Design and Analysis of High Sensitive Microcantilever Based Biosensor for CA 15-3 biomarker detection

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Abstract:

In Biomedical field, the Microcantilever is one of the promising bio-sensing device used for detection of various diseases. In this paper, analysis of the Long Paddle (T shape) Microcantilever Biosensor has been performed. CA 15-3 is the most widely used biomarker for the breast cancer diagnosis. CA 15-3 is a glycoisylated protein which have the molecular weight of around 400 KDa. It is secreted by the surface epithelia of cancer tissues and shed in to the blood stream. Free floating CA 15-3 at high level is detected in the blood of breast cancer patients. Various analyses with different microcantilever structures performed and from the results obtained total displacement of the microcantilever when it is interacted with CA15-3 biomarker on the surface of Microcantilever found and tabulated. This paper proposes the detection of breast cancer detection biomarker under the static mode of operation. The results shows that total deflection of $1.6865 \times 10^{-17}$ µm is produced when the biomarker is absorbed in the proposed microcantilever sensor. The most significant advantage of MEMS is their ability to communicate easily with electrical elements in semiconductor chips. Other advantages include small size, lower power consumption, lower cost, simplicity and specificity.

*Keywords: Microcantilever, Biosensor, Breast Caner, CA-153 biomarker detection*
I. INTRODUCTION

T. Thundat et al. in 1995 proposed the study of Adsorption induced surface stress and its effects on resonance frequency of microcantilever which shows the coating of microcantilever with two different materials like the metal coated and aluminum coated cantilevers upon vapor adsorption. In this, 'V' shaped silicon cantilever is used coated with gelatin where deflection measured using PSD (position sensitive detector). Then graphs were plotted between resonance frequency, relative humidity, Error voltage and Time in minutes followed with top and side view of 'V' shaped cantilever is shown. It gives the conditions that arise due to adsorption of molecules and resonance frequency shifts [1]. Christian Ziegler in 2004 proposed the study of "Cantilever based biosensor". It shows the introduction about biosensor and the three different transduction methods. In this paper spring constant, resonance frequency and corresponding quality factor is derived and also shows the schematic diagram of an active feedback circuit with a variable phase shifters and gain amplifier. The deflection is detected using optical detection method based on interference effect and the frequency spectrum of cantilever driven by thermal is shown. The aim is to design small cantilevers with low force that is sensitive [2].

Mohd. zahid Ansari and chongducho in 2008 proposed the study of design and analysis of a high sensitive Microcantilever Biosensor for Biomedical applications that shows the advancement in the design of conventional microcantilever with a narrow strip towards the fixed end of Rectangular microcantilever made of photoresist SU8 material instead of silicon material. It is said that the proposed design has better deflection when the concentration is extremely less. It shows the array conventional and proposed cantilever design for biomedical applications. Then, the simulation result is about 4% higher than experiment value of proposed design and this design is twice sensitive when compared with the conventional micro cantilever design[3].

V. Mounikareddy and G. V. sunilkumar in 2013 proposed the study of design and analysis of microcantilever with various shapes using Comsol Multiphysics software that explains the piezoelectric cantilevers made of silicon dioxide material with different types as Rectangular, Double legged and triangular under position sensitive detector (PSD). This paper shows the bending of cantilever beam in response to compressive and tensile stress, which gives the stoney and spring constant equation. The SiO2 material properties obtained in Comsol Multiphysics software is mentioned and the following simulation of microcantilever is shown, and analysed.
the sensitivity when same force is applied on different shapes of cantilever. [4]. Deep Kishore parsediya et al. in 2014 proposed the study of "Simulation and analysis of Highly Sensitive MEMS Cantilevers design for 'in vivo label free'biosensing" that shows the basic elements of biosensor and focused on optical Reflection method for monitoring the deflection due to its effectiveness. They have proposed the designs of four micro cantilevers like Rectangular, Trapezoidal, Trapezoidal with square step at fixed end and length wise symmetrical tree type cantilever, and comparatively found maximum deflection occur in Trapezoidal with square step design compared to Rectangular when small stress is applied at free end which has larger area than the fixed end[5]. Ayushkumar et al. in 2017 proposed the study of "shape optimization of microcantilever beam used as biosensors using resonance frequency shift method" shows that in order to increase the sensitivity; they reduced the thickness of microcantilever and explained the dynamic mode of operation based on resonant frequency. They showed the three basic structures of cantilever like Rectangular, Triangular and Trapezoidal cantilever and proposed the Trapezoidal shape with free end curved cantilever and they drawn the graph for frequency shift for the designs.[6]. In biomarker detection trapezoidal cantilever with paddle is proposed [7].

