

Microboats to the Rescue

Some medical treatments would be more efficient if medication could be transported via a tiny robot directly to the diseased area. **Peer Fischer** and his colleagues at the **Max Planck Institute for Intelligent Systems** in Stuttgart are developing microswimmers and nanoswimmers that are expected to one day make this possible.

TEXT **KARL HÜBNER**

A simple DIN A4 sheet of paper hangs beside the lab door. It reads: “Please don’t clean.” That should please the cleaning staff.

And the lab users are much more relaxed because they know that if no one is clearing away objects and wiping the tables, nothing important can go missing. That’s how it is when researchers work with objects that can’t be seen by the naked eye. This explains why the “Micro, Nano, and Molecular Systems” Research Group at the Max Planck Institute for Intelligent Systems in Stuttgart is protecting at least one of its labs this way.

The group is led by Peer Fischer, who is also a professor at the University of Stuttgart. In recent years, his research has resulted in a small fleet of miniature vehicles – microstructures

and even nanostructures that can move through liquids in various ways in a controlled manner, and that many already describe as tiny robots.

NO LIMIT TO HOW SMALL MACHINES CAN BE MADE

When Fischer describes the work his roughly 20-person team performs, he is happy to draw on a vision originally set out by Richard P. Feynman almost 60 years ago. On December 29, 1959, the American physicist delivered a lecture entitled “There’s Plenty of Room at the Bottom.” By this, Feynman meant that there is really no limit when it comes to designing the tiniest possible engines, machines and other objects. With that, he fired the starting shot, as it were, for nanotechnology, long before this term even existed. >

It’s simply a matter of principle: Bacterial motor systems, for example, can’t be replicated exactly for artificial microswimmers and nanoswimmers. The researchers in Stuttgart demonstrate this with models that they equip with batteries, engines and circuit boards. Because there is no room for these things in tiny robots, they implement biological drives differently, such as in the case of the magnetically driven nano-screw (far right).



