Microcantilever based Biosensor for Disease Detection Applications

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***Abstract*—The fast development of micro-electro-mechanical system (MEMS) technology has brought many great ideas in the field of biomedical applications. A biosensor is a chemical sensing device in which a biologically derived recognition analyte coupled to a transducer to allow the quantitative development of biochemical parameter. A biosensor consists of a bio-element and a sensor-element. The bio-element may be an enzyme, antibody, living cells, tissue, etc., and the sensing element may be electric current, electric potential, and so on and specificity of analyte is the important concept in biosensor. In this paper we review the principle of microcantilever, biosensing mechanism and applications of microcantilevers for bio detection for early detection of diseases accurately. Biosensors can have a variety of biomedical, industry, and military applications. The main advantages of MEMS based sensors are specificity, portability, simplicity, high sensitivity, potential ability for real-time and on-site analysis coupled with the high speed and low cost.**

***Index Terms*—microcantilevers, principle, mechanism of biosensors, biodetection applications, MEMS**

I. Introduction

Microelectromechanical systems (MEMS) is the technology of very small devices, MEMS are separate and distinct from the hypothetical vision of molecular nanotechnology or molecular electronics. MEMS are made up of components between 1 to 100 micrometres in size (i.e. 0.001 to 0.1 mm) [1]. Sensors are devices that detect or sense a signal and also a sensor is a transducer which transforms one form of energy into another or it responds to a physical parameter [2]. A biosensor have bio-element and a sensor-element. The bio-element used to attract the analyte and the sensing element for transduction into electrical quantity for measurement [3]. A class of MEMS sensors known as microcantilever based sensors came into existence as Atomic Force Microscopy probes [4]. Development of Bio sensing applications using microcantilever based sensors for wide range of applications gives interesting and challenging research problems to meet the requirement of low cost, high speed, miniaturization and sensitivity [5]. There are tremendous advances made in biosensor technology and these sensing technologies developed many new disease detection sensor applications. Sensor design and operation requires a cross disciplinary background likes electrical, mechanical engineering physics, chemistry, biology etc. MEMS Biosensor (Bio-MEMS) devices are used in detecting infectious diseases such as HIV, DNA analysis, proteins and genotypes. It have the advantage of low manufacturing costs, compact size, low weight and power consumption as well as increased multi-functionality. The characterization and identification of gases or vapors based on sequential position readout via beam-deflection technique from a microfabricated array of eight cantilever type sensors explained. Each of the cantilevers can be coated on one side with a different sensor material to detect specific chemical interactions [6]. The Stoney equation gives that for a given surface stress the deflection induced in the microcantilever is directly proportional to the cantilever length and inversely proportional to its thickness. In other words, by increasing the microcantilever length and/or reducing its thickness the deflection can be increased. These microcantilever based detection based physical, chemical and biological methods and Biosensor technologies offers great potential and have an interdisciplinary combination of approaches in Nanotechnology and medical science[24]-[34].

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II. Principle of Microcantilever Based Biosensor

The microcantilever based biosensors works on the principle of conversion of bio recognition into nanomechanical motion. These causes for nano mechanical motion can be caused due to free energy change on the surface of the cantilever due to the reaction of target analyte with probe coating molecule. In order to detect a specific analyte, the microcantilever transducer is fabricated with probe coating on the surface based on the nature of the analyte. The probe coating is a chemically sensitive layer that provides specificity for analyte recognition. The principle relies on transduction of chemical or physical processes into mechanical response. After exposure to analyte vapor, analyte molecules diffuse into cantilever coating, which begins to bend, jointly with the mass increase, a change of interfacial stress between coating and cantilever occurs resulting in a

