KINEMATIC ASSEMBLY OF SOFT-POLYMER BIOFLUIDIC CIRCUITS

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INTRODUCTION

Micro-scale biofluidic networks are providing researchers with a powerful new tool to perform useful biological assays. These Biofluidic Application Specific Integrated Circuits (BioASICs) can be designed for medical diagnostics, high throughput drug discovery, cell culturing, proteomics, functional genomics, protein crystallization, or any number of other important quantitative biology and medical applications [1-3]. Performing these tests using microfluidic technology not only makes them more portable when compared to their traditional counterparts, but also decreases testing time and cost.

One widely used method of creating BioASICs uses a soft polymer (Poly-dimethylsiloxane, PDMS) to replicate a silicon master mold in a technique known as soft lithography. This method can be used to create polymer microchannels rapidly and inexpensively, but complete assembly of these BioASICs requires precision alignment and bonding of the PDMS to a glass substrate that has proteins or metal electrodes patterned on the surface. PDMS' low modulus of elasticity makes it difficult to achieve this alignment by mechanical means, so the assembly must be performed manually under an optical microscope, leading to alignment errors that may be over an order of magnitude larger than feature dimensions in the BioASICs.

The paper presents a process that enables multiplexed assembly of PDMS/glass BioASICs with better than 5 μm precision, as compared to 20-40 μm error generated using current technology. By employing kinematic constraint and an integrated flexural bearing, the assembly device (shown in Figure 1) allows passive mechanical alignment and assembly of the microfluidic components. This decreases

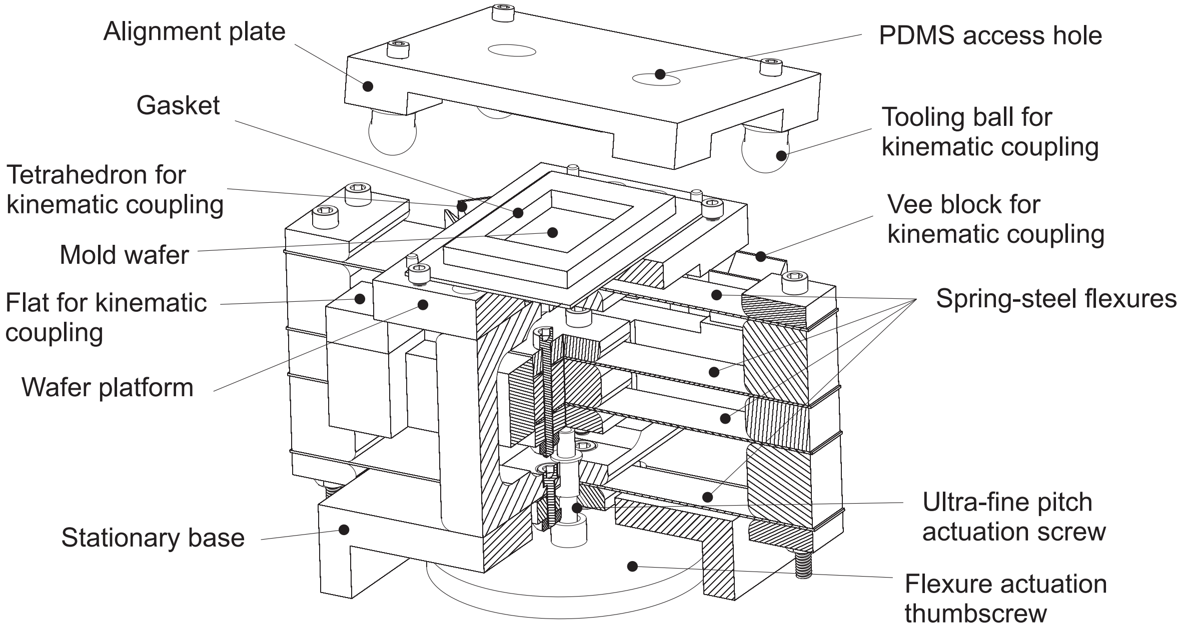

Figure 1. Sectioned diagram of kinematic soft-polymer alignment device.

fabrication time, increases alignment accuracy and eliminates the need for complicated optical alignment equipment. The necessary hardware for this system can be manufactured at a cost more than an order of magnitude smaller than comparable devices and it is possible to extend this technique to high-throughput automated assembly and use with other polymer materials.

PRIOR WORK

The first microfluidic and biofluidic devices were created in silicon and glass using semiconductor processing technology [4, 5]. This requires access to expensive etching machinery, and so was soon replaced in many labs by soft lithography [6]. This process requires a master mold created through the process shown in Figure 2, steps 1-4. A photosensitive polymer, such as SU-8 photoresist, is spin-coated onto a silicon wafer and then exposed to UV light through a patterned mask. The polymer which has not been exposed is subsequently removed during a developing step, leaving behind a positive relief mold.

