

# How Cells Make Waves

Researchers at the **MAX PLANCK INSTITUTE FOR THE PHYSICS OF COMPLEX SYSTEMS**

**DR. MARKUS BÄR**, head of the junior research group on "Pattern Formation", **DR. KARSTEN**  
in an astonishingly realistic way, how colonies of Myxobacteria behave in times of food

not only work with dead material: Using mathematical models,

**KRUSE** (Department of Biological Physics), and **UWE BÖRNER** are simulating,  
scarcity – or how a coli bacterium finds its midpoint before it divides.

The discovery and description of dynamic self-organization processes in inanimate nature has been part of daily work for chemists and physicists for a long time. They are familiar with many systems far from equilibrium – such as liquids or chemical reactions – in which atoms or molecules independently organize themselves into regular structures. "There has recently been more and more evidence that these processes are also important in biological events within cells and cellular structures," according to Markus Bär. "Apart from biological experiments, mathematical modeling is an important research tool."

Bär copies dynamic processes which, in nature, accompany the interplay between order and disorder. His research group on "Pattern Formation" works on living organisms. As a result of this work, models arise that give the scientists a deeper understanding of the mechanisms, which lie behind the formation of a given structure. This in turn makes it possible for biologists, biochemists and biophysicists to perform more specific and effective experiments in their laboratories.

One of the objects of study of the Dresden physicists is the social life of the bacterium *Myxococcus xantus*. Like Angela Stevens of the Leipzig Max Planck Institute for Mathematics in the Sciences, Bär and his colleagues Uwe Börner, Andreas Deutsch and Hans Reichenbach are

using their mathematical instruments to get up close to *M. xantus* (see MAXPLANCKRESEARCH 3/2002, p. 42 f.). The bacterium exhibits strange behavior under certain conditions. If a colony comes into an environment with low nutrient levels, up to 100,000 form a fruiting body, which can withstand long starvation periods. This is preceded by a fascinating spectacle: The colony contracts into waves of wandering cells. The wave pattern is highly regular: the peaks containing many bacteria and the valleys, in contrast, only a few.

## AN IMPULSE STIMULATES CONVERSION

The researchers believe that the cause of this characteristic pattern lies in both the type of movement and in the communication between the individual myxobacteria. The rod-shaped cells glide along the longitudinal axis until they frontally collide with a comrade. During the collision, they exchange a protein, which is sitting on their surface: the so-called C-factor. It is thought that this exchange causes the bacteria to alter their movement direction by 180 degrees, like a "bacterial bumper car".

Yet these simple rules alone are not enough to really cause the wave pattern (known as "rippling"). So scientists now want to know what the additional rules are that stimulate the bacterial society to dance the collective ripple ballet. For this pur-

pose, Bär and his colleagues are using another set of mathematical tools than those used by Angela Stevens – they are using "cellular automata". These split a mathematical space into cells of equal size, which behave according to certain rules. They are therefore an ideal instrument for the mathematical simulation of a starving culture of myxobacteria. A cube-shaped mathematical cell is used in the computer to represent an idealized bacterium. In the simulation these cells move in steps – like the individual pictures in a film. Exactly the same simple rules then apply as are thought to apply to the real myxobacteria.

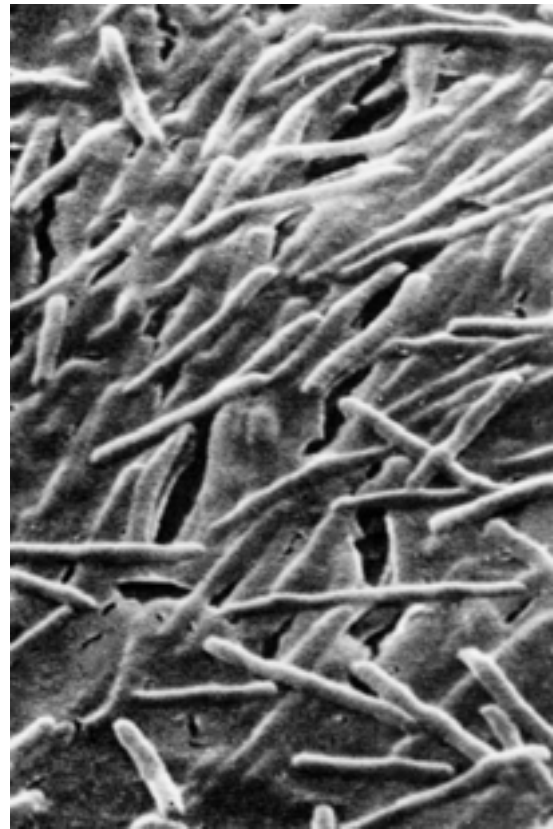
The Dresden physicists then tested under which additional conditions ripples as realistic as possible are caused. They discovered that the key could lie in the phase after the collision in which the C-factor exchange forces a reversal of direction. They therefore introduced a new rule, namely that the bacterium not be allowed to take up a new C-factor for a certain period of time after "inoculation" with the C-factor. If it collides with a new partner during this period of immunity, it marches further on, rather than turning around.

