# DNA origami suggests route to reusable, multifunctional biosensors

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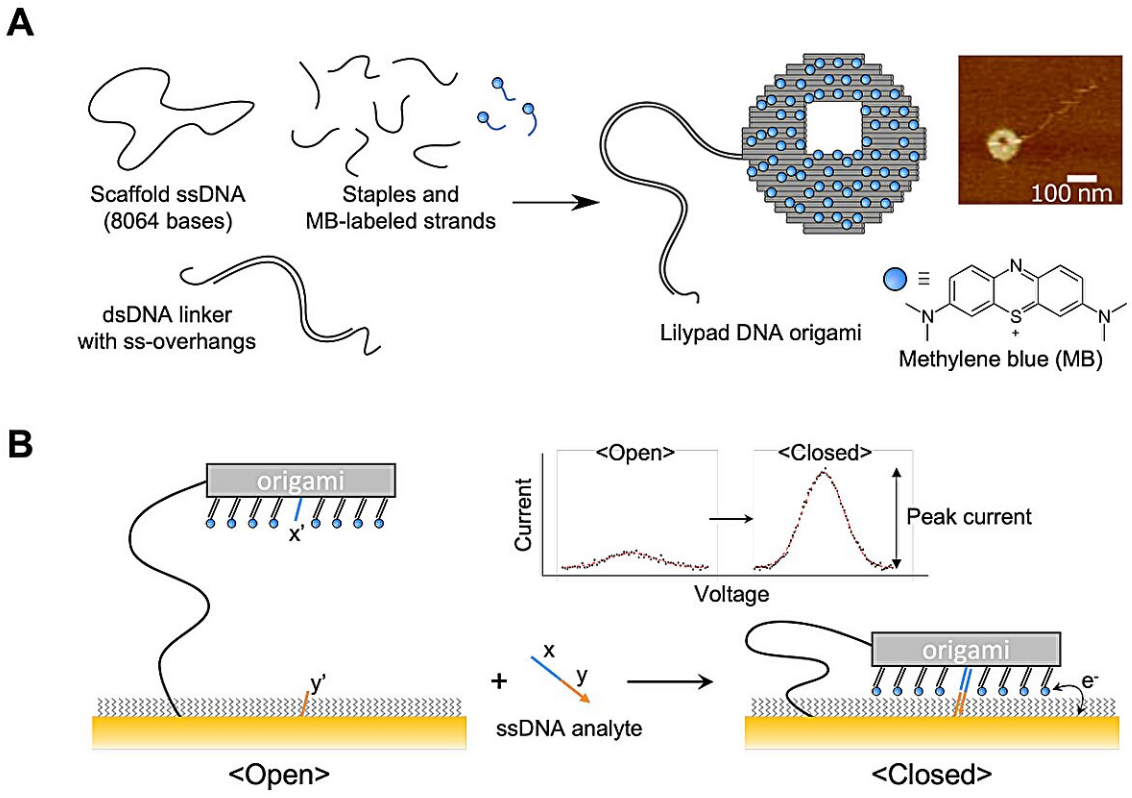



Lily pad sensors can be used for the electrochemical detection of biological analytes, here a DNA single strand. Credit: Byoung-jin Jeon et al

Using an approach called DNA origami, scientists at Caltech have developed a technique that could lead to cheaper, reusable biomarker

