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A Lego®-like swappable fluidic module for bio-chem applications

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A B S T R A C T

A Lego®-like swappable fluidic module (SFM) is proposed in this research. We designed and fabricated selected modular fluidic components, including functional and auxiliary types that can be effortlessly swapped and integrated into a variety of modular devices to rapidly assemble a fully-portable, disposable fluidic system. In practice, an integrated SFM uses finger-operated, electricity-free pumps to deliver fluids. Using a swirling mechanism, the vortex mixer can rapidly mix two liquids in a one-shot mixing event. We demonstrate the successful application of this SFM in several microfluidic applications, such as the synthesis of gold nanoparticles (AuNPs) from chloroauric acid (HAuCl4), and nucleic acid amplification from the Hepatitis B virus (HBV) with a capillary convective polymerase chain reaction (ccPCR).

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1. Introduction

Microfluidic devices have enormous potential in biological and chemical analysis applications [1–8]. Modular concepts to build integrated microfluidic systems have been a long-standing concern and an active area of research [9–12]. The advantage of a modular system is that each module can be designed and tested separately before integrating it into a larger system. Nevertheless, the main challenge in developing a modular microfluidic system is to ensure leak-free fluidic interconnections among individual components once the unit is assembled. Furthermore, the ability to build a customized multidimensional microfluidic system following a modular approach would be an advantageous platform to substantially enhance design flexibility, and improve the system performances of various bio-chemical processes.

Several researchers have proposed simpler fabrication methods aimed at the elimination of costly and time consuming clean-room lithography [13–17]. To replace the conventional chrome photomask, Glennon et al., for example, achieved direct printing of a lithographic mold by using laser toner as the fluidic structure [14]. Recently, modular architecture using fluidic breadboards and prefabricated microfluidic components have become popular [18–20]. These pre-fabricated components, which allow standardization and customization, appear to be an ideal solution for research scientists, and can be widely applied. However, breadboard applications limit system flexibility. Rhee and Burns recently developed a modular microfluidic assembly block (MAB) platform; using pre-fabricated polydimethylsiloxane (PDMS) blocks [21]. This allowed non-expert users to assemble fully customizable microfluidic devices at the point of use within minutes. However, this approach required a driving force control unit to activate the system, an additional glue-like, UV curable adhesive, as well as a PDMS mixture to connect components.

In this study, we demonstrate an advanced Lego®-like swappable fluidic module (SFM) concept using PDMS blocks with assorted channel geometries that effortlessly connect to form fully functional microfluidic devices. In addition, we applied the developed Lego®-like SFM to a nucleic acid amplification, using capillary convective PCR (ccPCR) experiments. Gold nanoparticles were also synthesized by rapid mixing and reactive chloroauric acid (HAuCl4) and sodium citrate (Na3C6H5O7) processes. The successful tests demonstrated the promising applications of the new Lego®-like SFM to achieve fully-portable, disposable fluidic systems.

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Table 1
Modular fluidic components used for integration of Lego®-like SFMs.

| Block Name          | Schematic          | Size(mm) | Block Name          | Schematic          | Size(mm) |
|---------------------|--------------------|----------|---------------------|--------------------|----------|
| Pump (P)            | ![Pump Schematic](image1) | L20 W20 H10.5 | Heating block (HB)  | ![Heating Block Schematic](image2) | L20 W20 H9 |
| (L10W10H10)         |                    |          | Reservoir (R)       | ![Reservoir Schematic](image3) | L15 W15 H10 |
|                     |                    |          |                     |                    |          |
| One-way valve (OWV) | ![OWV Schematic](image4) | L10 W10 H10 |                     |                    |          |
| (L10W10H10)         |                    |          |                     |                    |          |
| Vortex-type mixer (VM) | ![VM Schematic](image5) | L10 W10 H10 |                     |                    |          |
| (L10W10H10)         |                    |          |                     |                    |          |
| Cross tube-F (CT-F) | ![CT-F Schematic](image6) | L10 W10 H10 | Cross tube-M (CT-M) | ![CT-M Schematic](image7) | L10 W10 H10 |
| (L10W10H10)         |                    |          |                     |                    |          |
| T tube-F (TT-F)     | ![TT-F Schematic](image8) | L10 W10 H10 | T tube-M (TT-M)     | ![TT-M Schematic](image9) | L10 W10 H10 |
| (L10W10H10)         |                    |          |                     |                    |          |
| Straight tube (ST)  | ![ST Schematic](image10) | L10 W10 H10 | Corner tube (CT)    | ![CT Schematic](image11) | L10 W10 H10 |
| (L10W10H10)         |                    |          |                     |                    |          |
| Height tube (HT)    | ![HT Schematic](image12) | L10 W7.2 H7.2 |                     |                    |          |
| (L10W72H72)         |                    |          |                     |                    |          |

