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# Micro/Nano fabricated cantilever based biosensor platform: A review and recent progress

Aviru Kumar Basu[a,c,d], Adreeja Basu[b], Shantanu Bhattacharya[a,c,*]

[a] Design Programme, Indian Institute of Technology, Kanpur, U.P. 208016, India
[b] Department of Biological Sciences, St. John's University, New York, N.Y 11439, USA
[c] Microsystems Fabrication Laboratory, Department of Mechanical Engineering, Indian Institute of Technology, Kanpur, U.P. 208016, India
[d] Singapore University of Technology and Design, 487372 Singapore

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ABSTRACT

Recent trends in biosensing research have motivated scientists and research professionals to investigate the development of miniaturized bioanalytical devices to make them portable, label-free and smaller in size. The performance of the cantilever-based devices which is one of the very important domains of sensitive field level detection has improved significantly with the development of new micro/nanofabrication technologies and surface functionalization techniques. The cantilevers have scaled down to Nano from micro-level and have become exceptionally sensitive and also have some anomalous associated properties due to the scale. In this review we have discussed about fundamental principles of cantilever operation, detection methods, and previous, present and future approaches of study through cantilever-based sensing platform. Other than that, we have also discussed the past major bio-sensing efforts through micro/nano cantilevers and about recent progress in the field.

## 1. Introduction

In previous years, a significant amount of progress has been made in micro-/ nanoelectromechanical systems technology which has provided technologists and researchers advanced diagnostic tools for in situ biosensing applications. This high rate of progress in micro/nano electromechanical (MEMS/NEMS) technologies has become possible due to advancements in the micro/nano-technology tools and fabrication [1–11]methodologies. MEMS/NEMS based cantilever platforms provide higher sensitivity, compactness, low limits of detection, real-time detection and cost-effectiveness as compared to a standard assay based diagnostic tools. There have been significant of applications of cantilevers since its inception and applications to detection and sensing of many different biological entities like DNA, RNA, protein [12], viruses, pesticides, metal, antibodies, explosives [13], etc.

In cantilever based chemical and biological sensing, the target molecules are detected by conversion of extremely small mechanical displacements of the micro-cantilevers due to their bending (primarily from minuscule changes in surface energy) into distinguishable electrical signals and readouts. Receptor molecules that have a high affinity towards the target molecules are immobilized on one or both sides of the micro-fabricated cantilevers. When the receptor molecule gets exposed to the target molecules, molecular interactions occur on the surface of the sensor due to which there is a change in the surface energy. If the immobilization is just towards one side, there is a surface energy differential which may lead to a surface bending of the cantilever structure. In general, the interaction or binding between the target and the receptor molecules induce changes within the cantilevers either through a change in their resonance frequency (dynamic mode) or providing them short displacement by virtue of bending of the cantilever (static mode) [14]. The above-mentioned changes in the surface of the cantilever are used to determine in principle the binding of the target on the surface of the cantilever and this information of binding can be successfully used for assaying purposes of a variety of molecular species. Generally, the dynamic mode of measurements in cantilevers gives an overall higher resolution but it suffers from fluid damping issues, which badly effects the sensitivity of the cantilevers. In the static mode of measurements, the cantilever is placed in a polymeric, acrylic or Teflon based microfluidic chamber, with the inlet and the outlet port designed in such a manner to promote a laminar fluid flow around the cantilever so that the noise generated due to fluid turbulence reduces. A specific immobilization protocol and proper cleaning technique generally reduce both the cross-sensitivity and the noise in measurements. In the static mode, the deflection induced to receptor-target binding at

* Corresponding author at: Mechanical Engineering and Design Programme, Indian Institute of Technology, Kanpur, U.P. 208016, India
*E-mail address:* bhattacs@iitk.ac.in (S. Bhattacharya).

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0141-0229/ 

the molecular level is converted into an electrical signal or an optical signal in terms of a shift of the optical spot which occurs through a transducer like a piezoelectric crystal or a capacitive or piezo-resistive transducer. Typically, in an optical readout system, the nano-displacement of the cantilever is measured by focusing a laser beam on the tip of the cantilever surface. The reflection from the cantilever beams is recorded in a position sensitive detector assembly which calibrates the micro-cantilever deflection through a shift in the reflected laser spot which occurs due to bending of the cantilever. Another option is an integrated readout mechanism where the sensing is carried out by optics being guided through embedded waveguides. This optics-based mechanical readout can depict the nano-scale displacement of the cantilever with high accuracy and resolution.

The micro-cantilever-based sensing platform after its inception was routinely used in atomic force-based surface imaging through reconstruction data obtained by recording of cantilever deflections as the cantilever moved over a certain topography. The main applications of micro-cantilevers as chemical sensors have been demonstrated by Thundat et al. [15]. After this, in the past two decades the micro-cantilever based sensors have been heavily explored to carry out detection of various biological and chemical analytes. After its discovery, the sensing tip of an atomic force microscope (AFM) was fabricated through micromachining of solid state semiconductor materials. Following this period there has been great advancement in technology for fabrication of cantilevers and now they are being fabricated using other materials like ceramic, metals and polymers. The main motivation for the researchers to find alternative materials and processes are to curtail the huge expense of semiconductor fabrication. Previously, polymers like PDMS were heavily explored in the polymeric domain [16] following which the focus was slowly shifted to SU-8 based polymeric cantilevers which demonstrated much better performance in terms of cost and amenability of fabrication.

During the last decade, the development of cantilever based platform for as biochemical sensor and for various clinical applications have paced up and there have been various research groups from different places around the world contributing to this area [17–19]. A thorough review on past and recent trends in cantilever-based detection/diagnostic platform using various schemes is discussed in this paper. In Table 1, an attempt has been made to highlight and systematically document the major findings of the cantilever-based disease detection studies done by different research groups worldwide until now (2001–2019).

### 1.1. Working principle

#### 1.1.1. Stoney's equation

Cantilevers, with subnanometric resolution, are mechanical devices of high sensitivity which can detect and precisely measure mechanical stresses produced due to the binding of biomolecules [20]. Biomolecular interaction over the cantilever surface results in the mechanical bending of cantilever, either in the static mode or in the dynamic mode, which can be measured very easily shown in Fig. 1. [21,22]Cantilevers provide label-free detection of biomolecules with fast response and real-time data. The 1980s saw the use of microcantilever for the first time as a force probe in Scanning Force Microscopy [23]. Since then, micro-cantilever based biosensors have been effectively exploited for diverse biological applications like to measure mass off biomolecules and cells [24], nucleic acids, fungal and bacterial growth [21], etc.

The Stoney's equation is the main fundamental equation for the motion of a cantilever. It relates the residual surface stress per unit length of any thin film with the curvature that the film surface might take if there is a change in surface energy. The curvature has no relation with geometric properties of the film. This equation is mostly used for determining residual stress in thin films. The equation can be represented as

$$\kappa = \frac{6\Delta\sigma}{Et^2} \tag{1}$$

Where 'E' and 't' are the elastic modulus and thickness of the substrate. Since a cantilever plate is generally long and wide the young modulus 'E' is generally replaced by the biaxial modulus $\frac{E}{(1-\nu)}$ where '$\nu$' is the Poisson's ratio. The surface stress measurement is carried out in units 'N/m'. This surface stress induced deflection in the substrate is compared multiple times to the moment induced deflection of a thin plate. The surface stress and the concentrated moment is related as '$M_0 = \frac{\Delta\sigma t'}{2}$ where '$M_0$' is the applied concentrated moment, 'E' is the elastic modulus of plate and 'I' is the moment of inertia of the beam. Applying the Stoney's equation [25,26], the surface stress bends the plate with a uniform curvature. The following curvature relation for the plate bending can be represented as $\kappa = \frac{M_0}{EI}$ where '$M_0$ 'is the applied concentrated moment, 'I' is the moment of inertia of the beam and 'E' is the elastic modulus of the plate. For, a rectangular beam 'I = $bt^3/12$', where 't' is the thickness and 'b' is the width of the beam. The moment per unit length and the surface stress can be related as '$M_0 = \frac{\Delta\sigma t'}{2}$. This relation shows that the moment is directly related to the induced stress and the geometric properties of the plate. The governing differential equation for an isotropic thin plate which expressed bending and twisting in terms of curvature and deflection of the plate can be given as in equations 2∼4 below.

$$\frac{\partial^2 z}{\partial x^2} + \nu\frac{\partial^2 z}{\partial y^2} = \frac{M_x}{D} \tag{2}$$

$$\frac{\partial^2 z}{\partial y^2} + \nu\frac{\partial^2 z}{\partial x^2} = \frac{M_y}{D} \tag{3}$$

$$\frac{\partial^2 z}{\partial x \partial y} = \frac{M_{xy}}{(1-\nu)D} \tag{4}$$

Where D = $Et^3/12(1-\nu^2)$ is the flexural rigidity of the plate. It is assumed that $M_x = M_y = M_0$. and neglecting the shear component $M_{xy}$ the deflection 'Z' is illustrated in Eq. (5) below.

