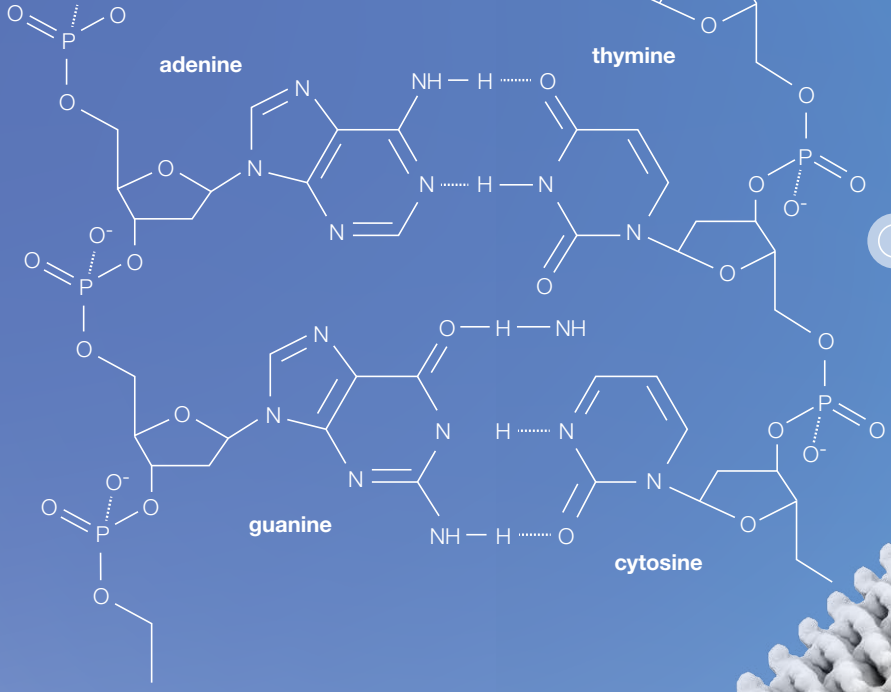
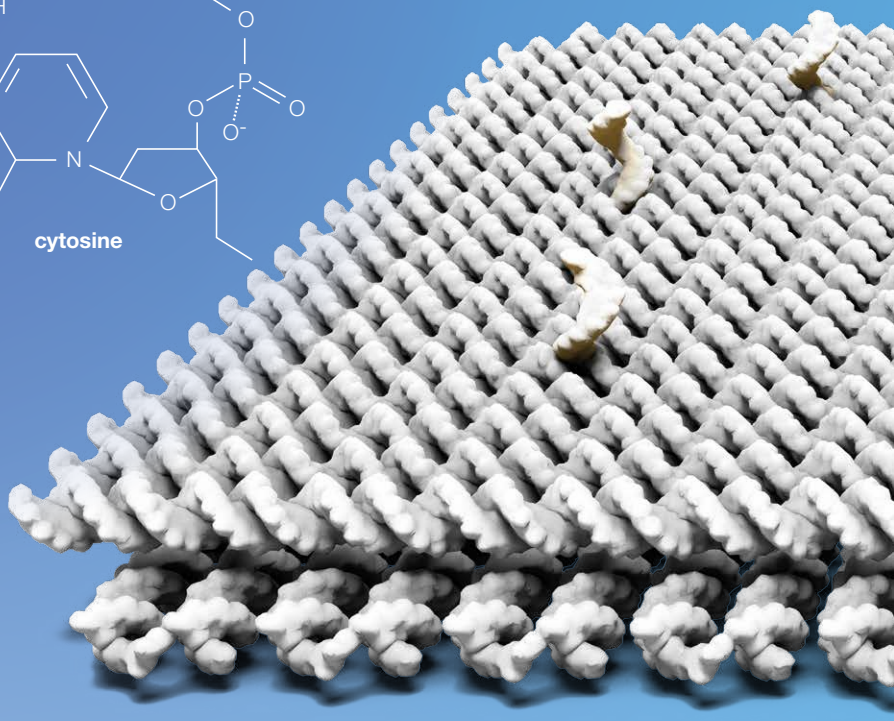
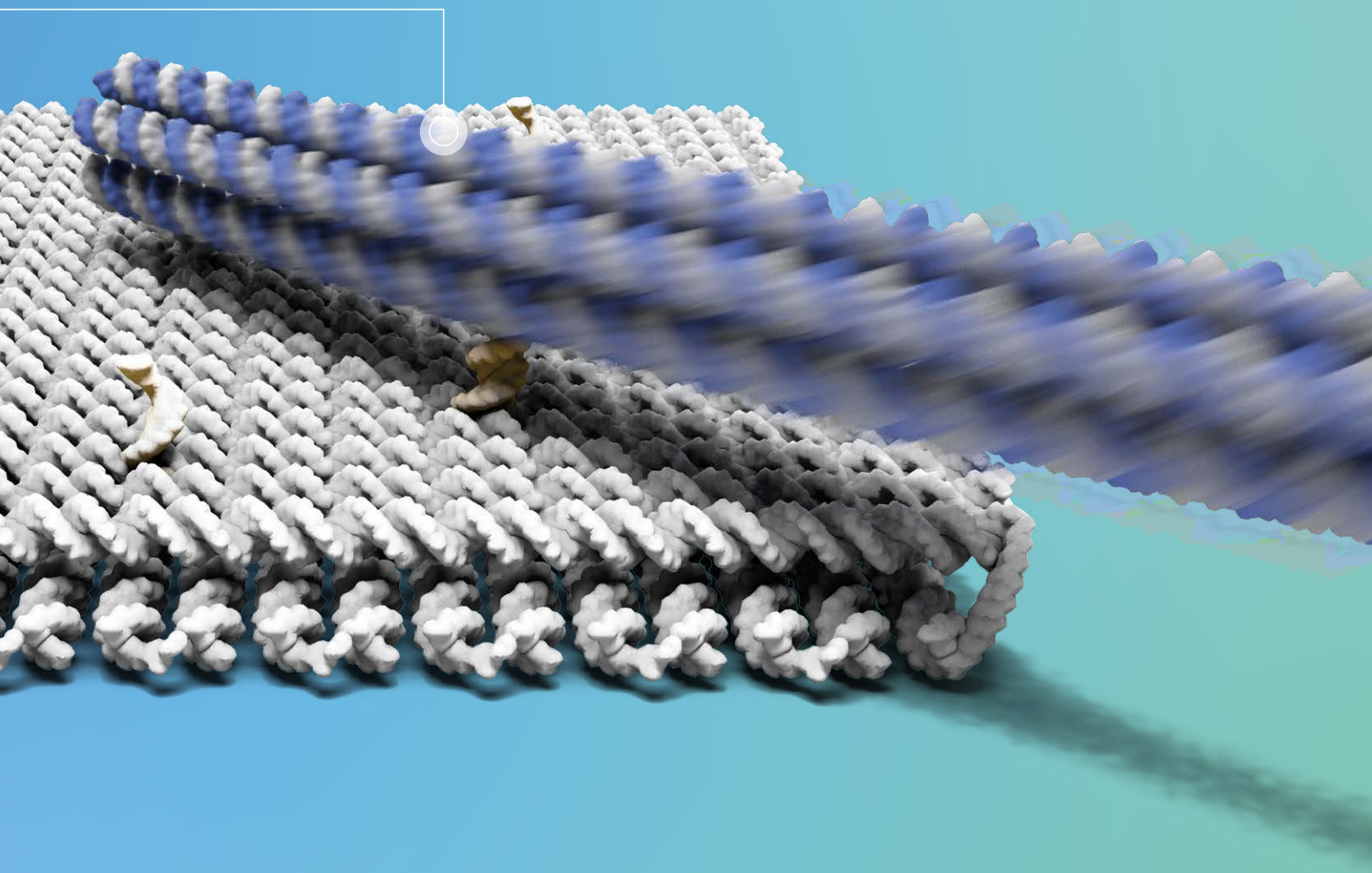


