DESIGN OF MEMS BASED MICROCANTILEVER FOR TUBERCULOSIS DETECTION

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ABSTRACT

Tuberculosis is infectious disease caused by various strains of *Mycobacterium tuberculosis*. The detection of tuberculosis is very difficult because their mechanism is not well understood and it is mainly based on the γ interferon which is normally secreted by the T-cell of the body. It consumes more time and it can detect various other strains like *Mycobacterium auerum* instead of virulent strains of tuberculosis.

The RD1 region is genomic and is present in all strains of *Mycobacterium tuberculosis*. The ESAT-6/CFP-10 complex is secreted by the ESX-1 secretion system, also known as the RD1 region. It is expressed as a surface antigen. The fusion protein of ESAT-6/CFP-10 antibody is 24KDa. It interacts with the surface antigen and enables detection. The cantilever structure on silicon substrate with gold-coated film has been simulated. The simulations results include the stress, displacement measurements, Eigen function study and the best suited type of cantilever for the detection.

Keywords: Finite Element Method, genomic, mycobacterium.

INTRODUCTION

TUBERCULOSIS is caused by a bacterium called Mycobacterium tuberculosis. In 2011, it has been estimated that 8.7 million new cases of TB (13% co-infected with HIV) and more than 5.7 million people died. In 2011-2012, the numbers of new TB cases had been brought down to 2.2%.Inspite of that, the prevalence of TB is high because of the increase in HIV patients [1]. Mycobacterium tuberculosis affects the lungs and occurs when the patient become immunodeficient [2]. Now-a-days, *Mycobacterium* is becoming a drug resistant and spreads quickly. The delay in recognizing and treating the disease has led to increased mortality, nosocomial outbreaks, and resistance to additional anti- tuberculosis drugs [3].

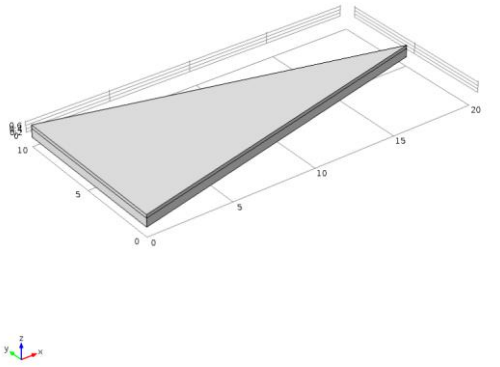
ESAT-6/CFP-10 is secreted by the extended region of RDX- 1 which encodes ESX-1, a novel protein secretion system and known to contribute to virulence and pathogenicity in the host because they are responsible for host-pathogen interaction [4]. ESAT-6 and CFP-10 form a tight 1:1 complex and adopt helix–turn–helix hairpin conformation and are orientated anti-parallel to each other. The interactions between the two proteins are mainly hydrophobic and Vander-Waals interactions [5].

The ESAT-6/CFP-10 heterodimer complex is targeted for secretion by a C-terminal signal sequence on CFP-10 that is recognized by the cytosolic Rv3871 protein. Rv3871 then interacts with the CFP-10 C-terminal, and escorts the ESAT-6/CFP-10 complex to Rv3870 and Rv3877, a multi-transmembrane protein which makes up the pore that spans the cytosolic membrane of the virulent host cell [7]. The sensitivity and selectivity for recombinant ESAT-6/CFP-10 is more compared to recombinant ESAT-6, recombinant CFP-10 and commercial ESAT-6 in diagnosis of tuberculosis [8]. The apparent molecular weight of the fusion protein was found to be 24 kDa [9].

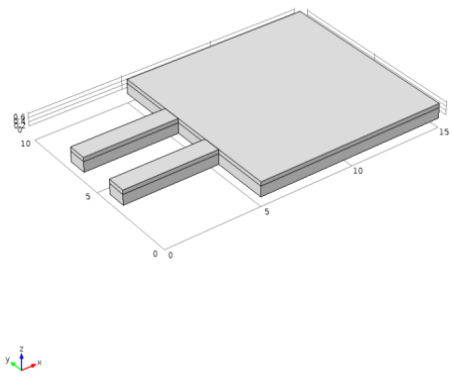
The cantilevers are highly sensitive structure. They enable easy detection and accurate measurement of number of molecules attaching to their surface. The detection below 1×10^4 cells is very difficult with electrochemical method. The main advantage over other methods is purification of the sample is not required and non specific interaction does not occur. Our aim was to select the best suited cantilever for tuberculosis detection.

