Chapter 2
That Was the Synthetic Biology That Was

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Contents

Abstract Visions of a synthetic engineering-based approach to biology have been a prominent and recurring theme in the history of biology in the twentieth century. Several major moments in this earlier history of attempts to redesign life are discussed: the turn-of-the-century prominence of experimental evolution and the coining of “synthetic biology” in 1912; early synthetic approaches to experimentally investigating the historical origin of life on the early earth; the goal of developing a “technology of the living substance” and the creation of life in the test tube as the ultimate epistemic goal for an engineered biology; the creation of synthetic new species in the first explicitly labeled efforts at “genetic engineering” in the 1930s; and the re-emergence of “synthetic biology” during the rise to prominence of novel recombinant DNA technology in the 1970s. The use of synthesis as a both mode of inquiry and of construction is highlighted. Aspects of the more recent history (the last decade) of contemporary synthetic biology are also explored.

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2.1 Introduction

"The first attempts to write the history of a scientific discipline often presage its imminent senescence" – or, in the case of synthetic biology, its imminent adolescence.[1] Most accounts of synthetic biology place its origin in the relatively recent past – if not just a few years ago, then perhaps in the 1990s or at a far reach in the 1970s. One frequently heard claim for the origin of the field dates to an editorial in *Gene* in 1978 describing the implications of the discovery of restriction enzymes, and making reference to "the new era of synthetic biology" (Szybalski 1978). Others trace the term back to less prominent pieces written a few years earlier, but all of which had been effectively forgotten and unknown to today's "founders" of the field.[2] Tracing a disciplinary label can certainly be a useful tool for uncovering the past of a field, but too exclusive a focus on the history of the label itself, rather than the field it represents, may exclude many more interesting and important developments.[3] Disciplinary godfathers have their purposes, but coinages alone do not a new field make.

The idea that a synthetic, engineering-based approach to life could serve both as an ultimate font of biological knowledge and that such knowledge could be directly and immediately applied to human purposes and for human benefit, is a prominent and recurring theme in the history of biology of the twentieth century. If "synthetic biology" is understood more broadly in this sense, then the twentieth century is replete with instances where this vision of biology led to important developments and transformations. Although the label was first coined shortly after the turn of the twentieth century, more significantly it was also at this time that a distinctively synthetic engineering-oriented standpoint to life gained dominance. The founding of the Carnegie Institution's Station for Experimental Evolution at Cold Spring Harbor serves as one useful entry point into this twentieth-century story of life by design.

Inaugurated on June 11, 1904, by the renowned Dutch botanist and author of *Die Mutationstheorie* Hugo de Vries, the Station was on the cutting-edge of biological research intended to turn the study of living things to the greater service of humanity. In his 45-min dedicatory address, de Vries was reported as saying that "evolution has to become an experimental science, which must first be controlled and studied, then conducted and finally shaped to the use of man."[4] At a time when Darwinism was relatively out of fashion as outmoded, slow, and incomplete as a

[1]The title of this piece and the first sentence are taken from Gunther Stent's landmark review (Stent 1968).

[2]"I didn't realize I was associated directly with invention," Szybalski said in an address delivered at the Synthetic Biology 4.0 conference in Hong Kong in October 2008. "I found out there was article in Wikipedia crediting me. . . I had to find it because I forgot about it."

[3]It will also include what may seem to be false positives, like (Huxley 1942) and (Reinheimer 1931) which – without much more interpretive work being done – seem at first glance to have relatively little to do with most contemporary understandings of "synthetic biology."

[4]"Scientists Assembled at Cold Spring Harbor: Formal Opening of the Carnegie Station for Experimental Biology," *Brooklyn Daily Eagle*, June 12, 1904.

description of evolutionary change – and when de Vries' own recently published mutation theory was in the ascendant – such vigorous proclamations that evolution could now come under experimental investigation and ultimately under human control matched the hopes of the new century. Here "[i]n this ten-acre plot" one newspaper reported, "man – long content with his part as caretaker and subjugator of living species – is now learning the new role of creator." Side by side with the human-focused interests of the other wing of the Laboratory, the Eugenics Record Office, the Laboratory's first director Charles Davenport declared that "the principles of evolution will show the way to an improvement of the human race" just as it would show "how organisms may be best modified to meet our requirements of beauty, food, materials and power."[5]

From the earliest years of the century, de Vries and other scientific breeders referred to their experimental breeding work as "synthetic" with the ultimate goal of creating novel, useful forms of life. "[Luther] Burbank crosses species," de Vries once said, referring to the traditional California breeder known for his almost magical ability to produce strikingly new and valuable varieties of flowers and fruits. "I seek to create new ones". Many of de Vries' contemporaries agreed, and declared of his work: "This is 'creating' life" (Huneker 1920). More than a sensational claim, it was precisely this "dissolution of the distinction between artificial and natural creations" that was de Vries' signature achievement, that guided much work at the Station, and that helped pave the way for the engineering of biology as a central goal of the twentieth century (Kingsland 1991).

