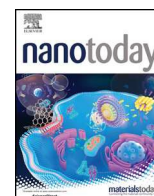




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Review

Point-of-care diagnostics for infectious diseases: From methods to devices

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ABSTRACT

The current widespread of COVID-19 all over the world, which is caused by SARS-CoV-2 virus, has again emphasized the importance of development of point-of-care (POC) diagnostics for timely prevention and control of the pandemic. Compared with labor- and time-consuming traditional diagnostic methods, POC diagnostics exhibit several advantages such as faster diagnostic speed, better sensitivity and specificity, lower cost, higher efficiency and ability of on-site detection. To achieve POC diagnostics, developing POC detection methods and correlated POC devices is the key and should be given top priority. The fast development of microfluidics, micro electro-mechanical systems (MEMS) technology, nanotechnology and materials science, have benefited the production of a series of portable, miniaturized, low cost and highly integrated POC devices for POC diagnostics of various infectious diseases. In this review, various POC detection methods for the diagnosis of infectious diseases, including electrochemical biosensors, fluorescence biosensors, surface-enhanced Raman scattering (SERS)-based biosensors, colorimetric biosensors, chemiluminescence biosensors, surface plasmon resonance (SPR)-based biosensors, and magnetic biosensors, were first summarized. Then, recent progresses in the development of POC devices including lab-on-a-chip (LOC) devices, lab-on-a-disc (LOAD) devices, microfluidic paper-based analytical devices (μ PADs), lateral flow devices, miniaturized PCR devices, and isothermal nucleic acid amplification (INAA) devices, were systematically discussed. Finally, the challenges and future perspectives for the design and development of POC detection methods and correlated devices were presented. The ultimate goal of this review is to provide new insights and directions for the future development of POC diagnostics for the management of infectious diseases and contribute to the prevention and control of infectious pandemics like COVID-19.

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Contents

Introduction	2
Detection methods for POC diagnostic applications	3
Electrochemical biosensors	3
Voltammetric/ampereometric biosensors	3
Impedimetric biosensors	5
Potentiometric biosensors	5
Field-effect transistor (FET)-based biosensors	5
Fluorescence biosensors	5
Direct fluorescence labeling biosensors	6

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"Signal-on" fluorescence biosensors	7
"Signal-off" fluorescence biosensors	8
Surface-enhanced Raman scattering (SERS)-based biosensors	8
Colorimetric biosensors	8
Chemiluminescence biosensors	11
Surface plasmon resonance (SPR)-based biosensors	11
Magnetic biosensors	12
POC devices for infectious disease detection	15
Lab-on-a-chip (LOC) devices	16
Parasite detection	16
Bacteria detection	18
Virus detection	21
Lab-on-a-disc (LOAD) devices	24
Parasite detection	24
Bacteria detection	24
Virus detection	25
Microfluidic paper-based analytical devices (μ PADs)	26
Parasite detection	27
Bacteria detection	27
Virus detection	28
Lateral flow devices	30
Parasite detection	30
Bacteria detection	30
Virus detection	32
Miniaturized PCR devices	34
Parasite detection	34
Bacteria detection	34
Virus detection	36
Isothermal nucleic acid amplification (INAA) devices	36
Parasite detection	36
Bacteria detection	36
Virus detection	37
Conclusion and future perspectives	39
CRedit authorship contribution statement	42
Declaration of Competing Interest	42
Acknowledgments	42
References	42

Introduction

Since the new coronavirus (SARS-CoV-2) caused pneumonia (COVID-19) outbreak occurred in December 2019, it has rapidly spread all over the world and caused a substantial threat to global human health [1–3]. Up to 22nd January 2021, there have been 96,012,792 confirmed cases of COVID-19 and 2,075,870 deaths all over the world, as reported by the World Health Organization (WHO) [4]. Looking back on history, none of the infectious diseases has not brought great disasters to mankind, especially for diseases caused by viruses, which have been one of the greatest existential threats to human beings [5–8]. For example, the 1918 influenza pandemic [9,10], the pandemic of human immunodeficiency virus (HIV) infection [11,12], the pandemic of severe acute respiratory syndrome (SARS) in 2003 [13–15], the pandemic of Middle East respiratory syndrome (MERS) in 2012 [16–18], and the current pandemic of COVID-19 were all deprived of thousands of lives [19–22]. All those appalling infectious diseases had significantly affected the global health, economy, social stability, and eventually the civilization process of human society, and as a result emphasized the importance of developing new novel point-of-care (POC) diagnostics to enhance timely recognition and intervention of those diseases.

Unlike other conventional diseases, infectious disease is a kind of disease caused by live pathogens such as bacteria, viruses and parasites, which is capable of rapid transmission and infection among human or animal vectors by inoculation, airborne or waterborne transmission [7,23–26]. For the management of infectious diseases, there are three strategies: 1) control of the infection source; 2) cutting off transmission routes; and 3) protection of

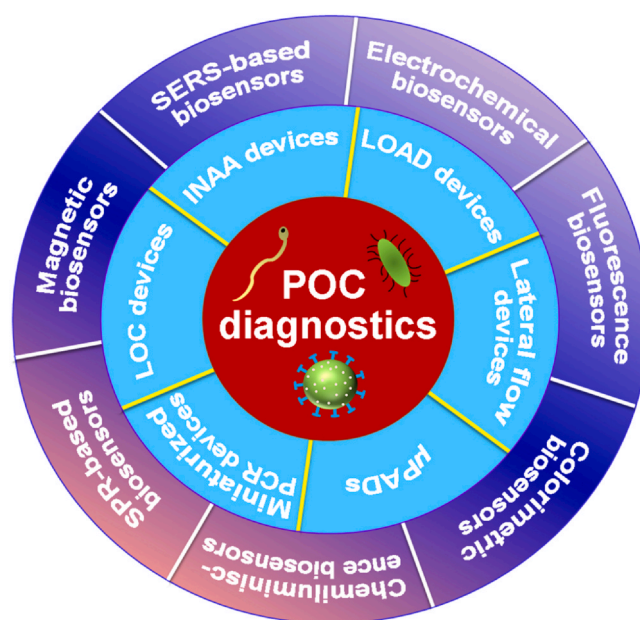
susceptible people. Among those strategies, control of the infection source is recommended to be the most important, which requires early detection, early isolation, and early treatment of correlated patients and calls for the development of rapid, sensitive and accurate detection methods and kits [27–33]. The common strategies for the clinical diagnosis of infectious diseases are majorly relied on the pathogen culture and identification or the detection of specific antigens, antibodies or nucleic acids of infectious pathogens [34–37]. However, the current conventional diagnostic methods, such as identification of microorganisms by observing characteristic features of cultures, enzyme linked immunosorbent assay (ELISA) and nucleic acid testing (NAT), are usually performed in medical laboratories, whose applications are always limited due to their shared disadvantages such as time-consuming, labor-consuming, high cost, expensive machine dependent, and inability to achieve rapid on-site detection. To achieve fast and highly sensitive NAT, various methods including photothermal nanomaterials-based PCR, isothermal nucleic acid amplification and biosensors [38–41], have been developed to increase the detection speed and sensitivity of NAT. Besides, though real-time quantitative polymerase chain reaction (qPCR) has been widely employed for NAT of infectious diseases in the past years due to its high sensitivity and accuracy, the qPCR machines and correlated reagents are always very expensive and skilled technicians are essential [42–44]. Those downsides of those above mentioned diagnostic methods make them inadequate to achieve fast, accurate and on-site diagnosis during the pandemic outbreak of infectious diseases, especially in resource-poor regions where infectious diseases are always the most widespread and serious.

POC diagnostic, refer to diagnosis done in the proximity of patient care, is a new intelligent strategy for real-time, rapid, accurate, and on-site detection at the patient's point-of-need [45–48]. In the past years, with high demand for on-site detection in clinical medicine, especially in resource-poor regions, POC diagnostics have attracted increasing attention since their emergences and there has been a huge market of POC devices. As coined by the WHO, the fundamental criterions of POC diagnostics are denoted to be “ASSURED”, that are affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end user [34,49]. Firstly, to develop POC diagnostics, design and establishment of novel sensitive and fast detection methods are among the most important. Up to date, there have been a variety of novel detection methods employed for the development of POC diagnostics, including electrochemical biosensors, fluorescence biosensors, surface-enhanced Raman scattering (SERS)-based biosensors, colorimetric biosensors, chemiluminescence biosensors, surface plasmon resonance (SPR)-based biosensors, and magnetic biosensors [50–53]. Moreover, empowered by the booming development of microfluidics, micro electro-mechanical systems (MEMS) technology, nanotechnology and materials science, all flowers are in bloom in the development of POC devices. Those POC devices including lab-on-a-chip (LOC) devices [54–56], lab-on-a-disc (LOAD) devices [57,58], microfluidic paper-based analytical devices (μ PADs) [59], lateral flow devices [60], miniaturized PCR devices [61], and isothermal nucleic acid amplification devices (INAA) devices [62,63], which substantially promoted the development of POC diagnostics. In particular, the seamless integration of those novel biosensors, advanced devices and recent artificial intelligence (AI) techniques would greatly accelerate the pace of progress in the development POC diagnostics toward labor-free and intelligent diagnosis.

Over the past decades, thanks to the efforts by us and others, there have been a large number of reports about POC diagnostic systems and some of them have been commercialized for clinical disease diagnostics either in hospital or resource-poor regions [64–80]. Hence, under the background of COVID-19 outbreak and the high demand for rapid, sensitive and accurate on-site diagnostics, it is necessary to review the recent progresses of the development of POC diagnostics for on-site diagnosis of infectious diseases, attempting to provide new approaches and research directions for the future development of POC diagnostics. Although there have been a couple of reviews about the applications of POC diagnostics for infectious diseases, most of them are mainly about the detection methods, nanomaterials employed and target detections, and are comparably one-sided [34,48,52,81–84]. Herein, both POC detection methods and correlated POC devices for the POC diagnostics of various infectious diseases were systematically summarized and discussed (Scheme 1). Firstly, various detection methods potentially for POC diagnostic applications were systematically presented. Then, the current progresses in the development of various POC devices and their applications in the detections of various infectious diseases were particularly reviewed. Finally, the challenges and future perspectives in the development of POC diagnostics were discussed in depth.

Detection methods for POC diagnostic applications

Detection methods are among the most important component in the development of POC diagnostic systems, which determine the efficiency, sensitivity and accuracy of the whole system. Therefore, developing novel detection methods for rapid and highly sensitive detections of infectious diseases is the foundation of design and fabrication of POC devices. Herein, various detection methods potential for POC diagnostic adaptation were summarized, including electrochemical biosensors, fluorescence biosensors, SERS-based



Scheme 1. Schematic illustration of point-of-care diagnostics for infectious diseases.

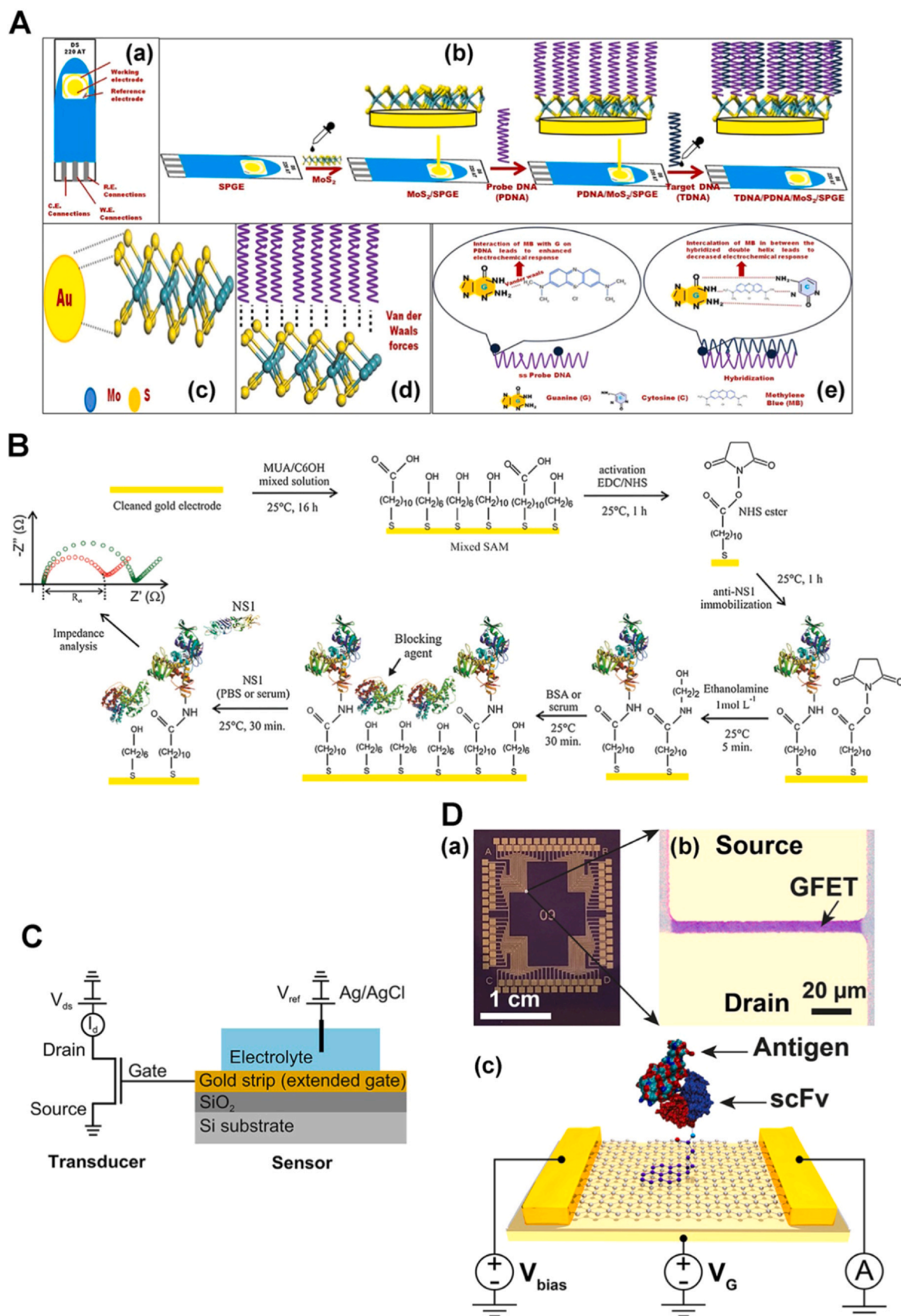
biosensors, colorimetric biosensors, chemiluminescence biosensors, SPR-based biosensors and magnetic biosensors.

Electrochemical biosensors

Electrochemical biosensors are one kind of the most popular detection methods for the detection of all kinds diseases, due to their advantages of short detection time, instrumental simplicity, low cost and portability, holding a great potential for POC diagnostic applications [85–89]. As a result, various electrochemical biosensors have been explored for the applications in the development of POC diagnostic platforms, including voltammetric/amperometric biosensors [90–94], impedimetric biosensors [95,96], potentiometric biosensors [97], and field-effect transistor (FET) based biosensors [98,99].

Voltammetric/amperometric biosensors

Voltammetric/amperometric biosensors are one of the widest employed electrochemical biosensors in the analyst detection due to their high sensitivity caused by the enzymes used [100]. Up to date, there have been various methods established for the development of voltammetry biosensors, including cyclic voltammetry, linear sweep voltammetry, square wave voltammetry, and differential pulse voltammetry [91,101]. Although both voltammetric and amperometric biosensors can achieve the detection of targets by measuring the current arising from electrolysis caused by an electrochemical oxidation or reduction at the working electrode upon being applied a potential to the indicator electrode versus the reference electrode, whose signals are determined by the mass transport rate of the reactant molecules from the solution to the electrode interface, the potential applied in a voltammetric biosensor is ramped at a given rate, while in an amperometric biosensor the applied potential is constant [98]. As a paradigm of POC diagnostic adaptation, Singhal et al. developed an electrochemical voltammetric biosensor based on molybdenum disulfide nanosheets (MoS_2 NSs) for POC detection of chikungunya virus DNA (Fig. 1A) [102]. Briefly, MoS_2 NSs were synthesized and subjected to physical adsorption onto the screen printed gold electrodes for immobilizing the probe DNA. Then, the magnitude of the voltammetric signal produced by the different interaction of methylene blue with the guanine bases of the single



(continued on next page)

Fig. 1. (A) Schematic illustration of MoS₂ NSs based biosensor for the POC diagnosis of chikungunya virus (a) Screen printed gold electrode (SPGE). (b) Stepwise representation of the fabrication of SPGE with MoS₂ nanosheets, probe DNA and target DNA. (c) Interaction of working electrode (Au) of SPGE and MoS₂ shows strong affinity between Au (SPGE) and S (MoS₂). (d) MoS₂ interacts with probe DNA via Vander Waals forces. (e) Principle for the detection of hybridization of target DNA via redox hybridization indicator, i.e., methylene blue. Reproduced with permission from Ref. [102] Copyright 2018, Springer Nature. (B) Schematic construction representation of the impedimetric label-free immunosensor based on an anti-NS1 modified gold electrode for POC dengue diagnosis. Reproduced with permission from Ref. [108] Copyright 2015, Elsevier. (C) Schematic of the potentiometric sensing device, consisting of two parts: a sensor part for signal generation and a transducer part for signal amplification and readout. Reproduced with permission from Ref. [114] Copyright 2016, Elsevier. (D) Schematic of graphene field-effect transistors (GFETs) nano-biosensor conjugated with single-chain variable fragment (scFv) antibodies for Lyme disease diagnosis. (a) Photograph of a sensor array with 100 GFET devices. (b) Optical micrograph of a GFET channel with dimension of 100 $\mu\text{m} \times 10 \mu\text{m}$, connected to source and drain electrodes highlighted in yellow. The light purple region is the 285 nm thick SiO₂ substrate, while the darker purple region is the graphene channel. (c) Schematic of a GFET functionalized with Lyme disease scFv through a 1-pyrenebutyric acid N-hydroxysuccinimide ester linker, with the bound antigen. Reproduced with permission from Ref. [121] Copyright 2020, IOP Publishing.

and double-stranded DNA was detected. The proposed electrochemical voltammetric biosensor exhibited a low detection limit of 3.4 nM [102]. In another work, Hiraiwa et al. developed an amperometric biosensor by a microtip immunoassay for rapid and POC detection of *Mycobacterium tuberculosis* (MTB) in sputum [103]. Briefly, a capture antibodies coated microtip was used to capture and concentrate the target bacteria by a coffee-ring effect to form immunocomplex on the microtip surface, which could be detected by electric current. The amperometric biosensor could achieve a highly sensitive detection of MTB in spiked human sputum with a detection limit of 100 CFU mL⁻¹, which was simple, portable, and very promising for POC detection in the resource-poor regions.

Impedimetric biosensors

Impedimetric biosensors are another kind of commonly used electrochemical biosensors due to its advantages of label-free and small amplitude perturbation, which employ electrochemical impedance spectroscopy (EIS) to realize target analysis [91,104,105]. Electrochemical impedance is the ratio of an incremental voltage change to the resulting current change, and the resistive and capacitive components of the circuit could be determined by EIS through a frequency changed small amplitude sinusoidal AC excitation signal. When the frequency is considerably high, there will be a rate limiting upon the migration of the redox species to the electrode surface, which can be blocked by the targets and generates a frequency-dependent phase lag between the AC voltage and current [98,106]. The EIS can be performed in Faradaic and non-Faradaic modes. Faradaic EIS involves charge transfer between the electrodes and requires the addition of a redox couple, while non-Faradaic detection requires no additional reagents, in which the capacitive behavior is produced through the separation of charges at the electrode-electrolyte interface [106,107]. As an example of applications of impedimetric biosensors for POC detection of infectious disease, Cecchetto et al. designed an impedimetric label-free immunosensor based on an anti-NS1, a non-structural dengue protein antibody, modified gold electrode for POC diagnosis of dengue by testing neat serum (Fig. 1B) [108]. Briefly, an impedimetric biosensor was fabricated by covalently immobilizing anti-NS1 to the gold electrode surface for NS1 binding. Then, the impedance spectrum was collected in the presence of a redox probe ([Fe(CN)₆]^{3-/4-}) to monitor the charge-transfer resistance changes caused by the target binding. The impedimetric label-free immunosensor could achieve high sensitive detection of NS1 with a detection limit of 30 ng mL⁻¹ in neat serum, suggesting its potential application in POC diagnostics of dengue [108].

Potentiometric biosensors

Potentiometric biosensors apply an electrochemical cell with two reference electrodes, largely ion-selective electrodes (ISEs), to measure the accumulation of a charge at an electrode while drawing negligible current flow [109,110]. For biological detection, enzymes are usually employed in the potentiometric sensors to catalyze chemical reaction and produce ions in the vicinity of the sensing ISE [111,112]. Potentiometric biosensors have several advantages of small size, rapid response, ease of use, low cost, resistant to color, turbid

interferences, and is independent of the sample volume [113], making it promising for POC diagnostic applications. As a paradigm, Tarasov et al. developed a novel potentiometric biosensor based on extended-gate field-effect transistors in a dual-chip configuration for on-site serological diagnosis of Bovine Herpes Virus-1 (BHV-1) (Fig. 1C) [114]. The potentiometric biosensor was then demonstrated to be highly sensitive and selective to detect BHV-1 in real serum samples from cattle, which could be easily integrated to POC devices for the POC diagnosis of a wide range of human and animal diseases [114].

Field-effect transistor (FET)-based biosensors

FET-based biosensors are a class of electrochemical biosensors that detect the change in source-drain channel conductivity in the electric field caused by the accumulation of charged target species at the sensor surfaces [115–117]. FET-based biosensors have attractive advantages of label-free, miniaturization, ease of mass production, high versatility and low cost, and thus have become an ideal candidate for the development of POC diagnostics [117–120]. For instance, Gao et al. developed a highly sensitive graphene FET-based nanobiosensor coupled with Lyme single-chain variable fragment antibodies for multiplexed detection of Lyme disease antigens of *Borrelia burgdorferi* bacterium, which exhibited a low detection limit of 2×10^{-3} ng mL⁻¹ (Fig. 1D) [121].

Fluorescence biosensors

Fluorescence biosensors are a type of biosensors that have been widely employed for POC diagnostics of infectious diseases due to their appealing advantages of high sensitivity, low cost, easily operation and rapid analysis [122–127]. Labeling of fluorophores, either fluorescent dyes or fluorescent nanomaterials, is always essential for the establishment of a fluorescence biosensor. For the design of a fluorescence biosensor, one of the most typical strategies is using fluorescence resonance energy transfer (FRET), which refers to the transfer of energy from a donor fluorophore to an acceptor fluorophore [87,128–130]. In addition, some nanomaterials can also produce fluorescence signals due to their unique physical, chemical, and electronic transport properties, and thus have attracted great attention for the development of fluorescence biosensors [131,132]. Based on the fluorescence generation or quencher in the detection, fluorescence biosensors can be classified into direct fluorescence labeling biosensors, “signal-on” fluorescence biosensors and “signal-off” fluorescence biosensors. For direct fluorescence labeling biosensors, the fluorescent tag is labeled to the specific ligand that selectively binding to the targets and generate corresponding proportional fluorescence signal. For “signal-on” fluorescence biosensors, the fluorescence signal is in proportional to the target quantity, and only negligible fluorescence intensity exists in the absence of the target. On the contrary, the fluorescence signal in a “signal-off” fluorescence biosensor is inversely proportional to the target quantity, and the fluorescence intensity is enhanced in the absence of the target. Herein, those potential fluorescence biosensors for POC diagnostics of infectious diseases were systematically discussed.

Direct fluorescence labeling biosensors

In direct fluorescence labeling biosensors, fluorescent dyes are labeled to the binding ligands that specifically recognize the targets and serve as the reporter signals. The fluorescence signals are proportional to the target amounts. Except for traditional fluorescent dyes, some nanomaterials have also been widely employed for developing fluorescence biosensors due to their excellent fluorescence properties, such as quantum dots (QDs) [133], carbon dots (CDs) [134,135], upconversion nanoparticles (UCNPs) [136], and metal nanoclusters (NCs) [137–139], which have been widely applied for the fabrication of fluorescence biosensors. Herein, various direct fluorescence labeling biosensors for POC diagnostics of infectious diseases were summarized.

Quantum dots-based fluorescence biosensors. QDs are a kind of nanoparticles with particle sizes less than or equal to their own exciton Bohr radius in three space dimensions, usually less than 10 nm, and have strong fluorescence properties [140,141]. Compared with other fluorescent materials, QDs exhibit several merits such as high quantum yield, tunable emission spectrum, and excellent photostability [141–143], and thus have attracted much attention for the development of POC diagnostic platforms for the detection of infectious diseases. As a paradigm, Hu et al. [144] encapsulated fluorescent QDs and Au nanoparticles into antibody and streptavidin modified RNs@Au multifunctional nanospheres (antibody-RNs@Au-streptavidin) and developed a sensitive and quantitative lateral flow assay for the POC detection of Ebola virus glycoprotein. In this strategy, fluorescent QDs were used for quantitative detection and Au nanoparticles were used for visual detection, which was able to achieve naked-eye detection of 2 ng mL⁻¹ glycoprotein within 20 min and a quantitative detection limit of 0.18 ng mL⁻¹. Takemura et al. [125] developed a new QDs-based immunofluorescence biosensor for the POC detection of nonstructural protein 1 (NS1) of Zika virus. In this biosensor, a localized surface plasmon resonance (LSPR) signal from plasmonic gold nanoparticles (AuNPs) was used to amplify the fluorescence intensity signal of QDs to achieve ultrasensitive, rapid, and quantitative detection of NS1 of Zika virus. The biosensor was able to detect NS1 of Zika virus in a wide concentration ranging from 10 fg mL⁻¹ to 1 ng mL⁻¹, and the detection limit was as low as 1.28 fg mL⁻¹.

Carbon dots-based fluorescence biosensors. CDs are a kind of well-known fluorescent zero-dimensional carbon-based nanomaterials with diameters less than 10 nm [145]. Due to their preferable attributes, such as excellent fluorescence properties and biocompatibility, CDs have been widely applied for various biomedical applications, including biosensing, imaging, drug delivery and therapy [146–149]. Among all those biomedical applications, fluorescence-based biosensing by leveraging their unique fluorescence properties has been extensively investigated for POC diagnostics of infectious diseases. For example, Xu et al. [150] developed a fluorescent lateral flow assay using CDs/SiO₂ nanospheres (CSNs) as reporters for ultrasensitive POC detection of severe fever with thrombocytopenia syndrome virus (SFTSV). The fluorescent lateral flow assay owned good reproducibility, high specificity and sensitivity due to the excellent fluorescent properties of CSNs, and was able to achieve a low visual detection limit of as low as 10 pg mL⁻¹ SFTSV nucleoprotein which was 2 orders of magnitude higher than that of the colloidal gold-based lateral flow test strip. Most recently, Wang et al. [151] developed a Eu (III) functionalized carbon dots (CDs-Eu)-based ratiometric fluorescent test paper for sensitive POC detection of dipicolinic acid (DPA), a biomarker of anthrax. This ratiometric fluorescent test paper exhibited excellent detection performance with high sensitivity which could achieve a linearity range from 0.5 nM to 5 μM and a detection limit of 0.8 nM. To make it a more convenient

approach for DPA detection, the ratiometric fluorescent test paper was further being combined with a smartphone and was able to achieve visualized POC detection of DPA with a detection limit of 67 nM, which was lower than other reported test paper for DPA detection, holding a great potential for the practical POC diagnostics of anthrax.

Upconversion nanoparticles-based fluorescence biosensors. Lanthanide-doped UCNPs are fluorescent inorganic nanomaterials that can absorb two or more low-energy photons light to produce higher energy photons and emit fluorescence signals [152–154]. Compared with conventional fluorescent materials, UCNPs have a variety of advantages, such as low toxicity, long luminescence lifetimes, high photostability, high signal-to-noise ratio, and high resistance to photobleaching [155–157], and thus have been regarded as a kind of very promising fluorescent probes for POC detection of infectious diseases. As a paradigm, Zhao et al. [158] developed an electro-driven immunochromatography assay using UCNPs for high-sensitivity detection of *Yersinia pestis* EV76. In this assay, UCNPs were used as the fluorescent tags and conjugated with monoclonal antibodies against *Yersinia pestis* EV76, and electroosmotic flow was applied to increase the assay speed. The electro-driven immunochromatography assay showed high specificity and sensitivity for the detection of *Yersinia pestis* EV76, and the whole process could be completed within 5 min. More importantly, the assay displayed good repeatability and high reliability in various conditions, and could achieve a low detection limit of 1.2×10^4 CFU mL⁻¹ in real soil samples, showing a great potential for on-site pathogen detection and other POC applications. In another study, Jin et al. [159] used aptamers functionalized UCNPs as probes and developed a lateral flow aptamer assay integrated smartphone-based portable device for highly sensitive and precise detection of *Salmonella*. Detailedly, aptamers were conjugated with the UCNPs to specifically bind with the targets and produced fluorescence signal at the test line, while a smartphone-based device was used to read the results, making the detection process rapid and portable. After optimization, the assay was demonstrated to be able to provide rapid and sensitive detection of *Salmonella* with a wide range of 150–2000 CFU mL⁻¹ and a detection limit of 85 CFU mL⁻¹, holding a great potential to be used as a sensitive, specific, convenient and stable platform for POC detection of *Salmonella* in various fields.

Metal nanoclusters-based fluorescent biosensors. Metal NCs are a type of ultrasmall nanomaterials consisting of several to tens of atoms, which have attracted a great attention for using as a new type of fluorescent probes for biosensing applications [160–162]. Compared with other fluorescent nanomaterials, metal NCs exhibit outstanding physical and chemical properties, well biocompatibility and strong fluorescence emission [162–164]. Over the past years, a variety of metal NCs, including AuNCs [165,166], AgNCs [167,168], and so on, have been synthesized and employed for the POC detection of infectious diseases. For example, Ji et al. [169] synthesized a protein-AuNC-based fluorescence sensor array for rapid identification of bacteria, which was able to realize discrimination of six kinds of bacteria, including two kinds of drug-resistant bacteria. Moreover, the sensor array could achieve 100% classification accuracy by using two protein-AuNCs probes with outstanding advantages of easy synthesis and convenient to use, demonstrating its promise for facile diagnosis of bacterial infection in resource-poor regions [169]. In another study, a label-free fluorescence biosensor based on DNA template AgNCs fluorescent probe was developed for the detection of clinical significant DNA fragments from human immunodeficiency virus type 1 (HIV-1). The proposed fluorescence sensor exhibited excellent selectivity and high sensitivity against mismatched target DNA and could achieve a low detection limit of 2.9×10^{-10} mol L⁻¹ HIV-1 DNA [170].

