

15. Nanomechanical Cantilever Array Sensors

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Microfabricated cantilever sensors have attracted much interest in recent years as devices for the fast and reliable detection of small concentrations of molecules in air and solution. In addition to application of such sensors for gas and chemical-vapor sensing, for example as an artificial nose, they have also been employed to measure physical properties of tiny amounts of materials in miniaturized versions of conventional standard techniques such as calorimetry, thermogravimetry, weighing, photothermal spectroscopy, as well as for monitoring chemical reactions such as catalysis on small surfaces. In the past few years, the cantilever-sensor concept has been extended to biochemical applications and as an analytical device for measurements of biomaterials. Because of the label-free detection principle of cantilever sensors, their small size and scalability, this kind of device is advantageous for diagnostic applications and disease monitoring, as well as for genomics or proteomics purposes. The use of microcantilever arrays enables detection of several analytes simultaneously and solves the inherent problem of thermal drift often present when using single microcantilever sensors, as some of the cantilevers can be used as sensor cantilevers for detection, and other cantilevers serve as passivated reference cantilevers that do not exhibit affinity to the molecules to be detected.

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15.1 Technique

Sensors are devices that detect, or sense, a signal. Moreover, a sensor is also a transducer, i.e. it transforms one form of energy into another or responds to a physical parameter. Most people will associate sensors with electrical or electronic devices

that produce a change in response when an external physical parameter is changed. However, many more types of transducers exist, such as electrochemical (pH probe), electromechanical (piezoelectric actuator, quartz, strain gauge), electroacoustic (gramophone

pick-up, microphone), photoelectric (photodiode, solar cell), electromagnetic (antenna), magnetic (Hall-effect sensor, tape or hard-disk head for storage applications), electrostatic (electrometer), thermoelectric (thermocouple, thermoresistors), and electrical (capacitor, resistor). Here we want to concentrate on a further type of sensor not yet mentioned: the mechanical sensor. It responds to changes of an external parameter, such as temperature changes or molecule adsorption, by a mechanical response, e.g. by bending or deflection.

15.1.1 Cantilevers

Mechanical sensors consist of a fixed and a movable part. The movable part can be a thin membrane, a plate or a beam, fixed at one or both ends. The structures described here are called cantilevers. A cantilever is regarded here as a microfabricated rectangular bar-shaped structure that is longer than it is wide and has a thickness that is much smaller than its length or width. It is a horizontal structural element supported only at one end on a chip body; the other end is free (Fig. 15.1). Most often it is used as a mechanical probe to image the topography of a sample using a technique called atomic force microscopy (AFM) or scanning force microscopy (SFM) [15.1], invented by *Binnig* et al. in the mid 1980s [15.1]. For AFM a microfabricated sharp tip is attached to the apex of the cantilever and serves as a local probe to scan the sample surface. The distance between tip and surface is controlled via sensitive measurement of interatomic forces in the piconewton range.

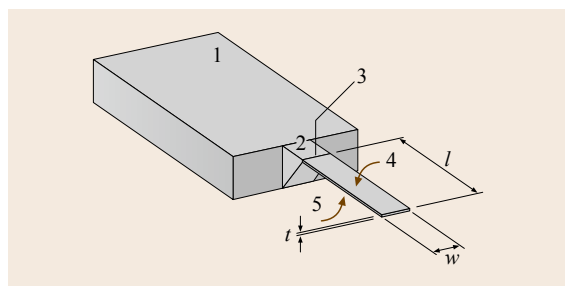


Fig. 15.1 Schematic of a cantilever: (1) rigid chip body, (2) solid cantilever-support structure, (3) hinge of cantilever, (4) upper surface of the cantilever, which is usually functionalized with a sensor layer for detection of molecules, (5) lower surface of the cantilever, usually passivated in order not to show affinity to the molecules to be detected. The geometrical dimensions, length l , width w and thickness t , are indicated

By scanning the tip across a conductive or non-conductive surface using an x - y - z actuator system (e.g. a piezoelectric scanner), an image of the topography is obtained by recording the correction signal that has to be applied to the z -actuation drive to keep the interaction between tip and sample surface constant. SFM methods are nowadays well established in scientific research, education and, to a certain extent, also in industry. Beyond imaging of surfaces, cantilevers have been used for many other purposes. However, here we focus on their application as sensor devices.

15.1.2 History of Cantilever Sensors

The idea of using beams of silicon as sensors to measure deflections or changes in resonance frequency is actually quite old. First reports go back to 1968, when *Wilfinger* et al. [15.2] investigated silicon cantilever structures of $50 \times 30 \times 8 \text{ mm}^3$, i.e. quite large structures, for detecting resonances. On the one hand, they used localized thermal expansion in diffused resistors (piezoresistors) located near the cantilever support to create a temperature gradient for actuating the cantilever at its resonance frequency. On the other hand, the piezoresistors could also be used to sense mechanical deflection of the cantilever. This early report already contains concepts for sensing and actuation of cantilevers. In the following years only a few reports are available on the use of cantilevers as sensors, e.g. *Heng* [15.3], who fabricated gold cantilevers capacitively coupled to microstrip lines in 1971 to mechanically trim high-frequency oscillator circuits. In 1979, *Petersen* [15.4] constructed cantilever-type micromechanical membrane switches in silicon that should have filled the gap between silicon transistors and mechanical electromagnetic relays. *Kolesar* [15.5] suggested the use of cantilever structures as electronic nerve-agent detectors in 1985.

Only with the availability of microfabricated cantilevers for AFM [15.1] did reports on the use of cantilevers as sensors become more frequent. In 1994, *Itoh* and *Suga* [15.6] presented a cantilever coated with a thin film of zinc oxide and proposed piezoresistive deflection readout as an alternative to optical beam-deflection readout. *Cleveland* et al. [15.7] reported the tracking of cantilever resonance frequency to detect nanogram changes in mass loading when small particles are deposited onto AFM probe tips. *Thundat* et al. [15.8] showed that the resonance frequency as well as static bending of microcantilevers are influenced by ambient conditions, such as moisture adsorption, and

that deflection of metal-coated cantilevers can be further influenced by thermal effects (bimetallic effect). The first chemical sensing applications were presented by *Gimzewski et al.* [15.9], who used static cantilever bending to detect chemical reactions with very high sensitivity. Later *Thundat et al.* [15.10] observed changes in the resonance frequency of microcantilevers due to adsorption of analyte vapor on exposed surfaces. Frequency changes have been found to be caused by mass loading or adsorption-induced changes in the cantilever spring constant. By coating cantilever surfaces with hygroscopic materials, such as phosphoric acid or gelatin,

the cantilever can sense water vapor with picogram mass resolution.

The deflection of individual cantilevers can easily be determined using AFM-like optical beam-deflection electronics. However, single cantilever responses can be prone to artifacts such as thermal drift or unspecific adsorption. For this reason the use of passivated reference cantilevers is desirable. The first use of cantilever arrays with sensor and reference cantilevers was reported in 1998 [15.11], and represented significant progress for the understanding of true (difference) cantilever responses.

15.2 Cantilever Array Sensors

15.2.1 Concept

For the use of a cantilever as a sensor, neither a sharp tip at the cantilever apex nor a sample surface is required. The cantilever surfaces serve as sensor surfaces and allow the processes taking place on the surface of the beam to be monitored with unprecedented accuracy, in particular the adsorption of molecules. The formation of molecule layers on the cantilever surface will generate surface stress, eventually resulting in a bending of the cantilever, provided the adsorption preferentially occurs on one surface of the cantilever. Adsorption is controlled by coating one surface (typically the upper surface) of a cantilever with a thin layer of a material that exhibits affinity to molecules in the environment (sensor surface). This surface of the cantilever is referred to as the functionalized surface. The other surface of the cantilever (typically the lower surface) may be left uncoated or be coated with a passivation layer, i. e. a chemical surface that does not exhibit significant affinity to the molecules in the environment to be detected. To enable functionalized surfaces to be established, often a metal layer is evaporated onto the surface designed as sensor surface. Metal surfaces, e.g. gold, may be used to covalently bind a monolayer that represents the chemical surface sensitive to the molecules to be detected from environment. Frequently, a monolayer of thiol molecules covalently bound to a gold surface is used. The gold layer is also favorable for use as a reflection layer if the bending of the cantilever is read out via an optical beam-deflection method.

15.2.2 Compressive and Tensile Stress

Given a cantilever coated with gold on its upper surface for adsorption of alkanethiol molecules and left uncoated on its lower surface (consisting of silicon and silicon oxide), the adsorption of thiol molecules will take place on the upper surface of the cantilever, resulting in a downward bending of the cantilever due to the formation of surface stress. We will call this process development of compressive surface stress, because the forming self-assembled monolayer produces a downward bending of the cantilever (away from the gold coating). In the opposite situation, i. e. when the cantilever bends upwards, we would speak of tensile stress. If both the upper and lower surfaces of the cantilevers are involved in the reaction, then the situation will be much more complex, as a predominant compressive stress formation on the lower cantilever surface might appear like tensile stress on the upper surface. For this reason, it is of utmost importance that the lower cantilever surface is passivated in order that ideally no processes take place on the lower surface of the cantilever.

15.2.3 Disadvantages of Single Microcantilevers

Single microcantilevers are susceptible to parasitic deflections that may be caused by thermal drift or chemical interaction of a cantilever with its environment, in particular if the cantilever is operated in a liquid.

