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Industry 5.0—The Relevance and Implications of Bionics and Synthetic Biology

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ABSTRACT

Bionics (the imitation or abstraction of the "inventions" of nature) and, to an even greater extent, synthetic biology, will be as relevant to engineering development and industry as the silicon chip was over the last 50 years. Chemical industries already use so-called "white biotechnology" for new processes, new raw materials, and more sustainable use of resources. Synthetic biology is also used for the development of second-generation biofuels and for harvesting the sun's energy with the help of tailor-made microorganisms or biometrically designed catalysts. The market potential for bionics in medicine, engineering processes, and DNA storage is huge. "Moonshot" projects are already aggressively focusing on diseases and new materials, and a US-led competition is currently underway with the aim of creating a thousand new molecules. This article describes a timeline that starts with current projects and then moves on to code engineering projects and their implications, artificial DNA, signaling molecules, and biological circuitry. Beyond these projects, one of the next frontiers in bionics is the design of synthetic metabolisms that include artificial food chains and foods, and the bioengineering of raw materials; all of which will lead to new insights into biological principles. Bioengineering will be an innovation motor just as digitalization is today. This article discusses pertinent examples of bioengineering, particularly the use of alternative carbon-based biofuels and the techniques and perils of cell modification. Big data, analytics, and massive storage are important factors in this next frontier. Although synthetic biology will be as pervasive and transformative in the next 50 years as digitization and the Internet are today, its applications and impacts are still in nascent stages. This article provides a general taxonomy in which the development of bioengineering is classified in five stages (DNA analysis, bio-circuits, minimal genomes, protocells, xenobiology) from the familiar to the unknown, with implications for safety and security, industrial development, and the development of bioengineering and biotechnology as an interdisciplinary field. Ethical issues and the importance of a public debate about the consequences of bionics and synthetic biology are discussed.

1. Another paradigm shift

Industry 4.0 and similar concepts, such as Make in China 2025 or Digital Industries, are all still incompletely defined and awaiting more development before they become an industrial reality. These concepts and their implementation have followed a well-known path: Initially limited in scope, they became hugely enlarged after some time, as the political, academic, consulting, and finally enterprise communities latched onto them and re-interpreted them to suit their own agendas. Practical considerations were addressed by dozens of essentially similar books that mixed the original limited concepts with digital disintermediation theory and practice, and included high use of the word "transformation" in word counts. However, these concepts have not yet

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deeply impacted the business models and shop floors of successful German and Chinese companies. Courses and programs to help companies implement these changes are now widespread. Predictably, public debates have begun on what Industry 4.0 and related concepts mean for societal change and, particularly, for jobs. The public appear to have shifted their attitude from indifference to mistrust, as April 2016 findings by the German Allensbach Institute show.

Cloaked at first as fairly harmless debates (often among human resources (HR) departments and unions) under headings such as "Industry 4.0 and the Future of Work," an alarmist variant of these debates now suggests that, at least in richer societies, we should immediately take action and provide everybody with a basic government-supplied income to prepare for the day when robots do all the work and essentially take over. Concrete figures for such a condition-less basic income are already being discussed.

This article explores at first bionics (the imitation or abstraction of the "inventions" of nature) and then focuses on synthetic biology—which, this author insists, will be as relevant to engineering development and industry as the silicon chip was during the last 50 years [1,2]. While concepts such as smart cities and Industry 4.0 shine a spotlight on the process states enabled by digital/Web-based technologies, the changes brought about by synthetic biology are more fundamental and foreshadow a tectonic, disruptive, and even geostrategic shift: Industry 5.0.

What have we learned from previous industrial transformations? Will our experiences help us to handle Industry 5.0 better, or will the transitions from one industrial paradigm to the next continue to be destructive, brutal, and socially upsetting? This author's action research with several industries, including Germany's premier industry, the automotive and mobility industry, indicates that the implications of these fields are still inadequately understood and hardly anticipated in strategic plans.

