REVIEW ARTICLES

# Development of novel and sensitive sensors based on microcantilever of atomic force microscope*

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**Abstract** Recently, the development of sensors based on microfabricated cantilevers of atomic force microscope (AFM) has attracted considerable attention from the designers of novel physical, chemical, and biological sensors. Many kinds of sensors have been developed taking the advantages of its high-resolution imaging, force measurement and force sensitivity, such as immunosensor and DNA biosensor and the sensors for detection of intermolecular interaction. This paper reviews the progress made in this field and discusses the signal transfer principles by which the design of the sensors is achieved.

**Keywords:** atomic force microscopy, microcantilever, sensor.

It is a challenge in sensor research to develop kinds of chemical sensors and biosensors with high selectivity, high sensitivity, good reproducibility and quick response. Microfabricated cantilevers have recently attracted considerable attention in the development of a wide range of novel physical, chemical, and biological sensors[1,2].

An atomic force microscope (AFM) is developed on the basis of a scanning tunnelling microscope, which can not only obtain surface topography at nanometer size and molecular level, but also measure intermolecular forces as low as the piconewton range. So AFM is becoming a rapidly developing technique, especially in biological science research. The AFM uses a cantilever, usually made from silicon or silicon nitride, with a very low spring constant, at the end of which a sharp tip is fabricated using semi-conductor processing techniques. When the tip is brought close to a sample surface, the forces between the tip and sample cause the cantilever to bend and this motion can be detected optically by the deflection of a laser beam which is reflected off the back of the cantilever. If the tip is scanned over the sample surface, the deflection of the cantilever can be recorded as an image, which in its simplest form represents the three-dimensional shape of the sample surface. The core of AFM is the force sensor, including microcantilever and tip.

Novel sensors based on AFM microcantilever mainly take advantages of its high-resolution imaging, force measurement and force sensitivity. With its high resolution, immunosensor and DNA biosensor have been developed by detecting the changes of surface coverage and height of samples; with the potential of AFM force measurement, kinds of novel microcantilever force sensors were developed to study intermolecular interactions; and by transformation of the force signals to nanomechanic response of the AFM cantilever, kinds of the sensors were also designed by virtue of cantilever sensitivity to very low force. This paper reviews the progress made in this field, and the signal transfer principle by which the sensor design achieved is discussed.

## 1 Novel AFM microcantilever sensor based on the topography difference

The ability for AFM to image sample at high spatial resolution can sensitively detect minute height difference or variation in surface roughness before and after analyte is injected. Therefore sensors can be designed by their topographic difference, which can be

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used to perform quantitative and qualitative analyses.

### 1.1 Height difference

Combining the height difference of biomolecules before and after interaction with a compositionally patterned array, an approach has been proposed to study interactions of biomolecules by investigating the change of height, such as immunoassays[3—6] and interaction of DNA with protein[7,8]. It is simple and direct.

Jones et al.[3] demonstrated the utility of combining the topographic imaging capability of AFM with the compositionally patterned array of rabbit IgG as an approach to perform immunoassays (Fig. 1). An internal reference plane for the detection of topographic changes is needed to perform height-based molecular recognition. Using the microarray technique, analytes are selectively immobilized on the active surface and the intert surface is used as reference plane for the detection of the topographic increase when a complementary antibody/antigen pair is formed. Immunoassay is performed by using rabbit IgG as an immobilized antigen and goat anti-rabbit IgG as a complementary antibody.

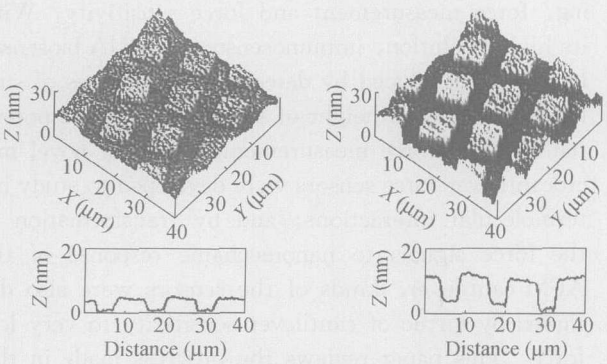

Fig. 1. Height-based immunoassay.

