Newtons of the leaves of grass

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Certain ethical implications of synthetic biology research go beyond those of genetic engineering.

Most of the ethical debates about synthetic biology have focused on the potential impact of uncontrolled self-replication and spreading of engineered organisms outside the laboratory or their deliberate misuse. But the move from engineering organisms in which mere fractions of genomes have been manipulated to the point where significant portions have been designed by humans poses several new ethical issues, which we attempt to explore here.

Synthetic biology and genetic engineering

Synthetic biology extends beyond genetic engineering by attempting to generate biological systems with new features that might never have existed before as part of any natural living system. To name an oft-cited paradigmatic example, the attempt can include the production of an organism stripped down to a few basic evolutionary functions onto which standardized genomic sequences can be mounted that express abilities tailor-made to specific human interests[1]. One of the latest steps toward this ambitious aim has been the Venter Institute's US patent application under the heading "minimal bacterial genome" in May 2007. In this application, ownership is claimed of an organism that contains a reduced version of the genome of *Mycoplasma genitalium* that is still capable of living freely, growing and replicating. The 'new' organism is meant to serve as a basic platform to be equipped with further, artificially produced genomic cassettes that eventually equip the organism with new capabilities and traits, such as the ability to produce alternative fuels such as ethanol or hydrogen.

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German philosopher Immanuel Kant believed that a "Newton of a leaf of grass" was not just unimaginable, but unthinkable. Today, synthetic biology is setting us down the path toward proving him wrong. (Painting by V.H.F. Schorr.)

It has been suggested that this kind of biology establishes a new field of scientific enquiry that far exceeds the potential of what has been possible from genetic engineering in the past. Whereas genetic engineering traditionally consists of the implantation of a genomic sequence taken from one organism into the otherwise unaltered genome of another organism and its expression in that context, synthetic biology promises to create organisms whose activity, beside basic functions of growth and reproduction, completely follows the scientists' visions. In short, synthetic biology does not just attempt to alter some characteristics of an existing organism: it can create new life forms whose key traits have been largely engineered by humans.

It deserves mention, however, that in contrast to the impression that bold statements in the lay press may give rise to, synthetic biology research is currently a good way off from the point where the creation of life as such will become feasible. After all, the platform organism that synthetic biology relies on when attempting to create new life forms is a modified, stripped-down version of an existing organism, not an organism assembled from separate small molecules in the laboratory. Notwithstanding the fact that researchers are willing to break this barrier too[2], such a project will involve considerable challenges and does not represent synthetic biology's most common aspirations at present.

From manipulation to creation

Given the possible future impact on society and the level of ambition at which synthetic biology is pursued, it does not come as a surprise that debate concerning ethical issues related to this new field of research is beginning to spread, albeit slowly. From an ethical perspective, the advance of synthetic biology might at first glance parallel the emergence of other novel fields of technological research. In these cases, ethical considerations are concerned, first and foremost, with potentially harmful, unintended effects of new technological abilities and, where applicable, with possible intentional abuse of the technology in question. Accordingly, statements and discussion to date referring to the ethical dimensions of synthetic biology have focused on risk evaluation and management. In the case of synthetic biology, specific risks in need of close scrutiny and monitoring are uncontrolled self-replication and spreading of organisms outside the lab, and deliberate misuse by terrorist groups or individuals or by "biodesigner-hackers"[3,4].

Nonetheless, we propose that synthetic biology raises other ethical questions, questions specific to the field. The shift from genetic engineering's 'manipulatio' to syn-

thetic biology's 'creatio' is a shift with considerable ethical significance. In general, it is a matter of unresolved philosophical speculation at what point an entity undergoing continuous changes turns from being one entity into being a new one. In the case of synthetic biology, though, we need not await a final solution to this problem to make plausible the claim that the envisaged synthesis of organisms constitutes an act of 'creation' rather than manipulation. Because synthetic biology's platform organism comprises only those characteristics that are seen as essential for life in general, all features that could more specifically embody an idea of the organism's identity are up to the researcher's intentions and inventions. In synthetic biology, the aim is not to amend an organism with a certain quantity of altered characteristics (that is, to manipulate); instead, it is to equip a completely unqualified organism with a new quality of being (that is, to create a new form of life).

Genetic engineering can be described as softening unpleasant edges of the activity of an organism or plant, or as adding extra value to a plant or an organism beyond the value that it already has for us—β-carotene–enriched 'golden rice' is a case in point. In other words, if we look at nature through the glasses of genetic engineering, we see a world filled with entities that are already useful to us in many respects and that just need some reshaping here and there to perfectly match our interests.

In contrast, synthetic biology does not soften edges, but creates life forms that are meant not to have any edges from the start. It does not add value to an existing organism; it brings into existence something that counts as valuable from our point of view. Seen from the perspective of synthetic biology, nature is a blank space to be filled with whatever we wish.

