biology was formally launched as a distinct discipline, the field has seen several developments e.g., (i) standard genomic parts that can be used to quickly build novel biological systems (ii) re-design existing biological parts and expand the set of natural protein functions for new processes (iii) engineering microbes to produce natural products and chemical compounds and (iv) design, chemical synthesis and construction of genome and chromosome.

Currently, synthetic biology products from several companies are on the horizon. These include, 1,3 Butadiene (Lanza Tech), 1,4 Butanediol (Bioamber), acrylic acid (Myriant, OPX Biotechnologies, Metabolix, Novozymes, Cargill), adipic acid (Verdezyne, Bioamber, Rennovia), antibiotic EV-035 (Evolva), biodispersants (Modular genetics), biobutanol (Green Biologics, Microvi, BP), bioisoprene (Dupont, Goodyear, Amyris, Michelin, LanzaTech), biopolymers (Metabolix), lactic Acid (Myriant), diabetes drug (Evolva), dodecanedioic acid (Verdezyne), fatty acids (OPX Biotechnologies), fumaric acid (Myriant), myristoyl glutamate (Modular genetics), patchouli oil (Amyris), pomecin (Evolva), sabacic acid (verdezyne), saffron (Evolva), Sitagliptin (Codexis), stevia and vanillin (Evolva).

Furthermore, a number of products are close to the market e.g., accelerate TRIO (Genencor, Dupont), bio based polyurethanes (Bioamber), biopolymer (Metbolix), cephalexin (Royal DSM), cottonase pectate lyase (Dupont, Verenium), D lactic acid (Myriant), encapso (Solazyme), eradicate alpha-amylase (Dupont, Verenium),

[46] WHO PIP Framework, section 4.2 at https://www.who.int/influenza/pip/WHA70108b_Analysis.pdf?ua=1

farnesene (Amyris), fuelzyme alpha-amylase (Dupont, Verenium), isobutanol (Gevo), Luminase PB-100 (Dupont, Verenium), nootkatone (Allylix, Isobionics, Evolva), pyrolase cellulase (Dupont, Verenium), Sorona (Dupont, Tate & Lyle Bio products), succinct acid (Bioamber, Myriant, Royal DSM), Susterra (Dupont, Tate & Lyle Bio products), ultra clean diesel (LS9), valencene (Allylix, Isobionics, Royal DSM), Xylathin Xylanase (Dupont, Verenium), zemea (Dupont, Tate & Lyle Bio products), zemea USP (Dupont, Tate & Lyle Bio products). In addition, synthetic biology software like product cyborg (Autodesk), cadano (Autodesk, Wyss Institute) and TeselaGen bioCAD/CAM platform (TeselaGen Biotechnology).

Overall the design and construction approach is significantly impacting biopharma (producing medically relevant drugs like artemisinin and small molecules). Some of the recent work like CAR-T cell therapy for cancer, synthetic tissues and synthetic organdies (Distributed Bio, Mammoth Biosciences, Synlogic and Precigen) are very interesting developments.

Several groups are working towards developing alternative biology based methods for industries that generate significant carbon emissions. Synthetic Genetics is engineering algae as bio factories for renewable fuel while Global Bioenergies are converting plant waste into petrochemical precursors. Kiverdi, Photanol, Visolis, LanzaTech and Global Bioenergies are some of the key synthetic biology companies to watch in the space of carbon recycling.

Synthetic Biology has started making significant inroads in the fashion industry as well. Companies like Tinctorium, PILI and Colorfix are exploring the possibility of dyeing jeans without producing the hazardous waste. Mango Materials is using bacteria to make bioplastics from methane, for applications in the garment industry. Bolt threads are making synthetic silk and faux leather from mushrooms. Likewise, AMSilk (Germany), Spiber (Japan) and Ecovative Design (US) use mushrooms to create a range of clothing and footwear.

Innovation frontiers are rapidly moving forward to generate applications in the cosmetics and fragrance industry. Synthetic Biology companies are focusing on areas

like makeup, skin creams, cologne and perfume. Collagen that has been traditionally sourced from animals is being replaced by synthetic substitutes / additives. Companies like Evolva are working towards producing nootkatone through fermentation. Similar Robertet Company is developing fragrances at a commercial level. Key companies in this sector are: Conagen, Geltor and Amyris.

Finally, the food sector is inviting a lot of attention from synthetic biology companies. Pivot Bio and Joyn Bio are engineering soil bacteria to deliver fixed nitrogen to plants and replace synthetic fertilisers. Congane is engineering microbes to synthesise food additives. Motif FoodWorks is using fermentation to brew proteins and nutrients to make food more delicious and sustainable.

Companies are also paying serious attention to the animal proteins. AquaBounty is working towards making sustainable salmon and AirProtein is using microbial fermentation processes from air. Other companies to watch are: Motif FoodWorks and Solar Foods.

Given the rapid emergence of technologies and products in synthetic biology, it is all the more necessary to provide guidance to funding and regulatory bodies to ensure responsible innovation. In this context, it is important to identify research priorities and bottlenecks and discuss how best to manage risk and earn public acceptance of this emerging and disruptive technology.

Inscripta has developed a bench top platform for genome engineering using CRISPR. Their Onyx platform can generate more than 10,000 edits per run with a single edit made per cell using the Mad7 nuclease. Companies use computational protein design to develop synthetic variants of molecules in a big way. Arzeda Company's platform generates the DNA sequences for creating enzymes of choice.

Japan based OriCiro have developed a cell free cloning method for up to 1MB of DNA, using a rapid two step enzymatic process. The first step uses homologous overlapping DNA ends linking up to 50 fragments. The second step amplifies the DNA – all outside of the cell. Though cell free cloning technology is less accurate than traditional cloning

method, the cell free method can be used in situations where the environment is toxic to the organisms.

MiProbes has developed a cell free biosensor (based on quorum sensing) embedded on a disk for testing food spoilage. Similarly, synthetic biology is driving critical advances in biomedicine, prompting groundbreaking developments in health care.

Synthetic biology researchers in industry report different usage rates for publicly available standard parts registries. Likewise, DNA synthesis technologies are reducing the cost of constructing DNA sequences along with achieving significant improvement in the length and error rate. As innovation in this field continues to advance the raw material, methods and tools considered enabling for synthetic biology may change with time. This will stimulate changes in the funding, regulation, patenting and licensing of these technologies. In future, it will be important to adopt policies and practices promoting transdisciplinary exchange of ideas, data and technology. It will be important to create structures for managing intellectual property, technology transfer and ensuring responsible innovation. By innovating the monitoring process, developing best practices and policies that can be implemented, synthetic biology will reach its full potential within the framework of responsible innovation.

4. GOVERNANCE, POLICY AND REGULATORY ASPECTS RELEVANT TO SYNTHETIC BIOLOGY

As with other developments in science and technology governance systems, across the world, synthetic biology is also impacted by discussions at international, regional and private-sector driven positions and interests. Countries are in need to considering several global, legally-binding, environmental treaties and conventions that provide guidance on the future of technologies such as synthetic biology. Currently, several international processes are considering options to deal with development and deployment of SYNTHETIC BIOLOGY products and organisms.

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)

Since 2010, the CBD has discussed whether synthetic biology should be classified as a new and emerging issue in the context of realizing the objectives of convention, namely, conservation, sustainable use and equitable sharing of benefits arising from use of the resources. An assessment of synthetic biology against the CBD's new and emerging criteria was carried out without any definite conclusions reached thus far. To date, the Convention on Biological Diversity (CBD) has been ratified by 196 states. Notable exception in terms of major players, using synthetic biology is the United States of America (US) which is a non-party to CBD.

Both 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. For the consideration of the parties at the 12th meeting, two reports on the potential impacts of the technology and possible gaps and overlaps with the Convention were released. [47]

The Parties decided to establish an Ad Hoc Technical Expert Group (AHTEG) and convened a moderated open-ended online forum to support its work[48]. The AHTEG has come up with an operational definition for synthetic biology which is a useful starting point for further deliberations.

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. [49]At the COP 14, Parties agreed on a need for regular horizon-scanning of the most

[47] https://bch.cbd.int/synbio/
[48] CBD COP decision XII/24,
[49] Ad Hoc Technical Expert Groups on Synthetic Biology, 2015, 2018

recent technological developments for reviewing new information regarding potential impacts of synthetic biology.[50]

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.[51] 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. [52]

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 Utilization (ABS) to the Convention on Biological Diversity. [53]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.[54]

ii. Food and Agricultural Organization (FAO)

The FAO International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) report commissioned in 2017examined the impacts of synthetic biology and

[50] CBD COP decision 14/19,
[51] CBD COP decision 14/19,
[52]Report Of The Ad Hoc Technical Expert Group On Synthetic Biology Montreal, Canada, 4-7 June 2019 at https://www.cbd.int/doc/c/b2bb/cf58/b09729bb00be6abf72325a1a/synbio-ahteg-2019-01-03-en.pdf
[53] Wynberg, R. and Laird, S.A. (2018). 'Fast Science and Sluggish Policy: The Herculean Task of Regulating Biodiscovery'. Trends in Biotechnology
[54] Recommendation Adopted By The Subsidiary Body On Scientific, Technical And Technological Advice CBD/SYNTHETIC BIOLOGYSTTA/22/ CRP.10, 2018 at https://www.cbd.int/doc/recommendations/synthetic biologystta-22/synthetic biologystta-22-rec-10-en.pdf

digital sequence information (DSI) on the Plant Treaty.[55] The report addresses the phenomenon of "dematerialization", 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.[56]

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. [57] Seventieth meeting of the CITES Standing Committee in October 2018 adopted a report on the "*Specimens Produced from Synthetic and Cultured DNA*."[58] 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.[59] 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.

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[55] Welch, E., Bagley, M., Kuiken, T. and Louafi, S.. Potential implications of new synthetic biology and genomic research trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or 'Treaty'). 2017.

[57] Decisions 17.89 to 17.91, 2016; SC69 Doc. 35, 2017

[58]Seventieth meeting of the Standing Committee Rosa Khutor, Sochi (Russian Federation), CITES, 1-5 October 2018at https://cites.org/sites/default/files/eng/com/sc/70/E-SC70-33.pdf

[59] Resolution 6.086

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 In accordance with TRIPS, patents should be available under national law of WTO members (other than LDCs) for innovative products/ processes in the field of synthetic biology, provided that they constitute inventions that comply with the general patentability standards. Select products of synthetic biology techniques may fall under the subject matter exclusions provided by Article 27, paragraphs 2 and 3 of the TRIPS Agreement and may therefore be excluded from patentability by some WTO members.

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)) when it comes to new plant varieties developed. 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, including varieties that are deemed essentially derived from a protected variety are 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 is being discussed.

Principles of International Law

Whether it is the international developments in defining the scope, governance and regulations related to synthetic biology products and organisms or national policies and regulatory frameworks related the same, there is a need to understand and apply, as appropriate, principles of international law.

A number of overarching rules and principles under international law can be applicable to the field of synthetic biology – the technology, components, organisms and commercialization. Treaties only apply to those States that are Party to them. In contrast, customary law which includes well established principles of international law applies to States regardless of whether they have ratified particular treaty.[60] The principles of international law relevant to the discussions on synthetic biology are:

i. The precautionary principle
ii. State sovereignty and prevention of transboundary harm.
iii. State responsibility and Environment Impact Assessment
iv. Principles of access to information, public participation and access to justice
v. People's right to self-determination and free prior informed consent
vi. Sustainable development and inter-generational equity

i. The Precautionary principle

Scientific uncertainty is a persistent characteristic of environmental governance. The precautionary principle or approach provides a tool for addressing uncertainty in decision making. The principle evolved as an approach to evaluate risks and benefits as a strategy for warding off environmental damage.

This means there is a shift in the burden of proof from those who raise concerns about a new project or technology to the ones promoting it to prove that the project doesn't cause harm. Usually there is not enough evidence for proving harm and in the case of synthetic biology it will be difficult to prove that it is entirely safe.

As formulated in the Rio Declaration on Environment and Development:
"*Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost effective measures to prevent environmental degradation.*" [61]

[60] https://legal.un.org/ilc/reports/2019/english/chp5.pdf
[61] Rio Declaration, Principle 15

This has been reformulated in the preamble of the Convention on Biological Diversity, which reads: "*Where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat*."

