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Cantilever Sensors: Nanomechanical Tools for Diagnostics

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Abstract

Cantilever sensors have attracted considerable attention over the last decade because of their potential as a highly sensitive sensor platform for high throughput and multiplexed detection of proteins and nucleic acids. A micromachined cantilever platform integrates nanoscale science and microfabrication technology for the label-free detection of biological molecules, allowing miniaturization. Molecular adsorption, when restricted to a single side of a deformable cantilever beam, results in measurable bending of the cantilever. This nanoscale deflection is caused by a variation in the cantilever surface stress due to biomolecular interactions and can be measured by optical or electrical means, thereby reporting on the presence of biomolecules. Biological specificity in detection is typically achieved by immobilizing selective receptors or probe molecules on one side of the cantilever using surface functionalization processes. When target molecules are injected into the fluid bathing the cantilever, the cantilever bends as a function of the number of molecules bound to the probe molecules on its surface. Mass-produced, miniature silicon and silicon nitride microcantilever arrays offer a clear path to the development of miniature sensors with unprecedented sensitivity for biodetection applications, such as toxin detection, DNA hybridization, and selective detection of pathogens through immunological techniques. This article discusses applications of cantilever sensors in cancer diagnosis.

Introduction

The detection of multiple target molecules in a small volume of sample has immediate relevance in the early detection of diseases, such as cancer. It is well known that many cancers can be curatively treated if diagnosed early when the tumors are still small and localized. However, the unfortunate reality is that a significant proportion of cancers are diagnosed only after the tumors have spread distally through blood or lymphatic fluid (metastasized) to multiple locations. Since cancer is a complex disease, its diagnosis will require monitoring for alterations in multiple parameters at molecular, cellular, and tissue levels to provide a comprehensive picture of the extent of the

disease process. Detection of a single biomarker has only limited specificity and therefore cannot be sufficiently informative. Hence, cancer diagnostics have been shifting from traditional monitoring of single biomarkers to the detection of multiple markers. Detection of multiple biomarkers is particularly important in screening for cancers of low prevalence, such as ovarian cancer. Ideally, these measurements would be done in a single readout with samples that are readily available and minimally invasive, such as blood serum. Therefore, a technique that can detect multiple biomarkers simultaneously using a single sensor platform and minimal sample volume would be

very attractive. Biosensing technologies based on cantilever arrays have the potential of satisfying this need for multi-target detection with high sensitivity and selectivity using very small volumes of sample.

Microcantilevers are micromechanical beams that are anchored at one end, such as diving spring boards, that can be readily fabricated on silicon wafers and other materials. Their typical dimensions are approximately 100 microns long, 20 microns wide, and 1 micron thick. The microcantilever sensors are physical sensors that respond to surface stress changes due to chemical or biological processes.¹ When fabricated with very small force constants, they can measure forces and stresses with extremely high sensitivity. The very small force constant (less than 0.1 N/m) of a cantilever allows detection of surface stress variation due to the adsorption (or specific surface-receptor interaction) of molecules. Adsorption of molecules on one of the surfaces of the typically bimaterial cantilevers (silicon or silicon nitride cantilevers with a thin gold layer on one side) results in a differential surface stress due to adsorption-induced forces, which manifests as a deflection. In addition to cantilever bending, the resonance frequency of the cantilever can vary due to mass loading. These two signals, adsorption-induced cantilever bending when adsorption is confined to one side of the cantilever and adsorption-induced frequency change due to mass loading, can be monitored simultaneously.²

Mass Detection Using Variation in Resonance Frequency

As described earlier, the resonance frequency, f , of a cantilever varies sensitively as a function of mass loading (Δm), according to:

$$f = \frac{1}{2\pi} \sqrt{\frac{k}{m^* + \alpha \Delta m}} \quad (1)$$

The spring constant of the cantilever is k , m^* is the effective mass of the cantilever, and α is a numerical constant. Increasing the surface area of a cantilever by nanopatterning can lead to higher adsorbed mass and higher sensitivity of detection. Lee et al. has demonstrated a cantilever with nanofabricated holes for increasing the adsorbed mass.³ Although mass detection using the cantilever resonance frequency is well suited for measuring mass in vacuum and air, its mass resolution is very poor when operated under solution.⁴ Resonance frequency variations, therefore, are generally not used for the highly sensitive detection of

adsorbed mass in liquid environments. Detecting surface stress variations is therefore a method of choice when biomarkers have to be detected in body fluids, such as serum. However, Burg et al. recently demonstrated a hollow cantilever concept called the suspended microchannel resonator (SMR) that is capable of detecting biological interactions in liquids with unprecedented sensitivity.⁵ (See the section on Suspended Microchannel Resonators later in this article.)