2.2 Coining "Synthetic Biology"

While the synthetic approach to life was already underway at Cold Spring Harbor, the earliest explicit reference to "la biologie synthétique" appears to come from the French professor of medicine Stéphane Leduc (1853–1939), who published his *La Biologie Synthétique* in 1912 after years of experimentation. Leduc's work is significant for more than the happenstance fact that he called his efforts by the same label we use today. As he grew a variety of osmotic and crystalline growths in solution in his various "jardins chimiques," Leduc hoped to show how basic physicochemical processes like osmosis and diffusion could produce new and complex, even recognizably "organic" forms. A distinctively "synthetic" approach to the problem of biological morphology, Leduc's approach and findings were contested by numerous contemporaries who saw in his osmotic growths merely pale imitations of life, irrelevant for a true and better understanding of living things.

In his role as one of the first to experimentally attempt to use *synthesis* as a means to understand the basic biology of organic growth and morphology, however,

[5] "Man as Creator, Wonders of New Station for Experimental Evolution," *Los Angeles Times*, "Illustrated Weekly Magazine," February 24, 1907, p. 11.

Leduc's early work provides a recognizable affinity with a primary goal of today's synthetic biology. Leduc was a firm believer in the epistemic virtues of synthesis, and not just analysis, in the progress of biology:

> Jusqu'à present la biologie n'a eu recours qu'à l'observation et à l'analyse. L'unique utilisation de l'observation et de l'analyse, l'exclusion de la méthode synthétique, est une des causes qui retardent le progrès de la biologie... [La méthode synthétique] devoir être la plus féconde, la plus apte à nous révéler les mécanismes physiques des phénomènes de la vie dont l'étude n'est même pas ébauchée. Lorsqu'un phénomène, chez un être vivant, a été observé, et que l'on croit en connaître le mécanisme physique, on doit pouvoir reproduire ce phénomène isolément, en dehors de l'organisme vivant.

Leduc also held that his book offered a new and powerful mode of approaching life by analogy:

> La biologie synthétique représente une méthode nouvelle, légitime, scientifique; la synthèse appliquée à la biologie et une méthode féconde, inspiratrice de recherches; le programme consistant à chercher à reproduire, en dehors des êtres vivants, chacun des phénomènes de la vie suggère immédiatement un nombre infini d'expériences, c'est une direction pour l'activité. Les résultats, les faits exposés dans cet ouvrage: la reproduction des cellules artificielles, des structures, des tissus, des formes générales, des fonctions, de la circulation centripète et centrifuge, des mouvements et des figures de la karyokinèse, de la segmentation, des tropismes, tous ces résultats d'expérience et les expériences elles-mêmes seraient sans signification, sans intérêt, dépourvus de sens, si ces recherches n'étaient pas inspirées par l'imitation de la vie. C'est à l'analogie avec ce que l'on observe chez les êtres vivants que ces phénomènes doivent tout leur intérêt. (Leduc 1912)[6]

Although Leduc's work was not entirely mainstream, it was far from bunk science. The celebrated William Bateson – the man who coined the very word "genetics" – even made use of Leduc's work as an illustration of his own theory of life (Bateson 1913, Coleman 1970).

Synthetic in method and analogical in conceptual approach, Leduc's method could aim at a better understanding of "natural" living things even while producing artificial life-like forms: "C'est la méthode synthétique, la reproduction par les forces physiques des phénomènes biologiques, qui doit contribuer le plus à nous donner la compréhension de la vie." It remained for other pioneers in the prehistory of synthetic biology to move beyond such an analogical synthetic approach to the development of an approach more directly related to the potentialities of life.

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[6]Leduc's name seems to have been unknown to all participants at the 1.0 and 2.0 conferences: "We didn't even *know* our field had a history," the organizers told me when I applied to present on the history of the field at 1.0. At the 3.0 conference I presented a poster highlighting Leduc's role; he was also mentioned by another speaker, and Leduc has been routinely cited as a founding figure of the field since about that time. For further details on Leduc's work and its reception, and references to contemporaries also attempting to mimic living forms in this period, see Keller's "Synthetic Biology and the Origin of Living Form" in (Keller 2002).

2.3 Creating Life in the Test Tube

> On June 20th [1905] the scientific world was startled by the sensational announcement that a momentous discovery concerning the origin of life had been made by an English scientist. Working experimentally at the famous Cavendish laboratory in Cambridge, Mr. John Butler Burke, a young man in the prime of life... succeeded in producing cultures bearing all the semblance of vitality....

John Butler Burke, a young Irish physicist working at the Cavendish Laboratory in Cambridge, also turned to synthesis as a means to better understand the nature of life. While Leduc's efforts were focused primarily on proximate questions of form and shape, Burke's work had the higher aim of understanding something deeper and more fundamental about life itself: could life be produced from nonlife? In line with contemporary debates over the possibility of spontaneous generation, reports of his experiments proved to have immense popular appeal.[7]

As reported to *Nature*, Burke's sensational experiments involved plunking a bit of radium into a petri dish of bouillon, with the resulting production of cellular forms that were, if not quite living, at least *life-like*. Appearing to grow and subdivide over a span of days and demonstrating other life-like phenomena at the cytological level, they nevertheless decayed in sunlight and dissolved in water, proving that they were not simply bacterial contaminants. Existing at the limits of vision, Burke's growths were also extraordinarily difficult to see.

