

## **Combined technique measures nanostructures 10 times better than before**

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Credit: TU Delft/Thomas Bauer

Researchers at Leiden University and TU Delft have combined two techniques that are used to measure the structure of biomolecules, creating a method that is 10 times more sensitive. With this new method, they hope to be able to better determine the structure of biomolecules. This is important, since a biomolecule's structure often determines its function. The same goes for more complex organic compounds such as



proteins, which can undergo multiple form changes during their life cycle, allowing them to perform different tasks.

Just as your <u>right hand</u> is the mirror image of your left hand, many <u>molecules</u> also have a mirrored version. And even though they look almost the same, a left-handed molecule often works very differently than a right-handed one. A well-known example of this is the drug thalidomide, which was marketed in the early 1960s as a safe sleeping pill, even for pregnant women. The drug consisted of a mix of lefthanded and right-handed variants of the active molecule, but only the left-handed molecule had the desired effect. The right-handed molecule turned out to be toxic, causing thousands of babies to be born with deformed limbs worldwide.

## Mirror image

Molecules that have a mirror image of themselves are called chiral molecules. And because of the difference in biological properties between left- and right-handed molecules, chirality is a phenomenon that is broadly studied in the natural sciences.

An important method to measure whether a molecule is left- or righthanded is <u>circular dichroism</u>. With this technique, researchers focus circularly polarized light that rotates left or right on a sample and then measure how the light is absorbed. Since differently handed molecules absorb light differently, researchers can use this technique to determine the ratio between these molecules in a sample. Using different colors (wavelengths) of light, they can even find out how a protein is folded. This is important since proteins often undergo structural changes during their <u>life cycle</u>, with these changes affecting their behavior.

## **Better signal**



The problem with circular dichroism is that the resulting signal is usually very weak. "This means you need a lot of time to collect your signal," explains TU Delft researcher Martin Caldarola. "You can compare it a to the shutter speed of a camera. The longer the shutter speed, the more light gets to the detector. Thus, dimmer objects can be seen." Increasing the number of molecules or proteins in a sample would also lead to a better signal. But in some cases that is very difficult to achieve.

The Leiden and Delft researchers have now combined circular dichroism with another existing technique, called photothermal imaging. This method can be used to measure how many photons a molecule absorbs. The experimental efforts of Michel Orrit's group at Leiden University led to the first working setup. An improved version that allows the researchers to take the next steps in the project was realized at TU Delft. "By combining circular dichroism with photothermal imaging, we achieved a sensitivity that is 10 times higher than with circular dichroism alone," says Caldarola. To prove that the method works, the researchers made left-handed and right-handed copies of a golden nanostructure that worked as an artificial molecule. They then successfully measured the handedness of these nanostructures.

The researchers' ultimate dream is to be able to detect the chirality of a single biomolecule. The great advantage of circular dichroism is that you are not dependent on the fluorescent labels that researchers now often attach to their molecules in order to follow them. "These labels work well, but they only work for a limited amount of time. After that, your experiment is over," says Caldarola. "In theory, our method should allow us to measure biological processes for as long as we want."

There is still much to be done before that becomes a reality, though. "Unfortunately, we are not yet able to detect single molecules," says Caldarola. "To do this, we need to improve the sensitivity by a factor of about a thousand. Sounds impossible? Maybe it isn't. "We already have



ways in mind to make the technique one hundred times more sensitive. From there it's only a small step."

**More information:** Patrick Spaeth et al. Circular Dichroism Measurement of Single Metal Nanoparticles Using Photothermal Imaging, *Nano Letters* (2019). <u>DOI: 10.1021/acs.nanolett.9b03853</u>

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