

MAR08-2007-001380

Abstract for an Invited Paper  
for the MAR08 Meeting of  
the American Physical Society

### **High-speed AFM for Studying Dynamic Biomolecular Processes<sup>1</sup>**

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Biological molecules show their vital activities only in aqueous solutions. It had been one of dreams in biological sciences to directly observe biological macromolecules (protein, DNA) at work under a physiological condition because such observation is straightforward to understanding their dynamic behaviors and functional mechanisms. Optical microscopy has no sufficient spatial resolution and electron microscopy is not applicable to in-liquid samples. Atomic force microscopy (AFM) can visualize molecules in liquids at high resolution but its imaging rate was too low to capture dynamic biological processes. This slow imaging rate is because AFM employs mechanical probes (cantilevers) and mechanical scanners to detect the sample height at each pixel. It is quite difficult to quickly move a mechanical device of macroscopic size with sub-nanometer accuracy without producing unwanted vibrations. It is also difficult to maintain the delicate contact between a probe tip and fragile samples. Two key techniques are required to realize high-speed AFM for biological research; fast feedback control to maintain a weak tip-sample interaction force and a technique to suppress mechanical vibrations of the scanner. Various efforts have been carried out in the past decade to materialize high-speed AFM. The current high-speed AFM can capture images on video at 30-60 frames/s for a scan range of 250nm and 100 scan lines, without significantly disturbing weak biomolecular interaction. Our recent studies demonstrated that this new microscope can reveal biomolecular processes such as myosin V walking along actin tracks and association/dissociation dynamics of chaperonin GroEL-GroES that occurs in a negatively cooperative manner. The capacity of nanometer-scale visualization of dynamic processes in liquids will innovate on biological research. In addition, it will open a new way to study dynamic chemical/physical processes of various phenomena that occur at the liquid-solid interfaces.

<sup>1</sup>This work was supported by CREST/JST.