II. BACKGROUND OF MICROCANTILEVER IN BIOSENSING APPLICATIONS

The detection of analyte is done by a device known as a biosensor which is a combination of a biological component and a physical detector. The biosensor is used to detect and analyse the unknown biological elements present in a medium. A general biosensor system is displayed in Figure 1. The detection of physical, chemical or biological changes is carried out with a mechanical device known as a micro cantilever using the principles of micro bending or resonant frequency. It is the miniaturized counterpart of a diving board that moves up and down at regular intervals. There is a distinct change in deflection when a specific analyte is absorbed on the surface of the microcantilever. The accuracy strongly depends on the determination of the surface stress induced deflections in micro cantilever based biosensors.

![Figure 1. Elements of biosensor](image_url)
The physical, chemical and biological sensing is carried out with micro cantilevers. Micro cantilevers have wide utility for applications in the field of medicine, in screening of diseases, detection of point mutations, blood glucose monitoring and detection of chemical and biological warfare agents [8]. Microcantilevers are micromechanical beams that are anchored at one end, such as diving spring boards that can be readily fabricated on silicon wafers and other materials. [9]. Bimetallic microcantilevers can exhibit static deflection as a result of thermal effects, including exothermic adsorption of chemicals on their surfaces [10]. Microcantilevers of different geometries have been used to detect two forms of prostate-specific antigen (PSA) over a wide range of concentrations from 0.2 ng/ml to 60 μg/ml in a background of human serum albumin (HSA) and human plasminogen (HP) at 1 mg/ml, making this a clinically relevant diagnostic technique for prostate cancer[11]. Reported a technique for micromechanical detection of biologically relevant glucose concentrations by immobilization of glucose oxidase (GOx) onto a microcantilever surface [12]. Due to the absence in need to attach fluorescent tags to molecules for detection and parallel operation [13] Cantilever sensors could be faster and cheaper. The biosensors are capable of detecting the target fungi in a range of 103–106 CFU ml−1. The measured shift is proportional to the mass of single fungal spores and can be used to evaluate spore contamination levels [14]. P-53 antigen is immobilized on the surface of the microcantilever as a recognition probe to detect p-53 antibody by measuring the deflection of the microcantilever using integrated piezoresistors, which is caused by the changes of the surface stress as a result of the specific bioaffinity between the antigen and the antibody [15]. SAM modified microcantilever can detect caesium ion concentrations in situ in the range 10211–1027 M [16]. Hepatitis B Virus (HBV) DNA detection using a silica nanoparticle-enhanced dynamic microcantilever biosensor proposed by [17]. Cholera O1 detection experiment is conducted in concentrations ranging from 1×10³ to 1×10⁷ CFU/ml. The micro cantilever-based sensor has a detection limit of ~1×103 CFU/ml and a mass sensitivity, ~146.5 pg/Hz, [18]. The peptide-functionalized microcantilever allowed efficient capture and detection of cancer cells in MCF7 spiked human blood samples emulating CTCs in human blood. A detection limit of 50–100 cancer cells mL from blood samples was achieved with a capture yield of 80% from spiked whole blood samples. [19]
III. REVIEW OF MICROCANTILEVER BASED BIOSENSOR

In the static mode of operation, the bending causes due to change in surface stress because of the molecular interaction on the surface of the micro cantilever. The principle of static mode of operation is displayed as Figure 2. Depending upon the surface deformation generated, the surface stress produced could be positive or negative. The work proposed by G.G Stoney in 1909 is the easiest model to understand the surface stress produced due to micro cantilevers [20]. Cantilevers by functionalized coating with bio chemical sensing layers respond very specifically using bio molecular key lock principles of analyte recognition.

