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SYNTHETIC LIFE: ETHOBRICKS FOR A NEW BIOLOGY

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8.1 INTRODUCTION

The purpose of this study is to bring the current state of gene synthesis and synthetic biology into the context of normative ethics, the branch of philosophy that classifies actions as good or bad. What are the demarcation lines between existing and new normative ethics as the technology evolves? What tools are needed by philosophers to capture and merge or resolve conflicting synthetic biology norms in a multicultural society, and how can we extend the conversation between philosophy and technology on these issues?

We here have no intent to review all the exciting new applications of synthetic biology. This information is already available in several outstanding reviews [1,2]. We further do not attempt to cover the significant regulatory and intellectual property issues brought to light by the rapidly escalating technology. Such discussions can be found elsewhere [3]. Our sole aim with this publication is to invite an open discussion on what, if any, consequences the rapidly increasing ability to build new genetic information has on our current normative ethics.

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8.2 HISTORICAL AND CONCEPTUAL BACKGROUND

In early nineteenth century, scientists of the era believed that compounds from living organisms could not be synthesized and that they possessed a nonphysical inner energy that could self-propagate (vitalism). Compounds derived from living organisms were labeled "organic" and most analytical efforts were instead focused on the inorganic types of compounds: metals, salts, and other nonbio materials. This vitalism myth was forever shattered in 1828 when Friedrich Wöhler synthesized urea, an organic molecule. This revelation changed much of chemistry from a discovery-based science to an engineering field devoted to the construction of novel organic molecules. Today there are almost no limits to the kind of organic molecules a good synthetic chemist can synthesize. The acceptance that organic materials can be made and modified to fit the need of mankind in conjunction with our significant understanding of organic chemistry has had far-reaching consequences in today's society, culture, and economy.

With the current advent of molecular biology, genomics, and most recently synthetic biology, we are again breaking through an imaginary barrier as now we have the ability to modify, edit, and create new biological entities by directly altering the biological source code—DNA. We are no longer limited to creating chimeras of naturally existing information, as is the case with "classic" genetic engineering. Instead, as the formal rules and grammar of biological information are gradually deconvoluted and gene synthesis technology improves, we now are able to create designed genetic templates for nonexisting proteins, replicative units, metabolic pathways, and, entire organisms (Table 8-1).

Synthetic biology is now emerging at the interface between chemistry, molecular biology, engineering, and computer science. The discipline is often suggested to be the "other half" of systems biology (Fig. 8-1) [4]. While systems biology is focused on cataloging all parts of biology, synthetic biology aims instead at building novel genetic circuitry and processes from scratch based on new or existing biological parts [5].

Our increasing ability to efficiently create any genetic information imaginable will transform life sciences into an engineering discipline just as what happened to organic chemistry more than a century ago.

Table 8-1 Historical milestones in creating increasingly larger and more complex synthetic DNA

First synthetic gene	1970	Yeast tRNA Ala (207 bp)	[8]
First synthetic peptide coding gene	1977	Human growth hormone (56 bp)	[54]
First synthetic protein coding gene	1981	Alpha interferon (514 bp)	[55]
First synthetic bacterial replicating unit	1995	Plasmid (2.7 kb)	[56]
Identification of minimal genome	1999	265–350 protein-coding genes of *Mycoplasma genitalium* are essential	[57]
First synthetic enzymatic pathway	1999	>50 erythromycin analogues	[58]
First synthetic genome	2002	poliovirus (7.4 kb)	[59]
First synthetic metabolic operon	2004	PKS gene cluster (32 kb)	[60]
First synthetic prokaryotic chromosome	2008	*Mycoplasma genitalium* genome	[61]

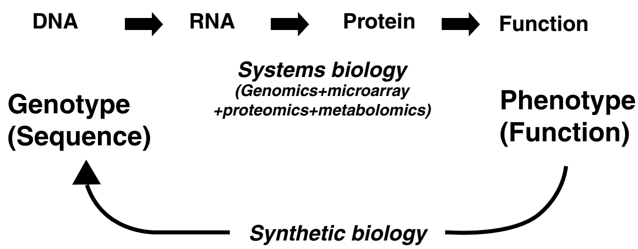

Figure 8-1 Systems biology, synthetic biology, and information flow. Information from genomics, proteomics, and metabolomics can be analyzed to create models describing biological activities. Systems biology develops methods to predict behavior of networks of these elements. Synthetic biology closes the loop by reversing the direction of information flow, creating novel genes, proteins, and organisms based on data from naturally occurring systems. This allows testing of predictive algorithms and the creation of new and useful biology. Figure previously published [62] and reprinted with permission from Elsevier.