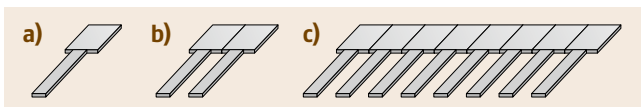


Fig. 15.2 (a) Single cantilever; (b) a pair of cantilevers, one to be used as a sensor cantilever, the other as a reference cantilever, and (c) an array of cantilevers with several sensor and reference cantilevers

Often, a baseline drift is observed during static-mode measurements. Moreover, nonspecific physisorption of molecules on the cantilever surface or nonspecific binding to receptor molecules during measurements may contribute to the drift.

15.2.4 Reference and Sensor Cantilevers in an Array

To exclude such influences, simultaneous measurement of reference cantilevers aligned in the same array as the sensing cantilevers is crucial [15.11]. As the difference in signals from the reference and sensor cantilevers shows the net cantilever response, even small sensor responses can be extracted from large cantilever deflections without being dominated by undesired effects. When only single microcantilevers are used, no thermal-drift compensation is possible. To obtain

useful data under these circumstances, both microcantilever surfaces have to be chemically well defined. One of the surfaces, typically the lower one, has to be passivated; otherwise the cantilever response will be convoluted with undesired effects originating from uncontrolled reactions taking place on the lower surface (Fig. 15.2a). With a pair of cantilevers, reliable measurements are obtained. One cantilever is used as the sensor cantilever (typically coated on the upper side with a molecule layer exhibiting affinity to the molecules to be detected), whereas the other cantilever serves as the reference cantilever. It should be coated with a passivation layer on the upper surface so as not to exhibit affinity to the molecules to be detected. Thermal drifts are canceled out if difference responses, i.e. difference in deflections of sensor and reference cantilevers, are taken. Alternatively, both cantilevers are used as sensor cantilevers (sensor layer on the upper surfaces), and the lower surface has to be passivated (Fig. 15.2b). It is best to use a cantilever array (Fig. 15.2c), in which several cantilevers are used either as sensor or as reference cantilevers so that multiple difference signals can be evaluated simultaneously. Thermal drift is canceled out as one surface of all cantilevers, typically the lower one, is left uncoated or coated with the same passivation layer.

15.3 Modes of Operation

In analogy to *AFM*, various operating modes for cantilevers are described in the literature. The measurement of static deflection upon the formation of surface stress during adsorption of a molecular layer is termed the *static mode*. *Ibach* used cantileverlike structures to study adsorbate-induced surface stress [15.12] in 1994. Surface-stress-induced bending of cantilevers during the adsorption of alkanethiols on gold was reported by *Berger et al.* in 1997 [15.13]. The mode corresponding to noncontact *AFM*, termed the *dynamic mode*, in which a cantilever is oscillated at its resonance frequency, was described by *Cleveland et al.* [15.7]. They calculated mass changes from shifts in the cantilever resonance frequency upon the mounting of tiny tungsten particle spheres at the apex of the cantilever. The so-called *heat mode* was pioneered by *Gimzewski et al.* [15.9], who took advantage of the bimetallic effect that produces a bending of a metal-coated cantilever when heat is produced on its surface. Therewith they constructed

a miniaturized calorimeter with picojoule sensitivity. Further operating modes exploit other physical effects such as the production of heat from the absorption of light by materials deposited on the cantilever (photothermal spectroscopy) [15.14], or cantilever bending caused by electric or magnetic forces.

15.3.1 Static Mode

The continuous bending of a cantilever with increasing coverage by molecules is referred to as operation in the static mode (Fig. 15.3a). Adsorption of molecules onto the functional layer produces stress at the interface between the functional layer and the molecular layer forming. Because the forces within the functional layer try to keep the distance between molecules constant, the cantilever beam responds by bending because of its extreme flexibility. This property is described by the spring constant k of the cantilever, which for a rectangu-

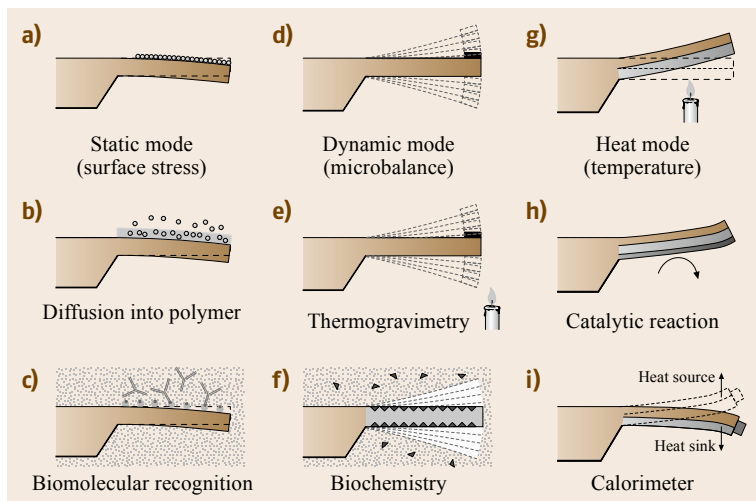


Fig. 15.3a–i Basic cantilever operation modes: **(a)** static bending of a cantilever on adsorption of a molecular layer. **(b)** Diffusion of molecules into a polymer layer leads to swelling of the polymer and eventually to a bending of the cantilever. **(c)** Highly specific molecular recognition of biomolecules by receptors changes the surface stress on the upper surface of the cantilever and results in bending. **(d)** Oscillation of a cantilever at its resonance frequency (dynamic mode) allows information on mass changes taking place on the cantilever surface to be obtained (application as a microbalance). **(e)** Changing the temperature while a sample is attached to the apex of the cantilever allows information to be gathered on decomposition or oxidation process. **(f)** Dynamic-mode measurements in liquids yield details on mass changes during biochemical processes. **(g)** In the heat mode, a bimetallic cantilever is employed. Here bending is due to the difference in the thermal expansion coefficients of the two materials. **(h)** A bimetallic cantilever with a catalytically active surface bends due to heat production during a catalytic reaction. **(i)** A tiny sample attached to the apex of the cantilever is investigated, taking advantage of the bimetallic effect. Tracking the deflection as a function of temperature allows the observation of phase transitions in the sample in a calorimeter mode

lar microcantilever of length l , thickness t and width w is calculated as

$$k = \frac{Ewt^3}{4l^3}, \quad (15.1)$$

where E is the Young's modulus [$E_{\text{Si}} = 1.3 \times 10^{11} \text{ N/m}^2$ for Si(100)].

As a response to surface stress, e.g. owing to adsorption of a molecular layer, the microcantilever bends, and its shape can be approximated as part of a circle with radius R . This radius of curvature is given by [15.15,16]

$$\frac{1}{R} = \frac{6(1-\nu)}{Et^2}. \quad (15.2)$$

The resulting surface stress change is described using Stoney's formula [15.15]

$$\Delta\sigma = \frac{Et^2}{6R(1-\nu)}, \quad (15.3)$$

where E is Young's modulus, t the thickness of the cantilever, ν the Poisson's ratio ($\nu_{\text{Si}} = 0.24$), and R the bending radius of the cantilever.

Static-mode operation has been reported in various environments. In its simplest configuration, molecules from the gaseous environment adsorb on the functionalized sensing surface and form a molecular layer (Fig. 15.3a), provided the molecules exhibit some affinity to the surface. In the case of alkanethiol covalently binding to gold, the affinity is very high, resulting in a fast bending response within minutes [15.13]. Polymer sensing layers only exhibit a partial sensitivity, i.e. polymer-coated cantilevers always respond to the presence of volatile molecules, but the magnitude and temporal behavior are specific to the chemistry of the polymer. Molecules from the environment diffuse into the polymer layer at different rates, mainly depending on the size and solubility of the molecules in the polymer layer (Fig. 15.3b). A wide range of hydrophilic/hydrophobic polymers can be selected, dif-

fering in their affinity to polar/unpolar molecules. Thus, the polymers can be chosen according to what an application requires.

Static-mode operation in liquids, however, usually requires rather specific sensing layers, based on molecular recognition, such as DNA hybridization [15.17] or antigen–antibody recognition (Fig. 15.3c). Cantilevers functionalized by coating with biochemical sensing layers respond very specifically using biomolecular key–lock principles of molecular recognition. However, whether molecular recognition will actually lead to a bending of the cantilever depends on the efficiency of transduction, because the surface stress has to be generated very close to the cantilever surface to produce bending. By just scaling down standard gene-chip strategies to cantilever geometry utilizing long spacer molecules so that DNA molecules become more accessible for hybridization, the hybridization takes place at a distance of several nanometers from the cantilever surface. In such experiments, no cantilever bending was observed [15.18].

15.3.2 Dynamic Mode

Mass changes can be determined accurately by using a cantilever actuated at its eigenfrequency. The eigenfrequency is equal to the resonance frequency of an oscillating cantilever if the elastic properties of the cantilever remain unchanged during the molecule-adsorption process and if damping effects are insignificant. This mode of operation is called the dynamic mode (e.g., the use as a microbalance, Fig. 15.3d). Owing to mass addition on the cantilever surface, the cantilever's eigenfrequency will shift to a lower value. The frequency change per mass change on a rectangular cantilever is calculated [15.19] according to

$$\Delta f/\Delta m = \frac{1}{4\pi n_l l^3 w} \times \sqrt{\frac{E}{\rho^3}}, \quad (15.4)$$

where $\rho = m/(lwt)$ is the mass density of the microcantilever and the deposited mass, and $n_l \approx 1$ is a geometrical factor.

The mass change is calculated [15.8] from the frequency shift using

$$\Delta m = \frac{k}{4\pi^2} \times \left(\frac{1}{f_1^2} - \frac{1}{f_0^2} \right), \quad (15.5)$$

where f_0 is the eigenfrequency before the mass change occurs, and f_1 the eigenfrequency after the mass change.

