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Synthetic Biology: Paradigm Revolution or Philosophical Eclipse? From *Bacillus subtilis* Genomics to Direct Design

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Abstract

Synthetic biology represents a profound transformation in the life sciences, shifting from reactive genetic manipulation to proactive, design-driven construction of biological systems. Using *Bacillus subtilis* genomics as a historical anchor, we trace the conceptual trajectory from genetic engineering through molecular biology to synthetic biology (SynBio), framing each transition through Thomas Kuhn's theory of paradigm shifts. We argue that SynBio constitutes a genuine revolutionary paradigm: Jacob's genetic program has become executable and editable through CRISPR, Hutchison et al.'s minimal genome (Syn3.0) defines the boundary between life and deliberate design and cheap DNA synthesis has compressed experimental timelines from months to days. However, this revolution carries the risk of a philosophical eclipse, the reduction of biological inquiry to pipeline optimization, unless accompanied by critical engagement with the perspectives of Keller, Haraway, and Jonas on emergence, ethics, and responsibility. We conclude that SynBio advances scientific understanding only insofar as it deepens, rather than bypasses, our engagement with the complexity of living systems.

Keywords: Synthetic Biology; Paradigm Shift; CRISPR-Cas9; Minimal Genome; Philosophy of Science; *Bacillus subtilis*

Introduction

Joshua Lederberg and Alexa McCray (2001) dissected the suffixes "-ome" and "-omics" as collective abstractions, *genome* echoing the rhizome's sense of wholeness [1]. This terminological genealogy reflects the successive reorientation of biological inquiry: from genetic engineering (1970s) through molecular biology (1950s–1990s) to synthetic biology (SynBio, 2000s onward). Thomas Kuhn's *The Structure of Scientific Revolutions* (1962) illuminates this sequence: each stage marks not just a technical upgrade, but a paradigm shift, in which the anomalies of "normal science" accumulate until a new conceptual matrix displaces the old [2].

François Jacob, in The Logic of Life (1973), introduced the powerful metaphor of the "genetic program": organisms as carriers of an inherited script, executed by molecular machinery [3]. This idea bridged classical genetics and molecular biology, translating Mendelian factors into informational sequences. Synthetic biology extends Jacob's framework in a consequential direction. SynBio takes this informational metaphor to its logical conclusion: the genome is not merely read and interpreted, but actively rewritten according to design specifications.

The complete sequencing of the *B. subtilis* subsp. Subtilis genome (4,214,810 bp; ~4,100 protein-coding genes; Kunst et al., 1997) exemplifies the achievements of molecular-biological approaches to genome characterization. It enabled secretion studies, for instance, the *sipS* signal peptidase, via manual cloning and YACs [4, 5, 6]. Yet the workflows of that era were deeply shaped by the genetic program metaphor as interpreted through molecular biology: the scientist as reader and incremental editor of an inherited script.

Synthetic biology pushes far beyond: de novo synthesis supplants the "one year to clone and express a single construct" paradigm. The Kuhnian question therefore emerges: are we witnessing a genuine paradigm revolution, or merely a technological acceleration that risks a philosophical eclipse of deeper biological questions?

Historical Trajectory: From Restriction-Based Cloning to Design-Driven Synthesis

Genetic engineering

Cohen et al. (1973) demonstrated the feasibility of recombinant DNA construction [7]. These approaches were characterized by low throughput, high failure rates, and substantial dependence on operator-specific expertise that was difficult to codify or transfer. In Kuhnian terms, this represented an extended pre-paradigm phase: powerful tools without yet a fully stabilized conceptual framework.

Molecular biology

The *B. subtilis* genome project (1993 - 1997) relied on lambda phage and YACs, revealing that 53% of protein-coding genes lacked detectable paralogs within the genome (singletons), and uncovering an expanded repertoire of transporters (77 ATP-binding proteins) [8]. Bioinformatics resources such as KEGG (Kyoto Encyclopedia of Genes and Genomes) enabled systematic functional annotation of the *B. subtilis* genome, linking gene catalogs to metabolic pathway data [9]. These insights required months of iterative cloning, plaques, screens, expression tests, and Sanger sequencing (1977) [10]. Sydney Brenner's championing of simple model organisms (*Caenorhabditis elegans*) and his framing of biology as a science of information were crucial in this phase [11]. Brenner's insistence that complex phenomena could be understood through minimal, tractable systems paved the way for today's minimal synthetic chassis, such as *Mycoplasma* Syn3.0.