Burke was well aware of and readily acknowledged many others' contemporary attempts to create artificial cells, cells that incorporated foreign material, and cells that appeared to grow. He held that his own growths were something else altogether, however, in that the sheer number of life-related phenomena they exhibited far surpassed earlier attempts to merely mimic life. Burke didn't want to just mimic life – he wanted to get at its underlying features. Of Leduc's earlier forms, Burke argued that "*they have not the inherent and characteristic directive power of the living organism*." A firm believer in the life-giving power of radium – a commonly held belief among both scientists and the public at this time[8] – Burke was convinced that he had produced something that was worthwhile even if not quite living, and contemporaries labeled his synthetic results "artificial life." Far enough from truly living things and yet just as far from being mere inorganic growths, he took his radium-induced growths to be new transitional forms of life with their own peculiar physical metabolism, and held that his growths were "suggestive" of both the nature and origin of life. It was far from mere wordplay to say that the element with a half-life (radium) had given rise to forms half-living.

Half-radium and half-microbe, these "radiobes" proved both immensely popular and controversial. The *New York Times* animatedly declared that these new forms existed "on the frontiers of life, where they tremble between the inertia of inanimate existence and the strange throb of incipient vitality." Burke himself said that

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[7] For more about Burke and further citations, please see (Campos 2006b), Chapter 2.

[8] For more on the connections between radium and life in this period, see (Campos 2006a) or (Campos 2006b) Chapter 1.

the interest his experiments unleashed "has been such that the brief note communicated to *Nature*, May 25th, 1905, and the few words uttered to a representative of the *Daily Chronicle*... have resounded from the remotest corners of the earth to an extent quite beyond the expectation even of my most apprehensive friends." Burke's experiments were hotly debated and contested on both sides of the Atlantic for months. By November 1906, Burke's findings were touted as "a discovery that has provoked more discussion, perhaps, than any event in the history of science since the publication of the 'Origin of Species,' for it has a direct bearing on all speculative theories of life."

Burke not only thought he had managed to produce at least "half-living" forms, somewhere on the border of life and not-life, but he used the controversy and fame that his work brought him to successfully reframe the terms of a contentious science-and-society debate about spontaneous generation with lasting effects. Although his experimental results were later discounted and explained away, and although he died unknown and almost completely ignored by the scientific community, he succeeded in laying the groundwork for the study of a new field: the experimental investigation into the historical origin of life. Synthesis was no longer about merely mimicking life; now it had been marshaled to help explore the more fundamental properties of life including its history and origin.

2.4 A Technology of the Living Substance

Not all pioneers in the prehistory of synthetic biology were interested in asking questions about the nature or history of life, however. Some – such as the German-American physiologist Jacques Loeb (1859–1924) – were much more interested in *doing* something with life, and in having full physiological and developmental control over it, developing new forms at will and as needed. As Philip Pauly has noted in his masterful biography, Loeb "considered the main problem of biology to be the production of the new, not the analysis of the existent" (Pauly 1987).

Loeb is most famed for, among other things, his mechanistic study of instincts and tropisms and his widely touted 1899 invention of "artificial parthenogenesis." This remarkable discovery, which cytologist and embryologist E. G. Conklin called "one of the greatest discoveries in biology," made Loeb a contender for the 1901 Nobel Prize. Loeb reported on his work in his *Mechanistic Conception of Life* (1912), the title punning on the new reality of artificial parthenogenesis and his own mechanistic view of life. The *Chicago Sunday Tribune* took similar license, trumpeting Loeb's work: "Science Nears the Secret of Life: Professor Jacques Loeb Develops Young Sea Urchins by Chemical Treatment – Discovery that Reproduction by This Means is Possible a Long Step Towards Realizing the Dream of Biologists, to Create Life in a Test Tube."[9] This was indeed not far from Loeb's own intentions. The discovery of artificial parthenogenesis – this "most vital discovery

[9] *Chicago Sunday Tribune*, November 19, 1899.

in the history of physiology," almost "the manufacture of life in the laboratory," as Loeb was reported to have said, meant that "we have drawn a great step nearer to the chemical theory of life and may already see ahead of us the day when a scientist, experimenting with chemicals in a test tube, may see them unite and form a substance which shall live and move and reproduce itself."[10] While Burke's forms may have had *some* but not *all* the properties of life, which was sufficient – indeed, exactly what was needed – for Burke's interests and purposes, Loeb's goal was otherwise. He dismissed Burke's attempts: understanding a phenomenon for Loeb meant being able to control that phenomenon. The test of ultimate control over life – Loeb's dream of "a technology of the living substance" – was not only to be able to do with life as one willed, but to eventually be able to create it oneself from scratch in the test tube.

