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LAMP-on-a-chip: Revising microfluidic platforms for loop-mediated DNA amplification

Haoqing Zhang [a], Ying Xu [a], Zdenka Fohlerova [b, c], Honglong Chang [a], Ciprian Iliescu [d, **], Pavel Neuzil [a, b, *]

[a] Northwestern Polytechnical University, School of Mechanical Engineering, Department of Microsystem Engineering, 127 West Youyi Road, Xi'an, Shaanxi, 710072, PR China
[b] Central European Institute of Technology, Brno University of Technology, Purkyňova 123, 61300 Brno, Czech Republic
[c] Faculty of Electrical Engineering, Brno University of Technology, Technická 3058/10, 61600 Brno, Czech Republic
[d] Biomedical Institute for Global Health Research and Technology (BIGHEART), National University of Singapore, MD6, 14 Medical Drive #14-01, 117599, Singapore

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ABSTRACT

Nucleic acid amplification for the detection of infectious diseases, food pathogens, or assessment of genetic disorders require a laboratory setting with specialized equipment and technical expertise. Isothermal deoxyribonucleic acid amplification methods, such as loop-mediated isothermal amplification (LAMP), exhibit characteristics ideal for point-of-care (POC) applications, since their instrumentation is simpler in comparison with the standard method of polymerase chain reaction. Other key advantages of LAMP are robustness and the production of pyrophosphate in the presence of the target gene, enabling to detect the reaction products using the naked eye. Polymerase inhibitors, presented in clinical samples, do not affect the amplification process, making LAMP suitable for a simple sample-to-answer diagnostic systems with simplified sample preparation. In this review, we discuss the trends in miniaturized LAMP techniques, such as microfluidic, paper-based, and digital with their advantages and disadvantages, especially for POC applications alongside our opinion of the future development of miniaturized LAMP.

1. Introduction

Polymerase chain reaction (PCR) [1] is currently the most widely used nucleic acid amplification test (NAAT) method. The integration of heating, and, especially cooling control modules used for thermal cycling to perform PCR increases the challenges and cost of the point-of-care (POC) system's design and operation. This demands careful design for the PCR system to optimize thermal properties, which directly influences its performance, as extensive transition times between temperature segments of each cycle could result in non-specific amplification results.

With an advent of microfluidics methods over the past 25 years, the PCR technique was one of the first utilizing this technology [2]. Since then, the microfluidics were extensively exploited for PCR applications in their conventional [3], quantitative [4], and digital form [5,6], including different POC assays [7,8]. Integration of a conventional PCR with pre- or post-processing samples is difficult, as it requires specially developed hybridization probes, which can pass the nucleic acid (NA) denaturation steps with a temperature of ≈95°C [9].

Isothermal amplification (IA) methods became promising alternatives [10] to PCR, especially for POC applications [11,12]. IA conducts deoxyribonucleic acid (DNA) amplification at elevated constant temperatures, simplifying the system design and operation. The temperature range required to perform IA is typically from ≈37°C to ≈65°C, lower than the one used for PCR denaturation, making the IA system simpler in comparison with PCR and suitable for integration with sample preparation [13–17].

The most widely used IA method is loop-mediated isothermal amplification (LAMP) as it provides excellent specificity in comparison with other IA methods [18]. LAMP utilizes six specific oligonucleotides sequences in the initial (material-producing) step and then four sequences during amplification, elongation, and

* Corresponding author.
** Corresponding author.
E-mail addresses: bigci@nus.edu.sg (C. Iliescu), pavel.neuzil@nwpu.edu.cn (P. Neuzil).

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recycling steps. The process is based on primer annealing followed by auto-cycling strand displacement. It was originally performed at elevated temperatures of ≈65°C [18–20] (Fig. 1). The LAMP is a rapid, sensitive technique for NA amplification, with applications in clinical diagnostics and pathogen detection [21–25], food safety testing [26], and others.

Here, we present the trends in the LAMP-on-a-chip systems for NAAT including its microfluidic, paper-based and digital variants. For each specific system, we reviewed their impacts and potentials. We also briefly described the detection methods used for LAMP techniques as well as LAMP applications. The potential of LAMP-on-a-chip technology relies on simplified hardware, easy options to integrate it with sample preparation steps, and LAMP detection capability. The insensitivity of the LAMP technique to the inhibitors presented in the clinical sample makes LAMP an exciting method for the detection of infectious diseases or genetic maladies.

2. Microfluidic approaches in NA amplification

Nucleic acids amplification methods are primarily required to be performed, as the original number of either DNA or ribonucleic acid (RNA) copies in the clinical sample is insufficient for their direct detection. They can be categorized according to the operating procedures, as either temperature cycling or isothermal.

2.1. Temperature cycling amplification

Polymerase chain reaction is the most common technique used for NA amplification [1,27]. The reagents are DNA polymerase, two sets of primers (oligonucleotides), and deoxynucleoside triphosphates. The PCR protocol requires a temperature-cycling process in three sub-steps: denaturation of a double-stranded DNA (dsDNA) molecule to two single-stranded DNA (ssDNA) molecules at ≈95°C, annealing of the target sequence of specific primers to ssDNAs at ≈55°C, and enzymatic elongation to finish the dsDNA at ≈72°C. The cycling is typically repeated 30–40 times to achieve a detectable number of DNA copies. The speed of the PCR process is defined mainly by the activity of DNA polymerase and the heat transfer rate defined by the hardware setup. The microfluidic PCR systems have rapid heat transfer due to a small sample volume and high surface-to-volume ratio. They can be divided into two major groups according to the temperature cycling method:

- *stationary chamber PCR* [28] is also called “time domain PCR” [29]. A defined volume of sample positioned in a chamber [5] or sealed in a droplet [30] is heated and cooled, either actively using an external element, or passively by simply switching the heater off with a stationary sample. Different heating methods are developed for a fast process, including infrared-mediated [31], plasmon-assisted heating [32], and ultrafast with active heating and passive cooling, achieving 40 cycles PCR in <6 min [33].