Mass-change determination can be combined with varying environment temperature conditions (Fig. 15.3e) to obtain a method introduced in the literature as *micromechanical thermogravimetry* [15.20]. A tiny piece of sample to be investigated has to be mounted at the apex of the cantilever. Its mass should not exceed several hundred nanograms. Adsorption, desorption and decomposition processes, occurring while changing the temperature, produce mass changes in the picogram range that can be observed in real time by tracking the resonance-frequency shift.

Dynamic-mode operation in a liquid environment is more difficult than in air, because of the large damping of the cantilever oscillation due to the high viscosity of the surrounding media (Fig. 15.3f). This results in a low quality factor Q of the oscillation, and thus the resonance frequency shift is difficult to track with high resolution. The quality factor is defined as

$$Q = 2\Delta f/f_0. \quad (15.6)$$

Whereas in air the resonance frequency can easily be determined with a resolution of below 1 Hz, only a frequency resolution of about 20 Hz is expected for measurements in a liquid environment.

The damping or altered elastic properties of the cantilever during the experiment, e.g. by a stiffening or softening of the spring constant caused by the adsorption of a molecule layer, result in the fact that the measured resonance frequency will not be exactly equal to the eigenfrequency of the cantilever, and therefore the mass derived from the frequency shift will be inaccurate. In a medium, the vibration of a cantilever is described by the model of a driven damped harmonic oscillator

$$m^* \frac{d^2x}{dt^2} + \gamma \frac{dx}{dt} + kx = F \cos(2\pi ft), \quad (15.7)$$

where $m^* = \text{const}(m_c + m_l)$ is the effective mass of the cantilever (for a rectangular cantilever the constant is 0.25). Especially in liquids, the mass of the comoved liquid m_l adds significantly to the mass of the cantilever m_c . The term $\gamma \frac{dx}{dt}$ is the drag force due to damping, $F \cos(2\pi ft)$ is the driving force executed by the piezo-oscillator, and k is the spring constant of the cantilever.

If no damping is present, the eigenfrequencies of the various oscillation modes of a bar-shaped cantilever are calculated according to

$$f_n = \frac{\alpha_n^2}{2\pi} \sqrt{\frac{k}{2(m_c + m_l)}}, \quad (15.8)$$

where f_n are the eigenfrequencies of the n -th mode, α_n are constants depending on the mode: $\alpha_1 = 1.8751$, $\alpha_2 = 4.6941$, $\alpha_n = \pi(n - 0.5)$; k is the spring constant of the cantilever, m_c the mass of the cantilever, and m_1 the mass of the medium surrounding the cantilever, e.g. liquid [15.21].

Addition of mass to the cantilever due to adsorption will change the effective mass as follows

$$m^* = \text{const}(m_c + m_1 + \Delta m), \quad (15.9)$$

where Δm is the additional mass adsorbed. Typically, the comoved mass of the liquid is much larger than the adsorbed mass.

Figure 15.4 clearly shows that the resonance frequency is only equal to the eigenfrequency if no damping is present. With damping, the frequency at which the peak of the resonance curve occurs is no longer identical to that at which the turning point of the phase curve occurs. For example, resonance curve 2 with damping γ_2 has its maximum amplitude at frequency f_2 . The corresponding phase would be $\varphi_{\text{res}}(\gamma_2)$, which is not equal to $\pi/2$, as would be expected in the undamped case. If direct resonance-frequency tracking or a phase-locked loop is used to determine the frequency of the oscillating cantilever, then only its resonance frequency is detected, but not its eigenfrequency. Remember that the eigenfrequency, and not the resonance frequency, is required to determine mass changes.

15.3.3 Heat Mode

If a cantilever is coated with metal layers, thermal expansion differences in the cantilever and the coating layer will further influence cantilever bending as a function of temperature. This mode of operation is referred to as the *heat mode* and causes cantilever bending because of differing thermal expansion coefficients in the sensor layer and cantilever materials [15.9] (Fig. 15.3g)

$$\Delta z = \frac{5}{4}(\alpha_1 - \alpha_2) \frac{t_1 + t_2}{t_2^2 \kappa} \frac{l^3}{(\lambda_1 t_1 + \lambda_2 t_2) w} P. \quad (15.10)$$

Here α_1, α_2 are the thermal expansion coefficients of the cantilever and coating materials, respectively, λ_1, λ_2 their thermal conductivities, t_1, t_2 the material thicknesses, P is the total power generated on the cantilever, and κ is a geometry parameter of the cantilever device.

Heat changes are either caused by external influences (change in temperature, Fig. 15.3g), occur directly on the surface by exothermal, e.g. catalytic,

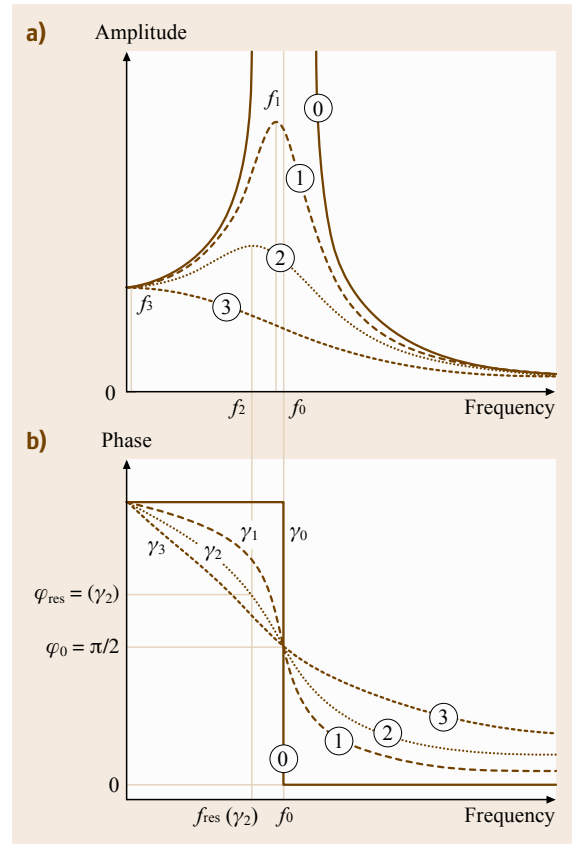


Fig. 15.4 (a) Resonance curve with no damping (0), and increasing damping (1)–(3). The undamped curve with resonance frequency f_0 exhibits a very high amplitude, whereas the resonance peak amplitude decreases with damping. This also involves a shift in resonance frequencies from f_1 to f_3 to lower values. (b) Corresponding phase curves showing no damping (0), and increasing damping (1)–(3). The steplike phase jump at resonance of the undamped resonance gradually broadens with increasing damping

reactions (Fig. 15.3h), or are due to material properties of a sample attached to the apex of the cantilever (micromechanical calorimetry, Fig. 15.3i). The sensitivity of the cantilever heat mode is orders of magnitude higher than that of traditional calorimetric methods performed on milligram samples, as it only requires nanogram amounts of sample and achieves nanojoule [15.20], picojoule [15.22] and femtojoule [15.23] sensitivity.

These three measurement modes have established cantilevers as versatile tools to perform experiments

in nanoscale science with very small amounts of material.

15.3.4 Further Operation Modes

Photothermal Spectroscopy

When a material adsorbs photons, a fraction of the energy is converted into heat. This photothermal heating can be measured as a function of the light wavelength to provide optical absorption data of the material. The interaction of light with a bimetallic microcantilever creates heat on the cantilever surface, resulting in a bending of the cantilever [15.14]. Such bimetallic-cantilever devices are capable of detecting heat flows due to an optical heating power of 100 pW, which is two orders of magnitude better than in conventional photothermal spectroscopy.

Electrochemistry

A cantilever coated with a metallic layer (measurement electrode) on one side is placed in an electrolytic medium, e.g. a salt solution, together with a metallic

reference electrode, usually made of a noble metal. If the voltage between the measurement and the reference electrode is changed, electrochemical processes on the measurement electrode (cantilever) are induced, such as adsorption or desorption of ions from the electrolyte solution onto the measurement electrode. These processes lead to a bending of the cantilever due to changes in surface stress and in the electrostatic forces [15.24].

Detection of Electrostatic and Magnetic Forces

The detection of electrostatic and magnetic forces is possible if charged or magnetic particles are deposited on the cantilever [15.25, 26]. If the cantilever is placed in the vicinity of electrostatic charges or magnetic particles, attractive or repulsion forces occur according to the polarity of the charges or magnetic particles present on the cantilever. These forces will result in an upward or a downward bending of the cantilever. The magnitude of the bending depends on the distribution of charged or magnetic particles on both the cantilever and in the surrounding environment according to the laws of electrostatics and magnetism.

15.4 Microfabrication

Silicon cantilever sensor arrays have been microfabricated using a dry-etching silicon-on-insulator (SOI) fabrication technique developed in the micro-/nanomechanics department at the IBM Zurich Research Laboratory. One chip comprises eight cantilevers, having a length of 500 μm , a width of 100 μm , and a thickness of 0.5 μm , and arranged on a pitch of 250 μm . For dynamic-mode operation, the cantilever thickness may be up to 7 μm . The resonance frequencies of the cantilevers vary by 0.5% only, demonstrating the high reproducibility and precision of cantilever fabrication. A scanning electron microscopy image of a cantilever sensor-array chip is shown in Fig. 15.5.

