# A Novel Plug N Play MEMS-Based DNA Microarray

K. Jindal*[1], V. Grover[1], and B. Nayak[1]
[1]Birla Institute of Technology and Science, Pilani
*Corresponding author: f2012811@pilani.bits-pilani.ac.in

**Abstract:** Microarrays are extensively used in modern biology as tools of multiplexed, high throughput analysis to study thousands of genes and their expression inside cells at once. The basic principle of a microarray is quantitative detection of fluorophore tagged DNA. Use of this method results in microarray experiments being expensive and complex due to fragile and costly fluorophores and instrumentation required to analyze them. Previously, MEMS based DNA sensors have been implemented, though at a small scale, sensing less than 10 DNA sequences. These sensors suffer from poor signal to noise ratio, cantilever to cantilever variation and impractical scaling of sensing techniques. In this report, we analyze and propose solutions to such problems and also propose a novel DNA chip of scale comparable to microarrays that does fluorophore free detection and also design circuitry to directly interface it to a computer, bypassing need of additional analysis instruments.

**Keywords:** DNA microarrays, Mass based resonant sensors.

## 1. Introduction

### 1.1 Traditional DNA Microarrays

DNA microarrays, also known as DNA chips are tools of high throughput biological experimentation. A typical DNA microarray involves a chip with a large number of dots arranged in an array like fashion. Each dot contains single stranded DNA probes of one kind. The probes on each dot are generally 20-25nt in length and are complementary to cDNA of a particular gene. The cells to be analyzed are taken, lysed and the mRNA is extracted. This mRNA is converted to cDNA via an enzyme called Reverse Transcriptase. Further, each cDNA molecule is end labelled with a fluorophore, typically Cy3 or Cy5. These labeled cDNA molecules are made to hybridize with the probes. The chip is then excited by the characteristic excitation wavelength of the fluorophore and each dot is analyzed for fluorescence intensity. The intensity of fluorescence is directly proportional to the number of cDNA molecules of the particular gene, hence the number of RNA molecules. This gives us an idea of the extent of up regulation or down regulation of various genes of a given cell population under specific environment, growth stage or infection [1].
Despite their popularity, microarray experiments are costly, lengthy due to the naturally slow throughput of fluorescence based detection and fragile, due to the use of expensive measurement instrumentation and photosensitive fluorophores. We feel that with the help of MEMS technology, microarray experiments can be made significantly faster, cheaper and much more robust.

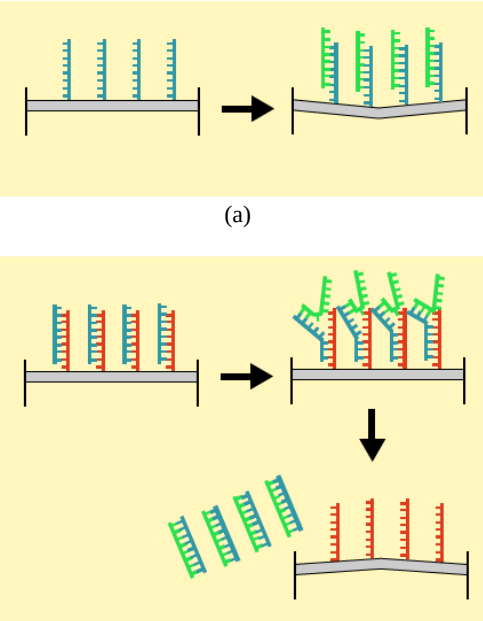
### 1.2 MEMS based DNA Microarrays

Herein, we model a MEMS based DNA sensor which is scalable for highly multiplexed applications such as the DNA microarray. The cantilever modelled is a resonant mass sensor, which resonates at a characteristic resonant frequency, which is a function of added mass. This resonance is converted to a sinusoidal voltage signal by a thin piezoelectric transducer and is conditioned and converted to a digital readout using an electronic circuit. The voltage is measured on the top face of the cantilever. Binding of DNA, present in the sample to be tested, leads to change in mass present on the cantilever and hence its resonant frequency. This change in resonant frequency is detected by the electronic circuit and is used to in turn determine the amount of DNA present in the sample.

