Plasmonic metamaterial based virus detection system: a review

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\textbf{ABSTRACT}

Our atmosphere is constantly changing and new pathogens are erupting now and then and the existing pathogens are mutating continuously. Some of these pathogens, such as SARS-CoV-2, become so deadly that they put the whole technological advancement of healthcare under challenge. Within this very decade several other deadly virus outbreaks were witnessed by humans such as Zika virus, Ebola virus, MERS-coronavirus etc. Though conventional techniques have succeeded in detecting these viruses to some extent, these techniques are time-consuming, costly, and require trained human-resources. Plasmonic metamaterial based biosensors might pave the way to low-cost rapid virus detection. So this review discusses in details the latest development in plasmonics and metamaterial based biosensors for virus, viral particles and antigen detection and the future direction of research in this field. Emergence of quantum properties in biosensing, application of machine learning, artificial intelligence and novel materials in biosensing is also discussed in brief.

\section{1. Introduction}

In late 2019, a unprecedented case of pneumonia was diagnosed in China which later was proved to be caused by a novel severe acute respiratory syndrome -coronavirus (SARS-CoV-2) or novel coronavirus\textsuperscript{Huang et al. (2020); Lu et al. (2020)}. This novel coronavirus disease (COVID-19) spread throughout the world in a very short time and was declared a pandemic by the World Health Organization (WHO)\textsuperscript{Organization et al. (2020)}. It is to be noted that this is the third large scale outbreak of coronavirus associated disease within a very short period after Severe Acute Respiratory Syndrome (SARS) in 2003\textsuperscript{Zhong et al. (2003)} and Middle East Respiratory Syndrome (MERS) in 2012\textsuperscript{Alhamlan et al. (2017)}. Apart from novel Coronavirus, a number of other virus related diseases also cause significant damage to the global population and it is needless to say that a rapid, reliable and accurate detection of viruses can contribute greatly to control the spread of the disease and prevent future pandemics like COVID-19.

Currently, several common methods are used for detecting infectious viruses. Serological testing \textsuperscript{Bastos et al. (2020)}, Immunofluorescence, Nucleic Acid Amplification Test (NAAT) are the most common genre of diagnosis \textsuperscript{Vemula et al. (2016)}. Hemagglutination inhibition assay (HI) and Enzyme Linked Immunosorbent Assay (ELISA) are the major serological testing \textsuperscript{Souf (2016)}. However, they have some major drawbacks which have hindered their ubiquitous usage for virus detection. For instance, preparation of antibody for ELISA is a costly technique and requires

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expert manpower Sakamoto et al. (2018). On the other hand, HI has low specificity under certain levels of agglutination and the sample may contain non-specific hemagglutinating factors Soares et al. (1999). Nucleic acid amplification based Reverse Transcription Polymer Chain Reaction (RT PCR) test is another technique to detect virus and till date it is the most widely used technique to detect novel Coronavirus Corman et al. (2020). RT–PCR technique is highly sensitive, specific and reliable diagnostic method. But this test typically takes longer than other detection methods and requires expert manpower and hence is expensive. Nucleic acid sequence-based amplification (NASBA), Loop-mediated iso-thermal amplification (LAMP), RT–PCR and q-PCR are in the genre of Nucleic Acid Amplification Test (NAAT). Most of these testing schemes are costly and require a lot of time and highly trained manpower. Other methods to detect viruses such as CRISPR Qin et al. (2019) and culture methods have apparently also failed to be a rapid and reliable method for satisfactory diagnosis of different viruses as they are not widely used yet. In such circumstances, real time and label-free biosensors have recently emerged as auspicious diagnostic tools for different infectious diseases. These sensors overcome the need for fluorescence or radioactive tagging for virus detection, thus enabling compact, robust, cost-effective point-of-care diagnostics. Different bio-sensing platforms based on optical, electrical Luo and Davis (2013), and mechanical Savran et al. (2004) signal transduction have been rendered for applications ranging from laboratory investigation to clinical diagnostics and drug development to combating emerging infectious diseases. Among these different genre of biosensors, optical detection platforms have gained considerable interest in recent years. Optical biosensors allow remote diagnosis scheme of the bio-molecular binding signal from the sensing volume without any physical connection between the excitation source and the detection media. Unlike mechanical and electrical sensors, these optical sensors are also compatible with physiological solutions and are not sensitive to the changes in the ionic strengths of the solutions. Among different optical biosensors plasmonic and metamaterial based plasmonic biosensors are highly potential in this regard due to their exotic properties like miniaturized sensor chip Yesilkoy et al. (2018), real-time sensing Guner et al. (2017), label-free sensing mechanism Maalouf et al. (2007).

The aim of this comprehensive review is to present the advances in plasmonic and metamaterial based plasmonic biosensors for virus or viral particles detection and highlight the scopes of future work in this field. There have been some recent review papers on plasmonic biosensors for virus detection Mauriz (2020), different methods of Coronavirus detection Samson et al. (2020); Yüce et al. (2020); Ji et al. (2020); Antiochia (2020) and recent progress in nanophotonic biosensors to combat the COVID-19 pandemic Soler et al. (2020). In this review, metamaterial based virus detection methods are discussed in details which is unprecedented and different plasmonic biosensors are classified in five broad fields on the basis of the detection technique and structure of the biosensors. Due to the ongoing COVID-19 pandemic, emphasis is given to the family of Coronavirus detection techniques and performance of different biosensors for different virus detection are also compared and summarized. Moreover, we have discussed the future trends in plasmonic and metamaterial based biosensing such as surface plasmon resonance imaging (SPRi),
incorporating quantum properties of materials in biosensing, novel materials based biosensors, artificial intelligence, and machine learning application in biosensing. As a non-destructive virus sensing platform, potential application of plasmonic and metamaterial based biosensors for rapid, multiplexed, point-of-care detection of virus is also highlighted.

2. Evaluation of plasmonic biosensors

To evaluate the performance of biosensors several figures of merit are widely used. Among them detection limits or limit of detection (LOD), sensitivity, selectivity or specificity are the most popular. Selectivity or specificity (S) is defined as the ability of a sensor to detect a particular virus from a sample containing admixtures of similar or other materials. Sensitivity and detection limit are two significant metrics that can be used to compare biosensors of different platforms. Sensitivity in the case of virus detection expresses how a sensor interacts in the presence of virus. For virus detection generally sensitivity of plasmonic biosensor is defined as-
Here $\Delta \lambda$ is the change in reflection/transmission wavelength of the plasmonic biosensor.

