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The development of a portable buoyancy-driven PCR system and its evaluation by capillary electrophoresis

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ABSTRACT

Rapid, low cost, and portable polymerase chain reaction system (PCR) can advance the diagnosis of infectious disease, especially for the third-world countries. Herein, we developed a compact PCR system based on Rayleigh–Bénard convection (RB-PCR). The optimal geometry parameters of the RB-PCR cell was obtained by finite element analysis. The amplification efficiency was improved by adding polyvinyl pyrrolidone into the PCR reagent and evaluated by detection of PCR products in capillary electrophoresis. Results demonstrate that λ-DNA was successfully amplified within 15 min, and the PCR products was identified within 6.0 min. 0.1% PVP (10 mg/9 ml) in PCR solution offers the best amplification efficiency for RB-PCR. The device is easy to assemble, and it is well suited for point of care applications.

1. Introduction

Polymerase chain reaction (PCR) is a powerful technology widely employed in genetic analysis, medical diagnostics, and forensic applications, because of its ability to amplify an initially dilute target DNA sample to a detectable concentration level [1,2]. Standard PCR cyclers involve three steps of repetitive temperature cycling: 95 °C (denaturation), 50–60 °C (annealing), and 72–77 °C (extension). However, conventional PCR thermal cyclers are sizable devices that accommodate many reaction tubes. They need large microliter volume solution and do not allow for very fast changes in the vessel temperature, which leads to long cycling time. Therefore, this kind of device cannot be developed in a portable format [3]. Although loop mediated isothermal amplification (LAMP) has the advantages of reaction simplicity and higher amplification efficiency, the primer design for LAMP is complicated and it is easy to produce false-positive [4]. Continuous flow PCR (CF-PCR) [5–18] and micro-chamber PCR [19–23] based on microfluidic can overcome those limitations and have the potential for developing portable PCR systems for point-of-care (POC) applications.

The CF-PCR was essentially dedicated laboratory apparatuses, often relying on integrated or nonintegrated pumping system (e.g., syringe) to actuate/load the fluid, complex microchannel design, and complicated manufacturing technology based on expensive manufacturing micro electro mechanical system (MEMS). The micro-chamber PCR is actually a kind of micro-miniaturization of conventional PCR. The thermal mass associated with the heater, PCR chamber and solution limits the flexibility to change the PCR speed, and complex control apparatus required to thermally cycle the PCR reagents among the desired temperatures hinders its prevalence.

PCR based on Rayleigh–Bénard convection (RB-PCR) had the potential to overcome these limitations [24,25]. Instead of repetitive heating and cooling, thermal convection was actuated by buoyance-driven instability in a reaction fluid between hot and cold part of the chamber. A continuous circulatory flow was achieved by a spatial temperature gradient and then PCR reagents are repeatedly transported through temperature zones for denaturing, annealing, and extension of DNA. Braun et al. performed the laminar convection PCR by heating an infrared source in the center of a disk, and the periphery of the chamber is kept at 52 °C [26]. Silicone oil was used as a cover to avoid evaporation [27]. RB-PCR was achieved in a capillary tube that heated only on the bottom by a single isothermal heater and cooled by the surrounding

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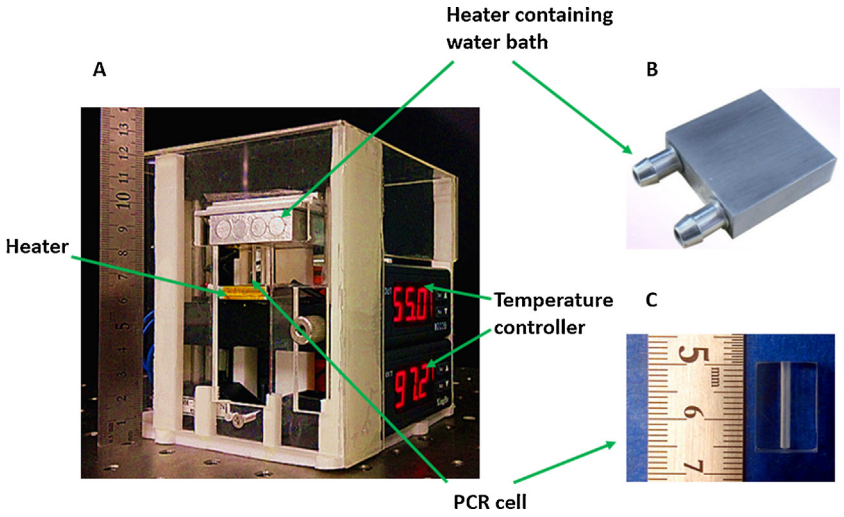