Loeb's goal was not to shock the public or to distance or entice his colleagues – though it may have had these effects – but came simply a concomitant of what he viewed as a thoroughgoing engineering approach to life. According to Pauly, for Loeb, "the very fact that creation of life was a nonnatural act made it possible to specify the steps necessary for production. Scientists should create life just because nature could not do so; and on the way to such an achievement they would find the power to reconstruct the living world according to the principles of scientific reasoning." It is thus not without reason that Loeb described his theory of a chemical basis for evolution as the development of a "synthetic physiology" and that he was intensely interested in "the artificial production of matter which is able to assimilate," and in "producing living matter artificially." A sampling of passages from Loeb's writings clearly reveal these elements of his research agenda:

> The idea is now hovering before me that man himself can act as a creator, even in living nature, forming it eventually according to his will. Man can at least succeed in a technology of living substance [*einer Technik der lebenden Wesen*].
>
> It is possible to get the life-phenomena under our control... such a control and nothing else is the aim of biology.
>
> And ten years ago, when I went to Naples, I dreamed that I must soon succeed in producing new forms at will!
>
> Perhaps the most fundamental task of Physiology... to determine whether or not we shall be able to produce living matter artificially.
>
> It is in the end still possible that I find my dream realized, to see a constructive or engineering biology in place of a biology that is merely analytical.
>
> There is, therefore, no reason to predict that abiogenesis is impossible, and I believe that it can only help science if the younger investigators realize that experimental abiogenesis is the goal of biology. (Pauly 1987)

While other biologists saw the production of abnormalities and monsters – precisely the kinds of organisms Loeb regularly succeeded in producing – as irrelevant to the study of biology, Loeb held much like de Vries that it was only in breaking down such distinctions between the natural and the artificial that a program for an engineering biology could be fully explored. As Pauly noted, by 1900 Loeb

[10] "Creation of Life," *Boston Herald*, 26 November, 1899.

> had come to symbolize both the appeal and the temptation of open-ended experimentation among biologists in America, and he became the center of scientific and popular controversies over the place of manipulation in the life sciences.
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> . . .The core of the Loebian standpoint was the belief that biology could be formulated, not as a natural science, but as an engineering science. More broadly, it means that nature was fading away. As biologists' power over organisms increased, their experience with them as 'natural' objects declined. And as the extent of possible manipulation and construction expanded, the original organization and normal processes of organisms no longer seemed scientifically privileged; nature was merely one state among an indefinite number of possibilities, and a state that could be scientifically boring. (Pauly 1987)

2.5 The Engineering of Experimental Evolution

This sort of celebration of the artificial did not sit well with many traditional biologists. "Thus one sitting in his study may blithely construct 'synthetic protoplasm' by 'a juggling of words,' or by a combination of ideas drawn from physics and chemistry," naturalist David Starr Jordan wrote scathingly in 1928 of newfangled attempts to engineer life.[11] The onetime president of Indiana and Stanford University, and an ichthyologist by training, Jordan was responding as most naturalists did to sensational claims like those of Loeb and others. Real biology was real biology: what Leduc, Burke, Loeb, and others were doing might be something interesting, but for Jordan it certainly wasn't biology. Many Progressive-era agriculturalists, breeders, and geneticists were more interested in altering protoplasm already in hand toward greater ends than they were in constructing synthetic protoplasm. Such concerns dovetailed in the American context not only with the establishment of new land-grant universities dedicated to the public good but also with the founding of experimental research stations like the one at Cold Spring Harbor. Gaining experimental control over evolution was seen as instrumental in such goods as improving crop yields or in developing new mutative varieties. Experiments in mimics of life, primitive life, or artificial life seemed less central.

Representing a parallel tradition in the engineering approach to life distinct from the work of Leduc, Burke, and Loeb, these investigators of a more traditional stripe – even as they ignored or derided artificial approaches – contributed in their own way to the development of an explicitly engineering-based approach to life, in their focus on improving species and varieties. Inspired by the work of de Vries, whose novel mutation-theory was sweeping biological circles in the first years of the century, many of these investigators began to envision a control of evolution that extended beyond the realm of basic *physiology* – where most of Loeb's research had concentrated – and into the phenomena of *heredity* and *evolution*.

In "The Aims of Experimental Evolution," his address at the dedication of Cold Spring Harbor, de Vries had suggested that organisms might mutate under the

[11] D. S. Jordan, "A Consensus of Present-Day Knowledge as set forth by Leading Authorities in Non-Technical Language that All May Understand," in Frances Mason, ed., *Creation by Evolution*, New York, The MacMillan Company, 1928, p. 3.

influence of "the rays of Roentgen and Curie" thus granting humanity control over evolution and leading to the production of new and useful varieties. Building on de Vries' suggestion, many investigators (including Loeb, for a time) began experimental attempts to induce mutations in plants, and later in animals, by means of radiations and chemicals. It was in precisely these attempts to induce mutation and to explore the possibility of what was widely termed "experimental evolution" that the engineering approach found some of its most widespread support in this period. Promising successes in synthetic genetics (and not just synthetic physiology) meant that newly synthesized "monstrous" forms could be viewed instead as "mutants." The study of mutation rapidly became central to the practice of classical genetics, as part of a vision of engineering evolution to suit human purposes.

