Eavesdropping on single molecules with light by replaying the chatter

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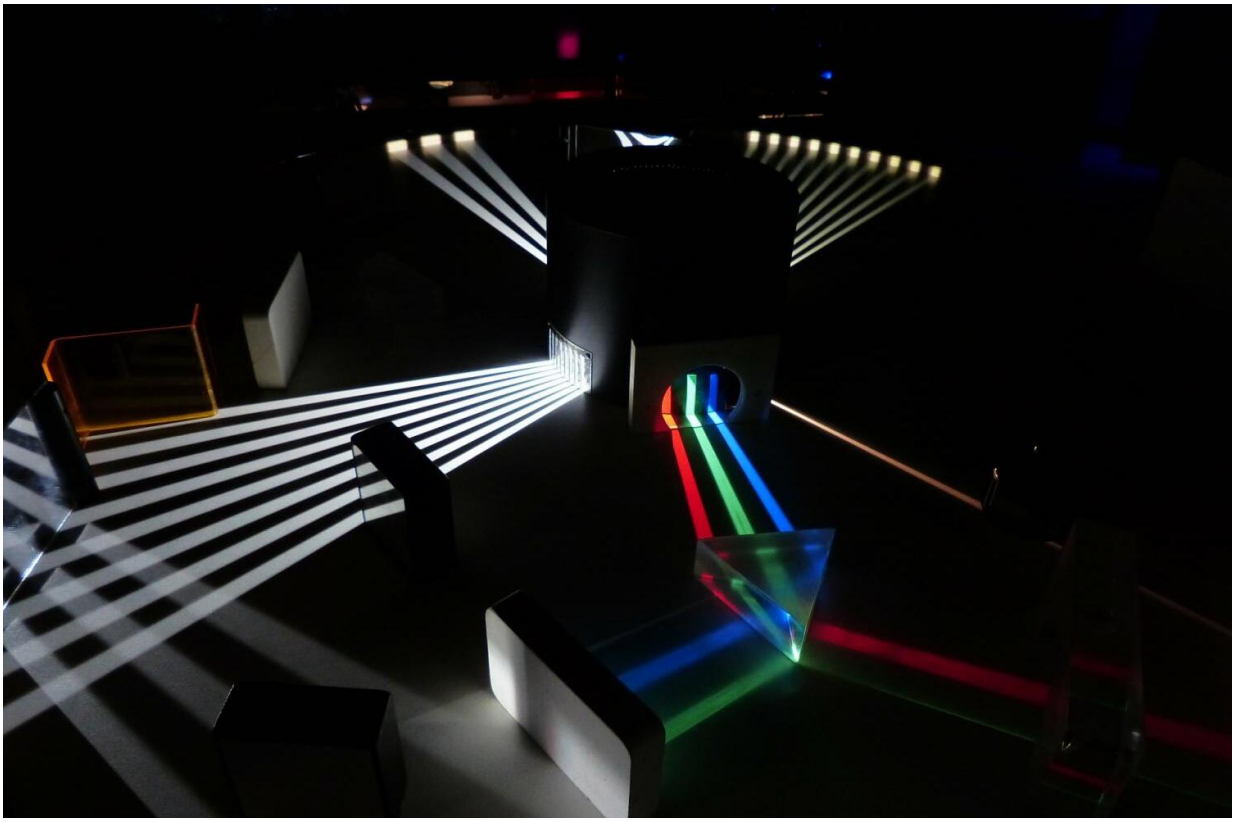

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Scientists have pioneered a new technique to expose hidden biochemical pathways involving single molecules at the nanoscale.

A team of researchers from the University of Exeter's Living Systems Institute used light to establish a means to monitor the structure and properties of individual molecules in real time.

This innovative approach has allowed the team to temporarily bridge molecules together to provide a crucial lens into their dynamics.

The study is published in the leading journal *Nature Communications*.

The structure of individual molecules and their properties, such as chirality, is difficult to probe.

In the new study, led by Professor Frank Vollmer, the group was able to observe reactions at the nanoscale which would otherwise be inaccessible.

Thiol/disulfide exchange—or the principal way disulfide bonds are formed and rearranged in a protein—has not yet been fully scrutinised at equilibrium at the single-molecule level, in part because this cannot be optically resolved in bulk samples.

However, light can circulate around micron-sized glass spheres to form resonances. The trapped light can then repeatedly interact with its surrounding environment. By attaching gold nanoparticles to the sphere, light is enhanced and spatially confined down to the size of viruses and amino acids.

The resulting optoplasmonic coupling allows for the detection of biomolecules that approach the nanoparticles while they attach to the gold, detach, and interact in a variety of ways.

Despite the sensitivity of this technique, there is lacking specificity. Molecules as simple as atomic ions can be detected and certain dynamics

can be discerned, yet we cannot necessarily discriminate them.

Serge Vincent remarks: "It took some time before we could narrow down how to reliably sample individual molecules. Forward and backward reaction rates at equilibrium are counterbalanced and, to certain extent, we sought to lift the veil over these subtle dynamics."

Reaction pathways regulated by disulfide bonds can constrain interactions to single thiol sensing sites on the nanoparticles. The high fidelity of this approach establishes precise probing of the characteristics of molecules undergoing the reaction.

By placing linkers on the gold surface, interactions with thiolated species are isolated for based on their charge and the cycling itself.

Sensor signals have clear patterns related to whether reducing agent is present. If it is, the signal oscillates in a controlled way, while if it is not, the oscillations become stochastic.

For each reaction the monomer or dimer state of the leaving group can be resolved.

Surprisingly, the optoplasmonic resonance shifts in frequency and/or changes in linewidth when single molecules interact with it. In many cases this result suggests a plasmon-vibrational coupling that could help identify individual molecules, finally achieving characterisation.

Professor Frank Vollmer said: "This excellent work by my Ph.D. student, Serge Vincent, paves the way for many future single-molecule analysis techniques that we have only been dreaming about. It is a crucial step for our project ULTRACHIRAL. ULTRACHIRAL seeks to develop breakthroughs in how we use light to analyse chiral molecules."

More information: Serge Vincent et al, Optoplasmonic characterisation of reversible disulfide interactions at single thiol sites in the attomolar regime, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15822-8

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