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Scenarios on the future of biotechnology

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Abstract

The major areas of research and development in biotechnology are maturing at a rapid rate, and may soon converge with one another. These emerging biotechnology areas range from the development of new medicines and drugs, genetically engineered foods, biologically controlled industrial manufacturing processes, and biologically based computing devices to the creation of new industrial materials and devices based upon biological structures and the use of biotechnology in food production. Each of these research areas carries the potential for strong societal reaction. To explore the potential impact of biotechnology on society, two fundamental drivers that influence societal acceptance of biotechnology are described. First, the extent to which technological integration proceeds may strongly impact the way society uses and perceives biotechnology. Second, the degree to which the public eventually accepts biotechnologically derived products and processes as legitimate and reliable alternatives to current products may shape both market demand and public policy. Taken together, these drivers suggest four discrete alternative scenarios for the future of biotechnology. Implications of these scenarios are discussed. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Biotechnology; Bioethics; Genetic engineering; Product development; Scenario planning

1. Introduction

From its earliest agrarian settlements onwards, humanity has consistently sought to control its natural environment. Crops were bred to provide for more nourishing foods, and in the process grass was bred into corn. Livestock and pets were domesticated through the hundreds

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of generations of controlled breeding. Healing salves and remedies were developed from cultivated roots and herbs. Although the principles of genetics were not known to these early pioneers, they still succeeded in planting the foundation for society as we know it today.

Many millennia later, as the industrial revolution swept across Europe, the theoretical and experimental groundwork for physics, chemistry, and modern engineering and mathematics blossomed amidst the literary, musical, and artistic enlightenment that revolutionized society. Biology was not left behind. From the 17th to the 20th centuries, a myriad of advances pushed forward our understanding of both our natural world and our place within that world. From the invention of the microscope to the founding of modern genetics, from the first observations of cells and chromosomes to the experimental studies on cellular biochemistry, biologists made substantial advances in their understanding of the cellular and molecular basis of life (see Fig. 1). The pace of discovery has only increased in this century, so that by the turn of the millennia, humanity is on the verge of mapping out every gene, protein, and cellular process within our body.

As our understanding of biology grew, the early and continuous desire of humanity to harness the world around us led several biologists and businessmen in the late 1970s to consider whether it might be possible to leverage the exponentially growing knowledge of molecular and cellular biology into products that could be sold on the open market. With that concept came the birth of the biotechnology industry. The biotechnology industry as we know it today was borne with the founding of Genentech in 1976. From that early and singular beginning, the number of companies focusing exclusively on biological products and processes increased globally to more than 5,500 today, an enormous increase in a relatively brief period of time. Only 25 years after the founding of Genentech, more than 2,200 products are in development, and there is explosive growth in both the development of technological platforms and in crossdisciplinary research.

2. Current state of the biotechnology industry

From a market perspective, there is substantial reason for optimism regarding continued industry growth. Worldwide product sales have increased 20% this year to \$13 billion [1,2], driven in part by growing alliances with pharmaceutical and fine chemical companies. Progressively greater market sophistication regarding valuation methods is gradually promoting greater stabilization of the share prices of public companies. With the age of the industry approaching 25 years, there is now a critical mass of strategic and operational knowledge available to guide senior management in charting the course of their companies. Finally, demographic shifts are influencing the need for life sciences products. In particular, the aging of our global population is contributing to a demand for health care products and services focused on sustaining the quality of life.

The biotechnology industry is being stressed by several threats and challenges. Historically, public perception regarding the use of biotechnology products has been ambivalent at best, and there is currently a wave of consumer caution and uncertainty regarding many products, especially for food products. Public bias against agricultural biotechnology