Studying mutations proved especially instrumental in the rise of the *Drosophila* school of genetics under Thomas Hunt Morgan at Columbia in the 1910s and 1920s (Kohler 1994). But it was the work of Albert F. Blakeslee, the second Director of the Station for Experimental Evolution, that established in the 1920s and 1930s the production of what he called "synthetic new species" as a result of chromosomal mutations – species that he said had been "made up to order, as it were, with definite plan and purpose" (Blakeslee and Bergner 1932). His contemporaries lauded this as the emergence of precisely the kind of evolutionary engineering that de Vries had envisioned. Some others even called it "genetic engineering" (this referred to the manipulation of chromosomes more than of genes, but Nikolai Timoféeff-Ressovsky had also used the term "genetic engineering" as early as 1934). Blakeslee's parts-based modular approach to chromosomal dynamics enabled him not only to characterize but to predict and to create novel types of species based on patterns of chromosomal rearrangement. Far from being opposed to an "engineering" approach, genetics in this period was much more than mere breeding – with the production of novel mutants, it was the site of some of the most interesting and enduring synthetic successes of the century.

2.6 Synthetic Biology and Genetic Engineering

Blakeslee's "genetic engineering" of the 1930s helped in the quest to create "synthetic new species" for human purposes. Synthetic biology and "genetic engineering" thus appear to have been closely related since at least this time. Similar sentiments and expressions existed in the Soviet Union: K. A. Timiryazev claimed that the highest state of Darwinism would be "to sculpture organic forms" (Zirkle 1959), while Nikolai Vavilov made tremendous efforts to improve agricultural yields through the establishment of seed banks, careful study of the centers of agricultural and botanical diversity of key genera, and through other efforts to also eventually "sculpt" crops to serve humanity. "By knowledge of the past, by studying the elements from which agriculture has developed, by collecting cultivated plants and domestic animals in the ancient centers of agriculture," Vavilov declared, "we seek to master the historical process. We wish to know how to modify cultivated plants and domestic animals according to the requirements of the day." Much like de

Vries' own similarly unabashed engineering approach to life, Vavilov declared that he wanted to be "directing the evolution of cultivated plants and domestic animals according to our will." He was but "slightly interested in the wheat and barley found in the graves of the Pharaohs of the earliest dynasties," he said. "To us constructive questions – problems which interested the engineer – are more urgent." Or, as he promised his students in an introductory lecture: "In the near future man will be able to synthesize forms completely unimaginable in nature." Such efforts at synthesizing new life forms took place in a distinct sociocultural context, of course – an exemplar of early Soviet science, Vavilov had declared: "I will quote Marx to you, 'Before scientists used to study the world to understand it; we study it in order to change it'" (Pringle 2008). But such claims of allegiance were to fail to prove to be enough: Vavilov was one of the many to suffer with the rise to power of Trofim Lysenko and his subsequent evisceration of Soviet agriculture and genetics.

In the West, however, synthetic approaches continued to emerge steadily throughout mid-century, even as Blakeslee's focus on chromosomal engineering faded with the ever-increasing attention given to H. J. Muller's successes with X-ray induced mutation of the gene. But even though such gene-centered work was not itself generally called "genetic engineering," the idea of precision control pervaded Muller's work. It was also a dominant theme in the thought of fellow traveler J. B. S. Haldane, whose worldview a critic once characterized as "the doctrine that the duty of the scientist is not to explain the world but to alter the world" (Langdon-Davies 1940). In line with this Marxist-*cum*-engineering philosophy, Haldane had delivered a paper at an international symposium on the origin of life entitled "Data needed for a Blueprint of the First Organism" (Clark 1968). And even the mid-century rise of molecular biology itself, as historian Lily Kay has noted, had "the goal of engineering life... inscribed into [its] program from its inception." Moreover, "this conceptualization of life as a technology was central to the empowerment of the molecular vision of life" (Kay 1993).

Other mid-century synthetic accomplishments include Stanley Miller's famed 1953 experiment into the origin of life, and the experiments of Arthur Kornberg and others concerned with the artificial synthesis of DNA. Both categories of experiments were routinely described as approaching near to the "creation of life in the test tube," in what had already been and would continue to be a recurring theme in the history of biology in the twentieth century. By the late 1960s and into the early 1970s, in the years just before the emergence of the new recombinant DNA technologies, the impact of imminent new biological techniques was already being debated and discussed, with particular reference to implications for humanity (Hotchkiss 1965). The re-emergence of the term "genetic engineering" in the mid-1960s, some 30 years after its first attachment to earlier techniques, was thus part and parcel of the larger eugenical goals and aims of the developing molecular biology, as Kay has shown (Kay 1996). But another more general term was felt to be needed to describe the powerful but more general potential of new techniques for the reconstruction of life beyond the human. With "genetic engineering" holding a fairly explicit eugenical valence by the early 1970s, "synthetic biology" was tapped instead to serve as the generic term of choice. Never a common term in this period, it was resurrected and redeployed from its earlier discursive home in the applications of chromosome engineering to now be used to describe the *gene*-level engineering of scientifically, agriculturally, or industrially important microorganisms using restriction enzymes.

Intriguingly, however, many of the dominant themes of today's synthetic biology – and particularly its emphasis on the genetic implementation of design principles and the uses of abstraction, not to mention the technosalvational rhetoric of promise and peril – echo quite strongly some of the claims of researchers of this earlier generation. "The essence of engineering is design," Robert Sinsheimer wrote in 1975, "and, thus, the essence of genetic engineering, as distinct from applied genetics, is the introduction of human design into the formulation of new genes and new genetic combinations," with new methods "supplementing" older techniques of experimental breeding. "For genetic engineering one would like to be able to rejoin such fragments in arbitrary ways," he noted (Sinsheimer 1975).

