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High-Resolution Imaging of Human Chromosomes Using Atomic Force Microscope

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We have integrated an atomic force microscope (AFM) with a conventional optical microscope into a system to study the structures of human chromosomes (Fig.1). This integrated system is very convenient for locating objects of interest in the AFM imaging processes. In addition, the system has the capability of directly comparing the chromosome images taken by AFM with those taken by the optical microscope. Though human chromosomes have been extensively studied by other microscopic techniques, such as optical microscopy and electron microscopy, each technique has its disadvantages. The optical microscope has only low power of resolution (around 1 micron), while the electron microscope requires elaborate procedures which may destroy natural states of the sample. It is considered that the structures reflect biochemical characters. Therefore, to understand the nature states of chromosome structures is very important.

The AFM, on the contrary, requires only minimum sample treatment and can give three dimensional surface configurations. It also reveals the chromosome structures at a high resolution around 50nm. However, in general, sample damage is a serious problem by using AFM to study the biological systems. We have tried out tips with four different force constants. The tips with 0.064 N/m force constant were finally selected because they gave better image resolution. In addition, the structures of the chromosomes were quite stable during scanning processes and good quality images can be easily reproduced.

There are four major findings in this study. First, chromosomes are observed with elastic properties, e.g., the images obtained depend greatly on the force applied by the tips. Secondly, AFM

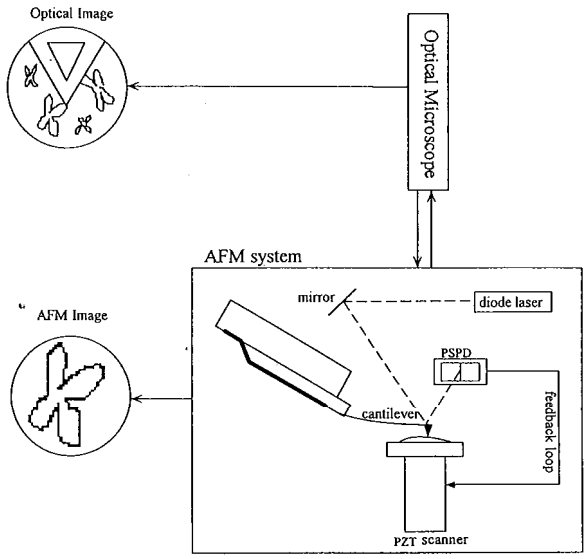

Fig. 1. Illustration showing the integrated optical microscope and the AFM system. From the optical microscope, an image of low resolution is taken. It also provides a sideway to look at the scanning processes. A high-resolution image is obtained by the AFM system.

images reveal the ends of loops of 30nm chromatin fibers, where the fiber reaches the surface and folds back into the body of the chromosome (Fig.2 (A.B)). These results confirm earlier electron microscope observations (Harrison et al. 1981, Adoph et al. 1983). Thirdly, there is a one to one correspondence between the height variations in the AFM image and the banding patterns observed after stained with Giemsa in the optical image. Finally, images of the bivalents isolated from sper-

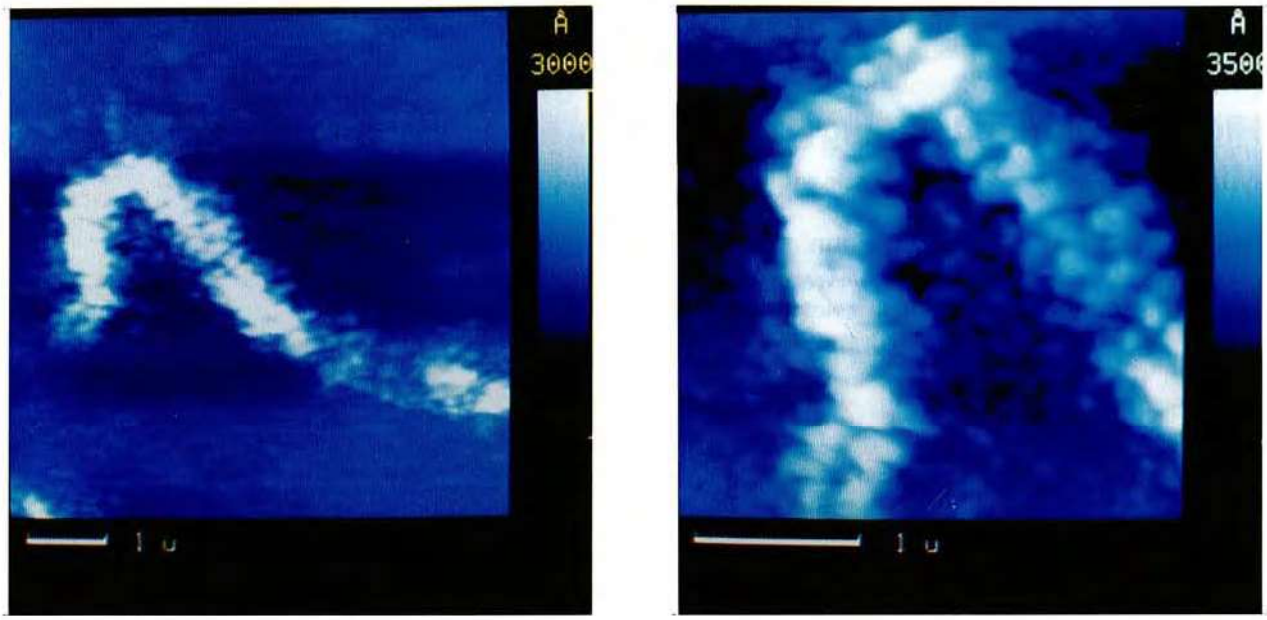

Fig. 2A. A typical AFM image of a human chromosome, with scan size 6.3 × 6.3 μm. **Fig. 2B.** The arc part of the same chromosome with scan size 3 × 3 μm. In these high-resolution images (resolution around 10nm), subunits with sizes in the range between 50nm to 100nm are predominant.

matocytes have shown twisted chromosome configurations which are not apparent in the optical image.

In conclusion, we have demonstrated that AFM is a useful and reliable tool for chromosome studies. This research is partly supported by National Science Council in Taiwan, R.O.C.

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