- *continuous flow PCR* method can be called, more generally, the “space domain PCR”. The sample moves between heaters with

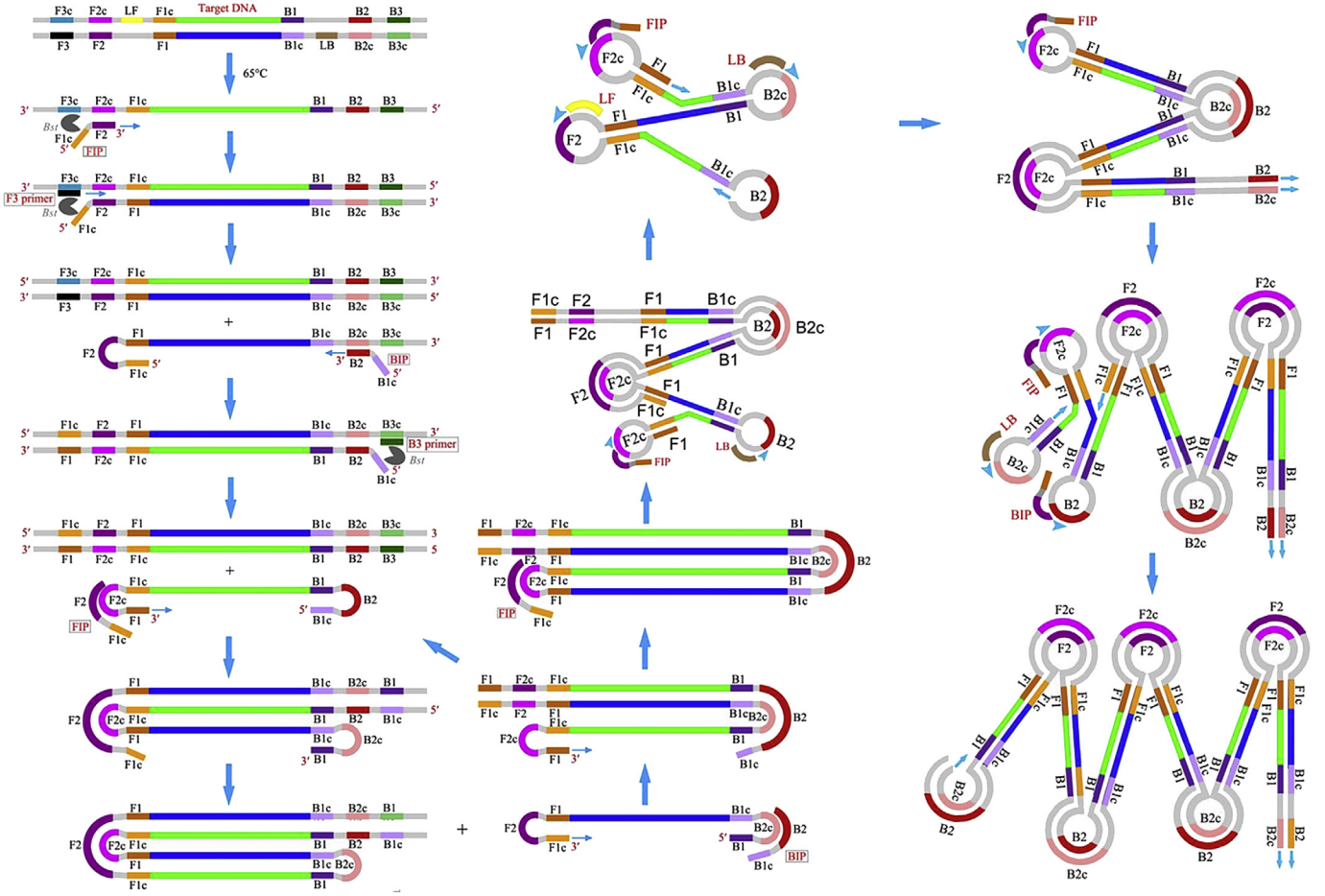

Fig. 1. Schematic of LAMP. Reproduced with permission from Ref. [20], open access.

different temperatures. The chip in early reported work [2] had a serpentine channel build over three heating blocks. Overall, the continuous flow PCR system does not need the temperature cycling from the heaters but does need an external pumping unit and an accurate flow control. Recently, a PCR system with an ultimate reaction time, was demonstrated achieving a cycle time of between ≈0.2 s and ≈0.5 s, resulting in the total time required for 40 cycles of PCR within an incredible range of ≈8 s to ≈20 s [34].

The PCR system's utilization for POC is limited by the system hardware and the sample-to-answer protocol complexity. Numerous steps are required to remove polymerase inhibitors from clinical samples.