Made up of DNA strands



The Best of **Both Worlds**

Friedrich Simmel has made it his mission to bridge the gap between the macroscopic world and the nano-world. His work deals with questions like “How can we utilize the benefits of molecular machines for systems adapted to the dimensions of our own macroscopic world?” and “How do we build interfaces between the two?” Three years ago, his team took a major step towards these goals when they succeeded in using electric fields to control nanostructures. The researchers are now exploring practical uses for this concept.



Graphics: ediundsepp/E. Kopperger (TUM)

Link
www.groups.ph.tum.de/en/e14/home

Kurzfassung · Langfassung: www.tum.de/faszination-forschung-26

Roboter im Nanomaßstab

D

Am Lehrstuhl „Physik synthetischer Biosysteme“ der TUM untersuchen Prof. Friedrich Simmel und sein Team die Frage, wie man Robotik auf der Grundlage von Molekülen oder Zellen realisieren kann. Zukunftsvisionen für die Anwendung solcher Systeme gibt es im Robotik- und im Medizinbereich. Man fragt sich beispielsweise, wie man Nanoroboter dazu bringen kann, dass sie Moleküle zusammensetzen, als kleine Messgeräte arbeiten oder Transportvorgänge durchführen. Diese neuen Technologien wären Grundlage für Nanofabriken der Zukunft. Andere Beispiele sind Mikrosysteme, die sich im Körper autonom bewegen und ihre Umgebung erkunden. Sie könnten Krankheiten erkennen oder gezielt Wirkstoffe freisetzen.

Da solche robotischen Nanosysteme sowohl eine gewisse eigene Intelligenz als auch eine Steuerung von außen benötigen, befassen sich die Forscherinnen und Forscher beispielsweise mit einer elektrischen Steuerung, die eine Schnittstelle zwischen Nano- und Makrowelt ermöglicht. Andere Projekte untersuchen, wie man biologische Systeme programmieren kann und wie zellähnliche Objekte autonom reagieren können. □

Friedrich Simmel, Professor of Physics of Synthetic Biosystems at TUM, describes the approach chosen by his team in 2017 as “a brutal solution”, and actually one solely “born of desperation”. They used an electric field to make a tiny molecular arm attached to a base unit consisting of DNA swing in a specific direction. Any initial doubts have long since been dispelled – their approach turned out to be a great success. It has now been patented and has given rise to an entirely new branch of nanomachine research – a branch of research in which the Munich team are now world leaders.

Nanorobot visions

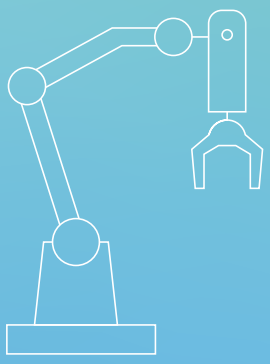
“Essentially, what we’re interested in is the question of how to create molecular or cellular robots,” explains the physicist. Scientists have been dreaming up applications for such robotic systems for years. Possible uses for nanorobots range from assembling molecules, to operating as tiny measuring instruments, to performing transport processes. These new technologies might one day enable the creation of nanofactories able to perform high-throughput biochemical analysis or manufacture complex drugs. The parts needed for these robots can already be manufactured inexpensively by way of DNA origami – a research field which Hendrik Dietz, a colleague of Simmel’s at TUM, has played a major role in shaping. This technique enables researchers to produce large quantities of nano-objects from deoxyribonucleic acid (DNA) – the genetic material shared by all cellular organisms – using what is essentially a programming technique. (see Faszination Forschung no. 21)

Simmel is himself a pioneer in this field. Some 20 odd years ago, as a young postdoc, he was involved in constructing the very first DNA nanomachines. “Back then, we made use of the fact that single-stranded DNA is flexible, whereas double-stranded DNA is relatively stiff. That meant that we could build mechanical elements representing either flexible connectors or rigid elements,” he explains. But how do you get these nanomachines to move in a specific way? “There are a number of established techniques for achieving this. Each sequence of bases along each section of DNA represents a precise ‘address’. We can use DNA control strands to target specific addresses and, for example, make one sequence move and another remain still. Alternatively, you can control this kind of process by changing the pH or changing the salt concentration.” ▷

“Essentially, what we are interested in is the question of how to create molecular or cellular robots.”