Mechanics of Cantilever Deflection

Adsorption of molecules on a surface results in a decrease in surface free energy. If the adsorption of molecules on a surface is restricted mostly to one side, for example, by making the opposite surface inert, a differential surface stress is generated between the two surfaces of a cantilever beam. Surface stress, g , and surface free energy, γ , can be related using the Shuttleworth equation:

$$g = \gamma + \frac{d\gamma}{d\varepsilon}, \quad (2)$$

where the surface stress, ε , is defined as the ratio of the change in surface area to the total area. Since the bending of the cantilever is very small compared to the length of the cantilever, the strain contribution is often neglected. However, this is a subject under active discussion in the literature.⁶⁻⁸

The differential surface stress created by molecular adsorption results in cantilever bending. Stoney's equation relates the difference in surface stress Δg between the chemically modified surface and the untreated surface with the cantilever deflection, Δh :

$$\Delta g = \frac{E\Delta h}{4(1-\nu)} \left(\frac{t}{L}\right)^2, \quad (3)$$

where, ν is the Poisson's ratio of the material, E is Young's (elastic) modulus of the cantilever material, and t and L are the thickness and the length of the cantilever, respectively. The surface stress also can be thought of as a change in surface energy density or a change in surface tension. It is clear that the longer the cantilever, the more sensitive the cantilever to measure surface stresses.

Modalities of Cantilever Deflection-Based Sensing

The motion of the cantilever response can be sensitively monitored using a variety of techniques, such as variations in optical beam deflection,⁹ piezoresistivity,¹⁰

piezoelectricity,^{11,12} embedded MOSFET (metal oxide semiconductor field-effect transistor),¹³ capacitance,¹⁴ and electron tunneling.¹⁵ In optical beam deflection, the cantilever motion is detected by reflecting a focused beam of light from the tip of a cantilever beam into a position-sensitive detector. In the piezoresistive technique, the resistance of an asymmetrically doped cantilever varies sensitively as a function of bending. The piezoelectric technique involves coating the cantilevers with piezoelectric materials, which develop a measurable charge due to cantilever bending. In the embedded MOSFET read-out method, a field-effect transistor is embedded at the base of the cantilever. The stress from the bending of the cantilever changes the carrier mobility and drain current. In the capacitance method, the capacitance between a bending cantilever and a fixed substrate varies as a function of cantilever bending. The electron tunneling method is extremely sensitive, and it is based on the tunneling of electrons between a cantilever and a fixed electrode.¹⁶

Piezoresistive Cantilever Array Fabrication

Piezoresistive materials, such as doped silicon, show piezoresistivity where the resistance of the material varies as a function of applied stress. A multilayer can-

tilever beam has been developed where the doped silicon layer is only on one side of the neutral axis of the cantilever beam and shows variation in its resistance as a function of the extent of the deflection.¹⁷ These cantilevers are composed of several layers of materials at different regions where single crystal silicon serves as an active functional element. The active silicon region is sandwiched between silicon nitride and silicon dioxide layers for insulation and protection, Figure 1a. These piezoresistive cantilevers are fabricated using predoped silicon with insulating layers of silicon nitride on both sides. The thickness of the insulating layers (silicon nitride and silicon oxide) is adjusted in such a way that the neutral axis of the bending cantilever is outside of the doped silicon. The cantilevers fabricated using this method have a higher signal-to-noise ratio, less cantilever drift, and increased sensitivity, as compared to piezoresistive cantilevers fabricated, where the neutral axis lies at the boundary between the doped and undoped regions of the silicon. Since the silicon nitride/silicon oxide layer is insulating, these piezoresistive cantilevers can be used in liquid environments.

