Beyond the organism versus machine dichotomy : a review of ethical concerns in synthetic biology

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Beyond the Organism versus Machine Dichotomy: A Review of Ethical Concerns in Synthetic Biology

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Abstract

Synthetic Biology (SynBio) is a technology that brings new possibilities and benefits as well as new ethical concerns. We have performed a systematic review and thematic analysis of papers that deal with the possible ethical and social issues surrounding SynBio. We found that articles mention deontological concerns related to tinkering with life and more consequentialist matters related to biosafety and biosecurity. At the same time, justice aspects, such as socio-economic and environmental impacts, are far less mentioned. Moreover, there is no systematic study of the ethical issues that SynBio researchers in the lab encounter on a day-to-day basis.

Keywords

Synthetic Biology, SynBio, Ethics, Justice, Review

Introduction

Synthetic Biology (SynBio) is a scientific field that has gathered much interest in popular media and scientific literature alike. A variety of areas of research are covered under this umbrella term. The term' synthetic 'biology' was first coined by Barbara Hoom to describe a specific class of genetically engineered bacteria [1]. Nowadays, SynBio refers to the building, modelling,

designing, and fabricating novel biological systems using customized gene components that result in artificially created genetic circuitry[1]. Research and applications that are considered SynBio often start from some pre-existing material or living system, which is then re-engineered for a desired purpose by synthesizing or transplanting entire genomes. At the same time, research that aims to create new, more straightforward kinds of minimal chemical, cellular life by using inanimate or lifeless materials is also often referred to as Synthetic Biology. The entities made from this approach are often called "protocells" [2]. While the risks from the former, top-down, approach include biosafety and biosecurity issues that may be similar to other approaches that are not usually thought of as 'SynBio', such as genetic manipulation, the creation of protocells may raise new forms of biosafety and biosecurity concerns since they would not resemble any other existing entities. Moreover, since these entities are human-made, from scratch, they would raise certain philosophical and anthropological concerns and may even challenge current views and perceptions of life [3,4-5]. Advocates of the technology state that it has great potential in addressing diverse applications such as the production of various bio drugs and the creation of tailor-made metabolic pathways, thereby potentially bringing direct and indirect transformation to human life [1]. At the same time, SynBio comes with its own set of ethical, legal, and social issues. SynBio has attracted the attention of philosophers, ethicists, anthropologists, and religious scholars, who warn about challenges surrounding the creation of de novo parts of biological processes and the potential unpredictability and uncontrollability of these components. Other ethical issues include SynBio's positive or negative impact on people's livelihoods and the environment. Moreover, the ethical frameworks used for SynBio will vary depending on the area of application and how the term is operationalized. To critically assess existing scholarship on the ethics of synthetic biology, we performed a systematic review of the papers discussing these issues in peer-reviewed journals. It is important to note that the term "SynBio" is used to denote different areas or fields such as Bioengineering, synthetic genomics, protocell synthetic biology, unconventional molecular biology, and in silico techniques, among others. However, our objective is restricted to the investigation of how papers discussing the term 'SynBio' conceptualize synthetic biology and its applications, as well as the specific ethical issues mentioned in the context of 'synthetic biology' in general.

Methods

We searched four databases in Nov 2021. The databases queried were PubMed, ERIC, Web of Science, and Google Scholar. Search terms used to retrieve articles were (Synthetic biology) AND (Ethics). Articles were limited to search terms in titles, keywords, and abstracts with an English abstract. After the removal of duplicate articles, all titles and all relevant abstracts were screened by both authors. We have included only papers that have SynBio in the abstract. Full-text articles were then read for inclusion eligibility. This search strategy has some limitations. We may have missed relevant literature that appeared in venues not indexed in the above-mentioned databases. We also did not include 'grey' literature because we wanted to focus on scholarly literature.

We performed a thematic analysis to identify essential themes from our data, interpret, and analyze them to summarize the critical ethical issues discussed in SynBio. We performed an inductive thematic analysis following the methodology described by Braun and Clarke [7]. We opted for an inductive approach because we aimed for the research to be data-driven and not heavily influenced by the researcher's theoretical interest or analytic preconceptions [7].

Both authors read each paper separately and coded inductively. Both authors discussed the themes they found for interrater compatibility and agreed on the following significant themes: Defining SynBio, Engineering life, and Assessing the impact of SynBio. Author 1 wrote the first draft of the results section, and Author 2 commented on it. The comments were then included in the results section. No software was used to analyze the texts.

Results

We found 39 articles from the time frame 2009 - 2020: an opinion paper, a policy forum, a book chapter from edited volumes, two dissertations, and 34 papers from peer-reviewed journals. Of these 39 papers, 16 papers talk about general ethical issues that arise in the case of SB, ten papers deal with governance and regulations, five papers approach SB from a religious perspective, three papers focus only on the philosophical aspects of SB, and five papers approach SB with different ethical theories.

We have distilled three clusters of themes – *Defining Synbio, Engineering life, and Assessing the impact of Synbio* with sub-themes within them. An overview of the papers and themes is provided in Table 1. We shall first provide a general overview of the themes covered in all the articles and then discuss the gaps and shortcomings in the discussion session.