An astonishingly realistic ripple pattern is produced in the virtual colony by a simulated C-factor immunity lasting a few minutes. On the other hand, no wave pattern is produced if the bacteria can take up the C-factor at any time during their



PHOTO: MPI FOR DEVELOPMENTAL BIOLOGY/JÜRGEN BERGER

Life under the magnifying glass: Using the bacterium *Escherichia coli* as an example, research workers at the Max Planck Institute for the Physics of Complex Systems have been examining how cells divide.



PHOTOS: SOCIETY FOR BIOTECHNOLOGICAL RESEARCH

A starving colony of *Myxococcus xanthus* takes on a characteristic wave pattern while it is drawing together to form a fruiting body. The bacteria are concentrated in the dark areas. A "wavelength" is the distance between the dark peak of one wave to the next light wave dent and is between 10 and 20 cell lengths.



A *Myxococcus xanthus* colony: A single bacterium is about 6 micrometers (millionths of a meter) long.

collision ballet. The Dresden model offers another advantage: As each of the hundreds of thousands of mathematical cells represents a bacterium, the research workers can observe the behavior of the individuals. The virtual cells do in fact move almost like the single cell organisms in a real myxobacteria colony. The model also shows that a precise choreography lies behind the collective ripple pattern. Most cells in a wave peak turn around in coordination when they meet a wave peak coming in the opposite direction. This resembles the experimental observations on real cultures – the model evidently gives a very realistic behavioral description of starving myxobacteria.

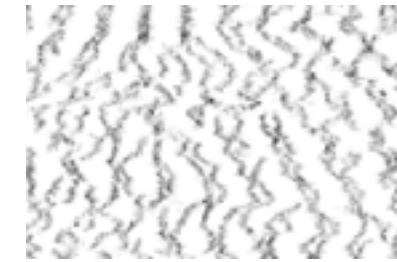
It has nevertheless not yet been concluded whether temporary immunity to the C-factor is the real decisive cause of the rippling. Angela Stevens and her colleague Frithjof Lutscher have suggested an alternative model and used analytical mathematics to demonstrate that a myxobacteria colony can ripple even without C-factor immunity. For this purpose, they laid down modified rules that involve other partners in

the vicinity of two colliding bacteria. If these can influence the decision of the partner in the collision as to whether he should turn round afterwards or not, then the virtual colony still performs an elegant ripple ballet.

The Dresden physicists are now attempting to find out which junction nature has taken through the use of an extended model. This is also based on cellular automata and tests the competitive rules. Bär and his colleagues do not even exclude the possibility that both rules together direct the ripple ballet of the myxobacteria.

In Frank Jülicher's neighboring Department of Biological Physics, Karsten Kruse is working not with colonies, but with a single bacterial cell: With *Escherichia coli*, which colonizes the human colon. *E. coli* is also one of the darlings of an international community of scientists who are using this and other bacteria to study cell division – an elementary life process.

Before it divides, a cell copies all-important components within itself and then distributes these among the new daughter cells – *E. coli* having two. Doubling of the DNA is particularly important. The mother cell must then find the right spot in her own body for the split. If she gets this wrong, she will seal off a daughter



The Dresden physicists' virtual *M. xanthus* colony: A very realistic wave pattern is formed if the bacteria are "immune" to the uptake of new C-factors for a few minutes after a collision.