For the cantilevers fabricated, there are two parallel silicon stripes (20 μm wide) in each cantilever (see Figure 1). Two gold/titanium metal leads connect silicon stripes at their base and end at the contact

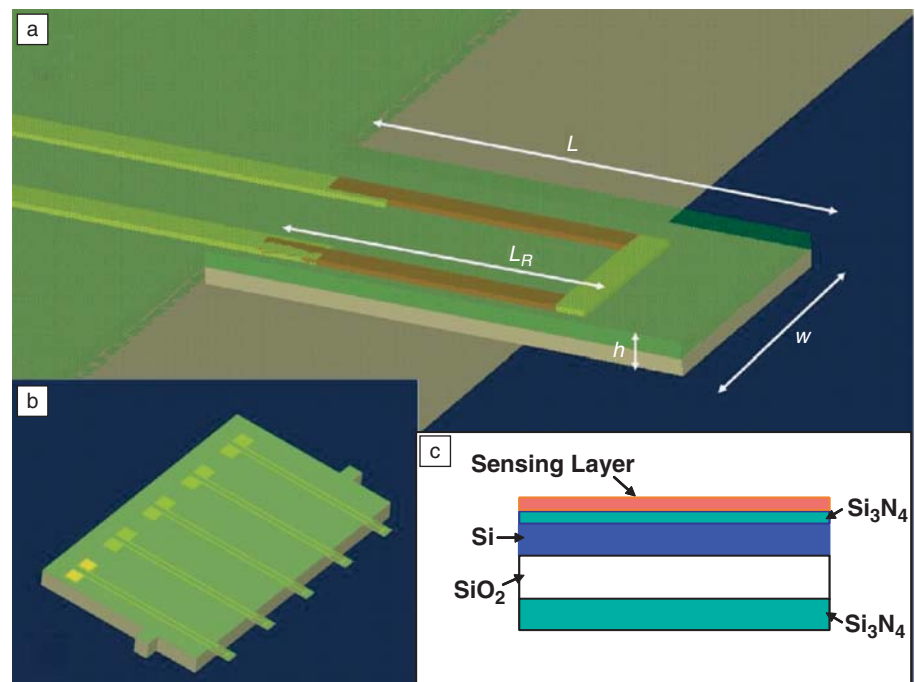


Figure 1. (a) Schematic diagram of a microcantilever indicating dimensions length, L , resistor length, L_R , width, w , and thickness, h . (b) An array of piezoresistive cantilevers. (c) Cross-sectional diagram through the layers of the microcantilever sensors.

pads at the edge of the chip. To complete the circuit, the silicon stripes are electrically shorted by a layer of gold at the free end. The resistivity of the silicon was designed at $3.4 \times 10^{-3} \Omega \text{ cm}$. The doping concentration was $2.2 \times 10^{19} \text{ cm}^{-3}$. The cantilever bending due to residual stresses in the buried oxide layer can be eliminated by depositing silicon nitride film on the back of the beam to create tensile stresses.¹⁸ The typical resistance of a piezoresistive cantilever is around a few kilo-ohms (1 and 5 k Ω depending upon the length).

The cantilever is shown in Figure 2. For piezoresistive cantilevers, higher sensitivity can be obtained when thickness of the cantilever is reduced.¹⁸ The piezoresistive coefficient of silicon is a function of the doping level and dopant type. Unlike a tip-loaded piezoresistive atomic force microscope cantilever, where *p*-type dopant is standard, with microcantilever sensors, a higher gauge factor (normalized change in resistance per unit stress) is achieved with *n*-type dopant.¹⁸