Table 1 Papers included in the study with themes and sub-themes identified in each

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
1	Synthetic Biology and Ethics of Knowledge 2010	New and novel	Playing God Role of Human beings Blurring lines b/w living & non-living Moral status	*Effect* • Knowledge related • Method related
2	Consequentialism and the Synthetic Biology Problem 2017	*n/a*	Role of media and metaphors	*Effect* • Method related *Governance* • Patenting • SynBio specific regulation
3	Synthetic Biology and Ethics Past, Present, and Future 2017	Form of construction New and novel	Creating life Role of Human beings	*Effect* • Method related
4	Research Translation and Emerging Health Technologies: Synthetic Biology and Beyond 2018	Multi-disciplinary Outcomes: Positive/ Negative	Blurring lines b/w living & non-living Creating life Role of media and metaphors	*Justice and equity* • Application related *Governance* • Transnational collaboration • Patenting • Public inclusiveness
5	Current ethical issues in Synthetic Biology: Where should we go from here? 2011	Form of construction New and novel	Moral status Creating Life	*Effect* • Method related *Justice and equity* • Application related *Governance* • Patenting • Academic awareness

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
6	Synthetic Biology Ethics at iGEM: iGEMer Perspectives 2018	Outcomes: Positive/ Negative	Blurring lines b/w living & non-living	*Effect* • Knowledge related *Governance* • Academic awareness
7	Synthetic biology ethics: A deontological assessment 2013	Outcomes: Positive/ Negative	Role of Human beings Playing God Role of media and metaphors	*Effect* • Knowledge related
8	Synthetic Biology between Self-Regulation and Public Discourse 2017	Form of construction	*n/a*	*Governance* • SynBio specific regulation Academic awareness • Public inclusiveness
9	The Ethics of Synthetic Biology: Next Steps and Prior Questions 2014	Form of construction	Role of Human beings Playing God Blurring lines b/w living & non-living Role of media and metaphors	*Effect* • Knowledge related • Method related *Justice and equity* • Application related • Transnational collaboration *Governance* • SynBio specific regulation • Public inclusiveness

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
10	A priority paper for the societal and ethical aspects of synthetic biology 2009	Form of construction New and novel	Creating life Moral status	*Effect* • Method related *Justice and equity* • Application related *Governance* • SynBio specific regulation • Academic awareness • Public inclusiveness • Patenting
11	A personalist ontological approach to synthetic biology 2016	New and novel	Creating Life Moral status Role of media and metaphors	*Effect* • Method related *Justice and equity* • Application related *Governance* • SynBio specific regulation • Academic awareness • Public inclusiveness
12	Whose ethics of knowledge? Taking the next step in evaluating knowledge in synthetic biology: a response to Douglas and Savulescu 2012	*n/a*	*n/a*	*Effect* • Knowledge related *Governance* • SynBio specific regulation • Public inclusiveness • Lived experience

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
13	Social and ethical checkpoints for bottom-up synthetic biology, or protocells 2009	Form of construction Outcomes: Positive/ Negative	Creating Life Playing God Blurring lines b/w living & non-living Role of media and metaphors	*Effect* • Method related *Justice and equity* • Application related *Governance* • SynBio specific regulation • Academic awareness • Public inclusiveness • Patenting
14	Playing God and the Intrinsic Value of Life: Moral Problems for Synthetic Biology? 2013	*n/a*	Creating Life Blurring lines b/w living & non-living Role of media and metaphors	*Governance* • Public inclusiveness
15	Engineering and ethical perspectives in Synthetic Biology 2012	Form of construction New and novel	*n/a*	*Effect* • Method related *Governance* • Public inclusiveness
16	Synthetic Biology: The Response of the Commission of the (Catholic) Bishops' Conferences of the European Community 2017	Form of construction	Playing God Creating life Role of Human beings	*Justice and equity* • Application related • Transnational collaboration *Governance* • Public inclusiveness • Patenting

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
17	Synthetic biology: Novel approaches for microbiology 2015	*n/a*	Role of media and metaphors	*Effect* • Method related *Governance* • Academic awareness
18	Synthetic biology, metaphors and responsibility 2017	Multi-disciplinary	Blurring lines b/w living & non-living Role of media and metaphors	*Governance* • Public inclusiveness
19	Synthetic Biology: A Jewish View 2012	*n/a*	Role of Human beings Creating life Playing God Role of media and metaphors	*Effect* • Method related *Justice and equity* • Transnational collaboration *Governance* • Public inclusiveness
20	Realizing the potential of synthetic biology 2014	Form of construction New and novel	Role of media and metaphors	*Effect* • Method related *Justice and equity* • Application related
21	Is There Anything Unique in the Ethics of Synthetic Biology? 2012	*n/a*	Creating life Playing God Role of Human beings Moral status Blurring lines b/w living & non-living	*Effect* • Knowledge related

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
22	Ethical Perspective on Synthetic Biology 2013	Form of construction	Creating life Role of Human beings	*Effect* • Method related *Justice and equity related* • Application related • Transnational collaboration *Governance* • SynBio specific regulations
23	The Ethics and Ontology of Synthetic Biology: a Neo-Aristotelian Perspective 2019	Outcomes: Positive/ Negative	Moral status Role of media and metaphors	*Governance* • SynBio specific regulation
24	Synthetic Biology Needs A Synthetic Bioethics 2012	*n/a*	Creating Life	*Justice and equity* • Application related *Governance* • Public inclusiveness • SynBio specific regulation
25	Ethical perception of synthetic biology 2011	New and novel	*n/a*	*Governance* • Public inclusiveness
26	Synthetic “Life,” Ethics, National Security, and Public Discourse 2010	Form of construction	Role of media and metaphors	*Effect* • Method related *Governance* • Patenting • SynBio specific regulation • Public inclusiveness

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
27	Integrating ethical analysis ‘‘Into the DNA’’ of synthetic biology 2015	Multidisciplinary	*n/a*	*Effect* • Knowledge related • Method related *Governance* • Academic awareness • SynBio specific regulation
28	Commercializing synthetic biology: Socio-ethical concerns and challenges under intellectual property regime 2009	Multidisciplinary Form of construction New and novel	Creating Life	*Effect* • Knowledge related • Method related Governance • Patenting • SynBio specific regulation
29	Ethical and Regulatory Challenges Posed by Synthetic Biology 2012	Outcomes: Positive/ Negative	*n/a*	*Effect* • Knowledge related *Governance* • Academic awareness
30	Synthetic Biology, Analytic Ethics 2010	*n/a*	*n/a*	*Effect* • Method related *Governance* • SynBio specific regulation

