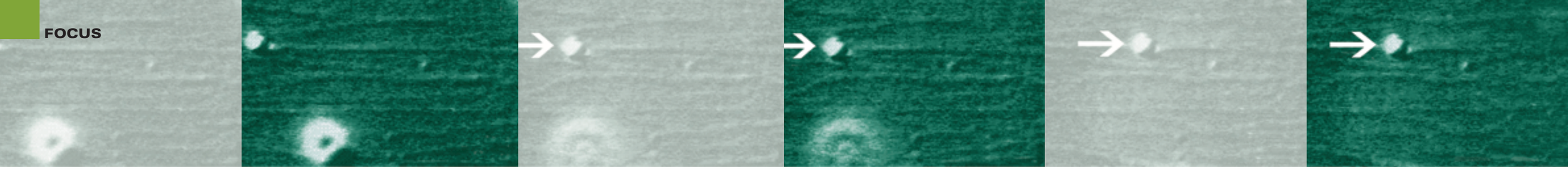
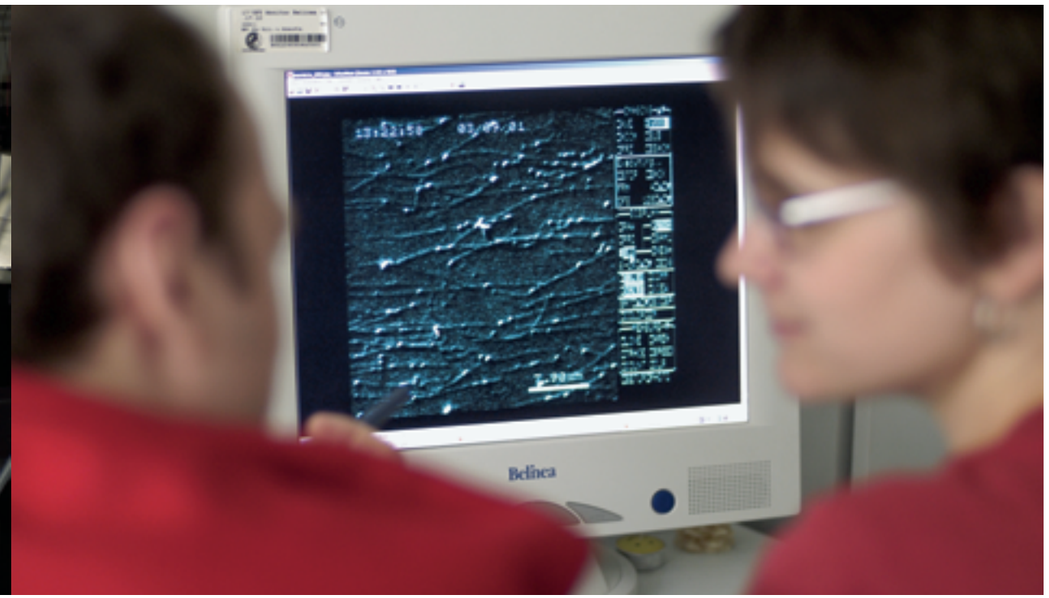


In biomimetic experiments (see also the photographs below), the motor molecule kinesin is bound to a small latex sphere that it moves along the microtubule from left to right with a speed of one micrometer per second (arrow).

Changing Tracks on the Molecular Rail Network

The ability of tiny particles to independently connect with each other and form ordered structures fascinates researchers. In connection with nanotechnology, scientists therefore like to call this self-organization. So-called molecular motors are also often seen from this point of view. **Stefan Klumpp** *at the* **Max Planck Institute of Colloids and Interfaces** *in Golm is investigating how these tiny cell motors move about.*



Photos: Norbert Michalke/MPI of Colloids and Interfaces – Klumpp

In the Institute's theory department, headed by Reinhard Lipowsky, Stefan Klumpp and his colleagues are investigating biomimetic model systems in which the cell's complexity is reduced to several components. The researchers want to track down the component processes of all the cellular events and possibly create the basis for non-biological applications for the tiny motors. Stefan Klumpp does not, however, want to reconstruct the cell motors. "There's no point," says the physicist, because nature is too complex. But he can envision using the molecules for other non-biological things, for example in nanotechnology.

How such motors work has been the subject of intense research during the last few years and is now well understood. The researchers know their structure, and know that they are related to complex proteins. With their "head" region – known as the motor domain – they attach themselves to the cellular rails, the so-called filaments. Each motor domain determines the kind of filament and the direction of movement, like a train with a particular gauge that can be used only on suitably laid tracks. The freight (and with it, the biological function of the individual motor) is determined by the motor protein's tail. This long double coil binds to corresponding loads – organelles, RNA or other cell components.