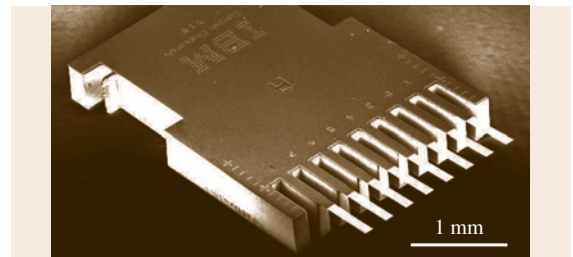


Fig. 15.5 Scanning electron micrograph of a cantilever-sensor array. © Viola Barwich, University of Basel, Switzerland

15.5 Measurement Setup

15.5.1 Measurements in Gaseous or Liquid Environments

A measurement set-up for cantilever arrays consists of four major parts: (1) the measurement chamber containing the cantilever array, (2) an optical or electrical

system to detect the cantilever deflection [e.g. laser sources, collimation lenses and a position-sensitive detector (PSD), or piezoresistors and Wheatstone-bridge detection electronics], (3) electronics to amplify, process and acquire the signals from the detector, and (4) a gas- or liquid-handling system to inject samples

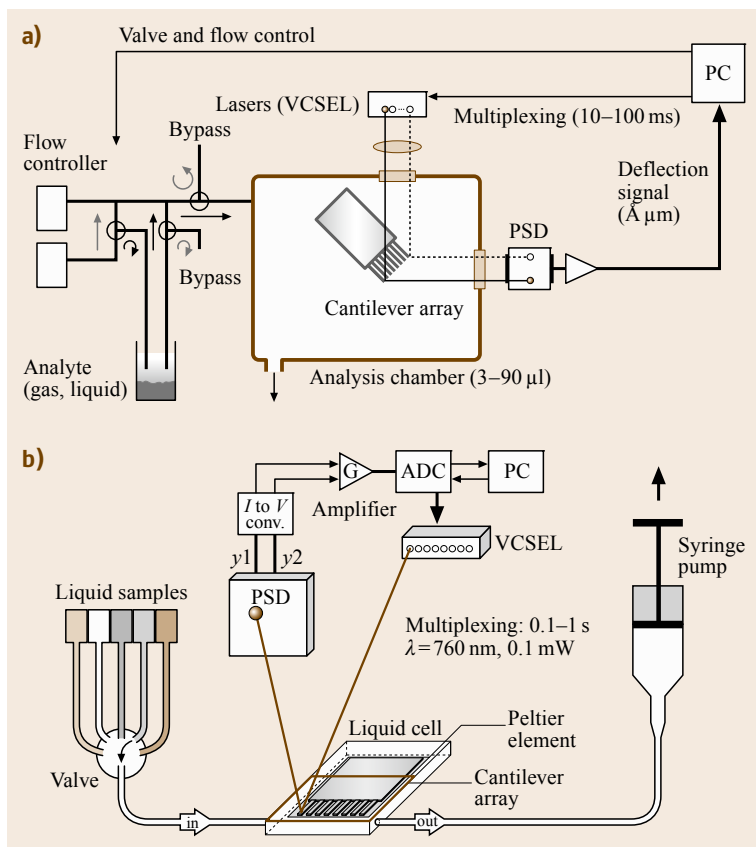


Fig. 15.6 Schematic of measurement setups for (a) a gaseous (artificial nose) and (b) a liquid environment (biochemical sensor)

reproducibly into the measurement chamber and purge the chamber.

Figure 15.6 shows the schematic set-up for experiments performed in a gaseous (Fig. 15.6a) and a liquid, biochemical (Fig. 15.6b) environment for the optical beam-deflection embodiment of the measurement set-up. The cantilever sensor array is located in an analysis chamber with a volume of 3–90 μl , which has inlet and outlet ports for gases or liquids. The cantilever deflection is determined by means of an array of eight vertical-cavity surface-emitting lasers (VCSELs) arranged at a linear pitch of 250 μm that emit at a wavelength of 760 nm into a narrow cone of 5 to 10°.

The light of each VCSEL is collimated and focused onto the apex of the corresponding cantilever by a pair of achromatic doublet lenses, 12.5 mm in diameter. This size has to be selected in such a way that all eight laser beams pass through the lens close to its center to minimize scattering, chromatic and spherical aberration artifacts. The light is then reflected off the gold-coated surface of the cantilever and hits the sur-

face of a position-sensing detector (PSD). PSDs are light-sensitive photopotentiometer-like devices that produce photocurrents at two opposing electrodes. The magnitude of the photocurrents depends linearly on the distance of the impinging light spot from the electrodes. Thus the position of an incident light beam can easily be determined with micrometer precision. The photocurrents are transformed into voltages and amplified in a preamplifier. As only one PSD is used, the eight lasers cannot be switched on simultaneously. Therefore, a time-multiplexing procedure is used to switch the lasers on and off sequentially at typical intervals of 10–100 ms. The resulting deflection signal is digitized and stored together with time information on a personal computer (PC), which also controls the multiplexing of the VCSELs as well as the switching of the valves and mass flow controllers used for setting the composition ratio of the analyte mixture.

The measurement setup for liquids (Fig. 15.6b) consists of a polyetheretherketone (PEEK) liquid cell,

which contains the cantilever array and is sealed by a viton O-ring and a glass plate. The VCSELs and the PSD are mounted on a metal frame around the liquid cell. After preprocessing the position of the deflected light beam in a current-to-voltage converter and amplifier stage, the signal is digitized in an analog-to-digital converter and stored on a PC. The liquid cell is equipped with inlet and outlet ports for liquids. They are connected via 0.18 mm inner-diameter Teflon tubing to individual thermally equilibrated glass containers, in which the biochemical liquids are stored. A six-position valve allows the inlet to the liquid chamber to be connected to each of the liquid-sample containers separately. The liquids are pulled (or pushed) through the liquid chamber by means of a syringe pump connected to the outlet of the chamber. A Peltier element is situated very close to the lumen of the chamber to allow temperature regulation within the chamber. The entire experimental setup is housed in a temperature-controlled box regulated with an accuracy of 0.01 K to the target temperature.

15.5.2 Readout Principles

This section describes various ways to determine the deflection of cantilever sensors. They differ in sensitivity, effort for alignment and setup, robustness and ease of readout as well as their potential for miniaturization.

Piezoresistive readout

Piezoresistive cantilevers [15.6, 20] are usually U-shaped, having diffused piezoresistors in both of the legs close to the hinge (Fig. 15.7a). The resistance in the piezoresistors is measured by a Wheatstone-bridge technique employing three reference resistors, one of which is adjustable. The current flowing between the two branches of the Wheatstone bridge is initially nulled by changing the resistance of the adjustable resistor. If the cantilever bends, the piezoresistor changes its value and a current will flow between the two branches of the Wheatstone bridge. This current is converted via a differential amplifier into a voltage for static-mode measurement. For dynamic-mode measurement,

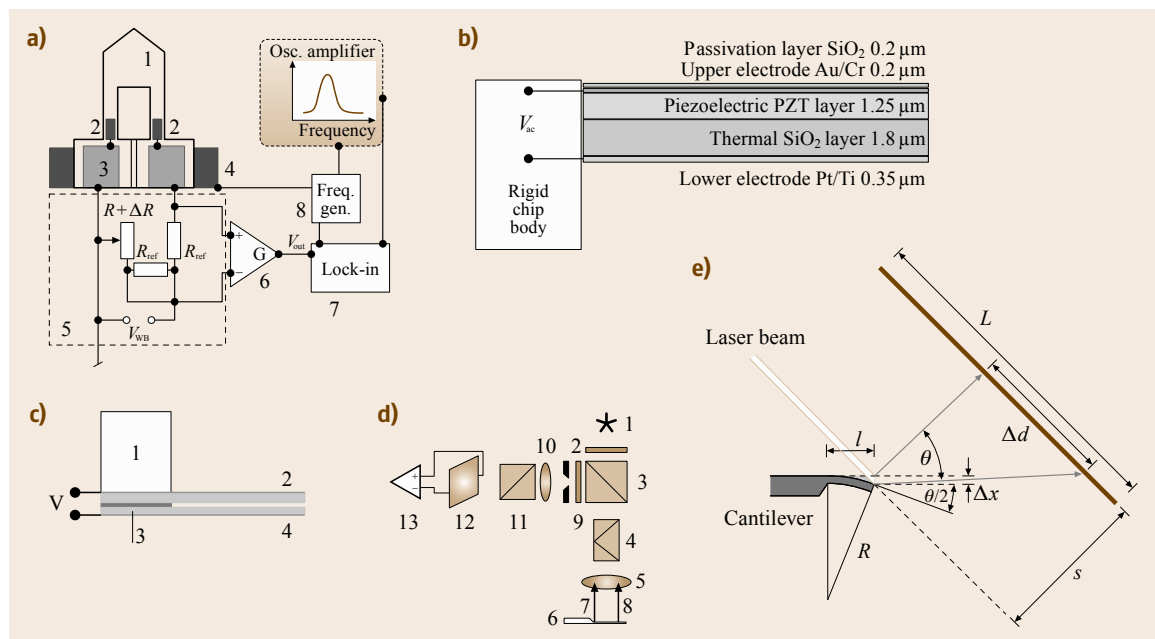


Fig. 15.7 (a) Piezoresistive readout: (1) cantilever, (2) piezoresistors, (3) Au contact pads, (4) external piezocrystal for actuation, (5) Wheatstone-bridge circuit, (6) differential amplifier, (7) lock-in amplifier, (8) function generator. (b) Piezoelectric readout. (c) Capacitive readout: (1) solid support, (2) rigid beam with counter-electrode, (3) insulation layer (SiO_2), (4) flexible cantilever with electrode. (d) Interferometric readout: (1) laser diode, (2) polarizer, (3) nonpolarizing beam splitter, (4) Wollaston prism, (5) focusing lens, (6) cantilever, (7) reference beam (near cantilever hinge), (8) object beam (near cantilever apex), (9) diaphragm and $\lambda/4$ plate, (10) focusing lens, (11) Wollaston prism, (12) quadrant photodiode, (13) differential amplifier. (e) Beam-deflection readout

the piezoresistive cantilever is externally actuated via a frequency generator connected to a piezocrystal. The alternating current (AC) actuation voltage is fed as reference voltage into a lock-in amplifier and compared with the response of the Wheatstone-bridge circuit. This technique allows one to sweep resonance curves and to determine shifts in resonance frequency.