$$Z = \frac{\Delta\sigma t\,(x^2+y^2)}{4D\,(1+\nu)} \tag{5}$$

If the cantilever beam is clamped so that movement in the 'y' direction gets restricted it can be further simplified as in (6) below

$$Z = \frac{3(1-\nu)\Delta\sigma}{E}\left(\frac{l}{t}\right)^2 \tag{6}$$

It is very well-known and comes from the variants of Stoney's equation used to determine the residual surface stress present in thin films by measuring the surface stress induced deflection. To include the clamped edge boundary condition Sader et al. [27] have proposed a modified Stoney's equation, viz.,

$$Z = \frac{3K(1-\nu)\Delta\sigma}{E}\left(\frac{l}{t}\right)^2 \tag{7}$$

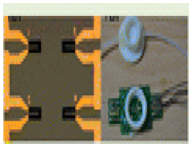
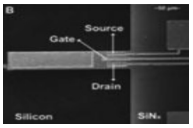
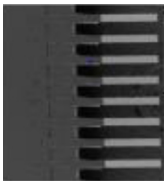
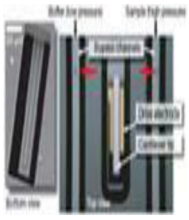
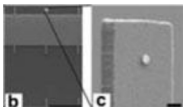
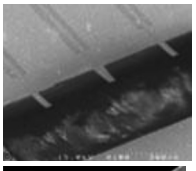
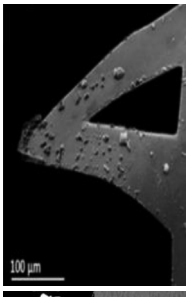
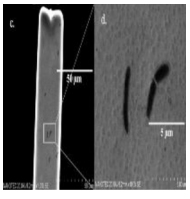
where 'K' is a constant dependent on material and geometric properties of cantilever.

### 1.2. Immobilization techniques

Immobilization of biomolecules onto surfaces is an important step for intermolecular interactions which occurs in high density. In, this kind of biosensing applications it is always a key challenge to get a high level of sensitivity with low limits of detection. It is dependent on the surface coverage of biomolecules on the surface of the cantilever sensor. The proper immobilization helps to maintain proper stability and increases binding efficiency for the analytes. As a result, it leads to higher surface stress on the cantilever and faster response/detection.

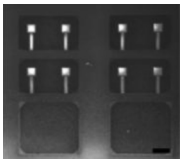
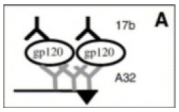
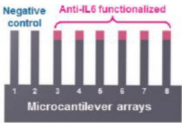
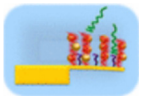
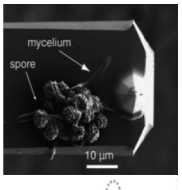
Inkjet Printing: An array of cantilevers can be easily immobilized by using the inkjet printing technology. A controlled deposition method

**Table 1**
An overview of significant works on cantilever based biosensors from past reported articles to recently reported articles is shown in Table 1 below [24,46,54–59,60–67].

| Institute | Device Figure | Detection Mode | Detection Mechanism | Analyte | Detection Limit | Medium | Reference |
|---|---|---|---|---|---|---|---|
| IIT BOMBAY |  | Static | Piezo resistive | TNT | n.m | Vapour | [54] |
| Northwestern University |  | Static | MOSFET Embedded | Biotin | 100 fg ml − 1 | Liquid | [46] |
| Oakridge Laboratory |  | Static | Optical deflection | SNP | n.m | Liquid | [55] |
| University of Alberta |  | Static | Optical deflection | HSA | n.m | Liquid | [56] |
| Massachusetts Institute of Technology |  | Dynamic | Resonance frequency shift | Single Cell | 100 ng | Vacuum | [24] |
| Cornell |  | Dynamic | Resonance frequency shift | dsDNA | 1.65ag | Vacuum | [57] |
| Korea Institute of Science and Technology |  | Dynamic | Resonance frequency shift | PSA | 10 pg $ml^{-1}$ | Controlled Air | [58] |
| Indian Institute of Technology Kanpur |  | Static | Optical deflection<br>Graphene based surface functionalisation | Cholesterol | 100 fM | Liquid | [59] |
| Mahidol University |  | Dynamic | Resonance Frequency shift | Vibrio Cholerae O1 | $10^3$ cfu/mL | Liquid | [60] |

(*continued on next page*)

**Table 1** (*continued*)

| Institute | Device Figure | Detection Mode | Detection Mechanism | Analyte | Detection Limit | Medium | Reference |
|---|---|---|---|---|---|---|---|
| UC Berkley |  | Static | Optical Deflection | DNA melting | n.m | Liquid | [61] |
| Trinity College, Dublin |   | Dynamic | Resonance frequency shift | Microbial cell growth (Aspergillus niger) | n.m | Liquid | [62] |
| Duke University |   | Static | Surface Stress | HIV-1 envelope glycoprotein gp120 | 0.4 μg/mL | Liquid | [63] |
| POSTECH |   | Dynamic | Resonance frequency shift | Interleukin Alpha-fetoprotein Interferon- γ | 0.1 pg/mL | Liquid | [64] |
| University of Alberta |  | Static | Optical deflection | Dopamine | $5 * 10^{-11}$mol/L | Liquid | [67] |
| University of Basel |   | Dynamic | Resonance frequency shift | A.niger and S.cerevisiae | $10^3$-$10^6$ cfu/mL | Liquid | [66] |
| Iowa State University |  | Optical detection | Surface stress | Mouse Lipocalin-2 | 4 nM | Liquid | [65] |

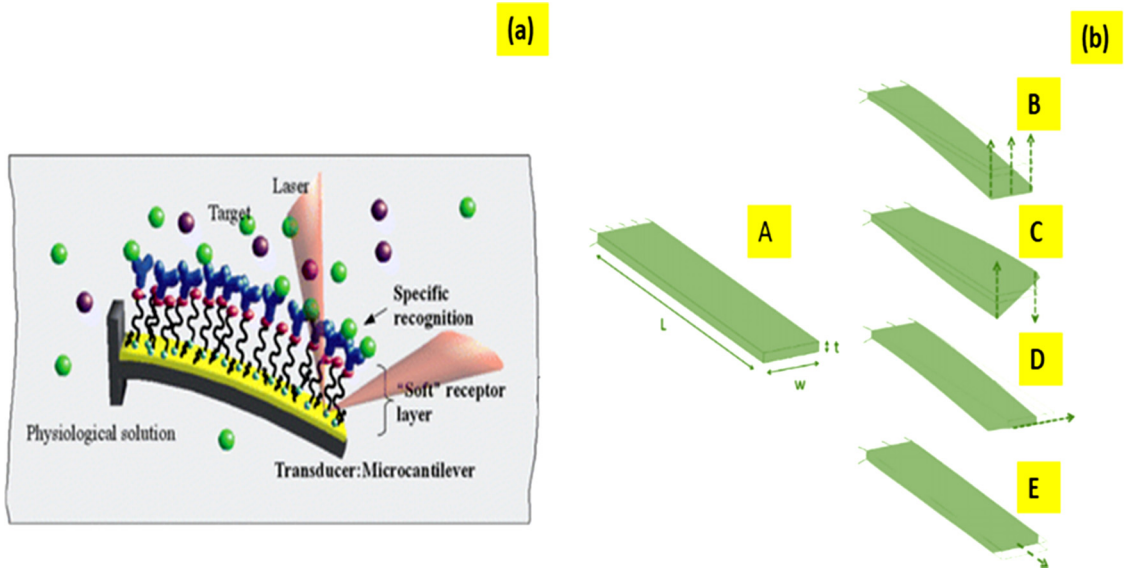



**Fig. 1.** Reprinted with permission from Alvarez and Lechuga [21]. Copyright (2010) Royal Society of Chemistry Reprinted with Permission from Biosensors and Bioelectronics (2012) [22].
(a) Basic sensing mechanism on the surface of microcantilever (b) Modes of cantilever operation in dynamic (resonance) mode (A) Basic cantilever structure (B) transverse mode, (C) torsional mode, (D) lateral mode, and (E) longitudinal mode Reprinted with Permission from Biosensors and Bioelectronics (2012) [22].

