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A PERSONALIST ONTOLOGICAL APPROACH TO SYNTHETIC BIOLOGY

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ABSTRACT
Although synthetic biology is a promising discipline, it also raises serious ethical questions that must be addressed in order to prevent unwanted consequences and to ensure that its progress leads toward the good of all. Questions arise about the role of this discipline in a possible redefinition of the concept of life and its creation. With regard to the products of synthetic biology, the moral status that they should be given as well as the ethically correct way to behave towards them are not clear. Moreover, risks that could result from a misuse of this technology or from an accidental release of synthetic organisms into the environment cannot be ignored; concerns about biosecurity and biosafety appear. Here we discuss these and other questions from a personalist ontological framework, which defends human life as an essential value and proposes a set of principles to ensure the safeguarding of this and other values that are based on it.

INTRODUCTION

Synthetic biology is an interdisciplinary field which combines molecular biology and engineering to obtain new biological systems.[1] It is an emerging field in which new developments and applications are appearing continuously. Thereby, the number of publications in this field multiplies year after year (Figure 1).

However, synthetic biology is not free of ethical issues, and these must be addressed while we are still in time to ensure safe progress. The number of publications on this aspect of the topic is limited and grows very slowly (Figure 1). Furthermore, a considerable absence of theoretical models that support bioethical argumentation in this field has been noted. While theories in bioethics are diverse, bioethical considerations will always require a rationally justified base to ensure hardiness. Thus, the bioethical study of synthetic biology must be conducted with a specific theoretical model providing principles to be applied which are based on a rationally validated ethical theory.

The aim of this work is to review the development of synthetic biology and to identify the ethical issues arising from this emerging discipline. Bioethical questions that appear around the different branches of synthetic biology are subsequently discussed by employing a particular ethical framework, namely ontological personalism.[2]

SCOPE OF SYNTHETIC BIOLOGY

Many definitions of synthetic biology have been suggested, but none is generally preferred by the entire synthetic biology research community.[3] This is an interdisciplinary field where biotechnology, chemistry and engineering, among others, converge to give rise to a new discipline. However, it has been said that it is most appropriate to consider synthetic biology as a derivation

[1] D. Endy Foundations for Engineering Biology. *Nature* 2005; 438: 449–453.

[2] E. Sgreccia, ed. *Personalist Bioethics: Foundations and Applications.* 1st edn. Philadelphia: The National Catholic Bioethics Center: 2012; 57–60.

[3] A.J. Newson. Current ethical issues in synthetic biology: Where should we go from here? *Account Res* 2011; 18: 181–193.

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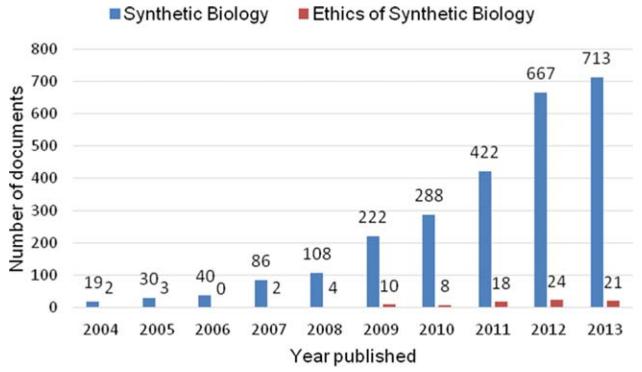

Figure 1. Historical distribution of documents related to synthetic biology and ethics of synthetic biology available in Pubmed.

of molecular biology.[4] What makes synthetic biology different from the technologies it has developed from is that its aim is the *creation* of something essentially new. Thereby, synthetic biology can broadly be defined as a scientific field which uses technology derived from molecular biology and applies engineering principles in order to obtain biological parts or systems not otherwise found in nature. These engineering principles are, basically, standardization, decoupling and abstraction[5].

No single definition of synthetic biology is clearly preferred due to the variety of approaches that can be followed within this field, which may vary in terms of methodology, materials and objectives.[6] Several authors have proposed different subdivisions or branches within synthetic biology. Benner and Sismour[7] classify synthetic biologists into two broad classes. One class focuses on assembling unnatural molecules to *create* lifelike artificial organisms. The second class focuses on assembling natural molecules in order to obtain systems that function unnaturally. Endy[8] subdivides synthetic biologists into biologists, chemists, 're-writers' and engineers on the basis of their aim. De Lorenzo et al.[9] also aim to differentiate the 'deconstructive' from the 'constructive' approaches. The first seeks for simplified and minimal forms that will improve our understanding of biological processes, while the second seeks to create artificial life. Forster and Church[10] divide synthetic biology into two classes, according to the type of projects that can be carried out: *in vivo* and *in vitro*. O'Malley et al.[11] define three broad approaches to synthetic biology: DNA-based device construction, genome-driven cell engineering and protocell *creation*. Deplazes[12] considers some of the above classifications to establish five categories: bioengineering, synthetic genomics, protocell synthetic biology, unnatural molecular biology and *in silico* synthetic biology. The criteria of this categorization are the scientific background, the stated goals, and the techniques that researchers use within each category. The advantage of this classification is that it can ease scientific and societal assessments by delimiting specific issues in each category. Bioengineering, synthetic genomics and unnatural molecular biology are the most relevant for bioethical study. Protocell synthetic biology, which seeks the *creation* of a fully artificial organism, using nonliving materials as raw ingredients, is much less developed and *in silico* synthetic biology involves the design of computational tools to be used in the other approaches.[13]

