# Detection of COVID-19: Biosensors for the rapid detection of SARS-CoV-2

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**Abstract- COVID – 19 pandemic has placed the world at stake. SARS-CoV-2 is rapid transmitting type of coronavirus and has already been spread across the world and between various species. Till date, there is no development in the form of drug or vaccine for the treatment. The infection remains asymptomatic for some and symptomatic for others which leads to fatal pneumonia and other health disorders. Therefore, prevention of exposure to the infected environment is very critical in this threatening scenario. One of the most commonly used method for detection of SARS-CoV-2 is reverse transcription-polymerase chain reaction (RT-PCR). Even if this method is accurate in giving results, it will not help in fast detection and hence preventing the infection. In this, we will be discussing about biosensors which could be used for COVID detection implementation in public places which will stand as an alerting system. Key advantage of this methodology is that, future viral interventions can also be prevented to a certain extend with this system as it is based on RNA detection.**

**Keywords- Coronavirus, Peptide Nucleic Acid Detection, Graphene Field Effect Transistor, Biosensors, Biomarkers, SARS-CoV2**

## I. INTRODUCTION

As of now, there are no exclusive antiviral drugs or vaccines for the SARS-CoV which is a betacoronavirus [1]. To cut short the epidemic graph of the pandemic a rapid detection method is imperative. The vigorous rate of transmission is due to the failure of the implementation of effective control measures. There are several modes of transmission ranging from droplet transmission and airborne to fomite transmission[2]. Improper disinfection of raw sewage containing patient's excrements in hospitals can also be a possible transmission path [3]**.** However, the WHO stated that the presence of viral RNA does not mean that a person is infectious enough to spread the disease [4]. Even asymptomatic cases have shown to exhibit viable viruses. SARS-CoV-2 virus primarily affects the lower respiratory system and may involve other organs and systems. To understand the pathogenesis of COVID-19 a proper analysis of tissue from human subjects is imperative. For identification of virus infected tissue and evaluation of its dispersal among different sites, immunohistochemical (IHC) and in situ hybridization (ISH) assays can be used [5]**.**

In Fig (1) the human transmission of Covid-19 is shown. When one or more in a group are affected by the coronavirus they are also exposed to healthy people who are likely to get the virus. It can be symptomatic or asymptomatic. Depending upon the immunity, each stage under symptomatic can be mild, severe, or critical. With adequate treatment,

people with mild and severe conditions can get cured as compared to patients affected with critical conditions which can be fatal. [6] Conversely, asymptomatic patients have more chance of recovering as their immune system is better as compared to others. Detection of coronavirus can be done in three main methods:- [7]a) Direct Detection, b) RNA/DNA Detection of virus, c) By the detection of antibody.

Several COVID detection methods have gained attention such as colorimetric, electrical, magnetic, plasmonic and lateral flow-based technologies. Evaluation of the role of rapid serological tests in the management of COVID-19 patients reveals that it may be a useful diagnostic tool besides RT-PCR [8].

Magnetic Technology uses magnetic nanoparticles to extract the biomolecules in the solution. Colorimetric and fluorescent sensors detect spectral change of presence of biomarkers. Through harnessing surface plasmons, plasmonic sensors detects proteins and nucleic acids[9]. Electrochemical sensors can monitor the living cells and interaction between other enzymes. The immobilization method is critical in terms of the nanomaterials and biological components to reduce the mistakes in virus detection. (EIS) or Electrochemical Impedance Spectroscopy is a competent technique which is capable of detecting even minute changes occuring at the solution–electrode interface and had gained popularity in characterizing materials, and for monitoring binding. This low cost method is even capable of obtaining low limit of detection (LOD) making it advantageous over conventional methods such as ELISA[10]. A handheld device has been developed recently which is based on the U-bent optical fibre, called as (P-FAB) Plasmonic Fiber Optic Absorbance Biosensor. It detects the types of endotoxins, proteinaceous and analyte moieties. The limit of detection is down to an attomolar (10^18M) of protein concentration. This device is very sensitive and a useful diagnostic method for detecting the biomolecular analytes [11]. Wearable devices a play vital role in alerting the patients when there are changes in the metrics which are matched with those associated with COVID-19 [12].