2.2. Isothermal amplification

Isothermal amplification techniques require simple hardware and they are rather insensitive to polymerase inhibitors, making the amplification process robust. They typically require a processing time within a range from ≈15 min to ≈60 min, significantly longer than microfluidic-based PCR running time. The most promising IA techniques suitable for conduction in microfluidic devices are nucleic acid sequence-based amplification (NASBA) [35], recombinase polymerase amplification (RPA) [36], helicase dependent amplification (HDA) [37], and LAMP [18].

NASBA [35] is an IA method operating at a temperature of ≈41°C, designed to amplify target RNA. NASBA can achieve up to ≈10^9 fold target amplification in ≈90 min [38]. This technique requires the initial removal of secondary structures from target RNAs to achieve specific amplification products conducted at ≈65°C. This method, integrated with a sample preparation, was demonstrated to detect the norovirus in oysters [39].

RPA [36] is an IA operating entirely at a relatively low temperature range from ≈37°C to ≈42°C. It can amplify a target sequence using a recombinase, single-strand binding proteins, and a strand-displacement polymerase. RPA has the advantage of a fast reaction with relaxed requirement for temperature control. This method has been demonstrated by the lab-on-a-foil system, based on a centrifugal microfluidic cartridge. The system was capable of detecting <10 DNA copies in ≈20 min [40]. Another RPA-performing device, constructed of a substrate comprising of a paper made from a combination of glass fiber and cellulose could detect human immune-deficiency virus (HIV). Results were detected by lateral flow strips achieving a limit of detection (LOD) of 10 copies in ≈15 min [41].

HDA [37] is another type of IA working in a temperature range from ≈45°C to ≈65°C using a DNA helicase for denaturation of dsDNA into ssDNA. Unfortunately, its speed of long-target sequence amplification is a limiting factor. The strength of this method is its combination with paper-based microfluidics, as demonstrated by the detection of *Mycobacterium tuberculosis* [42].

LAMP [18] is one of the IA methods for DNA amplification, operating at temperatures of ≈65°C. Its low running cost and the simplicity of the hardware makes LAMP one of the most promising techniques for genetic analysis in low-resource settings. The development of LAMP-on-a-chip techniques will be further elaborated in the next sections.

3. Classical microfluidics-based LAMP

Microfluidics-based LAMP chips with different structures were proposed for POC diagnostics. Here, we summarized the development of those chips based on single gene detection, multi-gene detection, and reverse transcription LAMP (RT-LAMP) (Fig. 2).

3.1. Single gene detection

A magnetic bead-based LAMP system, integrating NA extraction and temperature control, was proposed for the rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. 2A) [43]. The clinical samples, along with the specific nucleotide-coated magnetic beads, the washing buffer, and the reaction mixture were first loaded into the chambers of three different chips. The DNA was then extracted from the bacteria (cell lysis), bound to magnetic particles, and concentrated, using a magnetic field followed by LAMP. The fluids transportation and their mixing were assisted by a vacuum pump and a micro valve. The temperatures for cell lysis and LAMP were controlled by a built-in micro temperature control module. The results were analyzed using a spectrophotometer and the LOD was ≈10 fg μL^{-1}. This system was significantly faster in comparison with standard MRSA detection, as time-consuming cell culturing was eliminated. Also, the risk of contamination during cell culture was greatly suppressed as the system keeps the bacteria enclosed. Nevertheless, the solution movement in the chip and the optical detection were achieved by external components, such as the pump and spectrophotometer.

A microfluidic disk-based LAMP chip, integrating sample preparation and detection, was developed [44] (Fig. 2B). The disk consisted of a pressure-sensitive adhesive material film sandwiched between two poly(methyl methacrylate) (PMMA) layers. The LAMP reagents and the solution containing the DNA template were preloaded into respective chambers and sealed within the chip, prior to the experiment. The solution mixing was achieved by modulating the rotation rate of the disk, alternating the centrifugal force. The chip was kept at an elevated temperature using a hot air gun with a chip temperature monitored by an infrared camera. The results were optically detected as fluorescence change using SYBR Green I intercalating dye with achieved LOD of ≈5 pg μL^{-1}. The large size of the hardware, due to bulky temperature and disk rotation control systems, made it challenging for POC applications.

3.2. Multi-gene detection

Single gene detection using a compact integrated microfluidic LAMP chip is rather costly. Therefore, chip structures were modified to meet the requirements of multiplexed gene detection with high throughput. An octopus-like multi-channel chip was fabricated using the soft lithography method (Fig. 2C) [45]. The microchannels were connected to the related wells via gradient bridges. The designed microchannels present a low-mass-transfer coefficient to avoid the “cross-talk”. The different sample solutions were loaded into the chamber by capillary force and sealed. Then the LAMP was performed at ≈63°C. The results were detected using an optical sensor, obtaining LOD <10 copies·μL^{-1}. Nevertheless, the sample pre-treatment, heating, and optical detection was performed off chip.

Compared with the previous design, the LAMP disk system was proposed, integrated with DNA extraction and amplicon detection using a colorimetric lateral flow strip (Fig. 2D) [46]. It consisted of three major microfluidic layers from top to bottom for solution loading and transportation, DNA extraction and amplification, and lateral flow strip detection, respectively. The reagents for LAMP were loaded and sealed in the chamber. The chip was mounted on a centrifugal system, and the solution mixing and transportation via microchannels were controlled by operating different revolutions per min. Three identical units on the chip allowed simultaneous multi-gene detection with LOD of 50 colony-forming units. Nevertheless, the off-chip temperature control module limited its application for POC diagnostics.

