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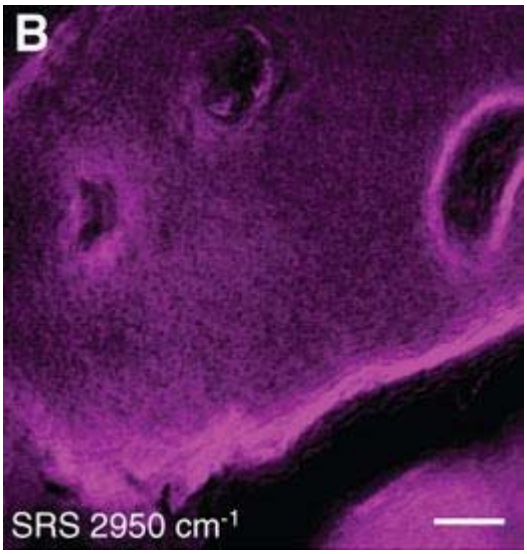
News

# Video microscopy reveals molecules in motion

**Technique tracks chemicals in living tissues without the need for fluorescent labels.**

Heidi Ledford

A microscope capable of imaging 'naked' molecules — without linking them to bulky fluorescent probes — has had an upgrade and can now gather images at high speed. The technique can be used to create videos of molecular motion in living animals (see videos of **a mouse's sebaceous gland** and **real-time blood flow**), and could one day transform medical imaging, for example by allowing surgeons to see specific molecules in tumours as they operate.

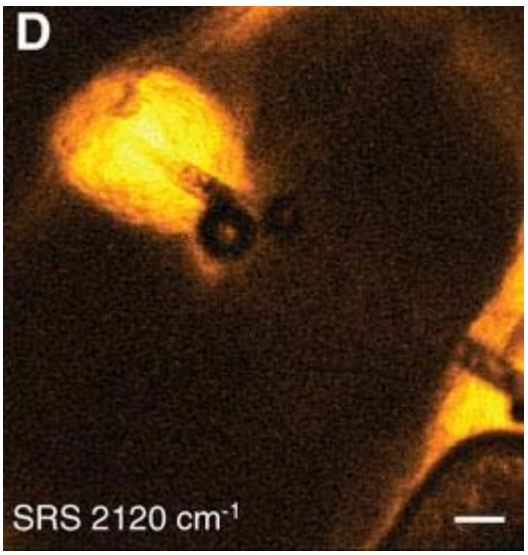



In living skin (shown) and other tissue, an advance in SRS microscopy allows molecular motion to be detected.

*Science/AAAS*

Called stimulated Raman scattering (SRS) microscopy, the technique is the culmination of more than a decade of work in Sunney Xie's chemistry lab at Harvard University in Cambridge, Massachusetts. The advance is reported today in the journal *Science*[1].

SRS microscopy detects molecules through the characteristic vibrations of their chemical bonds. The microscopes excite a target using two laser beams, carefully tuned so that the difference in the frequency of their light matches the vibrational frequency of the molecule of interest[2].




As the technique can image deuterated dimethyl sulfoxide penetrating living skin (shown), it might be used to monitor the entry of drugs into tissues or tumours.

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The shift in wavelength caused when chemical bonds in the molecule scatter the light can be used to track the target without resorting to the fluorescent labels often required for other types of microscopy. Although such labels allow more versatile and specific imaging than SRS — which cannot distinguish one protein from another, for example — they also tend to be bulky, and can interfere with the normal movement and function of biological molecules. That is not a problem with SRS.

But previous incarnations of SRS were limited by slow imaging times. With a rate of about 45 seconds per image, they were much too slow to image a live animal, says Christian Freudiger, a graduate student in Xie's laboratory and joint first author of the latest paper. Even an immobilized animal would move too much for the technique to provide a clear image.

### The need for speed

Xie's researchers decided to take matters into their own hands. Graduate student Brian Saar, now at the Massachusetts Institute of Technology Lincoln Laboratory in Lexington and the other joint first author, built a new amplifier that enabled the microscope to take 25 images per second.

The team also adjusted the instrument's light detector so that it was better able to detect scattered light, allowing the microscope to image thick samples. "If you look at your hand, you can't see through it — not because light is being absorbed, but because it is being redirected," says Freudiger. "If you want to look at thick samples, you can't image in transmission because the sample is simply too big." SRS microscopy offers a way to look at skin samples without needing light to pass through them.



The improvements are "impressive", says Andy Downes, a biomedical engineering fellow at the University of Edinburgh, UK, who works with similar microscopy techniques. He notes that the new microscope detects at least ten times more back-scattered light than with the SRS instrument reported by Xie's team in *Science* two years ago[2].

The increased sensitivity means that the technique could be used to monitor how well drugs penetrate into tissues and tumours. "It brings the label-free imaging of drugs closer," says Downes.

Freudiger says that his team is now working with Eric Seibel, a bioengineer at the University of Washington in Seattle, to miniaturize the set-up using fibre optics. They have already developed a prototype that is a centimetre wide, or roughly the size of a pen, says Freudiger, who is now consulting with neurosurgeons to learn more about how the microscope could be useful during surgery. "We're hoping we can even push it to a millimetre wide," he adds.

### References

1. Saar, B.G. *et al. Science* **330,** 1368-1370 (2010). | **Article** | **OpenURL**
2. Freudiger, C.W. *et al. Science* **322,** 1857-1861 (2008). | **Article** | **OpenURL**

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