DOI: 10.1002/anie.201300062

Chemistry Needed: Synthetic Biology as a New Incentive for Interdisciplinarity

*Petra Schwille**

Petra Schwille
Director at the Max Planck Institute for Biochemistry

Interdisciplinary research has been one of the great promises for decades. In fact, being interdisciplinary has not necessarily helped each and every young scientist in building his or her career, as many faculties, at least within Europe, still believe in traditional trajectories and canonical disciplinary knowledge. However, when writing research grant proposals, or for publishing in journals with a large outreach, interdisciplinarity is clearly beneficial, and raises great expectations of innovation and groundbreaking new insights.

It is fair to say that this perception is largely justified, and that indeed, interdisciplinary research has brought numerous great achievements and breakthroughs to the traditional subjects. In particular, biology has benefited tremendously in past decades from the growing attention of chemists, physicists, engineers, and recently even computer scientists. Here, interdisciplinarity has even led to the advent of new disciplines, and major subjects, such as biochemistry, biophysics, bioengineering, and bioinformatics, now with their own canonical knowledge and curricula.

However, with today's wealth of interdisciplinary research initiatives, what is missing can be more illuminative than what is actually there. Numerous scientific consortia bridge relatively distant disciplines, such as medicine and physics, biology and physics, or biology and informatics. But the obvious ties to synthetic chemistry, a field of eminent importance for biology, are still rarely made. Delighted as I am by the growing convergence of physics and biology, I wonder why chemistry, the natural mediatior between these fields, is often underrepresented in this collaborative research.

The obvious ties to synthetic chemistry, a field of eminent importance for biology, are still rarely made

It is not that chemistry itself has not developed greatly in the direction of biology. Many chemical disciplines, above all chemical biology, have delivered invaluable new concepts, methods, and useful molecules ("probes") to be utilized by life scientists. In turn however, life science faculties and consortia seem to have not so much embraced them, but extended more towards cellular and organismic biology, fields of eminent importance but with reduced controllability and accessibility to strictly quantitative concepts. As a consequence, the impact of cellular and molecular biology has grown at the expense of biochemistry.

Interestingly, biophysics has not been affected in the same way. Physics is obviously indispensable in quantitatively modeling biology and developing methods to subject biological phenomena to rigorous analytical treatment with a predictive approach . What it cannot offer, however, are genuinely synthetic strategies, something the life sciences are, however, increasingly in need of. After numerous highly successful decades of molecular biology, we have to realize that for many biomolecules, our efforts to functionally extract them from the cell and utilize them in the test tube are enormous, and often fruitless, and that new strategies are needed.

What we have learned about the function and structure of proteins are which particular motifs or modules encode specific functions. Therefore, an obvious question to be raised is whether it would, in principle, be possible to design simplified units, with functional motifs taken or adapted from complex proteins, and similar functions in a biochemical context. Based on our current knowledge, the design often seems to be more or less straightforward. But once they are designed, how do we actually build these units, that is, synthesize them from the bottom up, once the art of cloning and purification does not suffice? Clearly, such an endeavor would deserve the title "synthetic biology", in analogy to synthetic chemistry.

In fact, synthetic biology is the youngest generation of interdisciplinary research, advertised as a new generation of quantitative life sciences in which the construction aspect exceeds the traditional view of biology as a mainly analytical, descriptive subject. Some of the most visionary biologists have turned their attention to this field, and have been joined by engineers, computer scientists, and physicists. What appears, however, still to be quite underrepresented at conferences and workshops on this topic, is synthetic or general organic

[*] Prof. Dr. P. Schwille
Zelluläre und molekulare Biophysik
Max-Planck-Institut für Biochemie
Am Klopferspitz 18, 82152 Martinsried (Germany)
E-mail: office-schwille@biochem.mpg.de

chemistry. And this is rather surprising, considering the claims and self-conception of the new field. Chemical synthesis is obviously an indispensable tool if engineering of and with biomolecules beyond the limits of natural systems is intended.

After years of success in replacing chemical synthesis by biology, it is time to explore the reverse

To briefly recapitulate: What are the goals of synthetic biology, and why, in turn, should a synthetic chemist care about it? It views biology and biological entities through the eyes of an engineer, and raises the question of how natural systems could either be reconstructed from scratch, or, in a more application-oriented notion, how new biological systems or processes not present in nature could be designed by varying the existing ones. The visions are mostly known from industrial biotechnology, such as drugs, materials, and biofuels; but rather than focusing on a specific product, the new aspect is now the engineering of whole biological networks or pathways as production pipelines.

One of the most prominent characteristics of synthetic biology is the identification of modules, out of which a toolbox can be assembled. These modules can be single genes or protein motifs, but also whole cellular pathways or even functional subcellular structures. The concept culminates in the vision of a minimal cell: The implicit fundamental assumption is that what it takes for a complex biomolecular system to actually live should eventually be discernible.

Practically, synthetic biology can be dissected into a "top down" and a "bottom up" approach. In its "top down" representation, the unifying theme is to identify the necessary constituents of a living system such as a (microbial) cell, by successively eliminating gene by gene and pathway by pathway, eventually arriving at a minimal set to maintain living functions. The "bottom up" strategy, on the other hand, strives to find the sufficient constituents for life. Taken literally, this interpretation of putting parts together one by one reflects the true core of synthetic biology.

In keeping with the reductionist approach in science, it is predominantly (bio)physicists who adopted the vision of building biological systems molecule by molecule. Driven by technology provided by nanoscience, and inspired by the cutting-edge research of cell and molecular biology, we have already succeeded in reconstituting biological phenomena, including biological self-assembly and self-organization, as well as coupling of biological and nonbiological nanostructures. The biological functionalization of quantum dots or carbon nanotubes on one hand, and the construction of bio-nanodevices by the DNA origami technique on the other hand, are just two obvious examples of this cross-fertilization.

What has so far been largely missing in bottom-up synthetic biology, however, is the power of true chemical synthesis. If a biomolecular system cannot be reconstituted in a much-simplified environment because of the impossibility to clone and purify functional proteins, the purely biological bottom-up strategy faces a dead end. Additional know-how may be required in order to apply some of the essential functional features or "modules", such as switchable membrane-targeting groups, or domains to induce conformational changes, in the test tube. Here, joining forces with synthetic (bio)organic chemists trained in the de novo production or coupling of functional groups should be obvious.

To conclude, synthetic biology is one of the few fields where all of the main scientific disciplines, namely biology, chemistry, physics, mathematics, and engineering, will be equally important for success. It is a genuinely interdisciplinary field. Without the possibility of synthesis on the molecular level, efforts in reconstructing or engineering life are certainly bound to fail. Thus, after years of success in replacing chemical synthesis by biology, it is time to explore the reverse: whether innovative strategies of synthetic chemical biology can in fact help in engineering biological pathways in a more efficient way. A cross-fertilization of the synthetic disciplines thus seems to be highly desirable.