Piezoelectric Readout

Piezoelectric cantilevers [15.27] are actuated by applying an electric AC voltage via the inverse piezoelectric effect (self-excitation) to the piezoelectric material (PZT or ZnO). Sensing of bending is performed by recording the piezoelectric current change due to the fact that the PZT layer may produce a sensitive field response to weak stress through the direct piezoelectric effect. Such cantilevers are multilayer structures consisting of an SiO₂ cantilever and the PZT piezoelectric layer. Two electrode layers, insulated from each other, provide electrical contact. The entire structure is protected using passivation layers (Fig. 15.7b). An identical structure is usually integrated into the rigid chip body to provide a reference for the piezoelectric signals from the cantilever.

Capacitive Readout

For capacitive readout (Fig. 15.7c), a rigid beam with an electrode mounted on the solid support and a flexible cantilever with another electrode layer are used [15.28, 29]. Both electrodes are insulated from each other. Upon bending of the flexible cantilever the capacitance between the two electrodes changes and allows the deflection of the flexible cantilever to be determined. Both static- and dynamic-mode measurements are possible.

Optical (Interferometric) Readout

Interferometric methods [15.30, 31] are most accurate for the determination of small movements. A laser beam passes through a polarizer plate (polarization 45°) and is partially transmitted by a nonpolarized beam splitter (Fig. 15.7d). The transmitted beam is divided in a Wollaston prism into a reference and an object beam. These mutually orthogonally polarized beams are then focused onto the cantilever. Both beams (the reference beam from the hinge region and the object beam from the apex region of the cantilever) are reflected back to the objective lens, pass the Wollaston prism, where they are recombined into one beam, which is then reflected into the other arm of the interferometer, where after the $\lambda/4$ plate a phase shift of a quarter wavelength between

object and reference beam is established. Another Wollaston prism separates the reference and object beams again for analysis with a four-quadrant photodiode. A differential amplifier is used to obtain the cantilever deflection with high accuracy. However, the interferometric setup is quite bulky and difficult to handle.

Optical (Beam-Deflection) Readout

The most frequently used approach to read out cantilever deflections is optical beam deflection [15.32], because it is a comparatively simple method with an excellent lateral resolution. A schematic of this method is shown in Fig. 15.7e.

The actual cantilever deflection Δx scales with the cantilever dimensions; therefore the surface stress $\Delta\sigma$ in N/m is a convenient quantity to measure and compare cantilever responses. It takes into account the cantilever material properties, such as Poisson's ratio ν , Young's modulus E and the cantilever thickness t . The radius of curvature R of the cantilever is a measure of bending, (15.2). As shown in the drawing in Fig. 15.7e, the actual cantilever displacement Δx is transformed into a displacement Δd on the PSD. The position of a light spot on a PSD is determined by measuring the photocurrents from the two facing electrodes. The movement of the light spot on the linear PSD is calculated from the two currents I_1 and I_2 and the size L of the PSD by

$$\Delta d = \frac{I_1 - I_2}{I_1 + I_2} \cdot \frac{L}{2}. \quad (15.11)$$

As all angles are very small, it can be assumed that the bending angle of the cantilever is equal to half of the angle θ of the deflected laser beam, i. e. $\theta/2$. Therefore, the bending angle of the cantilever can be calculated to be

$$\frac{\theta}{2} = \frac{\Delta d}{2s}, \quad (15.12)$$

where s is the distance between the PSD and the cantilever. The actual cantilever deflection Δx is calculated from the cantilever length l and the bending angle $\theta/2$ by

$$\Delta x = \frac{\theta/2}{2} \cdot l. \quad (15.13)$$

Combination of (15.12) and (15.13) relates the actual cantilever deflection Δx to the PSD signal

$$\Delta x = \frac{l\Delta d}{4s}. \quad (15.14)$$

The relation between the radius of curvature and the deflection angle is

$$\frac{\theta}{2} = \frac{l}{R}, \quad (15.15)$$

and after substitution becomes

$$R = \frac{2ls}{\Delta d}, \quad (15.16)$$

$$\text{or } R = \frac{2\Delta x}{l^2}.$$

15.6 Functionalization Techniques

15.6.1 General Strategy

To serve as sensors, cantilevers have to be coated with a sensor layer that is either highly specific, i. e. is able to recognize target molecules in a key–lock process, or partially specific, so that the sensor information from several cantilevers yields a pattern that is characteristic of the target molecules.

To provide a platform for specific functionalization, the upper surface of these cantilevers is typically coated with 2 nm of titanium and 20 nm of gold, which yields a reflective surface and an interface for attaching functional groups of probe molecules, e.g. for anchoring molecules with a thiol group to the gold surface of the cantilever. Such thin metal layers are believed not to contribute significantly to bimetallic bending, because the temperature is kept constant.

15.6.2 Functionalization Methods

There are numerous ways to coat a cantilever with material, both simple and more advanced ones. The method of choice should be fast, reproducible, reliable and allow one or both of the surfaces of a cantilever to be coated separately.

Simple Methods

Obvious methods to coat a cantilever are thermal or electron-beam-assisted evaporation of material, electrospray or other standard deposition methods. The disadvantage of these methods is that they only are suitable for coating large areas, but not individual cantilevers in an array, unless shadow masks are used. Such masks need to be accurately aligned to the cantilever structures, which is a time-consuming process.

Other methods to coat cantilevers use manual placement of particles onto the cantilever [15.9, 20, 33–35], which requires skillful handling of tiny samples. Cantilevers can also be coated by directly pipetting solutions of the probe molecules onto the cantilevers [15.36]

or by employing air-brush spraying and shadow masks to coat the cantilevers separately [15.37].

All these methods have only limited reproducibility and are very time-consuming if a larger number of cantilever arrays has to be coated.

Microfluidics

Microfluidic networks (μ FN) [15.38] are structures of channels and wells, etched several ten to hundred micrometer deep into silicon wafers. The wells can be filled easily using a laboratory pipette, so that the fluid with the probe molecules for coating the cantilever is guided through the channels towards openings at a pitch matched to the distance between individual cantilevers in the array (Fig. 15.8a).

The cantilever array is then introduced into the open channels of the μ FN that are filled with a solution of the probe molecules. The incubation of the cantilever array in the channels of the μ FN takes from a few seconds (self-assembly of alkanethiol monolayers) to several tens of minutes (coating with protein solutions). To prevent evaporation of the solutions, the channels are covered by a slice of poly(dimethylsiloxane) (PDMS). In addition, the microfluidic network may be placed in an environment filled with saturated vapor of the solvent used for the probe molecules.

Array of Dimension-Matched Capillaries

A similar approach is insertion of the cantilever array into an array of dimension-matched disposable glass capillaries. The outer diameter of the glass capillaries is 240 μ m so that they can be placed neatly next to each other to accommodate the pitch of the cantilevers in the array (250 μ m). Their inner diameter is 150 μ m, providing sufficient room to insert the cantilevers (width: 100 μ m) safely (Fig. 15.8b). This method has been successfully applied for the deposition of a variety of materials onto cantilevers, such as polymer solutions [15.37], self-assembled monolayers [15.39], thiol-functionalized single-stranded DNA oligonucleotides [15.40], and protein solutions [15.41].

Inkjet Spotting

All of the above techniques require manual alignment of the cantilever array and functionalization tool, and are therefore not ideal for coating a large number of cantilever arrays. The inkjet-spotting technique, however, allows rapid and reliable coating of cantilever arrays [15.42, 43]. An *x-y-z* positioning system allows a fine nozzle (capillary diameter: 70 μm) to be positioned with an accuracy of approximately 10 μm over a cantilever. Individual droplets (diameter: 60–80 μm , volume 0.1–0.3 nL) can be dispensed individually by means of a piezo-driven ejection system in the inkjet nozzle. When the droplets are spotted with a pitch smaller than 0.1 mm, they merge and form continuous films. By adjusting the number of droplets deposited on the cantilevers, the resulting film thickness can be controlled precisely. The inkjet-spotting technique allows a cantilever to be coated within seconds and yields very homogeneous, reproducibly deposited layers of well-controlled thickness. Successful coating of self-assembled alkanethiol

15.7 Applications

15.7.1 Chemical Detection

Hydrogen

Early reports on detection of gases such as hydrogen involve nanomechanical detection of catalytic reactions of bimetallic microcantilevers coated with aluminum and a top layer of platinum in thermal mode [15.9]. The catalytic reaction of oxygen present in a reaction chamber with hydrogen being introduced into the chamber produces oscillatory chemical reactions resulting in mechanical oscillations of the cantilever due to heat formation related to catalytic conversion of H_2 and O_2 to form H_2O . By use of an array of four platinum coated and four uncoated microcantilevers, a change of the deflection signal due to bending of the platinum coated cantilever relative to the uncoated cantilevers is observed upon hydrogen adsorption in the presence of oxygen [15.11]. Similar responses are obtained with Pd coated glass cantilevers [15.46] and with Pd coated silicon microcantilevers using dynamic mode [15.47], capacitive readout [15.48] or beam-deflection readout in static mode [15.49].

