Application of nanomaterials-based optical sensors for virus detections

Jiahao (Carl) Shi
Saratoga Highschool, Saratoga, California, 95070, United States
shij3846@lgsstudent.org

Abstract. Contemporarily, the spread of virus has occurred in everywhere, which affect not only individual’s health but also society in the aspects of social relationships, cultural events, and families. In order to control the spread of the viruses, the rapid and accurate detection approach is crucial. Identified viruses with optical sensing techniques provides a rapid and effective judgement approach in the early diagnosis of patients. The review outlines the application of optical sensors based on nanomaterials for the detection of different viruses, e.g., colorimetric sensors, fluorescence sensors, and surface-enhanced Raman scattering (SERS) sensors. The substantial performances of these optical sensors including high sensitivity, high selectivity as well as high stability are also summarized. Moreover, besides virus recognition, the demonstrated virus optical sensors could also be widely used in detecting heavy metal ions, organophosphorus compounds, small drug molecules, tumor markers, cancer cells, etc.

1. Introduction
The virus can grow and replicate rapidly under the help of a host cell (e.g., bacteria, plants, and animals), though it is unable to reproduce by itself. Once a virus spreads within the general population, it will bring substantial harm to human life. For example, the ongoing COVID-19 pandemic has ruined many people’s lives, which leads to the unemployment and homeless. So far, the identification of the virus is becoming more and more urgent for preventing the spread of the virus as well as stopping the outbreak of disease. For the virus detection, indeed, there are many approaches such as immunoassay [1]. However, traditional detection techniques suffer from long testing periods, complicated operation, and high price. In order to effectively cut off the spread of virus, it is necessary to detect virus in the early diagnosis of patients with rapid and accurate identification techniques. Driven by this demand, many rapid detection techniques in the field of virus detection were greatly developed (e.g., ultrasensitive sensor technology [2]). Among these sensors, optical sensors have received increasing attention.

Using different types of nanomaterials as design elements, optical sensors (e.g. colorimetric sensors, fluorescence sensors, and surface-enhanced Raman scattering (SERS) sensors) are widely developed and utilized for virus detection because of their easy operation and low cost [3]. Therefore, without the need for multi-step sample preparation, the optical sensor is more suitable to be a practical monitoring tool that determines whether the patient is infected with the virus compared to traditional detection approaches. As shown in Fig.1(collected from Ref. [4]), the optical sensing mechanism is that the interaction between viruses and nanomaterials can lead to change of nanomaterials optical signals (e.g., solution color change and fluorescence intensity change). Moreover, these optical signals from different nanomaterials can be tuned by changing the experimental parameters. On the basis of these optical sensing mechanisms, different optical sensors with special nanomaterials as sensing probes are widely used to detect viruses.
In this review, the application of different optical sensors based on nanomaterials are illustrated for virus detection. More specifically, three types of optical sensors including colorimetric sensors, fluorescence sensors, and SERS sensors are introduced in the review for their applications in virus detection.

Figure 1. Schematic illustration of optical sensor components and classifications [4].

2. Application of colorimetric sensors for virus detection
A rapid, simple, and effective testing approach plays the most vital role in the field of virus detection, because it can help to control the spread of virus. In the aspect of virus detection, colorimetric sensors are constantly designed owing to their great advantages, such as quick response, high sensitivity, simple equipment, easy operation, and low cost. Virus detection with developed colorimetric sensors depends on the color change from colloidal nanomaterials solution. Two reaction phenomena are used to induce color change of such colloidal solutions. One is to use unmodified nanomaterials as colorimetric sending probes, and the other is to use biomolecule-modified nanomaterials. For example, unmodified gold nanoparticles (AuNPs), one of the most commonly used noble metal nanomaterials, can be used to indicate a change in the color of colloidal solution by target-induced AuNPs aggregation. The above-mentioned two phenomena are dependent on the inherent optical properties of nanomaterials. Once the colloidal solution changes color, one can detect it with human eyes, digital camera, and smartphone. Most importantly, there is a good linear relationship between color change and target concentration. Thus, the target can be detected by color change of solution. On the basis of such colorimetric sensing phenomenon, different colorimetric sensors with nanomaterials as sensing probes are designed and used to detect viruses [5].