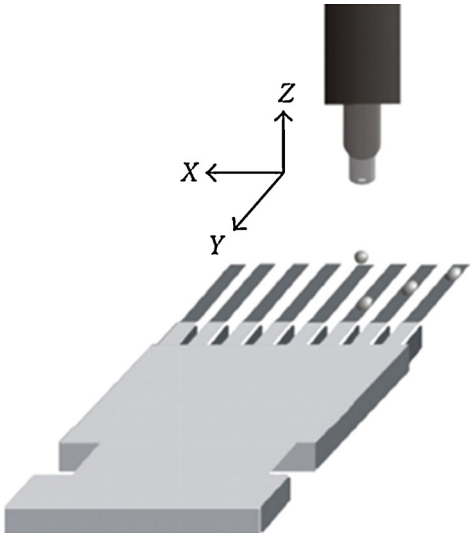



**Fig. 2.** An illustration of autodrop inkjet spotting system for cantilever array functionalizaation. [29].

[28] for surface coating of the fabricated cantilevers is the major key for converting the micro-nano cantilevers into chemical or biological sensors. A novel method of dispensing small amounts of liquid with a good spatial accuracy can be provided through the inkjet printing technology. The method is highly reliable and suitable for depositing SAMS or printing DNA microarrays, proteins etc. of a variety of surfaces. The inkjet printing method is much versatile, easy to use as well as faster for coating an array of microcantilevers than coating via micropipettes or capillaries. This method can be also utilized to coat arbitrary structures in non-contact mode. The inkjet printing has been utilized for cell deposition, above the surface of cantilever. Also, as inkjet printing technology by and large works on ink throw at distances it really does not damage or deform the substrate much which could have been the case with other needle based dispensing mechanisms. There are also some other techniques of selective coating on cantilever surfaces like capillary array and contact printing methods, but for selective coatings on only one side of the cantilever, inkjet printing technique is much superior to the others shown in Fig. 2 [29]. The chances of contamination on the backside of the cantilever is avoided [30]. In a comparative study between inkjet printing method and capillary coating method, Lukas et al. [29] showed that the inkjet printing method on the cantilever showed more precision as well as controlled way of cell deposition. Studies by few other research groups [30–32] have also affirmed the fact that the inkjet printing is a more reliable, less time consuming and specific technology for surface functionalization on the cantilever surface to obtain faster sensing and lower limits of detection.

### 1.3. Deflection sensing in micro-cantilevers: various detection methods

Several detection methods are deployed for finding out the minuscule movements and deflections within cantilevers. These cover various methods like Optical detection methods (through reflection, diffraction, interferometry etc.), Piezoresistive methods, Capacitive methods, MOSFET based methods etc.

### 1.4. Optical detection methods

#### 1.4.1. OBDT (Optical beam deflection technique)

The optical method is shown below in Fig. 3, where a focused laser beam of light with low power falls on the tip of the cantilever beam and gets reflected to the position sensitive detector (psd). The light does not affect the biomolecules coated on the other surface of the cantilever beam. As the deflection in the cantilever beam occurs there is a change in the position of the reflected beam of light and can provide geometric information related to the deflection of the cantilever beam. The advantage of this method is that very minuscule deflection of cantilever deflection of the order of nanometer to sub-nanometer levels can be easily obtained. The alignment of this kind of system is quite complex and expensive.

#### 1.4.2. Optical diffraction-based technique

Prior to this mostly optical beam-based deflection techniques were utilized for measurements of cantilever deflections. Another important optical phenomena, viz., Diffraction effects [33,9] have recently been utilized/incorporated in carrying out the optical measurements to monitor the static or dynamic bending of micro-cantilever structures. Illumination of the edges of the cantilever beam gives rise to asymmetric diffraction patterns and pattern shifts. This diffraction data can then be used to back calculate the tilt and curvature of the beam. In a way the problems associated with the optical alignment complexity etc. can be reduced. Fig. 4 (a) and (b) [33] show the optical detection of cantilever deflection through deflection in the reflected laser beam and similarly Fig. 5(a)–(c) show the diffraction-based bend sensing in micro-cantilevers.

#### 1.4.3. Interferometry

In the interferometer based optical deflection method, there is an interference of reflected beams from the tip of micro/nano cantilever and the reference cantilever beam. The interference of these beams with respect to each other may lead to fringes and the fringe data of geometry or fringe shift can then be utilized to back calculate the static or dynamic detection aspect of the cantilevers [33,9] This Interferometer technique is highly accurate and sensitive and can provide measurement of deflections upto sub nanometer levels. Though it can provide displacement upto 0.1 Å it does have many shortcomings and one principle shortcoming in this method lies in the placement of optical fibers in liquid medium to carry out the sensing by guiding the light past the medium is extremely time consuming. The drawbacks in this method are mainly due to mechanical vibration, noises and optical losses. The alignment of optical fiber setup is difficult, other than that the optical fibers can induce additional errors like stress during alignment as well as thermal drift at very low time scales [34]. As, a result accuracy in displacement measurements cannot be fully maintained in the liquid medium [35]. This kind of optical setup is generally extremely sensitive to acoustic and mechanical fluctuations, so proper isolation is required [34,36,37]

#### 1.4.4. Piezoresistive method

The piezo resistive method [38] has used a Wheatstone bridge orientation for detection of various analytes. The surface stress generated on the cantilever creates strain effects on the piezo-resistive material like doped silicon or doped poly-silicon. One cantilever with the resistor material interacts with the analyte of interest and the other cantilever (reference) filters out the signal. The deformation occurring on the cantilever due to surface stress can be easily co-related to the change in resistance of the piezo material. The advantage of this system is that the complexity of the optical equipment's which is normally there in optical sensing of deflection is easily avoided and this process of recording is more amenable to integration with microelectronics. The deflection readout for this piezoresistive system is a minimum of 1 nm (resolution). It is difficult to go beyond this deflection because it is difficult to fabricate thin cantilever with circuitry and isolation from the liquid is required [39]. Also, there is an additional effect of secondary deflection generated by a temperature change as there is a fluctuation in the current signal coming out of the piezo layer. The piezoresistive cantilever requires flow of current, through a current flowing circuit on the surface of the cantilever. The piezoresistance gives rise to heat dissipation and additional thermal drift during flow of current through the microcantilever [40–42]. This leads to parasitic cantilever deflection

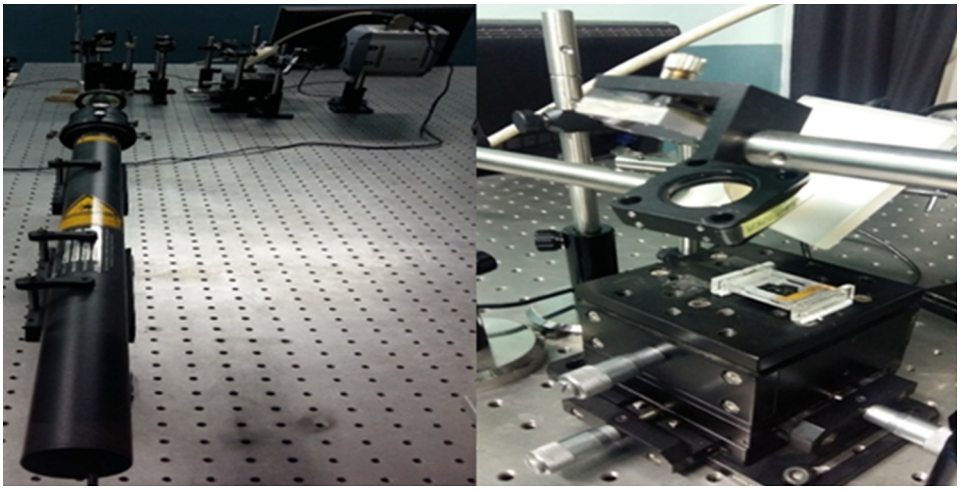


**Fig. 3.** OBDT setup for microcantilever deflection at IIT Kanpur.

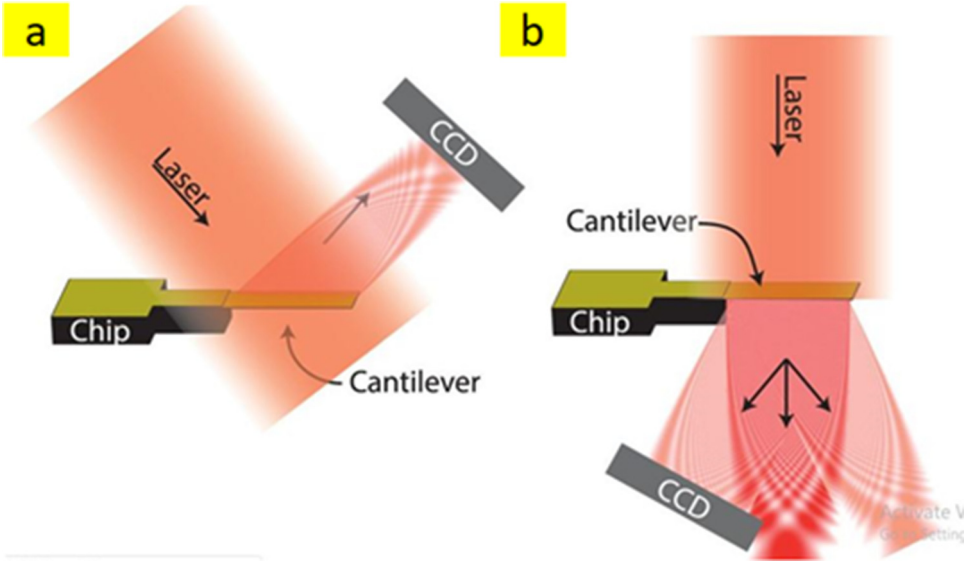



**Fig. 4. a** Diffraction from light reflected from cantilever. b Transmission from light transmitted through cantilever. [33] (Scientific reports, 2016 Rodolfo I. Hermans).