In sum, "synthetic biology" in the 1970s thus served as a somewhat rare but useful term that could capture the broader significance of the advent of recombinant DNA techniques – what we today would identify as "genetic engineering" – even as the term "genetic engineering" itself was until the mid-1970s associated more closely with a variety of other more eugenically loaded aims. Genetic engineering had remained synthetic in its aims from the 1930s to the 1970s, but by this later period the very common adjective "synthetic" could now be retooled by into a compound noun demarcating the "new era of synthetic biology."

2.7 Contemporary Synthetic Biology

Burke found fault with Leduc; Loeb criticized Burke; and other biologists and geneticists wondered just what Loeb thought he was up to. Artificiality and synthesis were always useful tools and yet also never sufficient to later investigators. In each case, an earlier investigator was applauded for an aspect of his accomplishments, but was still somehow seen as having failed in any ultimate sense to engineer life. Meanwhile, in the realm of experimental evolution, efforts towards the synthesis of new species – transforming "monsters" into "mutants" – proved the successful fulfillment of de Vries' dreams. By the end of the 1930s, synthetic new species could be produced at will. A generation later, with a shift toward engineering recombinant genes rather than chromosomes, recombinant DNA techniques were now hailed as bringing the dawn of a "new era of synthetic biology" – in contradistinction to the more direct eugenical and sometimes dystopian implications of the term "genetic engineering." An intriguing further terminological shift occurred once more by the mid-1970s, as "synthetic biology" seems to have disappeared from usage as a general term with the rise to prominence of "genetic engineering" in the sense with which we are now familiar. By the early 2000s, with the re-emergence of contemporary synthetic biology, efforts were made to distinguish this new engineered-based approach to life from earlier genetic engineering ("that's just breeding," said one participant at the 1.0 conference). Knowing these few details of the larger history of an engineering approach to life, and the ways in which terms like "synthetic biology" and "genetic engineering" have emerged, transformed, and sometimes been lost to history (at least for a time) helps to highlight a peculiar perception common among synthetic practitioners, and recurring over decades: that they alone have been the first to truly aim for – and possibly attain unto – a properly engineered biology.

Emerging around the new millennium, contemporary "synthetic biology" in its earliest years was frequently presented to interested audiences as novel, perhaps revolutionary, and cool. Biology was going to be rethought – for the "first time" – from foundational design principles with the ultimate goal of making it "easier to engineer." Such newfangled attempts to envision life as it could be shared certain rhetorical commonalities with and claimed insights from other near-contemporary efforts. Indeed, in an echo of events a century earlier, there are suggestive links between some of the first attempts at what would now be recognized as "synthetic biology" and other work in the mid- and late 1990s that had been explicitly referred to as "artificial life." Thomas Ray had published his "An Evolutionary Approach to Synthetic Biology" in 1995 at a moment when digital life was essentially co-extant with its code (Ray 1995), and by the late 1990s even complex biological systems were being eyed with a view to reading their code-equivalent, their genomes. Also by the late 1990s, Tom Knight, Gerald Sussman, Ron Weiss and other researchers had already begun to publish work in the realm of amorphous computing, an area that would also serve to bridge the gap between earlier work in artificial life, computer science, and biocomputing. With additional frequent references being made to analogous situations in the development of the software industry and what might be applicable from that case, a new vision for a re-engineered biology – synthetic biology as we understand it today – was emerging.[12]

From genetic algorithms in computer codes to genetic circuits being constructed from a digitized parts-based approach to biological systems, to an open-source ethos (or at least the aim of one), various threads were drawing together for an evolving but potentially coherent synthesis for the reengineering of life. Although a full history of

[12]For a brief philosophical overview of some of the conceptual linkages between artificial life of the late 1990s, and the efforts at amorphous computing in the nascent synthetic biology around 2000, see Keller 2002. Written just at the time of this transition, however, Keller's account wavers between seeking to claim a distinction between the artificial objects of intervention for computer scientists and the "actual practices" of "biologists who still live in a world of conventional biological objects... [and whose] activity remains grounded in material reality, and in the particular material reality of organisms as we know them." Keller also recognizes, however, that "mediums of construction can change, as they surely will. They might even come to so closely resemble the medium in which, and out of which, biological organisms grow that such a divide would no longer be discernable" (279, 288). The "hope" of Christopher Langton and others "to create artificial life, not just in cyberspace but in the real world" – in "some other (nonvirtual) medium" – might have now found its instantiation in the productive and provocative mix of metaphors and techniques in contemporary synthetic biology. After all, as Keller has noted, some of this early bridge work "draws its inspiration directly (and explicitly) from the early efforts" of various investigators in the realm of artificial life (285, 347, footnote 54).

this transition and the connections among investigators, technology, institutions, and research programs remains to be written, it is clear that today's synthetic biology is in no small measure the offspring of this unique confluence. And it found one of its first homes at the Computer Science and Artificial Intelligence Laboratory (CSAIL) at MIT where Knight, a senior research scientist, had come up with the idea of a "BioBrick" and where the "Registry of Standard Biological Parts" is still based today.