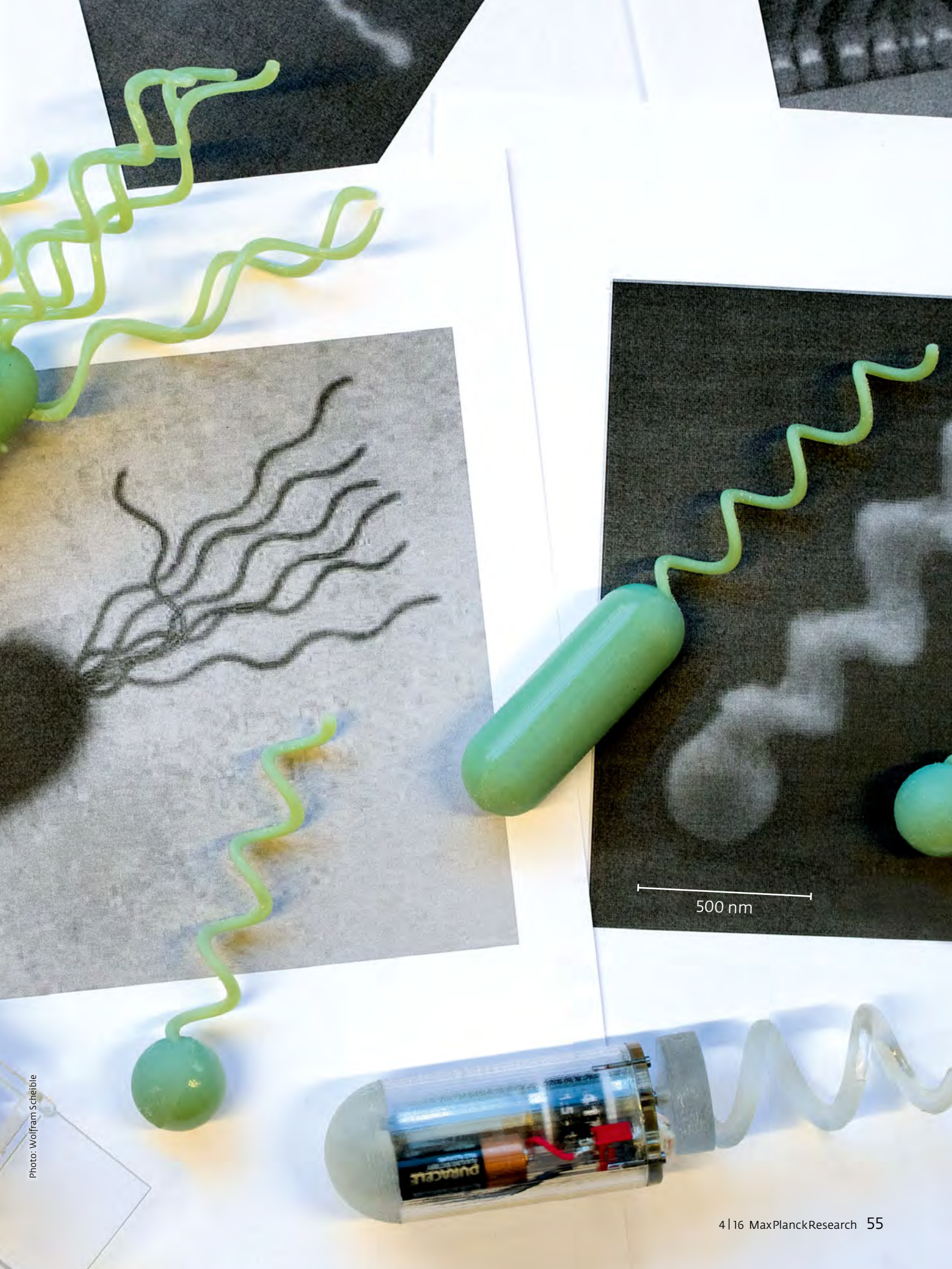
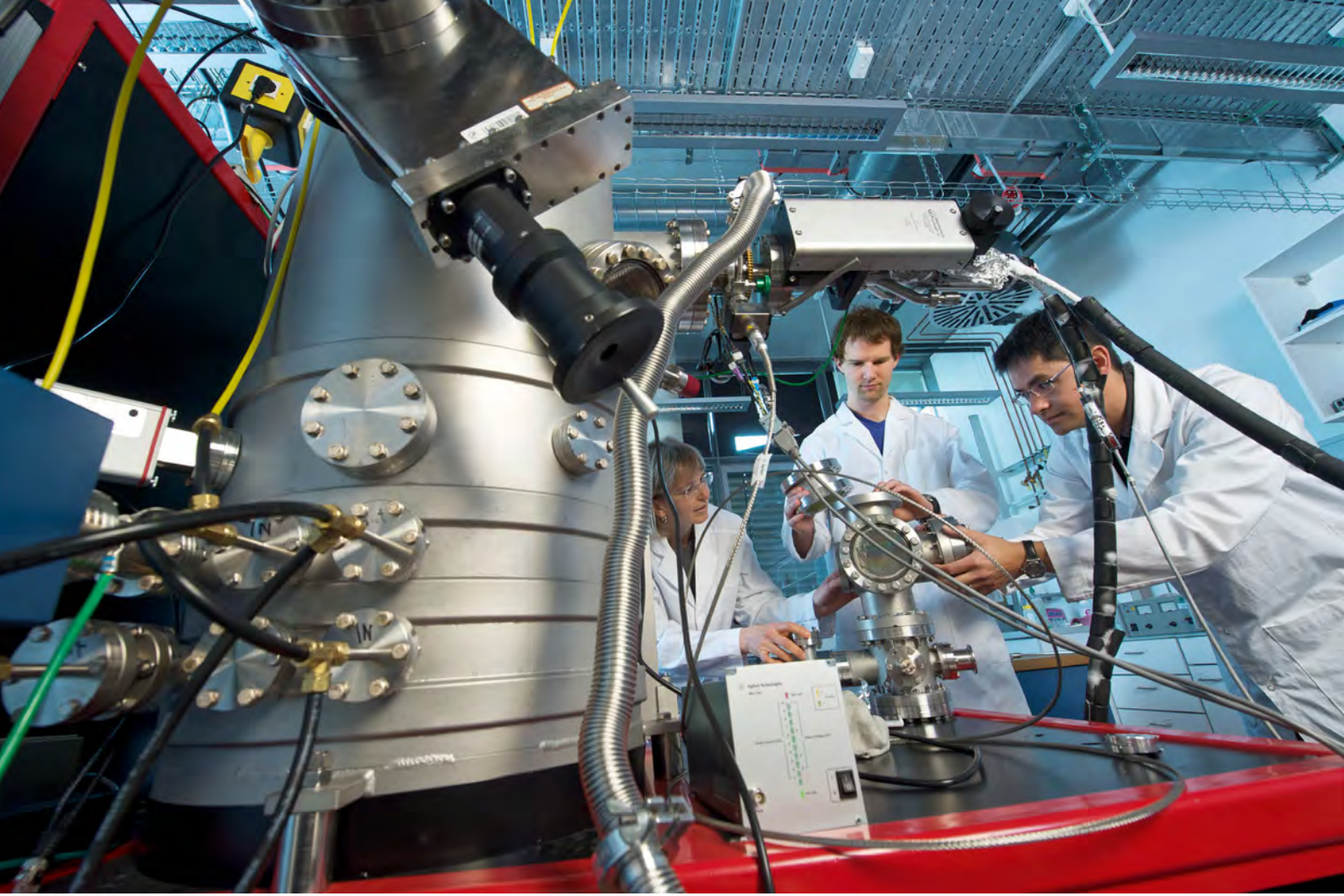