The energy-storing molecule adenosine triphosphate, or ATP, usually serves as "fuel" for the motor. The motor domain binds to this and converts it to ADP (adenosine diphosphate) by cleaving off a phosphate group. During ADP dissociation, the motor molecule changes its three-dimensional structure. In the process, the protein changes from a tightly-bound state on the filament track to an unbound state. This cycle of filament binding, change in the molecule's shape, detachment from the filament, regaining the molecular conformation and renewed binding causes the motor protein and its freight to move step by step along the cell's internal tracks.

Small Steps under the Microscope

This movement is minimal – it normally covers a distance of several nanometers (billionths of a meter); but along a molecular axis, it adds up. In this way, chemical energy is converted into mechanical energy. "Seen under the microscope and in real-time resolution, it really does look like the motor takes steps and walks," says Stefan Klumpp.

What functions so well experimentally – outside the cell as well – and was recently first visualized at high resolution by American scientists is what Stefan Klumpp has been trying to understand theoretically using his molecular models. He is

particularly interested in what happens when the process is observed over a longer distance. "Within the dimensions of a cell, the motor takes, on average, 100 steps, then falls off the filament," explains the Max Planck researcher. This is due to the fact that the binding energy to the filament is not much greater than the thermal energy resulting from fluctuations of the molecular components. Therefore, the bond to the filament is lost at some point.

Detached from the tracks, the motor molecule in solution participates in so-called Brownian motion, which is characterized by a diffusion coefficient that is measured in square centimeters per second. Since it also collides and bounces off other molecules in the cell, this movement is purely random. Scientists call this combination of random movement plus that directed along the filament "random walks."

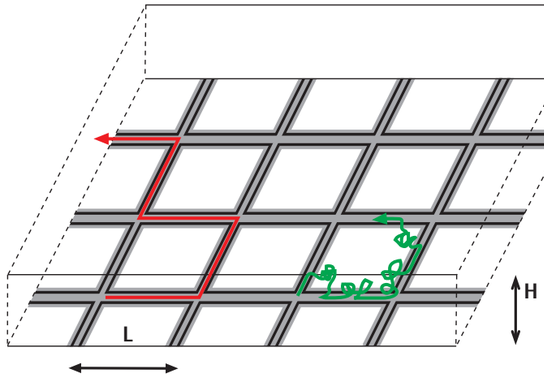
"Random walks" are interesting from both the theoretical and practical point of view. Klumpp believes that they could result in anomalous drift characteristics, as well as strongly accelerated diffusion of the molecule. "For certain applications, it could be useful to be able to increase molecular diffusion. In order to achieve this, one could possibly call upon the detachment process between the filament and the motor," says Klumpp, describing one possible idea. What he has in mind here are transport processes in a gel, where viscosity prevents hydrodynamic flow, and transport through normal diffusion would be too slow. But before considering specific applications, the theorists from Golm want to understand the effect and describe it physically.

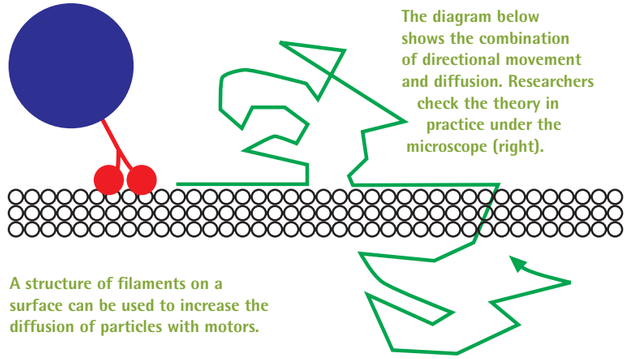
Stefan Klumpp has all he needs for his calculations. He views the filament as a one-dimensional grid. The motor sits at one location on this grid, along which, with a certain probability, it can walk. As parameters, he uses the walking speed and the average distance the motor will cover before it falls off, then the binding energy to the filament and the diffusion coefficient of Brownian motion. The researcher derives these parameter values from experimental observations. On the computer – and sometimes even with pencil and paper – he develops the algorithms that best allow the cellular process to be simulated. As yet, the results of these simulations could not be tested experimentally.

