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Chapter 30

Virus detection using nanosensors

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Chapter Outline

30.1 Introduction

The definition of a smart city is that a city that functions in an intelligent and sustainable direction by combining all its services into a cohesive unit and employing clever devices to control and monitor [1]. The global population is perpetually increasing and also importantly driving consumption of resources, which is the cause of climate change and resource deficiency. Especially, urban areas are responsible for the larger part of these resource consumption, prompting an increasing need to produce smart solutions that are environment friendly and more energy efficient [2]. Fig. 30.1 illustrated the solutions to these problems, which consist of advances to components of the smart city.

Recently, the concept of smart city has become more popular in international policies and literature [3]. Smart cities play an important role in economic and social prospects and have a tremendous effect on the environment [4]. The city metabolisms comprise of the remark of goods and the yield of waste with consonant adversary externalities that amplify economic and social troubles. In addition the standard of urban sustainability has increased and should respond to people's necessities through solutions for these aspects [5,6]. The smart city concept is far from being restricted to the utilization of technologies in cities. In point of fact, the use of the name is growing in several sectors without the agreement of definitions. It led to chaos among urban policy makers and hopes that the policies will make their cities smart. Cities search for solutions that allow mixed land uses, transportation linkages, and economical high-quality urban services all over the world. As shown in Fig. 30.2, this more efficient and high-quality transport that responds to economic requirements and associated labor is considered an essential element for the growth of cities [7–10].

Millions of people suffer from several diseases due to numerous medical problems [11]. Today, there is a noteworthy rise in the infectious diseases that affect humans, animals, and plants [12]. Particularly, in undeveloped countries, various diseases, including human immunodeficiency virus (HIV), malaria, and tuberculosis, affect a lot of people [13]. Viruses are parasites and require the host cell to generate and replication. Complex protection mechanisms have been developed by mammalian cells to detect and hinder viral replication. In response, they are capable of breaking down and controlling the host immune reactions. This has allowed the growth of viruses that are proficient at destroying host immune reactions [14].

The detection of pathogenic agents is important for point-of-care applications [15]. Several methods, including polymerase chain reaction [16], enzyme-linked immunosorbent assay [17], reverse-transcription polymerase chain reaction [18], and nanosensor technologies, can detect viruses [19–23], regardless of their drawbacks in terms of utilization and stability [24]. Because of the needs for prompt diagnosis in more stable, economical, and selective nanosensor

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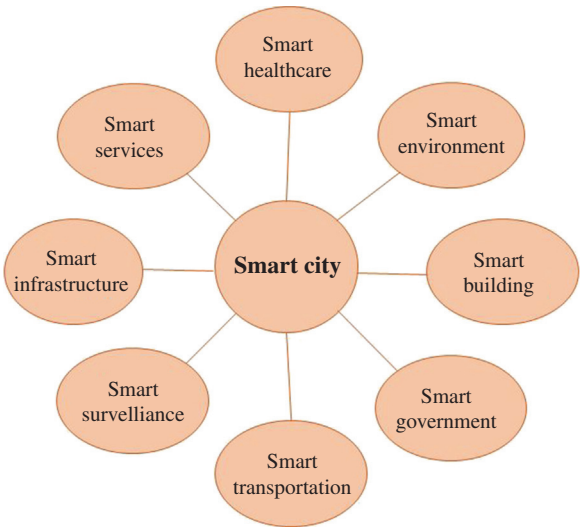

FIGURE 30.1 Components of a smart city.