8.3 DNA AS INFORMATION CARRIER

DNAs are discrete entities of coded information just as letters in the alphabet, musical annotation, and bits of computer code are all coded information. However, unique to genetic information and computational code is that the medium is also the message. The information carrier itself (be it ACGT or 100110) has the ability to perform a defined function (metabolize glucose or query a database) without any manual intervention. Similar to computational source code, the genetic code of synthetic biology captures an algorithm for a function and converts it to a step-by-step protocol.

DNA, as any type of coded information, can be both written and read. Reading is done by DNA sequencing and writing by gene synthesis. Most of the molecular biology over the last decades has focused on reading and analyzing naturally existing DNA sequences, as evident in the massive DNA sequencing effort of the human genome [6,7]. In contrast, writing new genetic information in the form of synthetic biology has only recently become commonplace. Although the first synthetic gene was made as early as 1970 [8], gene synthesis as a standard process to create completely synthetic genetic information only appeared over the last few years.

Today we are not only able to decipher the coding sequence of ourselves and of all other living organisms, but we are also in a position where we have the technology and knowledge to write synthetic genetic code that can operate new biological entities.

8.4 CREATING NEW BIOLOGICAL ENTITIES

A synthetic gene can be made to be an identical copy of a naturally existing gene sequence or it can be made to be a gene that has never existed before and not even be remotely similar to anything previously seen. Or it can be anything in between.

Currently, the majority of ongoing synthetic biology efforts are directed toward making minor deviations from existing genetic information. Typical synthetic biology applications today include efficiently making genetic constructs using ‘‘classic’’ genetic engineering that would be very labor intensive [9–12]. Even though the genes are completely synthetic, the coded information itself is identical or very similar to existing natural genetic information. This type of ‘‘synthetic–natural’’ genes is the application that today drives much of the technical development of gene synthesis.

Due to the degeneracy of the genetic code, a nucleotide sequence can be designed to be only ~60 percent identical to an existing gene, while the encoded protein is still an exact copy of a natural protein. This degenerate property of genetic information can be utilized to create synthetic genes for applications such as making genes for expression in foreign hosts [13–16] or for making RNAi-resistant mRNA transcripts [17]. Here the synthetic genes encode the natural protein information, but the corresponding DNA sequence has been recoded and can be drastically different on the DNA level to encode additional properties that are not found in the natural DNA information.

The availability and acceptance of ‘‘synthetic–natural’’ and recoded synthetic genes are important stepping stones on the path toward completely synthetic biological systems. The commercial demand for ‘‘synthetic–natural’’ and recoded synthetic genes today drives the technology to make all sorts of disparate synthetic genes faster at lower cost and without mutations. This type of synthetic genes are also critical in that they teach us the ground rules for what changes can and cannot be made in the genetic information.

Synthetic genes have also been used to create biological entities that have no precedence in the existing biological environment. These new entities can be completely new DNA or protein structures [18,19], genetic networks [20] with fascinating applications that include molecular computers [21], programmed pattern formation [22], an unbeatable Tic-Tac-Toe player [23], and even a bacteria that take pictures [24].

As our understanding of the rules and grammar of biological information increases, we expect synthetic biology constructs to deviate more and more from naturally existing sequences. But what does this new information imply? If a nanosized octahedron made from synthetic DNA encodes a replicon and can multiply in a surrogate host just as a virus, does it mean it is alive? Is the octahedron a complex organic molecule or is it an organism? And if a molecular DNA computer is built into a self-contained synthetic eukaryotic cell, is that a living calculator? The answers to these questions belong not only to science but also to ethics.