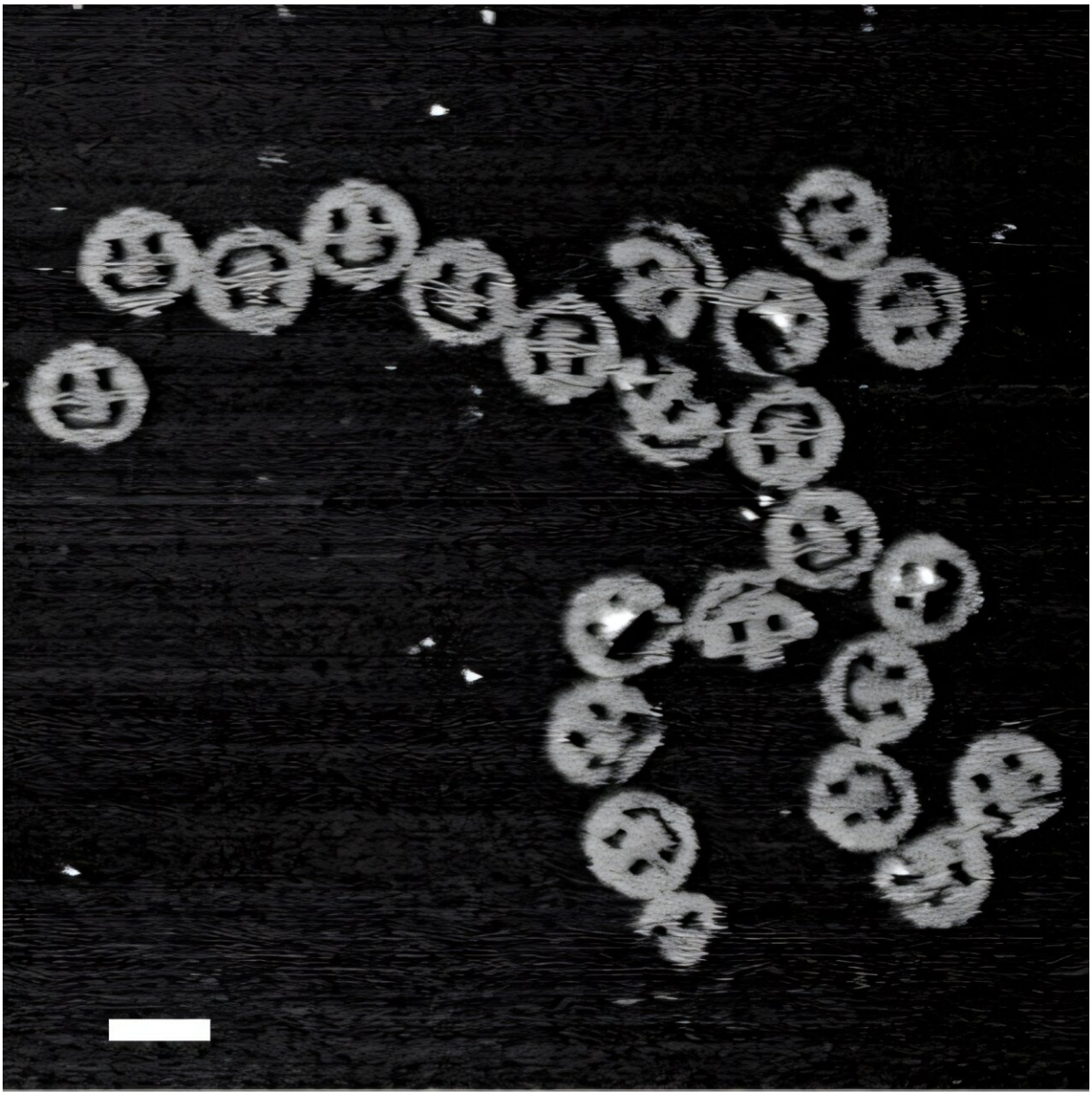
sensors for quickly detecting proteins in bodily fluids, eliminating the need to send samples out to lab centers for testing.

"Our work provides a proof-of-concept showing a path to a single-step method that could be used to identify and measure nucleic acids and proteins," says Paul Rothemund (BS '94), a visiting associate at Caltech in computing and mathematical sciences, and computation and neural systems.

A paper describing the work recently appeared in the journal *Proceedings of the National Academy of Sciences*. The lead authors of the paper are former Caltech postdoctoral scholar Byoung-jin Jeon and current graduate student Matteo M. Guareschi, who completed the work in Rothemund's lab.

In 2006, Rothemund published the first paper on DNA origami, a technique that provides simple yet exquisite control over the design of molecular structures at the nanoscale using nothing more than DNA.