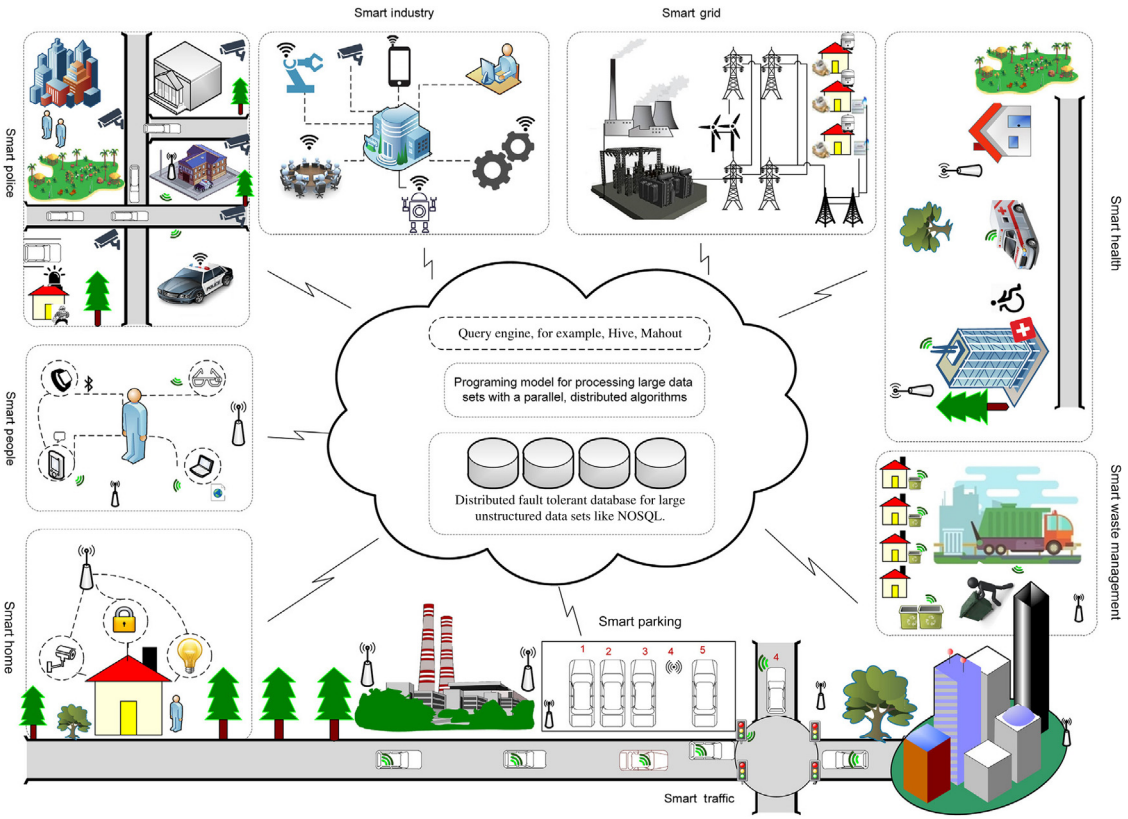

FIGURE 30.2 The landscape of the smart city [7].

technology, various recognition molecules have been analyzed to develop in sensing devices [25]. Nanosensors comprise recognition elements and transducers [26]. The principal bases on the capturing of target and conversion of responses to signals. Nanosensors can be classified into five classes: electrochemical [27], optic [28], piezoelectric [29], thermal [30], and magnetic [31]. Over the previous decades, nanosensors have evolved to be significant for identifying analytes from explosive [32] to protein [33], nucleic acid [34], carcinogens [35], bacteria [36], virus [37] and toxin [38] in food processing [39], environmental monitoring [40], clinical diagnostics [41], and fight against bioterrorism [42].

FIGURE 30.3 The modules of nanosensor.

In this chapter the fundamental concept and types of nanosensors are initially explained and then the use of nanosensor technology is widely reviewed according to the research studies for the assessment of smart utilizations in the diagnosis of infectious; conclusion and outlook are indicated as well.

30.2 Fundamental of nanosensors

A nanosensor has three main modules: a transducer, a receptor, and a detector with a digital output (Fig. 30.3). The target molecule connects with the receptor [43], and the biological detecting component identifies a biological molecule through a reaction. After that, the transducer converts changes to a signal quantified by the detector [44]. Nanosensors offer multiple abilities, including practicable operation, exceptional performance, high specificity and sensitivity, rapid response, condensed size, portability, and real-time analysis [45]. In these days, investigators improve the specificity and sensitivity of the methods by focusing on the nanosensor production quality, extending the affinity between the surface chemistries and employing nanocomposites, such as nanofilm [46], gold nanoparticle [47], or quantum dot [48], for signal amplification studies.