### 1.3 DNA strand displacement

Traditional MEMS based DNA sensors are sensitive to not only the number of DNA strands present, but also the length of the DNA strand [2,3]. In microarray experiments however, one is concerned only with the number of strands of different DNA sequences present in the sample. Thus, use of a traditional mass based resonant sensors is not ideal in such highly multiplexed applications and can give inaccurate results. To bypass this problem, we propose a novel strand

displacement based mass sensing of DNA which is only dependent on the number of DNA present and not its length (Figure 1). Use of this mechanism makes it possible to implement our design on a very large scale for a variety of target DNA sequences, without worrying about the difference in length of these sequences, hence enabling MEMS based DNA microarrays.



(a)

(b)

**Figure 1.** Novel strand displacement based DNA sensing on a microcantilever. Green: Target to be detected, length can vary from gene to gene; Blue: Probe complementary to target; Red: Probe binding DNA. (a) Conventional microcantilevers based DNA sensing approach, change in mass depends on both number and size of target strands. (b) Novel strand displacement based approach, decease in weight on cantilever is equivalent to N times weight of probe (known and equal for all cantilevers) where where N is number of target DNA. Hence change of weight does not depend on length of target, it depends only its number.

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## 2. Mathematical Modelling of the MEMS resonator

### 2.1 Geometric modelling

The cantilever designed is shown in Figure 2. The cantilever consists of a base, a thin piezoelectric transducer and a square patch on the top surface for oligonucleotide immobilization. The cantilever was fixed at both ends to create a clamped-clamped beam configuration. Capacitive excitation was used to induce resonance. The bottom face of the cantilever was grounded and acted as one plate of the capacitor, while voltage was applied to an electrode situated at a specific distance below it. The dielectric between the plates was taken as air only.

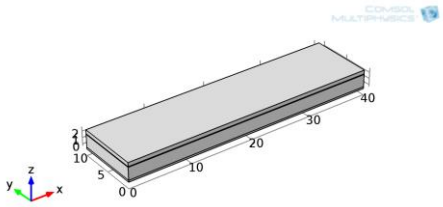


**Figure 2.** Model of the resonant mass sensor designed

### 2.2 Design of actuation circuit

A mathematical model of the actuating circuit was designed to compare the results of the simulation to those of the model. In brief, desired output voltage suitable for a low noise, linear readout from the electronic circuit was selected and the uniform force of actuation to achieve the desired voltage was calculated along with the center-point deflection of the sensor. The following equations were used to obtain the force and the actuating capacitor plate separation at the pre-stress voltage.

The fundamental equation for a piezoelectric material under the small field constitution is [4]:

$$\begin{bmatrix} D \\ \varepsilon \end{bmatrix} = \begin{bmatrix} e_\sigma & d_d \\ d_c & s_e \end{bmatrix} \begin{bmatrix} E \\ \sigma \end{bmatrix}$$

Where, vector D of size (3 × 1) is the electric displacement (Coulomb/m$^2$), ε is the strain vector (6 × 1) (dimensionless), E is the applied electric field vector (3 × 1) (Volt/m) and σ is the stress vector (6 × 1) (N/m$^2$). The piezoelectric constants are the dielectric permittivity $e_\sigma$ of size (3 × 3) (Farad/m), the piezoelectric coefficients $d_d$ (3 × 6) and $d_c$ (6 × 3) (Coulomb/N or m/Volt), and the elastic compliance $s_e$ of size (6 × 6) (m$^2$/N). A typical piezoelectric sheet can be treated as a

parallel plate capacitor, whose capacitance is given by [4]:

$$C = \varepsilon \frac{l.b}{t}$$

Where, C is the capacitance. l,b,t are the length breadth and thickness of the piezoelectric sheet respectively. The voltage across a parallel plate capacitor is written in terms of the charge on the plates and the capacitance as

$$V = \frac{q}{C}$$

The electric displacement D is related to the generated charge by the relation [4]:

$$q = \iint \begin{bmatrix} D_1 & D_2 & D_3 \end{bmatrix} \begin{bmatrix} dA_1 \\ dA_2 \\ dA_3 \end{bmatrix}$$