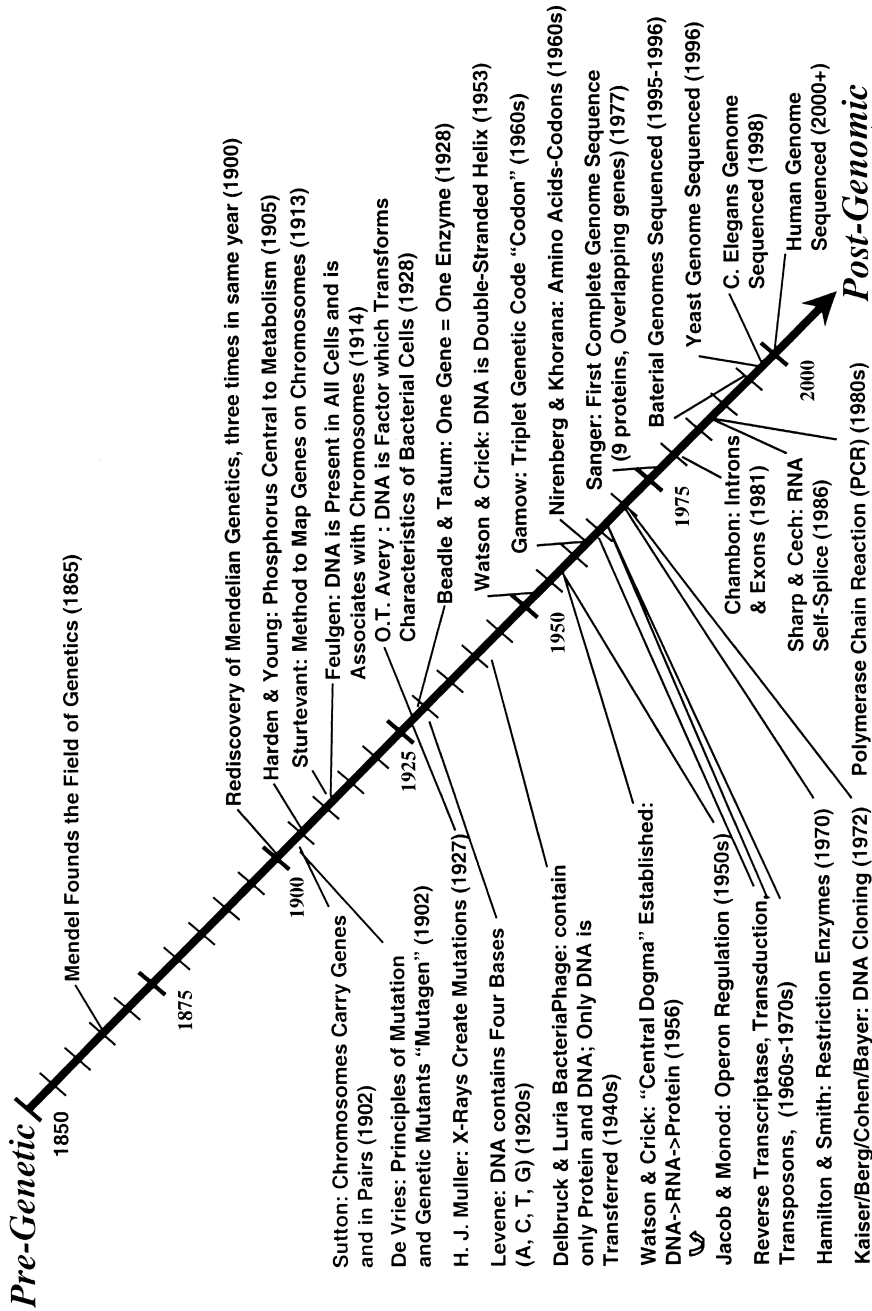


Fig. 1. A brief history of genetics and molecular biology.

products and services is especially strong in Europe. This situation is exacerbated by a limited public and legislative understanding of the scientific and technological infrastructure supporting the biotechnology industry.

Financial skepticism is ubiquitous as well. Investors may feel uncomfortable about the relatively long product development times (often up to 15 years) associated with biotechnology products, especially when compared with the hyperperformance and streamlined product development cycles characteristic of Internet-driven products and markets. This frustration can be heightened by the relatively long payoff period of biotechnology investments (often 10 years or more) when compared to investments in the electronic commerce marketplace (often measured in months or even weeks). As a result, many nascent ventures are experiencing higher hurdles as to the minimum investment size necessary for consideration by investment banks and institutional investors. Further, consolidation in the banking industry and limited analyst coverage of biotechnology companies can challenge emerging companies.

From a technological perspective, biology is not yet a mature science. The rate of scientific discoveries is rapidly increasing across many fields, and numerous technology advances have catalyzed growth. Systematic structural descriptions often precede profound functional discoveries, and both the past and current rush of descriptive work being carried out worldwide offers the promise of the emergence of a mature biology. Indeed, biology is transforming from a descriptive to a predictive science, and both the resolution and complexity of experimental questions and answers are continually increasing. Typical areas of present-day research topics range from cryptography of the information contained within our genes to the *de novo* construction of tissue and organs. An underlying framework for theoretical biology is developing concurrently in several fields, promoting in-depth studies as varied as the modeling of full-body physiology and the simulation of molecular evolution.

3. The future of biotechnology

The growing maturity of biotechnology is mirroring that of biology. Although there is currently a product focus on human therapeutic markets, an inversion of this market focus is likely within the next 20 years, by which time human therapeutic products may likely make up the minority of biotechnology products on the market. The converging and synergistic spectrum of emerging biotechnology areas range from the development of new medicines and drugs, genetically engineered foods, biologically controlled industrial manufacturing processes, and biologically based computing devices to the creation of new industrial materials and devices based upon biological structures and the use of biotechnology to sustain, improve, and nourish our global environment (see Fig. 2). Each of these areas is described below in greater depth.

4. Human therapeutics: developing new drugs

The therapeutic product pipeline has never been stronger: 438 human therapeutic drug products are currently in development [1,2]. These products fall into 16 major functional

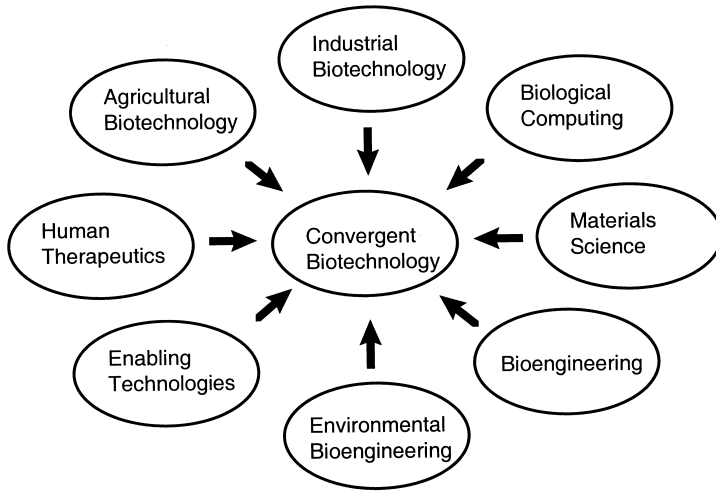


Fig. 2. Market sectors and technology convergence within the biotechnology industry.

classes (see Table 1), and they are targeted towards a variety of widespread disease states such as cancer, infectious disease, cardiovascular disease, and immunological and neurological disorders. By far the greatest number of products under development are focused on therapies for cancers. More than 18 discrete technological platforms are being leveraged in the study of human disease. The most prevalent technologies in use are vaccines (molecules

Table 1
Disease states under study: the pipeline of human therapeutics products under development [1,2]

