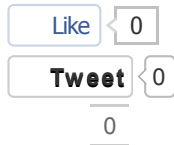


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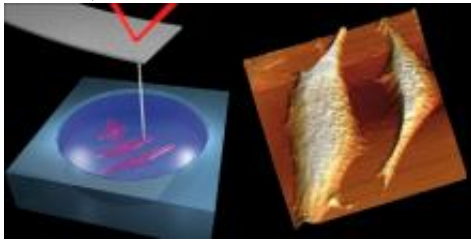
You are here: [Home](#) > [Science Overview](#) > [Scanning Probe Microscopy](#) > "Trolling"-Mode Atomic Force Microscopy

## "Trolling"-Mode Atomic Force Microscopy

### High-Resolution Imaging of Single Cells



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Imaging biological materials is one of the main branches of biomedical engineering. Particularly, imaging living cells at the single-cell level is highly important for fundamental understanding of cell behavior and its interaction with the extracellular matrix. The resolution of commonly used optical microscopy is limited by diffraction of light to ~200 nm. However, the major elements of the cell membrane such as transmembrane proteins, ion channels, cell adhesion proteins etc. are essentially nanostructures, which cannot be resolved with optical microscopy.

### Imaging Soft Surfaces in Liquids

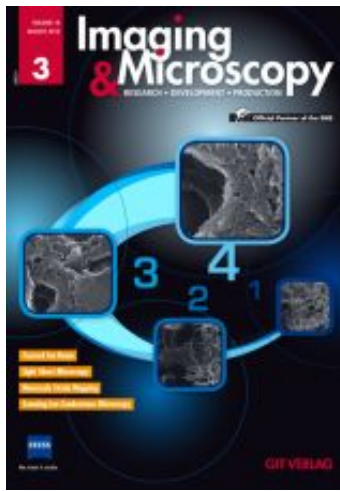
Atomic force microscope (AFM), introduced more than two decades ago, has reached angstrom resolution imaging in vacuum and in air. However, the resolution of AFM in liquid, particularly in imaging soft samples such as living cells has suffered. The main complication is the reduced sensitivity of the AFM cantilever in liquid due to large hydrodynamic drag between the oscillating micro-scale cantilever and the viscous liquid media. This reduced sensitivity expressed in terms of quality factor (Q-factor) of oscillations, drops by more than two orders of magnitude in air  $Q \sim 200-500$  to  $Q \sim 1$  in liquid. The force applied on the sample during AFM imaging has an inverse relationship with the Q-factor, (Formel 1). Although the applied force does not appear when imaging stiffer samples such as DNA, or supported membrane on a rigid surface, however, it manifests itself when imaging soft samples such as living cells. In the majority of the AFM images of living cells in the literature, the membrane is excessively deformed under the large applied force and the underlying cytoskeleton such as microtubules or actin filaments appear in the image, which is not the main purpose of live cell imaging.

### Active Q-control Increases Thermal Noise of the Cantilever

The commonly used active Q-control has not achieved much success in imaging soft samples such as cell membrane. Using external electronics, Q-control technique changes the apparent damping in the oscillating cantilever. However, this apparent boost in the Q-factor, essentially increases the thermal noise in the system leading to unchanged signal-to-noise ratio [1].

### Enhancing Cantilever Oscillation

We introduced the "Trolling"-mode AFM where the Q-factor of the cantilever oscillation is "intrinsically" enhanced by several orders of magnitude [2].



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This method does not need external add-on electronics and is essentially compatible with any type of AFM. Figure 1a shows the schematics of the "Trolling" mode AFM. There are two main components to this technique. The first one is an extended nanoneedle-probe (fig. 1b), and the second one is the shallow-level culture liquid. The extended nanoneedle-probe comprised of a long metallic nanowire grown directly on a regular AFM cantilever. The growth was done using the direct electrodeposition method [3]. The metallic nanowire could be grown longer than 100  $\mu\text{m}$  and with a diameter as low as 100 nm. The cells or other biological samples to be imaged are cultured or deposited in a culture dish with a medium level smaller than the length of the extended nanowire. As such, the bulky AFM cantilever stays outside of the media and only the extended nanowire is submerged into the liquid to image the sample. For high-resolution imaging, the tip of the nanowire is sharpened down to  $\sim 20\text{-}30$  nm in radius by using several seconds of ion beam milling (fig. 1b, inset). Since cantilever holder keeps AFM cantilever in  $\sim 12^\circ$  with the respect to the horizontal line, to ensure the nanoneedle enters the liquid vertically for imaging, the nanowire was deposited  $12^\circ$  inclined on the cantilever.

Figure 2 shows the performance of the method in terms of expected quality factor and dynamic response. Figure 2a shows the theoretical dependence of the quality factor on the nanowire diameter and immersion length into the liquid. The main damping associated with the nanowire-probe in liquid are the Stokes drag on the oscillating nanowire, and the energy dissipation associated with the nanomeniscus in the nanowire and liquid surface interface [2]. Both of the dissipations reduce with decreasing the diameter of the nanowire and reducing the depth of the shallow liquid medium. In principle, a Q-factor as high as 300 could be achieved in liquid without the need for external electronics such as Q-control. This is comparable to the quality factor obtained for operation of AFM in air ( $Q \sim 200\text{-}500$ ). Figure 2b shows experimentally obtained dynamic response of a probe with 600 nm in diameter for various immersion lengths into water. First observation is that only one peak appears in the dynamic response with minimal frequency shift respect to the natural frequency in air. Whereas in tapping mode imaging in liquid, dynamic response of the probe often shows many spurious peaks shifted to lower frequencies compared to the air natural frequency. For this 600 nm in diameter probe, Q-factor of 100 was obtained experimentally.

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