1 Introduction

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/978-3-319-73123-0_1) contains supplementary material, which is available to authorized users.

E.-K. Ehmoser-Sinner, C.-W. D. Tan, *Lessons on Synthetic Bioarchitectures*, Learning Materials in Biosciences, https://doi.org/10.1007/978-3-319-73123-0_1

1.1 Long-Term Vision and Objectives

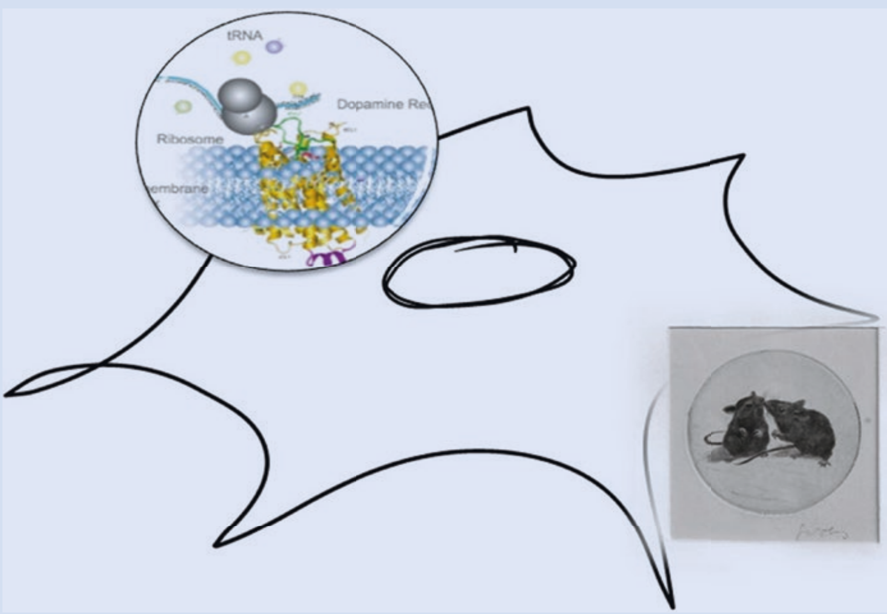
The objective of synthetic bioarchitectures as a field of research cannot be confined yet as it belongs to the converging sciences, still emerging; however, let us foresee one of the most relevant objectives of this field: the communication of life with synthetic matter.

What can we learn by talking to nature in the language of molecules? We can interfere with biological pathways in a much more "compatible" format than has ever been possible before.

For example, thinking about chemotherapy we might apply the German saying: "den Teufel mit dem Beelzebub austreiben"—which means that chemotherapy is about trading off: lacking specific tumor markers results in the attempt to stop proliferation in general and the result appears as treating "bad with similar bad": we kill various cells in the course of chemotherapy and eventually we succeed by hitting cancerous cells harder than benign tissue. The side effects are of course enormous and undesired.

But imagine a novel way to address such cancerous tissue. What a difference it would make if by means of synthetic biology—namely, bottom-up approaches—we were able to synthesize "communicators," talking only to the desired cells without toxifying them—rather, "convincing" them to get back into the healthy regulated routines of benign tissue. It still sounds naïve; however, we have come a long way in "understanding" biological architectures (◘ Fig. 1.1).

Can we think of a cell as communicateable object, where synthetic assemblies might integrate meaningfully into regualtory processes of diseased pathways and by this, cure, dysfunction?



◘ **Fig. 1.1** Cartoon of a (eukaryotic) cell with a graphic inset of an artificial bioarchitecture—namely a membrane protein, which might interfere with a diseased cell. This desired artificial assembly is available in vitro, made by the ribosomal complex with all the compounds needed (translocon machinery, chaperones, etc.) and energetic boundary conditions involved; however, instead of targeting the endoplasmic reticulum, as an example, colloidal membrane architecture can be addressed (e.g., membrane disks). On the other side of the cartoon, the whole organism is depicted, represented by two mice, eventually being cured by the introduction of such "synthetic assemblies"

Future vision: 'Communication'
between materials and living cells on all levels

Fig. 1.2 As time will tell, eventually, synthetic bioarchitectures will be targeted by scientists as novel therapeutics. (Composition images courtesy of D. Miklavcic, Ljubljana University, Slovenia; Tarek Mounir, CNRS, France; Ute Reuning, Technische Universität München, Germany)

We like to present, as an example, clinically relevant membrane proteins as such communicators, which are integrated into biocompatible polymeric islands as shuttle systems. Such orthogonal therapies would allow restoration of function at endogenous receptor levels. However, biofunctionalized surfaces, biohybrids, and novel gene-coding strategies point in the very same direction: bioarchitectures as novel approaches in communication with nature. Such fundamentally novel materials will be highly attractive for the pharmaceutical industry and molecular medicine. We present such pioneering technologies, which provide great opportunities for developing next-generation protein therapies in order to address fatal membrane protein–related diseases (Figs. 1.2 and 1.3).