Synthetic biology

SynBio, as articulated by Endy (2005), seeks standardized biological parts and composable design rules [12]. The Syn3.0 minimal genome, comprising approximately 473 genes [13], represents the culmination of this informational logic: a genome written almost entirely by design rather than assembled via classical cloning. This convergence reflects Brenner's foundational emphasis on minimal, tractable biological systems [11] and the goal, subsequently pursued by Venter and colleagues, of demonstrating that a functional genome could be defined, synthesized, and booted de novo [13, 14], a demonstration of what Feynman's maxim demands: that genuine understanding requires the capacity to build. SynBio eliminates many manual bottlenecks through sequence assembly via Gibson assembly [15] and Golden Gate cloning [16], combined with rapidly declining DNA synthesis costs (from ~$25/bp in the 1990s to below $0.35/bp by 2009) [17]. The exponential decline in synthesis costs, the so-called "Carlson Curve", represents not merely incremental improvement but a structural economic transition that has redefined what experiments are feasible [17]. This shift reorients the central experimental question from technical feasibility, whether a given construct can be assembled, toward rational design: what biological function should be engineered and how.

Our recent work in *Bacillus velezensis* genomics (2025) projects this logic forward: microbial genomes become platforms for future synthetic probiotics and antimicrobial resistance (AMR) interventions [18]. The conceptual distinction between these paradigms is fundamental: whereas genetic engineering and classical molecular biology operate reactively, modifying existing genetic sequences in response to empirical findings, synthetic biology proceeds proactively, designing novel biological functions from first principles prior to physical implementation (Table 1).

The three paradigm transitions outlined above are further illustrated in Figure 1, which illustrates the conceptual trajectory from genetic engineering through molecular biology to synthetic biology. Each transition is marked not only by new tools, but by a fundamental reorientation of biological inquiry, from discovering what exists to designing what could exist.

Synthetic Biology in Practice: Diagnostics, Proteins, and Accelerated Design

Synthetic biology revolutionizes research by suppressing intermediates and collapsing experimental timelines.

Diagnostics. Toehold RNA sensors and aptamer-based assays embody a "one protein, one diagnosis" logic; no longer are vast libraries strictly necessary [12, 19]. Transcriptomic studies of *Salmonella* Dublin infecting bovine epithelial cells have revealed serovar-specific gene expression patterns that guide the rational design of targeted detection constructs, moving beyond blind library screening approaches [20].

Proteins and vaccines. Direct synthetic cassettes now encode *Lactiplantibacillus plantarum* butyrogenic proteins with enteroprotective potential [21], as well as *Corynebacterium pseudotuberculosis* rPTS-based vaccine antigens [22].

Quantified gains. What once demanded a year of cloning now compresses into days or weeks, increasingly supported by cell-free systems that detach design from the constraints of specific host strains [12, 13, 23].

Craig Venter's insistence that crafting a minimal genome is a step toward "creating life" can be read in two ways: as an audacious claim to a new paradigm and as a provocation that forces us to ask what "life" means when its material instantiation is the output of a CAD pipeline [13]. George Church widens this perspective, envisioning SynBio as a platform for massive genome rewriting at scale, multiplex editing, recoding, and even species-wide interventions [24]. His work exemplifies both the democratizing potential and the dual-use risks of SynBio: from low-cost DNA synthesis for community laboratories to the possibility of DIY pathogen assembly [25].

Table 1: Overview of three successive paradigm phases in the life sciences, illustrated with representative workflows from B. subtilis research and characteristic institutional responses to each transition.

A Kuhnian Overview of Paradigm Transitions.