Friedrich Simmel

Two purposes for nanorobots



Nanofactories

Assembly line-like production of molecules to manufacture complex drugs, for instance

Nanomedicine

Intelligent nanoparticles navigating autonomously around the body, investigating their surroundings, detecting disease or releasing a drug

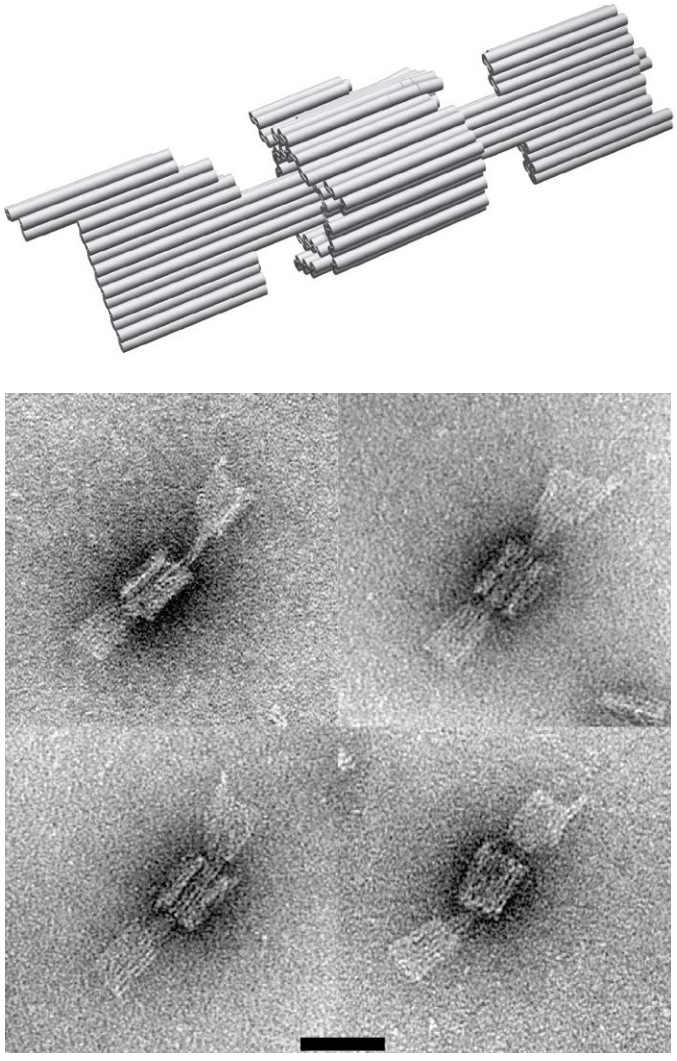
Graphics: ediundsepp (source: TUM); Picture credit: Stefan Woidig

Prof. Friedrich Simmel

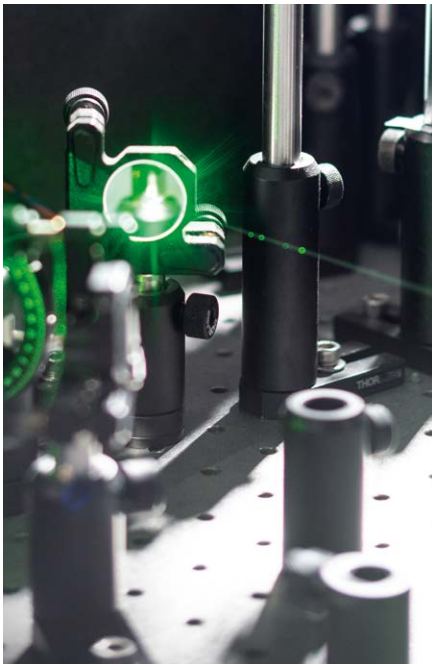
Friedrich Simmel embarked on his career as a solid-state physicist, joining the Center for Nanoscience at LMU Munich at its inception. In 2000, as a young postdoc, he worked on the project which built the first ever DNA nano-machines – long before origami entered the picture. Simmel then moved to Bell Labs in Murray Hill, NJ, USA, where he worked on biophysical systems. In 2002 he returned to LMU Munich, headed an Emmy Noether research group and completed his postdoctoral qualification period. In 2007 he took a professorship at TUM, where he has worked and taught ever since. Until October 2019, he was also co-coordinator of the Cluster of Excellence Nanosystems Initiative Munich.