**Connector Assembly**

- D2.75mm
- L2.5mm
- D2.5mm
- L2.5mm
2. Experimental

2.1. System description

Table 1 presents the modular fluidic components used to integrate Lego®-like SFMs. The functional components consisted of finger-operated, electricity-free pumps, a one-way valve, vortex-type mixer, reservoir, and heating block (with the associated block names P, OWV, VM, R, and HB), and the straight tube (ST), T-type tube (TT-F, TT-M with F, and M denoting a male to female type of sealing face), cross tube (CT-F, CT-M), corner tube (CT), and height tube (HT) were categorized as auxiliary components and the corresponding model numbers were listed below each schematic, which demonstrated the mass production feasibility of Lego®-like SFMs in several sizes. All components in this study were made of PDMS with the related design and fabrication methods described below. Fig. 1 shows a schematic of the fabrication process for vortex-type mixers. A two-piece assembled casting design allowed users to easily strip the outer mold down without damaging the product. We initially mixed the PDMS prepolymer and curing agent (10:1 w/w, Sylgard® 184 silicone elastomer, Dow Corning), poured the mixture into an aluminum mold, and the container was cured at 100 °C for 45 min to construct the configuration. The one-way valve (OWV) comprised three sections: chamber, reed, and base plate. The wet PDMS was coated on the base plate before assembly to function as an adhesive. During assembly, care had to be taken to ensure the appropriate attachment of the reed to one side of the chamber walls. For the inflow coming from the right, the left channel was blocked by the reed, configuring a no flow state from the right to left channel. On the other hand, when the flow came from the left side, the reed would be pushed, and thereby bent to the right, resulting in an open path for the fluid. Therefore, the flow was allowed to pass from the left to right channel. The pump was built with a featured hemispherical chamber to minimize dead space (with the dead-volume ratio down to 6%) and a thicker top diaphragm of the pump to enhance durability. The pump chamber was 11 mm in diameter for ergonomic efficiency, and the inlet and outlet diameters were both 0.8 mm. In the tests, the chamber was pressed down to expel the air inside the chamber. Since the OWV function could only move the internal fluid to the right side, the left side was thus blocked by OWV and not affected during the application of pressure [22]. Similarly, the vortex mixer consisted of three sections: a hemispherical chamber, two inlets and one outlet allowing the liquid passage. The inlets and outlet were located on the two sides and the bottom of the chamber. Those two streams from the inlets blended together along the coiled passage toward the center, and wound downwards to form a solid swirling vortex under high Reynolds Number conditions. The vortex agitation could further fold and stretch the fluids spirally to increase the interfacial area for mixing enhancement. In our previous studies, we have illustrated that the current vortex mixer needed only 0.1 s to attain mixing efficiency of 93% and maintained a good mixing performance during the period of 0.1–0.4 s for a one-shot event [23]. The heating block measured 20 × 20 × 10 mm, and the inner and outer capillary diameters were 1.8 and 3.0 mm, respectively. The device maintained a positive temperature coefficient (PTC) thermistor for heating. The reservoir was made using the same casting method as that of the chamber part of the pump. The diameter of the fluidic channel was 500 μm, while the volume values of pump (P), vortex-type mixer (VM) and reservoir (R) were approximately 956, 22 and 271 μl, respectively. All auxiliary components were used to allow channel stretch, turn around, congregate, segregate, and up and down movement. For bio-chem applications, the minimal volume of samples that could be processed in the devices is around 20 μl.

2.2. Connector description

This novel block design had self-aligning structures on both the male- and female-type Lego®-like SFMs for attaining the improved sealing at block junctions. The inter-block gaps were eliminated to maximize the functionality of SFM devices. The diameters of the male- and female-type Lego®-like SFMs were 2.75 and 2.5 mm,
respectively. This design can tightly seal the contact faces of the two linked SFMs in a state of higher compression, and thus minimize the possibility of forming gaps. The function tests demonstrated that the pass volume ratio of the male- and female-type Lego®-like SFMs was up to 99.8% based on the measurements of the inlet and outlet volumes of water with the back pressure held at least 0.35 atm. This design feature allowed non-expert users to rapidly devise and assemble the Lego®-like SFMs into a customizable microfluidic device in minutes. To perform the PCR procedures, we adapted the capillary convective PCR concept by Chou et al. with a capillary tube mounted on a heater at a constant temperature of 95 °C [24,25]. In operations, this concept doesn’t require complex microfluidic chip design, special tubing, or vessels. The constantly heated capillary base drove the lowest part of the sample fluids and raised them by convection while denaturing the template simultaneously. During the ascending of the sample, its temperature dropped because of the cooling effect from the surrounding air. As the sample reached the cool temperature zone near the top of the tube, it underwent annealing and extension, after which the DNA template descended and was heated again. Consequently, PCR cycles were achieved by natural convection.