Therapeutic Category	Phase I	Phase II	Phase III	NDA	Total
AIDS/HIV infection	10	15	4	1	30
Autoimmune disorders	9	8	2	0	19
Blood disorders	3	3	3	0	9
Cancer	97	39	20	7	163
Diabetes	3	5	4	1	13
Digestive disorders	1	6	1	1	9
Eye conditions	1	0	2	0	3
Genetic disorders	8	1	1	0	10
Growth disorders	1	1	2	0	4
Heart disease	13	11	4	3	31
Infectious disease	11	15	10	5	41
Infertility	1	1	2	0	4
Neurological disorders	12	9	4	2	27
Respiratory diseases	6	9	4	2	21
Skin disorders	5	7	2	0	14
Transplantation	9	6	0	1	16
Other	5	14	5	0	24
Total	195	150	70	23	438

Phase I, II, and III refer to the progression of drug candidates through a three-phase clinical trial study process. NDA refers to new drug application.

intended to trigger a specific immune response, creating immunity towards the physiological impact of that trigger), monoclonal antibodies (highly specific antibodies produced for unique targets), and directed gene therapy (alteration or replacement of improperly structured genes with those harboring enhanced function). Each of these and other techniques are being combined in highly innovative hybrid technology platforms, offering the probability of rapid, discontinuous improvements in the efficiency and efficacy of research and development.

Most of these products have been developed through a research and development process that often requires \$300 million and 15 years of product development and testing time. This development process is typically characterized by a sustained and high level of uncertainty regarding eventual market acceptance and limited “customer feedback,” often based solely upon the narrow results of carefully managed clinical trials. For this reason a fully developed product can and often does fail in the marketplace: widespread market acceptance of products can be unpredictable, and the marketplace itself is comprised of multiple tiers of demand channels: from pharmaceutical manufacturers to drug wholesalers, from pharmacy retailers to physicians, from patients and patient advocacy groups to managed care organizations and hospital management, the introduction of a new therapeutic product often depends upon a carefully balanced sales and marketing campaign leveraged through all these potential channels. When this campaign is unsuccessful, extraordinary waste can ensue. Several approaches are underway to improve the substantially therapeutic development process, including molecular breeding, pharmacogenomics, and embryonic stem cell technology.

4.1. Molecular breeding: turning biotechnology into nanotechnology

Ultimately, the current inefficiencies in the drug product development cycle stem from the highly convergent and linear product development tradition pursued by most pharmaceutical companies. In contrast to this approach, several new technologies offer divergent and very rapid discovery models. In particular, a paradigm shift is now underway, in which highly market-sensitive products may be developed by leveraging the diversity of evolution and designed through extensive front-end “customer” input. The breadth and diversity of evolution has been harnessed using a molecular breeding technology, in which the intrinsic molecular variability of sexual genetics has been reconstructed under hyper-efficient laboratory conditions. It is now possible to reengineer protein structure by shuffling the internal components within a protein and select for massively increased function in weeks, mimicking what occurs over the course of 10,000 years of natural selection. Proteins and enzymes can be reengineered to manifest 100-fold, 1,000-fold, and even 10,000-fold increases in functionality, whether for a specific binding affinity, the rate of catalysis of a chemical reaction, or for energy absorption, transfer, or emission [3,4]. Molecular breeding allows “end-users” requiring a particular function or set of functions to define their desired product and leverage the diversity of evolution to achieve that end-state without requiring a rationale for drug design; the diversity of evolution provides the creative materials, and a well-designed functional assay permits detection of an evolutionary solution. This “black box” approach to product development obviates the need for

extensive functional knowledge prior to product design, and in doing so eliminates the many years of incremental knowledge building and inefficient trial-and-error testing that so burdens the current product development process.

4.2. Pharmacogenomics: customizing medicine for the individual

The inherent individuality that defines each of us arises from a combination of our unique experiences and our biological makeup. Although we may debate the relative contribution of each factor to our self-definition, our individuality is a double-edged sword. Certain drug products and therapeutic protocols work well in some patients, poorly in others, and not at all for some unfortunate souls. Why? Our individual genomic makeup results in a similarly unique set of physiological pathways. The expression patterns of proteins in cells, tissues, and organs creates an ironic challenge for the pharmaceutical industry: How can a therapeutic product be mass customized?

Pharmacogenomics is the science of developing a customized and personalized medicine. By articulating and identifying the genetic uniqueness in each of us, the genetic variations separating us from one another can be used to refine the therapeutic strategies intended to treat a particular disease state, whether through a customized dosage regime or the design from scratch of a highly specific therapeutic [5,6].

The development of pharmacogenomic-based therapies with ultrahigh specificity for subpopulations of patients may require the acquisition and analyses of individual genomic data. The depth and breadth of this data stream may require a global infrastructure capable of transmitting, receiving, and processing a minimum of hundreds to thousands of terrabytes of multidimensional information each day. This informational scale may require new approaches to scaleable architecture, and carries with it significant (and already present) concerns regarding medical privacy and security. The use of the Internet as an extensible means of communication may be essential for the efficient and effective function of the biotechnology industry, perhaps more so than in any other field.

What benefits might we receive from this barrage of information? Pharmacogenomic data may be leveraged in several ways. The continuous mining of clinical trial and adverse event data may promote the development of individually tuned diagnostic tests for particular disease states and usher in an era of truly customized molecular medicine, in which individual genetic data may be used to guide specific therapies, the choice of drug classes, the determination of optimal dosage levels, and the creation of customized drug variants. Further, meta-analyses of pharmacogenomic data may drive substantial improvements in the efficiency of the clinical trial process, decreasing clinical testing times and improving experimental and clinical data resolution as a result of more tightly defined and presumably more homogenous patient populations.

Like the conditions from which it arose, the promise of pharmacogenomics also provides a double-edged sword. On the one hand, actualizing the concept of a customized medicine may profoundly impact medical care. On the other hand, a dangerous loss of privacy might ensue from the molecular articulation of our individuality. On the dark side, it might be possible to synthesize a molecular assassin targeted towards an ethnic group or even an individual. As

with all technology, the greatest danger and the brightest promise equally reside in the proper leverage of our collective wisdom.