Another important FOM limit of detection (LOD) or detection limit (DL) is defined as the minimum virus concentration that can be detected by the sensor. In other words, LOD is the minimum number of virus necessary to cause a detectable change in the output signal of the sensor. For determination of LOD a formula commonly used is:

\[
\text{LOD} = \frac{3\sigma}{S}
\]

Here $\sigma$ is standard deviation of the control without virus which is basically the system noise floor and $S$ is the slope of the linear fit for wavelength shift versus virus concentration plot which is basically the sensitivity of the sensor. LOD for virus detection can be specified in different units. But commonly used units are: (1) ng/mL (2) copies of virus/mL (3) PFU/mL (4) pg/mm² (5) EID/mL

### 3. From plasmonic to metamaterial based biosensor

#### 3.1. Plasmonic excitation in biosensing

In 1902 Wood observed an unusual distribution of light in diffraction grating. He introduced the idea of plasmonic excitation Wood (1902). Metal-dielectric contact has been one of the primary methods of generating excitation. Generally, it is a guided mode that propagates along metal/dielectric interfaces. Plasmonic excitations are characterized into two segments, namely Surface Plasmon (SP) and Localized Surface Plasmon (LSP). SP that propagates at the flat interface between a conductor and a dielectric are two-dimensional electromagnetic waves. It is the collective resonant oscillation of conduction electrons and incoming photons at the interface between metal and dielectric. On the other hand, LSPR is generated by a light wave trapped within conductive nanoparticles (NPs) smaller than the wavelength of light. The size of the NPs is typically in the region of Mie scattering. When an external electric field is applied to metallic NPs, the conduction electrons encounter combined harmonic oscillations causing strongly localized electromagnetic field which has very high intensity. Ever since the discovery of this unique characteristic, many exciting researches of biosensing has been conducted using this exotic property and it has been used in virus detection as well. Viruses like HIV, Coronavirus, Influenza, dengue, Adeno virus, Zika virus, hepatitis, Norovirus etc. have been reported to be successfully detected by employing various kinds of plasmonic biosensors.

To induce SPR in the boundary between metal and dielectric, the momentum of the incident photon must be matched with the momentum of the conduction band electrons. If the matching condition is met light can be coupled in the interface between metal and dielectric plane. For flat planar surfaces, this phase matching is fulfilled by the
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Attenuated total reflection (ATR). This usually requires a media of higher refractive index (RI). The matching condition can be interpreted from the dispersion relation given below Raether (1988):

\[ K_{spp} = \frac{2\pi}{\lambda_o} \sqrt{\frac{\varepsilon_m \varepsilon_d}{\varepsilon_m + \varepsilon_d}} = \frac{2\pi}{\lambda_o} n_p \sin \Theta_i \]  

where \( n_p \) is the refractive index of the coupling prism, \( \Theta_i \) is the incident angle of light, \( \varepsilon_m \) is the dielectric constant of metal, \( \varepsilon_d \) is the dielectric constant of dielectric, \( K_{spp} \) is the wave vector of surface plasmon.

As the refractive index of the analyte media changes, \( \varepsilon_d \) also changes, eventually altering the wave vector \( k \). When \( \varepsilon_m \) and \( \varepsilon_d \) are equal and opposite of each other, the wave vector is maximum which results in resonance. Here \( \varepsilon_m \) depends on the wavelength of incident light and \( \varepsilon_d \) depends on the refractive index of the dielectric environment. Diverse configurations are used to generate SPR or LSPR for bio-sensing. In this review, these plasmonic biosensors are broadly classified into five different groups based on their structure and sensing principle namely planar structure, opto-fluidic structure, nano particle based structure, quantum dot based structure and nano rod-based structure.

3.2. Emergence of metamaterials in biosensing

In recent years, to increase the sensitivity of plasmonic biosensors metamaterial based plasmonic biosensors have been employed. Advantages of using metamaterial based sensors are that a variety of geometric structures and different sensing principles can be utilized which were not feasible with conventional plasmonic biosensors.

In 1968, Russian physicist Victor Veselago first came up with the theoretical concept of left-handed materials Veselago (1968) which shows unusual refraction of light. Then in 1999, Pendry et al. theoretically showed that microstructures built from nonmagnetic conducting sheets which are much smaller than the wavelength of radiation exhibits an effective magnetic permeability and these structures can be tuned to show varying magnetic permeability Pendry et al. (1999) including imaginary component. Rodger Walser termed this type of substances as metamaterials in 1999. Smith with his colleagues experimentally demonstrated the first left-handed metamaterial at microwave frequency in the year of 2000 Smith et al. (2000). From then on metamaterials have been explored extensively for possible applications in optics Pendry (2000), photonics Fang et al. (2020), energy harvesting Yu et al. (2019), communication Turpin et al. (2014), sensing Chen et al. (2012); Beruete and Jáuregui-López (2020), biological imaging and spectroscopy Zhou et al. (2019). Primarily, electromagnetic metamaterials are utilized in biosensing applications and metamaterials based biosensors can be classified in three different groups based on their structure- two dimensional, three dimensional and meta-surface biosensors. Among them two dimensional and meta-surface biosensors have been successfully employed in virus sensing. Though usage of metamaterial in biosensing is still in its early stage, already detection of viruses like HIV Ahmed et al. (2020), Zika virus Ahmadivand et al. (2018), Avian Influenza Virus Lee
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**Figure 2:** Different stages of a bio-molecular reaction which can be observed by a planar SPR sensor. (A) Immobilized capturing molecules attach with sensor chip surface; (B) Association: Pumped viral surface protein starts to bind with capturing molecule; (C) Equilibrium: Almost all binding molecules binds with respective viral body; (D) Disassociation: After certain time viral bodies starts to unbind with capturing probes; (F) With proper treatment the chip is ready for reuse.

et al. (2017a), CPMV Sreekanth et al. (2017), PRD1 Park et al. (2017) using metamaterial based sensors have been reported and sensitivity has improved by approximately an order of magnitude Hong et al. (2018). Metamaterial based plasmonic biosensors have the potential to be a game changer in the field of label-free point of care virus detection.

4. Diverse plasmonic structures for biosensing

4.1. Bio sensing principle of plasmonic biosensors

Biosensor-based detection methods always utilize a specific bio-receptor surface to analyze either intact viruses or viral proteins. A common and widely explored bio-receptor is antibodies that originates in animal bodies against specific viral surface proteins or antigens. There are also diverse types of artificial capturing molecules that are developed in laboratory to capture certain virus. For example, laboratory made DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) aptamers D'Agata and Spoto (2012), Hairpin type mRNA Liu and Wilson (2010). The SPR system authorizes characterization of the binding kinetics of biomolecular interactivity in real time. To analyze the reaction between biomolecules, generally one interacting molecule is immobilized on the surface of sensor chip, and its binding partner (sample analyte) is injected constantly into the solution through the flow cell, resulting in analyte flowing over the capturing surface. As a result of the analyte reaction with the binding molecule, the analyte accumulates on the
surface and increases the refractive index. The change in refractive index is measured in real time, generating a plot of the response unit (RU) versus time. This entire process is depicted in figure 2. The resulting responses obtained at different analyte concentrations are integrated to derive the rate constants (association, $K_a$; dissociation, $K_d$; and equilibrium, $K_e$). Thus, by using the SPR signal, amount, and condition of analyte in the sample is diagnosed. SPR signal is usually measured in two ways for planar structures. Firstly, the change of incident angle with respect to generation of SPR. Secondly, change of wavelength about SPR occurrence. SPR sensors are also categorized in this regard as incident angle modulated SPR sensor Zhou et al. (2017) and wavelength modulated SPR sensor Liu et al. (2005) respectively.