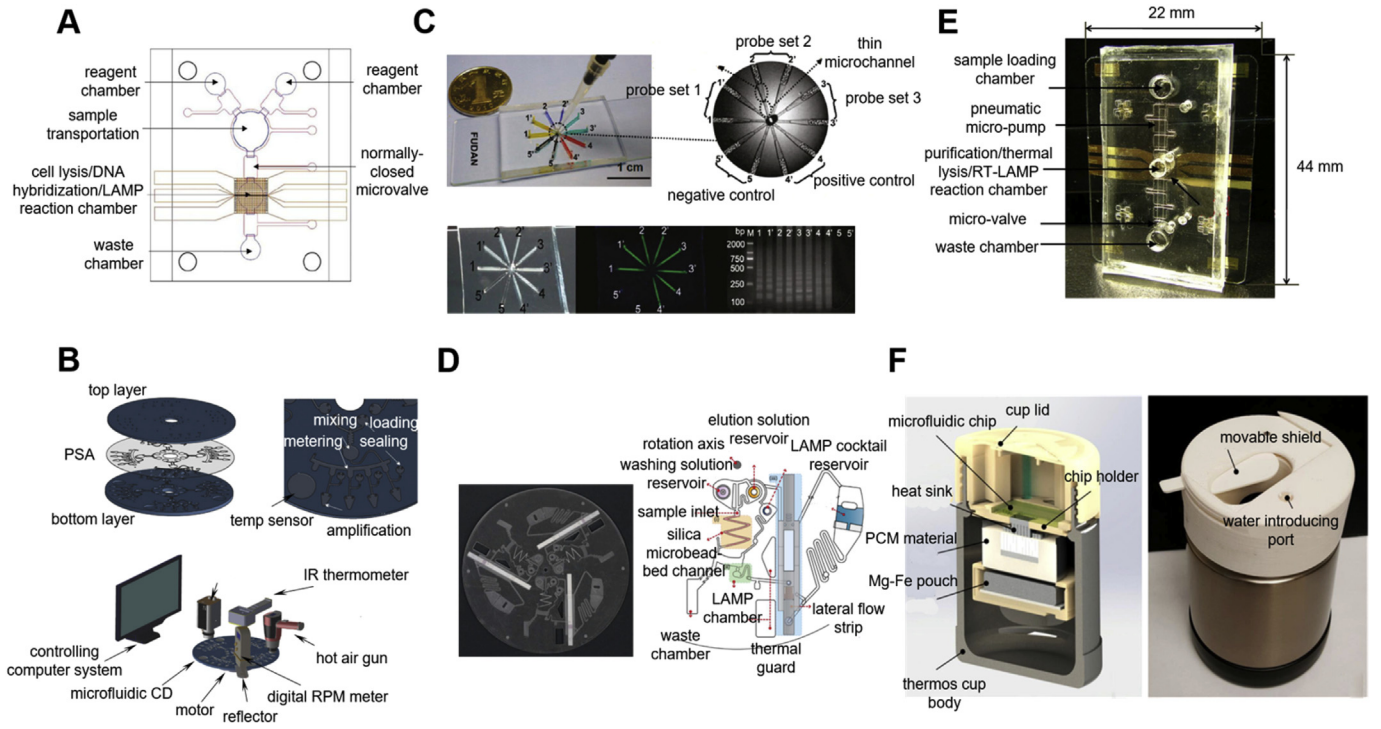

Fig. 2. Microfluidic LAMP systems in different gene detections. (A) Schematic of a magnetic bead-based assay for the rapid detection of MRSA. Reproduced with permission from Ref. [43], copyright 2008 Royal Chemistry of Society. (B) Schematic view of the lab-on-a-disc for detection of foodborne pathogens Reproduced with permission from Ref. [44], copyright 2016 Elsevier. (C) Octopus-like multiplex microfluidic LAMP system. Reproduced with permission from Ref. [45], copyright 2011 American Chemical Society. (D) Top view of an integrated rotary multi-LAMP system. Reproduced with permission from Ref. [46], copyright 2017 Elsevier. (E) A photograph of the integrated RT-LAMP system, consisting of a microfluidic control module and an IA module. Reproduced with permission from Ref. [47], copyright 2011 Elsevier. (F) Fully integrated RT-LAMP system to detect Zika virus. Reproduced with permission from Ref. [48], copyright 2016 American Chemical Society.

3.3. *Reverse transcription LAMP (RT-LAMP)*

An RT-LAMP system (Fig. 2E) [47], made from polydimethylsiloxane (PDMS), was designed to integrate RNA extraction and one-step RT-LAMP with an external temperature control. The sample was transported by operating the integrated pneumatic pump and valve. The RNA was extracted using specific probe-conjugated magnetic beads after sample loading. The RT and LAMP steps were performed using integrated micro-heater systems. This research presented a hands-off integrated system for virus detection from the sample containing RNA using the one-step RT-LAMP process. However, off-chip electrophoresis was performed for amplicon detection.Table 1.

An integrated RT-LAMP system for rapid detection of the Zika virus (Fig. 2F) was proposed [48]. The disposable chip consisted of four independent multifunctional reactors. The RNA was extracted and transferred into the amplification chamber. The chip was then placed inside a thermally insulated portable chamber, heated by an exothermic chemical reaction to perform LAMP. The results were recorded using a mobile phone camera, but it was also directly visible using the naked eye. This low-cost, simple, integrated sample-to-answer-based RT-LAMP system underlines the potential of this technology for POC applications.