![Figure 2. Principle of Static Mode of Operation](image)

Functionalization is not required on the surface of the micro cantilever in dynamic mode of operation. The total mass absorbed on both sides of the beam is the basis for changing the cantilever resonance frequency. The Principle of dynamic mode of operation is displayed in Figure 3 and in this mode of operation, the microcantilever is used as a microbalance and extremely high sensitivities can be obtained in the atto gram level. The spring constant, cantilever material and its geometry determine the sensitivity of the micro cantilever response. The cantilever stiffness change produces a change in resonance frequency as high as the force that is applied on the top surface.
Figure 3. Principle of Dynamic Mode of Operation

An Increase in the micro cantilever resonance frequency depends on the attached analyte density and cantilever length and thickness. For liquids environments, the quality factor of the microcantilever is lower than that in air, due to the damping effect of the viscous surroundings which decreases sharply the overall sensitivity. As a result, operation under dynamic mode is extremely difficult to implement and hence, most of the cantilever biosensors are based in the static mode only. A sensitive readout system is crucial for monitoring the nano or micro mechanical motion induced on the cantilever. Among the most extended readout schemes for biosensing are the optical, piezoelectric and the piezo resistive transduction mechanism.

The stoney equation is a basic expression relating the residual surface stress ($\Delta \sigma$) per unit length in a film to the curvature (k) of a substrate the film is deposited onto. The curvature does not depend on the material or the geometric properties of the film. This equation is used in determining the residual surface stress in thin films.

Radius of Curvature,

$$\frac{1}{R} = \frac{M}{E I} \rightarrow 3.1$$

The concentrated moment and the surface stress are related as under,

$$M = \frac{WT\Delta \sigma}{2}, \rightarrow 3.2$$

The moment of inertia for a beam of rectangular cross-section is given as,

$$I = \frac{WT^3}{12} \rightarrow 3.3$$

Where E is the elastic modulus, T is the thickness of the substrate and I, the moment of inertia. Substituting 3.2 and 3.3 in 3.1 equation,
\[
\frac{1}{R} = \frac{WT\Delta \sigma}{EWT^3} \]

\[
\frac{1}{R} = \frac{6\Delta \sigma}{ET^2} \quad \rightarrow 3.4
\]

Since,

\[
\Delta Z = \frac{l^2}{2} \left( \frac{1}{R} \right) \quad \rightarrow 3.5
\]

Substituting 3.4 in 3.5,

\[
\Delta Z = \frac{l^2}{2} \left( \frac{6\Delta \sigma}{ET^2} \right) \quad \rightarrow 3.6
\]

\[
\Delta Z = \frac{3l^2\Delta \sigma}{ET^2} \quad \rightarrow 3.7
\]

As the cantilever plate is long and wide, as a general practice E is replaced by the biaxial modulus \( E = \frac{E}{1-\nu} \), to accommodate the poisson's ratio(\( \nu \)) coupling,

\[
\Delta Z = \frac{3l^2\Delta \sigma}{(E\nu)T^2} \quad \rightarrow 3.8
\]

This is well known form of stoney equation[20] commonly used in predicting the residual surface stress in thin films by measuring the induced deflection.