2.1. Unmodified nanomaterials-based colorimetric sensors for virus detection
Colorimetric sensors with unmodified nanomaterials have been widely used to detect viruses. In the case of AuNPs, the dispersed AuNPs colloidal solution is red owing to inherent localized surface plasmon adsorption. In the presence of salt, the color of such colloidal solution changes due to salt-induced nanoparticles aggregation. Depending on color variation of AuNPs solution after adding salt, Wang et al. used AuNPs as colorimetric probe to detect maize chlorotic mottle virus (MCMV) [6]. 23.9 pg/μL of RNA of MCMV was detected in their work. Using a similar reaction mechanism, Wang et al. also developed a simple and sensitive label-free colorimetric sensing method for detection of cucumber green mottle mosaic virus (CGMMV), with unmodified AuNPs as colorimetric probe [7]. In this work, only through the NaCl-induced aggregation of AuNPs, 30 pg/μL of CGMMV RNA was detected without the help of other sophisticated instruments. Saleh et al. developed a colorimetric sensor for direct detection of spring viraemia of carp virus (SVCV) RNA with unmodified AuNPs [8]. Their results showed that detection of SVCV-RNA only took 15 min and the detection limit was $10^{-3}$ TCID$_{50}$/mL$^{-1}$.
2.2. Functionalized nanomaterials-based colorimetric sensors for virus detection
Nanomaterials functionalized with antibody, peptide, and other biomolecules are used as a new class of colorimetric probes to construct colorimetric sensors. These colorimetric sensors with functionalized nanomaterials can show better specificity for detection of virus than unmodified nanomaterials [5]. For example, Liu et al. reported a colorimetric sensor for detection of influenza A virus (IAV) using AuNPs that functionalized with monoclonal anti-hemagglutinin antibody (mAb) [9]. In their work, IAV-specific antibodies were used to modify AuNPs to produce colorimetric mAb-AuNPs probes, resulting in specific arrangement of mAb-AuNPs on the surface of IAV because of antigen recognition. Under the help of optimal experimental conditions, the detection limit for such colorimetric sensors was 7.8 hemagglutination units (HAU). Sajjarnar et al. used peptide-functionalized AuNPs to develop a sample and selective colorimetric sensor for visual detection of newcastle disease virus (NDV) [10]. Peptide-AuNPs exhibited high sensitivity for detection of the minimum number of NDV in such colorimetric sensors with the 0.125 HAU detection limit. Applying DNA modified silver nanoparticles, Liu et al. developed a one-step method to detect HIV DNA by sandwich strategy [11]. The aggregated silver nanoparticles are able to sense HIV DNA with ultralow concentration on account of their high scattering property where the detection limit was ~195 mol/L based on calculation. Using the strategy of one-step synthesis and modification, Lee et al. directly synthesized sialic acid stabilized AuNPs to design another colorimetric sensor for detection of influenza virus [12].

3. Application of fluorescence sensors for virus detection
Fluorescence-based optical sensors demonstrate excellent performances for the detection of viruses due to the utilization of commercial fluorescent probes and advanced optical elements. With regard to this kind of sensor, the change of fluorescence signal of the probe is measured to detect virus. However, it should be pointed out that photobleaching and photo quenching usually occur in fluorescent molecules under long-term illumination or high-power laser irradiation. Therefore, for the virus to be detected, an ultrasensitive fluorescence sensor is ought to be built for the sake of detection via screening the appropriate fluorescence molecules and adjusting the laser power. In addition, many experimental parameters including laser wavelength and illumination time in fluorescence sensors are supposed to be explored for detection of different viruses. With the development of nanomaterials, different kinds of nanomaterials are used to design virus fluorescence sensors to detect viruses, e.g., quantum dots, carbon nanomaterials, and some nanocomposites.

