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Biochemical IC Chips Fabricated by Hybrid Microstereolithography

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ABSTRACT

The world's first microstereolithography named "IH process" was developed by Ikuta et al. in 1992. Several types of micro stereo lithography including Hybrid-IH process, Super-IH process and Two-photon IH process, have been also developed. Three-dimensional (3D) resolution has reached to 140 nm in the two-photon IH process. The super-IH process and the two-photon process enable direct writing of movable micromechanisms without assembling process or sacrificial layer technique. The hybrid-IH process provides various types of composite devices with other functional elements such as actuators and sensors. These IH processes can be widely used for making polymeric microdevices. We have applied these techniques to create new micro chemical device named "Biochemical IC Chip" proposed by Ikuta et al. in 1994. IH process enables to make the biochemical IC chip including real 3D micro fluidic channels. Various kinds of Biochemical IC chip such as micro pumps, switching valves, reactors, concentrators, have already been fabricated. In chip cell-free protein synthesis has been demonstrated by using biochemical IC chips. The biochemical IC chips will open new bioscience and medicine based on innovative technology. In this paper, we introduce several types of IH process and its application to biochemical IC chips.

INTRODUCTION

Conventional micromachining such as surface micromachining and LIGA process have been widely used to make various kinds of sensors and actuators. However, these methods have some limitations on fabrication of 3D microdevices demanded in recent applications such as micro total analysis systems (μ-TAS) and lab-on-a-chip devices. On the other hand, we have developed several types of microstereolithography to make truly 3D microstructures. The world's first microstereolithography system called "IH process" was proposed and developed by Ikuta and Hirowatari in 1993 [1]. The IH process made possible the layer-by-layer process of 5 μm thickness with modifications to both the optical system and the characteristics of photopolymer. In 1996, mass productive microstereolithography named "Mass-IH process" was proposed and demonstrated [2]. Since this process uses an array of optical fibers to obtain multi-beam scanning with high accuracy, we can fabricate real 3D microstructures under mass and low cost production similar to silicon process. To fabricate functional microdevices, we have developed two-types of IH process named "Hybrid-IH process" and "Multi-polymer IH process". The hybrid-IH process provides a composite microdevice with functional elements such as chemical microparts and actuators [3, 4]. The multi-polymer IH process can produce all-polymer microdevices such as optical waveguides and microvalves using multiple kinds of photopolymer [5].

Conventional microstereolithography systems developed by us and other groups are based fixed surface methods [1, 6] and free surface methods [2-5, 7]. Since these techniques used a layer-by-layer process, the depth resolution and yield rate are limited due to the surface tension and viscosity of piling photopolymer layer. To improve both the resolution and yield rate of microstereolithography, we proposed a novel method named "Super-IH process" [8]. This method is based on pinpoint inner solidification, which is generated by focusing a blue laser beam inside a liquid photopolymer [9]. 3D scanning of the laser beam permits the fabrication of any 3D microstructure without layer-by-layer processes. The 3D resolution has attained to 430 nm in our latest fabrication system [10]. To obtain further higher resolution and yield rate, two-photon IH process was recently developed [11-15] and subsequently refined by other groups [16, 17]. In the two-photon IH process, a near infrared pulsed laser beam is used to generate two-photon-initiated polymerization, in contrast to UV or blue laser beam used in conventional microstereolithography. Since the rate of two-photon absorption is proportional to the squared intensity of light, the polymerization is strictly confined to a focal point. The resolution of the two-photon IH process attains to 140 nm in our latest fabrication system [18]. The two-photon IH process is also utilized for assembly-free, single-step fabrication of freely movable micro/nano structures [5, 15, 18, 19].

For the practical use of these microstereolithography techniques, we have developed a versatile microfluidic device named "Biochemical IC Family". The biochemical IC chip was proposed by Ikuta et al [20]. Several types of biochemical IC chips including a reactor [21], concentrator [3], homogenizer [22] and active valve and micro pump [4] have been already developed. Recently, in-chip cell-free protein synthesis was demonstrated by using biochemical IC chips [23, 24]. The palm-top protein synthesis devices are promising and powerful tools for not only order-made medicine but also implantable/wearable medical devices in the near future.

