# Making Knowledge in Synthetic Biology: Design Meets Kludge

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## Abstract

Synthetic biology is an umbrella term that covers a range of aims, approaches, and techniques. They are all brought together by common practices of analogizing, synthesizing, mechanicizing, and kludging. With a focus on kludging as the connection point between biology, engineering, and evolution, I show how synthetic biology's successes depend on custom-built kludges and a creative, "make-it-work" attitude to the construction of biological systems. Such practices do not fit neatly, however, into synthetic biology's celebration of rational design. Nor do they straightforwardly embody Richard Feynman's "last blackboard" statement (1988) that without creating something it cannot be understood. Reflecting further on the relationship between synthetic construction and knowledge making gives philosophy of science new avenues of insight into scientific practice.

## Keywords

construction, design, engineering, kludging, scientific knowledge, synthetic biology, systems biology



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*The dream is that well-characterized components can be easily assembled to generate novel genetic regulatory circuits. The reality is that this is hard to accomplish.*

— Haseltine and Arnold (2007: 15)

The aim of this article is to investigate the philosophical character of synthetic biology through an examination of its knowledge-making practices. I will ask a series of questions about how knowledge is made in synthetic biology, what sort of knowledge is produced, and what the relationship is, in fact, between knowledge and making. These are practical epistemic questions that are being discussed in very distinctive ways within synthetic biology, as those under its banner lay claim to a loosely bounded technological and epistemological territory. The answers to these questions have important implications for how scientists and philosophers think about knowledge making in general.

## Knowledge-Making Practices in Synthetic Biology

Synthetic biology is often given a potted origins narrative that emphasizes its historic dependence on DNA recombination techniques and genetic manipulation (e.g., Benner and Sismour 2005; Drubin et al. 2007). This observation is in part due to Waclaw Szybalski's announcement of synthetic biology in 1974 and 1978 (Szybalski 1978). As this issue demonstrates, a richer and deeper history may be in the making (see also Morange 2009). But for many purposes, synthetic biology can be straightforwardly described as an extension of the biotechnological capabilities of molecular biology, especially in the form of genomics. It is the latter field that most directly gives rise to a general notion of synthetic biology as biological engineering, and this is achieved on the basis of the molecular quantification afforded by large-scale sequencing and microarray projects. Roger Brent, now the president, CEO, and director of the independent, non-profit Molecular Sciences Institute (Berkeley, CA), anticipated the rise of synthetic biology as a consequence of the most basic achievements of genomics:

> The genome projects, with their promise of complete parts lists, have caused would-be engineers to start turning up in biology labs. It is unclear whether the first products of these cellular hackers, typically recreations of cellular clocks, switches, oscillators, etc., will themselves have any immediate positive impact on biology.. . . However, the engineers who build these devices will affect biology profoundly.. . . Even absent stimulus from biologists, this drive to perform engineering with a rigorous design component will spur development of biological simulations and the collection of information to populate them (Brent 2000: 176).

In this scenario, engineering approaches emerge as a response to parts lists, but in the process engineering becomes a shaper of techniques, data gathering, and research orientation: "The overwhelming physical details of natural biology . . . must be organized and recast *via* a set of design rules that hide information and manage complexity" (Keasling 2008: 65). It is in this sense of *rationally* engineering biological systems that synthetic biology finds its rallying cry, with the strong claim being made that never before has biology found itself in the position of being able to overcome the irrationality of nature with human-made rational design (e.g., Boyle and Silver 2009; Mukherji and van Oudenaarden 2009). The three engineering Rs of rationality, robustness, and reliability are contrasted with the whimsicality, inelegance, and variability of natural systems (Pleiss 2006). While engineering certainly contributes to the practices of synthetic biology, my claim is that it is doing this in more complicated ways than might be envisioned in the "pure" engineering ideal.

While it is common to talk about synthetic biology as if there were a distinctive and coherent set of practices under the label, in reality it consists of a number of different streams of practice. These differences have implications for how and what sort of knowledge is produced (O'Malley et al. 2008). The first stream is one that can be described as *DNA-based device construction*. It starts with DNA synthesis and works upwards. Many of its proponents emphasize standardization, decoupling, and abstraction as key routes to knowledge making in synthetic biology (e.g., Knight 2003; Endy 2005; http://parts.mit.edu). All of these practitioners are committed to decomplexifying biology in order to gain full control of the biological processes being synthesized (Ferber 2004; Guido et al. 2006; Voigt 2006).

