# Piezoelectric MEMS Micro-Cantilever Biosensor for Detection of SARS –CoV2

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***Abstract*— Piezoelectric MEMS (Micro-Electro-Mechanical Systems) are used in many applications now a day's including the diagnosis of diseases.COVID-19 is a pandemic recently affecting the entire world. Various techniques for detection are being used to date. Paper presents a simulation-based piezoelectric MEMS detection method for the virus, which is fast, portable, cost-effective, require less amount of sample, reliable, and can diagnose the stage for SARS-CoV-2(Severe acute respiratory syndrome corona virus 2) from the first day of virus infection. The design and analysis of cantilever-based MEMS biosensor is done COMSOL Multiphysics. Three cantilevers are used in the design, one each for viral load, IgM, and IgG. The bio-molecular reaction on the cantilever increases the mass at the end, changing the electrical and mechanical properties in the cantilever. Piezoelectric material generates the voltage proportional to the mass applied. From the values of voltage obtained from three cantilevers, the infection stage for symptomatic and asymptomatic can be diagnosed. Results show a linear relationship between the load applied and voltage generated. The proposed biosensor has a mass sensitivity of 20 copies /ml.**

***Keywords*— *Bio-MEMS, Biosensor, Coronavirus, COVID-19, diagnosis of SARS-CoV-2, MEMS cantilever, Piezoelectric MEMS, COMSOL Multiphysics***

## I. INTRODUCTION

Since the invention of MEMS in the 1960s, they have found applications in a wide area of applications. Due to ease of use, fast diagnosis, compatibility with bio-molecules, diagnosis of low concentration assay, MEMS have been widely used in bio-sensing [1]. Diagnosis of Swine flu [2], Hepatitis [3], viruses [4], using MEMS are just some examples in vast applications of disease diagnosis using MEMS.

COVID-19 was first detected on December 19 in Wuhan, China. Since then it has now spread in almost 200 countries and territories across the globe. It was declared a pandemic by the World Health Organization (WHO) in March 2020. It spreads from human to human via droplets of saliva or discharge from the nose. The novel SARS-CoV-2 is not deadly, but as it can spread undiscovered, it can affect people. As on 21st March 2021, there are 123,545,091 cases world-wise [5].

The most common COVID-19 diagnostic techniques for SARS-CoV-2 presently are RT-PCR(Reverse Transcription Polymerase Chain Reaction) and Immune Response Detection. RT-PCR technique detects the viral RNA present in the body. Antibodies are produced by the immune system of the body after the viral attack. Immune Response Detection techniques detect antibodies such as IgM(Immunoglobulin M) and IgG(Immunoglobulin G) in the body. The positive viral load in the sample shows the current infection state and no information whether or not the patient was infected in past, whereas Immune Response Detection techniques show the past infection in the patient with the added advantage of being cheap and no requirement of experienced professionals and Lab. Since antibodies do not appear before the 7th day of infection, Immune Response Detection techniques entirely miss the patients in the early stages of infections. Therefore, there is need of detection technique which can bridge the gap between existing diagnostic technologies.

## II. PRINCIPLE

Piezoelectric MEMS sensors are used as mass and viscosity sensors [6]. The principle involves bio-sensing, change in mechanical properties of the cantilever due to force/mass applied, and generation of electric energy via piezoelectric material.

The pits of the cantilevers are functionalized by applying the bio-receptor, and then the analyte is deposited. The bio-receptor and analyte form the bio-complex. The combination of analyte and bio-receptors is unique, as seen in Fig 1. Variation in mass depends on the number of complexes formed in the pit. The applied mass of the complex generates a force and the mechanical quantities of the cantilever like stress and displacement are changed proportionally to the force. Change in stress generates a voltage across the electrodes of piezoelectric material. The static analysis provides parameters such as displacement, stress, and Voltage, whereas Frequency analysis provides operating frequency for the sensor.