3.1. Quantum dots-based fluorescence sensors for virus detection
Compared to commercial fluorescent molecules, quantum dots (QDs), one of the colloidal semiconductor nanomaterials, have excellent optical properties, e.g., high quantum yield, anti-photobleaching ability, and adjustable emission wavelength [13]. For example, depending on quantum confinement effects, the used emission wavelength for QDs in fluorescence sensors can be tuned ranging from UV to near-infrared (NIR) region. Therefore, such QDs are chosen as an ideal fluorescence probe to develop fluorescence sensors. Pan et al. used NIR-emitting QDs to modify avian influenza H5N1 pseudotype virus (H5N1p) through biorthogonal chemistry [14]. Under the help of excellent optical properties of QDs, real-time visualization respiratory viral infection in a noninvasive and manner is realized. The intrinsic is that QDs-modified H5N1p exhibits stable and strong fluorescence signals in biological tissues. Selecting QDs as fluorescence labels, Zhang et al. developed a microfluidic device with integrated microbead array for detection of hepatitis B virus (HBV) DNA [15]. They designed microfluidic devices that could detect 1000 copies/mL of HBV virus in clinical serum samples with RNA as the target molecules. Chen et al. proposed a novel detection strategy to develop a homogeneous immunoassay for simultaneous detection of Human Enterovirus 71 (EV71) and Coxsackievirus B3 (CVB3) with different colored QDs [16]. The detection limit for EV71 and CVB3 were 0.42 and 0.39 ng/mL, respectively. Besides, such detection strategy could be considered as a promising clinical method for other virus detection.
3.2. Carbon nanomaterials-based fluorescence sensors for virus detection

Multiple novel fluorescence sensors based on carbon nanomaterials are developed for detection of different kinds of virus. Wu et al. illustrated up conversion fluorescence resonance energy transfer (FRET) strategy to design a sensitive and selective fluorescence sensor for the detection of anti-HIV-1 gp120 antibody in human serum [17]. In Zhang’s work, they design a graphene oxide (GO)-based fluorescence sensing platform to detect HIV-1 protease [18]. No fluorescence signals were detected in the absence of HIV-1 protease because the fluorescein was quenched by GO. Whereas, in the presence of HIV-1 protease, the substrate peptide was cleaved into short fragments, producing fluorescence signals. Thus, the detection limit for HIV-1 protease was 1.18 ng/mL. For detection of Ebola virus (EBOV), Wen et al. developed a simple and sensitive fluorescence sensing platform based on the rolling circle amplification (RCA) strategy and GO fluorescence quenching property [19]. The detection limit of such fluorescence sensing methods was 1.4 pM.

3.3. Nanocomposites-based fluorescence sensors for virus detection

Taking advantages of plasmonic properties of noble metal nanoparticles, Adegoke et al. devised a plasmonic nanoparticles-quantum dots (QDs)-molecular beacon (MB) sensing probe for detection of Zika virus RNA. Thereinto, localized surface plasmon resonance (LSPR) signals produced by plasmonic nanoparticles were used to mediate fluorescence intensity signals from QDs-based nanocomposites [20]. The detection limit of such fluorescence sensors was up to 1.7 copies/mL. Takemura et al. employed gold nanoparticles-induced QDs fluorescence signal change to invent another fluorescence sensor for immunofluorescence detection of influenza virus H1N1 [21]. This kind of fluorescence sensor based on nanocomposites shows high sensitivity for the detection of virus. The detection limit of influenza H1N1 virus was 0.03 pg/mL in deionized water and 0.4 pg/mL in human serum, respectively. Based on LSPR-induced fluorescence signal change between gold nanoparticles and QDs, Nasrin et al. synthesized a new class of nanocomposites to develop a fluorescence sensor to detect norovirus [22]. The detection limit for norovirus was 95.0 copies/mL.

4. Application of SERS-based optical sensors for virus detection

In this section, the application of surface-enhanced Raman scattering (SERS)-based optical sensors will be introduced for detection of different kinds of viruses. Compared to colorimetric and fluorescence sensors, SERS-based sensing method has been widely used in various fields such as plasmonic sensors construction, detection of environmental harmful substances, and nano-electrochemistry. This is because $10^6$ amplification of Raman scattering efficiency if the analyzed substance is close to the plasmonic metals surface [13]. Taking advantage of such high Raman scattering efficiency, SERS sensors based on different kinds of nanomaterials are applied to detect viruses [23].

Sivashanmugan et al. designed a SERS substrate with ordered Au/Ag multilayered nanorod arrays for detection influenza A virus strain [24]. The fabricated ordered Ag layer plays the most vital role to improve SERS mechanism by occurring the electromagnetic effect on the surface of Au layer. Thus, optimized Au/Ag multilayered nanorod arrays could be regarded as an excellent SERS substrate for virus detection. The detection limits for influenza virus were 106 PFU/mL. Depending on the excellent performance of SERS-based sensing method for multi-target detection, Neng et al. devised a sensitive SERS-based sensor for the detection of multiple viral antigens from the viral zoonotic pathogens West Nile virus (WNV) and Rift Valley fever virus (RVFV) [25]. In their work, a high sensitivity was obtained by introducing magnetic capture of SERS-active nanoparticles, Au nanoparticles and paramagnetic nanoparticles. Thus, the detection limit was $\sim 5$ fg/mL in phosphate buffered saline buffer (PBS) and $\sim 25$ pg/mL in the mixture of fetal bovine serum and PBS. Chang et al. utilized the inverted triangular Au nano-cavities arrayed to develop a new SERS-active substrate for qualitative detection of virus [26]. The detection concentrations for encephalomyocarditis virus or adenovirus and influenza virus were 106 PFU/mL and 104 PFU/mL, respectively.
Table 1. Summary of nanomaterials-based optical sensors for virus detection