Negative replicas of the mold are made by the process shown in Figure 2, steps 5-8; first, uncured PDMS prepolymer is poured over the entire mold. A single mold will generally contain multiple copies of the same pattern, thus the PDMS microfluidic networks for multiple BioASICs can be cast simultaneously. The PDMS is heat cured, removed from the mold and manually cut into individual components. Each PDMS microfluidic component undergoes optical alignment and bonding to a second substrate, forming closed channels. Patterned features—such as proteins or metal electrodes—on this second substrate make proper alignment between the components critical.

The current standard for BioASIC assembly involves using tweezers to manually suspend the PDMS microfluidic component over the glass substrate while they are aligned visually using a microscope. The PDMS is then released, bringing the two substrates into contact. The precision attained using this technique depends heavily on the user; even the most experienced technicians produce tens of microns of error during assembly.

Some researchers have attempted to improve assembly by replacing the hand-held tweezers with precision translation stages. This has increased the accuracy of optical alignment, but even with a very thoroughly designed multiple-stage setup it is difficult to attain less than 10 μm error [7]. Other drawbacks of this approach include high cost of the alignment machine and inability to process multiple BioASICs simultaneously.

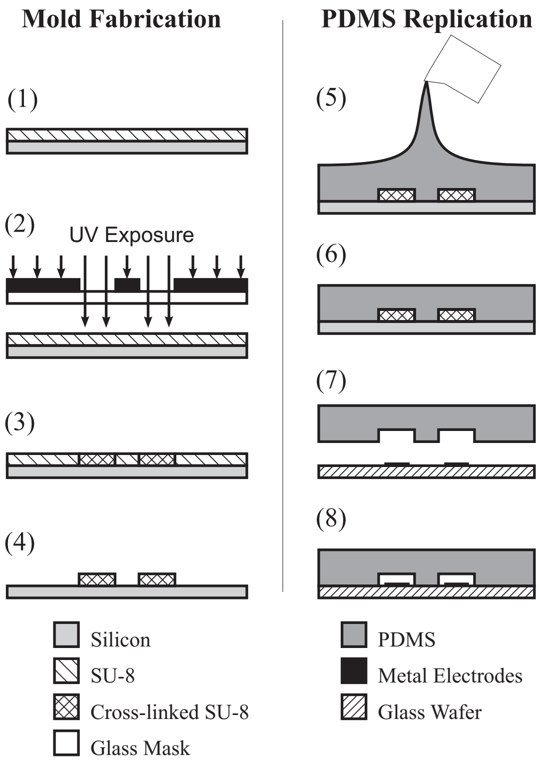

FIGURE 2. Traditional soft lithography: mold fabrication (a) begins by spin coating a silicon wafer with SU8 photoresist (1), then exposing it to UV through a patterned mask (2), causing exposed areas to crosslink (3). A chemical developer removes areas which have not crosslinked to leave a positive-relief mold (4). Mold replication is performed by pouring PDMS prepolymer over the mold (5) and curing until the material is rigid (6). The PDMS can then be removed from the mold (7) and aligned and bonded to a glass substrate (8).

Jo, *et al.* [8] reported 15 μm accuracy in aligning thin PDMS films by biasing them against a reference edge and using surface tension forces provided by a methanol surfactant. This approach removes the need for optical alignment, but the resulting error is larger than desired, and the approach is limited to use with components whose mass is small enough to be shifted via surface tension forces.

KINEMATIC ALIGNMENT DEVICE

The kinematic alignment device shown in Figure 1 removes the need for optical alignment, increases alignment accuracy, and is scalable to assemble multiple BioASICs simultaneously. The new technique, shown schematically in Figure 3, uses the same molds as traditional lithography. However, the difference lies in using a kinematic coupling to provide accurate placement in the horizontal plane and a flexural bearing to produce precise, repeatable motion in the vertical direction.

The novel soft lithography process starts by placing the mold onto the stationary base and assembling the gasket and alignment plate (steps 1-2). The PDMS prepolymer is poured into the mold cavity through an access hole in the alignment plate (step 3). The entire assembly is heated in an oven to cure the PDMS (step 4). After curing, the alignment plate is removed, retaining contact with the cured PDMS part (step 5). Then the mold is removed from the stationary base and replaced with a patterned glass substrate. The alignment plate/PDMS assembly is then mated with the base; the kinematic coupling provides passive alignment in the x-y plane. A flexural bearing in the base allows careful control of the gap between the two components, allowing them to be brought into precise contact (step 6). The assembled BioASIC can then be removed from the alignment mechanism.

The kinematic coupling is a deterministic mounting system that employs a set of three tooling steel balls and six contact points to exactly constrain the alignment plate in all six degrees of freedom. Thus, alignment between the two main components of the system is achieved with repeatability in the sub-micron range. [9] The optics-free nature of the system provides the opportunity to scale this technique to perform wafer-level assembly of BioASICs. Removal of optical alignment also means that the technique can be used with any number of polymers, even those that are not optically transparent.