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
32	From Homo Faber to Homo Creator? A Theological- Ethical Expedition into the Anthropological Depths of Synthetic Biology 2013	*n/a*	Playing God Creating life Blurring lines b/w living & non-living Moral status Role of media and metaphors	*n/a*
33	How to Address the Policy and Ethical Issues Emerging with New Technology. The Case of Synthetic Biology in a Small Country 2018	Multidisciplinary	Playing God Role of media and metaphors	*Effect* • Knowledge related *Justice and equity* • Transnational collaboration *Governance* • SynBio specific regulation
34	The Moral & Ethical Concerns of Synthetic Biology: The Reasons Why We Should Stop 2016	Form of construction New and novel	Role of Human being	*Effect* • Method related *Justice and equity* • Application related
35	Playing God? Synthetic Biology from a Protestant Perspective* 2013	*n/a*	Role of Human being Blurring lines b/w living & non-living	*n/a*
36	The Ethics of Synthetic Biology Respecting Life and Managing Risk - PhD thesis 2016	Form of construction	Moral status	*Justice and equity* • Application related Governance • Patenting • Public inclusiveness

No	Title and Year	Defining SynBio	Engineering Life	Assessing the impact of SynBio
37	The Defence of Artificial Life by Synthetic Biology From Ethical and Social Aspects 2015	Form of construction	Role of Human being Creating life Reductionism of life Blurring lines b/w living & non-living	*Effect* • Method related *Justice and equity* • Application related *Governance* • Patenting • SynBio specific regulation • Academic awareness
38	Artificial life and synthetic biology 2010	Form of construction	Blurring lines b/w living & non-living Role of media and metaphors	*n/a*
39	The Ethics of Synthetic Biology Research and Development: A Principlist Approach 2020	*n/a*	*n/a*	*Effect* • Knowledge related • Method related *Governance* • Public inclusiveness • Academic awareness

Defining Synbio

Thirty-two articles describe how they view the field and topic of SynBio. These include descriptions of Synbio as a form of construction, creating new and novel systems or entities, SynBio as a multi-disciplinary field, and SynBio as a field with the potential for positive or negative outcomes.

Fifteen papers described SynBio as a **form of construction.** They use terms such as design, redesign, and construct to describe the aim/function of Synbio [1,2,5,8–19]. While ten papers define the aim of SynBio to design and construct *new biological parts or systems* or to redesign the *existing* biological systems [1,8–11,15–19], three papers mention that SynBio aims to create complex *artificial biological systems* [2,5,12]. Two papers situate and equate SynBio within the engineering discipline [13-14]. One paper specifically mentions that SynBio, from a technical perspective, is more akin to a new engineering discipline where new cells or organisms are synthesized according to the design of human cells [13]. The other paper mentions that SynBio is an engineering discipline with a desire to build things that do not yet exist [14].

Ten papers use the terms **'new' and 'novel'** when describing the technology itself or the things created by it [1,8,9,14,15,17,18,20–2223]. However, while one paper mentioned *new and novel organisms* [20], seven papers mentioned *new and novel biological systems* [1,8,9,14,15,18,23]. 2 papers use both the terms *construction* of *novel biological systems* and *creation* of *novel organisms* as the aim of SB [17,21].

Five papers mentioned SynBio as a **multi-disciplinary field** involving the convergence of biology with engineering, creating a hierarchy of different research fields together representing a *powerful area of science* [1,22,24–26]. One paper specifically mentions the fluidity and vastness provided by SynBio to encompass a diverse range of possible technologies, thereby terming it as "the new technoscience" around which "socio-technical imaginaries" and promises of better health and benefit are built [22].

Six papers mention that Synbio has a great potential for **positive or negative outcomes** [2,4,27–30]. Of these six, four papers mention the consequences SynBio could have, such as setting great expectations and promises for a better future, providing a way for knowledge enhancement to investigate natural phenomena but also having disruptive potential [2,4,27,30]. While one paper mentions that SynBio also has the potential to change people's views on life and science [28], another paper explicitly states that, unlike previous technologies, "Synbio is

characterized by a drive to mastery that stands opposed to a due appreciation of the giftedness of life" more than any other technology [29].

Engineering Life

Twenty-eight papers describe their distinctive views on the role of human beings in SynBio. Nine papers have used the phrase **"Playing God"** [2,4,5,16,20,26,31–33]. However, the phrase has been used in different ways. While four papers used this term to emphasize the presence of a supreme power and the worries associated with human beings taking up the role of this supreme being [2,4,20,31], five papers used the phrase to either deny the statement of human beings acting like God or to point out that it is used to create a dystopian imaginary [5,16,26,32,33]. One paper specifically mentions that this phrase is not new in science and is instead used as a metaphor to describe the present significance and effect of technological development on the former ways of description found in our society [33].

Sixteen papers discuss **the role of media and metaphors** in SynBio [2,4,11,12,14,16,23,24,26,27,29,32–36]. Eleven papers describe the kinds of metaphors used in SynBio and their possible impacts on the development of this technology [4,11,12,16,23,24,29,32–35]. While four papers mention that terminology such as "hardware" and "living machines" could be damaging and misleading [4,24,34,35], two papers specifically talk about the negative influence computational and machine metaphors can have on societal attitudes and fear of reductionism of life [4, 24]. Six papers mention that avoiding confusing metaphors and using more accurate metaphors with clear language can help prevent public mistrust, misconceptions, and worries regarding Synbio [11,12,16,23,32,33].

