LEGO-like DNA Structures

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MATERIALS SCIENCE

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DNA "bricks" consisting of short sequences of single-stranded DNA self-assemble into a wide variety of shapes.

Parallels are often drawn between the construction of molecular structures and building toy models in LEGO bricks. This analogy is particularly suitable for the method reported by Ke *et al*. on page 1177 of this issue (*1*). The authors describe the construction of arbitrary and discrete three-dimensional (3D) DNA structures by self-assembly of single-stranded DNA "bricks." The method opens a new route to complex self-assembled (3D) nanostructures that may serve as addressable templates for placing guest molecules with high precision, with possible applications in biophysics, medicine, and nanoelectronics.

DNA nanotechnology evolved from Seeman's pioneering ideas in the 1980s about using immobile DNA junctions to create periodic DNA lattices (*2*) and bio-

electronic devices (*3*). The field has since advanced from assembling a few sequences to the assembly of large periodic lattices of repeated DNA tiles (*4*, *5*). However, the formation of large discrete DNA nanostructures with unique tiles in all positions posed a major challenge. The conventional wisdom was that such structures were difficult to form owing to the requirement for exact stoichiometry of the DNA strands and the formation of noncompatible partial structures.

In 2006, Rothemund overcame this problem through the development of DNA "origami" (*6*). Using a long single-stranded DNA sequence as a scaffold and over 200 shorter synthetic strands as "staples" to fold the scaffold, he assembled arbitrary and discrete 2D DNA nanostructures with dimensions of typically ~100 by ~100 nm.

The DNA origami method overcame stoichiometry problems by allowing use of the short synthetic DNA strands in excess. Later, the method was extended to 3D DNA structures (*7*–*9*). However, one drawback of

DNA origami is that the routing of the DNA scaffold in origami structures requires a new design and a new set of staple DNA strands for each new structure. Furthermore, the assembly of 3D origami structures is often slow and the yields low.

Yin and co-workers have challenged the conventional wisdom by using short single-stranded tiles (SSTs) to form large structures without a scaffold strand. Compared to conventional DNA tiles, the tiles are small, single-stranded, and have no ordered structure before they are incorporated in the superstructure (*10*). Recently, they used hundreds of SSTs to construct 2D structures with sizes comparable to those of 2D DNA origami (*11*).

In the latest work (*1*), the authors extend single-stranded tiles to single-stranded bricks and show that DNA brick assembly is a powerful method for constructing 3D structures. They show that arbitrary prescribed structures can be formed by selecting different subsets of strands from the same common pool of DNA sequences, making the design process more straightforward and enabling easy automation of the synthesis.

The basic building block in the structures is a 32-nucleotide single-stranded DNA, which contains four regions that can hybridize to four neighboring DNA strands (see the figure, panel A). To build 3D structures in a periodic way (panels B to E), the core design rule in this study is that the DNA bricks (resembling two-stud LEGO bricks) are connected with a 90° left-handed turn, resulting in layers of bricks that are shifted 90° relative to each other. Whereas LEGO structures are assembled by hand, brick by brick, the DNA structure forms by self-assembly: Each DNA brick is encoded with an individual sequence that determines its position and allows the structure to assemble by hybridization of complementary sequences. In a one-step annealing reaction in a magnesium-rich buffer, the cuboid structure (see the figure, panel C) formed over 72 hours.

The great advantage of the DNA brick method is that arbitrary structures can be sculpted from the same batch of DNA bricks by leaving out specific bricks and protecting the boundaries of the truncated structures with boundary and protector bricks. For example, the space shuttle–type of
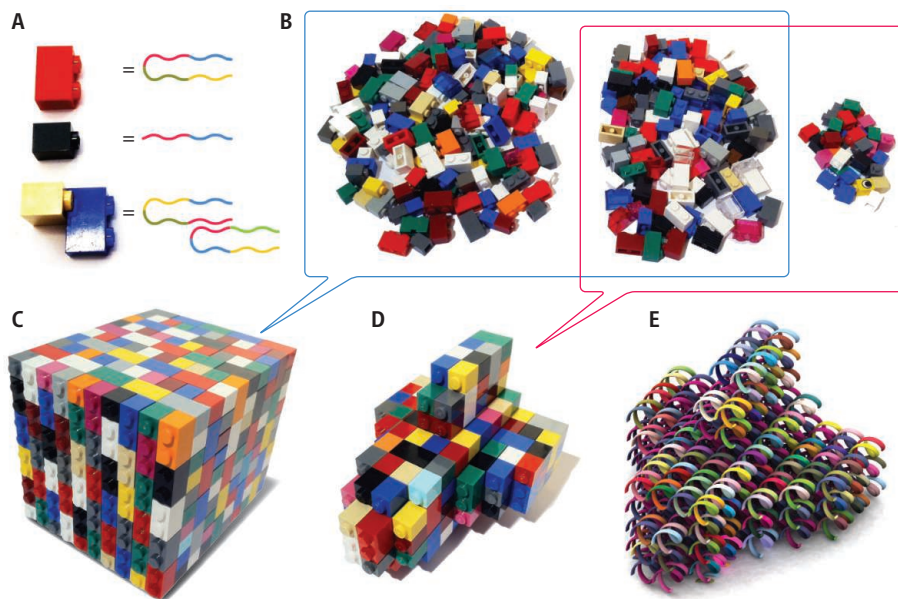
How to make DNA brick structures analogous to LEGO® brick structures. (**A**) A DNA brick consists of four regions of 8 nucleotides each and corresponds to a two-stud LEGO brick. Half–DNA-bricks corresponding to one-stud LEGO bricks are used for edges (*1*). DNA bricks are connected by an 8–base pair hybrid, causing a 90° shift between two layers. (**B**) Ke *et al*. used one- and two-stud bricks (represented by the LEGO bricks in the blue frame) to assemble a 10 by 10 by 10 voxel cuboid (*12*) (**C**). With subsets of the bricks used for the cuboid, the authors also assembled many other shapes, such as a space shuttle–like structure, shown both as a LEGO (**D**) and DNA model (**E**). The extra bricks in the red-framed section in (B) are the boundary and protector bricks required for formation of the space shuttle structure.

