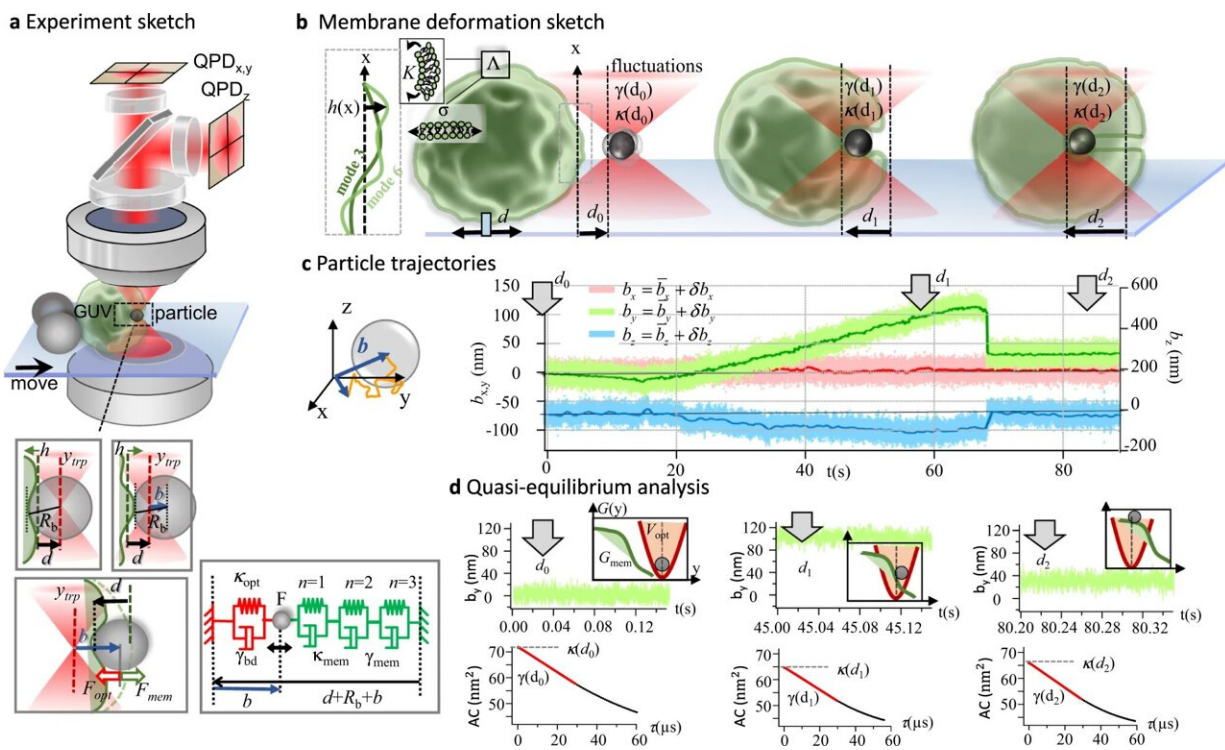


Thermal fluctuations and oscillation modes found to determine the uptake of bacteria in cells

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Particle trapping and tracking at different internalization stages. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-022-35302-5

How and with what effort does a bacterium—or a virus—enter a cell and cause an infection? Researchers from Freiburg have now made an important contribution to answering this question.

A team led by physicist Prof. Dr. Alexander Rohrbach and his collaborator Dr. Yareni Ayala was able to show how thermal fluctuations of a model [bacterium](#) and [membrane](#) oscillation modes of a model cell influence the energy with which the model bacteria dock and enter the membrane. The results have just been published in the journal *Nature Communications*.

Like a sticky piece of candy on a wobbly balloon

"To understand how a bacterium or virus enters a cell, you can imagine a sticky candy on a floppy, wobbly balloon. When a child shakes the rubber balloon around, the candy sticks even tighter to its surface," said Rohrbach, a professor of -Bio- and Nano-Photonics at the Department of Microsystems Engineering at the University of Freiburg.