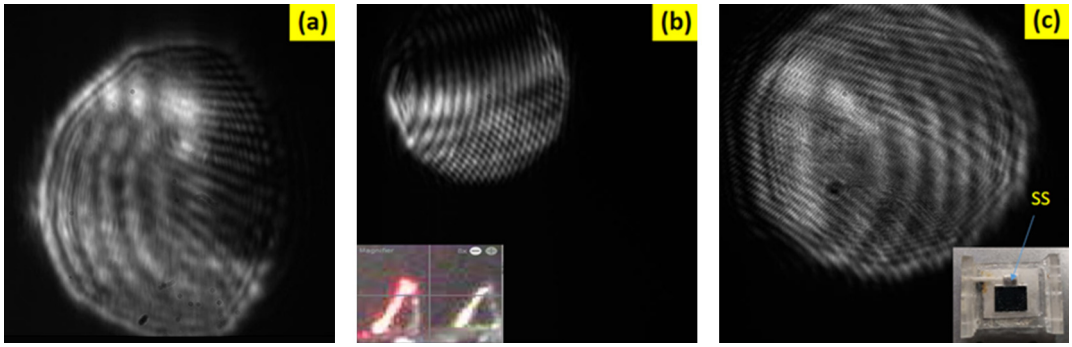



**Fig. 5.** a Diffraction pattern captured using CCD from a fully illuminated V-shaped microcantilever b. Diffraction pattern obtained from side edge of a V-Shaped cantilever c. Diffraction pattern obtained by illuminating the tip of V-shaped cantilever. Inset show microfluidic channel developed for diffraction, with thin layer of ss sheet attached as the base layer to obtain high resolution diffraction pattern from reflection. (Images were obtained at Biophotonics Laboratory, IITK with Mr. Amar Nath Shah).

along with the normal cantilever deflection and changes in piezo-resistance. This secondary deflection results into an erroneous measurement.

*1.4.5. Capacitance method*

The capacitance method [43] of measuring nano-displacements within cantilevers is yet another powerful detection methodology. The change in capacitance occurring from the displacement of the

conductor on the cantilever and on the substrate holding the cantilever may give absolute change in the capacitance values which can be related again to the deflection of the cantilever. The main problem with this setup arises from the use of electrolytic solutions which may give rise to faradic currents and undesirable signals.

### 1.5. MOSFET based cantilevers

The MOSFET (Metal oxide semiconductor field effect transistor) is a field effect transistor device which is widely used in switching and amplifying signals in electronic devices. It is a four-terminal device consisting of source, gate, drain and body terminals [44,45]. Presently MOSFETS [46] are integrated on cantilevers which generally give better sensitivity and low noise signals with direct readouts. MOSFETS are generally integrated on the base of the cantilever. The gate region becomes more active with surface stress and the drain current decreases due to deflection and bending of the cantilever. Table 1 indicates a list of microcantilever being developed by research groups in different parts of the globe with a summary of the mode of deflection, the analyte that these groups have been detecting, detection limit, the medium in which detection is carried out and the reference paper.

### 1.6. Lateral / Torsional mode of detection (Dynamic mode)

A few studies have suggested the utilization of torsional or lateral mode resonance nanocantilevers in biosensing research ([47–51]). Unlike the conventional bending mode, the shear stress generated in the torsional mode is free from the effect of volume tension or compression [47]. In an initial study, Sharos [48] et al. reported a detection method by eccentrically attaching a mass particle and observing the three-dimensional mode in the vibration spectrum obtained from the microcantilever. The cantilevers in the lateral and torsional frequency modes gave a greater magnitude of mass sensitivity. The Q-factors of the cantilevers also improved in a greater extent compared to traditional bending modes of the cantilever. Later, Johnson et al. [49] improved the method by developing novel cantilever designs, which showed ultrasensitive detection to mass change when self-assembled layers of gold were formed upon the cantilever. An asymmetric anchor design approach was followed for the design of the piezoelectric cantilever. This resulted in detection limit for mass change of up to 75 fg/Hz. The microcantilevers have also been widely used for detection of volatile organic compounds. The Q factor of the sensor increases in the lateral resonating mode with a detection limit of 1 ppm [52]. An intensive study reported the use of microcantilever resonators in torsion mode for on-the-spot detection of specific bio/chemical mass adsorption. The biotin/avidin interaction on the cantilever for 50 μm concentration resulted in a frequency shift of 433 Hz [47,50]. In another torsion mode-based study, a piezoresistive latin cross-shaped cantilever [51] was effectively used for precise detection of Alpha-fetoprotein (AFP) antibody-antigen binding. The authors concluded that the sensitivity of the cantilevers in second-torsion mode were much superior than the first torsion mode-based cantilevers.

The lateral mode bending of cantilever is also widely used in AFM technology and is commonly known as lateral force microscopy [53]. Lateral force microscopy is commonly used for real time detection of important physical and chemical properties like adhesion, surface energy change, intermolecular forces at nanoscale level, and affirming the presence of specific chemical groups of a particular substance. This techniques are mostly useful in creation of microfluidic and nanofluidic devices, intelligent bio-arrays, chips, sensors, and drug delivery devices [23]. The improvement in sensitivity in torsional and lateral frequency modes can be a good prospect for future biosensing applications shown in Fig. 6 [49].

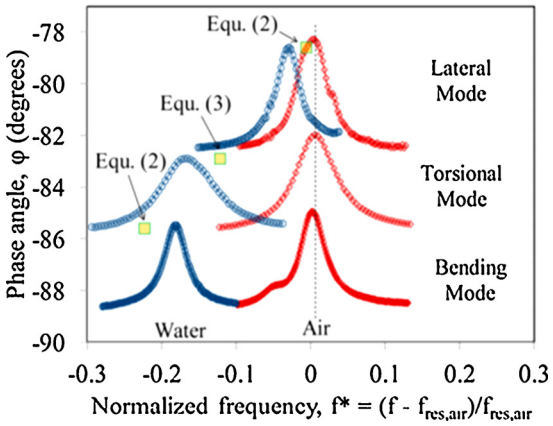



**Fig. 6.** Comparison of frequency response spectra of torsional (Δfair − liquid = 4.1 kHz, Qair = 23.3, ΔQair − liquid = 9.5, Ret = 5600) and lateral sensors (Δfair − liquid = 1.5 kHz, Qair = 37.4, ΔQair − liquid = 6.4, Rel = 190) in air and liquid with that of conventional bending modes present in sensors of design [49].

## 2. Biomolecular detection

Microcantilevers with nanomechanical deflections are applied to the detection of biomolecular agents. Static cantilever-based detection can occur in both aqueous and air medium. In case of the dynamic mode, only vacuum is preferable due to decrease in quality factor of the sensor because of viscous forces and damping behavior of the aqueous medium. In the following section, we discuss various bio-molecular sensing schemes according to the targets utilized.

### 2.1. Protein detection

The concentration of different kind of analytes that are present in human blood has been reported by Anderson using micro-cantilevers. He has reported in his article various disease biomarkers which are present below the nano-gram per-milliliter level. Cantilever based biosensors have been extensively used in protein detection in ultralow concentrations in several different applications. The following section provides a summary view into what biomolecular types have been detected through this approach.

#### 2.1.1. Prostate Cancer detectio

The prostate cancer markers are very important to keep an eye on progression of the disease. Prostate specific antigen (PSA) is one such marker serves as an important marker for both prostrate as well as female breast cancer. The PSA has been shown to be a validatory protein for cantilever based sensors by Arun Mazumdar's group long back at Berkley [68]. Wu and co-workers performed the quantitative detection of PSA through detection of both free PSA and complex PSA in the presence of human plasminogen and human serum albumin. Later, PSA was also detected in dynamic mode by Lee et al. using cantilever embedded with lead zirconate titanate (PZT material) with a limit of detection of 1 ng/mL in liquid and 10 pg/mL in controlled air.

#### 2.1.2. Myocardial infarction

Cantilever based sensors other than providing high sensitivity also provide a means of label-free detection without the binding of another secondary antibody. Arnz et al. ([69]) performed detection of two biomarkers myoglobin and creatin kinase related to acute myocardial infarction using cantilever sensors. The deflections were observed by them on differential basis with cantilevers in static mode by immobilizing one with the antibody and the other with BSA which acted as reference. The detection limits were obtained in this case as 20 μg/mL.

Similarly, in dynamic mode myoglobin was detected by Hwang et al. ([70]) using piezoelectric layer embedded cantilevers with detection limits in the range of 1 ~ 100 ng/mL).

Agarwal et al. [71] recently showed a technique to detect cardiac biomarkers through asymmetric functionalization of antibodies on one side of the cantilever. A comparison of functionalization symmetry (both side) and asymmetry (one side) of the cantilevers were done on silicon nitride piezoresistive cantilever. Preliminary studies were performed using immunoglobin protein. It was observed that the piezoresistance changes were higher in case of asymmetric bio-functionalized cantilever compared to the symmetric counterpart. Finally, this newly developed asymmetric cantilever platform was utilized to detect, important cardiac marker protein Troponin-I. The cantilevers were able to detect the biomarker with high sensitivity. A low detection limit of 250 ng/mL was obtained. The surface functionalization technique developed in this study has paved the way for clinical diagnostics of abnormalities in cardiac system at an early stage.

