NANOROBOTS

Reconfigurable self-assembled DNA devices

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Modular reconfigurable systems can be achieved with DNA origami, demonstrating the potential to generate molecular robots.

DNA nanotechnology makes it possible to construct precise nanometer-scale structures using self-assembly. Structures can be designed that sense, compute, and actuate in response to external signals. In this issue, Sarraf *et al.* (*1*) provide a detailed description of the design parameters for reconfigurable systems of DNA origami tiles. The work is a stepping stone on the route to reconfigurable molecular robotic devices built from DNA.

Two-dimensional (2D) DNA origami tiles with hundreds of unique DNA strands can be assembled with high yield (*2*). The glue that holds them together is Watson-Crick base pairing between DNA strands with matching (complementary) nucleotide sequences. The tiles, typically 100-nm square, can be used as an addressable molecular breadboard with a feature size of less than 10 nm. Adding protrusions and recessions to the edges of the tiles can create programmable lock-and-key interactions between tiles (*3*). The interactions are mediated by hydrophobic stacking between the ends of double-stranded DNA (*3*) or by combining stacking interactions with weak base pairing interactions (*4*). Joining many tiles using a set of orthogonal lock-and-key interaction rules allows access to larger length scales while retaining the same feature size. The interaction strength between tiles is controlled by the number of complementary interactions. Qian and colleagues (*4*) had previously noticed that their tile assembly experiments gave a good yield even when interactions were strong. This surprised them because they had expected kinetic traps where incorrectly placed tiles could not be removed. They proposed a repair mechanism called tile displacement: An incoming (correct) tile can displace a tile if it satisfies more complementary interaction sites than the (incorrect) tile in its place (*5*). The mechanism is a structural analog of toehold-mediated strand displacement seen with complementary DNA strands (*6*): The extra interactions fulfilled upon tile displacement are equivalent to the extra base pairs made by toehold binding (Fig. 1).

Sarraf and colleagues (*1*) extend the work by defining a large set of orthogonal interaction rules. In doing so, they map out the design space that is available for construction of reconfigurable DNA origami devices. Like any new molecular interface, there are multiple parameters that can be tuned to achieve specific binding and reconfiguration. The design rules build on previous work with DNA origami tile interfaces, but the addition of displacement complicates the design problem: Not only must tiles be made to interact specifically, but they must also be able to interact specifically with invader tiles to displace this and only this linkage. Drawing inspiration from DNA toehold–mediated strand exchange, Sarraf and colleagues first placed the toeholds either at the upstream or downstream end of the binding domain that links the tiles and found that both approaches work with similar specificity and speed. Unlike traditional DNA toehold exchange, tile interfaces can be designed with discontinuous toeholds distributed along the edge. Interestingly, this design strategy works at more or less the same speed as the terminal toehold. More importantly, it opens the design space up to over 800 possible orthogonal and displaceable interactions.

These interfaces are not limited to discrete assemblies; tiles that interact head-to-tail form ribbons. The linkages between tiles have some flexibility; this allows ribbons to fold on themselves to form barrel-like structures when the two ends of the ribbon join. Unlike previous lock-and-key tile growth models, the interactions can be broken via tile exchange. The authors show that they are able to break open the barrels to form ribbons by adding a specific invader tile.

Under the experimental conditions in the study, the tile displacement reactions happen on the order of hours, too slow for some applications. The authors note that the mechanical properties of the tile are likely to affect the speed of reaction and that making the tiles more flexible might improve the reaction rate. A more fundamental hurdle to overcome is that the tile exchange is not reversible, but, given that reversible toehold-mediated strand exchange reactions have been developed (*7*), it is reasonable to anticipate reversible tile exchange reactions.

Rudimentary sensing, switching, and computational modules have all been implemented using DNA as a construction material. These can be combined to make devices such as a logic-gated molecular robot that reveals its therapeutic cargo only when specific cellular conditions are met (*8*). DNA devices are relatively slow [if speed is what you are after, use an external electric field to drive them (*9*) or construct hybrid devices that integrate fast biological or chemical motors]. Although slow, DNA devices are unmatched in their ability to process information, and, because they are able to use biological inputs and outputs, they can be readily integrated with biological systems. The molecular machinery found in biological systems—from sensors and switches to motors and chemical assembly lines—provides both motivation by demonstrating what is possible and a benchmark against which to measure success.