MICROSTEREOLITHOGRAPHY

IH process (The world's first microstereolithography)

We proposed and developed the world's first microstereolithography named "IH Process (Integrated Harden Polymer Stereo-Lithography)" [1]. The fabrication principle of the IH process is based on the stereolithography which is used to make 3D mock-up model in macro size. Fig.1 shows the schematic diagram of fabrication apparatus. This system consists of an UV (ultra violet) lamp, XYZ-stage, shutter, lens and computer. To make a 3D microstructure, thin sliced cross sectional shapes of the final product are drawn by UV beam focused on photopolymer through transparent Z-stage. The cross sectional layers are piled up to fabricate the 3D microstructure. Fig. 2 show scanning electron microscope (SEM) images of a bending pipe (100 x 100 x 1000 μm) and a micro coil spring (diameter: 50 μm, length is 350 μm). The 3D resolution of this process attained to 5 μm in lateral and 3 μm in depth.

Unique features of the IH process were as follows: 1) Real 3D structure, 2) High aspect ratio, 3) Simple and low cost apparatus 4) Micrometer resolution etc. These features are much superior than conventional micromachining methods. The IH process has a great potential for various fields of applications.

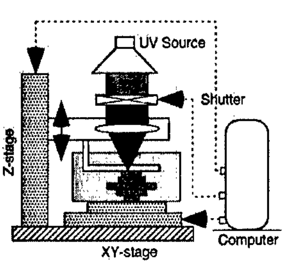
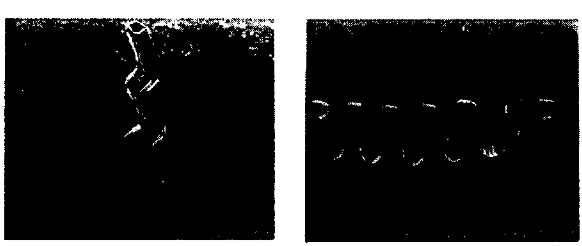


Fig. 1 Schematic diagram of IH process


(a) (b)
Fig. 2 3D microstructures made by IH process
(a) Bending pipe (b) Micro coil spring

Mass-IH Process

To improve the mass productivity of microstereolithography, we have developed a method named "Mass-IH Process" [2]. Fig. 3 shows the fabrication system of the mass-IH process. The main technology is the newly developed "Optical fiber Multi-beam scanning" which can satisfy both simultaneous scanning and uniform accuracy on all area. The array of optical fibers (4μm in core diameter) allows the multi-beam scanning. Fig. 4 shows a sample of 3D microstructures fabricated simultaneously. Five micro pipes (220 μm squire, 1150 μm high) with lateral windows were made within 40 minutes. Although the resolution at this time is not high compared to that of the IH process, feasibility as mass productive microstereolithography was verified. Increasing number of fibers and optimizing experimental conditions enable further mass productivity and higher resolution.

Super-IH process

Since conventional microstereolithography systems employ layer-by-layer process, the depth resolution is limited by surface tension and viscosity of photopolymers. To overcome the limitation caused by the layer-by-layer process, we proposed a new method named "Super-IH process" that was based on pinpoint inner solidification by using a tightly focused laser beam [8]. Fig.5 shows the fabrication principle of the super-IH process. The liquid photopolymer is solidified only at the vicinity of the focus, although that is solidified at the surface in the conventional method. By scanning the focus along the shape of the desired structure, any 3D microstructure can be made.

The pinpoint inner solidification results from the nonlinear response of photo polymerization to optical intensity with sufficiently low exposure [9, 10]. It is well known that the liquid/solid transformation of photopolymer is approximated by the threshold system. The photopolymer is not solidified unless the optical exposure exceeds the critical exposure. Accordingly, when a laser beam is highly focused inside photopolymer with optimum exposure conditions, the intensity near the focus is sufficient to solidify the photopolymer, even though the intensity is insufficient at out-of focus regions.

