This page is for a novel commercial product produced by a company RIBM based on the Biophysical instrument developed by researchers

High-speed Atomic Force Microscope

Toshio Ando, Noriyuki Kodera & Takayuki Uchihashi (Dept. of Physics, Kanazawa Univ.)

We long have had to infer how proteins function from the static snapshots of their structure and the dynamic behavior of optical makers attached to the molecules. Therefore, directly observing protein molecules in dynamic action at high spatiotemporal resolution has long been a holy grail for biological science. To make this long quested dream real, Ando embarked on the development of a high-speed atomic force microscope (HS-AFM) in 1993. AFM is a unique imaging tool that enables high resolution visualization of objects made of any material in any environment. However, it takes at least 30 s (usually minutes) to capture an image.

In the early stage, we focused on developing a fast scanner, a fast amplitude detector, small cantilevers with high resonant frequencies and small spring constants, and an optical beam deflection detector for the small cantilevers. The first prototypic HS-AFM setup built in 2001 [1] was tested for myosin V but found to be insufficient in both speed and low- invasive performances. Then, we developed active damping techniques to suppress the scanner's unwanted vibrations as well as to increase its response speed. Moreover, we devised a new feedback control scheme to make high-speed imaging compatible with low-invasive imaging. Through these long efforts, the HS-AFM of practical use was built at last in 2008 [2].

The feedback bandwidth has now reached ~100 kHz, and therefore, biological molecules can be imaged at ~12 frames/s (fps) or faster, without their function being disturbed. It is now rather becoming common to film dynamic processes of protein molecules by HS-AFM to find how the proteins act to function (see Review [3]). For example, bacteriorhodopsin showing photo-induced structural changes [4], myosin V walking on actin filaments [5], F_1-ATPase exhibiting rotary propagation of conformational changes [6] have been visualized with unprecedented clearness (Fig. 1). These video images newly uncovered molecular actions, bringing greater insights into their functional mechanism.

Reference

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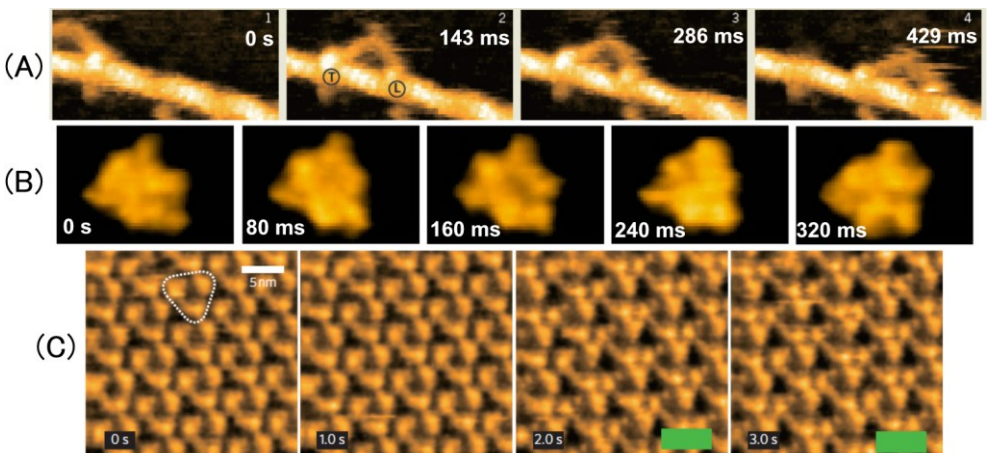

Fig. 1. Protein molecules in dynamic action captured by HS-AFM. (A) myosin V walking on an actin filament, (B) F_1-ATPase with rotating conformational changes, (C) bacteriorhodopsin responding to light. Imaging rate: 7 fps (A), 12.5 fps (B), 1 fps (C).

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NanoExplore™ (NEX)

Takao Okada, Norito Kotani & Takashi Morii (Research Institute of Biomolecule Metrology Co., Ltd.)

Noticing the potential of high-speed AFM and aiming at its commercialization, RIBM has been collaborating with Ando's lab of Kanazawa University since ten years ago. In cooperation with five oversea Universities, Ando's lab founded the international consortium on High-speed bio-AFM. RIBM joined this consortium by producing and supplying the prototypic high-speed AFM to the oversea members. Through these activities, RIBM learned techniques constituting the instrument, accumulated know-hows of producing them and also explored applications of HS-AFM. RIBM turned Ando's high-speed AFM into a commercial product, as NanoExplorer (NEX). Since 2011, we have been manufacturing and selling the product to domestic and oversea research institutes and providing the customers with support services.

In the world market, NEX is one of two commercial products that allow video capturing biomolecules in physiological solution. Its highest imaging rate is 0.05 sec per frame. As a side effect of this high-speed performance, NEX is less susceptible to floor vibrations and mechanical drift. Moreover, the effect of system parameter changes appears immediately on the acquired image, easing the system operation. Also in this regards, NEX is superior to conventional AFM.

The market of conventional AFM has been maturing, resulting in intense price competition and shrinking market. Under such circumstances, NEX that has brought a qualitative change from still to video imaging is now creating a new growing market. In fact, NEX has already been sold to a number of domestic and oversea institutions. The overseas countries include Australia, Canada, France, Netherlands, Switzerland, United States and others. There are overseas laboratories that have purchased

Fig. 2. High-speed AFM NanoExplore™

multiple units of NEX after recognizing its value. In addition, not only from United States and Europe, there are continuing inquiries also from countries in Middle East and Asia. Thus, further expansion of sales to overseas is expected.

The customer laboratories are using NEX to study dynamics of, for example, a variety of membrane proteins, membrane scission proteins, interaction of antigen-antibody, self-assembly of amyloid fibrils and membrane pore-forming proteins, interaction between DNA and DNA-related enzymes, opening and closing of ion channels and transport in nuclear pore. Also, some customers are using NEX to observe dynamics occurring in live cells including neurons. Other than NEX, there are no products allowing these studies and therefore, further expansion of NEX users is certain.

In 2015, RIMB started selling PS-NEX that scans the cantilever chip, rather than scanning the sample stage. PS-NEX can use large and heavy samples and be combined with fluorescent microscopes. From this capability it is expected that PS-NEX will contribute not only to basic research of biomolecules but also to life science in general as well as material sciences.

Biophysics has been advancing through creating and using new measurement techniques. RIBM hopes to be of more help in progress of Biophysics.