Water Vapor

First observation of microcantilever resonance frequency detuning is reported in [15.8]. A dependence on

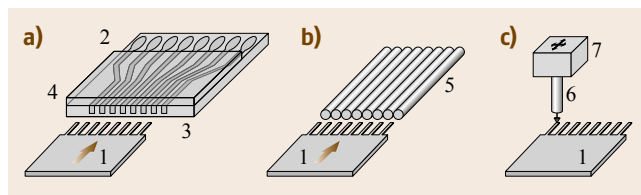


Fig. 15.8 (a) Cantilever functionalization in microfluidic networks. (b) Incubation in dimension-matched microcapillaries. (c) Coating with an inkjet spotter: (1) cantilever array, (2) reservoir wells, (3) microfluidic network with channels, (4) PDMS cover to avoid evaporation, (5) microcapillaries, (6) inkjet nozzle, (7) inkjet *x-y-z* positioning unit

monolayers, polymer solutions, self-assembled DNA single-stranded oligonucleotides [15.43], and protein layers has been demonstrated. In conclusion, inkjet spotting has turned out to be a very efficient and versatile method for functionalization, which can even be used to coat arbitrarily shaped sensors reproducibly and reliably [15.44, 45].

relative humidity of ZFM5 zeolites attached to resonating microcantilevers was observed in [15.50]. Relative humidity was measured with an accuracy of 1% using piezoresistive sensors embedded in polymer [15.51]. A detection limit of 10 ppm is achieved using Al_2O_3 coated microcantilevers [15.52].

Other Vapors

ZFM5 zeolites were used to detect vapor of *p*-nitroaniline dye in dynamic mode with picogram sensitivity [15.50]. A freon gas sensor using a piezoelectric microcantilever coated with MFI zeolite is described in [15.53]. Ethanol vapor detection in dynamic mode is described in [15.54].

Alkane Thiol Vapors

Surface stress changes and kinetics were measured in situ during the self-assembly of alkanethiols on gold by means of a micromechanical sensor, observing scaling of compressive surface stress with the length of the alkane chain [15.13, 55]. 65 ppb of 2-mercaptoethanol have been measured evaluating the response of gold-coated silicon nitride microcantilevers [15.56]. The mechanism of stress formation upon adsorption of thiol layers has been studied by exposing monolayers of alkanethiols on

gold to low energy Ar ions, resulting in formation of a large tensile stress [15.57]. The influence of surface morphology and thickness of the gold coating of the cantilever is discussed in [15.58, 59]. A multiple-point deflection technique has been used to investigate stress evolution during the adsorption of dodecanethiol on microcantilever sensors, allowing to assess the cantilever bending profile [15.60]. Using gold-coated, piezoelectric-excited, millimeter-sized cantilevers exposed to 1-hexadecanethiol (HDT) in ethanol, a detection range between 1 fM to 1 mM is claimed [15.61]. The formation of alkanedithiol (HS-(CH)₂SH) monolayers on gold in solution is monitored using microcantilever sensors [15.62]. The nanomechanical bending of microfabricated cantilevers during the immobilization of alkanethiols of different chain lengths has been investigated in the liquid phase [15.63].

Metal Vapors

Detection of mercury vapor was one of the first applications of microcantilever sensors in dynamic mode [15.10]. 20 ppb of Hg vapor was detected using a microcantilever with an integrated piezoelectric film [15.64]. A monolayer of 1,6-hexanedithiol has been identified as a unusually specific recognition agent for CH₃Hg⁺ [15.65]. 15 ppb detection limit for mercury is reported using microcantilevers that are thermally excited at the fundamental and first three higher order modes [15.66, 67]. Cs ion concentrations in the range of 10⁻¹¹–10⁻⁷ M were detected using a 1,3-alternate 25,27-bis(11-mercapto-1-undecanoxy)-26,28-calix[4]benzo-crown-6 caesium recognition agent bound to a gold coated microcantilever [15.68]. The crown cavity is highly selective to Cs, as compared to K or Na. An atomic force microscope cantilever has been used as a bending-beam sensor to measure surface stress changes which occur during electrochemical processes, such as the formation of a Pb layer on Au [15.69].

HF and HCN

Microcantilevers have been used as a gas sensor to detect hydrofluoric acid (HF) at a threshold of 0.2 ppm [15.70]. Femtomolar HF concentrations, which is also a decomposition component of nerve agents, were detected using a SiO₂ microcantilever. The high sensitivity is considered to be due to the reaction of HF with SiO₂ [15.71]. The etching rate is determined to 0.05 nm/min for SiO₂ and 0.7 nm/min for Si₃N₄ [15.72]. Sensor responses towards HCN at

at concentration of 150 ppm within seconds are reported [15.73].

Ion Sensing

Using microcantilevers coated with a self-assembled monolayer of triethyl-12-mercaptododecylammonium bromide on gold CrO₄²⁻ ions are detected at a concentration of 10⁻⁹ M. Other anions, such as Cl⁻, Br⁻, CO₃²⁻, HCO₃⁻ and SO₄²⁻ do not deflect such modified cantilevers significantly [15.74]. Hg²⁺ has been measured at a concentration of 10⁻¹¹ M using a microcantilever coated with gold. Almost no affinity to other cations exists, such as K⁺, Na⁺, Pb²⁺, Zn²⁺, Ni²⁺, Cd²⁺, Cu²⁺, and Ca²⁺ [15.75]. Adsorption characteristics of Ca²⁺ ions as a function of concentration in aqueous CaCl₂ solution was investigated in static and dynamic mode [15.76]. Microcantilevers functionalized with metal-binding protein AgNt84-6 are able to detect heavy metal ions like Hg²⁺ and Zn²⁺, but are insensitive to Mn²⁺ [15.77]. Hydrogels containing benzo-18-crown-6 have been used to modify microcantilevers for measurements of the concentration of Pb²⁺ in aqueous solutions [15.78]. Using different thiolated ligands as self-assembled monolayers (SAMs) functionalized on silicon microcantilevers (MCs) coated with gold allows to detect Cs⁺, Co²⁺ and Fe³⁺ [15.79]. A gold coated microcantilever is utilized as the working electrode to detect Cr(VI) [15.80]. Others use 11-undecenyltriethylammonium bromide [15.81] or sol-gel layers [15.82] for detection of Cr(VI). Based on the EDTA-Cd(II) complex and its binding capability to bovine serum albumine (BSA) and antibody-based Cd(II) sensor using microcantilevers is presented [15.83].

Volatile Organic Compounds

A microcantilever-based alcohol vapor sensor is described in [15.84] using the piezoresistive technique and polymer coating. They also present a simple evaporation model that allows determining the concentration. The detection limit found is 10 ppm for methanol, ethanol and 2-propanol. In [15.85] an integrated complementary metal oxide semiconductor (CMOS) chemical microsensor with piezoresistive detection (Wheatstone bridge configuration) using poly(etherurethane) (PEUT) as the sensor layer is presented. They are able to reversibly detect volatile organic compounds (VOCs) such as toluene, *n*-octane, ethyl acetate and ethanol with a sensitivity level down to 200 ppm. An improved version of that device is described in [15.86]. The sensitivity could be increased to 5 ppm for *n*-octane.

Later the technique has been refined by using electromagnetic rather than electrothermal actuation and transistor-based readout reducing power dissipation on the cantilever [15.87]. Piezoelectric readout in dynamic mode and electromagnetic actuation of cantilevers spray-coated with PEUT is reported in [15.88], achieving a sensitivity of 14 ppm for ethanol. In [15.89] a study is published how to prepare polyethylene glycol (PEG) coated microcantilever sensors using a microcapillary pipette assisted method. PEG coating is suitable for ethanol sensing as ethanol quickly forms hydrogen bonds with the OH groups of the PEG. Sensor operation is reported to be reversible and reproducible. In [15.90] artificial neural networks are used for analyte species and concentration identification with polymer coated optically read-out microcantilevers. The analytes detected are carbon dioxide, dichloromethane, diisopropylmethylphosphonate (DIMP), dioxane, ethanol, water, 2-propanol, methanol, trichloroethylene and trichloromethylene. In [15.91] the chemical sensing performance of a silicon resonant microcantilever sensor is investigated in dependence on the thickness of the sensitive coating. For a coating thickness of 1, 4 and 21 μm of PEUT a limit of detection of 30 ppm was found for ethanol. A new concept of parylene micromembrane array for chemical sensing is presented [15.92] using the capacitive method. The parylene membrane is suspended over a metal pad patterned on the substrate. The pad and part of the membrane that is metal-coated serve as electrodes for capacitive measurement. The top electrode located on the membrane is chemically modified by applying a gold layer and self-assembled thiol monolayers ($-\text{COOH}$, $-\text{CH}_3$ and $-\text{OH}$) for detection of analyte molecules. Successful detection of 2-propanol and toluene is reported. In [15.93] a sensitive self-oscillating cantilever array is described for quantitative and qualitative analysis of organic vapor mixtures. The cantilevers are electromagnetically actuated and the resonance frequency is measured using a frequency counter. Sensor response is reproducible and reversible. Using PEUT coating the smallest measured concentration is 400 ppm, but the limit of detection is well below 1 ppm. In [15.94] a combination of gas chromatography with a microcantilever sensor array for enhanced selectivity is reported. Test VOC mixtures composed of acetone, ethanol and trichloroethylene in pentane, as well as methanol with acetonitrile in pentane were first separated in a gas chromatography column and then detected using microcantilevers coated with responsive phases such as 3-aminopropyltriethoxy silane, copper

phtalocyanine and methyl- β -cyclodextrin. Analytes detected include pentane, methanol, acetonitrile, acetone, ethanol and trichloroethylene. In [15.95] results are presented on independent component analysis (ICA) of ethanol, propanol and DIMP using cantilever coated with molecular recognition phases (MRP), whereby ICA has proven its feature extraction ability for components in mixtures.

