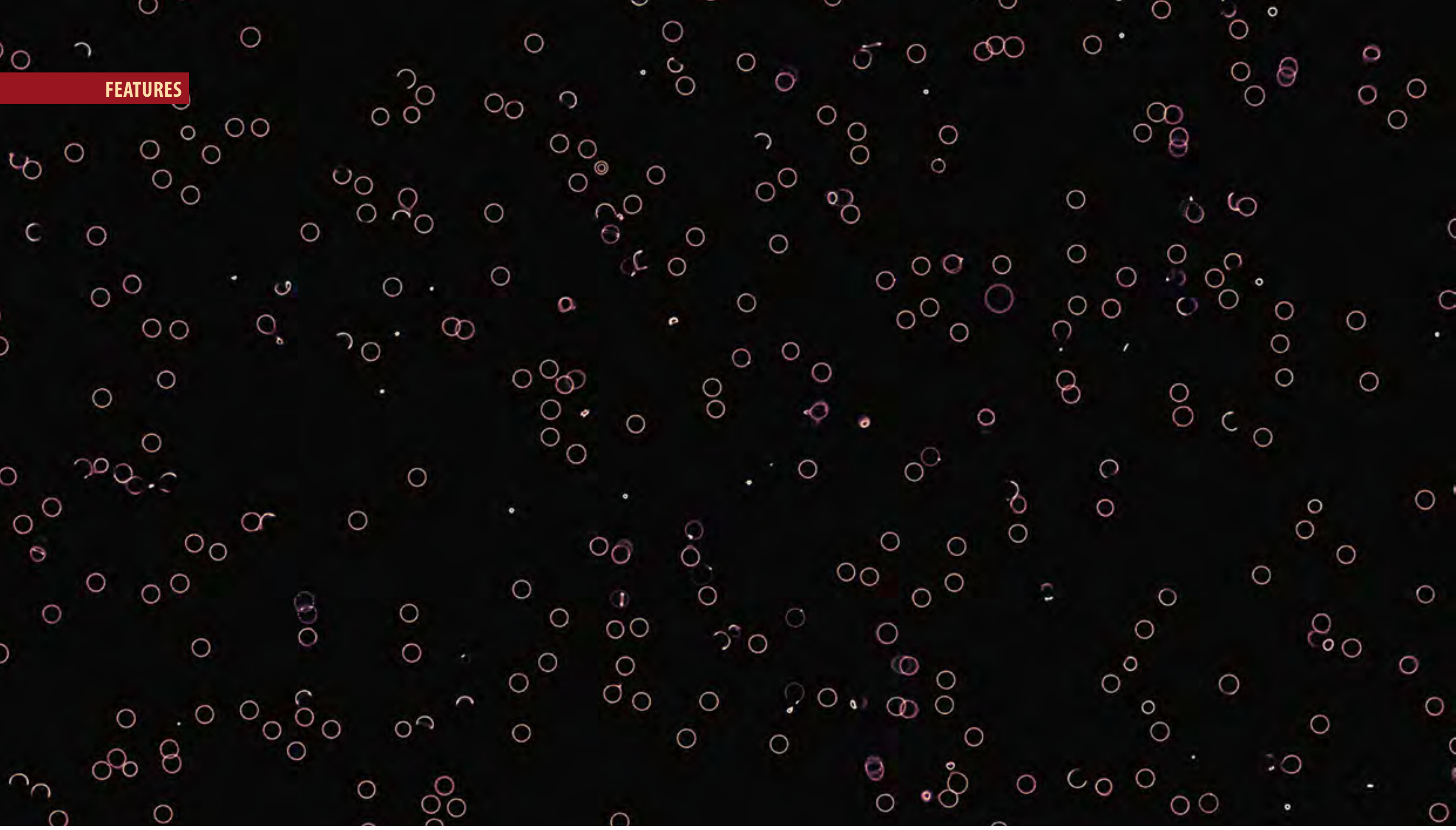

TINY ROBOTS
MADE FROM BIOMOLECULES

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Can we scale down robots to small scales and realize them with self-organizing molecules? As biological cells already act a little like robots – they sense, compute, move, and respond to their environment – the answer is probably "yes". But a wide range of interesting physical challenges have to be tackled.