Suspended Microchannel Resonators

As mentioned earlier, SMRs are cantilevers with microchannels fabricated inside the cantilever. Figure 3 shows a scanning electron micrograph of a SMR. Although the SMR cantilever is placed inside a vacuum for obtaining a high-quality factor (*Q* is defined as a ratio of resonance frequency and the full width at half maximum of the resonance amplitude) of resonance, liquid analytes can be pumped through the cantilever. This allows measuring masses of liquid and suspended biomaterials such as cells and cancer markers. At present, the SMR is fabricated in such a way that the hollow cantilever is vacuum sealed inside a chamber with an optical window for optical beam-based cantilever motion detection. Since the liquid is inside the cantilever, which is vibrating in a vacuum, a *Q* factor of 15,000 can be achieved for this device. High *Q* values enable mass to be measured with femtogram resolution in a 1 Hz bandwidth.⁵ The ability to circulate liquid through the cantilever allows for the monitoring of biological interactions between immobilized receptors inside the hollow cantilever and passing analytes. For example, changes in resonance frequency induced by the adsorption of cancer marker molecules and immobilized receptors can be used as a selective and sensitive method for monitoring the presence of cancer markers in the passing sample. Additionally, single cells can be weighed as they pass through

the suspended microchannel. Various methods for trapping an individual cell within the SMR so that the cell mass can be monitored as a function of time are currently under development. Such methods may be used to investigate how cell growth relates to progression through the division cycle and if the response of cancer cells to pathway-directed therapeutics can be classified according to subtle changes in growth.

Receptor Immobilization

Many approaches can be used to immobilize the molecular recognition agents to the microcantilever sensor, depending upon the final application. Generally, cantilevers are coated on one side with 2–3 nm of chromium then with 25–30 nm of gold using an e-beam evaporator. Chromium acts as an adhesion layer for the gold. Both the silicon side of the cantilever (using silane chemistry) and the gold side of the cantilever (using thiol chemistry) have been utilized depending on the final application for the molecular recognition assay. For thiol self-assembled monolayers (SAMs) and organosilane modification, dip coating is the preferred method for functionalization to allow for high density immobilization on the cantilever surface; all reactive surfaces of the cantilever and substrate that are exposed to the modifying solution(s) will have a coating. Thiol SAMs are self-limited to coverages of a monolayer of the thiol on a

gold film. Organosilane coatings also are of the order of a monolayer but can become multilayered upon extended exposure to the solution. Regardless of the

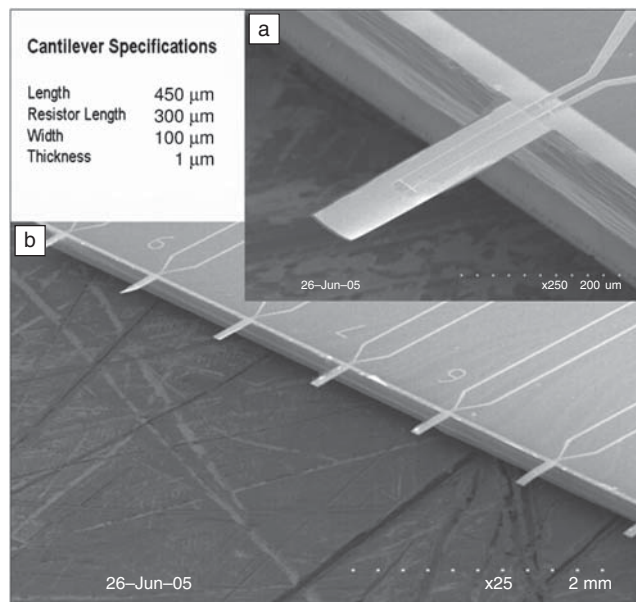


Figure 2. (a) Piezoresistive microcantilever and (b) 10-cantilever array. Resonant frequency ~ 20 kHz, spring constant ~ 0.003 N/m. (Image courtesy of P. Heskth, Georgia Institute of Technology.)