| Sensor types | Nanomaterials | Virus types | Detection concentration | Ref. |
|--------------|---------------|-------------|-------------------------|------|
| Colorimetric | AuNPs         | maize chlorotic mottle virus (MCMV) | 23.9 pg/μL | 6 |
|              | AuNPs         | cucumber green mottle mosaic virus (CGMMV) | 30 pg/μL | 7 |
|              | AuNPs         | spring viraemia of carp virus (SVCV) | $10^{-3}$ TCID$_{50}$/mL$^{-1}$ | 8 |
|              | AuNPs         | influenza A virus (IAV) | 7.8 HAU | 9 |
|              | AuNPs         | newcastle disease virus (NDV) | 0.125 HAU | 10 |
| Fluorescence | QDs           | avian influenza H5N1 pseudotype virus (H5N1p) | - | 14 |
|              | QDs           | hepatitis B virus (HBV) | 1000 copies/mL | 15 |
|              | QDs           | Human Enterovirus 71 (EV71) | 0.42 ng/mL | 16 |
|              | AuNPs-QDs     | Zika virus | 1.7 copies/mL | 20 |
| SERS         | Au/Ag nanorod | influenza virus | $10^6$ PFU/mL | 24 |
|              | Au nanomaterials | influenza virus | $10^4$ PFU/mL | 26 |

5. Conclusions
In conclusion, the application of optical sensors is introduced based on different nanomaterials for detection of viruses. In detail, the summarization of optical sensors is presented containing colorimetric sensors, fluorescence sensors, and surface-enhanced Raman scattering (SERS) sensors. The design principles of these optical sensors are discussed systematically for detection different kinds of viruses. Overall, these optical sensors have presented their inherent advantages in the field of virus detection as compared to conventional detection methods.

References
[1] Alam A, Hasan M, Anzar N, Suleman S, and Narang J 2021 Diagnostic approaches for the rapid detection of Zika virus–A review *Process Biochemistry* **101**, p156-68
[2] Ribeiro B V, Cordeiro T A R, and Freitas G R O, Ferreira L F, and Franco D L 2020 Biosensors for the detection of respiratory viruses: A review *Talanta Open* **2**
[3] Lukose J, Chidangil S, and George S 2021 Optical technologies for the detection of viruses like COVID-19: Progress and prospects *Biosensors and Bioelectronics* **178**
[4] Antiochia R 2021 Developments in biosensors for CoV detection and future trends *Biosensors and Bioelectronics* **173**
[5] Zhao V, Wong T, Zheng X, Tan Y, and Zhou X 2020 Colorimetric biosensors for point-of-care virus detections *Materials Science for Energy Technologies* **3**, p 237-49
[6] Wang L, Liu Z, Xia X, and Huang J 2016 Visual detection of Maize chlorotic mottle virus by asymmetric polymerase chain reaction with unmodified gold nanoparticles as the colorimetric probe *Anal. Method* **8** p 6959-64
[7] Wang L, Liu Z, Xia X, Yang C, Huang J, and Wan S 2017 Colorimetric detection of Cucumber green mottle mosaic virus using unmodified gold nanoparticles as colorimetric probes *J Virol Method* **243** p 113-9
[8] Saleh M, Soliman H, Schachner O, and El-Matbouli M 2012 Direct detection of unamplified spring viraemia of carp virus RNA using unmodified gold nanoparticles Dis Aquat Organ 100 p 3-10

[9] Liu Y, Zhang L, Wei W, Zhao H, Zhou Z, Zhang Y, and Liu S 2015 Colorimetric detection of influenza A virus using antibody-functionalized gold nanoparticles Analyst 140 p 3989-95

