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Design of Microcantilever Sensor for Detection of P24 Antigen in HIV Diagnoses

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***Abstract*—*The Human Immunodeficiency Virus is a dangerous virus that, when left untreated, causes the Acquired Immunodeficiency Syndrome - an infection that has a debilitating effect on the immune system; therefore, making the affected individual extremely susceptible to secondary infections such as tuberculosis, encephalopathy and numerous cancers. Almost 36 million people have died of complications due to HIV/AIDS since inception, and early detection of HIV helps in the prevention of AIDS. Commercial P24 antigen assays can measure only between 5-25 pg/ml, and this can lead to false negative to P24 antigen, which is the major protein in the HIV composition. This necessitates the detection of lower levels of P24 antigen; and we propose a microcantilever sensor model using COMSOL Multiphysics. The effect of varying design parameters such as shape, dimensions and materials on the sensitivity of the microcantilever is studied and an optimal design for the microcantilever is suggested.*

***Keywords*— *Microcantilever, deflection, HIV/AIDS, P24 antigens.*

I. INTRODUCTION

Microcantilever beams are MEMS devices that are used as sensors in various physical, chemical and biological applications. They are mechanical structures that are fixed at one end and are free at the other end. Two of the primary modes in which a microcantilever works are the static mode and the dynamic mode. The beam works in the static mode when the free end deflects from the natural position due to adsorption of mass, changes in surface stress and tension, and due to heat transfer [1], and this deflection is measured and is used to determine the amount of mass or stress that caused it. The cantilever is said to work in dynamic mode when there is a change in the frequency of the beam from the resonant frequency, and the difference is used to correlate and determine the amount of mass or surface stress that is acting on it [2].

To function as a biosensor, the microcantilever is generally not operated in the dynamic mode because the liquid medium results in the damping of cantilever and changes the resonant frequency of the beam. Additionally, static mode has higher sensitivity than dynamic mode for resonance frequencies in the kHz range [3], thereby making dynamic mode undesirable for our purpose. The beam is operated in the static mode, where the top surface of the cantilever is assumed to be covered with a single layer of antibody - P24 antigen's antibody, in our case - which specifically binds with the P24 antigen only. This results in mechanical bending of the microcantilever, with which the amount of antigen-antibody can be detected using simple electric readout methods [4]. With the advent of measuring instruments playing an imperative role at micro and nano scales, biosensors based on these instruments such as MEMS cantilevers, etc. have become a promising tool for biomolecular detection with relatively greater ease and accuracy. Microcantilevers transform the detection of biomolecules into a mechanical motion at nano levels [6]. This can then be converted to electrical energy for further processing.

Multiplexed, real-time detection of biomarkers having high sensitivity and selectivity levels has been discussed in [7]. The paucity of highly reliable biomarkers to detect complex diseases necessitate health professionals to carry out multiple tests for minimizing false positive cases. Thus, it is essential to develop a single device capable of multiple biomarkers even in very small concentrations. Multiplexed microfabricated cantilever array sensors are the potential candidates for their high sensitivity and throughput. With the advent of newer, improved methods in design and fabrication of microcantilevers has led from using single resonance cantilever for single analyte detection to using microcantilever arrays in for detection of more than one analyte, but at the cost of system complexity. Hence, design of multi-resonance microcantilever in makes use of adsorbing different analytes at different locations of the microcantilever beam [8].

Notable progress on the employment of MEMS cantilever beams for sensing equipment has been made for the applications such as detection of biomolecules, chemicals, diseases and explosives. Abundance of low-cost cantilever beams with materials like Si, SiN and other polymers has provided a promising avenue [9]. Choosing of right material, shape and size of these microcantilever beams itself is a determining task. Also, different readout methods are employed on an ad-hoc basis such as optical lever method, hard contact technique, piezo-resistive method, etc. out of which piezo-electric method provides direct translation to electrical forms.

HIV detection tests are very crucial as early detection can help in the prevention of AIDS diseases. The design simulations of MEMS microcantilevers carried out in COMSOL Multiphysics resulted in stress and displacement of the beam. The novel inflow methodology – though primarily used for in-time monitoring of water, as well as food products – can be used for detection of antigens and other pathogens with higher levels of sensitivity [10]. A microcantilever comprised of a thermally stable strain gauge along with a self-assembled monolayer fabricated using surface micromachining helped immobilize biomolecules on its

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surface. These biomolecules induce resistance on the strain gauge. It is then indicated in [11] that use of strain gauges proves an efficient method for biomolecule concentration detection. There are many commercial tests, one of which is Enzyme-Linked Immunosorbent Assays (ELISA), which is most commonly used as it is simple and can be used to simultaneously test huge sample numbers. But the disadvantage is that a larger sample of blood is required, causing difficulties in testing of infected infants.