2. Bionics

Bionics is a conceptual precursor to synthetic biology. In bionics, we try to imitate structures and processes created by evolution that we consider to be useful or from which we hope to learn. Bionics is a multidisciplinary field that involves scientists, engineers, architects, philosophers, and designers. Based on their various insights, we systematically investigate how nature has successfully solved a problem; then we attempt to copy or redesign the process or object under study in a manner that is divorced from nature. Bionics has branched off into many specialized fields, including construction bionics, sensor bionics, structural bionics, dynamic bionics, neurobionics, building bionics, process bionics, climate bionics, anthropobionics/robotics, and evolution bionics [3].

When classifying the astonishing inventions of nature that are imitated in bionics, a distinction is made between analogies in processes or products, and abstractions. Examples of analogies include airplanes, spiroid winglets, new car tire profiles that are modeled on cats' paws, and spiderlike robots with autonomous legs. Examples of abstractions include the lotus effect for self-cleaning surfaces, building elements that are modeled like trees or bones, riblet foils to reduce friction (in imitation of sharkskin), and Velcro (in imitation of burrs). Other examples of abstractions include swarm intelligence and ant algorithms, which create ant-like autonomous system behaviors (sometimes with ant-like robots, as showcased recently at the 2016 Hanover Fair).

3. Bioeconomy

The so-called bioeconomy is not the focus of this contribution. However, a brief mention should be made of the concept of bioeconomy, in order to delineate it from synthetic biology. For example, Germany has established a National Research Strategy BioEconomy 2030 with five priority fields of action: global food security, sustainable agricultural production, healthy and safe foods, the industrial application of renewable resources, and the development of biomass-based energy carriers. The general idea is to position Germany as a dynamic research and innovation center for bio-based products, energy, processes, and services. Research is supposed to meet responsibilities for global nutrition, as well as for the protection of the climate, resources, and the environment. Numerous pillars of German bioeconomy research, such as the Helmholtz Association of German Research Centers (HGF), which include plant, environmental, geological, climate, biotechnology, and engineering research; the Max Planck Society (MPS) in life sciences; more than a dozen institutes in the Gottfried Wilhelm Leibniz (WGL) science community; and institutes within the Fraunhofer Society (FhG) have all pooled their resources to establish a broad research environment. Over 30 000 scientists in Germany are currently pursuing biotechnical questions and issues across more than 200 research facilities, which include 63 universities, 26 technical colleges, 104 non-university research institutes, and nine government-affiliated sites.

4. White biotechnology

White biotechnology, also called industrial biotechnology, applies science to living organisms and their products. In contrast to synthetic biotechnologies, white biotechnology uses the existing biodiversity of nature in order to establish industrial processes, which are often linked to expectations of ecologically beneficial effects. White biotechnology has old roots; humans have used living microorganisms in the production of breads, cheeses, beers, and wines for centuries. Today, enzymes and microorganisms are contained in many everyday items, ranging from detergents to creams, and including high-value chemicals, drugs, and vitamins; they are also used in textiles, paper and leather production, and the production of antibiotics. White biotechnology has strong links with bionics; for example, in the use of enzymes, the recreation of spider silk with the help of bacteria, and the production of highly elastic rubbers from plants other than rubber trees. It encompasses many disciplines, including the bio-sciences, chemistry, physics, information science, and the engineering sciences. The research landscape of white biotechnology typically consists of institutes in collaborating clusters.

5. Synthetic biology

Synthetic biology dramatically shortens the time required for evolution to occur [2,4]. In German popular newspaper headlines, this engineering science has been variously labeled "Tailor-made Life," "Lego of Life," "Life from Nothing," and, ominously, "Remedy and Horror." The field attracts more and more attention; Oxford University Press announced a journal devoted to it in April 2016. In Germany, the Biotechnology 2020+ project (www.biotechnologie2020plus.de) brings together the major research institutions and networks in this field.

Synthetic biology is an attempt to reshape creation, and is part of a long tradition [3]. Wheat fields, for example, are not a natural phenomenon, but a human artefact. As scientists, we are continuously developing our understanding of the artificial. The nanoscale world of cellular building blocks is awe-inspiringly complex, and would be impossible to access without modern computers, data analytics, and vast storage capabilities. One important discipline of synthetic biology, DNA sequencing and synthesis, follows Moore's law and develops exponentially: While the first genome cost billions of dollars to sequence, an individual genetic test now costs only a thousand dollars and is expected to decrease in cost to just a few cents by 2022. The six years between now and then will likely see the equivalent of more than half a century of development and engineering advances, compared with past development.