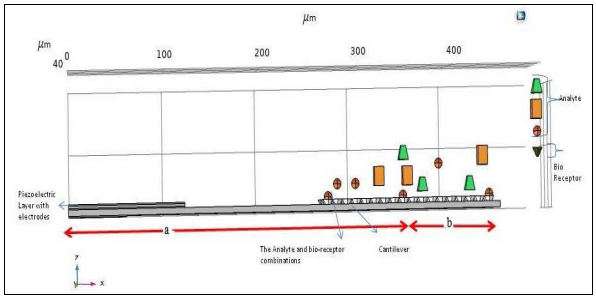


Fig 1. The analyte and bio-receptor combinations are unique. There are several analyte but only compatible bio-receptor will bind to form the complex. Coefficients for calculations are shown as *a* and *b*.

## III. DESIGN OF BIOSENSOR

Studies show that the SARS-CoV-2 virus in sputum and nasal swabs gives higher positive rates than blood.

Sometimes the viral load is higher in sputum and nasal swab but is not present in the blood [7]. Therefore, the sample type taken for analysis is nasal swab for viral load and serum for antibodies.SARS-CoV-2 Spike protein contains a receptor-binding domain (RBD, 60kDa) that specifically recognizes angiotensin-converting enzyme 2 (ACE2, 86kDa) as its receptor[8,9], IgM(970 kDa) binds with receptor-binding domain (RBD,60kDa) in spike protein, and IgG (150 kDa) binds with the S1(150 kDa) domain in spike protein[10]. These combinations for analyte and bio-Receptors are taken because of their higher binding affinities. Viral Load in corona varies from $10^4$ to $10^6$[11], higher viral loads($10^{11}$) also have been reported. Simulations are done for a viral load from 0 to $10^{11}$.

The design comprises three cantilevers: first one for viral load, the second one for IgM, and the third one for IgG. The design and dimensions are the same for all three beams. The cantilever beam has dimensions 450µm*90µm*5µm. The first layer is the silicon cantilever with a pit at a free end. At the fixed end, a piezoelectric material (PZT-5A) is placed with dimensions of 120µm*90µm*2µm. The piezoelectric material is sandwiched between upper and lower aluminum layers; they act as electrodes for measuring voltage.PZT-5A as the piezoelectric material is selected because of its ability of constant performance even in extreme temperatures and/or widely varying temperatures.

The pit of the cantilevers is coated with ACE2, RBD, and S protein, and then the analyte sample is deposited on respective pits. RBD-ACE2, IgM-RBD, and IgG-S1 complexes are formed on the first, second, and third cantilever respectively. Unattached proteins, immunoglobulin, and Enzymes are then eluted.

A bio-molecular complex on the surface will produce a force directly proportional to the mass of the complex. For simulations range of force values proportional to different bio-molecular complex is taken. Force will cause the cantilever to bend and cause deflection. This deflection produces stress on the cantilever. The stress causes piezoelectric material to deform and voltage is produced. Voltage can be measured between two aluminum plates.

Ranges and threshold values used in the simulation for Viral load, IgM, and IgG are given in Table I. Some sample simulation results with Analytical comparisons and threshold values are given in Table II. Simulated voltage values help to determine the negative or positive quantity of viral load, IgM, and IgG respectively. Finally, the stage of viral infection can be declared according to Table III. For ex. A person has positive values for viral load, IgM and IgG then he has active phase of infection.

## IV. Modeling Equations And Calculations

Let's assume one molecule of analyte binds with one molecule of bio-receptor. Force produced is calculated according to the mass of the bio-molecular complex. This force is used to calculate the maximum stress on the surface cantilever. This stress is then used to for calculating the voltage generated by the PZT-5A.Displacement and frequency is obtained by general equations. Some equations are used from reference 13.Some governing equations used for calculation are.