The second stream involves *genome-driven cell engineering*. Here, synthetic biologists focus on streamlining and modularizing genomes through minimal genome analysis, whole-genome synthesis, and the transplantation of "foreign" or modified genomes into cells (Cello et al. 2002; Smith et al. 2003; Gil et al. 2004; Chan et al. 2005; Glass et al. 2006; Pósfai et al. 2006; Lartigue et al. 2007, 2009). These practitioners conceive of the genome as a simplifiable, relocatable module that runs cellular processes and simply needs some easily obtained connectivity in order to be plugged into a cell chassis (Heinemann and Panke 2006).

The third stream focuses on *protocell creation*, using micelles, lipid self-assembly, and vesicles with ribozymes (Szostak et al. 2001; Deamer 2005; Noireaux et al. 2005; Forster and Church 2006; Luisi et al. 2006; Solé et al. 2007). Using top-down, bottom-up, and in-between approaches, these synthetic biologists work on constructions such as minimal cells, designed to approximate living cells at their most basic level. Although protocell synthesizers make many allowances for the complicated and unpredictable outcomes of evolution, they are keen to minimize such complexities because that makes artificial reconstruction more effective.

Another way of categorizing synthetic biology is to view it over time and see distinctions between the "first wave" of construction of very simple parts and modules, and a

second wave—only just begun—of whole system construction (Purnick and Weiss 2009). But just as important for this discussion as the differences in streams of practice are the shared knowledge-making dynamics in synthetic biology. One characteristic that brings the field together is the drive to replace or displace complexity with rationally determined, highly predictable systems. And although there are differences between the various schools of synthetic biology, all the approaches discussed above combine a similar set of steps in order to achieve the goal of constructing designed and decomplexified systems. Although these steps are carried out in different ways, they characterize today's efforts in synthetic biology and construct a certain attitude to biological knowledge production.

## Analogizing

Instead of channeling its flow of inquiry from the biological phenomenon of interest to its disassembly and then its modeling and comprehension, synthetic biology sets out from system design to gather and construct relevant components, and thereby create a biological machine that is regarded as the instantiation of knowledge (Ferber 2004). One of the most explicit accounts of why biological practice should work this way can be found in Yuri Lazebnik's classic 2002 discussion, "Can a biologist fix a radio?" In this article, Lazebnik sets out the biologist's view in contrast to the engineer's view, and argues that today's biologists must take the latter perspective in order to understand and do things effectively with biological systems. Traditional biological methodologies of cataloguing parts, finding connections between them, and qualitatively modeling function will not enable systems to be improved and understood, he argues (Lazebnik 2002). This will require the standardized, transferable language of engineers in reference to the total quantification of elements in the system.

Curiously, however, Lazebnik admits that the radio circuitry diagram he uses to exemplify his argument is not of the radio in the study. "The diagram of this radio was lost," he says (2002: Fig. 3, legend), and this explains why the radio is still broken. This is curious because Lazebnik claims that the radio is "an open book" to any engineer. The advantage of the engineering approach is meant to be that it would enable the engineer to fix the radio easily and quickly by detecting damage within the well characterized system through standard electronic tests and tools. Diagnosis should be followed by the repair or replacement of any dysfunctional components with standardized parts. One of the answers to Lazebnik's own question in his paper's title seems to be, "Engineers can only fix a particular radio if they have a plan of it." The fact his Russian radio is apparently unrepairable, despite Lazebnik's familiarity with radio circuitry, may say something about the problems of componentry and variability, and the need for more qualitative expertise in particular systems to be able to diagnose and intervene in the problem machinery.

The difficulties of finding identical replacement parts is not often addressed by the second type of analogizing, which focuses on components and levels of the systems rather than on practice itself. Electronic networks, pathways, circuits, and especially modules are used as conceptual templates for biological components (Andrianantoandro et al. 2006; Canton et al. 2008). Synthetic biology is in the process of shifting from the construction of individual components to the creation of functional modules. Its aim is eventually to construct entire complex systems composed of standardized modules, but at the moment this is still very much a hit-and-miss affair (Voigt 2006; Purnick and Weiss 2009). The context dependence of any designed part means that the uniformity and exact reproducibility of function—even in a redesigned and simplified system—cannot yet be expected (Andrianantoandro et al. 2006; Serrano 2007; Arkin 2008).

One of the best-known approaches to synthetic biology, the DNA-based device stream, conceptualizes biological devices as modular, standardized, interchangeable, stable, and predictable (Endy 2005; Canton et al. 2008; Shetty et al. 2008). Modularity poses many challenges—for this school and all synthetic biology. Part of the problem is the way in which modules are defined in engineering disciplines. As systems biologist Jeremy Gunawardena points out:

> In software engineering, modularity means "putting a boundary around some set of things" to set it apart from the rest of the system. Separated modules then communicate through controlled interfaces. This strategy breaks big problems into little problems. But are biological modules the same? Can they be enclosed and made to communicate in restricted ways? Or are biological modules just too permeable? (Gunawardena 2008)

In an innovative paper on experimental synthetic biology in bacterial networks, Mark Isalan and coauthors (2008) conclude that

> Our results indicate that partition of a network into small modules . . . could in some cases be misleading, as the behavior of the module is affected to a large extent by the rest of the network in which they are embedded.