Bioengineering aims to transform biotechnology into an engineering discipline by applying engineering principles to biology. This approach differs from traditional genetic engineering in that entirely new pathways are designed and introduced into organisms instead of inserting simple genes. It also differs from systems biology in that novel biological systems are designed instead of focusing on those which exist in nature. One example of this approach is the International Genetically Engineered Machine competition (iGEM), where student teams around the world use genetic parts of defined structure and function, called BioBricks, to build biological systems and operate them in living cells. BioBricks are a good example of the bioengineering approach to synthetic biology, since they fulfil the principles of standardization, decoupling and abstraction proposed by Endy.[14] In this context, the designing of a new fly species by Moreno[15] stands out. The author developed a transgenic fly population by genetic modification of *Drosophila melanogaster* using regulatory evolution. What is new here is that reproductive isolation, between the synthetic organisms and the *wild type*, was established, making it possible to talk about different species. It was achieved by combining some elements known to lead to this effect and it is highly significant because it provides the possibility of designing species boundaries, thereby preventing the interbreeding of

[4] M. Morang. A new revolution? The place of systems biology in the history of biology. *EMBO Rep* 2009; 10: S50–S53.
[5] Endy, *op. cit*. note 1.
[6] Newson, *op. cit*. note 3.
[7] S.A. Benner & M. Sismour. Synthetic biology. *Nat Rev Genet* 2005; 6: 533–543.
[8] Endy, *op. cit*. note 1.
[9] V. de Lorenzo, L. Serrano & A. Valenci. Synthetic biology: Challenges ahead. *Bioinformatics* 2006; 22: 127–128.
[10] A.C. Forster & G.M. Church. Synthetic biology projects in vitro. *Genome Res* 2007; 17: 1–6.
[11] M.A. O'Malley et al. Knowledge-making distinctions in synthetic biology. *Bioessays* 2008; 30: 57–65.
[12] A. Deplazes A. Piecing together a puzzle. An exposition of synthetic biology. *EMBO Rep* 2009; 10: 428–432.
[13] Ibid.
[14] Endy, *op. cit*. note 1.
[15] E. Moreno. Design and construction of 'synthetic species'. *PLoS ONE* 2012; 7: 39054.

natural species with transgenic ones, ensuring natural biodiversity.

Synthetic genomics involves the chemical synthesis of a minimal genome (a genome containing the fundamental genes that allow an organism to live) to transplant it into a living cell in order to reprogramme its metabolism to perform a new function. A potential application of this minimal genome is the construction of a 'chassis genome' to which other genes with specific functions can attach. Furthermore, essential genes are potential targets for novel antimicrobials, since they are necessary for bacteria to survive.[16] The ultimate goal of synthetic genomics was first achieved by researchers of the J. Craig Venter Institute who, besides synthesizing a simple bacterial genome, have successfully introduced it into a bacterium.[17] The 1.08 Mb *Mycoplasma mycoides* genome was synthesized based on two finished genome sequences. Cassettes of about 1080 bp were designed with 80 bp overlapping to adjacent cassettes. These constructions were assembled in three phases to obtain the entire synthetic genome, which was transplanted into a *M. capricolum* recipient cell. Finally, the synthetic transplants were characterized and it was proven that the synthetic genome controlled the new cells. More recently, in March 2014, a report on the first synthesis of a functional eukaryotic chromosome, *synIII*, based on the *Saccharomyces cerevisiae* chromosome III was published online.[18] The synthetic chromosome has some differences from the original, which makes it about 14% shorter. The amendments, without compromising its functionality in *S. cerevisiae*, give it a flexibility that will allow the introduction of different modifications in order to, for example, produce antibiotics or biofuels.

Unnatural molecular biology aims to design and construct genomes which are not found in nature, by means of new types of nucleic acids and their introduction into cells in order for them to function, which ultimately would lead to the obtainment of unnatural cells.[19] The C-G and T-A genetic alphabet has already been expanded *in vitro*.[20] However, very recently scientists at The Scripps Research Institute produced the first organism able to stably propagate an expanded genetic alphabet. They synthesized a plasmid containing natural C-G and T-A base pairs along with a new unnatural base pair: d5SICS-dNaM. Interestingly, when the plasmid was inserted into cells of *Escherichia coli*, it was replicated successfully without affecting organism growth.[21]

ETHICAL FRAMEWORK

Synthetic biology raises ethical questions that must be addressed in order to ensure that biotechnological progress leads to authentic human development. In 2009, the European Group on Ethics in Science and New Technologies published an extensive document in this regard in response to a request from the European Commission, where they divide these ethical issues into conceptual or specific.[22] By contrast, Parens et al. differentiate between non-physical and physical harms.[23] We think that the division proposed by Deplazes[24] is useful in associating ethical and societal issues arising from synthetic biology with each distinct approach to this discipline. This contextualization focuses, thus simplifying the bioethical discussion to be carried out, which in turn facilitates the development of an appropriate action plan. Table 1 shows the ethical issues arising from the different branches of synthetic biology.

Although several authors have approached the bioethical study of synthetic biology, only few examples were found in which a rationally developed philosophical theory was used or proposed as a basis for the ethical study of this field.