4.3. Embryonic stem cell technology: towards the fountain of youth

The fountain of youth has eluded hopeful explorers for centuries. Ironically, these explorers were carrying the objective of their quests within their own bodies. Using a combination of embryonic stem-cell technology and retroviral therapy, it may soon be possible to design new functions in aging or diseased organs, to grow new cells, tissues, and organs from scratch, and, potentially, to slow or even stop the molecular clock of aging [7,8]. A plethora of regeneration technologies may soon be possible. Diabetic patients may benefit from the implantation of nonimmunogenic, functioning pancreatic cells. Cardiovascular patients may enjoy potential benefits from newly grown blood vessels and arteries. Molecular cosmetic technologies might soon exist to repair or replace aging skin and hair. The limits to these technologies may be defined by our imagination, ethics, and collective wisdom.

While increasing the quality of life within the bounds of our current lifespan, the extension of the human lifetime beyond our current limits may lead to the discovery of new “post old-age” diseases, previously undetected and just as deadly for modern humanity as age-related neurological, cardiovascular, and physiological disorders would have been for a medieval woman or man had they lived as long a life as in modern times. While extending our quality of life, slowing the aging process carries with it the risk of “extreme age”-related metabolic and neurological disorders.

5. Agricultural biotechnology: towards efficiently grown and more nutritional food

From start-ups ventures to global corporations, many companies have embarked in significant research and development programs to exponentially accelerate the crop breeding efforts that began at the dawn of our civilization. More progress in agricultural engineering may be made in the next half-century than in the last ten thousand years.

Traditionally, food crops such as wheat, corn, and rice were bred for hardiness and yield through the slow and laborious crossing of different crop strains, and the ultimate results of these experiments took years to ascertain. Today, the highly refined genomic and genetic engineering of agricultural products may be carried out in weeks to months, compressing the breeding cycle from 100- to 1,000-fold [9,10].

A variety of traits are being targeted for genetic modification [11]. First, crops are being reengineered to yield increased environmental resistance (e.g., temperature and moisture extremes) and improved resistance to insects and pests. These enhancements may allow crops to be grown over a greater range of environmental conditions than ever before, ultimately increasing the carrying capacity of our environment. Second, plants may be structurally modified to yield alterations in leaf and petal shape and size and changes in stem, branch, root and seed structure. These structural modifications can reduce the energetic requirements of plants, further increasing crop yields. Third, the nutritional content

of crops can be substantially enhanced through the molecular tuning and adjustment of the relative percentages and distribution of oils, proteins, fats, and carbohydrates contained within fruits, leaves, flowers and seeds. In addition, it should be possible to alter the vitamin and mineral content of crops to further optimize their nutritional content. These modifications may create healthier and more tasteful food products as well as specifically formulated “nutriceutical” products. Fourth, the insertion of antigens into foodstuffs may create a new market for edible vaccines, in which foods can be used as the medium to immunize people against infectious diseases. Fifth, the breeding and growth cycles of the plants might be modified to allow for continuous growth, yielding an independence from or at least less dependence on seasonal growth cycles. Finally, it may soon be a straightforward process to grow materials in one species that had previously evolved within another, leading to far more sustainable and gentle manufacturing processes. For example, it may be possible to grow spider silk in corn kernels, and harvest the corn to purify the silk, ultimately fabricating extraordinarily strong fabrics and textiles. Taken together, these advancing fronts in agricultural biotechnology offer the possibilities of rapidly improving capacity to feed our growing population in a healthy, sustainable, and humane manner.

Although there has been and may continue to be considerable backlash and public skepticism regarding genetically engineered foods, ultimately such advances have been and may continue to be made for the improved health and welfare of our exponentially growing population: For the world to have enough food, the leveraging of agricultural biotechnology may be of enormous benefit. Nevertheless, the possibility of producing and consuming altered foods can trigger strong emotions and polarize thinking. It may be critical to educate and reassure those concerned in a manner that mutually respects the value systems of all involved.

6. Industrial biotechnology: replacing industrial-age manufacturing processes through biology

Industrial manufacturing processes have traditionally relied upon high temperature and energy, noxious chemicals such as acids, alkali, silicates, and surfactants, and have often incurred the excess production of phosphorus and the generation of hazardous metal wastes. In contrast, biotechnology offers both the promise and the reality of a far more gentle and sustainable manufacturing environment.

Enzymatic reactions serve the same role as high temperature and energy processes: to bring together reactants in space and time to promote the stability of the intermediate state of a reaction. The molecular structures of enzymes have evolved to catalyze body temperature reactions, while the typical noncatalyzed reaction equivalent might require a temperature of 3,000–5,000°C. This biocatalytic approach can be leveraged from the body and ported into a variety of manufacturing processes, in which enzymes such as lipases, proteases, cellulases, and amylases can be substituted in place of both noxious chemicals and high temperature and energy [12]. The range of manufacturing processes to which a biocatalytic approach can apply includes the production of detergents, starches, textiles, and grain processing. In each of

these and many other industry segments, biotechnology can be used to promote environmentally friendly, highly efficient and cost-effective alternative manufacturing processes.

Within the next 50 years it is probable that these biocatalytic manufacturing processes may evolve to an extent which permits the totally biological fabrication of consumer goods such as clothing, plastic goods, and building materials. Concurrently, biocatalytic approaches may assist in and support the assembly of more complex machine products such as appliances, automobiles, and perhaps even electronic components.

7. Biological computing: replacing silicon-based computer chips with living computers

Two complimentary approaches are underway to integrate computer science and biology. First, several initiatives are in progress to leverage computational power while deciphering biological encoding mechanisms ranging from the analyses and modeling of genome-scale structure and organization and simulations of genomic evolution at molecular resolution to the information patterns driving protein folding and the computation algorithms used within the human mind to perform multineuronal cognitive processing. These studies take advantage of the exponential increase in computing power and memory storage.