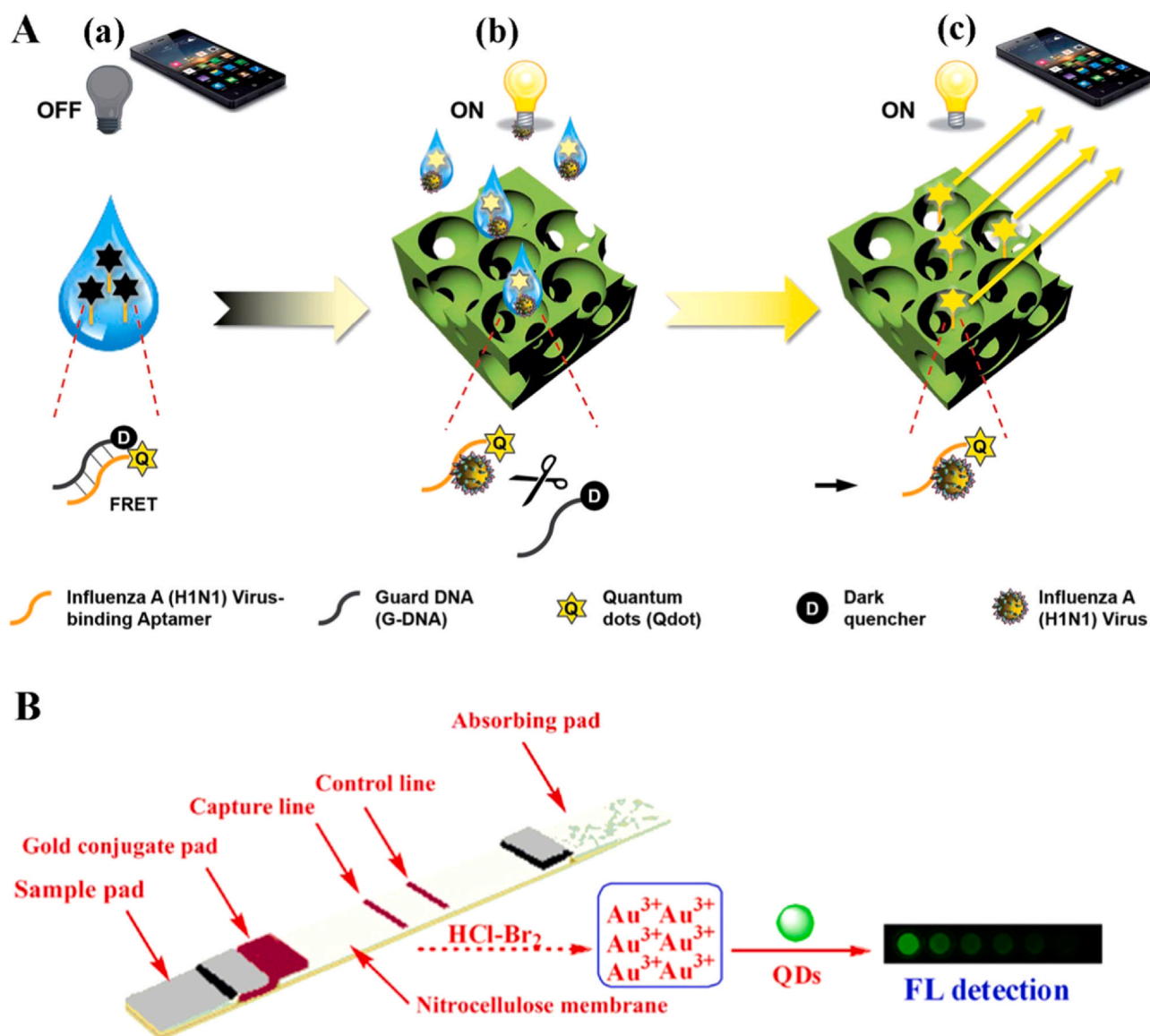


Fig. 2. (A) Schematic illustration of “Signal-on” fluorescence detection principle based on Qdot-aptamer conjugates and 3D nanoporous photonic crystal. (a) Loading the prepared quenched Qdot-aptamer conjugates (i.e., “OFF” state) for H1N1 virus detection in aerosol spray. (b) Capturing airborne H1N1 virus by aerosol spray and recovering Qdot signals by releasing G-DNA and preferred aptamer-virus binding (i.e., “ON” state). (c) Visualization of virus detection by enhanced Qdot signal owing to the emission light guide in 3D photonic crystals. Reproduced with permission from Ref. [171] Copyright 2018, the Royal Society of Chemistry. (B) Schematic illustration of “Signal-off” fluorescence immunoassay for the detection of AIV. Reproduced with permission from Ref. [173] Copyright 2012, Elsevier.

“Signal-on” fluorescence biosensors

In the past years, there have been a series of reports about the application of “signal-on” fluorescence biosensors for POC detection of infectious disease. For example, Lee et al. developed a fluorescent probe-based “signal-on” biosensor using the cooperation of quantum dot-aptamer beacons and light guides in a 3D photonic crystal for POC detection of influenza A (H1N1) virus [171]. Firstly, quantum dot-aptamer beacons and dark quencher-labeled guard DNA (G-DNA) were annealed for hybridization, which quenched the fluorescence signals of quantum dot to “OFF” state. In the presence of the H1N1 virus, the specific aptamers would preferentially bind to the virus and release G-DNA, resulting in recovery of fluorescence signal to “ON” state (Fig. 2A). The fluorescence intensity of the biosensor was quantitatively proportional to the concentration of the target H1N1 virus. The fluorescence biosensor was user-friendly, highly sensitive and selective towards H1N1 virus detection with an ultra-low detection limit of 0.138 ng mL^{-1} . Furthermore, the fluorescence biosensor could also

be adapted to a low cost portable home-made chamber for quantitative analysis of H1N1 virus with a smartphone camera [171]. While in another study, He et al. combined a powerful clustered regularly interspaced short palindromic repeats (CRISPR)-Cas assay with a “signal-on” fluorescence biosensor for rapid and POC detection of the nucleic acid of African Swine Fever Virus (ASFV) [172]. Specifically, this fluorescence detection system applied CRISPR-Cas12a programmed with a CRISPR RNA (crRNA) to specifically bind with ASFV target DNA to form activated Cas12a/crRNA/ASFV DNA complex, which then degraded the fluorescent single stranded DNA reporter probe that linked a fluorophore and a quencher, and thus generated fluorescence signal. Finally, the fluorescence signal was detected by a fluorescence-sensing unit aligned with an 80x disposable cartridge. This fluorescence biosensor could achieve rapid, accurate, and sensitive POC detection of ASFV DNA without nucleic acid amplification. The whole detection processes could be completed within 2 h and could achieve a low detection limit of 1 pM [172].

"Signal-off" fluorescence biosensors

As a paradigm, Li et al. integrated lateral flow test strip technique with a novel fluorescence immunoassay method for fast and ultra-sensitive POC detection of avian influenza virus (AIV), in which label-free and high luminescent quantum dots were applied as fluorescence signal output and gold ions released from gold nanoparticles were used as the fluorescence quencher [173]. In the presence of AIV, gold ions would be released from the gold nanoparticles and were captured in the test zone through the sandwich immunoreaction performed on the lateral flow test strip, which then quenched the fluorescence signals of quantum dots, resulting in "signal-off". Whereas, the fluorescence signals of quantum dots would recover in the absence of AIV (Fig. 2B). The proposed method could directly detect clinical samples without any pretreatment, and showed higher efficiency (90.0%), sensitivity (100.0%) and specificity (88.2%) against AIV compared with virus isolation (gold method), which was able to realize a linear range of 0.27–12 ng mL⁻¹ and a detection limit of 0.09 ng mL⁻¹, showing great promise for rapid, sensitive, and quantitative detection of AIV at POC [173]. While in another study, a rapid, low cost, and sensitive antibody-functionalized MoS₂-based "signal-off" fluorescence biosensor was developed for the detection of infectious bronchitis virus (IBV, an avian coronavirus), in which the FRET was utilized between the MoS₂ and fluorescence dye during the antibody-antigen interaction. The biosensor was performed on a low cost cotton thread-based microfluidic platform and could achieve a remarkable sensitivity of 0.023 ng mL⁻¹ for IBV standard solutions, which is very potential for POC detection [174].

Surface-enhanced Raman scattering (SERS)-based biosensors

Despite the outstanding attributes and extensive applications of the above mentioned fluorescence biosensors, they always have high background signals, limited sensitivity and inability to achieve multiplex detection [175]. SERS, which is a commonly used powerful sensing technique using enhanced inelastic light scattering by molecules adsorbed onto corrugated metal surfaces, can overcome those disadvantages of fluorescence biosensors due to its attributes of high sensitivity, well multiplexing capabilities, no photobleaching and low background [175–178]. More importantly, SERS-based biosensors can achieve single molecule detection by means of coinage-metal nanostructures [179]. Therefore, SERS has been extensively implemented for the development of biosensors in a wide variety of fields [180–183]. Meanwhile, SERS-based biosensors have also been widely investigated for the pathogen detection of infectious diseases at the POC, mainly including viruses and bacteria [175,184,185]. For example, Pang et al. developed a magnetically assisted SERS-based biosensor using aptamer and antibiotic molecules for dual-recognition of bacterial cells at the POC [186]. In this biosensor, aptamer-Fe₃O₄@Au magnetic nanoparticles were synthesized as magnetic and SERS activated substrate for specific bacteria enrichment, while vancomycin-SERS tags were prepared for the sensitive quantification of the pathogenic bacteria (Fig. 3A). The biosensor showed high specificity and sensitivity towards the target pathogenic bacteria with an ultra-low detection limit of 3 cells mL⁻¹ and a wide dynamic linear range from 10 to 10⁷ cells mL⁻¹, which is more sensitive than most of the current reported biosensors. Moreover, the whole process of the biosensor could be completed within 50 min and exhibited recoveries from 95.0% to 106.4% with relative standard derivation less than 5.3% in real samples [186]. Shi et al. designed a rapid SERS-based lateral flow immunoassay biosensor for the sensitive and quantitative POC detection of *Escherichia coli* (*E. coli*) O157:H7 in biological samples [187]. Firstly, novel gold-shell silica-core nanospheres (SiO₂/Au) with monodispersity, good stability, and excellent SERS activity were prepared and utilized as high performance tags. The SiO₂/Au SERS tags were then modified with two layers of Raman reporter molecules and monoclonal antibodies for

specifically and effectively binding with *E. coli* O157:H7 and forming sandwich immune complexes on the test lines. Under optimal conditions, this biosensor showed a detection limit of 50 cells mL⁻¹ in PBS solution and 100 cells mL⁻¹ in real samples, which are 2000 times more sensitive than colloidal Au-based lateral flow immunoassay strips [187]. Most recently, Lee et al. developed a PCR-coupled paper-based SERS biosensor composed of silver-nanowires (AgNWs) for rapid and sensitive determination of *Mycoplasma pneumoniae* DNA at the POC (Fig. 3B) [188]. In this system, a DNA intercalating molecule named EvaGreen dye was introduced to the low-cycled PCR product, whose difference in the intercalation of DNA structure could be quantified by Raman spectroscopy. The PCR-coupled SERS biosensor showed enhanced detection capability with a DNA detection limit of 3.12 pg μL⁻¹ with 10 cycles of target DNA amplification. Finally, the SERS substrate was prepared as a rapid kit containing a test line and negative and positive control lines, which could achieve specific discrimination of the target DNA and non-target DNA with statistically relevant after 10 cycles of amplification. Notably, the total assay time using the prototype SERS biosensor was only 30 min, including 20 min of thermal amplification and 10 min of SERS measurement, which is very promising to be used as a new detection method for the POC diagnostics of various bacteria and viruses [188].

Colorimetric biosensors

Colorimetric biosensors have long been investigated for POC diagnostic applications due to their superiorities such as easy preparation, easy readout, low cost, and portability [189–193]. Colorimetric detection can be achieved by the oxidation of peroxidase or peroxidase-like nanomaterials, aggregation of nanomaterials, or addition of dye indicators [193–196]. In the past years, peroxidase-like nanomaterials and aggregation of nanomaterials have been widely applied for colorimetric biosensor establishment such as gold nanoparticles (Au NPs), platinum nanoparticles, silver nanoparticles, magnetic nanoparticles (MNPs), and so on [196–200], among which Au NPs have attracted increasing interests for developing colorimetric POC diagnostic platforms for on-site detection of infectious diseases due to their simple preparation, easy surface modification, and interparticle surface plasmon resonance properties that can cause fast significant color changes through the nanoparticle aggregations [201–204].

As a paradigm, Zheng et al. developed a novel colorimetric biosensor based on AuNPs aggregation and smart phone imaging for the POC detection of *E. coli* O157:H7 (Fig. 4A) [205]. Specifically, MNPs modified with the capture antibodies against *E. coli* O157:H7, polystyrene microspheres (PSs) modified with the detection antibodies against *E. coli* O157:H7 and catalases were mixed with the sample containing the target *E. coli* O157:H7 cells in the first mixing channel of the microfluidic chip to form MNP-bacteria-PS complexes, which were then captured in the separation chamber by an external magnetic field. Then, the catalysate from the catalytic reaction of injected hydrogen peroxide by the catalases on the MNP-bacteria-PS complexes were mixed with the AuNPs and crosslinking agents in the second mixing channel, and incubated in the detection chamber. Finally, the aggregation of the AuNPs was triggered through the crosslinking agents, resulting in the color changing from blue to red, which was detected by a smartphone imaging APP to determine the amount of bacteria. The proposed biosensor exhibited rapid, high specific and sensitive detection of *E. coli* O157:H7 in chicken samples within 1 h, and the detection limit was as low as 50 CFU mL⁻¹ under optimal conditions, which owned several merits such as simple device for data processing, high integration for sample and reagent handling, low cost for microfluidic chip fabrication, and small size for POC detection applications [205]. However, the immune reaction efficiency was not very high with its detection limit and detection

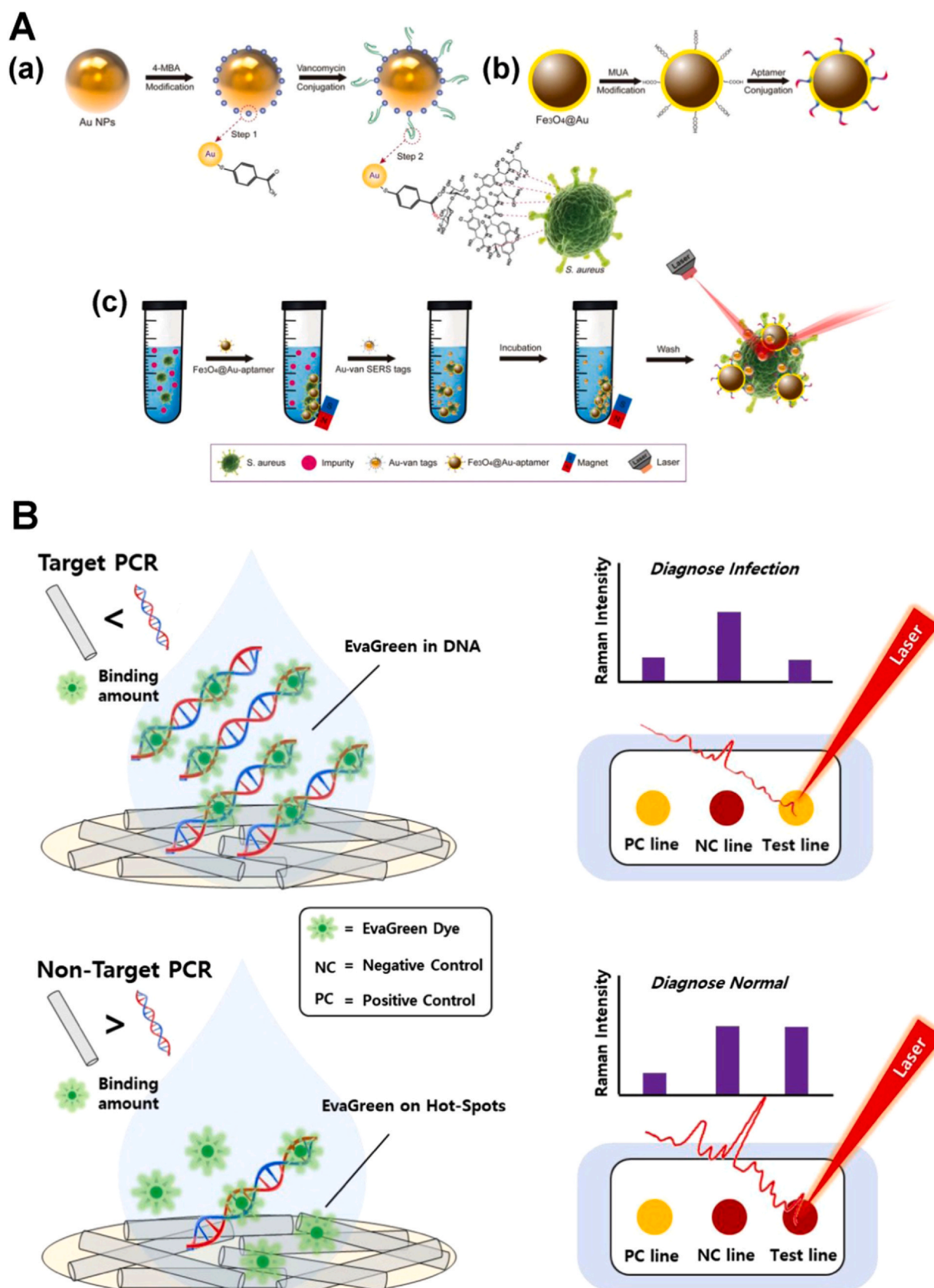


Fig. 3. (A) Schematic illustration of (a) the synthesis of Au-Van SERS tags, (b) the synthesis of aptamer-modified $\text{Fe}_3\text{O}_4/\text{Au}$ MNPs, and (c) the operating procedure for *S. aureus* detection via the dual-recognition SERS biosensor. Reproduced with permission from Ref. [186] Copyright 2019, Elsevier. (B) Schematic illustrations of diagnostic process for respiratory bacterial DNA using paper-based SERS substrate. In the presence of target, EvaGreen dye intercalation is dominant in DNA structure while in the presence of non-target or no-target, majority of EvaGreen is adhered on the hot-spots area of the AgNWs. The diagnosis can be made by comparing the Raman intensity between the test line and the control lines. Reproduced with permission from Ref. [188] Copyright 2021, Elsevier.

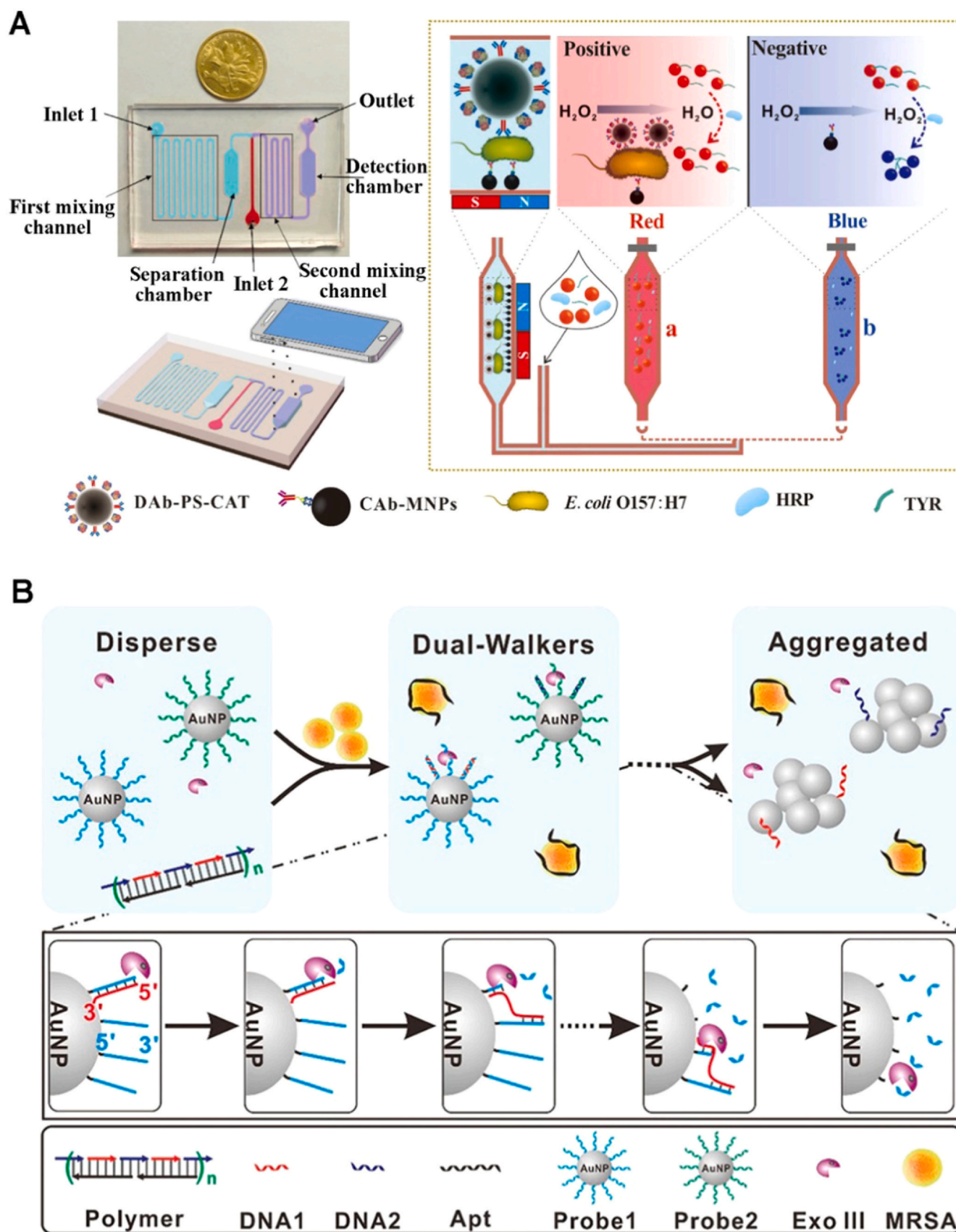


Fig. 4. (A) The principle of the proposed colorimetric biosensor for rapid detection of *E. coli* O157:H7 based on gold nanoparticle aggregation and smart phone imaging. Reproduced with permission from Ref. [205] Copyright 2019, Elsevier. (B) Schematic illustration of stochastic DNA dual-walkers for colorimetric detection of bacteria. Reproduced with permission from Ref. [206] Copyright 2020, American Chemical Society.

time needed to be further improved. To address this problem, a rapid, sensitive, and reliable stochastic DNA dual-walker-based colorimetric biosensor was developed for POC detection of bacteria (Fig. 4B) [206]. This colorimetric biosensor was composed of two kinds of well-dispersed thiol-tagged oligonucleotide-functionalized AuNPs probes and an aptamer specifically binding to the target bacteria. In the presence of the target bacteria, the aptamer would preferably bind to the target bacteria and concomitantly release two kinds of walking strands. Then, the released walking strands started multiple cycles of hybridization with the thiol-tagged oligonucleotides and allowed autonomous walk on the AuNP-based 3D track as propelled by Exo III through consumption of the thiol-tagged oligonucleotides, which eventually resulted in destabilized aggregation of AuNP-based probes and fast color change. Due to the operation of DNA dual-walkers in one system and multiple walking strands concurrently released from one polymer, the enzyme digestion reaction and reaction kinetics were significantly improved, thus shortening the response time and speeding the analytical procedure. The colorimetric biosensor was demonstrated to be very sensitive and specific for bacteria detection, which could be finished within 15 min with a linear response ranging from 100 to 1×10^5 CFU mL⁻¹ and a much lower detection limit of 1 CFU mL⁻¹. All these merits of this colorimetric biosensor such as rapid, sensitive, specific, and reliable analysis made it very promising for POC detection of bacteria [206].

Chemiluminescence biosensors

Chemiluminescence biosensors are very common sensors for disease diagnosis due to their high sensitivity, high signal-to-noise ratio, wide dynamic range, and simpler reader instruments, which have long been widely studied for POC diagnostic adaptations [207–213]. As early as in 2002, an accurate and sensitive chemiluminescence POC diagnostics, called the ZstatFlu®-II test, for the detection of influenza virus infections was developed, which has already been commercialized [214,215]. Besides, other commercialized chemiluminescence biosensors based POC devices, such as FastPack® IP system, PATHFAST®, OPTIGEN® systems, and so on, have also been developed [212,216,217]. However, those devices did not meet the “ASSURED” standard absolutely, which still required complicated operation and complex detector devices. Besides, multiplex detection has been another important challenge for POC detection of infectious diseases, especially for the targeted detection of emerging infectious diseases. Therefore, how to simplify the operations of chemiluminescence detection and signal acquisition, and increase detection flux has been the top priority in the development of POC devices based on chemiluminescence detection. In our previous work, we had established various chemiluminescence biosensors for the detection of infectious diseases, with expectations for advanced POC diagnostic applications [218–228]. As a paradigm, by combining magnetic separation technology for nucleic acid purification with a chemiluminescence technique for post-amplification detection, a DNA hybridization based chemiluminescence biosensor was developed for simultaneously multiple detection of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) (Fig. 5) [228]. First, the viral (HBV, HCV, and HIV) nucleic acids were extracted by silica modified MNPs, followed by one step multiplex reverse transcription PCR (RT-PCR) for amplification. Then, different amino modified capture probes for HBV, HCV, and HIV were attached to carboxyl coated MNPs, and incubated with biotin labeled RT-PCR products in different tubes for capturing HBV, HCV or HIV sequences, respectively. Finally, the chemiluminescence signal was recorded after the addition of streptavidin-modified alkaline phosphatase and substrate. The chemiluminescence biosensor was very specific, efficient and sensitive with a detection limit of 5×10^{-5} ng mL⁻¹ in serum samples in the monoplex detection of HBV, HCV,

and HIV, and low detection limits of 5×10^{-2} ng mL⁻¹ for HBV, 5×10^{-2} ng mL⁻¹ for HCV, and 50 ng mL⁻¹ for HIV in serum samples in the multiplex detection assay. This method could be modified into a high throughput automated set up for the simultaneous detection of multiple infections, which would dramatically decrease the cost of infectious diseases detection and showed a great potential for POC diagnostic applications [228].

Surface plasmon resonance (SPR)-based biosensors

SPR, which measures the changes in the refractive index caused by molecular interactions on the metal surface via a surface plasmon wave, has become one of the most powerful detection methods for the POC diagnostic applications due to its merits of real-time, label-free, high cost-effective, noninvasive nature, excellent reutilization performance and outstanding reproducibility [229–233]. And as a result, various SPR-based biosensors have been developed for POC detection of infectious diseases [82,168,234–238], among which some have already been adapted into POC devices [239–241]. However, the liquid sample volumes and power consumption of a SPR-based biosensor are still bulky, and the sensitivity and resolution of those SPR-based biosensors or devices need to be further improved, which have been the main bottlenecks in the fabrication of SPR-based biosensors for biomedical applications. To circumvent these drawbacks, nanomaterials, microfluidic devices, and compact as well as power-free pump systems have been attempted to integrate SPR-based biosensor systems [230,241–247]. In one example, an innovative SPR-based biosensor was developed for highly sensitive detection of HIV-related DNA based on entropy-driven strand displacement reactions and double-layer DNA tetrahedrons for SPR signal enhancement (Fig. 6A). In this biosensor system, hairpin probes were firstly immobilized on the surface of the SPR-based sensor chip in advance to bind with the target DNA via the terminal toehold region of three-stranded complexes, which then initiated the toehold-mediated strand displacement reactions and produced plentiful double stranded complex by the reuse of the target DNA. Subsequently, the generated double-stranded complex specifically hybridized with hairpin probes and captured double-layer DNA tetrahedrons nanostructure, forming three-decker composites on SPR-based sensor chip, which eventually amplified the SPR response signal significantly. The proposed SPR-based biosensor could detect HIV-related DNA sensitively and specifically with a wide linear range from 1 pM to 150 nM and a detection limit of 48 fM. More importantly, compared with the conventional methods and other sensing strategies, this SPR-based biosensor system have several advantages such as faster, simpler, lower-cost, more practical, and better stability, which is very promising for the POC detection of HIV infections [248]. In another example, a LSPR biosensor was fabricated for high sensitive detection and identification of dengue virus serotypes with CdSeTeS QDs and AuNPs regulation (Fig. 6B). Specifically, four different CdSeTeS QDs-conjugated hairpin nanoprobe were designed to exactly complement with the target analytes of four different DENV serotypes. Meanwhile, thiolated poly-C functionalized AuNPs were synthesized for complementary binding with the free poly-G region of the hairpin nanoprobe. In the presence of the complementary RNA of DENV, the hairpin structure of the nanoprobe would be opened due to the better hybridization of the nanoprobe ssDNA and complementary RNA of DENV in its loop region, and poly-C-functionalized AuNPs would then complementary bind with the poly-G region of the nanoprobe, resulting in the LSPR enhancement (at around 14 nm) or quenching (at around 3 nm) effect on the fluorescence of the QDs, which was determined by the distance between the QDs and the AuNPs. After optimization, the SPR-based biosensor could achieve the detection of standard dilutions of the target virus DNA from 1×10^{-9} to 1×10^{-4} μM with a detection limit of femtomolar range, demonstrating a great potential

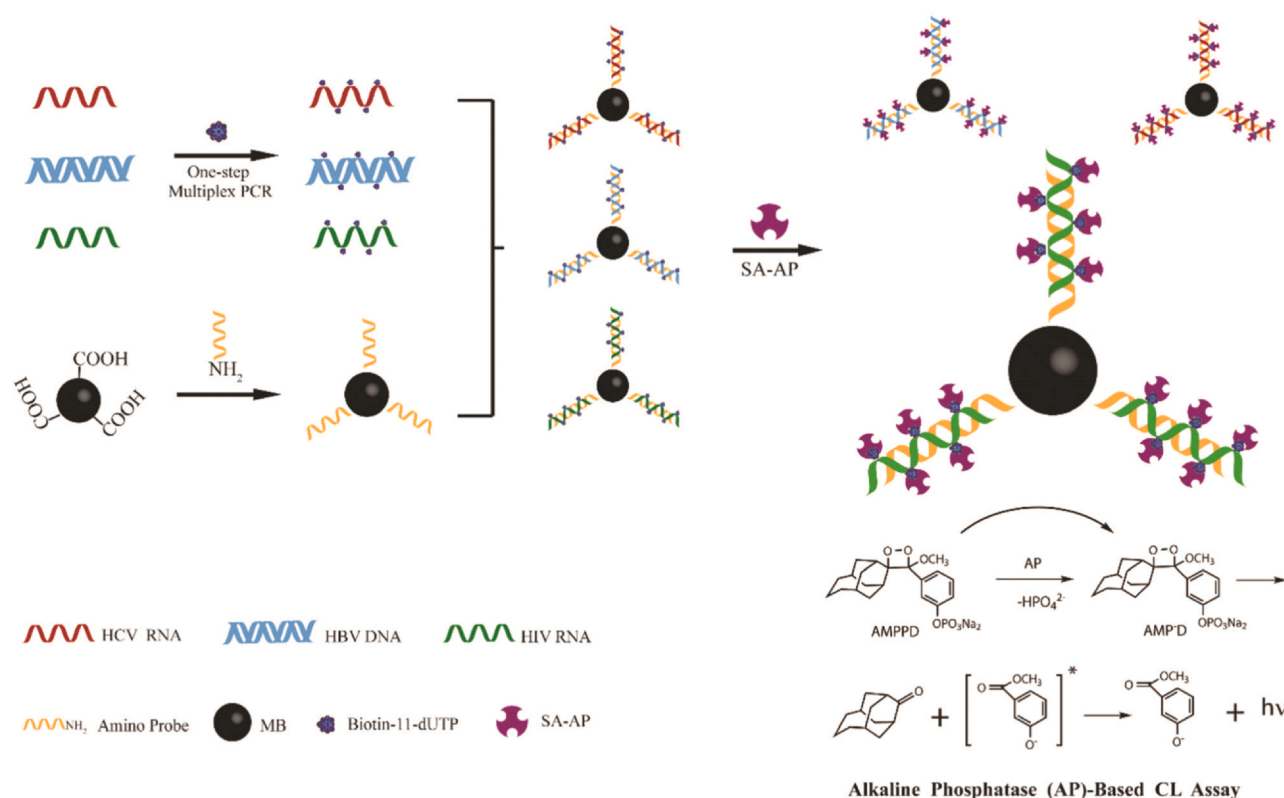


Fig. 5. Schematic illustration of one step multiplex RT-PCR and chemiluminescence detection of multiple viruses. Reproduced with permission from Ref. [228] Copyright 2017, the Royal Society of Chemistry.

for POC detection of dengue virus [249]. Moreover, a portable, multiplex, inexpensive microfluidic-integrated SPR platform was developed for rapidly POC detection and quantification of *E. coli* (Fig. 6C). Firstly, the disposable microfluidic chips with gold coated surfaces were functionalized with antibodies for efficient, selective and specific capture of *E. coli*. Then, the capture event happened in the microchannel induced a change in the local refractive index, which produced a signature on the reflected light and was captured by the SPR-based sensor. The platform presented reliable capture and detection of *E. coli* at concentrations ranging from 1×10^5 to 3.2×10^7 CFU mL⁻¹ in phosphate buffered saline and peritoneal dialysis fluid [250]. Furthermore, Trzaskowski et al. developed a portable SPR-based device for rapid detection of tuberculosis bacteria in sputum and cultures without bacteria lysis and purification [251]. Detailedly, miniature SPR sensor Spreeta 2000 (S2k) chips with gold surfaces were functionalized with anti-MTB secretory protein (Ag85) for specific Ag85 capturing, which was then connected to a SensiQ Discovery two channel manual SPR platform or self-built prototype SPR device. The device was able to detect MTB Ag85 in concentration of 10 ng mL⁻¹ and tuberculosis bacteria cultures in concentration of 1×10^4 CFU mL⁻¹ with no significant interfering response from two other bacteria species [251].