Yearley opines that principlism, which is the theoretical model that prevails in US biomedicine practice, does not provide the elements necessary to carry out the bioethical assessment of synthetic biology. He argues that the four principles of principlism (beneficence, nonmaleficence, autonomy and justice) are not enough to attend to concerns about whom to believe and are hardly applicable to such an innovative area, whose regulatory demands are very different from those of biomedicine. The author concludes that an ethical review of synthetic biology must integrate social and ethical reflection, rather than only focus on ethics, and it 'should be

[16] M. Juhas, L. Eberl & G.M. Church. Essential genes as antimicrobial targets and cornerstones of synthetic biology. *Trends Biotechnol* 2012; 30: 601–607.
[17] D.G. Gibson et al. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science* 2010; 329: 52–56.
[18] N. Annaluru et al. Total synthesis of a functional designer eukaryotic chromosome. *Science* 2014; 344: 55–58.
[19] Deplazes, *op. cit*. note 12.
[20] D.A. Malyshev et al. Efficient and sequence-independent replication of DNA containing a third base pair establishes a functional six-letter genetic alphabet. *Proc Nat Acad Sci USA* 2012; 109: 12005–12010; R. Yamashige et al. Highly specific unnatural base pair systems as a third base pair for PCR amplification. *Nucleic Acids Res* 2012; 40: 2793–2806; Z. Yang et al. Amplification, mutation, and sequencing of a six-letter synthetic genetic system. *J Am Chem Soc* 2011; 133: 15105–15112.
[21] D.A. Malyshev et al. A semi-synthetic organism with an expanded genetic alphabet. *Nature* 2014; 509: 385–388.
[22] R. Capurro et al. 2009. *Ethics of Synthetic Biology. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission*. Available at: http://www.coe.int/t/dg3/healthbioethic/cometh/ege/20091118%20finalSB%20_2_%20MP.pdf [Accessed 23 Nov 2014].
[23] E. Parens, J. Johnston & J. Moses. 2009. *Ethical Issues in Synthetic Biology: An Overview of the Debates. Synthetic Biology Project*. Washington, DC: Woodrow Wilson International Center for Scholars. Available at: http://www.synbioproject.org/site/assets/files/1283/synbio3.pdf? [Accessed 23 Nov 2014].
[24] Deplazes, *op. cit*. note 12.

Table 1. Ethical issues associated with different approaches to synthetic biology, modified from Deplazes (2009)

Approach	*Ethical issues*
Bioengineering	Moral status Biosafety Intellectual property rights Justice
Synthetic genomics	Concept of life and its creation Moral status Biosafety Biosecurity Justice
Protocell synthetic biology	Concept of life and its creation Moral status Intellectual property rights Biosafety Justice
Unnatural molecular biology	Biosafety Biosecurity Intellectual property rights Justice
In silico synthetic biology	Only as applied to other approaches

conducted in broader terms than those offered by the comfortable language of principlism.'[25]

Following the *M. mycoides* genome synthesis at the J. Craig Venter Institute,[26] the US president Barack Obama requested a study in which the implications of synthetic biology would be examined. The Presidential Commission for the Study of Bioethical Issues (PCSBI) carried out research and recommendations were offered in order to maximize public benefits and minimize risks. The commission considered it essential to use an ethical framework to carry out its task, but it found no suitable example. Therefore, the commission took into account alternative policy preferences and identified five ethical principles with which to construct an appropriate ethical framework to develop its recommendations. These principles are: public beneficence; responsible stewardship; intellectual freedom and responsibility; democratic deliberation; and justice and fairness.[27]

Heavey[28] thinks that no single ethical approach is able to resolve the issues raised by synthetic biology; it is necessary to apply a combination of several philosophical approaches, namely deontology, consequentialism, rights, duties and virtues.

Smith[29] analyses synthetic biology from a utilitarian perspective. The author concludes that, in order to maximize positive utility, a general laissez-faire stance must be adopted and, for those cases which pose substantial risks, the cost–benefit ratio must be determined.

The bioethical approach chosen in the current study is ontological personalism. Personalism cannot be defined as a bounded philosophy, but there are different currents and contributions from multiple authors that emphasize different issues. However, different versions have in common that they place the person in the core of his speech and give it a unique status superior to that of other beings.[30] Ontological personalism is an anthropological theory which defends the objective value of the person on the basis of its ontological structure. The person, as being endowed with reason, freedom and awareness, has a special value which is above that of other beings. The human person is the point of reference and measurement of what is lawful and unlawful.[31] From this approach personalistic environmentalism is derived, which considers it an ethical duty to preserve the environment, since it is an essential factor for human existence. The awareness that the human being has of her or his link with the cosmos, a relationship of interdependence, involves an ethical responsibility towards it.[32]

We have chosen ontological personalism to elaborate our ethical analysis of Synthetic Biology because we think that the principles derived from it may be broadly shared. This philosophical view recognizes the objective value of the person and, therefore, the ethical principles derived from it will always be at the service of every human life. Furthermore, it has already been developed from a bioethical point of view by Sgreccia in his renowned manual of bioethics,[33] greatly facilitating its application to develop bioethical studies.

Thus, on the basis of ontological personalism, Sgreccia proposes a triangular method of research in bioethics, which consists of performing an analysis that has three linkage points: (a) the explanation of the biomedical fact, the consistency of which must be proven; (b) the study of anthropological significance, which consists of analysing what values are at stake in relation to the life, integrity and dignity of the human person;[34] and (c) the

