Chapter 2
Synthetic Biology

2.1 Synthetic Biology

2.1.1 Definition of Synthetic Biology

2.1.1.1 Origin of the Term

Synthetic biology is an emerging scientific field that is increasingly featured in the public debate and in the media. This growing exposure is caused by the great benefits that this field promises to deliver in the health, energy, and food sectors, just to name a few, as well as to the concerns it raises from a scientific, ethical, safety and regulatory point of view.

While synthetic biology has only recently reached the spotlight, the origin of both the term and the concept has roots in the past.

In 1904, Dutch botanist Hugo de Vries declared that “evolution has to become an experimental science, which must first be controlled and studied, then conducted and finally shaped to the use of man”.1 With those words, de Vries highlighted what would become the pillar of synthetic biology: the transition from a descriptive and analytical approach to the study of life to one of synthesis and creation.

Another step in the direction of the principles of synthetic biology was set out in 1912, this time by German-American physiologist Jacques Loeb. While he argued that “we are not yet able to give an answer to the question as to how life originated on the earth... nothing indicates, however, at present that the artificial production of living matter is beyond the possibilities of science”.2 Therefore, in his opinion, “we must either succeed in producing living matter artificially, or we must find the

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1 Campos (2009, pp. 6–7).
2 Keller (2002, p. 18).
The ability to control life at need and at will is one of the cornerstones of Loeb’s position and, alongside his belief that biology could be construed as an engineering science rather than a natural one, it illustrates the similarities between his approach and that of modern synthetic biology.4

The term “synthetic biology” was also first coined in 1912. In that year, French biologist and chemist Stéphane Leduc wrote a book titled La biologie synthétique.5 In the section on Methods in biology, he postulated that biology is no different from other scientific fields. Therefore, biology will go through a descriptive, analytic, and synthetic phase.

The term “synthetic biology” in his current connotation reappeared in 1974 at the birth of the era of recombinant DNA. In that year, geneticist Waclaw Szybalski addressed the next steps of biology by stating:

Up to now we are working on the descriptive phase of molecular biology... But the real challenge will start when we enter the synthetic biology phase of research in our field. We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes. This would be a field with an unlimited expansion potential and hardly any limitations to building ‘new better control circuits’ and... finally other ‘synthetic’ organisms.6

The idea of an approach to biology based on wilful creation and engineering principles has permeated the twentieth century.7 Yet, the possibility to realise this goal became available only at the turn of the millennium. At that time, the completion of the human genome project and the decreased cost of DNA sequencing and synthesis offered the possibility to concretely realise the objectives of synthetic biology.

The first examples of applied synthetic biology surfaced in 2000, when two publications on a toggle switch and on a biological clock “illustrated the feasibility and predictability of engineering sophisticated functions into biological systems using standard components”.8

Only four years later, in 2004, the first conference on synthetic biology called Synthetic Biology 1.0 (First International Conference on Synthetic Biology) was organised in Cambridge, USA. The fact that the organisers of the conference chose to call it “synthetic biology” was “anything but inevitable or foreordained” considering that:

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3Keller (2002, p. 18).
4Campos (2009, pp. 10–12).
5Leduc (1912).
6Committee on Science, Technology, and Law et al. (2013, p. 9).
7For a more extensive overview of the history of synthetic biology (Campos 2009).
8SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 12), Gardner et al. (2000) and Elowitz and Leibler (2000).
Although the new field of ‘synthetic biology’ clearly shared significant aims and goals with the earlier ‘synthetic biology’ approaches... the new coinage seems to have come through no direct historical or verbal link to the earlier efforts to engineer biology.9

It took a while before the expression “synthetic biology” established itself as the name for this new technology. For instance, in 2006, the term “intentional biology” was employed and the expression “synthetic genomics” was still used in a number of publications between 2010 and 2013, albeit in much smaller numbers compared to “synthetic biology”.10

2.1.1.2 Range of Definitions

Despite having established itself as the term of choice for this new technology, synthetic biology is still devoid of a specific definition. Over time, more than 30 definitions have been formulated and no consensus was ever reached over the exact content of this expression and its boundaries.11 While this has not hindered the scientific development of the subject, it still caused uncertainties in the field. For example, one expert used the phrase “I know it when I see it”12 when asked to offer a definition of synthetic biology, while another scientist pointed out that, “if you ask five people to define synthetic biology, you will get six answers”.13

Although defining synthetic biology is problematic, it is a necessary step; otherwise, how could laws and regulations be effectively drafted if it is unclear what synthetic biology is and which activities fall within its scope14? Similarly, in the absence of an agreed definition, it would be possible for companies to set their own definition and thus to choose whether or not to include their products in the field of synthetic biology, with possible repercussions on regulations and public perception.15

9Campos (2009, p. 18). Scientists Drew Endy and Robert Carlson first considered the name “synthetic biology” in 2001 upon suggestion of scientist Carlos Bustamante, who had highlighted the analogies between this emerging field and the route taken by synthetic chemistry almost two centuries before (Carlson 2006).
10Some studies have considered the terms “synthetic biology” and “synthetic genomics” as interchangeable (Ribarits et al. 2014, pp. 8–82). Conversely, other reports considered synthetic genomics as a sub-field of synthetic biology (European Group on Ethics in Science and New Technologies to the European Commission 2009, p. 14).
11The interdisciplinarity of synthetic biology might also be responsible for this lack of consensus.
12This expression was coined in 1964 by Justice Potter Stewart of the US Supreme Court to describe his threshold test for obscenity in Jacobellis v. Ohio (U.S. Supreme Court 1964, p. 197).
13Ferry (2015) and “What’s in a name?” (2009, p. 1073).
14SYBHEL (2014, p. 16).
15This was the case for a cleaning products producer. In 2014, Ecover released a laundry detergent containing oil that had been manufactured by algae, whose genetic code had been modified via synthetic biology (Strom 2014). The use of an ingredient indirectly produced via synthetic biology—that is, the oil itself was not genetically modified, but had been produced via a synthetic biology algae—generated much press. This led the producing company to present its understanding
What clearly emerges from an analysis of the definitions currently used for synthetic biology is the ambiguous and uncertain use of this term not only amongst the general public, but also and especially in the scientific community.

Definitions of synthetic biology have spanned from broad formulations to lists of principles and parameters. Some researchers have opted for inclusion and exclusion criteria or suggested defining synthetic biology via its main research fields.\textsuperscript{16} The creation of a sliding scale model that would place works on a scale between classical biotechnologies and extreme synthetic biology was also considered.\textsuperscript{17} Equally, methodologies were used as defining elements.\textsuperscript{18}

16SCHER, SCENIHR, SCCS Scientific Committees (2014, pp. 11–16). Delimiting the scope of synthetic biology via its research areas has also been a common approach. The most frequent examples were bottom-up and top-down approaches, the design of minimal genomes, the fabrication of biological toolkits, and xenobiology research (Porcar and Peretó 2012, pp. 81–82; European Group on Ethics in Science and New Technologies to the European Commission 2009, p. 14; Schwille and Sundmacher n.d., pp. 2–8). A survey carried out amongst representatives of funding agencies from six European countries showed that only four areas were unanimously considered to belong to synthetic biology. Those are: biocircuits, both with and without standard biological parts, expanded genetic alphabet and DNA with a different backbone. Surprisingly, the quest for a minimal genome and the creation of artificial life were not universally considered as belonging to the realm of synthetic biology (Pei et al. 2012, p. 5). The variety of approaches is such that it would be problematic to find a common denominator between them and it may also be difficult, as well as highly controversial, to establish which research endeavours should be included. Definitions could also vary based on the desired outcomes or aims for which they are formulated such as, for example, funding and risk assessment (European Commission’s Directorate-General for Health & Consumers 2010, p. 28; European Group on Ethics in Science and New Technologies to the European Commission 2009, p. 13). Finding a definition is also complicated by the consideration that synthetic biology may just be an umbrella term (Kronberger 2012, p. 130; O’Malley et al. 2008, p. 57; de Lorenzo and Danchin 2008, p. 822).

17SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 26).

18Gaisser et al. (2008, p. 4). Most of the surveyed definitions did not explicitly mention quantitative or qualitative limits for the existence of synthetic biology. An exception was the working definition formulated by FERA (Food and Environmental Research Agency), which provided a two-prong definition for products and applications in the food and feed sector. The quantitative requirement concerned: “Substantially large synthetic parts of genetic material caused to function in a
An analysis of the definitions formulated so far illustrates the criteria that were most often considered as falling within the realm of synthetic biology. Those are: the application of engineering principles, the existence of a rational design, the use of standards, the construction of novel systems or novel functions, the intentionality and control over the creation. In addition to those, elements such as the size or complexity of the intervention in the biological system were also taken into consideration. On the other hand, ad hoc approaches, the absence of standards and of engineering features in the development of biological products were considered exclusion criteria given their incompatibility with the principles on which synthetic biology is based upon.\textsuperscript{19} No exclusion criteria were formulated on the basis of taxonomical categories (i.e. the different groups in which living beings are classified, e.g. bacteria and plants).\textsuperscript{20}

The principles behind synthetic biology have also been used as a reference point in trying to define this field. Synthetic biology is seen as move away from previous discovery-based biosciences, which relied on a descriptive approach, and as a step towards a hypothesis and synthesis methodology. Equally, the development of commercial outputs is fundamental in synthetic biology. This is confirmed by the fact that the majority of the research in this sector is geared towards commercial applications.\textsuperscript{21} Hence, synthetic biology aims to transform biology into a production technology. Lastly, the aims of synthetic biology were also considered in delimiting this discipline. For example, the EU TESSY project (Towards a European Strategy for Synthetic Biology) specifically mentioned that the purpose of synthetic biology is “to engineer and study biological systems that do not exist as such in nature”.\textsuperscript{22}

\textsuperscript{19}Porcar and Peretó (2012, p. 82).
\textsuperscript{20}Kuzma and Tanji (2010, p. 96).
\textsuperscript{21}Conference of the parties to the Convention on Biological Diversity (2014a, p. 9). Synthetic biology is certainly not the first science trying to exploit nature for commercial purposes. Still, its placing at the very centre of its investigative efforts and from the very beginning the development of new useful products and functions sets it apart from more descriptive sciences.
\textsuperscript{22}Gaisser et al. (2008, p. 4). TESSY defined synthetic biology as a discipline: “To engineer and study biological systems that do not exist as such in nature, and use this approach for (i) achieving better understanding of life processes, (ii) generating and assembling functional modular components, (iii) developing novel applications or processes” (Gaisser et al. 2008, p. 4). This definition
Those approaches sparked analogies between the world of synthetic biology and that of software and computers. From this perspective, DNA could be seen as a quaternary code—as opposed to the binary code of computer programming—thus suggesting that the work of synthetic biologists could somehow mirror that of software designers. Such perspective would fit with the notion that biological life can be seen and handled as information.\(^{23}\)

The aspects outlined above have been taken into consideration by scholars and authorities when formulating a definition of synthetic biology.\(^{24}\) One frequently cited definition states that synthetic biology is “(i) the design and construction of new biological parts, devices and systems, and (ii) the re-design of existing, natural biological systems for useful purposes.”\(^{25}\)

Similar to the above two-pronged definition is the one formulated by ERASynBio, which describes synthetic biology as “the engineering of biology: the deliberate (re)design and construction of novel biological and biologically based parts, devices and systems to perform new functions for useful purposes, that draws on principles elucidated from biology and engineering.”\(^{26}\) The reference to engineering principles is also present in the definition formulated by the Royal Academy of Engineering, which is used also by the OECD. In their opinion, “synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems.”\(^{27}\)

The purposes of synthetic biology were also cited in the definition formulated by the Scientific Committees appointed by the European Commission, which held that “synthetic biology is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic

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\(^{23}\)van den Belt (2009a, p. 259). This analogy explains the use of software metaphors in synthetic biology.

\(^{24}\)For additional definitions, SCHER, SCENIHR, SCCS Scientific Committees (2014, pp. 55–60), Conference of the parties to the Convention on Biological Diversity (2014a, pp. 9–11), British Food & Environment Research Agency (2014, p. 29), Ribarits et al. (2014, p. 9), OECD (2014, pp. 17–20), Kelley (2014, pp. 19–20), Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) 2010, p. 6).

\(^{25}\)Commentators noted that the vast majority of the definitions contain references to “biological systems” and avoid using to the term “life” (Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) 2010, p. 6).

\(^{26}\)ERASynBio (2014, p. 6).

\(^{27}\)OECD (2014, p. 18) and Royal Academy of Engineering (Great Britain) (2009, p. 6).
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materials in living organisms”. Yet another approach to synthetic biology could be found in the description provided by the ETC Group, an international civil society organisation, which dubbed this field “genetic engineering on steroids”. Likewise, the British Food and Environmental Agency used the formulation “extreme GM” as its “working understanding of synthetic biology”. Lastly, a detailed definition was formulated by the US Presidential Commission for the Study of Bioethical Issues. According to it:

Synthetic biology is the name given to an emerging field of research that combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavours that fall under its umbrella rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics. Whereas standard biology treats the structure and chemistry of living things as natural phenomena to be understood and explained, synthetic biology treats biochemical processes, molecules, and structures as raw materials and tools to be used in novel and potentially useful ways, often quite independent of their natural roles. It joins the knowledge and techniques of biology with the practical principles and techniques of engineering. ‘Bottom-up’ synthetic biologists, those in the very earliest stages of research, seek to create novel biochemical systems and organisms from scratch, using nothing but chemical reagents. ‘Top-down’ synthetic biologists, who have been working for several decades, treat existing organisms, genes, enzymes, and other biological materials as parts or tools to be reconfigured for purposes chosen by the investigator.

2.1.1.3 Radically New Technology or Extension of Earlier Practices

Ever since the inception of synthetic biology, questions have been raised on whether this discipline constitutes a revolutionary technology that will cause a paradigm shift in life sciences or whether it is merely an incremental change that represents the most recent highpoint in the development of biotechnologies. The approach taken on this matter has repercussions on the regulatory panorama of synthetic biology, since viewing this discipline as a revolutionary technology may lead to demands for additional specific norms on policy, safety, legal and ethical issues.

Scholarly opinions on this point are divergent. Those who believe that synthetic biology is an incremental technology have pointed out that rebranding traditional genetic and metabolic engineering as synthetic biology served funding purposes,

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28 SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 5).
29 ETC Group (2007, p. 1).
30 British Food & Environment Research Agency (2014, p. 52).
31 Presidential Commission for the Study of Bioethical Issues (2010, p. 36).
32 Viewing synthetic biology as an incremental technology has repercussions on the evaluation of the ethical questions posed by this field. In this case, it could be argued that these ethical issues will be for the most part similar to the ones already posed by other biotechnologies and that, consequently, the framework established until now would offer a valid point of reference (Parens et al. 2009, p. 11). From a safety perspective, it was mentioned that synthetic biology shares similarities with recombinant DNA technologies. For this reason, it was maintained that: “Placing a new name on an old technology does not create a new hazard” (OECD 2014, p. 123).
since one could take advantage of the hype surrounding this new technology to attract investment or serve as a marketing banner.33

Other authors have expressed more uncertain views on whether synthetic biology is indeed a truly innovative field.34 To add to the uncertainty, most current and near-term applications of synthetic biology are based on techniques connected to traditional genetic engineering.35

Notwithstanding this, the novel character of synthetic biology has also been defended, as a great degree of innovation in its “systematic, application-driven engineering perspective to biology” was detected.36

Interestingly, the divergent views expressed on the innovative nature of synthetic biology do not appear to be dependent upon the affiliation of the individuals or groups writing about it, but rather to be impacted by the topics and goals for which such formulations are being used. Indeed, it was claimed that:

There is no simple correlation between the nature of social groups (such as regulatory institutions, scientific community, NGOs, companies etc.) and their pronouncements about synthetic biology. In fact, views on whether synthetic biology should follow previous experience or be treated differently often vary even within the same report, depending on which topic (such as financial, ethical or environmental implications) is under discussion.37

2.1.1.4 Negative Connotation

Synthetic biology has been associated with negative connotations due to its name, its research endeavours and its connection to biotechnologies that have attracted criticism in the past. As synthetic biology products are now starting to reach the market, the consequences of these negative impressions are being acknowledged and are becoming more relevant.

Already at the dawn of synthetic biology, at the Synthetic Biology 2.0 conference in 2006, the negative connotations of the world “synthetic” were discussed, as this

33.“What’s in a name?” (2009, p. 1071). Ashcroft and Dawson pointed out the: “Tendency in the field to take a new sexy science, coin a neologism, start a journal and a society, and bid for Centre funding” (SYBHEL 2014, p. 17). Studies show that both journalists and the public viewed synthetic biology as a traditional gene technology (Gschmeidler and Seiringer 2012, p. 163). Others have gone even further and argued that, by observing the impact of synthetic biology on the distinction between artefacts and living organisms and other ontological questions, this new field may only be a: “Late and unexceptional offshoot” development in comparison to prehistoric agriculture (Greco 2013; Preston 2013, p. 649).
34Douglas and Stemerding (2014, pp. 1–2), Kronberger (2012, p. 130), Then and Hamberger (2010, p. 8), Deutsche Akademie der Naturforscher Leopoldina (2010, p. 5) and Balmer and Martin (2008, pp. 29–30).
35Conference of the parties to the Convention on Biological Diversity (2014a, p. 10).
36European Commission, Directorate-General for Research (2005, p. 10).
37Zhang et al. (2011, p. 7).
word could conjure up images of “monstrous life forms let loose by maniacal scientists”.