Where, $dA_1$, $dA_2$ and $dA_3$ are the components of the electrode area in the 2-3, 1-3 and 1-2 planes respectively. Thus, the voltage generated by the sensor can be expressed as [4]:

$$V = \left(\frac{d_{31} Yb}{C}\right) \int_l \varepsilon_1 dx$$

where, Y is the young's modulus of the material. $\varepsilon_1$ is the strain in the direction of the length of the cantilever. A suitable range for the voltage amplitude; where the signal to noise ratio was sufficiently high for the electronic circuit, was chosen as 100 uV. Evaluating the longitudinal strain as a function of the force (F) applied and distance from a fixed end (x), the actuation force was calculated as:

$$\varepsilon_1 = \frac{3F}{YbH^2}\left[1 - \frac{x}{l}\right]$$

Now, applying Castigliano's Theorem to a cantilever fixed at ends, the force and deflection of the center point of the cantilever can be related as:

$$\delta = 5\omega l^4 / 384EI$$

Where, ω is the force per unit length, δ is the deflection of the center point, E is the modulus of elasticity and I is the area moment of inertia about the bending axis. The force required for capacitive Transduction can be expressed as a function of the capacitance (C), inter plate separation (d), and the pre-stress and actuation voltages as:

$$F = \eta V_{AC}$$

Where,

$$\eta = \frac{V_{DC} C_0}{d} \quad and \quad C_0 = \varepsilon \frac{A}{d}$$

Thus, knowing the magnitude of actuation force needed, the distance between the base of the sensor and the microarray base was calculated.

### 2.3 Derivation of damping parameters

The Rayleigh mode of damping was used to estimate the damping in the cantilever structure. The values of the Rayleigh damping coefficients and can be expressed as [5]:

$$c = \alpha M + \beta K$$

Where, c is the damping matrix, M is the mass matrix and K is the stiffness matrix. The values of the Rayleigh damping coefficients can also be expressed in terms of the critical damping coefficient as [5]:

$$\begin{bmatrix} 1/4\pi f1 & \pi f1 \\ 1/4\pi f2 & \pi f2 \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = \begin{bmatrix} \xi 1 \\ \xi 2 \end{bmatrix}$$

Where, ξ is the critical damping ratio at a particular frequency 'f'. Using this, values of alpha and beta were calculated. Results of all mathematical analysis are listed in Table 1.

| Parameter | Value |
|---|---|
| Distance between base of cantilever and electrode | 286 nm |
| Alpha | 53615.8643 1/s |
| Beta | 1.2275e-11 s |

**Table 1.** Parameters derived from mathematical analysis

## 3. Use of COMSOL Multiphysics® Software

### 3.1 Model setup

Analysis and modelling of the sensor was done in COMSOL Multiphysics 4.4, electromechanics (emi) physics and Piezoelectric Devices (pzd) physics were used for simulation. A cantilever

was constructed in COMSOL Multiphysics (Fig. 1) as described in Sec. 2.1, the mesh type used was 'Free Tetrahedral'. The model has 63330 degrees of freedom.