[25] S. Yearley. The ethical landscape: Identifying the right way to think about the ethical and societal aspects of synthetic biology research and products. *J R Soc Interface* 2009; 6: S559–S564.
[26] Gibson, *op. cit*. note 17.
[27] Presidential Commission for the Study of Bioethical Issues. 2010. *New Directions. The Ethics of Synthetic Biology and Emerging Technologies*. Report. Washington, DC. Available at: http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf [Accessed 23 Nov 2014].
[28] P. Heavey. Synthetic biology ethics: A deontological assessment. *Bioethics* 2013; 27: 442–452.
[29] K. Smith. Synthetic biology: A utilitarian perspective. *Bioethics* 2013; 27: 453–463.
[30] T.D. Williams & J.O. Bengtsson. 2014. Personalism. *The Stanford Encyclopedia of Philosophy* Available at: http://plato.stanford.edu/archives/spr2014/entries/personalism/ [Accessed 31 Mar 2015].
[31] Sgreccia, *op. cit*. note 2.
[32] J. Ballesteros. 1995. *Ecologismo personalista*. Madrid: Tecnos.
[33] Sgreccia, *op. cit*. note 2.
[34] The explicit anthropocentrism of this view derives from a comprehensive dissertation carried out by Sgreccia in his manual. He specifically discusses the role of man within the natural world to compare the suitability of the anthropocentric ethical theories against the anti-anthropocentric ones, concluding that 'the preferable approach is

determination of values to safeguard and norms to apply to the action and agents on both the individual and social levels.[35] Thus, this anthropological point of view provides a criterion of discrimination between what is technically and scientifically possible and what is ethically permissible.

Sgreccia uses this method to derive some principles applicable to the specific case of genetic engineering,[36] which is particularly interesting for us given that its similarities with synthetic biology make these principles also suitable for the ethical discussion of this discipline. These principles are:

1. *Protecting the life and genetic identity of every human individual*: Bodily life is the fundamental human value, since it sustains all the others. Therefore, physical integrity must be maintained unless it compromises the life of the individual. Furthermore, the genetic heritage of the human individual must be considered untouchable, safeguarding *the therapeutic principle*.
2. *The therapeutic principle*: It is permissible to carry out a genetic intervention, even if it is invasive, on the living subject when it is necessary to correct a defect or treat an otherwise incurable disease.
3. *Protecting the ecosystem and the environment*: Humans are not only beneficiaries but also stewards of other living creatures and the environment. The environment and the living beings are necessary for human life and health. Furthermore, living organisms cannot be treated as mere instruments.[37]
4. *The ontological and axiological difference between man and other living beings*: There is a deep difference between humans and other living beings, since persons are endowed with reflective knowledge, freedom and responsibility. This implies that certain criteria cannot be applied to human and other living beings in the same manner. For example, the criterion of feeling pain, 'because the way that animals feel pain differs fundamentally from the way that man feels pain: animals suffer and man knows that he suffers and seeks meaning in the suffering'.[38]
5. *The competence of the community*: Questions about genetic interventions in terms of the genetic heritage of humans and even other organisms concern the whole of humanity, and their solution cannot be entrusted only to scientists or politicians, but populations need to share in the responsibility. Thus, while the freedom to conduct scientific research must be guaranteed, scientists must keep communities aware of relevant advances in order to make possible the development of a well-informed public opinion, which has to be taken into account by governments in decision making processes.

We used these principles to analyse some of ethical concerns posed above and others that we have estimated to be relevant in this context. We deepen the discussion to consider the ethical implications of synthetic biology in respect to the concept of life and its creation, the moral status of synthetic organisms and biosafety and biosecurity issues. Questions about intellectual property rights and justice, which largely fall within the field of biopolitics, are beyond the scope of this work. We think that human enhancement is also a relevant issue in the bioethical study of synthetic biology, so we also discuss it. Finally, the need to inform the public about the progress and ethical challenges of this discipline, in order to enable adequate social involvement in decision-making, is explained.

ETHICAL ASPECTS OF SYNTHETIC BIOLOGY

Concept of life and its creation

Synthetic genomics, the goal of which is the construction of a minimal genome, raises concerns about the reductionist understanding of life. Reductionism aims to deduce the properties or concepts of a complex scientific domain from a simpler scientific domain. A way to apply this approach to the understanding of the concept of life is to deduce the meaning of life, the properties shared by all that is alive, from genes. Thus, it is supposed that if the traits of an organism are given by its genome, then the special feature of being alive is given by a specific set of genes. The rest of the genome provides additional features to the living organism. However, Cho et al. find two problematic issues when following this approach. First, throughout history there have been cases where reductionist thinking has led to erroneous deductions, such as designating viruses as the phylogenetic precursors to cellular life. Second, the deductions that can be derived from a reductionist study of life, particularly

anthropocentric, understood to mean a moderate anthropocentrism that reserves for man the role of steward, thereby charging him with a serious responsibility' (Sgreccia, *op. cit*. note 2: 98).

[35] Ibid: 60.

[36] Ibid: 321–323.

[37] In order to better understand this principle, it may be useful to note the difference between intrinsic and instrumental value. Intrinsic value refers to the value that something has for its own sake, while instrumental value is the value that something has for the sake of something else. See: M..J. Zimmerman Intrinsic vs. Extrinsic Value. *The Stanford Encyclopedia of Philosophy* Spring 2015 edn. Available at: http://plato.stanford.edu/archives/spr2015/entries/value-intrinsic-extrinsic/ [Accessed 3 Apr 2015].

[38] Sgreccia, *op. cit*. note 2, pp. 322–323.

human life, may not fulfil the concept of life 'as something more than merely physical'.[39]

While different visions about what a living being is may be embraced, we believe that it is not possible to define the concept of life while focusing exclusively on a minimal set of genes. Whereas a minimal number of genes may be enough for a specific organism to survive, it will not be sufficient for the survival of a different organism. In fact, the set of essential genes is different for each organism, and it can guarantee the survival of the organism only under the most favourable conditions.[40] Furthermore, we find no justification for equating the concept of life to the concept of survival. Certainly, life involves being born, growing, dying and, eventually, reproducing, which requires not only the entire genome of the individual, but also the epigenome.[41] For these reasons, we think that essential genes cannot encompass the concept of life nor redefine it.