Photo: Wolfram Scheible



A production facility for nanorobots: The Max Planck researchers Conny Miksch, John Gibbs and Andrew Mark (left to right) examine the vacuum system in which complex nanostructures are evaporated layer by layer onto a silicon wafer.

And Feynman had very concrete ideas: “Although it is quite a wild idea, it would be interesting for surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and ‘looks’ around. [...] It finds out which valve is faulty and takes a little knife and slices it out.” This idea also inspired filmmakers. In the 1966 Hollywood movie *Fantastic Voyage*, a tiny submarine boat with a miniature-sized emergency crew on board ventured into the veins of a man to remove a blood clot in his brain.

Ideally, the miniature vehicles in Peer Fischer’s research group will also one day also be able to move through tissue, mucous membranes, the blood-brain barrier and the eye’s vitreous humor. These will hardly have miniature surgeons on board, but will perhaps carry, instead, pharmaceutical drug molecules, genetic blueprints or remotely controlled surgical instruments.

Nevertheless, Fischer isn’t too happy about having his work associated with *Fantastic Voyage*. According to him, too much of the film is scientifically “extremely dubious.” For example, “the active and controlled movement” of the mini submarines through the blood vessels. The top speed of 15 knots, which is equivalent to 30 kilometers per hour, also makes Fischer smirk: such a speed is very unrealistic for a miniature submersible vehicle.

A MEXICAN WAVE ON THE CILIATE

Hollywood doesn’t need to concern itself with the physical details of the micro world – with the fact that, for instance, small particles experience a high level of friction while their “inertia [is] of relatively no importance,” as Richard Feynman phrased it in his lecture. High friction in combination with low inertia simply means that a vehicle immediately comes to a stop as soon as

the engine is cut. After taking a stroke, a human swimmer glides through the water for a while due to inertia. However, according to Peer Fischer, a bacterium whose propulsion stops moves just one-tenth of a nanometer further before it comes to a halt, if one neglects Brownian motion. A bacterium swimming in water is like a human trying to swim through tar.

And yet single-celled organisms have clearly developed techniques for actively moving in various fluids. Many bacteria have a rotating flagellum that propels them. A sperm, on the other hand, makes a sort of whipping movement with its tail, which helps it to push off from its environment.