Precaution has been referenced in the preamble of the Cartagena Protocol and applied in the articles relating to decision making procedures. CBD COP Decision XI/11 explicitly applies the approach to synthetic biology, stating:

"*Recognizing the development of technologies associated with synthetic life, cells or genomes, and the scientific uncertainties of their potential impact on the conservation and sustainable use of biological diversity, urges Parties and invites other Governments to take a precautionary approach, in accordance with the preamble of the Convention and with Article 14, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations.*" [62]

In November 2018, the CBD COP further called upon Parties to apply a precautionary approach with regard to engineered gene drives.[63] In its decisions addressing biofuels, the Conference of the Parties also "*urged Parties and other Governments to apply the precautionary approach… to the introduction and use of living modified organisms for the production of biofuels as well as to the field release of synthetic life, cell, or genome into the environment, and to monitor technology associated with biofuels*".[64]

Beyond international instruments, national frameworks have also adopted the precautionary principle. In The European Union (EU), the precautionary principle is a key element in the Genetic Modification regulatory framework. The opinion on synthetic

[62] CBD COP decision XI/11, para 4

[63] Synthetic Biology Draft decision submitted by the Chair of Working Group II COP/14/L.31

[64] UNEP/CBD/COP/DEC/X/37 "X/37. Biofuels and biodiversity" 29 October 2010 at https://www.cbd.int/doc/decisions/cop-10/cop-10-dec-37-en.pdf

biology by three Scientific Committees of the European Commission [65] outlined that precautionary approach in accordance with domestic legislation and other relevant international obligations is required to prevent the reduction or loss of biological diversity posed by organisms, components and products generated by synthetic biology. It is also interesting to note the clash between freedoms of research anchored in Art. 13 of the EU Charter of Fundamental Rights and the precautionary principle. [66]

Other countries like the United States have not explicitly included the precautionary principle in their legal system and have resisted codification of the principle in international treaties but adopt the principle in practice. [67] "Product-based" or "trait-based" assessment is the pillar of the US policy for genetic modification process which exempted the GM products from regulations. [68]

In case of nanotechnology, there has been a paradigm shift in adopting precautionary principle while the Toxic Substances Control Act have not restricted the use of chemical substances unless the regulatory authority proves an unreasonable risk. [69] In Australia, there is case law in this area growing since 1990s. [70] The European Court of Justice (ECJ) and Court of First Instance have used guidelines about precautionary action and have been interpreted in case law. The ECJ examined the precautionary principle in risk assessment in relation to a regulation banning animal food additives. [71]

Applications of synthetic biology carry risk that is uncertain and potentially irreversible, making the precautionary principle applicable. Industry proponents have argued that it

[65] Scientific Committee on Health and Environmental Risks SCHER Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR Scientific Committee on Consumer Safety SCCS " Opinion on Synthetic Biology I Definition" (2014) available at https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf

[66] Würtenberger and Tanneberger (2014), "Futures of Technology, Science and Society"

[67] Jonathan B. Wiener, Michael D. Rogers "Comparing precaution in the United States and Europe"

[68] ENSSER Statement on New Genetic Modification Techniques (2017) https://ensser.org/publications/ngmt-statement/

[69] Jean Warshaw "The Trend Towards Implementing The Precautionary Principle In Us Regulation Of Nanomaterials" (2012)

[70] Telstra Corporation ltd v Hornsynthetic biology Shire Council (2006) 146 LGERA 10

[71] Alpharma Inc v Council of the European Union T-70/99, [2002] ECR II - 03495

is vague and an obstacle to scientific progress[72]. Despite being invoked consistently in environmental governance, there is no uniform formulation of the principle and its legal status in customary international law is not clearly established.[73]

Some civil society and scientific organisations have argued that the precautionary principle necessitates a "*moratorium on the release and commercial use of synthetic organisms, cells, or genomes until government bodies, with full participation of the public*" have conducted assessments and developed international oversight mechanisms.[74]

ii. *State Sovereignty and Prevention of Tran boundary Harm*

A basic principle of international law is that states have "*the sovereign right to exploit their own resources pursuant to their own environmental and developmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction.*" [75]

The Principle 2 of the Rio Declaration also has similar language.[76] State sovereignty provides the basis for states to make decisions regarding genetic resources and biological diversity within their territory. In the context of synthetic biology regulation, this does includes decisions regarding risk assessment and access and benefit sharing.[77]

State sovereignty includes risk assessment decisions relating to activities affecting natural resources in their territory, including decisions on introduction of modified

[72] Hastings Center "Carefully Precautionary about Synthetic Biology?" (2012) at https://www.thehastingscenter.org/carefully-precautionary-about-synthetic-biology/

[73] Beyerlin, Ulrich, and Thilo Marauhn. 2011. International environmental law. Hart Publishing. Oxford.

[74] ETC Group, Friends of Earth and International Centre for Technology Assessment "The Principles for the Oversight of Synthetic Biology" at ,Ihttps://www.etcgroup.org/files/The%20Principles%20for%20the%20Oversight%20of%20Synthetic%20Biology%20FINAL.pdf

[75] 11 IILM 1416,, Declaration of the United Nations Conference on the Human Environment Stockholm, 16 June 1972

[76] UNEP/ CBD/ COP/ 12/ INF/ 11

[77] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane, Jonathan S. Adams, IUCN "Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation"

organisms into the environment. States can also subject the access of natural resources to requirements for permits and benefit-sharing agreements.

States having sovereignty rights also have the duty not to cause transboundary harm. As held in the Pulp Mills case, it is an international customary rule that a state must prevent and provide compensation for damage wrongfully caused from its territory to other states.[78]

The International Court of Justice, in the Gabcikovo Nagymaros case, and in its advisory opinion on the Legality of the Threat or Use of Nuclear Weapons, confirmed the "*existence of the general obligation of States to ensure that activities within their jurisdiction and control respect the environment of other States or of areas beyond national control is now part of the corpus of international law relating to the environment*."[79]

Many synthetic biology research and commercial applications have the potential for transboundary impacts. However it does not mean that any activity that can cause environmental harm is generally prohibited. The duty only obliges a State of origin (of the product and/or organism in the case of SYNTHETIC BIOLOGY) to take adequate measures to control and regulate in advance potential sources of such harm.

States have to exercise "due diligence" before carrying out potentially harmful activities. In the synthetic biology context, release of mosquitoes developed using synthetic biology to reduce dengue and distribution of the Glowing Plant can all be environmental release of organisms. Whether such release will result in 'significant damage' and what was the "due diligence" expected of the State can only be ascertained on a case-by-case basis.

[78] Pulp Mills on the River Uruguay (Argentina v. Uruguay) International Court of Justice, 2010

[79] ICJ, Case concerning the Gabcikovo-Nagymaros Project (Hungary v. Slovakia), ICJ Reports 1997, 7, paragraph 53; and Legality of the Threat or Use of Nuclear Weapons (Advisory Opinion - General Assembly), ICJ Reports 1996, 22, paragraph 29.

iii. State Responsibility and liability of private actors

Synthetic biology techniques can be employed by both State and private entities. The laws of state responsibility constitute the principles governing when and how a State is held responsible for breach of an international obligation.[80] It also addresses the circumstances under which the conduct of non-State actors may be attributable to a State.

The International Law Commission has concretised the general rule by developing Draft Articles where there is an obligation to make reparation for "*any damage, whether material or moral, caused by the internationally wrongful act of a State*"[81]. Conduct of non- state actors are attributable to the State only if it is exercising elements of government authority or in any other relationship as articulated in the Draft articles.

A State can be under an explicit obligation to address private actors. Such an obligation has been partly applied to biosafety issues by the Nagoya- Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol to address private actors through domestic rules of liability. [82]

In addition to the "ex post" liability approach, the principle of state responsibility implicates an "ex ante" approach in the form of a responsibility to conduct environmental impact assessments (EIA) where there is potential for significant transboundary adverse impact[83]. Depending on scope, this could apply in cases where synthetic biology or engineered gene drives cross boundaries.

[80] as adopted by the Draft Articles on the Responsibility of States for Internationally Wrongful Acts by the International Law Commission in August 2001 at https://www.un.org/ga/search/view_doc.asp?symbol=A/56/10%28SUPP%29

[81] ILC Draft Articles 2001, art. 31, International Law Commission, United Nations, Draft articles on Responsibility of States for Internationally Wrongful Acts, with commentaries https://legal.un.org/ilc/texts/instruments/english/commentaries/9_6_2001.pdf

[82] https://bch.cbd.int/protocol/supplementary/

[83] Pulp Mills on the River Uruguay (Argentina v. Uruguay) International Court of Justice, 2010 United Nations Convention on Law of the Sea Art 206.https://www.un.org/depts/los/convention_agreements/texts/unclos/unclos_e.pdf

Article 14 of the CBD also requires Contracting Parties to introduce appropriate procedures requiring EIA when there is likelihood of "significant adverse effects."[84] The Cartagena Protocol to the CBD further stipulates that export of GMOs requires prior informed consent (PIC) of the importing state.

Some of the most active states in biotechnology are not among the 171 Contracting Parties of the Protocol, including the United States, Australia and Russia. Despite the absence of Treaty obligations, failure to comply with EIA and PIC obligations would possibly qualify as a wrongful act in the sense of the customary international law and Draft Articles described above.

Recognising the potential for harm in terms of accidents even in full compliance by the State, the International Law Commission also developed Draft Principles on the Allocation of Loss in the Case of Transboundary Harm Arising out of Hazardous Activities in 2006. It requires states to impose strict liability on operators of hazardous activities, and require operators to have financial security, such as insurance, to cover compensation claim[85]. It is however open to debate whether synthetic biology could be considered a "hazardous activity" as understood by the Draft Principles impacting biodiversity and the natural environment

iv. Access to Information, Public Participation and Access to Justice

The Rio Declaration recognized that procedural norms of good governance apply to decision making including that of biodiversity and sustainable development. Principle 10 of the Declaration and SDG 16 sets the fundamental elements: access to information; public participation in decision-making processes; and access to justice[86]. These components have a long tradition in several legal systems, including the United States.[87]

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[84] https://www.cbd.int/kb/record/article/6896?RecordType=article

[85] International Law Commission, Allocation of Loss in the Case of Transboundary Harm Arising out of Hazardous Activities 2006 https://legal.un.org/ilc/texts/instruments/english/commentaries/9_10_2006.pdf

[86] Sustainable Development Goals(SDG 16), Peace, Justice and Strong Institutions; https://in.one.un.org/page/sustainable-development-goals/sdg-16/
Rio Declaration on Environment and Development (Convention of Biological Diversity) https://www.cbd.int/doc/ref/rio-declaration.shtml

[87] Stewart J, International Journal of Training and Development; https://onlinelibrary.wiley.com/doi/abs/10.1111/1468-2419.00177. 2003

Emerging technologies like synthetic biology have far-reaching impacts on environment and human life, whether for good or ill. Thus every State should strive to champion fair and just systems to promote wide availability of accurate information and democratic deliberation over concerns. The principles relates closely to the distribution of benefits and burdens across society.[88] This prevents outcomes which are environmentally damaging, developmentally unsustainable and socially unjust.[89]

These principles are exceptionally relevant in the context of the European Union's approaches. The principles were further elaborated in the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters of 1998[90]. The Aarhus Convention, while European in scope, provides guidance on interpretation of the three aspects, that have been recognised as globally relevant[91].

According to the Aarhus Convention, the principle of access to information requires that any person has the right of access to environmental information held by public authorities, including private actors with public functions, notwithstanding exceptions concerning the protection of privacy, trade secrets and certain public interests[92].

The principle of public participation provides for a right of the public at large and particularly concerned persons to participate early in decision-making processes in

[88] "New Directions: Ethics of Synthetic Biology and Emerging Technologies (2010) https://bioethicsarchive.georgetown.edu/pcsynthetic biology/sites/default/files/PCSYNTHETIC BIOLOGYI-Synthetic-Biology-Report-12.16.10_0.pdf

[89] David Banisar Sejal Parmar Lalanath de Silva Carole Excell "Moving from Principles to Rights: Rio 2012 and Access to Information, Public Participation, and Justice" , Sustainable Development Law and Policy Volume 12 (2012)

[90] United Nations Economic Commission for Europe, Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters, https://www.unece.org/fileadmin/DAM/env/pp/documents/cep43e.pdf 1998

[91] Morgera, E., The EU Aarhus Regulation and EU Administrative Acts Based on the Aarhus Regulation: the Withdrawal of the CJEU from the Aarhus Convention, International Judicial Practice on the Environment, https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-9388.2005.00434.x 10.1017/9781108684385, (52-73), 2005.

[92] Aarhus art. 4, The UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters

relation to certain hazardous activities or environment-related plans, programmes and executive regulations.[93] This includes matters of negotiation and implementation of international agreements.

The principle of access to justice in environmental matters states that any person (which includes any environmental organisation) who considers their rights violated or interests affected by an environmental decision has access to a court or other independent and impartial review procedure to challenge the substantive and procedural legality of the decision.[94]

The Aarhus Convention explicitly applies these principles to matters related to genetically modified organisms. [95] The Convention links environmental rights to human rights and focuses on interactions between public and private authorities.

vi. Peoples' Rights to Self-Determination and Free, Prior and Informed Consent

Synthetic biology decision making can implicate rights of indigenous peoples and local communities in relation to natural resources and culture. For instance, the example of a population suppression of some wild species that cause undesirable ecological damage may affect the indigenous community that relies on it for food or cultural value.

The principle of self-determination of peoples, recognised in the Charter of the United Nations, the International Covenant on Civil and Political Rights, the International Covenant on Economic, Social and Cultural Rights, entails a right to control over natural wealth and resources[96].

The UN Declaration on the Rights of Indigenous Peoples and International Labour Organization (ILO) Convention 169 elaborate the rights of indigenous and tribal peoples

[93] Aarhus arts. 6-8 The UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters

[94] Aarhus art. 9 The UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters

[95] Aarhus art. 2(3)(a), art. 6(11)]. The UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters

[96] UN Charter art. 55, Repertory of Practice of United Nations Organs, United Nations Charter, Chapter IX https://legal.un.org/repertory/art55.shtml

to participate in the use, management and conservation of resources pertaining to their lands. ILO Convention 169 requires governments to "*respect the special importance for the cultures and spiritual values of the peoples concerned of their relationship with the lands or territories, or both as applicable, which they occupy or otherwise use...*"[97].

A series of international human rights cases (HRC "Lubicon Lake Band" 1984[98]; IACHR "Awas Tingni" 2001[99]; ACHPR "Endorois" 2009[100]) have highlighted the special relationship between indigenous peoples and their traditional territory and resources. It was found that interference with rights of communities related to their natural resources can implicate the human right to culture.

In practice, these rights are realised through procedural requirements for involvement of communities in decision making. The UN Declaration on Rights of Indigenous Peoples provides that indigenous peoples shall not be relocated from their lands or territories without their free, prior and informed consent[101]. The concept of free prior and informed consent (FPIC) has been extended to apply to any decision making related to activities affecting the territory or natural resources of indigenous peoples or communities.

Free, prior and informed consent has been largely discussed in the context of conservation for decisions impacting indigenous peoples and local communities. In its recent report, the CBD's Ad Hoc Technical Expert Group on Synthetic Biology (AHTEG)[102] noted that "*free, prior and informed consent of indigenous peoples and local*

[97] ILO Convention 169 art. 14, Indigenous and Tribal People's Convention,1989 No. 169, International Labour Organization https://www.ilo.org/dyn/normlex/en/f?p=NORMLEXPUB:12100:0::NO::P12100_ILO_CODE:C169

[98] Lubicon Lake Band v. Canada, Communication No. 167/1984 (26 March 1990), U.N. Doc. Supp. No. 40 (A/45/40) at 1 (1990).

[99] Case of the Mayagna (Sumo) Awas Tingni Community v Nicaragua IACHR Series C No. 79 [2001]

[100] Centre for Minority Rights Development (Kenya) and Minority Rights Group International on behalf of Endorois Welfare Council v. Kenya, 276/2003

[101] Art. 10

[102] Convention of Biological Diversity, Portal on Synthetic Biology, https://bch.cbd.int/synbio/

communities might be warranted in the development and release of organisms containing engineered gene drives"[103].