5.1. The look and "feel" of synthetic biology

What is the look and "feel" of synthetic biology? Examples are more illustrative than lengthy abstract descriptions. Here are some examples that already exist, or that indicate the directions of these novel technologies.

- Ginkgo BioWorks has an engineering platform with which it creates standardized microbes, or "biobricks," for all kinds of industries, while simultaneously contributing to an open-source registry of biological parts.
- Protein Sciences uses worm cells instead of chicken eggs in order to develop novel vaccines, and hopes to disrupt the vaccine market by being able to scale faster than older methods.
- National Aeronautics and Space Administration (NASA) has been investigating alternative foods for a long time. Seaweed has great nutritional value, and several algae companies, including Aurora Algae, Blue Marble Biomaterials, and Solazyme, are working on improving this value. Artificial meat grown in bioreactors is a very attractive commercial target.
- At the Centre for Synthetic Biology and Innovation at Imperial College London, scientists are trying to feed pigeons a harmless lab-created microbe in order to make pigeon droppings much more environmentally friendly—thereby saving cities' considerable cleaning costs.
- Under the title Living Foundries, the Defense Advanced Research Projects Agency (DARPA) is experimenting with repairing systems with the help of biology. Smart maintenance, indeed. One day, such technologies will be applied in disaster areas.
- Sample6 Technologies develops sensors that detect harmful bacteria in the food industry in real time. Future markets include healthcare, retail food chains, and water industries.
- Along with several industrial and public partners, Codexis is developing microbial genomes (bio-catalyzers) with the capability to capture extraordinarily large amounts of carbon dioxide, in order to reduce emissions and costs and to be able to store carbon in alumina and fertilizer products. Imagine earning money from carbon dioxide!
- With the introduction of a tube of frozen, synthetically altered microbes, Mars could be terraformed and colonized. Photosynthetic algae and bacteria would trigger the development of a Martian habitable environment. Bacteria and synthetic biology are the enablers of the colonization of other planets.

These vivid examples show the potential and scope of synthetic biology. The following sections focus on the engineering foundations of synthetic biology.

5.2. Virtual evolution

Code engineering in synthetic biology will lead to virtual, rapid, and often strange evolutions [5,6]. The structural analyses of proteins will be made easier because we will be able to change proteins artificially. Clustered regularly interspaced short palindromic repeat (CRISPR), a recent innovation that enables alterations to any part of the DNA chromosomes without introducing unintended mutilations and flaws, and an advance made in the creation of "genome vessels" by Craig Venter and his team (the latter innovation, which was publicized in March 2016, cost a paltry 60 million dollars) open up the perspective of targeting synthetic drugs directly at affected tissue, without the usual side effects to the whole human system. Proteins on a chip will serve as sensors in diagnostics. New biomaterials can be created as implants, bone replacements, or as dialysis minilabs, if not as outright kidneys. Industrial enzymes will help to replace fossil oil-based chemical processes with biological processes. New minimal organisms will emerge as building blocks for a new biological diversity. Bio-machines will turn straw into biofuel, and will capture carbon dioxide from the atmosphere. Our artificial evolution will create living, surviving artificial cells and new biological species.

5.3. Artificial nucleoid acid structures

The challenge lies in the programming of biological cells to create artificial cells with new functions, or cell-like structures called bioreactors. If we can reprogram the behavior of organisms, we might be able to deploy nanotechnologies to create totally new sensors, nano factories, and nano production lines; we could use nano containers that liberate their contents when triggered by the environment. Nano switches also seem possible.

However, DNA itself is determined and influenced by a complex environment of proteins, lipids, and polysaccharides, and much work needs to be done to fully understand these interrelationships.

