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Joachim Boldt *Editor*

Synthetic Biology

Metaphors, Worldviews, Ethics, and Law

Springer VS

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Diese interdisziplinäre Buchreihe ist Technikzukünften in ihren wissenschaftlichen und gesellschaftlichen Kontexten gewidmet. Der Plural „Zukünfte“ ist dabei Programm. Denn erstens wird ein breites Spektrum wissenschaftlich-technischer Entwicklungen beleuchtet, und zweitens sind Debatten zu Technowissenschaften wie u.a. den Bio-, Informations-, Nano- und Neurotechnologien oder der Robotik durch eine Vielzahl von Perspektiven und Interessen bestimmt. Diese Zukünfte beeinflussen einerseits den Verlauf des Fortschritts, seine Ergebnisse und Folgen, z.B. durch Ausgestaltung der wissenschaftlichen Agenda. Andererseits sind wissenschaftlich-technische Neuerungen Anlass, neue Zukünfte mit anderen gesellschaftlichen Implikationen auszudenken. Diese Wechselseitigkeit reflektierend, befasst sich die Reihe vorrangig mit der sozialen und kulturellen Prägung von Naturwissenschaft und Technik, der verantwortlichen Gestaltung ihrer Ergebnisse in der Gesellschaft sowie mit den Auswirkungen auf unsere Bilder vom Menschen.

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Preface

The results, arguments, and theses that are presented in this volume have been developed and discussed within the project *Engineering Life: An interdisciplinary approach to the ethics of synthetic biology*. The project was funded by the German Ministry of Research and Education (grant nr. 01GP1003). The following contributors were part of this project. In the order of appearance: Joachim Boldt, Oliver Müller, Harald Matern, Jens Ried, Matthias Braun, Peter Dabrock, Tobias Eichinger, Jürgen Robienski, Jürgen Simon, Rainer Paslack, Harald König, Daniel Frank, Reinhard Heil, Christopher Coenen.

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Freiburg, August 28, 2015 — Joachim Boldt

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An introduction to synthetic biology's conceptual and ethical challenges

Joachim Boldt

1 Novelty and conceptual framing of emerging technologies

Emerging technologies have a history. They do not emerge out of nothing but develop gradually and continuously. Synthetic biology is no exception. It is rooted in genetic engineering, and many observers maintain that synthetic biology is no more than a new label for just that: genetic engineering.

The inevitable question therefore arises: when is an emerging technology in fact a new technology and when is it only a gradual development of an already known technology? Part of the answer certainly does not lie in the technology itself but in the context of interests surrounding it. A supposedly new technology comes with new economic and societal opportunities – and new risks. That is to say, a new label suits researchers who are seeking to obtain grants just fine. At the same time, it suits technology critics, too.

Again, synthetic biology is no exception to this rule. Scientists use the label "synthetic biology" to set it apart from so-called traditional genetic engineering, which implies that synthetic biology is a non-traditional, modern, and particularly capable technology (Knight 2005). NGOs such as the ETC Group, on the other hand, equate the new label with "extreme genetic engineering", a description in which the adjective "extreme" leads to associations of highly risky undertakings (ETC 2007).

True as this may be, it nonetheless overstates the case if one explains the formation of a new emerging technology label entirely in terms of accompanying interests. Even if the technology itself is in a process of gradual development, the ways in which these technologies are understood and thus further developed, and the concepts in the light of which technologies are formed, may shift in leaps and bounds. Human beings are truth seeking animals, and their understanding of what concepts come closest to a true description of their study objects and intentions

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has an impact on the further development of a technology, just as economic or other interests that are only arbitrarily connected to a science and technology do.

Mainstream synthetic biology incorporates such a shift in conceptual framing. It aspires to move away from genetic engineering guided by trial and error towards a rational design process in which whole genomes can be constructed at the computer. Fast and cheap whole genome sequencing, reliable and affordable gene synthesis, and highly effective genome editing methods such as CRISPR/Cas9 pave the way towards realizing these objectives.