4.2. Planar structure

Many recent studies with SPR based planar structured virus detectors are in the spotlight of research. Mosquito borne dengue virus is a life-threatening pathogen. In 2020 Dengue Virus Type (DENV) 2 E-Proteins with high sensitivity and accuracy was successfully detected Omar et al. (2020). A SPR sensor based on self-assembled monolayer/reduced graphene oxide- polyamidoamine dendrimer (SAM/NH$_2$rGO/PAMAM) thin film was developed which detected the DENV-2 E-proteins with the lowest detection of 0.08 pM. This same research group also developed another sensor chip back in 2018 to detect dengue virus Omar et al. (2018). But in the later work they introduced a graphene-oxide(GO) layer in the sensor chip which significantly enhanced the overall performance of the sensor. In a similar work graphene-based material sensor chips were investigated for real time and quantitative detection of DENV protein. In this study the sensor chip was developed by accumulating cadmium sulfide quantum dots-reduced GO upon a thin gold plate. By changing the angle of incident light this graphene-based chip was able to detect DENV protein as low as 0.1 pM. Like dengue another deadly disease that causes hemorrhagic fever is ebola. Certainly, this virus has the full potential to create global pandemic. Recently a SPR chip was developed to diagnosis ebola virus with high specificity and sensitivity Sharma et al. (2020). To develop the sensor a gold SPR chip was modified with 4-mercaptobenzoic acid (4-MBA). Three different monoclonal antibodies (mAb1, mAb2 and mAb3) of Ebola virus were in the race. The interactions of antibodies were then investigated to determine the best mAb based on the affinity constant ($K_d$). After the screening mAb3 showed the highest affinity which was also confirmed by ELISA. This study also suggested the interaction was spontaneous, endothermic, and driven by entropy.

In 2013 a new type of avian influenza H7N9 virus emerged in China, causing human infection with high mortality taking 612 lives. A quantitively and real time diagnosis was crucial for eradicating the outbreaks of this emerging disease. A straightforward strategy for rapidly and sensitively detecting the H7N9 virus using an intensity-modulated surface plasmon resonance (IM-SPR) biosensor integrated with a new generated monoclonal antibody was proposed Chang et al. (2018). In another study a similar structure was developed to detect different respiratory viruses. In this
work a SPR-based biosensor was developed for specific detection of nine common respiratory virus including influenza A and influenza B, H1N1, respiratory syncytial virus (RSV), parainfluenza virus 1-3 (PIV1, 2, 3), adenovirus, and severe acute respiratory syndrome coronavirus (SARS) Shi et al. (2015). A significant challenge in this work was amplifying viral bodies by PCR (Polymerase chain reaction). But an advantage was the same sensor chip could be used to diagnose multiple times after washing with NaOH solution.

In a recent study HIV virus was also successfully detected by commercially available simple planar SPR biosensor. HIV-related DNA with hairpin type DNA aptamers was diagnosed. The proposed SPR biosensor could detect target DNA sensitively in a linear range from 1 pM to 150 nM with a detection limit of 48 fM. Diao et al. (2018). Lately a typical planar SPR biosensor for medical diagnostics of human hepatitis B virus (hHBV) has been developed Tam et al. (2021).
et al. (2017). A 7-fold higher limit of detection and 2-fold increase in coefficient of variance (CV) of the replicated results, were shown as compared to typical enzyme-linked immunosorbent assay (ELISA) testing.

4.3. Optofluidic systems

Another commonly used compact portable plasmonic bio sensing platform is optofluidic media. It is the combination of optoelectronics, optics and nanophotonic with fluidics. Such concoction constitutes a new perspective for manipulation of optical properties which incessantly scales the wavelength of light with applications ranging from fluidically adaptable optics to high sensitivity bio-detection. Many optofluidic plasmonic biosensors are based on nano apertures to enhance plasmonic sensing capabilities of fluidic viral analytes. These nano apertures hold capturing molecules (e.g., Antibody, aptamers) which increases binding potential between viral antigens and antibodies. One of the major recent breakthroughs in this regard is the detection of COVID-19 virus Funari et al. (2020). In this device the opto-microfluidic property is combined with plasmonic property. A serological testing with high specificity was devised. The refractive index (RI) sensitivity of the pure Au nanospikes in the opto-microfluidic device was precisely calculated by measuring the wavelength shift in the LSPR peak position when solutions with different refractive indexes (RI) are delivered to the microfluidic chip. The COVID-19 antibody presence was correlated with the LSPR wavelength peak shift of gold nanospikes caused by the local refractive index change due to the antigen–antibody binding.

In 2010 nano plasmonic biosensor chips was introduced which operated by utilizing the fluidic property of sample. Here the fluidic property was holding binding molecules by nano apertures. Detection and recognition of small enveloped RNA viruses (vesicular stomatitis virus and pseudo-typed Ebola) and large enveloped DNA viruses (vaccinia virus) was demonstrated. This platform opened opportunities for detection of a broad range of pathogens in typical biology laboratory settings. 220nm radius aperture was formed in a metal-dielectric layer. These apertures hold capture molecules for selective viral detection Yanik et al. (2010). Figure 4 illustrates various aspects of optofluidic plasmonic biosensor. In a more advanced work, programmable control systems for microfluidic analytes flow were used to develop a more efficient and portable plasmonic biosensor. In this study the 9 kinds of samples with different reflective index and antigen/antibody systems were utilized for characterization. By using these programmable optofluidic arrays, the biomarker of the liver cancer was tested in situ and real time Geng et al. (2014).

4.4. Nano particle enabled plasmonic structures

Nano particles (NP) are most used for development plasmonic sensor due to their easy fabrication process and cost-effectiveness. Gold (Au) and silver (Ag) nano particles are used for this purpose. Au NPs’ SPR wavelength is found around 520nm and Ag NPs show LSPR usually around 400nm Jans and Huo (2012). However, by changing the shape and size of the NPs, the SPR wavelength can be tuned Lee et al. (2011). NP based plasmonic biosensors play
a crucial role in virus sensing as they make label free detection possible. As a result, no fluorescence or colorimetric biomarker is required. Different immobilizing antibodies are used on to capture the viral particles or proteins.

