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Design for Values in Agricultural Biotechnology

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Abstract

Agricultural biotechnology dates from the last two decades of the twentieth century. It involves the creation of plants and animals with new useful traits by inserting one or more genes taken from other species. New legal possibilities for patenting transgenic organisms and isolated genes have been provided to promote the development of this new technology. The applications of biotechnology raise a whole range of value issues, like consumer and farmer autonomy, respect for intellectual property, environmental sustainability, food security, social justice, and economic growth. Hitherto the field has not yet witnessed any deliberate attempt at value-sensitive design or design for values. The reason is that under the influence of strong commercial motivations, applications have been developed first and foremost with simple agronomic aims in view, such as herbicide tolerance and insect resistance, traits which are based on single genes. The opportunities for value-sensitive design appear to be constrained by the special character of the biological domain. Many desirable traits like drought tolerance are genetically complex traits that cannot be built into organisms by the insertion of one or a few genes. Another problem is that nature tends to fight back, so that insects become immune to insect-resistant crops and weeds become invulnerable to herbicides. This leads to the phenomenon of perishable knowledge, which also calls the so-called patent bargain into question. The possibilities for value-sensitive design will likely increase with synthetic biology, a more advanced form of biotechnology that aims at making biology (more) "easy to engineer." Practitioners of this new field are acutely aware of the need to proceed in a socially responsible way so as to ensure sufficient societal support. Yet synthetic biologists are currently also engaged in a fundamental debate on whether they will ultimately succeed in tackling biological complexity.

Keywords

Intellectual property; Complex traits; Sustainability; Trade-offs; Perishable knowledge; Synthetic biology

Introduction

Modern agricultural biotechnology dates from the final decades of the last century. The adjective "modern" is sometimes added as an essential specification to distinguish contemporary biotechnology from age-old forms of human intervention with living nature such as traditional agriculture, conventional plant and animal breeding, and ancient fermentation techniques employed in making bread, beer, wine, cheese, and soy products. This linguistic usage may be slightly pedantic, however,

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as the lay public usually identifies "biotechnology" exclusively with its modern incarnation. While (modern) agricultural biotechnology is based on techniques of genetic engineering and thus involves manipulation on the level of DNA molecules, conventional breeding operates on the macroscopic ("phenotypic") level by selecting and crossing suitable individual organisms in order to create new varieties of plants and animals. As Charles Darwin already pointed out, agricultural practices automatically entail selection even when farmers do not consciously engage in deliberate breeding (Darwin 1972 [1859], p. 93). Similarly, while fermentation techniques are based on the activity of microorganisms (like yeasts), it is only since the investigations of Louis Pasteur that we are aware of this fact and that we can use our microbiological knowledge to improve these techniques. More recently, such knowledge has been supplemented with insights from genetics and molecular biology, thus opening a wide field of application to genetic engineering. Ancient fermentation techniques have thus gradually evolved into what is often called industrial biotechnology (or "white" biotechnology), which deals with the deployment of genetically engineered microorganisms and tailored enzymes for the optimization of industrial fermentation processes. In this chapter, I will however confine myself to agricultural biotechnology (sometimes referred to as "green" biotechnology). This area of biotechnology happens to be very controversial and to raise many ethical concerns. It may therefore be worthwhile to explore the possibilities of value-sensitive design (VSD) and design for values in this particular field.

Main Technologies

The so-called recombinant-DNA (or r-DNA) technology forms the technical core of modern biotechnology. It comprises a set of procedures by which segments of DNA from any organism can be "cut" at specific places and "pasted" together to form new recombinant-DNA molecules, which can be "inserted" into a recipient organism by using one or another method of gene transfer. This core technology uses two different groups of enzymes, which are involved in either "cutting" (restriction enzymes) or "pasting" (ligases). Those enzymes serve as the molecular scissors and glue by which genetic engineers perform their cut-and-paste work. There are a number of ways to insert the new r-DNA molecule (comprising one or more foreign genes from a distantly related or virtually unrelated organism) into the recipient organism. In the early years of genetic engineering, a relatively small piece of foreign genetic material (e.g., the human DNA sequence coding for the production of insulin) was often recombined with plasmids (i.e., circular pieces of bacterial DNA), and those plasmids were themselves used as vectors to be introduced into bacteria, where they would be replicated along with their bacterial hosts (bacterial cloning). The disadvantage of this method was that only relatively small stretches of DNA could be incorporated in plasmids. In the 1980s the introduction of the use of yeast chromosomes instead of plasmids allowed the multiplication or "cloning" of much longer segments of DNA. (Another breakthrough of the 1980s, the polymerase chain reaction or PCR, made it possible for the first time to multiply DNA sequences in vitro, that is, without the need to put those sequences into bacterial or yeast cells.) Other methods of gene transfer are microinjection, whereby the genetic material is injected into the host cell by means of a miniscule glass syringe, and bioballistics, whereby the foreign DNA is coated on tiny metal particles and then shot into the host cell with the aid of a device called a gene gun. Viruses and bacteria are also used as vehicles for transferring genes. In plant biotechnology, *Agrobacterium tumefaciens* has become a popular vector for mediating the transfer of genes to various plants. This bacterial species is a "natural genetic engineer" that transmits part of its own DNA to the plants it infects, all the while

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causing tumor crown galls at the wound sites. Modern plant biotechnology has turned disabled versions of this bacterium into a Trojan horse for the transfer of recombinant genes.