Electrochemical nanosensors have been applied in several applications. These nanosensors include screen-printed electrodes and semiconductors and monitor any changes in dimension, dielectric properties, charge distribution, and shape, while the complex is produced on the electrode. They can be separated into three groups, amperometric, impedimetric, and potentiometric transducers, and utilized to detect various targets [49–51]. Optic nanosensors measure the change of the reflective index of the transducer when the target and recognition element produce a complex. These nanosensors can be classified into two types. In the direct optic nanosensors, signal generation is based on the production of a complex on the transducer surface, whereas the indirect optic nanosensors are mostly designed with various labels to detect the binding and extend the signal. Although indirect sensing nanosensors can create higher signals, they suffer from high reagent cost of labeling step and nonspecific binding [52,53]. They have a multipurpose detection scale and sense various kinds of biomolecules from different specimens [54,55]. Piezoelectric nanosensors measure mass change and viscoelasticity by recording frequency and modifying a quartz crystal resonator [56,57]. The sensing needs isolation equipment that minimizes any hindrance effects because of the high sensitivity to environmental circumstances. These nanosensors have been used in a wide variety of applications to identify targets [58,59]. Thermal nanosensors exploit the fundamental property of biological reactions, such as absorption or evolution of heat. This is reflected as a change in the temperature within the reaction medium. In thermal nanosensors, heat is measured using sensitive thermistors that are frequently selected as temperature transducers. A number of instruments have been laid out in the past decades, and they integrated the fundamentals of enzyme catalysis, calorimetry, flow injection analysis, and immobilization on suitable matrices [60–62]. Magnetic nanosensors carry out magnetic beads coated with a ligand, and they can be detected within a magnetic field. They propose distinct advantages, such as when a sample selected for analysis does not contain any contaminating materials with magnetic properties, background signals are minimized. In addition, not only new avenues of research and clinical methods have been successfully formed, including hyperthermia treatment, magnetic actuation, targeted drug delivery, and the use of magnetic particles, but also bioassays based on fluorescent detection or well-established sequencing methods in genetics have been challenged [63,64].

30.3 Significance of virus detection

Infectious diseases still have a ubiquitous threat to health, especially in rural areas of cities. Underlying cases for such serious maladies can be summarized as the lack of available analysis methods and subsequent treatment strategies due to the limited access of centralized and equipped health-care facilities [65]. Many researchers, such as physicists, chemists, biologists, and medical doctors, have used nanosensors as applications in several fields, including doping analysis [66], diagnosis [67], food safety [68], and laboratory medicine [69]. Among them, clinical applications have been researched as an impressive field of application. Due to the necessity to enhance detecting properties and rapid analysis, new recognition molecules and organizations of them have been examined. With a different combinations, the detection

performance of the nanosensors can be improved. These properties make them suitable for clinical applications that can do rapid and multimolecule detection [70,71].

30.4 Applications of nanosensors in virus detection

30.4.1 Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a lentivirus that is a subset of retroviruses. Lentiviruses are slow viruses, which means that there is an interval between the beginning of the infection and rise of the symptoms. HIV infects the $CD4^+$ T cells and initiates to replicate after entering the bloodstream [72]. The resulting disease is AIDS that is one of the important public health issues. According to the WHO report, more than 35 million people have been infected up to now [73]. There are two classes of HIV, namely, HIV-1 and HIV-2, and HIV-1 is the most prevalent type of disease-causing agents.

Babamiri et al. promoted an electrochemiluminescence nanosensor to detect HIV-1 gene. After hybridization experiments, they observed the signal to be significantly increased. They accomplished a sensitive detection in a range from 3.0 fM to 0.3 nM. They showed that their nanosensor has a good specificity when compared with the noncomplementary sequences [74]. Lu et al. prepared a nanosensor with the aim of determining HIV-1-related glycoprotein 41 (Gp41). They modified the surface of piezoelectric nanosensor by a synthetic peptide, which has 579−613 residues of Gp41. They demonstrated that a nanosensor surface has an immense affinity to the target peptide and can selectively bind Gp41. They calculated the detection limit as 2 ng/mL [75]. Shafiee et al. exhibited an optic nanosensor for HIV-1 detection. They mentioned that the target was adsorbed and influenced a shift with 10 pM resolution and investigated ranging from 10^4 to 10^8 copies/mL [76].