The AHTEG also stated that the development of synthetic biology technologies "*should be accompanied by the full and effective participation of indigenous peoples and local communities*".[104] In 2018, the CBD COP called upon Parties and other Governments to obtain, as appropriate, free, prior and informed consent or approval and involvement of potentially affected indigenous peoples and local communities as a prerequisite to introducing engineered gene drives into the environment, in accordance with national circumstances and legislation[105].

vi. Sustainable Development and Inter-Generational Equity

Synthetic biology has potential benefits and potential effects that could affect resource management and economic development for future generations. The concept of sustainable development is defined as development that "*meets the needs of the present without compromising the ability of future generations to meet their own needs.*"[106] It recognises that economic/social development and environmental conservation are interdependent. [107]

Similar to the issue of climate change, synthetic biology also impacts the relationship of future generations with their living environment. The threat of irreversible or unpredictable damage takes away the choices of the future generation in enjoying the benefits of the natural world they inherit. Attitudes towards the natural world may

[103] para. 25, Convention of Biological Diversity, Report of the ad hoc Technical Expert Group on Synthetic Biology, Montreal, Canada, 5-8. https://www.cbd.int/doc/c/aa10/9160/6c3fcedf265dbee686715016/synbio-ahteg-2017-01-03-en.pdf December 2017

[104] Para 26, Convention of Biological Diversity, Report of the ad hoc Technical Expert Group on Synthetic Biology, Montreal, Canada, 5-8. https://www.cbd.int/doc/c/aa10/9160/6c3fcedf265dbee686715016/synbio-ahteg-2017-01-03-en.pdf December 2017

[105] COP declaration 14/L.31 paragraph 9-11, https://www.cbd.int/doc/c/2c62/5569/004e9c7a6b2a00641c3af0eb/cop-14-l-31-en.pdf

[106] Sustainable Development, Report of the World Commission on Environment and Development: Our Common Future https://sustainabledevelopment.un.org/content/documents/5987our-common-future.pdf 1987

[107] Principle 4, Rio Declaration on Environment and Development (Convention of Biological Diversity) https://www.cbd.int/doc/ref/rio-declaration.shtml

change over generations and the short-term benefits incurred by the current generation may accompany long-term risks to future ones.

It is linked to the principles of intergenerational equity, which entails an obligation of stewardship of the natural environment for future generations, and intragenerational equity which emphasises the need to meet the basic needs of current generations across circumstances and regions .[108]

The Sustainable Development Goals (SDGs) adopted in 2015 provide globally agreed upon targets for alleviating poverty, ensuring food security, combating climate change and conserving biological diversity. Certain applications of synthetic biology are intended to provide a means for realising sustainable development goals.

For example, applications to address invasive species could contribute to goals related to terrestrial and marine conservation (SDGs 14 and 1), while applications addressing human disease vectors such as mosquitoes support achievement of goals on human health and well-being as well as alleviation of poverty (SDGs 1 and 3).

Regulatory Frameworks Relevant To Synthetic Biology

Synthetic biology engages existing normative systems at the international, regional, national and sub national levels. Synthetic biology promises transformative benefits for human development but also poses risks of harm. Many of the existing regulatory frameworks were developed in the context of "traditional" fields such as biotechnology and genetic engineering and may have to be revised in order to cope with fresh challenges raised by synthetic biology.[109]

The SYNTHETIC BIOLOGY organisms will be more complex in substantial ways than previously developed recombinant DNA organisms , furthering uncertainty about their

[108] (Brown Weiss, 1993 [ICJ Nuclear Test Case, 1995, Weeramantry dissenting; ICJ Gabcikovo-Nagymaros, 1997, Weeramantry concurring; Minors Oposa, 1993).

[109] Laird, S. and Wynberg, R., A Fact-Finding and Scoping Study on Digital Sequence Information on Genetic Resources in the Context of the Convention on Biological Diversity and the Nagoya Protocol, https://www.cbd.int/doc/c/e95a/4ddd/4baea2ec772be28edcd10358/dsi-ahteg-2018-01-03-en.pdf 2018

human health and environmental impact. These organisms could persist in the natural environment for a long time and reproduce and spread. Along the process, such organisms might mutate or change their characteristics and potentially transfer their DNA to other naturally occurring organisms.

Regulating the Risks

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." [110] 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.[111] Intention is the key difference between both the two concepts and biosafety mostly refers to accidental events.

The 2001 Anthrax attacks warned the world about possible risks of biosecurity due to mishandling of pathogens. In countries like the U.S. it is possible for ordinary citizens to obtain different genetic DNA from thirty plus gene synthesis companies. For instance, during COVID-19 Twist Bioscience has been printing out genetic material for vaccine companies like Inovio. [112]

[110] Alexander Kelle, Security Issues Related to Synthetic Biology, in Synthetic Biology: The Technoscience And Its Societal Consequences 101, 102 (Schmidt et al. eds., 2009).
[111] Alexander Kelle, Security Issues Related to Synthetic Biology, in Synthetic Biology: The Technoscience And Its Societal Consequences 101, 102 (Schmidt et al. eds., 2009).
[112] https://www.twistbioscience.com/blog/science/raw-materials-tackle-coronavirus

The production and mailing of DNA parts, which could subsequently be combined to form dangerous viruses including the smallpox, was completely legal. In 2011, Fouchier and Kawaoka alarmed the world by revealing they had separately modified the deadly avian H5N1 influenza virus so that it spread between ferrets.[113] Enabling the easier spread of the virus among mammals, the experiments also raised fears that the pathogen could jump to humans.

The WHO intervened in 2011 calling for full publication of all details of two studies by Kawaoka and Fouchier on the H5N1 virus.[114] In the light of recent pandemics, there are speculations that such experiments may trigger global outbreaks if the organisms escaped from a lab or was intentionally released by a bioterrorist.

i. Risk Assessment- Biosafety and Biosecurity

With respect to biosafety, relevant international treaties that are applicable include the World Trade Organization's (WTO) 1995 Agreement on the Application of Sanitary and Phytosanitary Measures (SPS) and the 2000 Convention on Biological Diversity's (CBD) Cartagena Biosafety Protocol. The SPS measures limits 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.[115] Both the treaties seem inadequate to deal with the biosafety issues posed by synthetic biology.

The traditional biosafety frameworks were created in response to the issues raised by the recombinant DNA technology. Agricultural biotechnology can cause GM crops

[113] https://www.sciencemag.org/news/2019/02/exclusive-controversial-experiments-make-bird-flu-more-risky-poised-resume

[114] United Nations World Health Organization, World Health Statistics, https://www.who.int/gho/publications/world_health_statistics/EN_WHS2011_Full.pdf?ua=1 2011

[115] Regulatory Gaps and Synthetic Biology, 'Policy Brief Regulatory Gaps in the Global Governnace of Synthetic Biology '.(2014)

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". [116] 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 [117] 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".[118] Where LMOs are intended for introduction into the environment, the decision to allow import must be based on a risk assessment and apply precaution.[119]

The terminology "modern biotechnology" according to the Protocol drafted in 2000 does not include techniques like genome editing.[120] The Protocol does not concern itself with constituent parts like DNA under Article 3. The Cartagena Protocol will apply to most living organisms resulting from synthetic biology techniques. The definitions of "transfer" and "transboundary movement" do not include the possibility of local synthesis of DNA using publicly available sequence data.[121] The language of

[116] Article 3, Cartagena Protocol on Biosafety to the Convention on Biological Diversity
[117] Cartagena Protocol on Biosafety to the Convention on Biological Diversity, https://www.cbd.int/doc/legal/cartagena-protocol-en.pdf
[118] Arts. 15, 16
[119] Arts. 7, 10(6), 15
[120] "Modern biotechnology" is defined in the Cartagena Protocol as:
"The application of: a. In vitro nucleic acid techniques, including recombinant DNA and direct injection of nucleic acid into cells or organelles, or
b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection"
[121] Regulatory Gaps and Synthetic Biology, 'Policy Brief Regulatory Gaps in the Global Governnace of Synthetic Biology '.(2014)

"development, handling, transport, use, transfer and release" as laid down in Article 2.2 of the Protocol is applicable to physical specimens[122].

The "precautionary approach" in the Advance Information Agreement allowing for import restrictions can push highly risk adverse societies to refuse introduction of LMOs altogether. There can be no export unless the importing country allows, based on prior informed consent. It reverses the burden on importing countries since it establishes an international right to be notified of shipping of any LMOs. [123]

Synthetic biology involves large scale synthesis of DNA which can create new pathogens from scratch, recreate old pathogens, or engineer naturally occurring organisms to become a threat to biosafety. If a sequence coding for a toxin is made available on the Internet and anyone can print the gene or pathogen. The ability to transform from information to material and back can stress existing notions about biosafety regulation.

Annex III of the Protocol outlines the methodology of risk assessment, identification of potential adverse effects, evaluation of the likelihood and consequences of the effects, and estimation of overall risk.[124] It also lists points to consider, including the characteristics of the recipient or parental organism, the donor organism, the vector and modification, etc.[125] For LMOs that are intended for food, animal feed or for processing, a separate procedure applies; countries that make a final decision on domestic use must notify the Biosafety Clearing-House (BCH), a website portal operated by the Secretariat of the CBD Parties.[126]

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[122] Regulatory Gaps and Synthetic Biology, 'Policy Brief Regulatory Gaps in the Global Governnace of Synthetic Biology '.(2014)

[123] Lim Li Ching (2011) Third World Network " Synthetic Biology and Internaitonal Law"

[124] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane and Jonathan S. Adams "IUCN Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation" (2019)

[125] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane and Jonathan S. Adams "IUCN Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation" (2019)

[126] The Biosafety Clearing-House (BCH) is a mechanism set up by the Cartagena Protocol on Biosafety to facilitate the exchange of information on Living Modified Organisms (LMOs) and assist the Parties to better comply with their obligations under the Protocol.

With respect to biosecurity, the first effort in a treaty form was 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,). It was the first multilateral undertaking prohibiting the development or acquiring of biological agents or weapons for hostile purposes or armed conflict. [127] However the scenario is not adapted for the conduct of non-state actors apart from governments becoming biosecurity threats.

The chances of bioterrorist events happening can be rare but the regulation needs to take note of the gravity of the consequences. The increased securitization 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 organization in case of an unexpected or unusual public health event within its territory, irrespective of origin or source, which may constitute a public health emergency of international concern.[128] Proposals for screening customers who are ordering material which could be weaponized are made to commercial providers of synthetic DNA.

ii. National Biosafety Regulations

National biosafety regulations like that of India [129] may provide that certain activities require prior authorisation or notification, containment procedures or other forms of administrative oversight. 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. However, many countries have biosafety regimes in place that fully or partially follows the risk assessment framework outlined in the Protocol. The CBD

https://bch.cbd.int/

[127] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction 10 April 1972

[128] IHRs Article 7

[129] Biotech Consortium India Limited and Ministry of Environment, Forest and Climate Change, Regulatory Framework for Genetically Engineered Plants in India, https://biotech.co.in/sites/default/files/2020-01/Regulatory-framework-for-GE-plants.pdf

Biosafety Clearing House[130] and the ECOLEX legal database found 131 countries with national laws on risk assessment and management.[131]

National risk management legislation applicable to synthetic biology may include a range of legal instruments addressing different sectors and products. In addition to specific biosafety regulations, this may include legislation covering plant-breeding, food and drug safety, pesticides, toxic substances, sanitary and phytosanitary measures, and environmental protection. In India, 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 (DBT) under the Ministry of Science and Technology. 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. [132]

Some other countries don't follow the Cartagena Protocol and have multiple regulations covering biosafety issues. In the US, the biosafety framework that applies to research in institutions such as Universities has the status of regulation. The National Institutes of Health (NIH) has designed NIH Guidelines (for Research Involving Recombinant or Synthetic Nucleic Acid Molecules) which was amended in 2013 to include synthetic DNA.[133] Non-compliance can result in cancellation of NIH or any other federal funding.

The scope of applicability of the varying national regimes to synthetic biology, whether following the Cartagena Protocol or not, 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 under the Cartagena Protocol[134]. It

[130] Convention on Biological Diversity, Biosafety Clearing-House, https://bch.cbd.int/

[131] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane, Jonathan S. Adams "IUCN Genetic frontiers for conservation :An assessment of synthetic biology and biodiversity conservation"

[132] Sheetal Menon* and Shishir Kumar Jha (2016) National biosafety system for regulating agricultural biotechnology in India

[133] NIH Guidelines For Research Involving Recombinant Or Synthetic Nucleic Acid Molecules 2019 https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf

[134] CBD COP13 Decision 17, para. 7

can be a useful starting point but required adaptation considering the possibilities of synthetic biology. [135] 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 of LMOs[136]In November 2018, CBD COP14 extended the AHTEG, and emphasised the need for case-by-case risk assessments before organisms containing engineered gene drives are considered for release into the environment and recognised that specific guidance on such risk assessment could be useful.[137]

Two different approaches in addressing scope of applicability are employed by most national regulatory systems. These are often discussed in terms of "product" or "process" approaches. A "product" approach means that regulation is triggered by particular characteristics of products that may pose a risk, immaterial of the processes through which the product was generated. A "process" approach means that the product that is subject to oversight is defined by the certain characteristics pertaining to the process of its generation.

The US, Argentina, Canada, Philippines, Bangladesh etc have been categorised as having product-based approaches, while Brazil, India, China, Bolivia, Australia, Burkina Faso, the EU, New Zealand etc have taken a process-based approach.[138] Practically, product-based approaches often rely upon process-based distinctions, while process-based approaches often consider a combination of both product and process-based factors. The usefulness of the product/process dichotomy has therefore been questioned beyond the rigour involved in process-based risk assessment.[139].