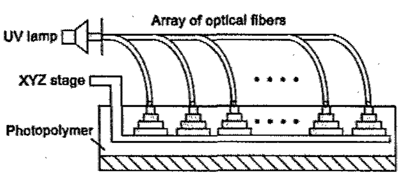


Fig. 3 Schematic diagram of Mass-IH process

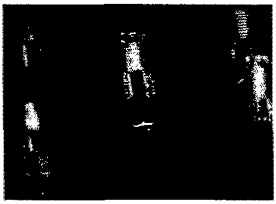


Fig. 4 Micropipes made by Mass-IH process

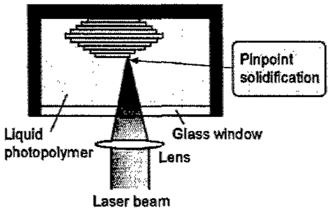


Fig. 5 Fabrication principle of Super-IH process

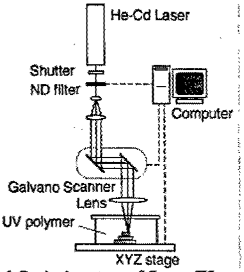


Fig. 6 Optical system of Super-IH process

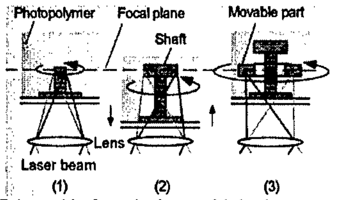


Fig. 7 Assembly-free, single-step fabrication process of movable microstructures


Fig. 8 Microgear made by Super-IH process

Fig. 6 shows a schematic diagram of our fabrication system, which consists of an He-Cd laser (Wavelength: 442nm), shutter, galvano scanners, xyz-stage, and objective lens (N. A.: 1.0 or 1.3). The beam from the laser is introduced into the galvano-scanner set to deflect its direction in two dimensions, and then is focused into the liquid photopolymer with the objective lens. As the beam scans laterally in the liquid photopolymer and the sample-cell stage vertically slides, any 3D structure can be formed in the photopolymer volume. The resolution of our latest fabrication systems attained to 430 nm [10].

The most important feature of the super-IH process is assembly-free, single-step fabrication of movable micromechanisms. In major microfabrication techniques such as surface micromachining and the LIGA process, sacrificial layers are indispensable to make a movable mechanism [25]. Even stereolithography needs supporting columns to hold movable components. On the other hand, the super-IH process requires neither sacrificial layers nor supporting columns, since movable microstructures can be fabricated merely by scanning a focus inside photopolymer as shown in Fig. 7. Fig. 8 shows an SEM image of movable microgear fabricated by the Super-IH process. A microgear (diameter: 47 μm) with an attached shaft was successfully fabricated.

Two-photon IH process

For the further improvement of resolution, we have developed two-photon IH process [11-14]. In the two-photon IH process, a liquid photopolymer absorbs two photons of near infrared simultaneously in a single quantum event whose energy corresponds to the UV region. The rate of two-photon absorption is proportional to the squared intensity of light. Accordingly, near infrared light is strongly absorbed only at the focal point within the photopolymer. This virtue of the two-photon process enables us to fabricate a 3D microstructure by scanning a focus inside the photopolymer.

The fabrication system of the two-photon IH process is similar to that of the super-IH process except for a laser source. In the fabrication system of the two-photon IH process, a mode-locked Ti: sapphire laser (wavelength, 710 nm; repetition, 82 MHz; pulse width, 130 fs) is used, because extremely high optical density is required for generating the two-photon absorption.

The two-photon IH process allows the fabrication of 3D microstructures directly from 3D CAD models. Fig. 9 (a)-(d) demonstrate SEM images of complicated 3D microstructures. The model of the microrobot (16 μm x 13 μm x 28 μm) and The micro V sign (10.4 μm x 10.4 μm x 21 μm) were solidified from the bottom to the top at an interval of 250 nm along the optical axis. The micro beetle and micro locomotive are fabricated in 20 minutes. These results clearly demonstrate the high efficacy of the two-photon IH process for fabricating 3D microstructures with submicron resolution.