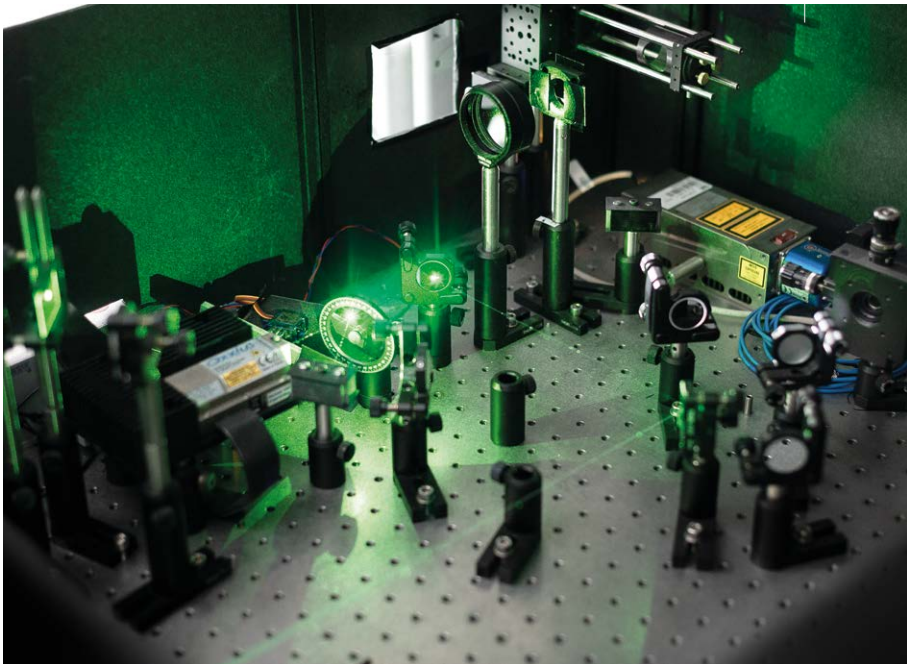
There's a fundamental problem with this type of chemical control, however – in practice it's extremely slow. It takes conventional DNA nanomachines minutes, sometimes even hours to perform these kinds of actions. "Working on these kinds of time scales, it's impossible to imagine ever being able to produce practical applications," laments Simmel. "That's why we decided to try using an electrical control. This offers the advantage of allowing rapid control from outside the system. In principle, it means you can control how a nanomachine moves using a computer." But this technique also has the disadvantage that it doesn't allow you to address specific DNA sequences – it moves all objects in the sample at the same time. "There's always a trade-off between speed and addressability, and this does of course have an effect on the possible applications," explains Simmel.

A research group in his department is now working to refine this approach and identify relevant applications. Dr. Enzo Kopperger, Dr. Martin Langecker and Dr. Jonathan List are now working to set up roboticDNA, a start-up aimed at harnessing this technology to build relatively inexpensive sensors. "We want to make use of the fact that you can attach biomolecules to the movable arm we have developed," says Kopperger. "If we then observe a large number of these devices simultaneously under a fluorescence microscope, we can see that the arm movement pattern changes when you add specific drugs. By analyzing the images automatically, we can even make quantitative measurements of the binding behavior of the individual nanorobots. This means that for each measurement we have a large volume of analyzable and usable data." This would represent one of the first applications for the team's electrical nano-drive technology. ▷



Molecular device produced via DNA origami. The rotaxane consists of an axis and a ring subunit that can glide and rotate on the axis. Top: 3D model; bottom: electron microscopy (TEM) image.

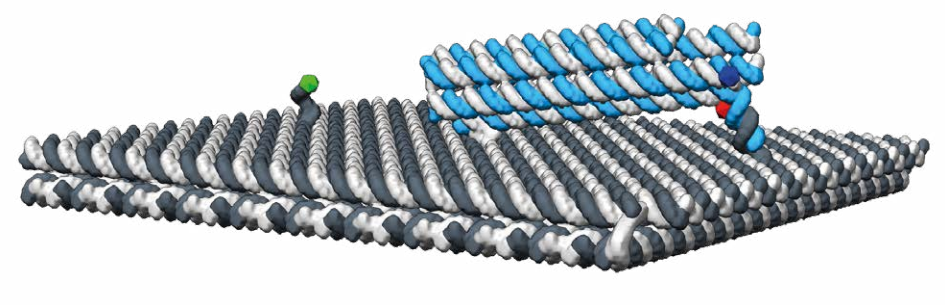




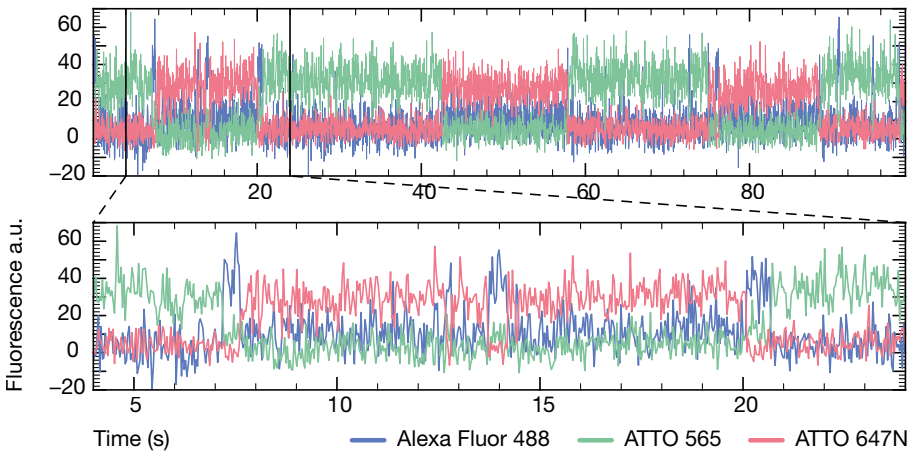
Laser-optical setup for determining the position and movement of DNA nanomachines using super-resolution microscopy and other single-molecule fluorescence methods.