In his lab, the laser and bio-physicists set up a similar experiment to study the physics of infection processes. The wobbly balloon corresponds to a giant uni-lamellar vesicle (GUV), which serves as a biological model cell. The membrane vesicle is the size of a tiny grain of sand about 20 micrometers in diameter.

The sticky candy here corresponds to a one-micrometer small, round particle that serves as a model bacterium and is brought into contact with the membrane. The researchers use laser tweezers to not only capture and hold the particle by means of optical forces, but also to approach it to the membrane in [small steps](#), to contact it and even to deform it until the particle slips into the membrane bubble.

Thermal fluctuations encode key information

Using optical tweezers and laser light scattering, not only the necessary forces and energies can be measured, but also the thermal motions of the

particle, which are necessary for its uptake. The membrane bubble and the particle are in aqueous solution at room temperature during the experiment. The [water molecules](#) shoot in all directions in the liquid, colliding with the particle and causing it to perform a characteristic quivering motion called Brownian motion or thermal fluctuations.

At the same time, the highly dynamic water molecules excite the membrane bubble to oscillate (so-called membrane modes) with different amplitudes and wavelengths, which arise and are damped again completely independently of each other.

"We assume," says Alexander Rohrbach, "that plasma membranes of living cells in our body also perform similar over-dampened oscillations and interact with the thermally moving bacteria, which under certain circumstances then leads to particle uptake and infection of the cell."

Fluctuation data on the laser trap

How strongly a candy wraps itself in a wobbly balloon depends on the stickiness of the candy and the condition of the balloon rubber. Similarly, a cell membrane has numerous receptors that bind specifically to ligands of for example approaching bacteria.

Here, the Freiburg physicists, in collaboration with the group led by Professor Dr. Winfried Römer, were able to both change the membranes of the model cell and vary the coating of the model bacteria in order to study the influence of thermal fluctuations at different adhesion forces ("stickiness"). Römer is a professor of synthetic biology of signaling processes at the University of Freiburg.

"At first, we were a bit disappointed," Rohrbach admits, "because the fluctuation data of the particle in the laser trap hardly differed visibly for different distances to the membrane or for different membranes."

This was despite the fact that the researchers recorded signals at microsecond intervals, allowing them to record minute changes in the particle's motion. It was only when they analyzed the data differently that significant differences in the [movement patterns](#) suddenly emerged, which now had to be understood—with the help of mathematical methods and computer simulations, which physicists use to test their conception of complex phenomena and the interpretations that follow from them.

Using the physics of stringed instruments as a comparison

In mathematical models, the superposition of many oscillation modes plays a decisive role. Here the physics of a guitar helps with the question which oscillation modes are suppressed and which are amplified: If you increase the tension of a guitar string, the frequencies of the oscillation modes become higher on average.

If the tension of the membrane bubble is increased by more internal pressure or a different chemical composition of the membrane molecules, the bubble oscillates in higher modes on average. If you shorten the oscillation length of the string of a guitar or violin with your finger, certain fundamental modes drop out or are suppressed, and the tone becomes higher again.

If the bacterium now comes into contact with the membrane bubble, fundamental oscillations are increasingly suppressed and only modes with higher frequencies, i.e. shorter oscillation lengths, survive. Since each oscillation mode of the membrane bubble has its own dampening or friction, computer simulations can be used to estimate the summed dampening and amplitude of all surviving modes.

Both the measurements and the [computer simulations](#) showed that the energy required for membrane deformation by the particle until its complete uptake will into the interior of the membrane bubble scales strongly with the stiffness and, above all, the dampening of the membrane motions.

Bacterium penetrates easier into membrane

These mathematical models and the movement measurements with one million particle positions per second can confirm, for example, why bacteria with certain proteins (ligands) on their surface bind more easily to cells with certain membrane receptors.

Most importantly, however, the mathematical models can be used to explain how a stronger fluctuating and less dampened membrane reduces the energy cost and thus increases the likelihood that the bacterium will be taken up, which corresponds to an increased risk of infection of the cell.

More information: Yareni A. Ayala et al, Thermal fluctuations of the lipid membrane determine particle uptake into Giant Unilamellar Vesicles, *Nature Communications* (2023). [DOI: 10.1038/s41467-022-35302-5](#)

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