Even though the existence of modules is crucial to the success of engineering approaches in biology (Hartwell et al. 1999; Andrianantoandro et al. 2006; Heinemann and Panke 2006), modularity may be a theoretical dictate that biology itself fails to obey (Wolf and Arkin 2003). A number of other disanalogies between engineered and biological systems have been suggested. The first is that evolution is not design, and that there are numerous overly complex products of evolution, many of which rational design processes cannot simply replicate (Arkin 2008). Connections between designated modules are often unknown, and the complexity of evolved systems is

not maskable. Abstraction from these systems and modules is therefore limited (Sorger 2005).

Many synthetic biologists hope that modularity issues can be overcome by greater standardization (e.g., Canton et al. 2008; Peccoud et al. 2008). There are also, however, more general objections to the engineering analogy. Lazebnik (2002) rebuts three commonly raised problems. In response to the objection that biology cannot handle simple systems so it will not be better at handling complex systems, he argues that engineers are undeterred by complex systems because they have developed formal languages and computational power. To the second objection, that engineering approaches are not applicable to cells because cells are fundamentally different from the objects studied by engineers, Lazebnik counters with the claim that biologists are superstitious and retain vitalist tendencies. Moreover, he says, radios and other designed systems have deep similarities to living systems. To the third common objection, that biologists know too little about cells to analyze them in the way engineers analyze their systems, Lazebnik says we know enough to put together formal models and find out at least the processes that are missing in our existing explanations.

While the assumptions underpinning these responses are questionable, the more important factor to note for my discussion is that Lazebnik is not advocating synthetic biology per se but the formal and quantitative mathematical modeling that often accompanies it. If anything is generally distinctive of synthetic biology at the rhetorical level, it is its claim to go beyond mere modeling and to treat biological systems as fully constructible objects.

## Synthesizing

Many discussions of synthetic biology contrast it to analysis, which involves the deconstruction or individualization of parts of systems (e.g., Benner and Sismour 2005). Such practices are often linked to "discovery-oriented" approaches. Synthesis, however, is characterized as being about the fabrication or construction of biological systems, in which parts are integrated into designed constructs (Ferber 2004; Marguet et al. 2007). In practice, of course, synthetic biology is as analytic as it is synthetic. To get started on their synthesizing activities, all synthetic biologists deconstruct systems into parts. In the footer of every Web page of the BioBricks site is the slogan "making life better, one part at a time" (http://syntheticbiology.org/). And, clearly, synthetic biology in general would not be possible without the knowledge base delivered by so-called analytic approaches. However, synthetic biologists do make a special claim for an epistemology of "constructing" or making as the source of real knowledge and see this as the trump statement of synthesizing (e.g., Drubin et al. 2007; Weber and Fussenegger 2009).

## Mechanicizing

Synthesis is too bland a word, however, to describe the efforts and rhetoric of construction synthetic biology. Another major characteristic of the field is its aim to put things together in a rational way and make them work predictably. This practice of making things work in a controlled manner is also an obvious descriptor of engineering practices. It involves the *art* of combining (re)constructed parts, often using circuit analogies, into predictably functioning devices. Transcriptional regulators are some of the best-known constructions so far produced by synthetic biologists (Becskei and Serrano 2000; Elowitz and Leibler 2000; Gardner et al. 2000), and a range of other devices have been built on the basis of other biological processes (Andrianantoandro et al. 2006; Issacs et al. 2006; Drubin et al. 2007; Purnick and Weiss 2009).

I have described these efforts to make things work as "art" for a number of reasons.[1] The first is that as paradigmatic instantiations of synthetic biology, such constructions are not a matter of copying biology, but of recreating it. Speaking of the famous three-gene repressilator, David Sprinzak and Michael Elowitz (2005: 443) say that such devices are "much simpler . . . and fail to operate as reliably [as natural clock circuits] but they provide a proof of principle for a synthetic approach." They did not aim to construct a natural biological system exactly as found in the "wild," but to make something with an approximately similar function and a more streamlined design. These engineers hope to learn more by constructing an oversimplified inaccurate pendulum clock than they can by disassembling a sophisticated Swiss timepiece (Sprinzak and Elowitz 2005: 447). This strategy is then applied to the pressing need to bypass evolutionary complexity.