$$F = m_{bio} g \tag{1}$$

$$\sigma = \frac{Fa}{Z} \tag{2}$$

$$V = \frac{d_{33} t_p \sigma A}{\varepsilon_0 \varepsilon_r w_p l_p} \tag{3}$$

$$\delta_{\max} = \frac{Fa^2(2a+3b)}{6EI} \tag{4}$$

$$f = \frac{1.8752}{2\pi} \sqrt{\frac{EI}{m_{eff}\, I_c^3}} \tag{5}$$

Where F is force, $d_{33}$ piezoelectric coefficient of PZT-5A, E is Young's Modulus of Silicon, V is voltage, I is the moment of inertia, A is cross-section area of cantilever, σ is stress near PZT-5A, Z is the section modulus of the cross-section of the beam, $\delta_{max}$ is a maximum displacement of cantilever, f is frequency, g is gravity constant, $\varepsilon_0$ and $\varepsilon_r$ is Permittivity of Free Space and Relative permittivity respectively. $l_c$, $l_p$, $w_p$, and $t_p$ are cantilever length, piezoelectric material Length, width, and height, respectively. *a* and *b* are distance from fixed end to pit middle point and from pit middle point to free end(Fig 1). $M_{eff}$ is an effective mass of the sensor and $m_{bio}$ is mass of the analyte and bio-receptor.

TABLE I
ANALYTE AND BIO-RECEPTORS WITH THEIR ORIGINAL VALUE AND QUANTITY IN 0.5ML SAMPLE FINALLY THRESHOLD VALUES.

| Quantity to be measured (Analyte) | Sample Type | Cantilever Pit (Bio-Receptor ) | SARS CoV2 values (Copies/ml) | Quantity in 0.05ml sample (Copies/ml) | Threshold Value for calculations (Copies/ml) |
|---|---|---|---|---|---|
| ACE2 | Throat Swab | Viral Load(RBD) | $10^4$ -$10^{11}$ | 500-5*$10^9$ | 450 |
| IgM | Serum | RBD | 100 (Mild), 500 (Severe), 700 (Critical) [12] | 5(Mild), 25(Severe), 35(Critical) | 3-11(Mild), 11-23(Severe), 23-35 (Critical) |
| IgG | Serum | S Protein | 350 [12] | 17.5 | 6 |

TABLE II

SAMPLE VALUES FOR VIRAL LOAD, IgM AND IgG VALUES. FORCE DUE TO BINDED COMPLEX, ANALYTICAL AND SIMULATION VALUES FOR STRESS, VOLTAGE AND DISPLACEMENT. LAST TWO ROWS GIVE THE THRESHOLD VOLTAGES TO DETERMINE POSITIVE AND NEGATIVE VALUES.

| | Values RNA / IgM / IgG | Force (N) | Stress (Analytical Value) | Stress (COMSOL) | Voltage (Analytical Value) | Voltage (COMSOL) | Displacement (Analytical Value) | Displacement (COMSOL) | Results Displayed |
|---|---|---|---|---|---|---|---|---|---|
| Viral | 400 | $9.51*10^{-19}$ | $1.85*10^{-06}$ | $1.8*10^{-06}$ | $3.79*10^{-15}$ | $3.65*10^{-15}$ | $1.51*10^{-19}$ | $1.5*10^{-19}$ | **NV** |
| | 25000 | $5.94*10^{-17}$ | $1.16*10^{-04}$ | $1.13*10^{-04}$ | $2.37*10^{-13}$ | $2.28*10^{-13}$ | $9.4*10^{-18}$ | $9.4*10^{-18}$ | **PV** |
| | 50000 | $1.19*10^{-16}$ | $2.31*10^{-04}$ | $2.25*10^{-04}$ | $4.74*10^{-13}$ | $4.57*10^{-13}$ | $1.88*10^{-17}$ | $1.88*10^{-17}$ | **PV** |
| IgM | 1 | $1.68*10^{-20}$ | $3.27*10^{-08}$ | $3.17*10^{-08}$ | $6.69*10^{-17}$ | $6.44*10^{-17}$ | $2.65*10^{-21}$ | $2.65*10^{-21}$ | **NIgM** |
| | 9 | $1.51*10^{-19}$ | $2.94*10^{-07}$ | $2.86*10^{-07}$ | $6.02*10^{-16}$ | $5.8*10^{-16}$ | $2.39*10^{-20}$ | $2.39*10^{-20}$ | **PIgM(M)** |
| | 17 | $2.85*10^{-19}$ | $5.55*10^{-07}$ | $5.4*10^{-07}$ | $1.14*10^{-15}$ | $1.1*10^{-15}$ | $4.51*10^{-20}$ | $4.51*10^{-20}$ | **PIgM(S)** |
| | 33 | $5.54*10^{-19}$ | $1.08*10^{-06}$ | $1.05*10^{-06}$ | $2.21*10^{-15}$ | $2.13*10^{-15}$ | $8.75*10^{-20}$ | $8.75*10^{-20}$ | **PIgM** |
| IgG | 5 | $1.19*10^{-20}$ | $2.31*10^{-08}$ | $2.25*10^{-08}$ | $4.74*10^{-17}$ | $4.57*10^{-17}$ | $1.88*10^{-21}$ | $1.88*10^{-21}$ | **NIgG** |
| | 13 | $3.09*10^{-20}$ | $6.02*10^{-08}$ | $5.85*10^{-08}$ | $1.23*10^{-16}$ | $1.19*10^{-16}$ | $4.89*10^{-21}$ | $4.89*10^{-21}$ | **PIgG** |
| | 35 | $8.32*10^{-20}$ | $1.62*10^{-07}$ | $1.58*10^{-07}$ | $3.32*10^{-16}$ | $3.2*10^{-16}$ | $1.32*10^{-20}$ | $1.32*10^{-20}$ | **PIgG** |
| | 7545 | $1.78*10^{-19}$ | $3.47*10^{-07}$ | $3.38*10^{-07}$ | $7.11*10^{-16}$ | $6.85*10^{-16}$ | $2.82*10^{-20}$ | $2.82*10^{-20}$ | **PIgG** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **PV** | Positive Viral RNA Voltage $>4.27*10^{-15}$ | **PIgM** | Positive IgM<br>$1.93*10^{-16}$< Voltage < $7.09*10^{-16}$ → Mild Case<br>$7.1*10^{-16}$<Voltage < $1.48*10^{-15}$ → Severe Case<br>$1.49*10^{-15}$<Voltage < $2.26*10^{-15}$ → Critical Case | **PIgG** | Positive IgG Voltage> $5.48*10^{-17}$ |
| **NV** | Negative Viral RNA | **NIgM** | Negative IgM | **NIgG** | Negative IgG |