Discussion in passing: Karsten Kruse, Markus Bär and doctoral student Uwe Börner (from left).



Simulation of the motion pattern and cell division: Karsten Kruse (left) and Markus Bär.

cell without the full complement of DNA. A mini-cell that has been maimed like this cannot survive. But just how does the mother cell find the right place to split?

### AND WHERE IS THE MIDDLE, IF YOU PLEASE?

Cell division is highly complex and is still hardly understood. However experiments have begun to reveal the first hints regarding a few of the important mechanisms. When a coli bacterium divides, it produces a partition, called a "septum", in the middle of its rod-shaped body. This grows from the external cell wall into the interior of the cell, like the shutter of an iris. There is a ring (Z-ring) at the inside edge of the still open septum, which is formed by a protein with the abbreviated name of FtsZ. Fts stands for the English term "filamentous temperature sensitive". The biologists were inspired to invent this name by mutations in the gene that carried the program sequence for FtsZ production. The mutated FtsZ protein prevents division at certain temperatures. Instead, the bacterium becomes continually longer, finally taking on a thread-like shape. The researchers believe that the correct FtsZ positions the growing septum at the correct place in the bacterium – namely, in the

middle. But how does the FtsZ know where the middle is?

Karsten Kruse is attempting to crack this hard nut with a mathematical model. This is intended to combine important experimental indices to give a useful overall picture. The "main actors" in septum formation are apparently three proteins, which the biologists call MinC, MinD and MinE. Min stands for mini-cell and points to a special property: Mutations in the Min proteins can cause the bacterium to split at one of its ends (poles) instead of the middle, cutting off an unfinished mini-cell. Experiments on *E. coli* show that MinC can prevent the formation of the Z-ring. Were the concentration of MinC in the middle lower than elsewhere, the Z-ring could only be formed there, which is the correct site. This is presumably exactly what happens when coli bacteria divide.

But how does the cell keep MinC away from the middle? This is where the proteins MinD and MinE have their part to play. MinD molecules like to settle within the cell near the cell wall. As they also like company, they accumulate at one of the two poles of *E. coli*. That would be the end of the story then, if MinE did not play its part. The following happens in its presence: After about 10 to 60 seconds, it evidently becomes

too uncomfortable for MinD at the pole of the bacterium. It is released and rapidly migrates to the other pole, where it is accumulated once again on the cell membrane. After the same interval, MinD is then shooed away once more and driven back to its old home.

This game is repeated again and again: Like a swing, the MinD molecule concentration at the two poles of the coli bacterium oscillates up and down. As the MinD molecules "race" back and forth, they spend most of the time at one of the poles. Therefore, if the average overall time is considered, the concentration at both poles is much higher than in the middle of the bacterium.

Now comes the third actor: the MinC, the "FtsZ brake". This follows the MinD like a dog on a leash. Owing to this close connection, the MinC simply copies the MinD concentration profile. The time average of the MinC concentration accordingly also has a dent in the middle of the bacterium. This dent makes it possible for the FtsZ to form the Z-ring there, and nowhere else – and this then forms the base for the septum. MinE is therefore the choreographer of this dynamic regulation of the correct division site.

The scientists have used several lines of evidence to develop the plot

PHOTOS: WOLFGANG FLEISER / MPI FOR THE PHYSICS OF COMPLEX SYSTEMS

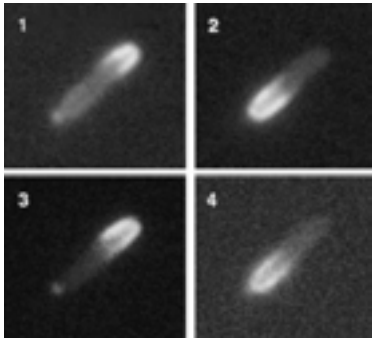
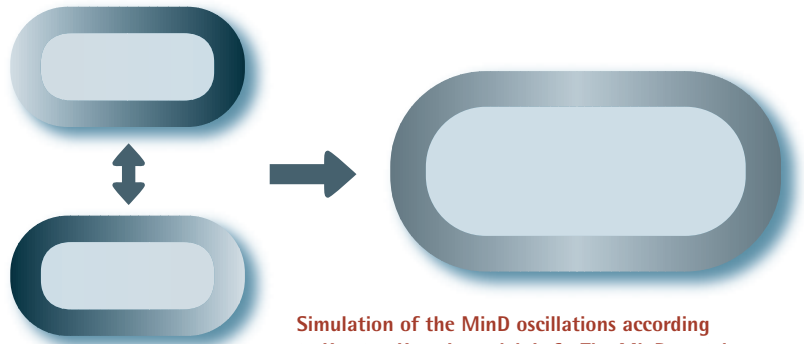