Fig. 1. The PCR apparatus: (A) all-in-one PCR apparatus with five modules. (B) The above heater containing water bath. (C) The RB-PCR cell.

air. Compared with the traditional PCR thermal cycler, this system is simpler and more convenient but it is extremely sensitive to the environmental temperature fluctuations [28,29]. Moreover, a micro RB-PCR chip consisting of micro heaters, micro temperature sensors, and one polydimethylsiloxane reaction chamber, was fabricated by MEMS [30]. Infrared-mediated temperature control was employed to accurately thermocycle microliter volumes in PCR microchip by Giordano et al. [31]. Although Wittwer's group realized the DNA amplification in 15–60 s, the system seems not portable [32]. Herein, we developed a compact PCR system based on buoyancy forces, and evaluated the reaction efficiency by capillary electrophoresis (CE). Such a low cost PCR system is easy to fabricate, and it is well suited for POC applications in third-world countries.

2. Materials and methods

2.1. Materials and reagents

SpeedSTAR HS DNA Polymerase and φX174-Hinc II digest were purchased from Takara (Shiga, Japan). Hydroxyethyl cellulose (HEC, 1300 k) was bought from Polysciences (Warrington, PA, USA). 10,000 × SYBR Green I was got from Invitrogen (Carlsbad, CA, USA). 10 × TBE (1 × TBE = 89 mM Tris/89 mM boric acid/2 mM EDTA, pH 8.4) buffer was bought from BIORAD (Hercules, CA, USA). 0.5 × Tris-broate-EDTA (TBE) was prepared by mixing 10 × TBE and distilled water with a ratio 1:19, 1 × SYBR Green I for DNA separation. 1 × SYBR Green I was obtained by diluting the 10,000 × SYBR Green I to a final concentration of 1/10,000.

2.2. RB-PCR system construction

Photographs of the assembled RB-PCR device are shown in Fig. 1. It mainly consists of two temperature controllers, two heating block units, and the natural convective PCR cell. A series of cylindrical holes were fabricated by a drilling machine. Polycarbonate was first chosen to be the substrate material, but it was found that internal surface of the hole was not smooth enough to achieve the lamina flow, then polymethylmethacrylate (PMMA) was selected to solve this problem and its good diathermancy was also useful for convection Then the block containing a cylindrical hole was sandwiched between two heaters (top: 55 °C, bottom: 97 °C). A schematic of the PCR cell is depicted in Fig. 1S. Both heaters were connected with two electronic devices to control the temperature more accurately. Water bath circulation was applied to cool down the reagent on the top due to its good heat capacity.

2.3. PCR protocols

PCR was performed in the RB-PCR system (Fig. 1). The reaction was performed with 0.7 μl λ-DNA and 34.3 μl reaction volumes containing 3.5 μl 10 × Fast Buffer I, 2.8 μl dNTP mixture (2.5 μM), 0.7 μl primer 1 (5′-GATGAGTTCGTGTCCGTACAACTGG-3′) and 0.7 μl primer 2 (5′-GGGCAATCAGTTCATCTTTCGTCATGG-3′), 0.175 μl Speed-STAR HS DNA Polymerase, 0.35 μl PVP (10%), and 26.075 μl pure water. The PCR product was directly analyzed for CE without any further sample preparation.