> Combinations of well characterized biological parts to create synthetic wholes not only drives towards applications faster but also finesses past the underdetermination and crosstalking nonmodularity of natural systems. With the advent of facile synthesis and reusable modules, the evolutionary bricolage can be studied or avoided as needed. (Church 2005: 2)

As well as recreating biological systems through simplified design, synthetic biologists have to cope with the heterogeneity of natural biological systems (Elowitz et al. 2002; Blake et al. 2003; Paulsson 2004; Raj and van Oudenaarden 2008). Biological synthesizers must compensate for (and sometimes take advantage of) the fluctuation of processes within cells, and the variability between genetically "identical" cells in "identical" environments. Andrea Loettgers (this issue) discusses the issue of "noise" in biological systems and how this is dealt with and reinterpreted by some synthetic biologists as facilitating the evolution of developmental mechanisms or robustness to environmental perturbation (Eldar et al. 2007; Çağatay et al. 2009). It is increasingly well accepted that combining different parts with known functions into a system

will not necessarily lead to predictable, additive functioning of the new system. Entirely new capacities and behaviors may emerge through such combination (Simpson 2004; Purnick and Weiss 2009).

A further complication is that the repositories for standardized parts are well known for the *non*-standard nature of their parts (Peccoud et al. 2008; Katsnelson 2009). In this respect, synthetic biology is not unlike software standardization. "The nicest thing about standards is that there are so many of them to choose from," joked operating system designer Andrew Tanenbaum (1988: 254).[2] All of this heterogeneity (natural and artefactual) has consequences, however, for the type of engineering that can be done in synthetic biology, and make it more similar to an intuitively creative "art" than the rational "plug and play" of predictable properties to which it is analogized (Koyabashi et al. 2004). The failure of designed systems due to molecular fluctuations and context dependence may greatly enable understanding of noisy phenomena and contextual interactions (Andrianantoandro et al. 2006), but design will have to become biologically flexible, plastic, and complex in order to work.

Combinatorial synthesis and directed evolution are likely, therefore, to be necessary complements to or even replacements of rational design, which—even when it works—requires multiple iterations of reconstruction and redesign (Blake and Issacs 2004; Haseltine and Arnold 2007; Michalodimitrakis and Isalan 2008; Koide et al. 2009). In *combinatorial design*, separate components are assembled *in vitro* and then placed in randomized combinations in cells, which are then screened for the desired function (Guet et al. 2002). This can work for simplified circuit behavior but may not be suitable for large networks with multiple functions, because of the extensive screening required (Haseltine and Arnold 2007). *Directed evolution*, a solution aimed against high failure rates in rationally engineered proteins, attempts to improve designed genetic circuits through targeting mutations and recombinations (Francois and Hakim 2004; Yokobayashi et al. 2002). High-throughput screening selects for the desired function from the variety of circuits generated in the first step. However, what is produced by these partly randomized design processes is something that is much more of a bricolage—it is a product of tinkering rather than of pure rational engineering. For this reason, some synthetic biologists continue to insist on the rational design of "proper safeguards *against* evolution," because evolution "interferes" with the design of cells (Hold and Panke 2009: 2; emphasis added).

## Kludging

Rational design is clearly taken seriously by advocates of engineering approaches in biology. Such design is usually taken to be the opposite of the kludge—a colloquial term for a workaround solution that is *k*lumsy, *l*ame, *u*gly, *d*umb, but *g*ood *e*nough (http://en.wikipedia.org/wiki/Kludge).[3] Kludging emphasizes the achievement of a particular function rather than the rational pathway to that function. It does not matter how inelegant the process is to get there, or how inefficient the relationships between some of the componentry and circuitry. If the system works, that is the ultimate vindication of construction. Synthetic biology's design processes always, so far, end up as iterative rounds of trial, error, and pragmatic solutions—sometimes referred to as "debugging," "tweaking," "retrofitting," or "parameter tuning"—to make systems behavior fit design specifications (Andrianantoandro et al. 2006; Barrett et al. 2006; Heinemann and Panke 2006; Marguet et al. 2006; Haseltine and Arnold 2007; Serrano 2007; Ellis et al. 2009). Kludging, therefore, may be the best way to understand the constructs so far produced within the field. Rather than exemplifying rational, elegant, and efficient design, many devices work because they are kludges.

> [U]nlike other engineering disciplines, synthetic biology has not developed to the point where there are scalable and reliable approaches to finding solutions. Instead, the emerging applications are most often kludges that work, but only as individual special cases. They are solutions selected for being fast and cheap and, as a result, they are only somewhat in control (Arkin and Fletcher 2006: 4).