30.4.2 Hepatitis B virus

Hepatitis virus has been known since the 1940s and causes transient and chronic hepatitis [77]. Hepatitis B virus (HBV) is one of the main infections evaluated to cause almost a million deaths every year due to cirrhosis and malignant liver growth. In addition, 15%−40% of infected patients will have liver failure, liver cirrhosis, or hepatocellular carcinoma, and 15%−25% will unfortunately die [78].

Hassen et al. published a study about the hybridization of DNA to detect the HBV by electrochemical impedance spectroscopy. First of all, they altered DNA probes with magnetic nanoparticles and immobilized nanoparticles into the gold electrode. Following the characterizations, they showed a good DNA immobilization and hybridization with different concentrations of complementary DNA. Moreover, they exhibited that this nanosensor has detected 50 pmol of HBV DNA, and saturation reached 12.65 nM [79]. Uzun et al. also detected an HBV surface antibody using optic nanosensor in human serum. They carried out kinetic studies employing HBV surface antibody−positive human serum samples. They calculated detection limit value and also showed that this nanosensor obeyed the Langmuir adsorption isotherm model [80]. İstek et al. provided an electrochemical nanosensor for sequence-selective DNA hybridization related to HBV detection. They performed the selectivity of the nanosensor in the presence of target and the other DNA sequences. They also calculated the detection limit value of 0.86 μg/mL [81].

30.4.3 Human papillomavirus

Human papillomavirus (HPV) has been studied for cervical cancer development, which is the second-most prevalent form of malignancy among women. Early diagnosis lets patients to be taken care of at an early stage. Hence, there is an extreme clinical utility of diagnostics even with binary positive and negative indications. The Pap smear is generally used for screening, but this method still suffers from low sensitivity and specificity [82,83].

Inan et al. developed a microfluidic nanosensor for detecting HPV-16 E7 antibodies. They observed detection down to 2.87 ng/mL. They validated the nanosensor in serum samples and supplied high responses as compared with control samples. They showed that this nanosensor can be implemented as a pretesting tool to diagnose for broad monitoring of HPV-associated cancers [84]. Teengam et al. reported a colorimetric nanosensor to screen synthetic HPV. They developed a DNA-dependent multiplex paper-based nanosensor (Fig. 30.4). The targets were determined by quantifying the color change of silver nanoparticles that gave a detection limit value of 1.03 nM. The nanosensor displayed high selectivity for the complementary oligonucleotides over single-base mismatch, two-base mismatch, and noncomplementary DNA targets [85]. Peng et al. demonstrated a nanosensor that depended on two-dimensional nanosheets for

