A vacuum manifold for rapid world-to-chip connectivity of complex PDMS microdevices†

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Received 19th November 2008, Accepted 22nd January 2009
First published as an Advance Article on the web 17th February 2009
DOI: 10.1039/b820683j

The lack of simple interfaces for microfluidic devices with a large number of inlets significantly limits production and utilization of these devices. In this article, we describe the fabrication of a reusable manifold that provides rapid world-to-chip connectivity. A vacuum network milled into a rigid manifold holds microdevices and prevents leakage of fluids injected into the device from ports in the manifold. A number of different manifold designs were explored, and all performed similarly, yielding an average of 100 kPa (15 psi) fluid holding pressure. The wide applicability of this manifold concept is demonstrated by interfacing with a 51-inlet microfluidic chip containing 144 chambers and hundreds of embedded pneumatic valves. Due to the speed of connectivity, the manifolds are ideal for rapid prototyping and are well suited to serve as "universal" interfaces.

Introduction

Microfluidic devices are becoming increasingly complex with advances in fabrication technology and the desire for high-throughput chemical and biological applications.[1] Devices are rapidly advancing beyond single-use "prototypes" with simple architectures to multipurpose systems with broad utility and computer-controlled valving (*e.g.* ref. 2). Strategies to simplify how benchtop fluid reservoirs and pneumatic controllers connect to microfluidic devices (termed "macro-to-micro" or "world-to-chip" connectivity) could greatly improve utilization of microfluidic systems that are currently tedious to assemble, load, test, and control.

A number of manifold designs have addressed world-to-chip connectivity, including socket-based mechanisms, sandwich configurations (see recent reviews[3]), glued-on microports (*e.g.* Upchurch), integrated tubing,[4] and direct incorporation of reservoirs or drops on the device.[5] Although useful for specific applications, these approaches either (*i*) require tedious assembly of consumable parts, (*ii*) need considerable fabrication and setup time for each manufactured device, (*iii*) are not amenable to incorporation of valves, or (*iv*) are unable to support applied pressure. Additionally, connecting to microfluidic manifolds can also require enclosing the chip, screwing down of fasteners/gluing, or application of pressure (*e.g.* from clamp or inserted needle) that can deform the device. Thus, despite these techniques, the most widely used method to world-to-chip interfacing consists of inserting blunt needles, one at a time, into devices.

Here we present a novel method to interface elastomeric devices containing numerous fluid inlets and pneumatic valves with the macro world using a vacuum manifold. This method has a number of advantages: (*i*) it allows for fast connections and sealing (seconds); (*ii*) valves can be actuated instantly and fluid can be introduced in seconds; (*iii*) it is reusable, *i.e.* the device can be removed from the manifold, and the same or a new device can be connected again easily; (*iv*) it is scalable to a large number of inlets without increase in setup time; (*v*) it can be used to rapidly test the quality of devices in a production line. We demonstrate the applicability of this approach by connecting a 51-inlet device, which has integrated microvalves that route fluids through 144 chambers,[6] to a rigid manifold that is permanently connected to fluid reservoirs and pneumatic valve controllers.

Results and discussion

The connection of microfluidic devices with numerous inlets to benchtop reservoirs and controllers is time consuming and sometimes difficult. Hours can be spent untangling, sorting, and connecting tubing one at a time to a single device (Fig. 1a), only to find that, if the device is not fully functional, the whole procedure must be repeated with a new device. This process is a bottleneck for quality control in a production line and also hinders rapid prototyping.

Here we introduce a manifold that make all-at-once connections to devices, analogous to a microchip in a printed circuit board (Fig. 1b). With this approach, a poly(dimethylsiloxane) (PDMS) device with inlets facing down is aligned and placed on top of a rigid manifold with matching outlets facing up (Fig. 1c). A network of trenches on the manifold distribute negative pressure (vacuum), holding the PDMS device against the manifold and allowing for the injection of liquid through the manifold and into the device without leakage.