This is not just the case for the engineering of biological systems, of course. Kludging of various sorts goes on constantly in electronic and software engineering. One such practice is the "debugging" of software to make it work more effectively. Working around the glitches in programs, called "patching," can contribute over half the cost of software development (Henkel and Maurer 2007). Microsoft's "Patch Tuesday,"[4] the monthly release of software kludges to repair dysfunctional or vulnerable programs, reached its highest levels ever in 2009 (Keizer 2009; Leffall 2009). Some software engineers use "adaptation" to describe the process of how a kludge fits, augments, and works around the constraints and shortcomings of systems and their operating environments (Koopman and Hoffman 2003). "Proper kludge building," says a tongue-in-cheek computational engineering discussion of it, requires a balance between producing "a completely impossible machine" and coming up with "just an ordinary computer" (Granholm 1962). In this aim of producing something novel and remarkable, excessive "departmentalization" can aid creative kludging, because little crosstalk between departments (or modules, or institutions) raises the likelihood of creative and even redundant design upon design (Granholm 1962). Pushing this suggestion a bit further leads to the idea that engineering, biology, and evolution all *need* kludging in importantly constructive ways.

My argument follows this line of thinking. Kludging should not be interpreted as a failure of synthetic biology, but as a highly creative and effective process. An alternative

"backronym" for kludge or kluge is, in fact, "*k*nowledge and *l*earning *u*sed for *g*ood *e*ffect" (Koopman and Hoffman 2003: 73). Not only does kludging make things work, often in the context of non-standardized parts and insufficient knowledge; it also provides the conceptual connection between biology, engineering, and evolution. Organisms can be conceived of as layers of "clever hacks" that are the product of ad hoc tinkering efforts that persist because they work (Huang and Wikswo 2006). As the philosopher of evolutionary kludging, Stephen Jay Gould, was fond of arguing, evolution constantly produces kludges: the history of evolution is in fact a history of kludging. He believed that kludges, which he termed exaptations and spandrels (using biological examples), increased with the evolved intricacy of the organism (Gould and Vrba 1982; Gould 1997). One of his favorite examples was bird feathers, which he argued were adaptations for thermoregulation, and subsequently exaptations for catching insects and, eventually, flight (Gould and Vrba 1982).

PZ Myers, well known as a biology blogger, also argues from code-writing experience that life should be understood as "a collection of kludges taped together by chance and filtered by selection for functionality" (2008). He offers an insightful discussion of evolutionary kludges in relation to the genetics of body segmentation in arthropods.

> If a fly were software, it's software that has been patched and patched, and patches have been put on patches, until almost all vestiges of the original code have been obscured in the tweaks. It's the antithesis of planning and design—it's *ad hoc* co-option and opportunistic incorporation of chance enhancements. It's evolution. . . . The complexity of developmental regulation isn't a product of design at all, and it's the antithesis of what human designers would consider good planning or an elegant algorithm. It is, however, exactly what you'd expect as the result of cobbling together fortuitous accidents, stringing together helpful scraps into an outcome that may not be pretty, but it works. That's all evolution needs from developmental processes: something that works well enough, no matter how awkward or needlessly complex it may seem. (Myers 2008)

In standard nonsynthetic biology, biologists kludge all the time in experimental situations. The general idea of experiment as a designed, efficient, and linear inquiry, conducted by narrowing a research question into a refined hypothesis that obtains a specific answer, is an over-idealized representation of practice (Radder 2003; Creager et al. 2007; de Regt et al. 2009). Certain philosophies of science have treated experimentation and "the" scientific method this way, and many scientists continue to believe this is how science should be practiced. Elegance is highly rated in experimental biology (e.g., Mazia 1953, on Lederberg; Botstein 2004, on Herskowitz; Oransky 2008, on Beadle, Tatum, and Horowitz), but this does not mean that it describes what goes on in practice. A few philosophers have discussed the kludging that goes on in biological and other sciences (Wimsatt 2007; Goodwin 2009; Lenhard and Winsberg forthcoming). If scientific experimentation is understood as kludging, then activities such as "ad hoc" hypothesis modification cannot be rejected solely because they deviate from the linear path to knowledge (e.g., Popper 1963; Bamford 1993). Building up and modifying auxiliary interconnected models is a crucial aspect of scientific activity, and this involves kludge-like logic (Lakatos 1968–69; Forster 2007). Especially when grappling with multiple data sets, fitting them together creatively is likely to produce more powerful results than will testing a single prediction (Gregory 2009).

Max Delbrück's (1979: 76–77) "principle of limited sloppiness" is relevant here. He used it to describe the necessity in scientific practice of not being too rigorous or controlled in experimentation because this could prevent novel insights. Being flexible and responsive to the system of study and its variability could lead to totally unexpected findings, he suggested (Delbrück 1979; see also Root-Bernstein 1989; Jan and Jan 1998; Grinnell 2009 for additional cases). Experimental kludging and model "fudging" do not make biologists inferior to engineers, however, because as I have already argued, many sorts of engineers kludge to make things work. The proclivity for kludging may be deeply rooted because of how the mind itself evolved as a kludge (Linden 2007; Marcus 2008), and many socio-mental activities, such as systems of morality, can be usefully described as kludges (see, e.g., Stich 2006).