The recent development is the fourth-generation assay in which the P24 antigen used. Antibodies which were detected 6-12 weeks after infection using the earlier generations of assays can be detected in fewer than 2 weeks using the P24 antigen essay [12]. The P24 is a capsid protein that has a molecular weight of 24 kDA, which is present at high amounts during initial infection, and it binds with monoclonal antibody, which has a mass of 29 kDa, as investigated by Sowmya Selvaraj et al. in [1]. A 500 µm, PZT-5A piezoelectric MEMS-based microcantilever was designed for the detection of viruses in the sizes of about 100 µm that included the likes of HIV and Herpes [13]. The changes caused in the mechanical vibrations of the microcantilever beam due to adsorption of the viral bodies at its surface tips were sensed by the production of output signals at different resonant frequencies.

In this paper, COMSOL Multiphysics has been used for simulation of the micro-cantilevers, and after a thorough analysis, the optimal micro-cantilever that can detect very low amounts of P24 antigen is suggested.

II. DEISGN

Micro-electro-mechanical systems consist of various specific devices, one of which includes the microcantilever that is hinged at one end and free at the other. The deflection of these devices depends not only on pressure but also on geometric considerations. The conventional rectangular microcantilevers, modified by sectional width variation enhances performance under low-level bio sensing [14]. The micro-cantilever beams for the detection of HIV antigen are designed and compared using COMSOL. The many advantages of these beams are that they are easy to fabricate, have high sensitivity, as well as, selectivity and offer good flexibility for on-chip circuits. It is also observed that they can be directly integrated with electro-mechanical systems and external circuitry is not necessary for detection [4], [5]. The microcantilever design in [15] is an arrangement of a two-level structure having perforations in circular and rectangular shapes at pre-decided locations along the length of the cantilever so that detection capabilities such as resolution, micro displacement and ease of bending is enhanced.

The origin, cause and effect, and the factors effecting surface stress experienced by microcantilevers along with adsorption based biomolecular detection methods are discussed in [16]. The surface stress developed was then calculated using Stoney's Equation. The deflection of the beam should not exceed half the thickness value, so as to maintain accuracy of Stoney Equation and avoid nonlinearity. The COMSOL Multiphysics software was used in analyzing and studying the dynamics of the micro-cantilever beam. Full electrical actuation and detection of the resonance behavior of piezo electric microcantilever, along with fabrication and material characterization is listed in [17].

The behavior of the microcantilever as sensor in the static mode can be completely described two equations. One of which is the Stoney's equation [1], which relates the change in the stress on the surface on the beam to the deflection caused in it; and is given by

$$\Delta g = \frac{E.\Delta h.t^2}{4(1-v)L^2} \tag{1}$$

where, Δg = Change in surface stress (N/m); Δh = Cantilever deflection (m); E = Young's Modulus (Pa); v = Poisson's Ratio; t = thickness of Cantilever (m); L = length of Cantilever (m)

The other equation is the spring constant equation [1] of the beam which is used to obtain the optimal sensitivity of the cantilever beam; and is given by

$$k = \frac{E.w.t^3}{4.L^3} \tag{2}$$

where, k = spring constant (N/m); w = width of Cantilever (m)

It can be observed that the structure length, width and thickness, along with the structural shape affect the deflection of microcantilever from the above two equations. It is also inferred from the above equations that the deflections of the microcantilevers are greatly influenced by the material used for fabrication.

A direct dependence of elasticity to the doping levels can be observed in silicon-based materials. This dependence function is observed by taking into account the measured resonance frequencies on a range of MEMS resonant devices whose wafers comprised of silicon bases with different dopants such as phosphorus, arsenic and boron [18]. Upon variations in the temperatures, the results found a temperature coefficient of shear elastic parameter varied linearly with the variations in the doping levels of the wafers. Experimental deductions were arrived at after assessing the variation of elastic modulus of silicon-based MEMS cantilever devices with the changing concentrations of near-surface carriers, occurring by means of UV irradiation or adsorption or otherwise [19]. It was conclusively stated that the modification of elasticity parameters in silicon was due to its subjection to UV radiations that caused de-passivation of bound H-B pairs, showing that the near-surface concentration changes affected the elasticity of silicon. The parameters that define the behavior of those materials are Young's Modulus, Poisson's Ratio and Density. The materials that have been chosen in this paper include Silicon Nitride (Si3N4), Silicon (Si) and Silicon Oxide (SiO2), as these are the materials used commonly in commercial purposes.