A combination of multiplexing and RT-LAMP has also been demonstrated detecting two RNAs, both from HIV, thus increasing the specificity of its diagnostics [59].

4. Paper-based microfluidic LAMP

Classical microfluidic LAMP devices require pumping systems and valves for fluid manipulation, increasing the cost and operational complexity of the system. The researchers explored the potential of much simpler paper-based devices, well-known for their robustness, cost-effectiveness, and user-friendliness [60,61]. In this section, we summarize their characteristics, showing their potential applications (Fig. 3). A critical aspect for paper-based NA amplification is the paper's material selection. The nonspecific binding of DNA molecules to the paper's fibers as well as paper self-fluorescence, negatively influence the noise level and thus the LOD. The most commonly used paper types are either nitrocellulose-based FTA [49–51] or glass-based [62].

A disposable cassette for the detection of HIV was proposed [49] (Fig. 3A). The cassette, made from PMMA, consisted of a single amplification chamber connected to the inlet and outlet ports. The FTA membrane was incorporated into the chamber for RNA isolation, concentration, and purification. As a result, the captured RNA was directly used as a template for RT-LAMP, without the elution or removal of the amplification inhibitors. A thin film heater, together with a conventional thermocouple, was mounted to the cassette holder to provide key components of a closed-feedback loop-thermal control system. The fluorescence of the sample was monitored in real-time using a portable and compact optical detector, achieving an LOD of <10 HIV virions. The system could be improved to detect nucleic acids related to other pathogens in saliva and urine, as well as in water.

A magnetic-based sliding-strip device [51] was fabricated for gene detection (Fig. 3B). A magnetic strip with an FTA-based disc was sandwiched between two magnetic layers, containing serial ports for sampling, washing, amplification, and detection. The linear motion of the sliding strip acted as a valve to control all processing steps. The probe's fluorescence was detected using a hand-held ultraviolet source, achieving an LOD of ≈5 cells.

Table 1
Characteristics of LAMP-on-a-Chip. FTA stands for Flinders Technology Associates, producing the FTA membranes, and LFA stands for lateral flow assays.

Technique	Ref	Target	Gene	Pre-treatment	Sample movement	Heating	Detection method	LOD
Microfluidic	[43]	DNA	1	on chip	vacuum pump off chip	heater on chip	spectro-photometer	10 fg μL^{-1}
	[44]	DNA	1	on chip	centrifugal force on chip	hot air gun off chip	visual	5 pg μL^{-1}
	[45]	DNA	3	off chip	capillary force on chip	heater off chip	optical sensor	10 copies $\cdot \mu L^{-1}$
	[46]	DNA	3	on chip	centrifugal force on chip	heater off chip	lateral flow strip	50 colony forming units
	[47]	RNA	1	on chip	pneumatic pump on chip	micro heater on chip	electro-phoresis	not stated
	[48]	RNA	1	on chip	silica membrane on chip	chemically exothermic reaction on chip	visual	not stated
			Material					
Paper-based	[49]	RNA	FTA	on chip		thin film heater on chip	optical sensor	<10 HIV particles
	[50]	DNA	FTA	on chip		oven off chip	visual	not stated
	[51]	DNA	FTA	on chip		heater off chip	grey value of image analysis	≈ 5 cells
	[52]	DNA	glass fiber-PDMS-FTA	on chip		heater off chip	LFA	≈ 5 pM
	[53]	RNA	PDMS on Al-coated paper	off chip		heater off chip	fluorescence	not stated
			Reaction chambers	Number of reaction chambers	Sample volume	Sample loading		
Digital LAMP	[54]	DNA	reaction wells	5000	≈6 nL	air pressure		
	[55]	DNA	reaction wells	384	≈6 nL	pressure difference		
	[56]	DNA	droplet	100,000	≈10 pL	droplet generator		
	[57]	DNA	droplet/wells	1280	≈6 nL	syringe and pipette		
	[58]	DNA	droplet	2000	≈31 pL	droplet generator		

Roll-to-roll thermal imprinting (molding) technology was proposed for the fabrication of integrated PDMS–paper microfluidic device for molecular diagnostics [53]. This technology enabled the scaling up of production to thousands of devices in an hour (Fig. 3C). The mold was made by photolithography on a nickel plate. The PDMS coating and pattern replication were performed on Al-coated paper. The metal coating effectively suppressed the paper's auto-fluorescence and enhanced fluorescence intensity, due to its high reflectivity. A rolling cylinder was used to transfer microfluidic structures in PDMS by thermal imprinting. The performance of this integrated device was validated by the detection of viral RNA by LAMP. The method created a bridge between academic research and industrialization in POC diagnostics, upscaling fabrication processes.

An integrated sample-to-answer microcapillary-based LAMP system [50] was presented for single nucleotide polymorphism genotyping (Fig. 3D). The FTA was placed inside this capillary as well as all reagents for DNA extraction, purification, and amplification. The sample flow was controlled by capillary forces as well as an external pressure. Once the sample pretreatment was completed, the glass capillary was kept at a temperature of ≈65°C for an hour, using an external heating source, to complete the LAMP and the results were subsequently observed by the naked eye.