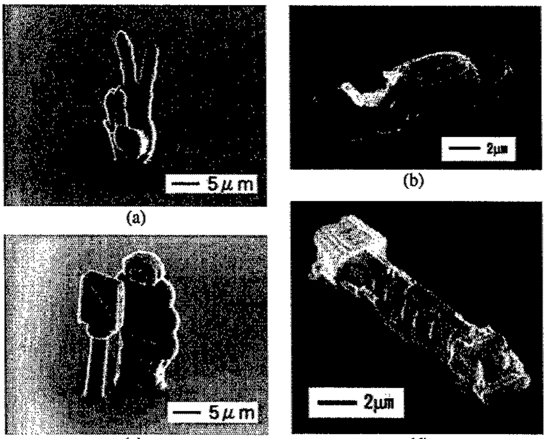


Fig. 9 3D microstructures made by two-photon IH process
(a) Micro V sign model (b) Micro beetle model
(c) Micro robot model (d) Micro locomotive model

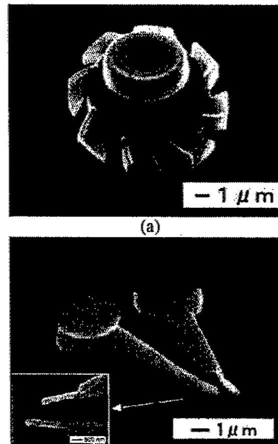


Fig. 10 Movable micromachins made by two-photon IH process
(a) Microturbine (b) Nanotweezers

Movable microstructures were also fabricated by using the direct laser writing method shown in Fig. 7. As shown in Fig. 10, various types of micromechanisms including microturbine, microgear train, and nanotweezers were successfully fabricated. The microturbine (external diameter, 14 μm) shown in Fig. 10 (a) was fabricated in only 13 minutes. The probe diameter of the nanotweezers (Fig. 10(b)) is 250 nm. These results demonstrate that two-photon IH process allows the rapid manufacturing of micro/nano machines.

In recent years, the two-photon IH process has been widely used to make complicated 3D microdevices such as photonic crystals and micromechanical components [16, 17]. We have developed optically driven micromachines by using the direct writing of movable micromechanisms. Our micromachines are driven by using a laser scanning manipulation technique [15]. We have already fabricated several types of light-driven micromachines such as microturbine, micromanipulators and nanotweezers [15, 18, 19]. The light-driven micromachines are promising and powerful tools for MEMS and μ-TAS. Although P. Galajda et al. have also used a two-photon process for making optical rotators in recent years [26], their rotators are simple wire-frame types and only offer rotary motion with continuous irradiation of light.

Multi-polymer IH process

We have developed a novel microstereolithography method for producing a hybrid structure using multiple photocurable polymers [5]. This method named "Multi-polymer IH process" has the potential to provide all-polymer functional microdevices. To confirm the validity of the multi-polymer IH process, we constructed a simple fabrication system with a single tank to store multiple kinds of photocurable polymers. The fabrication process is illustrated in Fig. 11. In this case, a 3D microstructure is formed with the polymer A, and then particular layers are formed with the polymer B. Each layer is leveled using a squeegee. By changing photocurable polymers layer-by-layer, a 3D structure consisting of multiple photocurable polymers can be easily formed.

As an example of an all-polymer microdevice, we fabricated several optical waveguides

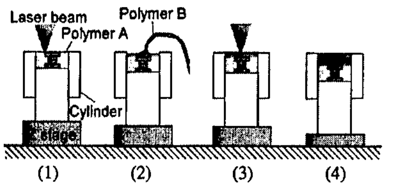


Fig. 11 Fabrication process of Multi-polymer IH process

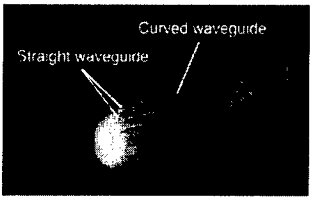


Fig. 12 Optical waveguides made by Multi-polymer IH process

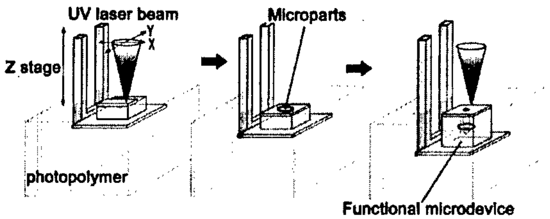


Fig. 13 Fabrication process of Hybrid-IH process.
Functional microdevices are produced without bonding process.