Second, innovative approaches to leveraging the parallel circuitry of biochemical reactions are in progress, with the ultimate objective of harnessing these reactions in a massively parallel computational engine [13,14]. In particular, nucleic acid synthetic chemistry is being used to form prototypical logical circuits [15,16]. These biological circuits offer the theoretical potential of vastly enhanced computational power: current estimates suggest that biological computers should be capable of a speed (measured in operations per second) seven orders of magnitude higher than that of modern-day supercomputers. Concurrently, it is estimated that biological computers should be capable of significantly decreased energy requirements: current supercomputers typically function at 10^9 operations per Joule, while biological computers should yield 10^{20} operations per Joule, at room temperature. Similarly the potential information storage capacity of biological computers (10^{12} Bit/nm³) is estimated to be as much as 12 orders of magnitude more dense than modern supercomputers.

Alternative technologies to electronically based computing engines may likely arise from the creative harnessing of photoreceptor chemistry. In particular, optical switching devices could be created based upon signal transduction molecules found within the human body. In particular, the chemical pathways present in the rods and cones within our eyes could be engineered and tuned to function as optical processing devices, offering the potential of vastly increased computational speed relative to that possible using electronic circuits.

A complimentary approach to centrally based biological computers would depend upon a convergence between distributed biological computers and distributed information processing devices such as Web appliances and embedded chip technologies. In particular, embedded computational devices could be synthesized upon or within biopolymers—resulting in wearable computers, highly distributed processing within household devices, and, in the extreme, information processing functions distributed through and on the scale of nanotechnology.

8. Materials science: developing biological materials for improved structure and function

The natural diversity inherent to biology provides for a bountiful pool of resources to draw upon in the enhancement and creation of novel materials. The reengineering of molecular and cellular processes to serve in roles and functions unrelated to the conditions in which these processes arose provides for an especially rich source of innovation [17–19]. From ultrastrong and lightweight materials based on hybrids between spider silk and insect exoskeletal materials, to adhesive materials based upon the adherent properties of insect pads, the materials resulting from natural evolution can be functionally redirected through the application of human creativity. Multiple organisms may serve in part as production assembly steps. For example, the molecular components comprising ultrastrong spider silk could be synthesized in bacterial cells and then purified from these cells and polymerized into ultrastrong synthetic textile structures. On another note, chitin derived from arthropod exoskeletons could be used to create lightweight structural frames (“chitinous chassis”) for a variety of products. In each of these cases, the properties that make these materials highly adapted for their respective environments can serve as compelling sources of value when removed from that environment.

Through the incorporation of biological components, substantial functional enhancements to existing materials are also likely. Structurally, fabrication materials, textiles, and device components may be manufactured that manifest environmental monitoring, in which embedded biomolecules sense fundamental aspects of the ambient environment such as temperature, humidity, and pressure, and adjust the properties of the material accordingly. The proliferation of self-regulating materials are also likely. For example, self-cleaning materials may soon exist, in which embedded biomolecules drive enzymatic processes that remove bacterial or chemical contaminants. Applications would vary from the hospital room to textiles to the personal care industry. Informationally, materials may be fabricated with embedded logical circuits or computational devices in the form of either electronic or biological information processing. With an embedded materials technology platform, interactivity with the environment would be possible, and could promote the development of highly coordinated, hyperefficient living and working spaces. For example, a person’s clothing might sense the body temperature of the wearer and send a signal to the environmental controls for the room, adjusting the temperature as appropriate. Many applications are possible, limited only by the imaginations of engineers and product designers.

9. Bioengineering: redesigning biological devices for new functions

The incorporation of biological components as design elements carrying out highly specific functions can be projected by considering the current uses of biological circuits within the living cells and extending these functions to devices outside of the body. For example, multiple biologically based mechanisms have evolved to capture and store

energy, ranging from the use of chlorophyll as a light-harvesting mechanism to the use of adenosine triphosphate (ATP) as an energy storage mechanism. In a bioengineering context, these structures could be used for their same function, yet in nonphysiological contexts. For example, chlorophyll could be used for a “generic” light sensory and capture function, while ATP could serve as the chemical basis of a biological battery. Similarly, energy transduction mechanisms such as touch-, light-, voltage-, and chemically gated ion channels and receptor proteins could be leveraged in the design of a wide range of reengineered sensory systems, all with myriad applications. For example, biological photochemistry could be harnessed in the development of optical computing circuits and for light sensor devices. Chemically gated ion channels and highly specific chemical receptors might serve as the core of customized and tunable chemical sensory devices. Similarly, touch- and voltage-gated ion channels could be used in the development of ultrasensitive analog processors, whose sensitivity thresholds could be biochemically adjusted in real time.

A complimentary approach to bioengineering involves the design of entirely novel functions for currently existing molecules whose structure has arisen through many millennia of natural selection. For example, micro-organisms have evolved to survive and even thrive in conditions ranging from solid ice within glaciers to ultrahigh pressure and temperature water near volcanic vents at the bottom of the ocean. In each of these cases, organism physiology has adapted to these conditions through alteration of specific molecular pathways. In the case of microbes living in boiling water at tremendous pressures, microbial enzymes have evolved for optimal function in this environment, and this natural optimization can be utilized for high-temperature, high-pressure processes in a test tube laboratory. Indeed, this approach was used to revolutionize molecular biology through a process known as polymerase chain reaction (PCR). The PCR process allows for the massive amplification of even minute quantities of DNA, and is made most effective by using enzymes that evolved in bacteria living near volcanic vents in the ocean. Similarly, research is currently underway to study and isolate the natural “antifreeze” compounds found in the blood of marine organisms, and to eventually leverage the underlying chemical modifications in applications as diverse as additives for the automotive engine fluids and tissue and cell storage media for cryogenic processes. Many potential applications may arise from the creative reuse of the present-day functional diversity found in nature [20,21].