Magnetic biosensors

Magnetic biosensors, which employ the magnetic phenomena of magnetic materials to achieve sensitive detections of the analytes, have received surging interests for POC detection applications in the past decades [53,123,252]. Compared with other biosensors, magnetic biosensors have a couple of advantages. Firstly, magnetic biosensors are of low cost and improved detection efficiency due to the elimination of expensive optics components and decreased sample preparation time by utilizing magnetic field [253–255]. Besides,

magnetic biosensors exhibit high specificity, sensitivity and high signal-to-noise ratio due to the negligible magnetic background signal of biological samples [256–258]. After several decades of development, there have been several classes of magnetic biosensors developed, such as giant magnetoresistance (GMR) biosensors, magnetic tunnel junction biosensors, magnetic particle spectroscopy (MPS) biosensors, and the nuclear magnetic resonance biosensors and so on [252,259]. Among them, GMR biosensors and MPS biosensors have been widely investigated for POC detection of infectious diseases in the past years.

GMR effect, which was discovered in 1980s, usually happens in a multi-layer structure in which ferromagnetic (FM) and non-magnetic (NM) thin films are deposited alternately [260–262]. However, subsequently studies demonstrated that GMR effect could also happen in inhomogeneous media, granular films for example, which expanded the biomedical applications of GMR biosensors [263,264]. Moreover, GMR effect can sense very low magnetic fields, making it very attractive for developing magnetic biosensors for highly sensitive POC detection of infectious diseases. For example, Wang et al. established a portable handheld GMR biosensor named Z-Lab for the POC detection of influenza A virus (IAV) (Fig. 7A) [265]. This GMR biosensor displayed high specificity and sensitivity towards IAV nucleoprotein and purified H3N2v with quantitative results in less than 10 min and low detection limits of 15 ng mL⁻¹ and 6.25×10^{-3} ng mL⁻¹ for IAV nucleoprotein and purified H3N2v, respectively. However, the detection processes of Z-Lab involved multiple washing and incubating steps, which were time-consuming and tedious, and thus the detection efficiency was limited. To solve this problem, Wang et al. further developed a wash-free magnetic bioassay to integrate with the Z-Lab platform for POC detection of both purified IAV nucleoprotein and IAV in nasal swab samples (Fig. 7B) [266]. The wash-free magnetic bioassay greatly simplified the testing process and significantly improved the detection

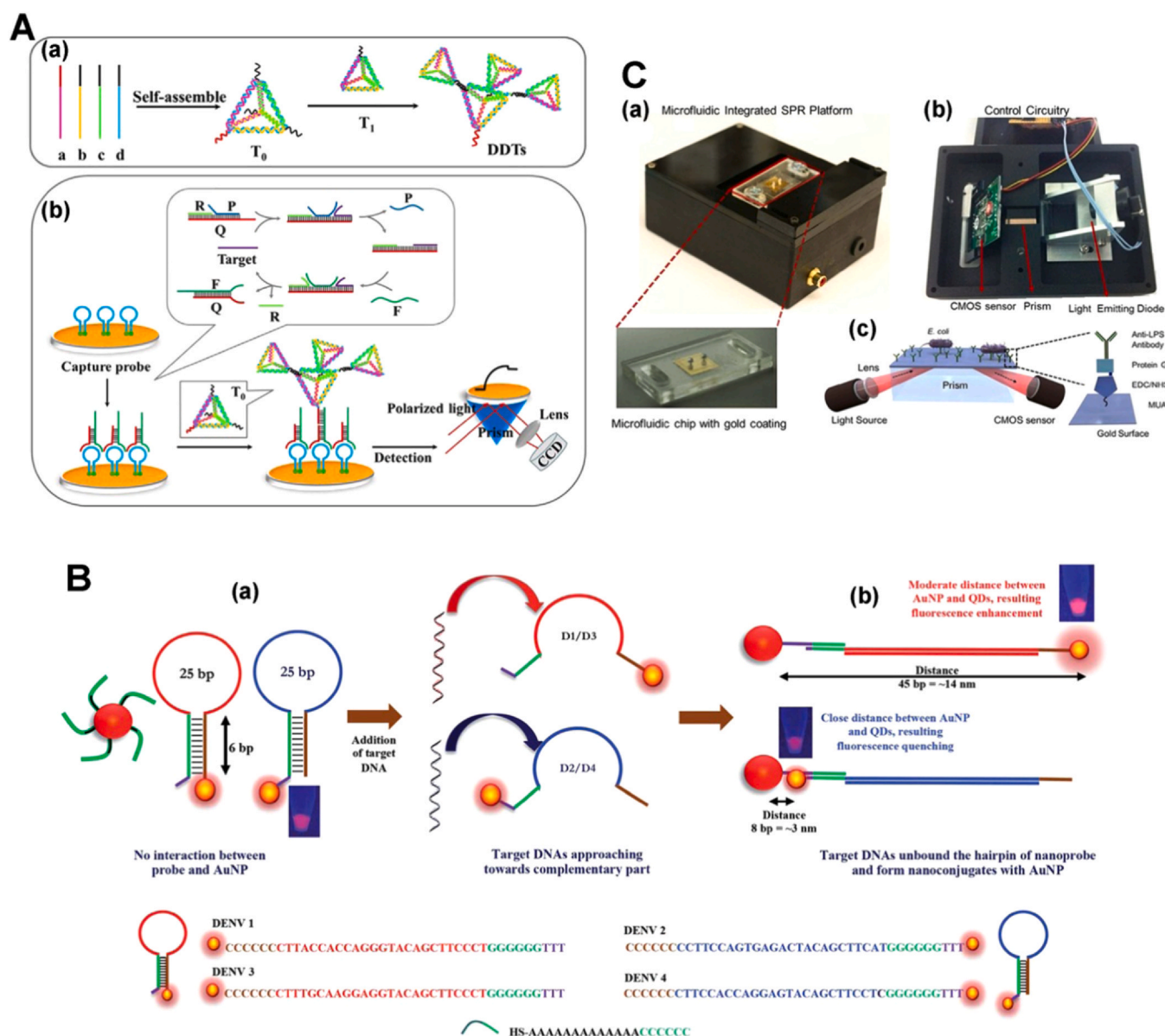
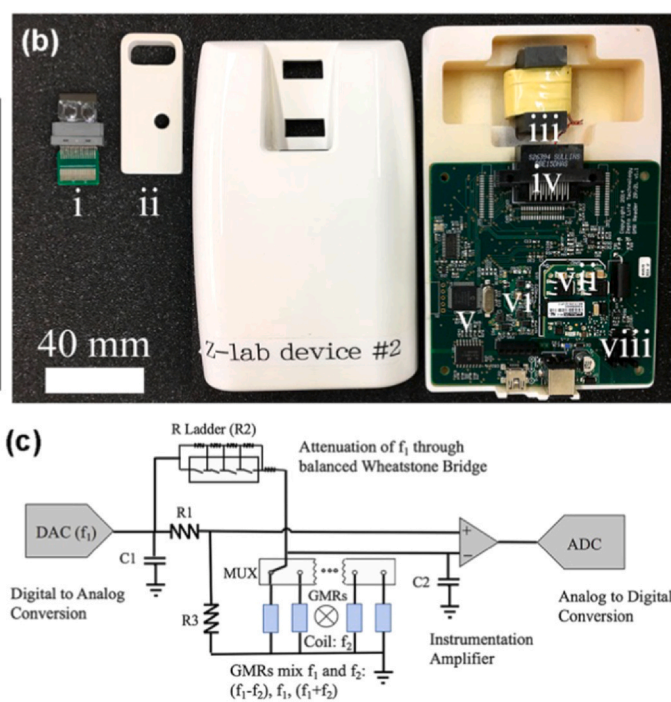
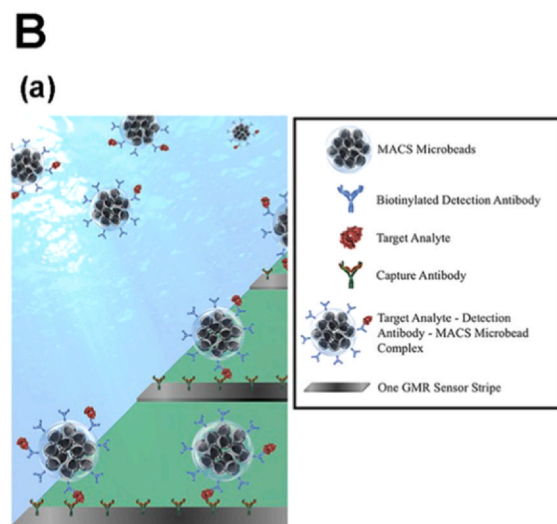
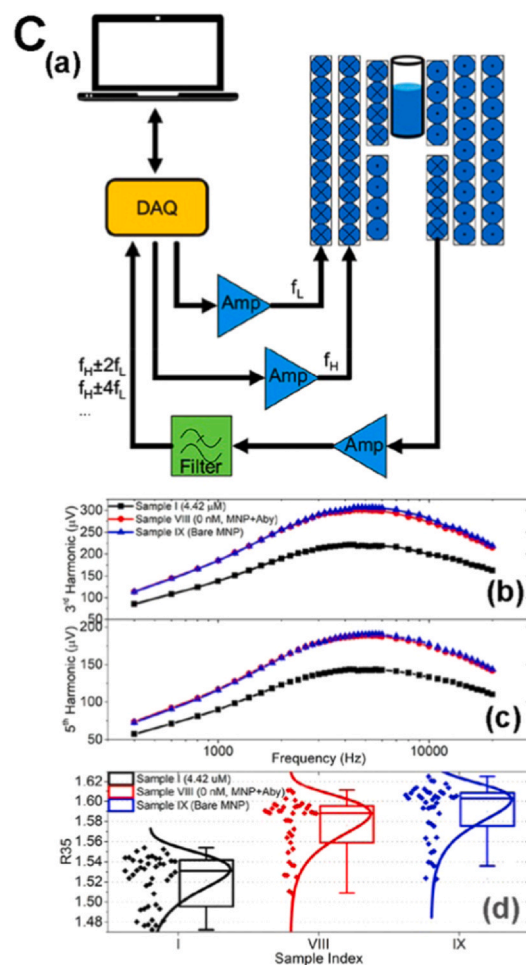
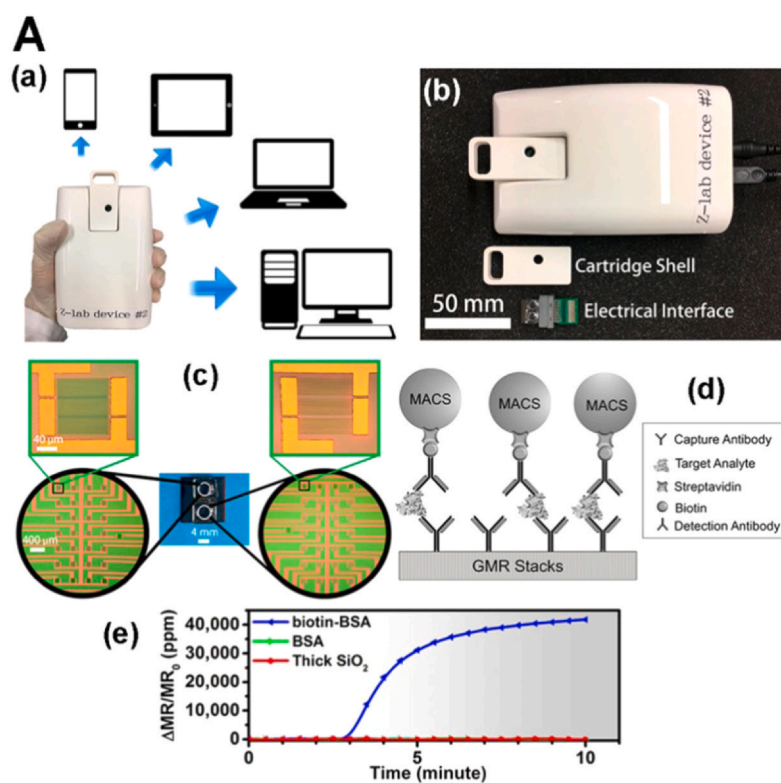


Fig. 6. (A) Schematic representation of SPR biosensor for POC detection of HIV. (a) Schematic illustration of the preparation of DDTs nanostructure; (b) Schematic representation of SPR biosensing strategy for HIV-related DNA detection based on ESDRs and DDTs nanostructure. Reproduced with permission from Ref. [248] Copyright 2018, Elsevier. (B) Schematic representation of the detection mechanism of dengue virus serotypes by AuNPs and hairpin ssDNA-CdSeTeS quantum dots. (a) Probe design for DProbe 1 and 2 and functionalized AuNPs. (b) Identification and fluorometric enhancement for dengue virus 1/3 serotype and quenching for dengue virus 2/4 serotype depending on the distance between the nanocomposite of AuNP-dsDNA-CdSeTeS. Reproduced with permission from Ref. [249] Copyright 2020, the Royal Society of Chemistry. (C) Schematic of Portable plasmonic platform for pathogen detection and quantification. Reproduced with permission from Ref. [250] Copyright 2015, Springer Nature.

efficiency, which was able to achieve high sensitive detection of purified IAV nucleoprotein and IAV with limits of detection of 0.017 ng mL^{-1} for IAV nucleoprotein and $1.25 \times 10^{-2} \text{ ng mL}^{-1}$ for IAV-spiked nasal swab samples. Although GMR biosensors can achieve POC detection of infectious diseases, the fabrication of GMR biosensors is very complex and the test is expensive. The further development of GMR biosensors may focus on their simplification and cost reduction.

MPS is a novel flourishingly researched detection method closely related to magnetic particle imaging, which can also be interpreted as a zero-dimensional magnetic particle imaging scanner that conducts spectroscopic studies on superparamagnetic iron oxide nanoparticles (SPIONs) [267,268]. In MPS, SPIONs are periodically driven into magnetically saturated regions in a sinusoidal magnetic field with sufficiently large amplitude and produce dynamic magnetic responses, which contain unique higher odd harmonics. Those

harmonics are then obtained and extracted by filtering and fast Fourier transform, which contain important information about the SPIONs solution for analysis [269,270]. Over the past years, MPS has been extensively explored as a portable, low cost and highly sensitive detection method for various biomedical detection applications, including POC diagnostics of infectious diseases. As a paradigm, a MPS biosensor was investigated for the POC detection of IAV subtype H1N1 nucleoprotein [271]. In this biosensing system, the oscillating harmonics of MNPs were measured by MPS, which was a metric of the freedom of rotational process that indicated the bound states of MNPs, and could be readily collected from nanogram quantities of MNPs within 10 s (Fig. 7C). In the presence of H1N1 nucleoprotein, IgG polyclonal antibodies anchored MNPs would specifically bind with H1N1 nucleoprotein molecules and trigger cross-linking between MNPs and H1N1 nucleoprotein, forming MNP self-assemblies. The MPS biosensor was finally demonstrated to be able to achieve



(continued on next page)

Fig. 7. (A) Schematic of Z-Lab diagnosis platform and magnetic sandwich assay mechanism. (a) Real-time data can be collected and transmitted to a smartphone, a tablet, a laptop and a desktop computer. (b) The Z-Lab platform consists of a plastic cartridge, an electrical interface connecting the electrodes from GMR chip to the circuit board, and a handheld device. (c) Schematic of the GMR chip. (d) Schematic of the magnetic sandwich assay. (e) Real-time binding curves of targeted binding. Reproduced with permission from Ref. [265] Copyright 2017, American Chemical Society. (B) Schematic of a wash-free magnetic bioassay based handheld GMR biosensors for POC detection (a) One-step wash-free magnetic bioassay based on a sandwich assay structure. (b) Photograph of one Z-Lab diagnosis platform. (i) disposable plastic cartridge; (ii) cartridge shell; (iii) Helmholtz coil with ferrite core; (iv) card edge connector; (v) microcontroller; (vi) UART to Bluetooth and USB; (vii) power supply; (viii) current source Helmholtz coil driver. (c) The circuit schematic of Z-Lab. Reproduced with permission from Ref. [266] Copyright 2019, Frontiers. (C) Schematic of the MPS biosensor for POC diagnostics (a) Schematic view of MPS system setups. (b) and (c) are the third and the fifth harmonics along varying driving field frequencies (only samples I, VIII, and IX are plotted) collected by the MPS system. (d) Boxplots of the harmonic ratios (R35) collected from samples I, VIII, and IX. Reproduced with permission from Ref. [271] Copyright 2020, American Chemical Society.

Table 1

Comparisons of the biosensors for POC diagnostics of infectious diseases.

Methods	Pros	Cons	Refs.
Electrochemical biosensors	High sensitivity, fast response and low cost	Weak stability and susceptibility to interference	[272–274]
Fluorescence biosensors	Rapid response, flexibility and experimental simplicity	High fluorescence background	[275–277]
SERS-based biosensors	High sensitivity, well multiplexing capabilities, no photobleaching and low background	Limited field of view	[177,178,278]
Colorimetric biosensors	Simplicity and visualized detection	Inability to achieve quantitative detection and limited sensitivity	[279–281]
Chemiluminescence biosensors	High sensitivity, wide linear dynamic ranges, simple instrument	Time-consuming, and enzyme-dependent	[87,282–284]
SPR-based biosensors	Label-free and real-time detection	Bulky equipment and expensive	[285,286]
Magnetic biosensors	low cost, and high signal-to-noise ratio detection	shortage of miniaturized magnetic readout systems	[123,258,259]

rapid, sensitive, and wash-free detection of H1N1 nucleoprotein and the detection limit was as low as 2.49 ng mL^{-1} , which could be further developed into a portable MPS-based device for the POC detection of H1N1 virus [271].

Despite the well performances of the above summarized biosensors, there are still many shortcomings of them. The detailed comparisons among them are illustrated in Table 1. Among the above biosensors, electrochemical biosensors are among the most widely investigated methods and show the most potential for POC diagnostic adaptation due to their high sensitivity, fast response and low cost. However, an electrochemical biosensor always displays weak stability and is susceptible to interference from environment [272–274]. Fluorescence biosensors are widely applied for POC detection because of their merits of rapid response and high sensitivity, flexibility and experimental simplicity. However, they are limited by high fluorescence background and limited fluorescence lifetime [275–277]. SERS-based biosensors can achieve single molecule detection of targets with high sensitivity, well multiplexing capabilities, no photobleaching and low background, the SERS-based biosensors still displayed limited field of view [177,178,278]. Colorimetric biosensors show the advantages of simplicity and detection by naked eyes without expensive instruments, which is the pioneered and most successful method for POC diagnostic applications, while it is difficult to achieve quantitative detection and the sensitivity is limited [279–281]. For a chemiluminescent biosensor, it has advantages of high sensitivity, wide linear dynamic ranges, simple instrumentation and has been widely employed in clinical detection, but it is limited by tedious washing steps, time-consuming, and is enzyme-dependent [87,282–284]. SPR-based biosensors exhibit extreme sensitivity, ability of detection in complex matrices, label-free and real-time detection, distinctive fingerprint capability and ability to achieve high-throughput analysis. However, the SPR equipment is too bulky and expensive [285,286]. With the booming development of nanotechnology and microfluidics in recent years, SPR-based biosensors have been attempted to be integrated with various POC devices to provide accurate, rapid, low cost and highly sensitive POC detection. Finally, a magnetic biosensor is able to achieve low cost, high-efficient and high signal-to-noise ratio detection without expensive optics components, there is a shortage of miniaturized magnetic signal readout systems. Thus, fabrication of miniaturized magnetic signal readout systems would contribute greatly to the development of portable devices to

integrate with magnetic biosensors for POC detection [123,258,259]. Notwithstanding the merits and shortcomings of those detection methods, how to simplify those methods and adapt them into POC diagnostics for infectious diseases with increased sensitivity, specificity, detection speed and easy-to-use remains a great challenge and the industry is still in its infancy. The fast development of nanotechnology, materials science, microelectronic techniques and microfluidic systems has made the integration of the above detection methods into portable POC devices to achieve specific and low cost POC detection with low sample volumes, increased speed and sensitivity, and ability of multiplex detection possible.

POC devices for infectious disease detection

Since the first POC device GeneXpert endorsed by the WHO in 2010 for the initial detection of HIV-associated tuberculosis, which integrated sample preparation, nucleic acid amplification, and detection into a single device that was able to complete nucleic acid detection with 2 h [287], there have been a series of POC devices fabricated for POC diagnostics of infectious diseases, such as the LIAT analyzer (IQum) for HIV detection [288], Truelab Uno® for malaria detection [289], GenePoC for Influenza A and B virus detection [290], and so on. Recently, due to the frequently spread of infectious diseases, especially at the circumstance of the COVID-19 outbreak, a research heat wave has been set off in the development of POC devices. As a result, there have been a series of POC devices developed for the detection of SARS-CoV-2 [291–293]. Part of current commercial available POC devices for infectious diseases can be found in Table 2 [48,294–297]. However, most of those established POC devices are just simple transplantation of conventional steps and most of them are not highly integrated and automated despite their high-cost and bulky instruments, there is still a huge space to develop portable, highly-integrated, rapid, sensitive, low cost, and fully-automated POC devices and the POC diagnostic industry is still in its true infancy stage. There are various problems remaining unaddressed, which call for more novel design and fabrication efforts to contribute to the development of POC devices. The most important challenge in developing such practicable POC devices is how to seamlessly integrate all the processes of detection methods into a complete automated instrument and achieve rapid, sensitive, and sample-to-result detection. Recent booming development of microfluidics, nanotechnology and MEMS technologies has greatly

Table 2
Current commercial POC devices for infectious diseases.

Devices	Types	Manufacturers	Pathogens	Time	Refs.
GeneXpert	Miniaturized PCR device	Cepheid	Tuberculosis and HIV	120 min	[287]
LIAT analyzer	Miniaturized PCR device	IQuum	HIV	60 min	[288]
FilmArray	Miniaturized PCR device	BioFire Diagnostics	Respiratory viruses and bacteria	60 min	[298]
mL FluAB-RSV assay	Miniaturized PCR device	Enigma	Influenza A and B viruses	95 min	[299]
ALERE i	INAA device	Alere	Influenza A and B viruses	15 min	[300]
Revogene®	LOAD device	Meridian Bioscience	Respiratory viruses and bacteria	70 min	[301]
Simplexa™	LOAD device	Focus Diagnostics	Influenza A and B viruses, respiratory syncytial virus	150 min	[302]
GenePoC	Miniaturized PCR device	GenePoC	Influenza A and B viruses	70 min	[290]
Truelab Uno®	Miniaturized PCR device	Bigtec Labs	<i>Plasmodium falciparum</i> and <i>Plasmodium vivax</i>	60 min	[289]
Elecsys® Anti-SARS-CoV-2	Lateral flow device	Roche	SARS-CoV-2	12 min	[291]
COVID-19 IgG/IgM Rapid Test Cassette	Lateral flow device	Zhejiang Orient Gene Biotech	SARS-CoV-2	10 min	[292]
COVID-19 IgM/IgG™	Lateral flow device	Truvian Sciences	SARS-CoV-2	10 min	[293]
Abbott Panbio™ COVID-19 IgG/IgM Rapid Test	Lateral flow device	Abbott Diagnostics	SARS-CoV-2	10–20 min	[303]
Alere™ Malaria Ag P.f RDT	Lateral flow device	Abbott Diagnostics	<i>Plasmodium falciparum</i>	15 min	[304]
SD BIOLINE	Lateral flow device	Abbott Diagnostics	<i>Plasmodium vivax</i>	15 min	[305]
RapidChek Select™	Lateral flow device	Romer Labs	<i>Salmonella</i>	22–30 h	[306]
Reveal® Salmonella 2.0	Lateral flow device	Reveal	<i>Salmonella</i>	24 h	[307]
Tubex® TF	Lateral flow device	IDL Biotech	<i>Salmonella</i>	22 h	[308]
Atlas® Salmonella SEN Detection Assay	Miniaturized PCR device	Roka Bioscience	<i>Salmonella</i>	24 h	[309]

facilitated the development of POC devices. Thus, a series of POC devices have been designed and fabricated for the detection of infectious diseases, including LOC devices, LOAD devices, μ PADs, lateral flow devices, miniaturized PCR devices, INAA devices, and so on.

In addition, thanks to the rapid development of hardware and software, smartphone has actually been a handheld miniature computer, which owns ubiquitous availability, extensive connectivity and appealing price. By using a smartphone as the primary user interface for detection, the total cost and overall time of detection are dramatically decreased owing to the elimination of centralized laboratory, specialized equipment and complex operation, making POC diagnostics more accessible and user-friendly [310–312]. Therefore, smartphone is always explored either as a detector or an instrumental interface to couple with other POC devices for the detection of various diseases due to its portability, wide accessibility, low cost and easily operation [313–318]. Herein, we will summarize the design and fabrication of various POC devices toward detections of various infectious diseases, which would contribute significantly to the applications of POC devices for urgent prevention and control of emerging public health events like COVID-19.

Lab-on-a-chip (LOC) devices

LOC devices are highly integrated and automated manipulation microfluidic devices that can rapidly conduct sample inlet and preparation, reagent manipulation, detection as well as result analysis in a unique platform, which have significantly facilitated the transformation processes of POC devices towards miniaturization, portability, integration, and automation of multiple assay functions into a single instrument [319–323]. Compared with conventional detection methods, highly integrated LOC devices exhibited several considerable merits such as rapid detection, ease of multiplexing and integration, small reagent volume consumption, cost effectiveness, high accuracy, and high portability [321,322,324,325]. As a result, LOC devices have attracted a good many attentions for POC diagnostic applications, especially for on-site detection of infectious diseases in resource-poor regions. Herein, fabrication and application of LOC devices for various infectious diseases detection were exhaustively discussed, including infections caused by parasites, bacteria, and viruses.

