# Yield, cooperativity, and prospects for nucleic acid nanofabrication

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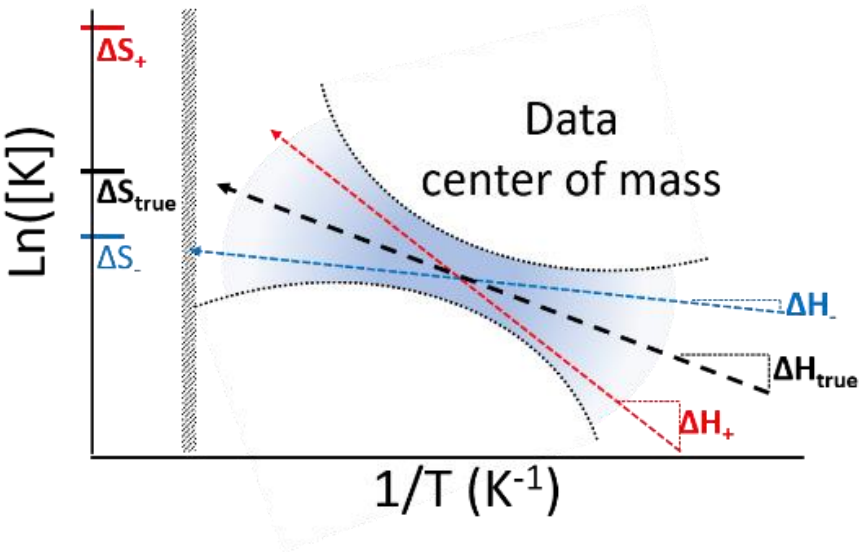
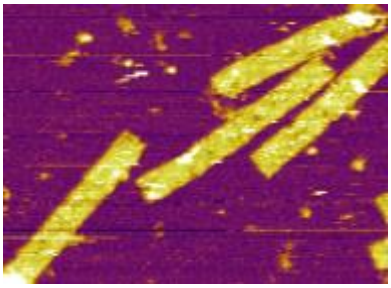
Nucleic acid nanofabrication (NAN), as exemplified by DNA origami, is capable of producing a myriad of structures and functional nanoscale devices. In addition, design tools are evolving that will enable a large community of researchers to explore the potential of this technology to control matter with molecular precision. An outstanding challenge for the field is determining where this technology may be applied to greatest effect. While there has been much speculation that self-assembling nucleic acid systems would be able to overcome lithographic barriers to semiconductor device fabrication, it is clear that, as we will describe and explain, the yield and placement precision are insufficient, resulting in a degree of disillusionment and concern about the future of the field. However, this concern is, we believe, misplaced, and arises from the attempt to try and take a still-developing technology and compete with an incumbent technology that has matured over decades to satisfy one very particular industry. For nucleic acid nanofabrication to realize its full potential, it is necessary to change the community's mindset, and break away from the notion of competing with successful incumbent technologies such as silicon nanofabrication or magnetic data storage. In addition, nucleic acid nanofabrication cannot compete directly against the full range of functionality provided by biological systems. However, NAN is uniquely positioned at the intersection of biological and semiconductor nanotechnology and can provide otherwise inaccessible combinations of their functionalities, either by aptamer emulation or directly, via covalent linkages. This enables the production of dynamic, reconfigurable nanoscale systems that can sense, perform logic, and actuate in response to a staggering variety of inputs. In addition, the assembly process is massively parallel, and recent work has shown that manufacturing at low cost and in high volume is eminently feasible.

Here, we describe some of the work that we are doing to enable NAN to be usefully combine semiconductor and biological systems. These include developing the measurement methodologies needed to understand the assembly process of nucleic acid systems, including precise determination of thermodynamics and assembly pathways that will allow the precise engineering of nucleic acid nanostructures with optimized yield and functionality.




Schematic showing the principles of van't Hoff analysis and the source of uncertainty in the determination of enthalpy and entropy.



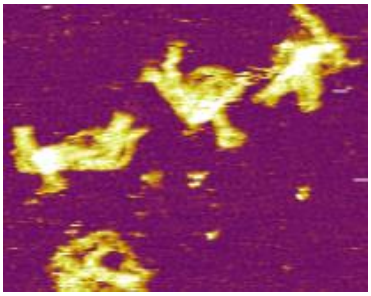


Illustration of the difference in folding yield for notionally similar structures having slightly different design details.

Summary: Nucleic acid nanotechnology will not compete with semiconductor manufacturing, but has great potential to act as a tool to enable the combination of microelectronic and biological functionalities. We describe the precise measurements of assembly pathways and system thermodynamics needed to enable the design and implementation of such semi-bio interfaces.