The engineering of novel functions for naturally evolved biological structures has allowed for the development of prototypical bioengineering at the nanometer scale (bio-nanoengineering). Prototypical designs have ranged from nanoelectronics to biological motors. In the realm of nanoelectronics, nucleic acids such as DNA and RNA have been used to complete nanometer-scale electrical circuits [22]. In the area of biological motors, artificially energized bacterial cells have been used to drive the rotation of bacterial flagella (hair-like molecular appendages) on a nanometer-scale through proton motive force [23]. Such prototypes represent the early adoption phase for bioengineering. In the next 20 years, it is likely that combination devices may arise containing both “classical” nanotechnology and embedded biological components, in applications as diverse as mechanical nano-engines, memory storage devices, and sensory transduction circuits. Such devices could be found in nanometer-

scale manufacturing processes, medical devices, personal care products, and consumer goods ranging from personal data appliances to telecommunications products.

10. Environmental bioengineering: repairing and sustaining our environment

Many environmental challenges have arisen from the unregulated use of technology developed from the time of the industrial revolution. Often, these technologies resulted in contaminated soil, water, and air, with far-reaching and unanticipated implications for our global ecology. These industrial era environmental challenges may be resolved through the wise application of biotechnology in the development of sustainable, environmentally friendly manufacturing processes. Such processes could generate minimal waste, and efficiently eliminate what little waste may be generated. In particular, microbial “cleaner” organisms may be designed to clean up contaminated soil, industrial effluent, groundwater, contaminated air, and petrochemical spills.

For each of these environmental challenges, the cleansing function of biotechnology would arise through highly controlled and localized biodegradation [24,25], in which the engineered microbe would consume the target waste over a discrete time window, after which the microbe would expire. This could be assured by having the microbial cleaner organism depend on a complex combination of extraordinarily scarce nutritional inputs not found in nature, so that when the small supply of artificially created nutrient is fully consumed, there is none available to sustain continued existence beyond the cleaning period. In this way it may be possible to both resolve current environmental issues and to anticipate potential problems without fearing that the solution may have more environmental impact than the original problem. As in many other fields, substantial crossimpact is expected from technological advances in industrial biotechnology, specifically in the directed evolution of the cleansing and nutritional dependence functions for the cleaner organisms.

A complimentary approach to the design of specific cleaner organisms would be to manufacture compounds of extracellular enzymes that carry out biochemical degradation reactions outside of a living cell. Although this approach minimizes any risk of releasing a living organism into the environment, ironically it also makes control of the extracellular compound more difficult, in that a powder or solution could be carried into the wind and distributed beyond an intended geographical region. For this reason it is likely that the microbial cleaner strategy may become more prevalent as the technology platform underlying this type of application continues to advance.

11. Technologies that drive the biotechnology revolution

A plethora of deeply powerful and synergistic technologies have been developed, and are being continually refined as their applications spread into numerous fields within biology. From high-resolution imaging to genomics, proteomics, and molecular breeding, these and

other technologies are driving scientific progress and industry growth to an unparalleled rate of expansion.

11.1. High-resolution imaging: seeing smaller and clearer than ever before

More than three centuries ago, Robert Hooke first used a simple microscope to study the structure of cork. That optical study marked the advent of cellular biology. A plethora of innovative and far more recent imaging technologies is rekindling this revolution. From magnetic resonance imaging to diagnostic ultrasound technology, a wide range of disease states can be sensitively diagnosed and often treated in concert with radiological therapies. In terms of spatial scale, this imaging revolution has now moved both inwards and outwards [26]. Moving inwards, the use of fluorescently labeled molecular tags is providing the opportunity to sensitively detect *in vivo* gene expression patterns as a function of position within cells, tissues, and organs. Moving outwards, the *in vivo* generation of light from light-producing animals is now permitting the rapid and noninvasive imaging of whole organs and body segments.

Coupled with highly resolved, three-dimensional structural data, the exponentially accumulating aggregate of finely resolved spatial and temporal gene and protein expression patterns has and may continue to drive the need to create multidimensional databases on the order of hundreds of terrabytes. Effective navigation and leverage of this information may require highly evolved and flexible pattern recognition and analysis algorithms. Further, this data may need to be distributed and communicated through a scaleable and extensible hardware communication network. One of many points of convergence of the information technology and biotechnology industries resides in the ever-adapting solution to this continual challenge.

11.2. Genomics and proteomics: mapping the complexity of the living cell

Mapping out the genetic and protein-based circuits driving our molecular physiology is critical to the efficient and effective treatment of disease. “Genomics” refers to the global effort underway to define and order the complete set of genes contained within our bodies [27]. Similarly, “proteomics” represents a characterization and mapping of the complete set of proteins present with our bodies [28,29]. These efforts are not entirely independent—proteins can bind to and regulate the expression of genes, and so their interactions can be critical in understanding the proper functioning of our physiology. Further, both mapping initiatives are making use of much of the same underlying technologies to both acquire and analyze massive amounts of data in highly parallel processes. As a result, several companies and organizations are concurrently involved in both initiatives. The collective output of these global projects may be a complete mapping of the molecular landscape of our cells. With this information as a guidepost, we may be well positioned to define both disease states and good health at a molecular level of resolution, leading to highly refined and sensitive diagnostic and therapeutic approaches to health care.

12. Implications for the maturation of biotechnology

Taken together, the emerging areas of research and development described above are laying the framework for extraordinary advances that may have far-reaching impacts on society, potentially dwarfing the current impact of the information technology revolution already in progress. Equally importantly, the maturation of biology as a science may provide a lens through which humanity may be enlightened as to the nature of two fundamental questions central to humanity: the uniqueness of life on our planet, and the basis for human consciousness.

