Chemical Specificity in Nanomechanical Sensors

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Advances in the field of micro/nano-electro-mechanical systems (MEMS and NEMS) now offer unique opportunities in the design of small and ultrasensitive analytical methods. MEMs/NEMs have demonstrated their unique advantages when they are combined with chemistry and biology, including fast, real-time responses. In addition, MEMs and NEMS are small enough to be integrated into other devices. One of the most promising MEMs is microcantilevers, which have been proven to be an outstanding transducer for chemical and biological sensors. This review summarizes the receptors and immobilization approaches reported for nanomechanical sensors and interpret the mechanism and dynamic relationship of recognition induced nanomechanical motions.

Since the three pioneer papers [1-3] published in 1994, the micro/nanocantilever sensor technology had boomed and become a promising sensor technology. Microcantilever sensors have several advantages over many other sensor technologies, including faster response time, lower cost of fabrication, the possibility of sensor arrays with small overall dimensions, the ability to explore microenvironments, and improved portability for field applications. SEM pictures of microcantilevers are shown in Fig. (1). Microcantilevers are miniature diving boards that are micromachined from silicon or other materials. The length of these cantilevers is often in the range of 100-200 microns while the thickness ranges from 200 –1000 nm; Recent advances in micromachining cantilever beams that can detect extremely small forces and mechanical stresses promise to bring about a revolution in the field of chemical, physical, and biological sensor development.

Fig. 1. Electron micrographs of microcantilevers fabricated in our group. The sizes of cantilevers on the right vary from 5 µm to 200 µm in extent from the support.
Cantilever resonance responses, such as frequency, deflection, Q-factor, and amplitude, undergo changes due to adsorption or changes in environment. In theory, cantilevers could be modified and optimized for sensitive and interference-free detection of chemicals and physical quantities.

Microcantilevers have two main signal transduction methods: bending and mass loading. In the mass loading mode, it behaves just like other gravimetric sensors such as quartz crystal microbalance (QCM) and Surface Acoustic Wave (SAW) transducers: its resonance frequency will decrease due to the adsorbed mass.

The unique characteristics of microcantilevers is that the device can be made to undergo bending due to molecular adsorption by confining the adsorption to one side of the cantilever. This bending is due to adsorption-induced differential stress on the cantilever. Using Stoney’s formula, the radius of curvature of bending of the cantilever due to adsorption can be written as:

\[
\frac{1}{R} = \frac{6(1-v)}{Et^3} \delta s
\]

where \(R\) is the radius of curvature for the cantilever, \(v\) and \(E\) are Poisson’s ratio and Young’s modulus for the substrate, respectively, and \(t\) is the thickness of the cantilever and \(\delta s\) is the film stress.

**Transduction methods:**

The advantage of the microcantilever sensor is that it works with ease in air and in liquid. Both resonance frequency and bending modes can be used in liquid. Since the cantilever structures are small they execute thermal motion (Brownian motion) in air and liquid. Therefore, no external excitation technique is needed for exciting cantilevers into resonance.

Since the advent of the AFM, several signal transduction methods have been explored for monitoring microcantilever deflections. These include optical, piezoresistive, piezoelectric, and capacitive methods. In the optical method, a laser diode is focused at the free-end of a cantilever. The reflected light is detected with a position-sensitive detector (PSD). In piezoresistive method, the silicon cantilever is doped with boron to half of its thickness. The electrical resistance of the boron channel changes as a function of cantilever bending. In piezoelectric method, cantilever bending causes a transient charge on a piezoelectric film, such as ZnO, on the cantilever. Since the signal is transient it is not ideal for static cantilever bending measurements. In capacitive method, the capacitance between the cantilever, which is micromachined with a space between the cantilever and the substrate, is measured.

While each of these methods have its advantages and disadvantages, from the studies conducted over the past decade, it is concluded that piezoresistive method may be the best approach for making an integrated, small scale sensor. This approach allows us to incorporate the how device into a single chip. Even though the optical detection could be somewhat superior in sensitivity, it involves alignment of a laser beam and thus is not convenient.
Surface Modification methods

Microcantilever bendings are generally induced by adsorption-induced surface stress change or film volume change. Adsorption of chemicals on the microcantilever surface changes the surface stress because of the repulsion or attraction of the molecules on the surface. The swelling or shrinking of the polymer film on the cantilever upon exposure to specific analytes could generally bend the microcantilever significantly.

