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An Automated, Pre-Programmed, Multiplexed, Hydraulic Microvalve

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Abstract
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An automated, pre-programmed, multiplexed hydraulic valve actuator is described. The valve is membrane-based and normally open. In contrast to the membrane-based pneumatic valve, the hydraulic valve uses hydraulic liquid to exert the control pressure. The line pressure is controlled with a roller moving over a prefabricated topology. Multiple rollers, each traversing its own track, are assembled into a single carriage, which can be actuated either manually or with a single computer-controlled motor. A valve manifold and roller actuators are designed, fabricated, and tested to demonstrate three-way valve actuation in a pre-determined sequence. The performance of the valve is evaluated and the utility of the valve in the operation of a micro thermal cycler was demonstrated. Hydraulic controllers of the type described here can be operated either manually or under computer control and provide an inexpensive means of controlling flow in lab-on-a-chip devices.

Introduction

With a growing interest in miniaturized point-of-care (POC) testing devices that perform rapid and accurate detection of infectious diseases,[1–4] a significant effort has been invested, in recent years, in developing simple, robust microfluidic components such as micropumps and microvalves for flow control. Not surprisingly, the literature contains many reports on microvalves using various actuation strategies such as magnetic,[5,6] electric,[7] piezoelectric,[8] rheological,[9] thermal,[10] pneumatic,[11,12] and phase change.[13,14] Among these actuation principles, pneumatic microvalves attracted much attention due to their simplicity, reliability, ease of control, and the feasibility of achieving a high degree of multiplexing.[15] One disadvantage of pneumatic microvalves is the need for multiple external pressure sources, which increases the complexity and cost of the system needed to control the flow in the lab-on-a-chip device. Recently, a multiplexed hydraulic valve,[12] analogous to a membrane-based pneumatic valve, was reported, in which an array of mechanically actuated Braille pins was utilized to operate multiple valves hydraulically.

Here, we report on an interesting alternative involving hydraulic pressure-controlled valve actuation that permits inexpensive, reliable, automated, multiplexed, pre-programmed control of multiple valves. A single valve or a group of valves is connected to a flexible tube laden with hydraulic fluid. Each tube is held in a track alternately patterned with flat "ground" and "recess" regions. A roller moving over the tube alternately squeezes and releases the tube to increase and release the hydraulic fluid's pressure. When the roller transverses a flat (ground) zone, it squeezes the flexible tube and pressurizes the hydraulic fluid that, in turn, deflects a flexible membrane, resulting in valve closure. When the roller moves to a recessed zone, the pressure is released, and the valve opens. The sequence of operations is "programmed" into the roller's track during the track's fabrication. The duration of valve closure/opening is dictated by the length of the features in the track and by the roller's speed. Many rollers can be connected to a single moving carriage, whose motion can be effectuated either manually or with a computer-controlled motor. To demonstrate the concept, we fabricated and tested a valve manifold and a valve actuator. The use of the valve manifold was explored in PCR amplification.

Concept

Our hydraulic valve is a conventional membrane-type valve as depicted schematically in Fig. 1. The valve assembly consists of a top part containing the pressure chamber and a bottom part containing the valve chamber. The pressure chamber is filled with hydraulic fluid (in our experiments, we used silicone oil, S159-500, Fisher Scientific) and is connected to the pressure line. The valve chamber includes inlet and exit ports. To reduce dead volume, it may be desirable, albeit not essential, to carve the valve chamber in a hemispherical shape. When the membrane is

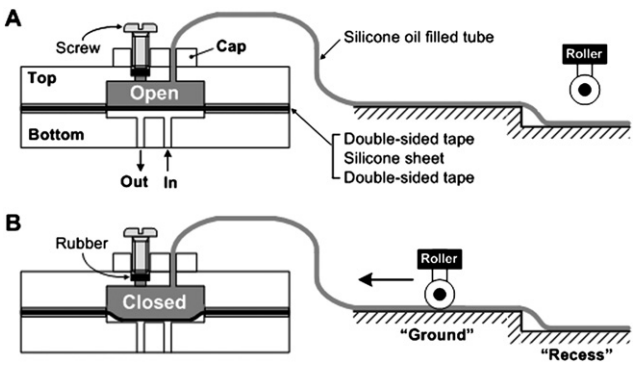

Fig. 1 Schematic depiction of the hydraulic valve actuation. (A) "Open" state when the roller resides within the recess region. (B) "Closed" state when the roller squeezes a tube in the ground region.

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in its normal, undeformed state, the valve is open and the working fluid flows freely from the inlet port to the exit port (Fig. 1A). When the membrane is partially deflected, flow of the working fluid is restricted and the valve operates as a proportional valve (see Fig. 3). When the membrane is fully deflected, the valve is closed and the path between the inlet and exit ports is blocked (Fig. 1B). The membrane deflection is facilitated by pressurizing the liquid in the pressure chamber above the membrane. The working liquid in the valve chamber can be either in direct contact with the membrane as depicted in Fig. 1 or separated with a secondary membrane. In the former case, the pressure chamber is a part of the microfluidic chip. In the latter case, only the bottom component needs to be part of the microfluidic chip and the upper component can be part of an instrument that controls the microfluidic chip.