Paradigm	Kuhnian Phase	Workflow (*B. subtilis* example)	Timeline	Resistance Today
Genetic Engineering	Pre-paradigm	Manual restriction/ligation; first recombinant DNA (Cohen/Berg, 1972–1973) [7]	6 - 12 months	Considered obsolete; survives in legacy "cookbook" laboratories
Molecular Biology	Normal science	Cloning via YACs/phage; PCR (*sipS* peptidase [5] Sanger sequencing [10]	3 - 6 months	"Students must clone manually!" - attachment to trial-and-error pedagogy
Synthetic Biology	Revolutionary	CAD design → DNA synthesis (<$0.35/bp [17]) Gibson/Golden Gate/CRISPR assembly [16,18] *Synthia/Mycoplasma* (2010s) [14]	Days - weeks [12,13]	"Why waste time cloning?" - generational divide among faculty [2]

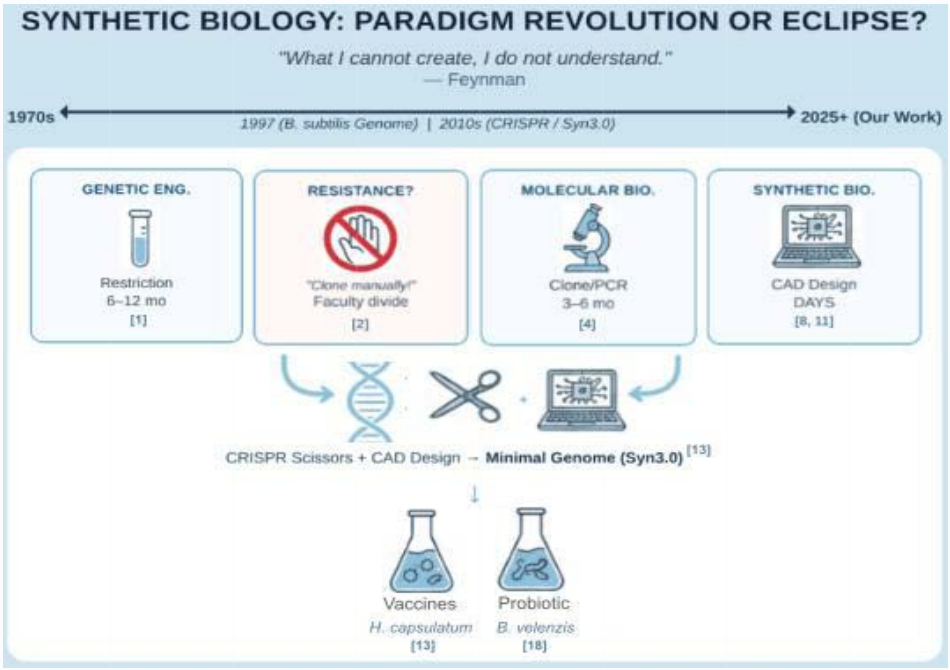

Figure 1: Conceptual overview of the three paradigm transitions in the life sciences: from genetic engineering through molecular biology to synthetic biology (SynBio), illustrating the shift from reactive manipulation to proactive, design-driven construction of biological systems.

CRISPR-Cas9 and the Transition to Precision Genome Editing

Jennifer Doudna and Emmanuelle Charpentier's development of CRISPR-Cas9 transformed genome editing into something very close to text editing [26]. Placed within Jacob's informational framework, CRISPR functions as a mechanism for targeted revision: specific nucleotides, regulatory elements, or entire loci can be altered, deleted, or replaced with unprecedented precision [26]. In practical terms, CRISPR short-circuits much of the manual "drudgery" of classical cloning.

Where older workflows required iterative restriction/ligation cycles and elaborate screening, CRISPR enables targeted, efficient edits that align perfectly with the SynBio ethos: design what you want, then implement it precisely. This shift mirrors a Kuhnian transition within experimental practice itself: from the craft of cloning to the abstraction of design. Resistance to CRISPR-based workflows often stems from a pedagogical attachment to the older paradigm, "students must learn restriction enzymes by hand", even when such training no longer reflects frontline research.