The product-based approach in the US is scattered across various domestic legislation including the Plant Protection Act (PPA), the Federal Food, Drug and Cosmetics Act,

[135] CBD COP decision 13/17, para 6
[136] Ad Hoc Technical Expert Group on Synthetic Biology, 2017, para. 28
[137] CBD COP decision 14/L.31para 9.a
[138] Ishii, T. and Araki, M., A Future Scenario of the Global Regulatory Landscape Regarding Genome- Edited Crops, https://pubmed.ncbi.nlm.nih.gov/27960622/ 2017
[139] Kuzma, J., Atitude towards Governance of Gene Editing, https://experts.umn.edu/en/publications/attitudes-towards-governance-of-gene-editing 2016

and the Toxic Substances Control Act[140]. A similar model is that of Canada, where the trigger for regulatory overview is a "novel product". [141] The Canadian Seed Regulations define a " Novel Trait"[142] while the Food and Drug Regulations refer to "novel food."[143] The US, Argentina and Canada are among the top countries of export for GM crops.[144]

In stark contrast, the process of genetic modification is the trigger for oversight in the European Union. A genetically modified organism (GMO) is defined as an organism "*in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.*"[145] The techniques that constitute genetic modification thus include both cisgenesis (reorganisation of genes within a species) and transgenesis (transfer of genes between species). [146]

iii. Regulatory Stages and Requirements

Biotechnology applications are subject to step-by-step regulation and monitoring at various levels in different jurisdictions. Right from the laboratory stage to potential field trials and finally, the environmental release of the organism can be subject to the approval of designated State agencies. Most countries require some sort of authorization system depending on the risk associated.

In Canada, the release of GM plants with "novel traits" has to pass through various stages including import (subject to permit); contained use in a laboratory or greenhouse (subject to biosafety guidelines); confined environmental release (subject to risk management conditions); unconfined environmental release (subject to risk

[140] Bergeson, L., Dolan, S.L. and Engler, R.E. (2015). 'The DNA of the US Regulatory System: Are We Getting It Right for Synthetic Biology?' Woodrow Wilson Centre Project on Synthetic Biology 41–43.
[141] McHughen, A., GM Crops and Foods: What Do Consumers Want to Know?, https://pubmed.ncbi.nlm.nih.gov/24051491/ 2016
[142] Seeds Regulations 107(1
[143] Canada Food and Drug Regulations, https://lawslois.justice.gc.ca/eng/regulations/c.r.c.%2C_c._870/index.html 2002
[144] Ishii, T. and Araki, M., A Future Scenario of the Global Regulatory Landscape Regarding Genome- Edited Crops, https://pubmed.ncbi.nlm.nih.gov/27960622/ 2017
[145] 2001/18/ EC Art. 2(2)).
[146] ECJ Case 528/16, 2018, paras 27–38 Confédération paysanne and Others v Premier ministre and Ministre de l'agriculture, de l'agroalimentaire et de la forêt C-528/16; 2018

assessment and management and monitoring); variety registration; and commercialisation.[147]

The Japanese legislation distinguishes between "Type 1 Use" and "Type 2 Use". Type 2 Use" describes use where measures are taken to prevent release outside the lab and requires confirmation of measures for containment. "Type 1" doesn't require any such measures and a ministerial determination suffices which declares the use will result in no adverse effect following approved procedures.[148]

Due to opposition from several interest groups in India, the proposed Biotechnology Regulatory Authority of India Bill is pending approval in the Parliament since 2013.[149] The current regulatory system under the Rules 1989 designates MoEF and DBT as authorizing agencies for approval. Various stages of regulatory approval include the manufacture, use, sale, import, export and storage of GMOs.[150] 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 and the Food Safety and Standards Act 2006.[151]

Three authorities are responsible for approval process at various stages of the biosafety system- (i) Institutional Biosafety Committees (IBSC), (ii) Review Committee on Genetic Manipulation (RCGM) and the (iii) Genetic Engineering Appraisal Committee (GEAC). [152]The monitoring at the State and district level is conducted by the (iv) State Biotechnology Coordination Committee (SYNTHETIC BIOLOGYCC) and (v) District Level Committee (DLC).[153]

[147]Canadian Food Inspection Agency
https://www.inspection.gc.ca/
[148] Japan, Act no. 97 of 2003, arts. 4–15
[149] https://www.prsindia.org/sites/default/files/bill_files/Brief-_BRAI_Bill_2013.pdf
[150] Biotech Consortium India Limited and Ministry of Environment, Forest and Climate Change, Regulatory Framework for Genetically Engineered Plants in India, https://biotech.co.in/sites/default/files/2020-01/Regulatory-framework-for-GE-plants.pdf
[151] RCGM Secretariat https://ibkp.dbtindia.gov.in/Content/Rules?AspxAutoDetectCookieSupport=1
[152] RCGM Secretariat https://ibkp.dbtindia.gov.in/Content/Rules?AspxAutoDetectCookieSupport=1
[153] RCGM Secretariat https://ibkp.dbtindia.gov.in/Content/Rules?AspxAutoDetectCookieSupport=1

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. After an in-depth evaluation of the forwarded proposals, the RCGM sends its recommendations to the GEAC.[154]

However, the responsibility of post-monitoring and field trials of GM crops is assigned to respective state governments. [155]In 2014, a ten-year moratorium was imposed on commercialization and release of Bt Brinjal. Several State governments like Andhra Pradesh, Maharashtra and Karnataka have approved field trials for few crops including food crops. [156]

Within the EU, member states have powers to "opt-out" and close areas and even the state borders to release of GM plants authorized for the EU market. [157] Also, EU has a stricter regulation framework (nature protection, seed protection and other laws) that can prevent the release of GMOs for specified areas. Areas under special nature protection can exclude the introduction of GMOs for reasons of maintaining GM-free reference sites. [158]

Most risk assessment methodologies are based on two main components:
(1) evaluation of intended and unintended effects, including probability and potential significance of the effects; and

[154] Sheetal Menon* and Shishir Kumar Jha (2016) National biosafety system for regulating agricultural biotechnology in India
[155] Choudhary, B., Gheysen, G., Buysse, J., Meer, P.v. and Burssens, S. (2014) 'Regulatory options for genetically modified crops in India', Plant Biotechnology Journal, Vol. 12, pp.135–146.
[156] Sheetal Menon* and Shishir Kumar Jha (2016) National biosafety system for regulating agricultural biotechnology in India
[157] 2001/18/EC Art. 26b
Winter, G., Cultivation Restrictions for Genetically Modified Plants: On Variety of Risk Governance in European and International Trade Law; https://www.cambridge.org/core/journals/european-journal-of-risk-regulation/article/cultivation-restrictions-for-genetically-modified-plants/0F6C85FACA0779560A06D37EADB826BB (2017)
[158] GMO-Free Europe (2016). 'Germany' (GMO Free Regions by Country, 2016). Available at: https://www.gmo-free-regions.org/gmo-freeregions/germany.html

(2) comparison of the modified product with existing counterparts.[159]

Several risk assessment frameworks do not focus on the benefits of the GMOs. Legal systems, such as the EU, have separate systems for risk assessment which is based on the precautionary principle. The EU Environmental Risk Assessment Methodology is one of the most detailed frameworks considering both health and ecological aspects. [160] States like the US applies cost-benefit analysis in the majority of their processes of environmental decision making. The major component of the cost-benefit analysis is the testing of alternatives and remains the US alternative to the precautionary principle. [161]

iv. 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 caused by LMOs (living modified organisms). Under the Supplementary Protocol, Parties should require operators to take certain actions in the event of damage- informing the relevant authority, evaluating the damage, and take reasonable s to restore affected biodiversity.[162]

Where the operator fails to take appropriate response measures, the competent authority may implement such measures and recover from the operator the associated costs. The national frameworks can provide for rules and procedures that address damage, including civil liability. The Supplementary Protocol has 42 parties to date and there are no binding obligations for establishing civil liability. The civil liability, according to the Protocol shall address (a) damage; (b) standard of liability (strict or fault-based), (c) channelling of liability; and (d) the right to bring claims.

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[159] Paoletti, P., Vila, I., Rife, M., Lizcano, J., Alberch, .J. and Gines, S., Dopaminergic and Glutamatergic Signaling Crosstalk in Huntington's Disease Neurodegeneration: The Role of p25/cyclin-dependent Kinase 5, https://pubmed.ncbi.nlm.nih.gov/18829967/ 2008

[160] https://www.eea.europa.eu/publications/GH-07-97-595-EN-C2/riskindex.html

[161] Paoletti, C., Flamm, E., Yan, W., Meek, S., Renckens, S., Fellous, M. and Kuiper, H. (2008). 'GMO risk assessment around the world: Some examples'. Trends in Food Science and Technology 19(SUPPL. 1):70–78.

[162] art. 2, 5

EU legal instruments apply a principle of strict liability, or no-fault liability, for any damage to the environment resulting from dangerous activities. The European Convention on Civil Liability for Damage Resulting from Activities Dangerous to the Environment[163] (The Lugano Convention) imposes no-fault liability on the operator of a dangerous activity.[164] "Dangerous activities" are creating significant risk for man, the environment or property, and covers the production, storage, use disposal or release of GMOs.[165]

Among the developing countries, Tanzania has adopted Biosafety Regulations in 2009 providing for strict liability concerning GMOs.[166] Damage to the environment or biological diversity is explicitly included as a type of harm covered by this provision.[167] It also applies to harm or damage caused to the economy, social or cultural principles, livelihoods, indigenous knowledge systems, or indigenous technologies[168] Harm caused by synthetic biology can lead to civil liability under tort or civil law in Tanzania.

In the US and Canada, farmers-initiated litigation against biotechnology companies alleging contamination of their fields with GM crops which reduced the value of yield or made it impossible to achieve organic accreditation.[169] To bring a similar tort suit

[163] Lugano Convention

[164] art. 6, European Convention on Civil Liability for Damage Resulting from Activities Dangerous to the Environment

[165] art. 2 European Convention on Civil Liability for Damage Resulting from Activities Dangerous to the Environment

[166] United Republic of Tanzania. 2009. The Environmental Management (Biosafety) Regulations. http://tz.chm-cbd.net/biosafety/nationalimplementation/national-biosafety-framework/tanzania-biosafety-regulations-2009.pdf
The Regulations states "Any person or his agent who imports, transits, makes contained or confined use of, releases, carries out any activity in relation to GMOs or products thereof or places on the market a GMO shall be strictly liable for any harm, injury or loss caused directly or indirectly by such GMOs or their products or any activity in relation to GMOs".[166]

[167] S. 56(2) United Republic of Tanzania. 2009. The Environmental Management (Biosafety) Regulations.

[168] S 59 United Republic of Tanzania. 2009. The Environmental Management (Biosafety) Regulations.

[169] For example, intrusion of modified organisms onto private property could give rise to claims of nuisance or trespass.
Rodgers, C.P. (2003). 'Liability for the Release of GMOs into the Environment: Exploring the Boundaries of Nuisance'. Cambridge Law Journal 62(2):371–402. https://doi.org/10.1017/S0008197303006354

alleging environmental harm from synthetic biology, the affected party requires to show standing, causation and damage, as well as a fault or strict liability.

Proving every one of these elements can be difficult in the context of synthetic biology. Where the damage is to an environmental interest rather than a private person, it may be difficult to prove standing in civil law. For synthetic biology, there may not be a sufficiently close causal link between the activity and the damage to show liability. Fault-based liability may be difficult to prove and if the substantial injury occurs despite due diligence, the cost may lie with the state. Strict liability is typically reserved for acutely dangerous activities or activities delineated in the national legislation or specified in case law precedents. Depending on the extent of damage, strict liability may not be available for injury caused by synthetic biology in most jurisdictions.[170]

Regulating the Benefits

Not all scientific developments turn out to have publicly beneficial uses, but with synthetic biology, there is immense potential in ensuring global needs for food, medicines, fuel and water. SYNTHETIC BIOLOGY products and related components are likely to attract protection on four of the mainstream forms of intellectual property rights (IP) such as patents, copyrights, trademarks and trade secrets. These propriety models offer an exclusive set of rights for the IP holder and third parties cannot exercise any of these rights without the permission or license from the IP holder.

Some of the synthetic biology components will have no ownership and will remain in the public domain- compilations of facts, abstract ideas etc. Some of the resources will be governed as a "commons" pool- comprising of rules and structures for accessing and sharing such information. The public domain and the commons-pool will remain in a symbiotic relationship with the proprietary rights over complex novel inventions capable through synthetic biology parts and techniques.

[170] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane, Jonathan S. Adams "Genetic frontiers for conservation" IUCN

With any information or material relating to genetic resources and traditional knowledge, there may be a strong case of appropriation of resources from provider countries and indigenous communities. Regulation of the benefits should be approached through the lens of all stakeholders whether it's private companies or indigenous people or scientists or hobbyists. Thus, the intellectual property and ownership of both final products and functional parts form only part of regulation of benefits. The access to the resources and the benefits that flow back to the communities and conservation are equally important in the discussion on benefits.

i. Patents and Ownership

Intellectual property decisions related to SYNTHETIC BIOLOGY inventions are made at national levels and countries deal differently with inventions that are linked to genetic resources. However international legal instruments and bilateral treaties on trade and investment considerably influence the regulatory space. The 1995 TRIPS agreement have led to the harmonization of minimum standards of patents and plant variety rights across WTO members. The goal of the patent system, in general, is to incentivize innovation. However, the opposite is also true for the biotechnology and pharmaceutical sectors.[171] Patents can spur or inhibit innovation or use of synthetic biology as the case is with other types of technology Broad access for the scientific community to the basic tools of synthetic biology like gene sequences is required to promote research in the field.

There are two major questions posed by the patenting of synthetic biology components and organisms. Firstly, there always have been different positions regarding the application of criteria for a valid patent on living inventions. Can genes and living organisms constitute patentable subject matter? Secondly, the debate has surrounded how the patent holder exercises its exclusive rights. Can the patent holder withhold the technology and give away exclusive licenses to a few? One major constraint in innovation architecture is patent trolls. Patent trolls are patent holders who do not

[171] Roger Brownswood and Morag Goodwin "Law and Technologies of the 21st century: Cambridge University Press, (2012)

have the intention to work their inventions, but files infringement suits against the ones using or building on the technology.

The main issue around patenting is that human-designed DNA sequences, systems, cells, and organisms may avoid criticisms about patents claiming "products of nature." Broad patents over foundational tools and technologies are excluded from the scope of patentable subject matters and gene sequences may fall under this umbrella. The EU harmonized patent law relating to biotechnological inventions and though excluding the discovery of a gene or gene sequence from patentability allowed for an isolated gene or gene sequence to constitute a patentable invention, if it met other patentability criteria.[172]

Since the 1970s, advances in biotech had led to patent applications on nucleotide sequences of genes in the global North. In 1973, the first patent was issued with "DNA" as a claim element.[173] After the *Diamond v. Chakrabarty* decision affirmed patentability of microorganisms engineered by humans in 1980, patent applications claiming DNA sequences increased rapidly in the US.[174] In the US, the isolated DNA or modified DNA was distinguished from genomic DNA which is naturally occurring for patentability.