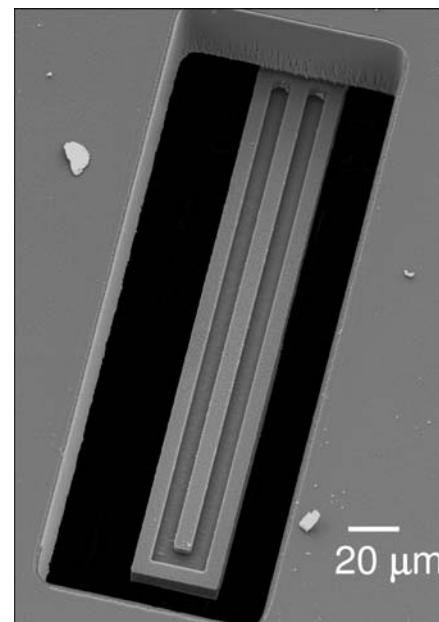


Figure 3. A scanning electron micrograph of a suspended channel microresonator. The channels can be seen inside the cantilever. The hollow cantilever vibrates inside a vacuum. (Image courtesy of S. Manalis, Massachusetts Institute of Technology.)

coating chemistry employed, typically all experimental surfaces are freshly prepared no more than 48 hours prior to assay. Stability studies to determine the effects of aging on the prepared surfaces remain to be done.

Biomolecular Detection Assays

Antigen-antibody interactions are a class of highly specific protein-protein binding that play a critical role in molecular biology. Since cantilever bending originates from the free energy change induced by specific biomolecular binding, this biomolecular detection assay offers a common platform for high-throughput, multiplexed label-free analysis of biomolecules, such as protein-protein binding, DNA hybridization, and DNA-protein interactions.^{19–27} When antibody molecules are immobilized on one surface of a cantilever, specific binding between antibodies and antigens produces cantilever deflection. Similarly, the cantilever undergoes bending when single-stranded DNA (ssDNA) probes are immobilized on the cantilever hybridized with complementary ssDNA (target) molecules in the solution. Such specific deflection was not seen when the incoming DNA strands were noncomplementary due to the absence of hybridization. Therefore, it is possible to design ssDNA probes specifically to detect mutations in the DNA sequence of target DNA responsible for many cancers. The following section briefly describes development of this assay.

Detection of Specific DNA Sequences

Several groups have shown cantilever deflections due to adsorption of ssDNA on virgin cantilevers as well as hybridization of complementary sequences.^{19,20,22,23,27} ssDNA can be immobilized on one side of a cantilever by coating that side with gold and using a thiol linker at one end of ssDNA. It has been experimentally found that adsorption of ssDNA on a cantilever results in a surface stress variation of 30–50 mN/m. Note that the surface stress variation is directly induced by the adsorption of sulfur atoms on the thiol chain on the gold substrate. The ssDNA bound to the cantilever acts as a probe (or receptor) molecule for the target complementary strands. The addition of noncomplementary ssDNA into the solution with immobilized ssDNA probes produces no mechanical signals. The cantilever bending signal also can be used for detecting mutations in the DNA sequence (single nucleotide polymorphism [SNP]), where a single nucleotide of noncomplementary nature appears in the sequence.²⁰

Figure 4 shows the surface stress variation of a piezoresistive cantilever as a function of time due to ssDNA (thiol link) immobilization and subsequent hybridization with complementary ssDNA. The specific binding between the complementary DNA strands on the cantilever results in a surface stress variation of 30–40 mN/m. Wu et al. investigated the origins of cantilever deflection due to biomolecular interactions and found that the deflection resulted from a change in free energy of one cantilever surface.²² The interplay between the energetic and entropic contributions determined the direction of cantilever motion.

Although both DNA hybridization and protein-protein (antigen-antibody) binding can be detected using cantilever deflections, what remained unclear for a while was whether this technique had sufficient specificity and sensitivity to be used for the detection of disease-related proteins at clinically relevant conditions and concentrations. To address this technologically critical issue, sensitive and specific detection of a prostate cancer marker, prostate specific antigen (PSA), was conducted as an example of both protein-protein binding in general and of a cancer diagnostic tumor marker detection in particular.²¹ Prostate cancer has emerged as the most common nonskin cancer and the second leading cause of cancer death in men in North America and Europe (www.cancer.gov). While transrectal ultrasonography and digital rectal examination are common clinical examinations, the most widely used biochemical test involves analyzing the presence of

PSA. PSA is a serine protease secreted by prostatic luminal epithelial cells. When used in population screening for the detection of elevated serum, PSA is credited with dramatic advances in the early diagnosis and management of men with prostatic carcinoma. The majority of the recently marketed assays are based on the commonly used reference range (<4 ng of PSA in a ml of blood), and almost all of them employ some variation of the technique of enzyme-linked immunosorbent assay (ELISA).