The Risk of Philosophical Eclipse: Keller, Haraway, and Jonas on the Limits of Design

Evelyn Fox Keller has long criticized the "genetic program" metaphor for smuggling in reductionist assumptions and obscuring the role of context, emergence, and interaction [27]. From a Kellerian perspective, SynBio's language of circuits, modules, and chassis risks intensifying this reductionism. When we treat cells as interchangeable hardware and DNA as clean software, we may lose sight of: the microbiome's ecological complexity; nonlinear, emergent behaviors that defy simple circuit metaphors; the historical contingency and material embeddedness of living systems.

Haraway's analysis of the politics of hybrid entities [28] is directly applicable here: synthetic organisms, minimal cells, and engineered probiotics are artefacts whose production raises questions of ownership, access, and the distribution of risk.

Hans Jonas, in articulating the principle of responsibility, provides a critical ethical counterweight to SynBio's technical optimism [29]. If we can rewrite genomes at scale (Church), create minimal cells (Venter), and distribute CRISPR tools widely (Doudna and Charpentier), then our obligations extend far beyond the laboratory. These fall into three categories: (i) dual-use risk, the same tools that enable diagnostics and vaccines can be applied to pathogen engineering; (ii) intergenerational responsibility, interventions at the level of ecosystems or germlines produce effects that extend across generations; and (iii) professional ethics, the risk that doctoral training reduces to workflow optimization, uncoupled from conceptual or ethical reflection [29].

From a Jonasian perspective, the SynBio revolution must be accompanied by an equally serious revolution in ethical education and governance, lest technical capability outpace the ethical and regulatory frameworks required to govern its responsible application.

Kuhnian Critique: Clinging to Cloning Amid Revolution

Kuhn's notion of incommensurability, that adherents of competing paradigms "live in different worlds", maps neatly onto the current divide between traditionalists in molecular biology and SynBio-oriented researchers [2]. Resistance to SynBio-oriented curricula has been observed in discussions of biology education, and frequently centres on the argument that proficiency in classical cloning procedures constitutes a prerequisite for conceptual understanding [30].

However, if we take Feynman's maxim seriously ("What I cannot create, I do not understand"), then the ability to design functional

biological systems may be a more appropriate contemporary criterion for understanding than the ability to operate legacy cloning workflows. SynBio's conceptual core lies not in mastering a specific enzyme kit, but in grasping how information, context, and dynamics interact to produce function - and then creating systems that realize these insights.

Our own trajectory, from *B. subtilis* genome mapper using YACs and phage to *Corynebacterium* pangenomist and SynBio practitioner, illustrates this transition [4, 6, 8, 31]. Where the *B. subtilis* project once required laborious mapping of regions such as *spo*VA-*ser*A [4,6], today CAD (Computer-Aided Design) tools simulate circuits and firms such as Twist or IDT synthesize custom constructs on demand. Educators therefore face a choice: continue to sacralize pipetting as the essence of training, or pivot toward design thinking, systems integration, and ethical reasoning as the new core competencies.

Paradigm Revolution, Not Philosophical Eclipse

Is synthetic biology a paradigm revolution or a philosophical eclipse? The answer, we argue, is both a conditional "yes" to the former and a preventable "no" to the latter.

On the side of revolution: Jacob's genetic program is now executable and editable at will [3]; Brenner's minimal models have evolved into minimal synthetic chassis (Syn3.0) that expose the boundary between life and nonlife [11]; Venter, Hutchison, and Church have demonstrated that genomes can be designed, synthesized, and massively rewritten, shifting biology from discovery to construction [13, 14, 24]; Doudna and Charpentier's CRISPR work made precise editing accessible and routine, bringing Feynman's ideal of understanding through creation into mainstream laboratory practice [26].