Parasite detection

As a typical and severe infectious disease caused by *Plasmodium* parasites continuously multiplying in human red blood cells, malaria has long been one of the severe worldwide health threats and caused hundreds of thousands of deaths every year [326–329]. However, the fast and accurate detection techniques for malaria are in quite shortage, requiring rapid, sensitive and accurate detection of *Plasmodium* parasites to improve the diagnosis and effective treatment of malaria. Under this background, on-site detection instruments such as POC devices are in greatly and urgent need for malaria diagnosis especially in resource-poor regions, where malaria outbreaks are most severe [328]. In recent years, LOC devices have attracted significant attention to be applied for POC detection of malaria caused by *Plasmodium* parasites. As a paradigm, Kadimisetty et al. developed a simple, inexpensive, disposable, fully 3D-printed microfluidic reactor array for rapid POC detection of *Plasmodium falciparum* gDNA (Fig. 8A) [330]. The 3D-printed microfluidic reactor integrated the extraction, concentration and isothermal amplification of nucleic acids in a variety of body fluids, yielding a multi-functional diagnostic platform, which was able to achieve both end-point colorimetric qualitative detection and real-time fluorescence quantitative detection. After being evaluated, the microfluidic reactor could detect *Plasmodium falciparum* in plasma samples by loop-mediated amplification (LAMP) within 50 min, and a low detection limit of 5.85×10^{-3} ng mL⁻¹ could be achieved [330]. While in another study, a complementary metal-oxide-semiconductor LOC platform integrated Ion-Sensitive Field-Effect Transistors (ISFETs) to facilitate direct chemical-to-electronic sensing and LAMP was developed for specific, quantitative detection of kelch 13 gene of *Plasmodium falciparum* and C580Y single-nucleotide polymorphism (SNP) associated with artemisinin-resistant malaria (Fig. 8B) [331]. The LOC platform demonstrated for the first time to realize DNA quantification on-chip by using DNA samples derived from clinical isolates of *Plasmodium falciparum*. The detection limits for kelch 13 gene and C580Y SNP were 1×10^2 copies mL⁻¹ and 1×10^3 copies mL⁻¹, respectively, which held significant potential for the development of a rapid, fully portable and sensitive POC device for quantitative malaria diagnostic and identification of mutations related to drug-resistance. Although those nucleic acid detection methods based on LAMP can provide highly accurate and sensitive diagnosis of malaria, the LAMP reagents are always very expensive

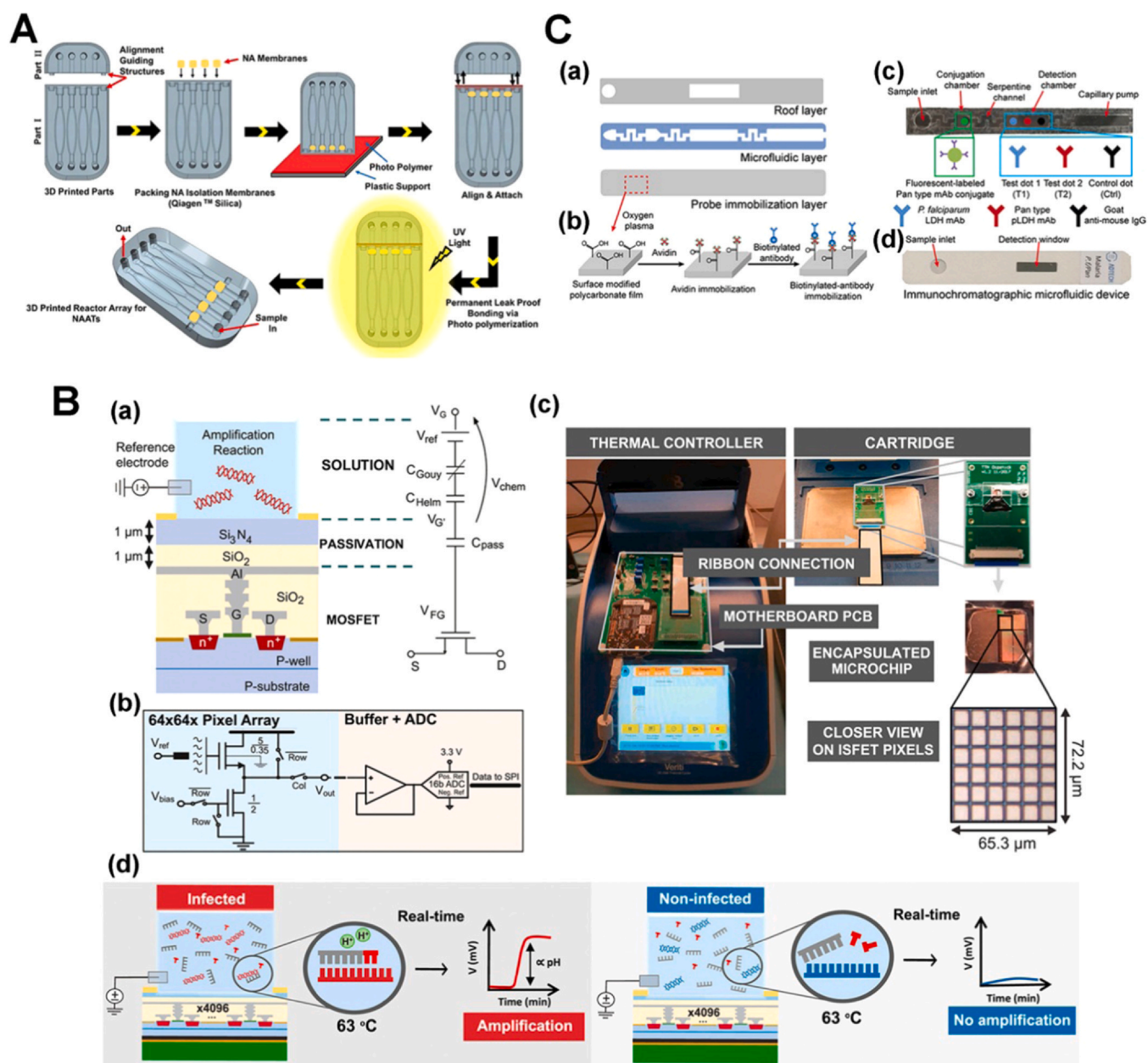


Fig. 8. (A) Schematic illustration of assembly of multifunctional 3D printed reactor array for rapid POC detection of *Plasmodium falciparum* gDNA. Reproduced with permission from Ref. [330] Copyright 2018, Elsevier. (B) Schematic of the metal-oxide-semiconductor LOC platform integrated ISFETs to facilitate direct chemical-to-electronic sensing and LAMP for malaria detection. (a) Cross-section of an ISFET fabricated in unmodified CMOS technology and equivalent circuit macromodel. (b) Schematic of the pixel circuit implemented as a source follower configuration where changes in V_{out} reflect changes in pH. (c) Setup showing the LOC platform including a motherboard printed circuit-board that facilitates data readout, a cartridge PCB hosting the microchip and microfluidic chamber, the microchip including an array of 4096 ISFET sensors and an external thermal controller. (d) Cross-section illustration of the LOC platform showing the reaction interface. Reproduced with permission from Ref. [331] Copyright 2019, Elsevier. (C) Schematic illustration of film-based immunochromatographic microfluidic device for malaria diagnosis. (a) An exploded view of the immunochromatographic microfluidic device. (b) Schematic illustration of the malaria parasite capture antibody immobilization procedure on the polycarbonate film. (c) The structure of the immunochromatographic microfluidic device. (d) Photograph of the IMD with a paper case. Reproduced with permission from Ref. [332] Copyright 2019, Springer Nature.

and trained personnel are necessary, which causes difficulties in on-site diagnosis. Therefore, a film-based immunochromatographic LOC device was fabricated for malaria diagnosis [332]. Firstly, a microfluidic channel was patterned on a polyethylene terephthalate double-sided adhesive film followed by being assembled with a polycarbonate film for the immobilization of capture antibodies against *Plasmodium falciparum* lactate dehydrogenase (LDH) or *Plasmodium vivax* LDH. Then, fluorescent labeled Pan-type monoclonal antibodies (mAbs) conjugates were prepared as the signal indicator. In the presence of *Plasmodium falciparum* LDH, three detection dots including test dot 1 (T1), test dot 2 (T2) and control dot

(Ctrl) revealed fluorescence signals where *Plasmodium falciparum* mAb, Pan-type pLDH mAb and goat anti-mouse IgG were immobilized, respectively. In the presence of *Plasmodium vivax* LDH, T2 and Ctrl dots showed fluorescence signals while no signal was detected with the negative control (Fig. 8C). This fluorescence-based immunochromatographic LOC device was able to detect *Plasmodium falciparum* LDH and *Plasmodium vivax* LDH successfully with detection limits of 50 ng mL^{-1} and 100 ng mL^{-1} , respectively [332].

Taking advantages of the high-resolution of the digital camera of a smartphone, a novel smartphone-coupled LOC device was designed to detect HRP-II antigen of *Plasmodium falciparum* from

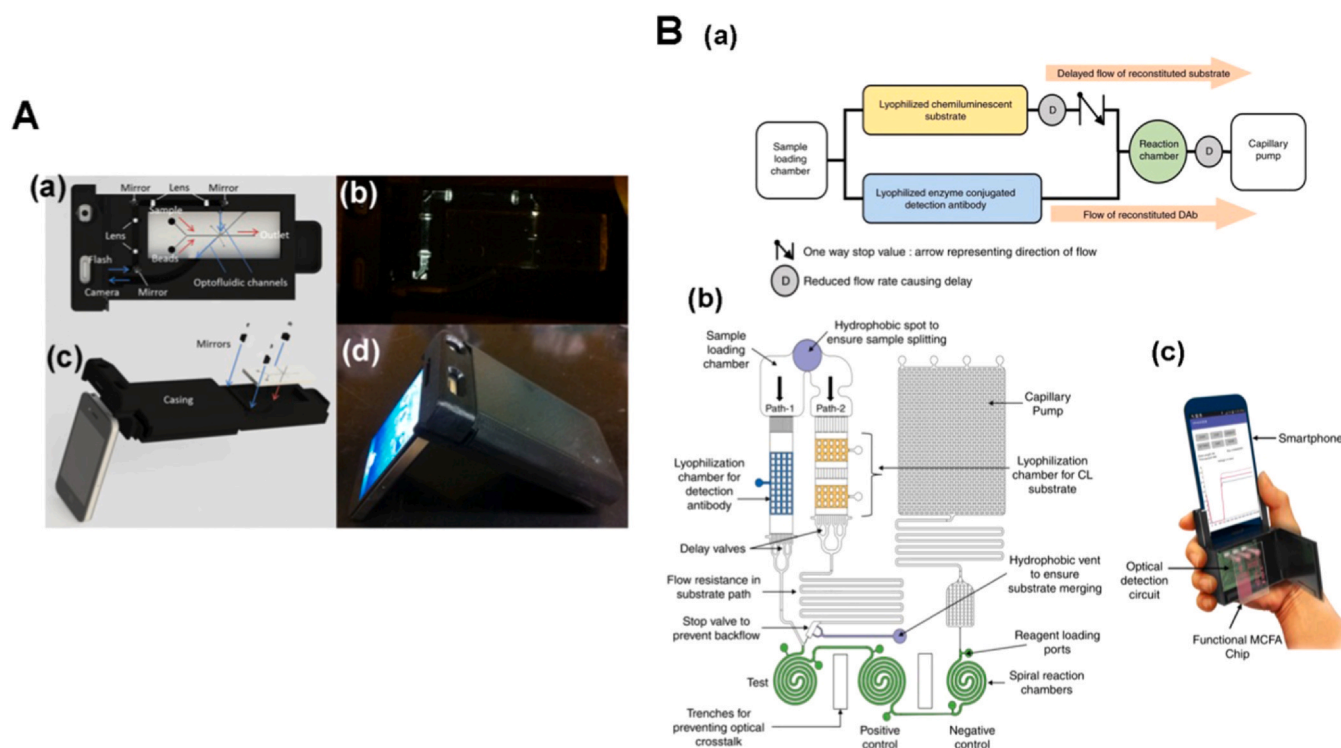


Fig. 9. (A) Schematic of the handheld smartphone-coupled LOC device for the detection of HRP-II antigen. (a) Isometric view of a rendering of the handheld device, less the case. (b) Top view of the handheld device. (c) Exploded view of the entire device. (d) Photograph of actual device with an iPhone 4 installed. Reproduced with permission from Ref. [333] Copyright 2014, SAGE Publishing. (B) Overview of the smartphone-based POC testing analyzer. (a) Functional concept of the MCFA lab chip with on-chip reservoirs in operation sequence to implement chemiluminescence based sandwich ELISA. (b) Schematic of the designed MCFA chip with detailed labeling of the microfluidic components and (c) Schematic of the developed smartphone-based POC testing analyzer. Reproduced with permission from Ref. [334] Copyright 2020, Springer Nature.

diluted (10%) human whole blood [333]. In this system, the white LED flash and digital camera of the smartphone were particularly utilized as an incident light source and a detector; anti-HRP-II-conjugated submicrobeads were applied for capturing HRP-II in blood samples in the LOC device; Mie scatter from the sample in the optofluidic channels was employed as the detection signal; and finally a handheld device fabricated by optical mirrors and lenses was attached to the single smartphone (Fig. 9A). After optimization, the device showed considerably high sensitivity to HRP-II antigen with a detection limit of $1 \times 10^{-3} \text{ ng mL}^{-1}$ in 10% blood and a linear range from $1 \times 10^{-3} \text{ ng mL}^{-1}$ to $1 \times 10^{-2} \text{ ng mL}^{-1}$, and the total assay time of the device was approximately only 10 min [333]. Although the digital camera of a smartphone can be used as a detector in a LOC device, it is not efficient enough for ultra-high sensitive optical detection required in immunodiagnosics. Therefore, more sensitive optical detectors are required to be integrated with smartphone-coupled LOC devices for immunodiagnosics, while the smartphone can serve as the power source, data transfer, storage and analysis, and display. As a paradigm, Ghosh et al. developed a smartphone-coupled LOC device using a microchannel capillary flow assay (MCFA) platform to perform ultra-high sensitive chemiluminescence based ELISA with lyophilized chemiluminescence reagents for the detection of malaria biomarker HRP-II [334]. The whole device was composed of a MCFA lab chip, a high-sensitive optical detector and a smartphone analyzer (Fig. 9B). Firstly, the MCFA platform with functionally microchannels was fabricated by thermoplastic COC for performing high sensitive chemiluminescence assay, which eliminated the liquid reagent handling, control of assay sequence and user intervention in a conventional chemiluminescent detection. Then, a custom designed high-sensitive optical detector, which was applied for detecting the chemiluminescent signal from the chip, was coupled with the smartphone via USB on-the-go port for real-time communication. Finally, the smartphone was mainly used for

display, data transfer, data storage and analysis, and also worked as the host and power source for the optical detector. This LOC device was able to detect HRP-II in artificial serum with a detection limit of 8 ng mL^{-1} , which is sensitive enough to detect active malarial infection [334].

Bacteria detection

Bacterial infection has long been one of the most common infectious diseases that threatens human health. Among various bacterial infectious diseases, tuberculosis has been one of the leading causes of death worldwide. What is worse, the multidrug-resistant tuberculosis (MDR-TB) always exhibits poor response to antibiotic therapy and bad clinical prognosis, and requires expensive systematical treatment [335–337]. Therefore, there has been an urgent requirement for fast, sensitive, and specific diagnosis of tuberculosis and MDR-TB. POC diagnostics using LOC devices show considerable advantages for the molecular detection of MDR-TB both in laboratory settings and resource-poor regions. In one study, Muhlig et al. developed a closed droplet based LOC device for the differentiation of six species of mycobacteria using SERS [338]. The platform consisted of a bead-beating module for disruption of bacterial cell and a LOC-SERS device for bacteria discrimination, which was able to differentiate mycobacteria in 1 h without extraction and further treatment of samples via the obtained SERS spectra by the LOC-SERS device. While in another work, Kukhtin et al. fabricated a Lab-on-a-Film disposable device for the detection of MDR-TB from sputum extracts [339]. The Lab-on-a-Film device was composed of 203 gel elements printed on a flexible film, including DNA sequences for 37 mutations, deletions, or insertion elements across 5 genes. Then, the film with printed gel elements was laminated to additional rollable films and formed a microfluidic flow cell (Fig. 10A). This device was an entirely closed-amplicon system that integrated multiplex amplification, hybridization and post hybridization wash steps into a single

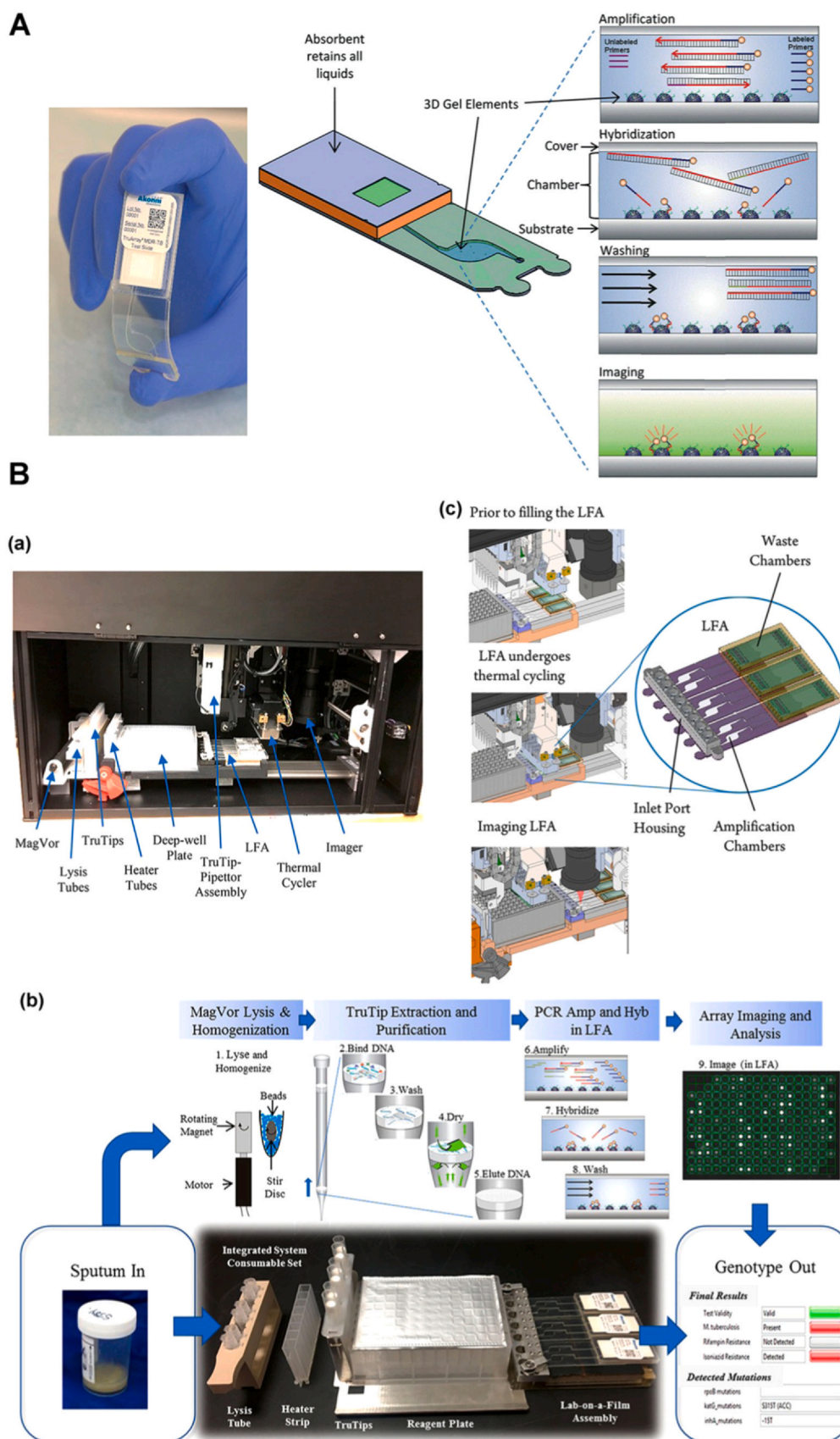


Fig. 10. (A) Schematic illustration of the Lab-on-a-Film disposable device for the POC detection of MDR-TB from sputum extracts. Reproduced with permission from Ref. [339] Copyright 2019, the Royal Society of Chemistry. (B) Schematic illustration of the benchtop automated sputum-to-genotype system using the LFA for the detection of MDR-TB. (a) Photograph of the interior of the analyzer depicting the MagVor for lysis and homogenization, the TruTip for purification, the deepwell plate so that all liquids are part of the consumable, pipetting station, the LFA, the thermal cycler, and the imager. (b) Layout of the consumable for six samples in which the following steps occur. (c) Illustration of the LFA on the system with the thermal cycler in the (1) “up” (disengaged) position, (2) in the “down” (engaged) position, and (3) with the imager capable of individually imaging and analyzing each array of gel elements. Reproduced with permission from Ref. [340] Copyright 2020, American Chemical Society.

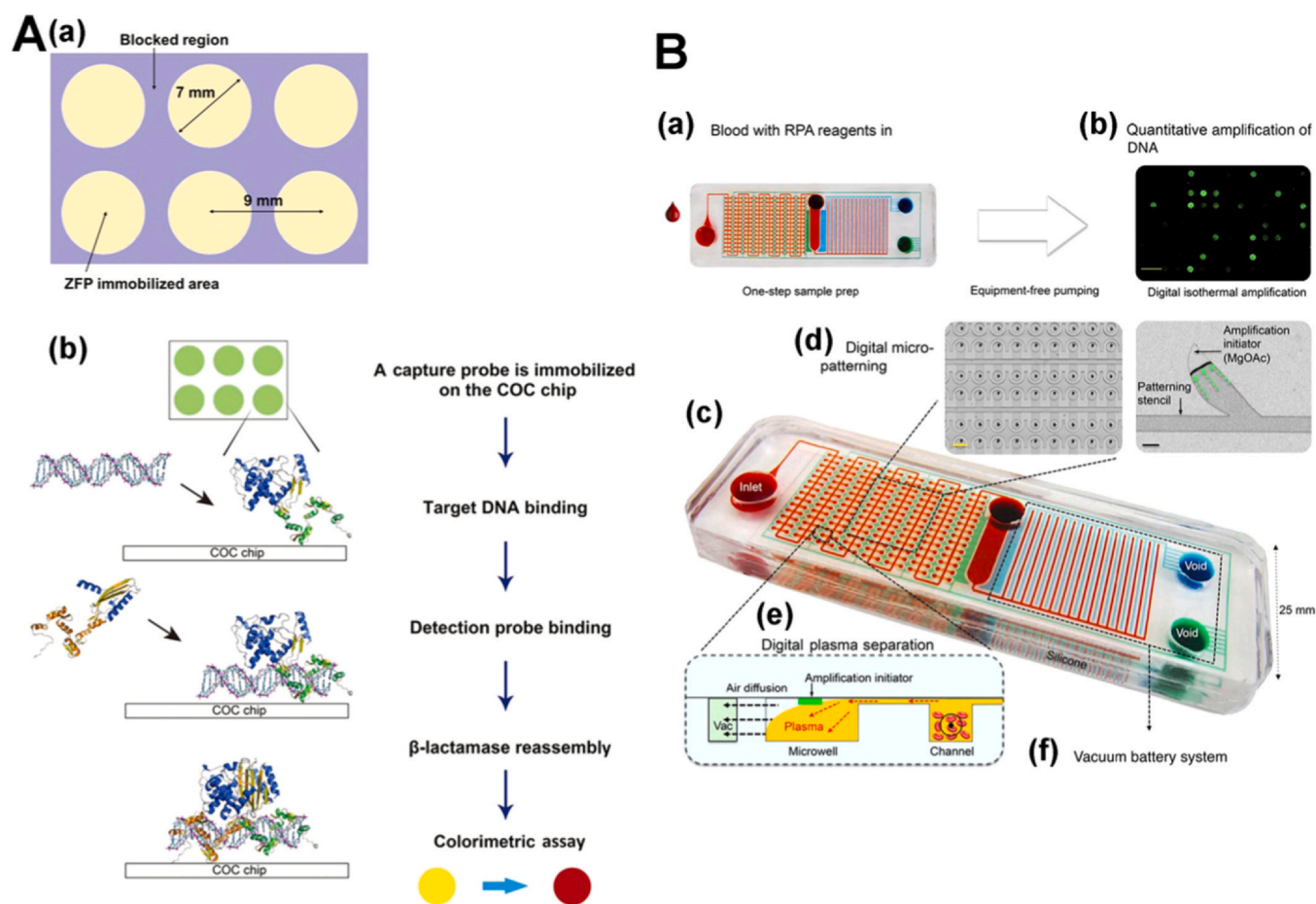


Fig. 11. (A) Schematic of a COC based LOC device using a ZFP array for POC detection of *E. coli* O157:H7. (a) An image of the COC array spot chip. (b) A schematic diagram of the ZFP array on the COC chip. Reproduced with permission from Ref. [344] Copyright 2018, the Royal Society of Chemistry. (B) Schematic illustration of the SIMPLE chip for low cost, quantitative, and portable nucleic acid testing. (a) Samples can be simply dropped into the inlet for automatic sample preparation with minimal handling and no external pumps or power sources. (b) The end-point isothermal digital amplification of nucleic acid was done (RPA) by incubating the chip on a reusable heat pack. Scale bar, 2 mm. (c) Dye-loaded chip for visualization of microchannels. (d) Digital microfluidic patterning enables reagent patterning with common laboratory equipment. (e) Side view of the digital plasma separation design. (f) The vacuum battery system frees the chip from external pumps or power sources for pumping. Reproduced with permission from Ref. [345] Copyright 2017, AAAS.

microfluidic chamber without buffer exchanges or other manipulations. The Lab-on-a-Film device was finally demonstrated to be capable of highly sensitive detection of MDR-TB from sputum extracts with a detection limit of 32 CFU mL^{-1} , and was able to genotype MDR-TB by computing ratios of mutant to wild-type hybridization signals from gel elements printed on unmodified and untreated film substrates [339]. However, the Lab-on-a-Film device was not able to achieve automatic and highly precise sample-to-result detection of MDR-TB without sample pretreatment. To achieve this goal, there are several challenges: 1) hard sample pretreatment due to the highly viscous and heterogeneous of the sputum; 2) difficulties in the lysis of acid-fast MTB bacilli; 3) diversity of MTB mutations; and 4) high-cost [340]. Therefore, to address those challenges in the POC diagnostic of MDR-TB and further make the Lab-on-a-Film device an automatic workstation, Kukhtin et al. then integrated and automated MagVor homogenization, TruTip purification, and Lab-on-a-Film assembly (LFA) amplification in a multi-sample, sputum-to-genotype system for automated genotyping of MDR-TB directly from raw sputum (Fig. 10B) [340]. Briefly, an automated MagVor using magnetic rotation of an external magnet to induce chaotic mixing of glass beads by the rotation of a disposable stir disc was used for sample homogenization and cell lysis. Then, a TruTip using a pipet tip with an embedded matrix was employed for nucleic acid isolation and purification. Finally, a Lab-on-a-Film device with 203 porous three-dimensional gel elements was utilized to

genotype multiple mutations and cut the cost of MDR-TB detection. Noteworthy, this LFA served as a platform for amplification, hybridization, washing, and fluorescent imaging in a closed format and thus prevented amplicon contamination of the workspace. The system was able to detect MDR-TB sensitively with a low detection limit of 43 CFU mL^{-1} from raw sputum [340].

Besides, *E. coli*, *Staphylococcus aureus*, and *Salmonella enterica* are also among the most common bacterial infectious diseases. In the past years, various LOC devices were developed for their rapid and sensitive detection [341–343]. As a paradigm, Ha et al. implemented a TEM-1 β -lactamase system engineered zinc finger protein (ZFP) arrays for the direct detection of pathogen-specific DNA sequences of *E. coli* O157:H7 using a cyclic olefin copolymer (COC) based LOC device (Fig. 11A) [344]. The engineered ZFPs were immobilized on the COC chip, which could function as a non-PCR based molecular diagnostic device, to directly detect double-stranded DNA of *E. coli* O157:H7 with high specificity and sensitivity. The system could achieve a low detection limit of 1 nM target DNA, which can be further developed into a simple and novel LOC device for the detection of various pathogens. In another study, for the purpose of simplifying the entire procedures from sample input to quantitative nucleic acid output without external power sources, Yeh et al. developed a self-powered, highly integrated LOC diagnostic device for direct POC quantitative detection of methicillin-resistant *Staphylococcus aureus* (MRSA) DNA from blood without separate sample

preparation steps (Fig. 11B) [345]. The device integrated three technologies into one chip: reagent microfluidic patterning, digital plasma separation for digital nucleic acid amplification, and an integrated vacuum battery on the chip. Briefly, an amplification initiator [magnesium acetate (MgOAc)] was prepatterned on the chip to enable digital nucleic acid amplification, followed by autonomous separation of the plasma into 224 microwells without any hemolysis via a simplified sample preparation step. Finally, an integrated vacuum battery was added to the chip to achieve self-powered microfluidic pumping without any external pumps, controllers, or power sources. This simple, autonomous, portable, LOC device allowed rapid quantitative detection of MRSA DNA directly from human blood samples in 30 min by isothermal recombinant polymerase amplification (RPA). The device was able to achieve a wide detection range from 1×10^4 to 1×10^8 copies mL^{-1} , providing promising foundations for future low cost molecular diagnostic assays [345].

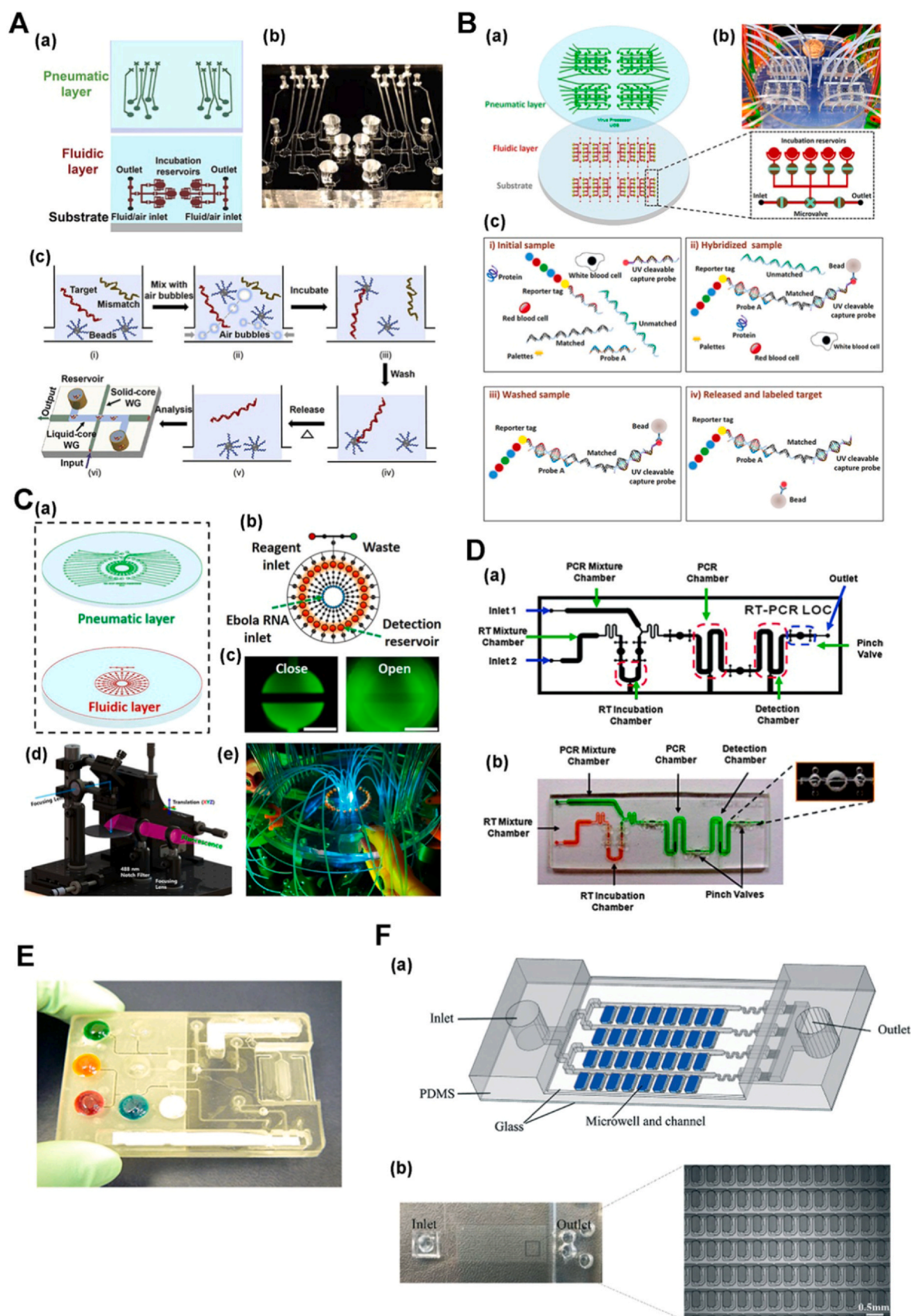
Virus detection

Viruses always cause very serious fulminating infectious diseases, such as Ebola, HIV, SARS, COVID-19 and so on. Therefore, rapid, sensitive and accurate detection of viral infectious diseases at POC is of significant importance for the prevention and treatment of those diseases. LOC device is one of the most popular alternatives to achieve such a goal. As one of the severe hemorrhagic fever viruses, Ebola causes a disease characterized by systemic viral replication, immune suppression, abnormal inflammatory responses, major fluid and electrolyte losses, and high mortality, which always leads to major epidemics in resource-poor regions [346]. Thus, portable POC detection is urgently needed for its control and treatment. Du et al. developed an automated microfluidic sample preparation multiplexer device combined with a sensitive liquid-core antiresonant reflecting optical waveguide biosensor chip for the detection of Ebola RNA (Fig. 12A) [347]. In this system, thermally stable 4-formyl benzamide functionalized magnetic beads with a high density of capture probes and metered air bubbles controlled by microvalves were used to enhance the hybridization of the target Ebola virus RNA with the capture probes bound to the beads. The system was able to achieve a wide dynamic range that covered the whole clinically applicable concentration range and the detection limit was as low as 1.05×10^{-6} ng mL^{-1} for clinical samples without target amplification. The whole detection process could be completed within 2 h [347]. However, this system is too complex and requires long sample preparation time, which is time-consuming and cannot meet the requirement of rapid detection. To simplify the approaches of the device and endow it with higher specificity and sensitivity, the authors then improved the system by using a sequence specific barcode fluorescence reporter and a photocleavable capture probe. The new device and protocol could detect Ebola virus RNA in raw blood with clinically relevant sensitivity by the sensitive and compact fluorometer (Fig. 12B). Exploiting a pneumatic multiplexing architecture, the device was able to run up to 80 assays in parallel samples on a single chip and achieved a detection limit of 3.37×10^{-3} ng mL^{-1} for Ebola RNA in raw blood within 90 min without target amplification. Importantly, this protocol did not require time-consuming and problematic off-chip probe conjugation and washing, which significantly simplified the sample preparation and detection procedures for POC detection Ebola virus [348]. Nevertheless, the fluorometer in this system was not integrated with the microfluidic systems, which cannot achieve automated detection without any external manipulation. Therefore, to further produce a simple, rapid, sensitive, and integrated LOC device for automated POC detection of Ebola virus, the authors combined an automated and multiplexing CRISPR microfluidic chip with a custom designed benchtop fluorometer for rapid detection of Ebola virus with very low volume ($\sim 10 \mu\text{L}$) (Fig. 12C). The device was capable of automated microfluidic

mixing and hybridization, after which the nonspecific cleavage products of Cas13a were immediately measured by a small custom integrated fluorometer. Exploiting the collateral cleavage of CRISPR technology, the integrated device was demonstrated to be able to detect total Ebola RNA in 5 min without solid phase extraction, and a considerably low detection limit of $\sim 1 \times 10^{-3}$ ng mL^{-1} was achieved [349].