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bending of cantilevers [7]. Chemical reactions are transduced by sensitivity of cantilevers with coatings such as metals, self-assembled monolayers, or polymer into a mechanical response. Reference cantilever sensors permit subtraction of background signals (differential measurement). Coating of each cantilever sensor with a different sensitive layer allows operation of the array-device as a new form of different analyte detection.[8]. Fig. 1 shows the elements of bio sensor consist of bio element, here microcantilever is used for biodetection. When specific biological reactions occur on one surface of a microcantilever, the resulting changes in surface stress deflect the cantilever beam. At the free end of the microcantilever, a small area is coated with probe coating to capture corresponding target antibodies. When the device is exposed to an environment with target antibodies, the antibodies coated on the free end of the microcantilever will capture them, resulting in a resonance frequency shift or static bending. This shift or bending is detected by different transduction mechanism. The mass resolution obtained with cantilevers in air is in the Pico and the femto gram range. Mass changes on the cantilever can accurately be determined by running the instrument in static mode and dynamic mode [9]

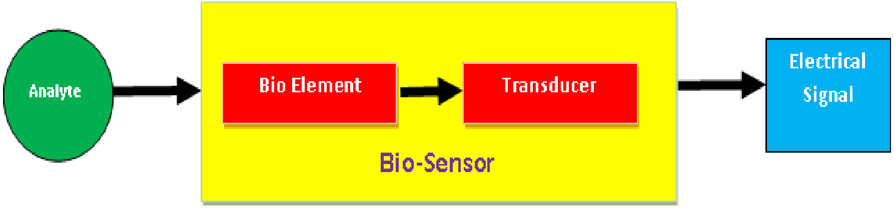

Figure. 1. Elements of bio sensor

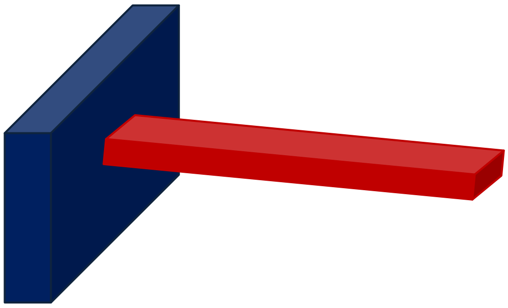

Figure. 2. Simple cantilever structure

Fig. 2 shows the simple micro cantilever structure and these Micro fabricated microcantilever array sensors for an artificial nose setup developed and each cantilever is coated on its top surface with a polymer layer. Volatile gaseous analytes are detected by tracking the diffusion process of the molecules into the polymer layers, resulting in swelling of the polymer layers and therewith bending of the cantilevers. From the bending pattern of all cantilevers in the array, a characteristic of the analyte is obtained [10]

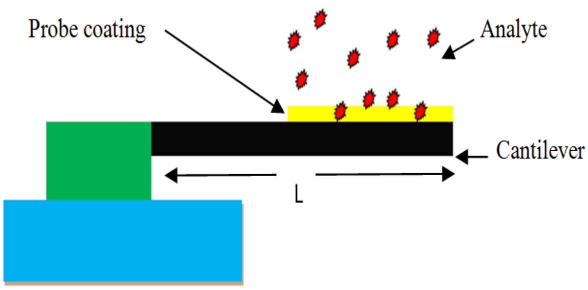

Figure 3 Schematic side view of a microcantilever showing cantilever length, L with probe coating and analyte