8.5 INTRODUCTION TO NORMATIVE ETHICS IN A GLOBAL COMMUNITY

From the very beginning of human societies, it was necessary to have a set of rules that could guide and regulate human behavior and actions. Such set of rules would define good as well as bad human actions in the context of society. A subset of these rules over time formed the basis for the judicial system. Most, if not all, of these early rules had a supranatural foundation, that is, the rules were perceived to have been defined by a God or set of Gods. Later, in the Ancient Greece (fourth century BC), philosophers like Plato and Aristotle designed rational normative ethics, a tradition followed later by the likes of Spinoza (and his geometrical style ethics), Kant (with his categorical imperative), or Moore (with his critics to the naturalistic fallacy and his stunning and absurd claim about "the direct object of Ethics is knowledge and not practice," *Principia Ethica,* 1903, Chapter 1, Section 14). Both positions, supranatural and rationalist, can be labeled as *foundationalist* approaches, because they find a clear foundation for their beliefs or ideas. For them, there is one and only one truth. Consequently, their moral codes are based on that absolute truth.

At the end of nineteenth and beginning of the twentieth centuries, several philosophers made new approaches to the ethical analysis: Nietzsche killed God and started an *Übermensch*'s ethics based on new myths, whereas Wittgenstein delimitated the possible rational, linguistic, and, therefore, thinkable spaces, excluding ethics from rational debate; to quote, "Ethics, if it is anything, is supernatural and our words will only express facts; as a teacup will only hold a teacup full of water and if I were to pour out a gallon over it" [25]. Wittgenstein continues to pragmatically point out the obvious in an ethical crossroad, "the absolutely right road would be the road which everybody on seeing it would, with logical necessity, have to go, or be ashamed for not going."

This new way of thinking led to the development of an antifoundamentalist ethics by philosophers like Eduardo Rabossi or Richard Rorty. Rabossi, for example, thought that the human rights phenomenon rendered human rights foundationalism outmoded and irrelevant [26]. From this perspective can be understood the claims of underdeveloped countries arguing about the imposition of Christian– Occidental values as if they were universal truths [27–29].

As monolithic religious/rationalist-based ethics is today losing its monopoly in contemporary developed societies, an intense blend of cultures and opinions is increasingly making its presence heard. This change is reflected in the increasingly global perspective of a multicultural society.

An additional ethical concept that has emerged over the last few years is the concept of risk society [30]. Risk society is often described as a systematic way of dealing with hazards and insecurities induced and introduced by modernization itself. Risk society specifically attempts to address how all human beings are connected by ecological and industrial risks, including everything from global warming to electromagnetic radiation from cell phones.

Although the globalized world now requires common global solutions for everything from economic markets to law enforcement, the moral pluralism is instead expanding and common ethics frameworks are diminishing on the contemporary ethical arena. This contradiction has been described as the "collapse of consensus" [31] and is making the efforts to find common solutions and compromises increasingly difficult to achieve.

The facts and promises of biological engineering and synthetic biology create conceptual problems about future decisions because they involve completely new and previously unexpected ways of changing reality. For that reason, opinions like those of Cho et al. [32], "Without prior discussion of ethical issues, the general public cannot develop a framework or common language to discuss acceptable issues of a new biomedical technology, or even whether it should be used at all,'' are premature as the general public does not share common normative ethics. Few words have in fact so disparate and ethically pregnant meaning as ''life.'' The meaning of the word varies widely in the global transnational community based on respective individual beliefs and historical and casuistic background.

Can there be a common ethical space or must we resign to a complete ethical anarchy? This is not a problem specific for the synthetics biology community but for any ethical problem affecting a global society. If it is true that bioethics is a specialized part of common ethics, with its own topics of interest, we must also consider that it belongs to the debate about sense and meaning among general ethics.

It could be argued that the general public should not decide on ethical aspects of synthetic biology, since several studies about risk perception and scientific literacy show that most citizens of our societies have a distorted, at best, or false ideas about science and the concept of risk [33–35]. The counter argument however is simple: A democratic society must rely on democratic principles as the foundation for ethical framework of any normative behavior.