On the side of a potential eclipse: Keller warns that circuit metaphors may intensify reductionism, sidelining emergence and ecology [27]; Haraway reminds us that synthetic organisms are political and cultural artifacts, not just neutral tools [28]; Jonas insists that the power to create and rewrite life demands a matching expansion of responsibility [29]; From our vantage point, SynBio democratizes biology: faster diagnostics (e.g., *Salmonella* spp.), rationally designed vaccines (*Histoplasma capsulatum*) and engineered probiotic formulations, including those based on *Lactiplantibacillus plantarum* [21], with potential activity against AMR pathogens [18, 20, 32].

Democratization without philosophical depth, however, risks exactly the eclipse we caution against: a landscape of highly skilled technicians executing pipelines whose broader implications they have never been invited or trained to question.

In Kuhnian terms, synthetic biology is indeed a revolutionary paradigm, but it will only count as scientific progress in the fullest sense if it also enriches our understanding of life, not merely our capacity to manufacture products. To avoid a philosophical eclipse, we must: teach students not just to pipette less, but to think more about systems, emergence, ethics, and responsibility; integrate the insights of Jacob, Brenner, Keller, Haraway, Jonas, and others into SynBio curricula, not as afterthoughts but as central to the discipline; embrace Feynman's demand that creation and understanding go together, while recognizing that creation at the scale of genomes and ecosystems entails duties that earlier generations of molecular biologists could scarcely imagine.

References

1. Lederberg J, McCray AT. 'Ome sweet 'omics - a genealogical treasury of words. The Scientist. 2001; 15(7): 8.
2. Kuhn TS. The Structure of Scientific Revolutions. Chicago, IL: University of Chicago Press; 1962.
3. Jacob F. The Logic of Life: A History of Heredity. Spillmann BE, trans. New York, NY: Pantheon Books; 1973.
4. Sorokin A, Azevedo V, Zumstein E, Galleron N, Ehrlich SD, Serror P. Sequence analysis of the Bacillus subtilis chromosome region between the serA and kdg loci cloned in a yeast artificial chromosome. Microbiology. 1996; 142 (Pt 8): 2005-2016. doi:10.1099/13500872-142-8-2005.
5. Bolhuis A, Sorokin A, Azevedo V, Ehrlich SD, Braun PG, De Jong A, et al. Bacillus subtilis can modulate its capacity and specificity for protein secretion through temporally controlled expression of the sipS gene for signal peptidase I. Mol Microbiol. 1996; 22(4): 605-618. doi:10.1046/j.1365-2958.1996.d01-4676.x
6. Azevedo V, Alvarez E, Zumstein E, Damiani G, Sgaramella V, Ehrlich SD, et al. An ordered collection of Bacillus subtilis DNA segments cloned in yeast artificial chromosomes. Proc Natl Acad Sci USA. 1993; 90(13): 6047-6051. doi:10.1073/pnas.90.13.6047
7. Cohen SN, Chang AC, Boyer HW, Helling RB. Construction of biologically functional bacterial plasmids in vitro. Proc Natl Acad Sci U S A. 1973; 70(11) :3240-3244. doi:10.1073/pnas.70.11.3240
8. Kunst F, Ogasawara N, Moszer I, et al. The complete genome sequence of the Gram-positive bacterium *Bacillus subtilis*. *Nature*. 1997; 390(6657): 249-256. doi:10.1038/36786
9. Kanehisa M, Goto S. KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 2000; 28(1): 27-30. doi:10.1093/nar/28.1.27
10. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977; 74(12): 5463-5467. doi:10.1073/pnas.74.12.5463
11. Brenner S. Nature's gift to science (Nobel lecture). Chembiochem. 2003; 4(8): 683-687. doi:10.1002/cbic.200300625
12. Endy D. Foundations for engineering biology. Nature. 2005; 438(7067): 449-453. doi:10.1038/nature04342
13. Hutchison CA 3rd, Chuang RY, Noskov VN, Assad-Garcia N, Deerinck TJ, Ellisman MH, et al. Design and synthesis of a minimal bacterial genome. Science. 2016; 351(6280): aad6253. doi:10.1126/science.aad6253
14. Gibson DG, Glass JI, Lartigue C, Noskov VN, Chuang RY, Algire MA, et al. Creation of a bacterial cell controlled by a chemically synthesized genome. Science. 2010; 329(5987): 52-56. doi:10.1126/science.1190719
15. Gibson DG, Young L, Chuang RY, Venter JC, Hutchison CA 3rd, Smith HO. Enzymatic assembly of DNA molecules up to several hundred kilobases. Nat Methods. 2009; 6(5): 343-345. doi:10.1038/nmeth.1318
16. Engler C, Kandzia R, Marillonnet S. A one pot, one step, precision cloning method with high throughput capability. PLoS One. 2008; 3(11): e3647. doi:10.1371/journal.pone.0003647
17. Carlson R. The changing economics of DNA synthesis. Nat Biotechnol. 2009; 27(12): 1091–1094. doi:10.1038/nbt1209-1091
18. Sousa EG, Campos GM, Viana MVC, Gomes GC, Rodrigues DLN, Aburjaile FF, et al. The research on the identification, taxonomy, and comparative genomics analysis of nine Bacillus velezensis strains significantly contributes to microbiology, genetics, bioinformatics, and biotechnology. Front Microbiol. 2025; 16: 1544934. doi:10.3389/fmicb.2025.1544934
19. Green AA, Silver PA, Collins JJ, Yin P. Toehold switches: de-novo-designed regulators of gene expression. Cell. 2014; 159(4): 925-939. doi:10.1016/j.cell.2014.10.002