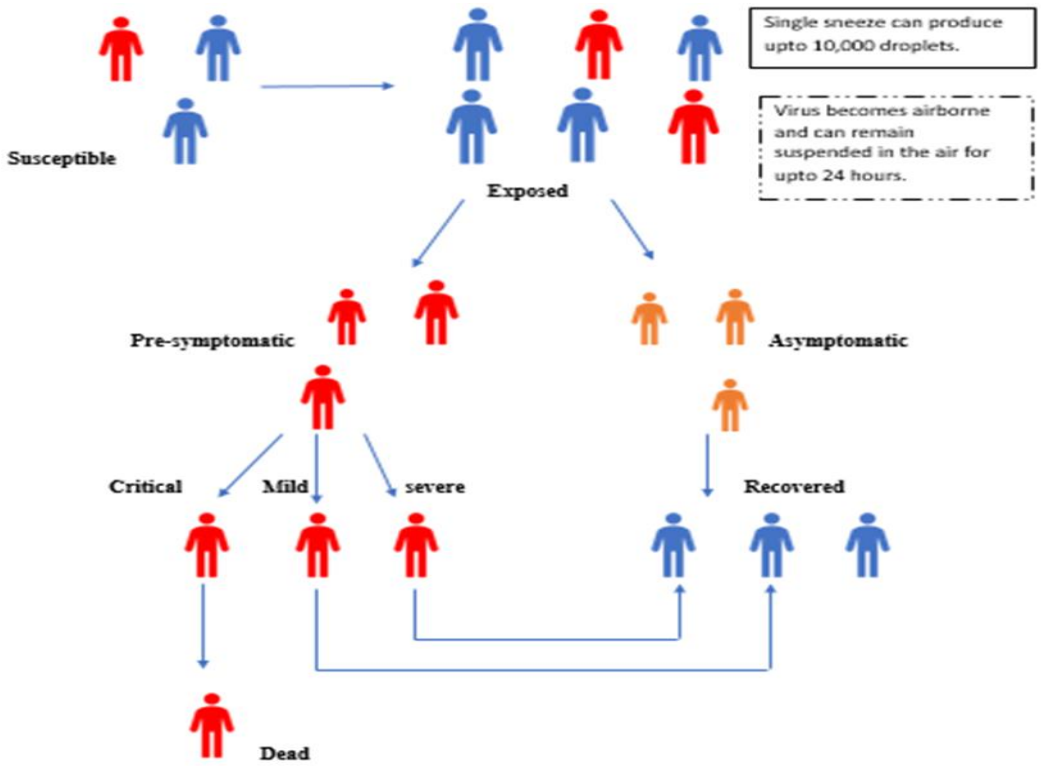



Fig.1. Schematic diagram of human to human transmission of Covid-19

## II. POTENTIAL DIAGNOSTIC METHODS AND BIOSENSORS

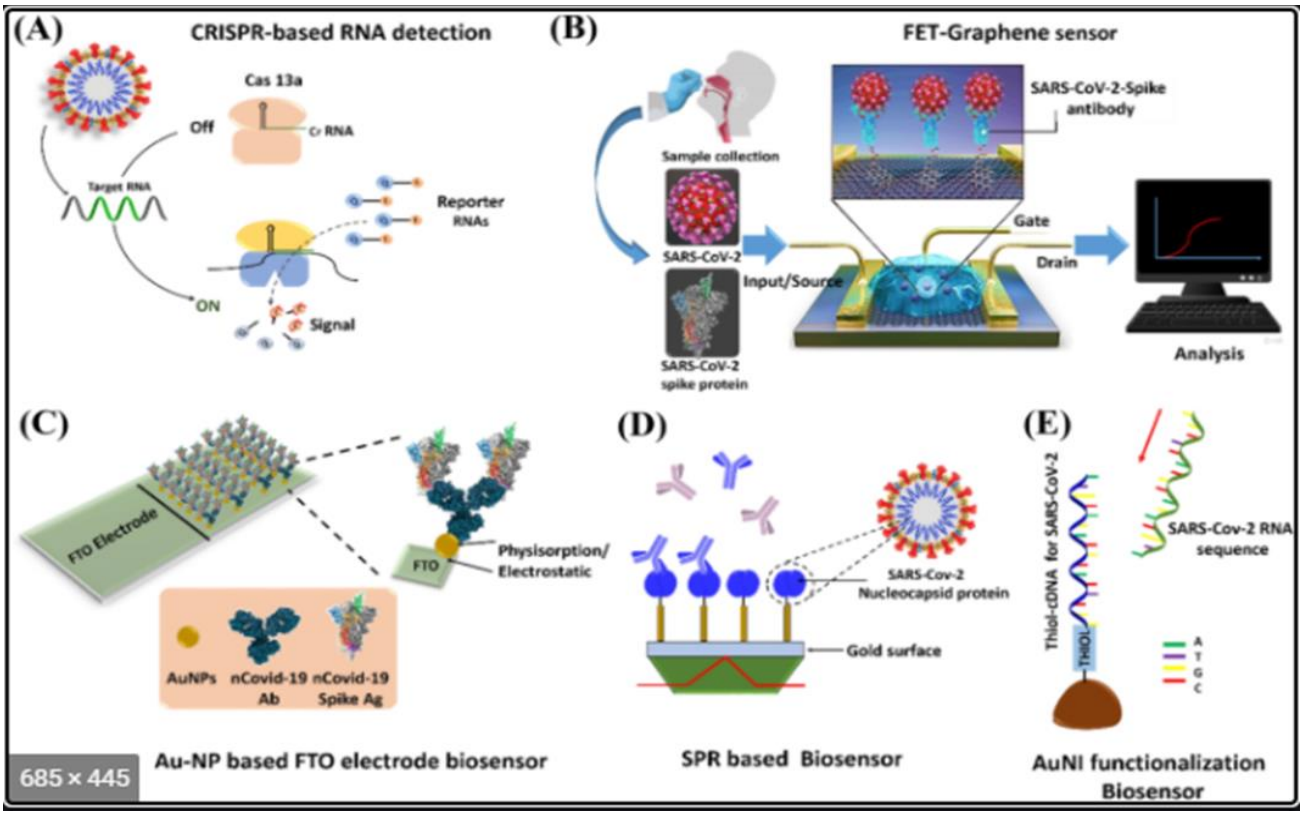
### *2.1 RT-PCR and Biosensors-*

RT-PCR is the most common method right now for SARS-CoV-2 detection. RT-PCR shows good sensitivity and specificity and results are obtained in a few hours. Here, for COVID-19 detection at first, the upstream oligonucleotides of the E gene (envelope gene) are screened and then the RT-PCR approach is used for the corroboration of the N gene (Nucleocapsid gene). Further testing using the sequencing of the RNA-dependent RNA polymerase gene is done only if the test results were negative initially[13] If further test results show positive then it confirms SARS-CoV-2. The major drawback of RT-PCR is that it needs professional staff to perform assay and interpret the result. It also needs expensive thermocycler.

For rapid detection of COVID-19 point of care (POC) devices that detect SARS-CoV-2 on-site needs to be developed. CRISPR based diagnosis might help in POC virus detection. It shows a favorable LOD range and has high specificity. CRISPR coupled with lateral flow assay reduces detection time [14]. CRISPR based biosensor helps to provide faster visual alternative to the method of RT-PCR with 100% negative predictive agreement [15]. Biosensors like LSPR (Localized surface plasmon resonance sensor) and graphene FET show promising results and can be a reliable alternative for real-time detection. As shown in Table (1), G-FET using the PNA probe gives promising results, better values, and is found to be comparatively better than other methods. Here, in this research, we will discuss it in detail.

| METHODOLOGY | BIOMARKER | LIMIT OF DETECTION | BIOLOGICAL SAMPLE FORM | RESULT | REF. |
|---|---|---|---|---|---|
| Self-assembled monolayer(SAM) | Zika-virus protein | 10 pM within 40 min | Saliva | Zika sensor with M-P interface was operated using a smartphone for diagnosis of POC and ease use. | [14] [16] |
| RT-PCR | Region SARSCoV2 RNA dependent – RNA polymerase-helicase gene | ~ | saliva | Viral RNA was not detected in the saliva of 3 out of 23 patients | [17] |
