Trends in Biotechnology

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Synthetic Biology and the United Nations

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Synthetic biology is a rapidly emerging interdisciplinary field of science and engineering that aims to redesign living systems through reprogramming genetic information. The field has catalysed global debate among policymakers and publics. Here we describe how synthetic biology relates to these international deliberations, particularly the Convention on Biological Diversity (CBD).

Synthetic biology or engineering biology is a fast-moving field that embraces and drives state-of-the-art technologies for designing and reconstructing livings systems at different scales, primarily by reprogramming cellular genetic information. As such, the field has catalysed global debate among the wider circles of legislative policymakers, including multiple international conventions, treaties, and protocols. Various international treaties and organisations are currently examining the impacts of synthetic biology and engineered gene drive systems on their respective agreements (Table 1). One main United Nations (UN) convention of importance to synthetic biology is the UN Convention on Biological Diversity (CBD). In simple terms, the CBD has three main objectives: (i) conservation of biological diversity, (ii) sustainable use of its components, and (iii) fair and equitable sharing of benefits arising from the use of genetic resources. Since 2010, the CBD has discussed whether synthetic biology should be classified as a new and emerging issue and its objectives and activities are of considerable importance to the synthetic biology research community. For example, one objective of the CBD is to grant sovereign rights of countries over their genetic resources. Furthermore, the CBD is also deliberating whether or not new/adapted regulations are needed for synthetic biology, how access and benefits sharing agreements (ABS) should be managed with digital sequence information (DSI) and also whether or not moratoriums on synthetic biology research and/or applications to the environment should be implemented (Table 1). The CBD is also debating whether the products of synthetic biology should be considered under the convention, in addition to the process or technology used to produce them. The synthetic biology community should follow these deliberations closely and take the opportunity to engage directly within these processes.

In addition, similar deliberations have been underway inside the International Union for Conservation of Nature (IUCN), the world's largest and most diverse environmental network. IUCN commissioned a broad assessment addressing mandates established at its 2016 IUCN World Conservation Congress: 'Development of IUCN Policy on Biodiversity Conservation and Synthetic Biology' (WCC-2016-Res-086). This assessment has recently been released [1].

In 2016, the Parties to the Nagoya Protocol adopted decision XIII/16, which established a science and policy-based process on DSI and genetic resources [*Decision XIII/16 Adopted by the Conference of the Parties to the Convention on Biological Diversity. Digital Sequence Information on Genetic Resources* (2016). Available at https://www.cbd.int/doc/decisions/cop-13/cop-13-dec-16-en.pdf; CBD synbio online forum can be found at https://bch.cbd.int/synbio/open-ended/discussion/]. Following the results of this process in 2018, the Parties to the Nagoya Protocol adopted decision 14/20 [*Decision 14/20. Adopted by the Conference of the Parties to the Convention on Biological Diversity. Digital Sequence Information on Genetic Resources* (2018) https://www.cbd.int/abs/dsi-gr/2019-2020/default.shtml]. This process entails the submission of views and information, the commissioning and peer review of four studies, and work by an expert group on how to address DSI on genetic resources in the context of the post-2020 global biodiversity framework. Over the next few years, these will be important decision-making processes for the synthetic biology community to observe and participate in, as the CBD and International Treaty for Plant Genetic Resources for Food and Agriculture negotiate issues surrounding both DSI and ABS.

These policies could have a significant influence on synthetic biology research and development internationally. For example, implementation of active ABS policies on genetic information could inhibit global commercialisation of public-funded research or promote 'get-arounds' to avoid ABS, both of which are not ideal scenarios. The policies could also fundamentally challenge the very nature and ethics of biological diversity, raising practical issues around ABS and risk assessment protocols. They also could lead to a moratorium on developing synthetic biology applications like gene drive (see below and Table 1).

Key Issue 1: Ownership (ABS/DSI)

The International Treaty for Plant Genetic Resources for Food and Agriculture (Plant Treaty) and the Nagoya Protocol

Table 1. International Legal Frameworks of Relevance to Synthetic Biology[a]

