Synthetic Biology. Many Meanings, Little New, and Not Needing Sociological Response

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Sociology seeks to understand why trademarks differentiate the value of products that are otherwise identical. The challenge to sociology is larger, however, when those trademarks apply to science and science funding. After all, science is supposed to be fact-based, rational, and different from non-science. Scientists should not be susceptible to branding. At least in theory.

Nanotechnology,[i] systems biology,[ii] and synthetic biology[iii] are recently coined trademarks in science. All have elements of novelty, of course. "Systems biology", for example, rests in the notion that the study of purified molecular components extracted from a living system (analysis) must lose some perspective on the "whole". Systems biology was offered as a way to reconstruct the "whole" by enumerating its parts, putting numbers on their interaction parameters, and building a computer model to reproduce the performance of the whole. Likewise, nanotechnology began as an effort to gain for molecules the kind of predictability that is displayed by microcircuit design.

Beyond their core ideas, these trademarks have not been particularly useful, however. Systems biology turned out to be not greatly different from what had previously been called "physiology", as Brent pointed out ("vague definition and unrealistic claims made for systems biology").[iv] Efforts to get predictive medicine from computer simulations failed, primarily because the simulations were not robust with respect to uncertainties in the measured input parameters. Biology, complex chemistry, is more complicated than can be managed this way.

Likewise, nanotechnology has not produced much different from research that previously was called "materials science" or, more simply, "chemistry". Molecules are, after all, nanoscaled. Further, the analogy between computer design and molecular design is flawed, in part because logic elements fixed at spots on a two dimensional surface do not diffuse to engage in uncontrolled interaction with other logic elements. Molecules in solution do just that. Indeed, for chemistry (biological and non-biological) to happen, molecules *must* do that.

Nevertheless, these trademarks attracted resources, often supporting quality science in the process. Thus, Leroy Hood founded the Institute for Systems Biology, which did excellent biological chemistry under his trademark. Harvard, whose own prestigious trademark allowed it to come late to the game, created *two* departments of systems biology. When the NIH awarded its first "pioneers" under its NIH Director Pioneer Award program in 2004, three of the first eight recipients carried the label "nanotechnology" in some form. It was the fad of those times.

Sociologists might look upon synthetic biology in the same way. Before they do, however, they must recognize distinct concepts associated with the trademark. For example, in 1912, Leduc published *La Biologie Synthetique*.[v] Notwithstanding the need to translate the trademark from the French, his meaning was clear: Synthetic biology was the field seeking to create artificial life. Leduc was ahead of his time, but little imagination was needed even then to appreciate that if the analysis then underway to determine the structures of molecules of living systems was taken to its logical conclusion, it should be possible to create something unnatural that had properties that we value in life.[vi]

Indeed, chemists were already practicing the art of synthesis with this intent. In the 19th century, when chemists determined the arrangement of atoms in a natural product, they often attempted to re-synthesize the same arrangement from simpler starting materials. At first, their goal was simply to show that they had deduced correctly the molecular structure of the natural product. However, chemists eventually began to synthesize new forms of their subject matter. This synthesis allowed them to test theories that related molecular structure to chemical behavior. This synthetic capability drove structural theory in chemistry. Just imagine how much faster geology would progress if geologists could synthesize new planets.

This was the meaning of phrase "synthetic biology" when it was used again in the 1970's by Waclaw Szybalski.[vii] Recombinant DNA technology was then becoming powerful enough to allow microbiologists to synthesize new forms of *their* subject matter. Szybalski recognized that this would open a new phase of research, where biologists would synthesize chemically altered microbes. By examining the resulting alteration in behavior, Szybalski expected to discover relations between biological parts and biological behaviors, just as chemist had done previously with their synthetic technology. Synthesis in biology would empower biological theory just as synthesis in chemistry had empowered chemical theory.

However, by the 1970s, chemists had discovered a still broader, and more powerful, role for synthesis. Famously articulated by R. B. Woodward in a 1968 lecture,[viii] synthesis can be part of a "grand challenge", where chemists are forced to synthesize something difficult to synthesize. Pursuit of the synthetic grand challenge forces scientists to cross uncharted grounds where they must solve *unscripted* problems using available theory. When theory is inadequate, the synthesis fails, and fails in a way that cannot be ignored. Thus, synthesis can force discovery and paradigm change in ways that analysis and "hypothesis-based research" cannot.[ix]

Woodward had spoken an important truth: *When scientists choose the hypotheses to test, they tend not to test hypotheses that challenge core theory*. And if a scientist nevertheless seeks to test a hypothesis that actually challenges theory, the test will not likely be funded.

Even today, Woordward's insight is not well appreciated by many biologists and the peer-review processes that they serve. Accordingly, "hypothesis-based research" remains the touchstone of "true science" across much of Federal science funding, outside of chemistry itself. Thus, relatively few resources support attempts to synthesize molecular assemblies that reproduce the behaviors of living systems, including their ability to reproduce, evolve, and adapt. Consequently, relatively little insight is emerging for biology in general, and natural biology in particular, of the type that could be provided by a Leduc-style "synthetic biology".