Objectives for Students

1. Relevance of the topic
2. Overview of the content
3. Connections with established disciplines
4. Visions and perspectives

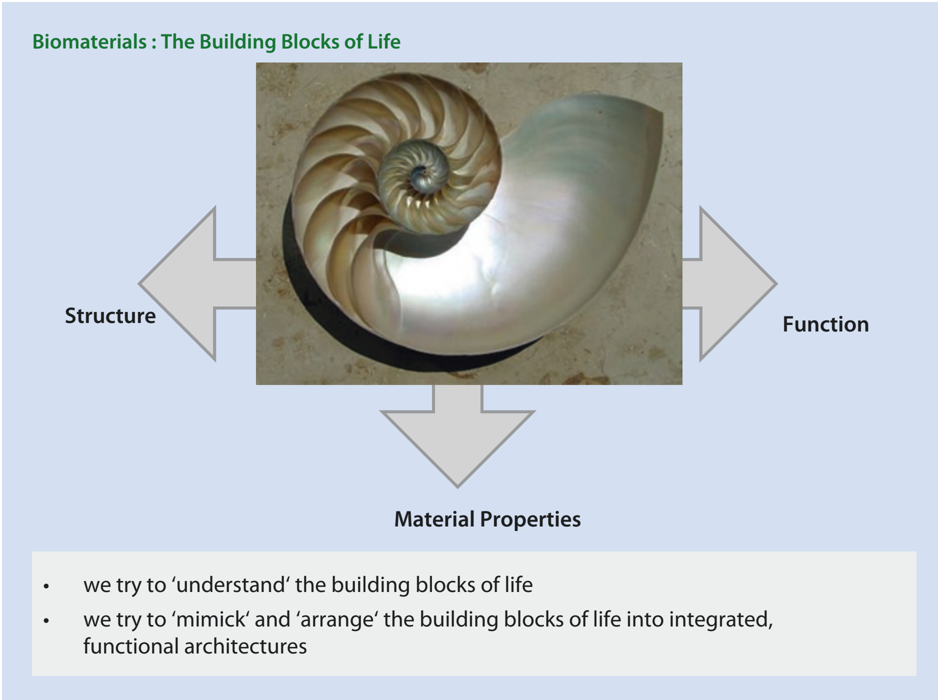


Fig. 1.3 Depicting the connection between structure and function and their consequence: material properties. And in the center: insight into the beautiful "functional structure of the nautilus shell". This Wikipedia and Wikimedia Commons image is from the user Chris 73 and is freely available at https://commons.wikimedia.org/wiki/File:NautilusCutawayLogarithmicSpiral.jpg under the creative commons cc-by-sa 3.0 license

Expected Outcomes

1. Students will know the term "synthetic bioarchitectures" with respect to bottom-up–top-down approaches in communicating with nature via materials/surfaces.
2. Relation to the "Roter Faden" of the book.
3. The history and the intra- and interdisciplinary future of such converging technology.
4. Putative goals and achievements in the field: the magic riddle of "regulation" in the context of cancer research.

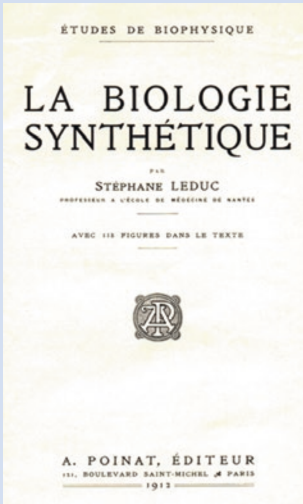
1.2 Synthetic Biology and Synthetic Bioarchitectures

"Synthetic biology" is a term describing the attempt to synthesize, manipulate, and—first of all—understand nature.

We know about proteins, lipids, and carbohydrates as the building blocks of life. As functional architectures, the building blocks of life have revealed impressive properties in the course of research that has even elucidated electron spin responses in biomaterials. In synthetic biology, several attempts have been made to use nature as a blueprint—for example, for bionic approaches on an engineering level—however, the closer

First time, the term "Synthesis" and "Biology" was put together: by Stéphane Leduc

'Il existe, pour expliquer les phénomènes de la nature, deux méthodes : le Mysticisme et le Physicisme. Le physicisme est la méthode des sciences physiques, le mysticisme règne encore sur la biologie.'