TABLE I. Parameters determining behavior of structural materials of microcantilever.

Material	Young's Modulus (GPa)	Poisson's Ratio	Density (kg/m^3)
SiO_2	70	0.17	2200
Si-Si	150	0.17	2330
Si_3N_4	250	0.23	3100

The appropriate pressure that has to be applied is determined by the molecular mass of the antigen and the

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antibody chosen. The correspondence between the number of molecules that get adsorbed is dependent on the pressure that is experienced on the surface of the microcantilever.

According to Sowmya Selvaraj et al. [1], 10 molecules each of P24 antigen and antibody is equivalent to a total pressure of $5.749892771*10^{-12}$ Pa. This pressure is applied to the top most surface of the cantilever, with the assumption that the antigens uniformly react with the antibodies present at the microcantilever.

The rectangular-shaped microcantilever beam model was the standard to which the other shapes were compared with, and the dimensions were chosen to be 200 µm, 40 µm and 2 µm. Following this, the T-shaped, Π-shaped, Triangular-shaped and V-shaped microcantilevers were modelled, having comparable dimensions.

Each of the micro cantilever was constructed using the three standard materials that are mentioned in table I. The deflections produced when subjected to a total pressure of $5.749892771*10^{-12}$ Pa were noted in each case and the results were tabulated in table II of the Results and Discussions section.

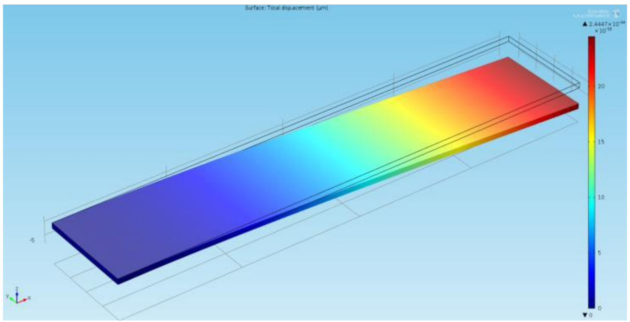

Fig. 1. Rectangular shaped microcantilever.

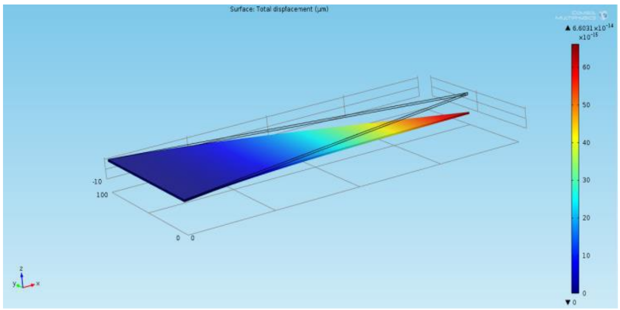

Fig. 2. Triangular shaped microcantilever.

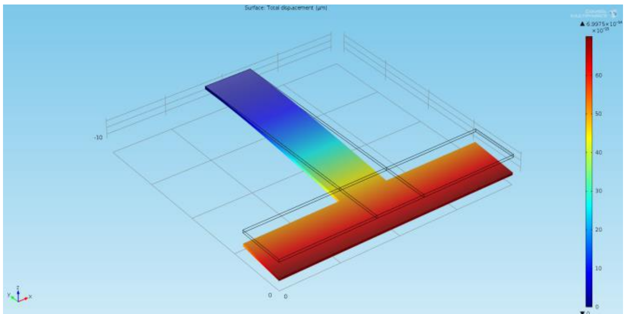

Fig. 3. T-shaped microcantilever.

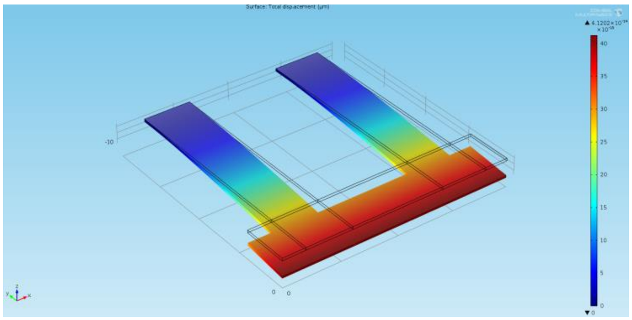

Fig. 4. Π-shaped microcantilever.