A PDMS-paper hybrid sample-to-answer device incorporating LAMP and LFA was proposed (Fig. 3E) to enhance LAMP sensitivity [52] using the shunt and PDMS barrier. It consisted of following four layers from top to bottom: a polyvinyl chloride for later flow, a glass fiber for performing LAMP, an FTA for sample loading and extraction, and a cellulose for waste absorption. The reagents for LAMP were pipetted onto the strip and then heated up using a hand-held heating system [62]. This device was capable of performing a simple colorimetric readout, achieving a LOD of ≈ 5 pM, 10-fold signal enhancement compared with the LFA strip without the shunt and PDMS barrier. This chip-based system is a good candidate for POC, due to its portability and simplicity.

These molecular diagnostic platforms generated a wide range of applications in medicine, healthcare, agriculture, environment, and water monitoring due to their low cost, rapidity, and accuracy.

5. Digital LAMP

Digital PCR (dPCR) was reported almost two decades ago [6] and sparked the interest of numerous applications primarily for early cancer detection and non-invasive, prenatal diagnostics. Naturally, the dPCR system has LAMP alternatives (Fig. 4). Based on the sample compartmentalization methods, digital LAMP (dLAMP) systems can be grouped into two categories: droplet-based and well-plate-based systems. The droplet-based dLAMP devices utilizes the sample droplets suspended in oil, thus preventing droplet-to-droplet cross-contamination. The chip-based dLAMP devices are of two types, both containing micro-reaction chambers. The sample is loaded into wells, either via a microfluidic network and then sealed by oil, or by pipetting it into wells and sealed by a lid. Results from both the droplet-based and chip-based dLAMP devices are analyzed in the same way as dPCR results, using either flow cytometry or digital image processing.

The first chip-based dLAMP system was proposed in 2012 [54]. This self-digitalized chip was fabricated based on the PDMS having 5000 microwells. The sample and the oil were sequentially loaded using force originated by air pressure (Fig. 4A). The chip with the loaded sample was placed into a water reservoir, keeping the temperature at ≈65°C to perform the LAMP process.

During the same year, a self-priming system for chip-based dLAMP was presented [55]. Its major advantage was the absence of external pumping or valves for the manipulation of the sample as