To rationally and reliably design and assemble a complex entity presupposes that the behavior and functions of the complex entity can be predicted on the basis of the behavior of its parts. Many artificial technological objects adhere to this requirement, as we know from experience. With regard to living beings, though, one may suppose that the case is different. After all, living beings are subject to evolutionary change; they interact in multiple ways with their environment; and we even attribute freedom of will to some of them, namely ourselves. Thus, to suppose that living beings can be reliably designed amounts to an ontological hypothesis claiming that the behavior of living beings can be explained in terms of the behavior of their physical parts.

By itself, this conceptual frame is far from new. It can be traced back at least to 17th century Cartesian philosophy and the mechanical animal models of the Renaissance. However, it was not until the discovery of DNA in the 20th century and today's advanced genome editing abilities that purposeful building and rebuilding of long DNA sequences and whole genomes became feasible (Keller 2002). Today, these assumptions form an epistemic, i.e., truth related, conceptual frame that is shaping synthetic biology and guiding it into the future. This frame differs from the guiding assumptions and goals of traditional genetic engineering, which are less systematic and less engineering and design oriented. It is precisely the specific conceptual frame of synthetic biology that adds a decisive element towards an exhaustive explanation of why synthetic biology bears a label of its own.

Building and rebuilding DNA differs from building mechanical animals. A mechanical animal may be regarded as being analogous to, but certainly not identical to, a natural animal, since its physical parts differ from the parts of a natural organism. Building the synthetic genome of a single-cell organism, by contrast, amounts to assembling parts that make up natural organisms as well. Again, in contrast to mechanical animals, the prospect of organisms created by synthetic biology urges the question of whether such a synthetic living being that is indiscernible from a natural living being with regard to its physical and, as one must assume, its emergent properties can be adequately understood as a quasi-mechanical object.

Organisms of synthetic biology inhabit a curious space between artificial objects and natural living beings because they are living beings, albeit constructed and treated as if they were not. If it is adequate to conceptualize living beings as quasi-mechanical objects, then synthetic biology is the technology that ultimately unsettles our – supposedly wrong, from synthetic biology's point of view – deeply entrenched everyday understanding that living beings are something different from, and more than, non-living entities. In addition, the synthetic biology conceptual frame has a bearing on the way in which one perceives ethical and societal impacts of this technology. It is an important task of bioethics, the social sciences, philosophy, and theology to identify, point out, and reckon with these impacts, especially in the early stages of a technological development.[1]

2 Synthetic biology, nanotechnology, and a conceptual challenge

In its quest to reveal the hidden secrets of an object in the object's basic parts, synthetic biology resembles nanotechnology. Nanotechnology, too, is animated by the idea of being able to build and rebuild complex objects by rearranging their parts. The title of the U.S. National Science and Technology Council's (NSTC) report "Nanotechnology. Shaping the world atom by atom" bears witness to this parallel. Unlike synthetic biology, though, nanotechnology literally aims to engineer machines. Nanoscale engineering objects are meant to be non-living entities that are put together at an atomic level. The NSTC does not go to great effort to assess the scientific feasibility of this ideal, but straightforwardly compares nanoscale objects to "Swiss watches": "The products of Swiss watchmakers even several centuries ago proved that human control over the material world had extended downward a thousandfold to the millimeter scale or so. Over the past few decades, researchers have pushed this control down another hundredfold" (NSTC 1999, p.5).

Synthetic organisms, by contrast, are by definition living beings whose nanoscale DNA components have been rearranged in novel ways. One may think of a synthetic cell as the "best shot at a general nanotech assembler, the dream of Eric Drexler and many nanotechnology enthusiasts" (Church and Regis 2012, pp.53f.), but the synthetic cell itself does not constitute a nanotechnology product as it is commonly defined. Even if one envisages the assembling of a functional cell from

1 The main focus of parts I and II of this volume is directed towards such normatively relevant conceptual issues within synthetic biology.

non-living molecules, this is a synthetic biology task, not a nanotechnological one. Nanobiotechnology, the area within nanotechnology closest to biology, comprises the engineering of nanoscale machines, i.e., non-living objects, that make use of or are inspired by biological molecules.