### 3.2 Size optimization of cantilever

During fabrication process, errors can occur which can result in cantilevers of slightly different dimensions than expected. This can lead to change in resonance frequency and hence response of a resonant sensor to a mass perturbation. To minimize this problem, a dual parametric sweep was run where both, length and width of the cantilever were varied from to and fundamental resonant frequency was calculated for each possible combination and plotted. Dimensions at which the slope of the curve (and hence its sensitivity to fabrication errors) were

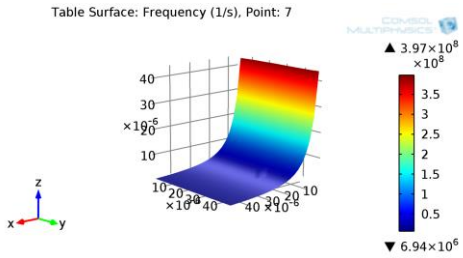


**Figure 3.** Parametric sweep for determining dimensions of the cantilever

minimum were chosen for further analysis. Figure 3 shows the curve obtained from the study. The final dimensions of each component are as listed in Table 2.

| Component | Dimensions (l x b x h) |
|---|---|
| Base | 40 x 10 x 2 um |
| Piezoelectric transducer | 40 x 10 x 0.1 um |
| DNA binding patch | 5 x 5 x 0.1 um |

**Table 2.** Dimensions of the sensor's components

### 3.3 Mechanical Characterization of the resonant sensor

Initial conditions using a prestressed voltage of 40V were obtained using stationary study. Fundamental frequency of the cantilever was obtained by Prestressed Eigenfrequency analysis under Rayleigh damping. Displacement of the cantilever at resonant frequency was computed using a Prestressed, Frequency Domain study under a harmonic perturbation of 1V on the electrode. The results of this study were used to compute the voltage generated by the piezoelectric transducer in the Z direction at resonance. The results of these studies are shown in Figure 4.

### 3.4 Variation of resonant frequency with added mass

The change of mass on the cantilever due to presence of target DNA was simulated by adding uniform mass per unit area of the silicon patch. Oligonucleotide density on the patch, required for mass calculation was used as previously reported. A parametric sweep was performed where the mass change was varied from zero to the maximum capacity of the cantilever and fundamental frequency was obtained for each case and plotted. Sensitivity obtained was 0.6Hz/fg of DNA. The results are shown in Figure. 5