| Field Effect Transistor | Antibody of SARS-CoV-2 spike | 1 fg per mL and 100 fg per mL In clinical transport medium | Nasopharyngeal swab | Good sensitivity | [18] |
| Field Effect Transistor | Antibody of SARS-CoV-2 spike | 0.2 pM | ~ | Good sensitivity | [19] |
| Graphene Field Effect transistor | PNA probe | 0.1 aM – 0.1 pM | ~ | Better detection than using DNA probe; increased sensitivity and specificity | [19] |
| MoS2-FET | DNA probe | 10 fM | ~ | Desired sensitivity | [19] |
| Reduced Graphene oxide (RGO)-FET | PNA probe | 100 fM | ~ | LOD of 10 fM was obtained by optimization | [19] |
| Surface Plasmon Resonance Biosensor | ~ | 58.2 ± 1.37 pg mL−1 | ~ | High sensitivity was obtained | [19] |

Table.1. The comparative study of various methods which is described in detailed in this paper and the best method for the detection of virus and implementation in public place – Graphene Field Effect Transistor using PNA as biomarker. This method has proved to provide a better LoD and other better parameters such as increased sensitivity, specificity and accuracy.




From [20] Fig.2. An illustration of the Biosensors for Covid-19 detection (2. A.) Clustered regularly interspaced short palindromic repeats- based RNA detection method. (2. B.) G-FET Biosensor and the process of Covid detection. (2. C.) FTO electrode biosensor with sensing area composed of AuNPs conjugated with nCovid-19 Ab. The conjugation can be done by physisorption or electrostatic bonding. (2.D.) Schematic diagram of Surface Plasmon Resonance biosensor. (2.E.) Gold nano-islands with complementary DNA ligands of thiol group.

In hospitals, samples are obtained from nasopharyngeal, oropharyngeal swab, or sputum. The collected sample tested using a diagnostic tool known as RT-PCR. RT-PCR is also known as a Reverse transcription-polymerase chain reaction that combines reverse transcription of the RNA into DNA, one such method routinely used for the detection of COVID-19.

Avidin and biotin molecules are molecules which exhibits most strongest and specific non-covalent interaction. Combining graphene with avidin-biotin gave a sensitivity of 0.37 pM [21]. Graphene has many outstanding features where electrical conductivity stands out. These properties make graphene field effect transistor an efficient diagnostic method.