When thought about in these broader ways, it becomes obvious that kludging can be understood as an inescapable aspect of a pragmatic approach to knowledge and construction. The intriguing fact remains, however, that synthetic biology is in many respects antikludge: it wants nature and engineering to be elegant and efficient (e.g., Endy 2006, in Economist 2006). This has to be understood within the broader context of scientific practice in which synthetic biology is located.

## Knowledge-Making Relationships

Looking at synthetic biology more widely, against the background of general biological practice, brings in the theme of disciplinary relationships, and the relationships between knowledge and making. Both of these broader views of synthetic biology are important to understand how it works and whether it is doing anything new or distinctive.

## Disciplinary Relationships

The abstract for the meeting on which this thematic issue is based suggested that "synthetic biology has emerged as a new discipline." The situation is not quite so straightforward, however, and as shown above there is a considerable variety of descriptions of what synthetic biology is. For some practitioners it is an *approach*—a way in which to gain a perspective on living systems and to be able to intervene in them more effectively (e.g., Drubin et al. 2007). For others, synthetic biology is

a *toolbox* that can be put to work in any relevant biological research program (Michalodimitrakis and Isalan 2008; Deamer 2009). For those with strong ideas about making biology into a type of engineering, synthetic biology is a *field*, *discipline*, or a *disciplinary nexus* (Arkin 2008; de Lorenzo and Danchin 2008). For many observers and participants, the salient feature of synthetic biology is its application power, in that it will enable the discovery and production of new drugs, forms of energy, and waste disposal (Church 2005; Serrano 2007; Weber and Fussenegger 2009).

Although it seems clear that new understandings of "discipline" are emerging with all the new fast-growing areas of postgenomic biological investment (Powell et al. 2007), it is also obvious that in order to be able to understand synthetic biology we need to conceive of it in relation to its cousin, *systems biology*. Systems biology is often touted as the necessary successor to genomics. Genomics is conceived of as being largely about sequencing, whereas systems biology is thought of as making sense of all the data in functional and integrated ways (Auffray et al. 2003; O'Malley and Dupré 2005; Deamer 2009). For many commentators, systems and synthetic biology are two sides of the same coin, embodying "fundamentally different but complementary outlooks" (Breithaupt 2006; Koide et al. 2009: 297; Minty et al. 2009). A number of distinctions are made to clarify this relationship; a key one is that systems biology is more concerned with formal abstractions whereas synthetic biology focuses on instantiated mechanisms (NEST 2005; Sorger 2005; Barrett et al. 2006). Another distinction on offer is that systems biology is knowledge driven and synthetic biology is application driven or pulled (Church 2005). In this formulation, genomics (conceived as data) enables systems biology (primarily producing models), which enables synthetic biology (focused on practical achievements).

Some of the most publicized achievements and applications of synthetic biology involve metabolic engineering. The biosynthesis of artemisinin, an effective antimalarial that is produced in sweet wormwood plants (*Artemesia annua*), is a case in point. Because plant extract production is costly, an alternative means of production was sought through engineering an artemesinin pathway into yeast and *Escherichia coli*, resulting in the production of precursor compounds (artemesinic acid and amorphadiene) that could then be synthesized with normal chemical techniques into artemesinin (Martin et al. 2003; Ro et al. 2006; Keasling 2008). The commercial production of proteins in cells has for some decades been a source of therapeutic enzymes (e.g., insulin), and now metabolic engineering has a list of other success stories in pharmaceutical and agricultural applications (Chatterjee and Yuan 2006; Marguet et al. 2006; Drubin et al. 2007). Metabolic engineering may deploy protein engineering and synthetic biology as tools through which to enhance metabolic performance (Tyo et al. 2007).

Many metabolic engineers describe their efforts as rational because they involve the knowledgeable and purposeful alterations of an organism's genome and biochemical pathways in order to achieve a specified metabolic output (e.g., Nielsen 2001; Khosla and Keasling 2003; Vermuri and Aristidou 2005; Tyo et al. 2007). Yet for some commentators, metabolic engineering is insufficiently rational and the sort of practice that synthetic biology has transcended.

> Metabolic engineering typically involves the exploitation of the whole cell. It also has to cope with a very high complexity that is typically not amenable to rational analysis. In other words, it has often relied on 'tinkering' rather than rational 'design-based' engineering, frequently leading to only minor re-engineering of cellular properties (NEST 2005: 28).