The legal position was clarified with the 2010 *Myriad* litigation which affirmed that "isolated" human genomic DNA is not patentable, based on the judicial exclusion of "products of nature".[175] However, the Myriad decision also clarified that cDNA which was not "found in nature" is the patent-eligible subject matter.[176] Synthetic genes will remain patentable for their origins in the human imagination. However, in 2015, Australia invalidated Myriad's patent claims on both isolated and synthesized DNA. It

[172] Kent H. Redford, Thomas M. Brooks, Nicholas B.W. Macfarlane, Jonathan S. Adams "Genetic frontiers for conservation" IUCN
[173] Diagnostic Method Utilizing Synthetic Deoxyrilionucleotide Oligomer Template, U.S. Patent No. 3,755,086 (filed Feb. 9, 1971) (issued
[174] Diamond v. Chakrabarty, 447 U.S. 303 (1980)
[175] 569 U.S. 576 (2013)
[176] Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, No. 09 Civ. 4515, 2010 WL 1233416, at *51 (S.D.N.Y. Mar. 29, 2010).

was held that such claims cover information that is "discerned" not made and thus failing the requirement of a man-made "manner of manufacture." [177]

The possibility of non-naturally occurring sequences and molecules being patentable may limit the developments in fields such as synthetic biology. The EU Biotechnology Directive explicitly allows for patents on some gene sequences that fail the Myriad test in the US. [178] Most developing countries, for example in Latin America, tend not to allow the possibility of patenting genes and gene sequences.[179] For example, in Brazil, biological material, including the genome or germplasm of living organisms, found in nature or isolated therefrom, is not considered an invention. [180]

Intellectual property in organisms, including genetically modified ones, is also treated differently by different states. Since most of the research is happening in the Global North, it is useful to take a look at the jurisprudence in the major powers like the US and EU. In the case of the 1984 Harvard OncoMouse, both product and process patents were granted in the US, EU, Canada and Japan. [181]The Oncomouse was a transgenic organism which expressed a gene that causes cancer in mammals and was used for studying anticancer treatments. With respect to claims on cloned animals, in the case of Dolly the sheep (In *re Roselin Institute*), the patent was rejected because it is not markedly different from what already exists in nature. [182]The Indian patent Act

[177] D'Arcy v Myriad Genetics Inc , [2015] HCA 35 (7 October 2015).
The Court noted that the isolated nucleic acid claims "[embrace] a nucleic acid sequence or protein removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesised analogs or analogs biologically synthesised by heterologous systems."
[178] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, Article 5(2), available at http:// eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:HTML
("An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element").
[179] Bergel, S.D. (2015). 'Patentability of human genes: The conceptual differences between the industrialised and Latin American countries'. Journal of Community Genetics 6(3):321–327. https://doi.org/10.1007/s12687-015-0228-2
[180] Industrial Property Law, art. 10
[181] Patenting of life forms, An Introduction to Ethical, Safety and Intellectual Property Rights Issues in Biotechnology.(2007)
[182] 750 F.3d 1333 (Fed. Cir. 2015). A related patent claimed the cloning methods used to produce Dolly the sheep.

specifically excludes plants and animals (except micro-organisms) from the patentable subject matter. [183]

However, the current position can be understood as the US provides for patent rights in plants and animals under certain conditions,[184] while the EU allows patenting of microorganisms but excludes patenting of plant and animal varieties.[185] In the EU, intellectual property in plant varieties is only possible in the form of plant variety protection. Farmers are allowed to further propagate their plants and develop new breeds.[186] The EU does not provide for product patents in animals, so that in practice protection in form of trade secret becomes the alternative. [187]

Following this position, the malaria vector mosquito (that is engineered to be non-reproductive) may be patentable in the US but not in the EU. The engineered blight-resistant chestnut would be suitable for the patent as well as plant variety protection in the US, but only for plant variety protection in the EU. Process patents for plant and animal modification are permitted in both jurisdictions. Modified microorganisms would be patentable in most jurisdictions and it is permitted under Article 27(3) of the TRIPS agreement. This is however excluded in the EU if the processes are "essentially biological".[188] In the case of synthetic DNA, the pertinent question is how different is it from a naturally occurring genome sequence.

Proponents of intellectual property protection within the industry view it as a tool indispensable to promote innovation in synthetic biology.[189] J. Craig Venter, the co-founder of "Synthetic Genomics", views intellectual property as fundamental for "*a vital and robust science and biotechnology industry*[190]. He claims that it is "*the first*

[183] Section 3(j), Indian Patents Act 1970
[184] Rimmer, M. (2008). Intellectual property and biotechnology: biological inventions. Edward Elgar Publishing. https://doi. org/10.4337/9781848440180
[185] European Union (EU). 1998. Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.
[186] Regulation (EC) 2100/94 Arts. 13 and 14
[187] EU Directive 98/44/EC Art. 4 (1) (1)
[188] EU Directive 98/44/EC Art. 4 (1) (2)
[189] Calvert, J. (2012). 'Ownership and sharing in synthetic biology: A "diverse ecology" of the open and the proprietary?'. BioSocieties 7(2):169–187. https://doi.org/10.1057/biosoc.2012.3
[190] Nelson, B. (2014). 'Cultural divide'. Nature 509(7499):152.

life form developed out of the computer and by humans, so it is much closer to a human invention".[191]

All of the above is compounded by the fact that the majority of SYNTHETIC BIOLOGY based research and development used DSI that may be publicly available. The next section delves on the protection of the DSI made available to researchers from material accessed from different countries.

ii. Copyright and Open Innovation

In general, private sector entities tend to be pro- IP, where the drive is to attract financial investments and patents help recoup returns on the investments. On the opposite end of the debate, several initiatives like the Biobricks community worry about the negative impacts of intellectual property. They advocate for an open innovation model in line with efforts in the open-software model. Under the "commons" model, there is collective ownership and management instead of private control over the resource and its use.

Several major initiatives are also supporting the synthetic biology commons" movement guided by the philosophy of "Get and Give". The iGEM Registry of Standard Biological Parts, for instance, is a fast expanding collection of genetic components. These parts can be accessed to build synthetic biology devices and systems by both researchers and amateurs. Users get parts, samples, data and tools and give back the new parts they have made. They also share user experiences within the open community.

The open-source software model witnessed tremendous innovation while presenting an alternative to proprietary rights.[192] Work can get copyright protection if it satisfies the criteria of originality, authorship and fixation in a tangible medium. Copyrights are can be extended to the DNA sequences if it can be treated like a computer program. DNA is composed of definite sequences of nucleotides comprising - A, G, T,

[191] J. Craig Venter ' Evidence tot United States House of Representatives Committee on Energy and Commerce (27 May 2010)

[192] Rai, A. and Boyle, J., Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons, https://journals.plos.org/plosynthetic biologyiology/article?id=10.1371/journal.pbio.0050058 2007

and C, whose specific order creates meaning in a polynucleotide sequence.[193] However, if the genes are derived entirely from a natural genome, both the criteria of originality and authorship can form a barrier. The mere labour exerted in sequencing the DNA cannot substitute the originality criteria and the mere discovery of a fact will not warrant copyright protection. [194]

However, any synthetic sequence "written" by a professional can qualify as an original work of authorship. Another possible barrier is the idea-expression merger doctrine. [195] The idea merges with the expression because DNA sequences can be expressed only in one manner. Independent invention of identical or similar synthetic DNA sequences would act as a counterbalance to any monopoly rights conferred on the first author. If a particular sequence is the only way to produce a polypeptide, then it will not get copyright protection. The Delhi High Court in the decision *Emergent Genetics India Pvt. Ltd. v. Shailendra Shivam and Ors* [196] held that there shall be no copyright protection of DNA.

Copyright if applicable, is capable of striking a balance of restricted and permissible uses of DNA sequences for society and the creators. It achieves this balance by replacing the strict liability regime of patent law with the more flexible fair use defence and a feasible open source regime.

The "modularity"[197] of synthetic biology makes it difficult to control the use, sharing and resharing of its various components.[198] The BioBricks Foundation, created in 2006, has developed tools such as BioBricks Public Agreement and OpenMTA, which facilitate access to SYNTHETIC BIOLOGY parts as an open-access resource, without corresponding obligations to return the derivative works to the common pool

[193] DNA Copyright in Andrew W. Torrance, Synthesizing Law for Synthetic Biology
[194] James G. Silva, Copyright Protection Of Biotechnology Works: Into The Dustbin Of History? (2011)
[195] James G. Silva, Copyright Protection Of Biotechnology Works: Into The Dustbin Of History? (2011)

[196] Ravindra Bhat J, Emergent Genetics India Pvt. Ltd vs Shailendra Shivam And Ors on 2 August, 2011
[197] degree to which a system's components may be separated and recombined, often with the benefit of flexibility and variety in use.
[198] Pottage, A. and Marris, C. (2012). 'The cut that makes a part'. BioSocieties 7(2):103–114. https://doi.org/10.1057/biosoc.2012.1

In terms of intellectual property rights, synthetic biology witnesses a tug-of-war between open and proprietary approaches. Tools such as the BioBricks Public Agreement and OpenMTA are leading to a "diverse ecology" of both proprietary and open systems[199]. While the databases may be protected as the copyright, the complex inventions building upon it may warrant protection under the patent system. The complementarity can protect the SYNTHETIC BIOLOGY component commons by increasing demanding for gene synthesizing services.[200]

Initiatives such as the Biological Innovation for Open Society (BIOS) created in 2005 strive to create a patent based commons despite patents being expensive.[201] An additional option is the creation of *sui generis* intellectual property systems like the ones that exist for traditional knowledge and plant varieties. . Contracts such as the 'clickwrap' license may also be used to guarantee access to synthetic biology parts and, eventually, to resulting products. This varied approach to different forms of property rights stems may coexist but even contribute to mutually flourishing. [202]

iii. Access and Benefit Sharing

The CBD affirms the sovereign rights of states over their natural resources extend to genetic resources. CBD mandates that any access to genetic resources except human genetic resources is subject to national authority and regulation. The Nagoya Protocol to the CBD affirms that these sovereign rights include the right to regulate access to genetic resources and negotiate terms for the fair and equitable sharing of benefits from their utilization.

The CBD- Nagoya framework also provides for rights of holders of traditional knowledge (TK) associated with the genetic resources to provide approval for the exploitation of such knowledge. Access and Benefit-sharing (ABS) provisions are

[199] Grewal, D.S. (2017). 'Before Peer Production: Infrastructure Gaps and the Architecture of Openness in Synthetic Biology'. Stanford Technology Law Review 20(1

[200] Pottage, A. and Marris, C. (2012). 'The cut that makes a part'. BioSocieties 7(2):103–114. https://doi.org/10.1057/biosoc.2012.1

[201] Kumar, S. and Rai, A. (2007). 'Synthetic biology: The intellectual property puzzle'. Texas Law Review.

[202] Calvert, J. (2012). 'Ownership and sharing in synthetic biology: A "diverse ecology" of the open and the proprietary?'. BioSocieties 7(2):169–187. https://doi.org/10.1057/biosoc.2012.3

relevant to synthetic biology as long as it is utilizing genetic resources.[203] The Nagoya Protocol establishes minimum standards to be laid down by provider countries from which the resources are accessed. It obligates each member to include prior informed consent (PIC) and mutually agreed terms (MAT).

An increasing number of countries have regulated ABS frameworks through national laws and regulations. Most countries that have introduced national frameworks for ABS distinguish between "biological" resources, that may be private or public owned and "genetic" resource territorially owned by the state.[204]

India's Biological Diversity Act (2002), that provides procedures and compliance needs for accessing the country's biological resources and associated traditional knowledge, call for strict measures when resources and associated knowledge are subject to commercialization, both by Indians and non-Indians. India's current stand within the Protocol negotiations is to include all genetic information, including DSI, under the ambit of ABS and be covered under the Act.

Since the US has not signed the Nagoya Protocol, US-based synthetic biologists will be subject to PIC/ABS/ MAT requirements of other countries even though the US has not a party to the CBD. Many developed countries such as the UK, Germany etc are parties to the CBD but decided against restricting access to their genetic resources. [205] However due diligence is to be exercised that any material is accessed in accordance with the applicable legislation of the providing country[206]

Some countries such as South Africa consider the state as a trustee of biodiversity, but it does not have ownership over genetic resources beyond public land.[207] The landowner or the local communities in South Africa own both the biological and genetic

[203] United Nations Convention on Biological Diversity, https://www.un.org/Depts/los/general_assembly/contributions_2015/SCBD.pdf
[204] The Access And Benefit Sharing Clearing House at https://absch.cbd.int/
[205] Kent H Redford and others, Genetic Frontiers for Conservation: An Assessment of Synthetic Biology and Biodiversity Conservation: Technical Assessment (2019).
[206] https://www.gov.uk/guidance/abs
[207] Republic of South Africa. 2004. National Environmental Management: Biodiversity Act, 2004. Cape Town. https://www.environment.gov.za/sites/default/files/legislations/nema_amendment_act10.pdf

resources on their property. However, researching on genetic resources in South Africa requires both the prior informed consent from the owner of the land and the competent authorities.[208] Access depends on permits from competent authorities and benefits arising from any utilization are mediated through the state. These requirements would extend to genetic resources accessed for synthetic biology.

The Nagoya Protocol aims at ensuring compliance with provider state requirements through corresponding user state obligations. User states are obligated to take "*appropriate, effective and proportionate legislative, administrative or policy measures*" to ensure that researchers within their jurisdiction have secured access according to provider state requirements.[209] There is no international harmonization but the 2002 CBD Bonn Guidelines is a non-binding instrument that encourages the Parties to adopt measures for ABS compliance.[210] The disclosure requirement in patent law can be a mechanism for ensuring compliance with ABS/PIC/MAT regulations of provider countries.