13. On the frontier

13.1. *Are we alone in the universe? exobiology, the structural study of nonterrestrial life*

A vigorous search for life off of our own planet is currently underway, both through the direct exploration of neighboring planets and moons, and through the systematic radiotelescopic monitoring of star systems [30–32]. Whether searching for signs of past or present water on Mars, life on a Jupiter moon, or artificially arisen radio signatures from distant planets, should extraterrestrial life be found, there may be deep implications for all of humanity.

Because living creatures are composed of highly coordinated molecular structures, including “informational” substrates (materials responsible for genetic processes such as DNA and RNA) and “structural” components (proteins and lipids, to name but a few), the analysis of life evolved from and present on another planet or non-Earth environment relative to Earth-based life may permit the most profound structural comparison in history. In particular, there may be significant implications for the understanding of our evolution if extraterrestrial life is based on similar molecular structures. For example, the hereditary structure of non-Earth life could be based on a similar nucleic acid chemistry (DNA and RNA). Alternatively, non-Earth-based life could have evolved using very dissimilar hereditary molecules, for example, based upon silicon-based chemistry.

In both cases, knowledge of an entirely independent evolutionary path may allow humanity to generalize on the core set of molecular features and physiological architectures required for life. These alternative and potentially more universal design criteria may likely stimulate thought in how we might leverage the best of each set of design principles and molecular chemistries in further enhancing the structure and function of our own physiological pathways. Such design principles could also impact the development of highly creative approaches to biotechnology, from the development of extraordinarily original biological computing devices to the creation of entirely unique biologically based manufacturing processes.

13.2. *“The molecular basis of regret”: towards an understanding of consciousness*

As our scientific community penetrates further into the mysteries of the mind, humanity may benefit from an increased understanding of the molecular and cellular basis of human

consciousness. Whether understanding the mechanism by which our minds bind our discrete sensory percepts in a unified whole (the “binding problem”), articulating the neurological basis of self-awareness, or deconstructing and reconstructing the molecular substrates of memory and emotion, continued progress may inevitably challenge the last remaining vestiges of “Vitalist” philosophy.

A popular philosophy in the 18th and 19th centuries, Vitalism presumed that the physical and chemical basis of our physiology could not be sufficient to fully define life. Rather, some fundamental life force existed beyond the inspection of science. Such debates raged around metabolic pathways for many decades, only gradually dissipating as laboratory reconstructions of biochemical pathways clearly showed function outside of the body. In modern times, Vitalism is the domain of philosophers and religious groups, who strongly feel that our mind is more than the sum of the underlying molecular, cellular, and electrochemical architecture.

We are now entering into an era of experimental philosophy. Upon reconstructing the molecular framework of a complex emotional or mental state outside of the body, we may finally be in a position to approach the age-old issues regarding the basis of the human soul. For example, consider the concept of regret. A deeply complex emotion, regret compares the memory of “what was” with a hypothetical prediction of “what could have been,” compares these two scenarios against one another, and generates an emotional response based upon this comparison. Should we be able to reconstitute regret in a test tube, we may be positioned to understand the chemical and cellular circuits that carry out this sequence of information processing operations. Through these and other experiments, we may begin to articulate the fundamental biochemistry and cellular biology that literally drives our thoughts. These experiments may usher in a new era of vigorous and emotionally charged debates regarding the nature of our souls.

Further insight into the nature of human consciousness may arise from a nascent electromagnetic wave monitoring technology. This emerging technology noninvasively detects the movements of electromagnetic waves within a human head and has been used to detect spiraling waves moving at 40 Hz within a conscious brain [33]. This wave movement pattern has been found to mirror that of the conscious state, in that the wave is consistently present when the subject is conscious, disappears when the subject is in non-REM sleep, and reappears when the subject dreams. Although these correlations do not demonstrate causality, they do suggest that these wave patterns may be a manifestation of some aspect of consciousness, perhaps in the binding of sensory percepts. Continuing work in this area may reveal more insights into the nature of these wave patterns. Further, the use of this and other technology to comparatively explore the limits of animal behavior and consciousness may allow a delineation of the relative cognitive spectrum of all animal species.

14. Scenarios on the future on biotechnology

Two fundamental drivers of biotechnology may play pivotal roles in the future of biotechnology. First, the extent to which technological integration proceeds may strongly

impact the way society uses and perceives biotechnology. If technological integration and crossfield convergence remains low, biotechnology products may remain relatively rare, and require discrete marketing and highly targeted sales campaigns. If, however, the integration and convergence of biotechnology rapidly proceeds, then humanity may experience a nearly seamless integration of biotechnology into agricultural, medical, engineering, and industrial products and processes.

Second, the degree to which the public eventually accepts biotechnologically derived products and processes as legitimate and reliable alternatives to current products may shape both market demand and public policy. If public acceptance becomes ubiquitous, then we might experience a substantial enthusiasm for the uses of potential biotechnology products and processes, leading to strong educational and legislative efforts focused on the appropriate use of biotechnology. Further, strong public support may likely be present regarding emerging ventures in biotechnology. If, however, the public ultimately rejects biotechnology products and processes, then a substantial public skepticism as to the uses of potential biotechnology products and processes may lead to weak educational programs and ubiquitous confusion regarding the appropriate use of biotechnology in everyday life.