Instrument	Description	Relevance for synthetic biology
UN Convention on Biological Diversity (CBD) https://www.cbd.int/ Adopted: 1992 Entered into force: 1993 Parties: 196	Global legal framework addressing conservation, sustainable use, and sharing of benefits of biodiversity. Creates obligations for each Party (Countries that have signed onto the Convention) to manage risks associated with living modified organisms (LMOs) that could have a negative impact on biological diversity [article 8(g)]. These obligations are captured, in part, under the Cartagena Protocol described below. Additional frameworks/requirements that address access and benefits sharing of genetic resources is also captured under the CBD and are described below (i.e., Nagoya Protocol). Decision XII/24 established an *ad hoc* technical expert group (AHTEG) on synthetic biology that has produced multiple reports and recommendations but has not as yet undertaken the robust assessment against new and emerging criteria as mandated by the Conference of the Parties [6]. These deliberations continue and have since added gene drives and genome editing to their mandate.	Since 2010, the CBD has discussed whether synthetic biology, which now includes gene drives and, potentially, gene editing, should be classified as a new and emerging issue. Defining it as such would enable the development of new guidance and risk assessments on how synthetic biology and its applications (separate from LMOs) could be utilised in the future by a member state. For synthetic biology researchers, this could result in limitations or even stopping research into some potential synthetic biology applications; there is a need to be aware of the origin/source of the genetic information they are using in their research, with potential limitations on commercialisation of some synthetic biology applications.
Cartagena Protocol on Biosafety to the Convention on Biological Diversity (Cartagena Protocol) https://bch.cbd.int/protocol Adopted: 2000 Entered into force: 2003 Parties:171	Protocol under the CBD intended to ensure the 'safe transfer, handling and use of LMOs resulting from modern biotechnology that may have adverse effects on biological diversity...' (article 1). It requires sharing of risk-related information between exporting and importing Parties and provides guidelines on methodologies for conducting environmental risk assessments and considerations in decision making.	Current deliberations are considering whether or not synthetic biology, including engineered gene drives, would fall under the definitions of LMOs and thus be subject to the risk assessment requirements of the Cartagena Protocol [7]. For synthetic biology researchers, note that the issues surrounding the classification of LMOs in relation to specific genome edits versus transgenes versus completely recoded synthetic genomes remains unresolved within the convention. In 2019 a study was commissioned to gather information from areas where LMOs containing engineered gene drives are produced and/or are expected to be used for either field testing or release, and any issues related to challenges for existing risk assessment methodologies and guidelines to assess the safety of LMOs containing engineered gene drives.
Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety (Supplementary Protocol) https://bch.cbd.int/protocol/supplementary/ Adopted: 2010 Entered into force: 2018 Parties: 42	Supplementary Protocol to Cartagena Protocol intended to provide rules and procedures for liability and redress relating to LMOs. Provides for national frameworks requiring response measures and assigning civil liability in event of damage resulting from LMOs that find their origin in transboundary movement.	Whether synthetic biology is classified as a new and emerging issue or is captured under the current LMO definitions under the Cartagena Protocol, the synthetic biology community would be held under the rules of this Protocol, pursuant to the member state in which they are operating. For the synthetic biology researcher, any accidental or deliberate release of an LMO that causes damage, the researcher/institution would be held as liable under the convention.
Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (Nagoya Protocol) https://www.cbd.int/abs/ Adopted: 2010 Entered into force: 2014 Parties: 105	The Nagoya Protocol is an international legal agreement for the fair and equitable sharing of the benefits [access and benefit sharing (ABS)] arising from sustainable utilisation of genetic resources to conserve and protect biodiversity.	Applies to genetic resources that serve as source material for synthetic biology research. Creates ABS framework based on traceability and transfer of material that could be undermined by use of digital sequence information. In 2017 the secretariat of the CBD commissioned a report examining the impacts of digital sequence information as it relates to the Nagoya Protocol [8]. The study found that the use of information on genetic resources, including in synthetic biology, could create opportunities for new forms of nonmonetary and monetary benefit sharing for the

Table 1. (continued)