20. Salaheen S, Kim SW, Haley BJ, Van Kessel JAS. Differences between the global transcriptomes of Salmonella enterica serovars Dublin and Cerro infecting bovine epithelial cells. BMC Genomics. 2022; 23(1): 498. doi:10.1186/s12864-022-08725-z

21. Dos Santos TG, Dos Santos KAG, de Oliveira EJF, Brenig B, Paulo EM, Marques PH, Azevedo V, et al. Genomic scale analysis foresees enteroprotective and butyrogenic properties in Brazilian isolates of Lactiplantibacillus plantarum. Probiotics Antimicrob Proteins. 2025. doi:10.1007/s12602-025-10495-5

22. Dorella FA, Pacheco LG, Seyffert N, et al. Antigens of Corynebacterium pseudotuberculosis and prospects for vaccine development. Expert Rev Vaccines. 2009; 8(2): 205-213. doi:10.1586/14760584.8.2.205

23. Pardee K, Green AA, Ferrante T, et al. Paper-based synthetic gene networks. Cell. 2014; 159(4): 940-954. doi:10.1016/j.cell.2014.10.004

24. Church GM, Regis E. Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves. New York, NY: Basic Books; 2012.

25. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science. 2002; 297(5583): 1016–1018. doi:10.1126/science.1072266

26. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014; 346(6213): 1258096. doi:10.1126/science.1258096

27. Keller EF. The Century of the Gene. Cambridge, MA: Harvard University Press; 2000.

28. Haraway DJ. Simians, Cyborgs, and Women: The Reinvention of Nature. New York, NY: Routledge; 1991.

29. Jonas H. The Imperative of Responsibility: In Search of an Ethics for the Technological Age. Chicago, IL: University of Chicago Press; 1984.

30. Smanski MJ, Zhou H, Claesen J, Shen B, Fischbach MA, Voigt CA. Synthetic biology to access and expand nature's chemical diversity. Nat Rev Microbiol. 2016; 14(3): 135-149. doi:10.1038/nrmicro.2015.24

31. Jesus HNR, Ramos JN, Rocha DJPG, Alves DA, Silva CS, Cruz JVO, Azevedo V, et al. The pan-genome of the emerging multidrug-resistant pathogen Corynebacterium striatum. Funct Integr Genomics. 2022; 23(1): 5. doi:10.1007/s10142-022-00932-x

32. Marques PH, Tiwari S, Felice AG, Jaiswal AK, Aburjaile FF, Azevedo V, et al. Design of a multi-epitope vaccine against Histoplasma capsulatum through immunoinformatics approaches. J Fungi. 2024; 10(1): 43. doi:10.3390/jof10010043