5.4. Biological sensors and toggle switches

We already use signal molecules in medical diagnostics, for example as so-called markers indicating early stages of illnesses. Synthetic biology will enable us to build very small toggle switches needing only a small amount of memory. New oscillometers, spectrometers, and other intelligent measurement devices will emerge from new types of biology-based signaling, including very small devices for immediate, instant, and personal use, with enough intelligence within the device or in the cloud to provide actionable advice—or even to take action and issue alerts when necessary. The switching mechanisms will have yet another function: They will switch off resistance to certain types of drugs, such as the antibiotics resistance of certain tuberculosis bacteria.

DARPA is currently coordinating an active competition calling for the creation of a thousand new molecules. How much "toy biology," that is, amateur activity, will these capabilities create?

5.5. The extremes of synthetic biology

Synthetic biology keeps the dream of everlasting data storage alive; digital data can be encoded onto strands of synthetic DNA.

In space, synthetic biology is expected to free astronauts from previous payload restrictions by allowing processes that can evolve over time and provide a synthetic environment of superior quality.

5.6. Creation of new metabolisms and biofuels

The creation of new food chains is one of the urgent challenges of synthetic biology; for example, the sustainable use of raw materials with the help of biotechnical processes [7]. In some cases, this will involve the genetic removal of toxic inhibitors, or the production of new combinations for new aromas and tastes. This premise goes far beyond artificial meat into strange yet exciting possibilities [8].

Combinations of technologies with enzyme engineering (e.g., fermenting processes) will provide cost-efficient new basic materials for the pharmaceutical industries, and will also create new biofuels. Major insights into as yet unknown or undetected biological principles can be expected as a byproduct of these new analytical and synthetic methods.

Because of their high energy density, we still need carbon-based fuels. With the help of phototrophic or future heterotrophic organisms—so-called bioreactors—second-generation biofuels will use the whole plant and not just 4% of it as is used today [9,10]. The production of oils and fatty acids might be genetically optimized at the molecular level, creating biodiesel and synthetic diesel. Photosynthetically active organisms will be used to produce isobutene and isoprene as bases for iso-octanes [11].

Through cloning and the combination of genetic groups, bacteria might be induced to produce and then secrete fatty acids in large quantities, as bioreactors. However, living cells will need to be kept stable and alive, despite these strong manipulations and interventions. We can expect a few bioreactor "meltdowns"!

6. Innovation and economic potential

In terms of turnover, industrial biotechnology as yet constitutes only a one-digit percentage of the overall turnover of the chemical industry worldwide. Biofuels, enzymes, antibiotics, vitamins, and amino acids are some of its products, for applications such as medicine, human food, animal feed, detergents, and other industries.

In the near future, second-generation bio-products will supplement classical methods of mutation and genetic selection. The new methods include metabolic engineering and system biology, that is, genetic changes in organisms, or the introduction of donor genes from other organisms. New metabolisms will help to generate building blocks for new, specialized plastics. Artemisinin (against malaria), hydrocortisone, and penicillin will be produced in yeasts, provided that this can be done naturally, in relevant quantities, and at acceptable cost.

Interdisciplinary work will accelerate these changes. Bioinformatics and genome research are already strongly linked. Many more chemicals will be produced with biotechnology rather than being extracted from the earth. New raw materials are emerging, such as the use of algae for photovoltaic coatings, in connection with light.

7. The heaven and hell of synthetic biology: Biosafety and biosecurity

Synthetic biology contains both "heaven," in terms of opportunities for a better world and untold benefits for humankind, and "hell," in terms of opportunities and possibilities for misuse. To understand the implications inherent in this field, it is useful to order the developments within synthetic biology [1,12] from the known to the unknown (with examples).

- Known: DNA synthesis, with the characteristics of synthetic genes, artificial chromosomes, synthetic viruses, and the synthesis of whole genomes;
- Known: bio-circuits, with genes, bio-building elements, biobricks, metabolic engineering (e.g., for medical drugs), and international competitions;
- Current: minimal genomes, involving synthetic top-down biology, the reduction of the genomes of living organisms, and the exploitation of transport functions for genetic circuits;
- Unknown: protocells, involving alternative biochemistry, artificial phospholipids, cellular vehicles without key elements of life, synthetic cells, synthetic bottom-up biology, the production of whole cells, and genetically engineered machines; and
- Totally unknown: xeno cells, involving alternative biochemistry, XNA ("alien" life), unknown amino acids, the rearrangement of genes, the development of new ribosomes, xeno organisms, and chemically modified organisms (CMOs).