The first virus detection using nano particle based plasmonic sensor was reported by Fatih Inci et. al in 2013 Inci et al. (2013). They used Au nano particles with immobilized antibodies to detect and quantify different subtypes of HIV viruses from unprocessed whole blood. Their limit of detection was $98 \pm 39$ copies/mL for HIV subtype D. They measured the shift in resonant wavelength when HIV virus was captured on the antibody immobilized biosensing surface as shown in fig. 5. Maximum wavelength shift of 9.3nm was reported for HIV subtype A virus concentration of $6.5 \times 10^5$ copies/mL.

During the same time, Yu et. al detected adenovirus particles by using Ag nanoisland-based localized surface plasmon resonance Yu et al. (2013). It is to be noted that this was non-specific detection of Adenovirus particles but based on numerical results they proposed specific detection models. They used rigorous couple wave analysis and transfer matrix method using effective medium theory for numerical analysis. Change in reflectivity was measured to

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**Figure 5:** (a) Nanoplasmonic biosensing platform for HIV detection Reproduced with permission from Inci et al. (2013) (b) Schematic diagram of optical set-up to detect adenovirus particles using gold nano island based plasmonic sensor reproduced with permission from Yu et al. (2013); Absorbance spectra of the biosensor immobilized with anti-NS1 antibody (red dashed line) exhibiting wavelength shift of peak absorbance after incubation with plasma separated on-chip from whole blood samples containing (c) 0.25 $\mu$g/mL and (d) 2 $\mu$g/mL of dengue NS1 antigen (green solid line). (e) Plot of variation of wavelength shift with concentration of NS1 spiked into whole blood showing linearity with R2 value of 0.84 reproduced with permission from Suthanthiraraj and Sen (2019)
detect adenovirus particles and the limit of detection was 109 viruses/mL.

In 2013, Jahanshahi et al. detected four diverse types of dengue virus using Immunoglobulin (Ig-M) based diagnostic test Jahanshahi et al. (2014). They used Au coating on glass substrate to excite surface plasmons. Antigens and amines in the form of NPs were used to immobilize four different types of dengue virus. Change in reflection angle of SPR was measured to detect the viruses. They achieved sensitivity of 83-89% and specificity of 100%. Their LOD was 10 antibody titres. In 2016, Valdez and his colleagues used LSPR shift to detect respiratory syncytial virus (RSV) using gold, silver and copper nano particles Valdez et al. (2016). They used anti-RSV polyclonal antibody to bind the virus with metallic NPs and they found copper NPs perform better in detecting RSV with LOD of 2.4 PFU.

A year later, Lee et al. Lee et al. (2017b) used Au NP and magnetic nano particle (MNP) decorated graphene (GRP) based hybrid structure to detect norovirus like particles (NoV-LP). Enhanced plasmonic and electrical properties exhibited by this hybrid structure were used to detect NoV-LP. The surface of Au/MNP-GRPs was functionalized with norovirus antibody to detect NoV-LPs and it performed well with high sensitivity and specificity. The change in resistivity was measured to detect NoV-LP in a concentration range from 0.01 pg/mL to 1 ng/mL and LOD was found to be 1.16pg/mL. At the same time, Kim and his group used gold nano particles in heteroassembled sandwich format to detect hepatitis B surface antigen (HBsAg) using anti-HBsAg antibody as the binding antibody Kim et al. (2018). These sensor was very specific to HBsAg and the LOD was 100 fg/mL.

In 2019, Heo et al. Heo et al. (2019) used gold nano particle based LSPR biosensor to detect noroviral protein and human norovirus. They used for the first time norovirus recognizing affinity peptides to bind noroviral proteins which is relatively inexpensive compared to the binding antibodies. From the change in absorption value they detected the presence of the virus. Their detection limit for noroviral capsid protein was 0.1 ng/mL and limit of detection for human norovirus was 9.9 copies/mL. Lee and his group utilized LSPR method using Au spike like NPs to detect avian influenza virus using a multi-functional DNA 3 way-junction Lee et al. (2019). They employed hemagglutinin (HA) binding aptamer and thiol group to bind the virus with NPs and achieved a LOD of 1 pM in two different environment of PBS buffer and diluted chicken serum.

At the same time Sen et al. Suthanthiraraj and Sen (2019) used thermally annealed thin silver film deposited onto silicon substrate to detect NS1 antigen of dengue virus in whole blood. Refractive index sensitivity of the biosensor was $10^{-3}$. A polyethersulfone membrane filter was used at the inlet of the sensor to separate blood cells from plasma and anti NS1 antibody was used to ensure specific binding of the NS1 antigen. Increase in absorption was found for antigen binding and for the highest 50 µg/mL concentration 108nm redshift in peak absorption wavelength was found. Sensitivity of this LSPR sensor was found to be 9nm/(µg/mL) and limit of detection was 0.06 µg/mL. Recently in 2020, Qiu et al. used dual functional plasmonic biosensor combining LSPR with plasmonic photothermal (PPT) effect to detect SARS Coronavirus 2 (SARS-CoV-2)Qiu et al. (2020). They used functionalized two dimensional gold...
nano islands for sequence specific viral nucleic acid detection. Local PPT heat generated from Au NIs is used to transduce the in-situ hybridization for highly sensitive SARS CoV-2 detection and they achieved a detection limit of 0.22pM. During the same time, Rippa et al. used two dimensional gold nano structures based on octupolar geometry to detect low concentration of rotavirus in water Rippa et al. (2020). They used rotavirus capsid (2B4) antibody to capture rotavirus for specific binding and detected the virus through change in LSPR extinction wavelength shift. They achieved maximum wavelength shift of 46nm for a virus concentration of $10^5$ PFU/mL and they achieved LOD of 126 ± 3 PFU/mL.
Quantum dots (QDs) are used as fluorescence signal amplifier to enhance the luminescent signals generated from the fluorescence probes attached to affinity reagents or viral targets. QDs generally have core-shell structure and are made of inorganic substances like CdSe as core and ZnS as shell. QDs possess exquisite optical properties and they exhibit stokes shift quantified up to hundreds of nanometers. Stokes shift is the difference between the maximum absorption wavelength and the maximum emission wavelength. QDs also have tunable broad absorption and narrow emission spectra and unlike traditional fluorescent dyes they can detect multiple signals simultaneously. Xuepu Li et al. (2012) used quantum dot fluorescence along with gold nanoparticles to detect Avian Influenza Virus (AIV). They didn't used plasmonic biosensor here but from then on QDs have been used in plasmonic biosensors to detect viruses as fluorescent signal enhancer.