In the past years, HIV had become one of the leading causes of human death from a single infectious agent, emphasizing the requirement of POC diagnostics for HIV infection [81]. Although rapid detection of HIV infection can be achieved using anti-HIV antibodies by lateral flow immunoassays, they cannot detect the disease during seroconversion with sufficient sensitivity [81,350,351]. LOC device shows the potential for enhancing the sensitivity and reducing the HIV acute phase detection window. For instance, Lee et al. designed an innovative disposable, polymer based LOC device for clinical POC diagnostics of HIV by RT-PCR based chemiluminescence assay (Fig. 12D) [352]. The device integrated on-chip RT-PCR with a portable analyzer that consisted of a non-contact infrared based temperature control system for reverse transcription process and an optical detection system for on-chip detection as well as monitoring the RT-PCR LOC. The developed polymer LOC device was demonstrated to be capable of achieving POC detection of HIV in shorter than 1 h with minimized cross-contamination. Besides, Chen et al. developed a self-contained, integrated, disposable and sample-to-result polycarbonate microfluidic cassette for nucleic acid detection of HIV at POC [353]. The cassette comprised on-chip sample lysis, nucleic acid isolation, enzymatic amplification, amplicon labeling, and detection, which was automatically controlled by an analyzer that provided pouch and valve actuation with electrical motors and heated for the thermal cycling (Fig. 12E). The device was finally demonstrated to detect HIV virus in saliva samples with a detection limit of 0.05 ng mL^{-1} . Most recently, Wang and Chiu et al. took advantages of fast, isothermal property and similar sensitive to qPCR of nucleic acid sequence based amplification (NASBA) and developed a digital format of nucleic acid sequence-based amplification using a self-digitization chip platform, a stationary water-in-oil nanolitre reactor generation chip with the ability to allow an incoming aqueous fluid spontaneously divides itself into an array of chambers that have been primed with an immiscible fluid [354], for the quantification of HIV-1 RNA (Fig. 12F) [355]. The self-digitization chip was demonstrated to be more sensitive and accurate than the real-time quantitative NASBA for quantifying HIV-1 RNA in plasma samples, and a low detection limit of 1 copy per μL of HIV-1 RNA was achieved, which is very promising for utilization in resource-poor regions.

Besides, LOC devices applied for other viral infectious diseases detection have also been widely investigated. In one study, an integrated LOC device using a magnetic nanoparticle immunoassay was developed for rapid detection of Hendra virus antibodies in dilute horse serum samples [356]. The device was characterized by the chaotic fluid mixing and the automatic liquid handling system, which was capable of detecting Hendra virus antibodies within 15 min and the detection limit was as low as 0.48 ng mL^{-1} . In another example, Zhu et al. designed a LOC device that integrated DNA extraction, solid-phase PCR and genotyping detection for high-risk HPV [357]. In this device, the chip size was significantly reduced by applying the pneumatic microvalves for organically combination of the fluid mixing and reagent storage. Moreover, to allow the spatial separation of the primers and reduce undesirable interactions in multiplex amplification, the solid oligonucleotide array were incorporated into the chip. After being tested using positive quality control samples and HPV patient cervical swab specimens, the LOC device was capable of detection of HPV virus within 1 h, whose detection limit was approximately 50 copies of HPV virus per reaction, providing great utility for the screening and monitoring of HPV



(continued on next page)

Fig. 12. (A) Schematic of an automated microfluidic sample preparation multiplexer (SPM) device combined with a sensitive liquid-core antiresonant reflecting optical waveguide biosensor chip for Ebola detection. (a) Design of the SPM with six incubation reservoirs for target preparation. (b) Photograph of the SPM. (c) Schematic of the solid-phase extraction process and assay. Reproduced with permission from Ref. [347] Copyright 2017, Elsevier. (B) Schematic of (a) Design of the SPM for on-chip solid-phase extraction with 80 incubation reservoirs. (b) Photograph of the SPM. (c) Schematic of the on-chip solid phase extraction experiment. Reproduced with permission from Ref. [348] Copyright 2017, American Chemical Society. (C) Schematic of automated CRISPR microfluidic chip for Ebola virus detection. (a) Design of the automated CRISPR microfluidic chip. (b) Blow up of design of the fluidic layer. (c) Open (left) and closed (right) states of a microvalve. (d) Design of a benchtop fluorometer system integrated with a microfluidic device for in situ virus sensing. (e) Photograph of chip and detection system. Reproduced with permission from Ref. [349] Copyright 2019, American Chemical Society. (D) LOC design for the RT-PCR: (a) design of the polymer RT-PCR LOC; (b) photograph of fabricated RT-PCR LOC including 5 different chambers; and (c) embedded micro pinch valves using silicone tubes. Reproduced with permission from Ref. [352] Copyright 2008, the Royal Society of Chemistry. (E) Schematic illustration of the assembled nucleic acid cassette. Reproduced with permission from Ref. [353] Copyright 2010, Springer. (F) Self-digitization chip for HIV detection. (a) Schematic of the self-digitization chip. 16×64 array of 6.5 nL microwells connected by channels is embedded in PDMS and covered with a PDMS-coated glass slide. (b) Photograph of the self-digitization chip. Reproduced with permission from Ref. [355] Copyright 2018, the Royal Society of Chemistry.

genotypes [357]. Furthermore, for the rapid and POC detection of H1N1 influenza virus, a self-driven microfluidic device integrated with a reverse transcription LAMP assay was developed [358]. The device comprised virus isolation via H1N1-specific aptamers conjugated magnetic beads, virus lysis, isothermal nucleic acid amplification, and colorimetric detection of the virus, which was capable of performing sample pretreatment, reverse transcription LAMP, and H1N1 virus detection on a single chip. The entire detection could be finished within 40 min and a low detection limit of 0.08 ng mL^{-1} was achieved, which was sensitive enough for clinical applications [358]. Most recently, to circumvent the elaborate and labor intensive sample preparation of PCR-based methods for the identification and quantification of viruses, Hügler et al. fabricated a LOC device for free-flow electrophoretic preconcentration of viruses and gel electrophoretic DNA extraction [359]. The device integrated free-flow electrophoretic preconcentration of viral particles with thermal lysis and gel-electrophoretic nucleic acid extraction on a single chip, which was able to achieve high sensitive detection of bacteriophage PhiX174 with a low detection limit of $0.5 \times 10^{-4} \text{ ng mL}^{-1}$. Further, to simplify the operation of the device, a custom-made chip holder

together with a compact peristaltic pump and power supply were introduced to the device, making it user-friendly, low risk of cross-contamination and high potential for automation [359].

In the past years, barcodes have been widely investigated for disease diagnostics due to their ability to allow simultaneous detection of multiple targets from patient samples with increased analysis speed and improved the precision and accuracy. However, their clinical applications were limited by the lack of sensitivity and expensive read-out device. To address this problem, Ming et al. engineered a simple and low cost chip-based wireless multiplex diagnostic device by combining quantum dot barcoding technology with a smartphone reader and isothermal amplification with expectation to detect multiple pathogens in patients with multiple blood-borne infections (Fig. 13) [360]. The results of analytical performances of this device demonstrated that the device was capable of rapid and simultaneous detection of HIV and HBV gene in a single test with a detection limit down to 1×10^3 copies mL^{-1} in less than 1 h, which could also be extended to develop molecular testing panels for other important pathogens by simply modifying the barcode recognition molecules to the target of choice [360].

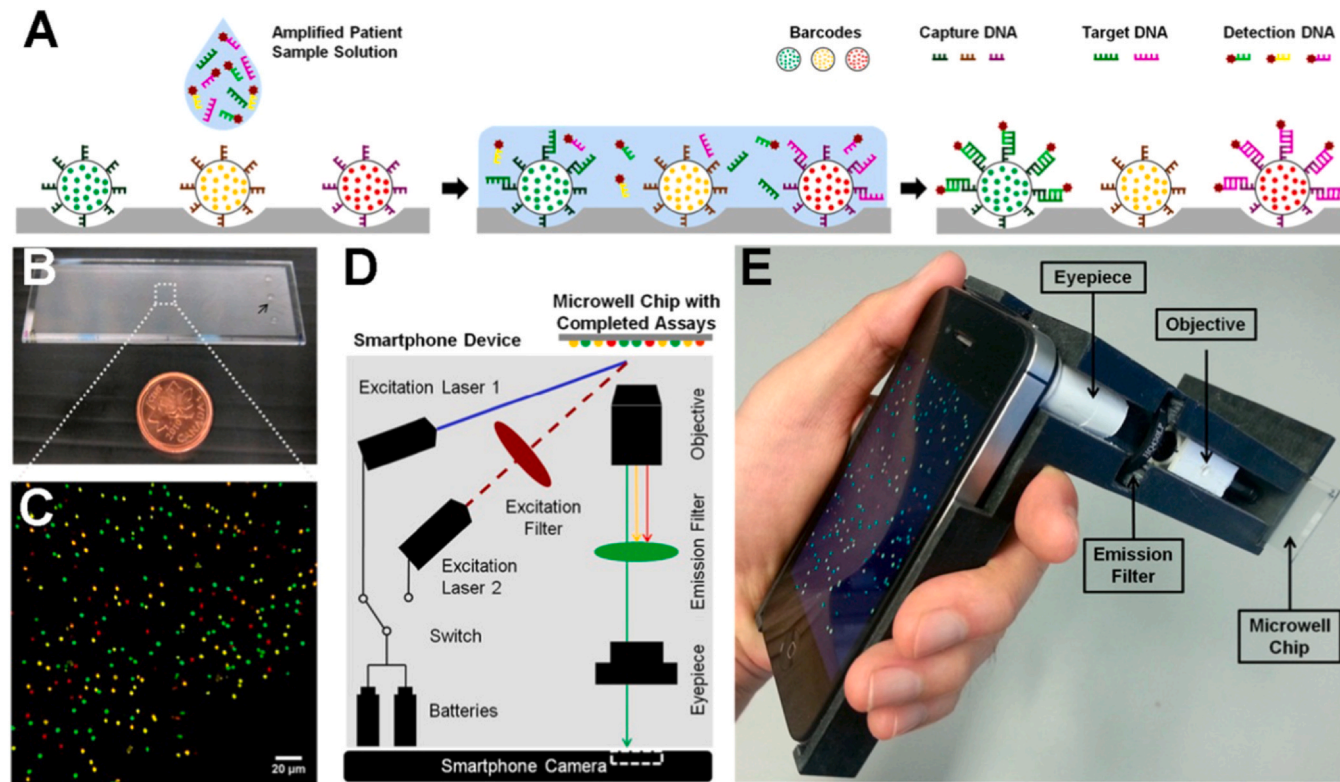


Fig. 13. Schematic illustration of the smartphone-coupled LOC device utilizing quantum dot barcodes. (A) Assay involves the addition of patient samples to a chip coated with microbeads, which are optically barcoded by quantum dots and are coated with molecules that recognize a target analyte. (B) Typical microwell chip containing different barcodes in each well. (C) Smartphone camera captures the image of four different quantum dot barcodes arrayed on the surface of the chip. (D) Two excitation sources excite the quantum dot barcoded chip independently. (E) Image of the smartphone device. Reproduced with permission from Ref. [360] Copyright 2015, American Chemical Society.

Lab-on-a-disc (LOAD) devices

LOAD device is a kind of centrifugal microfluidics, which integrates sample preparation, solution translocation, reagent mixing, separation and detection in a single device [57,58]. Compared with LOC devices, LOAD devices exhibit advantages of automatic fluid actuation without tubing, external pumping, actuators or active valves, a high degree of parallelization, and a huge capacity for total integration [361–367]. In a LOAD device, the movement of the solution is controlled by the synthetic action of centrifugal forces, capillary forces, Euler forces and Coriolis forces, which can be easily manipulated by modulating the spinning speed, spinning direction, valves or rotation actuated barriers, making the device be able to work smoothly and efficiently with a simple spindle motor and a sophisticated microfluidic design [57,58,367–370]. In the past years, LOAD devices have experienced great prosperity and development, which have been regarded as one of the most promising alternatives for the development of automated POC devices. As a result, LOAD devices have attracted considerable attention in the field of biomedical detection and diagnostics. Herein, recent progresses of LOAD devices for POC detection of infectious diseases were comprehensively provided.

Parasite detection

As described above, centrifuge-based LOAD device has shown great promising for integrated POC diagnostic application, but the centrifugal force is non-linear and energy-intensive due to the extremely high rotational frequencies upon the spinning [361]. Therefore, to circumvent those drawbacks, Choi et al. developed a real-time fluorescence LOAD device using energy efficient non-centrifuge based magnetic field interactions for field detection of *Plasmodium falciparum* and *Plasmodium vivax* with automated and scalable sample preparation capability [371]. The device was composed of a compact analyzer and a disposable microfluidic reagent compact disc, which seamlessly integrated parasite DNA sample preparation and subsequent real-time LAMP detection on a single microfluidic compact disc, and was driven by energy efficient non-centrifuge based magnetic field interactions (Fig. 14). There were four parallel testing units in each disc, which were able to automatically conduct the parasite DNA binding, washing, elution and immediate real-time isothermal amplification and fluorescence detection independently. Thus, the disc could be configured either as four identical tests or as four species-specific tests, increasing the testing throughput. After systematical evaluation, the LOAD device was demonstrated to be capable of rapidly processing four samples simultaneously within 50 min turnaround time and a detection limit of ~ 500 parasites mL^{-1} for whole blood was achieved, which was sufficient for the detection of asymptomatic parasite carriers [371].

Bacteria detection

Kim et al. developed a LOAD device, which integrated the DNA extraction, isothermal RPA, and detection onto a single disc, for the detection of *Salmonella* (Fig. 15A) [372]. The device applied a single laser diode for wireless control of valve actuation, cell lysis, and noncontact heating for the isothermal amplification, yielding a compact and miniaturized system. Meanwhile, antibody-coated magnetic beads were used in the detection system to enrich rare cells in large volumes of samples for the enhancement of sensitivity. Finally, lateral flow strips were utilized for the detection via direct visual observation. The device was capable of completing the entire detection procedures within 30 min automatically and rapidly, and low detection limits of 10 CFU mL^{-1} and $1 \times 10^2 \text{ CFU mL}^{-1}$ in PBS and milk were achieved respectively, indicating its great potential for molecular diagnostics of *Salmonella* [372]. In addition, Law et al. devised a robust LOAD device using RPA for automated real-time

detection of MDR-TB [373]. In this platform, real-time RPA was integrated on a LOAD with on-board power to maintain temperature for DNA amplification, and a fluorescence detector was applied for the final detection. After being tested using spiked sputa samples collected from healthy volunteers, the device was demonstrated to be able to detect MDR-TB fast and sensitively with a detection limit of $1 \times 10^2 \text{ CFU mL}^{-1}$ within 15 min. However, the sensors used in this RPA-based LOAD device are complicated. LAMP is another isothermal amplification method, which requires easier method than RPA to be integrated in a LOAD platform for sensitive target detection [364,374]. For example, Loo et al. developed a LOAD microfluidic platform using a real-time LAMP with SYTO-9 as the signal reporter to provide a sample-to-result solution for POC detection of MTB and *Acinetobacter baumannii* [375]. The microfluidic channels designed in this LOAD device was able to mimic sequential analytical steps in bench-top environment, in which the actuation of samples and reagents were automatically controlled by the centrifugation force. Notably, the LOAD system was self-contained, which seamlessly integrated DNA extraction, isothermal DNA amplification and real-time signal detection in a predefined sequence, thus making the LOAD device be able to achieve rapid and automated identification of MTB and *Acinetobacter baumannii* in 2 h with high sensitivity. The detection limits of MTB in sputum and *Acinetobacter baumannii* in blood were $1 \times 10^3 \text{ CFU mL}^{-1}$ and $1 \times 10^2 \text{ CFU mL}^{-1}$, respectively [375]. In another study, Seo et al. designed an integrated LOAD device for fully automated and colorimetric detection of *E. coli* O157:H7, *Salmonella typhimurium*, *Vibrio parahaemolyticus* and *Listeria monocytogenes* (Fig. 15B) [376]. The device integrated DNA extraction and purification, DNA amplification, and amplicon detection on a single disc closely. In this system, silica microbeads were incorporated in the disc for the extraction and purification of bacterial genomic DNA; LAMP was performed to amplify the specific genes of the targets; and a metal indicator (Eriochrome Black T) was used for the colorimetric detection via the color change of the LAMP mixtures from purple to sky blue. The whole detection processes could be rapidly completed in an automated manner by the LOAD device in 65 min with a low detection limit of 10 cells mL^{-1} . However, the samples used in this strategy are in small volumes. Therefore, to increase the amount of a sample, the authors further developed a fully integrated LOAD device based platform with a large-volume sample for POC genetic analysis for multiplex bacteria including *E. coli* O157:H7, *Salmonella typhimurium*, and *Vibrio parahaemolyticus* (Fig. 15C) [365]. The platform consisted of a portable genetic analyzer and a fully integrated LOAD device. The integrated LOAD was combined with a 3D-printed solution-loading cartridge for automated operation including the bead-based DNA extraction, isothermal amplification by an Eriochrome Black T-mediated LAMP, and amplicon detection by a colorimetric and UV-vis detector. Finally, the LOAD-based system was demonstrated to be capable of automatically finishing the whole processes in 1 h using a large sample of 1 mL and its detection limit was as low as $1 \times 10^2 \text{ cells mL}^{-1}$. Most recently, inspired by the fidget spinner toy, Michael et al. engineered a diagnostic fidget spinner (Dx-FS) based on an instrument-free LOAD platform for rapid, low cost, electricity-free and colorimetric detection of urinary tract infection (UTI) (Fig. 16) [377]. At the time of detection, just spun the Dx-FS, bacteria suspended in the sample would be enriched on a nitrocellulose membrane, which could be detected by the naked eye via colorimetric microbial detection. Moreover, a pressure equalization technique was used to circumvent the influence of operators because the Dx-FS was hand-powered. Finally, the Dx-FS was evaluated via a field test performed in India. The results showed that the Dx-FS was able to inform the presence of bacteria in urine within 50 min in contrast to turnaround times of several days, indicating the Dx-FS could be used in resource-poor regions as an inexpensive handheld POC device for the rapid concentration and detection of pathogens in urine samples [377].

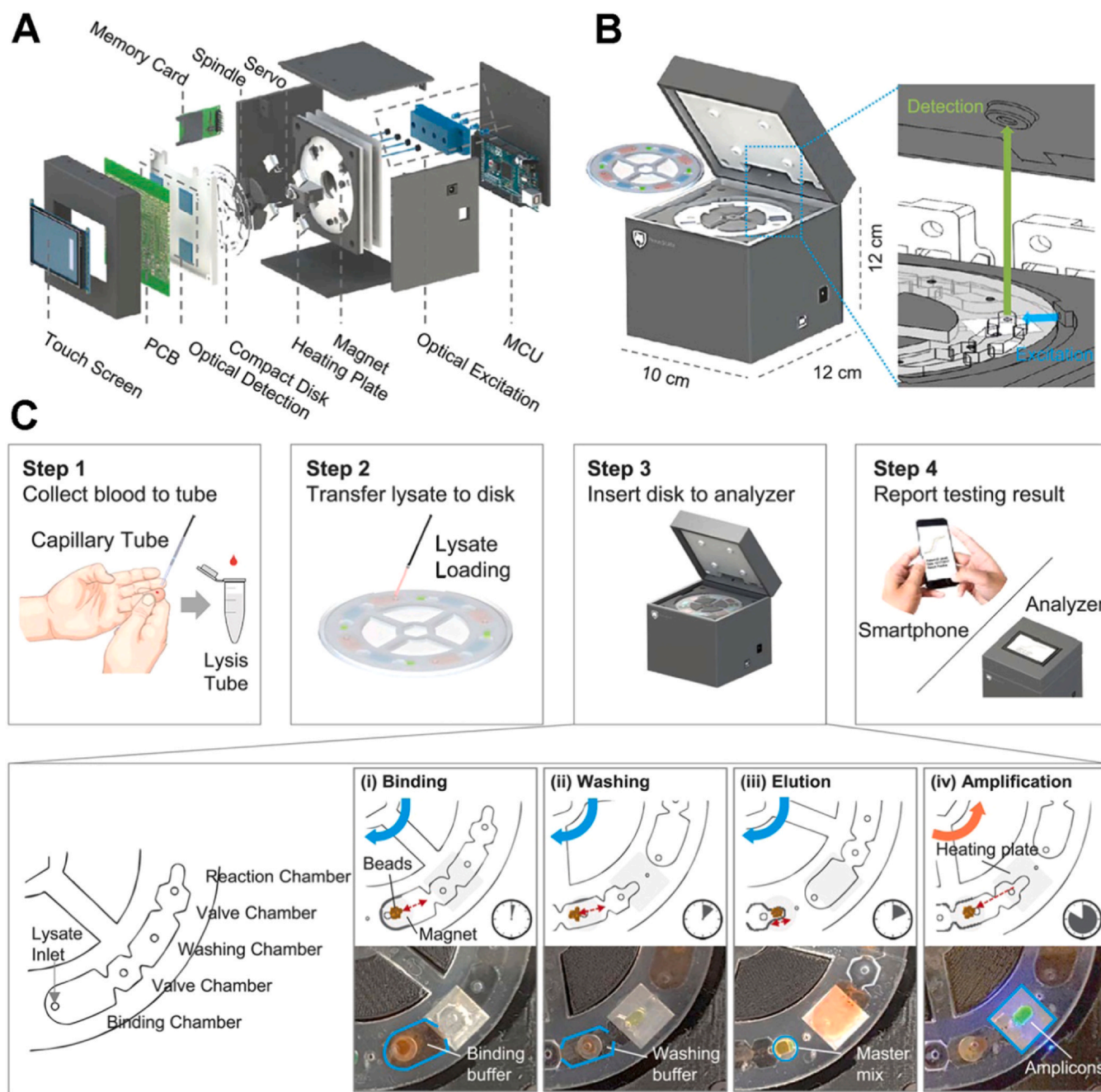


Fig. 14. Schematic illustration of real-time fluorescence LOAD nucleic acid testing device for malaria detection. (A) Exploded view of the device, showing the assembly of various components. (B) Schematic of the assembled device and the quadplex microfluidic reagent compact disc. The form factor of the analyzer is palm-sized. The reagent compact disc is secured to the spindle platter. A real-time fluorescence sensing scheme is integrated on the analyzer. (C) Workflow of the device. Reproduced with permission from Ref. [371] Copyright 2018, Elsevier.

Virus detection

As a paradigm, Liu et al. developed a novel LOAD platform integrated membrane-resistance (MemBR) valves for fully automated sample-to-result subtyping of highly pathogenic avian influenza viruses (HPAIVs) (Fig. 17A) [378]. In the LOAD platform, there were six MemBR valves utilized, which enabled reagent pre-storage and all the processes including sample lysis, RNA extraction and purification, and specific RNA detection by real-time reverse transcription LAMP to be seamlessly integrated on a single disc. After being evaluated using three HPAIVs H7N3, H7N9, and H9N2 and two other influenza A subtypes H1N1 and H3N2, the LOAD device could achieve automated subtyping of those HPAIVs within 70 min [378].

In another study, Li et al. fabricated an automated sample-to-result disc for rapid HBV detection from whole blood based on a double rotation axes centrifugal microfluidic platform (DRA-CMP) (Fig. 17B) [379]. The disc was capable of conducting the pre-storage of reagents and integrating serum separation from whole blood, magnetic bead-based DNA extraction, aliquot of nucleic acid, and qPCR into the disc. The device was then demonstrated to be able to successfully execute sample-to-result detection of HBV in a 500 μL whole blood sample with a low detection limit of 1×10^2 copies mL^{-1} . Besides, the whole detection process could be finished within about 48 min. All those properties of this device indicated its great potential for POC molecular diagnosis HBV in resource-poor regions [379].

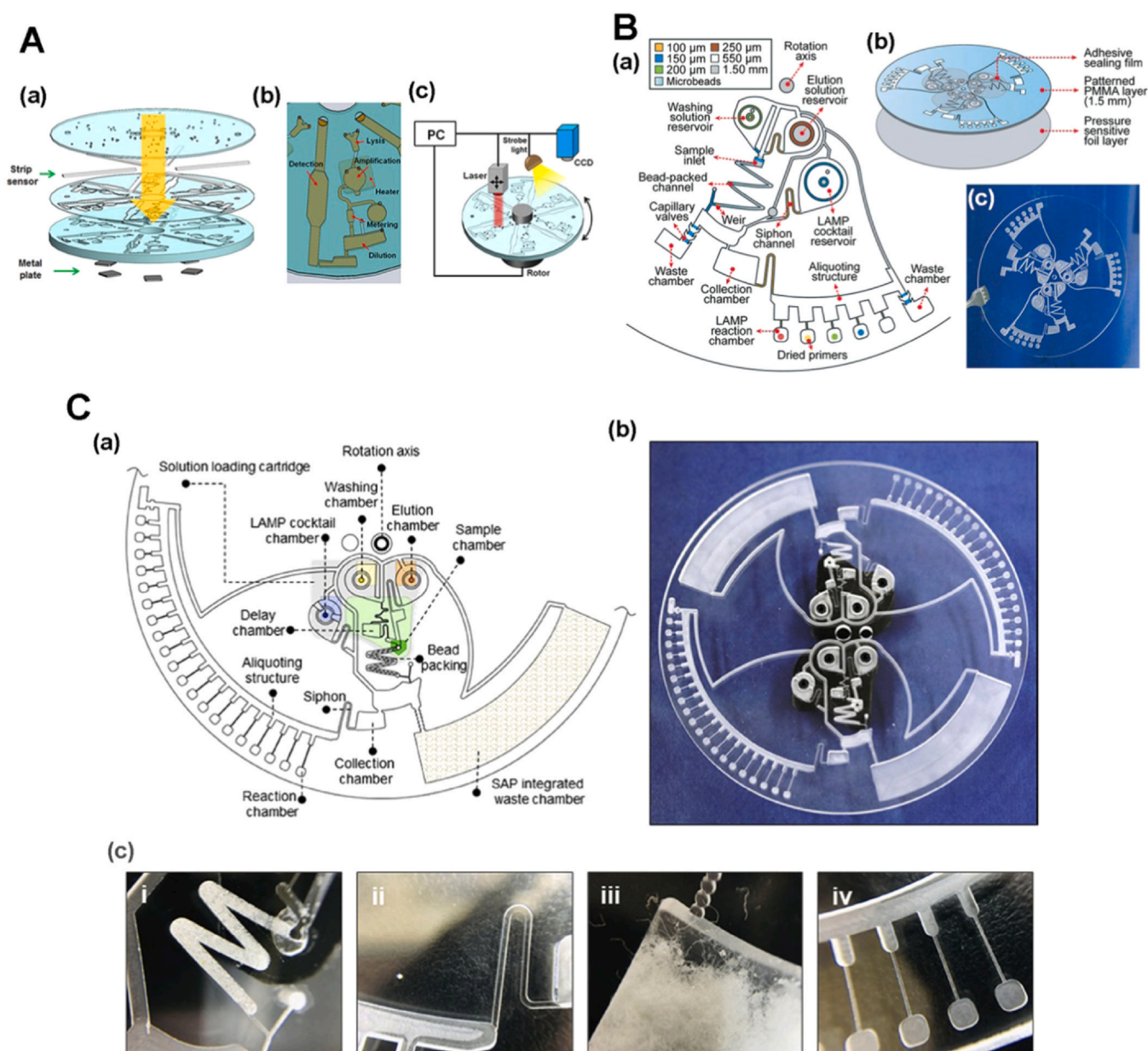


Fig. 15. (A) Schematic illustration of the LOAD device for POC detection of *Salmonella*. (a) Expanded view of the LOAD showing top and bottom plates made of polycarbonate, strip sensors, adhesive layer, and the metal heater. (b) Top view of a section of the disc featuring the chambers for cell lysis, isothermal amplification, metering, dilution, and detection. (c) Schematic illustration of the experimental setup. Reproduced with permission from Ref. [372] Copyright 2014, American Chemical Society. (B) Schematic illustration of the LOAD device. (a) The function components of the LOAD. (b) Assembly of the LOAD. (c) Photograph of the assembled LOAD. Reproduced with permission from Ref. [376] Copyright 2016, the Royal Society of Chemistry. (C) Schematic illustration of the integrated centrifugal disc. (a) The function components of the integrated centrifugal disc. (b) A digital image of the disc. (c) Components of the centrifugal microdevice. Reproduced with permission from Ref. [365] Copyright 2019, Elsevier.

Microfluidic paper-based analytical devices (μ PADs)

Since firstly introduced by Whitesides et al. in 2007, μ PADs have enjoyed booming development for POC diagnostic applications due to their inherent advantages provided by the paper-based substrates, such as hydrophilic and porous structure for microfluidic channels fabrication, low cost, fold ability, disposability, favorable biocompatibility, no need of external driven force for sample transportation, and equipment independence [380–386]. Typical μ PADs were composed of an arrangement of hydrophilic/hydrophobic microstructures patterned on paper substrates that integrated reagent storage, sample transportation, sorting, mixing, flow control and multiplex detection, making them ideal alternatives for automated field testing and POC diagnostic applications [385–387]. In

particular, μ PADs can be applied for target analysis in various aqueous solutions or biological fluids such as saliva, urine, serum, or even whole blood with simple operation and no external sources [382,388–390]. As a result, μ PADs have attracted increasing attention for POC diagnostic applications in the fields of biological detection, environmental protection, clinical diagnosis, and food safety, among which rapid POC detection of infectious diseases especially in resource-poor regions is one of the hottest fields.