*2.2. CSAb modified G-FET and Biomarkers-*

Through further research we find that these graphene FET modified with CSAb has higher affinity due to which they have better sensitivity to this antibody. This particular sensor showed an LOD of 0.2Pm. Although it is cost-effective, user-friendly, it does not help in the reduction of chance of virus transmission while diagnosing [18].

Biomarkers are biomolecules which are naturally occurring, specific to a particular disease. A protein-based biomarker is mostly used as it easier to isolate when compared with a nucleic acid or cell-based biomarker. Serum amyloid A, Serum ferritin, IL-1 beta, IL-6, and IL-10 are some of the COVID-19 biomarkers. With the help of integrating biomarker-based biosensor with microfluidics system, the sample amount is restricted from the chance of virus transmission.

*2.3. G-FET using PNA probe-*

The two-dimensional carbon material Graphene with single-atom thickness has wide-ranging physical and chemical properties like high specific surface area, high transparency, high electron mobility, and its ability to easily combine with various biomolecules via a pi – pi bond. These characteristics are mainly responsible for Graphene's unique role in the field of biosensors. Even though DNA probe-based biosensors are used to detect a range of analytes, they are seen to have created many problems such as electrical noise in the background, relatively poor specificity, and long hybridization time. It's mostly because of DNA molecules which are charged particles. This limitation can be overcome to an extent by graphene field-effect transistor (G-FET) using PNA (peptide nucleic acid) probes [22]. Peptic Nucleic Acid (PNA) is a non-charged DNA variant and the backbone is formed of a neutral amide bond. PNA can hence improve the specificity of the hybridization system and decrease the detection time.

Graphene is used as the conduction channel in Graphene Field Effect Transistor. The PNA probe is immobilized on the graphene surface using 1-pyrene butanoic acid succinimidyl (PBASE) which is an ester and it is used as a linker which helps in selective detection of RNA.

COVID-19 is a recently becoming apparent and prominent human infectious disease caused from severe acute respiratory syndrome(SARS).FET-based biosensing device detects COVID-19 with samples. The sensor is coated with graphene sheets with antibody protein. FET device identify COVID-19 spike at 100 fg/mL clinical transport medium. Evaluation of the performance is done by cultured virus, antigen protein, and nasopharyngeal swab specimens. FET device also identify COVID-19 spike at concentrations of the 1fg/ml in phosphate-buffered saline [23]. This device is a highly sensitive immunological diagnostic method for SARS-CoV-2.

*2.4 Plasmonic Biosensor-*

A dual functional plasmonic biosensor joined with (LSPR) localized surface plasmon resonance, and plasmonic photothermal effect sensing transduction would provide an optimized alternating and sound output to RT-PCR. The 2D gold nanoislands functionalized with complementary DNA receptors can detect selected sequences from severe acute respiratory syndrome through nucleic acid hybridization. The thermoplastic heat is generated on the same AuNIs chip when light up at their plasmonic resonance frequency for their better sensing outputs. [24] MERS-CoV was determined using an immunosensor on a carbon nanoparticles array mmodified with gold nanoparticles by using recombinant spike (S1) protein as the biomarker. This single step, sensitive and accurate method produced a detection limit of 1.0 pg.mL−1 for MERS-CoV [25].

The dual-functional LSPR biosensor manifests a high sensitivity toward the selected COVID, allowing precise detection and lower detection of the specific target in a multigene mixture. Fig. 3 shows the diagram of Covid detection methods such as RT-PCR, Surface Plasmon Resonance, and G-FET and their corresponding output graphs.