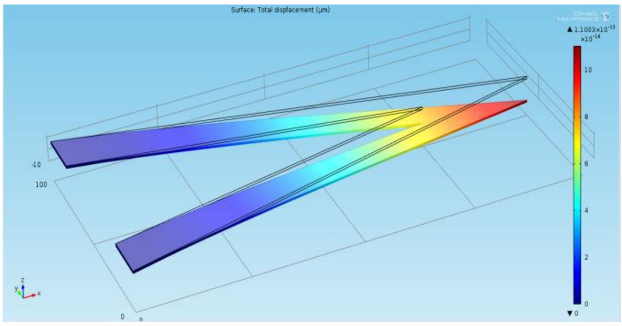

Fig. 5. V-shaped microcantilever.

Micro cantilever models and their respective deflection in each of the aforementioned shapes of SiO_2 material are as shown in the figures 1-5 above.

It can be observed that deflection can be increased by decreasing the thickness, but this results in problems in the structural integrity of the cantilever. From the above figures, it can be concluded that narrower the hinge-fixed support of the cantilever, greater is the deflection. Therefore, a design as proposed in [20] was modelled, which had notch supports and a wider free end to maximize sensitivity. This model is as shown in Figure 6; and, again, has comparable dimension to that of the initial rectangular beam, therefore validating the results. The deflection for the given pressure is observed to be very high, and is hence very suitable for the purpose of detecting low amounts of P24 antigens.

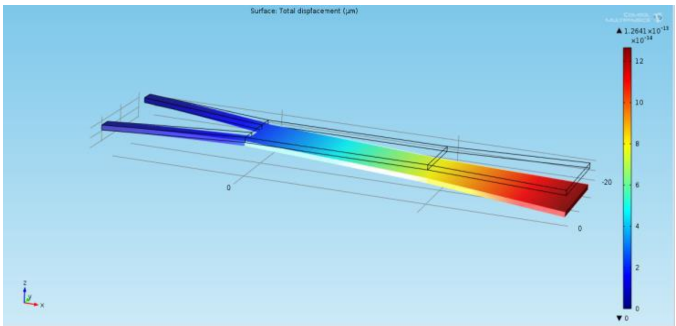

Fig. 6. Proposed design of micro-cantilever beam.

III. Results & Discussions

In order to arrive at the best material to be used for achieving maximum deflection, it can be inferred from the two equations concerning the deflections of the micro-cantilever – Stoney's equation and the Spring equation – that Young's Modulus and Poisson's ratio play key roles.

The detailed specifications of the various materials (SiO_2, Si and Si3N4) of different shapes (Rectangular-shaped, Triangular-shaped, T-shaped, Π-shaped, V-shaped and the proposed custom-shaped design) with comparable length, breadth and uniform thickness and their corresponding deflections on the application of a uniform total pressure of $5.749892771*10^{-12}$ Pa is as shown in the table II given below.

TABLE II. Deflections exhibited by various cantilever shapes with different materials having uniform dimensions.

Cantilever Shape	Cantilever Deflection(µm)		
	SiO_2	Si	Si_3N_4
Rectangular	2.4447e-14	9.9265e-15	6.7991e-15
Π-shape	4.1202e-14	1.6747e-14	1.1465e-14
Triangular	6.6031e-14	2.676e-14	1.8358e-14
T-shape	6.9975e-14	2.8424e-14	1.9463e-14
V-shape	1.1003e-13	4.52e-14	3.0786e-14
Suggested	1.2641e-13	5.2198e-14	3.5459e-14

IV. CONCLUSION

The readings obtained by force-deflection simulation of various microcantilevers are tabulated against different materials so as to arrive at the best set of parameters which result in maximum deflection of the microcantilever.

From the deflection readings tabulated above, it can be deduced that SiO2 is the best suited material as it gives larger amounts of deflection in the microcantilevers compared to the other materials used – namely, Si and Si3N4 – for a common load applied under same constraints.

Among the standard set of shapes of microcantilever that are considered for the study, which include Rectangle, Π-shaped, Triangular, T-shaped and V-shaped, it can be deduced that the microcantilever pertaining to V-shape exhibits the best deflection for a given amount of load under same test conditions.

The custom shape, as shown in Figure 6, is arrived at after the findings of the force-deflection behavior of the standard set of shapes. The free side of the custom-shaped microcantilever is made of a slightly larger area for enhancement of adsorption of molecules of interest. The fixed end is made narrower and is not kept completely attached to the bulk of the microcantilever; instead it is kept as two independent projections which thereby makes it flexible and sensitive. This custom shaped microcantilever, expectantly, gives the best results of deflection when SiO_2 is used as its structural material while the analysis was carried out for common load under similar test conditions. Thus, it can be concluded that, in order to achieve optimal deflections, the area of the free end of the microcantilever must be made large enough for enhanced adsorption; the fixed end must be made flexible enough to bring about more sensitivity, and the bulk material must preferably be SiO_2.

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