III. Biosensing Mechanism using Microcantilever

The life threatening diseases that destroy parts of human body which are detected only when the patients reach the critical stage, therefore there exists a need to constantly monitor the parameters in human body and provide medication to cure diseases. There are several diseases that can affect human body and therefore there must be means to accurately detect the diseases and subsequently classify them. Microcantilever based biosensor that are used to sense the presence of a certain particle or analyte are coated with a chemically sensitive material. This material needs to provide for a high degree of specificity in detecting certain particles or "analytes" within a sample. In some biomedical applications, bio molecules may be used as the cantilever coating so that they can better detect specific analytes within a small blood sample. Diseases classified, need to be treated by the selection of suitable drugs. The most common biosensor to detect the disease causing agent is the microcantilever. Bio sensors using microcantilever for a wide range of applications gives scope for miniaturization and parallelization. In medical diagnostics bio-sensors are used to analyze samples for substances such as antibodies, proteins, antigens and DNA. They are used for glucose monitors, pH sensors, protein binding, DNA detection and gene expression profiling. DNA or gene microarrays are biosensors used to analyze and measure the activity of genes. These arrays enables to analyze complex biological problems in identification of genetic variations that could play a role in diseases such as Alzheimer’s and Parkinsons. It also used to analyze and test for viruses that cause disease such as SARS(severe acute respiratory syndrome), HIV, tuberculosis and other infectious diseases. Microarrays can be used to measure changes in gene activity and thereby learn how cells respond to a disease. Surface reaction is when the analytes are confined to the surface of the probe coating. Microcantilevers are typically 10 to 500 µm long, up to 100 µm wide, and up to 2 µm thick. Fig. 3 Schematic side view of a microcantilever showing cantilever length, L with probe coating and analyte. The top or bottom surface or both surfaces are coated with a chemically reactive material designed specifically for the analyte targeted. By designing a cantilever biosensor with a different probe coating on each cantilever, a sensor can be used to detect several different substances with the same sample.

In cantilever based biosensor the target material is detected when it contact with a chemically sensitive material on cantilevers surface. The amount of target material is measured by monitoring a change in one or more of the cantilevers mechanical and electrical properties such as displacement, resistance or resonant frequency. when an analyte binds with the probe coating on a cantilevers surface, hence there is a change in the cantilevers mechanical or electrical properties which makes the transducer to change it property, when more target material attaches to the cantilevers surface, the resulting change is measured. The number of analyte atom or molecule binds in the probe coating is proportional to the bending of the microcantilever, This change is processed by integrated circuit or signal processing circuits of MEMS into relative data. This data is analyzed and compared to reference data to determine the type of analyte and its properties. The sensitivity of a microcantilever based biosensor depends upon the design sensitivity of the microcantilever and the measurement sensitivity of the deflection measurement system. A sensitive microcantilever design should have efficient conversion from the biomolecular stimulus into a large microcantilever deflection, the measurement sensitivity ensures the deflections measured are only induced because of the biomolecular interaction and not due to some source. The design sensitivity of the microcantilever can be improved by changing the cantilever design in such a way that for a given surface stress due to molecular interaction occurs a larger deflections. This can be achieved by reducing the bending stiffness of the cantilever or by changing the elastic modulus of the cantilever materials