2.3. Integrated reaction systems

Fig. 2 illustrates (a) a schematic, (b) a photograph of the integrated reaction system for the synthesis of gold nanoparticles, and (c) the operating procedures. The components on the left and right sides were reservoirs for the HAuCl4 and citric acid with the formed SFM as a sample loader to link to the in-line gold nanoparticles collection zone (pump). The vortex mixer was inserted between the reservoirs and the gold nanoparticles collection zone (pump). This connection array allowed the test fluids to flow through the mixer to set the mixing process in motion. To manipulate the finger-operated electricity-free pump, the mixed reagents were transferred to the gold nanoparticles collection zone (pump) to completing the swift synthesis of the gold nanoparticles experiment. To operate the finger-operated electricity-free pump again, the completed synthesis of the gold nanoparticles were pushed out of the system for collection of sample particles. The integrated system can be expressed in terms of the block names, as follows:
In demonstrating the ccPCR system to complete the prompt DNA amplification procedures, Fig. 3 illustrates (a) a schematic, (b) a photograph of the ccPCR system, and (c) the operating procedures. When the pump chamber is depressed, the interior air moves to the right side, as indicated by the blue arrow. When the external force is released, the low pressure inside will draw the fluids from the left side into the pump chamber. By depressing the pump again, the fluids inside can be driven to the capillary of the heating block (HB). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

In fact, PTC thermistors are thermally sensitive semiconductor resistors that exhibit an increase in resistance at a given temperature. Change in the resistance of a PTC thermistor can be effectuated either by a change in the ambient temperature, or internally, by self-heating resulting from current flowing through the device. A steady temperature for over 30 min can be maintained at the top surface of the heater after power is provided from the battery to the heater. To operate the finger-operated electricity-free pump, the mixed reagents were transferred to the DNA amplification zone for realization of the ccPCR experiments. Then, a medical syringe was used to suck up the sample from the glass capillary.
Fig. 4. Purification of AuNPs, using sodium citrate: (a) TEM images of AuNPs from the Lego®-like SFMs on the left side and commercial standard on the right side, and (b) absorption spectrum of purified AuNPs.
The combined model is depicted in terms of the block names, as follows:

\[
\begin{align*}
R & \rightarrow HT \rightarrow ST \rightarrow VM \rightarrow HT \rightarrow OWV \rightarrow HT \rightarrow OWV \rightarrow HB \\
R & \rightarrow HT \rightarrow ST
\end{align*}
\]

3. Results and discussion

3.1. Synthesis of gold nanoparticles

Gold nanoparticles were synthesized through a citrate reduction from aqueous HAuCl₄. In the experiments, 0.008 g of HAuCl₄ (Sigma Chemical, St. Louis, MO, USA) was dissolved in 80 ml of distilled water as a primer solution, and an additional 4-ml mixture of 3.4-mM (concentration of mini-Molar) citric acid and 15.9 ml of distilled water were utilized as a reducing solution. Fig. 4 illustrates the purification of AuNPs, using sodium citrate: (a) transmission electron microscopy (TEM) images of AuNPs from the Lego®-like SFMs on the left side and commercial standard on the right side, and (b) absorption spectrum of purified AuNPs. During operation, the HAuCl₄ and citric acid was fully heated through conduction at 100 °C for approximately 11 min to enhance the reaction. The TEM analysis demonstrated that the AuNPs obtained from the Lego®-like SFMs on the left side and commercial standard (10 nm diameter, OD 1, stabilized suspension in citrate buffer, Product No. 741957, SIGMA-ALDRICH) on the right side were mono-disperse with a mean diameter of 7.31 ± 2.34 nm and 9.31 ± 2.28 nm, respectively. The UV–vis spectra of the deep red AuNP suspensions indicated relatively narrow surface plasmon bands centered at \(\lambda = 523\) nm, revealing typical formations of largely non-agglomerated AuNPs and being similar to the experimental result of the commercial gold nanoparticles (\(\lambda = 524\) nm).