The chemical specificity can be achieved by selection of appropriate receptors that recognize the target analyte and the recognition event can be converted into a measurable nanomechanical signal. The receptors are categorized as chemical receptors and bioreceptors. So far, the chemical receptors used for nanomechanical sensors include crown ethers, calixarenes, specific functional groups, etc. Bioreceptors include enzyme, antibody, microorganism, cell, etc. Receptor immobilization methods applied to nanomechanical sensors include self-assembled monolayers, layer-by-layer technique, polymer doping approach, and conjugation chemistries.

Monolayer. Self-assembled monolayer method has been extensively studied for cantilever sensor development. To date, extremely sensitive sensors for species in aqueous solution, such as Cs\(^+\), CrO\(_4\)\(^{2-}\), Hg\(^{2+}\), Ca\(^{2+}\), Cu\(^{2+}\), organophosphorus, etc. have been developed in our research group using specific self-assembled monolayers on the microcantilever surface.

Microcantilever-based biosensors offer new, exciting opportunities in developing microscopic biomedical analysis systems with unique characteristics. Many microcantilever biosensors are based on surface conjugation chemistry. Current microcantilever-based biosensors can be generally grouped into the following types: DNA based sensor, antibody based sensor and enzyme based sensors.

Antibody-based microcantilever sensors have applications in detection of herbicide, prostate cancer, creatin and myoglobin for cardiac problems, enantioselective analytes, peptide, low-density lipoproteins (LDL), pathogens such as Escherichia Coli (E.coli), tularemia, Salmonella enterica. Because the relative large size and mass of the virus or bacteria compared to small biomolecules, the resonance of microcantilevers can also be used to detect those pathogens. Microcantilever is sensitive enough to measure the absorbed mass of individual vaccine virus particles with average mass of 9.5 fg. Based on this model, microcantilever modified with specific antibody was developed for detecting single cell, such as E. coli cell, and single virus, such as baculovirus.

Enzyme based biosensors have been widely used for specific chemical detection. However, enzyme modified cantilever sensors are still in its infant stage although several sensors have been developed recently. These work are focused on glucose measurement using glucose oxidase (GOx) and acetyl cholinesterase (AChE) for proof-of-concept study.

Multilayer. A novel approach was done by using layer-by-layer method. This was done by alternatively forming a positive charged polymer film and negatively charged polymer film on the gold side of microcantilever through electrostatic force between those layers. Poly(diallyldimethylammonium chloride) (PDDA) and
poly(sulfonatostyrene) (PSS) were used as positive polymer and negative polymer respectively in the process. Based on this approach, larger deflection amplitude was observed [7] for glucose measurement. This method provides an easy, practical approach for immobilization those enzymes or other biomolecules that may be difficult to be immobilized on microcantilevers through conjugate chemistries.

**Polymer** Hydrogels, composed of a solid and a liquid phase, are networked structures of polymer chains crosslinked to each other and surrounded by an aqueous solution. When immersed in a suitable solution, the chains in the network become solvated. By proper design, hydrogels modified cantilevers respond to pH [8], Pb\(^{2+}\), glucose, etc.

In summary, each modification methods have it advantages and disadvantages and different applications as summarized in the following table.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>Applications</th>
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<tr>
<td>Monolayer</td>
<td>Easy to modify; Fast response</td>
<td>Small bending amplitudes</td>
<td>Pathogens; large molecules; ion pair based</td>
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<tr>
<td>Multilayer</td>
<td>Ease; fast response, larger bending amplitude</td>
<td>Appropriate for enzyme based sensors</td>
<td>Protein based sensors</td>
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<tr>
<td>Polymers</td>
<td>Significant deflection</td>
<td>Preparation difficulty; slower responses</td>
<td>Small organic molecules and ions.</td>
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**References**


