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Lighting up DNA-based nanostructures

Most people know DNA as the carrier of genetic information. However, scientists now use DNA – based on their physical properties – as basic building blocks to produce complex, nanometer-sized objects. This technique is called DNA origami. Scientists from the Max Planck Institute of Biochemistry have now for the first time used a new variant of super-resolution microscopy to visualize all the strands of a DNA origami structure. The method promises to optimize the design of such structures for specific biological and biophysical applications. The work was published in the journal *Nature Communications*.

The term 'DNA origami' refers to a method for the design and self-assembly of complex molecular structures with nanometer precision. The technique exploits the base-pairing interactions between single-stranded DNA molecules of known sequence to generate intricate three-dimensional nanostructures with predefined shapes in arbitrarily large numbers. The method has great potential for a wide range of applications in basic biological and biophysical research. Thus researchers are already using DNA origami to develop functional nanomachines. In this context, the ability to characterize the quality of the assembly process is vital. Now a team led by Ralf Jungmann, Head of the Molecular Imaging and Bionanotechnology lab at the Max Planck Institute for Biochemistry and Professor of Experimental Physics at LMU Munich, reports an important advance in this regard. In the online journal *Nature Communications*, he and his colleagues describe a mode of super-resolution microscopy that enables all the strands within these nanostructures to be visualized individually. This has allowed them to conclude that assembly proceeds in a robust fashion under a wide range of conditions, but that the probability that a given strand will be efficiently incorporated is dependent on the precise position of its target sequence in the growing structure.

DNA origami structures are essentially assembled by allowing one long single-stranded DNA molecule (the 'scaffold' strand) to interact in a controlled, predefined manner with a set of shorter 'staple' strands. The latter bind to specific ('complementary') stretches of the scaffold strand, progressively folding it into the desired form. "In our case, the DNA strands self-assemble into a flat

rectangular structure, which serves as the basic building block for many DNA origami-based studies at the moment," says Maximilian Strauss, joint first author of the new paper, together with Florian Schüder and Daniel Haas. With the aid of a super-resolution technique called DNA-PAINT, the researchers are able to visualize nanostructures with unprecedented spatial resolution, allowing them to image each of the strands in the nanostructures. "Now, we can directly visualize all components of the origami structure and determine how well it puts itself together," says Strauss.

As its name suggests, the DNA-PAINT technique itself also makes use of the specificity of DNA-DNA interactions. Here, short 'imager' strands linked to dye molecules that pair up with complementary sequences are used to identify sites that are accessible for binding. Imager strands interact transiently but repetitively with their target sites, which results in a "blinking" signal. "By comparing the information in the individual fluorescence images, we are able to attain a higher resolution, so that we can inspect the whole structure in detail," says Strauss. "This phenomenon can be understood as follows. Let's say we're looking at a house with two illuminated windows. Seen from a certain distance, it appears as if the light is coming from one source. However, one can readily distinguish between the positions of the two windows if the lights are alternately switched on and off." Hence, the method allows the researchers to determine the positions of the bound staple strands precisely, and the specific blinking signal emitted by imager strands reveals sites that are available for binding.

The results obtained with the DNA-PAINT method revealed that variations in several physical parameters – such as the overall speed of structure formation – have little influence on the overall quality of the assembly process. However, although its efficiency can be enhanced by the use of additional staple strands, not all strands were found in all of the nanoparticles formed, i.e. not all available sites were occupied in all of the final structures. "When assembling nanomachines it is therefore advisable that the individual components are added in large excess and the positions of the modifications chosen in accordance with our mapping of incorporation efficiency," says Strauss.