Five papers point out the negative influence media has on technological acceptance and development, such as the potential for either overestimating the benefits of Synbio or dystopian fears associated with terms such as "Playing God" or "Creating Life" [2,14,26,27,32]. One paper explicitly mentions that one needs to be aware of the role played by marketing in promoting new health technologies, especially when commercial interests are involved [22].

Eleven papers have mentioned the **role of human beings in nature** [4,5,8,10,13,16,18,20,31,32,37]. Of these eleven papers, seven papers mention that human beings are in command of nature and therefore need to act as responsible stewards with an ethical obligation to preserve nature and fix the world [4,5,8,10,13,18,32]. At the same time, four papers state that human beings must recognize their limits and boundaries even if considered stewards to protect nature [16,20,31,37].

Fifteen papers use the phrase **creating life** [1,2,5,8,10,13,15,17,23,27,31-33,35,38]. In these papers, different authors use this phrase with other, sometimes, opposing meanings. On the one hand, six papers mention that the creation of life through SynBio raises concerns about the reductionism of life, human relationship with nature, and other living beings and also raises essential questions on the moral status of the new entities [2,10,13,17,23,27]. One paper mentions that the ability to create and manipulate protocells, for example, could profoundly impact our view of life and make us question our place in the universe [2]. Three papers state that interfering with the natural order to create entities that do not exist is entirely wrong and unnatural, which could lead to immoral activities such as the commoditization of life forms created by SynBio [1,31,38]. On the other hand, three papers mention that creating life is not new and has been happening since the dawn of time with human interference in agriculture and animal breeding [5,32,37]. In one paper, the author specifically mentions that the discussion on creating life can be postponed until scientists can build an organism using only inorganic chemicals [8].

Twelve papers describe the **blurring of lines** between natural and artificial and human being and machine in different contexts [2,11,13,16,20,24,27,30,31,33,35,37]. Ten papers feel that synthetic entities challenge a normative understanding of 'natural' and 'life' and alter the intuitive dichotomy between the living and non-living [2,11,13,20,27,30,31,33,35,37]. One paper uses the example of 'hybrid humans' created with SynBio in medicine to point out how they could have implications for understanding embodiment and its relationship to the 'natural' or 'biological' [27]. Two papers claim that the endeavor to understand life further and bridge the gap between non-life and life dissolves the boundary and blurs lines between 'nature' and 'culture' [11,24]. Only one paper discusses that SynBio brings no meaningful change in the human relationship to nature since the technology is still somewhat limited to modifying simple organisms [16].

Eight papers describe their views on the **moral status** of the presumed newly created entities [15,17,19,20,23,29,31,33]. All eight papers mention that synthetic entities would require a revaluation of their moral status because they fall in a "grey area," differing from natural organisms, machines, and genetically modified organisms. In one paper, the author specifically states that such re-evaluation is important "to maintain the principle of protecting the ecosystem and the environment, which states that living organisms cannot be treated as mere instruments" [23].

Assessing the Impact of Synthetic Biology

Thirty-five papers describe the effect, justice and equity-related issues in SynBio and ways of governance in SynBio.

Effect

Effects of the consequences of Synbio are described in terms of knowledge-related, method-related, and application-related issues.

Nine papers discuss **knowledge-related issues** that could arise in Synbio, such as the safe modes of creation, usage, transfer of knowledge, and the dual-use dilemma [1,4,16,20,25,26,28,30,31,39,40]. Of these nine, seven papers express the need to create an ethics of knowledge as a new branch of bioethics to go beyond research and investigate knowledge production and dissemination [1,16,20,25,28,31,40]. At the same time, three papers point out that the creation and operationalization of ethics of knowledge could be as alarming as what it seeks to prevent. It demands difficult trade-offs between liberty and human understanding versus safety and the impending uncertainty in predicting potential risks and benefits [28,39,40]. However, one paper stated that they are not highly worried about the use of SynBio knowledge by amateur scientists [26].

A dual-use dilemma arises in those technologies in which research and technology can be used for good and bad applications, such as for the benefit of mankind by inventing new medicines and for the danger of mankind, such as bioterrorism [41]. Although five papers have expressed their concerns over such **dual-use dilemmas** in SynBio, they do so by describing different scenarios [4,20,28,30,40]. Three papers mention that, unlike other areas of science, the risks of misuse might outweigh the beneficial uses of research in SynBio [4,20,30]. One article mentions that while all forms of SynBio research have at least some potential for dual use, dual use concerns are only applicable in cases where the risks are high, and the dangers very serious [40]. Two papers mentioned the concerns and worries associated with the publication of dual-use research articles and the availability of scientific equipment on the Internet [28,30].

Twenty-two papers describe **method-related issues** that could arise in SynBio, such as biosafety, biosecurity, and unpredictability in SynBio.

Biosafety has been discussed in thirteen papers with some differences [1,2,8,10,13,16–18,20,25,27,34,36]. While nine papers discuss biosafety regarding dangers for the environment and public life related to the creation and release of novel pathogens [1,2,8,18,20,25,27,34,36], four papers

discuss biosafety in the context of laboratory safety and dangers associated while working with unpredictable novel pathogens [10,13,16,20]. One paper also points out the risks to animals during animal experimentation, which is often overlooked in SynBio [18]. However, only one paper argues that it is essential "to explore how SynBio itself may contribute towards overcoming existing and possible future biosafety problems by contributing to the design of safer biosystems" [17].

Biosecurity as a concern of SynBio is mentioned in twelve papers [1,10,12,13,15–18,23,25,28,32]. Six papers associate bioterrorism with the creation of biological weapons and indicate the relative ease in obtaining materials for it [1,10,15,16,23,25]. Two papers also associate bioterrorism with the unintentional effects caused by well-meaning institutionally based scientists or amateur biologists and the unintended consequences of an organism escaping its controlled environment [12,18]. One paper mentions that most biosecurity issues manifest in the approach, application, and distribution of SynBio technologies [13].