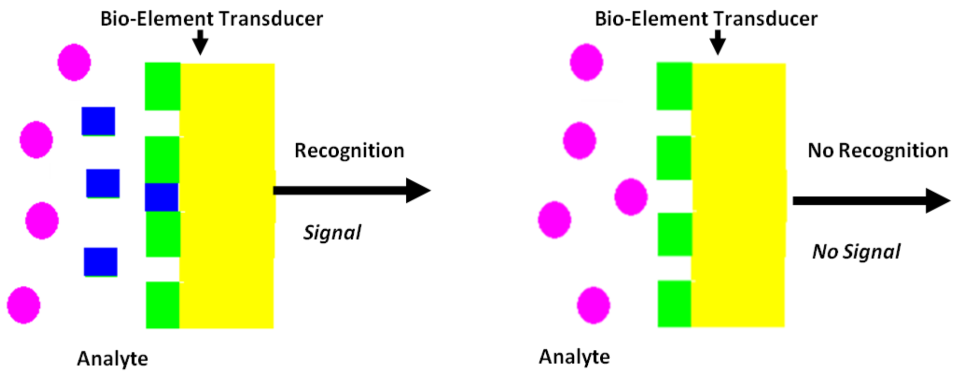

Figure 4. Specificity of analyte

IV. Biodetection Applications of Microcantilever Based Biosensor

A resonant cantilever-based Microsystems aimed at biochemical sensing which has sensor system comprises a magnetically actuated resonant cantilever sensor array integrated with the feedback circuitry, digital control circuitry and a serial interface on a single chip in 0.8 µm CMOS technology. The sensor system shows a frequency stability of better than 3 Hz in water corresponding to a detection limit of about 30 pg mass loading. The system has been used for the detection of antibody-antigen interaction on the cantilever surface. The possibility to actuate and operate cantilever arrays in a liquid environment opens up a variety of new applications for bio-chemical sensing. [11]. SU-8 is an interesting polymer for fabrication of cantilevers for bio/chemical sensing due to its simple processing and low Young's modulus, SU-8 cantilevers have a reduced sensitivity to changes in the environmental temperature and pH of the buffer solution and SU-8 cantilever surface can be functionalized directly with receptor molecules for analyte detection. [12]. A quick wireless label-free detection of disease related C-reactive proteins (CRPs) using a 200-µm-long microelectromechanical systems (MEMS) microcantilever designed and the deflection of the microcantilever due to specific CRP–antiCRP binding is detected using a position-sensitive detector. [13]. The sensors are validated using specific binding reaction of antigen and antibody of immunoglobulin G on the sensor surface, and the experimental results show that they are promising for portable and integrated sensing applications-[14]. Fig. 4 shows the specificity of analyte ie., only the biosensor attracts the required analyte and it does not capture the analyte not related to the experiment. MOSFET-embedded cantilevers are configured as microbial sensors for detection of anthrax simulants, Bacillus thuringiensis. Anthrax simulants attached to the chemically treated gold-coated cantilever cause changes in the MOSFET drain current due to the bending of the cantilever which indicates the detection of anthrax simulant. Electrical properties of the anthrax stimulant are also responsible for the change in the drain current [15].Carbon monoxide detection is required for various healthcare, environmental, and engineering applications, SU-8 microcantilever has been used as a CO sensor. The cantilever based sensor has exhibited a fast response and recovery times and is fully recoverable after repeated exposures. [16]. The sensor, named as "organic CantiFET," has a improved sensitivity, reliability, and also cost effectiveness of such sensor platforms by the use of polymer materials, along with the employment of smart and compatible transduction techniques. [17]. A simple practical method is presented to fabricate a high aspect ratio horizontal polydimethylsiloxane (PDMS) microcantilever-based flow sensor integrated into a microfluidic device. A multilayer soft lithography process is developed to fabricate a thin PDMS layer involving the PDMS microcantilever and the micro-fluidics network. [18]. A highly-integrated DNA detection SoC, where several kinds of cantilever DNA sensors, a readout circuit, an MCU, voltage regulators, and a wireless transceiver, are integrated by monolithically CMOS Bio-MEMS [19]. A COMSOL simulation is used for recent development micro and nanostructure cantilever [20]. Biosensors can be classified either by the type of biological signaling mechanism they utilize or by the type of signal transduction they employ. The application of surface plasma resonance-based (SPR) optical techniques could greatly enhance the understanding of HIV and lead to superior detection and quantification mechanisms [21] The nano-cantilevers is used in the detection of cancer cell, it would bond covalently with biomarkers or would be constructed with antibodies to detect the biomarkers. The cantilevers would then deflect as a result of the bonding with the biomarkers [22]. Fig. 5 shows the genral block diagram for analyte identification using microcantilever based biosensor. The microcantilever based biosensor can detect tuberculosis by immobilizing specific antibodies on the microcantilever. These antibodies are specific to TB antigen 85 complex. When the patient sample containing TB antigen 85 complex is placed on the cantilever biochemical interactions take place between TB antigens and the antibodies immobilized on the upper surface of the microcantilever. [23]