Feedback between Theory and Practice

"We look at what happens, for example, when several motors are in use and they meet up," says Klumpp. The problem of traffic jams and oncoming traffic is apparently not restricted to roads – according to the findings in Golm, they can also arise in molecular rail transportation systems. Stefan Klumpp's simulations have shown what such traffic jam profiles look like. If only a few motors are on the move, they collect at the end of a track. If there are a lot, they distribute themselves evenly along the route. "Whether there are traffic jams in the cell is not yet clear," says the 30-year-old post doc. It is assumed that a healthy cell might possess shutoff mechanisms: motors that are in the way are thrown off the filament.

The Golm theorists constantly seek feedback from colleagues doing experimental work, in order to check their model and keep it as realistic as possible. However, in the last few years, biologists and biophysicists have concentrated more on investigating individual molecules. "The many new methods for observing individual molecules have posed exciting questions and also brought great breakthroughs," agrees Stefan Klumpp. Although, in the process, it has been somewhat forgotten that things mostly involve lots of molecules, and that other effects have to be taken into account. For example, there have not yet been any experiments addressing the problem of oncoming traffic on the tracks – only hints about additional interactions. For Stefan Klumpp, investigating possible oncoming traffic is one of the interesting questions he wants to answer with his model calculations, as this could possibly be based on a form of cellular self-organization. "If several filaments are arranged parallel to each other, it could be that oncoming motors are initially blocked until one of them leaves the filament and changes to another track," says the physicist. In a model, the conditions under which this can function can be calculated. The theoretically calculated and simulated results provide a first glimpse of self-organization.





The diagram below shows the combination of directional movement and diffusion. Researchers check the theory in practice under the microscope (right).

A structure of filaments on a surface can be used to increase the diffusion of particles with motors.

Graphics: MPI of Colloids and Interfaces – Klumpp

Photo: Norbert Michalke

When theorists like Stefan Klumpp allow their thoughts to run wild, they quickly come up with other questions that could be answered with simulations. "For example, molecular motors could be reconstructed using genetic methods, thereby altering their properties in a specific way," says Klumpp. Using one of the models, it could be observed which change has a positive effect, thus making it desirable. However, a correlation between a specific property and a corresponding change in protein structure still seems to be a long way off. Accordingly, Stefan Klumpp turns to more immediate applications. "Traffic jams could be used, for example, to specifically slow down motors," he says. For example, to transport a reaction partner to a specific location where it should stay for a certain time to ensure that the reaction takes place.

The Golm-based scientist has, in any case, registered that research worldwide is now interested in interactions between several molecular motors. "This is indispensable for understanding biological transport processes and making targeted use of molecular motors," says Klumpp. After all, larger organelles are also normally moved in the cell by several motors working together. Such a situation can be reconstructed in an experiment as well as in a model. It simply has to be ensured that several motor molecules bind to the particle to be transported. Using his calculations, Stefan Klumpp can determine by what factor the path along which such a particle can be transported is elongated when it is carried by one, two or several motors. With several motors, there are always extra transporters when one motor falls off – the process stops only when all of the motors have lost their binding to the filament. Klumpp will soon receive an experimental analogy to these calculations. Janina Beeg, a doctoral student from Jena, has been working in Golm on precisely this question since December 2003. The theorists expect the first results soon. Theoretical model calculations form an important basis for understanding biological transport processes. With them, ways to avoid traffic jams and oncoming traffic can be tested. Both effects could, of course, become a problem for targeted application of motors in nanotechnology – for example, when the motors are to be used to lay cables and build electrical circuit boards. In the tiny dimensions in which it is barely still possible to work using optical lithography, this could be an alternative method for nanostructuring materials. While it may sound bold, Jonathon Howard's group at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden is already successfully working on it (see article on page 28ff).

Structures that Organize Themselves

Molecular motors could even contribute much more to self-organization of nanostructures. For example, when a motor binds to two filaments: it can run along one and transport the other. "The familiar aster structures of the cell division spindle are formed in this way," says Stefan Klumpp. It also seems possible that the motors initially lay their tracks parallel in the same way and then use them to avoid oncoming traffic. Other investigations show that molecular motors are also able to stretch a molecule such as DNA. Here, the DNA is fixed at one end and a motor molecule binds to the other end. When this motor moves off, it takes one end with it – and fascinating structures result.

A lot can certainly be learned from cells. And when a live experiment showing the workings of molecular motors isn't possible, a simulation is of great help. Researchers such as Stefan Klumpp use these models to penetrate deep into the mysterious world of "biological trolleys" – and who knows, perhaps one day it will be possible to reproduce them ...

Ina Helms