TABLE III
INFECTION PHASE FOR SARS- COV2.

| COVID Infection Phase | No Infection | Early Phase | Active Phase | Recovery Phase | Recovered | Initial Phase of Re-infection |
|---|---|---|---|---|---|---|
| **Viral RNA** | NV | PV | PV | PV later NV | NV | PV |
| **IgM** | NIgM | NIgM | PIgM | PIgM later NIgM | NIgM | NIgM/ PIgM |
| **IgG** | NIgG | NIgG | PIgG | PIgG | PIgG | High Value of IgG |

## V. Simulation Results

The design is simulated using MEMS module in COMSOL Multiphysics, which provides ease in setting a Multi-physics environment [14]. The COMSOL simulation environment is a stress-controlled and force-dependent. Geometry comprises four domains and twenty-seven boundaries. Single crystal isotropic Silicon, Lead Zirconate Titanate (PZT-5A), and Aluminum are used as materials for the cantilever, the piezoelectric layer, and electrode layers respectively. Piezoelectric Physics is used to set boundary conditions in the cantilever and PZT Layer. Finally, a linear static analysis with a parametric sweep is used to derive 2D and 3D graphs for the simulation.

Three simulations are carried out separately. The cantilevers with bio-complex are simulated for different force values according to the load of the analyte and bio-receptor binding. The cantilever bends because of this force value and stress is produced. This stress produces a voltage across PZT-5A, which can be measured between two aluminum layers. The static analysis yields the value for displacement, stress, and voltage

.

Fig 2 and 3 show simulated voltage and comparison of analytical and simulation voltage w.r.t viral load values. Fig 2 also displays the piezoelectric polarization direction for PZT-5A and the direction of load. Both of them are in the z-direction; hence $d_{33}$ mode is used for calculations. Fig 4 and 5 show simulated stress and comparison of analytical and simulation stress w.r.t IgM values. Fig 6 shows a comparison of analytical and simulation displacement w.r.t IgG values. Fig 7 shows the frequency curve w.r.t voltage for the cantilever.

Voltage, stress, and displacement graphs are obtained for viral load, IgM, and IgG. For reference, only selected values have been included in the Table II. Dynamic analysis for the cantilever resulted in a frequency of 74200 Hz, while the analytical value for the same is 75956.30 Hz. Analytical and simulated values are close to each other, as verified from Table II and graphs. There is a linear relationship between the load applied and physical quantities such as voltage.