Picture credit left: F. Simmel (TUM); right: Stefan Woidig

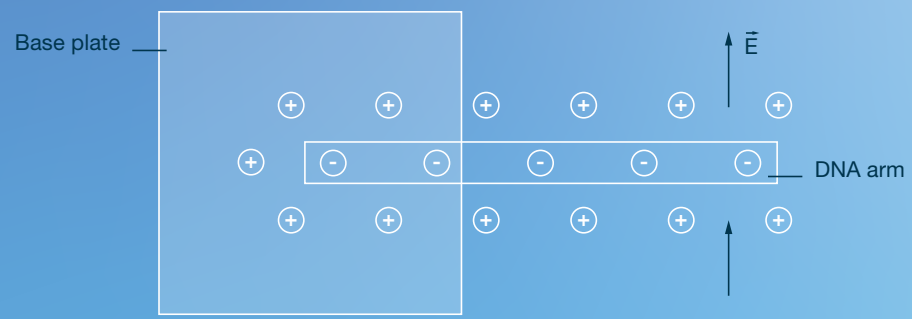
“We need to learn how to do robotics in the realm of Brownian motion.” *Friedrich Simmel*



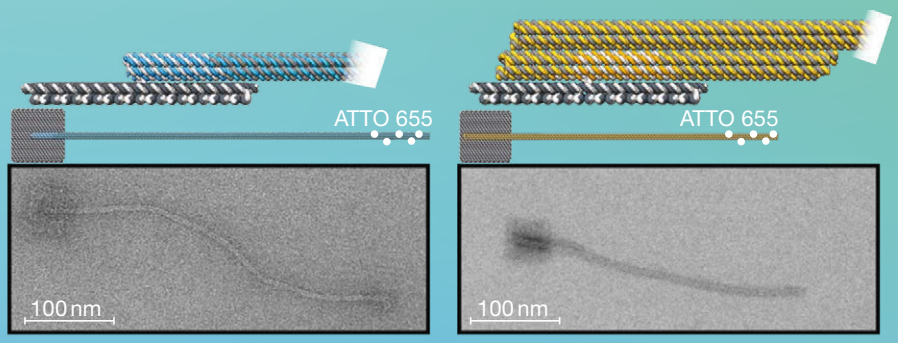
The DNA arm on the base plate can rotate and freely move between two docking sites (green and red). A fluorescent marker is attached to its free end. Like any molecular structure, the arm is always moving, just from thermal motion alone.



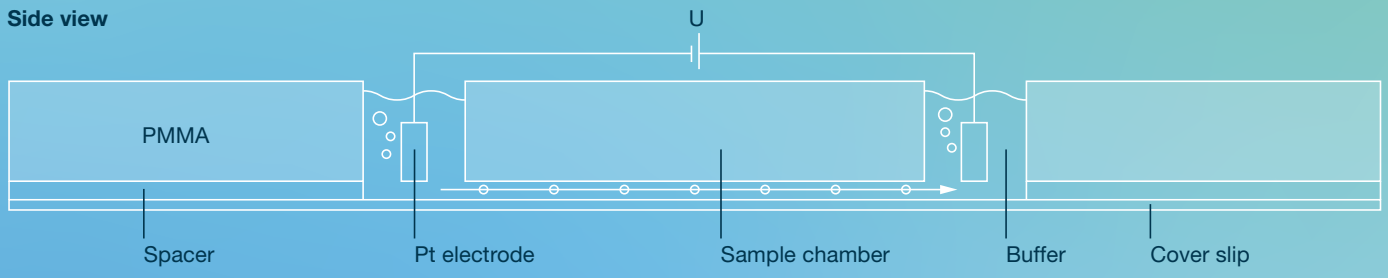
The fluorescence trace shows that thermal motion alone causes the arm to move back and forth between the two docking sites (green and red).

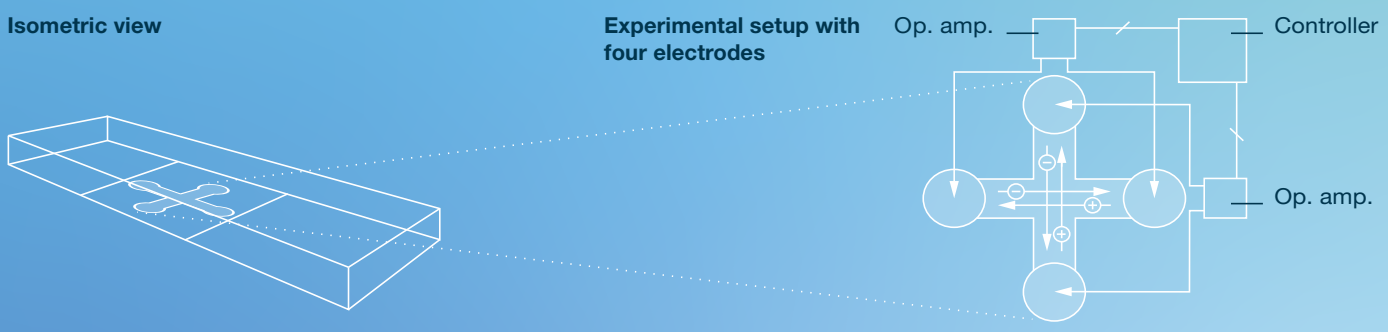


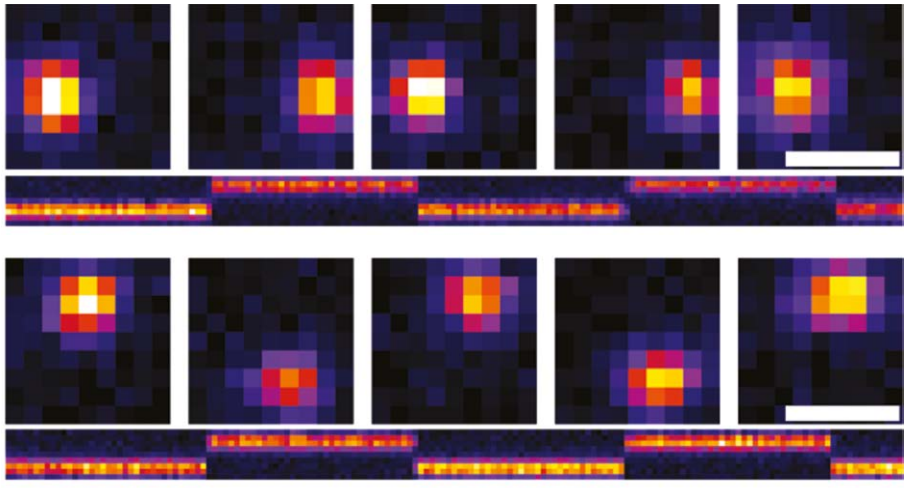
The researchers use an electric field to move the charged nanoarm in a specific direction.