▲ Fluorescence overlay image obtained from a large number of DNA robot arms such as that on the bottom of Fig. 2 that are rotating (the arms are fluorescently labeled at their tips, resulting in the circular shapes).

Robots have changed the way we work and live, and will continue to do so in the future. Robotic systems speed up and improve manufacturing processes, they assist in many areas such as health care or environmental regeneration. They can work at places which are inaccessible, or whose environments are too harsh or dangerous for humans. In science labs they perform large numbers of experiments in parallel and without getting tired. These robotic systems typically consist of three main units: sensors and actuators, which are coordinated by a computing device. The sensors collect information about the environment or the current state of the robot. This sensory information is then evaluated by a computer and used to decide on the necessary actions carried out by actuators - and these actions often mean mechanical motion. Most robots realized so far are rather large in size and utilize macroscopic mechanical parts and mechanisms combined with electronic control systems and computers.

Interesting questions and challenges arise, when we ask how far we can scale down robotic systems:

Is it possible to realize robots with just a few atoms, molecules, or nanoparticles? Without on-board electronics and power supply? How would one realize sensing, actuation and computation at such small scales? In fact, over the past years researchers in the physical sciences have begun to work on the development of molecular and cell-scale systems, in which robotic functions are realized, at least up to a certain degree. We are particularly interested in robotic systems based on biomolecules, which have the ability to work in biological environments and interact with biological entities. Among the most prominent goals of this research direction is the realization of nanomedical robots that autonomously detect and cure diseases at the earliest stages, but also the generation of molecular assembly lines that enable the programmable production of chemical compounds is one of its grand visions.

From biological inspiration to molecular and cell-scale robotics

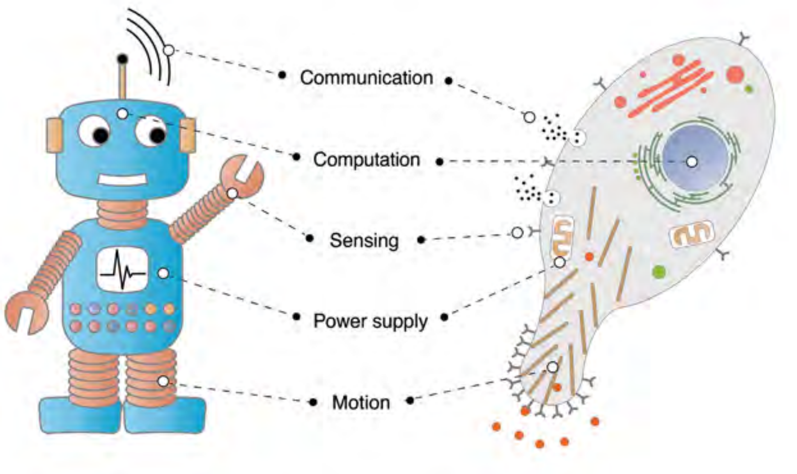
Biology has inspired the development of robotic systems at the macroscale in various ways. Their shapes and appearances are often derived from humans, dogs, or insects, *etc.*, and their movements and actions resemble those of their living counterparts. Roboticists are concerned with "motion planning", "cognition", *etc.* and therefore ask similar questions as neuroscientists. Another exciting example for biomimetics in this context is the field of swarm robotics, which is inspired by the observation of social interactions and dynamics among biological "agents".

At the cellular and molecular level, we can find inspiration for robots as well. Biological cells have sensors and actuators, they store and process information. They move, manufacture and interact with other cells. Other, specific examples are bacterial swimming and swarming, cell-shape changes, cell-cell communication, the immune system, muscle function, *etc.*

In the end, biology is a very different kind of "technology" than electronics and mechatronics. Biological systems are self-organized chemical systems existing far from thermal equilibrium, and if we want to build bio-inspired robots at this tiny scale, we will have to apply to other principles than those developed for "animal-scale" robotics. In the nano world, other physical laws are relevant than in our macroscopic world. For instance, gravity plays no role, but viscous friction is an important player. How should we think of or perform computation at this scale? Should we implement digital computation or develop molecular analog computers?