In 2016, Takemura et al. reported LSPR induces immunofluorescence nano biosensor by using CdSeTeS QDs with Au NPs to detect influenza virus Takemura et al. (2017). Here quaternary CdSeTeS QDs were used to enhance the fluorescent signal generated from the antibody antigen interaction on the thiolated Au NPs. Anti-neuraminidase antibody and anti-hemagglutinin antibody was conjugated with thiolated Au NPs and quaternary QDs respectively. They achieved limit of detection of 0.03 pg/mL for H1N1 influenza virus in deionized water, 0.4 pg/mL for influenza H1N1 virus in human serum and 10 PFU/mL for clinically isolated H3N2 virus. During the same time, surface plasmon resonance assisted CdSe-ZnS based quantum dots was first used to detect norovirus like particles Ashiba et al. (2017). Excitation wavelength of 390nm to excite SPR on an Al film of the sensor chip equipped with a V-shaped trench was used. To immobilize proteins a self-assembled monolayer (SAM) of phosphonic acid derivative was used. Then gold and silver plasmonic nano particles with semiconductor quantum dots were used by Adegoke et al. Adegoke et al. (2017) to detect Zika virus RNA. They used four different plasmonic NPs functionalized with 3-mercaptopropionic acid (MPA). MPA-AgNPs, MPA-AuNPs, core/shell (CS) Au/AgNPs, and alloyed AuAgNPs along with CdSeS alloyed Qdots were used to form the respective LSPR-mediated fluorescence nano biosensor. They achieved minimum LOD for alloyed Au Ag NP which is 1.7 copies/mL and it was very selective toward Zika virus RNA.

In 2018, Ahmed and his colleagues Ahmed et al. (2018) proposed and demonstrated a novel method by using Zr NPs with Zr QDs to detect Coronavirus. Zr QDs show blue fluorescence emission and by functionalizing them with anti-infectious bronchitis virus (IBV) antibodies, anti-IBV antibody-conjugated magneto-plasmonic nanoparticles (MPNPs) are formed. From the change in photo luminescence intensity they detected Coronavirus and their LOD was 79.15 EID/50μL. In another work, an immunofluorescence biosensor for the detection of nonstructural protein 1 (NS1) of the ZIKV by using gold NPs and QDs was made Takemura et al. (2019). The LSPR signal from the Au NPs was used to amplify the fluorescence signal intensity of quantum dots (QDs) from the antigen-antibody detection process. CdSeTeS QDs were used with four different thiol capped Au NPs. The biosensor achieved a LOD of 8.2 copies/mL.
and could detect the virus within the concentration range $10^{-10}$ to $10^{-7}$ RNA copies/mL. It could detect the ZIKV in human serum and showed good specificity for NS1 antigen against other negative control targets. At the same time, Omar et. al used CdS QDs with amine functionalized graphene oxide thin film to detect dengue virus E-protein Omar et al. (2019). They used used monoclonal antibodies (IgM) to bind the protein and achieved an outstanding LOD of 1pM.

Very recently, Nasrin and her group Nasrin et al. (2020) employed CdZnSeS/ZnSeS QD-peptide and gold nano particle composites to enhance the LSPR signal to detect different concentrations of influenza virus from $10^{-14}$ to $10^{-9}$ g/mL. They varied fluorescence intensity by changing the distance between the QD and NP by using different peptide chain lengths to find the optimized condition to detect the virus and achieve a detection limit of 17.02 fg/mL. Previously, the same group detected norovirus Nasrin et al. (2018) using the same mechanism and their LOD was 95 copies/mL. However, this system could not detect the small change in norovirus concentration due to the smaller crosslinker between two NPs.

### 4.6. Nanowire and nanorod based plasmonic biosensor

Nanowires and nanorods are usually used to enhance the properties of existing biosensors due to their ability of confining electromagnetic fields in a superior way.

Das and his colleagues designed and simulated a plasmonic immunoassay, in 2020, which comprised of sandwich plasmonic biosensor whose sensitivity was enhanced by using gold nanorod. They have varied the prismatic configuration and found that the BK-7 glass based sensor has sensitivity of 111.11 deg/RIU Das et al. (2020). They also varied the distance of the gold NRs and their aspect ratio and recorded their observations. This sensor was designed for SARS-COV-2 detection, the gold NRs and gold nanosheets are functionalised with SARS-COV-2 spike-protein antibody and shift is observed in the SPR angle. In 2010, A biosensor by functionalizing gold nanorods with monoclonal hepatitis B surface antibody (HBsAb) through physical adsorption was devised. The characteristic plasmon absorption spectra is then measured after placing these nanorods in the vial containing blood serum. The LOD of the sensor is 0.01 IU/ml Wang et al. (2010).

In 2006, a biosensor was fabricated by Shanmukh et al. where they obliquely deposited silver nanorods on surface. Three different human viruses were detected by the device namely adenovirus, rhinovirus and HIV. After depositing the virus Raman Spectrum is measured and from the change in the spectra viruses can be detected. This sensor mainly results in improved SERS detection;Ag nanorod substrates exhibit extremely high ($\sim 10^8$) SERS enhancement factors. The vibrational spectra of the molecule adsorbed on the sensor surface is enhanced as incoming laser beam interacts with the electrons in the plasmonic oscillation in the nanorodsShanmukh et al. (2006). In 2018, Hong et al. developed hybrid slot antenna structures in the THz frequency range, where silver nanowires (AgNWs) were employed to increase the sensitivity. They used this structure for virus detection. PRD1 bacteriophage virus was detected using this sensor.
5. Metamaterial based biosensors

5.1. Bio sensing principle of metamaterial based plasmonic biosensors

Metamaterials are engineered materials; they possess properties which are not found in naturally occurring elements Kshetrimayum (2004). These exotic properties depend on the geometry of the material hence can be tuned as

Figure 7: (a) Schematic representation of the synthesis of HBsAb antibody-functionalized GNRs and the detection mechanism for the biosensor immunoassay in capturing targets in different matrices reproduced with permission from Wang et al. (2010). (b) Representative scanning electron micrographs of the Ag nanorod arrays deposited with different lengths, (A) h= 868 nm and (B) h ) 2080 nm. The typical SERS substrate used for virus detection is represented in (A) i.e. 870 nm reproduced with permission from Shanmukh et al. (2006). (c) Representative SERS spectra of RSV, HIV, adenovirus and rhinovirus reproduced with permission from Shanmukh et al. (2006). (d) Normalized transmission amplitudes through hybrid slot antenna (INW= 1μm) with (red) and without (black) PRD1 viruses reproduced with permission from Hong et al. (2018)

The THz spectrum before and after placing the virus was used for the detection purpose Hong et al. (2018).
per requirement. Usually specific repeating patterns are created on the material and each pattern has size smaller than the wavelength they need to have an effect on.

Metamaterials enable the detection of biomeolecules in THz-GHz frequency regimes which is difficult otherwise, as microorganisms such as fungi, bacteria, and viruses have scattering cross-sections which are much smaller than THz/GHz wavelengths. Sensing biomolecules in the THz-GHz electromagnetic spectra has several advantages as it provides label-free, non-contact and non-destructive sensing.