Instead, most major Federal funding in "synthetic biology" has not moved conceptually beyond the 1980s. For example, DARPA is today investing tens of millions of dollars in its "Foundries 1000" program. This program seeks to rearrange natural enzymes in unnatural ways to create microorganisms that produce chemical products. The NIH has a parallel program entitled "Genomes to Natural Products", albeit with a more modest budget.

Both programs fit squarely within the classical field known as "metabolic engineering", a field that was already well developed in the 1980s. Examples from the 1980's include the Cetus-Chevron process to co-synthesize fructose and propylene oxide,[x] and the Genetics Institute-Chemie Linz process to manufacture phenylalanine.[xi] Both were gotten by rearranging enzymes from nature, the same process now funded by the DARPA and NIH programs.

The only distinction is one of scale. Today's metabolic engineers rearrange perhaps 5-10 enzymes, not the 2-3 enzymes rearranged in the synthetic biology work done three decades ago. Rapid DNA synthesis, whole gene and genome assembly,[xii,xiii,xiv] and improved bioinformatics, *inter alia*, all make metabolic engineering faster and cheaper. But since the biological parts still can diffuse in solution to freely interact with each other (rather than being pinned down at specific spots on a circuit board), the rearrangement involves much "tinkering". This was the word used a quarter century ago when engineers suggested that biological processing would be streamlined and vastly more productive once biological parts were altered via engineering strategies.[xv]

Intriguingly, synthetic biology appears to have created for itself a sociological problem by making claims of special powers for "engineering biology". Some members of the public have used the claims as grounds for alarum. For example, the Friends of the Earth recently objected to the use of the word "natural" to label products obtained by fermentation done with engineered microorganisms, evidently unaware that this has been the case 40 years.

It remains to be seen whether such claims will be realized, in particular, whether lay DIY individuals can engineer biology. Claire Maris in this symposium has a paper suggesting a very different reality. Among those who understand the supporting molecular sciences, is not clear that this claim can ever be realized. In any case, a new trademark does not create a new hazard.

References

[i] National Nanotechnology Initiative. http://www.nano.gov.

[ii] Ideker. T., Galitski. T., Hood, L. (2001) A new approach to decoding life: Systems biology. *Annu. Rev. Genomics Hum. Genet.* **2**, 343-372.

[iii] Benner, S. A., Sismour, A. M. (2005) Synthetic biology. *Nature Rev. Genetics* **6**, 533-543.

[iv] Brent, R. (2004) A partnership between biology and engineering. *Nature Biotech.* **22**, 1211-1214.

[v] Leduc, S. (1912) *La Biologie Synthetique*. *Etudes de Biophysique*, (Ed) Poinat, A.

[vi] Benner, S.A. (1987) *Redesigning the Molecules of Life.* Berlin, Springer*,* 175 pages.

[vii] Szybalski, W. (1974) In vivo and in vitro initiation of transcription. in: A. Kohn and A. Shatkay (Eds.), *Control of Gene Expression*, NY Plenum Press, pp. 23-24, 404-405, 411-412, 415 – 417.

[viii] Woodward, R. B. (1968) Recent advances in the chemistry of natural products. *Pure Appl. Chem*. **17**, 519-547.

[ix] Benner, S. A., Yang, Z., Chen, F. (2010) Synthetic biology, tinkering biology, and artificial biology. What are we learning? *Comptes Rendus* **14**, 372-387.

[x] Arena, B. J., Bruckner, A. H. (1985) Biological process for L-fructose synthesis. US. Patent: 4734366.

[xi] Johnsson, K., Allemann, R. K., Widmer, H., Benner, S. A. (1993) Synthesis, structure and activity of artificial, rationally designed catalytic polypeptides. *Nature* **365**, 530-532.

[xii] Nambiar, K. P., Stackhouse, J., Stauffer, D. M., Kennedy, W. G., Eldredge, J. K., Benner, S. A. (1984) Total synthesis and cloning of a gene coding for the ribonuclease S protein. *Science* **223**, 1299-1301

[xiii] Merritt, K. B., Bradley, K. M., Hutter, D., Benner S. A. (2014) Whole genes from autonomous self-assembly of synthetic oligonucleotides incorporating artificial nucleotides. *Beilstein J. Org. Chem*. **10,** 2348-2360.

[xiv] Gibson, D. G.; Benders, G. A.; Andrews-Pfannkoch, C., Denisova, E. A.; Baden-Tillson, H.; Zaveri, J.; Stockwell, T. B., Brownley, A.; Thomas, D. W.; Algire, M. A.; Merryman, C.; Young, L., Noskov, V. N.; Glass, J. I.; Venter, J. G.; Hutchison, C. A., III, Smith, H. O. (2008) Complete chemical synthesis, assembly, and cloning of a *Mycoplasma genitalium* genome. *Science* **319***,* 1215–1220

[xv] Knowles, J. R. (1987) Tinkering with enzymes. *Science* **236**, 1252-1258.