PHOTO: MPI FOR MOLECULAR CELL BIOLOGY AND GENETICS

The migration back and forth of MinD molecules (marked pale) within the *Escherichia coli* bacterium during an experiment at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden. The bacterium is two micrometers long. The time between the two illustrations is about 20 seconds.



Simulation of the MinD oscillations according to Karsten Kruse's model. Left: The MinD proteins (dark) oscillate back and forth between the two bacterium poles. Right: Averaged mean time, most MinD proteins are at the poles and the concentration in the middle of the bacteria is low.

of this protein drama. It is nevertheless uncertain whether they describe the real causes of cell division in a coli bacterium. There are many gaps in the experimental evidence and this is the point on which Karsten Kruse has begun. With his mathematical model he can use computer simulations to test whether this script produces the desired protein swing – or whether alternative scripts give better results.

Here the theoreticians are able to exploit a basic system property: Just as in the culture of myxobacteria, many participants – here the Min C, D and E molecules – produce a regular pattern. It was exactly these patterns that the Dresden physicists managed to model ably through clever use of the mathematical toolbox of the physics of complex systems. It was also a bit of luck, that *E. coli* allowed the use of some important simplifications, which made modeling easier. For example, Kruse only has to consider the concentrations of MinD and MinE, for MinC obediently follows MinD. Moreover, he was able to simplify the shape of *E. coli* through a mathematical cylinder, without forfeiting much accuracy. This allowed the researcher to only consider the concentrations of MinD and MinE along the bacterium's longitudinal axis in

his model: Out of three spatial dimensions, there is now one – which makes the mathematical equations much clearer.

Experts will be interested to note that Kruse's equations belong to the class of the "Reaction Diffusion Models". The brilliant English mathematician Alan Turing introduced models of this type in 1952. This computer science pioneer wanted even then to describe pattern formation in biological systems on a theoretical basis. Alfred Gierer and Hans Meinhardt of the Max Planck Institute for Developmental Biology in Tübingen have employed this approach to make a major contribution towards the understanding of the fresh water polyp hydra. This approach was also successful for Karsten Kruse: By correctly set concentrations of MinD and MinE in his model, oscillations, that were very close to the experimental data, were actually produced.

### WHICH SCRIPT IS AUTHENTIC?

The world of living organisms would be boring if complex life processes did not call for the development of alternative models. There are accordingly two different scripts for the MinC-D-E interplay from other research groups, one of these

led by Hans Meinhardt. These other scripts are based on similar basic concepts, but differ in essential points. All three scripts describe the mechanisms of the septum positioning differently, but each in its definite way. This gives rise to clear questions that can be answered by specific laboratory experiments on real bacteria.

For example, Karsten Kruse's script assumes that the MinD protein tends to clump together to form aggregates at the cell membrane. Two recent experiments have confirmed this prediction. In spite of this astonishing success, it will nevertheless be a long time before *E. coli* reveals the ultimate secrets of its cell division. The mathematical models will certainly provide more important impulses for new experiments.

The self-organization of bio-molecules or cells into collective patterns is of fundamental importance in many life processes. "Mathematical tools will also one day contribute to answering the question of how the cells in our body specialize during embryonic development and form different organs", says Bär. "However, the collaboration between theoreticians and experimental scientists will have to become even closer to make this possible."

ROLAND WENGENMAYR

PHOTO: MPI FOR THE PHYSICS OF COMPLEX SYSTEMS, MODIFICATION: ROHREK