In some cases, the alteration of an organism using well-established genetic engineering technology may certainly cause more ethical concerns than, for example, the creation of an organism that does not differ from a natural counterpart in any relevant aspect. Such cases notwithstanding, the general thrust of the two different perspectives points in another direction: because the starting point of manipulation is a given organism that is made to fit our demands more perfectly, such changes typically will not be as far-reaching as changes induced by the creation of new organisms, where the image of nature as a blank space almost automatically invites attempts to invent new organisms rather than just reinventing known ones.

The German philosopher Immanuel Kant confidently claimed at the end of the eighteenth century that a "Newton of a leaf of grass" would never see the light of day. The statement "Give me matter and I will assemble from it a living caterpillar" represented, for Kant, a world that was not just unimaginable, but unthinkable. Today, synthetic biology has made the first steps toward proving Kant wrong. Although the creation of life from smaller parts still is an unattained vision, the dividing line between the manipulation of organisms and the creation of life forms is about to be crossed. From an ethical perspective, this shift from 'manipulatio' to 'creatio ex existendo' is decisive because it involves a fundamental change in our way of approaching nature. In this context, the further advance—if ever possible—from 'creatio ex existendo' to 'creatio ex nihilo' would not constitute a whole new way of interfering with nature, but would still be part of the creation approach.

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Changes in the concept of life

Calling an object alive is deeply connected, both historically and systematically, with the conviction that the object in question is to be valued as a (more or less) autonomous agent, a status that artifacts do not share. As a consequence, the way in which newly created organisms are conceptualized has an ethical impact on how life in general is understood and valued.

When describing microorganisms and their signaling pathways, synthetic biology researchers often invoke the computer metaphor of 'hardware' and 'software'[5]. The platform organism that is stripped down to basic organic functions to be able to carry designed and synthesized DNA segments is described as a "chassis" of the complete new organism; standardized DNA segments are compared to "BioBricks" or "Lego bricks"[6,7]; and, as a last example, in a neutral description of the activities and aims of synthetic biology, the organisms in question appear without further discussion as "living machines"[8].

All of this vocabulary identifies organisms with artifacts, an identification that, given the connection between 'life' and 'value,' may in the (very) long run lead to a weakening of society's respect for higher forms of life that are usually regarded as worthy of protection. Researchers should be careful with their use of metaphors, the more so as attempts to actually rebuild life as such for the time being must count as fantasy.

Moreover, even if we ever achieve the goal of synthesizing 'life' from inert starting materials, it will be important to be clear about in what sense these new organisms are 'alive'. Scientific definitions of life[9] are working hypotheses—tools—used in the process of research that do not necessarily cover what counts as life from the everyday-life experience or other perspectives. Scientific definitions of life might be contestable from these perspectives. Again, keeping in mind the difficulties of defining life and the normative dimension of the concept of life, it is important not to prematurely conflate the concepts of 'life' and 'machine' in synthetic biology research.

Human self-conception as 'creator'

From the perspective of synthetic biology, we come to understand ourselves, justified or not, as creators of 'animuncula' (a term that we think captures very nicely the associations that accompany the creation of new forms of life), with all the implications that such a self-understanding might bring with it. 'Faust' or 'Frankenstein' are not just labels imposed on synthetic biologists by a frightened public, as we might tend to believe, but also form stereotypes around which, and in contrast to which, the self-conception of science and society as a whole—once being able to create new forms of life—will inevitably evolve, given the influence and suggestiveness of these ascriptions.

In fact, if synthetic biology as an activity of creation differs from genetic engineering as a manipulative approach, the Baconian *homo faber* will turn into a creator—a creator who does not have to smooth out nature's shortcomings but engineers a 'nature' without shortcomings. Using the abilities of nature through cultivation, manipulation or even exploitation differs from reinventing nature. Assuming all appropriate safety measures are in place, doing so might be justifiable in many specific cases. Nonetheless, taken as a general approach, it might lead to an overestimation of how well we understand nature's processes and our own needs and interests and of how best to achieve them.

Yet as long as the basic contrast between an outlook characterized by the filling in of a blank space with newly engineered organisms and an outlook that starts from what is given

to us has not been taken into account, there will be a danger of unduly overrating the range of applications of the creator's attitude as an ethically acceptable practical guideline.

An extended Asilomar?

In ethical statements on synthetic biology, a common proposal is to establish a code of ethics for synthetic biologists, following the model of the 1975 Asilomar meeting of biologists discussing risk assessment and management of recombining DNA[10]. A first step along this line was taken at the Synthetic Biology 2.0 conference in California in 2006 (ref. 11). If we take seriously the central ethical issues of synthetic biology that have been put forward here, such a code of ethics ought to include a reflection on how synthetic biology's researchers and engineers understand their own activities in the context of society and nature as a whole (in addition to topics of risk avoidance). Such an extended declaration will help to clarify what kind of basic attitudes synthetic biologists think ought to direct their research projects, making explicit at what point synthetic biology research reaches an ethical border. What is more, bearing witness to synthetic biologists' ability to reflect critically on their own role in research and society, such an extended declaration will help to facilitate constructive dialog with a public frightened by the prospect of a world inhabited by uncontrollable numbers of animuncula and their restless creators.

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