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structure (panels D and E) was created in this way.

Ke *et al*. demonstrate the generality and diversity of the method by creating 102 different structures out of subsets of the 10 by 10 by 10 voxel (*12*) cuboid. The structures have a wide variety of shapes, some with holes and closed cavities. There seem to be few limitations, except that a certain number of voxels must connect different parts of the structures to maintain the structural integrity.

It is puzzling that the structures form at all, instead of forming incompatible partial structures. The authors argue that seeding may be much slower than the growth of the structures, but it is not clear why this would be the case. Furthermore, the yields, at least for the larger structures, are relatively low.

Fortunately, the DNA brick and DNA origami methods are compatible; as Ke *et al*. discuss, it is likely that a combination of the two methods will pave the way for making even larger structures in higher yields.

Just as bricks of other shapes, other materials, and even small machines with matching sockets or studs can be integrated into LEGO structures, so can materials such as small molecules, nanoparticles, or proteins be integrated in DNA brick structures if these materials are conjugated to a DNA strand. Combined with the straightforward LEGO-like design principle of the DNA brick method and the possibility of integration with DNA origami, there is great potential for building advanced functional 3D nanostructures.

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12. Each 8–base pair interaction between bricks defines a voxel with dimensions 2.5 by 2.5 by 2.7 nm. In the LEGO analogy, one voxel corresponds to a one-stud brick.

Embers of the Distant Past

Detection of imprints from ancient star light places constraints on the evolution of the early universe.

Volker Bromm

Modern cosmology has come a long way in fulfilling its grand goal of reconstructing the entire history of the universe. The emergence of cosmic structure is governed by dark matter whose gravitational attraction led to the condensation of gas into galaxies, stars, and black holes. Whereas the evolution of the dark matter component is well understood (*1*, *2*), cosmic star and black hole formation is still subject to large uncertainties. The combined energy production from all stars and black holes, releasing radiation when gas is falling close to their event horizon, however, is preserved in a pervasive cosmic radiation background—the extragalactic background light (EBL). This radiation comprises wavelengths from ultraviolet (UV) to far-infrared (IR) and provides us with an independent check on how many stars and active black holes have existed. On page 1190 of this issue, Ackermann *et al*. (*3*) present a new measurement of the EBL with the Fermi Space Telescope, based on the attenuation of distant sources of gamma-ray photons when they travel through the sea of lower-energy, background EBL photons.

Such a consistency check on the census of luminous sources also provides crucial constraints to close the gap in our cosmic

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worldview, the first billion years after the Big Bang, when the first stars and galaxies formed (*4*). Our understanding of the first sources of light has to rely on theoretical studies, making predictions to be tested with the James Webb Space Telescope (JWST), to be launched around 2018. In the meantime, it is important to make progress by way of indirect constraints. Among them is the imprint left by the first stars on the EBL (*5*, *6*). The basic process involves the ionizing photons emitted from massive primordial stars (see the figure), which are reprocessed into Lyman-α photons; they in turn travel through the expanding universe for billions of years, eventually being redshifted into the optical and infrared part of the spectrum.

Complementary to the Fermi results by Ackermann *et al*., determining the strength of the EBL in the optical/UV, are measurements of the fluctuation power in the cosmic infrared background (CIB). Deep exposures with the Spitzer space telescope reveal hints of a highly clustered component that cannot be explained with any known sources, such as faint galaxies at intermediate redshifts (*7*). Light from the first stars and galaxies could account for the excess fluctuation signal, because the cosmological cold dark matter model naturally predicts that their formation sites are strongly clustered. A tantalizing new perspective has recently been provided by a possible correlation between fluctuations in the cosmic infrared and x-ray

backgrounds (*8*). Such a cross-correlation could be naturally accommodated by models of first star formation, where the emergence of massive binary systems is predicted, provided that a fraction of them would evolve into x-ray binaries (*9*, *10*). Such systems would contain a black hole remnant paired with a less-massive companion. The progenitor stars could contribute to the CIB, whereas the hard x-ray emission from their remnant would be deposited into the cosmic x-ray background. A correlated signal in the infrared and x-ray spectral region would naturally follow.

Both the Ackermann *et al*. Fermi and the CIB fluctuation results have as their prime goal to determine how many stars there were throughout cosmic time, including at high redshifts. This quantity is of crucial importance for a number of key questions in current cosmology. Among them is the problem of accounting for all the sources of ionizing radiation that, taken together, can reionize the universe at an age of about one billion years (*11*). There still seems to be a deficit, such that there must have existed an additional component of stars, or accreting black holes, in systems that are too faint, or too distant, to be detectable with current instrumentation. It is therefore crucial to constrain such "unseen" contributions. Theory suggest that at high redshifts, a mix of stellar populations was formed, including the elusive first generation of pure hydrogen/