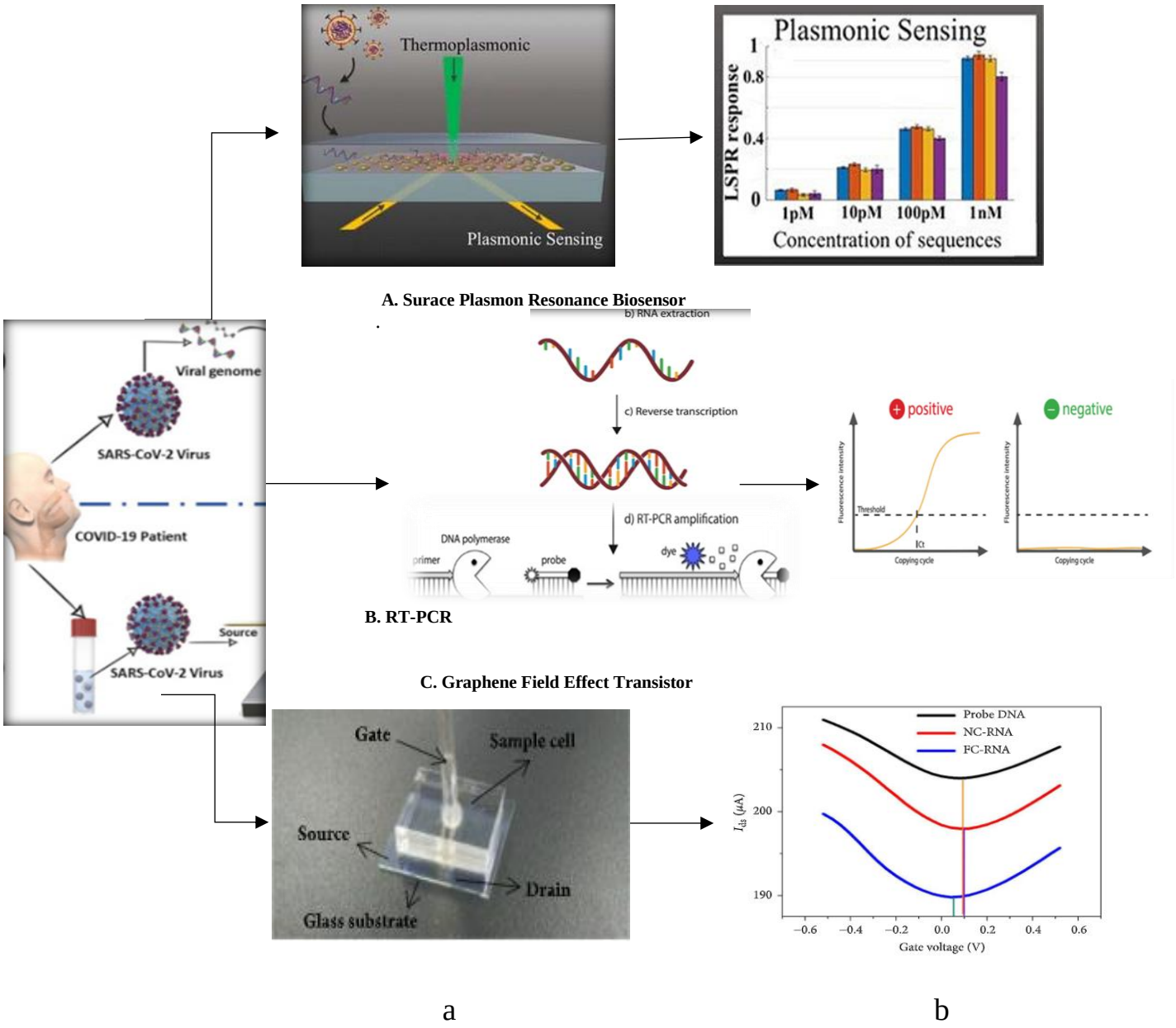



Fig.3. Diagrammatic illustration of the processes of A. Surface Plasmon Resonance Biosensor and it's concentration of sequences[22]; B. Reverse Transcriptase PCR [31] and C.Reduced Graphene Field Effect Transistor.[26] a. . Fabricated G-FET. b) Transfer characteristics of pristine DNA-modified G-FET biosensor (black) and after addition of NC-RNA (red) and FC-RNA (blue). [26]

As shown in Fig.3. which compares the various techniques like surface plasmon, RT-PCR, reduced graphene FET. The graph obtained in surface plasmon technique explains about a dual-functional plasmonic biosensor combined with the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing transduction. The LSPR provides an alternative and promising solution for the diagnosis of clinical COVID-19.

In RT-PCR the specimen is taken from the nose or throat of individual. The extracted DNA is transcribed into complementary DNA (cDNA). After the primers have bound to the DNA, they give a starting phase to the DNA polymerase to help duplicate it. DNA polymerase at that point debases the bound probe which brings about an increased

fluorescence signal. The fluorescence increments as duplicates of the infection DNA are made[27]. On the off chance that the fluorescence level crosses certain limit, the test is positive.
Reduced graphene oxide–based FET (rGO-FET) utilized for HPV-16 E7 detecting. XPS spectra of GO-FET previously (top) and after (base) decrease, by treating the GO layer for 4 h with hydrazine followed by warm tempering.

*2.5 RT-LAMP for SARS-CoV-2 Detection-*

Several studies demonstrate the potential of RT-LAMP (reverse transcription loop mediated isothermal amplification) to replace RT-PCR. Here dry swab is collected as sample and to maximise the target nucleic acid, magnetic bead capture is used. Subsequently RT-LAMP is used to amplify and detect SARS-CoV-2 genome by targeting the *ORFlab* gene alone. In real life clinical setting beside standard methods a RT-LAMP can produce results in under 30 min. Moreover, during large scale testing cost is a significant issue and LAMP instrument is cheaper than PCR machine. RT-LAMP method proves to be fast and is equivalent to RT-PCR and has the potential to be point of care device for COVID-19 detection [28].