Drew Endy, another early contributor to the field and a civil engineer by training, had first met Knight in the 1990s about five years after Knight had himself first started working on questions in biology. Endy's further discussions with Rob Carlson and Roger Brent at the Molecular Sciences Institute in Berkeley in 1999 about the nature of a new approach to biological engineering – tentatively being called "open source biology" in direct reference to the open source software movement – served as another root for the larger emergence of the new field (Cohn 2005).

Synthetic biology undoubtedly has many roots in many fields and contexts, including traditional molecular biology and in the various attempts by many others to engineer life in this period. Moreover, today's "synthetic biology" could well have come to be known by any number of different names including "constructive biology" or even "intentional biology," as Endy, Carlson, and others have noted. Such contingencies should help to illustrate how a basic search for the ancestors of the field by label alone is insufficient to capture the true complexity and multiple roots of any field. And yet, just as Leduc still has a role to play in any history of early synthetic biology so, too, the particular path taken in recent years toward the actual *naming* of contemporary "synthetic biology" by some of its founders remains of interest.

Already by October 2000 Carlson and Brent had drafted a letter on "open source biology" (Carlson and Brent 2000). By the following year, in a classic generational critique of genetic engineering as it had developed since the 1970s, Carlson developed this line of thought further: "When we can successfully predict the behavior of designed biological systems, then an *intentional biology* will exist. With an explicit engineering component, intentional biology is the opposite of the current, very nearly random applications of biology as technology" (Carlson 2001).[13] Or as he later recalled:

> Through predictive design, biological systems should be both easier to understand and more useful. These engineered systems would behave as *intended*, rather than displaying random and mystifying behaviors often encountered when genetically modified organisms are introduced into new environments or set loose in the wild; i.e., *unintended* behaviors. Roger Brent, Drew [Endy], and I, even organized a meeting to figure out how to make this happen. 'After the Genome 6, Achieving an Intentional Biology,' was held in Tucson, AZ, in December of 2000. Alas, that name had unintended consequences, namely that the

[13]From its basic and central conceptual concern to address matters of intellectual property and innovation, secure funding, integrate technological advances, and discuss the impacts of economies of scale, much of contemporary synthetic biology has been theorized in interrelation with commercial and industrial concerns.

> biologists attending the meeting thought we were asserting that all prior molecular biology had been unintentional. If rotten vegetables had been available, I'd have been pelted during my talk. (Carlson 2006)[14]

Endy tells a similar story:

> Rob Carlson and I had a birthday bid promoting intentional biology, like 'we want to engineer biology in accordance with our intentions'. Within the etymological landscape the words 'biological engineering' had already been occupied but the word 'intentional biology' went over like a lead balloon. When we talked to people about it in systems biology, they took offense that we were implying that they were doing unintentional biology.[15]

In a ripe echo of Erwin Chargaff a generation earlier, would-be "intentional biologists" stood accused of something like practicing molecular or systems biology without a license.

From such one-off contingent events, a hunt for a new name was underway. More direct inspiration for Endy and Carlson is said to have come during a *Nature* cocktail party in San Francisco in 2001, when Carlos Bustamante suggested analogizing from the term "synthetic chemistry." But despite an occasional wobble to other possible terms – Endy favored "natural engineering" for a time – Bustamante's suggestion seemed to take root.[16] Although the new field of "synthetic biology" clearly shared significant aims and goals with the earlier "synthetic biology" approaches over the preceding century, it was anything but inevitable or foreordained that this was the name that would be eventually settled upon. Indeed, the new coinage seems to have come through no direct historical or verbal link to the earlier efforts to engineer biology![17]

Plans were made for an inaugural "synthetic biology" conference to be held in the early summer of 2004 at MIT – what would later be known as "Synthetic Biology 1.0." Knight would later describe it "the first conference of its type, anywhere." And as Endy recalled, "we were expecting about 150 people, so we booked a room for 297. And 500 people wanted to come given 6 weeks of notice" (Endy 2008). The conference was in fact a rather small affair. Knight pitched the idea of a BioBrick standard biological part at 1.0, though he had already been

[14]Curiously, "intentional biology" has re-emerged as the term of choice in a report from the Institute for the Future in Palo Alto, California, which says "[i]ntentional biology, and its two main subfields, biomimicry and synthetic biology, treat nature not as a source of raw materials, but as source and code." See: "Intentional Biology: Nature as Source and Code." http://www.iftf.org/system/files/deliverables/SR-1051_Intentional_Biology.pdf

[15]Endy, personal communication, BioBricks Foundation Workshop, UCSF, March 2008.

[16]But as Carlson recalled, "The phrase 'Synthetic Biology' certainly isn't new, and was emerging from other sources at the same time (Steven Benner, in particular, if memory serves)" (Carlson 2006). By late 2008, others were also beginning to point more readily to putative parallels between the development of contemporary synthetic biology and synthetic chemistry in the nineteenth century.