Similarly, it was feared that synthetic biology may follow the path of Genetically Modified Organisms (GMOs) when it comes to public acceptance, especially in Europe. However, the situation may take a different course this time, considering that addressing ethical, safety, social, and legal issues has been central for synthetic biology ever since its inception.

2.1.1.5 Engineering Principles

Despite the lack of consensus over the definition of synthetic biology, one distinctive aspect of this discipline has unequivocally emerged: the application of engineering principles to biology. This approach is based on the idea that living systems are intrinsically complex, as they developed through evolutionary pressure. In particular, in the case of synthetic biology, reducing the complexity of biological systems is supposed to help controlling them, rendering their behaviour more predictable and designing them in a rational and systematic manner. The means to achieve these goals have been located in the core principles of engineering, which could be applied at all biological levels (e.g. molecules, cells, organisms).

This approach has led to analogies with the world of electronics, even though the characteristics of biological systems set synthetic biology apart from any other engineering-related discipline. Indeed, biological systems can self-replicate and repair, undergo mutation and evolution and are thus substantially different from other engineering objects. Such dissimilarities, coupled with the complexity of biological systems, led scholars to debate whether synthetic biology could ever successfully apply engineering principles to biology. While currently the consensus on this point is negative, some scholars have argued that it is merely a question of time before biology is transformed into an engineering discipline with the help of synthetic biology.

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38Cserer and Seiringer (2009, p. 31) and Balmer and Martin (2008, p. 6). Others noted that: "The term ‘synthetic biology’ is now tainted with negative connotations and should be avoided in public. Consumers prefer natural to synthetic, and ‘syn’ brings up negative connotations of ‘sin.’ The term ‘genetically engineered’ should also be avoided because it’s gotten too much public backlash. Some alternative terms suggested at the meeting were ‘fermentation derived’ and ‘nature identical’" (Perls 2014).
39Kronberger (2012, p. 132).
40Torgersen and Hampel (2012, p. 139).
41The actual use of engineering principles in current synthetic biology products is still quite limited (Davies 2019).
42Calvert (2010, pp. 98–99).
43Kronberger (2012, p. 130).
44“What’s in a name?” (2009, p. 1073) and Schwille and Sundmacher (n.d., p. 2).
45Jefferson et al. (2014a, p. 45).
A number of engineering principles have been considered relevant in this field. The most important one is the concept of standardisation. As hinted by the word itself, this principle demands the “definitive description and characterization of parts” and extends also to the standardisation of measurement protocols and documentation systems. Standardisation in biology is exemplified by the concept of BioBricks™, which are standard biological parts that can be assembled together in order to build new biological systems or devices. This approach facilitates exchanges amongst research groups as well.

Another important principle is decoupling, which relates to the “process of breaking down the construction of complicated entities into manageable semi-independent tasks”. On the other hand, abstraction refers to the possibility to separate “the overall system into meaningful subsystems, which in turn might be once more separated into meaningful subsystems, and so on”. Similarly, the decoupling of design and production aims at separating these two tasks and assigning them to specialised individuals, in the same way a car is not assembled by the people who have designed it. To enable decoupling, modularisation is needed. This concept, whose application is still hypothetical, predicts a “functional unit that is capable of maintaining its intrinsic properties irrespective of what it is connected to”. The concept of orthogonality describes instead systems “where modifying one component does not result in side effects to other components in the system”. This principle would be used to increase the predictability of the behaviour and of the interactions of the modified system within the cell and the environment.

2.1.2 Difference from Other Technologies

Understanding synthetic biology is understanding the connection between this field and other biotechnologies. This task is not trivial, considering the existing “overlap in terms of vocabulary, actors and concerns” and in terms of research endeavours.

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46 Panke (2008, p. 8) and O’Malley et al. (2008, p. 57).
47 On this, see Sect. 2.2.1.3.
48 O’Malley et al. (2008, pp. 57–58).
49 Panke (2008, p. 7).
50 Panke (2008, pp. 8–9).
51 Calvert (2010, p. 98). This concept is fundamental for BioBricks™. On this, see Sect. 2.2.1.3.
52 Conference of the parties to the Convention on Biological Diversity (2014a, p. 17). Refactoring refers instead to a software concept, which would be used in synthetic biology to: “Remove all uncharacterised functional elements and molecular interactions, which might lead to unpredictable system behaviour” (SCHER, SCENIHR, SCCS Scientific Committees 2014, p. 12).
53 Conference of the parties to the Convention on Biological Diversity (2014a, p. 17).
54 Kronberger (2012, p. 132).
Consequently, a clear separation between them is not always possible and it is likely that this uncertainty will persist in the future.

The principles that characterise synthetic biology are critical to the assessment of whether an activity falls within this area or not. Considering that both synthetic biology and related technologies operate in similar application and research areas, what sets synthetic biology apart from other biotechnologies are really its tools and approaches. Overall, it can be said that both synthetic biology and traditional biotechnologies aim at solving technological problems via the manipulation of biological material. However, prior biotechnologies have approached this task empirically and with an ad hoc methodology, whereas synthetic biology is implementing engineering principles in order to rationally manipulate biological systems.

2.1.2.1 Genetic Engineering

The methods used and the complexity of the modifications carried out by synthetic biology are often considered the core of what sets this field apart from traditional genetic engineering. Genetic engineering has been associated with the reading and analysis of DNA, whereas synthetic biology is connected to DNA writing and synthesis. Moreover, synthetic biologists intend to plan and manufacture new biological systems on the basis of engineering principles, whereas genetic engineers proceed through a trial and error method and have mostly focused on the adaptation and slight modification of already existing biological systems.

When it comes to the products of synthetic biology and genetic engineering, the discussion becomes more controversial, as it steps into the realm of GMOs. Synthetic biology products have been compared to GMOs for the high hopes and expectations they generate and for some possible overlaps on regulatory and policy issues. Nevertheless, from a biological perspective, differences between the products of synthetic biology and genetic engineering are poised to become more marked, as GMO products usually contain a single modification that is related to a new feature (e.g. pest resistance), whereas synthetic biology aims for more extensive ones. For instance, manipulations on the scale of whole genomes—either in terms of number of base pairs or loci—have been considered a main trait of synthetic biology, which is not present in traditional genetic engineering. Nevertheless, at this point in time, when the potentials of synthetic biology are only starting to be realised, examples from the food and feed sector show that there is still a large area of overlap between

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55.“What’s in a name?” (2009, p. 1073).
56.European Commission, Directorate-General for Research (2005, p. 11).
57.Conference of the parties to the Convention on Biological Diversity (2014a, p. 10).
58.Open Science (2012, p. 7) and Then and Hamberger (2010, p. 9).
59.Rousseaux (2015).
60.Ribarits et al. (2014, p. 111).
SynBio products and GMOs. Additionally, the tools used by synthetic biology build on the ones used by genetic engineering. Yet, it is to be expected that with time the gap between the two will widen, as synthetic biology achieves more complex modifications and further implements engineering principles.

### 2.1.2.2 Metabolic Engineering

The field of metabolic engineering is so closely related to synthetic biology that it is unclear whether it represents a discipline within it or rather a separate one. According to San Yup Lee:

> Originally, synthetic biology sought to redesign and rebuild biological parts and systems without specific biotechnological objectives, whereas metabolic engineering aimed at purposeful modification of metabolic and other cellular networks to achieve desired goals, such as overproduction of bioproducts. Recently, it has become more difficult to distinguish the two disciplines as each is employing the other’s approaches... and both are moving towards integration with systems biology.

Others have differentiated the two by stating that synthetic biology, contrarily to metabolic engineering, designs biological systems to make them perform tasks that are different from what they would normally do.

### 2.1.2.3 Synthetic Chemistry

Synthetic chemistry has been considered a precursor of synthetic biology in more ways than one. Before the advent of synthetic chemistry, organic chemistry was a discovery-based science focused on understating the properties of natural compounds by

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61. British Food & Environment Research Agency (2014, p. 49).
62. Recombinant DNA, Polymerised Chain Reaction and automated DNA sequencing are the tools of choice of genetic engineering. The first two are concerned with writing DNA, while the third with reading it out. Synthetic biology adds to these tools by using three additional approaches: automated construction of DNA, standards and abstraction (Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) 2010, p. 7).
63. Technically, it is hard to draw the line between this and more traditional recombinant DNA technologies. Indeed: “A piece of DNA can be synthesized, identical in sequence to an existing gene, and inserted into an organism. Such an organism could also be constructed using traditional rDNA techniques, and even the scientists who produced the organisms may be unable to tell which was produced with which technology. However, as synthetic DNA constructs become more and more complex... it becomes nearly impossible to accomplish the same engineering feats through traditional rDNA technology” (Carter et al. 2014, p. 9).
64. ERASynBio (2014, p. 7) and O’Malley et al. (2008, p. 62).
65. “What’s in a name?” (2009, p. 1072).
66. “What’s in a name?” (2009, p. 1071).
67. van den Belt (2009a, pp. 258–259).
examining compositions and reactions. The field proceeded along those lines, since it was commonly believed to be impossible to synthesise organic molecules. The situation drastically changed in 1828, when German chemist Friedrich Wöhler first synthesised the organic chemical Urea from an inorganic one.68 This experiment profoundly affected the world of chemistry, as it showed that even organic compounds could be built from scratch starting from simpler pieces. This led to discussions on the boundaries between natural and artificial, which are common also today in the field of synthetic biology.69

With time, synthetic chemistry moved from the synthetic reproduction of already existing substances to the creation of new ones. This trajectory is similar to the one synthetic biology is trying to explore nowadays, that is, the passage from reproducing natural systems to creating novel ones.70 According to Boldt and Müller:

> Synthetic chemistry has shown the way: from systematic analysis of chemical processes to synthesis of novel products. Synthetic biology does the same, but in the realm of the living.71

2.1.2.4 Systems Biology

Systems biology is a descriptive scientific discipline that aims to provide a “quantitative and predictive understanding of biological systems” by gathering information on the interactions of the various parts that compose a biological system.72 This field emerged at the turn of the millennium and focuses on systems rather than specific genes, just like synthetic biology.73

Systems biology lays the analytical and conceptual framework necessary for synthetic biology and provides the understanding of biological systems needed by the latter to develop new products and applications. Synthetic biology could thus be seen as the “design counterpart of systems biology”.74 Synthetic biology can be further distinguished from systems biology based on three aspects. First, modelling in systems biology is an expression of basic research, while in synthetic biology it is focused on the design of products. Second, large data gathering and integration is pivotal in systems biology, but not in synthetic biology. Lastly, synthetic biology tries to reduce complexity, whereas systems biology embraces it.75 Still, the two disciplines are strongly correlated and are bound to heavily influence each other in

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68Yeh and Lim (2007, p. 521).
69van den Belt (2009a, p. 259) and Carlson (2006).
70European Commission, Directorate-General for Research (2005, p. 11).
71“What’s in a name?” (2009, p. 1071).
72Health Council of the Netherlands (2008).
73O’Malley et al. (2008, p. 62).
74European Commission, Directorate-General for Research (2005, p. 11).
75O’Malley et al. (2008, pp. 62–63).
their development.\textsuperscript{76} It was even argued that “synthetic and systems biology are the ultimate synergetic partners for ushering in an era of rapid and probably systematic biological discovery” and that synthetic biology is “the other side of the coin of systems biology”.\textsuperscript{77}

2.1.2.5 Other Related Disciplines

Further disciplines overlap or contribute to synthetic biology. For instance, genomics is a discipline focused on the study of the genome (i.e. the genetic material of an organism).\textsuperscript{78} It analyses its interactions with the environment as well as diseases that could be connected to it.\textsuperscript{79} Genomics revolves around reading and understating the genome, whereas synthetic biology concentrates on the writing of the genome, which has proven to be a much more intricate task.\textsuperscript{80} Still, synthetic biology is benefiting from the knowledge gathered through genomics.

Lastly, synthetic biology must be differentiated from molecular biology. The latter adopts a descriptive approach to study biology at the molecular level, for example by analysing the structure and function of DNA, RNA, and proteins,\textsuperscript{81} while synthetic biology focuses on design and synthesis. Still, the existence and development of synthetic biology would not be possible in the absence of these discovery sciences.\textsuperscript{82}

2.2 Techniques, Research Areas and Applications

2.2.1 Techniques Used in Synthetic Biology

The realisation of the goals of synthetic biology depends on the progress of its enabling techniques. In recent years, programs for the design and optimisation of biological systems have improved and have become more user-friendly. Likewise, the production of those designs via DNA synthesis has improved in quality and speed, while becoming cheaper. Those techniques, coupled with the use of

\textsuperscript{76}Health Council of the Netherlands (2008, p. 19) and European Commission, Directorate-General for Research (2005, p. 11).

\textsuperscript{77}“What’s in a name?” (2009, p. 1073) and O’Malley et al. (2008, p. 62).

\textsuperscript{78}Genomics is not to be confused with genetics, which is the study of genes and their role in inheritance (National Human Genome Research Institute 2014).

\textsuperscript{79}National Human Genome Research Institute (2014).

\textsuperscript{80}OECD (2014, p. 20).

\textsuperscript{81}Mandal (2014).

\textsuperscript{82}O’Malley et al. (2008, p. 62).
standardised parts, facilitate the modelling and realisation of products of synthetic biology and will thus be examined in more detail in the following sections.

Such DNA design and production techniques are based on the premise that DNA is both an information storing medium and a sequence of chemicals. From a chemistry perspective, DNA is made up of chemical bases that are attached to a sugar molecule and a phosphate molecule. Hence, the synthesis of DNA consists of a chemical process to reproduce and assemble these different substances. On the other hand, these same chemical bases store hereditary material and information, much like an alphabet or a software code. As such, this code could be sequenced, amended and even reformulated. While emphasis could be placed on either one of these two aspects, the informational and chemical properties of DNA are inextricably intertwined.83

2.2.1.1 Designing Techniques

Design techniques used in synthetic biology enable the modelling of new biological circuits, which could be designed by scientists to achieve the best possible functionality. Such designed circuitry could be markedly different from anything found in nature. Although this is the ultimate goal, at the moment the ability to design new complex and functional biological systems is still limited, as natural circuits still represent the starting point of the work of synthetic biologists.84

The development of these tools is supported by bioinformatics, which offers the possibility to model circuits before using them in living biological systems.85 As in other engineering disciplines, Computer-Aided Design software (CAD) have been introduced. Such design programs, which are becoming increasingly sophisticated, support the gene assembly process and predict the behaviour and performance of the new system via simulations. They can also operate in conjunction with DNA databases and registries of standardised parts.86 For the moment, these bio-CAD programs have not reached the precision of their engineering counterparts given the complexity of biological systems.87 However, it will be fundamental for the development of synthetic biology to enhance these design techniques, as the existing gap between our limited ability to design and our evolved DNA synthesis skills is the main hurdle to fulfil the promises of this field.88

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83 On this, see Sect. 2.2.5.
84 Carter et al. (2014, p. 9).
85 British Food & Environment Research Agency (2014, p. 86).
86 Nowogrodzki (2018) and SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 13).
87 Yarris (2011).
88 Rice (2010).
2.2.1.2 Production Techniques

The gene-building field is doing for biology what Johannes Gutenberg did for printing – turning what was once a laborious and uneven artisanal effort into affordable and accurate mass production.\(^89\)

This quote shows the paradigm shift that occurred in the techniques for the production of DNA over the past decades: from methods that were expensive and labour-intensive to cheap and reliable techniques that permit the mass production of genes. Such techniques revolve around two concepts: DNA sequencing and DNA synthesis. The former is focused on determining the order of the nucleic acid sequence, while the latter is concerned with the actual artificial production of the DNA sequence. This differs from traditional recombinant DNA techniques. Prior methods allowed the rearrangement of genes and genomes, but did not offer the possibility to write specific DNA sequences, which is instead offered by DNA synthesis. A metaphor used to describe these two techniques compared synthetic DNA technology to a typewriter and recombinant DNA technology to copy/cut/paste/delete functions.\(^90\)

The cost and speed of DNA sequencing have been improving over time.\(^91\) Equally, when it comes to DNA synthesis, contemporary methods enable the synthesis of both completely new sequences as well as of sequences that are a duplicate of natural existing ones.\(^92\) The costs associated with this technique have drastically decreased in the past years.\(^93\) At the same time, the velocity of writing DNA strands increased exponentially.\(^94\) During this period, not only did the velocity and costs of production improve, but also the length of the sequences that could be manufactured.\(^95\)

Even the process for making DNA has undergone revolutionary changes in the last years. Nowadays, scientists have the possibility to type and then submit a DNA sequence via computer to a gene manufacturing company. After production, such genes are then shipped back to the scientists within a few days.\(^96\) According to American scientist and entrepreneur Craig Venter, a similar process could be devised to permit biological teleportation. In his opinion, it should be possible to make a “digital copy of an organism’s DNA in one place and sending the file to a

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\(^89\) Krieger (2015a).
\(^90\) Nista (2015).
\(^91\) OECD (2014, p. 57).
\(^92\) SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 37).
\(^93\) Krieger (2015a) and Zhang (2015).
\(^94\) ETC Group (2007, p. 6).
\(^95\) If in 2004 the longest strand amounted to 32,000 base pairs, in 2008 this number had already reached 580,000 base pairs. This size corresponds to that of viruses and minimal bacteria, which explains how by that time several viruses (e.g. the polio virus, the virus of the Spanish flu) could already be synthesised (Then and Hamberger 2010, p. 11).
\(^96\) Krieger (2015a).
device somewhere else that can then recreate the original life-form”. Interestingly, these creations via DNA synthesis might be identical to the ones found in nature and could not be distinguished from them.