Protocells, let alone xeno cells, are a possible source of infection. Once established in the environment, there are no adequate control mechanisms for these cells. National laws and international agreements are meant to safeguard against the unintentional liberation of new organisms. Scientists are agreed that a biological parallel world will have to be preserved in enclaves and protected by "genetic firewalls" [13].

Bioterrorists and developers of biological weapons may potentially use synthetic biology. This particular threat is often known by the remarkable euphemism, "dual use." In the past, there have been (benevolent) incidents of a deliberate increase in the virulence of a cowpox strain, the emergence of a new infectious virus in the production of a polio virus genome, and the deliberate lessening of virulence in an inoculation drug against smallpox.

The 2004 *A Synthetic Biohazard Non-Proliferation Proposal* is in need of international updating. Open-source biotechnology makes it difficult to self-regulate the industry, or mitigate safety and security concerns.

In another discipline, computer science, we considered the threat of misuse to be irrelevant for a very long time. This author organized a mobile telephone security conference at a time when nobody thought mobile phones could be attacked, and the conference was a failure. Today, the overwhelming majority of Internet traffic is spam, mobile telephones are under attack, and the costs of Web security are rising rapidly. By analogy, I would argue that—on top of an academic and public debate about the consequences of bionics and synthetic biology—we need much more radical, internationally agreed-on, and smart approaches to improve and maintain safety and security in the application of synthetic biology. Do we need international biosecurity oversight institutions? Yes, with robust competencies!

In the US, biosecurity against malicious activity is a major concern. The emphasis in Europe is on biosafety (safe research) and on engaging with the public. Are our current risk-management provisions sufficient? Probably not, in view of the unknown risks and potential military opportunities/threats from these technologies [14]. This author expects that self-destruct mechanisms will become an increasingly natural part of advanced synthetic biology research and practice in order to mitigate accidents.

Advisory bodies for the German Bundestag are currently working on a policy document intended to mitigate synthetic biology risk.

8. Geostrategic shift

Bionics industries exist in many countries. However, synthetic biology has a much more uneven distribution, and, as an important engineering industry, has a relatively feeble presence in Germany, even if policy documents seem to indicate otherwise. In Holland, three major universities have agreed to pool resources. China, in particular, stands to gain due to its massive investment in the field and to a more relaxed regulatory environment. However, as we have seen with digitization, unexpected results occur as industrial paradigms unfold, and it is yet to be seen which countries will take a lead role in Industry 5.0, and which countries will benefit most.

9. The necessity of an academic and public debate

From previous industrial paradigm shifts, we have—*post hoc*—learned the necessity of an engaged academic and public dialogue. Industry 4.0 has already triggered a debate about what it will be like to live alongside robots in the future. Industry 5.0 discussions touch on the very essence of humanity's existence, physical integrity, and relationship with nature. At the moment, this debate seems theoretical, yet it will soon come to the fore.

As usual, technical advances are ahead of the public debates. A synthetic biology open language (SBOL) is already in place. The field is defined by engineers, and the benefits are couched in engineering terms; that is, engineered biological systems will process information, manipulate chemicals, fabricate materials and structures, produce energy, provide food, and maintain and enhance human health and our environment [10].

Important questions remain as to control of and access to the products, and who will benefit. Should we grant patents on living organisms? How much bioengineering of human embryos is acceptable? How much biological retro-engineering of living humans can we afford or will we permit?

Through scenarios and case studies, we must create awareness of the implications of synthetic biology. As an interdisciplinary field, it needs to be integrated into many courses of studies. For example, the universities of Oxford, Bristol, and Warwick have founded a joint doctoral program that admits students from engineering, biology, biochemistry, physics, plant sciences, chemistry, statistics, mathematics, and computing. In addition, synthetic biology research should be developed with a global, open dialogue about the scientific, social, and economic implications, without shying away from a public debate about the ethical aspects of this emerging field.

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