Only one paper mentions the concern that bioterrorism can have human, agricultural, or environmental targets [16]. Two papers mention the role played by governments and big organizations. Both these papers mention that biological warfare is a possibility by rogue governments and terrorist organizations who can exploit the available information to engineer bioweapons [28,32]. One paper specifically points out that the discussion on the security aspect has been absent from discussions on the implications of the revolution in life sciences and that it is essential to think about the prevention of misuse through, for example, loss, theft, diversion, or intentional release of pathogens, toxins, and other biological materials [17].

The unpredictability of synthetic entities is discussed in four papers. These papers argue that the unpredictability of SynBio is much higher than other biosciences [1,9,40,42]. The unpredictable behavior of an organism outside its environment, unintended consequences on the individuals and environment, and difficulty in accurately predicting the potential risk posed by SynBio products make SynBio's risk-benefit assessment more complex than other sciences. One paper suggests using an approach that combines different moral theories for the ethical analysis of SynBio as a technology. This paper mentions that while a consequentialist analysis only tends to focus on the potential benefits and dangers in SynBio, a deontological analysis only helps assess the inherent morality of SynBio. These approaches complement each other and together can aid in obtaining an adequate ethical analysis [4].

Justice and equity-related issues

Application-related issues that could arise while trying to apply the products or technologies of SynBio in the public domain are mentioned in eleven papers [2,5,13,15–19,23,27,38]. The devastating effect SynBio can have, if not appropriately regulated, on justice and socioeconomic issues, such as the fair allocation of benefits and widening the prosperity gap between the advanced and developing world, is mentioned in nine papers [5,13,15–19,23,27,38]. Of these, two papers use examples of semi-synthetic artemisinin and synthetic vanillin to discuss SynBio's adverse effects on the social and environmental domains. One paper specifically mentions that SynBio production can affect the livelihood of those living in developing countries who currently harvest artemisinin and that deriving commercial benefits from semi-synthetic artemisinin production could give rise to conflict with the fair allocation of benefits [15]. Another paper also mentions how technological change leads to capital intensification and lowers the demand for labor, thereby potentially harming unskilled workers. The same paper also points out the environmental sustainability issues that could arise due to the large-scale demand for sugar to produce synthetic alternatives [19].

Three papers discuss the possibility that SynBio research becomes a highly privatized and monopolized market with detrimental effects on the equal distribution of benefits [2,18,19]. One paper mentions that the nature-devastating or nature-preserving potential of SynBio is dependent on the applications that would be developed and executed [16].

Six papers mention the importance of **transnational collaboration and global cooperation** in Synbio [5,10,16,26,27,32]. All six papers mention that it is essential to ensure an equal rate of progress among all countries, prevent research and health tourism, avoid technology and prosperity gaps between nations by enabling innovative developments, and tackle biosecurity issues. However, one paper also mentions that this would be challenging in the current divided and politicized climate [32]. One paper points out the importance of prioritizing the needs of small countries, thereby enabling them to contribute to the innovation and growth of Synbio in the global arena [26].

Governance

Thirty-one papers discuss the governance of SynBio and the possible ways of regulating it.

Patenting in SynBio is extensively discussed in ten papers [1,2,5,12,13,15,17,19,27,34]. The fear that the convergence of current IP laws with SynBio can lead to the creation of cartels and monopolies, thereby increasing the chances of commercialization of SynBio and leading to unjust scenarios, is mentioned in eight papers [1,2,5,13,15,19,27,34]. The need to rethink the current patent system and frame a proper risk-benefit analysis to encourage innovation through patenting while at the same time being attentive to the effects of such rights on the products and knowledge of SynBio is mentioned in four papers [5,12,15,17]. One paper mentions that patenting underlying biological processes might hinder the work of more efficient competitors and inhibit or shut down research in neighboring areas, thereby holding back science [34]. However, one author claims that scientific research remains a relatively unregulated activity; thereby, developing countries need not consider whether a developed country holds a patent to conduct scientific research, indicating that developed and developing countries have the same advantage and equal opportunities [13].

The need for a **SynBio-specific regulation** is mentioned in 16 papers. [1,2,10,12-14,16,17,19,23,25,26,38,39,42,43.] Eight papers mention the need for creating regulations specific to each application of SynBio significantly since the consequence of each application varies [2,13,14,16,19,23,25,26]. For example, one paper mentions that some applications might have a significant effect on our understanding of human relationships with nature more than the rest. Hence, each should be assessed on its own merits [16]. Also, another paper mentions that classifying technologies within Synbio can ease scientific and societal assessments by delimiting specific issues in each category [23].

Two papers mention the need to investigate the ethics of everyday research, specifically SynBio, and ensure progressing stage-wise regulation depending on each product's potential uses and applications [14,25].

Five papers mention some essential requirements to enable an ethical development of SynBio, such as preempting the impact of SynBio, a realistic assessment of likely benefits, and developing counter strategies to tackle unpredictable events. They also highlight the importance of having a flexible regulatory regime that can investigate IP rights on specific

products and applications of SynBio rather than grouping all applications within a single IP frame [1,12,13,17,26].

Two papers point out that there are better approaches than a general moratorium on the technology in SynBio since such a general moratorium does not make a sufficient distinction between the different types and applications of SynBio. Rather slow and careful consideration of application-wise consequences is needed [16,42]. Three papers state that in SynBio, there is a tension between self-regulation and stronger governmental regulation; therefore, there needs to be a broader interface between self-regulating scientists and `civil society to have a more nuanced government regulation guided by a well-informed public discourse [10,38,43]. One paper mentions the importance of using **lived experience** to create an ethics of knowledge that can also help regulate SynBio by adequately addressing procedural and distributive justice issues [39].

