BIOSENSORS

An origami chip of DNA

Nanoscopic DNA chips assembled using the DNA origami method enable target detection in solution and hold promise for single-cell gene expression analysis.

In 2006 Paul Rothemund of the California Institute of Technology 'folded' DNA to create two-dimensional shapes ranging from a basic rectangle to a personable smiley face (Rothemund, 2006). In this method—which he termed 'origami'—a long DNA molecule is folded into a predesigned shape by short oligonucleotide 'staples'. The components are heat-denatured, and they then self-assemble into the programmed shape as they cool. These shapes are placed on a mica surface and can be 'seen' by atomic force microscopy (AFM).

Discussing his results in a 2006 *Nature Methods* interview, Rothemund said the algorithm to design various shapes would be available, but most scientists "should just take the basic rectangle that I already made, and just start playing with that."

And that is indeed what Hao Yan at the Biodesign Institute and the Department of Chemistry and Biochemistry at Arizona State University has done in his effort to develop a tool for single-cell gene expression analysis. He says, "We thought that would be a really great platform to begin plugging in some probes, which can be RNA, DNA or other types of molecules—so there's no limitation."

In their work presented in *Science*, Yan and colleagues assembled origami rectangle tiles with 20-base-pair DNA tails attached to some of the staples (Ke *et al.*, 2008). Placed next to one another on a tile, two such tails comprise the probe for a target sequence. The researchers tested their system by adding these tiles to a solution containing three synthetic RNAs in a background of total cellular RNA. After dropping aliquots of the reaction mixture onto mica plates, they detected the targets that had hybridized in solution by AFM. Even if the tile lands probe-side down, AFM could still detect a bound target because of the flexible nature of DNA. "You can think of it as a ball underneath carpet," explains Yan.

Surprisingly, the targets bound differently to probes at various locations on the tile, and the researchers optimized the chips on the basis of this information. The precision of probe placement also opens the door to using these chips to study distance-dependent biomolecular interactions. Yan explains: "You can vary the distance between multiple ligands on the array, and see what spatial configurations will give best cooperative binding to a target."

Single-cell studies are also on the horizon. With the availability of microfluidic devices for single-cell analysis, the limitation now lies in placing the chips into a tiny spot for analysis. But Yan sees a potential solution to this in a commercially available molecular printer that can place small samples with nanometer resolution: "I cannot say for sure that this can be solved in a few months, but there is a promising future" for these chips.

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RESEARCH PAPERS

Ke, Y. *et al.* Self-assembled water-soluble nucleic acid probe tiles for label-free RNA hybridization assays. *Science* **319**, 180–183 (2008).

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