DNA-based robots

DNA-molecules turn out to be ideal to experimentally explore ideas for nanoscale robotic systems. DNA nanotechnology, especially the so-called "DNA origami" technique, makes it possible to assemble almost arbitrarily shaped molecular objects. Furthermore, various chemical and physical mechanisms have been used to switch these objects between distinct mechanical states. By doing so, linear or rotary molecular motors could be realized. DNA naturally lends itself for information storage and various computational schemes involving DNA have been developed. A wide range of DNA-based sensors – responding to nucleic acids, ions, small molecules or even light – are available. Thus, in principle, all of the aforementioned components of robotic systems can be realized with DNA alone. To name but a few, DNA robots have been created that act as smart drug delivery devices [2,3], DNA walkers have been shown that make decisions, sort, transport and assemble cargo [4-6], and DNA nanomechanical devices have been realized that can be actuated with magnetic or electric fields [1,7], or that themselves actuated soft robotic devices [8].



▲ **FIG. 1:** Robots and cells have similar functional modules and capabilities (the image only highlights a few examples). Can we create cell-scale robots that perform non-biological tasks or use biological cells themselves as robots?

While DNA-based robot prototypes are very promising, many challenges remain, and these will also have to be tackled by robots based on molecules other than DNA. First, the information processing capabilities of individual molecular structures are quite limited. Second, most realizations of DNA robots so far are slow and cannot quickly respond to external inputs. Thirdly, molecular robots are, of course, small. This makes it hard to integrate them into larger systems, let them move across larger length scales, and to operate many of them in parallel. Another challenge relates to the question how to best fuel the robots at this scale, whether they can be autonomous or must be externally controlled, *etc.*

Biological molecular motors

Proteins are another promising class of biomolecules which might be used to construct nanorobots. In biology, a plethora of molecular motors exist. For instance, processive motors such as kinesin walking along protein filaments or rotary motors that drive the flagella of bacteria. Protein-based motors on their own or in combination with DNA have already been utilized to create active materials [9,10] and "swarms" [11]. But autonomously moving particles or components alone will not make a robot. The challenge will be to integrate such active behavior with other functions, and it would be desirable to find ways to control and program active behavior. For example, after sensing the environment the output of a sensor module could be used to control a physicochemical parameter that is important for movement. Active particles that move in chemical gradients need to

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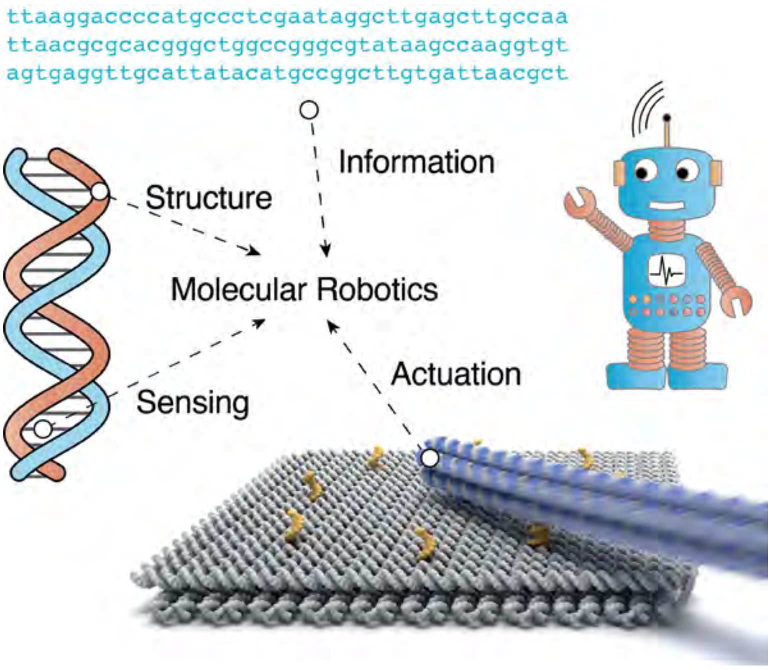

▲ **FIG. 2:** DNA is an ideal molecule for exploring molecular robotics. It inherently stores information, it is a structural rigid molecule, and it can be used for sensing (*e.g.*, via base-pairing interactions). DNA has already been used to create nanoscale structures and machines (the example at the bottom is an image of a rotatable robotic arm made with the DNA origami technique [1]).