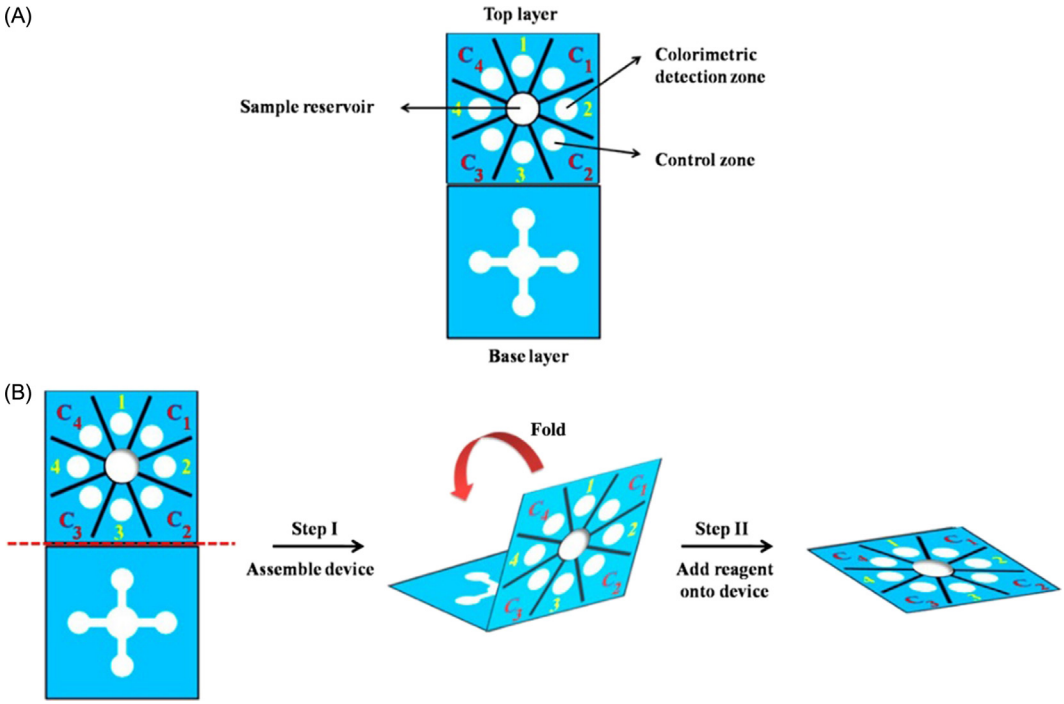

FIGURE 30.4 (A) Design and (B) the principle of paper-based colorimetric nanosensor [85].

HPV detection. These nanosheets were acquired by exfoliating their layered etched powder and exhibited high fluorescence quenching ability to dye-labeled single-stranded DNA and different affinities for single-stranded and double-stranded DNA. They observed that the single-stranded DNA probe showed minimal fluorescent emission under the fluorescence quenching effect of nanosheets. This nanosensor for HPV-18 detections showed high specificity and a low detection limit of 100 pM [86].

30.4.4 Ebola

Ebola virus infections generate severe illness in humans, and after an incubation time, patients at first present with general influenzas before a fast progression to a progressive disease characterized via shock-like syndrome, multiple organ failure, and hemorrhage [87]. The largest outbreak of Ebola virus infection is discussed in Ref. [88]. Such advanced superiorities would be perfect for fast, point-of-care detection of Ebola virus [89]. Natesan et al. produced a digital nanosensor to detect Ebola virus. Their nanosensor had a flow cell assay that captured specific antibodies with microarrayed recombinant antigens and a smartphone fluorescent reader for high-performance clarification of results. They showed that the smartphone reader utilized a hardware attachment that snapped at the back of a smartphone and provided a user interface to handle the operation, communicate with cloud service, and acquire test results. They also developed a secure cloud service for the tele-monitoring of results. They tested these nanosensor results with sera from nonhuman primates that received a live attenuated Ebola vaccine [90]. Ilkhani et al. invented an electrochemical nanosensor to identify Ebola virus. They first marked it with a streptavidin−alkaline phosphatase conjugate and optimized all the steps and then received a low detection limit value. They finally accomplished selectivity and reproducibility [91]. Yanik et al. constructed an optofluidic nanosensor that detects whole viruses. Their nanosensor was based on a light transmission impact and used group-specific antibodies. They applied in a range spanning three orders of magnitude. They modified antibodies against the Ebola glycoprotein on the nanosensors, and transmission spectra were collected after the cleaning process [92].

30.4.5 Zika

Zika virus is a mosquito-borne virus. Some sporadic human sickness cases were listed in Asia and Africa before 2007. The first report was in the Federated States of Micronesia in 2007 [93]. Emerging infectious illnesses, such as the Zika

virus epidemic spanning the Western Hemisphere, have demanded renewed studies regarding the requirement to produce simplified diagnostic tests [94].