Taken together, these drivers suggest four discrete alternative scenarios for the future of biotechnology (see Fig. 3). The present-day reality of biotechnology is that of low public

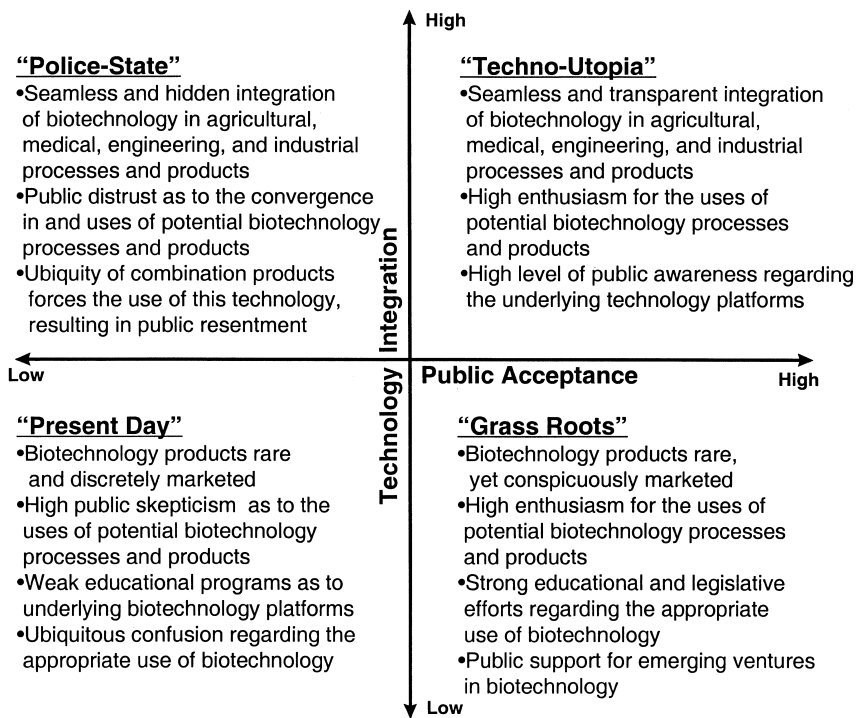


Fig. 3. Scenarios on the future of biotechnology.

acceptance and low technology integration, with the ramifications of public confusion and uncertainty regarding the use of biotechnology products and processes (“Present Day”). Under conditions of high technology integration and high public acceptance, society would embrace biotechnology and use its products and processes in a sophisticated, enthusiastic manner (“Techno-utopia”). Concurrently, the industry would vigorously and transparently demonstrate the origins of its products and processes as a means of further market penetration. Should society embrace biotechnology in the absence of significant industry integration and convergence, then a high value may be placed on the relatively rare biotechnology goods and services that enter the marketplace. Further, the public might strongly support the continued expansion of the industry (“Grass Roots”). On the darker side, should society reject biotechnology in the presence of significant industry integration and convergence, then a low value may be placed on the relatively common biotechnology goods and services in the marketplace. In this scenario, public resentment and distrust of biotechnology might drive behaviors that mask the true nature of the goods and services provided by the industry (“Police-state”). Which of these scenarios most accurately reflects our society in the near-future strongly depends upon our present-day actions and behaviors. To avoid the technologically “constrained” scenario may require that the currently polarized factions within society enter into an open and constructive dialog with one another, in which the value systems of each group are respected as common ground is sought. To minimize the potential frustrations of the grass-roots scenario, visionary cross-industry business development may require broad support from a wide range of funding sources even in the absence of near-term revenue. To move into a utopian scenario, society may need to invest in a vision of the future while simultaneously wrestling with and resolving the antagonisms of the present. Through this duality, the full potential of the biotechnology industry can be realized.

15. Conclusions

There is an explosive synergy present in biotechnology, a synergy that is driving medical, agricultural, computational, engineering, and industrial processes to substantially elevated levels of efficiency, efficacy, and environmental sustainability. The rapid convergence of biotechnology, nanotechnology, and information technology is impending, and may lead to profound changes in the way a wide range of products are designed, manufactured, and used. Furthermore, we are entering into an era of hyper- and self-directed evolution, where humanity is positioned to design and create entirely new molecules, biochemical pathways, tissues, organ systems, and life forms. The ethical and societal implications of these technological advances may be staggering.

There was a time late in the last century when technological progress imparted a similar societal impact. The industrial revolution concurrently crystallized three fundamentally new concepts for humanity.

First, a large portion of our population discovered that humanity was not at the center of the universe. Indeed, several hundred years of advances in telescope technology and

astronomical analyses revealed that the universe did not revolve around the earth, but rather, that the earth was a small planet located in a solar system rotating on the distant fringe of one small galaxy. The universe took on an unimaginable and sublime spatial scale, relegating humanity to one distant edge of a far greater whole.

Second, it became known that humanity probably evolved from apes and not from a discrete divine creation. The deep impact of Charles Darwin and his theory of natural selection put humanity on par with all the other species on the planet, forcing us to consider ourselves as but one species within the animal kingdom.

Third, a rapid demographic shift transformed whole populations from agricultural to industrial work, resulting in their physical relocation to densely packed, poorly planned, and nonhygienic urban centers. The resulting poor working and living conditions promoted rampant disease. Concurrently, the widespread use of the microscope revealed that the source of this disease in many cases might be from small, invisible microbial organisms. This revelation created a feeling of loss of control, that humanity was relatively feeble and vulnerable to even the smallest of invisible creatures.

Taken together, these fundamental concepts changed the way humanity perceived itself. A “symbolist” era ensued, in which the literary, decorative, and fine arts focused on both a near worship of nature and on a nostalgic view of a more simple agrarian past [34]. This aesthetic movement was a manifestation of a profound alienation within society, an alienation based on an abrupt and unanticipated reconsideration of self.

Given the breadth and depth of advances underway in biotechnology, there is a strong potential for a reemergent, neosymbolist era. Similarly, fundamental drivers may shape this new era of self-reconsideration. The complete decoding of our physiology down to individual genes, proteins, and even individual thoughts and emotions may profoundly impact our self-perception of health, disease, aging, personality, and soul. Alteration of the carrying capacity of our planet through agricultural biotechnology may fundamentally change our relationship with the ecology in which we live. Rapid improvements in industrial manufacturing, materials science, and bioengineering may deeply impact both the nature and flow of information and materials through our economy. In each of these endeavors, emotions may run high as we further articulate our common societal values. Special interest groups may feel antagonized and polarized as these conversations proceed. Ultimately our ability to use biotechnology to create a better world for all the creatures on the Earth depends upon our ability to exercise wisdom, compassion, and respect for one another.

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