The insertion of a foreign gene into a particular organism only makes sense, of course, if the gene and its function or the protein for which it codes are known. The background knowledge about genes and their functions across a wide array of biological species and taxa is still expanding. Thanks to spectacular advances in the techniques for sequencing DNA, the human genome and the genomes of various other organisms have been completely mapped. The advance of genomics has also shown that many of the older theoretical conceptions of molecular biology (like the Central Dogma that genetic information always flows from DNA via RNA to protein or the idea that a gene is always represented by a fixed stretch of DNA and always codes for one and only one type of protein) are often far too simplistic. In fact, the functioning of genomes has turned out to be exceedingly complex (Griffiths and Stotz 2013). The new discipline of bioinformatics has been brought into being to handle and process the enormous and constantly increasing mass of genomic data. Some of the new insights gained have resulted in new molecular tools, which can be deployed for the benefit of genetic engineering but also to enhance conventional breeding, as happens, for example, in marker-assisted selection (MAS).

History

When the unprecedented possibilities that would be opened up by recombinant-DNA technology were first realized in the early 1970s, molecular biologists declared a temporary moratorium on further experiments in this area to discuss the possible consequences of this new line of work and to devise measures that would allow it to be continued in a responsible way. This unleashed a broad societal debate in which issues of safety and security but also more remote ecological and social consequences of r-DNA technology were extensively discussed. The researchers who were most directly concerned with this type of work finally agreed among themselves that r-DNA experiments could be conducted safely in the confined environment of specially secured laboratories, but large segments of the lay public remained unconvinced. At the end of the 1970s, however, biotechnology was increasingly perceived by governments as an exciting field of technological innovation that would lead to renewed economic growth and restore international competitiveness for western countries. The production of human insulin by genetically modified bacteria, realized in 1978 by the first biotech company, Genentech, was the key event that aroused high expectations.

The huge economic potential of this new field of technology would however only be unlocked, it was thought, if biotechnological inventions were to receive proper legal protection. In the landmark case of *Diamond v. Chakrabarty* concerning the patentability of a genetically modified oil-consuming bacterium, the US Supreme Court ruled in 1980 that “anything new under the sun that is made by man,” whether living or nonliving, can be patented. In subsequent years US jurisprudence explicitly extended patentability to multicellular organisms like plants (1985), oysters (1987), and mammals (1988). Other western countries ultimately followed the American example, albeit with some delays and hesitations. In 1988 the patent offices of the USA, the European Union, and Japan proclaimed the new policy line that DNA sequences and genes would also be eligible for product patents. Their justification was that sequences and genes, when isolated and purified, would be essentially different from their natural counterparts and therefore qualify as inventions rather than discoveries. (This standpoint was later incorporated in the European Directive on the Legal Protection of Biotechnological Inventions of 1998, Directive 98/44/EC.) In a parallel move, the legal protection of plant varieties resulting from conventional breeding by so-called plant breeders’

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rights would also be tightened up. In 1961 a handful of western (mainly European) countries had concluded the first international agreement on plant variety protection, called UPOV after its French acronym (*Union internationale pour la Protection des Obtentions Végétales*). This agreement gave the originators exclusive rights on commercializing their plant varieties but granted other breeders the right to use these varieties as starting material for further breeding (breeder's exemption) and left farmers the freedom to save seed from their harvest for the next planting season (farmer's privilege). In 1991 a new international agreement was concluded (referred to as UPOV 1991), which drastically curtailed the breeder's exemption and virtually annulled the farmer's privilege, bringing plant breeders' rights more in line with patent law (GRAIN 2007). In the eyes of its main beneficiaries, the intellectual property regime also needed to be globalized. Driven by an influential business lobby in the pharmaceutical, biotech, and entertainment industries, the US and European governments used their clout in international trade negotiations to "persuade" reluctant developing countries to accept the (for them often disadvantageous) terms of the *TRIPS Agreement*, which was concluded in 1994 as part of an overall WTO package. The TRIPS agreement (standing for *Trade-Related aspects of Intellectual Property rights*) sets worldwide minimum standards for the protection of intellectual property rights (including patents, copyright, and breeder's rights). It mandates that, with few exceptions, "patents shall be available for any inventions, whether products or processes, in all fields of technology" (art. 27.1). Countries are allowed to exclude plants and animals (other than microorganisms) from patentability, but "Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof" (27.3b). Breeder's rights are an example of a *sui generis* system of plant variety protection. Many developing countries have meanwhile joined the UPOV 1991 agreement to fulfill their TRIPS obligations. In the USA and the European Union, genetically modified crops may even be doubly protected by patents and by plant breeder's rights.