In another work Agarwal et al. [72] detected another cardiac biomarker- heart type fatty acid binding protein. SU-8 polymeric cantilevers were functionalized with amine molecules by a hot wire chemical vapor deposition technique. The antibody-antigen interaction study through the piezoresistive cantilever was carried out inside a PDMS flow cell. The immobilization protocol on surface of the cantilever developed by this group led to detection of crucial cardiac biomarker even at a low concentration of 100 ng/mL.

The study of viscosity and density measurement is important in biological samples, specifically in blood samples. The blood samples coagulate due to polymerization of fibrinogen which increases the viscosity of plasma. The coagulation of blood samples occurs due to series of biological reactions leading to the formation of clot. The enzyme thrombin plays the key role in blood coagulation. It converts the fibrinogen to fibrin leading to the formation of a protein network. Presently, a detailed coagulation analysis is usually performed by most of the research groups [73] by observing the prothrombin aprothrombin time which are mentioned through a parameter called international normalized ratio levels (INR). In previous studies, the physical properties for blood clot, viscosity and density were not measured. Padovani et al. [74] made an excellent attempt to measure the three important parameters - viscosity, density and the coagulation rate by fabricating an array of resonating cantilevers. Precise knowledge about these parameters are quite essential to know before performing any normal or cardiovascular surgery in a patient. In this study, the cantilevers were able to detect the analyte even at a very low volume of only 4 μL. The aprothrombin detection by the cantilever is obtained at 47 s only, which is within the clinical range. A recent investigation by Oyunbaatar et al. [75] has also affirmed the use of cantilever arrays as a promising technique for high throughput drug screening in cardiovascular studies.

Bashir et al. [76] detected a single vaccinia virus particle by scaling down the cantilever thickness to less than 100 nm shown in Fig.7 [77]. MOSFET embedded cantilever based detection have also been carried out by detection of biotin upto 100 fg/mL by recording the changes in drain current due to biomolecular interaction between biotin and streptavidin [77].

### 2.1.3. Protein conformation

The orientation and conformation change in protein are key factors which generally play a pivotal role in various types of biological processes. There are many spectroscopic techniques which are utilized to study the conformational change like FTIR, CD, NMR, Fluorescence spectroscopy etc. Microcantilevers based platform attracted the researchers due to higher sensitivity and label-free detection. Mukhopadhyay et al. [78] detected structural changes in protein upon a multiplexed cantilever platform at nanoscale level. The readout from cantilever in form of changes in piezo resistance distinguishes the changes in conformation between oestrorgen receptors (ER) in free

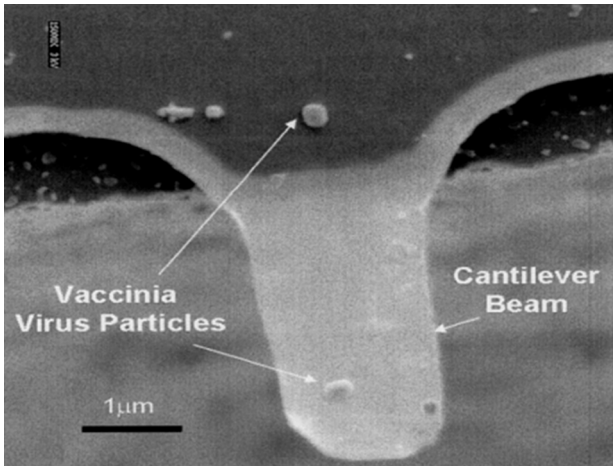



**Fig. 7.** FESEM image of Vaccina virus particle detection. [77].

form and oestradiol (E2) bound form. A conformational change occurs in oestrogen when binds to ligand binding domain of oestrogen receptors. The conformational changes are sensed here through peptide specific binding.

In another study, Braun et al. [79] reported a conformational change on surface membrane proteins. This article adopted Bacteriorhodopsin proteoliposomes as a model system and explored membrane protein-based ligand receptor interaction upon microcantilever arrays. The retinal in bacteriorhodopsin(bR) remains completely bound to the protein during the proton translocation cycle. The photoactivated retinal in bacteriorhodopsin is chemically removed by a process called bleaching, which leads to structural changes in bR protein. Here, microcantilevers are applied to detect the quantity of retinal removal from bR protein, based on mechanical surface stress upon the cantilevers.

### 2.2. DNA detection

Nucleic acids with simple repeating units (A, G, C and T) have always been the subject matter of detection due to easy modifiability, robust nature and ability to be successfully immobilized on a variety of surfaces.

Hybridization based detection of Nucleic Acids : Fritz and coworkers [80] have reported for the first time detection of nucleic acids through hybridization by using optical beam deflection over a cantilever. Differential deflection signals of the cantilevers were used between two oligomers over which DNA hybridization was carried out to detect DNA concentrations as low as at 400 nmol creating a surface stress of 5 mN/m with an actuation force of 300 pN. The authors also showed that the discrimination of single nucleotide polymorphism (SNPs) were made possible through cantilevers [80,81]. This group was unable to explain the lesser deflection in longer chain DNA hybridization (20 mer) as compared to shorter chain hybridization (16 mer).

Wu et al. [82] started a work of DNA hybridization, the nanomechanical motion of the cantilever during DNA hybridization occurred due to the changes in configurational entropy as well as intermolecular energetic changes occurring during biomolecular interaction. Further, Hansen et al. [55] showed the capability of the cantilevers to find the SNPs. In his paper he also reported that cantilever deflection in positive or negative direction was found to be dependent on the number of mismatches and the location of SNPs along the double stranded DNA molecule. The upward deflection on the cantilever occurs due to a decrease in compressive stresses on gold coated side of the cantilever. The decrease in stress on the cantilever occurs due to a sudden decrease in configurational entropy of double stranded DNA with respect to single stranded DNA. The terminal mismatch in the probes does not contribute much in the deflection whereas the internal mismatch can contribute to

stresses and downwards deflection of the cantilever. The greater the number of mismatches in base pairs, greater is the repulsive forces. The repulsive force generates from the partial hybridization of the probes at either end of the target, with a greater repulsive force at the point of internal mismatch. The configurational entropy decreases only at the partial hybridization sites, but the unhybridized region results in increase in charges and forces. The combined effect of these two regions caused huge increase of repulsive forces, resulting in deflection of the cantilever. This study of cantilever deflection with the various length of the DNA molecules showed that deflection of the cantilever was dependent on the entropy and bio-molecular interactions.

Mishra et al. [83] performed a real time detection of oligonucleotides in a very low concentration without labeling and amplification, in a complicated background of total cellular RNA (Ribonucleic acid) extracts obtained from the cell lines. The microcantilevers were surface functionalized with ssDNA and reference ssDNA respectively and were exposed to complementary ssDNA strands which were spiked in a cellular RNA solution. The nanomechanical response of cantilever beams were studied in a competitive background. This study is essential for pharmacokinetics, biomarker assay and miRNA quantification for disease diagnosis. The authors were able to detect the oligonucleotides up to femtomolar concentration.

A schematic on the classification of cantilever based on detection schemes is shown below in Fig. 8. The figure shows various detection mechanisms, principles, detection of diverse range of biomolecules past and present, as well as a view on future trends on cantilever based biosensing/diagnostic platform.

## 3. Recent progress in cantilever based bio-sensor

### 3.1. Cancer derived exosome detection

Thundat et al. recently detected cancer cell derived exosomes on cantilever [84]. The exosomes from the breast cancer were identified by the over expressed antigens or the membrane proteins like CD63, CD24 and EFGR with high selectivity and sensitivity. An array of cantilever sensors was used for realtime detection of exosomes. The cantilevers were used to distinguish between tumorigenic and non-tumorigenic exosomes, also exosomes samples were spiked in human serum and detections were carried out successfully. This technique may be a good way for early on detection of tumors.

### 3.2. Breast Cancer cell detection from aptamer peptide functionalized cantilever

Ligand-directed capturing [85] and targeting of cancer cells is presently a new methodology for detecting circulating tumor cells. Hashem et al. ([85]) reported peptide functionalized micro-cantilever arrays for detection of circulating tumor cells. Cantilevers were exposed to both cancerous cells (MCF-7) and non-cancerous cells (MCF 10A), deflections observed were more for breast cancer specific peptide 18 − 4 functionalized cantilevers. The detections were also performed by spiking cancer cells in human blood. A detection limit of 50–100 cells/mL from blood samples were achieved shown in Fig. 9 [85].

In another article, Chen li et al. [86] reported the detection of tumor biomarker MUC1 and diagnosis of human breast cancer cells (MCF-7). The thiol functionalized aptamers were surface functionalized on the cantilever surface. The target analytes interacted with the surface of the cantilever and as a result differential deflection were obtained. The biomarker MUC1 was detected with low detection limit up to 0.9 nm concentration. The MCF-7 cancer cells were detected even at the lowest detection limit of 213 cells/mL. This aptamer based reported work showed a way of precise detection of both tumor biomarkers and breast cancer cells using highly sensitive aptamer molecules.