● ● ● be asymmetric. And this asymmetry could be controlled by a decision-making molecular circuit. Another challenge will be to find the "right chemistry". It should allow active processes and other robotic modules to operate under realistic environmental conditions - *e.g.*, inside a living organism.

Synthetic cells as robots

Maybe there is a "complexity threshold" above which robotic functions can be realistically implemented in molecular systems, and single molecules or small supramolecular assemblies are simply below that threshold. On the other hand, biological cells – more complex assemblies of molecules – really already behave like microscale robots (see above). Biology has successfully tackled the "systems integration" challenge and realized out-of-equilibrium systems that sense, compute and respond to their environment. In cells, various functional modules play together, behave in a context-dependent manner and are controlled by molecular programs.

When envisioning the realization of small robots, we might therefore ask whether we can either build synthetic systems that imitate cells but perform technologically relevant, non-biological functions? Or whether we can engineer biological cells to become more like robots? Essentially both of these approaches to engineer biological systems are already pursued in the (closely related) field of synthetic biology.

The bottom-up approach - putting together all the necessary molecular parts to generate a synthetic life-like system - poses a huge systems-engineering challenge. In order to realize such systems, metabolic processes need to be compartmentalized and coupled to information processing, movement, and other types of actuation, which has not been entirely achieved so far. The second approach circumvents the challenge of realizing a consistent multifunctional molecular system, but engineering of extant cells is difficult due to the sheer complexity of these systems. Engineered modules put additional load on a cell, which compromises their fitness, and they also often suffer from unexpected interactions with other cellular components.

Applications envisioned for micro- and nanorobots

Where can we find applications for such tiny robotic systems? Most likely, micro- and nanorobots will be used when a direct physical interaction with the molecular or cellular world is required. One of the main applications envisioned for such systems will be in nanomedicine, *e.g.*, as highly advanced drug delivery vehicles. Such devices could sense their environment, release drugs on demand, or stimulate cell-signaling events. They may potentially be equipped with simple information-processing capabilities that can integrate more complex sensory information; for instance, to evaluate the presence of a certain tissue or cell type, and thus location in the body, and apply diagnostic rules such as "if condition X is met, bind to receptor Y, release compound Z", *etc.* Given the limited capabilities of small-scale systems, it is not clear how programmable such robotic devices will be. Autonomous robots will have to find their location by themselves, which for some applications may be achieved by circulation and targeted localization in the organism. Alternatively, hybrid approaches are conceivable, which allow for active control from the outside, *e.g.*, by magnetic or laser manipulation. There are many additional challenges for such devices, which are similar to those for conventional drugs, *e.g.*, degradation, allergenicity, dose, or circulation time.

Apart from nanomedical robots, for which the first examples are already emerging, a wide range of applications can be envisioned in biomaterials and hybrid robotics. Hybrid robots (composed of "classical" and molecular components) could use an interface to the environment that is equipped with biomolecular sensor and actuator modules, which would allow, *e.g.*, to release or present molecules in response to an input. Here, the overall robot would be macroscale, but with the ability to act on the microscale. In materials applications, surfaces or particles could be modified with active molecular robotic devices, which can then be programmed and change their properties in response to environmental signals in various ways.

Conclusions

The realization of biomolecular robots is a highly interdisciplinary endeavour with a potentially huge technological impact. First examples of tiny robotic systems have been realized, but real-world applications will require further development. Apart from its more applied aspects, the field is also interesting for physicists, as it touches upon fundamental questions, which are related to the basic robotic functionalities: What are the physical limits of sensing? What is the computational power of a molecule or a cell? How can we generate autonomous motion at the nano- and microscale, in the presence of Brownian motion? How can we realize collective behaviors and decision-making processes in systems of many interacting agents? How do we supply these systems with energy? These are questions naturally asked also by researchers in biophysics, statistical physics and complex systems. ■

About the Authors

Tobias Pirzer obtained his PhD in biophysics at the Technical University Munich (TUM) in 2010. Since 2012 he is working as senior scientist in the group of Friedrich Simmel.

Friedrich Simmel obtained his PhD in physics at the Ludwig-Maximilians-University Munich (LMU) in 1999. After a postdoctoral stay at Bell Labs, he started an independent junior research group at LMU Munich and became a full professor of physics at the Technical University Munich in 2007. His research focuses on biophysics and its applications in bionanotechnology and synthetic biology.

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