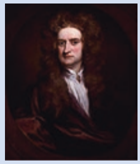
■ **Fig. 1.4** If we take a biomaterial in the focus of synthetic bioarchitectures, we have to view the composition of living objects from the perspectives of chemistry, physics, and biology; only then might we reveal the structural–functional relationships and, as a consequence, we might be able to control and eventually mimic the material properties presented by nature

methodological approaches have come to the level of atomic resolution of functionalized assemblies in living cells, the more subtle and ambitious scientists have become worldwide about the vision of mimicking nature (■ Fig. 1.4).

Going back in history, the term "La Biologie Synthetique" was coined by a French scientist named Stephane Leduc (see ■ Fig. 1.5). It was a commitment to phenomenologically driven aspects of biology, which in contrast to physics were annotated as being of a "mystical" nature—too complex to ever be understood and described by laws and numbers.

In this context, the origin of attempts to understand and manipulate biology was in alchemy—a descriptive view of our world—attempting to transform the elements of the periodic system and by this to "control" nature.

If we look back in history, the extent to which scientists at the respective times with respective methods were able to understand interaction and relevant processes even on the atomistic level is impressive. For the topic of synthetic bioarchitectures, it became interesting after Boyle, Dalton, and Newton set out the atomistic model, when the periodic system was anticipated by Berzelius, and the elements as components of our world were able to be put on one sheet of paper; even though it was clear that some were still


Boyle - (1627–1692) **Newton - (1642–1726)** **Dalton - (1766–1844)**

And then....

…as a history moves on, alchemy turned into chemistry and in human followed the idea of atoms being turned into molecules (lat. moles, f.: mass, molecula: small mass)

Jöns Jakob Berzelius, 1779–1848

Fig. 1.5 The key researchers in transforming Alchemy into modern chemistry: the ground work for the periodic system

When Chemistry and Biochemistry meets...

Friedrich Wöhler,1800–1880

Fig. 1.6 Friedrich Wöhler: a capable student crossing borders from synthetic and 'biogenic' materials

missing, the consecutive order of elements according to their mass, defining their properties and interactive capacity, became clear (see Fig. 1.6).

However, Berzelius's own student, Wöhler, already thought beyond the border of the periodic system as he performed a transformation of ammonium cyanate into urea by mere heating. This observation was interpreted by him as a transformation from an "unliving" material into a very much "living" material—insofar as he claimed rightfully to have crossed the borders between the inorganic and organic worlds and that there would be

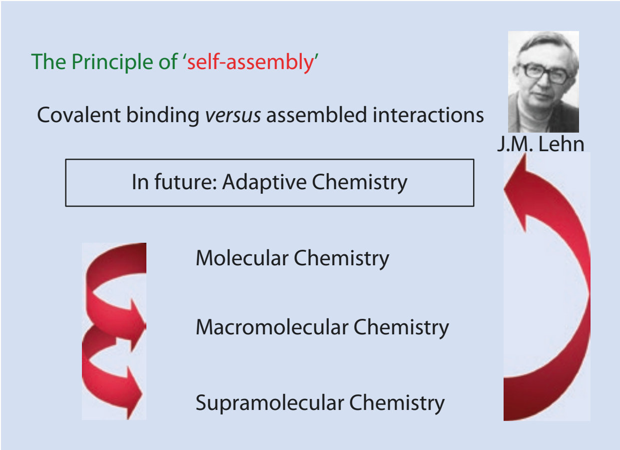


Fig. 1.7 Interpreted from Jean Marie Lehn as he proposes in his presentation at the Journal Angewandte Chemie at its anniversary in Berlin (2012): today's chemistry might become 'adaptive'

connections between elements, which were not describable by the mere periodic system. The letter he wrote to Berzelius, his teacher, is worth reading to see his beautiful spirit of respect and joy about his discovery. And maybe even more acknowledgeable is the response of Berzelius as a supportive and sovereign mentor, even though his student—to a certain extent—had diminished the relevance of his own life's work: the periodic system of the elements as a "sorting table" (see ► http://www.chemieunterricht.de/dc2/tip/brief.htm for the original text of the letter and our attached translation into the English language).

Without transition possibilities among the elements themselves, however, as Wöhler demonstrated on the molecular level, materials can be transformed into different combinations and thus the borders between the living and nonliving worlds are not as narrow as was claimed before his observation.

At the beginning of the eighteenth century, it was high time for great discoveries in chemistry, especially in regard to the era of industrialization. The finding of polymeric reactions indeed paved the way for generating materials, which were quite tedious to isolate from natural sources or even impossible to find in nature.