Progress is not limited to the production of DNA, but extends also to its editing. In recent years, a wide array of genome-editing tools to alter virtually every existing DNA sequence in a reliable and fast manner have emerged. Such tools can be applied to higher organisms (e.g. plants and animals) and allow the introduction of several modifications, even at the same time.

Notwithstanding the above improvements, the synthesis of new genomes remains a complex task due to biological complexity and errors in the design and production of biological systems. Mistakes and inaccuracies can emerge at every stage of the preparation and even low error rates (e.g. 1 in 10,000 base pairs) can be highly problematic. This explains why testing and debugging newly-made genomes constitutes one of the most challenging and time-consuming tasks in their production, even accounting for 95% of the time spent on projects. Hence, the assembly of a genome ex novo is more complex than merely editing an already existing one.

2.2.1.3 Standardisation

Standardisation of biological parts is one of the main goals of synthetic biology. It is based on the assumption that biological components can be assembled to create more complex systems and that these parts could become standardised enough to be exchanged between different devices and laboratories. Such characteristics have sparked analogies with Lego. Still, the possibility to standardise biological parts has not been univocally accepted.

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97 Corbyn (2013).

98 SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 37) and Then and Hamberger (2010, p. 11).

99 SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 37). The most revolutionary and promising methods include Zinc-Finger Nucleases (ZFNs), Transcription Activator-Like Effector-Based Nucleases (TALENs) and CRISPR-Cas (Gaj et al. 2013, p. 397). The technology behind CRISPR-Cas has been at the centre of a heated patent battle between scientists and universities claiming priority in the invention (Cynober 2019).

100 Ribarits et al. (2014, p. 11) and OECD (2014, p. 58).

101 OECD (2014, p. 62). While the availability of cheap DNA synthesis is bound to help scientists and companies experimenting with different gene combinations, it still does not remove the complexity of synthetic biology. Indeed, it has been pointed out that: “Making DNA is not the hardest part of synthetic biology. Synthetizing a gene is chemistry; getting a gene to work in a cell is biology, and that comes with all of biology’s messiness” (Zhang 2015).

102 Ribarits et al. (2014, p. 11).

103 Helman et al. (2007, p. 6).

104 Commentators noted that: “The idea… is either dismissed as a research question because it’s irrelevant or dismissed as a research question because it’s impossible” (Frow and Calvert 2013, p. 44), while others pointed out that: “There is no such thing… because even a standard component
The best-known example of standard biological parts was initiated by American scientists Drew Endy and Tom Knight and is known under the name BioBricks™. Such standard biological parts perform a specific task (e.g. turn genes on and off, transmit signals between cells) and are compatible with other BioBricks™, which offers the possibility to combine them to produce longer circuits.\textsuperscript{105} The term BioBricks™ refers not only to the parts themselves, but also to the assembly standard used to make sure that parts are compatible with each other. BioBricks™, which are available in an open source format, are collected in physical form at the Registry Repository, while information on them is stored in the Registry of Standard Biological Parts.\textsuperscript{106}

In spite of this, researchers rarely use parts contained in repositories. Indeed, most of the sequences mentioned in publications do not operate in the same vectors and do not have standardised cloning sites. This is the reason why most standards exist only within companies or research groups.\textsuperscript{107} Nevertheless, the setting of precise and agreed standards is fundamental for the development of synthetic biology.\textsuperscript{108} For this reason, standardisation efforts were undertaken on both sides of the Atlantic by national institutions.\textsuperscript{109}

### 2.2.2 Current Research Areas

Engineering living systems is proving more complex than traditional engineering. The complexity of the living, coupled with our limited understanding of the inner workings of nature, currently impede the full implementation of engineering principles in biology. This is exemplified by the unpredictability of the interactions between cells, their parts and the environment and by the fact that biological systems seem to be devoid of any logical formula. Indeed, studies show that ample sections of the genome may be deleted without damaging the functioning of an organism, while minor mutations could prove fatal for it.\textsuperscript{110}

In order to devise biological systems that are reliable, predictable and perform desired functions, synthetic biologists developed two approaches: the bottom-up and the top-down. These processes, while complementary and partially overlapping,

\textit{works differently depending on the environment. The expectation that you can type in a (DNA) sequence and can predict what a (genetic) circuit will do is far from reality and always will be”} (Endy 2013, p. 19).

\textsuperscript{105}ETC Group (2007, p. 16) and iGEM (n.d.-a).
\textsuperscript{106}Ribarits et al. (2014, pp. 39–40). Related to the BioBricks™, is the BioBricks Foundation, which aims to ensure that the engineering of biological systems is performed ethically and openly (BioBricks Foundation n.d.-a).
\textsuperscript{107}SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 12).
\textsuperscript{108}Jain (2015).
\textsuperscript{109}Parliamentary Office of Science and Technology (POST) (2015, p. 2) and Basulto (2015a).
\textsuperscript{110}OECD (2014, pp. 62–63).
stem from opposing starting points. The top-down approach tackles biological complexity by stripping an existing organism of genetic elements that are not essential to its functioning and is performed in vivo. Conversely, the bottom-up approach, which is performed in vitro, intends to build living systems from scratch using as components non-living building blocks or standard parts. This innovative and challenging approach, based on the engineering concept of modularity, postulates that biological systems can be built by assembling independent functional modules, whose characteristics will determine the features of the final biological product.111

2.2.2.1 Minimal Genome

The quest for a minimal genome represents the best example of the top-down approach of synthetic biology and, as hinted by its name, it is focused on determining the smallest number of genes needed to support basic life functions.

Based on the assumption that even the genome of the smallest organism contains redundant sections, synthetic biologists are trying to strip those genomes to a minimum in order to “minimise the metabolic burden on the cell” so that “the remaining cellular energy can be directed toward the manufacture of a desired industrial product”.112 This should also make the cell easier to control. The purpose of this approach is to redesign genomes to render them more efficient or to make them perform new functions.113 On the down side, the removal of genes usually affects the robustness of the organism and its ability to survive in the wild.

The starting point of this approach is understanding which genes support basic metabolism and cell replication. In the past, theoretical studies postulated that as few as 206 genes would be needed for the minimal genome, while other scientists believed that a viable cell could exist with 256 genes.114 Others, such as Kitney, argued instead that “there is in fact no universal minimal cell, only a minimal cell for a given set of conditions”, while Koonin argued that the minimal genome might be something to which synthetic biologists get closer and closer to without ever reaching it.115

Empirical studies showed that these predictions on the size of the minimal genome were too optimistic. Of the 482 genes that compose the organism with the

111 Presidential Commission for the Study of Bioethical Issues (2010, pp. 43–46) and European Group on Ethics in Science and New Technologies to the European Commission (2009, pp. 19–20).
112 SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 29).
113 Tucker and Zilinskas (2006, p. 27).
114 Ribarits et al. (2014, pp. 20–21) and Mushegian and Koonin (1996, p. 10268). There are also examples of naturally reduced genomes. A number of free-living prokaryotes in different environments have all about 1400 genes. This circumstance was seen as an indication that nature itself was able to reduce the genome of those free-living prokaryotes to a minimum number of genes (Porcar et al. 2011, p. 3).
115 Coghlan (2016) and Twilley (2016).
shorter known genome, *Mycoplasma genitalium*, only 100 could be removed.\textsuperscript{116} Their deletion had a positive effect on the growth rates of the organism, possibly due to the reduced amount of energy allocated to non-essential processes.\textsuperscript{117} The study of the minimal genome of this bacterium was first undertaken by Craig Venter during his Minimal Genome Project. In 2008, Venter and his team removed the non-essential genes and then assembled a new version of the bacterium, this time using chemically synthesised DNA.\textsuperscript{118} Subsequently, Craig Venter applied for a patent on the 381 genes that were believed to constitute the minimal bacterial genome.\textsuperscript{119} This sparked controversy, as some commentators viewed those claims as contrary to public morality, safety and as too wide.\textsuperscript{120}

In 2016, Venter and his team made further progress in the quest for the minimal genome. Taking as a starting point the *Mycoplasma laboratorium* bacterium they designed in 2010 (so called JCVI syn1.0) and its 901 genes, they identified the essential, nonessential and quasi-essential genes that made it up.\textsuperscript{121} They achieved this by deleting one by one sections of the genome to see which repercussions it would have. At the end, a 473-gene genome was achieved and was named JCVI syn3.0. Interestingly, 149 of these 473 genes do not have a known function.\textsuperscript{122} This lack of understanding was addressed by Koonin by stating that “anyone who claims that she or he understands how a cell works is either ignorant or ridiculously arrogant”.\textsuperscript{123} At the moment, scientists are attempting to install the genome of JCVI syn3.0 into a synthetic liposome containing the machinery needed to convert DNA into protein. The goal is to see whether a cell with both synthetic “hardware” and “software” could survive.\textsuperscript{124}

Venter and his team filed patents covering both JCVI syn3.0 and the process to make it.\textsuperscript{125} Some commentators doubted the practical relevance of such research, as

\begin{itemize}
\item \textsuperscript{116}For comparison, humans have approximately 23,000 genes (Specter 2009).
\item \textsuperscript{117}OECD (2014, p. 63).
\item \textsuperscript{118}Specter (2009).
\item \textsuperscript{119}The ETC Group nicknamed this invented bacteria *Synthia*, in order to provide the public with an easier and catchier name (The Economist 2007).
\item \textsuperscript{120}The Economist (2007). The ETC group was also very critical of the work of Venter and his team and demanded the withdrawal of the related patents or, otherwise, their rejection on public morality and safety grounds (Balmer and Martin 2008, p. 16).
\item \textsuperscript{121}Quasi-essential genes are needed for growth, but are not absolutely required to keep the organism alive. Some of these genes were left in the genome of JCVI syn3.0 in order to guarantee a workable growth rate of the bacterium.
\item \textsuperscript{122}Twilley (2016), Coghlan (2016), Lowe (2016), NewScientist.com (2016) and Dvorsky (2016).
\item \textsuperscript{123}Twilley (2016).
\item \textsuperscript{124}Powell (2018).
\item \textsuperscript{125}Dvorsky (2016).
\end{itemize}
other organisms (e.g. yeast) have been successfully used and studied by man, although their genome is not minimal.\textsuperscript{126}

Attempts to achieve a minimal genome have also been applied to \textit{E. coli}, which is one of the most used organisms in biology. This led to the deletion of parts of the genome, which had a positive effect on the properties of the bacterium.\textsuperscript{127} This was achieved despite the fact that more than 20\% of its genes do not have a proper functional characterisation, although \textit{E. coli} is one of the best-known and studied organisms.\textsuperscript{128}

The quest for the minimal genome serves also another purpose. Considering that organisms evolved due to evolutionary pressure rather than to be fit for industrial processes, it was considered ideal to develop a \textit{chassis} organism. The word chassis, which was originally used in mechanical engineering, describes a simplified cellular structure in which modular biological parts can be inserted.\textsuperscript{129} This biological production platform would operate efficiently and would not contain any features that would interfere with the purposes for which it is designed.\textsuperscript{130} The hope is that in the future those chassis could be combined with BioBricks\textsuperscript{™} to provide platforms in which the latter could be embedded to create new organisms or functions.\textsuperscript{131}

\subsection*{2.2.2.2 Synthetic Life}

One of the main promises of synthetic biology is the creation of artificial life. This entails the development of synthetic organisms, which are bound to have a revolutionary effect not only in scientific terms, but also from an ethical perspective.

Bottom-up approaches have been devised with the aim to build functional genomes using synthesised DNA. The difference in this line of research compared to traditional genetic engineering lays in the manufacturing of cells using genome sequences that are computer-designed.\textsuperscript{132} Recent experiments have shown that “genomes can be designed in the computer, chemically made in the laboratory

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\textsuperscript{126}\textsuperscript{126}Twilley (2016). Syn3.0 is tailored to grow on a specific diet and in a petri dish, which would make it more complex to use in comparison to other organisms that are easier to maintain (e.g. yeast) (Twilley 2016).
\textsuperscript{127}\textsuperscript{127}SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 30), Conference of the parties to the Convention on Biological Diversity (2014a, p. 15) and Ribarits et al. (2014, p. 23).
\textsuperscript{128}\textsuperscript{128}Panke (2008, p. 6).
\textsuperscript{129}\textsuperscript{129}Conference of the parties to the Convention on Biological Diversity (2014a, p. 15) and Frow and Calvert (2013, p. 48).
\textsuperscript{130}\textsuperscript{130}Schwille and Sundmacher (n.d., pp. 3–4).
\textsuperscript{131}\textsuperscript{131}Calvert (2010, p. 102).
\textsuperscript{132}\textsuperscript{132}Conference of the parties to the Convention on Biological Diversity (2014a, p. 15).
\end{tabular}
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and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome.”

The steps undertaken in this field are remarkable. In 2002, researchers first synthesised the poliovirus, producing the first synthetic organism. Soon after, in 2003, Craig Venter announced the creation of a synthetic virus from scratch in just 14 days and in 2007 his team transplanted the genome of one organism into another. This last research showed that a foreign genome could take control of another living cell. At the time, Craig Venter considered this step as pivotal towards the creation of synthetic life. Other scientists were instead more critical and believed that, while his studies might be interesting, they still concerned organisms that were unsuitable for industrial purposes. In 2008, Craig Venter and his team reached another relevant milestone in the road towards creating the first synthetic organism by synthesising from scratch the genome of a bacterium. This last achievement was saluted as a new approach to reach the minimum genome, this time from the bottom-up.

In 2010, Craig Venter and his team announced a new and controversial milestone towards the creation of artificial life. By announcing the creation of the world’s first synthetic cell, he and his team declared that they had produced the first self-replicating synthetic genome that was inserted into a cell of a different species. This achievement, called JCVI syn1.0, marked the first time that a synthetically produced genetic material completely replaced the natural existing one in a bacterial cell. This cell was also the first one controlled entirely by human-made genome, which means that all the features and characteristics of the cell were determined by scientists. In describing their work, Venter and his team highlighted the main points of their research:

We report the design, synthesis, and assembly of the... Mycoplasma mycoides JCVI-syn1.0 genome starting from digitized genome sequence information and its transplantation into a M. capricolum recipient cell to create new M. mycoides cells that are controlled only by the synthetic chromosome. The only DNA in the cells is the designed synthetic DNA sequence.

133Then and Hamberger (2010, pp. 6–7). In spite of this, some commentators noted that: “There’s no such thing as an artificial gene. DNA is DNA. What matters to a gene is sequence, not how you made it” (Garthwaite 2014).
134European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 18).
135Balmer and Martin (2008, p. 15) and Health Council of the Netherlands (2008, pp. 34–35).
136Wade (2007).
137Wade (2007).
138Singer (2008).
139Panke (2008, pp. 48–50) and Singer (2008).
140Palca et al. (2010) and Presidential Commission for the Study of Bioethical Issues (2010, pp. 20–42).
141McLennan and Rimmer (2012).
142Gibson et al. (2010, p. 52).
In lay terms, their work could be described as follows. Scientists used very accurate sequences of the 1 million-base-pair long genome of a bacterium called *Mycoplasma mycoides* to produce a synthetic version of its genome.\(^{143}\) This synthetic genome was then inserted into a cell (*Mycoplasma capricolum*) that had previously been emptied of its own genome. After the insertion, this new cell was booted up and showed the ability to grow and reproduce. The new cell behaved just like a *Mycoplasma mycoides* one and it no longer contained sequences that previously existed in the *Mycoplasma capricolum* cell, which meant that the cell was run by its wholly artificial genome.\(^{144}\) This project costed approximately $40 million.\(^{145}\)

The main struggles connected to this work related to the complexity of producing an error-free genome, to jump-start life and to boot up a genome in a different cell.\(^{146}\) Those characteristics led commentators to compare the synthetic DNA to software that is being booted up in a new hardware.\(^{147}\) On this, *Venter* stated that "*bacterial cells are software-driven... machines. If you change the software, you build a new machine*”.\(^{148}\) To differentiate the artificial genome from the natural one, scientists inserted watermark sequences in it and disabled the part of the genome that rendered it infectious to humans.\(^{149}\) This was needed because Venter and his team reproduced exactly the genome of an already existing organism and it would otherwise be impossible to distinguish the two. Such similarity was necessary, given that our limited understanding of biological complexity precludes the construction of completely new genomes. According to the scientists, this work:

> Stands in sharp contrast to various other approaches to genome engineering that modify natural genomes by introducing multiple insertions, substitutions, or deletions. This work provides a proof of principle for producing cells based on computer-designed genome sequences. DNA sequencing of a cellular genome allows storage of the genetic instructions for life as a digital file. The synthetic genome described here has only limited modifications from the naturally occurring *M. mycoides* genome. However, the approach we have developed should be applicable to the synthesis and transplantation of more novel genomes as genome design progresses.\(^{150}\)

While *Venter* announced this result as the "*first... species... whose parent is a computer*” and believed that this was both a philosophical and technical

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\(^{143}\)For comparison, the genome of fruit flies is approximately 165 million base-pair long, while the human genome contains more than 3 billion base pairs (Presidential Commission for the Study of Bioethical Issues 2010, p. 39).