2.4. Capillary electrophoresis

The self-built CE system was previously described [2,33]. It was driven by a high-voltage power supply (MODEL 610E, TREK, Medina, NY, USA). The excitation wavelength from a mercury lamp was filtered to be 460–495 nm, which was the wavelength of the excitation maximum of the conjugate of SYBR Green I and the nucleic acid by the optical filter (U-MWIB-3, Olympus, Japan). The fluorescence emission was collected by a 60 × objective (PlanApo/IR, Olympus), and then was detected by a photomultiplier tube (R928, Hamamatsu Photonics, Japan). Power supply and data collection were controlled by LabVIEW (National Instrument, Austin, TX, USA). A certain length (100 cm) fused-silica capillary with ID/OD = 75/365 (μm/μm) was covalently coated with polyacrylamide [34,35], and then it was divided by diamond cutter. The entire detection system was enclosed in a dark box. DNA sample was electrokinetically introduced into the capillary at 100 V/cm for 1.0 s. After each run, the capillary was flushed with sterilized water by pump for 1.0 min. All separations were performed at 26 °C in the clean room controlled by air-conditioner.

3. Results and discussion

3.1. Optimization of the geometry of the RB-PCR cell

Numerical simulation on the temperature and flow distribution in the cell was carried out by COMSOL Multiphysics to obtain the optimal geometry parameters. Cylindrical holes were considered to be an ideal reactor well for natural convection PCR. The spatial velocity and temperature distributions within the reactor