Protocell synthetic biology goes beyond the synthesis of a minimal genome; it aims at the production of living organisms from inanimate materials. This objective, if achieved, could be understood as *creating* life. For this reason this approach also raises questions about the concept of life and, moreover, about the concept of the creation of life[42]. Nevertheless, we think that it would be more accurate to talk about designing, constructing or recreating life than about creating it, since what is being done in protocell synthetic biology and synthetic genomics is recreating existent organisms and constructing new forms of life from previous organic materials and knowledge. The use of these terms would be more precise and would avoid unnecessary misconceptions and worries.

However, the production of a living being exclusively from inorganic materials could be achieved in the future and it is debated whether in such a case it would be correct to use the term *creation* or whether this also requires that the organism produced does not exist in nature[43]. In our opinion, ethical evaluation should be developed based on the moral status of the resulting being rather than on to what extent the process of production approximates to the notion of creation.

Moral status

Until now, the boundary between organisms and nonliving entities has been clear, and the moral status of each was clearly differentiated, i.e. ascribing no moral status to nonliving entities. Since bioengineering, synthetic genomics and protocell synthetic biology open the possibility of *creating* new entities not found in nature, concerns about the moral status of these entities appear. It has been said that we have to assign a moral status to any product of synthetic biology before we *create* it, in order to make it clear from the beginning which treatment it will deserve.[44]

Deplazes and Huppenbauer compare organisms and machines as the opposite ends representing the living and the nonliving worlds. They found that these entities differ in terms of four properties: composition (organic material *vs.* inorganic material); origin (uncertain *vs.* clearly defined); development (change *vs.* permanence); and purpose (own purposes *vs.* external, i.e. human, purposes). Taking into account these features, they placed the different products of synthetic biology between these ends, where before there was nothing.[45]

Questions about the moral status of these new entities must be addressed in order to maintain the principle of *protecting the ecosystem and the environment*[46] which states that living organisms cannot be treated as mere instruments. Deplazes and Huppenbauer propose designating those products of synthetic biology which fulfil human purposes as machines, to which no moral status is granted.[47] However, it is contradictory to attend to human purposes in order to determine the moral status of an organism, since it is humans, as unique moral beings, who recognize a moral status onto organisms and, based on this, limit the fulfilment of their purposes. Thus, their argumentation does not seem able to resolve the questions about the moral status of synthetic products. In fact, they conduct their argumentation on the basis that these synthetic products are very simple forms of life (toward which no

[39] M.K. Cho et al. Ethical considerations in synthesising a minimal genome. *Science* 1999; 286: 2087–2090.

[40] R. Zhang & Y. Lin. DEG 5.0, a database of essential genes in both prokaryotes and eukaryotes. *Nucleic Acids Res* 2009; 37: D455–D458.

[41] R.R. Kanherkar, N. Bhatia-Dey & A.B. Csoka. Epigenetics across the human lifespan. *Front Cell Dev Biol* 2014; 2: 49. doi:10.3389/fcell.2014.00049.

[42] A. Balmer & P. Martin 2008. *Synthetic biology. Social and Ethical Challenges. An Independent Review Commissioned by the Biotechnology and Biological Sciences Research Council (BBSRC)*. Available at: http://www.bbsrc.ac.uk/web/FILES/Reviews/0806_synthetic_biology.pdf [Accessed 23 Nov 2014]; M. Bedau & E. Parke. 2009. *The ethics of protocells. Moral and social implications of creating life in the laboratory.* Cambridge: MIT Press; T. Douglas & J. Savulescu. Synthetic biology and the ethics of knowledge. *J Med Ethics* 2010; 36: 687–693; ETC Group. 2007. *Extreme genetic engineering. An introduction to synthetic biology.* Available at: http://www.etcgroup.org/sites/www.etcgroup.org/files/publication/602/01/synbioreport-web.pdf [Accessed 23 Nov 2014]; M. Schmidt et al. SYNBIOSAFE e-conference: Online community discussion on the societal aspects of synthetic biology. *Syst Synth Biol* 2008; 2: 7–17; H. van den Belt. Playing God in Frankenstein's footsteps: Synthetic biology and the meaning of life. *Nanoethics* 2009; 3: 257–268.

[43] B. Baertschi. Defeating the argument from hubris. *Bioethics* 2013; 27: 435–441.

[44] Douglas & Savulescu, *op. cit*. note 41.

[45] A. Deplazes & M. Huppenbauer. Synthetic organisms and living machines. Positioning the products of synthetic biology at the borderline between living and non-living matter. *Syst Synth Biol* 2009; 3: 55–63.

[46] Sgreccia, *op. cit*. note 2, p. 322.

[47] Deplazes & Huppenbauer, *op. cit*. note 44.

moral status is recognized) and conclude that if higher forms of life were discussed 'the moral meaning of their self-interest might have be revisited and contrasted to machines.'[48]

Douglas and Savulescu explain that moral status is conferred to an organism if it has certain characteristics, such as sentience, consciousness, self-consciousness or rationality[49], while Jaworska and Tannenbaum contend that 'an entity has moral status if and only if it or its interests morally matter to some degree for the entity's own sake, such that it can be wronged.'[50] From this it may be argued that what matters when talking about the moral status of an organism are the consequences that actions have on its interests, which often are given by the features of the organism itself (capability of feeling pain, etc.). At this point, we think that distinguishing between merely living organisms without interests, sentient organisms and rational beings could be helpful. Therefore, the moral status of an organism is given by those features that determine the consequences that actions have on it. As the principle of *the ontological and axiological difference between man and other living beings* states, persons are endowed with special features (reflective knowledge, freedom and responsibility).[51] Here it is important to note that morality is a unique feature of human beings. All this rationally justifies the highest moral status of person.