Instrument	Description	Relevance for synthetic biology
		owners of genetic resources but noted the risk that DSI would undermine existing approaches to benefit-sharing by avoiding the need for access to genetic resources themselves [8]. Deliberations on this topic continue. For the synthetic biology researcher, policy developments around DSI could affect their 'freedom to operate'.
International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA) http://www.fao.org/plant-treaty Adopted: 2001 Entered into force: 2004 Parties: 145	International regime recognising sovereign rights over plant genetic resources for food and agriculture. The treaty facilitates access to the genetic material of the 64 crops in the multilateral system for research, breeding, and training for food and agriculture. Those who access the materials must be from the treaty's ratifying nations and they must agree to use the materials totally for research, breeding, and training for food and agriculture. The treaty prevents the recipients of genetic resources from claiming intellectual property rights over those resources in the form in which they received them, and ensures that access to genetic resources already protected by international property rights is consistent with international and national laws. Those who access genetic materials through the multilateral system agree to share any benefits from their use through four benefit-sharing mechanisms established by the treaty.	It is currently unclear how the technological change occurring in synthetic biology that is enabling the manufacture, manipulation, and use of genomic sequence data should be considered under the ITPGRFA. Although the treaty addresses ABS for physical material it does not take an ABS approach for genetic data. The evolving technological, legal, and institutional context surrounding the exchange and use of DSI for synthetic biology and genomic research may affect ABS frameworks under the ITPGRFA. The availability of sequence data through decentralised data libraries and organisations may challenge the multilateral system set up by the ITPGRFA. Other factors, including partial sequence combinations, and the fact that the same sequence may occur in multiple organisms, further challenge the ABS principles. For the synthetic biology researcher, policy developments around ABS could affect their 'freedom to operate'.
UN Convention on International Trade in Endangered Species (CITES) https://www.cites.org/ Adopted: 1973 Entered into force: 1975 Parties: 183	Multilateral environmental agreement establishing regulations and permitting system covering trade in listed species.	CITES has begun discussions related to synthetic biology products that substitute or resemble products from a CITES listed species in international trade (e.g., synthetic rhino horn or other ivory products). CITES is also examining what the status of a genetically modified species, a completely novel species, or a de-extinction species would be under the Convention. For example, would a 'new' species or a de-extinction species created though synthetic biology be given the same protections under CITES.
UN Convention on the Law of the Sea https://www.un.org/depts/los/ Adopted: 1982 Entered into force: 1994 Parties: 168	Codification of law of the sea, including activities and resources in areas beyond national jurisdiction. Provides basis for ongoing negotiation of international agreement on marine biodiversity in areas beyond national jurisdiction, including sharing of benefits from marine genetic resources.	While these discussions are in the early stages, issues around ABS, ownership, and protections are similar to the negotiations/discussions currently underway in the CBD, Nagoya, CITES, and ITPGRFA. It could have an impact on genetic resources that could serve as source material for synthetic biology research. For the synthetic biology researcher, policy developments around the availability and usage of genetic resources could affect their 'freedom to operate'.

[a]Adapted from [1].

have begun to examine the broad themes and potential implications of synthetic biology and genomic research; specifically, how evolving technological, legal, and institutional contexts surrounding the exchange and use of DSI affects its ABS frameworks.

Science and Technology Dimensions

The recent report commissioned by the Plant Treaty has a number of key findings [2]. There are three main broad themes: (i) mining plant genomic information for gene editing in agriculture, (ii) mining for use outside of agriculture, and (iii) using the plant as a 'workhorse' to produce other products. A large amount of DNA sequence data is already widely available and easily exchanged, which raises significant challenges to the ABS logic of identification and the different expectations of monitoring. With new genetic technologies,

the ABS system cannot rely on the link between physical material and data to identify ownership and location, so monitoring DSI exchange is very challenging. Other complications are the use of partial sequence combinations and duplication of sequences in multiple organisms.

Legal Challenges in ABS

Access to material under the multilateral system [MLS; Article 12.3(a)] is solely for purposes of 'utilization and conservation for research, breeding and training for food and agriculture', and excludes 'chemical, pharmaceutical and/or other non-food/feed industrial uses'. Researchers can effectively use DSI from MLS material in any kind of research, including chemical and/or pharmaceutical, without such usage being easily monitored. Moreover, by using DSI from identifiable published material, the chain of transmission is not transparent nor documented, and there are no indications that legal innovations such as open material transfer agreements will improve DSI monitoring or assess benefits. While some patents incorporating DSI may provide geographic origin information, others may not, or the information may be hidden (e.g., trade secret protection).

To encourage equitable sharing and access to genetic materials, researchers generally use *ex ante* investment to facilitate access to genetic material, public funding for infrastructure investment, facilitated access for research community building, structured research collaboration, and education and training. These strategies could be considered in relation to the Nagoya Protocol and Plant Treaty [3], as both acknowledge the importance of fair and equitable sharing of benefits arising from genetic resources, through exchange of information, access to and transfer of technology, and capacity-building.

Key Issue 2: Biocontainment

In some cases, synthetic biology applications could ultimately involve environmental release of living modified organisms (LMOs) that would interfere with evolution and natural biodiversity [4] (see below). To address this, a number of novel biocontainment strategies have been described, although their utility is still under debate [4,5]. Several use auxotrophy, which limits a cell's ability to survive in the absence of defined chemical or nutrients. Others involve genetic 'kill-switches', which control the viability of cells in response to defined internal or external stimuli. In contrast, physical containment directly limits contact of LMOs with the surrounding environment. The release of LMOs directly into the environment is a central topic within the CBD. Concerns are based around lack of predictable organism behaviour and influence on its surroundings. Certain criteria would need to be met to ensure the LMO would not restrict or outcompete native organisms, nor interfere with the natural evolutionary process. A major problem is the adaptive response of living organisms to their environment where, to survive, cells can evolve escape mechanisms such as mutational drift or horizontal gene transfer, or acquire essential nutrients from the environment [5].

