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DNA-Encoded Synthetic Systems: Coding More than Life

Damien Baigl

From chiseled silica-crafting diatoms to migrating blue wildebeests, living matter manifests itself in an exceptional diversity of morphologies and functions. Perhaps even more amazing is that this astonishing diversity is encoded in the same and highly conserved molecule, DNA, the molecular code of life. Structurally, DNA can be primarily described as a double helix held by hydrogen bonds through specific base pairing. Functionally, naturally occurring DNA is essentially the support of the genetic code that is translated into proteins. In the course of evolution, living systems have thus reached a high degree of complexity and versatile functionality while having encoded them in a rather simple and robust molecular entity.

On a separate path and through years of scientific exploration and industrial development, human-made synthetic materials have steadily improved to achieve broader, more sustainable, and/or higher-performance functionality. Based on a vast repertoire of known chemical reactions and processes, synthetic materials are typically designed, fabricated and shaped by judiciously combining building blocks from a rich alphabet of atoms, molecules, or supramolecular entities, through synthesis, assembly and/or formulation. Unlike their living counterparts, synthetic materials have a perfectly well-defined composition and known mechanisms of operation, but they are rarely able to achieve some of the properties characteristic of living systems such as communication, adaptation, reproduction and evolution.

Interestingly, in recent years we have a witnessed a technological twist, since now virtually any synthetic DNA of any desired sequence or length can not only be synthesized in a rapid, user-defined manner, but can also be purchased at very low cost. Exploiting synthetic DNA as a molecular program to build and design synthetic systems thus appears to be a particularly timely and relevant strategy: i) to generate a variety of user-defined structures and functions in a generic and highly programmable manner; ii) to build well-defined systems in which all components are perfectly known and assembled; iii) to interrogate living systems in a rational manner; iv) to realize synthetic systems with life-like properties such as communication, adaptation, reproduction or evolution. It is precisely this rich territory that this special issue aims to explore. It presents a selection of research articles pushing the boundaries of current knowledge, as well as reviews providing original perspectives on the field, all reports having in common the construction, exploitation, study or analysis of synthetic systems encoded by DNA.

Several scientific fields are more particularly involved. This is the case for structural DNA nanotechnology, which exploits specific base pairing to build sophisticated synthetic DNA-based nanostructures with programmable morphologies and site-specific functionalities. In this special issue, structural DNA nanotechnology is expanded by examining its advantageous coupling with additive manufacturing (article adbi.202200195). It is also revisited by considering programmable liquid-state structures (article adbi.202200180) and finds new applications for fundamental research, especially in mechanobiology sensing (article adbi.202200224). In addition, the emergence of synthetic biology has prompted researchers to convert synthetic genes into functions through cell-free protein synthesis, leading to the emergence of new synthetic systems capable of biological functions. These systems not only provide insight into the functioning of living matter, but also create new biocompatible tools for diagnostics and biomedical applications. In this issue, cell-free expression is better controlled, understood and predicted through original experiments (article adbi.202200164) and simulation tools (article adbi.202200177). The novel reconstitution of important proteins in minimal systems allows a better understanding of the spatio-temporal organization of cellular components involved in cell division (article adbi.202200172) as well as the development of animal-free and ultraminiaturized immunoassays (article adbi.202200266). In addition to encoding structures and functions, DNA has also been recognized as an active code capable of performing logic operations, leading to the development of DNA-based molecular computing. In this issue, this approach explores promising prospects for sample classification and pattern recognition that can be applied to diagnosis (article adbi.202200203). All of these different articles not only share a common interest in exploiting synthetic DNA as a molecular program in their own specific research areas. They also have cross-cutting goals, including understanding information-based assembly (adbi.202200180, adbi.202200195, adbi.202200203), studying spatio-temporal organization at the molecular (adbi.202200177, adbi.202200164) and cellular (adbi.202200172, adbi.202200224) levels, the rational construction of functional architectures (adbi.202200266, adbi.202200172, adbi.202200195, adbi.202200224), as well as the development of original tools for biotechnological and biomedical applications (adbi.202200266, adbi.202200203).

In article adbi.202200195, Simmel and colleagues expose an original overview for improving the structural resolution of additive manufacturing by combining it with bottom-up DNA self-assembly. They demonstrate that implementing DNA

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programmability constitutes a great perspective for the future of bioprinting to achieve hierarchical assembly of synthetic biomaterials with molecular resolution up to supra-cellular levels.