with two kinds of photopolymer having different refractive indexes. Fig.12 shows a prototype of the straight waveguides and a curved waveguide. The width of the core was about 150 μm. The clad and core were made of a low refractive index polymer (n: 1.51) and a high refractive index polymer (n: 1.55), respectively. Both photopolymers are transparent to visible and near-IR light. To verify the performance of the waveguide, we measured the propagation loss of a straight waveguide by using the prism-coupling method with an He-Ne laser. The propagation loss of the waveguide was about 14 dB/cm.

Hybrid IH Process

Another approach to make functional microdevices is to integrate existing elements such as actuators and sensors into a polymeric microstructure. To perform the integration of microparts, we have developed a simple method named "Hybrid-IH process" [3]. The fabrication process of the hybrid-IH process illustrates in Fig. 13. Microparts such as microactuators and membranes are inserted in a polymeric microstructure during the fabrication process. Unlike conventional micromachining techniques, since this process doesn't need additional bonding process, leak-free packaging is easily realized. This process is widely used to make transparent, functional polymer microdevices. We have utilized this process to fabricate micro chemical devices such as micropump [4], microvalves [4] and microconcentrators [3]. In the following chapter, we introduce the micro chemical devices fabricated by using the hybrid-IH process.

BOCHEMICAL IC CHIP

Concept of Biochemical IC chip

The authors have been conducting unique biochemical micro devices named "Biochemical IC" proposed by Ikuta et al. in 1994 [20]. This device originally named "MIFS (Micro Integrated Fluidic System)" contains both miniaturized fluidic circuits made of polymer and silicon circuits in one chip. Although the concept for miniaturization of chemical systems on a chip seems similar to μ-TAS and Lab-on-a-chip, the biochemical IC differs from these chips in various meanings.

Fig. 14(a) shows basic concept of the biochemical IC consisting of 3D micro fluidic channels (upper part) fabricated by the IH process and electric parts (lower part) made by silicon process. Fig. 14(b) shows the modular IC concept of "Biochemical LSI" which satisfies more complicated capability at higher level. [2, 27]. The biochemical IC has the following features in comparison with other micro chemical devices.

1) Modular device architecture
2) 3D micro integrated fluidic system
3) Containing micro fluid driving devices
4) Hybrid structure of polymer, silicon and other materials
5) User assembled chip-set family
6) Wearable/implantable applications

This biochemical IC is based on modular IC concept similar to the today's IC/LSI family (C-MOS/TTL). Each biochemical IC chip in a disk (or cell) shape contains different functional devices such as multiple micro valves, pumps, chemical concentrators and micro reactors. Users can construct their own biochemical systems by using several types of biochemical IC chips. Since active fluidic devices such as pumps and valves are miniaturized in chips, the biochemical IC chips will be applied to wearable and implantable microdevices unlike general μ-TAS and lab-on-a-chip.

Prototypes of Biochemical IC chips and experimental verification

By using the hybrid-IH process, we have already developed several types of biochemical IC chips including a reactor [21], concentrator [3], homogenizer [22] and active valve and micro pump [4]. In this section, we present fluid driving chips such as pump and active switching valve.

Fig. 15 (a) shows a prototype of a micropump chip (size: 14 x 14 x 3.0 mm) containing three micropumps driven by shape memory alloy (SMA) actuators. Each pump designs are reciprocating pumps, consisting of two check valves, a deformable chamber and a SMA actuator as shown in Fig. 15 (b). Pump rate for water are in the order of 10 μl/min.

Fig. 16 (a) shows a prototype of a switching valve chip to select direction of flow dynamically. This valve chip is actuated by two SMA actuators as shown in Fig. 16(b). This valve design is one inlet-two outlet connection valve, consisting of two silicone rubbers as valves and SMA actuators. The switching time in active phase was better than 0.5 seconds and the response time of the opposite way in the passive phase was about 2 seconds.