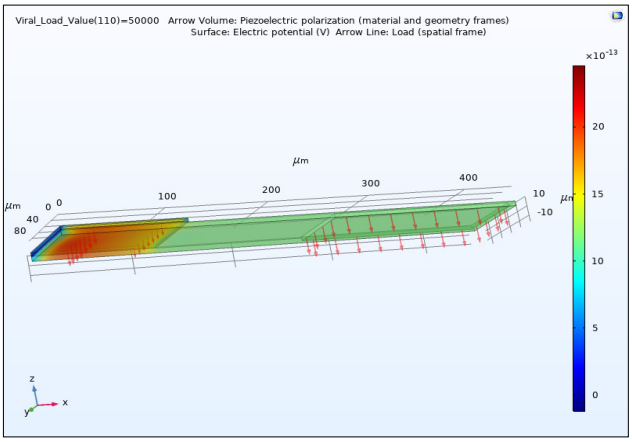


Fig 2. COMSOL Voltage profile, Force applied direction and piezoelectric polarization for viral load

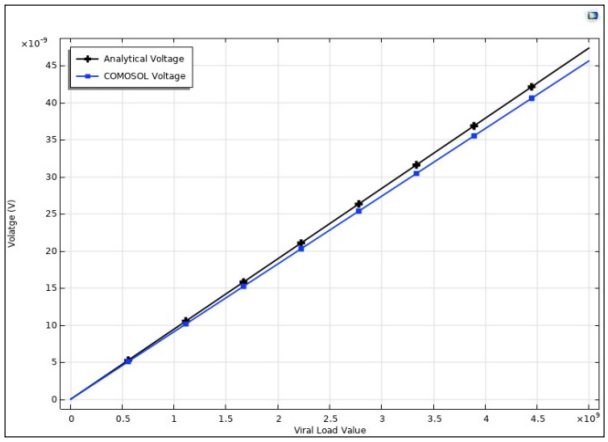


Fig 3. Analytical and COMSOL curve for Viral Load Values vs.Votage

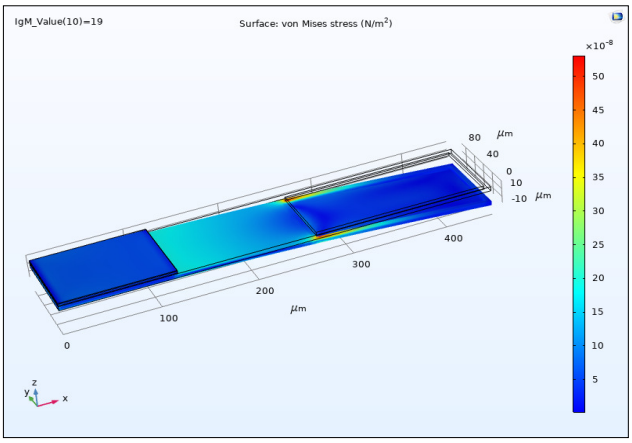


Fig 4. COMSOL Stress profile for IgM

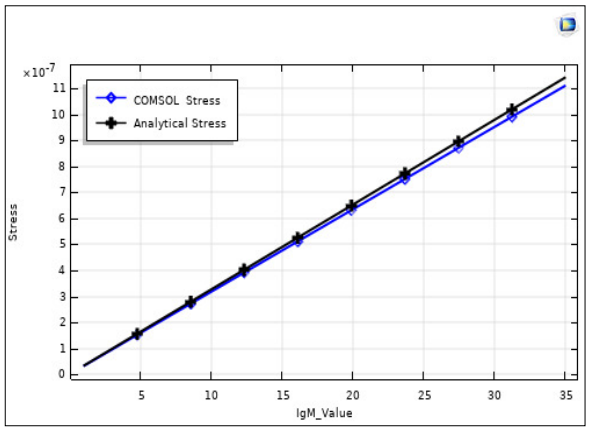


Fig 5. Analytical and COMSOL curve for IgM Values vs. Stress

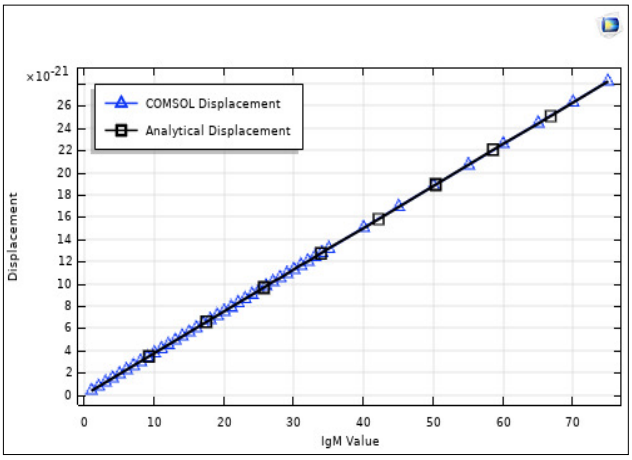


Fig 6.Analytical and COMSOL curve for IgG Values vs. Displacement

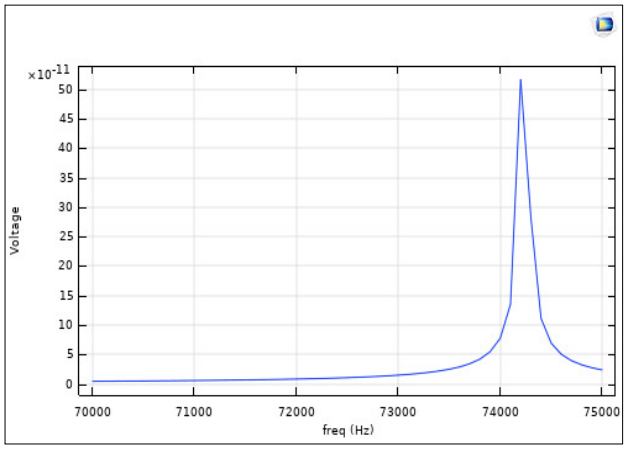


Fig 7. COMSOL Frequency verses Voltage curve

## VI. Conclusion And Future Scope

Proposed Piezoelectric MEMS Cantilever sensor detects Viral Load, IgM, and IgG values for SARS-CoV-2. It combines the great features of existing diagnostic methods. Its main advantage is that it can determine infection from the first day to months afterward, relative to RT-PCR, which provides positive results only till 25 days of illness. Immune Response Detection techniques display positive results after seven days of infection.

The design gives results in 5 to 10 minutes, which is quicker than RT-PCR and almost equivalent to other tests. The MEMS biosensor offers the reusability advantage, as they can be cleaned and functionalized again. The bio-receptors proposed in the system may cross-react with older strains of an equivalent virus, reducing the selectivity of the system. Using Monoclonal Antibodies can eliminate the likelihood of Cross-Reaction. The proposed sensor offers good mass sensitivity of 20 copies/ml.

Added benefits are reliable, cost-effective, easy to use, portable, require less amount of sample and may diagnose analytes in low concentration. It doesn't require extensive laboratory and technicians leaving professionals to worry for more patients. To understand the entire infection effect on the patient's body, both viral load and antibody results should be known. Laboratory tests for both RT-PCR and Immune Response Detection techniques combined are expensive. The proposed sensor detects viral load and antibodies with less cost and provides rapid results. Mass productivity further allows the reduced cost of the systems. Recent studies show that patients who had a higher viral load in the first week are often critical in the second week and needed hospitalization [15]. The design gives viral load values in 5 to10 minutes compared to one day of RT-PCR test result. Some of the severe and critical cases can be handled within the first week of infection. The proposed system will help in avoiding unnecessary quarantine of 14 days who don't have the virus, which may save time and money. In comparison with optical detection methods used for disease diagnosis, it provides a plus, because it doesn't require expensive microscopic components, less calibration time, and its performance isn't suffering from changes in medium properties. The sensor is simulated at room temperature; the temperature dependence simulation for the system can be done in future scopes. Metals and Polymers are often used for MEMS Cantilever material rather than Silicon. Both metals and Polymers have shown good bio-compatibility and better leads to the past.

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