*2.6 SARS-CoV-2 Detection using Functionalized $TiO_2$ Nanotube based Electrochemical Sensor-*

SARS-CoV-2 can be rapidly detected with the help of cobalt functionalized $TiO_2$ nanotubes (Co-TNTs) based electrochemical sensor. This sensor detects SARS-CoV-2 by sensing the spike receptor binding domain (S-RBD) present on the surface of the virus. Electrochemical biosensors sense biomolecules by detecting biomarkers with great accuracy, high sensitivity and specificity. For TNT synthesis a one-step electrochemical anodization route is used which is simple and cost-effective. An incipient wetting method is used to carry out Co functionalization of TNTs platform. Co-TNTs based electrochemical sensor can detect SARS-CoV-2 even at very low concentration of 14-1400 nM and also gives a linear response in the detection of S-RBD protein of SARS-CoV-2 over the concentration range. This sensor can detect S-RBD protein of SARS-CoV-2 in approximately 30s and has the potential to be used as a point of care device for COVID-19 diagnosis. [29]

## III. METHODOLOGY

*3.1 G-FET fabrication-*

Low pressure chemical vapor deposition on a 50µm thick Copper foil is used for the synthesis of Graphene film. Firstly, acetone, alcohol and DI water is used in sequence for 20 min at room temperature to clean the copper foil which is then dried using nitrogen. As copper foils with larger grain size produce higher quality graphene films therefore the copper foil is annealed for 15 min at $1050^0$C under 30 sccm of hydrogen to enlarge the size of copper crystals before the actual growth of graphene. [22] For graphene growth, $CH_4$ is used as a source of carbon. After the annealing process, the quartz reactor is injected with 15 sccm of $CH_4$ for graphene growth for 10 minutes and during this process the flow rate of $H_2$ is unaltered.

After the completion of growth process, the quartz reactor is exposed to air directly to cool down the samples to room temperature at a rate of 100-$200^0$C/min. The graphene film is now transferred to a glass substrate with patterned ITO electrodes for G-FET fabrication. Now, with a thin layer of poly methyl methacrylate (PMMA) the as-grown graphene on copper is spin-coated. To make the PMMA tightly adhere to the graphene surface the PMMA/Graphene/Cu is baked at $150^0$C for 30 min after the PMMA coating. Afterwards, using a 1 M $FeCl_3$ solution the underlying copper substrate is etched away to obtain PMMA/Graphene film.

Before transferring onto the glass substrate with the patterned ITO electrodes, the obtained PMMA/Graphene film is cleaned with DI water. To remove the moisture on the transferred PMMA/Graphene/glass substrate, it is then baked at $180^0$C for 30 minutes. [22] At last, PMMA is removed by immersing the PMMA/Graphene/glass substrate in acetone, ethanol and DI water. A sample cell is added onto the graphene/glass substrate for sample detection and a reference electrode like Ag/AgCl electrode is used to provide gate voltage. The graphene surface can also be chemically functionalized using PBASE as it is an efficient interface coupling agent used as a probe linker [23].

*3.2 Antigen Selection and Antibody Validation-*

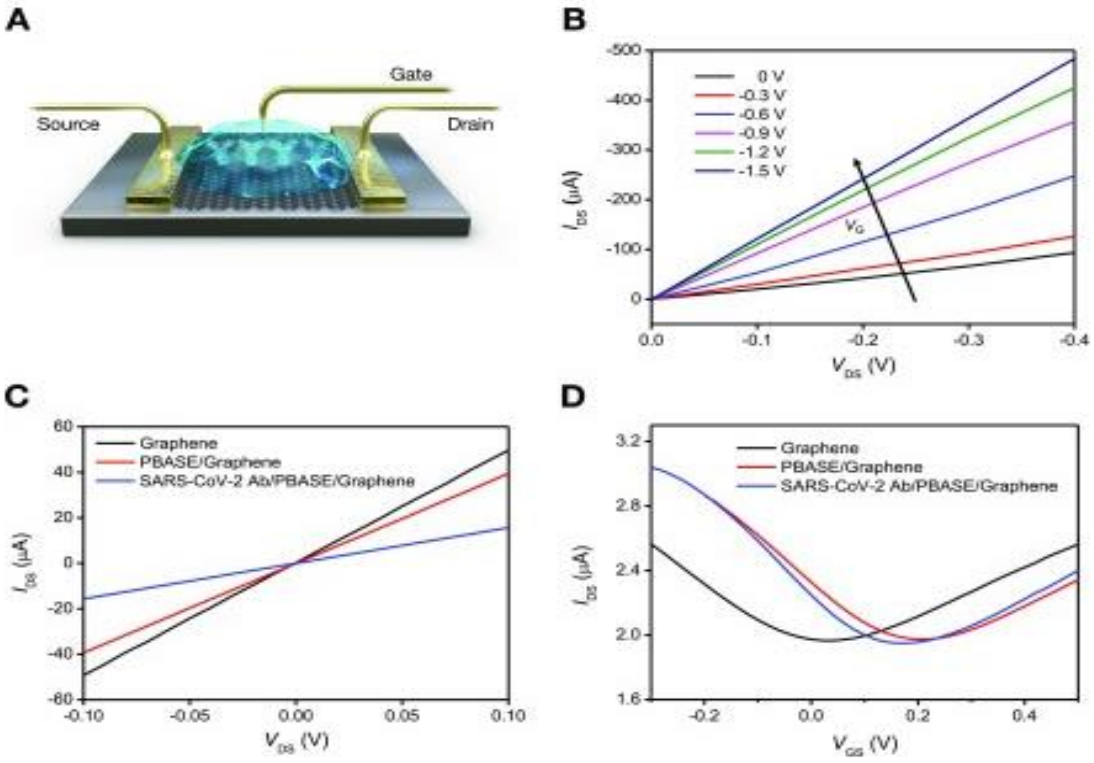
The four structural protein encoded in SARS-CoV-2 are: spike, matrix, envelope and nucleocapsid. Of all the four structural protein, spike protein is a vital transmembrane protein and is highly immunogenic. It also displays amino acid sequence diversity among coronaviruses. Because of all these reasons SARS-CoV-2 spike antibody is used as a receptor to detect the virus. Enzyme Linked Immunosorbent Assay (ELISA) is used to verify the performance of the antibody before immobilizing SARS-CoV-2 spike antibody onto the graphene field effect transistor. [23]