### 1.2 Surface coverage difference

Theoretically, AFM has a high lateral resolution. However, in principle, its resolution is typically lower than that because of the influence of instrument, experimental operation and sample preparation, etc. Labels can be used to enhance signals when the sample size is ultrasmall. Colloidal gold has been applied extensively to labeling. It is an effective method to combine AFM imaging with gold labeling in the histochemistry[9,10] and nucleic acid[11—14] study.

Casáki et al.[11—13] investigated the DNA immobilization and hybridization on gold substrates using colloidal gold as label. Our group introduced the use of colloidal gold particles as topographic labels to develop molecular beacon (MB) biosensor and study hybridization specificity when MBs were immobilized on the substrate. It was found that the surface coverage of colloidal gold increased with the increase of concentration of labeled target DNA. So a method that could measure the concentration of target DNA with a relatively low detection limit was proposed.[1)]

## 2 AFM microcantilever force sensor

Because it is possible to measure intermolecular forces as low as the piconewton range, AFM is becoming a rapidly developing technique for probing affinity and recognition of properties at the molecular level, such as antigen/antibody[15—17], ligand-receptor complexes[18—20], DNA-DNA[21—23], DNA-protein interaction[24], interactions of terminal group[25,26], and covalent bond strength[27], etc.

Gaub et al.[18] studied the single molecular force of biotin/avidin complex. The interaction of biotin/avidin is the model system of ligand-receptor pairs. The results showed that the single molecular force of biotin/avidin complex was $160 \pm 20$ pN.

Nucleic acid hybridization is the essential molecular recognition in the process of gene replication, gene transcription and gene translation. There have been several reports of AFM force measurements for studying nucleic acid hybridization. For example, Lee et al.[21] were the first to report the measurement of single molecular forces between complementary DNA molecules in 1994. Their data suggested that the magnitude of the interactions depends on the base number of nucleic acid strand.

Taking the advantages of the capability of determination force as low as piconewton rang, our group[23] investigated specific recognition of MB from the micromechanics viewpoint. The rupture force of the MB interaction with the target DNA (complementary and single-base mutation) was measured and compared to the interaction force between a linear

1) Jin Y., Wang K. M., Tan W. H. et al. A novel biosensor for surface-immobilized molecular beacon hybridization studies based on gold nanoparticle labeling and atomic force microscopy. In preparation

DNA probe and the target DNA. The results indicated that the specific discrimination capability of the MB is higher than that of linear DNA probe. The principle is illustrated in Fig.2. MB and different target DNAs were attached to AFM tips and substrates, respectively. The force measurement between MB and target DNA was performed in a hybridization buffer.

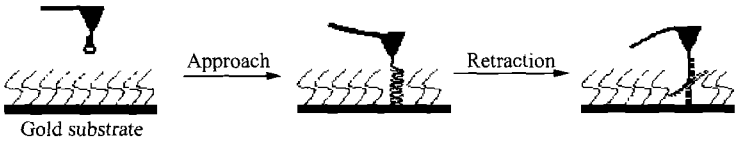


Fig. 2. Schematic representation of the AFM force measurement of MB/cDNA.