Legislation on intellectual property rights is only part of the legal framework regulating biotechnology. The recombinant-DNA controversy of the 1970s had been "resolved" (or at least temporarily closed) by the introduction of strict safety and security rules for the research labs in which gene-splicing experiments were to be conducted. This set of rules obviously no longer sufficed when in a next stage the new technology was also applied to the creation of transgenic crops and farm animals, which had to grow and live in much less confined settings than secured labs and were often ultimately destined to enter the human food chain. The first field trials with GMOs (genetically modified organisms) occurred in the 1980s. This new stage in the development of biotechnology presented a huge challenge to the regulatory authorities. Largely for historically contingent reasons, the United States and the European Union have devised sharply contrasting policy answers to this challenge. The US response, by and large, has been to treat agricultural and food biotechnology as business as usual, to regulate its final products in the same manner as those of any other technology, and to declare the process by which the products are made (i.e., genetic engineering) irrelevant for regulatory purposes. This type of policy response has been characterized as the "product frame" (Jasanoff 2005). The EU approach to regulation has been completely different. European policymakers consider agricultural and food biotechnology as more than just business as usual and see the process of genetic modification itself as a relevant factor for regulation. This type of policy response has been characterized as the "process frame" (Jasanoff 2005). It implies a much more "precautionary" approach to the possible ecological risks and health hazards of GMOs, separation of GM and non-GM (conventional and organic) product flows, monitoring and traceability, and mandatory labeling of GM foods to ensure freedom of choice to consumers. A similar approach was adopted by policymakers in Japan and South Korea. On the global scale, the

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confrontation of these two opposed policy frames has led two "regulatory polarization" (Bernauer 2003) and given rise to fierce disputes before the World Trade Organization.

Transgenic crop varieties were first commercialized in 1996. Since then a suite of different GM crops have spread to different parts of the world in a rather uneven pattern, determined by varying socioeconomic and agroecological conditions but also by different regulatory frameworks and intellectual property arrangements. The area planted with biotech crops has increased 100-fold from 1.7 million hectares in 1996 to 170.3 million hectares in 2012 (James 2012). The two traits that have most often been inserted into GM varieties are herbicide tolerance and insect resistance. The main agricultural crops involved are soybean, canola, maize, and cotton. Transgenic crops are mostly grown in North and South America and in Asia (especially China and India), while Europe and Africa are the continents with a very low adoption rate in terms of the number of approved varieties as well as of planted area. In Europe, stringent regulation and public distrust are retarding factors, while in Africa it is the very lack of indigenous regulatory capacity and the fear of losing product markets in Europe, along with a shortage of GM crops suitably adapted to African agroecological conditions, which explain the low adoption rate. Adoption may also be influenced by the vicissitudes of intellectual property protection and biosafety regulation, as is illustrated by the case of GM soybeans in South America. At an early stage, Argentina eagerly adopted the so-called "Roundup-Ready" soybean, which had been developed by the US company Monsanto as a GM variety resistant to its proprietary herbicide glyphosate (trade name "Roundup"). The variety was actually without legal protection in Argentina and therefore formally in the public domain, as Argentine law did not allow patents on plants and Monsanto had failed to apply for a plant breeder's right (Correa 2006). This did not prevent Monsanto to claim royalties from Argentina for the use of its "proprietary technology." The US company even went so far as to seize shiploads of Argentine soy meal in European ports and sue for patent infringement there (in the end, European courts rejected Monsanto's claims). Through illegal smuggling from Argentina, glyphosate-resistant soybeans also reached farmers in Paraguay and Brazil, where the new GM variety had not yet been approved by the regulatory authorities. Widespread adoption by farmers in those countries created a *fait accompli*, which was subsequently legalized by a formal approval not based on a careful biosafety assessment. Something similar happened in India with insect-resistant Bt cotton (containing a gene from *Bacillus thuringiensis* that produces a toxin against insects). This variety had been developed by Monsanto and its Indian subsidiary Mahyco. These companies proved unable to retain their intellectual property control over the new variety, after Gujarat farmers had somehow appropriated the transgenic seeds (possibly from testing fields), crossed it out with indigenous varieties, and in the process created a huge market for "stealth seeds" (Herring 2007). The farmers' actions also defied the Indian supervisory agency charged with biosafety regulation, but state and federal authorities in India did not dare to alienate their farmer constituencies by ordering the destruction of GM cotton harvests.

Values and Value Issues

Agricultural biotechnology is still highly controversial. Some objections are ostensibly based on religious views, like the charge that by crossing species boundaries, man is *playing God*. There is also the stigma of *unnaturalness* that is often attached to GMOs. Both charges can be readily combined, as is shown in the work of Jean-Jacques Rousseau, the precursor of modern romanticism. His *Émile ou de l'éducation* can actually be read retrospectively as a radical condemnation of modern biotechnology. The opening sentence states: "God makes all things good; man meddles with

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them and they become evil" (Rousseau 1966 [1762], p. 35). In a later chapter, Rousseau claims that it is definitely nature's (or God's?) intention to keep the various species apart and distinct: "The insurmountable barriers that Nature has placed among the various species, so that they will not become mingled, make her intentions abundantly clear. She has not simply established order: she has also taken effective measures to prevent it from being disturbed" (ibid., p. 359). There is thus no doubt that Rousseau would have opposed attempts to recombine genetic material from different species.