The DNA-PAINT method thus provides a means of optimizing the construction of DNA nanostructures. In addition, the authors believe that the technology has great potential in the field of quantitative structural biology, as it will allow researchers to measure important parameters such as the labelling efficiency of antibodies, cellular proteins and nucleic acids directly. [göd]

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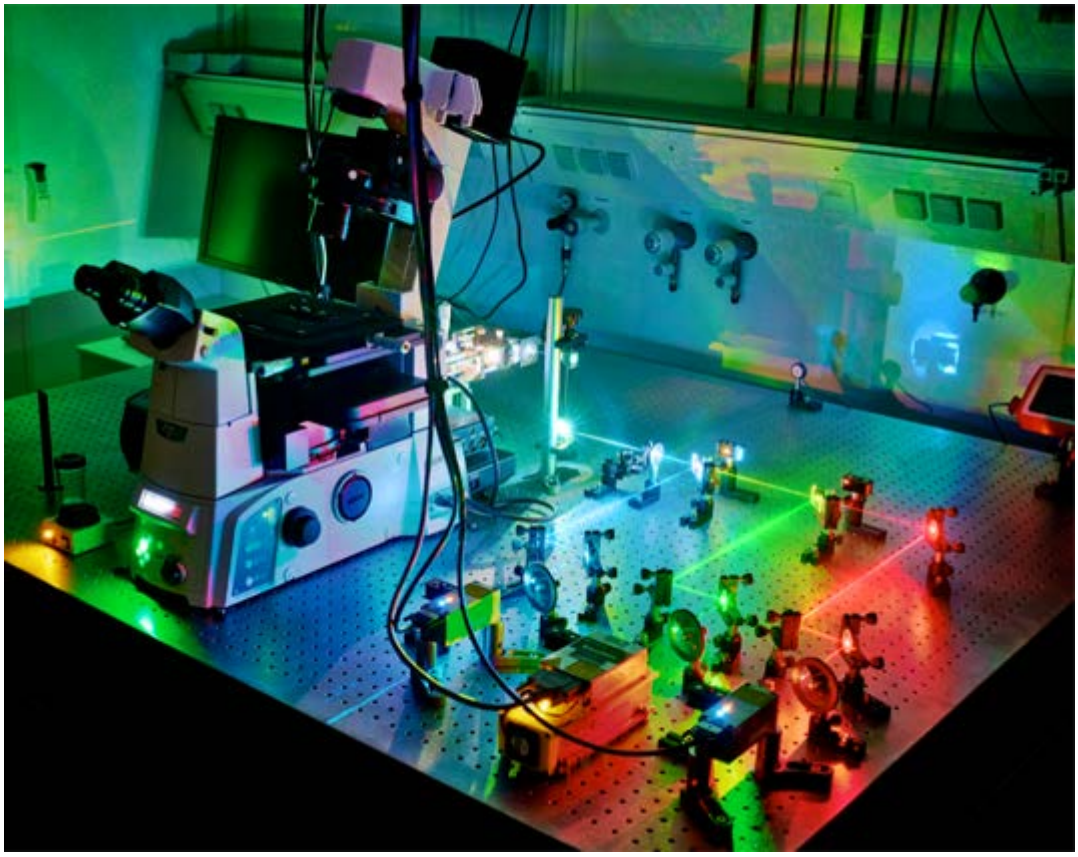

Caption:
Super-resolution microscopy. With DNA-PAINT it is possible to visualize all the strands in DNA nanostructures individually.
Photo: Maximilian Strauss, © Max Planck Institute for Biochemistry.

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About Ralf Jungmann
Ralf Jungmann studied physics at Saarland University in Saarbrucken from 2001 to 2006. After graduating from the University of California Santa Barbara, USA, he earned a doctorate from the Technical University of Munich in 2010. This was followed by a postdoctoral fellowship at the Wyss Institute for Biologically Inspired Engineering at Harvard University. Since 2014, he has been head of the independent Molecular Imaging and Bionanotechnology Research Group at the Max Planck Institute for Biochemistry in Martinsried and Ludwig Maximillian University (LMU) in Munich. He

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has held a professorship in experimental physics at LMU since 2016. In 2016 Jungmann was awarded the ERC Starting Grant of the European Research Council. Since 2017, he is a Paul Allen Distinguished Investigator and was awarded an HFPS Young Investigator Award in 2018.

About the Max Planck Institute of Biochemistry (MPIB)
The Max Planck Institute of Biochemistry belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top level basic research. As one of the largest Institutes of the Max Planck Society, 850 employees from 45 nations work here in the field of life sciences. In currently eight departments and about 25 research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus where two Max Planck Institutes, a Helmholtz Center, the Gene-Center, several bio-medical faculties of two Munich universities and several biotech-companies are located in close proximity. www.biochem.mpg.de/en

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