Based on the fabrication methods of μ PADs, μ PADs can be classified into 2D μ PADs, and 3D μ PADs. 2D μ PADs can be fabricated by patterning physical or chemical hydrophobic boundaries on the paper to produce liquid channels [380]. Besides, other strategies, including photolithography, laser treatment, plotting, cutting, inkjet etching, plasma etching, wax printing, screen printing and so on

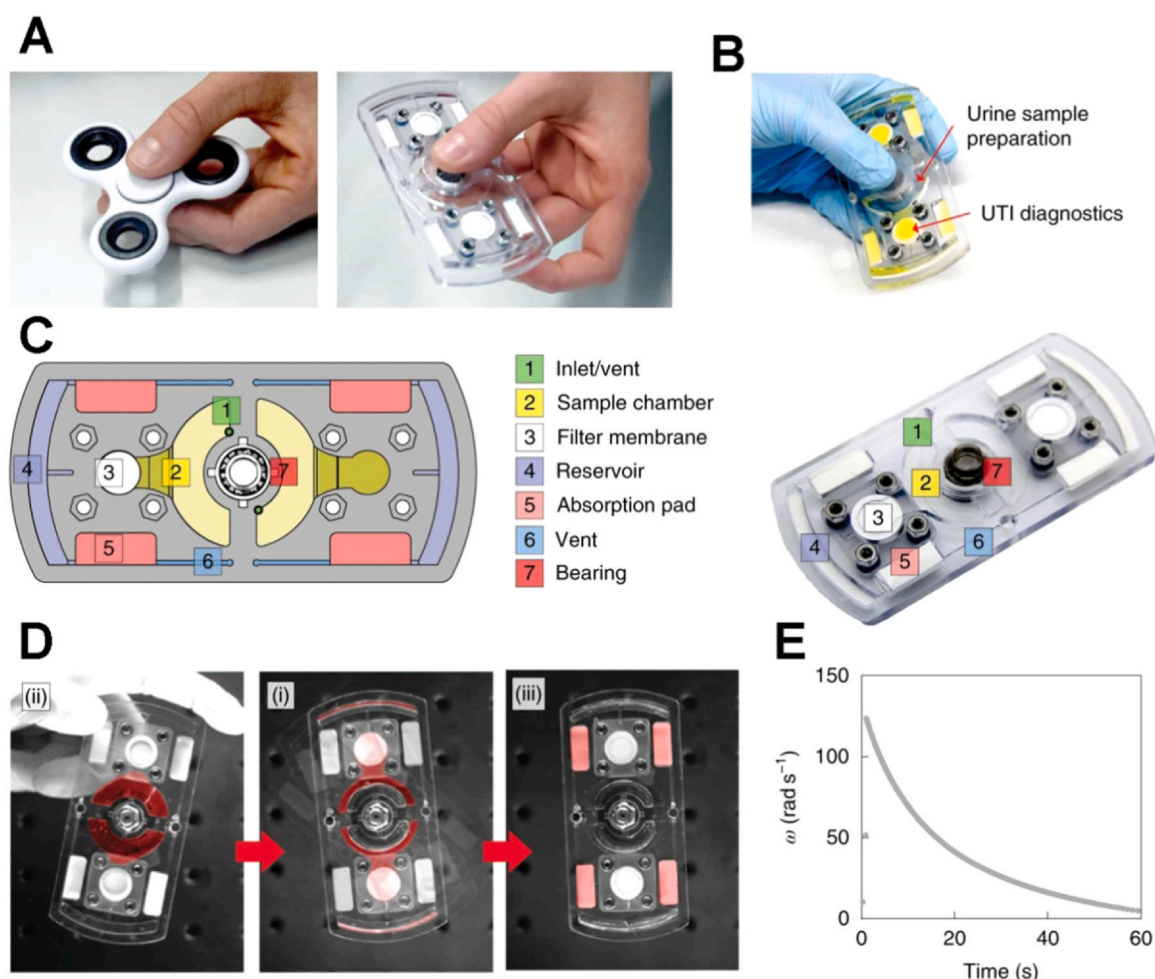


Fig. 16. The Dx-FS as a POCT device for low-resource settings. (A) Fidget spinner (left) and Dx-FS (right). (B) Sample enrichment (urine sample preparation) and UTI diagnostics performed by a Dx-FS. (C) Design of the Dx-FS with labeled parts. (D) Images from a high-speed video showing the operation of a Dx-FS: the device was (i) hand-spun, (ii) spun for 1 min and (iii) stopped. The areas colored in red denote the liquid flow during the process. (E) Angular rotational frequency of the Dx-FS versus time. Reproduced with permission from Ref. [377] Copyright 2020, Springer Nature.

[391–394], have been attempted for 2D μ PADs development. Compared to 2D μ PADs, the fabrication of 3D μ PADs is more complicated to achieve more complicated reaction process and multiple functionalities, which are usually obtained by stacking the layers of 2D microfluidic paper [59]. Meanwhile, some newly developed methods can also be employed for the development of 3D μ PADs, such as origami, slip techniques, open-channel, 3D-printing, and so on [59,393–396]. In the past decade, there have been a large number of novel μ PADs reported for the detection of various infectious disease, which will certainly contributed to the prevention and control of the disease spreads. Herein, the development of μ PADs for POC detection of infectious diseases was discussed.

Parasite detection

Taking malaria detection for an example, Chakma et al. developed a novel label-free spectrophotometric detection method following an indicator displacement assay for the detection of malarial biomarker histidine-rich protein II (HRP-II) [397]. Then, they incorporated this assay into a μ PAD for simple POC detection applications in resource-poor regions. The μ PAD was fabricated by printing hydrophobic alkyl ketene dimer on a chromatographic paper to create hydrophilic microchannels, test zone, and sample application zone. The device was able to achieve rapid and favorable detection of HRP-II within 5 min with a detection limit of

30 ± 9.6 nM. In particular, the sample used was as low as 20 ± 0.06 μ L. These properties of this μ PAD made it a promising POC device for rapid, selective, simple, portable, and inexpensive POC diagnostic of malaria [397]. In another study, Xu et al. developed a μ PAD using the paper-folding technique of origami via wax printing to integrate the sequential steps of DNA extraction, LAMP, and array-based fluorescence detection for multiplexed malaria diagnostics from whole blood (Fig. 18A) [398]. The device was demonstrated to be capable of rapid and sensitive detection of *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium pan* directly from a finger-prick volume of whole blood in 45 min with minimal user intervention.

Bacteria detection

As a paradigm, Costa et al. fabricated a μ PAD by an eco-friendly wax printing technology for colorimetric detection of MTB nucleic acids through their hybridization with species specific gold labeled oligonucleotide probes (Fig. 18B) [399]. Firstly, the wax printed 384 well plate was impregnated with a predetermined concentration of salt (MgCl_2) to induce Au nanoprobe aggregation. In the presence of the complementary MTB DNA sequence, Au nanoprobe aggregation would be prevented and the paper surface remains red; in the absence of complementary MTB target, Au nanoprobe aggregation would be induced by the presented salt, resulting in a visible color change from red to blue in the paper surface. Besides, by using wax

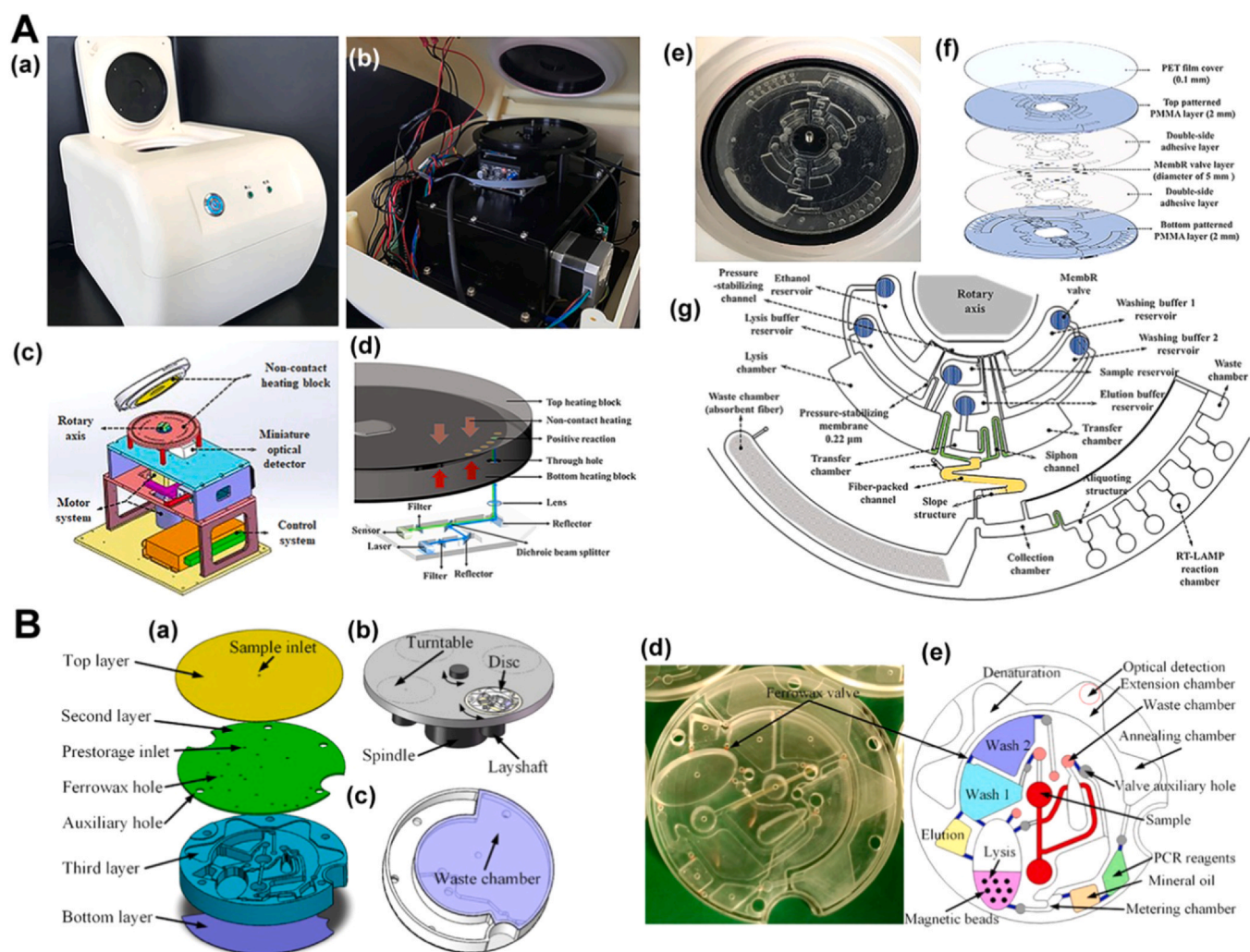
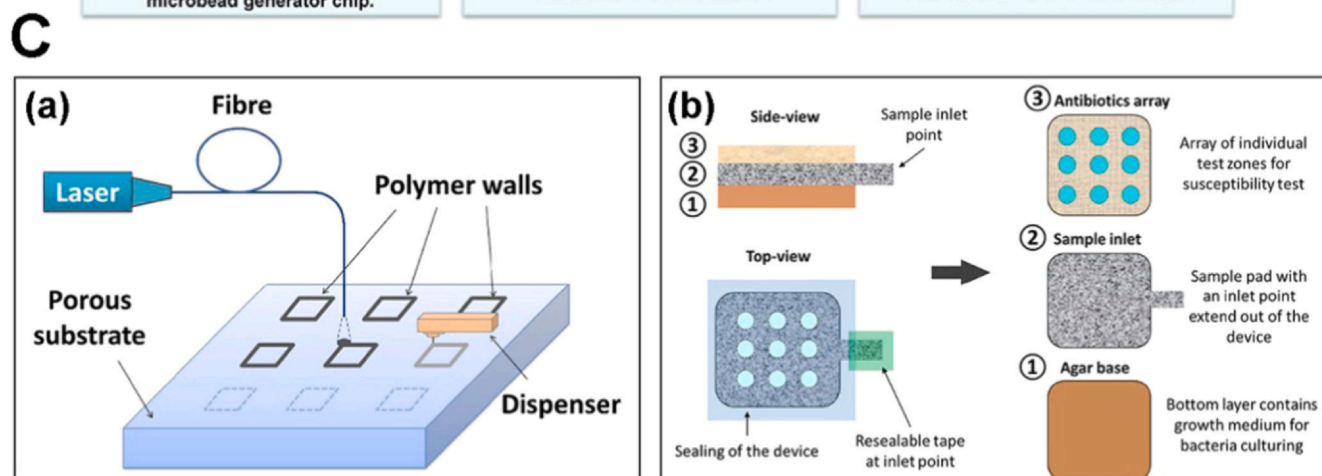
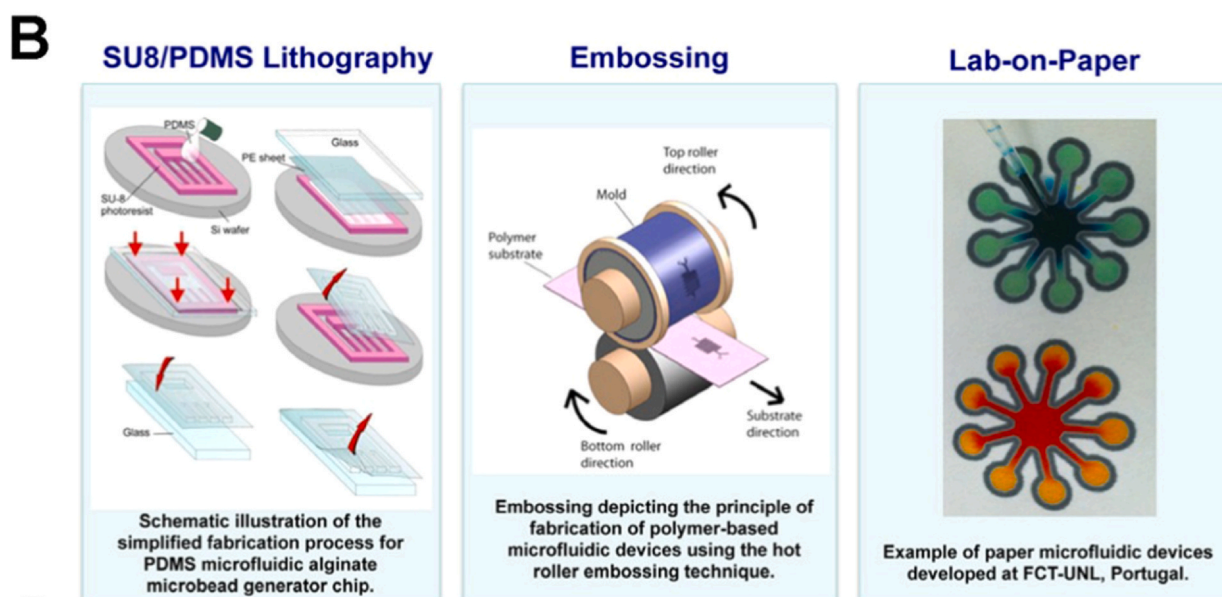
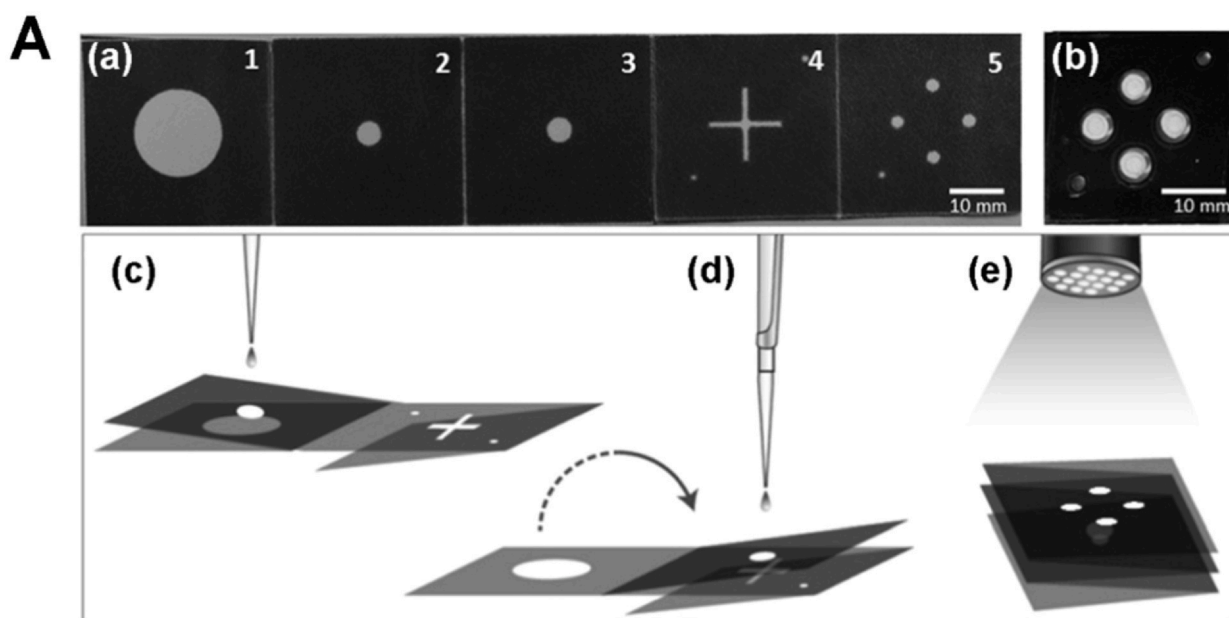


Fig. 17. (A) Schematic illustration of the sample-to-result LOAD platform. (a) Image of the platform appearance. (b) Photograph of the internal modules. (c) Schematic diagram of the main modules in the platform. (d) Schematic diagram of the non-contact heating and the optical module with the dichroic beam splitter. (e) Photograph of the assembled disc mounted on the rotary axis. (f) Assembly of the disc. (g) Design of the diagnostic disc. Reproduced with permission from Ref. [378] Copyright 2018, Elsevier. (B) Schematic illustration of the DRA-CMP for HBV detection. (a) Exploded view of the chip contains four layers. (b) Schematic illustration of the flow control module consisting of a DRA-CMP and a disc. (c) Schematic illustration of the waste chamber of the disc. (d) Picture of the disc. (e) Schematic of the microfluidic layout for sample-to-result HBV DNA detection from whole blood. Reproduced with permission from Ref. [379] Copyright 2019, American Chemical Society.

printing, Srisa-Art et al. developed a colorimetric μ PAD coupled with immunomagnetic separation (IMS) for the detection of *Salmonella typhimurium* [400]. In this device, IMS anti-*Salmonella* coated magnetic beads were applied to capture and separate bacteria from the sample matrix for preconcentration and sample loading. Then, a sandwich immunoassay was conducted using β -galactosidase (β -gal) as the detection enzyme for bacteria quantification. After being tested using culturing solution and spiked bird fecal samples and whole milk, the device was demonstrated to be able to detect *Salmonella typhimurium* sensitively with detection limits of 1×10^2 CFU mL⁻¹ for culturing solution, 1×10^5 CFU g⁻¹ for starling bird fecal samples, and 1×10^3 CFU mL⁻¹ for whole milk. In the past years, antimicrobial resistance (AMR) has been one of the global threats to human health, which has resulted in hundreds of thousands death all over the world every year [401,402]. Therefore, to control infections caused by AMR bacteria better, He et al. developed a laser-patterned μ PAD for the detection and susceptibility testing of *E. coli* via a simple visualized color change in resource-poor regions (Fig. 18C) [403]. The results indicated the μ PAD a promising device for POC detection of bacterial infections, providing a novel tool for tackling the global challenge of AMR.

Virus detection

In the past decade, there have been a number of articles reported about development of μ PADs for POC detection of virus infections, including influenza virus [404], chikungunya virus [405], HCV [406], West Nile virus [407], HBV [408], HPV [409], HIV [410], and so on. For example, Srisomwat et al. developed a pop-up DNA based 3D μ PAD platform for label-free electrochemical detection of HBV DNA [408]. The 3D μ PAD platform integrated multi-step operation of detection into a single device with facile sample introduction, avoiding contamination and minimizing biofluids exposure. The fluidic path, incubation time and electrical connectivity of the 3D μ PAD platform were precisely controlled by the pop-up design through simply folding. Moreover, to achieve electrochemical detection, a pyrroli-dinyl peptide nucleic acid, acpcPNA, was covalently immobilized onto the modified cellulose on the working electrode for target DNA capture. After systematically optimization, the device was demonstrated to be capable of sensitive detection of HBV DNA with high specificity and a wide linear range of 50 pM–100 nM, whose detection limit was as low as 1.45 pM. In another study, to avoid the fussy washing steps of conventional heterogeneous immunoassays, Tenda et al. developed an integrated “sample-to-result” 3D μ PADs based on



(continued on next page)

Fig. 18. (A) Schematic of paper-based multiplexed LAMP detection of malaria in blood. (a) Foldable paper devices: dark areas are printed with hydrophobic wax. The device consists of five panels (1–5) folding onto each other, and a plastic cover for LAMP processing to avoid evaporation. (b) The design incorporates alignment marks on two corners to assign the results. (c) Illustration of the extraction process. (d) By folding the device, the sample is transferred to the LAMP spots where the reaction is carried out. (e) The signal is read out using a UV flashlight (365 nm). Reproduced with permission from Ref. [398] Copyright 2016, Wiley. (B) Illustration of the main microfluidic technologies. The complexity/cost decreases from left to right. Reproduced with permission from Ref. [399] Copyright 2014, IOP Publishing. (C) Schematic illustration of laser-patterned paper-based device. (a) Schematic of the laser-based direct-write setup. (b) Schematic of the laser direct-write fabricated three-layer paper device for bacteria identification and antibiotic-resistance testing. Reproduced with permission from Ref. [403] Copyright 2020, Elsevier.

bioluminescence resonance energy transfer (BRET) switches for multiplex colorimetric detection of anti-HIV1, anti-HA, and anti-DEN1 antibodies in whole blood [410]. The device was composed of multiple paper layers that vertically arranged through lamination. The first layer served as the sample pad for cellular components separation. The second layer was impregnated with furimazine, which would be dissolved into the vertically flowing sample liquid and transported to the third layer immobilized with the BRET-switching protein (LUMABS). The design of the device enabled an automatic detection with sample volume independent and fully reagent-free operation. The only operation for users was limited to the introduction of a single drop of sample and acquisition of a photograph after sample introduction. All the procedures could be completed within 20 min without requirement for precise pipetting, liquid handling, or analytical equipment except for a camera, making it ideally suit for user-friendly POC diagnostics in resource-poor regions [410]. Recently, detection of influenza with antiviral treatment effectiveness indication is of great significance in reducing the treatment decision time, shortening the impact of symptoms, and minimizing transmission. However, current technologies cannot achieve this goal very well. To address this problem, Murdock et al. developed a novel, POC μ PAD by wax printing for influenza detection with the ability to determine antiviral susceptibility of the strain for treatment decision [411]. The μ PAD consisted of two wax-patterned filter paper layers and two outside layers of lamination. For specific and sensitive detection, the enzymatic activity of surface proteins present on all influenza strains were employed in this platform. Upon the sample introduction to the device, it would be distributed to 4 different reagent zones, and the results could be read either by eyes or through a colorimetric image analysis smartphone due to the development of the enzymatic substrate under different buffer conditions took place on the bottom of the device [411].

Lateral flow devices

Lateral flow devices are one of the most widely used POC diagnostic tools for the detection of infectious diseases owing to their advantages of simplicity, easy operation, rapidness, durable stability, cost-effectiveness, and minimum user intervention [412–414]. Since the first lateral flow device developed in the 1980s for pregnancy self-testing, there have been various lateral flow devices developed for all kinds of applications, including biomarker detection, disease diagnosis, food safety, environment monitoring and so on [415–420]. A typical lateral flow device consists of a nitrocellulose membrane, sample pad, conjugate pad, and absorbent pad with all the required chemicals and reagents pre-stored in the test strip [393,421]. The sample pad is designed for sample fluid loading and adsorption; the conjugated pad is impregnated with specific molecule-conjugated biolabels for binding to the analyte and signal generation; the nitrocellulose membrane immobilized with capture molecules is the core component for testing; and the absorbent pad provides the driven capillary forces and collects excess sample fluid [422].

Commonly, there are two formats of lateral flow devices, sandwich and competitive lateral flow devices. In a sandwich lateral flow device, a small volume of sample is loaded to the sample pad, which then flows across the conjugate pad, nitrocellulose membrane, and absorbent pad through capillary forces. The target in the fluid will specifically recognize the specific molecule-conjugated biolabels

pre-stored on the conjugate pad and form target-molecule-conjugated-biolabels complexes, which are then captured by the capture molecules immobilized on the test zone and generate test and control lines, which can be directly read by the naked eye [412,422]. Therefore, in a sandwich lateral flow device, the target concentration is proportional to the test line signal. In a competitive lateral flow device, the analyte target will compete with the capture molecules immobilized on the test zone to bind to the specific molecule-conjugated-biolabels pre-stored on the conjugation pad. Thus, in the presence of the analyte target, the test line will not display the signal, while in the absence of the analyte target, there will be signals at both the test line and control line [421,423]. Thus, the target concentration is inversely proportional to the test line signal. Both sandwich and competitive lateral flow devices can be used for qualitative and quantitative detection of targets. The difference is that a sandwich lateral flow device is usually utilized for the detection of targets with multiple antigen epitopes, while a competitive lateral flow device is more suitable for the detection of a single antigen epitope targets [393].

Parasite detection

The past years have witnessed a booming development of lateral flow devices for POC detection of infectious diseases. Taking malaria detection as a paradigm, Pereira et al. developed a lateral flow device that integrated the concentration and detection steps into a single step for POC detection of a malaria biomarker named *Plasmodium* lactate dehydrogenase (pLDH) [424]. In this lateral flow device, a micellar aqueous two-phase system was applied in the 3D paper design to reduce the macroscopic phase separation time, which allowed simultaneously concentrate and detect pLDH within 20 min at room temperature. After systematic optimization, the device was capable of sensitive detection of pLDH with a low detection limit of 1.0 ng mL^{-1} , which is 10-fold lower than a conventional lateral flow device. While, dos Santos et al. developed a simple, sensitive and low cost lateral flow device for the early diagnosis of *Plasmodium falciparum* malaria via an enzyme-based colorimetric detection of HRP-II, a specific biomarker for identifying the *Plasmodium falciparum* malaria contamination [425]. In this device, the colorimetric detection was achieved by the catalytic reaction of TMB substrate using a detection antibody labeled with the peroxidase enzyme, which could generate a colorimetric signal by the production of an insoluble product. The lateral flow device was able to detect HRP-II with a very low detection limit of 5 ng mL^{-1} .

Bacteria detection

Roskos et al. developed a compact and inexpensive lateral flow device for the detection of MTB genomic DNA through the execution of isothermal DNA amplification in a mesofluidic cartridge that attached to a portable instrument [426]. In the device, one-way passive valves, flexible pouches, and electrolysis-driven pumps were used for the fluid handling inside the closed-system disposable cartridge, and the isothermal DNA amplification occurred in a two-layer pouch that permitted high-efficient heat transfer. Notably, the lateral flow device performed the detection in a closed-system cartridge also prevented workspace amplicon contamination. Finally, LAMP and Exponential Amplification Reaction (EXPAR) assays were coupled in this device for MTB genomic DNA detection, which could be completed within 20 min for LAMP based detection and 70 min

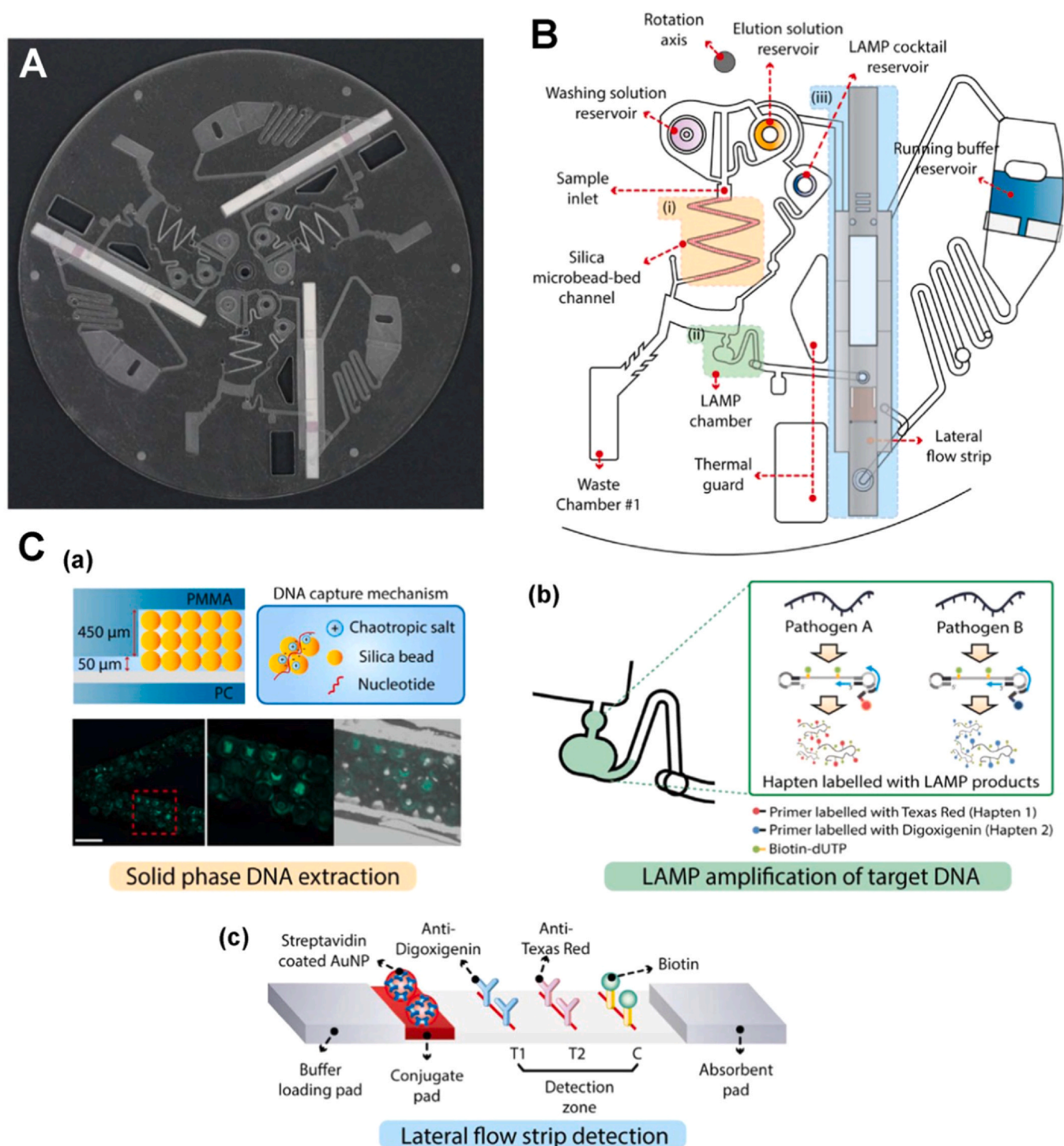


Fig. 19. Schematic of the integrated lateral flow device on a rotary microfluidic system for POC colorimetric detection of *Salmonella Typhimurium* and *Vibrio parahaemolyticus*. (A) A digital image of the integrated rotary microdevice (B) Schematic illustration of the integrated rotary microdevice for the DNA extraction, the LAMP reaction, and the lateral flow strip detection. (C) Schematic illustration of the solid phase DNA extraction unit and the fluorescence images of the FAM-labeled DNA adsorbed glass microbeads (a), the LAMP amplification of target DNA (b), and (c) the lateral flow strip detection. Reproduced with permission from Ref. [427] Copyright 2017, Elsevier.

for EXPAR based detection with detection limits of $30 \text{ copies mL}^{-1}$ and $2 \times 10^4 \text{ copies mL}^{-1}$, respectively [426]. However, the sample preparation step was not integrated in the device, limiting its application for automatically sample-to-result detection. To develop a fully integrated device for POC nucleic acid detection of infectious diseases, Park et al. designed an integrated lateral flow device on a rotary microfluidic system for POC colorimetric detection of *Salmonella Typhimurium* and *Vibrio parahaemolyticus* [427]. The device was

a highly integrated detection platform, which was able to conduct glass microbead based DNA extraction, LAMP, and colorimetric strip based detection in a sequential manner under a rotational speed control (Fig. 19). Then, the device was applied for the multiplex detection of *Salmonella Typhimurium* and *Vibrio parahaemolyticus* in contaminated water or milk. The results showed that all the processes could be completed within 80 min and a low detection limit of $1 \times 10^4 \text{ CFU mL}^{-1}$ was achieved [427]. However, the above device