Echoes of Rousseau's romantic celebration of nature are ubiquitous today, especially in food adverts (Doorman 2012). Thus a big Dutch dairy company advertises one of its products, "pure" milk from cows in grassy pastures, as "milk such as Nature intended it to be." But the proponents of modern biotechnology can also speak Rousseau's language, as is testified by the CEO of the industrial biotech company DSM, Feike Sijbesma, in an interview on second-generation biofuels: "We are on the threshold of a green revolution to return to a society living from and with nature" (quoted in Banning 2012). The fact that the most divergent causes can apparently be justified by an appeal to nature should make us wary of the validity of any argument invoking the presumed naturalness or unnaturalness of GMOs.

A value that enjoys wide endorsement in liberal-democratic market economies is *freedom of choice* for consumers. Even if one does not share the religious objections against biotechnology or finds the charge of unnaturalness inappropriate, one would still grant people the right to act on their personal convictions in their personal lives. Mandatory labeling of GM foods might be seen as a straightforward way to secure this right. If consumers are to be given a free and informed choice between GM and non-GM foods, however, then in practice a compromise has to be struck. It is impossible to guarantee that foods that are not labeled "GM" will be 100 % GM-free in situations where both categories of food are admitted to the market. The solution is to set an upper threshold for "contamination" (such as the 0.9 % limit in the EU). A further departure from an ideally free choice for the consumer results from the fact that the whole regulatory machinery set up to secure this choice – proper distances between fields with GM and conventional or organic crops ("coexistence"), separation and tracing of product flows, and adequate liability rules – tends to discourage the production and marketing of GM foods. Ultimately the consumer may end up having only the option of "choosing" non-GM foods. At present, this is by and large the situation in the EU. From a moral point of view, it is far from ideal. In the USA, the situation with regard to consumer freedom is entirely different but not ethically more satisfactory. Here the adopted regulatory model (the "product frame") has effectively excluded mandatory labeling and thus denied consumers the possibility to exercise their right of an informed choice between GM and conventional foods.

The EU regulatory framework is predicated on the assumption that "coexistence" and separation are viable options. Critics of agricultural biotech contest that assumption. Wherever GM crops are being grown and processed into food or other products, inadvertent transfer of transgenes to conventional crops and weedy relatives through pollen transport and the mixing up of seeds in the processing chain are bound to occur. Organic farmers in particular can be economically harmed when their harvest becomes "contaminated" and no longer satisfies customary certification requirements. The risk of contamination becomes especially troublesome with some newer generations of biotech crops. It would hardly be acceptable, for example, when GM plants engineered to produce "biopharmaceuticals" entered the human food chain. Researchers and biotech companies are therefore exploring various possibilities of biological containment (e.g., by making GM seeds sterile) to address the issue of unwanted fallout from the growing of GM crops. The old ethical principle of Hippocrates may apply here: *First, do no harm!*

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A value to which biotech companies attach great importance is *respect for intellectual property*. For them, patents and plant breeder's rights are a just reward for their inventive efforts and allow them to recoup the costs and expenses incurred in creating new GM varieties. Hence they very much lament any unauthorized use of "their" technologies, for example, by farmers who grow "pirated" GM crops without paying them any royalties. Although patents, plant breeder's rights and other intellectual property rights are territorially based, it is striking that companies tend to see their inventions as proprietary also in those countries in which no patents or breeder's rights have been filed. Thus Monsanto claims royalties on the use of GM soybeans in Argentina even though their invention is not legally protected in that country. It is also not unusual for biotech companies to magnanimously "donate" their technologies to humanitarian initiatives for use in countries where they have no markets (as with the WIPO World Intellectual Property Organization Global Responsibility Licensing Initiative), but what exactly do they give away if they have no patents in such countries in the first place? For farmers, property rights are also at stake, but their concern is rather that modern *intellectual* property threatens to erode their *tangible* property. In the old days, when a farmer bought seed from the seed merchant, it truly became his property, that is, he could do with it whatever he liked. He could use it to grow his crop and save seed from the harvest for replanting in the next season (or he could exchange it with his neighbor or even sell it on the market). This age-old practice of seed saving (and seed exchange) has traditionally been at the core of an informal system of crop improvement (De Schutter 2011). Even the first international agreement on plant breeder's rights (UPOV 1961) still recognized the farmer's privilege or the right to save seed on-farm. The rise of agricultural biotechnology would drastically change this. New interpretations of patent law, followed by a drastic revision of plant breeder's rights (UPOV 1991), no longer allow on-farm seed saving. When a farmer buys GM seed from a biotech seed company, it no longer becomes his full property because he no longer acquires the right to make use of an inherent biological characteristic of the seed, i.e., its natural capacity to reproduce itself. In fact, it would be more appropriate to say that the farmer "rents" the GM technology incorporated in the seed for the duration of only one growing season. Or as was stated in a US Supreme Court case, the biotech company "sells the seeds subject to a licensing agreement that permits farmers to plant the purchased seed in one, and only one, growing season" (Bowman v. Monsanto Co. 2013).

