Docket #: S26-054

Interferometric Image Scanning Microscopy for Label-Free High-Resolution Imaging of Live Cells

Scientists at Stanford have developed a novel imaging approach that enables high-resolution, label-free visualization of subcellular structures in living cells.

Current microscopy approaches for label-free imaging of subcellular structures in live cells are restricted by the diffraction limit (which limits spatial resolution), sensitivity and poor image contrast for nanometer size objects. Existing super-resolution microscopy techniques can overcome these challenges, but they require fluorescent labels, specialized sample preparation and high light intensities which may damage biological samples.

The Moerner lab at Stanford has developed an interferometric image scanning microscopy (iISM) system that combines image scanning with interferometric detection of light scattered by intracellular structures to enable label-free, high-resolution imaging of subcellular structures in living cells. The approach builds on a laser scanning microscope architecture that is compatible with existing commercial confocal microscope platforms. This technology has broad implications for cell biology and drug development by enabling minimally perturbative, high-resolution imaging of dynamic processes in living systems.

Stage of Development: *prototype/proof of principle*

Applications

- Imaging of samples that are sensitive to photobleaching, require high spatial resolution, or are not suitable for use with fluorophores/dyes
- Applicable to live-cell imaging and intracellular nanoparticle tracking/localization

Advantages

- Uses laser scanning microscope architecture that is compatible with commercial confocal instruments
- Enables imaging of intracellular structures in living cells with reported lateral resolution on the order of ~120 nm
- Provides improved contrast and resolution relative to conventional confocal/ISM for scattering specimens by exploiting interferometric detection and phase accounted reconstruction
- Reduces phototoxicity and sample perturbation compared to fluorescence-based super-resolution approaches

Publications

- Liang, Q., Ren, W., & Xi, P. "Interferometric image scanning microscopy enables label-free super-resolution imaging of live cells." *Light: Science & Applications*, vol. 15, article 248, 2026.
- Michelle Küppers and W. E. Moerner (2026). Interferometric Image Scanning Microscopy for label-free imaging at 120 nm lateral resolution inside live cells. Light: Science & Applications, 15, 129.

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