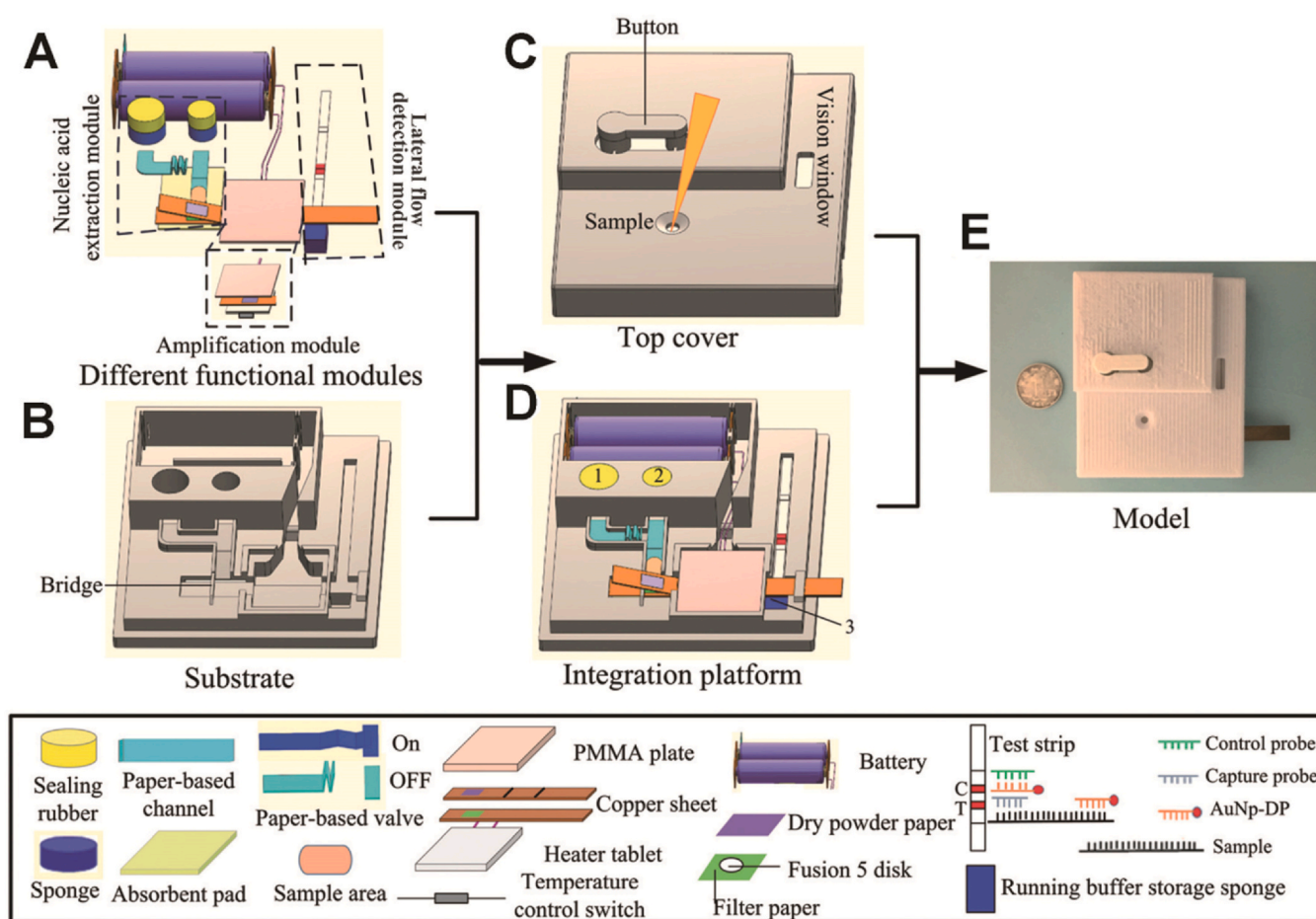


Fig. 20. Schematic of a disposable and integrated lateral flow device for nucleic acid extraction, amplification and detection. (A) The different functional modules of the device, including nucleic acid extraction, amplification by the battery heat blocker and lateral flow detection. (B) The substrate and a bridge that was used to separate the upper layer copper sheet from the bottom layer to prevent the lysis buffer and washing buffer from flowing to the dry powder paper. (C) The top cover of the integrated lateral flow device. (D) The integration platform of the different functional modules and the substrate. (E) The model of this device. Reproduced with permission from Ref. [428] Copyright 2017, the Royal Society of Chemistry.

requires off-chip reagent storage, complex operation steps and equipment-dependent nucleic acid amplification. To overcome these challenges, Tang et al. designed a fully disposable and integrated sample-to-result lateral flow device for POC nucleic acid detection of *Salmonella typhimurium* (Fig. 20) [428]. This established device was composed of a sponge-based reservoir and a paper-based valve for nucleic acid extraction, an integrated battery, a positive temperature coefficient ultrathin heater, temperature control switch and on-chip dried enzyme mix storage for isothermal amplification, and a lateral flow test strip for colorimetric detection, which was capable of integrating nucleic acid extraction, helicase-dependent isothermal amplification and lateral flow assay detection into one paper device and allowing on-chip dried reagent storage and equipment-free nucleic acid amplification with simple operation steps. After being tested using spiked samples, the device was demonstrated to be able to sensitively detect *Salmonella typhimurium* with a detection limit of as low as 1×10^2 CFU mL⁻¹ in waste water and egg, and 1×10^3 CFU mL⁻¹ in milk and juice in about 1 h, indicating its great potential for future POC detection applications in resource-poor regions [428].

To make lateral flow device more user-friendly, convenient and intelligent, a smartphone-coupled dual lateral flow immunoassay device was developed by Cheng et al. using mesoporous core-shell palladium@platinum (Pd@Pt) nanoparticles as a signal amplifier for simultaneous detection of *Salmonella* Enteritidis and *E. coli* O157:H7 [429]. The system exhibited several attractive features: 1) using

nanozyme (mesoporous Pd@Pt nanoparticles) for improving the sensitivity and stability; 2) using dual lateral flow immunoassay for simultaneous real-time detection of targets; and 3) a smartphone for imaging and results recording. After optimization, the device was capable of achieving simultaneous real-time detection of *Salmonella* Enteritidis and *E. coli* O157:H7 with greatly improved sensitivity and the detection limits were calculated to be ~ 20 CFU mL⁻¹ for *Salmonella* Enteritidis and ~ 34 CFU mL⁻¹ for *E. coli* O157:H7, respectively [429].

Virus detection

There has been a long history in the development of lateral flow devices for POC detection of viruses, which have also been applied for rapid and cost-effective detection of SARS-CoV-2-specific antibodies. For example, a lateral flow immunochromatography assay was employed for the detection of SARS-CoV-2 IgG/IgM in symptomatic patients presenting to the emergency department. The results displayed a satisfactory analytical performance in clinical practice, indicating the device a potential supplemental serology testing tool for the rapid diagnostic of COVID-19 [430]. Nucleic acid detection is the most commonly used and effective method for specific detection of viruses, which has been widely incorporated in the lateral flow devices to achieve simple, rapid, sensitive and user-friendly POC detection. For example, simple lateral flow devices based on reverse transcription LAMP had been developed and applied for rapid

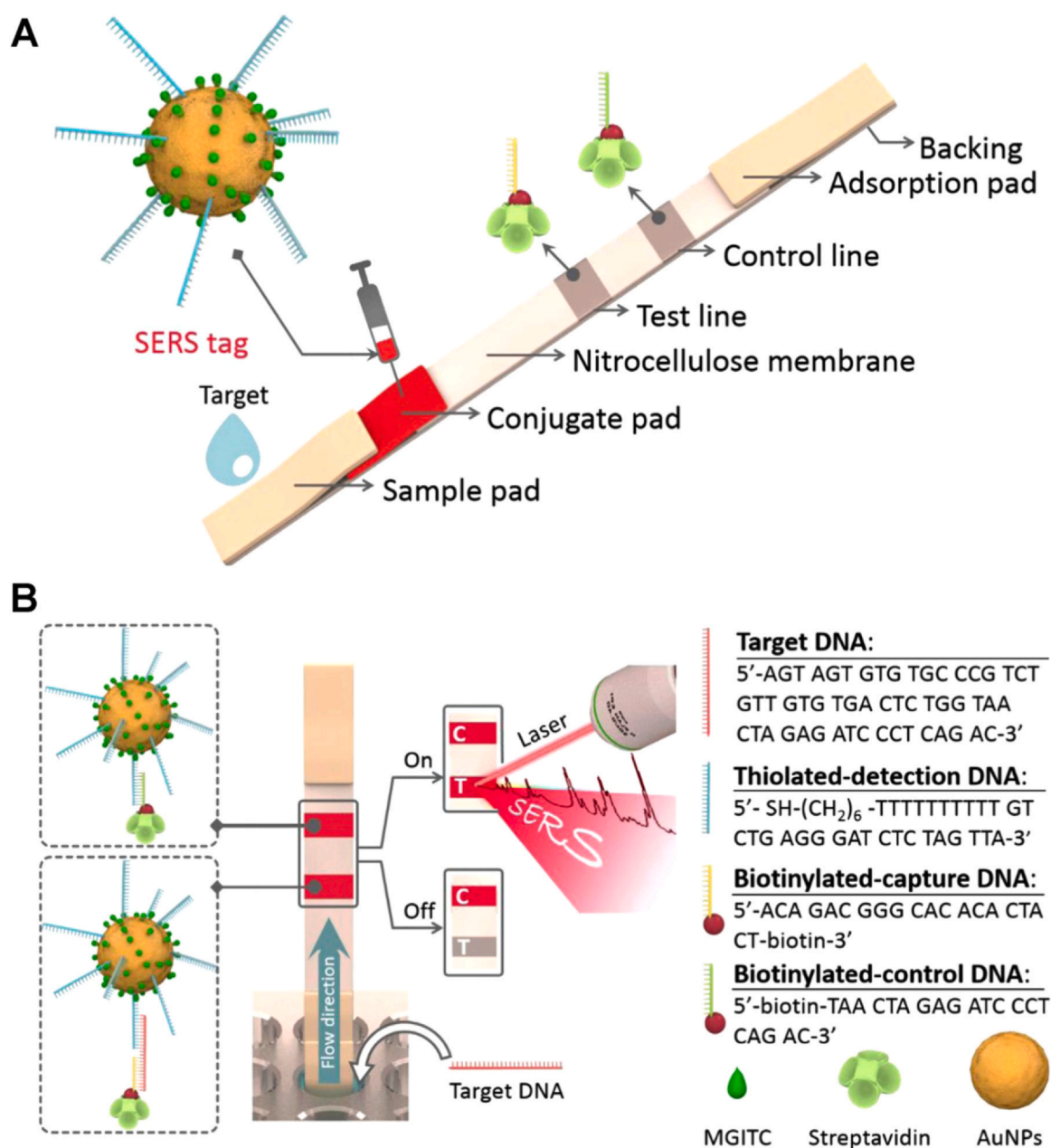


Fig. 21. (A) Schematic illustration of the configuration and (B) the measurement principle of the SERS-based lateral flow device for quantification of HIV-1 DNA. (C is the control line and T is the test line). Reproduced with permission from Ref. [433] Copyright 2016, Elsevier.

clinical detection of H7N9 virus and foot-and-mouth virus [431,432]. However, conventional lateral flow devices have limited sensitivity and quantitative analysis, which can only identify targets of high cut-off values via colorimetric detection. To address those problems, nanomaterials were used to enhance its sensitivity and quantitative ability. Fu et al. developed a SERS-based lateral flow device for highly sensitive detection of HIV-1 DNA in the low concentration range (Fig. 21) [433]. Raman reporter-labeled AuNPs were employed as SERS nano tags for targeting and detecting the HIV-1 DNA marker in the device. After optimization, the device showed favorable ability for the detection of HIV-1 DNA with a considerably low detection limit of 0.24 pg mL^{-1} . Besides, Gong et al. developed a miniaturized and portable upconversion nanoparticle (UCNP)-based lateral flow device for POC detection of HBV DNA, which was composed of a lateral flow assay detection system, an UCNPs-lateral flow assay reader and a smartphone-assisted UCNPs-lateral flow assay analyzer

[434]. The device displayed highly sensitive and quantitative detection capability of HBV DNA with a detection limit of lower by approximately 10 folds than the clinical cut-off value. Moreover, the precision and accuracy of the UCNPs-based lateral flow device were also comparable to the gold-standard method with correlation coefficients of 0.922 and 0.995, respectively [434].

For the purpose of realizing more accurate, faster and networked on-site monitoring and detection of avian influenza viruses (AIVs) with high sensitivity, Yeo and Park et al. developed a coumarin-derived dendrimer-based fluorescent lateral flow immunoassay device coupled with an efficient reflective light collection module and a smartphone (Fig. 22A) [435]. The lateral flow immunoassay device exhibited a two-fold higher detectability as compared to that of the table-top fluorescence strip reader for H5N3, H7N1 and H9N2 subtypes, and could achieve rapid and highly sensitive detection of H5N1 virus within 15 min with a sensitivity of

96.55% (28/29) [95% confidence interval (CI): 82.24–99.91] and a specificity of 98.55% (68/69) (95% CI: 92.19–99.96) in a clinical study of H5N1-confirmed patients. Furthermore, the collected results measured by the smartphone in this system were able to be wirelessly transmitted to a centralized database system for further information processing and data mining via short messaging service. All those properties of the device made it a powerful tool for agile identification and efficient control of infectious diseases dissemination [435]. However, this fluorescent lateral flow immunoassay device was single channel designed and could only detect one pathogen at once, thus limiting its application for simultaneous multiplex analysis. To solve this problem, the authors then improved the lateral flow immunoassay device to a multiplex AIVs detection toolkit and readout system, which was equipped with a portable smartphone-based rapid dual fluorescent diagnostic system (SRDFDS) using two emission filters (Fig. 22B) [436]. The system was designed for simultaneously detection and quantification of both influenza A and its H5 subtype on a single strip using two QD signals (580 nm and 650 nm). The results demonstrated that the system was able to achieve a high sensitivity of 92.86% (13/14) and 78.57% (11/14), and a specificity of 100% (38/38, $P < 0.0001$) and 97.37% (37/38) for the detection of influenza A and H5 subtype respectively, indicating the system could be used for accurate and early diagnosis of influenza viral infections [436].

Miniaturized PCR devices

PCR is one of the most popular detection methods and gold standard of molecular diagnosis for infectious diseases, which enables the exponential amplification of one or a few copies of a particular sequence of DNA or RNA, making it very powerful, specific and sensitive [437–439]. Typical PCR processes were always conducted in an airtight tube with a small volume of no more than 100 μL , and the reaction were performed at temperatures cycled among around 60 $^{\circ}\text{C}$, 72 $^{\circ}\text{C}$ and 95 $^{\circ}\text{C}$. However, the common PCR machines are usually complex, bulky and expensive, which can only be used in resource-intensive centralized laboratories, thus precluding their applications for POC detection. The advent of microfluidics in combination with micro electro-mechanical systems (MEMS) technology, have enabled the miniaturization of PCR processes in a chip device with potential merits of ultra-fast speed, low cost and low sample consumption, portability, high throughput, high-integration and automation to be possible [440,441], which would empower PCR-based diagnostics to be used for POC diagnostic applications in resource-poor regions. However, conventional PCR processes integrate precise heating and cooling control modules to perform thermal cycling increase the challenges and cost for miniaturization, which calls for more sophisticated and careful design to optimize thermal properties [442,443]. The emergence of qPCR have realized nucleic acid amplification and quantitative real-time detection in a single step without electrophoresis or hybridization steps, which has been the pioneer of PCR-based integrated NAT despite its complex and precise heating and cooling control [444–446]. To realize rapid or ultrafast NAT, simplifying and shortening the conventional PCR processes are the two key challenges to be addressed. Due to the fact that the heating/cooling rates of conventional PCR systems are only a few degrees centigrade per second and a long time of 1–2 h is needed to complete the whole PCR processes, it is quite slow and the speed is urgently needed to be improved to achieve fast detection. Strategies including increasing the rate of heat transfer, using more efficient heaters, and shrinking of sample volume are the most commonly employed approaches [446–448], among which a small volume of sample is the most attractive option due to its cost-effective and increased heating/cooling rates, and the application of microfluidics enables very small volume samples used in PCR to be possible. In this part, the design

and fabrication of miniaturized PCR devices either based on conventional PCR or qPCR for the POC detection of infectious disease were discussed.

Parasite detection

In a typical example, a handheld, battery operated, chip-based Truelab Uno[®] microPCR device was developed by bigtec Labs, Bangalore, India, for differential identification of *Plasmodium falciparum* and *Plasmodium vivax* parasites. The device was developed based on qPCR method, which was able to detect *Plasmodium falciparum* and *Plasmodium vivax* with similar sensitivity and specificity to the WHO nested PCR protocol based on the evaluation of 100 samples, and the detection limit was of $< 5 \times 10^3$ parasites mL^{-1} for both *Plasmodium falciparum* and *Plasmodium vivax* [289]. In another study, Zaky et al. developed a novel backpack PCR methodology for molecular detection of *Brugia malayi* in mosquitoes, which integrated a rapid NaOH-based DNA extraction methodology, a portable battery powered PCR platform and a test strip-based DNA detection assay [449]. This backpack PCR diagnostic platform eliminated reliance on expensive and bulky instrumentation without compromising sensitivity or specificity of detection, providing an alternative to cost-prohibitive column-dependent DNA extractions that are typically coupled to detection methodologies requiring advanced laboratory infrastructure, and thus holding a great potential for POC detection of various pathogenic parasites.

Bacteria detection

In the past years, multiplex nucleic acid detection of pathogens has attracted special attention due to its benefits of rapid identification of pathogens and high clinical sensitivity [450,451]. Manage et al. developed a multiplex cassette PCR device for the detection of enterohemorrhagic *E. coli* [452]. The cassette PCR contained 10 trenches with a total of 50 capillaries with microliter volumes of LCGreen dye loaded desiccated acrylamide gels to pre-store all the reagents required for the PCR. Finally, the detection was performed by taking CCD images of the entire cassette at each PCR cycle and melt curve analysis at each temperature. The device was capable of simultaneously detecting up to 10 targets of 8 samples within 75 min [452]. Moreover, Salman et al. developed a shunting PCR microfluidic device for nucleic acid detection of *E. coli* [453]. The device comprised a polycarbonate microfluidic PCR chip, a shunting thermal cycler and a highly sensitive lock-in fluorescence detector, which enabled rapid nucleic acid amplification with heating and cooling rates of 1.8 $^{\circ}\text{C}/\text{s}$ and 2 $^{\circ}\text{C}/\text{s}$, respectively. The developed shunting PCR microfluidic device allowed performing low cost PCR amplification with annealing temperatures ranging from 54 $^{\circ}\text{C}$ to 68 $^{\circ}\text{C}$ and the detection limit was 700 ng mL^{-1} , which showed great potential to quantify PCR products in real-time without performing slab gel or capillary electrophoresis [453].

Up to date, the diagnosis of tuberculosis is still a challenge in the clinical medicine by using available conventional methods and it is more difficult to detect extra pulmonary tuberculosis (EPTB) due to the low yield of bacilli in the clinical specimens. For the purpose of addressing this challenge, a chip based TrueNAT device using RT-PCR was introduced for the diagnosis of pulmonary tuberculosis (PTB) and EPTB [454]. A systematic evaluation of the device was conducted using a total of 145 clinical samples including both PTB (80) and EPTB (65). All the results demonstrated that the sensitivity and specificity of TrueNAT device is 93.1% and 72.5% for the diagnosis of PTB and 96.77% and 76.4% for EPTB, respectively. Besides, the device was able to achieve fast detection of PTB and EPTB as well as rifampicin resistance within 2 h, which is portable and compatible for POC detection of *Mycobacterium tuberculosis* [454]. Moreover, an integrated continuous flow PCR (CF-PCR) and electrophoresis bio-chip based all-in-one microfluidic device was recently developed by Li and his coworkers for the detection of *Porphyromonas gingivalis*,

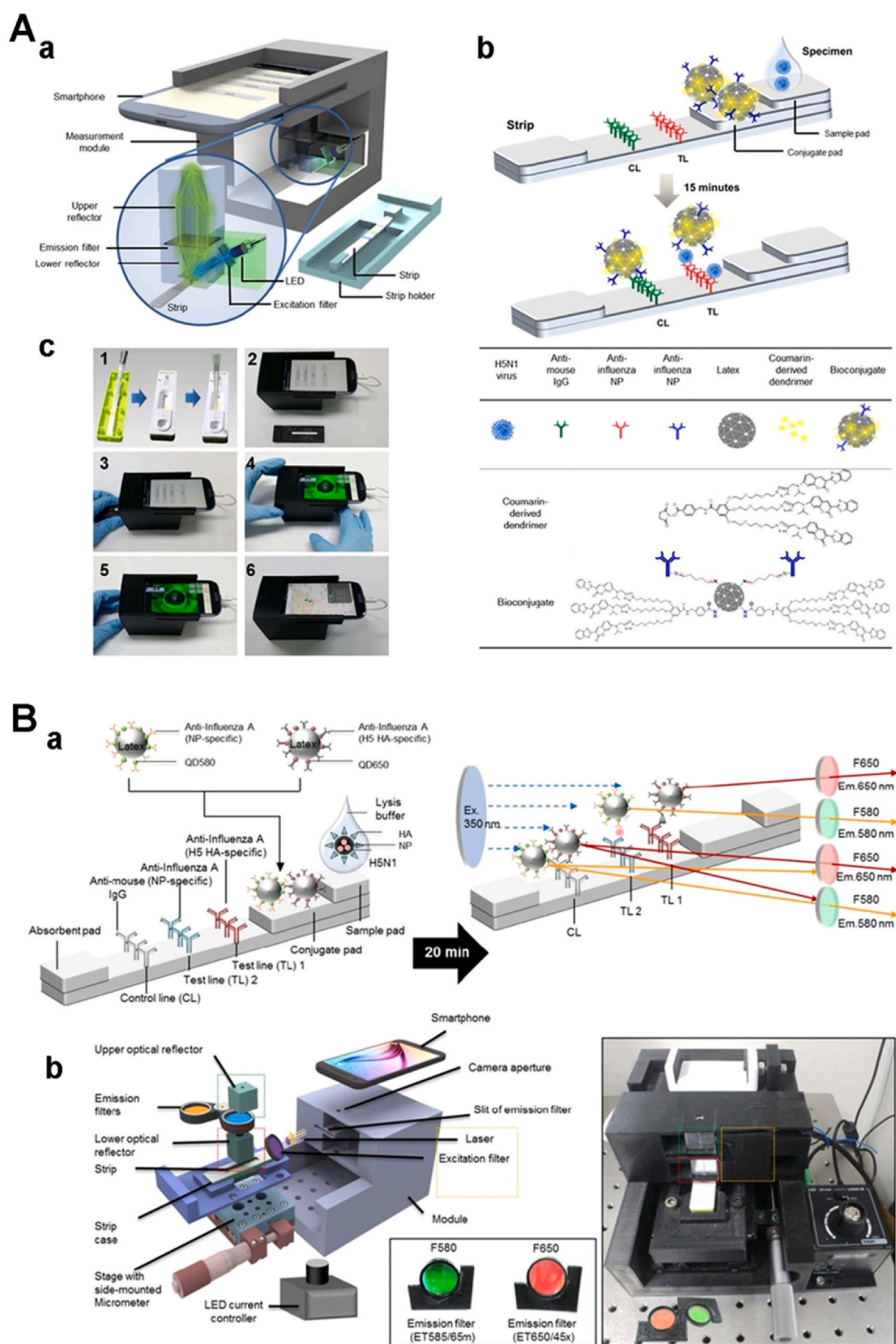


Fig. 22. (A) Schematic of smartphone-coupled fluorescent lateral flow immunoassay device. (a) Schematic description of a smartphone-based fluorescence detector with a reflective light concentrator module. (b) Schematic of a fluorescence detector flow strip for the detection of AIVs, whose fluorescence signal is measured by the smartphone-based diagnostic device. (c) The detection processes of this device. Reproduced with permission from Ref. [435] Copyright 2016, Ivyspring International Publisher. (B) Overview of the smartphone-coupled rapid dual fluorescent lateral flow immunoassay based diagnostic system. (a) Schematic presentation of the multiplexed lateral flow strip with two simultaneous conjugates. (b) Schematic representation of the smartphone-based fluorescence detector with a reflective light concentrator module and two emission filters. Reproduced with permission from Ref. [436] Copyright 2018, Ivyspring International Publisher.

Treponema denticola and *Tannerella forsythia* [455]. The all-in-one device consisted of an innovative pumping unit, two aluminum heaters and an integrated CF-PCR and electrophoresis microfluidic chip (Fig. 23), which was able to achieve automated sample injection, rapid DNA amplification, and on-site PCR product detection in sequence without costly external precision syringe pump. The results showed that the target DNA amplification could be finished as short as 2'31" and the detection of PCR products could be completed within 3'43" with the minimum number of bacteria to be amplified as low as 1.25×10^5 CFU mL⁻¹, indicating its great potential for POC NAT of pathogens [455].

Virus detection

As a paradigm, Zhou et al. developed a home-made microfluidic chip system for sensitive detection of SARS coronavirus [456]. This system was composed of a laser-induced fluorescence microfluidic chip analyzer, a glass microchip for both PCR and capillary electrophoresis, a chip thermal cycler based on dual Peltier thermoelectric elements, a RT-PCR SARS diagnostic kit, and a DNA electrophoretic sizing kit. This system could allow efficient cDNA amplification of SARS-CoV and followed electrophoresis on the same a glass microchip. Subsequently, the results of electrophoresis on the microchip were collected and analyzed via the laser-induced fluorescence microfluidic chip analyzer. The test results of this system showed that 17 positive samples were obtained from 18 samples of nasopharyngeal swabs from clinically diagnosed SARS patients, compared to only 12 positive results from the same 18 samples by the conventional RT-PCR with agarose gel electrophoresis detection, indicating the high positive rate, accurate and rapidity of the microfluidic chip system for SARS diagnosis [456]. Furthermore, due to the significant advantages of qPCR and its gold standard for molecular detection, miniaturizing qPCR devices would contribute to the POC detection of infectious diseases much. Ahrberg et al. developed a handheld qPCR device with an approximate size of 100 mm × 60 mm × 33 mm for on-site detection of H7N9 virus [457]. The device was capable of simultaneously performing four reactions in virtual reaction chamber form on a glass cover slip with a sample volume of ≈ 200 nL. The qPCR device was capable of detecting a single DNA copy of H7N9 virus, and the standard curve slope of the device was -3.02 ± 0.16 cycles at threshold per decade corresponding to an amplification efficiency of 0.91 ± 0.05 per cycle, suggesting its potential for rapid detection of infectious diseases in small clinics [457]. Moreover, in one of our previous work, a qPCR based POC device coupled with magnetic nanoparticle nucleic acid extraction was developed for automated sample-to-result detection of adenovirus [458]. The device comprised a 3D-printed closed cartridge and an automated instrument communicated with a computer via Bluetooth, which weighed 6.5 kg with dimensions of 27 × 27.5 × 25 cm (length × width × height). All the liquids and reagents needed were able to be pre-packaged in the cartridge to achieve fully automated sample-to-result detection. The magnetic separation based nucleic acid extraction and qPCR detection were conducted in the cartridge to avoid contamination. Due to the fact that there are five main steps for nucleic acid extraction based on magnetic separation (lysing, binding, multiple washing and elution), the first five centrifuge tubes (4 × 1.5 mL, 1 × 0.2 mL) of the cartridge were used to hold the nucleic acid extraction reagents, while the next three 0.2 mL centrifuge tubes were employed for the qPCR detection. After systematic evaluation, the device showed similar performance to commercialized qPCR device and manual method, indicating its promising for on-site detection of pathogens [458].

Isothermal nucleic acid amplification (INAA) devices

To circumvent the complex heating and cooling control in conventional PCR devices and increase the detection speed, a series of

isothermal nucleic acid amplification methods have been developed for POC diagnostic applications, such as rolling circle amplification (RCA) [459–461], LAMP [354,462–464], RPA [465,466], strand displacement amplification (SDA) [467,468], helicase dependent amplification (HDA) [469], NASBA [355], multiple cross displacement amplification [470–472] and so on. These isothermal nucleic acid amplification methods were conducted at a fixed temperature without complex thermal cycling equipment, making them more applicable for POC diagnostics [294,442,473,474]. To achieve POC diagnostics, those INAA devices must integrate sample preparation, nucleic acid amplification, detection and even result analysis into one to realized sample-to-result detection, which are portable and can be friendly used by any unskilled personnel. Up to date, there have been a number of reports about INAA devices designed for POC nucleic acid detection of infectious diseases, and some INAA devices have already become commercially available [475–480]. Herein, POC devices using isothermal nucleic acid amplification methods were systematically discussed.

Parasite detection

NAT of parasites is currently one of the most precise and accurate methods for the diagnostics of correlated infectious diseases. However, to achieve POC detection, various INAA methods have been coupled with microfluidic techniques to develop INAA devices due to their outstanding merits. However, manipulation of droplets in the channels of traditional microfluidic devices always needs external valves, pumps or pressure supplies, making the devices complicated. Digital microfluidics (DMF) can address this problem via an electrowetting force to manipulate an individual microdroplet on an array of electrodes and has been employed in the development of INAA devices. As a paradigm, Wan et al. developed a LAMP based handheld, automated and detection system free thermal DMF device called LampPort for the DNA detection of blood parasite *Trypanosoma brucei* (Fig. 24A) [481]. Firstly, droplet manipulation and real-time temperature control systems were integrated into the handheld device. Then, the control software was installed on an external control system to communicate with the device via Bluetooth. In the experimentation, samples were loaded by an electrowetting force into sandwich-structured DMF chips for an on-chip LAMP reaction, followed by addition of a highly concentrated SYBR Green I droplet to mix with the reaction droplet for visualized detection. Notably, the device was able to prevent aerosol contamination due to the absence of air inside the reaction chamber in the DMF chip. This low cost and compact device can achieve sensitive detection of *Trypanosoma brucei* DNA without bulky optical system, and a similar detection limit of 4×10^3 copies mL⁻¹ to a commercial thermal cycler was achieved [481].