Figure 1: Proposed Geometry of the Cantilever array

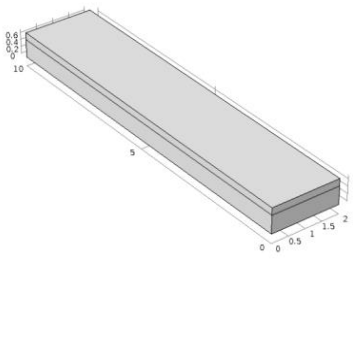
a. Triangular Shape



b. Pi-Shape



c. Rectangular Shape



MODEL DESCRIPTION AND ANALYSIS

The simulation modelling has been done using COMSOL Multiphysics software because it has the capability for design, modelling, and simulation of MEMS based models. In this simulation, the cantilever is constrained at one end and is suspended free at the other end. The length of each type of cantilevers is 100µm. Two layers i.e, polysilicon layer of 0.5µm and gold layer of 0.2µm are sandwiched together. The Stoney's formula, which relates cantilever end deflection 'δ' to applied stress 'σ':

$$\delta = \frac{3\sigma(1-\nu)}{E}\left(\frac{L}{t}\right)^2 \quad \text{--- (1)}$$

Where 'ν' is Poisson's ratio, 'E' is Young's modulus, 'L' is the beam length and't' is the cantilever thickness. Polysilicon layer is used to avoid non specific interaction and gold layer enables the immobilization of antibodies by gold thiol interaction and detection of cantilever deflection by S*urface Plasmon resonance*.

The physics employed is Solid Mechanics. The total force is being applied to the cantilever is correlated with the number of analyte molecules attaching to the thiolated gold surface of the cantilever. The resonance frequency (f) in the dynamic working mode of the cantilever is given by:

$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m_{eff}}} \quad \text{--- (2)}$$

Where, 'k' is the spring constant,

'm_{eff}' is the effective or dynamic mass.

The stationary study and Eigen study are performed to obtain a best suited cantilever. The result verifies the Hooke's law which states that stress is directly proportional to strain. Mathematically,

$$\mathbf{F = -kx} \quad \text{--- (3)}$$

Where, x is the displacement in Z-direction,
F is the restoring force,
k is the spring constant.

RESULTS AND DISCUSSION:

(i) STATIONARY STUDY:

Figure 2 a: Triangular shaped cantilever

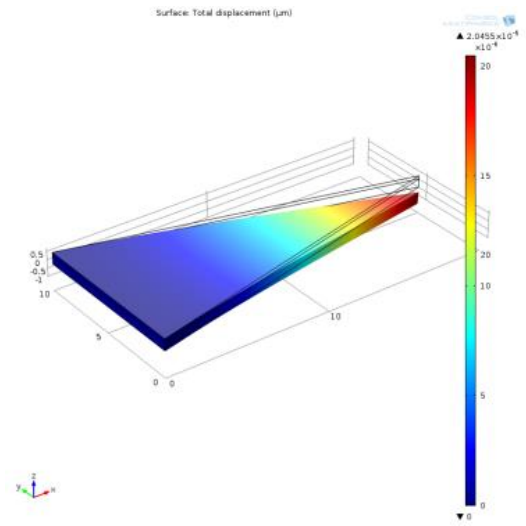


Figure 2 b: Pi shaped cantilever

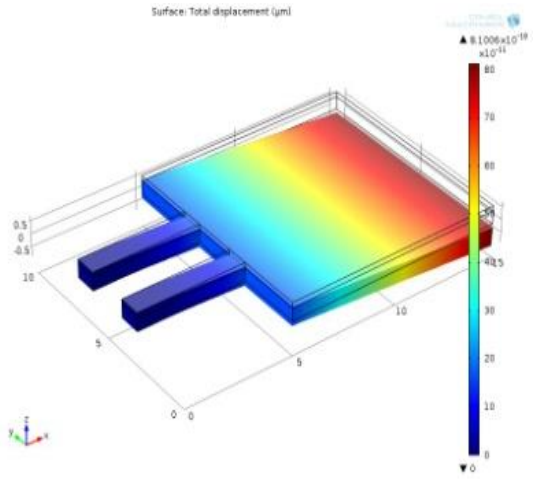


Figure 2 c: Rectangular shaped cantilever

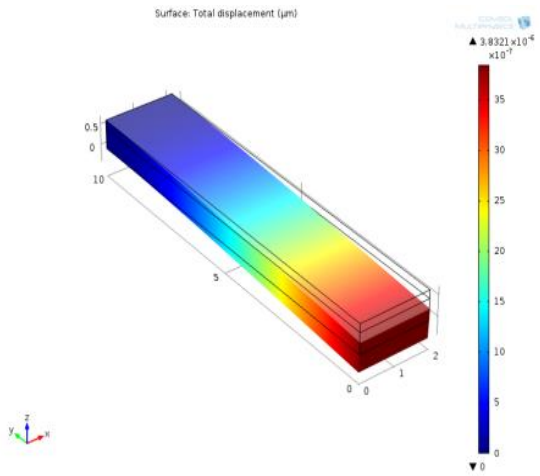
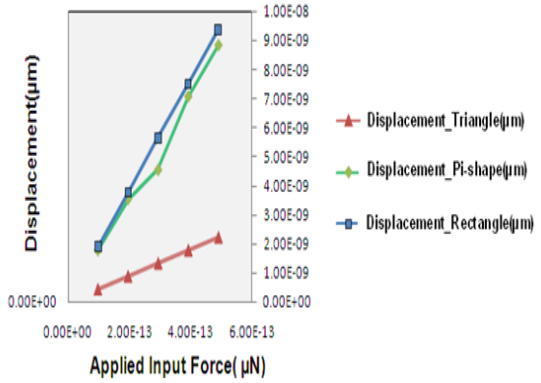


Figure 3: Displacement Vs Input force for different Cantilever types

Cantilever type	Displacement (µm)	Eigen Frequency (Hz)
Triangular shape	$1.0023*10^{-13}$	9.86225
Pi- shape	$3.9693*10^{-21}$	$1.8115*10^{7}$
Rectangular shape	**$9.3887*10^{-9}$**	**$4.5078*10^{6}$**



The maximum displacement of $9.3887*10^{-19}$ was observed in rectangle-shaped cantilever for an input mass of 50 antigens which means that it is highly sensitive. The Eigen frequency simulation study of the different types of proposed cantilever are given in figures 4 a, b and c.

Figure 4 a: Triangular shaped cantilever

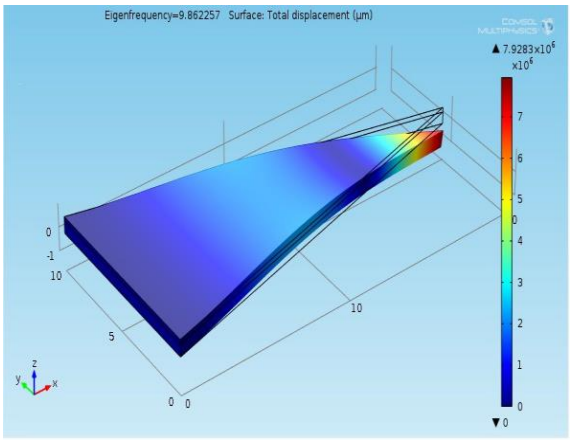


Figure 4 b: Pi - Shaped cantilever

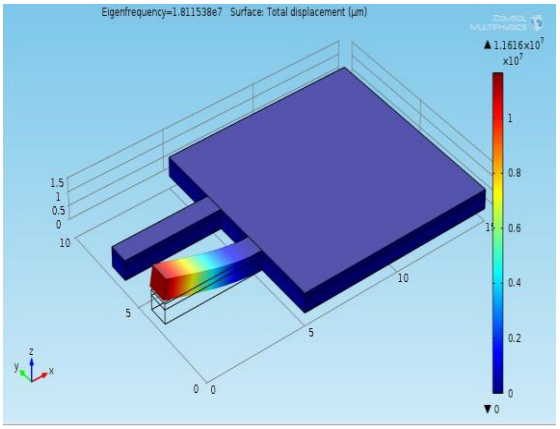
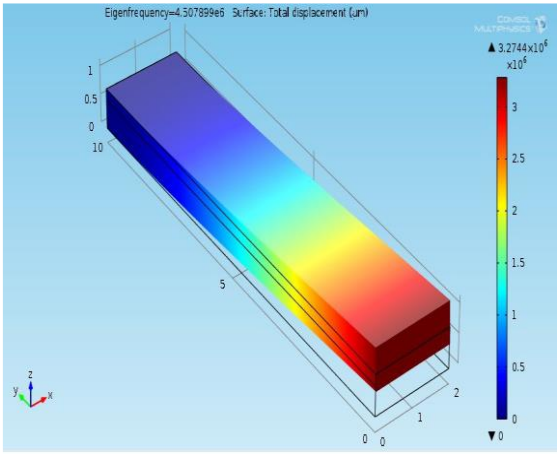


Figure 4 c: Rectangular shaped cantilever



CONCLUSION:

The Eigen frequency and the maximum displacement were observed for rectangular shaped cantilever sensor. The sensor is highly sensitive since it can detect even attomolar concentration of the analyte molecules. For an input mass of *50 ESX-1 antigens*, a maximum displacement of **$9.3887*10^{-19}$** was observed. Thus, a highly sensitive and selective sensor based on cantilever is simulated using COMSOL Multiphysics 4.3b software.

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