Figure 5 shows the potential of microcantilevers as a platform for developing a sensitive and specific assay for PSA using the optical beam deflection method for cantilever bending. The cantilevers were immobilized with polyclonal anti-PSA antibodies. Binding of PSA on the immobilized polyclonal antibody resulted in a deflection of the cantilever. Furthermore, changes in surface stress were related quantitatively to the concentration of PSA. Results in Figure 5 are from a model solvent system prepared with phosphate-buffered saline and shows steady-state cantilever deflection as a function of PSA concentration against a much higher background of bovine serum albumin. Similar tests were performed against high backgrounds of human serum albumin and human plasminogen, both of which are found abundantly in human sera. Of note was the finding that PSA concentrations can be detected below 4 ng/ml, the clinical threshold for prostate cancer. In fact, concentrations down to 0.2 ng/ml were detected. Since for the same PSA concentrations cantilever deflections varied with their geometry, it is important to standardize these measurements in terms of surface stress rather than cantilever deflections using Stoney's formula. The technique is simpler and potentially more cost-effective than ELISA, the current "gold standard" assay for PSA detection, because it does not require labeling and can be performed in a single reaction without additional reagents.

Challenges of Cantilever-Based Detection

Despite the unprecedented sensitivity demonstrated using microcantilever sensors, the selectivity performance and robustness are not consistent, and the full potential remains to be developed and validated. There are a number of challenges to overcome before cantilever sensors come into widespread use. It is possible to achieve higher selectivity, sensitivity, and robustness through optimization of cantilever geometries, immobilization techniques, and analyte delivery schemes.

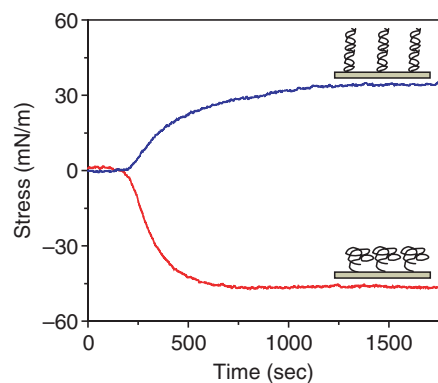


Figure 4. A plot of the surface stress variations of a piezoresistive cantilever as a function of time due to the immobilization (red) and hybridization with complementary ssDNA (blue). The immobilization and hybridization response curves are superimposed to show the response direction. Inset schematics show configurations of ssDNA (below) and double stranded DNA (above).²²

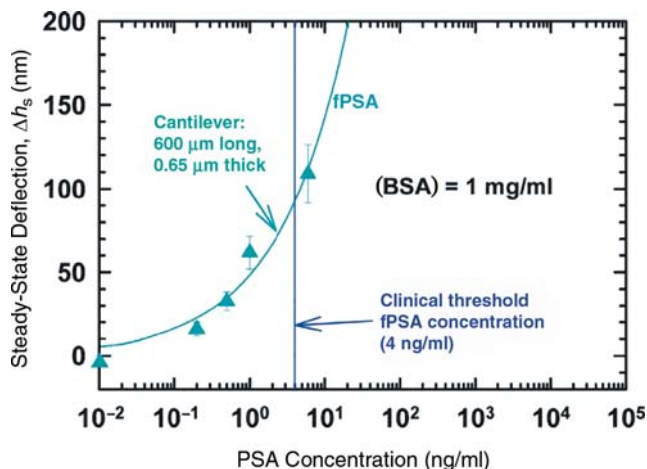


Figure 5. Steady state cantilever deflection (measured using optical beam deflection) as a function of the concentration of free prostate specific antigen (fPSA) in the solution. The responses from five different concentrations are shown. BSA, bovine serum albumin. Please note the width of the cantilever is 20 μm .