**IV. DESIGN OF PROPOSED MICROCANTILEVER FOR CA 15-3 BIOMARKER DETECTION**

Cancer diagnosis and treatment are of great interest due to the widespread occurrence of the diseases, high death rate, and recurrence after treatment. According to the National Vital Statistics Reports, from 2002 to 2006 the rate of incidence (per 100,000 persons) of cancer in White people was 470.6, in Black people 493.6, in Asians 311.1, and Hispanics 350.6, indicating that cancer is wide-spread among all races. [21]. Formal definitions of nanotechnological devices typically feature the requirements that the device itself or its essential components be man-made, and in the 1–1.00 nm range in at least one dimension. Cancer-related examples of nanotechnologies include injectable drug delivery nanovectors such as liposomes for the therapy of
breast cancer [22]. CA 15-3 is the most widely used marker for the breast cancer diagnosis. CA 15-3 is a glycoisylated protein of molecular weight of around 400 KDa. It is secreted by the surface epithelia of cancer tissues and shed into the bloodstream. Free floating CA 15-3 at high levels is detected in the blood of breast cancer patients. Proposed microcantilever designs with paddle structure for the detection of CA 15-3 biomarker detection. A finite element analysis software Comsol Multiphysics is used for analyzing the deflection of the conventional and proposed microcantilever beam designs. In this analysis, the same element as per [5] is taken as reference for designing the sensor and the properties in given in Table 1. In this proposed design the paddle is introduced in the end of the rectangular structure for better sensitivity and deflection. The pressure produced by the surface stress of the CA 15-3 biomarker is calculated and it is applied at the top surface of the proposed microcantilever structure. All the microcantilever beams are designed with the uniform surface area of 50,000 μm².

Table. 1 Material Properties-SiO₂

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Density</td>
<td>2200 kg/m³</td>
</tr>
<tr>
<td>2.</td>
<td>Youngs Modulus</td>
<td>70e9 Pa</td>
</tr>
<tr>
<td>3.</td>
<td>Poisson’s ratio</td>
<td>0.17</td>
</tr>
<tr>
<td>4.</td>
<td>Electrical Conductivity</td>
<td>0 (S/m)</td>
</tr>
<tr>
<td>5.</td>
<td>Co-efficient of thermal expansion</td>
<td>0.5e-6 (1/K)</td>
</tr>
<tr>
<td>6.</td>
<td>Heat capacity at constant pressure</td>
<td>730 J/(kg.K)</td>
</tr>
<tr>
<td>7.</td>
<td>Relative permitivity</td>
<td>4.2</td>
</tr>
<tr>
<td>8.</td>
<td>Thermal conductivity</td>
<td>1.4 W/(m*K)</td>
</tr>
</tbody>
</table>
V. RESULTS AND DISCUSSION

A Rectangular shape design is taken with the length and breadth 500 μm x 100 μm respectively with the thickness is 50 μm which is taken as a reference simple microcantilever structure. Figure 4 shows the Rectangular Microcantilever structure with the surface area of 50,000μm².

![Figure 4. Rectangular Microcantilever structure](image)

Figure 5 shows the free end displacement of the Rectangular Microcantilever structure with the surface area 50,000μm² using Comsol Multiphysics software by applying the equivalent stress of CA 15-3 biomarker on the top surface of the microcantilever. Corresponding to this applied stress, the rectangular beam design produced a free end deflection of 1.4000 x 10^{-18} μm.

![Figure 5. Simulation result of Rectangular Microcantilever structure](image)
A Rectangle with circular shape paddle Microcantilever structure design is taken with the length and breadth 200 μm x 100 μm (Rectangular beam) and 112.83μm (circular Paddle diameter) respectively with the thickness is 50 μm which is taken for the analysis. Figure 6 shows the Rectangle with circular shape paddle Microcantilever structure with the surface area of 50,000μm²

![Figure 6. Rectangle with circular shape paddle Microcantilever structure](image)

Figure 7 shows the free end displacement of the Rectangle with circular shape paddle Microcantilever structure with the surface area 50,000μm² using ComsolMultiphysics software by applying the equivalent stress of CA 15-3 biomarker on the top surface of the microcantilever. Corresponding to this applied stress, the Rectangle with circular shape paddle design produced a free end deflection of 9.1418x 10⁻¹⁸ μm.