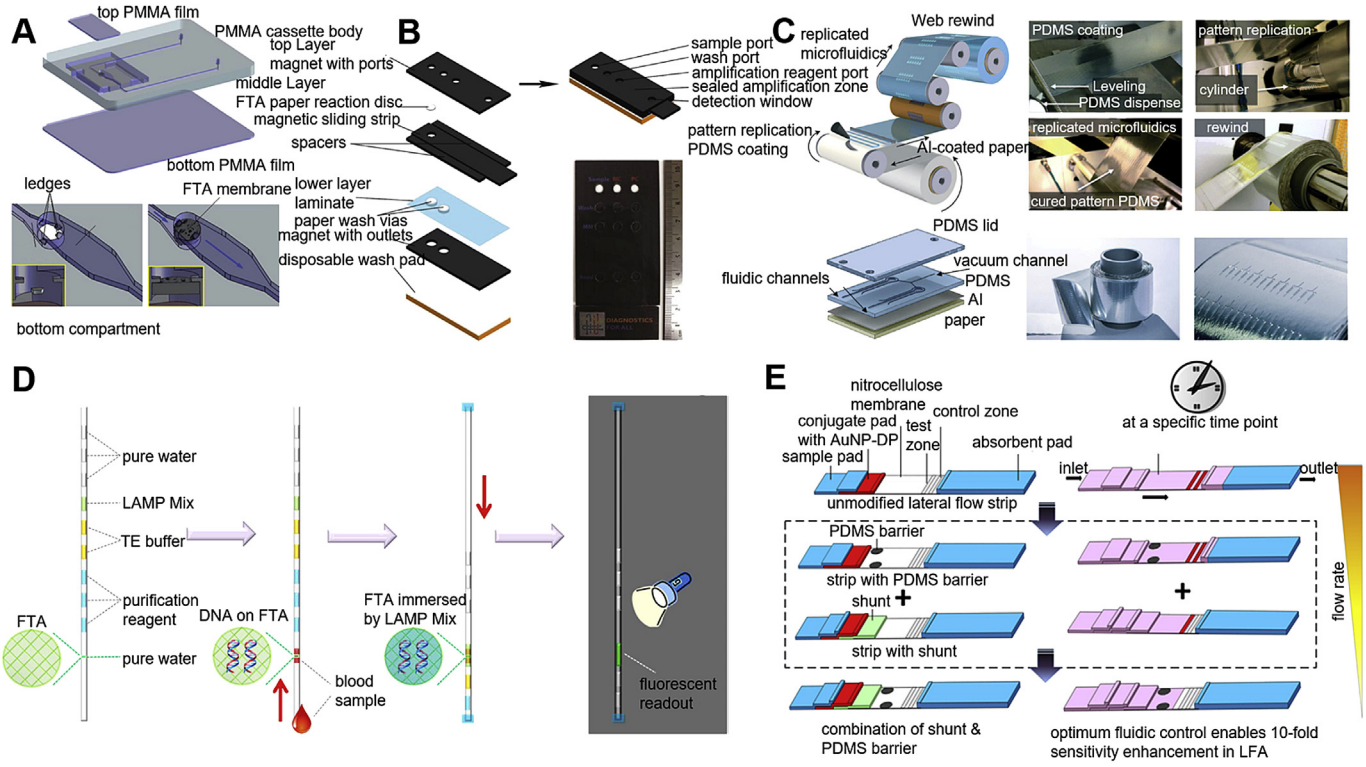

Fig. 3. Paper-based LAMP systems with different structures. (A) The integrated LAMP cassette. Reproduced with permission from Ref. [49], copyright 2011 Royal Chemistry of Society. (B) Schematic of sliding-strip device. Reproduced with permission from Ref. [51], copyright 2015 American Chemical Society. (C) Flow of roll-to-roll replicated PDMS microfluidics on Al-coated paper. Reproduced with permission from Ref. [53], copyright 2018 Royal Chemistry of Society. (D) Principle of integrated capillary LAMP device with preloaded reagents. Reproduced with permission from Ref. [50], copyright 2014 American Chemical Society. (E) An integrated paper-based device incorporating LAMP and lateral flow assays. Reproduced with permission from Ref. [52], copyright 2016 American Chemical Society.

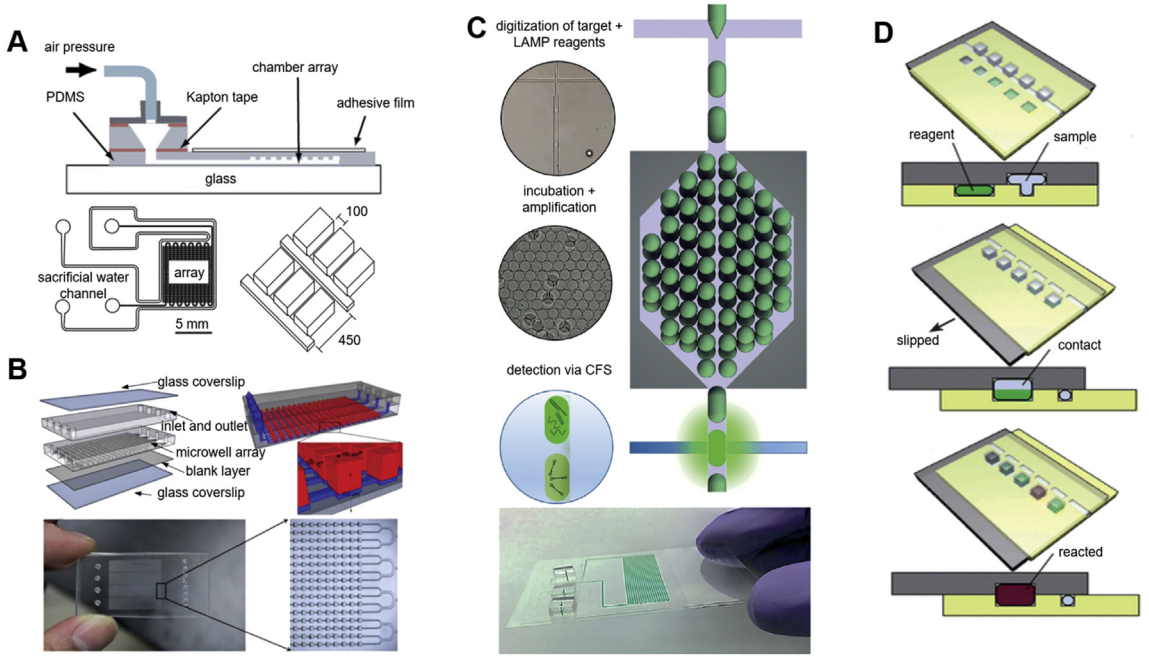

Fig. 4. Digital LAMP approaches: (A) Self-digitalized chip. Reproduced with permission from Ref. [54], copyright 2016 Royal Chemistry of Society. (B) Self-priming digital LAMP. Reproduced with permission from Ref. [55], copyright 2016 Royal Chemistry of Society. (C) Droplet-based LAMP. Reproduced with permission from Ref. [56], copyright 2016 Royal Chemistry of Society. (D) LAMP using Slip-Chip technology. Reproduced with permission from Ref. [57], copyright 2016 Royal Chemistry of Society.

well as the oil. The PDMS chip was kept in a vacuum environment to remove air from the PDMS. The sample was loaded into the chip and pulled into the chambers due to the force caused by pressure difference between the external ambient and low internal pressure with degaussed PDMS working as a sorption pump (Fig. 4B). However, the system independence on fluidic elements, such as

pumps and valves, was compromised by a low "digitalization" level having only 384 wells.

A droplet-based dLAMP device was presented in 2015 [56] (Fig. 4C). The droplets were generated using a classical cross between two microfluidic channels and then transferred into a heated region to perform amplification. The droplet volume was ≈10 pL with a processing time of ≈110 min required for a volume of ≈10 μL. That is equivalent to amplifying DNA in $\approx 10^6$ droplets in 2 h. The elevated temperature of ≈63°C was achieved by placing the dLAMP device on a thermoelectric element. An optical setup was used for fluorescence detection, using a dual excitation wavelength and a dual detection band. Results monitoring was performed by two methods: DNA binding to EvaGreen and calcein dye-based indicators.

Another method was introduced using disposable polymeric DropChip, generating the droplets by centrifugal force [58]. Once the droplet generation was completed, the chip was transferred to a thermal cycler to perform LAMP in ≈1 h and the amplification results were monitored by a microarray scanner.