Ciliates have mastered another technique. These protozoa are covered with countless tiny hairs that move in an elaborately choreographed sequence. The tiny hairs make synchronized movements that somewhat resemble our arms when doing the breaststroke.

» Fischer's group is currently concerned primarily with finding and testing drive principles for the microstructures.

Together, all the hairs perform what looks like a Mexican wave that runs along the entire body of the ciliate, propelling it forward.

It is precisely this complicated mechanism that inspired Peer Fischer and his colleagues to create a biomimetic microswimmer. It quickly became clear that it wouldn't be possible to produce an exact artificial copy. "After all, there is no electronic control system or even a battery that would be small enough to propel structures the size of an individual tiny hair," explains Fischer. "So we try to understand the essence of the principle, simplify it, and then apply it with all the resources available to us."

In the lab in Stuttgart, the biological template, the ciliate protozoa, became a one-millimeter-long cylinder made from a special material known as a liquid crystal elastomer: a plastic that exhibits the characteristics of both a liquid crystal and an elastic solid. "It's a type of molecular muscle in which individual sections expand as soon as they are exposed to light of a certain wavelength," explains Fischer.

Specifically, this means that the cylinder expands at the places where the researchers in Stuttgart expose it to green light. When the light disappears, these areas contract again. In their experiments, the researchers use a complex mirror system to project stripes of green light onto the tiny cylinder. The ultra-thin strips of light cause wave-like rings to travel through the vehicle, similar to the process of peristalsis that occurs in earthworms. And just as an earthworm pushes the earth behind it, the pulsating cylinder pushes past the surrounding water/glycerol mix and

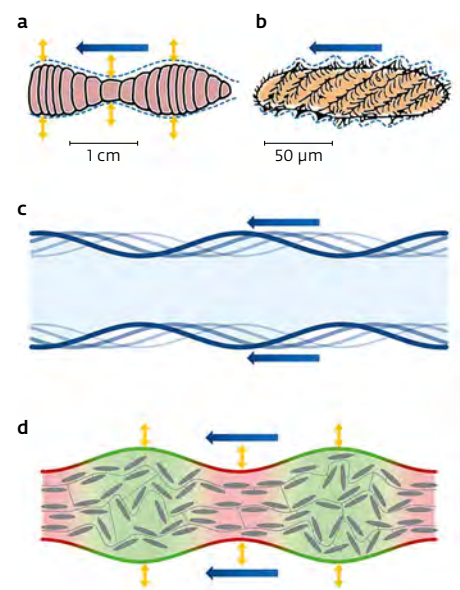
moves forward, traveling at a speed of around one centimeter per hour.

Of course the real ciliate moves considerably faster, but this is due to the fact that it simply sends many more waves over its surface per second. In any case, the researchers managed to transfer the movement principle to their microswimmers. What's more, they can use their special mirror to vary the light profile any way they want, and thus also change the direction of movement of their cylindrical submarine body – in this way, they made it swim along defined trajectories, for instance.

A MICRO-SCALLOP WOULD MAKE NO HEADWAY

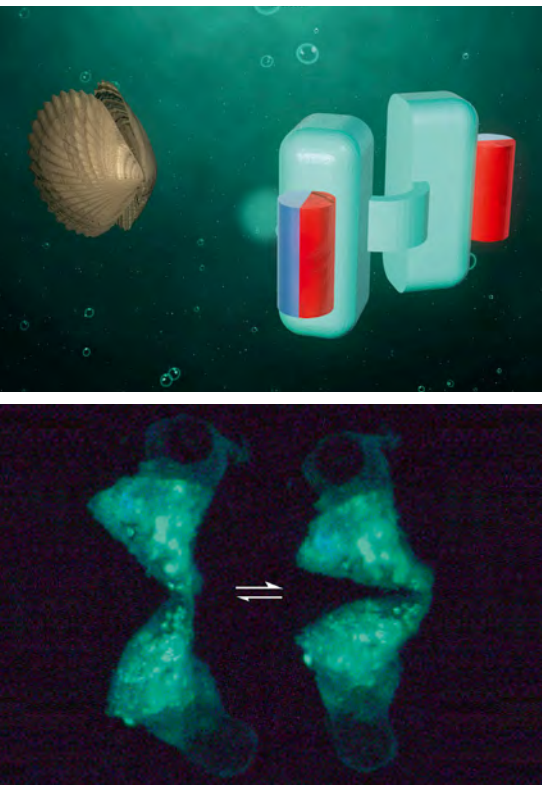
"That was the first time ever that an artificial microswimmer was able to use only shape changes to power itself without any external mechanical or magnetic forces having to be applied," says Peer Fischer. The tiny swimming robot needed only to be exposed to light. "In order to use such light-activated, liquid crystal elastomer constructs, they would perhaps one day be attached to the ends of glass fibers," says Fischer. In such cases, instead of acting as artificial microswimmers, they would act as artificial muscles that could move soft robot arms, for example at the end of an endoscope. But that's still in the distant future. At the moment, Fischer's group is concerned primarily with finding and testing principles to actuate and power microstructures.