8.6 EMOTIONS AS THE BASE FOR SYNTHETIC BIOETHICS?

The interest in the ethical aspects of synthetic biology is not only due to the moral implications of this kind of research but also due to the cognitive implications of ethical values for scientific practices. As previously discussed [36], theoreticians of science studies consider nonepistemic values (specifically ethical and moral values) as alien to the scientist's process of making rational decisions [37]. However, neuroscience and the emerging field of neuroethics propose that epistemic values are inherent to natural science [38–40]. At the same time, analysis of the emotional aspects of human reasoning suggests that most of the moral actions imply emotional attitudes and responses [41–43]. From an anthropocentric perspective, information is not just information, a state, but an active quantity of data meaningful for action. We are not perfect rational robots, nor strange Mr. Spock without emotions [44]. Minds have not been evolutionarily designed to just capture the neutral realities but to interpret them in a framework based on previous experiences and in the context of other related pieces of information. Only by categorizing and sorting new information into an existing framework can we start to interact with the captured information through behavior and actions. Emotions shape thoughts and how to relate to and acknowledge new information. And as we now are able to create new biological data, we need to find meanings for those pieces of information to build a framework for our understanding of living entities and biological systems.

Results from neuroethics are suggesting that nonepistemic values, formerly considered alien to the scientific praxis, are instead anchored in the scientist's neuronal processes and are determining their actions. Several investigations in neuroimaging have shown the central role of emotions in the formation of rational judgments [45–47] and in how moral dilemmas initiate cerebral activity in the areas associated with emotion and moral cognition. These emotions are also socially distributed among human communities [48,49].

It can thus be concluded that rational decisions are cognitively processed through emotional elements that can be explained from insights derived from new advances in neuroethics. Therefore, any kind of bioethics that can be thought must be developed from the sentimental frame. The relationships between ethics and sentimentality were initially developed by Rorty [50], at the same time when contemporary discoveries about the limits of rationality (beyond the formal incongruence of the logical classic research, as was demonstrated by Gödel and Russell) and the basic role of emotions in human thinking were made, led contemporary efforts on ethics toward an ethics based on emotions with strong limitations of fundamentalist positions.

8.7 ETHOBRICKS

From the perspective of the collapse of the consensus in contemporary ethics and after the historical failures to achieve a universal ethical code, we here propose a simple project: Create an ongoing ethical frame that can offer answers to the synthetic biology community, a kind of ethical Nash equilibrium based on simple and shared ethobricks. This would be an open and collaborative project (like an universal *wiki*), in which different social agents (scientists, artists, civil society organizations, and so on) define basic ethical pieces for configuring the action's puzzle [5].

The current ethical frame for synthetic biology was defined through the social contemporary circumstances at the time of inception. We can see the early pioneers in this effort when reading the personal writings of the Dolly sheep's creators [52] or we can see it in the Critical Art Ensemble's conflictive artistic works (http://www.critical-art.net). Specially interesting is the use of synthetic biology and genetic engineering techniques by Eduardo Kac, an artist, on his *Move 36*, an open reflection on the limits between artificial and human intelligence through the visual results of the incorporation of a synthetic gene on a new plant (http://www.ekac.org/move36.html).

Currently we have not defined meanings for those genetic information realities, and we are afraid of what to do with it. This is a good starting point: We feel uncomfortable with our actual ideas and the language with which we have developed them, and we are looking for a new way to understand (and modify or create) that biological reality. Before genetic engineering and synthetic biology, humans created names for existing semantic genetic meanings. Chimeras such as mermaids and centaurs were part of the imaginary realm and not a real world. Ethics is an integral part of scientific decision making (e.g., stem cells). There were clear roads in the scientific framework. But our capacity to create new biological meanings require that we create new names and new ethical frameworks to shape the future of living systems, including ourselves, humans. For this we have no references, because those realities were not previously thinkable by whatever philosophical or religious ideas we could consider. As Benner and Sismour state, "A synthetic goal forces scientists to cross uncharted ground to encounter and solve problems that are not easily encountered through analysis. This drives the emergence of new paradigms in ways that analysis cannot easily do'' [53]. This is the situation for synthetic biology and, as consequence, for synthetic bioethics.

The origin and justification of the proposed value do not matter. Dividing the ethical concepts into minimal building ethobricks alleviates the need to discern between the truthfulness of different religious, traditional, and cultural beliefs. Ethobricks can be used to define the consensus among beliefs and how to apply ethics to the scientific question asked. Ethobricks would be, then, small ethical blocs with which we could regulate our present and future relationship with synthetic biology research.