Afsahi et al. developed graphene-based nanosensor to detect the Zika virus. They quantified as low as Zika viral antigens concentration (450 pM). They exhibited a potential diagnostic tool by detecting Zika antigen in human serum. They validated the selectivity with Japanese encephalitis NS1 [95]. Kaushik et al. represented an electrochemical nanosensor to detect Zika virus. They applied electrochemical impedance spectroscopy to measure the response and showed that the nanosensor detected Zika virus in a range of 10 pM−1 nM, and the detection limit value is lower than 10 pM [96]. Song et al. published a study based on reverse-transcription loop-mediated isothermal amplification to determine Zika virus. They exhibited the usefulness of this nanosensor by detecting Zika virus in real samples with a sensitivity of 5 pfu [97].

30.4.6 Influenza

Influenza is an infectious disease regarded as a wellhead of several clinical issues and enormous economic interruptions [98]. As common methods are insufficient for in-field detection and usually suffer from being time-consuming and difficult, it is essential for researchers to develop effective options to conventional methods [99].

Tam et al. published an article about the immobilization of DNA employing carbon nanotubes to detect influenza. They modified a DNA probe onto the nanosensor surface and characterized the fundamental interaction. They detected the DNA probe hybridization and the target DNA and found the limit of detection as 0.5 nM [100]. Vollmer et al. studied an optic method to detect influenza virus. They performed the binding experiments of single virions from changes of discrete in the resonance frequency of a whispering-gallery mode. They also supported the sensing mechanism with the virus-sized nanoparticles [101]. Bai et al. developed a portable optic nanosensor by employing an aptamer to detect avian influenza virus (AIV) H5N1. The immobilized aptamers by capturing AIV H5N1 cause an improvement in the refraction index. Following the optimization of experimental parameters, their results displayed that the refraction index value was linearly associated with AIV concentration [102].

Emir Diltemiz et al. prepared piezoelectric and optic nanosensors for the detection of hemagglutinin that is the main protein of the influenza virus. They employed 4-aminophenylboronic acid to bind sialic acid. As depicted in Fig. 30.5, they modified the nanosensor surfaces with thiol groups and then immobilized 4-aminophenylboronic acid and sialic acid. Also, they calculated detection limits as 4.7×10^{-2} and 1.28×10^{-1} μM for piezoelectric and optic nanosensors [103].

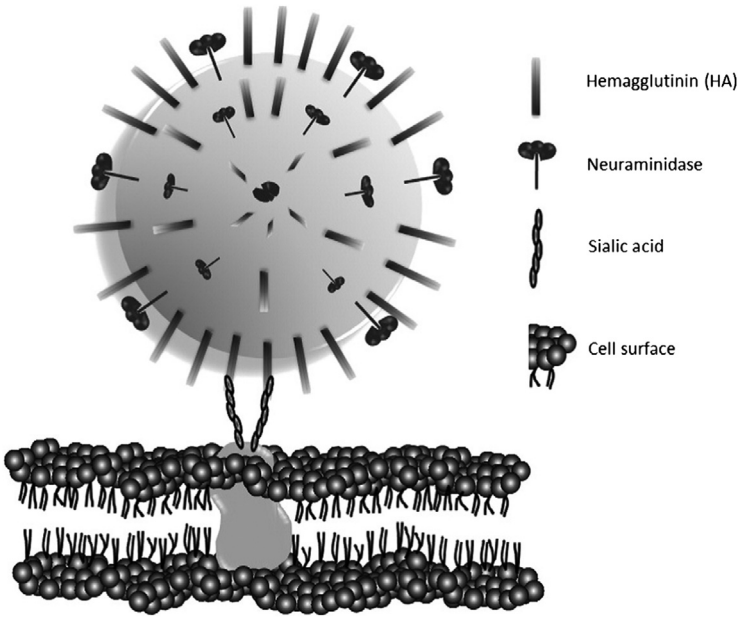

FIGURE 30.5 Schematic representation of binding of influenza to sialic acids [103].

30.4.7 Other viruses

The real-time virus detection has a high interest in various fields, such as biosecurity, biomedicine, and environmental science [104]. Nanosensor does not need trained personnel and expensive equipment, especially if obtained results can be read by naked eyes [105,106].