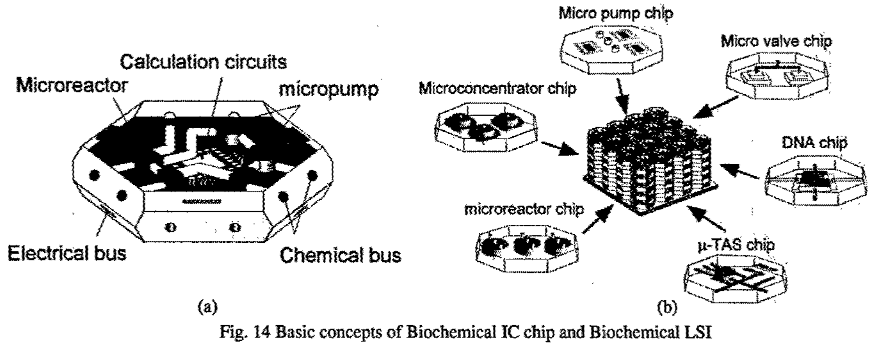
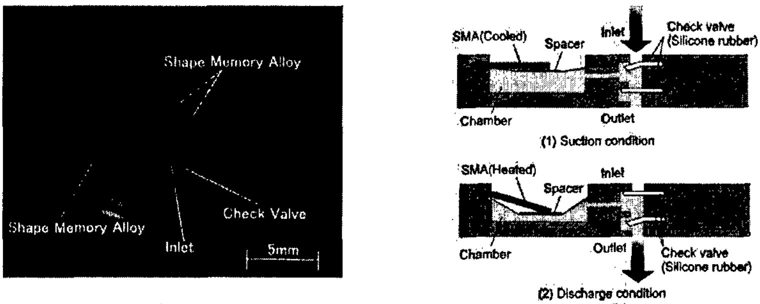


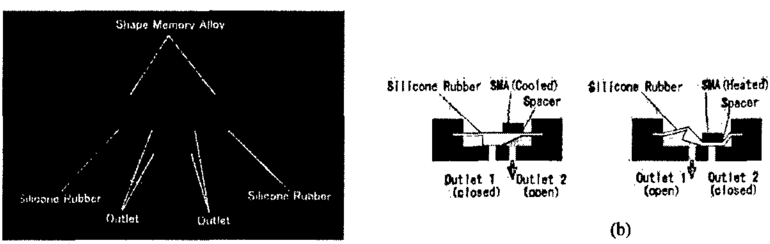
Fig. 14 Basic concepts of Biochemical IC chip and Biochemical LSI
(a) Bicochemical IC chip (b) Biochemical LSI

To demonstrate the validity of these chips, a simple experiment of neutralized reaction using sodium hydroxide and phenolphthalein was demonstrated. Fig.17 (a) shows an experimental setup using biochemical IC chips. The first upper layer is a micro pump chip to supply sodium hydroxide through the inlet. The second layer is a micro reactor chip. The third layer is a micro switching valve chip to switch to another outlet. The fourth layer is a connector chip. Fig. 17 (b) shows biochemical IC chips held in a holder unit. Each chip is connected with thin silicone rubber films, and held by spring force. Our original coupling method named "silicone rubber coupling" enables good sealing under high pressure (>400 kPa) [28, 29].



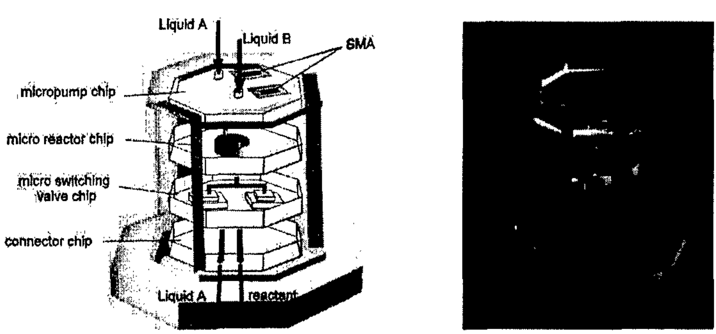
(a) (b)

Fig. 15 Micropump chip (a) Prototype (b) Operation principle



(a) (b)

Fig. 16 Switching valve chip (a) Prototype (b) Operation principle



(a) (b)