When we think about aniline, the finding of Wöhler took place in the context of an era of identification of new materials with high commercial potential: polymer chemistry. The famous Staudinger reaction took place by condensation of small building blocks—monomers—into polymeric materials, thus the first "plastics" were achieved (Fig. 1.7).

The idea of Wöhler—namely, transforming nature's materials easily into controllable, cost-effective, daily life products—was an intriguing thought. Indigo, formerly isolated from plants, provided a perfect example of the potential of synthetic biobased chemistry. In conventional synthetic chemistry, macromolecules are formed by transforming starting molecules into the desired macromolecular material in laboratory conditions by pushing against equilibrium constants and often orchestrating solvent conditions in order to achieve the desired product. As a chemical layman, successful synthesis strategies look to me like cartoons of a spider network, as bypassing the obstacles of accessibility, reaction conditions and, in the end, stability and purity are the factors of turning nonworking into working chemistry. Synthesis blueprints from nature are already guiding open-minded chemists into new spheres of combinatorial organic chemistry, often as a consequence of intensive collaboration with medicine. Often, questions from molecular medicine are answered with strategies and ideas from peptide biochemistry; as an ongoing example.

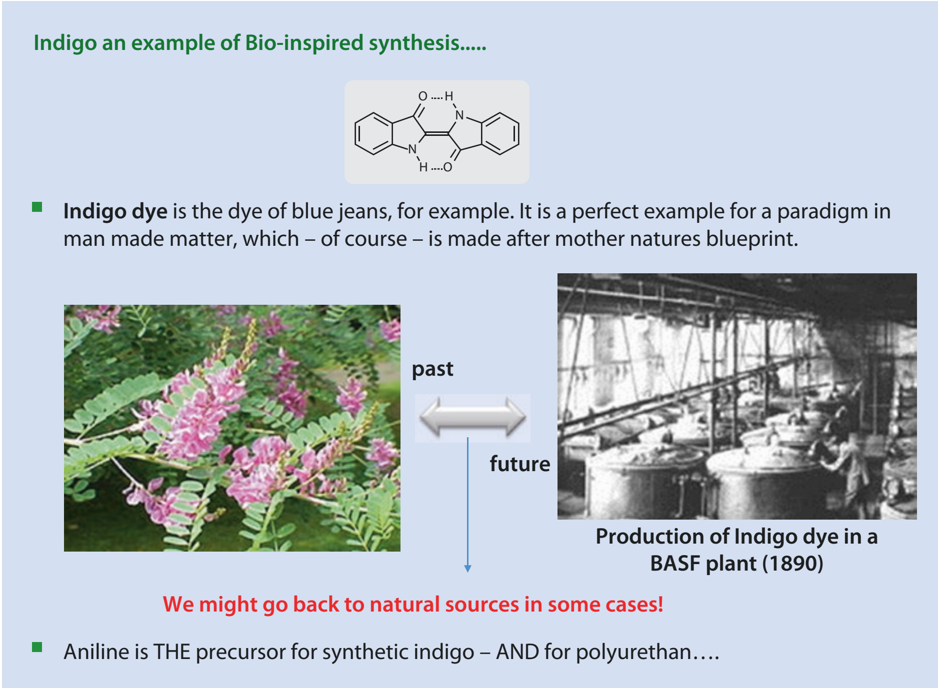


Fig. 1.8 The dye "indigo" originally was isolated from the plant named indigofera. However, the synthetic version of indigo was developed as the world needed much more indigo and chemical synthesis based on Aniline precursors enabled a less expensive source. However, the 'blueprint' of this powerful dye came from nature

In the future, we assume that there might not be such a difference between synthetic chemistry and biobased chemistry, as there are already some channels and valves in between, where complex starting blocks are already consequences of the synthesis performed by "active little house elves" in the lab.

No, it is not you, dear students, to which we refer, but bacterial species, which build reliably and reproducibly peptidic/lipid or carbohydrate composites, which can be isolated and further purified in conventional biotechnological down-processing for synthesis reactions.

The advance from macromolecules into supramolecular chemistry is already considered a breakthrough in history—these days the adventure goes on as J.M. Lehn developed the concept of self-assembly (see Fig. 1.8), and the borders between "man-made" and nature-derived materials seem to fade out once more. As adaptive materials respond to their environment on the molecular scale, what difference is there between an enzyme finding its substrate and a macromolecule with catalytic properties being tunable via pH changes?

The underlying processes in molecular recognition are the same in both cases, and no difference can be found in the consequences of molecular transformations.