Metamaterial was first used in biosensing by Lee et al. In 2008 Lee and Yook (2008). They used gold split ring resonator (SRR) array to detect biotin and streptavidin to show the biosensing capability of the metamaterial. SRR worked as biosensor as it can be considered as a simple LC circuit with simple resonant frequency of

$$f_0 \approx \frac{1}{2 \pi \sqrt{LC}}$$

(2)

So, the resonant frequency of the system changes as the capacitance or inductance changes. As biotin and streptavidin binds to the system the capacitance of the SRR changes which is reflected in the resonant frequency thus it can be used as a biosensor. In 8 the equivalent LC representation of a specific metamaterial with rectangular geometry with a split is shown. In this way the metamaterials with nanogaps can be modeled and their sensing mechanism can be understood using 2.

### 5.2. Different metamaterial based biosensors for virus detection

In 2017, S.J. Park and his group created a metamaterial surface using gold rectangular structure on quartz. Metamaterial has certain capacitance and inductance equivalent parameters. Presence of virus particles within the capacitor gap changes the resonance frequency which can be explained by a simple LC circuit. Hence different viruses were detected by observing the THz transmission spectra. They detected bacteriophage viruses PRD1 (60 nm) and MS2 (30 nm). Sensitivity was 80 GHz/ particle Park et al. (2017). Ahmadivand and his colleagues designed a toroidal metamaterial based biosensor they sensed zikavirus envelope protein by measuring the spectral shifts of the toroidal resonance in 2018. They also added gold nanoparticles to see the effect in the sensitivity and observed enhancement in the performance of the sensitivity Ahmadivand et al. (2018). In 2018, A THz biosensing metamaterial absorber for
virus detection based on Spoof Surface Plasmon Polariton (SSPP) Jerusalem cross apertures metamaterial absorber was devised. They determined the shift in absorption and resonant frequency as the alpha beta parameters of the viruses were changed. Analyte thickness of H9N2 was also changed to see the variation in resonant frequency and absorption. From these they claimed that virus subtypes can be uniquely identified using this sensor. H5N2, H1N1, H9N2 viruses were detected Cheng et al. (2018). In 2017, Ahmadivand and his group used 2D micro-structures composed of iron (Fe) and titanium (Ti) for the magnetic and electric resonators (torus), respectively to design a set of asymmetric split resonators as meta-atoms to support ultra-strong and narrow magnetic toroidal moments in the THz spectrum. Limit of detection of 24.2 pg/mL and sensitivity of 6.47 GHz/log(pg/mL) their system resulted in toroidal response.

Figure 9: (a) Schematic of THz nano-gap Au metamaterial sensing of viruses reproduced with permission from Park et al. (2017). (b) Normalized THz transmission amplitudes of THz metamaterials after deposition of PRD1 at various surface densities for gap width of 200 nm reproduced with permission from Park et al. (2017). (c) 3D schematic diagram of the THz biosensing metamaterial absorber for Al virus detection reproduced with permission from Cheng et al. (2018). (d) Schematic demonstration of ZIKV envelope protein binding with respective antibody on the toroidal THz plasmonic metasurface reproduced with permission from Ahmadivand et al. (2017). (e) Schematic of THz detection of virus samples in liquid state using a nano slot-antenna array based sensing chip reproduced with permission from Lee et al. (2017a). (f) Transmittance spectra through multi-resonance nano-antenna with and without virus sample onto the antenna reproduced with permission from Lee et al. (2017a).
lineshape extremely sharp, narrow and deep. They analyzed the sensitivity of the dip with Zika virus envelope protein attached to the system Ahmadivand et al. (2017). In 2017, Lee et. al. used a multi-resonance and single resonance nano antenna sensing chip which was fabricated using gold nano antennas printed on silicon wafer to sense different types of Avian Influenza viruses. H9N2 was sensed using a multi resonance sensor. By using a single resonance nano antenna they demonstrated that viruses can be classified in terms of resonance frequency and decreased transmission ratio Lee et al. (2017a). In 2019 Vafapour and his colleagues developed a biosensor using metamaterial comprising of H-shaped graphene resonator on a semiconductor film which they used to detect Avian Influenza Keshavarz and Vafapour (2019). Ahmed et al. developed a cost-effective metasurface based biosensor in 2020. They used a Digital Versatile Disc which already has built-in periodic grating where they deposited multilayers of gold, silver and titanium and showed that the device exhibits fano-resonance. When the HIV virus particles were captured they observed a shift in the fano resonance peak from which HIV can be detected Ahmed et al. (2020).

In 2016, Aristov et al. devised a 3D metamaterial based biosensor composed of woodpile structure which has not yet been used in virus detection but showed sensitivity greater than 2600nm/RIU and phase sensitive response is more than $3 \times 10^4$ degrees/RIU for analytes which is very high. In the same year Sreekanth et al. designed a biosensor with grating coupled hyperbolic metamaterial which is a bulk 3D sub-wavelength structure that enhances angular senistivity of plasmonic biosensor. They detected cowpea virus with it and obtained a maximum sensitivity of 7000 deg per RIU Sreekanth et al. (2016).

6. Plasmonic Biosensors for Coronavirus Detection

Currently, diagnosis of COVID-19 is primarily accomplished by three techniques- quantitative reverse-transcription polymerase chain reaction (RT-qPCR) Corman et al. (2020) and gene sequencing, a lateral flow immunoassay, which is a common point-of-care (POC) diagnostic approach that detects antibodies against SARS-CoV-2 in patient samples Böger et al. (2020); Bastos et al. (2020), and chest computed tomography (CT) Zhang et al. (2020). Quantitative reverse transcription polymerase chain reaction (RT-qPCR) is widely used as the confirmatory test for COVID-19 detection and it is considered as the gold standard in this regard. However, RT-qPCR method requires long and difficult processing method. It also demands highly trained manpower and cost which hinder the large scale testing for COVID-19. Although RT-qPCR test is highly sensitive, may give false negative reports especially if the specimen is collected from the upper respiratory tract after a certain period from the onset of symptoms Tahamtan and Ardebili (2020). Therefore, there is an ongoing demand for an alternative detection method for novel coronavirus.

