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Guest Editorial: Nucleic Acid Nanotechnology

When we first thought about writing an introductory editorial to this special issue devoted to Nucleic Acid Nanotechnology, we went through the contributions with the idea that we could describe them by sorting them into a few buckets, much like a Chinese menu: 8 from column A, 10 from column B, 6 from column C. Much to our surprise, we found minimal overlap between the Accounts: The diversity that Nucleic Acid Nanotechnology has achieved in the 30+ years of its existence is remarkable, even to those of us who have watched the development of the field from its origins. The initial goal of the field, simplified crystallization of biological macromolecules, has yet to be achieved, although self-assembled designed crystals have been built with resolution better than 3 Å. Nevertheless, like the European search for the Northwest Passage, there has been a huge number of spinoffs, ranging from applications in programmable materials, logical operations, nanoelectronics and nanophotonics organization, and nanorobotics to toolboxes for biophysics, biomimesis, diagnostics, and chemical catalysis. All of these applications are a consequence of the robust nature of being able to place molecular, supramolecular, and macromolecular species at specific locations owing to the structural robustness and relatively large size of the DNA components doing the job. These are among the areas covered in this issue, but they certainly do not define the entire interdisciplinary scope of the Accounts collected here.

The central feature of Nucleic Acid Nanotechnology is the programmability of nucleic acid structure using the same Watson−Crick base pairs that are responsible for the information content of all living systems. These secondary structure recognition interactions are reliable, reversible, and responsive, with low error rates and tractable rules. The existence and success of the field is clearly a consequence of the convenient availability of specific sequences of nucleic acids, owing to the development of phosphoramidite chemistry by Marvin Caruthers in the early 1980s. As can be seen in many of the articles, DNA structures, although robust, are not necessarily static constructs. They can be modified readily to yield machines based on intramolecular and intermolecular motion. Beginning with two-state constructs, such simple DNA nanomechanical systems today are often components of larger cascades. These are predicated on a staged series of isothermal strand displacements that work by removing strands with unpaired segments ("toeholds") when their full complements are added.

One of the major developments in Nucleic Acid Nanotechnology has been the advent of DNA origami, originated by Paul Rothemund. This is an intermediate-resolution technology, in that a naturally occurring "scaffold" strand ~7500 nucleotides in length is typically paired with ~200−250 short synthetic "staple" strands in a simple reaction. The iconic origami construction was a smiley face in the introductory article, but the ability to make shapes is not the key importance of the method. Rather, it permits one to create a surface of ~7500 nm^2 with 100−200 addressable points using a simple hybridization protocol. These points can be used to organize other species ranging from nanoparticles to DNAzymes to binding moieties. Many of the workers in the field were first attracted to it by seeing how easy it was to achieve the large extent of addressability that DNA origami presents on the nanometer scale. The ability to generate many of the features of an origami construct without staple strand purification has opened the area to those unskilled in such procedures; even so, most workers in the area have found that staple strands that interact with strands external to the origami construct need to be purified.

Throughout most of its history, Nucleic Acid Nanotechnology has been involved intimately with molecular computation. DNA sequence availability and the Watson−Crick structural rules have enabled the use of DNA tiles and toehold-based cascades as logic gates. In this fashion, they can be used to construct aperiodic arrays or to perform calculations using DNA as the computing material. Using the same types of logic that are visible in biological systems, workers in this field are using DNA molecules to make decisions, often as a consequence of a sensing function that has been built into a DNA construct. Many of the workers in this field began their careers in computer science and their presence is a major component of its growth.

Although the bedrock of Nucleic Acid Nanotechnology is the Watson−Crick B-DNA double helix, that is certainly not the only component of use in the field. For example, Z-DNA was a component of the first robust nanomechanical device. The i-motif and the G-tetrad are prominently used in a variety of applications. In addition, RNA and modified DNA backbones are currently being exploited in numerous places within the field. Single strands and tertiary interactions are now being exploited in both the molecular engineering of tensegrity structures and the formation of RNA targets.

This is an appropriate time for a large selection of the workers in Nucleic Acid Nanotechnology to review their work and their perspectives on the area. There is no doubt that the field is approaching maturity, but there are many fundamental questions that remain to be answered before its full value to nanoscience can be exploited. These range from previously unasked questions about the molecular physics of DNA molecules, to the spatial and temporal limits of molecular programming. These are issues that have not previously arisen, because there was no need to address them. Thus, in addition to foreshadowing a whole variety of nanoscale applications, Nucleic Acid Nanotechnology is also stimulating basic science by opening lines of inquiry that will lead to greater understanding of the molecules at the center of life. Richard Feynman's final blackboard contained the line, "What I cannot create, I do not understand." As workers in Nucleic Acid Nanotechnology try to exploit these molecules in more and more complex applications, we are finding that there is much

Special Issue: Nucleic Acid Nanotechnology

Published: June 17, 2014

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that we do not understand, often things that we thought that we did understand. Thus, the field is pushing both technology and science forward at an increasingly rapid pace.

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Notes

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dx.doi.org/10.1021/ar500159g | *Acc. Chem. Res.* 2014, 47, 1643−1644