Toxins

Detection of the organochlorine insecticide compound dichlorodiphenyltrichloroethane (DDT) is reported using a synthetic hapten of the pesticide as recognition site conjugated with bovine serum albumin (BSA) covalently immobilised on the gold-coated side of the cantilever by using thiol self assembled monolayers [15.96].

Explosives, Chemical Warfare and Biohazards

Security measures require inexpensive, highly selective and very sensitive small sensors that can be mass-produced and microfabricated. Such low cost sensors could be arranged as a sensor grid for large area coverage of sensitive infrastructure, like airports, public buildings, or traffic infrastructure. Threats can be of chemical, biological, radioactive or explosive nature. Microcantilever sensors are reported to offer very high sensitivities of explosives detection. Photomechanical chemical microsensors based on adsorption-induced and photoinduced stress changes due to the presence of diisopropyl methyl phosphonate (DIMP), which is a model compound for phosphorous-containing chemical warfare agents, and trinitrotoluene (TNT), an explosive are reported [15.97]. Further explosives frequently used include pentaerythritol tetranitrate (PETN) and hexahydro-1,3,5-triazine (RDX), often also with plastic fillers [15.98]. These compounds are very stable, if no detonator is present. Their explosive power, however, is very large, and moreover, the vapor pressures of PETN and RDX are very low, in the range of ppb and ppt. By functionalizing microcantilevers with self-assembled monolayers of 4-mercaptobenzoic acid (4-MBA) PETN was detected at a level of 1400 ppt and RDX at a level of 290 ppt [15.99]. TNT was found to readily stick to Si surfaces, suggesting the use of microcantilevers for TNT detection, taking advantage of the respective adsorption/desorption kinetics [15.100, 101]. Detection of TNT via deflagration on a microcantilever is described by *Pinnaduwa* et al. [15.101]. They used piezoresistive microcantilevers where the cantilever deflection was measured optically via beam deflection.

TNT vapor from a generator placed 5 mm away from the microcantilever was observed to adsorb on its surface resulting in a decrease of resonance frequency. Application of an electrical pulse (10 V, 10 ms) to the piezoresistive cantilever resulted in deflagration of the TNT vapor and a bump in the cantilever bending signal. This bump was found to be related to the heat produced during deflagration. The amount of heat released is proportional to the area of the bump in the time versus bending signal diagram of the process. The deflagration was found to be complete, as the same resonance frequency as before the experiment was observed. The amount of TNT mass involved was determined as 50 pg. The technique was later extended to the detection of PETN and RDX, where much slower reaction kinetics was observed [15.99, 102]. Traces of 2,4-dinitrotoluene (DNT) in TNT can also be used for detection of TNT, because it is the major impurity in production grade TNT. Furthermore DNT is a decomposition product of TNT. The saturation concentration of DNT in air at 20 °C is 25 times higher than that of TNT. DNT was reported detectable at the 300 ppt level using polysiloxane polymer layers [15.103]. Microfabrication of electrostatically actuated resonant microcantilever beams in CMOS technology for detection of the nerve agent stimulant dimethylmethylphosphonate (DMMP) using polycarbosilane-coated beams [15.104] is an important step towards an integrated platform based on silicon microcantilevers, which besides compactness might also include telemetry [15.105]. Cu²⁺/L-cysteine bilayer-coated microcantilever demonstrated high sensitivity and selectivity toward organo-phosphorus compounds in aqueous solution. The microcantilever was found to undergo bending upon exposure to nerve agent stimulant DMMP at concentrations as low as 10⁻¹⁵ M due to the complexation of the phosphonyl group and the Cu²⁺/L-cysteine bilayer on the microcantilever surface [15.106, 107].

15.7.2 Biochemical Environment

pH

Control of pH is often important in biochemical reactions. Therefore this section concerns measurement of pH using microcantilevers. The interfacial stress of self-assembled monolayers of mercaptohexadecanoic acid and hexadecanethiol depends on pH values and ionic strength [15.39]. SiO₂ and silicon nitride microcantilevers were also found to exhibit a deflection dependence with

pH when coated with 4-aminobutyltriethoxysilane, 11-mercaptoundecanoic acid and Au/Al-coated over a pH range 2–12. Aminosilane-modified SiO₂/Au cantilevers performed robustly over pH range 2–8 (49 nm deflection/pH unit), while Si₃N₄/Au cantilevers performed well at pH 2–6 and 8–12 (30 nm deflection/pH unit) [15.108]. Microcantilevers with poly(methacrylic acid) (PMAA) and poly(ethylene glycol) dimethacrylate coating showed to be sensitive to pH changes [15.109]. Also hydrogel coatings were found to be sensitive to pH [15.110]. The dependence of the micromechanical responses to different ionic strength and ion species present in the aqueous environment is discussed in [15.111], highlighting the critical role of counter- and co-ions on surface stress.

Glucose

Glucose sensing via microcantilevers is achieved by coating the cantilevers with the enzyme glucose oxidase on gold [15.112] or via polyethyleneimine (PEI) conjugation [15.113]. Glucose concentrations between 0.2 and 20 mM could be detected [15.114]. In another study a detection range between 2 and 50 mM is reported for glucose. No signal is observed for fructose, mannose and galactose [15.115].

Hydrogen Peroxide (H₂O₂)

Hydrogen peroxide is detected at the nM level using multilayer modified microcantilevers functionalized through a layer-by-layer nanoassembly technique via intercalation of the enzyme horseradish peroxidase. The magnitudes of bending were found to be proportional to the concentrations of hydrogen peroxide [15.116].

DNA, RNA

Specific DNA hybridization detection was observed via surface stress changes related to transduction of receptor-ligand binding into a direct nanomechanical response of microfabricated cantilevers without the need for external labeling or amplification. The differential deflection of the cantilevers was found to provide a true molecular recognition signal despite large responses of individual cantilevers. Hybridization of complementary oligonucleotides shows that a single base mismatch between two 12-mer oligonucleotides is clearly detectable [15.17]. The findings were confirmed or modeled by several groups [15.117, 118]. Hybridization in a complex nonspecific background was observed in a complement concentration range between 75 nM and 2 μM [15.40], following Langmuir model kinetics [15.119]. Enzymatic processes were directly

performed on a microcantilever functionalized with DNA incorporating a Hind III restriction endonuclease site, followed by digestion with Hind III to produce DNA comprising a single-stranded end on the cantilever surface. Ligase was used to couple a second DNA molecule with a compatible end to the DNA on the cantilever [15.120]. Using gold nanoparticle labeled DNA, microcantilevers have been used to detect DNA strands with a specific sequence in dynamic mode, whereby a concentration of 23 pM could still be detected, as well as a single basepair mismatch [15.121]. Whereby adsorption of thiol functionalized single-stranded DNA is easily observed, hybridization cannot be observed if long hydrocarbon spacer molecules between single strand DNA and thiol anchor are used [15.122]. DNA hybridization is also observed using piezoresistive cantilevers [15.119, 123]. A different technique to read out the microcantilever deflections in an array is reported in [15.124]. There the optical beam deflection technique is combined with the scanning of a laser beam illuminating the cantilevers of an array sequentially. DNA hybridization is also reported using polymer SU-8 cantilevers [15.125]. *Mukhopadhyay* et al. report 20 nM hybridization sensitivity using piezoresistive cantilevers and DNA sequences with an overhang extension distal to the surface [15.126]. A larger array comprising 20 microcantilevers is described in [15.127]. Moreover, the authors present integration of the array with microfluidics. Surface stress changes in response to thermal dehybridization, or melting, is reported [15.128]. The dependence of salt concentration and hybridization efficiency is discussed in [15.129]. Two different DNA-binding proteins, the transcription factors SP1 and NF-kappa B are investigated [15.130]. Phase transition and stability issues of DNA are discussed in [15.131]. Differential gene expression of the gene 1-8U, a potential marker for cancer progression or viral infections, has been observed in a complex background. The measurements provide results within minutes at the picomolar level without target amplification, and are sensitive to base mismatches [15.132].

Proteins and Peptides

Microfabricated cantilevers were utilized to detect adsorption of low-density lipoproteins (LDL) and their oxidized form (oxLDL) on heparin, and to detect adsorption of bovine serum albumin and Immunoglobulin G (IgG) [15.133]. In [15.134] the activity, stability, lifetime and re-usability of monoclonal antibodies to myoglobin covalently immobilised onto

microfabricated cantilever surfaces was investigated. Using piezoresistive microcantilevers the interaction of anti-bovine serum albumin (a-BSA) with bovine serum albumin (BSA) was studied [15.135]. Continuous label-free detection of two cardiac biomarker proteins (creatin kinase and myoglobin) is demonstrated using an array of microfabricated cantilevers functionalized with covalently anchored anti-creatin kinase and anti-myoglobin antibodies [15.41]. Label-free protein detection is reported using a microcantilever functionalized with DNA aptamers receptors for Taq DNA polymerase [15.136]. Label-free detection of C-reactive protein (CRP) using resonant frequency shift in piezoresistive cantilevers is described in [15.137], utilizing the specific binding characteristics of CRP antigen to its antibody, which is immobilized with Calixcrown SAMs on Au. Receptors on microcantilevers for serotonin, but insensitive to its biological precursor with similar structure tryptophan are described in [15.138]. Using single chain fragment antibodies instead of complete antibodies allowed to lower the limit of detection to concentrations of about 1 nM [15.139]. In [15.140] detection of prostate specific antigen (PSA) and C-reactive protein is reported. Detection of the human oestrogen receptor in free and oestradiol-bound conformation can be distinguished [15.141]. The Ca^{2+} binding protein calmodulin changes its conformation in presence of absence of Ca^{2+} resulting in a microcantilever deflection change [15.142]. No effect is observed upon exposure to K^{+} and Mg^{2+} . Detection of activated cyclic adenosine monophosphate (cyclic AMP)-dependent protein kinase (PKA) is performed in dynamic mode employing a peptide derived from the heat-stable protein kinase inhibitor (PKI) [15.143]. Detection of streptavidin at 1–10 nM concentration is reported using biotin-coated cantilevers [15.144]. Using GST (glutathione-S-transferase) for detection of GST antibodies, a sensitivity of 40 nM was obtained [15.145]. A two-dimensional multiplexed real-time, label-free antibody–antigen binding assay by optically detecting nanoscale motions of two-dimensional arrays of microcantilever beams is presented in [15.146]. Prostate specific antigen (PSA) was detected at 1 ng/ml using antibodies covalently bound to one surface of the cantilevers. Conformational changes in membrane protein patches of bacteriorhodopsin proteoliposomes were observed with microcantilevers through prosthetic retinal removal (bleaching) [15.147]. Using an analog of the myc-tag decapeptide, binding of anti-myc-tag antibodies is reported [15.148].