The researchers even worked on a particular form of motion that shouldn't work for swimmers at low Reynolds



Modeled after nature: An earthworm (a) uses peristalsis to generate a wave on the surface of its body (c) in the same way a ciliate (b) moves the tiny hairs on its surface in a coordinated manner. The researchers in Stuttgart implement this principle by projecting stripes of green light onto a cylinder of a liquid crystal elastomer, which expands at the illuminated locations (d).

» Finding drive techniques for tiny artificial swimmers is a challenge for the researchers in Stuttgart. Another challenge they face is fabricating microswimmers.



Modeled on the scallop: Peer Fischer's team designed a microswimmer whose two halves are joined by a hinge and fitted with magnets (top). By opening and closing the two halves in a magnetic field (bottom), the researchers move the micro-scallop through biological fluids.

numbers: that of the scallop. The scallop swims through water by opening and closing both halves of its shell in a uniform motion. Scallops are a few centimeters in size and this technique works perfectly for their dimensions. The smaller a scallop is, however, the more friction becomes an issue. The viscosity of the water then seems to them to increase. The movements resulting from the uniform opening and closing of the shells ultimately cancel each other out – and a microscopic scallop would make no headway at all. Edward Purcell formulated this relationship in a rule that is named after this bivalve mollusk: the scallop theorem.

DIFFERENT THAN WATER: BIOLOGICAL FLUIDS

This rule applies not only to the opening and closing of two scallop shells, but very generally to mirror-symmetrical movements in extremely viscous environments. The microcosm of nature thus contains exclusively asymmetrical powering techniques, such as the rotating bacterial flagellum or the movements of tiny hairs on a ciliate.

Nevertheless, Fischer's group had set out to propel microswimmers using a mirror-symmetrical motor function, as the corresponding motor systems are usually based on simpler mechanisms and are easier to create. The researchers saw an opportunity for a symmetrical drive, because many biological fluids behave differently than water. "In synovial fluids, or vitreous humor in the eye, for example, the hyaluronic acid molecules are arranged in network-like structures, and this is precisely why the viscosity can change,"

explains Peer Fischer. As soon as a microswimmer moves around in these gel-like structures, the viscosity decreases because it breaks up the network. However, if the microswimmer persists, the bonds between the molecules are immediately reestablished. It is therefore possible to subvert the scallop theorem in such fluids.

Fischer's team demonstrated this for the first time in 2014: the researchers designed a 0.3-millimeter scallop-like body in which the two shells were connected by a hinge. They attached micro-magnets to the shells. When the scientists exposed the micro-scallops to an external magnetic field, the shells closed. When they removed the magnetic field, a sort of resetting mechanism in the hinge opened the artificial scallop again.

"The key is to open the shells much faster than we close them," explains Fischer. "This temporally asymmetric movement cycle results in the surrounding fluid being less viscous during the opening process than during the slow closing process." The scallop thus covers a greater distance when the shell is opening than when it is closing. The bottom line is that it makes progress – but only in liquids that act like a synovial fluid, the vitreous humor, or many other biomedically relevant fluids.