Bacteria detection

For the NAT of bacteria, nucleic acid extraction and amplification are very important, which have not been seamlessly integrated in the INAA devices. How to seamlessly integrated the two procedures and achieve automated, portable, highly-sensitive, fast and easy-to-use POC detection remains a great challenge in this field. In the past years, the advent of microfluidic cartridge has presented an effective solution to address this problem. As a paradigm, Liu et al. developed a LAMP based self-heating cartridge for visual fluorescent detection of *E. coli* DNA [482]. The device was fully self-contained without any external instruments, which integrated water-activated exothermic heating with temperature regulation facilitated with a phase change material (PCM) and LAMP (Fig. 24B). Porous paper was used to control the rate of exothermic reaction by modulate the water supply to the exothermic reactor, whose temperature was maintained by the PCM material to range from 20 °C to 40 °C, supplying the power for LAMP. Finally, the visual fluorescent detection was achieved by using a reusable, keychain-mounted UV light. The

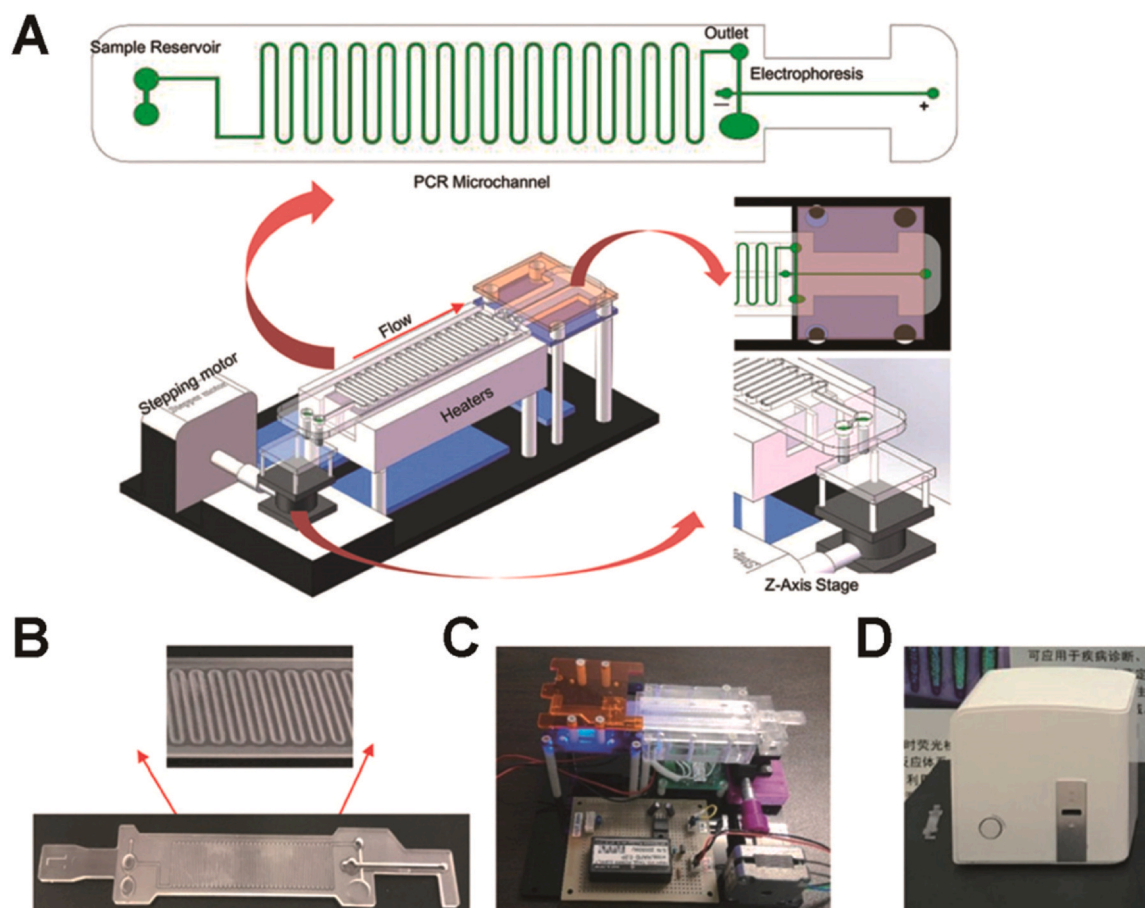


Fig. 23. The schematic for the (A) integrated CF-PCR-electrophoresis microfluidic chip and the all-in-one device. The photos of the (B) microfluidic chip, (C) prototype system, and (D) all-in-one device. Reproduced with permission from Ref. [455] Copyright 2019, the Royal Society of Chemistry.

easy-to-use device was able to detecting *E. coli* DNA consistently with a detection limit of as few as 2×10^3 copies mL^{-1} , which was suitable for use at home, in the field, and in resource poor regions [482]. In another work, Kaur et al. developed a modular fluorescent paper-based LAMP device for the POC detection of MTB gDNA [483]. The device was very user-friendly and cheap with a 12-test-zone device cost of \$0.88 and one reaction reagent cost of \$0.43, which could be operated by an untrained user. Moreover, all reagents could be dry-stored in the device, facilitating storage and transportation without cold chains. Finally, the device was coupled to an inexpensive imaging platform, which enabled filter-free fluorescence detection of amplified DNA via a cell-phone camera. The device exhibited high specificity to MTB in various complex samples with a low detection limit of 10 copies of MTB gDNA. More importantly, the clinical sensitivity and specificity of the device in clinical sputum samples were 100% (zero false negatives) and 68.75% (five false positives), respectively ($N=30$), when utilized Xpert MTB/RIF assay as the reference standard. All those results demonstrate that the device has the potential to provide affordable and accessible molecular diagnostics of MTB at the POC [483].

Virus detection

Rapid detection of virus by NAT is the good standard of the diagnostics of virus caused infections. INAA exhibits many superiorities compared with traditional PCR and qPCR, which has been widely investigated to develop INAA devices for POC diagnostics of infectious diseases caused by viruses. Recently, digital INAA has been one of the hottest research fields, which can be highly integrated

with microfluidic devices to achieve miniaturization of the devices, and highly sensitive and precise detection of target nucleic acids. In one previous work, Yu et al. designed a self-partitioning SlipChip (sp-SlipChip) microfluidic device that could generate droplets by slip-induced flow to perform digital LAMP for POC detection and quantification of human papillomavirus (HPV) DNA [484]. Firstly, the sp-SlipChip containing a designed “chain-of-pearls” continuous microfluidic channel was designed to establish the fluidic path for liquids to be introduced into the device. When one simple manual slipping step was added, the aqueous solution could robustly self-partition into individual droplets by capillary pressure-driven flow. Then, digital LAMP was applied by this sp-SlipChip to perform quantitative analysis of HPV-16/18 nucleic acids extracted from clinical swab samples without cross-contamination observed between adjacent droplets, indicating the digital LAMP based device to be a promising diagnostic tool for POC quantitative analysis of viral load, especially in resource-poor regions [484]. Song et al. developed a microfluidic cassette based device using reverse-transcription LAMP for visualized detection of ZIKV virus [485]. The device was powered a chemically heated cup and achieved visualized detection via the leuco crystal violet dye without external instruments. After evaluation, the device was demonstrated to be able to complete rapid and highly sensitive detection of ZIKV in oral samples with a detection limit of 2.5×10^{-3} ng mL^{-1} within 40 min. Moreover, a portable, smartphone-controlled, automated LAMP based self-driven microfluidic device was developed for rapid colorimetric detection of H1N1 virus (Fig. 25) [486]. The device integrated magnetic beads based sample purification, pathogen lysis, isothermal nucleic acid

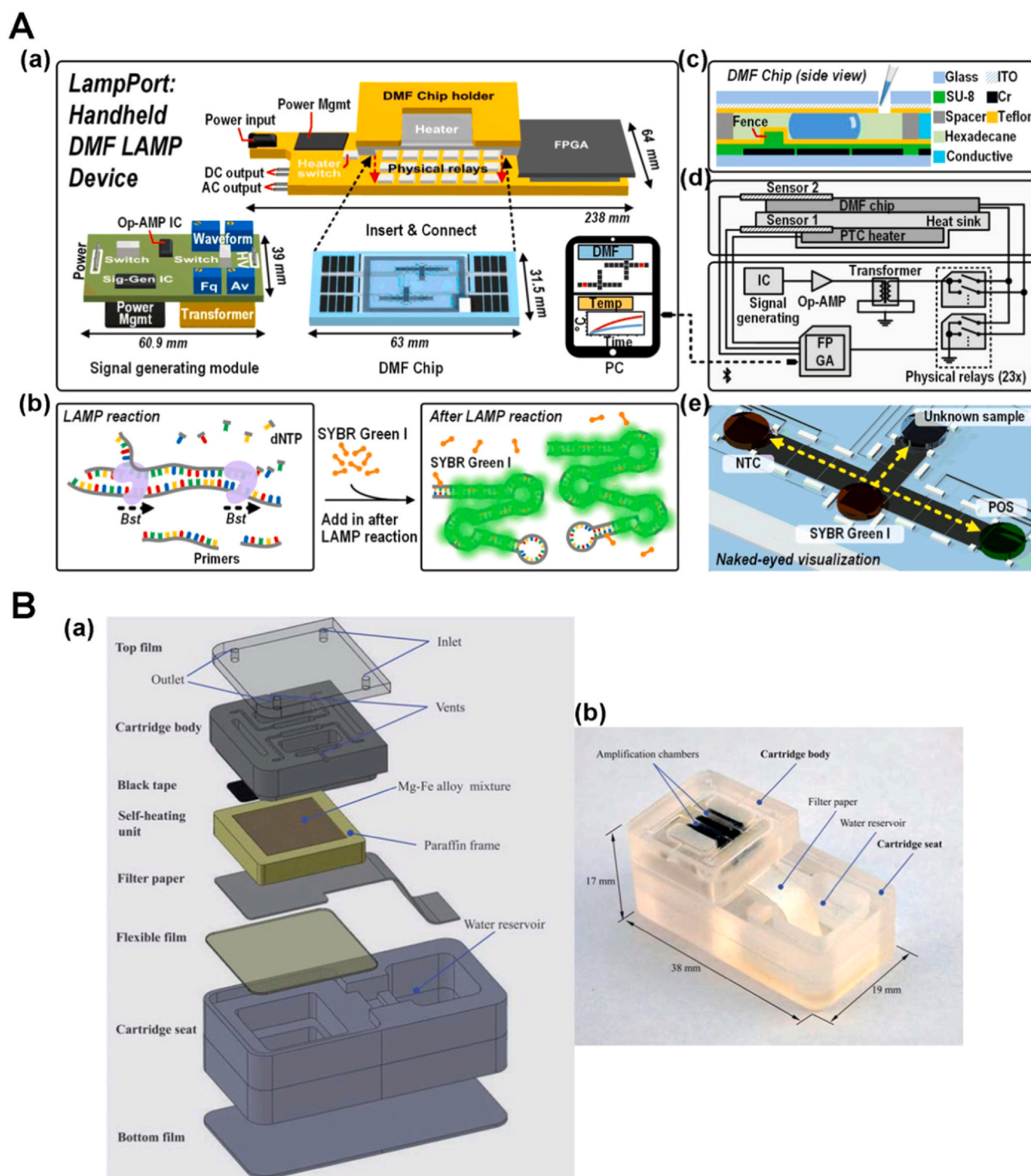


Fig. 24. (A) Schematic illustration of the handheld DMF LAMP device for the DNA detection of blood parasite *Trypanosoma brucei*. (a) 3D schematic of the components of the device. DC: direct current. (b) Schematic of the LAMP reaction and endpoint SYBR Green I denotation of positive LAMP products. (c) Side view of the DMF chip. (d) Droplet actuation and heating control electronics. (e) Schematic of the naked-eyed visualization of the LAMP results. Reproduced with permission from Ref. [481] Copyright 2019, Springer Nature. (B) Schematic illustration of the water-activated, self-heating, non-instrumented cartridge based LAMP device. (a) Exploded view and a photograph (b) of the water-activated, self-heating, non-instrumented cartridge for isothermal amplification of nucleic acids. Reproduced with permission from Ref. [482] Copyright 2011, the Royal Society of Chemistry.

amplification, and colorimetric detection in one, which could be completed within 40 min and controlled by a smartphone. Finally, the device was demonstrated to achieve accurate and sensitive molecular diagnosis of H1N1 virus, whose detection limit was 0.8 ng mL^{-1} , which is sensitive enough for clinical adoption.

In addition, taking advantages of LAMP, we then developed a portable multi-channel turbidity device for rapid nucleic acid detection of H7 subtype avian influenza virus [487]. The device was composed of a temperature control unit, photoelectric detection unit, turbidity calibration unit, power management unit, human

machine unit, communication unit and ARM-based microcontroller with dimensions of 21 cm in length, 15.5 cm in width and 11.5 cm in depth. The testing results demonstrated that the LAMP-based POC device was capable of rapid and highly sensitive nucleic acid detection of H7 subtype of H7N9 avian influenza virus within 60 min, and a low detection limit of 10 copies mL⁻¹ could be achieved. Owing to the current PCR devices require stable electricity and are not portable, Snodgrass et al. developed a portable LAMP based device called TINY for isothermal nucleic acid quantification with power from electricity, sunlight or a flame and the ability to store intermittent energy sources for operation when electrical power is not available or reliable, enabling the device to be used either in a centralized laboratory with electricity supply or in the field when electricity is unavailable [488]. The TINY was able to quantify target nucleic acid in a handheld package with both weight and volume approximately to be an order of magnitude smaller than commercial qPCR machines (Fig. 26). Besides, the latent heat inside TINY was able to keep isothermal amplification for over an hour in case of power outages. Then, the TINY device was tested in two Ugandan health clinics to evaluate the system against commercial machines performing both qPCR and LAMP using the detection of Kaposi's sarcoma-associated herpesvirus DNA as a model. The results showed that TINY device was of equivalent performance either powered by sunlight or electricity and an agreement of 94% with commercial qPCR machines for detection of Kaposi's sarcoma-associated herpesvirus DNA using samples from 71 Ugandan patients was achieved [488]. Most recently, Sun et al. developed a portable LAMP device coupled with a smartphone to perform POC detection of live virus from nasal swab media, using a panel of equine respiratory infectious diseases as a model system for corresponding human diseases such as COVID-19 [489]. In this system, LAMP on a microfluidic chip was applied for target nucleic acid amplification and the smartphone was used as a detector for detecting at the end of reactions. The total assay could be completed in 30 min with high accuracy and sensitivity, whose detection limit was comparable to that of traditional lab-based test and PCR, indicating its great potential for clinical POC detection of infectious diseases such as COVID-19 [489].

In the field of POC devices, development of portable easy-to-use devices that allow sample-to-result detection is the ultimate goal. Thanks to the fast development of nanotechnology, microfluidics and MEMS technology, a couple of portable devices integrated with various POC detection methods have been investigated for the detection of infectious diseases. In this part of this review, fabrications and applications of POC devices including LOC devices, LOAD devices, μ PADs, lateral flow devices, miniaturized PCR devices, and INAA devices for the POC diagnostics of various infectious diseases were systematically presented and discussed. Despite all the distinct merits of those POC devices, they all failed to fully satisfy the ASSURED criterions, leaving many challenges in developing POC devices toward clinical applications. As illustrated in Table 3, LOC devices have advantages of faster, high-throughput and multiplex analysis, smaller sample volume, less power consumption and more efficient control and manipulation, despite the existing challenges in fabricating, sealing and interfacing LOC devices, and difficulty of multiplexing [56,490–492]. LOAD devices displayed particular advantages of: 1) the liquids can be easily handled by centrifugal force via a low cost and controllable spinning motor; 2) can be easily applied for large-scale parallelization and multiplexing. But they are still limited by their relatively short shelf life, difficult on-board reagent storage, and are hard to deal with samples of very small volumes [492–495]. μ PADs are attractive POC devices that are very potential toward commercialization due to their low cost, easy fabrication and operation, no need of external pumps or power sources, and well compatibility. However, they are currently limited by their inherent shortcomings such as lack of flow control, difficulty

of multiplexing and multi-step assays, limited sensitivity, inability of instant response and repeatable use [386,496,497]. Lateral flow devices have been widely deployed POC diagnostics due to their superiorities of user-friendly, low cost, easy miniaturization and development, and independent on equipment, they have limited capability to achieve quantitative detection, and the multiplexing capability and throughput need to be further improved [421,498,499]. For miniaturized PCR devices, they own common merits of traditional PCR devices of accurate quantification, small sample and high sensitivity, the deficiencies are high production cost, expensive complex device, and trained professional person are needed [294,441,500]. Finally, INAA devices are simple and high sensitive devices that can achieve fast POC detection. However, current POC diagnostics based on INAA devices are limited by high requirements for the primers and expensive reagents [501–503]. Among all those challenges, the most important challenge in the fabrication of POC devices for the detection of infectious diseases is how to integrate all the detection steps into a compact single device, including sample pretreatment, reaction, signal amplification and acquisition, and data analysis and display. The other important challenge is how to miniaturize the device and keep all its functions as well, which requires the cooperation work of several research areas such as nanotechnology, MEMS, microfluidics, 3D-printing, and materials science. Moreover, guaranteeing the performance and clinical utility of the device comparable to the gold standard methods used in the laboratory settings is also very crucial, which needs very precise design and fabrication. Besides, reducing the fabrication cost and making it an individual affordable device would guarantee the device to be very popular and own a broad market. Finally, in consideration of the complex situation of clinical diseases and mixed infection, achieving high throughput and simultaneously detection without any interference and minimal human intervention is very attractive and fascinating, and efforts have been made to achieve this goal.

Conclusion and future perspectives

The current outbreak of COVID-19 worldwide has exposed our deficiencies in the prevention and control of infectious diseases, especially in the aspects of rapid detection and early screening, which urgently require portable POC diagnostics and correlated devices to contribute to rapid discovery of infections in time, especially in resource-poor regions where the medical conditions are always limited. In this review paper, we systematically summarized recent progresses in the development of POC detection methods and correlated POC devices for the diagnostics of various pathogens caused infectious diseases including parasites, bacteria and viruses. In the first part, detection methods for POC detection of infectious diseases were summarized, including electrochemical biosensors, fluorescence biosensors, SERS-based biosensors, colorimetric biosensors, chemiluminescence biosensors, SPR-based biosensors, and magnetic biosensors. Then, the progresses in the development of various POC devices and their applications in the detections of various infectious diseases, including LOC devices, LOAD devices, μ PADs, lateral flow devices, miniaturized PCR devices, and INAA devices, were particularly reviewed.

Despite the fast development of POC detection methods and correlated POC devices for infectious diseases, achieving fast, highly sensitive and accurate POC diagnostics of infectious diseases remains a big challenge in this field. The performances of a good practicable POC device should meet the “ASSURED” standard, which requires the device to be of fast detection, high accuracy, low detection limit, low cost, good repeatability and stability, and to be user-friendly. To achieve those goals, a highly integrated POC device able to achieve sample-to-result detection that can conduct sample pretreatment, reaction, signal amplification, detection, data analysis

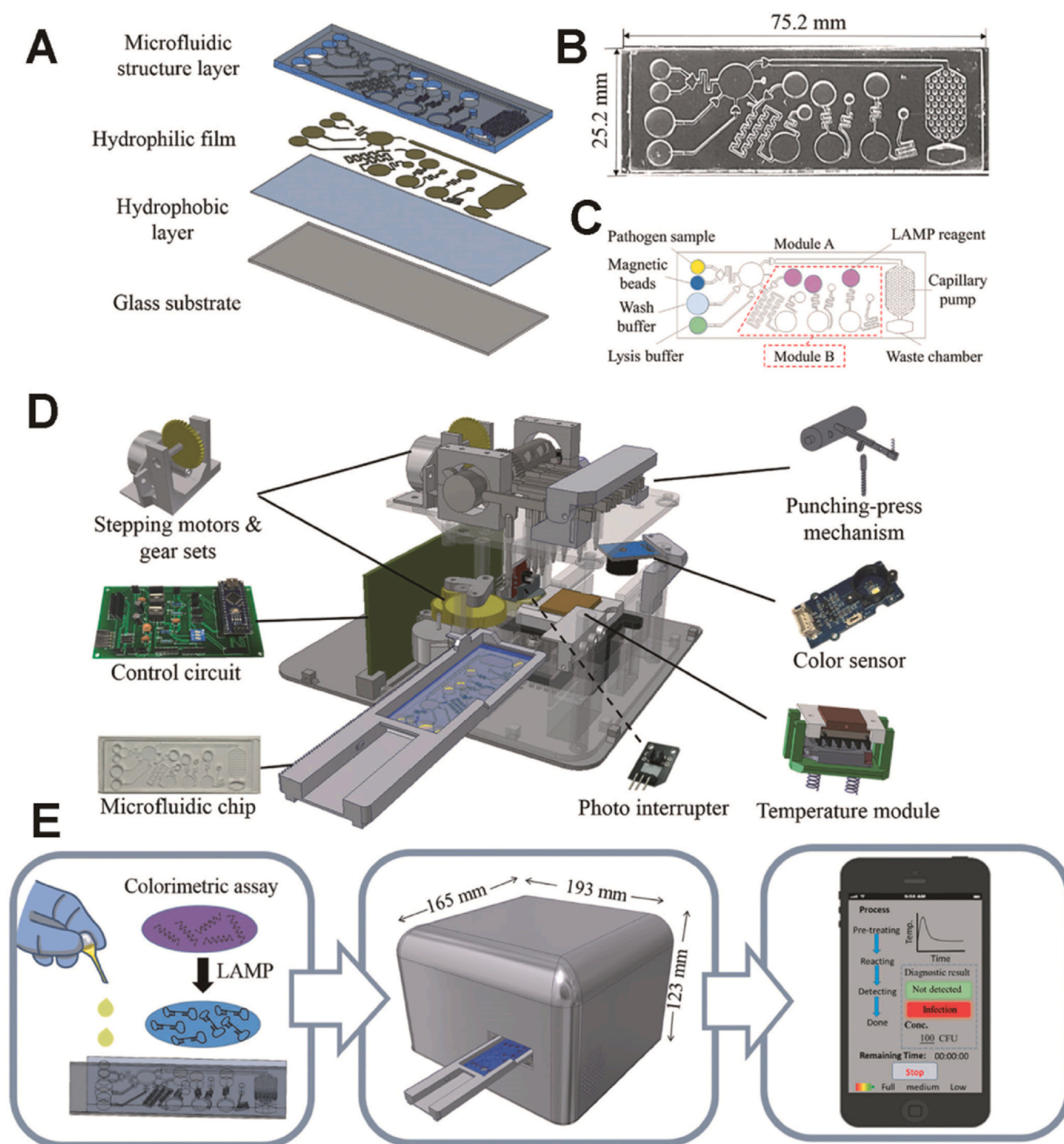


Fig. 25. (A) Exploded view of the self-driven microfluidic chip consisting of a PDMS microfluidic structure layer, a hydrophilic film, a PDMS hydrophobic layer, and a glass substrate. (B) A photograph of the chip. (C) Schematic illustration of the chip design. The area enclosed by the red dotted line represents the LAMP reaction module (module B), with the other area being used for sample pretreatment (module A). (D) Illustration of the portable system composed of two stepping motors, two sets of gears, two photo-interrupters, a punching-press mechanism, an Arduino-based microcontroller circuit, a thermal control module, a color sensor, and a microfluidic chip. (E) Experimental workflow of a sample-to-answer, portable platform for rapid pathogen detection. Reproduced with permission from Ref. [486] Copyright 2019, the Royal Society of Chemistry.

and reader automatically is the most essential [353,504]. However, to achieve detection without sample pretreatment is always very hard especially for infectious diseases due to their complex components with human body fluids, which can interfere the detection results. Therefore, the future development of POC diagnostics for infectious diseases may focus on designing assays using original clinical samples with no need of sample pretreatment. The second challenge is that the detection speed and sensitivity of current POC

devices should be improved, which mainly depends on the design of novel detection methods [505,506]. The third challenge of the development of POC devices for infectious diseases is that the costs need to be decreased. Only when the costs of the devices are widely affordable can the POC devices realize their social values and benefit human health [507,508].

The fast development of mobile networks, internet of things (IoT), machine learning and AI has facilitated the development of

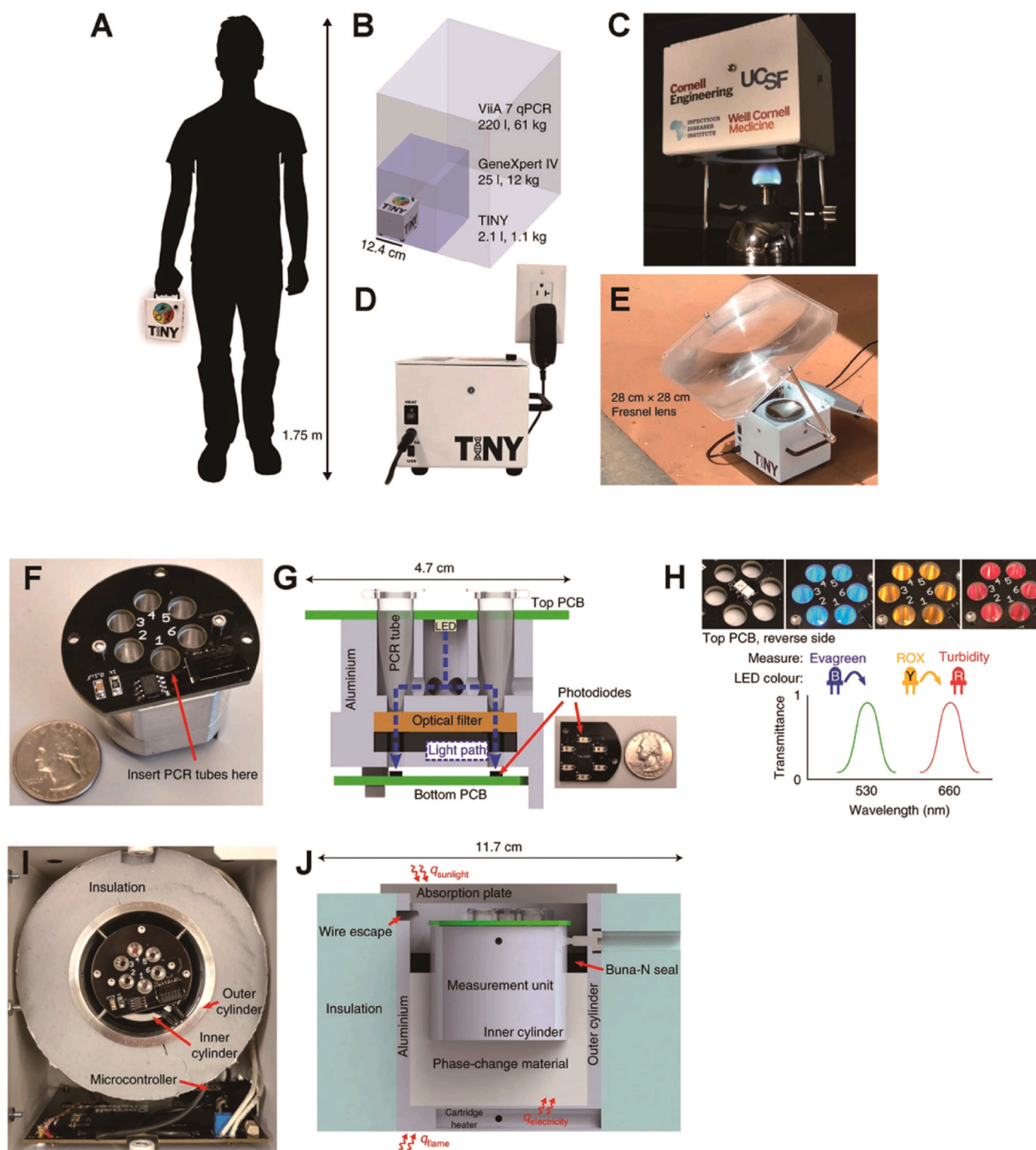


Fig. 26. Schematic illustration of the portable LAMP based device called TINY for isothermal nucleic acid quantification with power from electricity, sunlight or a flame. (A) TINY is portable and easily carried in one hand, which is far smaller than the GeneXpert IV by Cepheid (footprint outlined by the dark purple box), or the ViiA 7 Real-Time PCR System by Thermo Fisher Scientific (light purple box) (B). (C) TINY heated by a Bunsen burner through an opening in the bottom of the system. (D) TINY heated via electricity, using an integrated cartridge heater. (E) TINY heated via concentrated sunlight at the infectious diseases institute in Uganda. (F) A photograph of the measurement unit separated from the temperature-regulation unit. (G) A cross-section of the measurement unit. (H) LEDs are placed on the bottom side of the top PCB. (I) Looking down into the TINY system with the solar absorption plate removed. (J) A cross-section of the temperature-regulation unit. Reproduced with permission from Ref. [488] Copyright 2018, Springer Nature.

POC devices towards remote assay operation and interpretation, more user-friendly and convenient operation, fully automated and intelligent detection, and high-efficient result readout, enabling personalized diagnosis and therapy in a fast, low cost and

high-efficient way [509–514]. By using IoT, POC devices would be able to communicate with centralized location remotely, provide important information to the operators, and speed up the data transmission for big data analysis, which can contribute greatly to

Table 3
Comparisons of the POC devices for the diagnostics of infectious diseases.

Devices	Pros	Cons	Refs.
LOC devices	High-throughput, multiplex and faster analysis, small sample volume, less power consumption and more efficient control and manipulation	Difficulty of fabricating, packaging and interfacing, and difficulty of multiplexing	[56,490–492]
LOAD devices	Low cost and easy control by centrifugal force, simple and independent liquid handling, large-scale parallelization and multiplexing	Short shelf life, difficult on-board reagent storage, and hard to work with very small volumes	[492–495]
μ PADs devices	Low cost, easy fabrication and operation, no need of external pumps or power sources, and well compatibility	Lack of flow control, difficulty of multiplexing and multi-step assays, limited sensitivity, inability of instant response and repeatable use	[386,496,497]
Lateral flow devices	Low cost, user-friendly, independent on equipment easy miniaturization and development	Difficulty of achieving quantitative detection, limited multiplexing capability and throughput	[421,498,499]
Miniaturized PCR devices	Accurate quantification, small sample and high sensitivity	High production cost, expensive complex device	[294,441,500]
INAA devices	Fast, simple device, and high sensitivity	High requirements for the primers and expensive reagents	[501–503]

the prevention and control of pandemic such as COVID-19 [515,516]. The current commercialized fifth generation of mobile network will provide a massively increased data rate and accelerate the application of IoT for POC detection. Besides, due to the mushrooming of machine learning in recent years, it has also been harnessed with POC devices to improve the medicine practice by integrating clinical detection and disease diagnostics based on big data and intensive evidences [511,517,518]. Finally, the deep learning methods in AI would advance the fabrication of POC devices towards AI-based devices, which will revolutionize medical diagnostics and endow them the ability to achieve automated and intelligent medical practice with precise diagnostics in complex biological environments at POC and provide personalized therapeutics in time. Those approaches will contribute to realize earlier identification of infectious diseases, which is more effective than that at the advanced stages, thus helping the prevention of pandemic outbreak [519–522].

Finally, the data processing of POC devices is also very important. In the past years, the fast growth in cloud computing has made the data transmission, storage and analysis easier and more efficient and convenient. POC devices combined with cloud computing would accelerate the detection speed, enhance diagnosis accuracy and efficiency, which is of great significance to the control of infectious diseases and enables precise personalized medicines [314,523,524]. However, by using cloud computing, all the healthcare data concerning personal privacy will be uploaded to the cloud storage, which can be downloaded by different platforms, parties and even individuals. Thus, how to keep data safety of cloud computing is a great challenge. To address this problem, on the one hand, internet laws are essential to guide the data storage by cloud computing servers. On the other hand, new sophisticated encryption methods should be developed for cloud computing to guarantee the data safety.

CRedit authorship contribution statement

Chao Wang: Conceptualization, Writing-original draft. **Mei Liu:** Conceptualization, Writing-original draft, Review & Editing, Supervision. **Zhifei Wang:** Review & Editing, Supervision. **Song Li:** Review & Editing. **Yan Deng:** Review & Editing. **Nongyue He:** Conceptualization, Writing, Review & Editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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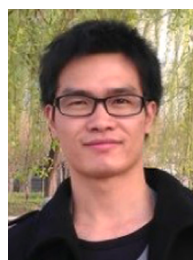
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