While biotech companies demand respect for intellectual property, others fear that the *autonomy* and *independence* of farmers will be increasingly undermined by more stringent IP restrictions on saving seed. The famous report on the International Assessment of Agricultural Knowledge, Science and Technology for Development (IAASTD) expresses "concern about present IPR instruments eventually inhibiting seed-savings and exchanges" (IAASTD 2008, p. 42), thereby restricting the capability of farmer communities to develop locally adapted varieties and to maintain gene pools through in situ conservation – essential to local practices that enhance food security and sustainability (ibid., pp. 43–44).

Debates on agricultural biotechnology also turn on values like *environmental sustainability*, *food security*, *energy security*, *social justice*, *health*, *wealth*, and *economic growth*. The beauty of this beneficent technology, according to some of its adherents, is precisely that it allows us to have it all. From the very outset, biotech champions have raised expectations about unlimited wealth creation along with promises about incredibly benign environmental and socioeconomic effects. It is not unusual, of course, for newly emerging technologies to fuel high expectations, but in the case of agricultural biotechnology, the "cycles of hype and hope" seem to be exceptionally tenacious. In 2008 Hugh Grant, CEO of Monsanto, stated that in his view sustainability means that "we produce more and conserve more simultaneously" (Grant 2008). Biotech makes this possible. It allegedly allows us to produce more food, more feed, more fiber, and more energy all at once and also to protect the environment, thus finally enabling us to escape from Hermann Goering's eternal dilemma of guns versus butter. No hard choices are necessary. Rather than the grim choice "food *or* fuel," so much impressed upon us by the backlash caused by first-generation biofuels, we can have "food *and* fuel" (and much else besides). Even more, agricultural biotechnology contains an internal code that is inherently pro-poor: "The novel thing about biotech is that it's scale neutral. Seeds deliver scale neutrality whether you're a one-acre smallholder in Uganda or a 1,000-acre grower in the Mississippi Delta. And the benefits of using biotech seeds are roughly the same" (ibid.). That may sound too good to be true, and it probably is (for a criticism of the hidden assumptions behind the framing of agricultural biotechnology as pro-poor, see Scoones (2002) and Glover (2009)). At any rate, in 2008 Grant held out the prospect of a new generation of *drought-tolerant* maize varieties, which his company intended to launch in the US Midwest in 2012 or 2013, and which it would subsequently make available to farmers in sub-Saharan Africa with the least possible delay through the WEMA (Water Efficient Maize for Africa) public-private partnership. Meanwhile, African regulatory capacity is being built up in the form of the African Biosafety Network of Expertise (ABNE) in Burkina Faso, nominally an "Africa-based, Africa-owned, and Africa-led" initiative (Vaidyanathan 2010), but funded by the Bill and Melinda Gates Foundation. This network is supposed to smooth the way for the arrival of drought-tolerant GM crops.

In December 2011, the US Department of Agriculture "deregulated" (approved) Monsanto's so-called *DroughtGard* maize, a GM maize variety containing the cold-shock protein gene *cspB* derived from the bacterium *Bacillus subtilis*, which is said to confer drought tolerance. WEMA expects to release adapted versions of this transgenic drought-tolerant maize in sub-Saharan Africa as early as 2017 (James 2012, p. 10). Given the increasing vulnerability of agricultural harvests to extreme weather conditions due to climate change, enhanced drought tolerance of crops might be considered a highly desirable trait. The same holds for improved water use efficiency (WUE), in view of the circumstance that already 70 % of global freshwater is currently being used by agriculture. The key question is whether and to what extent agricultural biotechnology can indeed contribute to the alleviation of periodic drought stress and water scarcity.

Hype Versus Caution

There are several reasons for striking a skeptical or at least cautionary note with regard to the expected environmental and socioeconomic performance of new generations of GM crops. It is a sobering thought that the possibility to insert genes for nitrogen fixation derived from nitrogen-fixing bacteria into nonleguminous crops was already announced in 1981 as a "promise" of the new biotechnology, that this possibility has not been realized until now, and that a recent forecasting exercise (Charles et al. 2010) sets the expected arrival of nitrogen-fixing GM crops beyond a 20-year time interval. So when this early promise is finally realized (if it is to be realized), it will have taken more than 50 years! Surely it would be extremely attractive, both from a socioeconomic and environmental point of view, to have the trait of nitrogen fixation in our crops. Other early promises already made in 1981 were drought tolerance and salt tolerance of plants. But perhaps biotech companies had other priorities during the past 20 or 30 years, such as making crops resistant to their proprietary herbicides – as Monsanto first did by creating GM "Roundup-Ready" varieties of canola, maize, and soybean that would tolerate its registered glyphosate herbicide, an example of strategic behavior that was to be quickly followed by its main competitors Syngenta, DuPont, Bayer, and BASF and that clearly made economic sense (Harhoff et al. 2001).