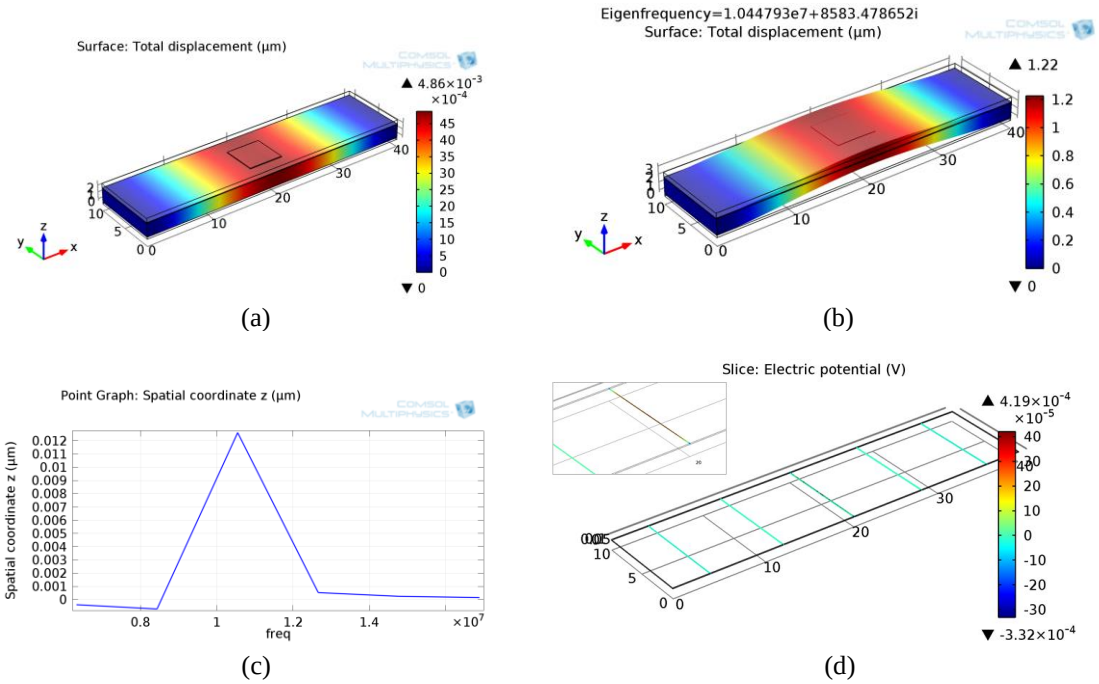


**Figure 4.** (a) Stationary study of the prestressed cantilever. (b) Eigenfrequency analysis to find first resonant mode. (c) Frequency sweep around the resonance frequency. (d) Peak voltage generated across piezoelectric layer at resonance (inset shows a zoomed in view of the center point).

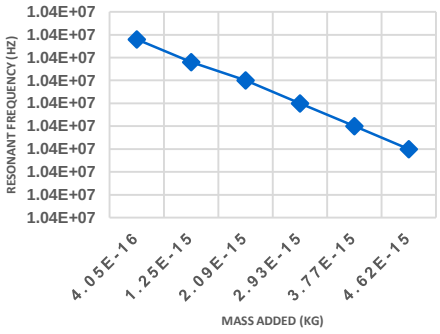


**Figure 5.** Response of the DNA sensor to added mass.

## 4. Electronic circuit design for readout generation

A signal conditioning circuit was designed to generate meaningful digital readout from the AC signal generated by the resonating cantilever. Piezoelectric sensors have high output impedance. Hence circuits having input impedance much higher than the output impedance of the sensor must be used to ensure minimal loss of the signal. Several signal conditioning circuits for piezoelectric sensors have been previously reported [6][7]. [6] and [7] used a current to voltage converter or current amplifier, cascaded by an inverting amplifier.

The signal conditioning circuit used in our design is shown in Figure 6. The piezoelectric sensor was modeled as a charge generator in parallel with $C_{int}$, which is the internal capacitance of the sensor. $C_c$ is the equivalent capacitance of the cables connected between the sensor and the amplifier and is in parallel to $C_{int}$ [4]. The high frequency gain of the amplifier is determined by the value of the feedback capacitance, $C_f$. The feedback resistance, $R_f$ provides a path for current flow at low frequencies when $C_f$ becomes open circuited leading to the amplifier being in open loop. At high frequencies, when the impedance of $C_f$ is low, role of the $R_f$ path is reduced. A pole is introduced in the circuit due to the $R_f$ and $C_f$ components and the circuit effectively acts as a high pass filter with the pole value set at

$$f_p = \frac{1}{2\pi R_f C_f}$$

After setting the value of $C_f$ to get the desired gain, the value of $R_f$ was set to obtain the desired frequency response. A low value of $R_f$ is desirable for a high value of pole frequency. The output voltage of the charge amplifier is unaffected by the sensor capacitance or the cable capacitance. The output depends only on the value of feedback capacitance. The charge amplifier stage is cascaded by a Schmitt trigger whose output now switches between two states.

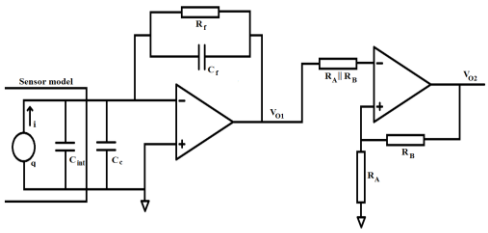


**Figure 6.** Circuit for processing output of MEMS sensor

## 5. Conclusion

The study demonstrates design and analysis of a linear MEMS based DNA sensor which has relatively higher scalability, tunable sensitivity with the help of DNA strand displacement and a ready interfacing to digital devices. We feel that such a device if practically implemented, would be instrumental in improving existing microarray technologies and also making it available to a wider group of researchers.

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