[17]It bears emphasis that this is only one historical path to contemporary synthetic biology, the one that supplied the current name of the field and some of its initial conceptualizations. There are, of course, as many conceptual and practical roots to the field as there are practitioners.

developing it for years, noting that while engineers often found the concept exciting, "[m]ost biologists simply glaze over. They are not excited. Nor should they be. It's a different agenda." But by tying in this new concept of a BioBrick "part" with the ingenuity and energy of undergraduate students during a January course at MIT, the seed of the International Genetically Engineered Machines competition (iGEM) had been planted and the reunification of synthetic biology with genetic engineering – arguably a century-long association – became possible. Synthetic biology soon had an initial, youthful, and powerful new engine for ongoing part development, even as discussions about what exactly constituted a part continued apace.

The full history of the 1.0 conference, and the many important technical developments and gatherings that have followed, also remains to be written. What is clear is that in only four years since its official debut, the field has taken on a wide variety of concerns and research agendas and even begun to differentiate as it has spread across the globe into different cultural and institutional contexts, and allied with already existing research efforts to engineer life. Just what counts as synthetic biology has even become an issue in some quarters.

The 2.0 conference held at the University of California, Berkeley in June 2006 was easily double the size of 1.0, with some applicants being turned away to due to space limitations (including several nonscientific observers). Fascinating new synthetic approaches were described at 2.0 and a sense of vitality and rapid growth pervaded the conference. Also by the time of this meeting, various civil society groups had begun to take notice of the new field and raised concerns about both the new bioengineering endeavors as well as about a proposed model of "self-governance" that they perceived to be without public participation or oversight. Thirty-six of these civil society groups teamed up to issue an open letter calling for a broader public dialogue. Engagement in real-time politics had both expectedly and unexpectedly become the order of the day.[18] Upon learning of the letter, conference organizers decided not to proceed with a general vote on any sort of principles of self-regulation or a code of conduct, things that had been offered as a model for engagement in discussions at 1.0. While an "Asilomar"-style action had been floated in discussions in 2004 as a forward-thinking move that synthetic biologists might do well to consider, the new reality on the ground in 2006 meant that any such "self-regulatory" actions ran a real risk of being perceived as "closed-shop" governance. (Indeed, this was to become a refrain of the ETC Group, one of the more vocal civil society groups, as well as the theme of their devastatingly creative "Little Closed Shop of Governance" poster at the 3.0 conference, inspired by the "Little Shop of Horrors.") Important and far-reaching large-group discussions about risk, safety, and public involvement were held at 2.0 as planned, but ultimately no action on "self-governance" was taken.

By the time of the 3.0 conference in June 2007, held at ETH in Zürich, Switzerland, the meaning of "synthetic biology" was already beginning to expand

[18] At 1.0, a researcher had wondered aloud to me during a coffee break whether "the activists" might not be "a few years behind the advances in the sciences." Attempts at 1.0 to prepare for a possible public "misunderstanding" of the field and the backlash this might generate – a discussion conducted in a session on "risk management" – proved to be prescient.

in different directions as ever-increasing numbers of researchers learned about the field and worked to integrate their own research programs with some of its larger goals. Some established researchers claimed to have been doing "synthetic biology" for years already and to good effect, wondering just what was supposed to be so new; others, generally younger, seemed full-fledged converts who had found a new religion. Several additional main schools began to emerge in Europe following this conference: in addition to parts and metabolic engineering, synthetic biology could now be understood to be engaged in the construction of minimal genomes or minimal cells, conducting research into the origin of life, or as creating orthogonal biochemistries – and more besides. At the 2.0 and 3.0 conferences, it had become clear that just what counted as synthetic biology, who had been doing it, how the community could govern itself, and who should count as a member of the larger "synthetic society," were all issues that had come to the fore.

At these conferences and at other workshops, issues of biosafety and biosecurity, of "bioterror and bioerror," also emerged, as did questions about intellectual property structures for the further development and commercialization of the field, leading in part to the founding of the BioBricks Foundation. Six months after 3.0, participants at an ESF-sponsored European conference on synthetic biology proposed that perhaps there was a need for an explicitly "European" approach to synthetic biology, based on the coordination of a broad array of existing areas of research under one umbrella (another meaning of "synthesis"), or that perhaps a "European strategy" might be devised by deciding upon a strategic initiative for success in one focused area of research. Synthetic biology was not only becoming internationalized – it was becoming situated in particular cultural, national, and institutional contexts.

Much more could be said about these developments and many more besides. Through all the current diversity of the field, it seems clear that the inaugural "flagship" 1.0 conference had unleashed a new and powerful movement to re-engineer biology, unfurling in many different directions at once. Interest has continued to grow, and only four years later, at the 4.0 conference in Hong Kong in October 2008 – a destination and locale carefully chosen to signal the international scope and intended destiny of the field – more than 600 participants came from around the world, more than double the number anticipated. With the announcement of new academic positions in synthetic biology, novel funding opportunities, talk of updating regulatory and governance structures, and a remarkable and growing level of interest from institutions and the broader media, synthetic biology by the start of 2009 had clearly attained a significant and growing level of prominence. As both its proponents and critics alike seem to envision, this adolescence is only the beginning of the shape of things to come.

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