Key Issue 3: Interference with Evolution

Synthetic biologists directly engage with molecular evolution, from simple genetic point mutations to whole gene deletions, additions, and replacement. More recently, work has expanded to *de novo* genome synthesis as a result of decreasing DNA costs and the ease of large-scale DNA assembly (e.g., bacterial genomes and yeast chromosomes). There are now a range of reverse genetics strategies available in the synthetic biologist's toolkit, with the gene drive approach (Box 1) causing particular concern within the CBD and other international conventions. Resolution of these concerns could result in a moratorium on the release into the environment of engineered organisms for specific applications.

Concluding Remarks

Synthetic biology has the potential to catalyse a new biotechnology revolution, but with these opportunities comes a duty to ensure safety. There is now an urgent need for scientists, policy makers, and broader stakeholder communities to engage with one another to collectively evaluate and decide how synthetic biology research should be conducted, with the aim of conserving biological diversity whilst providing benefits to all. We strongly recommend that the synthetic biology community monitor the CBD debates, which will include an opportunity to review the findings of the *ad hoc* technical expert group of synthetic biology and participate in future online forums on synthetic biology and DSI (refer to the UN Portal on Synthetic Biology for more information: https://bch.cbd.int/synbio/).

Box 1. Gene Drives

A gene drive is a system of biased inheritance where the ability of a genetic element to pass from a parent organism to its offspring through sexual reproduction is enhanced. Unlike the population dynamics of normal genomic alterations, gene drive systems promote the spread of genetic elements through populations by ensuring inheritance at a higher frequency than Mendelian segregation would predict [9]. Of particular relevance is the Cas9-mediated gene drive study of the malaria vector mosquitoes *Anopheles stephensi* and *Anopheles gambiae* showing potential as an intervention in malaria control [9]. Cas9-mediated gene drives have also been demonstrated in mice [10]. Whilst this technique has potential to address global problems in health, agriculture, and conservation, the capacity to alter wild populations outside the laboratory has caused significant concerns [11,12]. Therefore, it is essential to ensure that any self-propagating system has multiple biocontainment strategies in place to minimise any risk of contamination of natural biodiversity.

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T.K. is a current observer member (P.F. and Z.S. were past members) of the Ad-Hoc Technical Expert Group (AHTEG) on Synthetic Biology within the CBD.

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References

1. Redford, K.H. *et al.*, eds (2019) *Genetic Frontiers for Conservation: An Assessment of Synthetic Biology and Biodiversity Conservation. Technical Assessment*, IUCN
2. Welch, E. *et al.* (2017) *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')*, International Treaty on PGRFA, FAO
3. Bagley, M.A. (2016) Digital DNA: The Nagoya Protocol, Intellectual Property Treaties, and Synthetic Biology. *SSRN* Published online February 2, 2016. ssrn.com/abstract/=2725986
4. Torres, L. *et al.* (2016) Synthetic biology approaches to biological containment: pre-emptively tackling potential risks. *Essays Biochem.* 60, 393–410
5. Mandell, D.J. *et al.* (2015) Biocontainment of genetically modified organisms by synthetic protein design. *Nature* 518, 55–60
6. Convention on Biological Diversity (2018) *Report of the Ad Hoc Technical Expert Group on Synthetic Biology*, CBD
7. Convention on Biological Diversity (2018) *Risk Assessment and Risk Management of Living Modified Organisms*, CBD
8. Laird, S.A. and Wynberg, R.P. (2018) *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*, CBD
9. Kyrou, K. *et al.* (2018) A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. *Nat. Biotechnol.* 36, 1062–1066
10. Grunwald, H.A. *et al.* (2019) Super-Mendelian inheritance mediated by CRISPR-Cas9 in the female mouse germline. *Nature* 566, 105–109
11. Esvelt, K.M. *et al.* (2014) Concerning RNA-guided gene drives for the alteration of wild populations. *eLife* 3, 03401
12. Akbari, O.S. *et al.* (2013) A synthetic gene drive system for local, reversible modification and suppression of insect populations. *Curr. Biol.* 23, 671–677