\(^{144}\)Gibson et al. (2010, pp. 52–56) and Dillow (2010).

\(^{145}\)Nista (2015).

\(^{146}\)Krieger (2013a) and Gibson et al. (2010, p. 55).

\(^{147}\)Nista (2015) and Rousseaux (2015).

\(^{148}\)Rice (2010).

\(^{149}\)Ballantyne (n.d.).

\(^{150}\)Gibson et al. (2010, p. 55).
landmark, others were more sceptical. Venter responded to claims that he did not create life from scratch, by stating that:

A baker who starts with flour, sugar, and eggs gets credit for his creation, not accusations that he should have begun with atoms and molecules. Besides... once the original cell reproduced, the question should be considered settled... in what we call the synthetic cell there is not a single molecule of the original form.

Aside from the reactions of the scientific community on whether this work was truly ground-breaking, also the general public weighted heavily in the debate, especially on whether synthetic life was actually created. Commentators expressed doubts on how to define life in the age of synthetic biology, especially considering that this field blurs the line between what is natural and what is synthetic. Vitalism-inspired philosophies and “playing God” arguments featured prominently in media headlines.

Venter and his team are not the only ones working on synthetic life projects. At the moment, a new research endeavour promises to bring forward our knowledge of biological systems, while laying the foundation for the future design of genomes for specific purposes. This project, known as Synthetic Yeast Genome Sc2.0, aims to synthesise the entire genome of a yeast (around 6000 genes) with “a built-in diversity generator that will enable researchers to discover how yeast, as a model organism, deals with genetic change and how genomes might be improved to create more robust organisms”. This project involves several universities worldwide and is attempting to synthesise for the first time the genome of a eukaryotic cell.

This line of research holds a very high potential. Differently from the bacterium used by Venter’s team, yeast represents a more complex organism that has often been used as a model for genetic manipulation due to its resistance. Yeast is also well-known and widely employed by men for industrial purposes (e.g. production of beer and bread) and shares several chromosomes with humans.

By 2014, the first artificial yeast chromosome had already been prepared. It was based on the smallest of the 16 yeast chromosomes and presented some differences compared to the natural version. Unnecessary sequences were removed and landing sites to create on-demand mutations were added. Such insertions should be helpful in

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151 Wade (2010).
152 Wade (2010), Palca et al. (2010) and Presidential Commission for the Study of Bioethical Issues (2010, pp. 1–2).
153 Corby (2013).
154 Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) (2010, p. 5) and Balmer and Martin (2008, p. 4).
155 Corby (2013) and van den Belt (2009a, p. 264).
156 GenScript (n.d.).
157 Eukaryotic cells contain membrane-bound organelles, such as the nucleus, and are more complex. Humans belong to this category. Conversely, prokaryotes do not have a nucleus and have a much simpler structure.
158 Villa (2011) and Helman et al. (2007, pp. 16–17).
determining which mutations can be borne by it and to discover useful variations. Apart from the development of foundational tools, the project is likely to lead to the development of new chemicals and to the streamlining of old production methods. Furthermore, research on the most industrially relevant microbe is likely to have major commercial repercussions. This is confirmed by the fact that some companies have already expressed their interest in this line of research. Nonetheless, the results of this project will be shared under an open access format.

In 2016, researchers considered the possibility to synthesise the human genome from scratch. This project, known as Human Genome Project-write (HGP-write or GP-write), would have enormous potential in the health sector (e.g. growing transplantable human organs, new and improved gene therapies) and could be financed via a large public-private initiative similar to the one used for the HGP. The project, managed and directed by a consortium, is currently ongoing. The promoters of the projects have claimed that the “intellectual property developed in GP-write will encourage broad access and use through the use of patent pooling and common licensing agreements”.

2.2.2.3 Xenobiology

Xenobiology is the “design, engineering and production of biological systems with non-canonical biochemistries and/or alternative genetic codes”. It investigates unusual life-forms based on a biochemistry which is not available in nature. The main goals of this line of research are understanding the origin of life, how and why DNA and organisms are shaped the way they are and whether life could have taken other forms. Researchers see in xenobiology a possibility to create new and industrially interesting compounds and an advanced form of biocontainment. Furthermore, this technology could be used for medical purposes in the fight against...
diseases such as Ebola and HIV. However, commercial applications in this field are still years away. Another advantage of this line of research is connected to the concept of orthogonality, as those unnatural materials can exist next to natural ones (e.g. XNA and DNA) without interacting or interfering with them.

An interesting research area in this field is the expansion of the genetic alphabet. As known, DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) are at the basis of the hereditary and the evolutionary process of all creatures on earth and represent the code of life. DNA is composed of four bases A (adenine), G (guanine), C (cytosine), T (thymine), which pair together as A-T and C-G to form a double helix structure. RNA follows the same structure, except for the fact that it contains a U base (uracil) instead of the T one. Short sections of DNA create genes, which in turn constitute chromosomes. This new research field increases the number of base pairs, by introducing new ones that are not found in nature. For each new base pair, the genetic alphabet increases twofold.

In 2014, two bases called X and Y were created. A single pair of them was inserted in an E. coli bacterium where they were able to reproduce, albeit at a slower rate than usual. The reproduction continued for almost a week and at the end of it the bacterium substituted these “alien” bases with natural ones. This represents the first time that unnatural synthetic DNA built in a lab was inserted in a cell, where it was accepted and duplicated instead of being destroyed. By 2019, scientists had developed four new DNA letters. Commenting on this line of research, scientists stated that a wholly unnatural-DNA-based cell could be possible, while the creation of a wholly synthetic organism may prove very problematic due to the degree of integration of natural DNA into cellular systems and in the environment. Still, the potential of this field is remarkable considering that, as Romesberg said:

If you read a book that was written with four letters, you’re not going to be able to tell many interesting stories. If you’re given more letters, you can invent new words, you can find new ways to use those words and you can probably tell more interesting stories.

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169 Connor (2014).
170 Conference of the parties to the Convention on Biological Diversity (2014a, p. 17).
171 On this, see Sect. 2.1.1.5.
172 RNA is generally considered to be single stranded. However, in some cases, RNA can form double strands and, in some cases, even double helices.
173 SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 34).
174 Pollack (2014). However, strictly speaking, it would be the DNA that contained the bases that reproduced.
175 Callaway (2014).
176 Rita et al. (2014). Even before this, in 1989, modified forms of Cs and Gs were created and this expanded bases system, called AEGIS, was commercially licensed to a company that produced short DNA molecules for genetic testing (Callaway 2014; ETC Group 2007, p. 21).
177 Dengler (2019).
178 Callaway (2014).
179 Callaway (2014).
The advantages of this extended code have also been pointed out by those who believe that the earth will soon undergo a sixth wave of extinction and who believe that xenobiology could recreate biodiversity across the globe.\textsuperscript{180} Other research groups focus instead on changing the backbone of DNA. This entails moving away from deoxyribose or ribose acid and use instead another chemical structure (e.g. TNA if threose is used as a backbone substance). Such non-DNA or RNA structures are generally called xeno nucleic acids (XNA).\textsuperscript{181} To our knowledge, natural evolution on earth has never generated any XNAs.\textsuperscript{182} Interestingly, the use of a different backbone renders XNA invisible to natural biological systems. This effectively impedes the exchange of genetic information between them and the environment. This feature constitutes a very powerful bio-safety tool, a so called “genetic firewall”.\textsuperscript{183} Still, given its novelty, commentators have pointed out that both XNAs and new base pairs would need to be tested to make sure that they do not pose risks for humans or for the environment.\textsuperscript{184}

The possibility of creating non-canonical amino acids is also being explored in order to go beyond the 20 found in most species, which in turn would have repercussions on the number and type of proteins available. This field is also likely to be affected by research on the expansion of DNA bases, as the introduction of two additional bases could raise the number of amino acids from 20 to 172.\textsuperscript{185}

Industry-wise, a number of companies tapped into this market. For example, Maxygen developed a synthetic DNA sequence that encodes novel proteins, whose metabolising properties are far stronger than those of naturally existing ones.\textsuperscript{186} This approach was taken even further by the company Amunix, which devised synthetic proteins not based on naturally existing ones.\textsuperscript{187}

### 2.2.3 Futuristic Research Areas

Having been pinned as the solution to the problems of mankind, synthetic biology is not only focused on projects that have direct present relevance, but is also engaging in research endeavours that are still theoretical and that could be realised only

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\textsuperscript{180}Krumins (2015) and Rousseaux (2015). However, the same authors expressed concerns over the idea of a diversity triggered by scientists in a lab and the possible negative effects of such unnatural organisms on native ones.

\textsuperscript{181}SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 34).

\textsuperscript{182}Schmidt (2010, p. 328).

\textsuperscript{183}SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 15), Deutsche Akademie der Naturforscher Leopoldina (2010, p. 12) and Schmidt (2010, pp. 325–327).

\textsuperscript{184}SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 35).

\textsuperscript{185}SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 35) and Krumins (2015).

\textsuperscript{186}Holman (2015, pp. 429–430).

\textsuperscript{187}Holman (2015, p. 430).
decades from now. Amongst those various research areas, the two that seem to have caught the attention of the public and scientific community the most are the possibility to bring back to life extinct organisms and the possibility of building completely autonomous and artificial cells using non-living raw materials.

### 2.2.3.1 De-extinction

Concerns over a possible sixth great extinction wave affecting a vast number of species have sparked suggestions to use synthetic biology to restore biological diversity. Such attempts include not only currently endangered species, but consider also bringing back to life animals that have been extinct for thousands of years. This quest is facilitated by discoveries indicating that fossils might be able to preserve cells much longer than expected. For example, soft tissues were discovered in the bones of a *Tyrannosaurus rex* as well as in the relatively more recent mammoth. While this is no guarantee to find intact DNA in those fossils, it still opens some futuristic scenarios.

In 2005, researchers were able to sequence part of the genome of a mammoth. On a similar note, one year later, a research group announced that it had partially sequenced the genome of a Neanderthal man. While these are interesting developments, they do not guarantee that scientists will be able to organise and place the genome into chromosomes and to recreate the apparatus needed for life. Still, an American research group has tentatively discovered how to place mammoth DNA into the egg of an elephant and was investigating whether the extinct animal could be birthed by an elephant mother.

But it was the possibility of bringing back to life our ancestor, the Neanderthal, that caused the biggest uproar in the public. In an interview in 2013, George Church mentioned that technical improvements might enable the creation of a Neanderthal clone. In particular, in an interview, he explained that:

Church: The first thing you have to do is to sequence the Neanderthal genome, and that has actually been done. The next step would be to chop this genome up into, say, 10,000 chunks and then synthesize these. Finally, you would introduce these chunks into a human stem cell... We developed the semi-automated procedure required to do that in my lab. Finally, we assemble all the chunks in a human stem cell, which would enable you to finally create a Neanderthal clone.

Spiegel: And the surrogates would be human, right? In your book you write that an ‘extremely adventurous female human’ could serve as the surrogate mother.

Church: Yes.

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188 Takahashi (2016).
189 Tennant (2015).
190 Wilson (2008).
191 Anthony (2013).
192 Specter (2009).
193 Bethge and Grolle (2013).
The public outcry that followed this statement led to a retraction from George Church, who clarified that he was not working on cloning Neanderthals, but was merely discussing the possibilities opened by future synthetic biology.\textsuperscript{194}

Technology-wise, three methodologies could be employed to reach those results: cloning, genetic engineering and artificial selection. The first would come closer to truly recreating the extinct species, whereas the second would provide a hybrid between the genome of the extinct species and that of one of its closest living relatives. The third option would instead use living species to recreate extinct ones.

The methodology behind the cloning method resembles the one used in the field of synthetic life. A cell is deprived of its DNA and, in its place, the nuclear DNA of another organism is added. This would then be developed into an embryo. The resulting organism would have the nuclear genotype of the donor and the mitochondrial genome of the egg donor. While this method offers the closest realisation of an extinct organism, it still does not offer a perfect copy of it, since the egg would affect the expression of the genes. For this technique to work, it is also necessary to find a close egg donor for the creation and gestation of the organism. Furthermore, the complete and viable nuclear DNA of the extinct species is needed. Therefore, this method is applicable to recently extinct organisms. In 2009, a \textit{Pyrenean ibex} was recreated via this method. This represents the first viable birth of an extinct animal.\textsuperscript{195}

By contrast, genetic engineering could make use of a partial gene sequence to integrate and change the genome of a similar species. This process, which has not yet successfully been performed, would generate hybrids that have some of the genome of the extinct species, but are not identical to it. Lastly, artificial selection would use selective breeding techniques to cross living organisms from other species that have some characteristics of the extinct ones. In light of this, the final organism would still belong to the donor species rather than the extinct one.\textsuperscript{196}

None of the above techniques would thus lead to the recreation of an exact copy of the extinct organism. In particular, the last two techniques could be considered as either something completely new or as a modified version of a living species.\textsuperscript{197}

Lastly, keeping in mind the risks connected to a mass extinction, the Frozen Ark Consortium started collecting DNA and viable cells from endangered species and to preserve them. Although these samples could not be used to re-create extinct animals under current technology, the founders of this project imagine that such technologies could become available in the future, thus enabling the cloning of extinct species.\textsuperscript{198}

\textsuperscript{194}Spiegel Online (2013).
\textsuperscript{195}Carlin et al. (2014, pp. 8–9). Still, it has to be noted that the animal survived only a few minutes and that this species had died out in 2000.
\textsuperscript{196}Carlin et al. (2014, p. 11).
\textsuperscript{197}Carlin et al. (2014, p. 16).
\textsuperscript{198}ETC Group (2007, p. 38).
2.2.3.2 Protocells

Research endeavours connected to protocells seek to “construct new simple forms of living systems, using chemical and physical processes and employing as raw ingredients only materials that were never alive”. In other words, protocells are the precursor to building wholly artificial cells by using non-living materials. This approach, which is strictly bottom-up, aims to reduce biological complexity at the cellular level while creating new biological systems.

Such attempt to reduce biological complexity is inspired by the same idea behind the research on the minimal genome. However, in this case, efforts are concentrated at cellular level, instead of genome level. Equally, in comparison to the work on minimal genomes, this area of research appears more complex, given that protocells cannot take as example or be based upon already existing biological systems. On the contrary, they require “a detailed master plan, or at least a convincing hypothesis about the minimal set of functional modules to ‘jump-start’ life – a true intellectual act of synthesis.”

So far, protocells that interact with living cells were devised, but no truly autonomous and artificial cell could yet be developed. Equally, protocells are not yet capable of replication. However, scientists are currently actively working on constructing cell-like growing and dividing systems.

Protocells are expected to act as chemical containers and it is auspicated that in the future they could be employed as chassis in which to insert synthetic DNA to form new living organisms. To reach this goal, protocells must first become functionalised enough to support reproduction, self-maintenance and evolution. Furthermore, since protocells originate from non-living materials, much of the research in this field is connected to chemistry and physics rather than to biology.

Considering that protocells are built via materials that were never alive, they blur the line between living and non-living matter and raise both ethical and safety questions. This explains why commentators have defined protocells as “artificial..."
cells that have some properties of living systems but are not yet fully alive”. However, for the moment, those concerns have only a theoretical relevance. Indeed, even though protocells could be seen as precursors of truly synthetic cells, this field is still in its infancy. Therefore, it is unlikely to yield relevant commercial applications in the near future.

2.2.4 Applications

The hype connected to synthetic biology stems from its promise to profoundly affect an array of disciplines and industries and, ultimately, our lives. Being a platform technology that could cut across a variety of industrial sectors, synthetic biology has been pinned to address climate change and environmental protection, energy concerns, food and land shortage as well as health conditions.

As the field is still in its infancy, most of these expectations have not yet materialised. Still, failures to deliver some highly expected products have increased the pressure on synthetic biologists. Indeed, commentators expressed their concerns on the matter by stating that “the field has had its hype. Now it needs to deliver”.210

2.2.4.1 Health

The development of medicinal treatments for a large number of diseases is one of the strongholds of synthetic biology. By consulting the Synthetic Biology Project database, it emerges that more than 20 products are currently being developed as medicaments. The release of the majority of these medicines is only “on the horizon”, as only a single product is close to or on the market already.211 At the same time, other drugs are undergoing trials.

