CHEMICAL BIOLOGY

A new twist for DNA

A computer-aided design strategy allows scientists to 'staple' DNA molecules into a wide variety of two-dimensional shapes, generating precisely arranged scaffolds that could serve as promising platforms for nanoscale research applications.

DNA: it's not just for geneticists anymore. This has been a gradual realization over the past decade or so, as a small but growing cadre of nanotechnology-oriented researchers have begun working with the double helix as a building material for a variety of nanoscale structures. One such researcher, Paul Rothemund of the California Institute of Technology, got an early start in the field when, as an undergraduate in 1992, he undertook a project exploring the idea of DNA-based computing—a technology he continues to explore 14 years later.

Precise molecular patterning is important for the design of higher-order DNA-based devices, but most techniques for building complex DNA structures require the laborious assembly of many small oligonucleotides in multiple reaction steps. In a recent article in *Nature*, however, Rothemund presents an alternative—the use of many short oligonucleotides to anchor a single, long 'scaffold' DNA molecule into any of a variety of two-dimensional shapes—a process he terms 'DNA origami'. The process is relatively simple. In the design phase, the scaffold molecule (Rothemund used the 7.2-kilobase M13 virus genome) is virtually 'woven' into a specific shape, with linkage points designed into the model to stabilize the folded DNA. This folding path data is then fed into an algorithm, which optimizes the blueprint and designs oligonucleotide 'staples' that reinforce these linkage points by base-pairing with the scaffold. The completed design has no bases unpaired. The scaffold DNA and an excess of staple molecules are mixed together in solution, heat-denatured and then slowly renatured. This results in a far simpler assembly process, in which rapid synthesis takes place in a one-pot reaction that requires essentially no titration of components.

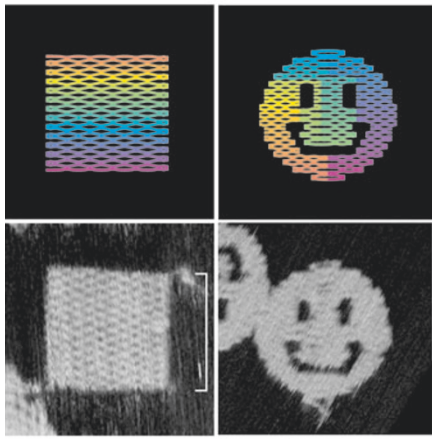

Figure 1 | Examples of DNA origami. Computer-generated diagrams of DNA molecule patterning (top), and atomic force microscopy images of actual folded DNA structures (bottom). Reprinted with permission from *Nature*.

Within 2 hours, the origami is folded, and even though the results might not be tiny cranes or turtles, they are nonetheless impressive—a variety of shapes, ranging from simple squares to cheerful smiley faces (**Fig. 1**), all of which show high fidelity to the originally computed designs. Rothemund also demonstrates the potential to decorate these DNA platforms with sequence-addressed functionalities by working with modified staples for his 'rectangle' design. Using hairpin-containing staples, which can be visualized as 'pixels' via atomic force microscopy, he has generated surprisingly complex and accurate patterns on the rectangle surfaces, including lettering and even a map of the Americas. A bit showy, perhaps, but also a strong demonstration of the precision with which one can target the attachment of molecules to these scaffolds.

Since publishing this work, Rothemund has found that if he works with well-purified scaffolding, he can routinely achieve reactions in which 70–90% of the shapes are properly folded, regardless of the complexity of the design. One of the main challenges now is developing methods for precisely arranging folded origami on solid substrates. "We need to get them down where we want them," says Rothemund, "not just splattered down willy-nilly..., and that's a challenge, to go from them being in solution like that, down onto a surface."

Nonetheless, this initial work has already aroused the interest of several scientists interested in using this approach to precisely arrange quantum dots, gold nanoparticles and proteins, among other things. Rothemund will be making his design algorithm available to the public, but also feels that most scientists should already have all that they need at their disposal: "The thing is that most people who want to use this stuff don't want to use the program. They should just take the basic rectangle that I already made, and just start playing with that."

For molecular biologists, DNA nanotechnology can still be a bit of a hard sell—so far, the most active interest has come from physicists and chemists—but Rothemund suggests that any biologist interested in the nanoscale arrangement of molecules could benefit from taking up a little origami. "There are some multienzyme systems in biology where a substrate gets passed from one enzyme to the next," he says, "so if somebody wants to re-engineer such a protein 'factory', to have the proteins occur in a particular order, this is something that they might be interested in." He now hopes to reach out to biologists who might be interested in trying somewhat unconventional approaches to address their research questions. "There's this whole toolkit that we have, and hopefully there will be people who want to have some imagination for their experiments and have us help them—because it's really not that hard—to do interesting biology experiments," he concludes. "It just takes some imagination to work that out."

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RESEARCH PAPERS
Rothemund, P.W.K. Folding DNA to create nanoscale shapes and patterns. *Nature* **440**, 297–302 (2006).