It may happen that human interests are opposite to the interests of another organism which also has moral status, which is usually the case in scientific research. Given the highest moral status of human beings, our interests morally matter more than the interests of any other being and thus prevail when deciding the course of action. It is morally right to act in order to accomplish human interests even if it involves the frustration of the interests of other organisms, provided that such human interests are morally right themselves.

Bringing these conclusions to the case of synthetic biology, it would be necessary to attend to the features of its products, regardless of their purpose, to determine what their interests would be, whether their interests morally matter and whether the intended use of them could contravene these interests. Then the morally right way to behave towards them can be defined, preserving their interests as far as possible.

According to the principle of *protecting the life and genetic identity of every human individual*, the genetic heritage of the human individual may not be subject to manipulation, with the exceptions stated in *the therapeutic principle*.[52] Therefore, it should not be the case that the moral status of a supposed 'synthetic human' has to be defined.

Biosafety

Biosafety measures aim at the prevention of risks to public health and the environment that could be produced by unexpected interactions between synthetic organisms and other organisms or the environment. Taking these interests into account, several questions arise in terms of safeguarding them from unintended exposure to synthetic biological organisms.

The risks that could derive from unexpected interactions between the products of synthetic biology and other organisms or the environment must be addressed. Following the principle of *protecting the life and genetic identity of every human individual,*[53] it is necessary to assure that synthetic biology will not infringe on human life, integrity and dignity whether directly, by means of medical applications, or indirectly, due to interactions with synthetic organisms accidentally released into the environment. Furthermore, according to the principle of *protecting the ecosystem and the environment,*[54] the environment and natural organisms must also be preserved from damaging interactions with synthetic biological products.

Future biosafety problems may be avoided through the design of synthetic safety systems such as less competitive organisms with modified metabolic pathways; organisms dependent on external biochemicals; evolutionary robust biological circuits; biological systems based on an alternative biochemical structure to avoid, e.g., gene flow; and protocells lacking key features of living entities.[55] Some measures have already been proposed in this area. The PCSBI propose the introduction of 'suicide' genes into the genome of synthetic organisms, which would prevent their survival outside a contained environment.[56] However, much remains to be investigated before this technique can be safely applied, since its effect may be voided by mutation or genetic interchange processes.[57] As explained before, Moreno devised a system to reproductively isolate synthetic species from

[48] Ibid.
[49] Douglas & Savulescu, *op. cit*. note 41.
[50] A. Jaworska & J. Tannenbaum. 2013. The grounds of moral status. *The Stanford Encyclopedia of Philosophy* Available at: http://plato.stanford.edu/archives/sum2013/entries/grounds-moral-status/ [Accessed 23 Nov 2014].
[51] Sgreccia, *op. cit*. note 2, pp. 322–323.

[52] Ibid: 321.
[53] Ibid.
[54] Ibid: 322.
[55] P. Herdewijn & P. Marliere. Toward safe genetically modified organisms through the chemical diversification of nucleic acids. *Chem Biodivers* 2009; 6: 791–808; M. Schmidt. Do I understand what I can create? Biosafety issues in synthetic biology. In M Schmidt et al., eds. *Synthetic biology. The technoscience and its societal consequences*. Berlin: Springer; 2009.
[56] Presidential Commission for the Study of Bioethical Issues, *op. cit*. note 27.
[57] T.H. Murray. *La ética y la biología sintética: Cuatro corrientes, tres informes*. Available at: http://www.fundaciogrifols.org/polymitaImages/public/fundacio/Publicacions/PDF/informe5.pdf [Accessed 23 Nov 2014].

wild type species, which may guarantee the preservation of natural biodiversity.[58]

In this regard, the do-it-yourself (DIY) movement generates important concerns. DIY synthetic biology is synthetic biology practised by amateur or professional individuals at home laboratories, outside of institutional settings. In the study carried out by the PCSBI, it was noted that DIY synthetic biologists pose some potential risks that 'must be identified and anticipated [. . .] with systems and policies to assess and respond to them'. The report concludes that for now there is no reason to stop this movement, but the DIY scientist must be educated in the 'culture of responsibility'.[59]

The principle of *the competence of the community*[60] must also be considered here. Scientists have to inform society about the factors involved in biosafety, such as risks of synthetic organism release (biodiversity damage, horizontal gene transfer or unexpected side effects on the environment and other organisms),[61] the advances made in safety systems (physical containment or engineering synthetic organisms to limit their survival to specific conditions),[62] the achievements of the DIY movement, etc., so that society can participate in the debate and help in the establishment of appropriate regulations.

Biosecurity

Biosecurity has been defined as that which 'refers to the protection, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information, to prevent unauthorized possession, loss, theft, misuse, diversion or intentional release'.[63] Examples of potential misuses of synthetic biology include the production of biological weapons, engineering synthetic organisms to produce toxins[64] or the designing of novel pathogens. In fact, *de novo* syntheses of the polio virus[65] and the Spanish influenza virus[66] have already been achieved.