Because of their specific hairpin structures, MBs are extraordinarily target-specific, ignoring nucleic acid target sequences that differ by as little as a single nucleotide[28,29]. To systematically investigate MB hybridization with different target DNAs, we combined AFM force detection with flow injection analysis to establish a new method. It is based on the difference of adhesive force between MB-modified tips and mercaptopropanic acid (MPA)-immobilized gold surface before and after hybridization. All of the different target DNA solution, hybridization buffer, and regeneration buffer could be changed directly in a flow system using a peristaltic pump. Therefore the detection of DNA hybridization, regeneration of the modified tips, and non-specific adsorption can all be performed consecutively. So the method is time-saving and easy to handle.[1)]

## 3 AFM microcantilever sensor based on nanomechanics of AFM cantilever

In 1994, two research teams, one from Oak Ridge National Laboratory, USA and the other from IBM Zurich, converted the same mechanism that caused the unwanted interference into a platform for a new family of sensors[30,31]. They found that a standard AFM cantilever could function as a microcalorimeter, offering femtojoule sensitivity and a substantial improvement over more traditional approaches. By measuring shifts in the resonance frequencies of microcantilevers, the researchers were able to show that microcantilevers are mass-sensitive devices that outperform more conventional piezoelectric gravimetric sensors. The sensitivity of microcantilevers was minute quantities of adsorbates. It was superior to that of the traditional quartz crystal microbalance (QCM) and surface acoustic wave (SAW) transducers. The aforementioned research generated substantial interest in cantilever as a new platform for a variety of physical and chemical sensors.

AFM microcantilever sensors are mainly based on the cantilever deflection or resonance frequency shift before and after molecular recognition to achieve quantitative or qualitative detection of analytes. The novel microcantilever sensors provide significant advantages such as fast response, high sensitivity, and label-free, etc.

### 3.1 Mass-sensitive AFM microcantilever sensors

Nanomechanical deflection due to biomolecular interactions is the characteristic signal in cantilever biosensors. The origin of nanomechanical cantilever motion has been attributed to the change in mass induced by molecular interactions that are restricted to one surface of the cantilevers. Capitalizing on this motion, microcantilevers have been used as sensors in a wide variety of physical, chemical, and biological applications, for example, detections of inorganic ions[32,33], humidity[34], thoils[35] salts[36], protein[37—39], nucleic acid hybridization[40—44], and interaction between DNA and protein[45], etc.

#### 3.1.1 Inorganic ion detection

Ji et al.[33] proposed a sensitive method to detect trace amounts of $Hg^{2+}$ using a microcantilever coated with gold. The microcantilever undergoes bending due to accumulation of $Hg^{2+}$ on the gold surface. It was found that a concentration of $10^{-11}$ mol/L $Hg^{2+}$ could be detected using this technology. This method has a high selectivity and good reproducibility.

#### 3.1.2 Protein analysis

Microcantilevers have been extensively applied to protein analysis by virtue of their advantages that

1) Jin Y., Wang K. M., Tan W. H. et al. Realtime and online monitoring nucleic acid hybridization in flow system by atomic force microscopy. To be published.

they are label-free and of high sensitivity[37—39]. Majumdar et al.[37] have used a cantilever to detect prostate-specific antigen. The principle is illustrated in Fig. 3. Gold was coated on one side of the silicon cantilever and the property of the two sides was different. Probe molecules were selectively immobilized on the gold-coated side and nonspecific adsorption was avoided. Polyclonal anti-prostate antibody was covalently linked to the cantilever surface with a thin coating of gold as a ligand. The cantilever deflection due to free prostate-specific antigen (fPSA) binding with this antibody allowed them to detect fPSA concentration from 0.2 ng/mL to 60 μg/mL, which covered the clinically relevant diagnostic PSA concentration range.

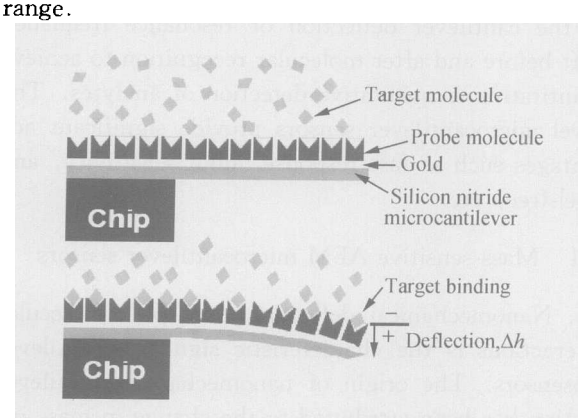


Fig. 3. Schematic representation of an AFM microcantilever immunosensor.