The benefit-sharing agreement between TBGRI and the Kani people in India is acclaimed as an effective model for benefit sharing. A trust fund was established to share the benefits arising from the commercialization of the patented medicine "Jeevani" produced using the TK of the Kani tribal community over the use of the plant *Aarogyapachha*." [211]

Applicants based on synthetic biology will have to disclose the origin of genetic resources utilized for the invention. In case of microorganisms, the WIPO Budapest Treaty of 1980 allows for the deposit of microorganisms at an international depositary authority to be recognized to satisfy the disclosure requirement of patent law. While the EU Directive has a requirement for voluntary disclosure,[212] countries such as Switzerland have provision for mandatory disclosure like that of India. The obtaining

[208] art. 3, 81, 85, Republic of South Africa. 2004. National Environmental Management: Biodiversity Act, 2004. Cape Town. https://www.environment.gov.za/sites/default/files/legislations/nema_amendment_act10.pdf
[209] Art 15 of Nagoya Protocol
[210] https://www.cbd.int/abs/infokit/revised/web/factsheet-bonn-en.pdf
[211] https://www.wipo.int/ipadvantage/en/details.jsp?id=2599
[212] Directive 98/44/EC on the Legal Protection of Biotechnological Inventions of July 6, 1998

and preservation of patent will depend on proper disclosure and non-compliance can invite sanctions. [213]

Internationally, thirty-plus countries have established specific disclosure requirements related to genetic resources and/or TK for patent applications.[214] The Chinese Patent Law, for instance, will reject the patent application if the direct and original source of the genetic resources. [215] The Indian Patents Act section 10(4) (ii) (D) requires mandatory disclosure in the complete patent specification. Non-disclosure or wrongful disclosure of the source or geographical origin of biological material used for the invention will be a ground for both opposition and revocation of patent. [216]

Beyond the CBD framework, the UNCLOS, FAO ITPGRFA and WHO PIP framework also concern themselves with ABS provisions on genetic resources. The WHO Pandemic Influenza Preparedness Framework (PIP) was adopted in 2011, to improve and strengthen the sharing of influenza viruses with human pandemic potential; and to increase the access of developing countries to vaccines and other pandemic related supplies.[217] The Standard Material Transfer Agreements (SMTAs) regulate the transfer of biological material and issues of ABS with respect to the WHO PIP framework. [218] The expeditious sharing of pathogen genome and resultant fair and equitable sharing of benefits has major public health implications. Including India[219], more than 30 WHO Member States impliedly include pathogens within the scope of ABS instruments. [220]

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[213] Article 81(a) of the Swiss Federal Act further states: "Any person who wilfully provides false information under Article 49(a) is liable to a fine of up to 100,000 francs. The court may order the publication of the judgment."

[214] World Intellectual Property Organization (WIPO) (2017). Key Questions on Patent Disclosure Requirements for Genetic Resources and Traditional Knowledge. Geneva, Switzerland: WIPO. https://www.wipo.int/edocs/pubdocs/en/wipo_pub_1047_19.pdf

[215] Implementing Rules of the Patent Law of the People's Republic of China (promulgated by Decree No. 306 of the State Council of China on June 15, 2001, and revised by the Decision of January 9, 2010, of the State Council on Amending the Rules for the Implementation of the Patent Law of the People's Republic of China) (http://www.wipo.int/wipolex/en/details.jsp?id=6504)

[216] Article 64 Revocation of patents and Article 25 Opposition to the patent, Indian Patents Act 1970

[217] https://www.who.int/initiatives/pandemic-influenza-preparedness-framework

[218] Section 4.1. of the PIP Framework, Article 6 of the Standard Material Transfer Agreement 1 (SMTA 1 available at https://www.who.int/ influenza/resources/pip_framework/en/

[219] Section 2(c): means plants, animals and microorganisms or parts thereof, their genetic material and by-products

[220] https://www.who.int/influenza/pip/governance/OP1bReport_14Mar2020.pdf

UNCLOS has an ongoing negotiation on a new international agreement on marine biodiversity in areas beyond national jurisdiction, including questions of sharing of benefits from genetic resources originating in the high seas or the deep seabed.[221] The implications of synthetic biology and associated tools such as digital sequence information have become part of the discussion.

iv. "Nagoya Plus "Approach

The CBD – Nagoya framework addresses the issue of "biopiracy" where exclusive patent rights are enjoyed over the genetic resources that are indigenous to a foreign country without compensating the conservators of the genetic resources and/or the holders of related traditional knowledge. With the advent of the Digital DNA, databases with genetic information are no more bound by territorial limitations of the member states.

Synthetic biology can disrupt and can even make the Nagoya Protocol redundant. The digitization of sequence information can replace the need to have physical access to any genetic resource and the provider countries have no control over the subsequent use. Such digitized information falls outside the scope of "territoriality" under the definition of "genetic resources" in the CBD and Nagoya Protocol. Thus, the Nagoya framework was not construed to accommodate the digitization possibilities and as a direct consequence, effective benefit sharing on these patented synthetic biology products are far more difficult to ascertain compared to tangible genetic resources.

Synthetic biology tools such as DSI challenge ABS frameworks by making traceability of such information impossible. These challenges increase over time as sequences pass through multiple improvisations and the direct link for benefit sharing erodes. Key question in such situations is whether the benefit sharing shall apply to an indefinite number of transactions or is there an expiration point. The digital libraries allows any entity to access genetic information for private use which can be sold back as commercialized patented inventions.

[221] United Nations General Assembly (UNGA). 2017. A/Res/72/249. http://www.un.org/en/ga/72/resolutions.shtml

The global ABS mechanism is premised on benefit sharing being a rightful incentive for conservators and a source of funding for conservation efforts. The challenges raised by synthetic biology could impact this intended contribution to CBD's goals of conservation and sustainable use[222].

To accommodate these concerns, some countries have started explicitly expanding or interpreting genetic resources to include DSI. We can find some examples of these in the national implementation of ABS in countries like Costa Rica and Namibia and the members of the Andean Community that are now enforcing access requirements for DSI. [223] However, they do not include any benefit sharing possibilities.

On the contrary, countries like Brazil have opted for benefit sharing for the utilization of DSI. Brazil, have in their domestic legislation, clauses exerting their rights over DSI even if held outside their borders. Brazil has adopted the "Nagoya plus" approach defining the term "Genetic Heritage" that includes information on "Genetic Resources". 'The Brazilian law of 2015[224] has expanded "access' to all research or "technological development" conducted on a sample of genetic heritage or associated traditional knowledge. Some Nagoya Protocol "Plus" mechanisms have also been adopted by developed countries such as the EU and Japan.[225]

Another challenge for benefit-sharing is when inventions combine genetic elements from multiple living organisms, both within and beyond national jurisdiction. Often,

[222] Sachin Sathyarajan and Balakrishna Pisupati 2019 The need for a Nagoya Protocol 'plus'. FLEDGE, India.
[223] Fact-finding Study on How Domestic Measures Address Benefit-sharing Arising from Commercial and Non-commercial Use of Digital Sequence Information on Genetic Resources and Address the Use of Digital Sequence Information on Genetic Resources for Research and Development, As requested by decision 14/20 (paragraph 11 (e)) from the Fourteenth Conference of the Parties to the Convention on Biological Diversity ,(25 October 2019)available at https://www.cbd.int/abs/DSI-peer/Study4_domestic_measures.pdf
[224] Law (13.123/15) Provisional Act, No 2,186-16 2001 (Brazil), Title II, Art 7, para I Law No. 13.123 of May 20, 2015 (Access and Benefits Sharing of Genetic Resources and Associated Traditional Knowledge) available at http://www.wipo.int/wipolex/en/details.jsp?id=15741
[225] Under the EU Regulation 511/2014
"[u]sers shall exercise due diligence to ascertain that genetic resources and traditional knowledge associated with genetic resources which they utilise have been accessed in accordance with applicable access and benefit-sharing legislation or regulatory requirements, and that benefits are fairly and equitably shared upon mutually agreed terms, in accordance with any applicable legislation or regulatory requirements."

genetic elements are functionally identical in different organisms, and elements which are used in the research process but not found in the resulting invention[226]. The availability of digital tools such as BLAST facilitates finding the same DNA sequence in other possible organisms found in other jurisdictions. The tool finds regions of local similarity between query sequences and those in the databases by searching every record. [227]

Academics and companies can now easily take genetic code that has been uploaded to the internet and using a DNA synthesizer, recreate and modify that code to produce new substances, tests, and perhaps even new organisms, with no meaningful way to track the origin of the genetic information that formed the basis for the discovery. The disclosure requirement cannot help address this issue, as it is impossible to determine the origins of genetic information.

Another pertinent issue is the usage of fragments of DNA sequences from many different species in designing new biosynthesis pathways to generate new or enhanced compounds.[228] The value of digital sequence information is often found in the aggregate, rather than an individual sequence with increasing complexity of the research. The multilateral benefit-sharing fund and non-monetary options like access to databases, capacity building, technology transfer etc[229] are great on paper but the practical application is highly constrained by political and economic realities.

The "dematerialization" and transfer or use of DSI for SYNTHETIC BIOLOGY is threatening the ABS framework of the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA). Three possible uses of Synthetic biology have

[226] Bagley, M. A. (2016). Digital DNA: The Nagoya Protocol, Intellectual Property Treaties, and Synthetic Biology.
[227] Margo A. Bagley "Towering Wave or Tempest in a Teapot? Synthetic Biology, Access & Benefit Sharing, and Economic Development", 2017, Susy Frankel and Daniel Gervais eds., The Internet And Intellectual Property: The Nexus With Human And Economic Development ,Victoria University Press
[228] Margo A. Bagley "Towering Wave or Tempest in a Teapot? Synthetic Biology, Access & Benefit Sharing, and Economic Development", 2017, Susy Frankel and Daniel Gervais eds., The Internet And Intellectual Property: The Nexus With Human And Economic Development ,Victoria University Press
[229]Article 10 of Nagoya Protocol https://www.cbd.int/doc/c/ae6c/05f2/805fea62acc7deee055850d0/synthetic biologyi-02-05-en.pdf

implications for the FAO's Treaty (1) mining plant genomic information for gene editing purposes in crops; (2) mining for use outside of agriculture; and (3) using the plant as a 'workhorse' to produce other products.[230] Dematerialization is "the information and knowledge content of genetic material [could increasingly be] extracted, processed and exchanged in its own right, detached from the physical exchange of the plant genetic material.[231]"Similar to the CBD framework, "dematerialization" makes identification of the users and monitoring of downstream usage challenging for the FAO's ITPGRFA framework.

Open source agreements are being developed as a solution to avoid the high transaction and legal costs associated with traditional material transfer agreements (MTAs) and other licensing agreements. MTAs have been used by biotechnologists to define terms and conditions for sharing biomaterials since the pre-internet era. From an ABS perspective, MTAs have been instrumental in provenance tracking, disallowing re-distribution of biomaterials and prohibition of commercial uses of the same. [232] MTAs constrained several socially beneficial sharing resources such as Addgene which shares plasmids to several research institutions. Open source agreements like the OpenMTAs (developed by the BioBricks Foundation) include provisions for attribution of provenance while protecting access, redistribution and reuse. They are intended to facilitate the free exchange of information, technology and materials, and support collaborative research.

Another solution is a blockchain mediated model mooted by the Earth Bank of Codes. The Earth BioGenome project, aims to sequence and characterize the genomes of all eukaryotic biodiversity between the 2018-2028 periods. [233]The Earth Bank of Codes aims to create an open library of Amazon's biological data with blockchain enabled

[230] Eric W Welch and others, 'Potential Implications of New Synthetic Biology and Genomic Research Trajectories on the International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA or 'Treaty"). Draft Study Prepared for Special Event on Genomics Information, 28 Oc'.
[231] FAO, IT/GB-5/13/4
[232] Linda Kahl and others, 'Opening Options for Material Transfer' (2018) 36 Nature Biotechnology 923.
[233] Harris A. Lewin and others , "Earth BioGenome Project: Sequencing life for the future of life", April 24, 2018, Proceedings of the National Academy of Sciences of the United States of America 115 (17) p 4325-4333 available at http://www.pnas.org/content/115/17/4325

provenance tracking.[234] The transfer will be facilitated by "Smart contracts" that assign rights and revenues automatically and any future commercial use of the data requires sharing of the value with the country of origin. [235]

User agreements including provisions for ABS are being increasingly used by targeted databases and research institutions. The Global Initiative on Sharing All Influenza Data (GISAID) has developed a Database Access Agreement (DAA) that issues licenses for the use of data on viral genetic information and includes benefit sharing provisions. The J Craig Venter Institute (JCVI) has negotiated Memoranda of Understanding (MOUs) that address DSI as part of marine microbe collections inside territorial waters. [236] Several research groups undertaking such field collections, include specific language in their agreements clarifying that DSI will be uploaded to public databases.

Non-state Regulation

Non-state actors like the industry and specialized communities play an important role in regulating new technologies. In synthetic biology, there is a need for specialized knowledge from the industry and self-governance has been recommended as a solution. With the growth of hobbyists in the synthetic biology sector, the self-governance does not hold ground. The risks and benefits with synthetic biology are uncertain and hence the impact on indigenous peoples and local communities has to be studied.

i. Industry Governance and Regulation

In relation to synthetic biology, there is a growing body of standards created and imposed by industry, researchers and communities of practice. The emerging private sector of synthetic biology uses the so-called 'soft' standards, which can facilitate responsible behaviour within the sector[237]. Strong self-governance regimes have been

[234] Ben Schiller, "How a bank of all the Worlds Genetic Codes Hopes to Save Nature" Feb 2 2018 available at https://www.fastcompany.com/40534363/how-a-bank-of-all-the-worlds-genetic-codes-hopes-to-save-nature

[235] Earth Bank of Codes available at https://earthbankofcodes.worldsecuresystems.com/

[236] https://www.jcvi.org/sites/default/files/assets/projects/gos/collaborative-agreements/Ecuador_MOU_English.pdf

[237] Parks, S., Ghiga, I., Lepetit, L., Parris, S., Chataway, J. and Jones, M.M. (2017). 'Developing standards to support the synthetic biology value chain'. RAND Corporation. https://doi.org/10.7249/RR1527

mooted where the industry self regulates without any governmental influence in countries like the US. Government agencies are touted as ill-equipped in understanding the complexities in the technologies and organization of the industry.