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It is also plausible that biotechnology is as yet simply unable to deal with serious biological complexity. We have to take account of the fact that the two traits that have been introduced into the currently most widely used GM crops – herbicide tolerance and insect resistance – are relatively simple *single-gene* traits. Traits such as drought tolerance, salt tolerance, and other forms of abiotic stress tolerance (heat tolerance, cold tolerance, light tolerance, etcetera), by contrast, are (genetically and physiologically) *complex* traits involving many genes and complex gene-environment interactions. Moreover, there is also a subtle interplay between different abiotic stress conditions, occasionally reinforcing or mitigating each other. As a recent review article summarized, "The acclimation of plants to abiotic stress conditions is a complex and coordinated response involving hundreds of genes. These responses are also affected by interactions between different environmental factors and the developmental stage of the plant . . ." (Mittler and Blumwald 2010, p. 444). There may therefore be reasonable doubt about the claim that agricultural biotechnology can come to grips with this complexity, despite Hugh Grant's confident announcement that Monsanto's drought-tolerant maize varieties will alleviate production losses from periodic drought occurring in the American Midwest (Grant 2008). Grant referred to field trials showing yield increases of 8–10 % "in dry land corn [maize] environments," but this is of course no guarantee that the same yield increases will actually be obtained in the maize fields of Midwestern farmers, and still less so in sub-Saharan maize fields (African Centre for Biosafety 2013). Supporters of transgene-based drought tolerance have already adjusted their initial high expectations downward (Edmeades 2013, p. 27). It is not even sure that GM drought-tolerant crops will ultimately turn out to be the best answer to the problem of drought stress. Significantly enough, other companies including Monsanto's biotech rivals DuPont and Syngenta have meanwhile launched drought-tolerant maize varieties, in which the desired trait has not been created by genetic engineering but by conventional breeding informed by the molecular technique of marker-assisted selection (Edmeades 2013, pp. 16–20). A critical report issued by the Union of Concerned Scientists concludes that transgene-based drought-tolerant maize is not superior to maize in which this trait has been obtained through conventional means, that Monsanto's variety offers modest protection only under moderate but not under severe drought conditions, and that it shows no advantages at all with regard to water use efficiency (Gurian-Sherman 2012). The lackluster performance of these new biotech maize varieties should not be surprising, as drought tolerance is controlled by many different genes and genetic engineering so far has manipulated only a few genes at a time.

There is a further reason to be cautious about claimed and expected environmental benefits of GM crops. This reason may be summed up in the slogan: *Nature fights back* (Carson 1962, chapter 15). While environmentalists' fears about GM crops often concentrate on the risk that transgenes outcross with wild plants and inadvertently create nasty superweeds, there is also the classical Darwinian scenario that continued use of certain herbicides on a massive scale, enabled and even encouraged by the herbicide tolerance engineered into the crop plants themselves, could act as a selection pressure favoring the development and spread of resistant weeds. What is currently happening in US soybean and maize cultivation is a case in point. Monsanto's "Roundup-Ready" (glyphosate-tolerant) crops have been immensely successful in the USA, where they currently cover 90 % of the soybean area and 80 % of the maize area. In comparison with some older and more aggressive herbicides, glyphosate is relatively benign in its effects on wildlife. Another environmental advantage is that the combined use of glyphosate and glyphosate-tolerant crops enables many farmers to practice low-tillage agriculture, with much less soil degradation and fuel use. Many successive years of glyphosate use, however, have now resulted in at least nine nasty weed species that have gained immunity to this herbicide. The expectation is that by 2015 some 40 % of the cultivation area will harbor resistant weeds. Farmers have to resort to older and less ecologically benign herbicides such as 2,4-D and dicamba, in addition to using Roundup, to kill the new invaders. Agrochemical and biotech companies are meanwhile developing new herbicide-tolerant varieties of soybean and maize with "stacked" transgenes that will not only tolerate glyphosate but also other herbicides (Kilman 2010; Keim 2012). We are thus witnessing an ongoing "arms race" between biotech and nature, which shows that the environmental benefits of agricultural biotechnology are sometimes only temporary rather than durable or truly "sustainable."

For the biotech companies involved, this may be a blessing in disguise. A cynic might even argue that the evolution of weed resistance makes once highly successful herbicide-tolerant cultivars obsolete over time, thus clearing the way for new cultivars to enter the market and reducing the chance that an effective invention reaches the public domain as a generic cultivar after the end of the patent term. For a company like Monsanto, the emergence of glyphosate-resistant weeds at a time when its patents on glyphosate-tolerant crops are about to expire is definitely not something to be deplored (although company scientists had earlier dismissed this very possibility as highly improbable). This process of creative destruction favors private "innovation." Industry scientists claim that the use of new transgenic crops with stacked tolerance traits for glyphosate and other herbicides like 2,4-D and dicamba is not likely to accelerate the evolution of multiply resistant weeds, but other researchers argue that sooner or later the emergence and spread of such superweeds is precisely an outcome that is to be expected (Mortensen et al. 2012). The whole agricultural system seems to be set on "transgene-facilitated herbicide treadmill" (ibid., p. 83). Unfortunately, the knowledge structure needed to practice integrated weed management, which would enable farmers to escape from this treadmill, is simultaneously atrophying, because the relevant type of knowledge does not lend itself to being packaged in patentable and salable products (ibid., pp. 81–82).

