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Socrates Untenured

Ethics, Experts, and the Public in the Synthetic Age

Three tools have transformed biotechnology over the past decade and a half. Gene reading has made it possible to quickly sequence the genome of any living creature. Gene synthesis has made it possible to construct DNA sequences in the lab from constituent chemicals. Gene editing has made it possible to place those sections into an existing DNA sequence at any point a technician chooses.

Having these tools at your fingertips transforms how you look at the living world. Organisms are no longer strictly limited by their genetic inheritance. They can be altered, redesigned, and made to do new work. With these technologies, the living world can look more like a self-sustaining, self-maintaining tool for human use than it has ever looked before.

The technicians working with these tools might be driven by their determination to solve problems, by visions of societal good, or simply by their desire for riches beyond imagination. J. Craig Venter, one of the scientists at the center of the development of these technologies, likes to say that the world's first trillionaire will be the person who designs and markets a globally useful bacterial organism. The idea of self-maintaining, biodegradable tools made from organic materials has plenty of appeal. As a result, synthetic biology is booming. Around the edges of this field lie some truly radical possibilities.

MADONNA, a research and innovation project funded by the European Commission, sees biotechnology as the key to a sustainable human future. (According to the project page at www.madonnaproject.eu, the name MADONNA represents "microbial deployment of new-to-nature chemistries for refactoring the barriers between living and non-living matter.") Traditional industry is an "artificial metabolic system" that fails spectacularly to do what natural metabolic systems do with ease: recycle. To create the biochemistry needed for recycling industrial wastes, the MADONNA teams plan to use "chemo-robots" inserted into an existing bacterial chassis to generate the desired metabolic reactions. Over time, the chemo-robots will force the instructions for the desired reaction into the bacterial blueprint, taking advantage of the fact that tweaks to metabolic biochemistry can drive changes in DNA. This direction of change—from metabolism to DNA—means the central dogma of molecular biology (in which DNA is the driver of all organismic activity) becomes only a partial truth. According to the project's website, such an upending of how science thinks about the flow of information in biology will enable giant leaps forward in tackling pressing challenges such as carbon capture, nitrogen fixation, and plastics degradation. MADONNA researchers expect its breakthroughs will "open the door to revolutionary and Earth-friendly products and processes."

Visionary ideas such as these are exciting. They drive innovation forward and motivate people to put in long hours and to think creatively and unconventionally. Advanced biotechnologies may become essential tools to support a human population projected to hit ten billion by mid-century, and advocates seem to believe that they will do so in a way that creates equitable benefits for all.

Such boldness does, however, raise the ethical stakes for these types of biotechnologies far above the standard instrumental considerations about harms, costs, and efficiencies. Kevin Esvelt, a researcher in the Sculpting Evolution group at the Massachusetts Institute of Technology, recognizes the significance of the moral challenges. When discussing gene drives, a technology capable of using gene editing and gene synthesis to crash wild populations of

organisms, Esvelt insists the public should have both a seat at the table and an absolute veto power over development and deployment of such a powerful technology.

"The only way to conduct an experiment that could wipe an entire species from the Earth is with complete transparency," he said in the *New Yorker*. "For both moral and practical reasons, gene drive is most likely to succeed if all the research is done openly." What's more, Esvelt thinks these heightened standards for transparency and process apply far beyond the technology he is currently working on: "if we can do it for gene drive," he says, "we can do it for the rest of science."

Esvelt's willingness to put make-or-break decisions about whether to proceed with a technology in the hands of the public has riled some scientists. They worry about technological development being hampered by the whims of a fickle and potentially ill-informed public. From my perspective, as important as whether the public has veto power over a technological development is the question of whether the full breadth of ethical questions are on the table. Some of the questions that need asking are straightforward and obvious. Others are more veiled.

To begin with the straightforward ones, if technology is thought of as only an instrument, then the obvious questions are whether a proposed technology will prove to be an effective instrument. Can it reliably achieve what it is designed for? Can it achieve those goals without serious undesirable unintended side effects? In a number of cases, answers to these two questions can be elusive. Modeling can supply only so much information. Field-testing can be either too small in scale to provide adequate information or so big that it creates unacceptable risks. This so-called research-deployment dilemma haunts other powerful emerging technologies as well, such as climate engineering.

In the case of gene drives, one of the biggest concerns about their deployment into a wild population is whether a natural resistance will quickly build up and thwart the spread of the engineered organism. Almost all alterations made by humans will convey a selective disadvantage to the organism, something that will work against its distribution through a population. It is not known if evolutionary resistance or population dynamics of a wild species such as a mosquito would permit the spread of a gene drive. But neither does it sound safe to try to find this out on a large scale.

If it turns out the technologies do work as hoped, the next question is whether unintended ecological ramifications will overwhelm the intended benefits. Perhaps an engineered bacterium will swamp a native, beneficial bacterial species. Perhaps a crashed insect population will create room for a virulent alternative disease vector to take its place. When technologies that disrupt long-established biological processes are deployed into complex ecological systems, surprising things happen. For example, one recent study showed that genetically modified mosquitoes deployed on an experimental basis in Brazil changed the genetic makeup of the local mosquito population in ways they weren't supposed to.