*3.3 Preparation of G-FET Biosensor-*

Electrical measurement is done to evaluate the presence of SARS-CoV-2 spike antibody. Current-Voltage (I-V) curves of the graphene device prior to and following attachment of antibody is shown in Fig (3C) and the differences in slope display the successful introduction of SARS-CoV-2 spike antibody. Aqueous solution gated FET as shown in Fig (3A) can detect SARS-CoV-2. The detection is based on the changes in surface potential and the equivalent effects on the electrical response. [23]

The transfer curves of G-FET after each modification process is shown in Fig (3D). Because of p-doping effect of pyrene group a positive shift is observed after PBASE functionalization. But, a n-doping effect is exerted on graphene after the immobilization of antibody and the negative shift of transfer curve indicates this effect and the output of G-FET sensor as a function of gate voltage ($V_g$) is represented in Fig (3B). This linear I-V curve shows that the FET sensor gives a good electrical signal for the detection of target analytes like SARS-CoV-2 antigen protein.

Therefore, G-FET sensor is highly sensitive for SARS-CoV-2 spike antigen protein [23] [30]. G-FET also show high specificity for SARS-CoV-2 spike antigen protein and when tested with MERS-CoV spike protein did not show any response [23].




From [23] Fig. 4. (A) Schematic diagram of COVID FET sensor using antibody conjugated Graphene. 4. (B) Current - Voltage output curves with gating voltage ranging between 0 V to −1.5 V. 4. (C) I-V characteristics of G-FET in functionalizing process for the revising antibody. 4. (D) Transfer curves during antibody conjugation

*3.4 Process of Detection of SARS-CoV-2 using G-FET-*

Firstly, the sample is obtained from the patient which is then placed on G-FET based biosensor. For the particular detection of targets, the gate surface of field effect transistor (FET) is supplemented with a layer of biomolecules. To distinguish SARS-CoV-2 spike protein S1, the gate surface is adorned with SARS-CoV-2 spike S1 subunit protein (CSAb) antibody. The S1 protein holds a minute positive charge. After the attachment of S1 protein with CSAb receptors on the graphene surface a change in the conductance/resistance of G-FET is observed. This is considered as the basis of detection of COVID-19 using graphene-FET [18]. The change in conductance/resistance of G-FET indicates the presence of virus.