Lipid Bilayers, Liposomes, Cells

Cantilever array sensors can sense the formation by vesicle fusion of supported phospholipid bilayers of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) on their surface and can monitor changes in mechanical properties of lipid bilayers [15.149]. Liposomes are detected based on their interaction with protein C2A which recognizes the phosphatidylserine (PS) exposed on the surface of liposome [15.150]. Individual *Escherichia coli* (*E. coli*) O157:H7 cell-antibody binding events using microcantilevers operated in dynamic mode are reported [15.151]. The contractile force of self-organized cardiomyocytes was measured on biocompatible poly(dimethylsiloxane) cantilevers, representing a microscale cell-driven motor system [15.152]. Resonating cantilevers were used to detect individual phospholipid vesicle adsorption in liquid. A resonance frequency shift corresponding to an added mass of 450 pg has been measured [15.153].

Spores, Bacteria and Viruses

Micromechanical cantilever arrays have been used for quantitative detection of vital fungal spores of *Aspergillus niger* and *Saccharomyces cerevisiae*. The specific adsorption and growth on concanavalin A, fibronectin or immunoglobulin G cantilever surfaces was investigated. Maximum spore immobilization, germination and mycelium growth was observed on the immunoglobulin G functionalized cantilever surfaces, as measured from shifts in resonance frequency within a few hours, being much faster than with standard Petri dish cultivation [15.154]. Short peptide ligands can be used to efficiently capture *Bacillus subtilis* (a simulant of *Bacillus anthracis*) spores in liquids. Fifth-mode resonant frequency measurements were performed before and after dipping microcantilever arrays into a static *B. subtilis* solution showing a substantial decrease in frequency for binding-peptide-coated microcantilevers as compared to that for control peptide cantilevers [15.155].

Medical

A bioassay of prostate-specific antigen (PSA) using microcantilevers has been presented in [15.156], covering a wide range of concentrations from 0.2 ng/ml to 60 µg/ml in a background of human serum albumin (HSA). Detection has been confirmed by another group using microcantilevers in resonant mode [15.157, 158]. The feasibility of detecting severe acute respiratory syndrome associated coronavirus (SARS-CoV) using microcantilever technology is studied in [15.159] by

showing that the feline coronavirus (FIP) type I virus can be detected by a microcantilever modified by FIP type I anti-viral antiserum. A method for quantification of a prostate cancer biomarker in urine without sample preparation using monoclonal antibodies is described in [15.160].

15.7.3 Microcantilever Sensors to Measure Physical Properties

Besides chemical and biochemical sensing, microcantilevers can also detect changes in physical properties of surrounding media, such as gas or liquid, or of layers deposited on the cantilever itself.

Density and Viscosity

A piezoelectric unimorph cantilever as a liquid viscosity-and-density sensor was tested using water-glycerol solutions of different compositions, whereby the resonance frequency decreased while the width of the resonance peak increased with increasing glycerol content [15.161]. The viscosity of complex organic liquids with non-Newtonian behavior is studied in [15.162] in a wide range from 10 to 500 mm²/s. Simultaneous determination of density and viscosity of water/ethanol mixtures based on resonance curves of microcantilevers is reported in [15.163]. A detailed theoretical study of viscoelastic effects on the frequency shift of microcantilever chemical sensors is given in [15.164]. Microcantilever deflection as a function of flow speed of viscous fluids is investigated in [15.165]. Viscosity of sugar solutions is tested using microcantilevers [15.166].

Gas and Flow Sensing

Gas sensing does not only involve chemical detection, but also pressure and flow sensing. *Brown et al.* [15.167] have studied the behavior of magnetically actuated oscillating microcantilevers at large deflections and have found hysteresis behavior at resonance. The amplitude at the actuation frequency changes depending on pressure due to damping. The authors have used cantilever in cantilever (CIC) structures, and have observed changes in deflection as gas pressure is varied. At atmospheric pressure, damping is large and the oscillation amplitude is relative small and hysteresis effects are absent. At lower pressure, abrupt changes in the oscillation amplitude occur with changes in the driving frequency. Since the change of amplitude and driving frequency, at which they occur are pressure dependent, these quantities can be used for accurate determina-

tion of gas pressure, demonstrated in the range between 10^{-3} and 10^2 Torr. *Brown et al.* [15.168] emphasize that microelectromechanical system pressure sensors will have a wide range of applications, especially in the automotive industry. Piezoresistive cantilever based deflection measurement has major advantages over diaphragms. The pressure range has been extended to 15–1450 Torr by means of design geometry adaptation. *Su et al.* [15.169] present highly sensitive ultrathin piezoresistive silicon microcantilevers for gas velocity sensing, whereby the deflection increases with airflow distribution in a steel pipe. The detection principle is based on normal pressure drag producing bending of the cantilever. The minimum flow speed measured was 7.0 cm/s, which is comparable to classical hot-wire anemometers. *Mertens et al.* [15.170] have investigated the effects of temperature and pressure on microcantilever resonance response in helium and nitrogen. Resonance response as a function of pressure showed three different regimes, which correspond to molecular flow, transition regimes and viscous flow, whereby the frequency variation of the cantilever is mainly due to changes in the mean free path of gas molecules. Effects observed allow measurement of pressures between 7.5×10^{-5} and 7500 Torr. *Mortet et al.* [15.171] present a pressure sensor based on a piezoelectric bimorph microcantilever with a measurement range between 75 and 6400 Torr. The resonance frequency shift is constant for pressures below 375 Torr. For higher pressures the sensitivity is typically a few ppm/mbar, but depends on the mode number. *Sievilä et al.* [15.172] present a cantilever paddle within a frame operating like a moving mirror to detect the displacements in the oscillating

cantilever using a He-Ne laser in a Michelson interferometer configuration, whereby the cantilever acts as moving mirror element in one path of the interferometer. A fixed mirror serves a reference in the other arm of the interferometer.

Thermal Expansion

The thermal expansion of TaO_xN_y thin films deposited on a microcantilever was measured to examine the residual stress and the thermal expansion coefficient by observing the changes in radius of curvature [15.173]. Thermal drift issues of resonating microcantilevers are discussed in detail in [15.174].

Infrared Imaging

Microcantilevers can also be used as uncooled, microcantilever-based infrared (IR) imaging devices by monitoring the bending of the microcantilever as a function of the IR radiation intensity incident on the cantilever surface. The infrared (thermal) image of the source is obtained by rastering a single microfabricated cantilever across the image formed at the focal plane of a concave mirror [15.175–177]. The method has later been refined such that photons are detected using the stress caused by photoelectrons emitted from a Pt film surface in contact with a semiconductor microstructure, which forms a Schottky barrier. The photoinduced bending of the Schottky barrier microstructure is due to electronic stress produced by photoelectrons diffusing into the microstructure [15.178]. The performance of IR imaging via microcantilevers has been enhanced by one-fold leg and two-fold legs beam structures with absorber plates [15.179–181].

15.8 Conclusions and Outlook

Cantilever-sensor array techniques have turned out to be a very powerful and highly sensitive tool to study physisorption and chemisorption processes, as well as to determine material-specific properties such as heat transfer during phase transitions. Experiments in liquids have provided new insights into such complex biochemical reactions as the hybridization of DNA or molecular recognition in antibody–antigen systems or proteomics.

Future developments must go towards technological applications, in particular to find new ways to characterize real-world samples such as clinical samples. The development of medical diagnosis tools requires an improvement of the sensitivity of a large number of genetic tests to be performed with small amounts of single

donor-blood or body-fluid samples at low cost. From a scientific point of view, the challenge lies in optimizing cantilever sensors to improve their sensitivity to the ultimate limit: the detection of individual molecules.

Several fundamentally new concepts in microcantilever sensing are available in recent literature, which could help to achieve these goals: the issue of low quality factor of resonating microcantilevers in liquid has been elegantly solved by fabrication of a hollow cantilever that can be filled with biochemical liquids. Confining the fluid to the inside of a hollow cantilever also allows direct integration with conventional microfluidic systems, and significantly increases sensitivity by eliminating high damping and viscous

drag [15.182]. Biochemical selectivity can be enhanced by using enantioselective receptors [15.183]. Other shapes for micromechanical sensors like microspirals could be advantageous for biochemical detec-

tion [15.184]. Miniaturization of microcantilevers into *true* nanometric dimensions, like by using single wall carbon nanotubes [15.185] or graphene sheets [15.186] will further increase sensitivity.

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