In article adbi.202200180, Takinoue and colleagues present what is probably one the first reviews specifically dedicated to DNA droplets. They showcase in particular the emerging interface between DNA nanotechnology and dynamic soft matter systems. They also highlight the unique properties of this new state of programmable matter made of liquids with sequence-specific recognition and programmable mechanical properties.

In article adbi.202200224, Bellot and colleagues analyze the current state-of-the-art of constructing sophisticated force-sensitive DNA nanodevices and their exploitation for mechanobiological investigations. They discuss the challenges and opportunities raised by this new class of man-made and finely engineered nanomachines interacting with biological systems.

In article adbi.202200164, Yoshikawa and colleagues report an original and systematic study on the role of monovalent cations in regulating cell-free expression in the TX-TL system. They unveil in particular a marked promoting role of Rb^+.

In article adbi.202200177, Shimizu and colleagues describe the development of a protein synthesis simulator. Their tool allows for large-scale model construction based on cell-free protein synthesis, with user-specified conditions (nucleic acid sequence, component concentrations, decoding rules), and can advantageously simulate the cell-free synthesis of full-length proteins.

In article adbi.202200172, Danelon and colleagues use cell-free expression to produce the basal division membrane-binding protein FtsA from its coding DNA inside synthetic cells. In the presence of the purified FtsZ protein partner, FtsA-FtsZ cytoskeletal structures that constrict the cell membrane are formed without inducing its division.

In article adbi.202200266, our group describes a novel fully synthetic bio-assay where functional single-domain antibodies (VHH) are cell-free expressed from their coding DNA with concomitant antigen binding assessment inside picoliter drops. This new purification-, animal- and culture-free format produces a fast and ultraminiaturized immunoassay with improved ethical acceptability and high-degree of programmability.

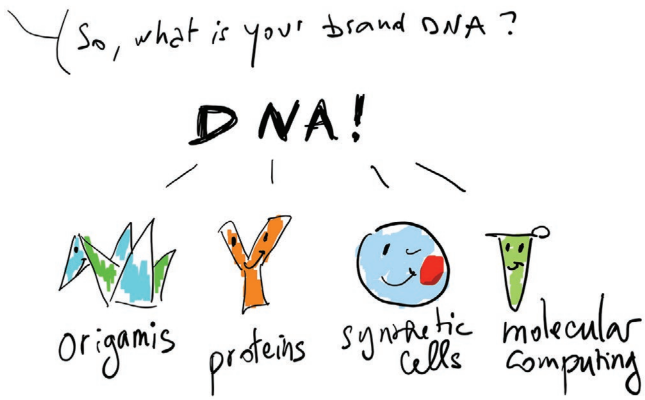

Figure 1. Author's illustration of the variety of synthetic systems that can be advantageously encoded with DNA.

In article adbi.202200203, Rondelez, Gines and colleagues survey the recent advances in DNA-based molecular programming for sample classification and disease pattern recognition, a particularly promising approach for one-pot and low-cost smart diagnostics. They focus in particular in recent experimental implementations of molecular circuits using Boolean operations or neural networks.

In summary, because of its simple and robust base-pairing principle, its capacity for gene coding and molecular programming, its stability, and its ease of being synthesized at virtually any length and sequence, synthetic DNA is emerging as a highly versatile and convenient molecular code that can rationalize and expand the repertoire of synthetic systems in terms of design, properties and applications (**Figure 1**). Nadrian Seeman (1945–2021), the inspirational founder of DNA nanotechnology, regularly gave a lecture entitled "*DNA: Not Merely the Secret of Life*". This issue demonstrates once again how true and promising this statement is.

Conflict of Interest

The authors declare no conflict of interest.

Damien Baigl is exceptional class professor of chemistry at Ecole Normale Supérieure (ENS-PSL) in Paris, France and senior member of the Institut Universitaire de France (IUF). Curiosity-driven, he is exploring original and interdisciplinary ways to observe, manipulate, control, or build a variety of soft matter systems. His current research interests include dynamic DNA nanotechnology, reconfigurable self-assembly, soft synthetic biology, coffee-ring effect for patterning and diagnostics, colloidal organization at fluid interfaces, synthetic cells, and genetic encoding of soft matter properties.