Seventeen papers mention **public inclusiveness and engagement** as important in creating awareness, preventing, or handling biosafety issues, avoiding misinterpretations, garnering support for SynBio's further development, and solving ethical dilemmas [2,5,9,12,16,17,19,21,23,24,27,32,35,38–40,43]. Two papers mention that public engagement and responsible innovation are essential elements that are value-laden in the connection between science and society [24].

Two papers point out how public engagement can provide us with the vision of lived experiences to view and understand how science might or might not change "our" understanding of the human relationship to nature [16,39]. While all seventeen papers mention the role and importance of the public in the development of SynBio, only one paper notes the importance of the research participant's perspective. One paper mentions the role potential participants should be given in decisions over what sort of research should go ahead since they are part owners and active stakeholders in research, thereby respecting their autonomy [22].

Eleven papers mentioned the importance of **academic awareness** regarding ethical issues in SynBio [2,13,15,17,23,25,28,30,36,40,43]. Ethical education of young scientists as part of Human Practice (HP) work, biosecurity awareness among students, scientists, and the public, and cooperation between SynBio scientists, the biosecurity community, and all stakeholders have been pointed out as essential requirements in these papers. The term Human Practice (HP) was first used in 2006 by Rainbow and Bennet as part of the Synthetic Biology Engineering

Research Centre's founding process. HP meant transferring, adapting, and extending adapting of ethical considerations into SynBio [30]. The role of funding agencies in shaping the course and conduct of SynBio research has been mentioned in one paper [2].

While one paper points out Tuija Takala's view that ethicists trained in philosophy can contribute to enriching the discussions and decision-making in complex ethical issues arising in SynBio [43], another paper mentions that apart from having a significant number of ethicists who are trained in the biological sciences, scientifically literate enough to follow SynBio's trends, a more formal degree of integration of science and ethics may help guide a safe and ethical science [25]. Such integration would allow the ethicists to be scientifically literate enough to follow SynBio's trends, enabling the application-wise decision-making process. This form of integration of ethicists and social scientists into SynBio research can already be found in the Imperial College London's Centre for Synthetic Biology and Innovation (CSynBI) [25].

Three papers point out the need to develop codes of conduct for scientists to consider their work's societal and ethical dimensions and understand their research's social and cultural aspects to create a generation of responsible scientists with accountable and thoughtful action in the field [2,24,28].

Discussion

Synthetic biology: what are we talking about?

The articles we found did not provide one standard definition for SynBio. Articles that did give a definition all included references to designing *novel* biological systems. Moreover, papers were divided on whether SynBio is a "new technology" or a "gradual development" of previous technologies. However, different interpretations of SynBio may yield differences in how ethical issues are presented and produce different conclusions. For example, suppose Synbio refers to an extension of existing gene editing techniques, such as CRISPR/Cas9; one could argue that ethical discussions on SynBio are not that different from ethical discussions on gene editing. If one considers SynBio a new paradigm in biotechnology, as some authors do, this may imply a whole new type of ethics as well. The conceptual frame of Synbio plays a vital role in how one perceives the ethical and societal impacts of this technology [44]. Hence, it is an essential task for all stakeholders to analyze this conceptual framework stage by stage,

describe its benefits and limits and compare it to alternative accounts before it advances to a stage where it becomes impossible to evaluate single applications [44]. This applies even to the analysis of the dual-use dilemma that is often being spoken about in SynBio. While most applications of technologies like SynBio are possible candidates for dual-use research of concern, the potential for dual use must be explicitly analysed for each product and application and logically be applied only in cases where the risks and dangers are high [40].

Metaphors play an essential role in communicating and interpreting reality and structuring the world, providing orientation, and leading to action (Lakoff and Johnson: 2003)[33]. However, the usage of engineering and computational metaphors in SynBio has created contrasts in the acceptance and perspectives of Synbio.

Scientists sometimes describe the function of synthetic cells as "like a machine," and some even refer to their products as “genetically engineered machines” [13]. Synthetic biologists also often discuss microorganisms in the context of SynBio in terms of ‘hardware’ and ‘software’; some refer to these as ‘living machines’ or describe synthetic DNA segments as ‘BioBricks’ and living “chassis” organisms [4]. As pointed out by Brian Johnson, media debates on controversial technologies and products are inevitable and often involve exaggerated claims about their benefits and risks. He references the case of protocells, but this also applies to other cases, such as the European debate on GM crops[47,p.23.] Engineering and machine metaphors influence one’s perspective on the abilities of Synbio and the function and behavior of its objects [44]. It is true that metaphors are indispensable tools for performing, communicating, and implementing science and its applications [45]. However, using terms such as designing, constructing, or recreating life rather than using words such as “creating life” would be more appropriate to explain the work being conducted in labs. This is especially relevant since the research work in SynBio labs mostly deals with recreating existent organisms and constructing new forms of life from previous organic materials and knowledge. These terms would be more precise and avoid unnecessary “misconceptions and worries” [23].

The use of reductionist terms such as “programming life” or “artificial life” is questionable scientifically and ethically because they vastly overstate our current ability to control biological processes at the organismal level [12]. Responsible usage of metaphors, both by scientists and the media, is an ethical requirement for the development of Synbio.

The ontological and moral status of life versus non-life

The fact that humans—or, more specifically: synthetic biologists—are now at the threshold of constructing biological life, or parts of biological life, from scratch raises questions about the authority to create life from scratch. Several authors discuss which category these entities fall under – 'natural' or 'artificial.' This seems to be linked to the idea that natural living entities may have some unique type of intrinsic value, whereas created, artificial or machine-like entities do not. Indeed, Synbio falls in a "grey area" created by the overlap of the "natural" and the "artefactual." The natural aspect of SynBio comes and goes out of existence completely independent of human desire and manipulation, but the artefactual embodies an intentional human structure' [38]. Some authors are therefore arguing that the entities that are the result of SynBio should be attributed a "special status" [29, 20].