The best-known synthetic biology application in the medical field is the production of a semi-synthetic version of the anti-malaria drug Artemisinin. After resistance against previous treatments spread, a new cure containing Artemisinin in combination with other drugs was developed. However, this treatment has also its drawbacks, given that *Artemisia annua* is not easy to cultivate and that the price and availability of Artemisinin are subject to heavy fluctuations.213 For this reason, a research group

208 Conference of the parties to the Convention on Biological Diversity (2014a, p. 16).
209 SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 15).
210 European Commission’s Directorate-General for Health & Consumers (2010, p. 8).
211 The information is available at the website www.synbioproject.org in the section on applications of synthetic biology.
212 Kelley (2014, p. 40).
213 The plants are mostly cultivated by small farmers in Asia and in Africa (ETC Group 2014a, pp. 1–4; European Commission’s Directorate-General for Health & Consumers 2010, p. 10).
supported by the Gates Foundation engineered a bacterium to produce artemisinic acid (the precursor of Artemisinin) microbially and in a streamlined manner.\textsuperscript{214} The product was then manufactured on a larger scale in collaboration with a pharmaceutical company and is now available on the market.\textsuperscript{215}

While Artemisinin is the best-known example of the use of synthetic biology in the health sector, considerable research is also being carried out in other directions. Xenobiology is being used to develop new diagnostic tests and researchers are working on SynBio-derived cancer treatments. Smart drugs and vaccines are also being investigated, as they could deliver targeted treatments and produce a specific immune response when needed.\textsuperscript{216} Equally, phage are being engineered to provide an alternative to antibiotics and to treat certain bugs, which is especially relevant considering the growing resistance to antibiotics.\textsuperscript{217} Furthermore, faster and more accurate production of vaccines is also being studied.\textsuperscript{218}

Progress has also been made in the field of microbial factories that could manufacture molecules needed for pharmaceutical purposes. If used as little production machines, they could lead to the quicker manufacturing of the required product (e.g. painkillers) in a contained environment that is not vulnerable to external conditions, which would reduce the risk of environmental contamination.\textsuperscript{219} The situation would be different in case the synthetic biology organism would be the drug itself, which is engineered to survive for some time in the body of the patient, as this would increase the uncertainties connected to exposure and release.\textsuperscript{220} Lastly, researchers have cultured an animal body part (in this case, a rat foreleg) and generated a bio-limb. This could open great possibilities for transplants, as cells could be grafted from the body of the patient.\textsuperscript{221}

In conclusion, the role of synthetic biology in the health sector could be summarised as follows:

While the benefits of synthetic biology to health care may prove monumental, significant hurdles remain. With the exception of semi-synthetic Artemisinin and potential, near-term improvements in vaccine design, most of the anticipated health benefits of synthetic biology remain in the preliminary research stage. We are unlikely to see commercial applications

\textsuperscript{214}Health Council of the Netherlands (2008, p. 34).
\textsuperscript{215}Simone (2014). Even though the availability of another source of Artemisinin has been saluted as a great improvement by many, critics have highlighted the negative impact that semi-synthetic Artemisinin could have on the livelihood of the farmers that produce the natural version. They also dissented with the idea that the synthetic version would provide a cheaper option (ETC Group 2014a, p. 1; Marris 2013). Those statements need to be read in conjunction with reports arguing that the promises made by synthetic biology on this malaria treatment have backfired (Marris 2013).
\textsuperscript{216}Maynard (2016) and Simone (2014). Scientists are also using synthetic biology to tackle Coronavirus (Cumbers 2020).
\textsuperscript{217}The Economist (2015).
\textsuperscript{218}Conference of the parties to the Convention on Biological Diversity (2014a, p. 44).
\textsuperscript{219}Krieger (2015b) and Henry (2014).
\textsuperscript{220}Paradise and Fitzpatrick (2012, p. 61).
\textsuperscript{221}Hanel (2015).
from much of the biomedically oriented synthetic biology research for many years, although the pace of discovery is unpredictable.  

2.2.4.2 Food and Agriculture

The population of the world is set to reach 9.5 billion by 2050. 40% of the world’s ice-free land is used for agriculture, which also accounts for about 70% of the water consumption on the globe. The use of fertilisers is responsible for the pollution of water wells. Additionally, between 1964 and 2007, the global production of cereals shrank by 10% due to droughts and extreme weather conditions.

To feed a growing population notwithstanding increasingly unstable weather conditions and limited land availability, researches have been considering synthetic biology as a solution to the problems posed by food and agriculture. Reports have identified five areas in which synthetic biology is likely to make an impact on the food industry. Those are health products and processing aids, preservatives, flavours, biosensors (e.g. artificial noses), and food waste processing.

Meat has been in the focus of synthetic biology companies. The environmental effects of meat production as well as the growing request for meat-alternatives have sparked a great interest in the production of meat via synthetic biology techniques. This interest has then led to the founding of around 1000 cultured meat companies around the globe, despite the problematic issue of public acceptance. Milk has also been eyed as a product whose manufacturing chain could be streamlined by using synthetic biology.

Another area that is evolving under the influx of synthetic biology is food flavouring. Recently, many synthetic biology companies shifted their focus from fuels to fine chemicals for food and fragrances, since those products take less time and money to develop and command higher prices in the market ($1 per kg of biofuel compared to the $10–10,000 per kg of fine chemicals). On the other hand, these products may face consumer rejection, especially if the label “natural” usually attached to them is perceived as deceitful by the public.

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222 Presidential Commission for the Study of Bioethical Issues (2010, p. 67).
223 Garthwaite (2014).
224 Ulivieri (2016).
225 British Food & Environment Research Agency (2014, p. 45) and OECD and The Royal Society (2010, p. 19).
226 Burningham (2016). Reports showed that only one fifth of Americans would try lab-grown meat and these types of products have already been dubbed by the press as “Frankenmeat” or “test tube burgers” (Kerr 2016; Harman 2014).
227 A team of DIY biologists is trying to replicate cow milk via yeasts. Such milk, which would be indistinguishable from the bovine molecule, could be used as milk or to produce vegan cheese (Kerr 2016). The regulatory aspects of such lab-grown meat are also challenging (Mayhall 2019).
228 Check Hayden (2014, p. 598).
229 Check Hayden (2014, p. 598).
The first synthetic biology flavour to hit the market was vanillin. In this case, synthetic biology was used to engineer an organism to make it produce vanillin. This means that the vanillin itself was not a synthetic biology product, but rather a product of synthetic biology. For this reason, it would not be subjected to the GMO labelling and could be considered a natural flavour. This situation generated ample controversy. Other SynBio products that are being developed are saffron (the most expensive spice in the world), cocoa butter and synthetic biology alternatives to palm oil.

Agriculture is another field that is likely to be impacted by synthetic biology. Supported by heavy government funding, synthetic biology should be able to enhance crop yield and resistance to external factors (e.g. drought, pest), while reducing the negative environmental impact of agriculture. Similarly, a new generation of targeted pesticides that do not linger in the environment after their use is being developed and so are crops that do not need nitrogen fertilisers altogether. Even though it is unclear whether any synthetic biology products for agriculture have already been commercialised, some suggest that their implementation should be carefully considered, as it could have a negative impact on biodiversity or it could lead to unintended consequences due to the release of engineered organisms into the wild. Lastly, ornamental plants that glow in the dark or grass that is greener and requires less mowing and herbicides have also been manufactured.

2.2.4.3 Energy and Fuel

The production of biofuels has been at the centre of the synthetic biology discourse since the very beginning. The development and manufacturing of biofuels embodied the great hopes and hype of synthetic biology and represented some of its greatest

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230 Watson (2015a), van der Hoeven (2015), McEachran (2015) and Check Hayden (2014, p. 598).
231 The environmental organisation Friends of the Earth was critical of this product and contacted companies, asking them whether they were planning to use this ingredient (Colwell 2015; Barclay 2014). The producing company countered these claims by adding that they: “Synthetize genes as a part of that process, but we’re not ‘printing fake DNA’. All genes are just sequences of data and these sequences change all the time in nature anyway” (Watson 2015b).
232 Johnson (2014). In both cases, critics of the projects fear that these products might negatively affect the livelihood of the local populations who manufacture the natural version of these two materials and add further pressure on the manufacturing of sugar feedstock, which is necessary for synthetic biology’s fermentation processes (ETC Group 2014b, p. 1; ETC Group 2014c, p. 1).
233 Kelley (2014, pp. 43–44).
234 ETC Group and Heinrich Böll Stiftung (2015, p. 11) and Conference of the parties to the Convention on Biological Diversity (2014a, p. 26).
235 Conference of the parties to the Convention on Biological Diversity (2014a, p. 26).
236 Synthetic Biology Project (n.d.-a, p. 2).
disappointments. For years, generous funding and investors have been attracted by the possibility of substituting petroleum-based oils with new generations of fuels based on renewable and greener energy sources. Biofuels could be extracted from biomass. Several types of biofuels are currently available. However, current biofuels have considerable drawbacks, such as high production costs and inefficiencies.

Synthetic biology alternatives are thus being devised to overcome those hurdles. For example, the production of butanol via the fermentation of sugars and starches or via cellulose is being assessed, especially considering that this biofuel could be inserted directly into engines powered via traditional gasoline. In this case, synthetic biology is used to enhance the natural butanol production capacity of some enzymes.

Similarly, much hope resides in the use of algae as biofuels. Algae would be an ideal source of fuel as they are low-input, biodegradable, can mitigate greenhouse emissions and can grow both on land and water, even in areas that could not otherwise be subjected to agriculture. Furthermore, algae have a very high yield and are believed to be compatible with already existing technologies. Still, despite heavy investments and intense research in the field, algae biofuels will probably be amongst the last to reach the market due to high technical hurdles. Similar developments are also envisioned for biohydrogen fuels.

By examining the funding and companies behind these projects, it emerges that governmental agencies, major corporations (e.g. ExxonMobil, DuPont) as well as companies specialised synthetic biology (e.g. Amyris, Solazyme) have been involved in the quest to develop biofuels. However, these investments have not paid back mostly because of the competition with other fuels and the inability to reach the anticipated targets for industrial-scale production. The struggle to render biofuels cost-effective (especially if oil prices are low) and to produce at a large scale have hindered the development of many SynBio companies in this sector.

Yet, a number of products reached the market already. The US navy bought biofuels in 2010, while 300 buses in Brazil are fuelled via biodiesel produced through synthetic biology techniques via yeast. Equally, another start-up engineered microorganisms to produce ethanol. To achieve this goal, the genome of these organisms was stripped to a minimum in order to increase their productivity

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237 Kelley (2014, pp. 44–46).
238 Presidential Commission for the Study of Bioethical Issues (2010, pp. 56–57).
239 Presidential Commission for the Study of Bioethical Issues (2010, pp. 59–60).
240 Presidential Commission for the Study of Bioethical Issues (2010, p. 60).
241 OECD (2014, p. 36).
242 Presidential Commission for the Study of Bioethical Issues (2010, pp. 61–62).
243 European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 20) and Balmer and Martin (2008, pp. 11–12).
244 Kelley (2014, pp. 44–46).
245 LaMonica (2014) and Savage (2007).
246 Conference of the parties to the Convention on Biological Diversity (2014a, p. 18).
and make sure that their metabolism was focused on ethanol production rather than growth.\footnote{Bullis (2012).}

### 2.2.4.4 Environment

Synthetic biology is displaying its potential in environmental applications. In particular, synthetic biology is likely to make a contribution in the detection of contaminants and pathogens as well as in onsite degradation.

For example, a team of scientists has developed a biosensor that detects arsenic in water by engineering bacteria to produce acid, which can be revealed via a simple pH test.\footnote{European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 22).} Equally, researchers devised an organism to degrade pesticides.\footnote{European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 22).} In addition, resources are being devoted to research on bioremediation, which could be used to restore an environment by using organisms capable of degrading poisonous substances. So far, the use of bioremediation has been limited, possibly due to its perception as a less reliable method that requires extensive site assessment.\footnote{European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 22).} Nevertheless, this technology is particularly promising. Lastly, bacteria engineered via synthetic biology have also been considered in the race to stop desertification, since they could boost the growth of plant roots.\footnote{Stinson (2015).}

### 2.2.4.5 Data Processing and Storing

DNA is the code of life and via its four bases—A, C, G and T—encodes the information necessary for organisms to function. Believing that the features that render DNA such a great code could be used for engineering purposes, researchers have programmed cells and DNA to be used for data storage and computational purposes.\footnote{Scudellari (2015, p. 15771).} The idea of using DNA for data storing was sparked by the ever-increasing amount of data that is being generated and that needs to be stored. It is estimated that by 2020 about 35 Zettabytes of data—1 Zettabyte equals $10^{21}$ bytes—will have been produced. Although other storage devices are available, their size,
maintenance, cost and risk of decay have led researchers to investigate other options.253

Biostorage represents an ideal candidate due to the characteristics of DNA. DNA is a high-density storage medium that is particularly stable over time and can be read and reproduced without becoming obsolete. Furthermore, it represents a static offline system, which protects it from remote internet access. These features render DNA storing ideal for maintaining information that needs to be available long-term, does not need to be accessed frequently and where security is pivotal. Indeed, DNA could be seen as an encryption system that is invisible to the naked eye.254 This storage method uses the four DNA bases as a code, similar to the binary code used in software. This allows the storing of any sort of information and data.255 The concentration of DNA storage devices is impressive. A human body could store up to 150 Zettabytes, 70 million copies of a book could be fitted into one drop of liquid and 7 litres could contain all the data in the world.256 The data are generally inserted in the non-coding areas of a gene and therefore they do not affect the workings of the biological system or its functions.257

Given the challenges related to it, biostorage is not likely to replace other types of storage devices any time soon.258 Nonetheless, the technology is very promising, especially if the cost and speed of reading and writing DNA would improve and if a DNA language were developed.259

Biological computers represent another field that is quickly evolving and gaining relevance. Researchers have developed transistors made of DNA and RNA that operate from inside a living cell. They have the ability to reply in a true or false manner to almost any biological question that could emerge within a cell. They could detect the presence of a substance and communicate their findings by changing colour or smell. Similarly, such cell computers could identify how many times a cell divides. This would be important for cancer treatments, as cells that replicate at an abnormal rate could indicate the presence of a tumour.260 According to Endy, these cellular computers will “work in places where we don’t have computing now” and “in places where silicon would never work”.261

253Limbachiya and Gupta (2015, pp. 1–2).
254Zakeri and Lu (2015, p. 10).
255Limbachiya and Gupta (2015, pp. 2–3).
256Limbachiya and Gupta (2015, p. 3) and Brown (2015).
257There are also storing systems where the information is expressed in DNA outside and independently of any biological system.
258Limbachiya and Gupta (2015, p. 14).
259Zakeri and Lu (2015, p. 10).
260Krieger (2013b) and Myers (2013).
261Krieger (2013b).
Notwithstanding the leaps made by researchers in this field, no highly functional biological computers are expected in the near future. Still, simpler biosensors that detect and record changes in a cell will be available in the short term.262

2.2.4.6 Others

Synthetic biology could be used for a variety of applications that go beyond the ones listed above. In particular, synthetic biology has been employed in the cosmetic and fragrance sector, for fabrics and textiles, for the production of rubber, for mining and is even being considered for space missions.