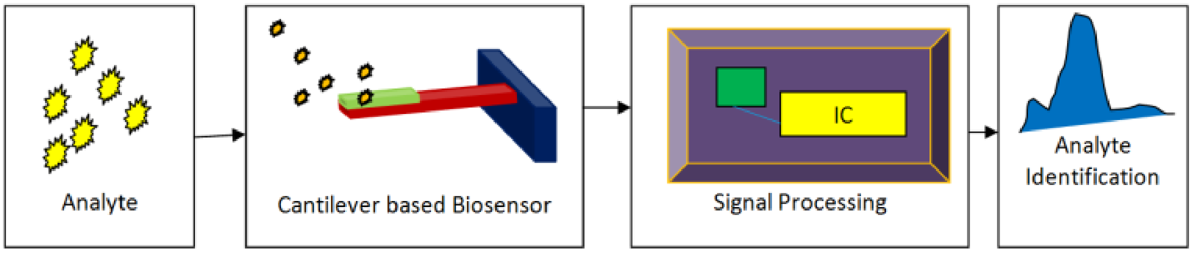

Figure. 5 General block diagram for analyte identification using cantilever based biosensor

V. CONCLUSIONS

This concludes our study of microcantilever and its application on bio sensor which is a device for biosensing. The overall goal of this device is to become a portable platform for biodetection, detecting various bio analytes for disease identification. These MEMS sensors hold advantages such as low cost of production due to lesser materials, easy integration, greater portability, robustness and low power consumption.

REFERENCES

[1] WIKIPEDIA. Microelectromechanical Systems. [Online]. Available:http://en.wikipedia.org/wiki/Microelectromechanical_systems

[2] H. P. Lang, M. Hegner, and C. Gerber, "Nanomechanical cantilever array sensors," *Handbook of Nanotechnolgoy, Springer*, pp. 443-459.

[3] S. P. Mohanty and E. Kougianos, "Biosensors: A tutorial review," *IEEE Potentials*, 2006, pp.1-16

[4] W. P. King *et al*, "Design of atomic force microscope cantilevers for combined thermomechanical writing and thermal reading in array operation," *Jouranl of Microelectromechanical System*, vol. 11, no. 6, pp. 765-774, 2002.

[5] J. Fritz *et al*, "Translating biomolecular recognition into nanomechanics," *Scieces*, vol. 288, 2000, pp. 316-318.

[6] H. P. Lang *et al*., "A chemical sensor based on amicromechanical cantilever array for the identification of gases and vapors," *Appl. Phys*., A66, 1998, pp. S61–S64

[7] F. M. Battison *et al*., "A chemical sensor based on a micro fabricated cantilever array with simultaneous resonance-frequency and bending read out," *J. Sensors and Actuators*, vol. B77, pp. 122-131, 2001.

[8] H. P. Lang *et al*., "An artificial nose based on a micromechanical cantilever array," *Elseveir Analytica Chimica Acta 393*, 1999, pp. 59- 65

[9] S. Logeshkumar *et al*., "FEM based estimation of biological interaction using a cantilever array sensor," in *Proc. COMSOL Conference*, Bangalore, 2011.

[10] H. P. Lang *et al*., "An artificial nose based on microcantilever array sensors," *Journal of Physics: Conference Series*, vol. 61, pp. 663–667, 2007.

[11] Y. Li, C. Vancura, and K. U. Kirstein, "Monolithic resonant-cantilever-based CMOS microsystem for biochemical sensing," *IEEE Transactions on Circuits and Systems*, vol. 55, no. 9, pp. 2551-2560, October 2008.

[12] M. Nordström *et al*., "SU-8 cantilevers for bio/Chemical sensing; fabrication, characterisation and development of novel read-out methods," *Journal Sensors*, vol. 8, pp. 1595-1612, 2008.

[13] C. H. Chen *et al*., "A wireless bio-MEMS sensor for C-reactive protein detection based on nanomechanics," *IEEE Transactions on Biomedical Engineering*, vol. 56, no. 2, pp. 462-470, February 2009.

[14] Y. Z. Zhou *et al*., "A front-side released single crystalline silicon piezoresistive microcantilever sensor," *IEEE Sensors Journal*, vol. 9, no. 3,pp. 246-254, March 2009.