To demonstrate the simplicity and scalability of this approach (Fig. 2a), we created a manifold with a distributed vacuum network that matched the inlets of a PDMS device with 21 positively pressurized fluid inlets, 4 multipurpose inlet/outlets, and 26 pneumatic valving inputs (Fig. 2c). This device was designed to multiplex chemical perfusions through 144 distinct 750 μm × 750 μm chambers.[6] The vacuum network was formed by milling a common vacuum line to connect all vacuum annuli milled around each inlet port.

We connected the manifold to fluid reservoirs and pneumatic controllers *via* needles and tubing in the back of the manifold,

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† Electronic supplementary information (ESI) available: Table and figures of delamination and point of leakage through the PDMS/PMMA seal as a function of fluid pressure, as well as videos showing loading of a device onto the vacuum manifold. See DOI: 10.1039/b820683j

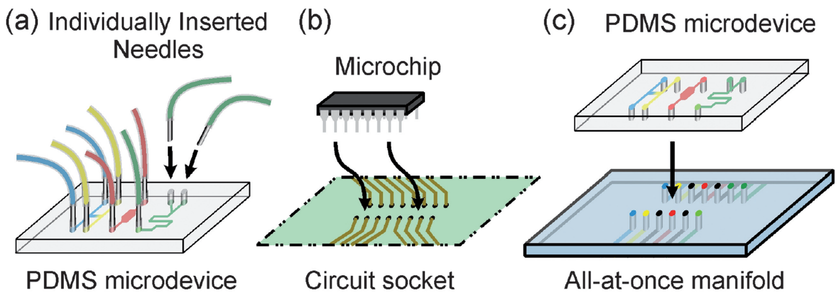

Fig. 1 (a) Illustration showing standard connections to a PDMS device. Individual tubings are inserted into microfluidic devices using blunt needles as connectors. (b) An electronic microchip with several pins is inserted all at once into a socket on a printed circuit board. (c) An "all-at-once" manifold approach with pre-fabricated interface that connects, in one step, the microfluidic chip to inlet lines that are permanently attached to the manifold.

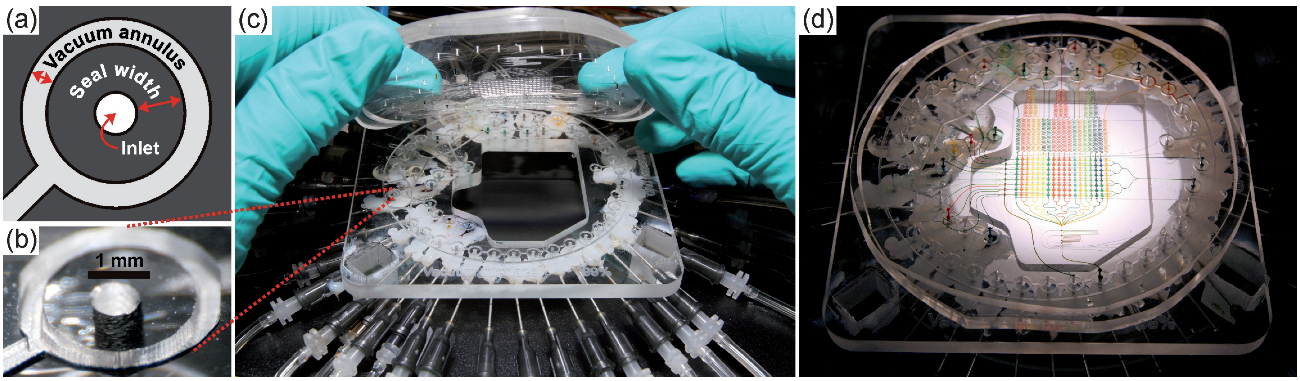

Fig. 2 (a) The basic unit of the manifold consists of a vacuum annulus milled around an inlet. Conformal contact seals the PDMS to the PMMA (see Experimental) in the region between the inlet and the vacuum annulus. Suction applied to the vacuum network provides a net force that holds the device and the manifold together. (b) Photograph - with tilted perspective - showing a 0.4 mm wide and 0.8 mm deep vacuum trench surrounding a ≈ 0.8 mm inlet port. (c) Photograph of the PDMS device peeled up from the manifold. The inlet ports on the manifold align directly to the inlets on the PDMS device. Needles glued into the back of PMMA inlet holes connect permanently to fluid reservoirs and pneumatic controllers *via* tubing. (d) Alignment and connection of the PDMS device onto the manifold was simple and fast; it took only seconds (see Video S1).† The image shows the device loaded with dyes and functioning at 7 kPa (1 psi) fluid pressure. For a panned view of the manifold, see Video S2.†

aligned by eye and placed the PDMS device on the manifold (Video S1),† and applied vacuum to the manifold. Immidiately we could actuate valves and prime the device with fluids (Video S1). Full functionality of the device was achieved with normal fluid driving pressures (<21 kPa (3 psi)). Overall, we observed the following advantages of using this approach:

(1) Fast connectivity. Valves could be actuated immediately after alignment of the device onto the vacuum manifold.

(2) Quick loading. Within 1 min of pressurizing fluid inlets to 7 kPa (1 psi), the device was nearly filled with dye (See Video S1).†

(3) Reversible sealing. Though seals began to fail at 41 kPa (6 psi), lowering the pressure restored function without removal from the manifold.

(4) Reusable. No loss of function upon removing and replacing a device from the manifold.[7]

(5) Scalable. For a given hole size, increasing the number of inlets did not increase setup time. Devices with a single inlet (see below), 9 inlets (not shown), or 51 inlets (see Video S1),† required just seconds to align and connect.

Manifold characterization

We tested single-inlet PDMS devices with 0.5 mm and 0.75 mm diameter holes, seal widths from 0.6 mm to 1.9 mm, and vacuum annuli widths of 0.4 mm and 1.4 mm. None of these parameters were found to significantly impact the pressure at which devices leaked ($n = 23$, see Table S1).† Thus, depending on the particular application, one could choose between ease of fabrication and alignment (larger features) vs. inlet packing density (smaller features). We note, however, that as seal width increased, more dead volume formed in regions of delamination between the PDMS and PMMA prior to leakage (see Fig. S1).† All devices withstood 41 kPa (6 psi) up to a maximum of 145 kPa (21 psi); the average leakage pressure was 101 kPa ± 28 kPa (14.7 psi ± 4.1 psi) (see Fig. S2).†

This pressure range exceeds the pressure generally needed to keep pull-open valves[8] closed against fluid driving pressure.[2] We also explored modifications that might make the manifold more suitable for devices that use push-closed style microvalves,[9] which require higher operating pressures to keep closed (40 kPa to 100 kPa (5.8 psi to 14.5 psi) or more). To this end, we hypothesized that adding rigid backing to a *thin* PDMS device would redistribute the stresses within the PDMS and allow stronger holding forces. Accordingly, we tested the holding strength of 0.22 mm, 0.63 mm, and 2 mm thick PDMS layers (all bonded to glass slides) against a PMMA manifold with ≈1.0 mm wide seal and 1.35 mm wide vacuum annulus. As PDMS thickness decreased from 2 mm to 0.63 mm to 0.22 mm, leakage strength increased from 100 kPa (15 psi) to 186 kPa (27 psi) to more than

345 kPa (50 psi), respectively. In fact, with no applied vacuum, the 0.63 mm thick PDMS devices stayed sealed up to fluid pressures of 96.5 kPa (14 psi), compared to <28 kPa (4 psi) for unsupported 5 mm thick PDMS. Other opportunities for improving the device performance might include use of more rigid materials in fabrication, such as using a higher density of cross-linking reagent in the PDMS prepolymer[10] or adding fillers.[11]

Conclusions

We have introduced a robust and reusable manifold design that facilitates easy alignment of large, multipurpose PDMS devices. Importantly, macro-to-micro connectivity can be achieved in a few minutes rather than many hours because the approach does not require sorting or affixing ports, needles, or tubing into the PDMS and does not involve any clamping or sandwiching to hold parts together. We predict that the technology can be readily scaled to devices having hundreds to thousands of inlets without increasing setup time. These advantages make the vacuum manifold a powerful tool for microfluidics in the realm of truly high-throughput experiments. Further optimization of the design and fabrication of thin PDMS devices will also likely ensure the applicability of this approach to pushed-closed valving systems, which require higher pneumatic pressures. Finally, this approach could lead to "universal" interfaces that can accommodate many different microdevice designs. In addition to the size, complexity, and control inherent to microfluidic devices, we believe this simple plug-and-play platform will facilitate the application of microfluidics to multiparameter experiments of biological phenomena.

Experimental

PDMS device fabrication

Poly(dimethylsiloxane) PDMS (Sylgard 184, Dow Corning) substrates were made by pouring 1 mm to 5 mm thickness over silicon wafers or by spin coating PDMS at 100 rpm for 60 s and 31.4 rad/s (300 rpm) for 45 s, yielding thicknesses of 0.63 mm and 0.22 mm, respectively. Inlet ports into PDMS devices were created with 0.5 mm or 0.75 mm micropunches (Harris Uni-Core, Ted Pella). PDMS layers were bonded to glass slides and membranes after exposing each to 100-W oxygen plasma for 30 s (Plasmod Plasma System, March Instruments, Inc.). Multilayer PDMS device were fabricated by soft lithography, as previously described.[2] A 25-gauge needle was inserted into the fluidic inlets to rupture the membrane so that fluid could pass through the pneumatic layer into to the fluid layer.

Vacuum manifold fabrication and testing

We used a programmable milling machine (MicroMill 2000, MicroProto Systems) to cut patterns for the vacuum manifolds at 99% original size to account for PDMS shrinkage. Inlet ports were drilled with a #67 bit (0.8128 mm) through 6 mm thick poly(-methylmethacrylate) (PMMA) stock. Larger drill bits (*e.g.* #58; 1.0668 mm) were spun over each hole to smooth out rough edges on the PMMA. Vacuum channels were milled 0.8 mm deep and 0.4 mm wide centered 1.5 mm around the edge of the drilled inlet port, which defined the "seal" of PDMS/PMMA contact. Blunt 22-gauge needles were epoxied into the back of the manifold and connected to fluid reservoirs or pneumatic controllers *via* 0.625 mm ID microbore Tygon tubing. Pinch clamps on the tubing prevented leakage of the manifold prior to sealing the PDMS device. For the manifold characterization tests, we employed shallow drilling with a hole mill that had a fixed cutting width (1.5 mm) and an adjustable inner diameter (Genessee Manufacturing Co, Inc.).

A vacuum pump was connected to the suction port of the vacuum manifold −91 kPa (≈ −27 in Hg). Inlet ports were filled with dye and tested for holding strength. Air pressure driving each inlet was increased at a rate of 7 kPa/min to 14 kPa/min (1 psi/min to 2 psi/min) until dye was observed leaking into the vacuum ring around the inlet. Observation of the PDMS/PMMA seal was observed under a stereomicroscopy (SteREO Discovery V20, Zeiss) fitted with a digital camera (Powershot G7, Canon).

Disclaimer

Certain commercial products are identified in this report to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

Acknowledgements

GAC acknowledges a postdoctoral fellowship from the National Research Council. We thank Gregory Vogl and Joan Savall for helpful discussions.

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7 Fluid pressure and vacuum were turned off and the device was removed from the manifold. It was immediately functional upon replacement and return of vacuum and fluid pressure. The reusability of the manifold is especially valuable for quality control, which permits rapid testing of many devices in a short time. For technical experiments, which may involve exchanging fluids, a user-specific cleaning protocol may need to be implemented, and could involve, for example, rinsing off the surface of the manifold, unplugging or replacing luer-connected tubing from the needles in the manifold, and rinsing parts with sterilized water or ethanol. To keep the manifold "ready" during long periods of inactivity (*e.g.* days), inlet lines were pinched closed, valves were turned off, and the manifold was submerged in water.
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