The chip consisted of two loosely connected plates, enabling them to slip over each other, thus named "SlipChip" technology [57] (Fig. 4D). The sample droplets were generated and then mixed by layer slipping. The SlipChip contained 1280 wells and was used to test antimicrobial susceptibility, measuring the phenotypic response of *Escherichia coli* (*E. coli*) present in a clinical sample of urine. The results of SlipChip technology showed a fast processing time of <7 min.

6. Detection methods for LAMP-on-a-Chip

Monitoring methods used for LAMP are commonly adopted procedures developed earlier for PCR and other bio-molecular techniques. Their utilization for LAMP has been extensively studied and was summarized [63].

Mainstream detection methods of LAMP results often rely on naked-eye monitoring to observe precipitates [22], DNA-binding dyes [64], and colorimetric indicators [65]. Off-chip end-point detections are commonly conducted by performing gel electrophoresis [66]. There are also real-time monitoring optical methods, such as turbidity measurement monitoring optical attenuation of the fluid [67] and fluorescence with a suitable dye [68]. Electrochemical methods can also be either real-time or end-point detected, and they are also commonly used for LAMP monitoring, either in form of a sensor [69] or biosensor [70]. Finally, there are antibody-based methods such as immunochromatic technique (lateral flow dipstick) [71] and the gold standard for protein detection such as antibody enzyme-linked immunosorbent assay [72].

Besides these major techniques, researchers have also tested numerous other methods based on a nano-Au probe [73], field effect transistors [74], surface plasmon resonance [75], bioluminescence [76,77], or the giant magnetoresistive effect [78]. Nevertheless, compared with mainstream detection methods, these techniques are not commonly used as they require chemical preparation or additional instruments to perform product detection.

7. Applications of LAMP-on-a-Chip

The LAMP method is an innovative technique for gene amplification, due to the simplicity of its hardware [79]. It has been utilized in a wide range of applications, including infectious disease diagnostics [22,23] and food safety tests [26]. In particular, LAMP is an effective gene amplification method for POC devices [19].

7.1. LAMP for infectious diseases and clinical diagnostics

With the progression of globalization, the spread of infectious diseases is threatening people's health and lives around the world, regardless of regions' wealth or development status. It is essential to diagnose and cure infected patients to prevent the spread of diseases. Rapid, accurate, and sensitive diagnostic tools to identify pathogens, ideally in POC format, are vital to tackle the spread of infectious diseases [80].

LAMP was first recognized as a potent alternative to PCR in 2003, when it was shown to detect the RNA of a severe acute respiratory syndrome virus [23]. Since then, it has attracted a lot of attention and has become an increasingly popular method for clinical diagnosis. So far, LAMP has been employed for rapid detection of both DNA and RNA possessing human- and non-human-carried viruses, such as MRSA [43], pseudorabies [24], tuberculosis [72], influenza A [21], Zika [48], nervous necrosis [47], and aqua pathogens in fish [81].

7.2. LAMP in food safety test

Food safety and food quality control are, inevitably, an important part of the public-health system. LAMP has been used in food safety detection [26,82–84] including *Staphylococcus aureus* [85], *Salmonella* [86–89], *E. coli* O157 [90], and *Vibrio parahaemolyticus* [91], as well as food allergens [65].

8. Conclusions and perspectives

LAMP is an isothermal amplification technique that can detect target sequences with high specificity and sensitivity. Its technology has been further developed recently, having advantages over classic PCR techniques, such as isothermal operation. The specificity of the PCR achieved by annealing at an optimized temperature is substituted by LAMP technology with more complex primer designs. However, a processing time of a single sample LAMP cannot compete with ultimate PCR systems, capable of performing the amplification in <1 min [34]. The dLAMP technique seems different, as its conduction was reported in <7 min, a difficult time to achieve for dPCR [57].

Therefore, LAMP has its merits, as the heating system is simpler, and there is no temperature cycling and cooling as required for PCR. Also, the sample pretreatment module is easier to incorporate due to a more robust LAMP process compared to PCR. The results analysis of LAMP is also much easier, as the resulting fluorescence after amplification can be observed by the naked eye. A lower LOD can be better achieved by LAMP in food-borne pathogen detection than PCR [26]. Moreover, the simple structure of LAMP chips provides opportunities for mass production and industrialization. As a result, LAMP-based integrated systems [92] are more suitable for application in POC diagnostics [93] than PCRs. LAMP-based diagnostics are not likely to replace conventional techniques such as PCR; they will coexist in parallel, as each one has its strengths and weaknesses.

Since its discovery, LAMP has been further developed, often involving the combination of this technique with other molecular approaches, such as reverse transcription and multiplex amplification. LAMP is easy to handle, and is compatible with multiple detection methods, including turbidity detection, real-time fluorescence detection, and end-point visualization.

In previous sections, we discussed LAMP's potential based on its specificity, efficiency, speed (more related to the dLAMP), and practical implementations. The utilization of LAMP was demonstrated for the diagnosis of viruses, bacteria, and allergens in food. Nevertheless, there is still much room for improvement in

detection methods for the integration of LAMP in POC applications. Ideally, the detection modules have to be miniaturized and integrated with the on-chip LAMP system. Thus, developing a mobile biosensor with a LAMP technology application may result in significant advancement towards the detection of pathogens directly from clinical samples, which is especially important in cash-strapped countries or when working with highly contagious clinical samples. Due to its high specificity, LAMP can also be used for the early detection of genetic disorders, an important aspect of prevention diseases associated with them and their treatment. In summary, LAMP could be the ideal method for diagnostics in an everyday POC setting.

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