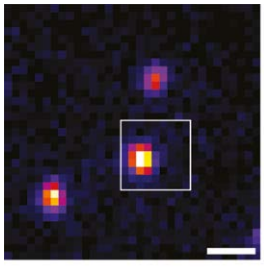
Two different nanoarms and the corresponding electron microscope images. Four electrodes connected to the sample chamber allow the researchers to controllably move the arm in a certain direction.





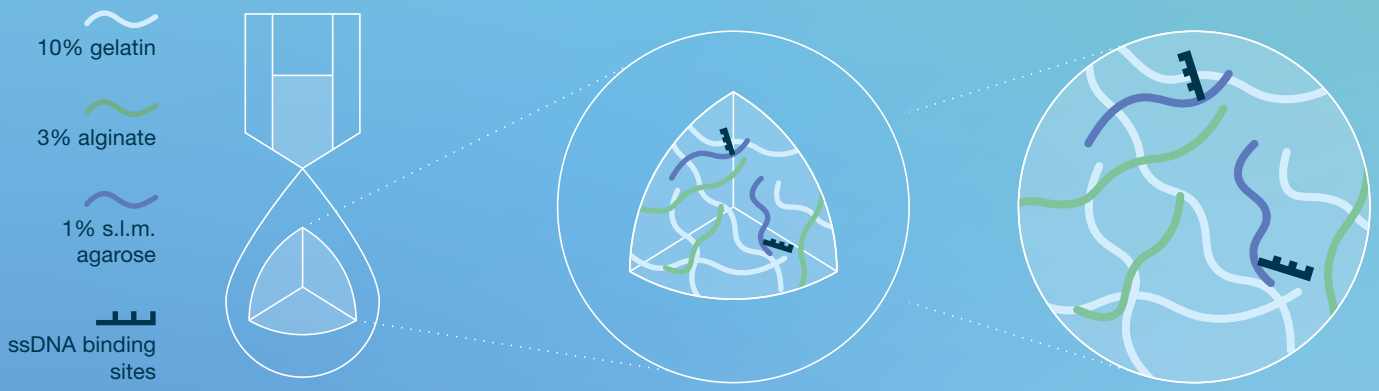


Fluorescence microscopy images of three structures that are switched in the electric field. Movements for the highlighted particle are shown left. Top row: switching the electric field left and right. Bottom row: switching up and down.

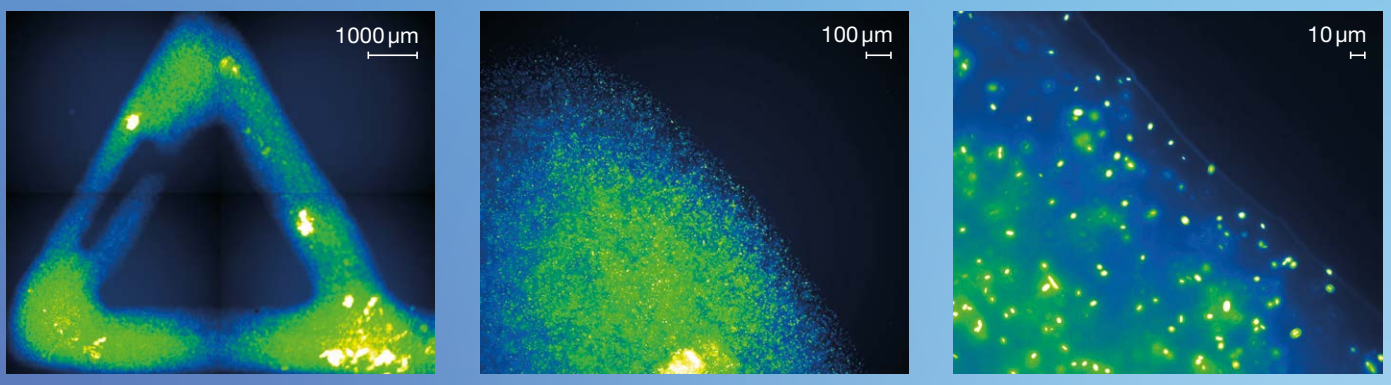


Graphics: ediundsepp (source: TUM); Picture credit: F. Simmel (TUM); left middle: F. Simmel (TUM), D. Lamb (LMU)

