With light into the nanoworld

How optical microscopes allow detailed investigations of nanoparticles for biosensing

It sounds like trying to scan a vinyl record with a hammer: Light is actually too "coarse" to image small particles on the nanometer scale. However, in their project "Supercol"- funded by the European Union - scientists want to achieve just that: The investigation of nanoparticles with light. To make this possible, they are combining Nobel Prize-winning methods with modern computer processes. The goal: the development of novel nanoparticles for biomedical applications such as biosensing. The results of the SuperCol project will be presented at an event of the European Materials Research Society on June 1st in Strasbourg.

Using a combination of super-resolution microscopy and computer simulations, scientists can now determine the position of molecules on the surface of nanoparticles much more precisely. In the future, this could enable new biomedical applications.

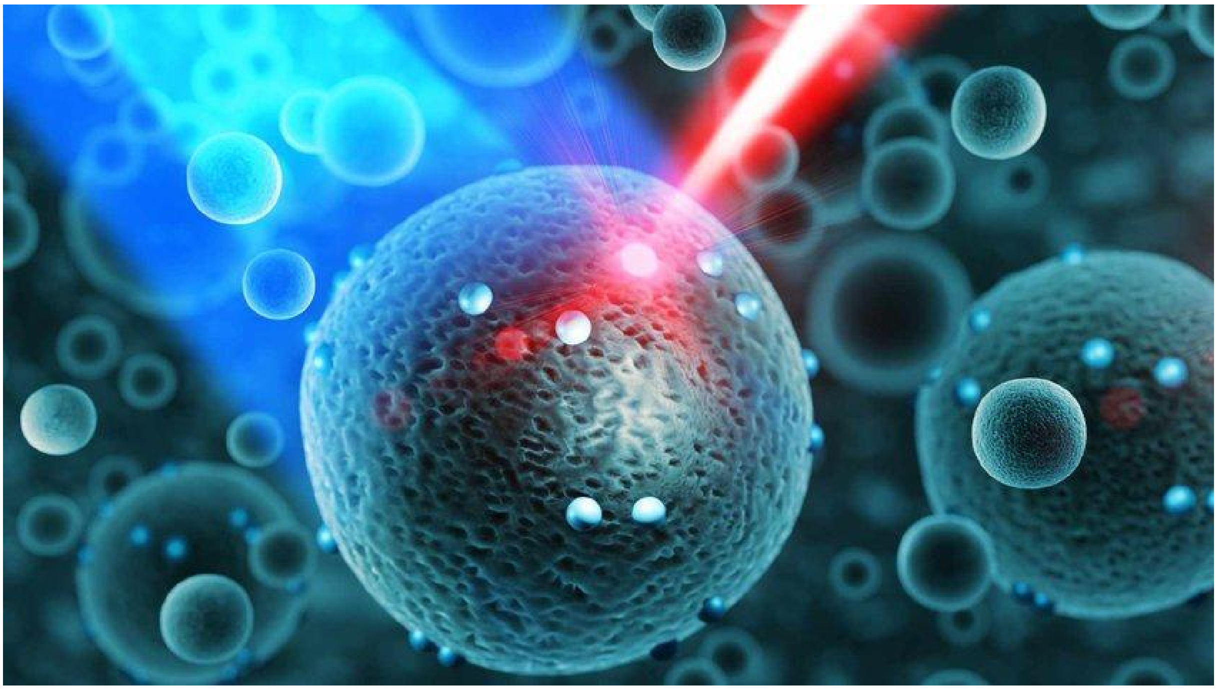

Figure 1 *Using a combination of super-resolution microscopy and electron microscopy, scientists can now determine the position of molecules on the surface of nanoparticles much more precisely. In the future, this could enable new biomedical applications. Copyright MPI-P.*

Nanoparticles - i.e. small particles with a size in the range of a few tens to hundreds of billionths of a meter - are a wide-ranging field of research. For example, they make the latest biomedical applications possible by acting as a kind of container to transport active ingredients to their target. Ideally, their surfaces are "functionalized" - i.e. provided with a molecular puzzle piece, which allows them to dock only to desired target cells in the body.

However, studying such particles and the molecules on their surface is difficult: light is basically too "coarse" to image such particles in a normal light microscope. Visible light in the range from UV to infrared can at most resolve particles with a size of 200 nanometers - 200 billionths of a meter. Too large to determine where, for example, a molecular puzzle piece sits on its surface or to determine their number.

Light emitted from point sources is not optically imaged as a single clearly defined point but more like a spread spot. Thus, common microscopes cannot resolve (and count) individually many nearby light sources, their extended spots overlap. “The situation is like trying to 'not see the forest for the trees', the details (say individual light sources or individual trees) are completely blurred out,” explains Rodrigo Rivas Barbosa, Supercol Fellow, pursuing a Phd at the Physics Department of La Sapienza.

On to higher resolution

Therefore, the researchers used a method that won them the 2014 Nobel Prize in Chemistry: In what is known as "super-resolution microscopy," small fluorescent particles - called fluorophores - are used and, in the case of nanoparticles, attached to molecules on its surface. These fluorophores have the property of blinking statistically in a microscope. Given the stochastic nature of the fluorophores, two very close fluorophores will not blink at the same time, light from the single blinking fluorophore will still be detected as a spreaded spot but it will not be blurred out by other nearby light sources. The position of this blinking signal can be detected much more accurately than would be possible with conventional optical microscopy.

To understand this, it might be easier to think of it like two people standing side by side on a dark mountain, shining their flashlights in your direction. If they are both shining at the same time, it is hard to tell that there are two flashlights. But if the lights are blinking, the difference between them becomes much clearer.

Using computer power to get to the truth

However, the image of the nanoparticle obtained in this way is only half the truth: Nanoparticles have properties that can distort this image - for example resonance phenomena that bring also part of the nanoparticle to glow, and not only the fluorophore. The Sapienza node therefore models similar nanoparticles to the ones studied experimentally within Supercol. Rodrigo, under the supervision of Francesco Sciortino and Emanuela Zaccarelli, uses computer simulations to gain full control over the investigated particles and to obtain a description of the experiments. This information is used as a benchmark, allowing to correct measurement artifacts and to achieve a more accurate description of the nanoparticles and of their assembly.

Biosensing

The researchers now hope to use their method to study nanoparticles in the light microscope, which delivers faster results. This will allow nanoparticles to be studied more precisely and comprehensively in the future, leading to new biomedical applications. One of these applications is biosensing, a technology that has become vitally important in the past years during the pandemic. New biosensors are urgently needed for a wide range of diseases, as is explained in the video below:

https://www.youtube.com/watch?v=fWCyIHWQUSs