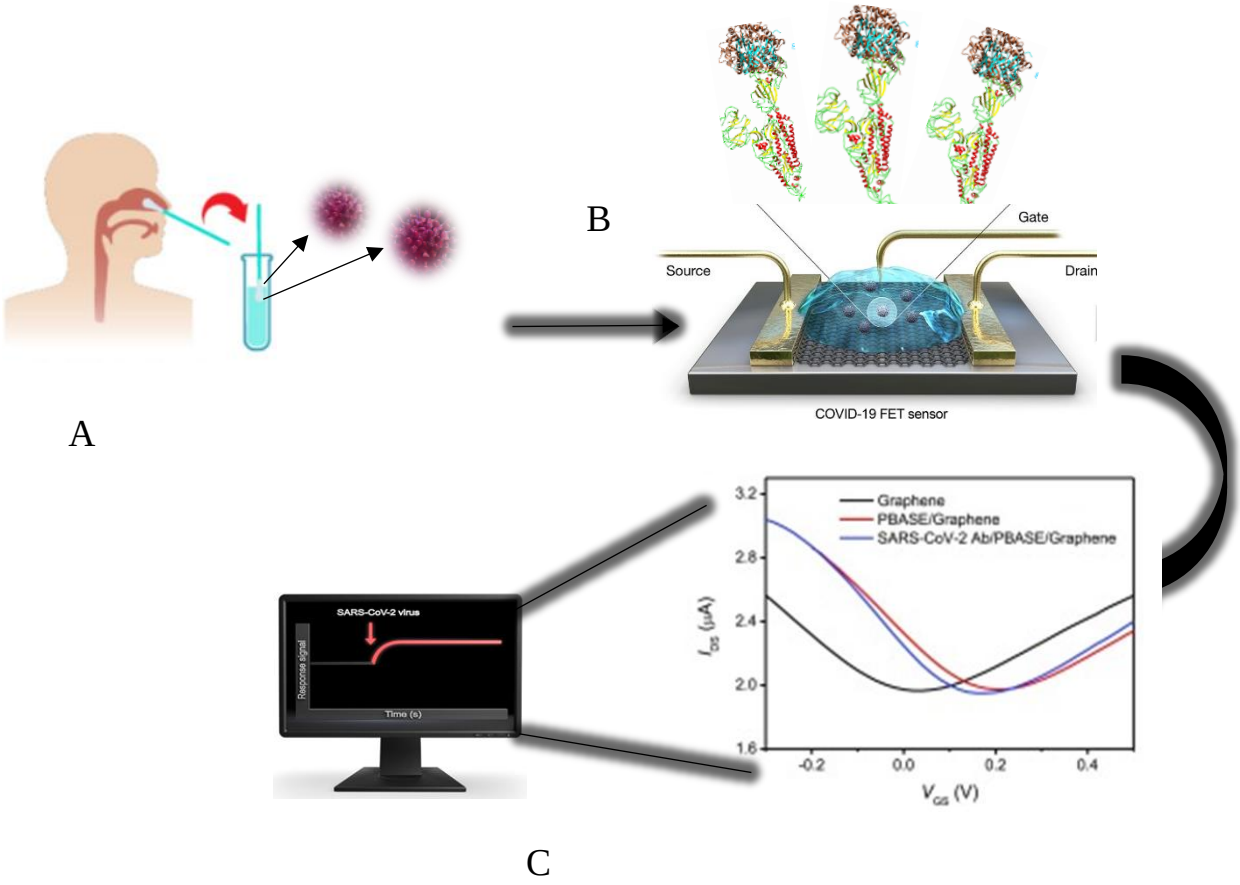



Fig.5. Schematic diagram of operation procedure of Covid-19 FET biosensor. A. Collection of swab specimen. B. Conjugation of SARS-CoV-2 spike antibody onto the graphene sheet via the probe linker, 1-pyrenebutyric acid N-hydroxysuccinimide ester. C.Electrical characterization of pristine, modified PBASE and Covid-19 spike antibody-immobilized graphene and measurement of transfer curves. [23]

Fig (5) demonstrates the process of detecting COVID-19 Causative Virus (SARS-CoV-2) with the help of Graphene field effect transistor-based biosensor. The sample is obtained which is then placed on Graphene Field Effect Transistor. After the functionalization of PBASE which is an efficient interface coupling agent used as a probe linker, noticeable positive shift was observed due to the positive doping effect of pyrene. Whereas the transfer curve shifted negatively which clearly shows that the positive charge of the antibody exerted negative doping effect on graphene after the antibody was immobilized. The graphene-field effect transistor with a limit of detection of 0.1aM-0.1pM helps

in the detection of SARS-CoV-2 antigen protein. At the end, we obtain the result – presence of virus indicates positive while absence indicates negative.

## IV. RESULTS AND DISCUSSION

So far more than 1 million deaths have been reported worldwide and till date no vaccine with an efficacy rate of 100% has been found. The only way to cut short the viral transmission of COVID-19 is through the development of point of care device. Diagnostic methods like RT-PCR can detect the presence of SARS-CoV-2 successfully but is time consuming and can only be operated by a professional. This is where point of care devices comes into play. POC devices are not time consuming and does not require the presence of a trained professional.

Out of all the potential POC devices mentioned in this paper G-FET has a favourable LOD range (0.1aM - 0.1pM). $TiO_2$ Nanotube based Electrochemical Sensor detects SARS-CoV-2 in under 30s but G-FET has a better LOD range. G-FET using PNA probes outperforms G-FET using DNA probes as DNA probe-based biosensors created many problems such as electrical noise in the background, relatively poor specificity, and long hybridization time. PNA probe-based biosensor improve the specificity of the hybridization system and decrease the detection time as PNA is a non-charged DNA variant and its backbone is formed of a neutral amide bond. Moreover, G-FET biosensor also shows high specificity and sensitivity for SARS-CoV-2 spike protein compared to other biosensors.

## V. CONCLUSION

During the COVID-19 pandemic, there is a need for point of care devices to cut-short the viral transmission. Based on our research G-FET proves to be the best point of care (POC) device as it has a better LOD range when compared to other POC devices. Moreover, this sensor shows no cross reactivity with MERS-CoV and is therefore highly specific and also exhibits high sensitivity for SARS-CoV-2 spike protein. Therefore, G-FET provides a rapid and highly responsive detection of SARS-CoV-2 virus. Furthermore, this method can also be handed down for the detection or diagnosis of other future viral diseases.

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