With that approach, we can create a common ethical space while avoiding discussions of the foundational basis of ethics. Instead of an ethics of confrontation between deep truths, ethobricks means a ''common sense'' ethics based on basic emotions, flexible and adaptable to continuous changes. Once synthetic biology community reaches a stable set of ethobricks, it will be transformed into an ethical core with an external belt of concepts under day-to-day supervision. All, core and external ethical belt, are provisional but accepted ways to regulate action.

Like biobricks, basic biological synthetic pieces with which to create new life forms or processes, ethobricks are basic ethical points of departure for a common ethical background. Very important for our approach is the consideration of synthetic biology problems as radically new questions about life for which we have no answers (otherwise, it would not be a problem!). And a crucial problem: We know that people who have values based on divine beliefs or supposed universal principles cannot convince all others the truth of their beliefs (based on divine truths as well as on ''rational'' ones). Absolute ethics is only possible from absolute beliefs. This is an exclusionary project that separates between those who have the (ethical) truth and those who have not.

Multicultural and democratic societies must develop ethical agreement tools to be able to have coordinated responses to the contemporary ethical dilemmas such as synthetic biology.

8.8 APPLYING ETHOBRICKS

Our project on ethobricks is not just as an engineering code of ethics for practitioners. Bioethics is part of ethics, and we must always remember that ethics is a practice and not an intellectual or mere regulatory process. It is a way of life if considered personally, but a merged moral state if considered socially.

The question is how to find common ways of life and practice? From our perspective, it would be illusory to pretend to find a unique and absolute moral code for all humans. Instead, we must negotiate provisional but reasonably stable codes for deciding our actions. There are many application fields of ethics into synthetic biology, such as bioterrorism, biosafety, patents, life definition, right to manipulation, and control over research (http://openwetware.org/wiki/Synthetic_Society#Synthetic_Society.2FUnderstanding.2C_Perception_.26_Ethics). These concepts will change in different societies due to the transformations of their sciences, industry and technology.

Therefore, we should try to find provisional ways to develop our activities as scientists, as citizens, as artists, or whatever role we have in our societies.

Ethobricks cannot be regulated by a metaorganization, because it would imply that there is an upper lever from which certain experts know the truth about the discussed facts. Ethobricks is instead an open and continuous project that is gradually implemented on legal traditions. However, there is not only one channel of debate, because it would exclude most of the interested participants from the debate. The equilibrium of an independent ethobrick is achieved if, for continuous space of time, there is not a deep debate about its ethical values. Accordingly, our approach does not imply a different way to define ethics on synthetic biology issues, but it requires a commitment to avoid absolute values. One may think that this leads to a weak ethical frame, but it is the only possible path forward inside true democratic societies.

Can we define the first ethobrick? Certainly yes, *trust*. We can and should trust the fact that all implied participants in this ethical debate seek the best for them and their societies (the basic *pleasure of happiness*). The point is, then, to harmonize for *common* ethical spaces in this increasingly globalized world.

BOX 8-1 MAKING SYNTHETIC LIFE

Current list of examples where genomes have been synthesized *de novo*. In all cases but the T7 phage below, the synthetic genomes are very similar to the natural counterpart. For the T7 phage genome, only a quarter of the genome was synthesized and subsequently combined with the remaining natural three quarters. The synthetic quarter of the T7 genome was redesigned and is significantly different from the natural T7 genome counterpart.

- In August 2002, Dr Wimmer (SUNY) announced that his research team had assembled an infectious poliovirus (7.4 kb) *de novo* using DNA sequence of the viral genome available from GenBank [59].
- In 2003, Dr Smith and colleagues at the Venter Institute developed a two-week selection-based method for the *de novo* synthesis of a phage genome, the 5.4 kb bacteriophage φX174 [63].
- In 2005, Dr Tumpey and colleagues at the U.S. Centers for Disease Control in Atlanta synthesized the 1918 pandemic flu virus genome (13.5 kb) and showed they were infectious in mice [64].
- In 2005, Drew Endy and coworkers at MIT redesigned and synthesized 12 kb of the 40 kb T7 phage genome to make the virus simpler to model and more amenable to manipulation [65].
- In 2008, the J. Craig Venter Institute published the first synthetic prokaryotic chromosome (~600 kb). The DNA was synthesized by three commercial gene synthesis companies (DNA2.0, Blue Heron Bio, and GeneArt) and stitched together by scientists at the J. Craig Venter Institute [61].

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