### 3.3. BRAF mutation detection total RNA from Melanoma cells

Malignant melanoma, one of the deadliest forms of skin cancer, is developed from melanocytes. Recent researches have delineated that majority of the metastatic or unresectable melanomas are associated with genetic mutations in BRAF genes of which $BRAF^{V600E}$mutation is most common. BRAF mutation is an important predictive biomarker for determining the course of treatment in advanced melanoma patients [87].

In recent years, few drugs have come to operation which target this tumor carrying mutation. In a recent study, Huber et al. [88] showed that using surface-immobilized BRAF specific V600E_short (thiolated 13-mer oligonucleotide) as probe can results in microcantilever array based label-free detection of BRAF mutation in total RNA extracted from cancer cell lines. The mutant is detected up to low concentration

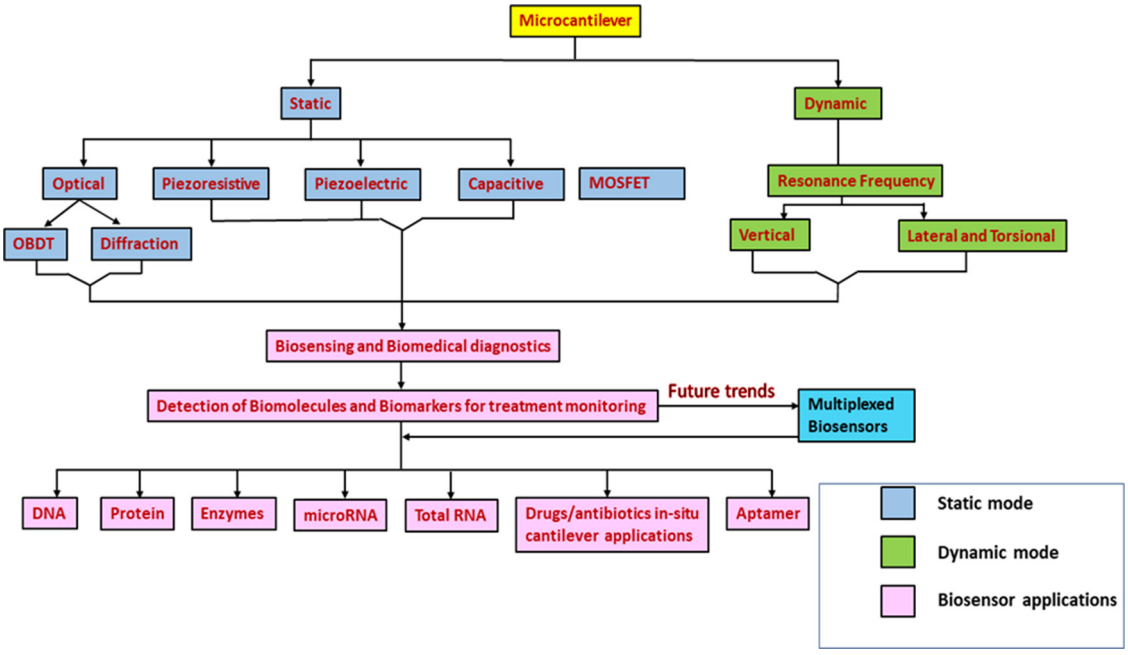



**Fig. 8.** A schematic on micro/nano cantilever based biosensing platform.

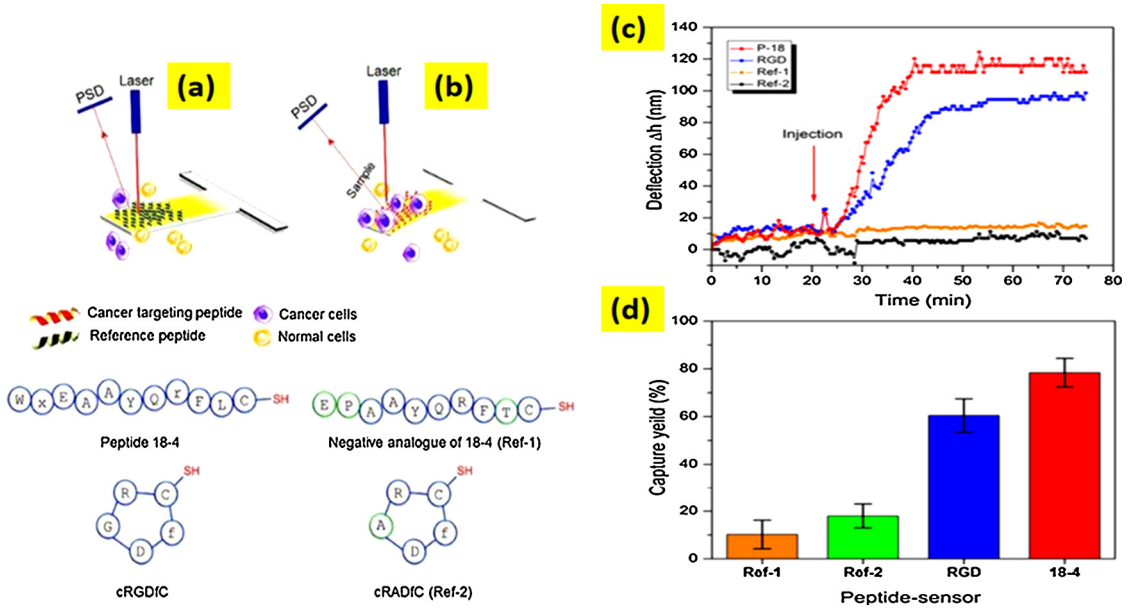
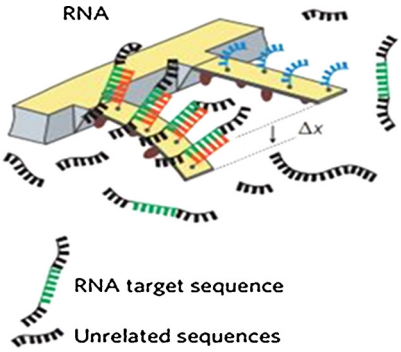



**Fig. 9.** a Microcantilever surface coated with non-specific peptide, no deflections obtained with normal or cancer cells b. Microcantilever surface coated with specific peptide, significant deflections obtained with cancer cells c. Real time detection of NCF7 human breast cancer cells d. Capture yield of cancer cells for each peptide coated cantilever [85].




**Oligonucleotide probes used in the study.**

| Probe | Sequence | Use |
|---|---|---|
| V600E_short | 5′-CTACAGAGAAATC-3′ | Detection of 621 bp mutated cDNA PCR product |
| polyAC_short | 5′-ACACACACACACA-3′ | Reference for detection of 621 bp mutated cDNA PCR product |
| V600E_long | 5′-GAGATTTCTCTGTAGCTA-3′ | Detection of *BRAF*$^{V600E}$ in total RNA |
| polyAC_long | 5′-ACACACACACACACACAC-3′ | Reference for *BRAF* RNA detection |
| wt_long | 5′-GAGATTTCACTGTAGCTA-3′ | Additional reference in *BRAF*$^{V600E}$ detection |

**Fig. 10.** Cantilevers functionalized with probe oligonucleotides in blue and nonspecific nucleotides in red [88] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

of 500 pm. The cantilevers were able to distinguish melanoma cells carrying mutation from the wild type of cells using only 20 ng/μl RNA, without PCR amplification (shown in Fig. 10 [88]).

### 3.4. Liver Cancer diagnosis

Liver cancer is the sixth most commonly occurring cancer having the fourth highest fatality rate worldwide in 2018 [89]. Diagnosis of liver cancer at an early stage has surge interest worldwide as it has high significance in determining the course of cancer treatment. In a first attempt to detect liver cancer biomarkers, Wang et al. [90] proposed batch-fabricated microcantilever biosensors. In a subsequent study, Wang et al. [91] reported label-free cantilever arrays for the detection of multiple biomarkers. They designed a microcavity near the tip of the cantilever where the interaction between antigen and antibody occurs. This significantly reduced the changes in adsorption induced coefficient k. Additionally, pillar arrays were also fabricated for increasing the detection upper limit for the diagnosis of early liver cancer. The cantilever arrays were used for the detection of three biomarkers, alpha-fetoprotein, glutamyltranspeptidase II and Hepatocyte growth factor, with frequency shift of cantilever (shown in Fig. 11 [91]).