Finding drive principles that propel tiny artificial swimmers is a challenge for the researchers in Stuttgart. Another challenge they face is fabricating microswimmers like the tiny magnet-driven scallops in the most simple manner feasible. Their shells should be as thin as possible, but at the same time, they must be robust enough to withstand



Dust obstructs: In the clean room, the researchers use photolithography to create microstructures, such as the micro-scallop. It is crucial that they avoid even the tiniest impurities in the air.

the constant opening and closing in a relatively viscous environment. The researchers ultimately chose to make the micro-scallop from a solid siloxane polymer. This material was used in a 3-D printer to build the tiny structure, including the hinge, which was just 60 micrometers thick, or roughly the diameter of a human hair.

Creating the delicate copy of the scallop required great precision, but producing the smallest-ever vehicle in the Stuttgart fleet was even more difficult. This is a 400-nanometer-long screw made from quartz glass and nickel. The corkscrew-like spiral strand is just 70 nanometers thick – almost 1,000 times thinner than a human hair. It was only thanks to a process the researchers had developed themselves (see box at right) that they ultimately managed this complicated feat.

There is a simple reason why the researchers in Stuttgart are even puzzling over vehicles that are smaller than any

DESIGNING AND BUILDING NANOCOMPONENTS TO SPEC

It's not exactly an everyday achievement to manufacture high-precision components in the nanometer range, such as the corkscrew-like nano-screw. The Max Planck researchers in Stuttgart build such nanostructures layer by layer. They first cover a silicon wafer with a dense grid of gold dots measuring just eight nanometers in diameter. They position the wafer in a vacuum chamber in which they evaporate the desired materials. The substances then make their way to the wafer, which the researchers position in such a way that the particles can't reach the wafer surface, but only the gold particles, and are deposited there. (Just like the slanted rays of the evening sun in the mountains illuminate only the mountain ridges and peaks, but not the valley floors.) In this way, fine, clearly separated structures grow.

By rotating the wafer in various directions during the deposition process, the researchers can also generate complex geometries – they just have to ensure that the evaporated substances don't reach the wafer surface. By continuously rotating the wafer, they create the corkscrew-like nano-screws. When they tilt the wafer abruptly, the evaporated structure produces zigzag shapes. Since the structures grow atomic layer by atomic layer, the Stuttgart-based researchers can interrupt the process at any time and continue with another material. In this way, they can, for example, integrate magnetic nickel into a nanostructure that otherwise consists of silicon dioxide or titanium dioxide.

»» A microswimmer was successfully maneuvered through a viscous biological medium for the first time.



An opener for the stomach lining: The researchers in Stuttgart coated the quartz glass corkscrew-shaped micro-screw with enzymes that are used to liquefy the mucous locally, allowing the vehicle to swim through this gel-like network.

bacterium: they are looking for a swimming device that is small enough to swim through the three-dimensional hyaluronic acid network without having to break it apart. “So of course a swimmer must be smaller than the molecular mesh size of these networks, which is a few hundred nanometers,” says Fischer.

Once again, the researchers used a template from nature for their screw-shaped design. This time they used the bacterial flagellum, which works just like a corkscrew except that the microbes bore through fluids instead of through cork. That is precisely what the nano-screw from Stuttgart can do, too. The necessary rotation is ensured by an external magnetic field that acts on the nickel in the screw.

The researchers placed their nano-swimmers in a model fluid composed of water and hyaluronic acid, applied the rotating magnetic field and – were delighted. Using a microscope, they were able to watch how effortlessly the little screw pushed its way through. That this really was due to the tiny size of the vehicle was proven by running a comparison with a micrometer-scale screw, which got undeniably stuck after just a few rotations.

A MICROPROPELLER THAT LIQUEFIES MUCOUS

Slipping through the meshes is one way of penetrating a tightly woven molecular network. However, the scientists in Stuttgart had another idea: they wondered whether it would be possible to simply chemically dissolve the gel-like structure – essentially to liquefy it. This could be interesting, for instance, for using a swimming vehicle to transport drugs through the mucous membrane of the stomach, intestine or lungs directly to the diseased area.