What is notable about these sorts of uncertainties is how, if they are resolvable at all (and they may not be), resolution is possible primarily through concerted scientific research. Whereas members of the public can ask the questions about effectiveness and about harms, they cannot provide the answers. They must rely on scientists to inform them about the practicality and safety of a technology. Too often members of the public will be told, in essence, to "shut up and listen to the experts." (Of course, they may or may not comply.)

Hard on the heels of these questions comes another ethical concern about the instrumentality of the technology. Biotechnologies that create new functions in bacteria (e.g., entirely new synthetic organisms or new-to-nature reactions inserted into existing bacteria) or distort the rules of Mendelian inheritance (e.g., gene drives) raise the specter of dual-use. The technology could potentially be co-opted by malicious individuals or groups to cause harm. Diseases could be synthesized and spread indiscriminately, food supplies could be disrupted, and toxins could be added surreptitiously to water supplies. New technologies with global reach targeting basic biological function make the dual-use possibility particularly worrisome.

These types of fears featured prominently in the ethical analysis sponsored by the Woodrow Wilson Center when synthetic organisms first started attracting attention. On one side, this analysis implied, are the research scientists seeking to do good and to solve problems. On the other are the people seeking to use these technologies to cause harm.

As with concerns about the efficacy and potential side effects of a proposed biotechnology, these dual-use concerns are real and ethically significant. Mechanisms need to be in place to prevent malicious use. But similar to the functionality and side-effects questions, the dual-use worries mostly cannot be resolved by the public. To the extent it is possible, regulatory and governance frameworks need to be in place in order to prevent harms. Rigorous enforcement protocols must accompany the technology every step of the way. Once again, the public can raise the ethical concerns, but laypeople often cannot themselves determine when or how these concerns have been adequately addressed. They have to cede the ground to another type of expert, those with governance and regulatory experience.

The ethical concerns mentioned so far, in other words, quickly exit the public domain. They are focused on the instrumentality of the technology. Is it a good instrument? Is it an instrument that can be abused? Experts are needed to answer both.

Such ethical concerns are significant, but they do not exhaust the ethical terrain. There is a different type of ethical question that is not only important, but its capacity for resolution may sit uniquely in the public's lap.

Big technologies don't just serve purposes; they also dramatically reset people's expectations and transform relations with the surrounding world. The automobile was not just an instrument to help people move quickly from *A* to *B*. It changed where people could live and work, what those places looked like, and what people could expect to do with their time. As well as being instruments, technologies are mechanisms for social transformations, transformations of material, economic, and conceptual structures. Like the car, the smartphone, and the home insulin test, synthetic biology will reshape how members of the public interact with each other and change how they think.

Given that emerging biotechnologies such as those envisioned in Madonna are in very early stages of research and development, it may not yet be possible to say how they will change the way people and societies do things. Much of this will depend on the particular form they take and the scale at which they are deployed. It is certainly possible, however, to glimpse how they might change the way people conceptualize their surroundings.

Until this time, genomes were molecular structures mostly inherited over long stretches of evolutionary time. Although humans had nudged these structures in certain directions for millennia and bent them toward their needs through domestication, artificial selection, and (more recently) direct genetic modification, the vast majority of the genome of any living form was always inherited (together with a surprising portion that moved laterally into the cell through viruses and bacteria).

The trio of technologies described above change the contours of this long-standing relationship. Genomes may increasingly be created, designed, and built according to an engineer's express purpose. If these technologies pan out as their promoters are predicting, then the biological world that is *found* will begin to be replaced by one that is *made*. In more and more respects, organisms will be tweaked to serve humans rather than simply be part of the existing context surrounding them.

A decade ago, Joachim Boldt and Oliver Müeller, professors of medical ethics and history at the University of Freiburg, called this development the beginning of the conflation between life and machine. They suspected this conflation would lead to a devaluing of life. More recently, I have characterized it as the onset of a "Synthetic Age." This is an age in which fundamental earth processes that used to be governed by forces outside human power increasingly become an expression of it. This is not just humans being careless with their pollutants and making a global mess. It is a redesign of some of the biosphere's most fundamental processes.

People no doubt will differ vociferously on whether transformations of this kind are desirable. What is essential to note, however, is that these issues are ethical to their core. They are about what relationship humans ought to have with their surroundings, when humans should intervene, and what kind of world they want to live in. They do not speak to the instrumental elements of a technology, but to the conceptual ones. In arenas such as biotechnology, these can be the concerns on which policy is made. Think of the prohibitions on human cloning or human germline editing.

Note also how, viewed through this lens, the desirability of the technology is not something that scientific researchers can resolve simply by conducting more experiments. Nor is it something that regulatory and governance frameworks alone can settle. It is something that the public must resolve through difficult and inclusive conversations. Of all the ethical issues presented by new technologies, then, this is the one that falls most fully and exclusively into the public's hands.

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When the MIT researcher Kevin Esvelt contemplates the power of today's biotechnologies, his insight is to recognize how transformative these technologies are. He is convinced that they demand a serious change in how to practice science. "The single most important application of gene drive is not to eradicate malaria or schistosomiasis or Lyme or any other specific project," Esvelt says. "It is to change the way we do science."

I submit that of equal importance is how these technologies must change the way society thinks about the ethics of emerging biotechnology. Ethics must be open, public, and inclusive. It must address hidden questions of relationship and meaning. It must probe the type of world people want to surround themselves with. These ethical determinations are not, thankfully, the province of experts. They are accessible to all those whose lives will be affected.

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