Another example of "nature fighting back" is provided by the use of insect-resistant *Bt* cotton in China, which for a series of seven successive years brought lower spraying costs and improved health to Chinese farmers, until in the 8th year a formidable resurgence of "secondary pests" necessitated a much greater and very costly use of previously abandoned pesticides, completely eroding the advantages of *Bt* cotton (Wang et al. 2006). A final example is provided by South Africa, where the African maize stem borer (*Busseola fusca*) eventually developed such widespread resistance to Monsanto's *Bt* maize expressing the so-called Cry1Ab gene (MON810), that the cultivation of this hitherto extensively grown food staple variety had to be abandoned in 2013. Maize farmers in South Africa now pin their hopes on "stacked" varieties that combine the Cry1A.105 and Cry2Ab toxin-producing transgenes, but it might be just a matter of time before pest resistance to these new varieties emerges, especially when appropriate pest management strategies (like maintaining refuges planted with non-*Bt* crops) are not complied with (Van den Berg et al. 2013).

Design for Values?

The foregoing discussion shows that many different values may be at stake in the development of agricultural biotechnology. The question is whether value-sensitive design or design for values can be said also to play a part in this field of technology. Insofar as agricultural biotechnologists deliberately try to "build" certain "traits" into existing crop varieties, their work can undoubtedly be described as a form of design. Yet there are some difficulties that would militate against a straightforward application of value-sensitive design.

One major complication is that this "building" activity occurs mainly at the *molecular* level of DNA, while the intended traits represent *phenotypic* properties of entire organisms that are also

Handbook of Ethics, Values, and Technological Design
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dependent on environmental conditions and genetic background (other genes already present). At first sight it might appear hardly deniable that a gene construct derived from *Bacillus thuringiensis* that codes for the production of an insecticidal toxin actually confers the trait "insect resistance" to the plants in which it has been inserted, but this holds only so long as the target insects have not become immune to the relevant toxin (and also, of course, on condition that the *Bt* transgene will be "expressed" in the plant in sufficient quantity). Thus Monsanto's *Bt* maize based on the Cry1Ab gene no longer protects, as it once did, against the African maize stem borer after the insect developed resistance against the Cry1Ab toxin. With the complex traits involved in various forms of abiotic stress tolerance, the links between genes and traits are even more tenuous and complicated. This is actually a major reason for critics to cast doubt on the expected performance of drought-tolerant GM crops, especially as long as the desired trait is created through the insertion of a single gene. The underlying issue here is whether and to what extent "biology" is indeed amenable to "engineering."

The fact that, say, a new insect-resistant crop can only be temporarily successful but will normally not be a durable innovation, marks a characteristic feature of technological design in the biological domain. The new crop does not simply become obsolete due to further technological change; its untimely depreciation is as it were biologically preordained. In 1973, at a time of rising environmentalist awareness, some German philosophers of science already criticized the scientific-technological view of nature as an infinite reservoir for technical intervention and the concomitant assumption of the endless reproducibility of experimental effects. They used an interesting example to make their point: "The validity of the claim that the chemical substance DDT has an insecticidal effect is warranted by a reproducible experiment. Actually, the experiment has been repeated millions of times, albeit not in the laboratory but through the technical application of DDT. But precisely this large-scale repetition invalidates the claim that DDT is an insecticide, as the massive use of DDT leads to the selection of resistant insect strains" (Böhme et al. 1973, pp. 141–42). This peculiarity of technological design in the biological realm is obviously highly relevant with regard to the *sustainability* of our innovations. We can ill afford to prematurely exhaust the limited natural arsenal of *Bt* toxins by developing GM crops that set up selection pressures accelerating the appearance of resistant insect strains. The fact that much biotechnological innovation represents "perishable knowledge" also undermines the rationale of intellectual property protection. In the standard account of the fictitious contract that is concluded between an inventor and society (the so-called patent bargain), the inventor who discloses his invention by giving a full description of it receives in return the exclusive right to use his invention for a limited period of time. After the expiration of the patent, his invention is supposed to fall into the public domain, that is, it has to be made freely available to society. If, however, the invention "perishes" in the course of the protection period, society will in the end see itself robbed of its part of the bargain. The problem of the "vanishing public domain" is not only relevant for agricultural biotechnology; it also plays a prominent role in the development of new antibiotics and the preservation of the usefulness of existing antibiotics (Outterson 2005). It would seem that the problem calls for some institutional redesign of the system of intellectual property.

The fact that agricultural biotechnology has predominantly been developed in a commercial setting also helps explain the virtual absence of any serious design for values. In the past 20–30 years, most biotech applications have been designed with *agronomic* traits in view. To make GM seeds attractive to farmers, they must offer benefits like increased yields, more resistance to insect pests, or reduced labor needs. The introduction of herbicide-tolerant and insect-resistant GM varieties clearly made sense from this perspective. The development of herbicide-tolerant crops that could in particular withstand the company's own proprietary herbicide (Roundup in the case of

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Monsanto) was also economically smart: it allowed Monsanto to make a relatively smooth transition from an agrochemical to a biotech company. Roundup-Ready soybean, maize, and canola also brought environmental benefits, especially because they stimulated low-tillage or zero-tillage agriculture, although these benefits had not been originally designed, but resulted from farmers' initiatives. One could argue that it would have been morally better to develop new varieties that would not need any herbicide spraying at all, but in the absence of evidence that such options were really within the available design space, the argument remains rather hypothetical. There is a lot of historical contingency in innovation.

