**Exploiting weak interactions in DNA self-assembly**

Weak stacking interactions allow dynamic assembly and disassembly of DNA origami shapes

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Many dynamic biomolecular complexes, such as actin filaments or microtubules, are formed through the assembly of numerous subunits that can disassemble again after a modest input of energy. To achieve structural integrity, the interfaces between domains must be relatively large. At the same time, the overall adhesion energy of each interface must be sufficiently low so that it can be readily broken on command. On page 1446 of this issue, Gerling et al. report a framework that satisfies these conditions for the programmable dynamic assembly and disassembly of rigid three-dimensional (3D) structures built from DNA origami. Such devices could prove useful for applications such as sensors and therapeutic delivery vehicles.

Structural DNA nanotechnology exploits the robust sequence complementarity of DNA strands to program the assembly of complex shapes. One powerful variant, DNA origami, enables one-pot self-assembly of 2D or 3D custom shapes with up to 10,000 independently addressable base pairs. In this method, a long scaffold strand with a nonrepetitive sequence is combined with hundreds of shorter staple strands to fold together via base pairing into bundles of double helices in the desired configuration.

Hierarchical assembly between bundles has been explored using not just base-pairing interactions, but also blunt-end stacking interactions, which are weak adhesions between the ends of two double helices that each lack single-stranded overhangs. Specificity can be provided by “jigsaw” bundle ends, where the constituent double helices protrude to variable extents. Only bundle ends with shape-complementary sets of protrusions can then dock in a manner to satisfy all blunt-end stacking interactions. In earlier studies, the origami pieces were linked along the helical axes of the 2D bundles. In contrast, Gerling et al. designed interfaces between bundles that face each other laterally. This has the advantage that, at low to moderate salt concentrations, electrostatic repulsion greatly exceeds generic attractive interactions. This net repulsion provides an energy barrier that only target interactions can overcome at moderate ionic strength, and no potential interactions can overcome at low ionic strength.

To engineer a specific attractive interaction, the authors designed a “plug” (a pair of double helices of defined length, terminating in pairs of blunt ends) on the side of one bundle and a corresponding “hole” (two flanking pairs of double helices that also terminate in pairs of blunt ends) on the side of the conjugate bundle. Together, a “plug” and a “hole” then form four blunt-end stacking interactions. An individual stacking interaction is only about half as strong as a base-pairing interaction; a single plug-hole interaction is therefore quite weak yet provides long-range registration, because the bonding is distributed between the two distant termini of the plug. The authors programmed shape-complementary distributions of plugs and holes that were designed to sterically exclude nontarget interactions.

Because the interaction energies of the interfaces are much lower than those holding together each bundle, external conditions can be used to modulate hierarchical assembly without compromising bundle integrity. The authors were able to cycle the assembly and disassembly of interfaces through altering cation concentrations or by shifting the temperature. In the latter case, they achieved more than 1000 cycles of opening and closing of a scissor motif over the course of 4 days with no detectable degradation. Closure upon cooling to 25°C took an average of 4 s, whereas opening after heating to 50°C was much more rapid.

The authors also demonstrate allosteric control via strand hybridization. Here, they engineered a single-stranded loop in the middle of a plug, such that when a complementary strand was added in trans, the plug was deformed, disrupting the interface. Subsequent removal of the complementary strand was achieved by toehold-mediated hybridization to a recovery strand added in trans. (A toehold is an additional 9-base single-stranded domain that gives strand displacement a thermodynamic advantage as well as a kinetic boost.) In the future, chemically powered autonomous cycling could be implemented with catalytic strand-displacement cascades.

Gerling et al. demonstrate the generality of their method through the assembly of example architectures, including a single-threaded filament of rectangular blocks, a 2D hexagonal array versus a dual-threaded filament of hexagonal blocks, a 2D array of scissor motifs, and sheets that fold up into hexagonal or rectangular blocks. One particularly delightful example involves a “nanorobot” that assembles from three separate components, reminiscent of the Voltron mecha cartoons from the 1980s.

One limitation of the current design is that the length of the plugs is restricted to...
integral numbers of double-helical turns. If future designs could modulate plug length to single-base-pair resolution, a much larger set of orthogonal interfaces could be constructed relative to a given bundle size. This would allow assembly of larger, more complex, and therefore more sophisticated devices.

The authors note some challenges for including base-pairing interactions, instead of only stacking interactions, to drive dynamic interfacial recognition. For example, the interaction energies may be too large when long sequences are used. Nonetheless, one can imagine interesting possibilities where base pairing is involved. For example, the use of short sticky ends (double-helix termini with single-stranded DNA overhangs available for base pairing) may be exploited to increase the combinatorial possibilities, although compensatory repulsive interactions may be required in conjunction to prevent the specific interfacial energy from becoming too large. Longer sequences could be used together with competitor displacement strands (12), where the specific interfacial energy can be tuned according to length, sequences, and concentrations of the latter strands. For example, Rogers and Manoharan (14) recently reported programming reentrant melting of DNA-functionalized colloids (which interact only within a specified temperature band) by exploiting competitive strand displacement schemes.

Given the great advances in static self-assembly of highly complex DNA shapes over the past decade, the time is ripe to explore how these architectures can be controlled dynamically. Through their pioneering forays into shape complementarity, weak interfacial energies, and remotely tunable repulsion energies, Gerling et al. point the way toward reconfigurable, rigid DNA nanodevices that may one day rival the functional sophistication of the biomolecular machines of the cell.

**REFERENCES**


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**NEUROSCIENCE**

**Treating brain disorders with neuromodulation**

Nanoparticles, magnetic fields, and heat-sensitive ion channels are harnessed to manipulate brain activity to other magnetic fields that one confronts in daily life? The more immediate value for magnetothermal neuromodulation is in its use as a tool to excite specific subpopulations of neurons by remote control.

The development of new tools for intracranial neuromodulation (see the figure) evokes a concept hypothesized by Nobel Laureate Antônio Egas Moniz in the first half of the 20th century—that a dysfunctions circuit of Papez (medial limbic circuit that connects the hypothalamus to the cortex) underlies major affective disorders. He and others intervened surgically with lesions of the frontal cortex by a transorbital route (lobotomy). The idea was to destroy connective nerve fibers or specific brain tissue, but the procedure only improved symptoms in some patients temporarily, and the risks included serious affective

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“…magnetothermal neuromodulation...could...enhance our knowledge of the brain’s microcircuitry in normal and disease states.”

and cognitive side-effects such as apathy. Shortly after the introduction of the human stereotaxic apparatus in 1947 (2), which used a three-dimensional coordinate system to locate specific regions in the brain, surgeons approached deeply situated motor regions with more precise lesions to treat patients with movement and psychiatric disorders.

In the second half of the 20th century, electrodes placed temporarily in deeply situated areas of the brain became more popular. Limbic regions were thus stimulated to modulate affective behaviors of patients (3). A well-known animal study demonstrated that an attacking bull could be stopped instantly when an electrode, placed in its caudate area, was activated by a remote controller (4). Although these methods were hypothesis-driven, their main weakness was the lack of a robust scientific base, and they