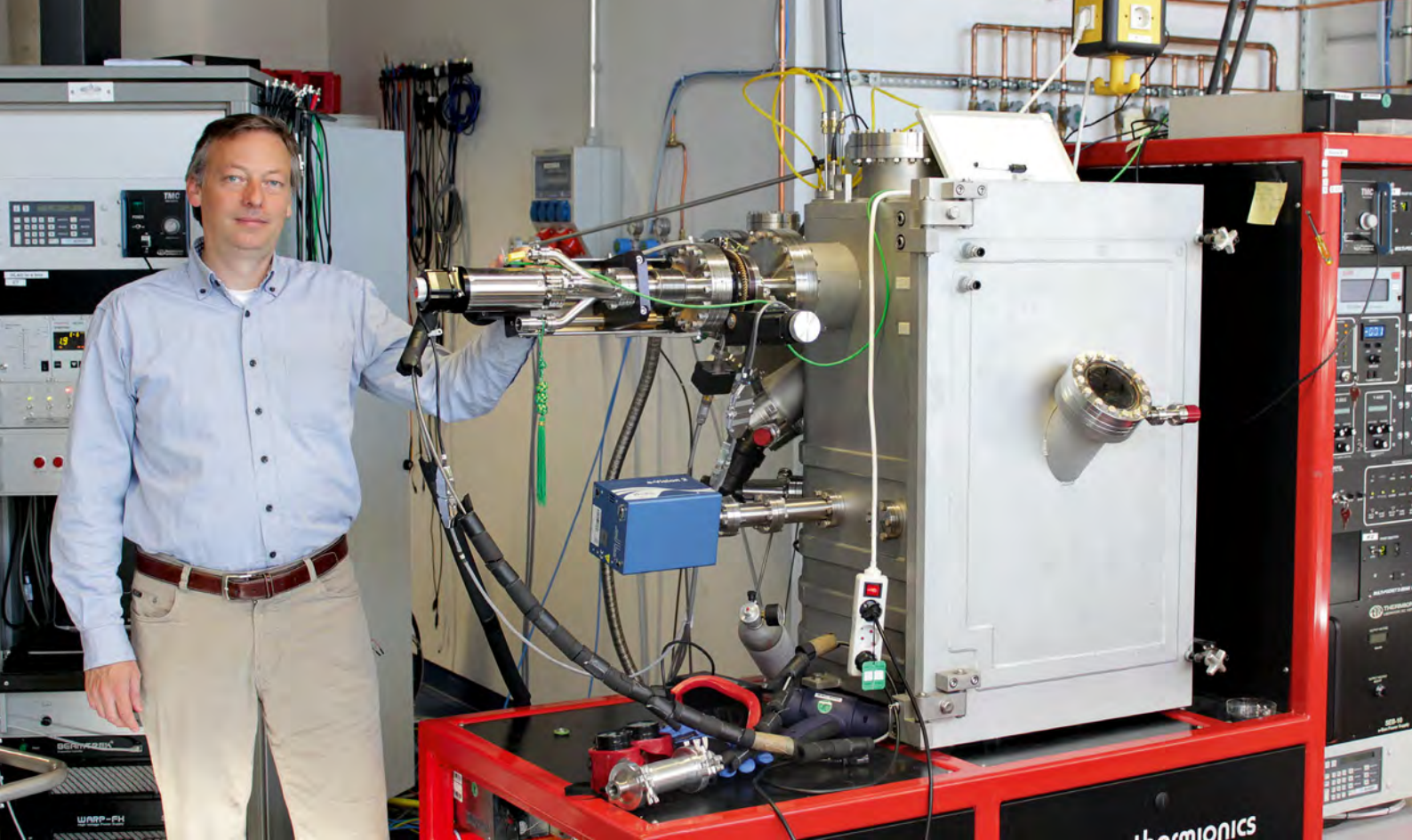
In order to create a tiny submarine that liquefies mucous, once again, a glance at nature helped the researchers. A bacterium known as *Helicobacter pylori* provided the crucial hint. Anyone who has heard of this bacterium certainly wouldn’t associate it with anything positive: researchers have known for about 25 years that *H. pylori* can cause inflammation and ulcers in the human stomach wall. It manages to make its way through the stomach lining by secreting an enzyme known as urease. This enzyme breaks down the urea that is present in the gastric fluid. In the process, ammonia is released – a