Fig. 17 Experimental setup for neutralized reaction using biochemical IC chips
(a) Schematic diagram (b) Biochemical IC chips held in a holder unit

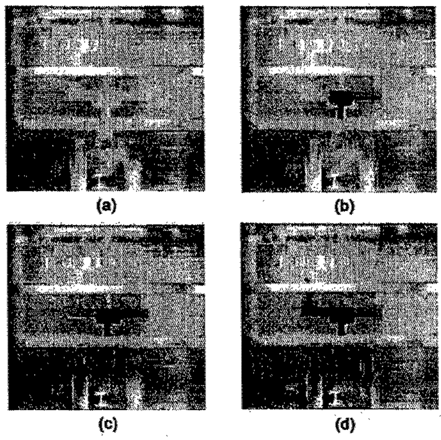


Fig. 18 Experimental results of neutralized reaction using biochemical IC chips
(a) Before neutralized reaction (b) After neutralized reaction
(c) Flow through left outlet (d) Flow changed to right outled

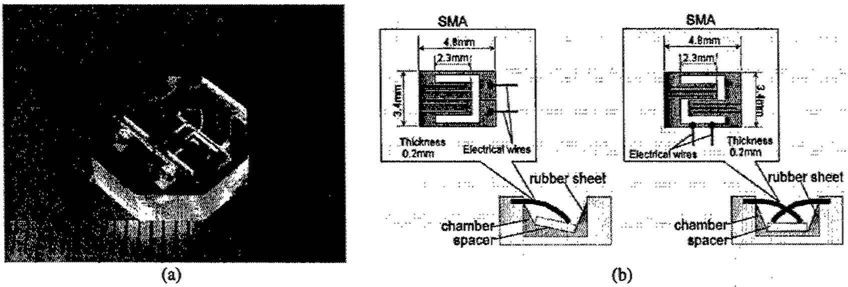


Fig. 19 High-performance micropump chip applicable to liquids and gases
(a) Prototype (b) Modification of SMA cantilevers

Fig.18 is the sequential photos for the demonstration while the neutralized reaction is proceeding in transparent biochemical IC chips. Phenolphthalein and sodium hydroxide were supplied by using the micropump chips, and then they were mixed in the reactor chip. Finally, the mixed reagent was successfully divided into two outlets by using the switching valve chip. The experiments indicates the validity of the modular concept of the biochemical IC chips.

Recently, we have developed a high performance micropump chip that can flow not only liquids but also gases (12 μl/min, 25kPa for water, 11 μl/min., 5 kPa for air) [30]. Fig. 19 (a) shows a prototype of the micropump chip. Two micropumps are included in a chip. To achieve such high performance, we improved the design of SMA actuators, check valves and chamber. The modification of the SMA actuators are illustrated in Fig. 19 (a). The SMA cantilevers can push down the spacer stably compared to the former design shown in Fig. 15.

Cell-free protein synthesis by using biochemical IC chips

Cell-free protein synthesis is one of key technologies in post genome research and tailor made examination. We have first demonstrated cell-free protein synthesis from DNA by using biochemical IC chips [23]. A luminous protein of firefly called "Luciferase" was synthesized

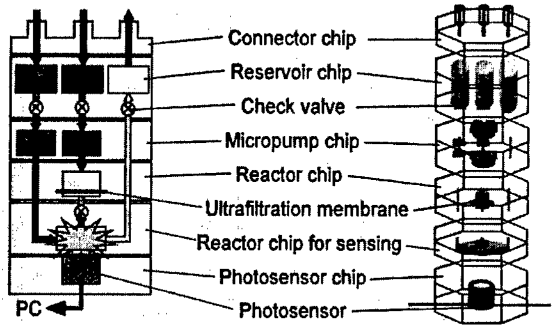


Fig. 20 Biochemical IC chip-set with a built-in micropump chip for cell-free protein synthesis