Plasmonic biosensing is a promising field for the detection of Coronavirus, as it can enable rapid testing and also reduce the manpower needed for performing the diagnosis. There are already many ongoing and reported works on plasmonic detection of novel Coronavirus. The schemes that were developed for detecting other Coronaviruses can be
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useful for SARS-CoV-2 detection as well. Commercially available surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) sensors are already being used for viral strains detection such as SARS, MERS and influenza Bhalla et al. (2020). In May, 2020 Moitra et. al. reported a work on COVID-19 detection using plasmonic nanoparticles which produced result within 10 minutes Moitra et al. (2020). Ahmadvand et. al. reported in June, 2020 their work using toroidal plasmonic metasensor for femto-molar detection of COVID-19 spike protein. They claimed that their sensor had a limit of detection of around 4.2 fmol and sample to result duration was around 80 minutes Ahmadvand et al. (2020). In the same year Das et al designed a gold nanorod-based plasmonic sensor to detect COVID-19 with a sensitivity of 111.11 deg/ RIU Das et al. (2020). In 2018, Ahmed et. al. devised a sensor using magneto-plasmonic nanoparticle for coronavirus detection. The fluorescence properties of immuno-conjugated QD MP NPs nanohybrids through separation by an external magnetic field enabled biosensing of Coronavirus with a limit of detection of 79.15 EID/50 mL Ahmed et al. (2018). In August, 2020 Uddin et. al. proposed a surface plasmon resonance sensor for COVID-19 detection which they claimed to have a sensitivity of 130.3 degrees/RIU Uddin et al. (2020). Previously, in 2009, Huang et. al developed a localized surface plasmon coupled fluorescence fiber-optic biosensor for the detection of SARS-CoV Huang et al. (2009). Funari et al. devised a detection system which combined opto-microfluidic chip with lspr to detect antibodies against SARS-COV-2 spike protein in December, 2020 Funari et al. (2020). In addition to that, several works have been mentioned in this article in which viruses with diameter smaller than coronavirus (120 nm) are detected e.g. PRD1 (60 nm) MS2 (30 nm), Avian Influenza Virus (80 nm - 120 nm), Zika Virus (50 nm) etc. using plasmonic and metamaterial based biosensors with promising sensitivity, these schemes might be useful for the detection of Coronavirus as well and further investigation can be done to prove their usefulness in coronavirus detection. It is noteworthy that there is still no reported work of Coronavirus detection using metamaterial based biosensors.

Table 1: Performance comparison of plasmonic biosensors for virus detection.

| Sensor type | Sensor configuration | Virus detected | Binding molecule/antibody | LOD/Sensitivity |
|-------------|----------------------|----------------|---------------------------|-----------------|
| Au/DSU/NH2rGO-PAMAM | DENV-2 E-proteins | DENV-2 E-proteins monoclonal antibody | 0.08 pM |

 Planar structure
| Sensor type            | Sensor configuration | Virus detected                  | Binding molecule/antibody                        | LOD/Sensitivity |
|-----------------------|----------------------|---------------------------------|--------------------------------------------------|-----------------|
| Au/CdS-QDs-rGO        | Omar et al. (2018)   | DENV-2 E-proteins               | DENV IgG (developed in Rabbit)                   | 2ng/mL          |
| Au(plate)             | Chang et al. (2018)  | Avian Influenza H7N9            | Monoclonal Antibody(IgM)                         | 144 copies/mL   |
|                       |                      | Influenza A,B H1N1, RSV, PIV1, 2, 3, Adenovirus, SARS | No antibody was used as viral bodies was amplified by PCR |                 |
|                       |                      |                                 |                                                  |                 |
| Au/4-MBA              | Sharma et al. (2020) | Ebola Virus                    | Three Monoclonal antibody(mAb1, mAb2 and mAb3)  | 0.5 pg/ml       |
| Biacore X (Commercial name) | Diao et al. (2018) | HIV                            | Hairpin DNA captureprobes                        | 48 fM           |
|                       |                      |                                 |                                                  |                 |
|                       |                      | Hepatitis B                    | HBsAg (derived from Pichia pastoris)            | 980ng/L         |
| Sensor type       | Sensor configuration                        | Virus detected                          | Binding molecule/antibody                          | LOD/Sensitivity |
|-------------------|--------------------------------------------|----------------------------------------|---------------------------------------------------|-----------------|
| Au/SiNx(with nano holes)/Si | VSV, vaccinia virus                        | 8G5 antibodies, A33L antibodies.       | 0.5mg/mL                                             |
| Yanik et al. (2010) |                                            |                                        |                                                   |
| Optofluidic Structure | Au/SiNx(with nano holes)/Si/SiNx | protein A/G                              | IgG                                                | 0.055M          |
| Coskun et al. (2014) |                                            |                                        |                                                   |
| Au NPs on Si inside PDMS pipe | Liver cancer antigen | Liver cancer antibody | 25 to 42ng/ml                                       |
| Geng et al. (2014) |                                            |                                        |                                                   |
| Au NPs            | HIV                                        | Immobilizing antibody with NeutrAvidin | 1346 ± 257 copies/mL for HIV A                     |
| Inci et al. (2013) |                                            |                                        | 10609 ± 2744 copies/mL for HIV B                  |
| NP based          |                                            |                                        | 14942 ± 1366 copies/mL for HIV C                  |
| Ag nanoislands    | Adenovirus                                 | pDE1sp1A/GFP                            | 404 ± 54 copies/mL for HIV G                       |
| Yu et al. (2013)  |                                            | adenovirus shuttle vector              |                                                   |