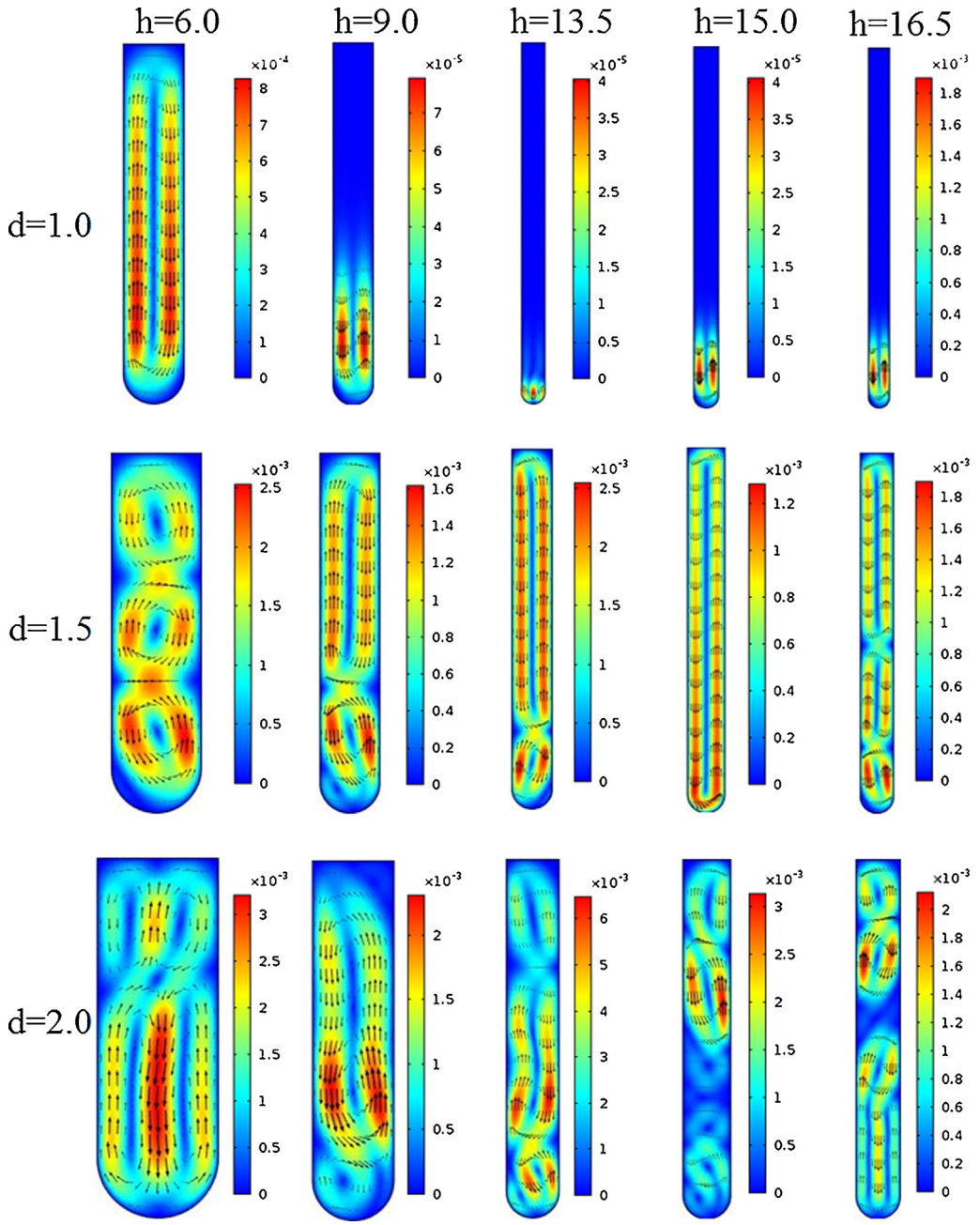

Fig. 2. Numerical results for the velocity distribution in the RB-PCR cell with different dimension. Where *d* is the diameter of the cross section, *h* is the height of the cell. Arrow denotes flow lines in the solution. All scale bars represent the velocity of the water in the cylindrical hole, and the unit is m/s. The unit of *d* and *h* is mm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

determine whether the PCR reagent can sequentially occupy the temperature zones for PCR during sufficient period of time. The velocity and temperature field in a cylindrical hole is characterized by the Rayleigh number (*Ra*) [24],

$$\mathrm{Ra} = \frac{g\alpha\Delta\mathrm{Th}^3}{\nu\kappa}$$

where g, α, ν and κ are the acceleration of gravity, the coefficient of thermal expansion of the fluid, the dynamic viscosity and the thermal diffusivity, respectively. ΔT is the temperature difference between the top (T_{top}) and bottom (T_{bottom}) heaters. Ra can be adjusted by changing the height of the cylindrical hole (h). T_{top} and T_{bottom} were maintained at 55 °C and 97 °C, respectively. The physical properties of the fluid in the system was assumed to be the same as pure water [36]. Model parameters for the simulations are summarized in Table S1 (see the Supporting information).

The Rayleigh number indicates the transition between laminar and turbulent flow. It should be lower than 10^9 if the fluid moved in laminar flow manner. Here, we analyzed the fluid flow and temperature distribution in RB-PCR cell with various heights from 6.0 mm to 16.5 mm with an increments of 1.5 mm (delete?). The diameter for the cross section was 1.0 mm, 1.5 mm and 2.0 mm, respectively. Ra was 1.1762×10^5, 3.9698×10^5, 1.3398×10^6, 1.8379×10^6 and 2.4462×10^6, corresponding to the height of 6.0 mm, 9.0 mm, 13.5 mm, 15 mm and 16.5 mm, and thus laminar regime was expected. The simulation results are demonstrated in Fig. 2. Single