In the case of artemesinin, the metabolic engineering that was carried out required the addition of a number of genes of different origin in order to produce the relevant enzymes and the desired reactions (Prather and Martin 2008). In an enhanced version of the engineered host cell, the introduction of extra protein scaffolds was able to control metabolic flux and reduce overproduction stress and toxicity build-up (Dueber et al. 2009). And, even though the production of the desired precursors has been achieved, all the reaction steps have still to be understood (Muntendam et al. 2009). The main reason for all the acclaim of this exemplar is that it *did* work, despite the cobbling together and imperfect knowledge. It is difficult, therefore, to see metabolic engineering as an inferior type of engineering—especially if strictly rational engineering would have been unable to produce the desired result.

What we see in the rise of synthetic biology is the development of genetic and metabolic engineering in the context of the integrating approach of systems biology (Purnick and Weiss 2009). This ramping up of engineering efforts through systems knowledge includes many more general and older practices than the "newness" of synthetic biology indicates. There is no denying, however, that for many practitioners it is valuable to distinguish the activities of synthetic biology from this broader context of practice and knowledge. Making such distinctions enables disciplinary formation, channels attention (positive and negative), and, above all, funding (always positive) to particular characterizations of the bodies of practice associated with synthetic biology.

But another, more epistemic, distinction can be made by thinking about metabolic and other biological engineering strategies in relation to synthetic biology.

> metabolic engineering generally requires more than simply throwing enzymes together in a cell. Achieving a synthetic goal (here, a strain that produces a particular product) requires the management of complex metabolic and regulatory processes. In pursuit of this goal, one cannot help but learn about metabolism and its emergent behaviors, including the regulation of metabolism and the extent to

which enzymes drawn from various sources can be combined independently. So, synthesis drives discovery and learning. (Benner and Sismour, 2005: 538)

Here, the links that are being drawn between construction and knowledge are the hallmark of synthetic biology's distinctiveness: its focus on *making* as true knowledge, usually uttered with the intention of distinguishing constructive synthesizing practices from more general processes of data gathering and the generation of model-based understanding.

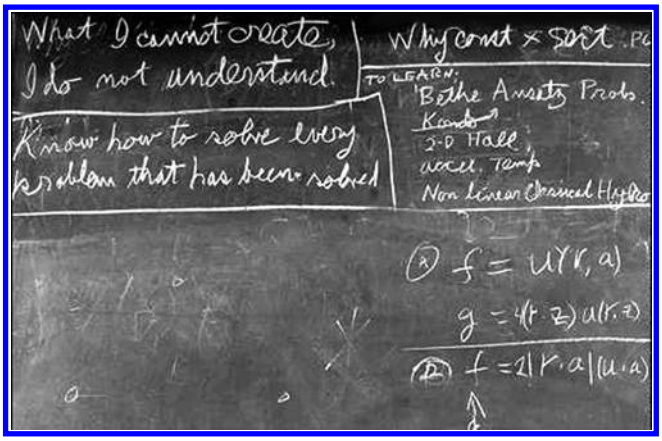


**Figure 1.**
Richard Feynman's "last blackboard," written at Caltech shortly before his death in 1988. The relevant quote is in the top left-hand corner. Courtesy of the Archives, California Institute of Technology.

## Making is True Understanding

Synthetic biologists frequently cite the Nobel Prize winning theoretical physicist Richard Feynman for his statement that "What I cannot create, I do not understand" (Feynman 1988; Fig. 1; see also Drubin et al. 2007: 252; Marguet et al. 2007: 608).

This adage echoes (and is perhaps an unacknowledged use of) a claim made by the Italian philosopher Giambattista Vico (1668–1744), that "truth and making are reciprocal" (1710, in Miner 1998: 63).[5] Only the Maker, in this case a divine one, can have true knowledge of phenomena from the inside; humans can gain knowledge only from the outside, first by dissecting, then by constructing (Miner 1998; Costelloe 2008).

There are many oddities about how this statement is used, even when its theological implications are set aside. Astrophysicists have considerable understanding of the physical characteristics of far away galaxies despite their inability to construct them materially. Biologists appear to understand a great deal about biological systems even when they "merely" observe and experiment rather than construct them *de novo*. And synthetic biology does not yet have the ability to create enduring reproducing life from scratch, and may never develop such capabilities. Does this diminish its achievements and mean that useful biological understanding has not been and will not be produced? Perhaps this limitation means that synthetic biologists are thinking of partial rather than comprehensive understanding. But if we think of a factory producing electronic products and see assembly-line workers putting together componentry, neither synthetic biologists nor anyone else would think of the workers as having a thorough understanding of the electronics of the parts they construct. Even if a factory worker produces a whole system, it is unlikely that all the knowledge that went into the design and invention of the item somehow becomes available to the assembler through assembling (some of which will be done mechanically or even robotically). This sort of assembly is, in fact, a standardization potential celebrated in synthetic biology, where it is argued that engineers at different levels of the synthesized system will need only to know the inputs and outputs of the device, not how it works (Alon 2007; Endy 2008; Canton et al. 2008; Yildirim and Vidal 2008). But for most scientists and philosophers, knowledge and construction appear to have much more complex, iterative, and inclusive relationships, such that giving an epistemically privileged role to "making" cannot be warranted.