Aptamers are the artificial single-stranded DNA or RNA molecules having extremely high affinity and specificity to specific targets. Specific target binding aptamers are synthesized by using cell-SELEX (systematic evolution of ligands by exponential enrichment) method [92]. Due to its high affinity and specificity, presently aptamer-based biosensors or aptasensors are finding widespread application in sensing and targeting ions, small biomolecules and proteins. Nowadays, they are widely used in diagnostics, imaging and therapeutics. In a recent research, Chen [93] et al. reported detection of liver hepatocellular

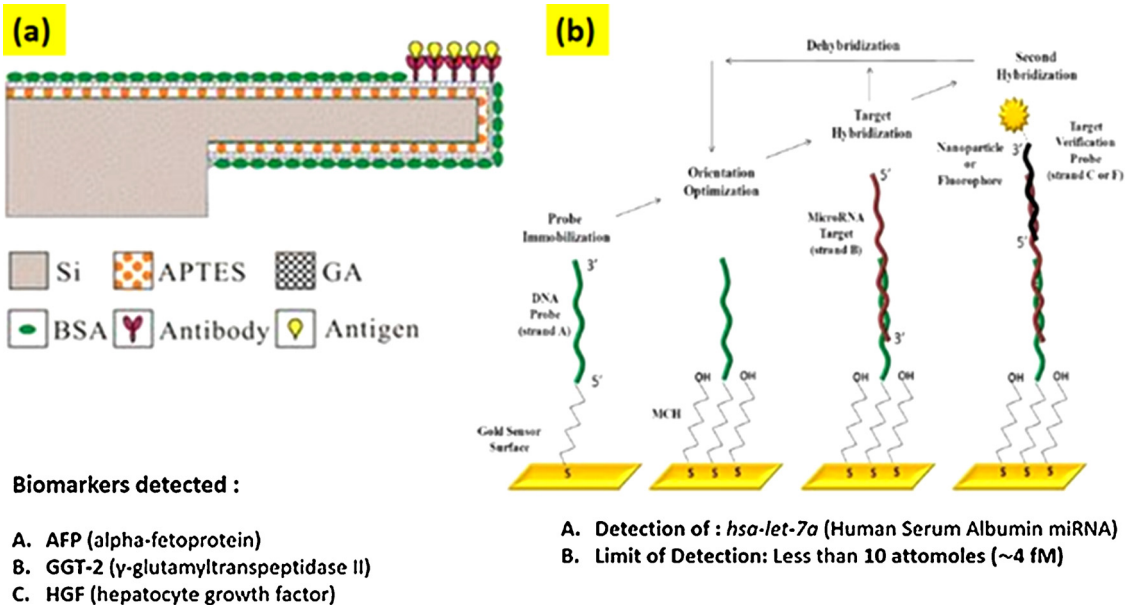



**Fig. 11.** a A schematic diagram of modified cantilever with locally immobilized antibodies b. Schematic of microcantilever-based assay protocol for detection of microRNA, showing the main steps of probe immobilization, probe orientation optimization, target hybridization, and target hybridization verification and amplification. [91].

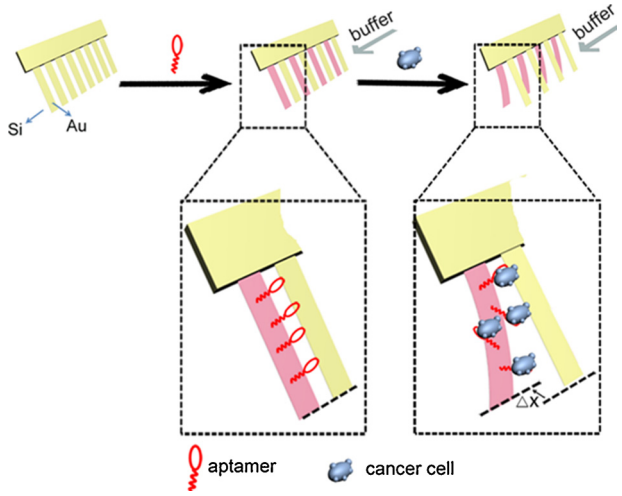



**Fig. 12.** Schematic illustration of HepG2 cells binding with the aptamer functionalized cantilevers. The cantilevers in pink color are surface functionalized with aptamer and in grey color are the reference cantilevers [93].

carcinoma (HepG2) cells by surface functionalizing microcantilever arrays with HepG2 cells specific TLS11a aptamer probe. In this label-free microcantilever aptasensor, the differential comparison in bending was performed by modifying the surface of reference microcantilevers with 6-mercapto-1-hexanol self-assembled monolayers. The cantilevers were able to detect with a detection limit up to 300 cells/mL. The aptasensors also showed high specificity over other cancer cells like breast, bladder and cervix (shown in Fig. 12 [93]).

In a subsequent study, Chen et al. [94] showed aptamer based detection of two biomarkers for liver cancer α-fetoprotein and carcinoembryonic antigen. The aptamers of CEA and AFP were respectively functionalized on the surface of the cantilevers. The surface stress on the cantilevers were obtained through the sandwich structure of aptamer-antigen-antibody interaction. Simultaneous detection of two biomarkers were performed and real time data of the bending of the cantilever was recorded. The detection limits of 0.6 ng/mL for AFP and 1.3 ng/mL for CEA were reported respectively. This work showed a path for simultaneous detection of biomarkers for cancer at low concentrations for faster clinical diagnosis.

### 3.5. MicroRNA detection from human serum

MicroRNAs (miRNAs) are a large class of small non-protein coding RNA molecules (18–25 nucleotides long) which serve as a post-transcriptional regulator of the expression of the target gene using the RNA interference (RNAi) mechanism [95]. Till date, information of about 2300 true human mature miRNAs are available in the most comprehensive miRNA database, miRBase 22 (http://www.mirbase.org/) [96,97]. Characterization of human miRNAs has revealed that miRNAs can function either as oncogenic factors or tumor suppressors [98]. Furthermore, some of the recent studies have shown that circulating miRNAs in human serum or plasma can be effectively used as novel biomarkers and their expression level can be used for diagnostic screening and prognosis of cancer [99,100]. Low abundance, short length and high sequence similarity with miRNAs of the same family, has posed several constraints in circulating mRNA profiling [101]. A recent study has proposed a highly sensitive and efficient method using microcantilevers in dynamic mode operation for measurement of micro RNAs in human serum and buffer [42]. The response of the sensor related to a labeled DNA hybridization, gold nanoparticle functionalized DNA hybridization and has-let-7a hybridization is studied in realtime using flowcell. The assay successfully detected has-let-7a with a limit of detection upto 10 attomoles. The sensor also showed extremely good selectivity in comparison with similar microRNAs differing by only one single nucleotide and also with random microRNAs.

### 3.6. Mechanical study of multiple number of cells

Study of cell mechanics using PDMS integrated cantilevers [102] are shown below in a microfluidic channel. Intentionally, macrorestriction are created inside the channel so that a deformation study can be done for normal and abnormal cells (cancer cells in metastasis), with the cantilever acting as a force sensor. The advantage of this device lies in testing a high number of cells in a very small amount of time, compared to single cell mechanical testing devices (shown in Fig. 13 [102]).

A cantilever based mechanical study was performed by Tian et al.

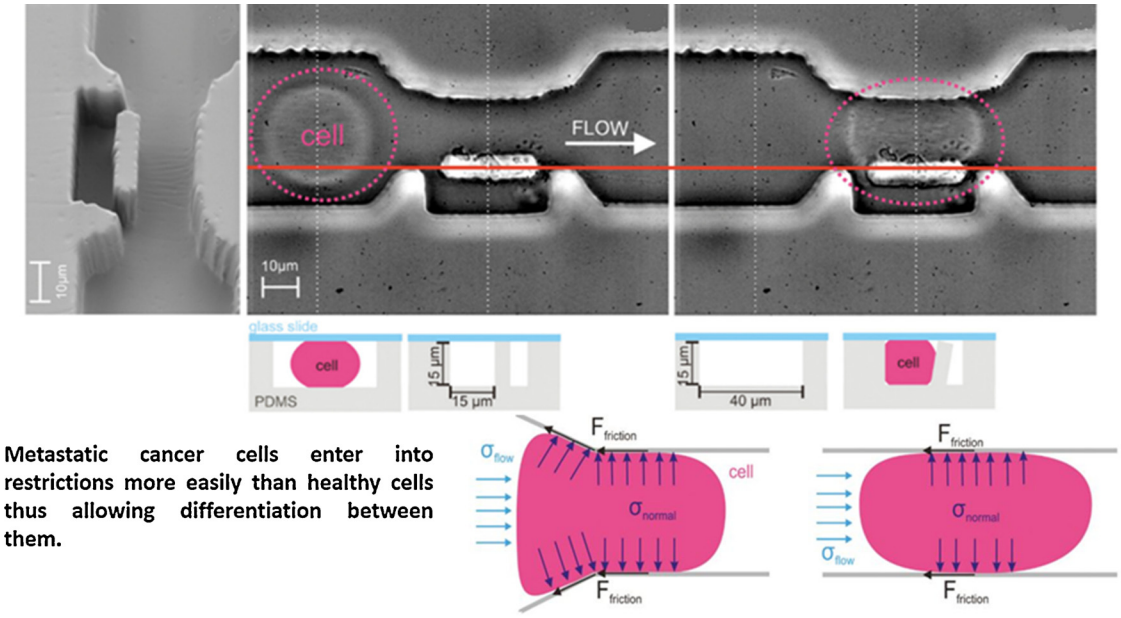



**Fig. 13.** Study of cell mechanics via cantilever based PDMS force sensor [102] (Reprinted with permission from Biointerphases, 2011).