### 3.1.3 Nucleic acid hybridization[40—44]

Characterization of single-nucleotide polymorphisms is a major focus of current genomics research. Hansen et al.[42] demonstrated the discrimination of DNA mismatches using an elegantly simple microcantilever-based optical deflection assay, without the need for external labeling. Gold-coated silicon AFM cantilevers were functionalized with thiolated 20- or 25-mer probe DNA oligonucleotides and exposed to target oligonucleotides of varying sequence in static and flow conditions. Hybridization of 10-mer complementary target oligonucleotides resulted in net positive deflection, while hybridization with targets containing one or two internal mismatches resulted in net negative deflection. Mismatched targets produced a stable and measurable signal when only a four-base pair stretch was complementary to the probe sequence. This technique is readily adaptable to a high-throughput array format and provides a distinct positive/negative signal for easy interpretation of oligonucleotide hybridization.

### 3.1.4 Protein-DNA interaction

Stevenson et al.[45] reported the first study describing the enzymatic manipulation of immobilized DNA on gold/silicon microcantilevers and the resultant mechanical motion. Two enzymatic reactions were conducted: a restriction digestion of immobilized DNA and subsequent ligation of a compatible DNA sequence to the remaining immobilized DNA. Fig. 4 shows a schematic of the digestion and ligation reactions. Double-stranded (ds) DNA incorporating a *Hin*d Ⅲ restriction endonuclease recognition site was attached to the silicon side of a gold-coated cantilever. DNA-coated cantilevers were then exposed to *Hin*d Ⅲ restriction enzyme, and deflection was monitored before, during, and after exposure to the enzyme. *Hin*d Ⅲ cut the DNA on the cantilever at the specific recognition site, leaving a 5-base single-stranded "sticky end" that can be used to attach a piece of DNA with a complementary end. After addition of the complementary strand and ligase, double-stranded DNA formed again. For both restriction and ligation reactions, a permanent deflection of the cantilever was observed even after the enzymes were washed away. This repeatable digestion/ligation procedure opens up possibilities for control and manipulation of DNA-coated microcantilevers for use in molecular interaction sensing of nucleic acid with protein.

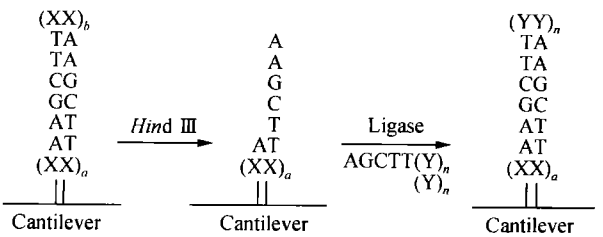


Fig. 4. Schematic illustration of the interaction between DNA and protein.

## 3.2 AFM microcantilever sensor based on volume change of hydrogel

The key to microcantilever sensor development is to choose appropriate coatings for the identification of chemically specific species. A good coating candidate is stimuli-response hydrogels, which change the volume in response to small changes in the environment. Taking the advantage of the volume-changeable property of hydrogel, Zhang's group[46] reported a sensor based on a hydrogel-coated microcantilever. Tetraalkyl ammonium groups were used to form an ion pair with $CrO_4^{2-}$. These microcantilevers underwent

bending deflection upon exposure to solutions containing various $CrO_4^{2-}$ concentrations as a result of swelling or shrinking of the hydrogels. The microcantilever deflection was nearly linear to the concentration of $CrO_4^{2-}$ ions in most concentration ranges. It was found that a concentration of $10^{-11}$ mol/L $CrO_4^{2-}$ could be detected with good selectivity using this technology in a fluid cell.