The uniqueness of synthetic entities is that they have been synthesized artificially from naturally occurring products, but would that make them artificial? [16]. While they are not entirely artificial, these entities fall under a "special category". They possess an internal, "organismal" teleology like other natural microbes but also possess an external "artefactual" teleology imposed by the designer and defined by their goals and purposes in designing the organism. As pointed out in one paper, irrespective of the 'natural' or 'artefactual' categorization, these entities possess some form of "organismal" teleology since they are synthesized from naturally occurring products, which calls for moral standing, thereby, moral respect [19].

With the development of technologies like SynBio, there might be a change or a challenge in our common understanding of what we refer to as living and non-living while also blurring the boundaries between what is natural and artificial. However, does this imply that there would be a reductionism in the value of life? For example, one paper mentions that respect for life does not imply that we are incapable of understanding, controlling, reshaping, and transforming life. Because if not, humanity could have never got the benefits of such research, including improvements in animal husbandry, pest control, elimination of pathogenic microorganisms, etc [13].

SynBio is an example of how concepts such as 'synthetic' and 'natural,' rather than immutable categories, are actively constituted, negotiated, and re-valued through scientific practices and scientific ideals. For example, the possibility of creating hybrid organisms or even hybrid

humans that are a combination of 'natural' and 'artificial' biological components has implications for our understanding of embodiment [22].

In many of the papers we have analysed, authors reflect on the permissibility of SynBio to tinker with nature and to provide answers to the classification of entities created by SynBio. As such entities blur the boundary between biology and machine, it may lead to the objectification and instrumentalization of biology. SynBio is an example of how such existing dichotomies between the natural vs. artificial, biology vs. engineering, and biological entity vs. machine may be problematic. Given the normative implications of such distinctions, it may be worthwhile to probe the dichotomies themselves. Is a dualistic perspective necessary to view the world, or can non-Western non-dualist ontologies inspire us? Thinking beyond dualisms may also yield opportunities to see this 'blurring of boundaries' not solely as a reduction but also as an enrichment. Indeed, many non-western philosophies, such as Hinduism, revolve around a non-dualistic view that emphasizes a synergetic relationship between the living entities around us[49]. It provides us with necessary and alternative perspectives to apply an ecocentric vision and move beyond the barriers separating human life from other forms of life. This perspective can enable us to find different ways of addressing the man vs. machine or life vs. non-life philosophical conflicts in SynBio. Non-dualistic philosophies may provide us a direction to move forward in our ethical discourse on SynBio while also generating a more inclusive and diverse public opinion.

Regulation

Besides investigating the conceptual schemes that underlie many discussions on SynBio, several papers also discuss the features of its products and their purpose of determining why they are worth developing, whether the applications of these products morally matter, and whether the intended use of them could contravene these interests. While the unpredictability of microbes in general and the newly created synthetic entities specifically are significant concerns in Synbio, there are many technical barriers that exist to creating a predictable and robust microbe. The common approach in engineering is to use a top-down approach for creating complex systems. This approach breaks down the complex system into units, and then they are designed and implemented using existing and well-characterized modules that solve these sub-problems [9]. But such an approach is not always straightforward

when dealing with biological systems, mainly because breaking them down into distinct modules, with a clear understanding of their connections, is not always possible. A possible way would be to define a modular structure in natural genetic circuits through 'network motifs.' These are interaction patterns that frequently occur in complex networks and could be associated with specific functionalities. Despite various algorithms being developed to identify such motifs in protein-protein and genetic networks in *Escherichia coli* and *Saccharomyces cerevisiae,* the relationship between network motifs and the dynamic functionality of the whole network is still unclear. Such a conceptual gap must be resolved if we systematically use natural modules to redesign predictable and robust synthetic organisms [9]. SynBio needs to progress into being approached as a full-fledged engineering discipline that entails standardization, modularization, and regularization. A standardized approach to biological engineering will require a re-assemblage of scientific subdisciplines, varied forms of funding, the involvement of institutional networks, and governmental and non-governmental agencies, among others [48,pp.15-16].

Apart from the technical barriers, the impact of SynBio is not restricted to one area of study, and the effect can be found at different levels. Consider something 'benign' such as creating artificial vanillin or semi-synthetic artemisinin. We are more likely aware of its benefits, but this is accompanied by multiple environmental and livelihood issues. The ecological risk that synthetic organisms pose has been discussed in two papers [18,38]. However, the socio-economic impacts are also equally important to consider. For example, semi-synthetic artemisinin has already had a cascading socio-economic impact on the livelihood of many wormwood growers who have been the source of commercially available artemisinin[38]. While it is understandable that chemically synthesized semi-synthetic artemisinin may temporarily solve the unstable artemisinin market, one tends to forget the justice issues it creates. Semi-synthetic artemisinin negatively impacts the livelihood of wormwood growers, who have been the sole source of the most commercially available artemisinin [38]. Similarly, in the case of vanillin, most of the native producers who are poor farmers get affected due to technological change leading to capital intensification and lower demand for labor [19]. This implies that a bottom-up approach in SynBio starts from understanding specific research protocols and applications and directly engages with research in the lab. Further discussion on the distribution of products and knowledge arising from SynBio research related to social justice, power relations, and the current global divide should be encouraged. Particular

attention should be given to the debate about intellectual property rights and the effect of such rights on access to the products and knowledge of SynBio [17].

Most applications of Synbio, to a large extent, are covered by several existing national or international regulations [44]. However, in the long run, rapid advancements would lead to increased scope of areas where Synbio can be applied. This would mean that future SynBio products may fall outside the current regulatory schemes, thereby calling for new forms of ever-evolving SynBio regulations. An example of one way to annul the risk assessment challenge may be to encourage step-by-step genome changes to ensure that every novel synthetic organism has a similar and known predecessor [44].