[15] S. Mostafa, I. Lee, S. K. Islam, S. A. Eliza, G. Shekhawat, *et al*., "Integrated MOSFET-embedded-cantilever-based biosensor characteristic for detection of anthrax simulant," *IEEE Electron Device Letters*, vol. 32, no. 3, pp. 408-410, March 2011.

[16] C. V. Bhaskar Reddy *et al*., "Piezoresistive SU-8 cantilever with fe (III) porphyrin coating for CO sensing," *IEEE Transactions on Nanotechnology*, vol. 11, no. 4, pp. 701-706, July 2012.

[17] V. Seena, A. Nigam, P. Pant, S. Mukherji, and V. Ramgopal Rao, "Organic CantiFET: A nanomechanical polymer cantilever sensor with integrated OFET," *Journal of Microelectromechanical Systems*, vol. 21, no. 2, pp. 294-301, April 2012.

[18] A. S. Nezhad, M. Ghanbari, C. G. Agudelo, M. Packirisamy, R. B. Bhat, and A. Geitmann, "PDMS microcantilever-based flow

sensor integration for lab-on-a-chip," *IEEE Sensors Journal*, vol. 13, no. 2, pp. 601-609, February 2013.
[19] Y. J. Huang *et al*., "A CMOS cantilever-based label-free DNA SoC with improved sensitivity for hepatitis B virus detection," *IEEE Transactions on Biomedical Circuits and Systems*, pp. 1-12, 2013.
[20] M. W. Al-Mufti, U. Hashim, and T. Adam, "Simulation of nano lab on chip devices by using COMSOL multiphysics," *Journal of Applied Sciences Research*, vol. 9, no. 2, pp. 1056-1061, 2013.
[21] D. W. G. Morrison, M. R. Dokmeci, U. Demirci, and A. Khademhosseini, "Clinical applications of micro-and nanoscale biosensors," *John Wiley & Sons Publications,* Text Book Chapter 17, pp. 139-183, 2008.
[22] N. Oakes *et al*, "Review article on nanotechnology with biomedical applications-cancer," Online Article, pp. 1-32, 2011.
[23] P. Sangeetha and A. V. Juliet, "Biosensor for Tuberculosis detection using MEMS device," in *Proc. 3rd International Conference on Electronics, Biomedical Engineering and its Applications*, China: Hong Kong, January 26-27, 2013, pp. 52-56
[24] National Space Biomedical Research Institute, "Building a Hand-Held Lab-on-a-chip to Simply Blood Tests," *ScienceDail*, April 11, 2006.
[25] H. S. Lang, M. Hegner, and C. Gerber, *Cantilever Array Sensors*, Materials Today, 2005.
[26] Electronic Nose. Science Article from NASA. (2004). [Online]. Available: http://science.nasa.gov/science-news/science-at-nasa/2004/06oct_enose/
[27] MEMS Cantilevers Participant Guide, Southwest Centre for Microsystems
[28] A Manz, N Graber, H. M. Widmer, "Miniaturized total chemical analysis systems: Anovel concept for chemical sensing," *Sensors and Actuators*, 1990.
[29] K. M. Hansen and T. Thundat, "Microcantilever biosensors," *Methods*, vol. 37, pp. 57–64, 2005.
[30] M. Nordstrom, S. Keller, M. Lillemose, A. Johansson, S. Dohn, D. Haefliger, *et al.*, "SU-8 cantilevers for bio/chemical sensing; fabrication, characterisation and development of novel read-out methods," *Sensors*, 2008.
[31] NEMS/MEMS Cantilever based Biosensor, Yael Nemirovsky.
[32] R. C. Jaeger, *Introduction to Microelectrical Fabrication*, Addison-Wesley, 1997.
[33] K. M. Hansen and T. Thundat, "Microcantilever biosensors," *Methods*, vol. 37, pp. 57–64, 2005.
[34] S. M. Sze, *Semiconductor Sensors*, S. M. Sze, Ed., New York: Wiley, 1994.

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