From an ethical perspective, nanotechnology and nanobiotechnology thus present issues of technological control and risk assessment. When confronted with nanotechnology one has to ask: can we responsibly do what we aim to do? Synthetic biology leads to the further question: do we know what we are talking about when we conceptually align the living world with the non-living world? Synthetic biology – bionanotechnology, if you like – is a challenging enterprise not only with regard to risk assessment but also with regard to the use of concepts and metaphors.

If one distinguishes nanotechnology and synthetic biology in this way, the distinction hinges upon the difference between non-living and living entities being as clear-cut as possible. Notwithstanding the everyday self-evidence of this distinction, attempts to spell out precisely what sets the living world apart from the world of non-living entities have kept philosophers and scientists busy since the ancient beginnings of philosophical and scientific thinking.

Biology textbooks typically offer open lists of criteria for what counts as life. These include, for instance, metabolism, homeostasis, growth, stimulus response, reproduction, and adaptation and evolution. When one looks for necessary and adequate properties to explain and sort these criteria one often comes across concepts such as "self-organization" or "self-preservation" (Bensaude Vincent 2009). The prefix "self" is important here because it carries the idea that the behaviors of living objects cannot be explained purely with reference to determining causal forces but need to include the notion of something *reacting to* something else outside of itself. Living beings require a shift from causal explanations towards telos-oriented ones, it is assumed (Boldt 2013).

Which kind of abilities justify such a shift to a telos-oriented explanatory scheme, and whether we are able to reliably detect their presence, remains a debatable issue. Nonetheless, if one maintains that there is indeed a difference between living and non-living entities, the difference will have to be spelled out in terms of these notions.

Heuristically at least, synthetic biology itself maintains the distinction. It is a biotechnology explicitly aiming at restructuring and reinventing the molecular basis of *life*. It does so because objects that possess metabolism, reproduce, and undergo evolutionary change can be more efficient and more powerful technological tools than non-living technologies. At the same time, these properties come with a price. Besides the fact that growth is energy-consuming and reproduction can be unreliable, evolution implies a certain degree of independence of the engineered object's behavior and development from the engineer's initial plans and intentions, to name one ethically relevant property of living beings.

Applying the synthetic biology conceptual frame may lead to an underrating of the relevance of the above point. As long as synthetic biology has not advanced to a stage at which it becomes possible to evaluate single applications, it is one of the most important tasks of bioethics to analyze the conceptual framework of this technology, describe its limits, and compare it to alternative accounts. The engineering and machine framework of synthetic biology and the faith that synthetic biologists place in it certainly deserve such scrutiny, as indicated by statements such as the following:

> Originally, you pretty much had to take organisms as they came, with all the inherent design flaws and limitations, compromises and complications that resulted from the random working of evolution. Now we could actually preplan living systems, design them, construct them according to our wishes, and expect them to operate as intended – just as if they were in fact machines (Church and Regis 2012, p.182).

As becomes evident, the machine metaphor and the engineering framework of synthetic biology shape one's perspective on the abilities of synthetic biology and on the function and behavior of its objects. DNA segments that appear redundant and DNA expression pathways that seem to be unnecessarily complicated are not deemed to call for closer analysis but are classified as flaws. In the same vein, the future behavior and development of a synthetic organism is thought to be safely following the engineer's intentions, disregarding the possibility of unexpected evolutionary change. The synthetic biologists de Lorenzo and Danchin, who otherwise share an optimistic outlook for synthetic biology's general and long-term ability to design reliable synthetic organisms with predictable properties and behaviors, object to the mainstream conceptual frame of their research field: engineering metaphors for gene expression, for example, "represent a straight and overtly simplistic projection of electric engineering concepts into supposedly biological counterparts," they write (Lorenzo and Danchin 2008, p.824).