Cosmetics, creams and detergents were amongst the first SynBio products to be placed on the market. This included the aroma of oranges and grapefruits used for perfumes and cosmetics, as well as the moisturising agent squalene which was obtained via engineered algae.263 Laundry detergents have also been listed amongst the goods that contain synthetic biology products. For example, a company manufactured a detergent containing oil obtained from engineered algae. The use of this oil, which was a replacement for palm oil, sparked controversy not only because it was labelled as natural, but also because this was the first time that a company publicly confirmed the use of synthetic biology for the manufacturing of a specific product.264

Synthetic biology is also being used to manufacture textiles. Projects for the development of spider silk, which would be a very strong and elastic fabric, have been initiated and carpets made via bacteria have already entered the market.265 Synthetic biology companies are also heavily investing in the production of rubber for tyres.266

The extraction of copper from mines is also being addressed by synthetic biology. Traditional technologies require considerable amounts of energy and chemicals and cannot reach all copper in a mine. To counter these problems, synthetic biologists are designing microorganisms that boost the solubility and extraction of this metal and thus allow extractions that were either not possible before or not commercially feasible.267

Futuristic and speculative uses of synthetic biology for space exploration have also been imagined. Scientists noted that during long space missions it would be

262Anthony (2013) and Sankin (2013).
263Check Hayden (2014, p. 598), Strom (2014), Janicki (2014) and Synthetic Biology Project (n.d.-b, pp. 1–2).
264De Nieuwe Band (2015) and Strom (2014). The oil itself can be considered natural, as it was not genetically engineered. It is instead the organism that produced the oil that was engineered (Strom 2014).
265Leproust (2015), OECD Development (2011, p. 80) and European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 21).
266ETC Group (2014d, p. 1) and OECD Development (2011, pp. 76–77).
267Synthetic Biology Project (n.d.-c, p. 1).
ideal to have renewable sources of fuel, food, and medicine, which could save costs as well as improve the well-being of astronauts.268

2.2.5 **Technical Background: The Chemical and Informational Content of DNA**

Human genes are sections of DNA contained in chromosomes in the nucleus of a cell.269 Genes contain the instructions to create the amino acids that are used by the body to produce proteins.270 Each gene can produce more than one protein and have multiple functions.271 Interestingly, a gene does not present differences based on its natural or synthetic origin.272 Structurally, the gene is composed of two sections: introns and exons. Exons correspond to the sections that code for amino acids and are separated by introns, which instead do not perform any known coding activity. Approximately 98% of DNA does not encode proteins and was thus referred to as “junk DNA”. However, scientists noted that parts of it are still transcribed into RNA; the reason behind this structure is still unknown. Similarly, RNA performs a number of functions that are still unclear and that are unrelated to the coding of proteins.273

DNA found in nature is called genomic DNA or gDNA.274 gDNA contains both exons and introns. cDNA is complementary DNA that can be manufactured in the lab. It contains only the relevant exons and no introns. cDNA is particularly useful in the production of proteins (via the insertion into bacteria) or for preparing diagnostic probes and it can perform its functions even in the absence of the introns found in gDNA.275 Generally, cDNA does not occur in nature.276

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268Yarris (2014).
269There exists no unique definition of “gene”, as its meaning changed over time and varies according to the discipline involved (Lesser 2011, pp. 328–329; Calvert and Joly 2011, p. 166). As noted by Burk, the notion of gene is a product of human classification (Burk 2013a, p. 95). Similarly, it was held that scientific facts are essentially judgements about what should be considered relevant in a certain situation (Burk 2013a, p. 96).
270More specifically, they contain instructions on the order in which amino acids should be linked to produce a functional protein. The creation (or synthesis) of amino acids is regulated on various other levels.
271Calvert and Joly (2011, p. 166) and Dutfield and Suthersanen (2008, p. 304).
272Falcone (2012, p. 5).
273Dutfield and Suthersanen (2008, pp. 303–304).
274Schertenleib (2003, p. 125).
275Authors held that the issue of function should be addressed with the requirement of industrial application rather than in connection with the notion of invention (Bostyn 2004, p. 42).
276“Brief for the United States as amicus curiae in support of neither party in Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al. before the U.S. Supreme Court (Myriad)” (2013, p. 9).
Related to cDNA is messenger RNA (mRNA), which naturally conveys genetic information from the DNA to the ribosomes. There, the mRNA sequence is translated into the amino acid sequence needed to produce functional proteins. mRNA does not contain all the sequences that are present in gDNA and, therefore, the two are not identical. \textsuperscript{277} cDNA is reverse-transcribed from mRNA via a number of man-made techniques. \textsuperscript{278} Therefore, since cDNA derives from mRNA, the former will not be identical to the DNA found in the human genome. This latter point is the reason why cDNA has been considered as non-naturally occurring by some commentators. \textsuperscript{279} Those who oppose this conclusion argue that the “\textit{genetic structure of the human body remains part of it even after the reconstruction as a cDNA sequence}” and that cDNA maintains the same coding information found in gDNA. \textsuperscript{280}

The status of cloned genes has also been extensively debated. The process employed to clone genes is complex and the final result is not identical to the naturally occurring gene. Indeed, such gene has been copied several times. Hence, it has been argued that cloned genes could be considered as translations or versions of a text rather than a photocopy of it. \textsuperscript{281} Cloned genes can be of genomic DNA (i.e. gDNA) or of complementary DNA (i.e. cDNA).

DNA is isolated from its surroundings by cleaving the covalent bonds that are found at each end of a DNA sequence. Despite this cleaving, the resulting DNA fragment maintains its genetic information. The severing of the covalent bonds is performed via a routine and conventional process that creates a molecule that does not normally exist within the cell. Commentators held that isolated DNA is not markedly different from gDNA, considering that they have an identical sequence and genetic information. \textsuperscript{282} In particular, “\textit{isolating or removing the gene from the body does not chemically alter the gene... the chemical information, compared to DNA in its natural state, is identical}”. \textsuperscript{283} Additionally, experiments have shown that if isolated DNA is reinserted into the cell, it continues to function as it did before. \textsuperscript{284}

One of the most controversial points regarding the patentability of DNA concerns the nature itself of this molecule. Specifically, whether DNA should be considered a chemical substance (the notation ATCG of DNA is actually a representation of its

\textsuperscript{277}DNA sequences undergo significant alterations in their transcription into mRNA, to the point that this creates a: “\textit{Substance that is new and different}” (“Brief for the United States as amicus curiae in support of neither party in Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al. before the U.S. Supreme Court (Myriad)” 2013, p. 18).

\textsuperscript{278}Schertenleib (2003, p. 125).

\textsuperscript{279}Taliadoros and Muratore (2000, p. 125).

\textsuperscript{280}Cornish et al. (2019, p. 909); “Brief for the United States as amicus curiae in support of neither party in Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al. before the U.S. Supreme Court (Myriad)” (2013, p. 19).

\textsuperscript{281}Resnik (2002, pp. 150–151).

\textsuperscript{282}Farias-Eisner (2014, p. 15).

\textsuperscript{283}Farias-Eisner (2014, p. 15).

\textsuperscript{284}Farias-Eisner (2014, p. 16).
chemical structure\textsuperscript{285}) or a carrier of information.\textsuperscript{286} The approach adopted on this point is particularly significant, as it leads to different attitudes on ownership and patentability.\textsuperscript{287} Equally, a patentee might highlight one of the two aspects in order to facilitate patent eligibility in that specific case.\textsuperscript{288} No clarifications are generally offered as to why a subject matter was characterised in a specific way.\textsuperscript{289}

Genes have generally been construed as chemicals in order to fit them into the pre-existing categories of patentable subject matter. This approach was first adopted in the USA and later reached other jurisdictions. In Europe, genes and chemical substances have been ranked side by side, despite the fact that genes are more complex and dynamic than chemicals and that there is only a limited number of genes possible.\textsuperscript{290} While some authors stated that there was no clear evidence that this approach was not valid, other scholars considered this perspective as “fundamentally flawed or at least as partial and one-sided”.\textsuperscript{291} Specifically, it was held that this constitutes an ontological and legal reduction, which is no longer appropriate given the current attitude of the scientific community.\textsuperscript{292} For example, Nobel laureate John Sulston argued that “the essence of a gene is the information – the sequence”.\textsuperscript{293} Equally, Rai criticised the qualification of DNA as a mere chemical molecule as “fundamentally misconceived” and stated that “although DNA is, obviously enough, a chemical compound, it is more fundamentally a carrier of information”.\textsuperscript{294}

From an historical perspective, molecular biologists have often thought about DNA in informational terms.\textsuperscript{295} Examples of this can be found in the language

\textsuperscript{285}Burk (2013b, p. 748).
\textsuperscript{286}Viewing DNA as information will have an impact of the scope of protection accorded to it (Lesser 2011, p. 362).
\textsuperscript{287}Committee on Science, Technology, and Law of the National Academies of Science, Engineering and Medicine (2013, p. 3).
\textsuperscript{288}The problem with this is that, once a patent on the product has been issued, the inventor is able to claim also the other use (e.g. genetic, even though he previously emphasised the chemical traits of the product) (Sherman 2015, p. 1220).
\textsuperscript{289}Sherman (2015, p. 1225).
\textsuperscript{290}Jacobs and Van Overwalle (2001, p. 505).
\textsuperscript{291}van den Belt (2009b, p. 1326).
\textsuperscript{292}A similar point was made concerning the reduction of living organisms to mere compositions of matter (Calvert and Joly 2011, p. 167).
\textsuperscript{293}Sulston and Ferry (2002, p. 269).
\textsuperscript{294}Rai (1999, pp. 835–836).
\textsuperscript{295}The heated debate on whether DNA could be seen as a chemical or as an information carrier started only in recent times. Eisenberg noted that, at the beginning, DNA patenting was not controversial. This is possibly attributable to the fact that patenting genes was considered like patenting drugs, given that many claims were directed to tangible materials used in the pharmaceutical sector (“Molecules vs. information: Should patents protect both?” 2002, pp. 191–192). The situation changed when the informational value contained in the sequences gained more relevance that the molecule itself. Hence, she argued that: “That shift in perceptions of where the value lies is leading to new intellectual property strategies for appropriating that value. The patent system has
employed in this field, which refers to code, translation, transcription, editing, expression and messenger.296

In spite of the above, the majority of businesses and patent practitioners share the idea that DNA is a chemical.297 Equally, the informational view of DNA is not universally accepted in biology.298 Authors who criticised the centrality of the concept of information in biotechnologies did so by stating that:

not come close to digesting this shift. I think forward-thinking patent lawyers are digesting this shift, but the patent office has not really grappled with it yet” (“Molecules vs. information: Should patents protect both?” 2002, p. 197). A number of strategies to protect the chemical and informational value of genes have been considered. It has been argued that patent protection might be appropriate for the chemical molecule, but inadequate for its information value. Indeed, once the patent has been issued, the information regarding the DNA will become freely available and it would not be possible to prevent others from using this information. Since this approach seems problematic, other strategies suggested restricting access to databases containing such DNA information. Others advised instead to claim sequences that are stored in a computer-readable medium (“Molecules vs. information: Should patents protect both?” 2002, pp. 198–199). However, it is debatable whether this latter solution would be appropriate from a patentability perspective (“Molecules vs. information: Should patents protect both?” 2002, pp. 199–200). An extreme consequence of this would be that patents would be infringed merely by storing, retrieving and analysing information rather than by the production and sale of the molecules (Eisenberg 2002, p. 6). Lastly, it would raise questions concerning which IP rights are appropriate for the protection of information. On this, Eisenberg affirmed that patents might be: “A very dangerous form of intellectual property rights for information because there are so few safety valves built into the patent system that constrain the rights of patent holders” (“Molecules vs. information: Should patents protect both?” 2002, p. 201). Another approach suggests that the DNA molecule itself could be seen as a tangible medium for the storage of the biological information. This would lead to question why information is patentable when stored in the gene, which is readable by living cells, and not when it is stored in a computer, which is readable by humans. Eisenberg replied to this by pointing out that the information stored in a computer is read by man and, by tying it up, it would undermine patent disclosure and, consequently, the patent bargain (Eisenberg 2002, pp. 8–9). Similarly, other scholars have argued that the genetic code itself could be considered a law of nature, with obvious repercussions for its patentability (Kane 2004, p. 751). The characterisation of DNA as an information carrier has an impact on the fundamental patent bargain set by the law. Time-limited exclusivity is conferred to the patentee by the law, but, in exchange for that, the inventor must disclose his invention so that others can build upon it. However, if patents are granted on DNA and DNA is classified as information, this system might break down (Andrews 2014, p. 555). In fact, in this case, the patentee could prevent others from using the information disclosed in the patent, thus blocking their possibility to build upon it. The pre-emptive effect of these patents can thus be substantial, given that further innovation could be dis-incentivised and that genes cannot be invented around (Andrews 2014, p. 555). It has been argued that this conclusion does not apply to cDNA (“Brief for the United States as amicus curiae in support of neither party in Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al. before the U.S. Supreme Court (Myriad)” 2013, p. 10).

296 For example, Sulston wrote that: “It makes more sense to think of genes as software rather than chemical entities. The information can just as well be held in a computer or written in a book; composition of matter is irrelevant, because the conversion of the information from one form to another is unsurprising” (Sulston 2006, p. 412).

297 Dutfield and Suthersanen (2008, p. 303).

298 Griffiths (2001) and Sarkar (1996).
The whole idea of the ‘informatisation’ of life or the ‘digitising’ of biology would be no more than a rhetorical construction or, insofar as it is actually believed by many involved, a collective delusion. Sure, bioinformatics plays such a prominent role in modern biological research, because there is a huge amount of data to be analysed. But these vast amounts of information about genes should not... be assimilated with information encoded in genes.299

The introduction of novel technologies, such as microarrays and gene chips, poses new challenges. In particular, it was noted that the difference between the computer-readable and molecular version of a DNA sequence is becoming increasingly complex to determine. Indeed, those new technologies enable the use of computers:

To perceive information stored in DNA molecules... when contemporary technology blurs the distinction between computer-readable and molecular forms of DNA, what logic is there to drawing this distinction in determining the patent rights of DNA sequencers300?

2.3 Market and Players

2.3.1 Market

No univocal and precise estimates are available to determine the size of the synthetic biology market. The discrepancies detected in several studies could derive from difficulties to determine exactly which products belong to synthetic biology. This is aggravated by ongoing doubts about the definition of synthetic biology and by the reluctance of companies to explicitly mention if they manufacture goods using this technology.

In 2012, the global market for synthetic biology was valued at approximately $1.8 billion, with the largest market share by sector being healthcare.301 Other studies placed instead the value of the market for 2013 at $3 billion and pinned biofuels to be the most promising field for investment given their growth potential.302 Indeed, studies showed that, while in 2016 the healthcare segment is bound to retain its predominance, the energy sector is the one displaying the highest compound annual growth rate.303

By 2020, the size of the synthetic biology market should have reached $38.7 billion.304 Geographically, Europe is considered to be the largest market, while the Asia-Pacific region is forecasted to be the fastest growing one.305 Other prognoses

299van den Belt (2009b, pp. 1310–1311).
300Eisenberg (2002, p. 10).
301Industry Today (2015).
302Allied Market Research (2014).
303SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 12).
304Rizzuto (2014).
305Global Industry Analysts, Inc. (2015).
predict that the global synthetic biology market will reach the $100 billion mark in 2025.\textsuperscript{306}

### 2.3.2 Players

#### 2.3.2.1 Governments

Since the inception of synthetic biology in the early 2000s, governments have invested heavily in this field to support research on fuels, medicaments and, overall, sustainable development.\textsuperscript{307} So far, States have been the main contributors to the funding of synthetic biology.\textsuperscript{308}

European institutions were slower than their US counterparts in embracing this discipline, but several steps have been taken in the past years to invert this trend and to take advantage of the pool of expertise available in the old continent.\textsuperscript{309} Yet, the amounts invested in Europe are considerably smaller than in the US (10s of millions instead of 100s of millions).\textsuperscript{310} Over time, the European Commission has supported synthetic biology through its framework programmes (FP) for research and technological development, albeit with slightly different approaches.

The first FP to address synthetic biology was FP6, which spanned from 2002 to 2006. During this time, it funded NEST (New and Emerging Science and Technology) and its projects dedicated to the application of synthetic biology. Everything started in 2003, when synthetic biology was identified as a promising research area,\textsuperscript{306} ERASynBio (2014, p. 8).

For an extensive overview per country and region of the projects, funding and authorities involved in synthetic biology, Kelley (2014, pp. 50–90) and OECD (2014, pp. 133–154).

Calvert and Martin (2009, pp. 201–202).

European Commission, Directorate-General for Research (2005, p. 5). Recently, China has also been investing in synthetic biology and the country is currently setting up a professional committee for this subject (Xinhua 2018).

In the US, no single coordinated funding plan for synthetic biology exists. Numerous agencies are involved. Overall, while no precise estimates are available, it is believed that these sources contributed between $500 million and $1 billion to research on synthetic biology (Kelley 2014, p. 50). The US and Europe have collaborated on several projects (ERASynBio 2014, p. 11) and instituted a joint task force for biotechnology, which has a synthetic biology working group (British Food & Environment Research Agency 2014, p. 35). The legislative branch was also active in this field. In 2015, an Engineering Biology Research and Development Act was presented in order to ensure that America maintains its leadership in this field. The act does not refer to synthetic biology, but rather to engineering biology, and aims to advance this field, increase the number of researchers, accelerate the commercialisation of products, support social sciences related to it and improve coordination between agencies (HR 591) (Johnson 2015). In 2019, a similar act was passed by Congress. Its goal is to promote US national security, sustainability and productivity. It also considers the acceleration of the commercialisation of this type of R&D (Boyd 2019; Johnson 2019).
although no synthetic biology community was yet present in Europe at the time.\textsuperscript{311} Soon after, in 2005, a NEST High-Level Expert Group reported on this innovative research area and outlined its challenges, its possible lines of development for the next 10–15 years as well as the actions that could be taken to promote its growth in Europe.\textsuperscript{312} As a result, several projects related to synthetic biology were founded via FP6. Amongst those, there were scientific research endeavours on energy, biological computers, and medical applications.\textsuperscript{313} Interestingly, these projects were not exclusively dedicated to scientific research, but included also project on policy, strategy and safety.

FP7 began in 2007 and it included a number of specific initiatives targeting synthetic biology. SYBHEL was another project funded via FP7, which was focused on assessing the ethical, legal and policy issues deriving from synthetic biology.\textsuperscript{314}

The 8th FP—called Horizon 2020—provided funding for biotechnology and was based on the idea that smart and sustainable growth are pillars for the development of Europe.\textsuperscript{315} Specific projects related to synthetic biology have been funded via this mechanism.\textsuperscript{316}

European countries are also active individually in the support of synthetic biology, albeit with different approaches. The UK and Switzerland have set up programmes dedicated to synthetic biology, while in France and in Germany synthetic biology projects are funded via general biotechnology programmes.\textsuperscript{317}

### 2.3.2.2 Universities and Research Institutions

The first synthetic biology department was inaugurated in 2003 in Berkeley.\textsuperscript{318} Nowadays, more than 40 countries are involved in this area, with almost 700 organisations active in this field, the majority of which are universities and research institutions.\textsuperscript{319}

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\textsuperscript{311}Parliamentary Office of Science and Technology (POST) (2008, p. 2).