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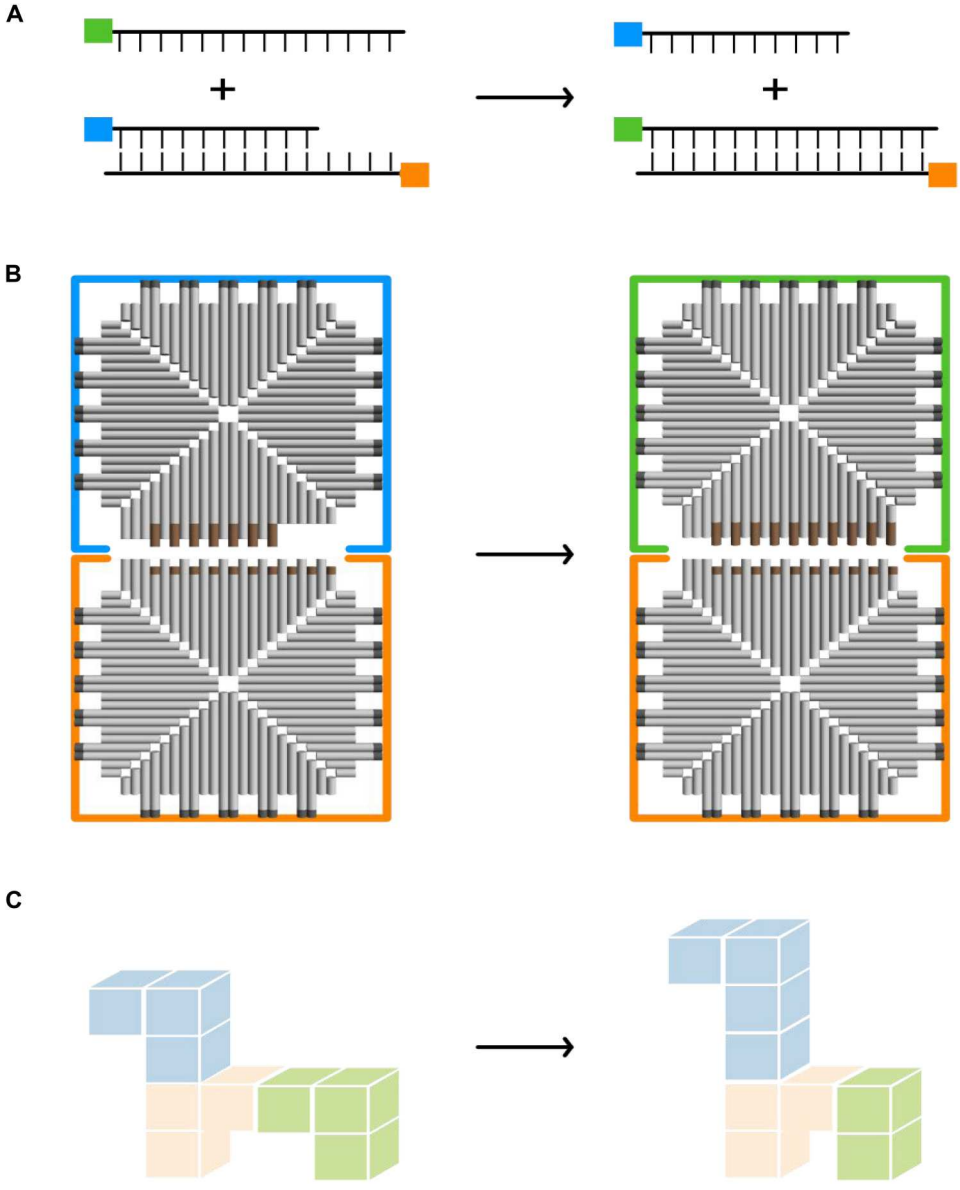

Fig. 1. Reconfigurable DNA nanostructures. (**A**) A DNA strand (blue) bound to a partially complementary strand (orange) can be displaced by addition of a fully complementary strand (green). This mechanism is driven thermodynamically by a short single-stranded "toehold" of base pairing interactions that are only satisfied once the reaction is complete. (**B**) The mechanism can be extended to much larger DNA origami tiles by replacing bases between tiles with partially complementary shapes at the interface between them. (**C**) The mechanism can be further extended to allow rearrangement of 2D and 3D structures.

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