However such soft standards applied by the industry are neither binding nor legally enforced. Security issues have been discussed in the community since early development stages. The second International Meeting on Synthetic Biology (2.0) opened a draft declaration for public comment as early as 2006. The draft consists of resolutions addressing the dual-use implications of DNA synthesis and included a proposal for establishing a working group for creating software tools for cross-checking orders of synthetic DNA. [238] On the wake of such attempts, the ETC Group warned against self governance and called for a global societal debate warranting governmental action in 2006.[239]

Scientists working on engineered gene drive applications have led several attempts at self-governance and good practices for safe and responsible research. In 2015, prominent engineered gene drive researchers working on different projects published recommendations for safeguards to contained experiments of engineered gene drive[240]. Several attempts to organize a formal coordination of researchers working on engineered gene drive technology are ongoing. One such instance is the Gene Drive Research Consortium convened by the Foundation for the National Institutes of Health to discuss communication and safe testing in relation to gene drive technology.[241]

The control of synthesized, ordered and distributed DNA sequences is required to identify requests of concerns. This framework should include both customer screening and sequence screening from the part of major companies. Two separate industry

[238] Alisson McLennan "Regulation of synthetic biology: BioBricks, Biopunks and Bioentrepreneurs'" (2018)
[239]ETC Group (May 18, 2006) Global Coalition Sounds the Alarm on Synthetic Biology https://www.etcgroup.org/content/global-coalition-sounds-alarm-synthetic-biology
[240] Akbari, O. S., Bellen, H.J., Bier, E., Bullock, S. L., Burt, A., Church, G.M., Cook, K.R., Duchek, P., Edwards, O.R., Esvelt, K.M., Gantz, V.M., Golic, K.G., Gratz, S.J., Harrison, M.M., Hayes, K.R., James, A.A., Kaufman, T.C., Knobich, J., Malik, H.S., Matthews, K.A., O'Connor-Giles, K.M., Parks, A.L., Perrimon, N., Port, F., Russell, S., Ueda, R. and Wildonger, J. (2015). 'Safeguarding gene drive experiments in the laboratory'. Science 349(6251):927–929. https://doi.org/10.1126/science.aac7932
[241] Foundation for the National Institutes of Health (FNIH) (2018a). Gene Drive Research Consortium. Available at: https://fnih.org/what-wedo/current-research-programs/gene-drive-research-consortium

groups published guidelines regarding control of distributed genetic sequences- The International Association Synthetic Biology (IASYNTHETIC BIOLOGY) issued "The IASYNTHETIC BIOLOGY Code of Conduct for Best Practices in Gene Synthesis" [242] and the International Gene Synthesis Consortium (IGSC) published "Harmonized screening protocol: gene sequence & customer screening to promote bio- security".[243] Both guidelines require the human screeners to participate in the process of identification of sequences. [244]The collaboration with national intelligence agencies for reporting suspicious customers is integral in this effort.

The safety board of the International Genetically Engineered Machine (iGEM) international student competition has established a policy with a specific focus on biosafety and developed a separate policy on work related to engineered gene drive systems and how to prevent accidental gene drive release.[245] Gene Drives are not allowed in iGEM projects without a special exception from the Safety Committee. iGEM however aaccepts common research Anti-microbial resistance (AMR)-related parts into the registry, citing low public health risk.

Another significant player in the ecosystem is the do-it yourself (DIY) biology community and they have developed a code of conduct, broadly drawing from good practices applied by the scientific community[246]. DIY biologists may not be held to the same standards of safety as formally trained biologists[247]. In some countries, licensing

[242] International Association Synthetic Biology (IASYNTHETIC BIOLOGY). (2009). The IASYNTHETIC BIOLOGY code of conduct for best practices in gene synthesis. Retrieved from http://op.bna.com.s3.amazonaws.com/hl. nsf/r%3FOpen%3djaqo-7xqpnr International

[243] International Gene Synthesis Consortium (IGSC). (2009). Harmonized screening protocol— Gene sequence & customer screening to promote biosecurity. http://www. genesynthesisconsortium.org/images/pdf/IGSC%20Harmonized%20Screening%20Protocol-11_18_09.pdf

[244] Lucía Gómez-Tatay and José M Hernández-Andreu, 'Biosafety and Biosecurity in Synthetic Biology: A Review' (2019) 49 Critical Reviews in Environmental Science and Technology 1587 <https://doi.org/10.1080/10643389.2019.1579628>.

[245] International Genetically Engineered Machine Foundation (iGEM) (2017). Safety Policies. Available at: http://2017.igem.org/Safety/Policies

[246] DIYbio (2011). Codes. Available at: https://diybio.org/codes/

[247] Garrett, L. (2013). 'Biology's Brave New World: The Promise and Perils of the Synbio Revolution'. Foreign Affairs, 92(6):28–46.

requirements on laboratory biologists, including training in safety and ethics, may not apply to community laboratories[248].

However, in the EU, community laboratories, like other laboratories, need licenses to undertake experiments involving genetic engineering[249]. The DIY biology community has also developed its own safety standards[250] and continues to evaluate their effectiveness and develop additional resources associated with biosafety and biosecurity.[251] However, there are still limits on the capability of DIY-community laboratories to create organisms that would cause significant environmental damage.[252] Much of the concern around DIY bio-centers revolves around questions of biosecurity.

The role of funding organizations is also important for the regulation of research. In its report on gene drives, the American National Academies of Sciences, Engineering and Medicine recommended several actions including the need to collaborate with scientists and regulators "to develop oversight structures to regularly review the state of gene drive science and its potential for misuse" [253]. In addition, the Presidential Commission for the Study of Bioethical Issues established the responsibility of funders to promote some key principles for responsible research and use of synthetic biology[254]. In response to these calls, a number of organizations sponsoring or supporting gene drive research have agreed to a set of principles for responsible

[248] Kolodziejczyk, B. (2017). Do-it-yourself biology shows safety risks of an open innovation movement, Techtank. Available at: https://www. brookings.edu/blog/techtank/2017/10/09/do-it-yourself-biology-shows-safety-risks-of-an-open-innovation-movement/

[249] Seyfried, G., Pei, L. and Schmidt, M. (2014). 'European Do-it-yourself (DIY) Biology: beyond the hope, hype and horror'. Bioessays 36(6):548–551. https://doi.org/10.1002/bies.201300149

[250] Guan, Z., Schmidt, M., Pei, L., Wei, W. and Ma, K. (2013). 'Biosafety Considerations of Synthetic Biology in the International Genetically Engineered Machine (iGEM) Competition'. BioScience 63(1):25–34. https://doi.org/10.1525/bio.2013.63.1.7

[251] Yassif, J. (2017). 'Genspace — DIYbio Labs Project' (Open Philanthropy Project, 2017). Available at: https://fnih.org/what-we-do/currentlectures-awards-and-events/gene-drive-research-forum

[252] Lentzos, F. (2016). 'Biology's Misuse Potential'. Connections: The Quarterly Journal 15(2):48–64.

[253] Recommendation 8.7, National Academies of Sciences, Engineering, and Medicine (NASEM) (2016a). Gene Drives on the Horizon. Washington, D.C.: National Academies Press. https://doi.org/10.17226/23405

[254] Weiss, R., Gutmann, A. and Wagner, J. (2010). New directions: The ethics of synthetic biology and emerging technologies. Washington, D.C.

research.[255]Beyond the key principles, the forum of supporters and sponsors holds regular meetings to discuss key issues around gene drive research, including topics like data sharing, regulatory capacity, etc.[256]

i. Indigenous and Customary Laws

The statutory frameworks are not the only sources of law and regulation relevant for synthetic biology. Legally binding norms governing research and use of synthetic biology can derive from indigenous or customary systems. Many countries formally recognize indigenous or customary law as well as civil and common law in national legal systems.

More than half the world's countries have constitutional provisions relevant to customary law, ranging from provisions that protect cultural practices to provisions that define customary law and its legality (including India).[257] Indigenous authorities can be legally granted exclusive or shared jurisdiction over specific territory or subject matter, or granted the right to participate in national decision making.

The CBD- Nagoya Protocol framework considers Indigenous peoples and local communities (IPLCs) not only as custodians of biodiversity but also as the holders of traditional knowledge (TK) – which can lead researchers to potential uses of genetic resources (GR).[258] The core link between the utilization of genetic resources for research in synthetic biology with the associated traditional knowledge of indigenous peoples cannot be ignored.

The preamble of the Protocol contains seven paragraphs relevant to IPLCs including reference the diversity of circumstances in which TK is owned or held, the

[255] Emerson, C., James, S., Littler, K. and Randazzo, F.F. (2017). 'Principles for gene drive research'. Science 358(6367):1135–1136. https:// doi.org/10.1126/science.aap9026

[256] Foundation for the National Institutes of Health (FNIH) (2018b). 'Gene Drive Research Sponsors and Supporters Forum'. Available at: https://fnih.org/what-we-do/current-lectures-awards-and-events/gene-drive-research-forum.

[257] Cuskelly, K. (2011). Customs and Constitutions: State recognition of customary law around the world. Bangkok, Thailand: IUCN. Available at: https://portals.iucn.org/library/node/10144

[258] The Nagoya Protocol on Access and Benefit-sharing and Traditional Knowledge at https://www.cbd.int/traditional/Protocol.shtml

identification of the rightful holders of TK, the U.N. Declaration on the Rights of Indigenous Peoples and the non-extinguishment of existing rights.[259]

The CBD AHTEG has noted that customary law of indigenous peoples and local communities should be considered in implementing risk management measures for synthetic biology[260]. Researchers and users of synthetic biology may be faced with a maze of legal rules from different sources, and this legal pluralism can be a significant challenge with respect to regulation. Failure to navigate these rules can result in violations that lead to conflict between different stakeholders and entities.

CBD COP10 established the Tkarihwaié:ri Code of Ethical Conduct to Ensure Respect for the Cultural and Intellectual Heritage of Indigenous and Local Communities.[261] The Code identifies general ethical principles, including: prior informed consent and/or approval and involvement; the fair and equitable sharing of benefits; precautionary approach, including relevant ILCs and the use of local criteria and indicators in the prediction and assessment of potential harms to biodiversity.[262]

The crux of the problem with respect to synthetic biology techniques is once the genetic information is placed in the "public domain" or through "open access" that does not respect the rights of the genetic resource providers, the ability of IPLCs to protect their traditional rights could be permanently impaired. It would be counter-intuitive to exempt public or private academic users from benefit sharing obligations when several inventions based on synthetic biology techniques are being granted patents in developed countries.

The trade of resources from provider countries can be fast replaced by synthetic biology products. The synthetic alternatives can wipe away the economic demand of the original biological resource and can impair the livelihoods of the IPLCs that are

[259] The Nagoya Protocol on Access and Benefit-sharing and Traditional Knowledge at https://www.cbd.int/traditional/Protocol.shtml
https://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf
[260] CBD/SYNTHETIC BIOLOGYSTTA/22/CRP.10 (2018). Digital sequence information on genetic resources. Note by the Executive Secretary. Available at: https://www.cbd.int/abs/dsi-gr/ahteg.shtml#peerreview
[261] Decision X/42.
[262] Decision X/42, Annex A, Section 2(A)

dependent on these resources. Synthetic biology copies of rare and expensive natural products including saffron, vanillin, artemisinin, stevia, and several others are already on the market or in development.[263]

Also within synthetic products, there is a distinction between "Naturally unnatural" products and "Unnaturally natural" products. Naturally unnatural products use a natural host but the final end product is unnatural. The case of artemisinin, vanilla, stevia and saffron falls within "unnaturally natural" products, where the end products are natural. The status of 'unnaturally natural' products created from synthetic biology organisms remains as "biological resources" and this needs further clarification at a labelling and regulatory level.

If these products are referred as 'nature identical', then consumers could be confused regarding the origin of the product. It follows that IPLCs could witness replacement of natural products with the proliferation of SYNTHETIC BIOLOGY products on the global market. In both the US and Europe, Synthetic Biology products can be labelled as 'natural' ingredients, but this is not necessarily consistent with consumer perceptions.[264]

There is a dearth of case studies on the influence of indigenous or customary law on synthetic biology. The study from New Zealand on Maori perspectives of synthetic biology looks at how perceived potential benefits of the technology may vary according to the intended use. Moving genes between species, introduction of genes from non-native species, extraction of genetic material from an organism and other practices associated with synthetic biology would have direct implications on Maori values.[265]

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[263] ETC Group, "Synthetic biology, Biodiversity and Farmers", April 2016 at http://www.etcgroup.org/sites/www.etcgroup.org/files/files/etc_synbiocasestudies_2016.pdf

[264] Stephen Gardner, Amanda Howell & Erika Knudsen, "A Natural Solution: Why Should FDA Define 'Natural' Foods?" (2014) Food and Drug Policy Forum

[265] "There is a general consensus that whakapapa (genealogy) sits as the key concept for Māori communities. The second most commonly acknowledged cultural value is mauri (life essence), followed by mana (power/authority) and kaitiakitanga (guardianship)."
Mead, A. T., Hudson, M. and Chagne, D. (2017). Maori perspectives and gene editing: A discussion paper.

5. CONCLUSION

This compilation is intended to provide a foresight for further developing a national policy framework for India. This is supported by the two annexes that are to be considered as a part of this report in understanding the state of play in the area of synthetic biology with regard to research and development (annex 1) and the involvement of private sector, globally, in dealing with synthetic biology (annex 2).

Though it is not customary to elaborate the principles of international law and policies, as presented in this compilation, it is important to consider these elements while developing the national policy, especially since the science and regulatory framework related to use of the science is driven by global considerations and decisions.

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 policy on the other.