\textsuperscript{312}European Commission, Directorate-General for Research (2005).

\textsuperscript{313}European Group on Ethics in Science and New Technologies to the European Commission (2009, pp. 24–26).

\textsuperscript{314}SYBHEL (2014, p. 1).

\textsuperscript{315}Deutsche Akademie der Naturforscher Leopoldina (2010, p. 28).

\textsuperscript{316}Kelley (2014, p. 68). The European Science Foundation (ESF) has also funded projects related to synthetic biology (e.g. EuroSYNBIIO) to foster multidisciplinary research and to advance fundamental knowledge (Kelley 2014, pp. 71–72; Deutsche Akademie der Technikwissenschaften et al. 2009, p. 25).

\textsuperscript{317}OECD (2014, p. 82).

\textsuperscript{318}European Academies Science Advisory Council (EASAC) and Swiss Academies of Arts and Sciences (2011, p. 3).

\textsuperscript{319}Conference of the parties to the Convention on Biological Diversity (2014a, p. 10) and ERASynBio (2014, p. 11).
As far as publications are concerned, the majority of papers—including a high proportion of the most significant ones—originates from the US. Nonetheless, the gap between publications in Europe as a whole and in the US is closing. The number of researchers in this area is still limited. These experts operate predominantly in research institutions, with a meagre 7% working in industry. The background of these experts reflects the interdisciplinarity of the field, as 37% of them were biologists, 14% chemists, and about 10% each informatics and engineers. This interdisciplinarity is a challenge to the traditional education system and, therefore, ad hoc classes and programmes for synthetic biology have been introduced at both graduate and undergraduate level.

A key aspect to train young synthetic biologists and to form a community around this subject has been the creation of the international Genetically Engineered Machine (iGEM) competition. The annual iGEM competition, established in 2004, sees the participation of high school, undergraduate and graduate students, who compete in the design and implementation of biological systems. iGEM administers also a Registry of Standard Biological Parts, to which the participating teams shall contribute new parts in case they want to compete for iGEM prizes and medals. Such parts must follow the BioBricks™ assembly standard. The competition attracts an increasing number of teams from all over the world.

Another forum that greatly contributed to the development of this field is the Synthetic Biology x.0 conference series. The BioBricks Foundation organises a series of international conferences addressing both scientific and policy related aspects of synthetic biology. The first gathering was organised in 2004. In the eyes of its proponents, the SB 1.0 conference was “consciously designed to facilitate the emergence of a tight-knit, cooperative international community of synthetic biology researchers”.

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320ERASynBio (2014, p. 11) and ERASynBio (n.d.).
321European Commission’s Directorate-General for Health & Consumers (2010, p. 7).
322OECD (2014, p. 22) and British Synthetic Biology Centre for Doctoral Training (n.d.).
323SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 53).
324Frow and Calvert (2013, p. 49). On this, see Sect. 2.2.1.3.
325iGEM (n.d.-b). On this, see Sect. 2.2.1.3.
326At the beginning, in 2004, 5 teams participated in the competition and submitted approximately 50 parts to the Registry. In 2010, 128 teams took part in iGEM and submitted more than 1800 parts. By 2015, the number of participating teams reached 280 (iGEM n.d.-c).
327Bensaude Vincent (2013, pp. 369–371).
328BioBricks Foundation (n.d.-b).
329Kelley (2014, p. 137).
2.3.2.3 Companies

The companies active in the synthetic biology market operate at different levels of the production chain. Some focus on enabling technologies, while others specialise in enabled products. Amongst the first group are companies manufacturing synthetic genes. A considerable number of companies active in the enabled products sector have been founded by researchers and professors. During early funding rounds between 2005 and 2006, many of these companies were able to raise millions of dollars in capital from wealthy individuals as well as venture capitalists. This led to an increased media attention and to articles placing synthetic biology companies in the list of the hottest start-ups. This trend has continued, as promising start-ups were recently able to obtain several million dollars from venture capitalists.

Venture capital is not the only source of funding of synthetic biology, as some high-profile investors entered this field. Studies show that six of the top ten chemical, energy, and grain corporations and the top seven pharmaceutical companies in the world have all invested in synthetic biology. For example, companies like Bayer, Intel, Microsoft, Total, Exxon, L’Oréal and PepsiCo, just to name a few, are directly investing in synthetic biology or have integrated it into their R&D processes and partnerships. This is a change from the initial reluctance of pharmaceutical companies to invest in this field due to a lack of proof of utility.

Some synthetic biology companies have also gone public during the past few years, taking advantage of its market potential, reducing operating costs and improved business models. Lastly, synthetic biology has been promoted via crowd funding initiatives.

Product-wise, companies are increasingly moving away from the production of fuels and are instead focusing on the manufacturing of chemicals.

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330 Rousseaux (2015) and Presidential Commission for the Study of Bioethical Issues (2010, pp. 40–41).
331 Balmer and Martin (2008, p. 11). Wealthy individuals, especially tech founders, are still heavily investing in synthetic biology (Cumbers 2019).
332 Ferry (2015).
333 Interestingly, venture capitalists are increasingly investing in this field, with $500 millions being raised in the first three quarters of 2015, which is more than the total amount raised in 2013 and 2014 combined (Basulto 2015b). For 2018, Nanalyze (2018).
334 ETC Group (2012).
335 ETC Group and Heinrich Böll Stiftung (2015, pp. 10–18), Mistbreaker News (2015), Rousseaux (2015), Ferrari (2014) and Kelley et al. (2014, p. 141).
336 European Commission’s Directorate-General for Health & Consumers (2010, p. 22) and OECD and The Royal Society (2010, p. 24).
337 Philp (2014, p. 23) and OECD (2014, pp. 88–89).
338 For example, the Pink Army project to devise personalised medical treatments has appealed to crowd-funding, while the Glowing Plant one initiated a Kickstarter campaign (Hanel 2015; Callaway 2013, p. 15).
339 van den Belt (2009b, p. 13).
beginning companies pivoted towards lower value chemicals (chemicals that yield between $3–30 for kg), they have now geared towards high value chemicals (spanning between $30–3000 for kg) in order to remain in business. The start-ups of today have learned from the struggles of the first wave of industrialisation of synthetic biology and have steered clear of highly complex and regulated fields (e.g. energy) in order to concentrate their efforts on niche areas, where products could be quickly brought to the market.  

2.3.2.4 Public

The success of synthetic biology will depend on if and how this technology will be embraced by the public. After the experience with GMOs, there is a risk of rejection of this technology due to environmental, safety, health and policy concerns.

Until 2010, only 17% of people who participated in a survey commissioned by the European Commission knew of the existence of synthetic biology.  

Specifically, 16% had either only heard of this discipline or discussed it and researched it occasionally. Only 1% had researched and discussed the topic frequently. With its 17%, synthetic biology had by far the lowest percentage of familiarity amongst the five technologies surveyed by the Commission (i.e. GM food, animal cloning for food production, nanotechnology and biobanks). This trend was consistent all over Europe, albeit with some variations.

EU-wide studies showed that people would like to be more informed about the risks and benefits of this technology. When it comes to the conditions for approving synthetic biology, 17% of interviewees did not approve of synthetic biology under any conditions, while 21% approved in special circumstances and 36% approved only if this discipline were regulated by strict norms. Those approval ratings varied between countries. Overall, the number of disapproving States was basically equal to that of approving ones.

Another report compiled in the UK on the basis of workshops with citizens and interviews with stakeholders showed a number of interesting findings on the perception of synthetic biology. Overall, it was noted that there is:

Conditional support for synthetic biology – while there was great enthusiasm for the possibilities of the science; there were also fears about control; who benefits; health or environmental impacts; misuse; and how to govern the science under uncertainty.

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340 Check Hayden (2015, p. 19).
341 Bensaude Vincent (2013, p. 369). For US surveys, Pauwels (2013, pp. 81–87).
342 In Switzerland, the percentage of people claiming familiarity with this discipline peaked at 29%, while in France and in the Czech Republic it sunk at 12% (Gaskell et al. 2010, p. 82).
343 A high percentage of interviewees (23%) choose not to reply, as they did not have a clear opinion on the matter.
344 Gaskell et al. (2010, p. 34).
345 Bhattachary et al. (2010, p. 7).
The participants mentioned the need for scientists to properly take into consideration the implications of their work and believed that citizens should be involved in discussions on synthetic biology and its funding from an early stage. On a more abstract level, they perceived a tension between the concepts of “biological” and “synthetic” and some had the impression that science was transgressing nature. They were also sceptical of the notion that nature can be reduced to parts that can be assembled. Similarly, concerns were expressed over the fast rate of development, unknown long-term impact and possible uncontrolled release in the environment.346

Related works showed that participants negatively reacted to the name synthetic biology, so that this term might become a liability for the field. They also indicated that the reaction of the British public towards synthetic biology was more positive than in the US.347

All reports examined above detected a connection between the area of application of synthetic biology and its acceptance. For example, health applications were generally seen as more desirable than food-related ones. Indeed, UK studies showed that medical applications were considered to be the most morally acceptable, useful and to be encouraged, while bioremediation and food applications fared more negatively.348 Other studies have assessed the connection between the acceptance of synthetic biology and religious beliefs, concluding that the latter seems to increase the disapproval for this technology.349

To overcome the doubts and fears of the public, numerous approaches have been proposed. Entrepreneurs have argued that the more consumers understand synthetic biology, the better the situation will be.350 However, the familiarity argument (postulating that public backlash is a result of an informational deficit) has been rebutted by scholars and studies alike.351

The media are another factor that will greatly influence the way synthetic biology is perceived. Overall, the media attitude towards synthetic biology has been predominantly positive both in Europe and in the US, with the American press

346Bhattachary et al. (2010, pp. 8–13).
347OECD and The Royal Society (2010, p. 40).
348Philp (2014, p. 30).
349Dragojlovic and Einsiedel (2013, p. 869).
350Harman (2014).
351Pauwels (2013, p. 79).
displaying an even more optimistic view of it.\textsuperscript{352} As for their content, articles have often focused on potential future applications rather than on current ones.\textsuperscript{353}

Safety concerns related to synthetic biology have also featured prominently in the news. A study focused on English speaking newspapers found that a quarter of the articles mentioning synthetic biology included also references to the words “bio-weapon” or “terror”.\textsuperscript{354} Older studies, covering the period between 2003 and 2008, showed that the European press focused on ethics as well as biosafety and biosecurity, whereas US newspapers tended to focus mostly on biosecurity issues.\textsuperscript{355} Metaphors on “playing Lego”, creation, re-designing life and religion were instead very present in the German media portrayal of synthetic biology.\textsuperscript{356}

Stories about scientists “playing God” and the debate between what is natural or not are already recurring in the media and so are associations with previous technologies. For example, studies showed that people tend to associate synthetic biology with other more conventional gene technologies and, in particular, with biotechnology.\textsuperscript{357} It was even stated that synthetic biology is “not perceived as different enough from biotechnology to merit special attention and is supposed to raise the same questions as biotechnology”.\textsuperscript{358}

2.3.2.5 DIY Movement

Synthetic biology is not being developed only in institutional settings, but also within a new and heterogenic community known as do-it-yourself biology or biohacker community.

The term biohacker, which should not be read in a negative connotation, refers to individuals who work either alone or in groups to design and manufacture biological systems outside of institutional settings.\textsuperscript{359} Participants do not necessarily have a

\textsuperscript{352}Gschmeidler and Seiringer (2012, p. 164). German-speaking print media presented synthetic biology as a field with great benefits (83% of articles), especially for energy, health and environmental applications. On the other hand, risks were only mentioned in half of the surveyed articles (Gschmeidler and Seiringer 2012, p. 166). Another study showed that only 21% of the examined German articles assessed the pro and contra of this technology and its classification (Lehmkuhl 2011, p. 25). Similar results emerged from an analysis of the Scandinavian press, which showed that the tone of the articles was mostly balanced or positive, with only 13% of publications that expressed a cautious or negative approach (Ancillotti et al. 2015, p. 5).

\textsuperscript{353}Cserer and Seiringer (2009, p. 33).

\textsuperscript{354}Jefferson et al. (2014a, p. 16).

\textsuperscript{355}European Group on Ethics in Science and New Technologies to the European Commission (2009, p. 38). On this, see Sect. 2.4.1.2.

\textsuperscript{356}Gschmeidler and Seiringer (2012, p. 169) and Cserer and Seiringer (2009, p. 29).

\textsuperscript{357}Gschmeidler and Seiringer (2012, pp. 169–170) and Kronberger et al. (2012, p. 179).

\textsuperscript{358}Gschmeidler and Seiringer (2012, p. 170).

\textsuperscript{359}Dietrich and Steen (2007, p. 4).
biology background and are inspired by the open-source movement. Hence, they generally judge negatively the use of intellectual property rights in this field.\footnote{McLennan and Rimmer (2012).}

The number of biohackers is controversial. While some believe that their number is quite limited, other sources argued that they could have hundreds or even thousands of members.\footnote{SCHER, SCENIHR, SCCS Scientific Committees (2015a, p. 39), Meyer (2012, pp. 312–314) and Schmidt (2008, p. 2).} Their communities are active around the world, including in less developed countries.\footnote{Tatalovic (n.d.).}

Three factors contributed to the rise of the DIY movement in synthetic biology. First, the reduction of the costs associated with DNA synthesis. Second, the Registry of Standard Biological Parts offered a basis to build new biological devices in an easier and cheaper manner. Third, information on biological devices and their modification is now largely available on the internet.\footnote{Dietrich and Steen (2007, p. 5).}

Biohackers are said to operate in an environment which is almost completely devoid of any regulatory or enforcement oversight.\footnote{Rousseaux (2015) and Schmidt (2008, p. 2).} Because of this, biohackers are considered as a possible threat to safety. Reports have described them as a community in which “lone individuals develop dangerous organisms much as they currently create computer viruses”.\footnote{European Commission, Directorate-General for Research (2005, p. 18).} By contrast, other commentators pointed out that the skills needed to produce this kind of organisms are much beyond the abilities of most biohackers.\footnote{Ledford (2015, pp. 398–399).}

\section*{2.4 Risks, Concerns and Regulations}

\subsection*{2.4.1 Risks and Concerns Connected to Synthetic Biology}

\subsubsection*{2.4.1.1 Ethics}

Ethics are an integral part of the debate surrounding synthetic biology. Scholars have considered whether synthetic biology poses new ethical questions. Although it was argued that “synthetic biology does not create any ethical dilemmas that have not already been raised”, this does not exclude or reduce the complexity of such issues.\footnote{SYBHEL (2014, p. 16) and Heyd (2012, p. 581).} To address these complex points, studies were undertaken by the European Group on Ethics in Science and New Technologies, the US Presidential
Commission for the study of bioethical issues, and the Nuffield Council, just to name a few.368

Amongst the most debated issues is the question of whether it would be ethical to produce goods via synthetic biology knowing that this might negatively affect ecosystems and disrupt the livelihood of the farmers that currently grow the natural versions of these goods in some of the poorest regions on the planet.369 Concerns are not limited to the livelihood of local producers, but extend also to the legal status of the genetic resources found in these countries. The Convention on Biological Diversity supports the equitable sharing of the benefits connected to local knowledge and resources. However, this sharing might be affected by synthetic biology.370

From an ethical morality perspective, the two most intricate questions posed by synthetic biology concern the blurring of the line between natural and artificial and claims that scientists are “playing God” and creating life.

On the first issue, Calvert argues that, although synthetic is often considered a synonym of artificial, this does not imply that all creations of synthetic biology will be seen as such. The line separating the natural from the artificial could thus become a “receding horizon”.371 Still, consensus exist that, independently from their natural or artificial method of creation, these entities shall have equal moral status and rights.372

The second issue was often raised in the media, as headlines referred to scientists “playing God” and disrupting the natural course of life.373 Different opinions have been expressed on whether synthetic biology really invites this accusation more than other technologies and, if so, why. Campos pointed out that controversies about the

368Nuffield Council on Bioethics (2012), Presidential Commission for the Study of Bioethical Issues (2010) and European Group on Ethics in Science and New Technologies to the European Commission (2009). Papers have also been commissioned by synthetic biologists themselves. For example, in 1999, Craig Venter commissioned an article on the ethical aspects of the synthesis of a minimal genome (Yearley 2009, p. 561; Cho et al. 1999).
369Friends of the Earth (n.d., p. 1).
370Teller (2015, p. 8) and Conde (2012).
371Calvert (2010, p. 108).
372Newson (2015, p. 48) and Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) (2010, p. 28).
373It could be suggested that this argument is not strictly religious. In a report, the Commission of the Bishops’ Conferences of the European Community (COMECE) argued that Craig Venter had not created life, but he rather: “Obtained a new life form, but to do that he has only exploited, after long and costly efforts, the natural properties of a bacterium which certainly did not owe its existence to him”. Hence, the production of new biological entities does not necessarily amount to “playing God” (Commission of the Bishops’ Conferences of the European Community (COMECE) 2016, p. 7). Similar conclusions over the non-religious character of this objection have been raised also by van den Belt. He held that the “playing God” argument is generally used by secular organisations and that synthetic biology is seen as an affront to nature rather than to a divine entity (van den Belt 2009a, pp. 263–265).
creation of artificial life and the pushing of its boundaries are not new. On the other hand, it has been argued that synthetic biology pushes these statements even further. Indeed, while “many a technology has at some time or another been deemed an affront to God... perhaps none invites the accusation as directly as synthetic biology”. According to Preston, the construction of organisms from scratch using BioBricks™ severs the connection between the organism and the evolutionary process in a way that prior technologies did not, thus infringing the Darwinian principle of natural selection.