Still it is relevant to understand the origin of materials derived from nature, even as we buy them from catalogs in the lab; we should know well the difference, for example, between synthetic peptidic materials and isolated ones, as impurities and stability are major concerns with bioderived materials!

It is not only about impurities being present; it is also about stability and chemical robustness. Materials from biological sources need to be handled accordingly—they are often temperature sensitive and sensible in their structural–functional integrity. This is often ignored when such materials are employed in the interface between disciplines—antibody materials are a prominent example. Antibodies are famous as precise recognition labels and as such are often part of imaging and tracing experiments on the molecular scale. However, they are quite complex biological entities with a limited time of activity and inherent (though often ignored) impurity content as they are isolated from a cell culture supernatant.

The example of antibodies as "major players" in molecular recognition shows the limitation and strength of natural-derived materials.

This example is very useful to show the parallel development of synthetic bioarchitectures as a subfield of synthetic biology; in certain aspects, history repeats itself. As chemistry started from defining the compounds and elements, moving forward to macromolecular and supramolecular chemistry, the field of biomaterials will follow such developments—with the example of antibodies, the field started with defining the material of such protein molecules, the structural features, and modification possibilities. At present, researchers think about artificially copying the binding characteristics of antibodies, either by chemical modification of the present antibodies or by employing alternative materials, such as nucleic acids, aiming to preserve the outstanding capacity in molecular recognition of monoclonal antibodies and at the same time replace the inherent drawbacks with regard to stability, reproducibility, and animal origin.

In this regard, synthetic bioarchitectures seem to follow the field of chemistry with an approximate 30-year gap. However, as already established products, especially based on fossil fuels, are in everybody's hands and minds, it seems difficult to repeat the momentum of the "chemical revolution" from 100 years ago.

Introducing cost- and resource-effective alternatives seems more likely to describe the actual and ongoing movement of synthetic biology in everyday products. Funding schemes, opting for engineered, rational design of commercial alternatives to fossil fuel–based products, are already active and will contribute to hunting down "easy to establish" biobased products, which hopefully will make their name to finally become interesting "stakeholder's darlings."

Why is this a favorable scenario? In our world, the driving momentum will only happen when the common incentives of money and/or power are in place. In research, one can look out for "biomimicking concepts"; impulses from self-organization concepts—known for a long time—are at present being "reinvented" to justify projects in various fields. In synthetic bioarchitectures, we are obliged to start from Feynman's statement, "What I cannot create, I do not understand"—e.g., in his spirit of being able to solve every problem that has been solved and continue with systematic steps toward sustainable, integrated, and intelligible (responsive) functional biomaterials. In summary, this sounds to us like synthetic bioarchitectures.

The putative goals and achievements in this field depend very much on the exact example of choice. In today's biotechnology, the investment in large-sized fermenters is an interesting example to show just one potential of synthetic bioarchitectures: materials from natural sources provide the backbone source for any material processed from our industry. In the beginning of each process, there is a contribution from nature, which in most cases is not even known to the consumer. A "breakthrough invention" from the field of microbiology was the development of single organism–derived cultivation (fermentation), enabling control and foresight in (productive) metabolism. The principle behind it is quite old: knowing the optimal conditions to grow a specific (desired) organism was the ultimate start for human-controlled production of cheese, beer, wine, and many more goodies, where we need biochemical input from the "little helpers" around us—namely bacteria, yeast, and fungi.

In large-scale fermentation, one can find the organism of interest in a monoculture environment, optimized for the production of commercial compounds. In some cases, this concept has taken care of the synthetic chemistry procedures—at least partially—by providing high-purity and cost-effective building blocks of various (industrial) products. Such "organism-based" (or let us call it "cell-based") synthesis still bears some risks and drawbacks, as living species naturally change—for example, as mutations continuously occur. Knowledge about desired biochemical pathways, the enzymes involved, engineering of proteins, and the regulatory interactions between and within microorganisms on very complex levels has been elucidated in the research field of systems biology in the past decades. Already some examples have been applied to address real-world problems, such as synthesis from interesting compounds, engineering of therapeutics (e.g., humanization of antibodies), and green algae turning wastewater into biofuel, just to name a few "dreams" that are about to become reality. One can think about systems biology as a field in which the blueprints of life are elucidated—this is naturally a very important inspiration for any "synthetic" architecture, deriving or making use of such natural building blocks.

In summary, it will be knowledge about molecular interactions and structures of living species that will transform the relevance of synthetic bioarchitectures as an inherent consequence of the idea of synthetic biology into research questions directed toward sustainable, economical, logical, and responsible biotechnological research and industry, which will optimistically be quite integrated into our ethical and societal networks.

Further Reading

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