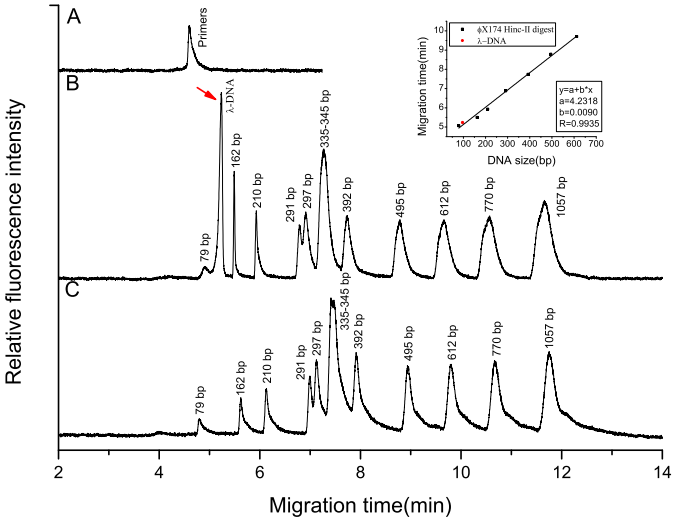

Fig. 3. The electropherogram of PCR of λ-DNA (A) without template (negative control); (B) φX174-Hinc II digest containing λ-DNA RB-PCR product (C) φX174-Hinc II digest in HEC. Electrophoretic conditions: polymer (0.5%HEC, 1300 k), total and effective length of the capillary (6.0 cm/9.0 cm), electric field strength (80 V/cm), loadings (100 V/cm, 1 s). (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

convection loop is observed when d is 1.0 mm, but the solution was kept above 77 °C (see Fig. S2 in the Supporting information), making the PCR reagent impossible for annealing during PCR process. Furthermore, it is not easy to load the PCR reagent when the diameter of the cross section is so small. Multiple convection loops are observed when d are 2.0 mm and 1.5 mm, except when the dimension (h/d) is 15/1.5, which was selected to be the optimal height and diameter of the RB-PCR cell.

3.2. Amplification of λ-DNA in RB-PCR cell

We performed the PCR of λ-DNA in both self-assembled RB-PCR system (Fig. 1) and conventional PCR thermal cycler (see the Supporting information). The reaction time was 25 min. Experiment demonstrated that the amplification signals were strengthen when the internal surface of the PCR chips were treated by polyvinyl pyrrolidone (PVP) because of its passivation effect [37]. Therefore, we added PVP (1300 k) into the PCR reagent for RB-PCR. The RB-PCR products were diluted by 50% prior to analysis by CE. The size of the PCR products was determined by φX174-Hinc II digest. Negative PCR control (without template) was carried out to check out the selectivity and specificity of the primer. Results showed that the DNA smaller than 612 bp was baseline resolved within 10.0 min (Fig. 3C). CE of negative PCR control (without template) showed that only peak corresponding primer was observed (Fig. 3A). CE of positive PCR control showed that one peak at 4.606 min was observed (Fig. 3B). The size of the PCR product was determined by calibration plot of DNA size versus its migration time (see insert of Fig. 3). The linear regression fit for DNA size and migration time was achieved with correlation coefficient R = 0.9935, and thus the size of PCR product of λ-DNA was determined, which was marked with filled red arrow in Fig. 3. It is interesting to note that the fluorescence intensity of the PCR product in RB-PCR was 3 times as the one in conventional PCR (see Fig.S3 in the Supporting information), although the reaction time was nearly the same, indicating that it was possible to obtain yields comparable with conventional PCR tubes by such a portable RB-PCR. In addition, experiments demonstrated that PCR failed in RB-PCR cell with other dimension (see Fig.S4 in Supporting Information), which were consistent with the numerical simulation results.

3.3. Methods to improve the amplification efficiency

We investigated the effect of reaction time and PVP on the volume of PCR product, which was evaluated by calculating the peak area of λ-DNA in the electropherogram. PCR of λ-DNA was performed in a RB-PCR cell (h/d = 15 mm/1.5 mm). The top and bottom of the cell maintained at 55 °C and 97 °C, respectively. The total volume of the PCR reagent was about 26.5 μl. The PCR products were directly introduced into the capillary after PCR. Each PCR was carried out 5 times, and then the PCR products were introduced into CE for separation. The electropherogram was sum-