It does not always make sense to represent the work of agricultural biotechnologists as if it occurred in some abstract "design space." Such a design space, if it existed, would ideally delineate the various possible combinations of "traits" in plants that can be realized with the available tools of the trade at hand and would also suggest ethically relevant "trade-offs" between different traits (insofar as these traits can be linked to important values). However, in cases where complex traits are under consideration, as with various forms of abiotic stress tolerance, the links with the multiple relevant genes are so complicated that the idea of a clearly circumscribed design space loses its analytical utility. Even a seemingly simple single-gene trait like insect resistance starts to look more complex once we also take into account the likely indirect effects of its prolonged large-scale use on the evolution of the target insects.

Although the alleged inadequacy of a single-gene approach for tackling complex traits is prominently cited by critics to cast doubt on the promises of drought-tolerant GM crops, this point of criticism is also partly accepted by some of the proponents. Thus an otherwise favorable report on drought tolerance in maize comments: "Drought tolerance is a genetically complex trait, so it is reasonable to expect that a successful transgenic strategy will rely on transcription factors and cascades of genes, or transformation with several transgenes affecting different but key processes. *However, current attempts appear to be focused on single genes*" (Edmeades 2013, pp. 20–21; my italics). Here it is admitted that the current biotech approach falls short of what is considered the ideal strategy. What is described as such ("cascades of genes . . . affecting different but key processes") actually looks quite similar to what is also known as *metabolic engineering*, whereby entire biochemical pathways controlled by networks of concatenated genes are being installed in a host organism. Metabolic engineering is an important set of tools for the emerging field of synthetic biology. A famous example is the creation of a complete new biochemical pathway, controlled by 12 genes from three different organisms, in yeast cells for the production of a precursor of artemisinin, a medicine against malaria, by Jay Keasling's team in Berkeley, California – a landmark achievement that figures as a poster child for synthetic biology.

Synthetic biology is described by many of its practitioners as the attempt to make biology (more) easy to engineer. In their eyes, what passes for "genetic engineering" in classical biotechnology hardly deserves this term at all or can only be considered a very primitive form of engineering. Critical NGOs like the ETC Group, by contrast, tend to portray synthetic biology as "extreme genetic engineering," thus emphasizing the continuity with biotechnology. It is useful to keep in mind that no clear dividing line can be drawn. Synthetic biologists aim to create standard biological systems from standard devices which in turn are produced from well-characterized standard parts. Their designs have to satisfy the engineering requirement of modularity, so as to ensure predictable performance when different parts are assembled together to form a new system. Currently, the program of synthetic biology is more a promise than a reality, although many synthetic biologists all over the world are trying hard to turn the promise into a reality. The success of a new paradigm, as Thomas Kuhn already famously noted, is "at the start largely a promise of success" (Kuhn 1970, p. 23). Only time can tell whether synthetic biologists will ultimately succeed in effectively taming

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unwieldy biological complexity. It is clear, however, that this effort is confronted with huge challenges (Kwok 2010). Practitioners respond differently to those challenges. Some reaffirm their confidence that the new field will indeed rise to the occasion (Kitney and Freemont 2012), while others profess the value of humility in the face of the overwhelming complexity and unpredictability of the biological world (Agapakis 2014). The dominant attitude in synthetic biology is arguably still one of Promethean overconfidence, as testified by the frequently repeated claim that the range of useful applications that synthetic biology potentially holds in store is "only limited by our imagination." This attitude may boost confidence but is not conducive to a serious evaluation of the moral dilemmas to which the application of synthetic biology may give rise. It easily leads to a denial of all constraints, so that everything is possible and no hard choices need to be made between different ends. This is not to deny that technology, including biotechnology and synthetic biology, may relax existing constraints and thus help to create room for striking more acceptable trade-offs between competing values. What offers grounds for hope is that serious attention to ethical and social aspects of new applications forms an integral part of the international iGEM International Genetically Engineered Machine student competition, which works as a training ground for attracting new recruits to synthetic biology. Practitioners may thus gradually learn to overcome their overweening confidence. In Europe, finally, the wish to avoid another GMO debacle (the rejection of GMOs by a large part of the population) is a strong motive for policymakers to support initiatives for what is currently called Responsible (Research and) Innovation. This too affects the social matrix in which synthetic biology will evolve.

In the near future, gene technologists may become more fully aware that "design for values" is the name of the game. One major technological challenge for biotechnology and synthetic biology is to solve the harsh dilemma of "food *or* fuel," which gained visible prominence by the backlash of higher food prices and deforestation that followed the first wave of enthusiasm for "first-generation" biofuels. More advanced (second, third, or fourth) generations of biofuels, based on various foreseeable breakthroughs and milestones, are expected to loosen up or even overcome the trade-off between the two major competing uses of the world's biomass. Such expectations could be no more than merely the beginnings of another cycle of hope and hype (Bindraban et al. 2009), but the adherents of biotechnology and synthetic biology are convinced that the dilemma is ultimately going to be solved, so that in the end we can have our fuel and eat it too (Graham-Rowe 2011). It would make an excellent test case for design for values.

Cross-References

► Conflicting Values in Design for Values
► Design for Sustainability
► Ibo van de Poel

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