base that increases the pH value locally in the otherwise acidic milieu of the stomach. When this happens, the gel-like network of molecules in the stomach lining is broken up, and bacteria can swim through it.

Fischer’s team simulated this effect and designed a glass screw – similar to the previously mentioned nano-screw, only bigger. The researchers bound urease enzymes to the thread of the screw. This swimmer also contained some nickel so that it would rotate when a magnetic field was applied. The team finally tested this enzyme-coated microrobot in a milieu of pig stomach lining – and was actually able to pass it through the lining. It was another premiere: “A microswimmer was successfully maneuvered through a viscous biological medium for the first time,” says Peer Fischer, visibly pleased about the result.

The urease example shows that chemistry, too, offers a box of tricks that can open the door to opportunities for the movement of microswimmers. The scientists in Stuttgart want to make even greater use of it in the future. They plan to develop miniature vehicles that autonomously generate their own propulsion. In all previous projects, the researchers had to use external means to move the submarines, whether magnetic fields or light. “If we could equip our nanorobots with a chemical fuel, then they would have an engine on board, so to speak,” says Peer Fischer.

An initial approach has already been made: a microparticle that has two faces. The surface of one half is coated with a catalyst, while the surface of the other half isn’t. This Janus-head-



At the helm of nanoproduction: By tilting and rotating a silicon wafer in the vacuum unit when evaporating material onto it, the researchers generate nanostructures in the form of screws or zigzag lines. Peer Fischer holds the manipulator they use to adjust the wafer.

ed particle propels itself through a fluid containing a substance in which the catalyst triggers a chemical reaction. This chemical reaction changes the concentrations of the substances in the fluid in the environment of the microparticle half with the catalyst, creating a difference in concentration compared with the environment of the other microparticle half.

“As in the case of osmosis, the system wants to balance out this difference in concentration,” explains Peer Fischer. This means that fluid moves along the microparticle, generating a force in the process, and moves the microparticle forward in parallel with the concentration gradient. Fischer and his team would now like to transfer this principle to biological environments and replace the metallic catalyst with suitable enzymes. The end result could be a sort of biological self-driving chemotaxi. And when such a vehicle is one day roaming about the lab in Stuttgart, the cleaning staff will occasionally have to stay out again. Better safe than sorry. ◀

TO THE POINT

- **Microrobots and nanorobots that can be maneuvered through the body and transport active substances to the diseased area could make medical treatments more efficient.**
- **Max Planck researchers in Stuttgart are designing drive systems for such tiny vehicles, and developing methods for producing them.**
- **To do this, they simulate mechanisms from nature, such as the concentrated movement of tiny hairs on a ciliate, or the mucolytic effect of *Helicobacter pylori*, and implement them with technically feasible means.**

GLOSSARY

Liquid crystal elastomer: A plastic whose shape can be changed elastically and that exhibits the structure of a liquid crystal. Liquid crystals are liquid, but their molecules don't form a disordered structure like liquids, but rather arrange themselves at least in one dimension with a preferred orientation, making them resemble crystals.

pH value: A measure of how acidic or basic a liquid is. The pH value is low in an acidic milieu and high in a basic milieu.

Scallop theorem: According to this rule, in most liquids, such as water, very small swimming bodies can't be propelled using symmetric movements. For example, they can't move in the same way a scallop does. This is because the effect of friction in nanoswimmers and microswimmers is much greater than the effect of inertia, with the result that symmetric movements move the swimmer exactly the same distance forward and backward. However, this rule can be subverted in gel-like biological fluids.