3.2. Polymerase chain reaction

In this study, we used a specific 122-bp segment of HBV. Each PCR reaction consisted of a 30-μl DNA template, 7.5 μl of LightCycler® FastStart DNA Master Hybridization Mixture (including Taq DNA polymerase, PCR reaction buffer, 10 mM of MgCl₂, and dNTP mixture, Roche, Germany), 9 μl of 25-mM MgCl₂, 1.5 μl of 10-μM primers (HBV F: ‘5′-CCCTAGCGTTCGGTTCGAGCCG-3′; HBV R: ‘5′-CCCTAAGCGAGCAGCGAGCAGC-3′), 25.5 μl of ddH₂O, and 10 μl of mineral oil. During the experiments, the reagent was thoroughly heated for 10 min through conduction to activate the Taq DNA polymerase. The tube was heated only at the bottom to generate natural convection for DNA amplification within 30 min.

Fig. 5 shows the electrophoresis gel test results (Lane 1, 100-bp ladder). The traditional device (Biometra, Germany) results are presented in the Lane 2 and the results in the Lane 3–6 repeat four tests from the samples loaded using the Lego®-like SFMs. The cycling program of the traditional device (Biometra, Germany) comprised an initial predenaturing step at 95 °C for 10 min, followed by 45 amplification cycles. Each cycle included three stages: denaturing at 95 °C for 20 s; annealing at 53 °C for 30 s; and extension at 72 °C for 30 s. Each PCR run ended with a final extension at 72 °C for 7 min. The DNA strands were successfully amplified using the Lego®-like SFM device as the sample loader. We could operate the proposed Lego®-like SFMs without using an additional centrifugal machine with a reaction time retained to 30 min, which was not possible for the cases of adopting traditional PCR.

4. Conclusion

A new Lego®-like SFM, consisting of functional and auxiliary components, was designed, fabricated, and tested to integrate into a fully-portable, one-use modular fluidic device for various biochemical applications. The finger-operated electricity-free pump delivered the working liquids in operations without the use of additional power sources, such as costly syringe pumps or air compressors. Because of the concurrent actuation of the pumps, a strong swirling flow developed in the core of the mixer chamber, and achieved a high mixing performance in a one-shot event. The proposed Lego®-like SFM was therefore applied as a sample loader to amplify the nucleic acid through the ccPCR experiments. The AuNPs were synthesized from the rapid mixing and reactive processes of HAuCl₄ and sodium citrate. The ccPCR results demonstrated that the DNA sequences in 30 min from HBV 122 bp at the DNA concentration of 10⁵ copies/μl were successfully amplified. The TEM analysis and surface plasmon bands centered at \(\lambda = 523\) nm revealed the production of gold nanoparticles with a mean diameter of 7.31 ± 2.34 nm, within 11 min. Compared to conventional microfluidic devices, the Lego®-like SFMs can be effortlessly swapped and integrated into a variety of modular devices for quick assembly and the replacement of certain components to realize a fully-portable, disposable fluidic system with great potential for diverse bio-chemical applications.
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Biographies

Yi-Fan Hsieh received his master (2005) and PhD (February, 2014) degree in mechanical engineering from the National Taiwan University. He joined Biomedical Technology and Device Research Laboratories at Industrial Technology Research Institute as a biotechnology researcher. His current research interests include the micro-fluidic system for biology and real time PCR system for DNA quantitative sequencing.

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Pei-er Chen received PhD degree from the University of Pennsylvania in 1987. Afterwards, he joined the Graduate Institute of Clinical Medicine of National Taiwan University as a professor. His main research areas include animal models of hepatitis B and D infection and replication, liver tumor related gene mutation, development and clinical trials of novel treatments for hepatitis B and C and New strategies for liver tumor management, including combination therapy, chemo-, immune, and gene therapy.

Ping-Hei Chen received his bachelor degree in mechanical engineering from National Taiwan University in 1980. After completing his military service, he went to U. of Minnesota for his graduate study. He received his master and PhD degree in mechanical engineering from U. of Minnesota in 1984 and 1988, respectively. In 1988, he joined the Department of Mechanical Engineering of National Taiwan Uni- versity as an associate professor. He was appointed to full professor in 1996, and serve as the vice-chairman of the Department from 1996 to 2008, and as the chair- man from 1998 to 2001. His excellent achievement in sensors-related researches has won him the honor of a distinguished professorship by the National Taiwan University in 2008. He also serves as the Executive Secretary of the Office of Science and Technology, the taskforce to support the Board of Science and Technology of the Executive Yuan to review national science and technology policy guidelines and research management. His major research areas are in MEMS, biomedical devices, nanotechnology, and energy harvesting chips, highly efficient energy systems, and sensors.