3 Synthetic biology and existing GMO regulation

Before turning to the possible ethical and societal impact of the current synbio conceptual frame in more detail, it is worth noting that the emergence of synthetic biology takes place within a set of existing laws and regulations, nationally and internationally. Exaggerated promises and expectations notwithstanding, synthetic biology may indeed soon offer useful applications. There are promising approaches within the field of medicine, and energy and the environment are further fields of application.[2] Each application will of course have to conform to established legal and ethical regulation. With regard to short-term applications of synthetic biology, the relevant fields are covered to a large extent by a number of existing national or international regulations.[3]

In the long run, however, synthetic biology's research agenda may lead to products that fall outside the field of established risk assessment procedures and current regulation. Synthetic organisms whose genomes stem from a large number of different sources, for example, aggravate the task of risk assessment. Established risk assessment procedures for genetically modified organisms rely on an evaluation of the known behavior and risk profile of the natural counterpart organism. If the genome of the synthetic organism no longer resembles the genome of any natural species, the basis for a risk assessment procedure of this kind is lacking. What is more, if synthetic biologists one day engineer a synthetic cell containing only non-natural DNA molecules, it will be difficult to classify such an organism as a "genetically modified" one. Most probably, any such organism will not fall within the scope of current GMO regulations (Pauwels et al. 2012).

In all cases it holds that the more encompassing genetic modification and replacement become, the more difficult it will be to assess the risks and apply existing regulations. One way out of the risk assessment challenge may be to encourage step by step genome changes in order to ensure that every novel synthetic organism does have a like and known predecessor. With regard to non-natural DNA organisms, modification of legal regulations will be unavoidable.

4 The synbio story, ethics, and the diversity of research approaches

Assessing applications according to legal and ethical standards is an important ethical, societal, and political task, but not the only one. Given synthetic biology's powerful self-narrative that is shaping the future of this emerging technology as well as its perception of its objects – it is equally important to be attentive to this

2 Societally relevant synbio application scenarios are described by König (in this volume).

3 An overview of legal regulations is supplied by Robienski, Simon, and Paslack (in this volume). Cf. also Kuzma and Tanji (2010).

very narrative, its limits, and alternative accounts of what synthetic biology may be and become.

The constraints of the machine metaphor and the engineering framework of synthetic biology are ethically relevant. For example, how one rates the threat to an existing ecosystem posed by a synthetic organism depends on, among other assumptions, how accurately one believes oneself able to predict the development of the synthetic species. To name another example, thinking along the lines of the design and engineering approach does not restrict synthetic biology to engineering single-cell organisms. On the contrary, it appears natural from this perspective to expect synthetic biology to extend its scope to higher organisms, including humans, as soon as this appears technically feasible. From the contested biocentrist's point of view, ethical questions regarding inherent value and instrumentalization are relevant – to a higher or lesser degree – whenever living beings are subjected to technological interventions according to ends that do not conform to the ends and interests of the organism itself (Deplazes-Zemp 2012). Nonetheless, when one considers human beings, issues of instrumentalization inevitably become relevant, regardless of whether one is operating from a biocentric or anthropocentric ethical foundation. From an organism-as-machine standpoint, these issues are difficult to recognize and understand, let alone tackle.

Paying attention to the current synbio self-narrative, its limits, and alternative accounts of what synthetic biology may be, could contribute to developing accounts of synthetic biology that put less emphasis on the strong design and engineering framework found today. Synthetic biology need not be understood as a technology aiming to rationally design a second nature (Keller 2009). It can also be framed as a technology inspired by and mimicking natural organisms and natural processes of DNA change. Such an interpretation and its application ideals may, for example, help to alleviate safety concerns. One may also envisage synthetic biology as a technology that aims to use DNA and its products without relying on those energy consuming and difficult to control processes such as evolution and growth that are inherently bound to the phenomenon of life (Giese and Gleich 2014). In this case, cell-free systems would count as synthetic biology's poster child. Again, this approach may be seen as safer when compared to synthetic organisms. Cell-free approaches are obviously also less likely to fall victim to concerns that, once single-cell organisms have been equipped with novel synthetic genomes, animals and humans come next.

What the search for alternative stories to describe the core aims and sources of synthetic biology amounts to, then, is an appeal for a diversification of research