Programming Folding Pathways and Chemical Synthesis with DNA

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DNA is not only a wonderful material for nanoscale construction, its hybridization or hydrolysis can be used to provide energy for synthetic molecular machinery. With DNA it is possible to design and build three-dimensional scaffolds, to attach molecular components to them with sub-nanometre precision – and then to make them move. I shall describe our work on DNA origami assembly pathways and the use of synthetic molecular machinery to control covalent chemical synthesis.

Assembly Pathways[1] DNA origami is a robust molecular assembly technique by which a single-stranded DNA template is folded by annealing with hundreds of short 'staple' strands.[2] There is a strong analogy with protein folding: both are governed by information encoded in polymer sequence.[3] We present an origami structure that has the unusual property of having a small set of distinguishable, well-folded shapes that represent discrete and approximately degenerate energy minima among 10^{23} disordered alternative staple configurations. We obtain a high yield of well-folded structures, demonstrating that efficient folding pathways exist,[4] and show that the assembly pathway can be steered by rational design. We identify similarities to protein folding: assembly is highly cooperative; reversible bond-formation is important in recovering from transient misfoldings; and the early formation of long-range connections can be very effective in forcing particular folds.

Programmable Synthesis[5] We report the programmed synthesis of peptides and unnatural oligomers using synthetic molecular machinery made from DNA to control and record the formation of covalent bonds[6]. DNA-templated covalent bond formation[7] is controlled by an autonomous cascade of DNA hybridization reactions which brings reactants together in a controlled sequence defined by a reconfigurable molecular program. The sequence of assembly reactions, and thus the structure, of each oligomer synthesized is recorded in a DNA molecule which enables this information to be recovered by PCR amplification followed by DNA sequencing. We apply this technique to the programmed synthesis of two families of oligomers with different backbone chemistries: peptide, with the potential for biomimetic synthesis, and Wittig, creating bio-orthogonal linkages. The system can also be programmed to achieve combinatorial assembly, opening up the possibility of applications in drug discovery.

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