Patenting

Patenting in SynBio is a critical topic of discussion in SynBio governance. The patenting process in SynBio is likely to create complications that were not encountered with other technologies. A SynBio-specific scenario could involve the potential granting of patents for a biological process leading to knock-on issues, especially because the biological process can have various offshoots that can have multiple fields of application. For example, patenting an underlying biological process of biomass could hinder the development of more efficient competitors, leading to high prices and a monopoly where an organization owns the fuel itself rather than its sources. Such patenting may also inhibit or shut down research in neighboring areas [34]. Patenting in SynBio can also lead to cartelization and monopolization. This was evident from the patent text published by the Venter Institute for Mycoplasma laboratorium. Besides critical commentary around common issues such as ecological corruption and bioterrorism, there was also a sharp focus on if the Venter enterprise was positioning itself to put foundational technologies under monopoly ownership and control [47,pp.172-173]. While patenting is important to ensure continued research and advancement, as pointed out by Cho et al., it is equally important to ensure that new models of patenting rights are regularly discussed to ensure the protection of both commercial and public interests [12].

As pointed out by Gibson et al., the current intellectual property structures remain a potential barrier to synthetic biology research and development, thereby raising several important ethical problems in terms of global justice and transnational regulation of health technologies. This sparks a debate on the effects of intensive patenting and the need for an appropriate or optimal mode of managing intellectual property in this area of research [22].

It is not just the method and application of Synbio that needs concrete, ever-developing governance and regulation but also knowledge production and dissemination. Creating an ethics of knowledge to regulate SynBio can be difficult to implement and achieve, as pointed out by R.L Pierce [39]. Trying to constrict knowledge production and dissemination would not only be in direct contrast with respecting the autonomy of scientists but could also be seen as deskilling the development of science. Finding a balance between providing the scientific freedom to use resources for the development of science and ensuring that these resources do not get into the wrong hands is challenging but essential.

Most importantly, the way SynBio is developed impacts its eventual applications and consequences. Indeed, concentrating on novel concepts and problems specific to each application of SynBio with a joint inter-disciplinary investigation can help in a justice-based safe development of the technology [15]. An ethically well-informed group of researchers and project investigators with other stakeholders would be able to deliberate the possible future consequences and therefore lead the research and its applications by regularly considering not only biosafety and biosecurity issues but also concerns about justice [16]. Initiatives such as the Nagoya Protocol, which about 139 countries have ratified, can be leveraged to help achieve such an outcome [46]. It would be highly beneficial to have more of such initiatives, which ensures that SynBio follows a justice-based approach, reflecting on its undesirable effects on the environment and livelihood.

At the same time, it would be incorrect to state that discussions on justice and environmental impacts are completely absent from the ethical literature on the modification of organisms. For example, in the genetic modification and adaptation space, authors such as Bier and Sober[50] and Rulli[51], among others, have all written on gene-drive ethics for human health and conservation. Some other authors have also written on genetic adaption and de-extinction in the environmental space [52,53,54]. Many social justice groups have long talked about the implications of synthetically generated crops on emerging economies and farmers. Ethicists reflecting on the impact of SynBio may find inspiration in the discussions in these and adjacent fields.

It is a matter of justice that the process considers the interests of all members of society and not only those near or at the table. Unlike regulatory authorities who focus mainly on risk per se, the public also considers the real and perceived benefits to themselves. Acting as individuals, many people are prepared to take relatively high risks if the benefits are attractive

enough [47,p.20]. Public inclusion and engagement enable the inclusion of lived experiences and opinions, which are essential in creating ethics of knowledge [39].

Conclusion

Synthetic Biology, in all its forms, gives rise to different ethical concerns besides biosafety, biosecurity concerns, and deontological concerns about the acceptability to 'tinker with biology'. Indeed, we believe that ethics, and certainly ethics of synthetic biology, should also include justice and even political considerations. At the same time, it should also take into account the actual practices of researchers in the lab. Even though SynBio is considered a technology that poses a dual-use dilemma, ensuring that it is a net positive technology depends on various factors. First, Synbio must be approached stage-wise and research area-wise rather than as an umbrella technology. This would mean that the ethical issues should be analyzed and addressed at different stages of research development (knowledge, method, and application) and attended to separately based on various research areas. Second, ethical considerations should prioritize environmental and livelihood justice issues that may arise from implementing SynBio technologies. Third, Synbio as a technology can benefit from general ethical awareness, which, when maintained, can transform into creating a general ethical discourse. This is especially important when integrating early-stage researchers and students. This allows them to start considering the ethical ramifications of their research from the outset, which then transforms into the mindset being applied to future projects. On an even broader note, we also need to consider how such attitudes can help push organizations to take the proper steps in placing ethics as a critical parameter in research projects. While it is true that political and corporate gain coerces governing bodies and political institutions in deciding the direction of the development of any technology, it should not stop us from pushing forward in trying to create awareness and engage the public on ethical practices. This ensures checks and balances on research organizations and thereby guarantees that we, as a society, work towards ensuring a net positive gain of significant scientific development in Synbio. Moreover, the current ethical discourses on SynBio revolve around a dualistic thought process and rely on dichotomies such as nature versus machine or life versus non-life as normatively relevant, often leading to a stalemate between those who consider synthetic entities as machines and those who consider them as biological. We believe there is much to

gain for ethics of technology in general, and ethics of SynBio specifically to engage with non-dualistic frameworks as they exist in non-Western philosophies.

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Both authors reviewed the search strategy and read and discussed the resulting paper. The first draft of the manuscript was written by Varsha Aravind Paleri with revisions by Kristien Hens.

Notes

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