[10] Sajjanar B, Bhuvna K, Deepika B, Saxena S, Singh A, Joshi V, Tiwari A, and Kumar S 2015 Peptide-activated gold nanoparticles for selective visual sensing of virus Journal of Nanoparticle Research 17

[11] Liu Y and Huang C 2012 One-step conjugation chemistry of DNA with highly scattered silver nanoparticles for sandwich detection of DNA Analyst 137 p 3434-3436

[12] Lee C, Gaston M A, Weiss A A, and Zhang P 2013 Colorimetric viral detection based on sialic acid stabilized gold nanoparticles Biosens Bioelectron 42 p 236-41

[13] Maddali H, Miles C, Kohn J, and O’Carroll D 2020 Optical Biosensors for Virus Detection: Prospects for SARS - CoV - 2/COVID - 19 ChemBioChem

[14] Pan H, Zhang P, Gao D, Zhang Y, Li P, Liu L, Wang C, Wang H, Ma Y, and Cai L 2014 Noninvasive visualization of respiratory viral infection using bioorthogonal conjugated near-infrared-emitting quantum dots ACS Nano 8 P5468-77

[15] Zhang H, Xu T, Li C W, and Yang M 2010 A microfluidic device with microbead array for sensitive virus detection and genotyping using quantum dots as fluorescence labels Biosens Bioelectron 25 p 2402-7

[16] Lu C, Zhang X, Zhou G, Xiang X, Ji X, Zheng Z, He Z, and Wang H 2012 Simultaneous Determination of Human Enterovirus 71 and Coxsackievirus B3 by Dual-Color Quantum Dots and Homogeneous Immunoassay Analytical Chemistry 84 p 3200-7

[17] Wu Y, Chen Y, Huang L, Yu R, and Chu X 2014 Upconversion fluorescence resonance energy transfer biosensor for sensitive detection of human immunodeficiency virus antibodies in human serum Chem. Commun. 50 p 4759-62

[18] Zhang Y, Chen X, Roozbahani G, and Guan X 2018 Graphene oxide-based biosensing platform for rapid and sensitive detection of HIV-1 protease Anal Bioanal Chem 410 p 6177–85

[19] Wen J, Li W, Li J, Tao B, Xu Y, Li H, Lu A, and Sun S 2016 Study on rolling circle amplification of Ebola virus and fluorescence detection based on graphene oxide Sensors and Actuators B: Chemical 227 p 655-9

[20] Adegoke O, Morita M, Kato T, Ito M, Suzuki T, and Park E Y 2017 Localized surface plasmon resonance-mediated fluorescence signals in plasmonic nanoparticle-quantum dot hybrids for ultrasensitive Zika virus RNA detection via hairpin hybridization assays Biosens Bioelectron 94 p 513-22

[21] Takemura K, Adegoke O, Takahashi N, Kato T, Li T C, Kitamoto N, Tanaka T, Suzuki T, and Park E Y 2017 Versatility of a localized surface plasmon resonance-based gold nanoparticle-alloyed quantum dot nanobiosensor for immunofluorescence detection of viruses Biosens Bioelectron 89 p 998-1005

[22] Fahmida N, Ankan D, Chowdhury, Kenshin T, Jaewook L, Oluwasesan A, Vipin K, Fuyuki A, Tetsuro S, and Enoch Y 2018 Single-step detection of norovirus tuning localized surface plasmon resonance-induced optical signal between gold nanoparticles and quantum dots Biosensors and Bioelectronics 122 p 16-24

[23] Luo S-C, Sivashanmugan K, Liao J-D, Yao C-K, and Peng H-C 2014 Nanofabricated SERS-active substrates for single-molecule to virus detection in vitro: A review Biosensors and Bioelectronics 61 p 232-40

[24] Sivashanmugan K, Liao J-D, You J-W, and Wu C-L 2013 Focused-ion-beam-fabricated Au/Ag multilayered nanorod array as SERS-active substrate for virus strain detection Sensors and Actuators B: Chemical 181 p 361-7

[25] Neng J, Harpster M H, Wilson W C, and Johnson P A 2013 Surface-enhanced Raman scattering (SERS) detection of multiple viral antigens using magnetic capture of SERS-active
nanoparticles *Biosens Bioelectron* 41 p316-21

[26] Chang C, Liao J, Shiau A, and Yao C 2011 Non-labeled virus detection using inverted triangular Au nano-cavities arrayed as SERS-active substrate *Sensors and Actuators B: Chemical* 156 p 471-8