As mentioned earlier, the cantilevers can be fabricated in such a way as to increase their detection sensitivity. For sensing methods based on adsorption-induced cantilever deflection, longer and thinner cantilevers with small force constants show higher sensitivity. However, as in the case of all surface adsorption-based sensors, larger area cantilevers show faster detection time for low concentrations of target molecules. Therefore, the optimal cantilever dimension will depend on the dimension of the cantilever chamber and the analyte delivery system. Since most measurements are carried out using a reference cantilever, the common mode rejection (differential measurement with respect to a reference cantilever) basically improves sensitivity. New designs of piezoresistive cantilevers show less drift and improved signal-to-noise ratios.²⁸ Godin et al. demonstrated that the bending of a cantilever beam strongly depends on the surface roughness of the gold film.²⁹ Vacuum-deposited gold films with larger grain sizes on the cantilever show increased bending sensitivity. The sensitivity of bending also depends on the uniformity of the immobilization layer and cleanliness of the sensing surface.³⁰

Selectivity of detection in complex samples still remains to be solved. It must be noted here that while PSA detection, described previously, yielded a clinically relevant level of sensitivity when tested in a model protein-containing buffer solution system, its sensitivity was much lower in actual human serum. This decreased sensitivity may be a result of one or more of the following factors. Since serum contains thousands of various bio-

molecules, many of them at much higher concentrations than the target analyte, there is a likelihood of false positives due to binding of the immobilized antibody to a nontarget molecule that has a similar structural motif. The number of false positives may increase further if polyclonal antibodies are used for capture. Another potential limitation for an optical readout sensor is the turbidity of serum.

Some of the ways to alleviate these problems include use of capture reagents with significantly higher specificity (such as single chain antibodies or aptamers), allowance for multiple wash steps similar to an ELISA procedure, or preconcentrating the serum for the target analyte by reducing the concentration of the abundant nontarget proteins in serum. The latter, for example, can be achieved by affinity chromatography to remove as many as 12 abundant protein species such as serum albumin, actin, or immunoglobulins.

One of the challenges in translating cantilevers as practical sensors for biological applications is the sensor reproducibility. Since selectivity is achieved by coating the cantilever with selective receptor coatings such as antibodies, peptides, DNA, or enzymes, the specificity of the receptor-target interaction controls the selectivity and sensitivity. The cantilever response also depends on the uniformity of the coating on the cantilever surface. Often, coverage of surface immobilized receptor molecules can vary from cantilever to cantilever due to contamination, resulting in irreproducible responses. Consequently, more work is urgently needed to develop more reliable immobilization techniques

for microcantilevers, which are a universal platform to base electromechanical sensors for selective and sensitive detection of cancer markers.

Future Trends and Summary

The trend in miniaturization of sensor arrays for multiplexed detection couples very well with the versatility of cantilever arrays. Currently available microfabrication technologies could be used to make multitarget sensor arrays involving multiple cantilevers, electronic processing, and even local telemetry on a single chip. The technology for designing and simulating electronic chips is well advanced. Integration of electronic, mechanical, and fluidic designs, however, is still in its infancy. Additional receptors and immobilization methods will need to be developed and added to the libraries. These could include improvements such as the application of aptamers or molecular imprinting polymers as surface-bound capture receptors. The stability of immobilized receptors is an issue that potentially limits shelf life and long-term reliability of the sensors and will need to be addressed. Here, the advances could come in the form of regenerating receptors. Using multiple cantilevers for single target detection will lower noise, greatly increase selectivity, and increase robustness.

Cantilever arrays have the potential of satisfying the need for multitarget detection necessary in cancer diagnostics with high sensitivity and selectivity using very small volumes of sample and not requiring repeated body fluid sampling. Because cantilever sensors report on the existence of biomarkers in a label-free manner, they can be employed in a relatively inexpensive assay format, requiring fewer manipulative steps compared to the currently available diagnostic platforms such as ELISA assays for proteins or microarrays for nucleic acids. Also, since the turnaround times for assays can be shortened due to multiplexing, substantial savings are possible in diagnostic workup schedules. Ultimately, all of these advantages, including early detection, will have significant implications in reducing the assay costs and hence costs to the patient and healthcare providers.

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