Jin et al. published a study about a virus diagnostic tool that combined with an optic nanosensor and microfluidic system to detect human adenovirus. They detected 10 copies of human adenovirus in 30 minutes. They also validated the clinical utility and declared that this tool proposed a sensitive and rapid detection with simplicity, low cost, and short assay time [107]. Guerreiro et al. exhibited a genetically encoded switch-on fluorescent nanosensor comprising acyclized green fluorescent protein (cVisensor) with an adenoviral protease cleavable site (Fig. 30.6). They first optimized nanosensor and then established virus detection by stable expression in mammalian cells and utilized for live-cell monitoring of adenovirus infection. They obtained a flow cytometry-based assay using cVisensor cells 48 hours postinfection and showed the limit of detection value as 10^5 infectious particles/mL [108].

Kim et al. proposed a colorimetric nanosensor that depended on various forms of dsDNA-shielded gold nanoparticles to detect Middle East respiratory syndrome coronavirus. They demonstrated that their nanosensor was capable of verifying the existence of viral molecules and color changes of gold nanoparticles in the UV−vis wavelength range. They planned a pair of thiol-modified probes at either the 5′ end or 3′ end to coordinate complementary base pairs with upstream of the E protein gene and open reading frames. In addition, they reported that colorimetric nanosensor could discriminate down to 1 pmol/μL of 30 bp Middle East respiratory syndrome coronavirus [109]. Trzaskowskia et al. investigated the possibility of using optic nanosensor in the detection of tuberculosis in sputum. First, they designed a portable surface plasmon resonance apparatus and referred its performance with a standard desktop surface plasmon resonance platform via measuring the response to tuberculosis secretory protein. Then, they examined samples of suspended *Mycobacterium tuberculosis* cultures and sputum samples of tuberculosis patients. They claimed that this nanosensor was able to detect *M. tuberculosis* secretory protein and also able to determine tuberculosis bacteria cultures in the concentration of 1×10^4 cfu/mL with no significant interfering response from two other bacteria species [110]. Weerathunge et al. offered a colorimetric nanosensor to detect infective murine norovirus. They integrated the gold nanoparticles that have enzyme−mimic catalytic activity with a murine norovirus aptamer and noticed that this nanosensor created a blue color in the being of norovirus. They also found the detection limit as three viruses per assay, which is equal to 30 viruses/mL of the sample [111].

30.5 Conclusion and outlook

Clinical diagnostic systems have a huge research area that still has to deal with many unmet disputes necessary to develop and commercialize the nanosensors. They should be stable, simple, robust, reliable, and affordable and also have high detection capability, especially in clinical applications. Nanosensor feasibility also seems to begin leaving the proof of concept, and several analytes have already been detected to demonstrate the versatility of the nanosensors. In some particular cases the validation with real samples in clinical scenarios strengthens nanosensors suitability. There are still some doubts to overcome as some portable nanosensors have recently been studied at the research level. Though the progression is quite slow, a significant advancement in smartphone technology has helped mobile health diagnostics to deploy at developing countries. The exponential increase in mobile application development and the affordability of these platforms have revolutionized health delivery and opened a new window in global health access.

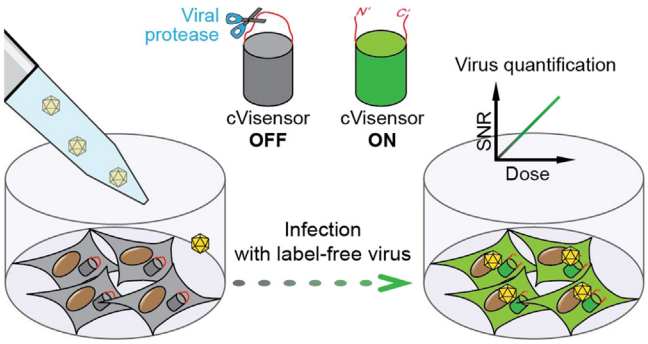

FIGURE 30.6 Scheme of the working principle of cVisensor [108].

In this review the current developments of nanosensors were summarized in clinical application for virus detection. In comparison with conventional techniques, these nanosensors demonstrate more favorable applications to improve human health.

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