The principles to be preserved are the same as those for biosafety: i.e. the principle of *protecting the life and genetic identity of every human individual*, the principle of *protecting the ecosystem and the environment* and the principle of *the competence of the community*.[67]

With regard to biosecurity in this field, it has been said that the most important issue for bioethicists to address is the concern that knowledge from synthetic biology will be deliberately misused.[68] We agree with the authors in that, despite the potential benefits of synthetic biology, the possibility of a misuse raises a number of risks dangerous enough to doubt whether pursuing and disseminating knowledge from this field is right at all. They quote Selgelid[69] to argue that the misuse of knowledge from synthetic biology could be more dangerous than that from nuclear technology, given that synthetic biology is likely to become quite cheap and that there is a tradition of open access in life sciences which is not present in nuclear technology research. Douglas and Savulescu suggest developing an 'ethics of knowledge'[70] to deal with what is known as the dual use dilemma.[71] It would not merely focus on the ethics of how scientific knowledge is produced, but also on the ethics of pursuing and disseminating certain kinds of knowledge. Certainly, when pursuing and disseminating knowledge may be too risky, it must be restricted, in order to safeguard the *principle of protecting the life and genetic identity of every human individual* and the *principle of protecting the ecosystem and the environment*.

The possibilities of misuses of synthetic biology are definitely a biosecurity matter. In addition to restrictions on the dissemination of knowledge, other measures must be taken. Schmidt et al.[72] propose cooperation of DNA synthesis companies in screening the ordered sequences, improvement of the technical means of DNA screening and a future balance between security gains and feasibility as three important measures to be implemented. Kelle suggests a governance structure based on five policy intervention points (the 5P strategy): the principal investigator, the project, the premises, the provider of genetic material and the purchaser.[73] We think that an oversight strategy is necessary to follow the DIY research. This movement has a high potential to improve science education and, although it is not still clear what its capacity to produce scientific breakthroughs is, it can certainly inspire innovation in unprecedented ways. Furthermore, the DIY community has proven to be proactive in

58 Moreno, *op. cit*. note 15.
59 Presidential Commission for the Study of Bioethical Issues, *op. cit*. note 27.
60 Sgreccia, *op. cit*. note 2, p. 323.
61 Capurro, et al., *op. cit*. note 22.
62 Ibid.
63 The White House. Available at: http://www.whitehouse.gov/administration/eop/ostp/nstc/biosecurity [Accessed 23 Nov 2014].
64 Capurro, et al., *op. cit*. note 22.
65 J. Cello, A.V. Paul & E. Wimmer. Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template. *Science* 2002; 297: 1016–1018.
66 T.M. Tumpey, C.F. Basler & P.V. Aquilar. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* 2005; 310: 77–80.
67 Sgreccia, *op. cit*. note 2, pp. 321–323.
68 Douglas & Savulescu, *op. cit*. note 41.
69 M. Selgelid. A tale of two studies: Ethics, bioterrorism, and the censorship of science. *Hastings Cent Rep* 2007; 37: 35–43.
70 Douglas & Savulescu, *op. cit*. note 41.
71 S. Miller & M. Selgelid. Ethical and philosophical consideration of the dual-use dilemma in the biological sciences. *Sci Eng Ethics* 2007; 13: 523–580.
72 M. Schmidt et al. A priority paper for the societal and ethical aspects of synthetic biology. *Syst Synth Biol* 2009; 3: 3–7.
73 A. Kelle. Ensuring the security of synthetic biology—towards a 5P governance strategy. *Syst Synth Biol* 2009; 3: 85–90.

addressing biosafety and biosecurity concerns.[74] However, the risk of misuse of the means that this movement makes available to citizens cannot be ignored. Government oversight could prevent unfortunate consequences and it would not have to imply the cessation of this movement.

Despite the relevance of these issues, the debate on synthetic biology biosecurity did not take place at the beginning of the synthetic biology movement; it took some time to emerge and it mainly did so in the US.[75] According to the principle of *the competence of the community,*[76] scientists must inform society about the factors involved in biosecurity, such as the risk of misuse (biological terrorist attacks, biological war or biohacking), the advances made in safety systems, etc. Once all the parties are well informed, legislators must attend to them to develop useful laws. Biosecurity awareness among scientists must also be increased, for which cooperation between the synthetic biology and biosecurity communities is necessary.[77] Furthermore, biosecurity education must be a part of undergraduate life sciences curricula[78] and the active involvement of all stakeholders is necessary to avoid too severe restrictions.[79]

Synthetic humans

For the time being, synthetic biology is focused on microbial life. However, important representatives of this field have already expressed their excitement about the possibilities of a direct application of synthetic biological techniques to the human genome. Drew Endy has suggested that it could enable us to skip evolution by designing our own offspring[80] and George Church has written that it could be used to obtain virus-proof humans or bring Neanderthals back to life.[81] Thus, this discipline seems to have the potential to *improve* humans and to develop what it has been called *subhumans*, a kind of humanoid organism which would serve several purposes, such as being sources of transplantable tissues and organs, experimental subjects or crash test dummies and landmine defusers.[82]

Despite the relevance of the transhumanism topic in bioethics, we note a complete lack of references about the ethics of using synthetic biology for these purposes. We think that the bioethical study of this discipline must take into account these possibilities in order to prevent an unethical scenario.

The principle of *protecting the life and genetic identity of every human individual*[83] advocates the untouchability of the human genetic heritage. Thus, it denies the legitimacy of both the modification of the genetic composition of human populations in order to promote the reproduction of more desired traits and any type of meiogenic practice, that is, the production of humanoid organisms to be used by humans. However, an exception must be observed for the cases of genetic interventions with therapeutic purposes, so as to maintain *the therapeutic principle.*[84]

Social awareness

Although synthetic biology has developed rapidly, social ignorance is still very high. As the 2010 Eurobarometer evidences, the awareness of synthetic biology among Europeans is very low.[85] The percentage of respondents who had heard about synthetic biology was much lower than those without awareness of this discipline. Only 17% of respondents were aware of synthetic biology at the time of the survey, while the remaining 83% had never heard about it. Furthermore, out of those aware of it, only 9% had talked about or searched for information on it.[86] Figure 2 shows that synthetic biology is not clearly approved of.