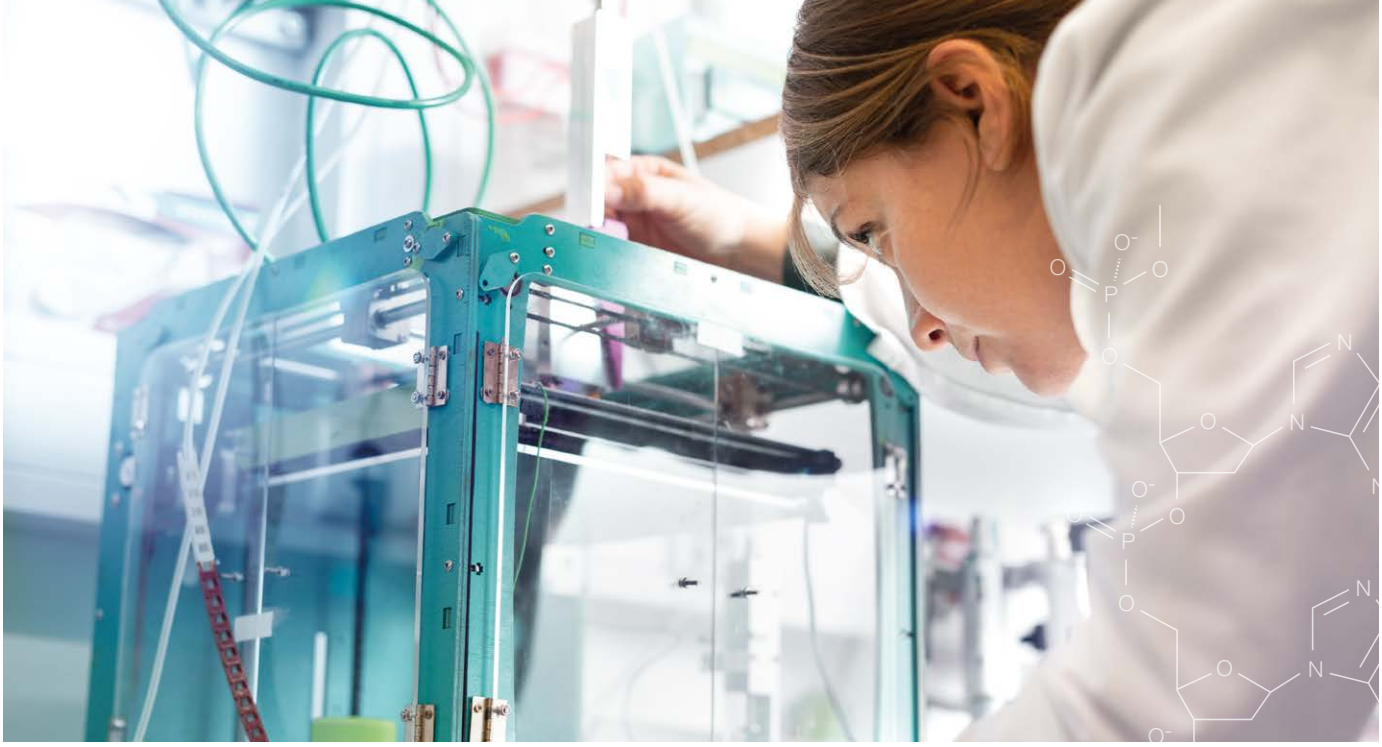
Julia Müller (right) employs a 3D printer to produce tiny, DNA-programmable gel droplets. A hydraulic syringe, which is controlled by the printer, dispenses the tiny samples.



The DNA bioink consists of three components: gelatin as the main component providing structural stability, alginate as a viscosity enhancer, and super low melt agarose as the DNA-functionalizable component.



Tiny gel droplets containing living bacteria are printed in a predefined structure. The encapsulated bacteria produce fluorescent proteins and make the triangular structure become visible over time.



Nanoscale robots

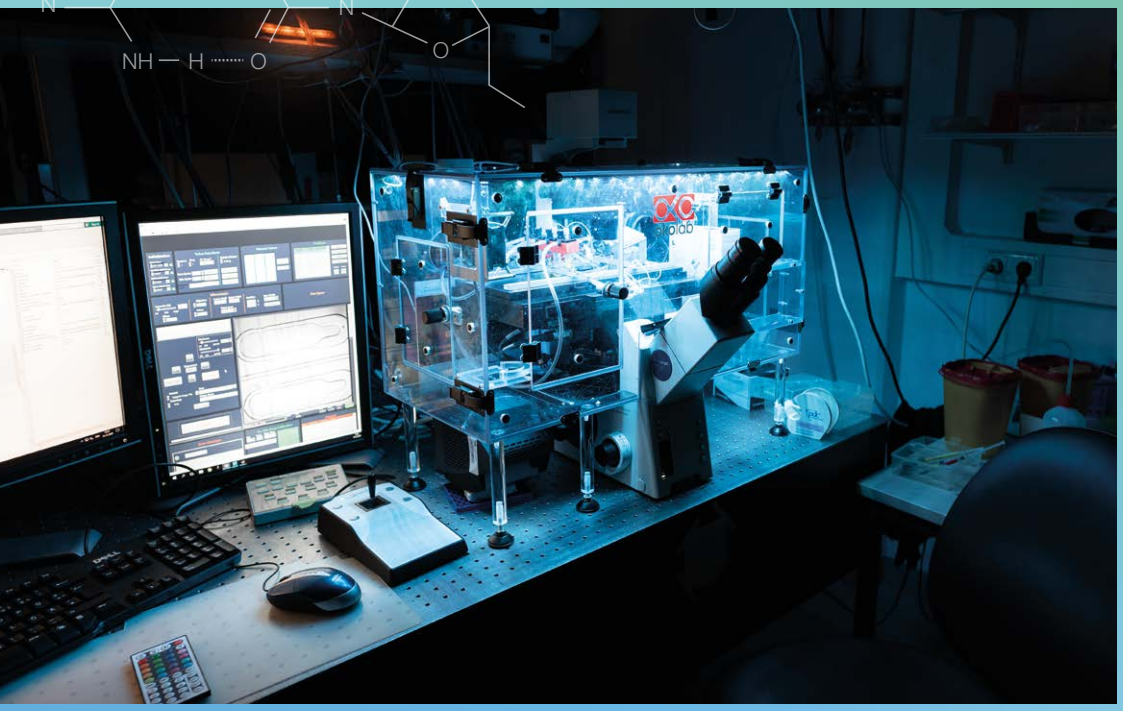
But the research being carried out by researchers in Simmel's group – who come from a range of academic backgrounds spanning physics, chemistry, biology and even electrical engineering – is in general more fundamental in nature. They might be studying how we can make tiny structures function as robots, for example. Their electrically controlled arm is a first step in this direction. "Even a classical robotics specialist would call what we have created here a robot," opines Prof. Simmel. "For our robotics specialist working on a macroscopic scale, connecting rigid elements using joints and controlling this using electrics would be entirely natural. From a robotics perspective, however, a single movable DNA arm is just an actuator. It only becomes something like a robot once it's linked up with some electrodes and a control computer. It's my hope that we will one day be able to build macroscopic robots that also contain biomolecular nano-elements."