Other arguments criticise the idea of biological building blocks as mechanical entities that can be controlled and dominated, as this would constitute a reductive view of life and would prove that the goal of synthetic biology is not to understand nature, but rather to exploit it. The quest for a minimal genome could also be seen as a reductionist approach to the origin and meaning of life. Equally, authors wondered whether organisms synthesised by men could be considered machines. Relatedly, questions have been raised on which responsibilities mankind has for the repercussions of its synthetic creations.

2.4.1.2 Safety

Synthetic biology postulates the creation of new biological systems that could be used to fulfil tasks set by humans. Although these tasks are usually associated with benign targets, malicious use represents a risk. Those risks can be the result of either wilful or inadvertent dissemination. Given the potential of synthetic biology, these dangers could affect large sections of the population and the environment. Hence, scientists, organisations, governments and companies have developed different strategies to assess and address these threats, keeping in mind that absolute risk removal is generally unattainable.

An open question is whether synthetic biology poses unique safety risks. Some commentators replied in the negative, believing that this discipline is based on the same practices of genetic engineering. Nevertheless, debates have emerged over...

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374 In 1905, similar claims were made about an experiment that, by adding radium to a petri dish containing bouillon, resulted in the creation of life-like cell forms or to works done in the sixties on artificial DNA synthesis (Campos 2009, pp. 9–10).
375 “Meanings of ‘life’” (2007).
376 Preston (2008, p. 35).
377 Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) (2010, pp. 11–12).
378 Raho (2012, p. 298).
379 For example, if machines are intended as devices that are externally controlled and that are used for purposes set by humans, this would raise the question of whether “biological machines” should be considered as such or as living systems (Gregorowius 2012).
380 Commissione federale d’etica per la biotecnologia nel settore non umano (CENU) (2010, p. 19).
381 Moe-Behrens et al. (2013, p. 1).
whether current safety procedures and regulations are effective also for synthetic biology. Synthetic biologists and regulators have often argued that they are, especially in the biosafety field.382

The level of risk mitigation to be applied to synthetic biology has been a contentious topic. The discussion reverted mostly around whether the precautionary principle or the prudent vigilance one should be applied. The precautionary principle shifts the burden of proof on the possible risks connected to a project from those who are against it to those who are promoting it. In other terms, those who propose a project should be able to show that it does not pose any risks, which—some say—would lead to the paralysis of the project as absence of risk is complex and lengthy to prove.383 Nonetheless, the Conference of the Parties to the Convention on Biological Diversity urged its parties to adopt it “when addressing threats of significant reduction or loss of biological diversity posed by organisms… from synthetic biology”.384 This view was shared by a number of civil society organisations.385 This led to requests for a “moratorium on the release and commercial use of synthetic organisms until a thorough study of all the environmental and socio-economic impacts of this emerging technology has taken place”.386 Equally, a number of States supported resolutions to prevent the release of synthetic biology products into the wild.387 By contrast, the US Presidential Commission for the Study of Bioethical Issues believed that the principle of prudent vigilance would be better suited in this case.388 This position was also supported by proponents of synthetic biology, as the application of the precautionary principle would hinder the development of the field.

Risks in the field of synthetic biology are usually divided into threats to biosecurity and biosafety. Biosafety, which is often at the centre of the debate in Europe and represents a more novel field, targets the “unintentional exposure to harmful or potentially harmful biological agents and material, or their accidental release”.389 Conversely, biosecurity, generally a focus in the US and a more established concept, concentrates “on preventing the misuse through for example loss, theft, diversion or intentional release of harmful or potentially harmful

382OECD and The Royal Society (2010, p. 32).
383Kaebnick (2012) and ETC Group (2007, p. 50).
384Convention on biological diversity (2018), Conference of the parties to the Convention on Biological Diversity (2014b, p. 6) and Convention on biological diversity (1760 UNTS 79) (1992).
385Friends of the Earth et al. (2012, p. 3).
386Friends of the Earth et al. (2012, p. 1), ETC Group (2012), Sharma (2012a) and Gutmann (2011, p. 21).
387During a 2010 meeting of the Conference of the Parties to the Convention on Biodiversity, the Philippines as well as a number of African countries favoured the precautionary principle for the field release of synthetic biology products (Sharma 2012b).
388Gutmann (2011, p. 21).
389Kelle (2009, p. 85) and Parliamentary Office of Science and Technology (POST) (2008, p. 3).
biological agents and materials”. In lay terms, they have been described as “keeping bad bugs from people” and “keeping bad people from bugs” respectively. A third problematic topic is dual-use research, that is, research that could be used for either benign or malevolent purposes. Some research studies have led to the development of pathogens, thus raising concerns that these same research endeavours could be used for malign purposes.

Biosecurity threats could in theory be posed by States, terrorist organisations and lone wolves alike. Some scholars believe that governmental programmes are the likeliest source, given their resources and history. Still, historical precedents show that even state funded programmes spanning years and involving thousands of scientists encountered many difficulties in trying to develop biological weapons, especially new pathogens. This has been attributed to the difficulty of turning living, mutating organisms that are sensitive to their environment into reliable weapons.

Terrorist organisations have been pinned as possible users of biological weapons developed via synthetic biology. While some authors argue that the employment of such weapons by terrorist groups is inevitable, others have cautioned against the exaggeration of this threat. For example, it has been doubted that terrorists would focus time and resources on new artificial biological agents, when there are plenty of dangerous natural ones available.

The preparation of synthetic biology weapons by terrorist groups or lone wolves has been attributed to the de-skilling of biology, which would allow any layman to design and produce dangerous pathogens and weapons. This idea has been judged as misleading by some commentators. First, it was noted that synthetic biology is not easy and that it would be wrong to believe that anyone can engineer an organism. Also, the skills possessed by DIY-biologists have been considered as grossly overstated. Likewise, despite DNA synthesis becoming cheaper and being outsourced to third companies, it is not easy to assemble a functional genome.

The intentional release of synthetic biology organisms into the environment for benign uses has also raised concerns. First, those organisms could displace already existing ones and become invasive or polluting. Second, they could exchange genetic materials with natural organisms, possibly resulting in unpredictable variations in both the natural and the synthetic organisms. Third, fears over synthetic biology organisms with “unpredictable and emergent properties” have also been

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390 Kelle (2009, p. 85) and Parliamentary Office of Science and Technology (POST) (2008, p. 3).
391 OECD (2014, p. 117).
392 European Commission’s Directorate-General for Health & Consumers (2010, p. 19) and Kelle (2009, p. 86).
393 Jefferson et al. (2014a, p. 23).
394 Kelle (2009, p. 86).
395 European Commission’s Directorate-General for Health & Consumers (2010, p. 19).
396 Marris and Jefferson (n.d., pp. 1–2).
Additionally, worries have emerged over the possibility that synthetic biology organisms could cause allergic reactions in the population. However, for the moment, synthetic biology organisms are generally unfit to survive in the wild, thus decreasing the risk of contamination. Still, evolutionary pressure might change this.

To prevent the accidental spreading of synthetic biology organisms and avoiding unintended contacts with natural environments, containment strategies have been devised. Such containment methods are either physical or biological and, though helpful, cannot guarantee absolute safety. Physical containment strategies include—as the name suggests—physical barriers to the release of the organisms, for instance by restricting use only to laboratories or closed industrial settings. On the other hand, biological containment comprises controls that are intrinsic to the organism; that is, biological systems should be designed with safety in mind. Biological mechanisms are apt for applications that require the spreading of synthetic biology organisms into the wild (e.g. bioremediation). For instance, induced lethality mechanisms, or “kill switches”, would cause a cell to self-destruct in certain conditions or when a specific time is reached, thus preventing it from further interacting or spreading. However, evolutionary pressure might disarm those genes or cause them to mutate, thus defeating their purpose. Another possibility is trophic containment. In this case, organisms are designed to make them unable to synthesise a compound needed for their survival. If the organisms are in a safe environment, such compound could be fed to them, thus keeping them alive. Conversely, the release of the organisms in the wild would cause them to die due to their inability to either synthesise or obtain this necessary compound. Still, also this method does not offer absolute reliability. Other strategies rely instead on the prevention of gene transfers. This would block organisms from taking up or inheriting altered genetic materials. Moreover, xenobiology is also being considered to shield the environment from synthetic biology organisms. This strategy, called semantic containment, uses unnatural backbones or nucleotides to prevent communication between natural and synthetic organisms. Research in this field is in its infancy and thus the effect of xenobiology organisms on natural ones is still unclear.

The topic of security has been addressed by the synthetic biology community since its inception. Already at the Synthetic Biology 1.0 conference in 2004, some discussions were hosted to explore biological risks. However, a study carried out in Europe in 2007 regarding the level of risk-knowledge of 20 synthetic biologists

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397 Conference of the parties to the Convention on Biological Diversity (2014a, p. 30).
398 SCHER, SCENIHR, SCCS Scientific Committees (2015b, pp. 9–10).
399 Parliamentary Office of Science and Technology (POST) (2008, p. 3).
400 European Commission’s Directorate-General for Health & Consumers (2010, p. 21).
401 Moe-Behrens et al. (2013, p. 3).
402 Conference of the parties to the Convention on Biological Diversity (2014a, pp. 32–33) and Moe-Behrens et al. (2013, p. 6).
403 Maurer et al. (2006, p. 4). On safety issues connected to synthetic biology, Maurer (2011).
showed a low to medium awareness. In the DIY field, codes, guidelines and web portals dealing with safety questions have been established.

2.4.2 Synthetic Biology in the Normative and Regulatory Framework

Several international conventions and agreements cover the area of synthetic biology. Some of the most relevant focus on the maintenance of biological diversity and on the safety and security issues related to this discipline.

The 1992 Convention on Biological Diversity aims to conserve biological diversity, guarantee sustainable use as well as the fair and equitable sharing of the benefits obtained from genetic resources. The Conference of the Parties to the Convention deemed synthetic biology to fall within the realm of biotechnology as defined by the Convention and recognised that this new discipline could have both positive and negative effects on the conservation and sustainable use of biodiversity. The Convention on Biological Diversity addresses also the use and release in the environment of organisms that have been modified and that might have an adverse impact on biodiversity. The Conference of the Parties to the Convention noted that synthetic biology organisms fall within the definition of “living modified organisms resulting from biotechnology” and that the provisions on biosafety of the Convention are thus applicable to them. For the same reason, the norms of the Cartagena Protocol on biosafety are applicable to synthetic biology as well.

The creation of biological weapons is the subject of legislation. The Biological Weapons Convention prevents States from developing and producing biological agents that do not have any justification for peaceful purposes. It covers agents that have been developed via natural or artificial methods, thus including developments in synthetic biology.

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404 Kelle (2007, p. 27).
405 Jefferson et al. (2014b, p. 6).
406 For an overview of applicable international and European regulations, Falcone (2014, pp. 62–65).
407 Conference of the parties to the Convention on Biological Diversity (2014a, pp. 8–9). For an overview of the potential implications of synthetic biology on biotrade and access/benefit-sharing, see the study presented by UNCTAD, United Nations Conference on Trade and Development (2019). For an overview of a number of issues raised by synthetic biology within the framework of the Convention on Biological Diversity (Lai et al. 2019).
408 Conference of the parties to the Convention on Biological Diversity (2014b, p. 6) and Cartagena Protocol on Biosafety to the 1992 Convention on Biological Diversity (2226 UNTS 208) (2000).
409 Conference of the parties to the Convention on Biological Diversity (2014b, p. 7), Schmidt and Giersch (2012, p. 288) and Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (1015 UNTS 163) (1972).
At EU and US level, synthetic biology is currently regulated by the norms previously set for GMOs. In Europe, Directives 2001/18/EC and 2009/41/EC regulating deliberate release and contained use of GMOs are applicable to synthetic biology. The GMOs directives are based on a case-by-case assessment of risks, on the precautionary principle and adopt a comparative approach. The comparative principle dictates that GMOs are compared to a natural equivalent to assess the possible risks and changes introduced by the mutation. However, this principle could be problematic in synthetic biology, given the growing distance between natural organisms and synthetic biology ones. Also, the high demands and costs associated with existing GMO regulations could discourage innovation, especially by smaller companies. Innovation may thus be redirected towards areas with lower regulatory hurdles (e.g. cosmetics).

These issues raised the question of whether the norms regulating GMOs are sufficient and appropriate for synthetic biology. While this issue is still much debated, commentators noticed that the use of the processes established for GMOs has both positive and negative aspects. On the one hand, it offers a solid background of expertise. On the other, discussions on synthetic biology might be influenced by negative public views associated with GMOs and might be subjected to an onerous regulatory framework. The consensus seems to be that the regulatory and risk assessment regimes for GMOs can be applied to synthetic biology in its current form. However, as the discipline evolves, those regimes might need to be revised.

The commercialisation of synthetic biology products is also raising a number of questions, especially concerning the commercial release and labelling of the

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410 The US legislation on GMOs presents some differences in comparison to its European counterpart. For an overview of the regulatory and oversight competences, Presidential Commission for the Study of Bioethical Issues (2010, pp. 80–102).

411 For an overview of the regulatory framework applicable to specific applications and requirements (e.g. labelling) (British Food & Environment Research Agency 2014, pp. 8–9; OECD 2014, pp. 122–127; SCHER, SCENIHR, SCCS Scientific Committees 2014, pp. 60–63). Directive 2001/18/EC and Directive 2009/41/EC define a Genetically Modified Organism (GMO) and a Genetically Modified Microorganism (GMM) 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”. However, while the Directives apply to: “Any biological entity capable of replication or of transferring genetic material” and thus cover most of the current developments of synthetic biology, some doubts have emerged on whether they would also encompass protocells and xenobiology inventions. On this, see Sect. 4.2.2.1.

412 SCHER, SCENIHR, SCCS Scientific Committees (2014, p. 18).

413 SCHER, SCENIHR, SCCS Scientific Committees (2015b, pp. 31–60).

414 Douglas and Stemerding (2014, pp. 8–9).

415 OECD (2014, p. 127). Other sources doubted whether the GMO regulatory framework is suitable for synthetic biology (SCHER, SCENIHR, SCCS Scientific Committees 2014, p. 8). This idea was shared by the European Group on Ethics, which suggested that the Commission should reassess the legislation applicable to synthetic biology to establish whether it is fit to address the issues raised by this field (SYBHEL 2014, p. 5; European Group on Ethics in Science and New Technologies to the European Commission 2009, p. 53). For further discussions, Seitz (2018).

416 Conference of the parties to the Convention on Biological Diversity (2014a, p. 35).
products. For instance, commentators in Europe were arguing over whether products might be labelled as natural and whether they should bear a “synthetic biology” tag.417

Lastly, questions were raised on the regulatory approach that should be adopted in this discipline. On the one hand, authors advised against the over-regulation of this field as well as regulations that might be too specific and thus not able to cover various methodologies and applications. On the other hand, it was noted that a specific oversight for synthetic biology could reduce problems and consolidate the trust of stakeholders.418 In its report, SYBHEL warned against the risks of “exceptionalism” and argued that “synthetic biology should be regulated like any other commercial engineering endeavour”.419 Another debated point concerned the issue of self-regulation. Some argued that self-regulation was appropriate, as the scientific community is able to adhere to voluntary standards, as shown with Asilomar.420 A proposal for self-regulation along the lines of Asilomar was presented at the SB 2.0 conference in 2006. This proposal was however withdrawn due to the strong criticism it raised amongst civil society organisations.421 Public response to self-regulation was also sceptical.422

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417British Food & Environment Research Agency (2014, p. 15). Questions on commercialisation and labelling have been particularly prominent in the US. The fact that discussions over the adequacy of current regulations are more predominant in the US than in Europe has been attributed to the more restrictive regulatory framework already existing in the old continent (OECD and The Royal Society 2010, p. 37).
418Newson (2015, p. 53).
419SYBHEL (2014, p. 13).
420Maurer et al. (2006, p. 4). Asilomar refers to the International Congress on Recombinant DNA Molecules held in Asilomar in February 1975. In that occasion, scientists evaluated the nature and level of risk deriving from newly discovered recombinant DNA techniques and agreed on guidelines to perform research in this field.
421ETC Group (2006, pp. 3–4).
422A British study highlighted that: “There was a strong view that scientists should not be allowed to regulate themselves and people should not be allowed to do synthetic biology in their ‘back gardens’. Given the stakes, voluntary standards developed through industry were also not seen as appropriate. A robust and independent regulator was considered to be fundamental in this area” (Bhattachary et al. 2010, p. 42).
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