Initial testing of the kinematic coupling placement accuracy was performed using Lion Precision C1 capacitive sensors. The data from n=10 trials has a range of just under 1 µm in each direction, with standard deviation of 0.33 and 0.34 µm in the x- and y-directions, respectively.

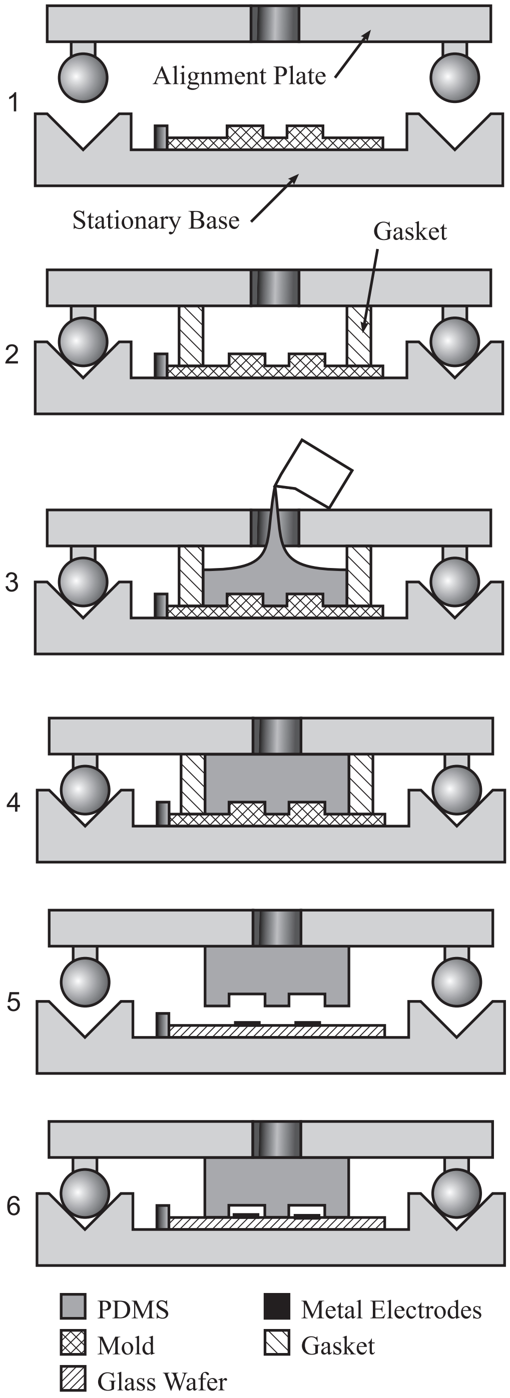

FIGURE 3. Soft lithography with kinematic alignment. A mold is aligned to the stationary base (1); a gasket and the alignment plate form a closed cavity (2). PDMS prepolymer is added via an access hole in the alignment plate (3), and PDMS is heat cured (4). The PDMS is removed from the mold and gasket, but retained with the alignment plate; the mold is replaced with a glass substrate (5). The alignment plate is reseated, bringing the PDMS and glass substrate into contact (6).

A double-compound flexural bearing is integrated into the stationary base of the alignment device. The bearing is actuated using an ultra-fine pitch screw (100 tpi, from ThorLabs) connected to a thumbwheel, which are both also integrated into the stationary base. By actuating this system, one can manually control the spacing between the alignment plate and the mold or glass substrate. This provides accurate control over PDMS thickness during the casting process and contact pressure during alignment and bonding steps. The system has a travel range of over 1 mm and was chosen because its geometric symmetry minimizes error due to long time scale thermal fluctuations.

Use of the alignment plate as a backbone during the PDMS curing and assembly process also allows better control over thermal expansion of PDMS. The large coefficient of thermal expansion (310 μm/m/K) of this material makes it very sensitive to ambient temperature fluctuations: change of a single degree Kelvin leads to an expansion of 3 μm over a standard 1 cm x 1 cm die size. Constraining the PDMS to the alignment plate forces the PDMS to conform to the thermal deformation of the stiffer (and less thermally expansive) backing material [10], thus increasing its dimensional stability with respect to temperature fluctuations by at least an order of magnitude. Careful matching of material CTE and thermal centroid location in future generations of this device should reduce thermally induced error even further.

CONCLUSIONS AND FUTURE WORK

A novel kinematic system for PDMS-based microfluidic casting and alignment has been developed for creation of biofluidic integrated circuits. Precision machine design techniques such as kinematic constraint can be used to provide low-cost passive alignment device capable of better than 5 *μ*m precision. Initial testing of the kinematic coupling alignment has shown submicron placement repeatability. The elimination of optical alignment and ability to simultaneously assemble multiple BioASICs provides a significant improvement in efficiency and opens the door to automated and wafer-level assembly. This technique could easily be extended to other uses PDMS devices, such as microcontact printing; it could also be adapted for use with any number of other soft polymers.

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