ANNEXURE I

TABLE 1: LIST OF EXPERTS INVOLVED IN THE SYNTHETIC BIOLOGY FORESIGHT / POLICY DISCUSSION

(includes tracks, leads and advisors)

S.No	Name	AFFILIATION	Track 1 Food and Agriculture	Track 2 Biotechnology and Bioinformatics	Track 3 Non Pharma including Industry	Track 4 Academia and Research
1	Ajay Wamanrao Tumaney	Principal Scientist, CFTRI, Mysore	x			
2	Amit Ghosh	Assistant Professor Grade-I, Energy Science and Engineering P.K. Sinha Centre for Bioenergy and Renewables	x			
3	Anindya Majumdar	Reliance Industries Limited	x			
4	Anirban Bhaduri	Calcutta Medical Research Institute Kolkata		x		x
5	Anu Raghunathan	Senior Scientist Chemical Engineering and Process Development Division (NCL) CSIR - National Chemical Laboratory Pune		x		x

6	**Archana Chugh**	**Associate Professor, Kusuma School of Biological Sciences IIT Delhi, New Delhi**		**x**		**x**
7	**Ashish Misra**	**Assistant Professor Department of Biochemical Engineering and Biotechnology, IIT Delhi Phone: +91-11-26591003**		**x**		**x**
8	**Ashish Paradkar**	**Director & Head, Research and Technology at Novozymes**			**x**	
9	**Arun Shukla**	**Associate Professor Wellcome Trust-DBT Intermediate Fellow & EMBO Young Investigator Joy-Gill Chair. Department of Biological Sciences and Bioengineering, IIT Kanpur**			**x**	
10	**Balakrishna Pisupati**	**Chairperson FLEDGE, Chennai.**	**Principal Investigator**			
11	**Baskar Bakthavachalu**	**National Centre for Biological Sciences (NCBS) Tata Institute of Fundamental Research**		**x**		**x**
12	**B. Sesikeran**	**Former Director National Institute of Nutrition Hyderabad**	**x**			

13	**Chaitanya Athale**	**Associate Professor IISER Pune Phone:**		**x**		**x**
14	**Dayananda C**	**E2E BIOTECH PVT LTD, Bangalore Bioinnovation Centre Electronic City Phase-I Bengaluru**				
15	**D. Sundar**	**Professor, Department of Biochemical Engineering and Biotechnology IIT Delhi**		**x**		**x**
16	**Ezhil Subbian**	**Founder/CEO at String Bio Pvt. Ltd.**		**x**		
17	**Guhan Jayaraman**	**Professor Room No. BT 501 Department of Biotechnology IIT Madras**		**x**		**x**
18	**H. S. Subramanya**	**Director IBAB & Biocon Chair Institute of Bioinformatics and Applied Biotechnology, Biotech Park, Electronic City Phase I, Bengaluru**		**Lead Facilitator**	**ADVISORY COMMITTEE**	
19	**H.V. Thulasiram**	**Scientist Organic Chemistry Division CSIR-National Chemical Laboratory, Pune**				**x**

20	**Jagadish Mittur**	**Biotechome Facilitation Cell, Department of IT BT and S&T, Government of Karnataka Bengaluru**			**Lead Facilitator**	
21	**Kartik Raman**	**Associate Professor BT 104, Department of Biotechnology IIT Madras, Chennai**		**x**		**x**
22	**Malathi Lakshmikumaran**	**Executive Director and Practice Head, Lakshmikumaran & Sridharan, Attorneys Safdarjung Enclave New Delhi**	**X**			
23	**Mrinal K. Maiti**	**Professor Department of Biotechnology, IIT Kharagpur West Bengal**		**x**		**x**
24	**MS Swaminathan**	**M S Swaminathan Research Foundation. 3rd Cross Street, Institutional Area, Taramani. Chennai**	**x**			
25	**Muthusamy**	**Department of Biotechnology, PSG College of Technology, Peelamedu, Coimbatore**		**x**		
26	**Nagasuma Chandra**	**Professor, Molecular Biophysics Unit,**		**x**		

		Indian Institute of Science, Bengaluru				
27	**Nalinkanth V. Ghone**	**Assistant Head Room No 12-208 Chemical Engineering Adjunct Professor, Department of Biotechnology, Sri Venkateshwara College of Engineering, Chennai**				**x**
28	**Naveen Kulkarni**	**CEO, Quantumzyme LLP Lal Bagh Main Rd, Krishnappa Layout, Bengaluru, Karnataka**			**x**	
29	**Pawan K. Dhar**	**School of Biotechnology Jawaharlal Nehru University, New Delhi**	**Principal Investigator**			
30	**Pradip Nair**	**Chief Scientific Manager BIOCON RESEARCH LIMITED, Novels Bengaluru, Karnataka**		**x**		
31	**Pranesh Badami**	**Reliance Industries Limited**				
32	**P.M. Murali**	**Chairman, Jananom Private Limited Kovaipudur, Coimbatore**			**x**	

33	**Prabodh Kumar Trivedi**	**Director, CSIR-Central Institute of Medicinal and Aromatic Plants, P.O-CIMAP, Near Kukrail Picnic Spot Lucknow-226015**				
34	**Pramod Wangikar**	**Professor, Chemical Engineering, IIT, Bombay**		**x**		**x**
35	**Push Vanam**	**Joint Director (Standards), Food Safety and Standards Authority of India (FSSAI)**	**x**			
36	**Rajam MV**	**Professor, Department of Genetics University of Delhi South Campus New Delhi**		**x**		**x**
37	**Rajiv Ranjan**	**Assistant Professor, Plant Molecular Biology Lab, Department of Botany, Faculty of Science Dayalbagh Educational Institute Agra**				**x**
38	**Rakesh Mishra**	**Director, CCMB, Hyderabad**		**x**		
39	**Ram Kaundinya**	**Board Director, Advanta Limited**	**x**			
40	**Ram Rajashekaran**	**CFTRI, Mysore**	**x**			

41	Raman Parkesh	Principal Scientist, IMTECH, Chandigarh				x
42	Ramanujam Srinivasan	Reader, School of Biological Sciences, National Institute of Science Education and Research, Bhubaneswar, Odisha				x
43	Ramesh V Sonti	Director, NIPGR, Aruna Asaf Ali Marg, New Delhi, Delhi 110067		x		
44	Rangarajan P N	Professor, Dept. of Biochemistry, Indian Institute of Science, Bengaluru 560 012	x			
45	Rohini Garg	Assistant Professor, Department of Life Sciences Shiv Nadar University, G.Noida				x
46	Sachin Chaturvedi	Director General, Research and Information System for Developing Countries (RIS) New Delhi	ADVISORY COMMITTEE			
47	Sachin Sathyarajan	RCE Thiruvananthapuram, Centre for Innovation in Science and Social Action (CISSA), Thiruvananthapuram, Kerala	Legal Consultant			

48	**Sangita Kasture**	**Department of Biotechnology, Ministry of S &T, New Delhi**	**ADVISORY COMMITTEE**			
49	**Sangram Bagh**	**Associate Professor, Biophysics and Structural Genomics Division Saha Institute of Nuclear Physics, Kolkata,**		**x**		**x**
50	**Sanjay Ghosh**	**Institute of Bioinformatics and Applied Biotechnology, Biotech Park, Electronic City Phase I, Bengaluru**			**x**	
51	**Santanu Dasgupta**	**Senior Vice President at Reliance Mumbai, Maharashtra**			**x**	
52	**Seema Mishra**	**Assistant Professor, Department of Biochemistry, School of Life Sciences, University of Hyderabad, Gachibowli, Hyderabad**				**x**
53	**Seetharam Annadana**	**Syngenta India Limited, Bangalore**	**Lead facilitator**			
54	**Saurabh Joshi**	**Senior Executive at Syngene**		**x**		

		International Limited, Yavatmal, Maharashtra				
55	Shaikh Z. Ahammad	Associate Professor, Department of Biochemical Engineering & Biotechnology, IIT Delhi, New Delhi ,Phone: 91-11-26591006				x
56	Shaibal K, Dasgupta	INSTEM, Bangalore			x	
57	Shambhavi Naik	Research analyst, The Takshashila Institution, Bangaluru		x		
58	Shashank Tripathi	Assistant Professor, Wellcome Trust India Alliance Intermediate Fellow Microbiology & Cell Biology Department, Indian Institute of Science		x		
59	Shams Yazdani	Group Leader, Microbial Engineering, ICGEB, New Delhi, India	ADVISORY COMMITTEE			Lead Facilitator
60	Shashi Kumar	Group Leader, Metabolic Engineering (Biofuels and Industrial Biotechnology), ICGEB, New Delhi				x

61	Shibani Ghosh	Fellow, Centre for Policy Research New Delhi				x
62	Shireesh Srivastava	Group Leader- Systems Biology & Biofuel ICGEB, New Delhi			x	x
63	Shriram Raghavan	Jananom Private Limited, Kovaipudur, Coimbatore		x		
64	Shivakumara Swamy	IBAB, Bengaluru			x	
65	Sivaprakash Ramalingam	Senior Scientist & Head, Genome Engineering & Stem Cell Group IGIB, New Delhi		x		x
66	S.K.Barik	Director, NBRI, Rana Pratap Marg, Lucknow				
67	Somenath Roy Chowdhury	Research Associate, IICB, Kolkata, Guest Faculty (Biotechnology) University of Engineering and Management, Kolkata				x
68	Souvik Maiti	Senior Scientist, IGIB, New Delhi				x
69	Sundar. D	Professor, IIT Delhi				
70	S. Ramalingam	Associate Professor, Centre for			x	

		Biotechnology Anna University, Chennai				
71	**Suvendra N Bhattacharya**	**Principal Scientist & Head, Molecular Genetics Group CSIR - IICB, Kolkata**				**x**
72	**Utpal Mohan**	**Assistant Professor, Department of Biotechnology NIPER Guwahati**				**x**
73	**Umesh P**	**Lecturer, Kerala**		**x**		
74	**Vijai Singh**	**Associate Professor, Department of Biosciences Indrashil University, Gujarat**				**x**
75	**Vikas Jain**	**Associate Professor, Department of Biological Sciences IISER Bhopal, Bhopal, Madhya Pradesh**				**x**
76	**Tapas R. Kundu**	**Director, CSIR-CDRI, Sitapur Road, Lucknow**				

ANNEXURE II

SUMMARY OF THE ONLINE MEETING HELD ON DEC 09, 2020

More than 70 experts from Industry, Academia and Administrative backgrounds (Table 1) were invited for deliberations on developing a national foresight analysis and policy framework on synthetic biology. The aim was to develop a national consensus on the definition, regulatory aspects, industry trends and emerging needs of the nation. An elaborate foresight document was circulated beforehand for further discussions. It was conveyed that the outcome will be provided to DBT for further action on developing national policy related to synthetic biology.

The exercise was important given that the United Nations Convention on Biological Diversity (CBD) is negotiating an international framework on synthetic biology, focusing on both regulatory and policy components. The purpose of online consultation was to seek inputs from experts to ensure wider participation of experts and practitioners in the area of synthetic biology so that the policy framework can be inclusive and responsive.

This consultation focused on the issues of developments in synthetic biology and its application from academic and related research components. Consultations were organized on topics such as agriculture and food, bioinformatics, industry and applications (including pharma), international developments and related aspects.

To ensure full confidentiality of inputs, the report followed Chatham House Rules. The meeting led to following observations.

1. There is a pressing need to define synthetic biology from the Indian perspective. A clear boundary should be marked between synthetic biology and the Recombinant DNA technology so that the policy gaps in synthetic biology are clearly visible. It was emphasized that exclusion criteria was important in this context.

2. The distinction between genetically manipulated systems falling under the ambit of IBSC, RCGM and GEAC and synthetic biology must be evident. Should one strengthen the existing policy framework rather than creating a new one for Synthetic Biology, is an open question.

3. Terms like 'Unintended consequences' and 'Unpredicted events' may be avoided as they may hinder the growth of synthetic biology. One may consider “predicted unfavorable events” and measures to facilitate the responsible growth of synthetic biology.

4. The genome-editing technology should be regulated because of its power and far-reaching impact. However, the governance norms may be dynamic and adapted to the needs of the society.

5. There should be minimal Indian government restrictions under the 'research mode'. We may consider moderate regulation in 'human and animal health sector' and relatively stricter regulation in the 'environment and biodiversity' sectors.

6. Extending the regulations of GMO to synthetic Biology merits detailed discussion. GMO regulations are under dispute and the outcome may affect the development of synthetic biology. This has to be avoided. One may consider unique framework considering the unique features of synbio, regulatory and governance norms and use existing policy framework and incorporate the synthetic biology plug-in, instead of desgining a brand new regulatory framework for synthetic biology.

7. Synthetic biology research may have come under a broad policy framework and appropriate sub-policies based on the Intention of use. Each subcategory may have a separate set of data requirement and approval processes, if needed. Sometimes the prior intention vis a vis real outcome is not always easy to detect and demarcate. As far as possible, the policy should be comprehensive and cover all aspects taking into account the biosafety and biosecurity needs of the country.

8. The international Synthetic Biology community emphasizes sharing and open access, which may make the ABS framework (Access and Benefit Sharing) irrelevant or very difficult to implement. An example of this is artemisinin production using engineered yeast. The discussion may be taken up under digital sequence information group.

9. India can take the lead in establishing a 'Biodiversity Commons', which, while promoting open access to genetic resources between countries, can also provide for a binding 'share-alike' mechanism. This can be in the form of establishing production facilities in countries that have provided genetic resources, as well as educating and training the local population to empower them to utilize their own natural resources. India has 7-8% of the total biodiversity in the work, with being one of the 17 mega diverse countries. We may need Indian science to be more mature before we open our biodiversity to the world freely. One may focus on capacity building but the idea of commons should not end up as a facilitator for free riding and piracy.

10. We should make regulatory policies proportionate to the risk. The risk may be assessed based on the kind of synthetic organism, IPR, Biodiversity, safety, and ethical issues. Furthermore, the regulation may include synthetic DNA, synthetic chromosome, synthetic chromosome, synthetic biomolecular circuits, synthetic cell or synthetic cell consortia, for which we don't know what will be the final impacts. Risk governance is critical (e.g., gene drives) taking into account all aspects of risks.

11. The concept of 'force majeure' or 'act of God', which is well-accepted in contract law, may be studied for possible adoption in synthetic biology.

12. Potential risks associated with technological innovations cannot be precisely determined; synthetic biology-enabled innovations are no exceptions. Insisting on the precautionary principle may be too conservative an approach, and such a policy environment may not be conducive for the progress of the synthetic biology discipline.

13. We need detailed discussion on incorporating sustainable and ‘contained synthetic biology’ processes like fermentation-based products in the new regulatory framework.

14. Active and knowledgeable researchers should be part of the team that formulates the Indian synthetic biology governance framework in future. Stakeholder engagement is very important.

15. Appropriate measures may be discussed and adopted for synthetic biology which would not hamper the progress of getting approval for simple gene manipulation methods.

16. We need a national plan and strategy that takes into account Synbio's potential for socio-economic development. The Sub-group in XII th plan has made some observations on this.

17. The foresight paper may include the discussions on patentability and ownership from the Indian perspective.

18. It was recommended that the draft paper may be uploaded on the DBT website for public opinion.

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the report on policy and research planning for synthetic biology ends here

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March 6, 2021

JNU, New Delhi