Moreover, the Feynman statement needs to be understood within the context of his own, complex attitude to science and engineering. Feynman did not by and large construct the systems he sought to understand. But he did advocate a "Babylonian" approach to physics in which the emphasis was on making mathematical systems work, rather than on their rigor and deductive beauty (Feynman 1965). Babylonian logic works along these lines:

> I happen to know this, and I happen to know that, and maybe I know that; and I work out everything from there. . . . The [mathematics of physics] is like a bridge with lots of members, and it is overconnected; if pieces have dropped out you can reconnect it another way (1965: 47; order of sentences reversed).

This pragmatic bent allows mathematical kludging at the expense of formal elegance, and illustrates the potential for the design process to be quantified and mathematical without starting from fundamental axioms and being rational from beginning to end.

Feynman also suggested, however, that the production of kludges in engineered systems did *not* mean causal knowledge had been produced: "Naturally, one can never be sure that all the bugs are out, and, for some, the fix may not have addressed the true cause" (1986: Appendix F). Feynman wrote this in his appendix to the report on the Challenger disaster in 1986, in which he criticized top-down design. After playing a pivotal role in the investigation into the disaster (Feynman and Leighton 1988; Vaughan 1996), Feynman wrote his own appendix to the official report (1986). In it, he argued very much against the spirit of the "knowledge = making" statement in relation to top-down engineering. He did seem to hold out hope of detailed causal knowledge arising from bottom-up engineering. His criticism of top-down engineering and his distinction

between causal knowledge and practical construction provide limited support for the "knowledge = making" claims being made by synthetic biologists and attributed to Feynman. From mathematical and engineering perspectives, Feynman seemed to be suggesting that knowledge production is only sometimes driven or assisted by the construction of objects, and that design should be attuned to phenomena and practical necessity, not the elegance of the relationships between principles.

## Knowledge Making Conclusions

Synthetic biology is an interesting exemplification of the tension between rational ordering and untidy making do. The rhetoric of pure engineering appears to function as a strategy of discipline formation, which needs to be contrasted against the technical achievements (quite remarkable) and failings (less advertised) of synthetic biology so far. This question of whether kludging can be overcome or whether it lies inseparably at the heart of both life and biological practice is perhaps the general research question that synthetic biology is addressing (even if the "field" does not see it that way). The issue of whether synthetic biology can continue to work within these tensions or whether it needs to resolve them may not need to be addressed while the tension is as productive as it currently is. A corollary, of whether synthetic biology needs a special epistemological and disciplinary status in order to deliver its promises, is probably more pressing. Disciplinary status brings about social achievements, such as financial and institutional investment, without which even the best approaches never become practical realities. This question will repay philosophical and historical scrutiny as we seek to understand the nature and implications of disciplinary formation in the postgenomic era of biology.

Synthetic biology has resurrected some old philosophical debates about the nature of life, and given them a rather different set of answers. These have more to do with the ability of scientists to intervene in biological systems than the nature of the phenomena themselves. Through its very practical approach, synthetic biology is offering highly informative lines of insight into the philosophical understanding of scientific practice. The notion of kludging, tied to iterativity and exploration (O'Malley, in review), may more aptly describe scientific endeavors than do standard notions of rigorous hypothesis testing and methodological principles. Philosophy will certainly have to focus on the actual practices of synthetic biology if it wants to work out what is being achieved and how. In that process, a great deal about scientific knowledge and its making may be learned.

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## Notes

1. For an interesting discussion of synthetic chemistry as an art, see Nicolaou et al. (2000).
2. This quote is also attributed to Ken Olsen, founder of Digital Equipment Corp (e.g., Arkin 2008: 774), who is more famous for having predicted in 1977 that homes would not need computers (for details, see http://www.snopes.com/quotes/kenolsen.asp).
3. There are several competing accounts of the origin and meaning of kluge (commonly used in North America) or kludge (more common in the UK), and the Wikipedia entry brings together most of these accounts with original references.
4. Patch Tuesday is often followed by "Exploit Wednesday," when hackers anticipate and subvert the patch releases to expose Microsoft even further (Leffall 2007).
5. Vico's statement is often interpreted to mean *verum ipsum factum*—"the true is the made" (e.g., Costelloe 2008: 7). I am indebted to Werner Callebaut for making this very interesting connection between Feynman and Vico.

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