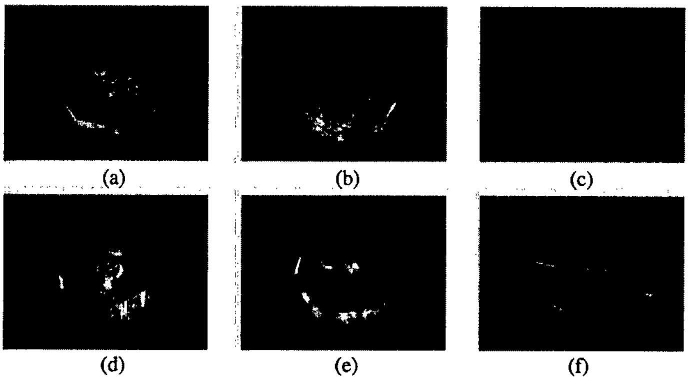


Fig. 21 Prototypes of Biochemical IC chips (a) Connector chip (b) Reservoir chip (c) Micropump chip (d) Reactor chip (e) Reactor chip for sensing (f) Photosensor chip

without living cells in 8 hours. In the first demonstration, however, we used external pumps to supply reagents. Recently, we succeeded in developing a micropump chip for cell-free protein synthesis [24]. Since the micropump chip used new check valves with double silicone rubber films, it has sufficiently long lifetime for protein synthesis.

Fig. 20 shows the basic design of biochemical IC chip-set for cell-free protein synthesis. This synthesis system is constructed with six types of biochemical IC chip: connector chip, reservoir chip, micropump chip, reactor chip, reactor chip for sensing, photosensor chip. The micropump chips supply reagents from the reservoir chips to the reactor chip. The reactor chip includes an ultrafiltration membrane to synthesize protein, which is then introduced into the reactor chip for sensing with the micropump chip. The protein is optically detected at the detection chip, which has a built-in a avalanche photodiode, by mixing an assay reagent for luminescent detection. Fig. 21 shows the prototype chips. By using the hybrid-IH process, micropart such as an ultrafiltration membrane, silicone rubber, SMA actuator, are hybridized with a polymeric structure.

To perform the experiments, each chip is set in a holder unit. Since each chip is connected with thin silicone rubber films by using our proposed silicone rubber coupling method [28, 29], dead volume is minimized without any leakage. Fig. 22 shows the entire experimental setup for

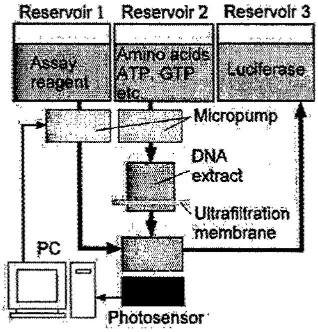


Fig. 22 Experimental setup for cell-free protein synthesis

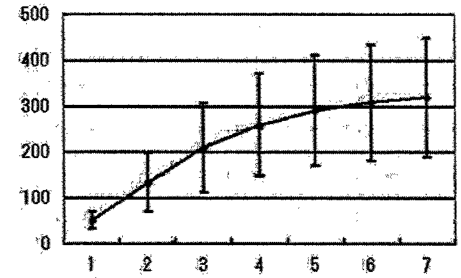


Fig. 23 Experimental result of cell-free protein synthesis

DNA-originated cell-free protein synthesis. Solution A (DNA, S30 Premix, Amino acid complete, SW) and solution B (S30 Extract) are mixed in the reactor and synthesized. Luciferase is filtered through the ultrafiltration membrane (YM100). An assay regent is mixed to measure the protein concentration via luminous intensity. Fig. 23 shows an experimental result of Luciferase synthesis. We succeeded in synthesizing protein in 7 hours by using the built-in micropumps. The palm-top protein synthesis device is promising tools for not only tailor made medicine but also bioscience researches.

CONCLUSIONS

We have developed several types of microstereolithography such as the IH process, the super-IH process, the two-photon IH process and the hybrid IH process. The resolution of the microstereolithography techniques are scalable from 100 μm to 100 nm. By using these techniques, we can fabricate functional polymer microdevices such as the biochemical IC chips as well as micro/nano machines such as microgears and nanotweezers. We have already demonstrated the validity of our modular approach of biochemical IC chip with chemical and biochemical experiments such as cell-free protein synthesis. In the near future, the biochemical IC chips should contribute not only the biomedical applications but also basic science.

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