[103] using silicon nitride cantilevers through nanoindentation techniques to detect Hepatocellular carcinoma(HCC). Tian et al. [103] reported that nanomechanical signatures/responses from the liver tissues can be directly correlated to HCC. The mechanical profiles of the liver cancer tissues obtained from the indentation directly varied with the tumor progression. This profile can provide a platform for early diagnosis of HCC.

### 3.7. Drug resistant bacteria and antibiotics for humans

A high throughput screening and detection is essential for drug resistant bacteria [104]. To study the bacteria with antibiotics in situ upon cantilever, cantilevers were fabricated with channels. A change in resonance frequency occurs due to bacterial adsorption. The trapped E. coli bacteria inside the channel gives a significant amount of mechanical response when exposed to antibiotics. This detection mechanism was able to capture and detect the changes in bacteria for *L. monocytogenes* upto single cell per microliter (shown in Fig. 14 [104]).

Ndiyera [20] reported similar kind of work on surface stress based sensors, described about the mechanical responses obtained during interaction between surface receptor and different antibiotics in presence of competing ligands in the solution. The drugs used for this purpose mostly FDA approved vanciomycin and oritavancin. The findings in this article can provide a layout on further studies to know the role of mechanics and chemistry in membrane bound proteins and receptors, to synthesize better drugs in pharmacokinetics and plan a proper sensing based diagnostic platform shown in Fig. 15 [20].

Gentamycin is a broad spectrum antibiotic which is generally used for treating pneumonia, bone infection and endocarditis in patients. Excess of this drug in blood can lead to hearing loss, dizziness, vertigo, kidney damage and nerve damage [105]. Gentamycin prevents the growth of gram-negative bacteria in our body. Growth of this bacteria often leads to peritonitis, i.e. inflation of the inner wall of the abdomen. If not treated at an early stage, peritonitis can often become life

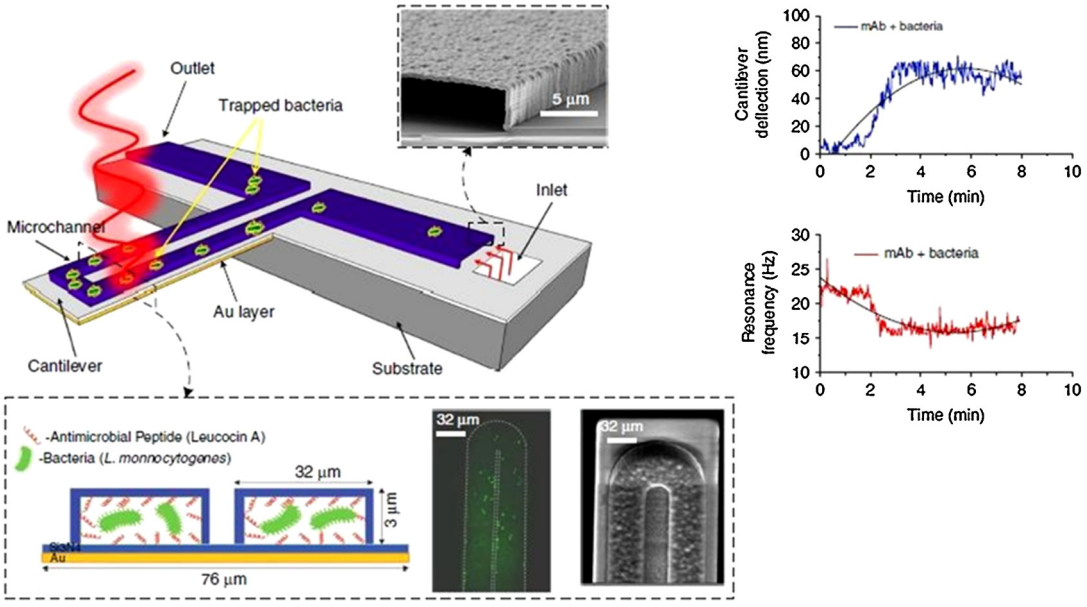



**Fig. 14.** Schematic representation of a bimaterial cantilever with microfluidic channel upon it and its multimode operation. [104].

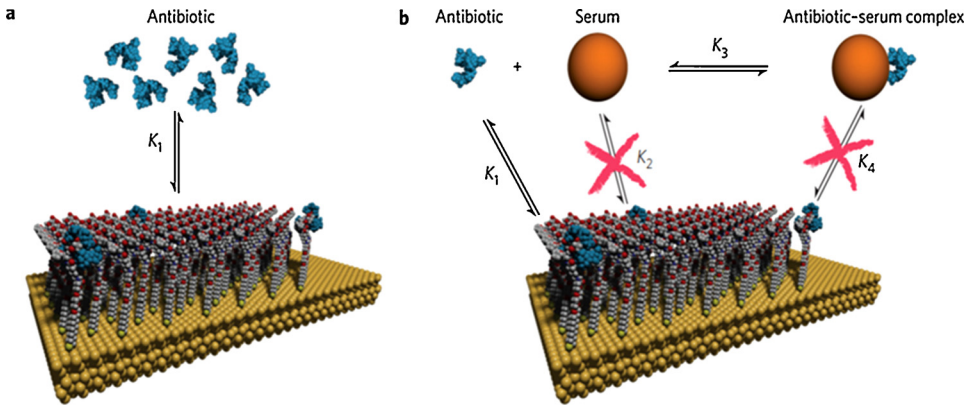



**Fig. 15.** The nanomechanics of drug–target interactions upon cantilever surface to explore the impact of dosing and competing ligands on the functionality of drug molecules [20].

threatening. In a recent research, Kuan Wei Li et al. [106] developed a CMOS based piezoresistive cantilever for detection of small molecules of Gentamicin directly from the blood sample of affected persons. The capture antibodies were surface immobilized on the cantilever, which were able to detect small molecules (< 2 kDa) of Gentamycin directly. The drug- antibody interaction results in nanomechanical bending of the cantilever. The study reported a limit of detection of 9.44 μg/mL.

## 4. Conclusion

Cantilevers-based biosensors have widespread clinical applications in biodetection. These cantilevers can be fabricated in micro/nano scale of various shapes with variety of materials. Several types of electrical and optical cantilever sensors have been reported for diverse wide range of applications in air, vacuum and liquid. Cantilevers, due to high flexibility, can be used as array for high-throughput detection of bioparticles, DNA, RNA and proteins. The cantilever based biosensing platform can further be customized for environmental monitoring and clinical diagnosis. In this paper we have summarized the basics of microcantilever principle, the surface functionalization techniques and the methods to measure microcantilever deflections. Furthermore, we have also made a comprehensive review about the detection of analytes and different biomolecules like protein, DNA, RNA fragments and measuring anomalies in the level of biomarkers through the cantilever based biosensing platform. Mostly, these cantilever sensors are label-free, highly multiplexed and can quite easily miniaturized from micro to nanoscale. Due to miniaturization, nanocantilevers, which are now mostly used for disease diagnosis, have high mass sensitivity. The recent researches corroborated in this review depicted that bio cantilever is emerging as a powerful tool for accurate measurement of the mass of bioparticles. The different cantilever-based sensors are highly suitable for point of care diagnostics and application.

## 5. Future scope

Over the last decades, recent advancements in nanobiotechnology due to innovation as well as improvement in medical tools has demonstrated tremendous benefit in disease detection and will undoubtedly be the unique key for future developments in diagnosis. Furthermore, recent progress in human molecular biology has revealed plethora of information contained within human cells and thus resulted in discovery of novel biomarkers. Initial laboratory-based attempts have also delineated that cantilever based nano biosensors are emerging tools for precise detection of trace concentration of cancer and other disease related biomarkers. Thus, it can be inferred that employment of nanocantilevers in medical institutes and hospitals will result in early stage diseases diagnosis, monitoring and on time treatment in patients. Multiplexed biosensors are another elusive area of research. However, until now, not much studies have been done for exploring multiplexed biosensors. A few studies have demonstrated that microarrays of cantilever sensors with integrated microfluidics are capable to act as multiplexed biosensor with extremely high level of sensitivity, faster detection of different miRNA targets and anomalies of multiple biomarkers or biomolecules with minimum intervention of the user [107]. The commercialization of this nanosensor tool will help patients to get a quick picture of the state of disease by complementing the information about multiple biological parameters concurrently. This will also help the medical practitioners to determine the right course of treatment and proper dosage of medicines. Thus, it can be inferred that the commercial application of this devices will also decrease the mortality rate of patients. In future, the advent of nanodevices with simultaneous detection and treatment of disease can open new windows in the world of medical sciences. The successful implantation of this kind of devices in the body, with wireless sensing capabilities for disease detection, can prove highly beneficial for patients and doctors. However, implantation of this devices in point of care diagnostics will require further clinical analysis, miniaturization, biocompatibility and proper signal readout mechanism. Thus, complementation of molecular biology with nanobiosensor based research will probably open new avenues in theranostic studies.

## Declaration of Competing Interest

The authors declare no conflict of interest.

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