The concentration of the MRI contrast agent is proportional to the signal intensity of the T1-weighted sequences, whereas gradient echo is fast and can detect temperature elevations. They assessed tissue damage resulting from the ultrasound by histological examination of the mouse brains.

The researchers opened the barrier at a minimum pressure of 0.6 MPa and did not detect tissue hemorrhage at this pressure. At 0.8 MPa, blood cells leaked in small, scattered areas.

In eight of nine of the control mice, the amount of Herceptin that entered the brain was below the limit of detection. However, 1032 ng/g of tissue entered the brain in one of the control mice because of experimental uncertainty and biological variation. Using ultrasound at 0.6 MPa and 0.8 MPa, 1504 and 3257 ng of the drug per gram of tissue entered the brain, respectively.

The researchers believe that they can translate this method to human treatment. They previously evinced that a focused array can safely disrupt the barrier in humans, and they believe that they can use this technique to deliver other antibodies to the brain, such as those against β-amyloid, which some evidence suggests may cure Alzheimer's disease. □

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## MEMS-based scanning device facilitates microendoscopy

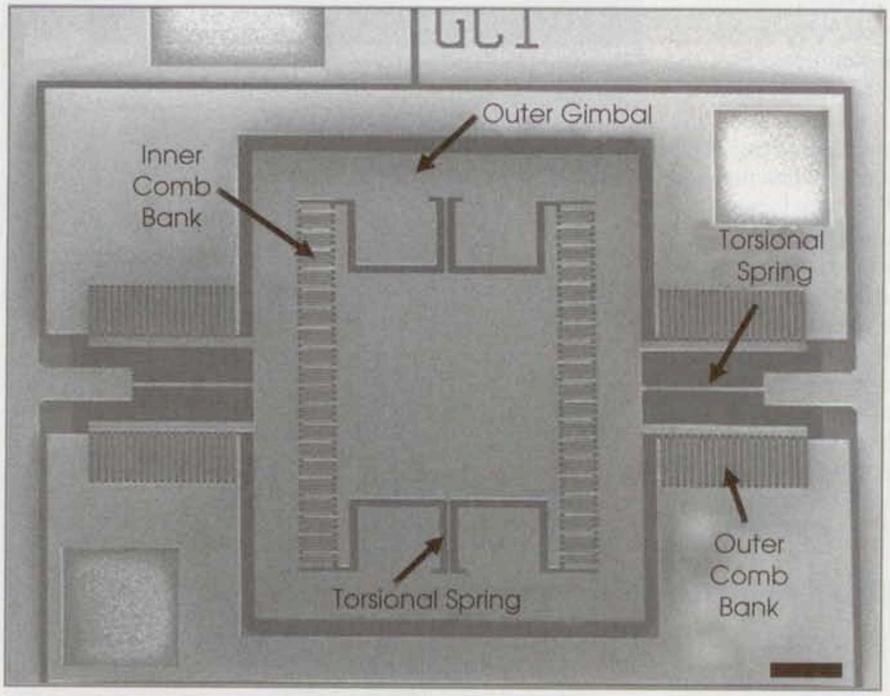
Line-scanning rates of up to 1 kHz are important for imaging fast biological processes such as blood flow and neuronal activity. However, conventional scanning mechanisms that offer fast acquisition rates, including galvanometer, spinning polygon and acousto-optic scanners, cannot readily be miniaturized for incorporation into microendoscopes for minimally invasive imaging procedures.

Most miniaturized scanners explored for confocal and two-photon fluorescence imaging have been cantilever mechanisms, such as a vibrating optical fiber mounted on a piezoelectric actuator. Although inexpensive to fabricate, these mechanisms offer limited scanning rates, are not easily mass-produced and cannot be reduced to millimeter sizes.