![Figure 7. Simulation result of Rectangle with circular shape paddle](image)
A Short Paddle (T Shape) Microcantilever structure design is taken with the length and breadth 300 μm x 100 μm (Rectangular beam) and 300 μm x 100 μm (Paddle structure) respectively with the thickness is 50 μm which is taken for the analysis. Figure 8 shows the Short Paddle (T Shape) Microcantilever with the surface area of 50,000 μm$^2$

![Figure 8. Short Paddle (T Shape) Microcantilever structure](image)

Figure 8. Short Paddle (T Shape) Microcantilever structure

Figure 9 shows the free end displacement of the Short Paddle (T Shape) Microcantilever structure with the surface area 50,000 μm$^2$ using ComsolMultiphysics software by applying the equivalent stress of CA 15-3 biomarker on the top surface of the microcantilever. Corresponding to this applied stress, the Short Paddle (T Shape) Microcantilever produced a free end deflection of $1.0066 \times 10^{-18}$ μm.

![Figure 9. Simulation result of Short Paddle (T Shape)](image)
A Trapezoidal Microcantilever structure design is taken with the length of 500 μm and front and back breadth of 150 μm and 50 μm respectively with the thickness is 50 μm which is taken for the analysis. Figure 10 shows the Trapezoidal Microcantilever structure with the surface area of 50,000μm².

![Figure 10. Trapezoidal Microcantilever structure](image)

Figure 10. Trapezoidal Microcantilever structure

Figure 11 shows the free end displacement of the Trapezoidal Microcantilever structure with the surface area 50,000μm² using ComsolMultiphysics software by applying the equivalent stress of CA 15-3 biomarker on the top surface of the microcantilever. Corresponding to this applied stress, the Trapezoidal Microcantilever structure design produced a free end deflection of 2.5664 x 10⁻¹⁸ μm.

![Figure 11. Simulation result of Trapezoidal Microcantilever structure](image)

Figure 11. Simulation result of Trapezoidal Microcantilever structure
A Long Paddle (T Shape) Microcantilever structure design is taken with the Rectangular area of (length of 800 μm and breadth 50μm) 40,000μm² and front and paddle area of (length of 200 μm and breadth 50μm) 10,000μm² respectively with the thickness is 50 μm which is taken for the analysis. Figure 12 shows the A Long Paddle (T Shape) Microcantilever structure design with the surface area of 50,000μm².

Figure 12. Long Paddle (T Shape) Microcantilever structure

Figure 13 shows the free end displacement of the A Long Paddle (T Shape) Microcantilever structure with the surface area 50,000μm² using ComsolMultiphysics software by applying the equivalent stress of CA 15-3 biomarker on the top surface of the microcantilever. Corresponding to this applied stress, the A Long Paddle (T Shape) Microcantilever structure produced a free end deflection of 1.6865 \times 10^{-17} \text{µm}.

Figure 13. Long Paddle (T Shape) Microcantilever structure
Table 2 shows total Deflection with different shapes of microcantilever which is simulated and Figure 14. Performance Comparison of different structures of Microcantilever which shows that the Long Paddle (T Shape) have the better deflection and sensitivity with respect to the biomarker.

Figure 14. Performance Comparison of different structures of Microcantilever
VI. CONCLUSION

In this paper, presented the study of biosensor, microcantilever based sensor for CA 15-3 biomarker detection. From the results the proposed structure may be used for the detection of CA 15-3 biomarker for the diagnosis of breast cancer detection biomarker under the static mode of operation. The results show that total deflection of $1.6865 \times 10^{-17} \, \mu m$ is produced when the biomarker is absorbed in the proposed microcantilever sensor. In future, by implementing with polymer material and by modifying the shape at the tip of the microcantilever structure, results ie., the total displacement due to antigen can be expected higher and also by choosing appropriate mode could be achieved more to detect the cancer antigens present in the sample at early stages to save the human lives.

REFERENCES:


