Modular microfluidic systems using reversibly attached PDMS fluid control modules

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Abstract
The use of soft lithography-based poly(dimethylsiloxane) (PDMS) valve systems is the dominating approach for high-density microscale fluidic control. Integrated systems enable complex flow control and large-scale integration, but lack modularity. In contrast, modular systems are attractive alternatives to integration because they can be tailored for different applications piecewise and without redesigning every element of the system. We present a method for reversibly coupling hard materials to soft lithography defined systems through self-aligning O-ring features thereby enabling easy interfacing of complex-valve-based systems with simpler detachable units. Using this scheme, we demonstrate the seamless interfacing of a PDMS-based fluid control module with hard polymer chips. In our system, 32 self-aligning O-ring features protruding from the PDMS fluid control module form chip-to-control module interconnections which are sealed by tightening four screws. The interconnection method is robust and supports complex fluidic operations in the reversibly attached passive chip. In addition, we developed a double-sided molding method for fabricating PDMS devices with integrated through-holes. The versatile system facilitates a wide range of applications due to the modular approach, where application specific passive chips can be readily attached to the flow control module.

(Some figures may appear in colour only in the online journal)

1. Introduction
The use of highly integrated soft lithography-based poly(dimethylsiloxane) (PDMS) systems for on-chip valving has long been the dominating approach for high-density and combinatorial microfluidic systems [1–4]. These systems have the advantage of enabling a vast number of simultaneous experiments for high-throughput studies [3, 5]. Modular systems consisting of a number of interfaced components can be an attractive alternative to the integrated system approach. In principle, a given number of standard modules can be reused and connected in different system configurations for the price of one, bypassing the need to redesign entire new integrated systems for each new task. Also, the fabrication of PDMS valve systems is a more complicated process than mass production technologies such as injection molding applicable for fabrication of passive polymer devices. For conducting serial experiments it can thus be attractive to reuse the PDMS microvalves and dispose cheaper, single-use components. Reuse or disposal of different system parts has also been pointed out by Krulevitch et al [6] who demonstrated different combinations of hybrid systems combining custom-made and off-the-shelf components. Modularity is also beneficial for combining different material platforms. For instance chips containing advanced sensors are typically based on silicon rather than polymers [7, 8].

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However, in order to create modular systems it is important to be able to interface the different components in an easy and reliable manner. Examples of hybrid systems interfacing PDMS with other material platforms have been presented [9–13]. These systems, however, rely on irreversible bonding and cannot exploit the advantages of modular systems. Dimov et al [14] presented a hybrid system integrating a glass capillary in one chip and fluidic networks in another. However, the system relies on PDMS-PDMS self-sealing for low-pressure applications and does not present high-density interconnectivity. Cooksey et al [15] have demonstrated a chip-to-world manifold based on vacuum sealing to interface PDMS chips with multiple fluidic inlets permanently glued to the poly(methyl methacrylate) (PMMA) manifold. The manifold facilitates rapid connection to peripherals but the vacuum approach limits the portability of the device, since the sealing strength, depending on the design, can be significantly decreased when unplugged from the vacuum. Portability is an important feature for systems to be compatible with standard cell culture lab routines in order to ease transfer between workstations such as laminar flow benches, incubators and microscopes. Another important aspect for adoption of configurable microfluidic systems into biology labs is ease of use for users not being trained in microengineering. Langelier et al [16] have shown an example of such usability by demonstrating easy construction of highly configurable systems using standard PDMS assembly blocks. These assembly blocks however rely on an irreversible assembly method and only contain passive fluidic networks not offering the same amount of complex fluid handling as active valves. An example of a modular system comprising both components with active valve circuitry and components with passive fluidic networks has been presented by Shaikh et al [17] Utilizing an intermediate silicon layer this approach however can pose an increased production cost over the fully polymeric system presented in the following. We have recently presented a complete component platform, entitled MainSTREAM [18], allowing for quick and flexible creation of a variety of systems from a library of components and a standardized interconnection scheme.

In this paper, we present a modular system featuring a universal soft lithography-based PDMS fluidic control module which feeds an externally attached hard passive polymeric chip. The system is based on a reversible sealing between the PDMS fluid control module and the passive chip using self-aligning PDMS O-ring features previously presented [18, 19]. The modularity concept and interconnection standard is in this paper extended by direct integration into a module containing active fluid control valves. To demonstrate the concept, we have fabricated a PDMS fluid control module featuring pneumatically actuated valves leading to 32 central chip connections in four blocks of 8. By tightening four screws the 32 fluidic chip-to-control module interconnections are readily formed and we show the stability of the interconnections through flow rate characteristics with three different chips attached. Using fast prototyped chips of PMMA we demonstrate how the universal PDMS fluid control module can be used for control of fluid flow patterns in the passive external chip.

Figure 1. Schematic overview and annotation of passive microfluidic PMMA chips with (a) 8 individual lines (b) common chamber with 2 × 8 interconnections and (c) common chamber with 4 × 8 interconnections. Each chip has a footprint of 25.25 × 25.25 mm² and eight inlet holes of 0.8 mm diameter are equidistantly distributed with 2.25 mm spacing along each edge.

2. Materials and methods

2.1. Hard passive chips

Hard passive chips of PMMA with microfluidic networks were fabricated by mechanical micromilling (Folken, Glendale, CA, USA). PMMA sheets (Plexiglas XT 20070, Röhm GmbH, Germany) of 2 mm thickness were used for both top layer containing channels and chambers and bottom layer containing fluidic inlets. Chips were sealed by UV-assisted thermal bonding. In short, the bonding surfaces were exposed to UV (DYMAX, 5000 EC with bulb 36970, CT, USA) for 85 s. Subsequently the two layers were aligned by integrated pins and placed between two glass plates in a preheated laboratory press (PW 10 H, P/O/Weber, Germany). Heat bonding was carried out at 85°C for 16 min with an initial bonding pressure of 1.2 MPa.

The inlets are holes with a diameter of 0.8 mm spaced with a center-to-center distance of 2.25 mm to conform to 1536 well microtiter plate spacing standards. Each chip has a footprint of 25.25 × 25.25 mm² and contains 8 inlets along each of the four sides. Three different designs shown in figure 1 were fabricated and exploit either 16 or all 32 fluidic interconnections. Chambers have a footprint of 6.4 × 6.4 mm² and channels have a width of 400 μm. Both structures have a nominal depth of 100 μm.

2.2. Interconnection scheme

Integrated O-rings protruding from the PDMS control module (figure 2(c)) enable fluidic interconnection with the PMMA chips. Each O-ring consists of a 240 μm through-hole centered in a 1.6 mm diameter and 0.5 mm tall cylinder capped with a 0.8 mm semispherical protrusion for self-alignment of chip and control module. These semispherical O-ring features can also minimize dead volumes of interconnection [18, 19]. Reversible sealing between chip and control module is obtained by mechanically compressing the chip against the O-rings supported by a clamping system.

2.3. Clamping system

A clamping system to mechanically support the chip-to-control module interconnections was made in polycarbonate (PC) by mechanical milling. The system consists of a top
Figure 2. Overview of a hard/soft modular microfluidic system. (a) Exploded perspective showing the PC top and bottom clamp system enclosing a PDMS fluid control module with 32 protruding O-rings and a separate, passive PMMA chip. (b) Side view showing a cross-sectional view of the multilayered PDMS fluid control module comprising a fluidic layer, membrane and control layer compressed against a hard passive chip. Peripheral connection to control and fluid inlets are implemented with press fitted needles. Fluidic channel depth directly under the O-rings is increased to avoid pinching off channels upon compression. Drawing is not to scale. (c) Close-up image of two O-ring structures showing the O-ring on the topside of the fluid control module and through-hole leading to fluidic channels in the fluid control module.

2.4. PDMS fluid control module

The three-layer PDMS fluid control module consists of a thin PDMS membrane (the middle layer) sandwiched between a pneumatic control line layer and a fluidic network layer. The geometry of control and fluid channels was defined by lithographic masters for soft lithography. 4\textquoteright\ diam. silicon wafers were spin coated with SU-8 photoresist (MicroChem Corp., MA, USA). The SU-8 was prebaked at 95 °C and UV exposed through pattern defining photomasks before post exposure baking at 95 °C and development for up to 15 min in SU-8 developer (MicroChem Corp., MA, USA). Subsequently the wafers were hard baked at 180 °C. Next, wafers were exposed to perfluorinated trichlorosilane (T2492-KG, United Chemical Technologies, Bristol, PA, USA) for minimum 30 min in a desiccator under house vacuum to aid subsequent PDMS release. The master for the control channel layer was spin coated with SU-8 2035 at 4000 rpm to a final thickness of 15 μm. The fluidic channel master was spin coated, baked and exposed in two steps. The first step with SU-8 2035 at 2250 rpm to a final thickness of 25 μm defined main channels and the second step with SU-8 2075 at 1650 rpm to a total thickness of 100 μm defined interconnection base sites. The interconnection base sites placed under the O-ring features serve to avoid pinching off the channels during mechanical compression on the O-rings.

PDMS membranes were made from PDMS prepolymer (Sylgard 184, Dow Corning, MI, USA) 10:1 (wt:wt) base:curing agent mixed with hexane in a 3:1 (wt:wt) PDMS:hexane ratio and spin coated on a silanized silicon wafer at 4000 rpm followed by curing on a hotplate at 85 °C to a final thickness of 9 μm.

Molding of the fluid control module channel layers was done through two different methods. The fluidic layer was molded by pouring PDMS prepolymer over the master, degassing in a desiccator under house vacuum followed by curing at 68 °C over night (figure 3(a)). Subsequently, the fluidic layer edge was trimmed with a scalpel and peeled off the master (figure 3(b)).

For the fabrication of the pneumatic control layer we used a double-sided mold made from PMMA and silicon/SU-8 layers to mold PDMS. PMMA features were fabricated by micromilling and used to produce the O-ring features [18, 19] by threading with 240 μm optical fibers (FVP200220240, Polymicro Technologies, AZ, USA). The SU-8 layer was fabricated by traditional photolithography and used to pattern microchannel features in the PDMS replica. To mold a replica, the SU-8 master was mounted at the bottom of a mold and fibers were threaded through the O-ring array which aligned them with the SU-8 interconnection features. Degassed PDMS prepolymer was manually injected into the mold via a syringe (figure 3(c)) to create a double-sided replica. With this method, a single molding step produced replicas featuring micron-scale control channels on one side and closely packed O-rings features on the opposite side. The structure was cured at 68 °C
Figure 3. Fabrication of the PDMS fluid control module. Soft lithography of the fluidic layer (a)–(b). Fabrication of the double-sided control layer with O-rings and through-holes (c)–(e). Assembly by bonding of the control layer and membrane (f)–(g) followed by bonding to the fluidic layer (h).

over night (figure 3(d)). The mold was disassembled and SU-8 master, PDMS and fibers were removed (figure 3(e)). Any residual PDMS layers between SU-8 master and fiber inserts were removed manually from the through-holes. Inlet holes for attaching external tubing were punched (Harris Uni-Core™, Whatman plc, UK) in the control layer and the microchannel featured side was subsequently cleaned with adhesive tape (Scotch Magic Tape 810, 3M, MN, USA) prior to plasma treatment to remove particles. The thin PDMS membrane was bonded to the cleaned pneumatic control layer by treating both parts with air plasma (22 s, 700 W) (Plasma-Preen II-973, Plasmatic Systems, Inc., NJ, USA), bringing the pieces gently into contact, and baking at 85 °C on a hot plate for 15 min (figure 3(f)). The bonded assembly was cut out from the wafer and manually released. With a pair of tweezers the membrane was peeled away from the inlets which feed through into the fluidic layer (figure 3(g)).

The fluidic layer and membrane-capped control layer were cleaned with adhesive tape and afterwards plasma-treated and subsequently aligned and brought into contact under a stereo microscope (figure 3(h)). Vacuum was applied to the control inlets and the assembly was baked on a hot plate at 85 °C for 35 min. The control lines were then pressurized to release valves and an alternating pressure and vacuum sequence was executed for a minimum of 90 min to ensure proper valve function.

2.5. Assembly and control

The system is assembled by mounting the fluid control module in the clamp and mounting external fluid and control lines by press-fitting prebent 25 gauge needles (Small Parts, Inc. WA, USA) connected to tubing. To ensure bubble-free operation of the impermeable PMMA chips both PDMS fluid control module and PMMA chips were primed before press-fitted together. The PDMS fluid control module was primed by pressurizing the inlets with valves opened until small droplets appeared at the O-rings where after flow was stopped by closing the valves. The PMMA chip was primed manually using a syringe from one or more of the inlets depending on chip design. Fluid flow in the system was established by pressurizing 50 ml conical tubes (430290, Corning, NY, USA) containing food-coloring dye solutions connected by tubes to a manual pressure controller (Conoflow GH10XTHCXXXB, ITT Conoflow, SC, USA) and the PDMS fluid control module. Valves were operated by pneumatics through an external, custom-made control box containing 24 solenoid valves (LHDA0511111H, The Lee Company, CT, USA) and a digital I/O device (NI USB-6501, National Instruments, TX, USA) computer controlled by a custom-made LabView program (LabView, National Instruments, TX, USA).

2.6. Visualization and measurements

Fluid flows were visualized by micrographs of food-coloring dye solutions recorded with a high-resolution digital color camera (EOS 5D, Canon, Japan) mounted on a stereo microscope (SMZ1500, Nikon, Japan). Control of fluid flow and switching in two directions was controlled by the state of outlet valves. Flow rates were measured by weighing the pumped fluid with a precision balance (PB303-S DeltaRange, METTLER TOLEDO, Switzerland) supporting a 50 ml waste reservoir (430290, Corning, NY, USA). A freely suspended tube fitted with a 16 gauge needle, which was immersed into the water, was fed through a cap with a 4 mm access hole. To minimize evaporation the water was capped with a thin layer of mineral oil (330779, Sigma-Aldrich, MO, USA). Flow rates were measured with three different chips mounted at three different pressures. Five readings over a 10 min period were recorded for each chip and pressure combination and repeated three times. Mean and standard deviations on the flow rate for all nine chip and pressure combinations were calculated. Conversion from mass to volume flow rate assumes a fluid mass density of $10^3 \text{ kg m}^{-3}$.

2.7. Fluid control module design

The fluidic control module is designed for individual switching of eight pairs of inlets in one direction (inlets (a), figure 4). In the transverse direction all eight chip interconnections are connected to a shared pair of inlets (outlets (b), figure 4) giving...
Figure 4. Layout of the central part of the PDMS fluid control module containing (a) valve pairs for bottom inlets, (b) one valve pair for side inlets, and (c) and (d) single valves for controlling outlet direction. The 32 central circles are interconnection bases for through-holes to the O-rings. Fluidic channels are marked with blue and valves and control channels are red with the valve pads shown as red circles. The fluidic circuit is closed by connecting the external chip, sketched as the dashed square, to the 32 central circular interconnection pads.

Figure 5. Total flow rate versus pressure through the PDMS fluid control module and three different PMMA chips. Each measurement is based on a total of 15 readings and the error bars indicate the standard deviation. The flow direction is from (a) to (c), cf figure 4, and the legends correspond to the convention in figure 1. The solid line corresponds to theoretical estimate.

3. Results

3.1. Flow rate measurements

The reproducibility of clamping on the PDMS fluid control module to three different chips was investigated. The measured variance in flow rate is low with relative standard deviations below 8% (figure 5) suggesting that the clamp-on solution did not significantly affect the hydraulic resistance. The relationship between pressure and flow rate deviates from theoretical estimates assuming that PDMS is fully rigid (figure 5). The relative difference between measured flow rates and theoretical estimates increases with applied pressure. Since the dominating hydraulic pressure drop in the system is in the channels in the PDMS control module, we therefore assume that the channels cross-section increases with increasing applied pressure. Increased cross section will lead to higher flow rate. This trend is in line with previous work investigating effects of pressure on the geometry of channels defined in PDMS and the resulting flow rate [20, 21].

3.2. Flow control

Examples of flow control in two directions using external valves are given in figure 6. In (a)–(c) a preestablished interdigitated pattern was translated and removed from the chamber by a wash from the shared, left inlet over a time period of 29 s. Establishment of an interdigitated striped pattern following a chamber wash is shown in figure 6(d). The flow pattern in figure 6(e) demonstrates symmetric flow confined in one direction. Finally, an alternating flow between loading stripes in the y-direction and flushing in the x-direction could create a dynamically developing wave pattern.

To demonstrate contamination-free multistep exposure of the chamber to different combinations of patterns, a sequence with three different exposure steps and intermediate wash steps is shown in figure 7. Blue and yellow represent active compounds in the y- and x-directions, respectively and red represent washing buffers. Figure 7(a) initiates with an interdigitated flow along the y-axis followed by a wash step along the y- and x-directions in (b) and (c), respectively. Subsequently an exposure along the x-direction is given in
Figure 6. Close-up of a common chamber of the design given in figure 1(c) demonstrating fluid flow control in two directions. The symbols indicate the state of upstream (colored) and downstream (black) valve(s). The filled circles indicate open valves and the crossed lines indicate closed valves. (a)–(c) the removal of an interdigitated pattern (red and blue) by flushing with a shared buffer from left at \( p = 30 \text{kPa} \). Relative times are \( t = 0 \text{s}, t = 12 \text{s} \) and \( t = 29 \text{s} \) for (a), (b) and (c), respectively. The onset of an interdigitated pattern following a wash of the chamber is shown in (d). A steady flow in a single direction is given in (a). (f) establishment of dynamic wave patterns by alternating flow in the \( x \)- and \( y \)-directions by dynamically changed valve states. The valve states shown in (f) only indicate the states at the time of image acquisition.

4. Discussion

Here we have demonstrated a reliable solution to create PDMS-based fluid control modules and interface these to a hard chip through incorporation of O-ring features in the PDMS part for creation of modular systems. The interconnections demonstrated between the PDMS fluid control module and the hard chip showed that numerous (here 32) interconnections could be secured leak-free by tightening four screws. In this work we inserted needles into the PDMS to connect the PDMS fluid control module to peripheral liquid reservoirs and solenoid control valves. Inserting needles is both cumbersome and also poses a risk to induce damage to the PDMS devices. This could be avoided by adding another bank of O-ring-based interconnections that connect to chips that handles liquid I/O in accordance with the modularity concepts demonstrated in [18]. Hence it would be feasible to make all connections for fluidic inputs and pressure control lines by tightening a few screws, a significant advantage compared to inserting needles into PDMS chips. Other approaches for easy attachment of peripherals to soft lithography-based devices have been proposed recently, for instance using the previously mentioned vacuum manifolds [15] or premounted steel pins with PDMS gaskets and intermediate carrier plates [22].

4.1. Stability of operation

For widespread use of microfluidic technologies it is of key importance that the systems and employed methods demonstrate a consistent performance. One of the concerns with nonintegrated systems is that the assembly of the different components may affect the performance if interconnections and components are not well matched. For the presented system, however, the flow rate measurements demonstrate that the modular system is insensitive to the mechanical O-ring-based interconnection scheme since the flow rate is independent of the attached chip (figure 6). It should furthermore be noticed that the consistence is sustained even though the assembly and compressive sealing is done manually without any gauges.
Figure 7. Example of a bi-directional exposure sequence with intermediate wash steps. The arrows designate flow direction. Red represents buffer, and blue and yellow represent active compounds in the y and x-directions, respectively. The symbols indicate the state of upstream (colored) and downstream (black) valve(s). The filled circles indicate open valves and the crossed lines indicate closed valves. An initial exposure pattern along the y-direction (a) is followed by a wash along y (b) and x-direction (c). A common exposure in (d) is followed by a wash step and a new exposure along the y-direction (f).

The main reason for the independence of the manually attached chip is a proper distribution of hydraulic resistance throughout the system. The total fluid control module resistance is four orders of magnitude higher than the hydraulic resistance of the attached passive chips. Changes in pressure and flow rate relation caused by chip-to-chip variation are hereby to a large degree eliminated. Attachment of a number of different chips with different designs can therefore be facilitated without altering or recalibrating the hybrid system as long as the hydraulic resistance is dominated by the fluid control module.

Another important feature is the use of a double layered photolithographic process for the fluidic channel layer. Hereby we gain an interconnection base under the O-ring with a height of 100 μm combined with the remaining high-resistance fluid control module based on a 25 μm channel height. Due to the cubic scaling of resistance with channel height, the higher interconnection base reduces the hydraulic resistance to about 2% of a corresponding single-layer channel geometry; therefore the influence of local channel deformation under the O-ring interconnections during compression is negligible. A similar design without increased interconnection base height has been tested and found to be vulnerable to changes in mechanical compression (data not shown). The O-ring design has previously been reported [18] to have an average leak pressure of 470 kPa and thus compatible with the typical pressure range of miniature solenoid control valves [23, 24].

4.2. PDMS fluid control module fabrication

A commonly employed method for making fluidic access in PDMS devices is to use manual punching combined with needle press fittings which was done for the attachment of peripherals in this device. Despite the versatility and ease of use for rapid prototyping, this method is far from desirable for making high-density interconnections. It is labor intensive to hook up and does not provide a satisfactory quality due to the manual positioning of each hole. Furthermore, the method is prone to tear the PDMS and leave residues both during punching and subsequent needle insertion, which can possibly clog the device. Approaches to avoid the punching step have been presented including a method for integrating access holes through the use of PU plastic masters with integrated steel pins [25]. An example of a method for combined fabrication of PDMS replicas with micro and macro scale features, including integrated inlet holes and reservoirs, has also recently been demonstrated [26]. These two examples allow for a single-step molding of fluidic channels and through-holes without the need for manual finishing of the through-holes. However, the process is a single-sided molding and manual insertion of individual needles or tubing is still needed for interconnections. Multilayered PDMS devices often require bonding steps to combine single-side molded structured layers [27]. A method for double sided microscale PDMS structuring reducing the need for bonding has been shown [28].
method presented in this paper differs by combining double-sided, micro-macro scale molding with integrated through-hole precursors. Manual peeling of through-hole residual layers is time consuming but can be done in the same step as membrane peeling, which in any case is needed for fluidic access. An approach to eliminate residual layers could be to integrate holes in the SU-8 into which the fibers can be irreversible glued. Membrane peeling can be circumvented by positioning the fluid layer on top of the membrane and the control layer below the membrane in contrast to the layout in figure 2. This would entail the pneumatic lines to be attached from the bottom side but eliminate the need for either pneumatic or fluidic lines to pass through the membrane.

4.3. Valve network design

The PDMS fluid control module has been designed to dominate the fluid flow by having a significantly higher hydraulic resistance than the hard passive chips. An example of the control capabilities is demonstrated in figure 6(e) where the balanced outlet design of the control module, cf figures 4(c) and (d), results in a satisfactory degree of flow symmetry in the chamber of the passive chip.

Despite the lack of valves in the hard passive chip the external fluid control module is capable of producing complex on-chip fluid patterns as demonstrated in figure 6. The lack of on-chip valves, however, can cause diffusive contamination in chip designs with merging perpendicular inlets, e.g. as featured in figure 1(c). As demonstrated in figure 7 this contamination in stagnant perpendicular inlets can be eliminated by dedicating the leftmost channel to a common buffer. Thereby it is possible to create exposure patterns in two directions without diffusively induced contamination in a fully passive microfluidic chip. Such approaches could potentially be attractive for combinatorial cell culture assays requiring time-dependent change of exposure conditions to study cell-cell communication, migration or effect of exposure to soluble compounds. The flow control for the latter is demonstrated in figure 7.

The layout of the fluid control module has been chosen to demonstrate that a soft lithography-based fluid control module can control the flow in two directions in an externally attached passive chip. To exploit the modular approach the design of the control module is kept as versatile as possible in the form of an array of individually controlled valves, where the specific use of the valves depends on the attached chip. Here we demonstrate and verify the concept by showing fluid control in open chambers in the passive chip. The control module would as an example also support chips and assay requiring sequential injection of up to 18 different compounds or mixtures thereof, e.g. to test the impact of factor addition sequence on cell differentiation. Alternatively, two compounds could be sequentially switched in between nine individual chambers in a parallel assay.

The materials used, PDMS and PMMA, are widely used in cell culture and other microfluidic applications [29–33]. However, the modular approach described here enables use of any hard chip (polymeric, glass or silicon) providing that the chip has the corresponding holes to accept interconnections. The modularity makes it very easy to adapt the system to a variety of applications by simply exchanging the passive hard chip. It is therefore possible to employ different kinds of electrical sensors where electrical connections can be integrated in the upper part of the clamping system. Such implementation of contacts would allow for rapid attachment of both fluidic and electrical lines to an external chip for applications employing impedance spectroscopy or similar sensing methods.

Another advantage of the hybrid system approach is the possibility for applying mass production methods such as injection molding for fabrication of the hard passive polymer chips. Such fabrication methods are especially suited for applications where the fluid control module can be reused. In this case passive chips containing a sample can be attached as a cheap single use device, which is attractive both to reduce costs in commercial applications as well as minimizing fabrication in research laboratory settings.

Compared to fully integrated microfluidic systems the presented modular approach does due to the separation between valve system and passive chips induce a larger volume between fluid control sites and downstream reaction or analysis sites. Combined with the need for interconnection ports between the modules, the presented system does therefore not offer the same integration density as monolithic systems [5, 34] but excels in flexibility. In the demonstrated configuration the PDMS fluid control module is a single structure containing all valves for inlets and outlets on the same PDMS base. However, as a functional element the fluid control module consists of four independent units each handling one of the four chip interconnection groups. To exploit the modular concept even further a possible future option would be to mold each functional unit as individual elements with standardized O-ring-based connections for both control module-to-world and chip-to-control module interconnections. The anticipated advantages of this would be increased yield and flexibility due to separation of elements. Combining a number of standard fluid control modules containing independent or shared valves or more advanced elements such as mixers, titrating gradient generators or valving multiplexers [1, 35] could be envisioned to be integrated into the previously demonstrated modular platform [18] for even higher flexibility and levels of fluid control options. We imagine that replacing application specific integrated systems with a set of standard off-the-shelf fluid control modules, which can be freely combined by the end-user, can be a promising way of introducing the microfluidic technology to a wider audience in research fields such as cell biology. A key element for this to be practically feasible is easy and stable establishment of interconnections, which we have demonstrated possible.

Conclusion

We have presented a method for creating modular systems combining active, soft lithography-based PDMS fluid control modules with passive microfluidic chips. The method relies on mechanical sealing through combined micro and macroscale
PDMS structures, which can be fabricated through double sided molding. The method is useful for achieving a high interconnection density as demonstrated through the rapid connection of 32 fluidic connections to a 6.4 cm² microfluidic chip. The modular mechanical connection approach opens up for a highly flexible design concept by exchanging the externally attached passive chip depending on application and combining with other elements from an existing platform conforming to the same interconnection standards. The presented fluid control module has a versatile design, which facilitates fluid control in two directions. With this design we have demonstrated that the fluid control module is able to control the fluid flow with high fidelity in an externally attached passive chip and that the interconnection method shows consistent performance independently of the attached chip.

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