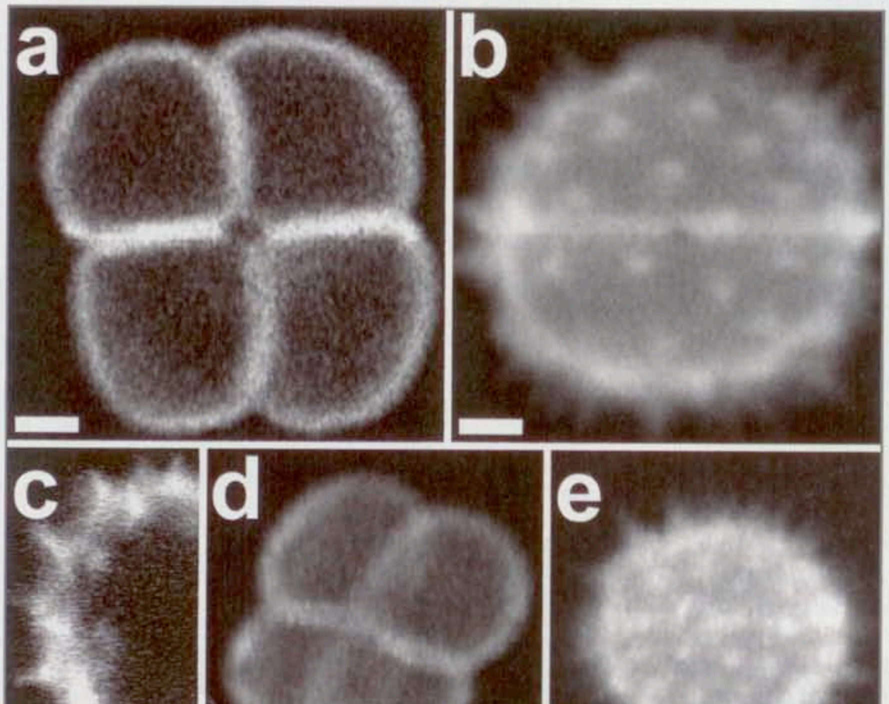
Now, a team of optical scientists and engineers led by Mark J. Schnitzer, Olav Solgaard and Wibool Piyawattanametha at Stanford University in California has developed a device that is based on microelectromechanical systems (MEMS) scanners and that achieves adjustable, fast-axis acquisition rates of up to 3.52 kHz.

Using reactive ion etching methods, the researchers fabricated 750 × 750-μm single-crystalline silicon scanning mirrors on a double silicon-on-insulator wafer. Six banks of electrostatic vertical comb actuators and a gimbal design enabled rotation of the scanning mirror in two dimensions with minimal crosstalk (Figure 1). The mirror, movable comb teeth and inner torsional springs were fabricated in the upper device layer, and the frame, fixed comb teeth and outer torsional springs were fabricated within both the upper and lower layers, each measuring 30 μm thick.

The layer thickness is important because it affects the performance of the MEMS scanner; thicker mirrors can reduce




*An electron micrograph shows the key components of a two-dimensional MEMS scanner developed for two-photon microscopy and microendoscopy applications. Images reprinted with permission of* Optics Letters.




*Two-photon fluorescence images of pollen grains were captured using instrumentation incorporating the MEMS scanning mirror. Images were acquired using a microscope objective (a-c) or a GRIN microendoscope probe (d,e).*

flexure of the mirror when scanning it at high speeds, and the pronounced thickness of the comb teeth raises the electrostatic torque that can be applied to the mirror, increasing its angular range to up to 16°.

To test the feasibility of optical imaging based on MEMS, the scientists constructed a two-photon microscope that employed their scanner. A Spectra-Physics Ti:sapphire laser provided an 850-nm excitation beam with a pulse width of 100 to 150 fs and a repetition rate of 80 MHz. The beam passed through two lenses that decreased its diameter before reflecting off the scanner, then expanded and passed through a dichroic mirror until it filled the back aperture of the microscope objective. Fluorescence was detected with a Hamamatsu photomultiplier tube. The instrumentation can be additionally equipped with a compound gradient refractive index (GRIN) microendoscope probe, placed after the objective lens, for microendoscopy applications.

Using two-photon microscopy and microendoscopy, the team captured images of pollen grains with micron-scale detail (Figure 2). Acquiring data on both the forward and return scanning paths enabled acquisition rates of up to 3.52 kHz.

Given the measured ranges of the two axes and 850-nm excitation, the number ($N$) of distinguishable focal spots for any imaging system based on the researchers' MEMS scanner is ~250 × 90. The largest field of view that can be obtained without sacrificing imaging resolution ($R$) is about $N \times R$. Given the highest lateral resolution demonstrated for GRIN endoscope probes, ~1 µm, the MEMS scanner offers a maximum field of view of 250 × 90 µm. For typical microscopy applications in which $R = \sim 0.5$ µm, fields of view of ~125 × 45 µm are obtainable.

The value of $N$ for the MEMS scanning mirror is smaller than that of galvanometer mirrors and other scanning mechanisms. Modest gains in $N$ might be achieved by increasing the maximum scanning angle or the diameter of the mirror, but the latter option would decrease the mirror's scanning speed. The researchers are working on incorporating the MEMS scanner into a miniaturized fiber optic instrument to be used for portable two-photon microendoscopy. □

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