CHEMICAL REVIEWS

Editorial

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Introduction: Nucleic Acid Nanotechnology

What is all the hubbub about DNA nanotechnology? Ever since the original description of using DNA as a scaffold to organize other molecules in 1982 in a paper in the *Journal of Theoretical Biology* by Nadrian C. Seeman,[1] DNA nanotechnology has experienced a growth trend that is reminiscent of a bacterial growth curve that is currently in the log phase. In the early 1990s, with the iconic demonstration of the construction of a molecule with the connectivity of a cube made entirely out of DNA—outlined in *Nature* by Chen and Seeman[2]—a molecule that had primarily held the fascination of biologists crossed over into the hands of chemists. Chemists saw this molecule as a water-soluble polymer whose growth could be controlled and whose branching, or cross-linking, could be rationally manipulated. Thus, several structural motifs were co-opted from biology to create exquisite shapes, all made out of DNA. The birth, evolution, and future trajectory of one of these motifs, the paranemic crossover, is outlined by Wang et al.

The next step-change that showcased the capabilities of this polymer was the creation of assemblies that could switch their conformations. Again, Ned Seeman exploited the ability of DNA to exist in alternative, non-B-DNA conformations and showed that one could elicit specific shape changes from structured DNA assemblies.[3] Unusual four-stranded motifs such as G-quadruplexes and i-motifs have been used as building blocks to make such chemically responsive DNA-based molecular switches, which is authoritatively reviewed by Jean-Louis Mergny and Dipankar Sen. In another major development around the same time, Yurke and co-workers showed that one could induce such targeted shape changes using DNA strands, laying out the concept of toehold-based strand displacement as a tool in the field.[4] The principal advance in our understanding of the capability of the DNA scaffold was that it opened up the possibility to achieve isothermal switching of specific assemblies from among a collection of DNA-based nanodevices. Strand displacement thereafter underwent an explosive growth resulting in the creation of a plethora of sensors, its use in molecular computation, and the creation of molecular robots, as well as the assembly and actuation of diverse nanomaterials. This area is reviewed by two of the pioneers of strand displacement, Fritz Simmel and Bernie Yurke.

All biological systems are the result of molecular computation on a massive scale; this computation gives rise to fairly robust patterns that dynamically evolve with remarkable reproducibility. The growth of organisms from a single cell occurs because of biochemical reaction networks that also have the ability to adapt in response to external cues. The power of strand displacement, in terms of assembly-specific addressability, has seeded the rational design of synthetic chemical reaction networks based on DNA. Such synthetic chemical reaction networks are a breeding ground for adaptive materials and promise fundamental knowledge of how to rationally design them and are reviewed by Wang and Ellington in this thematic issue.

The ability to create these adaptive materials also hinges on our capacity to derivatize DNA with other functional entities—fluorescent molecules, metal nanoparticles, and biologics. The residue level addressability of the DNA polymer is one of its greatest advantages. This allows us to position functional groups on DNA in ways that are highly tunable. At the center of these advances lie the development of reliable and robust functionalization chemistries. In fact the whole field of DNA nanotechnology has been made possible because of pioneering work by Robert Letsinger and Marvin Caruthers, who enabled the synthesis of virtually any imaginable sequence. The next layer is the development of a panoply of chemistries to attach functional groups precisely to individual DNA strands as well as fully formed nanodevices. Enabling nucleic acid chemistries lie at the very heart of the success of all DNA nanotechnologies and are reviewed by Kurt Gothelf.

A new direction for DNA-based nanodevices emerged when Krishnan first demonstrated that synthetic DNA-based molecular switches could function autonomously inside the complex milieu of a living cell[5] and then inside a living organism.[6] Thereafter DNA nanodevices gained rapid traction as biotic−abiotic interfaces that could be manipulated to study living systems as well as manipulate them. Key to achieving this has been the development of methods to target simple DNA- and RNA-based architectures to specific locations in living systems and release payloads based on molecular logic. Robust delivery routes have been exploited to deliver therapeutics and probes and are outlined by Chunhai Fan.

In summary, the field has moved in many directions and grown beyond the original vision of Seeman, which was to use this scaffold to prearrange molecules in space for structure determination. DNA origami and DNA brick systems, not covered in this thematic issue, resulted in the democratization of architecture construction on the multinanometer scale with DNA. It is worth pointing out that the success of origami and bricks are a direct consequence of the dramatic decreases (hundreds of US dollars/nucleotide to about $0.10 today) seen in the price of oligonucleotides. One of the concerns with DNA origami that is currently being addressed by leading practitioners is how one can stabilize these massive structures yet retain their functionality when introduced into living systems. Another is how one can scale construction as well as maintain practical yields for materials applications.

Even so, nonorigami based nucleic acid technologies are already delivering on several fronts, so what might a glimpse of the future hold? In a recent breakthrough this year, Krishnan revealed how functional imaging with DNA nanodevices reported on the responsiveness of individuals to therapeutics by directly analyzing cells derived from patients, thereby catapulting DNA nanotechnology into the world of precision medicine.[7] Lessons from toehold exchange or chemical reaction networks might be applied in concert with next

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generation sequencing to achieve DNA or RNA sequencing with subcellular spatial resolution. Innovative chemistries might impact applications in epigenetics by sequencing reversible RNA or DNA modifications *in situ* in cells. It will not be surprising at all to see nucleic acid nanotechnology providing the next generation technologies for biological analysis or the next generation of smart, adaptive, and precisely built materials.

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Notes

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Biographies

Yamuna Krishnan has been a Professor of Chemistry at the University of Chicago since 2014. Prior to that she was an Associate Professor at the National Centre for Biological Sciences, Bangalore. She received a Ph.D. in Organic Chemistry in 2002 from the Indian Institute of Science, Bangalore and was an 1851 Research Fellow at the University of Cambridge, UK from 2001−2005. While at the National Centre for Biological Sciences, she pioneered the application of DNA-nanotechnology to cell biology. At the University of Chicago, she expanded on this application, launching DNA-nanotechnology into the world of precision medicine. Selected honors include the Infosys Prize for Physical Sciences in 2017, Scientific Innovations Award from the Brain Research Foundation, and the Shanti Swarup Bhatnagar Award. She was featured on *Cell*'s 40 under 40 of scientists that are shaping current and future trends in Biology.

Nadrian C. Seeman is the Margaret and Herman Sokol Professor of Chemistry at New York University. He obtained his BS in biochemistry from the University of Chicago and a Ph.D. in biological crystallography from the University of Pittsburgh in 1970. His postdoctoral training, at Columbia and MIT, emphasized nucleic acid crystallography. He was the founding president of the International Society for Nanoscale Science, Computation and Engineering (ISNSCE). He is the recipient of the Sidhu Award, the Feynman Prize, the Emerging Technologies Award, the Rozenberg Tulip Award in DNA Computing, the World Technology Network Award in Biotechnology, the NYACS Nichols Medal, the SCC Frontiers of Science Award, the ISNSCE Nanoscience Prize, the Kavli Prize in Nanoscience, the Einstein Professorship of the Chinese Academy of Sciences, a Distinguished Alumnus Award from the University of Pittsburgh, the Jagadish Chandra Bose Triennial Gold Medal, and the Benjamin Franklin Medal in Chemistry. He received a Prose Award in Biological Sciences for his 2016 book, *Structural DNA Nanotechnology*, written during a John Simon Guggenheim Fellowship; he is a Thomson-Reuters Citation Laureate and a Fellow of the AAAS, the Royal Society of Chemistry, the American Crystallographic Association, and the American Academy of Arts and Sciences.

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