On the basis of previous work, Liu et al.[47] reported that microcantilevers coated with a benzo-18-crown-6 moiety containing hydrogel could be used for the detection of $Pb^{2+}$. The principle is shown in Fig. 5. When solutions containing various concentrations of $Pb^{2+}$ were injected into the fluid cell, the microcantilever bent down. The microcantilever deflection increased as the concentration of $Pb^{2+}$ increased. The effects of other cations, such as $Na^+$, caused a slight microcantilever deflection at high concentrations. $K^+$, on the other hand, could interfere with $Pb^{2+}$, but only when the $K^+$ concentration was $>10^{-4}$ mol/L. This hydrogel-modified cantilever could selectively respond to $Pb^{2+}$ at concentration as low as $10^{-6}$ mol/L. It is expected that such hydrogel-coated microcantilevers could be used to prepare many microcantilever-based chemical and biological sensors when different molecular-recognition agents are immobilized in the hydrogel.

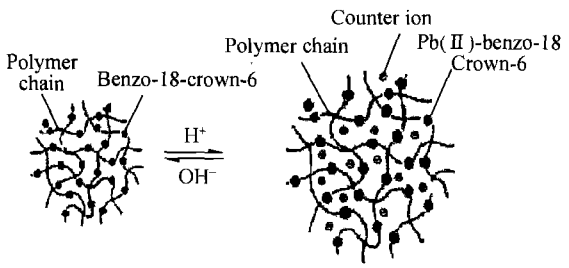


Fig. 5. Schematic of $Pb^{2+}$ microcantilever sensor.

### 3.3 AFM microcantilever sensor based on surface stress variation

The micromechanical detection of pH using surface-modified microcantilevers has been reported. The technique is based on the ionization of surface species on a microcantilever as a function of solution pH[48]. As one surface of the cantilever accumulates charge proportional to the pH of the surrounding liquid, the cantilever undergoes bending due to the differential surface stress. Results of chemically modified (4-aminobutyltriethoxysilane, 11-mercaptoundecanoic acid) and metal-modified (Au/Al) surface over a pH range 2—12 were presented. Aminosilane-modified $SiO_2$/Au cantilevers performed robustly over pH range 2—8 (49nm deflection/pH unit). While $Si_3N_4$/Au cantilevers performed well at pH 2—6 and 8—12 (30nm deflection/pH unit). Therefore cantilever surfaces can be selectively modified to respond within a specific pH range.

AFM cantilevers have been used to measure surface stress by changing medium (ionic strength or pH)[49—51]. For example, Raiteri et al.[49] demonstrated the possibilities of using the bending of cantilever to determine surface stress changes at solid-liquid interfaces. The bending radius of curvature is directly proportional to changes of the differential surface stress. Cantilevers were coated on both sides with gold and different thiol monolayer formed on gold. Changes in the surface stress for the different thiol monolayers were due to specific proton adsorption. Surface stress changes were measured with a cantilever coated on one side with octadecanethiols and on the other side with 3-mercaptopropionic acid. When referring to the carboxylic side, the surface stress showed a minimum around pH 4—5. When the pH increased to above 5 or decreased to below 4, the cantilever bent toward the mercaptopropionic acid side, that is, its surface stress increased. The proton dissociation of the carboxyl group was probably an important factor. The dissociation constant, p$K$, of propoionic acid is between 4 and 5. Binding of a proton to a carboxylate group lowers its free enthalpy. This could explain the increase in surface stress with increasing pH. In the case of 2-aminoethanthiol and 2-mercaptoethanol, only the increase of surface stress with increasing pH was observed. The side groups of these molecules can dissociate with p$K$ values of 10 and $>10$.

## 4 Future perspectives

Microcantilever-based sensor technologies have grown rapidly over the last several years in an attempt to develop sensitive and selective detection of biological and chemical substances and environmental factors. It provides a new platform to develop novel sensors although there are several limitations such as signal instability, the effect of nonspecific adsorption, and the difficulty in mechanism interpretation. Microcantilever sensor systems will continue to evolve with improvements in sensitivity and specificity, as

well as smaller size and cost, and achieve great breakthrough in the theoretical and practical applications.

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