Essentially, DNA origami enables long strands of DNA to fold, through self-assembly, into any desired shape. (In the 2006 paper, Rothemund famously used the technique to create miniature DNA smiley faces measuring 100 nanometers across and 2 nanometers thick).



DNA origami smiley faces, each 1/1000 the width of a human hair, demonstrate that virtually any shape can be folded from DNA. (atomic force microscopy image; scale bar: 100 nanometers) Credit: Paul W.K. Rothemund/Caltech

Researchers begin with a long strand of DNA, the scaffold, in solution. Because the nucleotide bases that make up DNA bind in a known way

(adenine binds to thymine, and guanine binds to cytosine), the scientists can add hundreds of short sequences of complementary DNA knowing they will bind to the scaffold on either end at known locations.

Those short, added pieces of DNA fold the scaffold and give it shape, acting as "staples" that hold the structure together. The technique can then be used to create shapes ranging from a map of North and South America to nanoscale transistors.

In the new work, Rothemund and his colleagues used DNA origami to create a lilypad-like structure—a flat, circular surface about 100 nanometers in diameter, tethered by a DNA linker to a gold electrode. Both the lilypad and the electrode have short DNA strands available to bind with an analyte, a molecule of interest in solution—whether that be a molecule of DNA, a protein, or an antibody.

When the analyte binds to those short strands, the lilypad gets pulled down to the gold surface, bringing 70 reporter molecules on the lilypad (which indicate that the targeted molecule is present) into contact with the gold surface. These reporters are redox reactive molecules, meaning they can easily lose electrons during a reaction. So, when they get sufficiently close to an electrode, an electric current can be observed. A stronger current indicates that more of the molecule of interest is present.

Previously, a similar approach to making biosensors was developed using a single DNA strand rather than a DNA origami structure. That earlier work was led by Kevin W. Plaxco (Ph.D. '94) of UC Santa Barbara, who is also an author of the current paper.

Caltech's Guareschi points out that the new lilypad origami is large compared to a single DNA strand. "That means it can fit 70 reporters on a single molecule and keep them away from the surface before binding.

Then when the analyte is bound and the lilypad reaches the electrode, there is a large signal gain, making the change easy to detect," Guareschi says.

The relatively large size of the lilypad origami also means that the system can readily accommodate and detect larger molecules, such as large proteins. In the new paper, the team showed that the two short DNA strands on the lilypad and the gold surface could be used as adapters, making it a sensor for proteins rather than for DNA.

In the work, the researchers added the vitamin biotin to those short DNA strands to turn the system into a sensor for the protein streptavidin. Then they added a DNA aptamer, a DNA strand that can bind to a specific protein; in this case, they used an aptamer that binds to a protein called platelet-derived growth factor BB (PDGF-BB), which could be used to help diagnose diseases such as cirrhosis and inflammatory bowel disease.

"We just add these simple molecules to the system, and it's ready to sense something different," Guareschi says. "It's large enough to accommodate whatever you throw at it—that could be aptamers, nanobodies, fragments of antibodies—and it doesn't need to be completely redesigned every time."

The researchers also show that the sensor can be reused several times, with new adapters added each round for different detections. Although the performance slightly degrades over time, the current system could be reused at least four times.

In the future, the team hopes the system might also be useful for proteomics—studies that determine what proteins are in a sample and at what concentrations. "You could have multiple sensors at the same time with different analytes, and then you could do a wash, switch the analytes, and remeasure. And you could do that several times,"

Guareschi says. "Within a few hours, you could measure hundreds of proteins using a single system."

Additional authors of the paper, "Modular DNA origami-based electrochemical detection of DNA and proteins," are Jaimie M. Stewart of UCLA; Emily Wu and Ashwin Gopinath of MIT, Netzahualcóyotl Arroyo-Currás of Johns Hopkins University School of Medicine, Philippe Dauphin-Ducharme of the Université de Sherbrooke in Canada; and Philip S. Lukeman of St. John's University in New York.

**More information:** Byoung-jin Jeon et al, Modular DNA origami–based electrochemical detection of DNA and proteins, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2311279121. On *arXiv*: DOI: 10.48550/arxiv.2312.06554

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