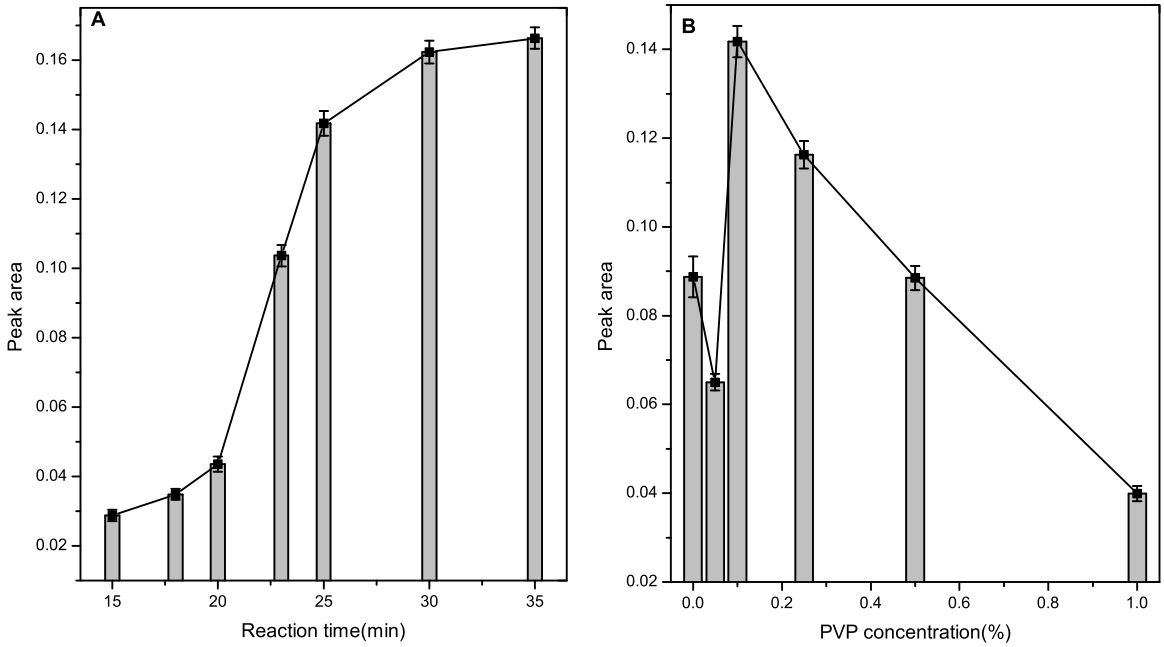

Fig. 4. The relationship between volume of PCR products and (A) reaction time in the RB-PCR cell; (B) the concentration of PVP in the PCR reagent. Electrophoretic conditions: total and effective length of the capillary (4.0 cm/6.0 cm), electric field strength (100 V/cm). Other electrophoretic conditions were the same as those in Fig. 3.

marized for data analysis if the signal/noise is above 3. The peak was considered unreliable if the signal/noise is lower than 3. The relationship between the amount of PCR products and reaction time is depicted in Fig. 4A. The volume of PCR products was predominantly increased if the reaction time was longer than 20 min, and the volume became stable if the reaction time is more than 30 min, indicating that PCR was finished. PVP is a dynamic coating material which may improve the PCR, which was widely used in the continuous flow PCR chip [38]. Fig. 4B shows that 0.1% PVP in PCR reagent offered the best PCR efficiency for RB-PCR, and then the volume of PCR products decreased with the increase of PVP volume.

4. Conclusions

We demonstrated a self-assembled portable RB-PCR system for the amplification of DNA in this work. Experiments demonstrated that λ-DNA was amplified less than 20 min and the amplification efficiency was greatly improved by adding PVP into the PCR reagent. Furthermore, the volume of the PCR products was much more than the traditional PCR thermal cycler although the amplification time was the same. Compared with CF-PCR chip, the RB-PCR cell is easy to fabricate without MEMS technology. The low cost RB-PCR system in this work is easy to operate, and is well suited for POC applications.

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.snb.2016.02.143.

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