Therefore, given this lack of knowledge, clear acceptance by citizens is far from being a reality. If society does not approve of synthetic biology, progress in this promising field will be significantly slowed, or even halted, as has happened with traditional genetic engineering.

The principle of *the competence of the community,*[87] which states that scientific research must take into account the common weal and the involvement of public opinion, has been seen to be relevant for the solution of a considerable number of the ethical issues raised by synthetic biology. Interactive communication among scientists, legislators, bioethicists, industries, the public, etc., is fundamental.[88] In order to foster the debate on synthetic biology and improve public opinion, an informative

[74] T. Kuiken. DIYbio: Low risk, high potential. *The Scientist* 2013; 3: 26–27.
[75] Kelle, *op. cit*. note 72.
[76] Sgreccia, *op. cit*. note 2, p. 323.
[77] Schmidt et al., *op. cit*. note 71.
[78] G. Mancini & J. Revill. 2008. Fostering the biosecurity norm: Biosecurity education for the next generation of life scientists. Available at: http://www.centrovolta.it/landau/content/binary/LNCV%20-%20BDRC_Fostering%20Biosecurity%20Norm.pdf [Accessed 23 Nov 2014]
[79] Schmidt et al., *op. cit*. note 71.
[80] M. Specter 2009. A life of its own. Where will synthetic biology lead us? *The New Yorker*, September 28, 61.
[81] G. Church & E. Regis. *Regenesis. How Synthetic Biology will Reinvent Nature and Ourselves*. New York: Basic Books; 2012.
[82] S.A. Newman. 2012. *Meiogenics: Synthetic Biology Meets Transhumanism*. Council for Responsible Genetics. http://www.councilforresponsiblegenetics.org/genewatch/GeneWatchPage.aspx?pageId=411 [Accessed 23 Nov 2014].
[83] Sgreccia, *op. cit*. note 2, p. 321.
[84] Ibid: 322.
[85] TNS Opinion & Social. 2010. *Biotechnology. Special Eurobarometer* 341/wave 73.1.
[86] G. Gaskell et al. 2010. *Europeans and Biotechnology in 2010. Winds of Change?* EUR 24537 EN. Publications Office of the European Union, Luxembourg. ISBN 9789279168789.
[87] Sgreccia, *op. cit*. note 2, p. 323.
[88] Schmidt et al., *op. cit*. note 71.

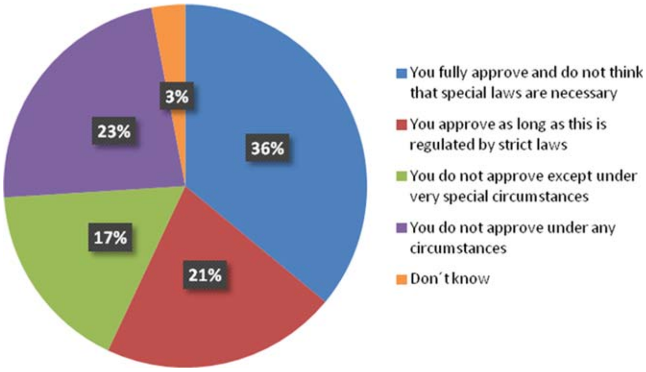

Figure 2. Answers to the question 'Overall, what would you say about synthetic biology?' modified from TNS Opinion & Social (2010).

initiative must be carried out in which both terms and tone are used carefully.

CONCLUSIONS

Synthetic biology is an emerging field with great potential to lead to unprecedented applications. However, some ethical concerns arise from the different branches of this promising discipline. With the aim of carrying out an exhaustive analysis in this area, we chose the principles of personalism as our ethical framework, since they are based on robust anthropological study and could lead to conclusions that can be broadly accepted.

With regard to the implications of synthetic biology for the concept of life and its creation, two conclusions were drawn. Protocell synthetic biology and synthetic genomics are very useful for obtaining chassis organisms with multiple applications, and the search for essential genes may help in the identification of new drug targets. Nevertheless, reductionist reasoning about the concept of life would lead to such oversimplification that it would entail loss of the meaning of the whole, focusing only on one part. The terms *designing*, *constructing* or *recreating* are more appropriate than *creating* when referring to what is made in these branches of synthetic biology, and their use would avoid unreasonable concerns.

Apart from its potential benefits, synthetic biology poses real risks to human health and the environment. On one hand, their products may accidentally interact with other organisms and with the environment with unknown consequences. Thus, biosafety measures are necessary to be developed while new developments and applications in this field are achieved. On the other hand, potential misuses of synthetic biology, such as the production of biological weapons, engineering synthetic organisms to produce toxins, or the designing of novel pathogens, also pose risks to be considered. These biosecurity issues must be prevented by means of restrictions to the research to be carried out and to the dissemination of knowledge, legislating control over the market of genetic material and establishing some sort of bureaucracy that will monitor the DIY movement. Here it is also important to note that the human genetic heritage should not be manipulated either for transhumanist purposes or for the production of *subhumans*, since interventions on the human genome are only morally right when applied for therapeutic purposes.

Finally, we think that an informative initiative involving the synthetic biology community, citizens and legislators is necessary in order to foster a properly informed debate, which could enable the establishment of the necessary regulations to ensure the safe, optimal and fair progress of synthetic biology, so that it leads to true human development.

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