109 viruses/mL
| Sensor type                        | Sensor configuration          | Virus detected  | Binding molecule/antibody | LOD/Sensitivity |
|-----------------------------------|-------------------------------|-----------------|---------------------------|-----------------|
| Au coating on glass substrate     | Jahanshahi et al. (2014)      | Dengue virus    | Amine NPs                 | 10 antibody titre |
| Au, Ag and Cu NPs                 | Valdez et al. (2016)          | Respiratory syncytial virus | anti-RSV polyclonal antibody | 2.4 PFU |
| Au NP and Magnetop NP decorated   | Lee et al. (2017b)            | Norovirus       | Norovirus antibody        | 1.16pg/mL       |
| Au NP monolayer                   | Kim et al. (2018)             | Hepatitis B virus antigen | anti-HBsAg antibody       | 100 fg/mL       |
| Au NP                            | Heo et al. (2019)             | Norovirus       | Norovirus recognizing affinity peptide | 9.9 copies/mL |
| Au spike like NP                   | Lee et al. (2019)             | Avian influenza virus | Hemagglutinin (HA) binding aptamer | 1 pM |
| Thermally annealed silver film    | Suthanthiraraj and Sen (2019) | Dengue virus    | NS1 antibody              | 0.06μg/mL       |
| Au Nanoislands                    | Qiu et al. (2020)             | SARS CoV-2      | Thiol cDNA receptor       | 0.22 pM         |
| Sensor type | Sensor configuration | Virus detected | Binding molecule/antibody | LOD/Sensitivity |
|-------------|----------------------|----------------|---------------------------|-----------------|
| Au nanostructure in octupolar geometry | Rotavirus | Rotavirus capsid (2B4) antibody | 126 ± 3 PFU/mL |
| Rippa et al. (2020) | QD fluorescence | CdSeTeS QDs with Au NPs | Influenza virus | anti-neuraminidase antibody and anti-hemagglutinin antibody | 0.03 pg/mL for H1N1 in deionized water; 0.4 pg/mL for H1N1 in human serum; 10 PFU/mL for clinically isolated H3N2 |
| Takemura et al. (2017) | CdSe-ZnS based QD on Al film with V shaped trench | Norovirus | SAM phosphonic acid | .01ng/mL |
| Ashiba et al. (2017) | Gold and silver plasmonic NP with CdSeS QDs | Zika virus | 3-mercaptopropionic acid (MPA) | 1.7 copies/mL |
| Adegoke et al. (2017) | Zr NPs with Zr QDs | Coronavirus | anti-infectious bronchitis virus (IBV) antibodies | 79.15 EID/50µL |
| Sensor type | Sensor configuration | Virus detected                     | Binding molecule/antibody                      | LOD/Sensitivity |
|-------------|----------------------|------------------------------------|-----------------------------------------------|-----------------|
| Gold NPs with CdSeTeS QDs | Take-mura et al. (2019) | Zika virus | Anti-NS1 antibody | 8.7 copies/mL |
| CdSeTeS QD with Au NP | Nasrin et al. (2018) | Norovirus | 11-mercaptopendecanoic acid | 95 copies/mL |
| CdS QDs with graphene oxide thin film | Omar et al. (2019) | Dengue virus E protein | Monoclonal antibodies (IgM) | 1pM |
| CdZnSeS/ZnSeS QD-peptide-Au NP composite | Nasrin et al. (2020) | Influenza virus aspartic acid residue and anti HA antibody | 17.02 fg/mL |
| SSPP Jerusalem Cross Aperture | Cheng et al. (2018) | AIV | Not Stated | 0.5 THz/RIU |
| Rectangular Au metamaterial | Park et al. (2017) | PRD1,MS2 | Not Stated | 80 GHz/particle/μm² |
| Sensor type                  | Sensor configuration                                   | Virus detected     | Binding molecule/antibody | LOD/Sensitivity              |
|-----------------------------|--------------------------------------------------------|--------------------|----------------------------|------------------------------|
| Toroidal metasensor         | Ahmadivand et al. (2017)                               | Zika Virus         | Immobilized antibody       | 6.47 GHz/log (pg/mL)         |
| Au nano-antenna             | Lee et al. (2017a)                                     | H1N1, H9N2, H5N2  | Not Stated                 | 0.35 THz/RIU                 |
| Hyperbolic metamaterial     | Sreekanth et al. (2016)                                | cowpea virus       | Not Stated                 | 7000° per RIU                |
| Toroidal metasensor         | Ahmadivand et al. (2018)                               | Zika Virus         | Immobilized antibody       | 5.81 GHz/log(pg/mL)          |
| Au NR                       | Wang et al. (2010)                                     | Hepatitis B virus  | HBsAB                      | Shift in LSPR of upto 30nm   |
| Nanorod/Nanowire            |                                                       |                    |                            |                              |
| Ag NR Arrays                | Zhao et al. (2006)                                     | RSV,HIV            | Not Stated                 | Not Stated                  |
| Ag NR                       | Das et al. (2020)                                      | SARS=COV-2         | COVID-19 spike-protein antibody | 111.11 deg/RIU              |
7. Future perspective

Researchers are always on the quest of finding new methods of pathogen detection which is faster, accurate and sensitive and also can be used as POC device because the population is increasing at a fast pace and epidemics are materialising more frequently than ever. Relatively newly discovered materials like graphene Cucci et al. (2019); Gong et al. (2019), carbon nanotube Wang et al. (2020), and nanodiamond Miller et al. (2020) are being used in the sensing. Researchers are also using machine learning in sensing to get better results Moon et al. (2020). In addition to that, topological insulator has been used to enhance the sensitivity and detection limit of surface plasmon resonance based sensor Zhu et al. (2019). These methods and many others are yet to be explored extensively in biosensing field.

Almost all plasmonic biosensors works on the basis of antigen-antibody binding. Though there has been much research on antigen antibody binding but there was very little focus on antibody adsorption with the sensor chip. Typically metallic plasmonic materials like Au, Ag are used on the top layer sensor chip. Therefore, capturing molecules like antibody is adsorbed onto the plasmonic materials. Systematic numerical model of adsorption might open up new possibilities in this regard Osborne (2018). Quantum enhanced plasmonic sensing is an state of the art idea which can be explored as well. Quantum properties can amplify the sensitivity of a sensor and thus has the potential to shake up the plasmonic sensing scheme through the development of quantum-enhanced sensors Dowran et al. (2018). Machine learning and artificial intelligence assisted plasmonic biosensing can be also applied for virus sensing. Recently researchers has started to blend neural network algorithms with plasmonic diagnosis Li et al. (2019). Surface plasmon resonance imaging (SPRi) is another emerging field that has been applied in detection and monitoring of biomolecular events Puiu and Bala (2016). There has been a study of apple stem pitting virus (ASPV) by imaging the aptamer binding with the coat protein using SPR Lautner et al. (2010). Recently, researchers have achieved sub-100nm resolution using this technique Ohannesian et al. (2020) which can be applied for virus detection as well.

Finally, sensitivity of plasmonic and metamaterial based biosensors have reached femtomolar detection limit but
here limiting factor is the specificity of the biosensors which requires attention. Although employing aptamer and peptide based binding molecules specificity has improved significantly their application is still not suitable for all biosensors. Moreover, the biosensors may detect viruses successfully in laboratory environment, their performance need to be evaluated from clinical samples. Another problem for metamaterial based biosensors can be mass production for which the sensing platform needs to be compact. Multiplexing capability for detecting multiple viruses Sánchez-Purrà et al. (2017) using the same sensing platform using plasmonic and metamaterial based biosensors can be developed as well.

8. Conclusion

The world is currently fighting with the pandemic caused by SARS-CoV-2, there is no assurance when will this pandemic end let alone the next one. Disease diagnosis in the early stage is one of the main weapon in this ongoing fight against the pandemic. Though during last few years there has been significant improvement in disease diagnosis by optical biosensors, even COVID-19 has been successfully detected by LSPR based biosensors there is still room for development. Plasmonic and metamaterial based biosensors exist in many different forms and each form has one or more supremacy over conventional techniques, some are already being used in laboratories for drug and vaccine developments Myszka and Rich (2000). Some of the plasmonic biosensors like planar metal-dielectric interface based biosensors have simple fabrication techniques and give pretty good sensitivity and low LOD. Plasmonic biosensors like those based on metamaterial allow label-free, non-destructive sensing. Nanoparticle based plasmonic biosensors allow a broad-range of antibody binding. Addition of metamaterials in plasmonic biosensors have increased the sensitivity manifolds. Most importantly all the biosensors make rapid detection possible. However, plasmonic and metamaterial based biosensors need to be robust and reproducible to become mainstream virus caused disease diagnosis method. Also biosensors need to be developed as a lab-on-a-chip system in order to make them ubiquitous. Many of the researchers are already working on lab-on-a-chip configuration of plasmonic biosensors. If these shortcomings can be overcome in near future then plasmonic and metamaterial based biosensors will enable faster and more accurate detection of pathogens which will greatly help to prevent outbreaks in future.

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