The interfaces required for this are now under development. They might be electric, but could also operate with light or magnetic fields. Simmel takes great pleasure in aesthetic phenomena in physics and biology, and he is always on the lookout for elegant solutions. As a former solid-state physicist, in the course of his transformation into an interdisciplinary biophysicist he learned that physics and biology have quite different cultures. "Physicists are sometimes quite playful, and will do something just because they find an effect interesting or beautiful. This might give rise to a unique structure, an unusual model, something like that. In biology, by contrast, there's more of a tendency to ask, 'What's the biological question we're trying to answer?' or 'How is this biomedically relevant?' This more playful approach is probably less common among biologists than among physicists and chemists." Simmel still takes this approach, however, and applies it to the field of biomolecular computing, a field concerned with the issue of how we can use and program biological structures and processes to perform computations. In 2016 he received the Rozenberg Tulip Award in DNA Computing.

Julia Müller is another of Friedrich Simmel's co-workers. To help with such experiments, her team recently developed a method for employing a 3D printer to produce tiny gel droplets with precisely defined properties. The gel consists of a bioink containing, among other things, strands of DNA. These can be programmed and made to form patterns.

For Simmel, what makes the bionanotechnology field really interesting is that it is concerned with producing entirely novel objects. He finds this far preferable to investigating a biological process in painstaking detail. "For traditional biological scientists, DNA nanomachines might come across as pointless gimmicks." Despite this, in January 2018 the highly respected journal "Science" featured an article on electrical control of a nanorobot as its cover story. ▷

Graphics: ediundsepp (source: TUM); Picture credit left: J. Müller; right: Stefan Woidig



Fluorescence microscope with a microfluidic setup for investigating synthetic biochemical “circuits”.

“In the long term, we envision autonomous systems which can also evolve.”

Friedrich Simmel

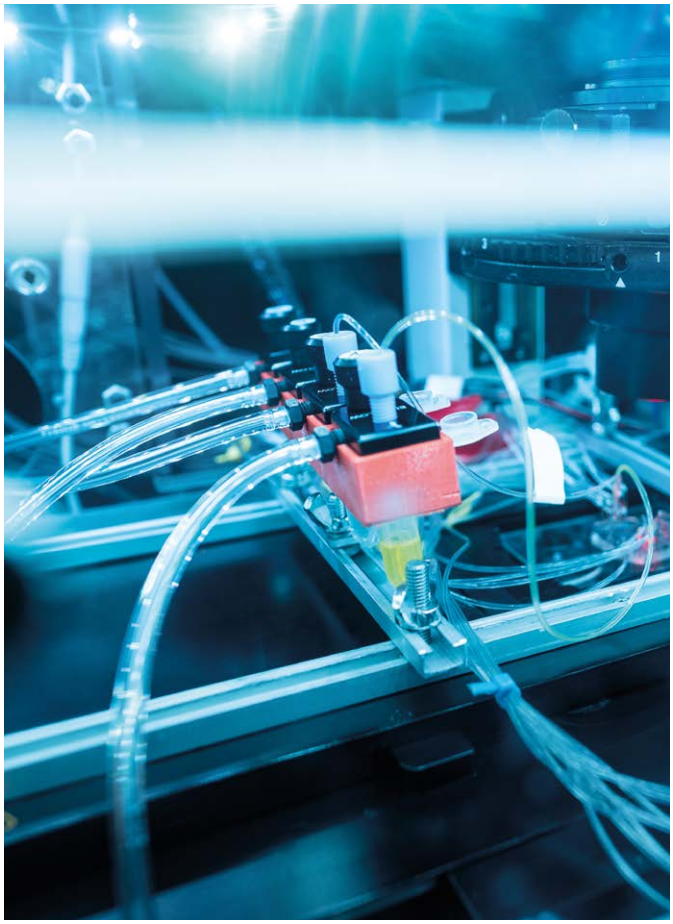
Intelligent nanoparticles

Another important pillar in Friedrich Simmel's group is synthetic biology. Although much of their work might sound like science fiction, they are in fact performing real experiments. One potential medical objective might be to develop an autonomous system able to carry out specific tasks such as navigating around the body, investigating its surroundings, detecting disease or releasing a drug. "The best option for achieving this is probably multifunctional nano or microparticles, or chemically propelled cell-like objects," reckons Simmel. "Our objective here is to create self-organizing molecular and cellular systems that can react to their environment, process information, move and act. Longer term, we envision autonomous systems which can also evolve."

In addition to cell-based synthetic biology, the last few years have also seen the rise of cell-free synthetic biology. This involves cell extracts which play host to genetic processes. "Cell-free synthetic biology involves systems that are much more complicated than DNA nanotechnology systems. They are not living systems, however, which makes them easier to engineer." Kilian Vogele, a student of Simmel's, is currently working on a new start-up project called Invitris. Invitris aims to use cell extracts to produce bacteriophages for use in phage therapy, an alternative approach to tackling antibiotic-resistant bacteria.

Friedrich Simmel and his team are certainly not short of ideas for new projects. Sometimes he takes his inspiration from biology, sometimes ideas just appear, for example when a lab experiment works out much better than originally expected. "Some projects develop entirely by chance," he says. "Sometimes you have something that has got completely bogged down and then you go away and think about whether you might not be able to take a great leap, whether you can do something in a completely new way. Then there are also – albeit rarely – moments of pure inspiration."

Brigitte Röthlein



The tubings (front) are used to supply cell-free reactions in a microfluidic chamber (background right) with nutrients and chemical signals.

Graphics: ediundsepp; Picture credit: Stefan Woidig