The tube that is connected to the pressure chamber is filled with hydraulic liquid and part of its length is held in a patterned track containing ground and recessed regions as shown in Fig. 1. A roller moves along the track. When the roller is in the "recessed" region, it does not contact the tube, the liquid in the tube is not pressurized, and the valve is open (Fig. 1A). When the roller transverses the elevated, "ground" region, its squeezes the tube and pressurizes the hydraulic liquid, which in turn leads to valve closure (Fig. 1B). The roller's motion can be effectuated either manually (as in our experiments) or with a motor. The track can contain multiple "ground" and "recess" regions to allow for multiple valve closings and openings. Finally, multiple valves can be connected to the same line, allowing one roller to effectuate concurrent opening and closing of multiple valves.

Fig. 1 featured a single roller and a single track. The concept can be expanded to facilitate concurrent actuation of multiple valves, each with its individual control. This is accomplished by an array of tracks, each with its own pattern of ground and release states and its individual roller. All the rollers are mounted on the same carriage. Fig. 2 provides a three-dimensional depiction of an actuator that was fabricated in our lab. The actuator contains seven tracks, each with a different pre-programmed sequence of operations. In other words, the actuator can concurrently control seven different valve sequences through the motion of a single carriage. Of course, the number of tracks can be increased as needed. Fig. 2A features linear tracks that are laid in a straight line. It is possible, if desired, to fabricate the tracks as closed loops.

Experimental apparatus

To demonstrate the concept, we constructed a few prototypes. The hydraulic valves were fabricated using layered manufacturing and consisted of six layers (Fig. 1). A cap; a top polycarbonate layer containing the displacement chamber (800 μm in height, 4 mm in diameter); a double-sided adhesive tape (~150 μm thick, 9474LE, 3M™); a middle silicone sheeting layer (125 μm thick, 40 durometer, Specialty Manufacturing Inc., MI); a second double-sided adhesive tape, same as the first one; and a bottom polycarbonate layer containing the valve chamber. The top polycarbonate layer also contained a polycarbonate cap to facilitate interfacing with the tubing (Fig. 1). All polycarbonate sheets were milled with a CNC machine (Haas Automation, Inc., CA).

The silicone sheeting was treated with oxygen plasma (Diener, electronic, PA) for 5 min at 200 W to enhance its bonding with the double-sided tapes.[16] The plasma-treated sheeting was applied to patterned double-sided tapes in which disks at the position and size of the displacement chamber were cut out with a CO_2 laser. The double sided tapes facilitated the bonding of the upper and lower polycarbonate parts.

A thin layer of acetonitrile (Fisher Scientific) was applied to the bottom of the polycarbonate cap. Subsequently, the polycarbonate cap was aligned with and bonded to the top polycarbonate layer. Then, the flexible tubes (silicone, 0.040″ ID, 0.085″ OD, 51845K52, McMaster-Carr, IL) were connected with an insert to the bonded polycarbonate cap.

The roller carriage (71.1 mm × 19 mm × 9.5 mm) and the actuator base (122 mm × 53 mm × 9.5 mm) (Fig. 2A) were machined from polycarbonate sheets using a CNC milling machine. The roller carriage housed equally spaced, snugly fitted, stainless steel rollers mounted along a stainless steel shaft. The actuator base contained multiple tracks, each with a series of "ground" and "recess" regions. The flexible tubes were held on

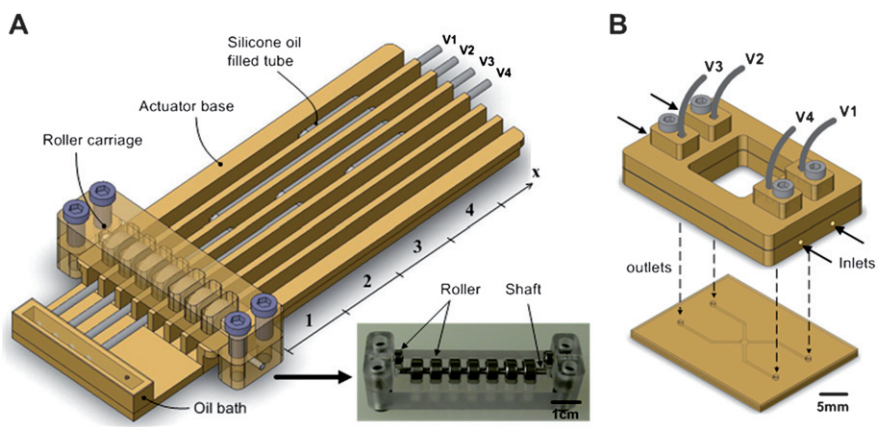

Fig. 2 Three-dimensional depiction of the multiplex valve actuator and valve manifold. (A) The roller carriage moves along the actuator's base to actuate the various valves in a pre-programmed sequence. (B) The valve manifold is aligned and clamped to a microfluidic chip for three-way flow control.

the flat regions using double-sided adhesive tapes and further locked down with a thin layer of PDMS.

Air bubbles were occasionally trapped in the displacement chambers during hydraulic liquid filling. To remove air from the system, we utilized "bleeding" ports consisting of thick rubber pads pressed against the outlet of the displacement chamber with a screw (see Fig. 1). As a hydraulic liquid, we used silicone oil (polydimethylsiloxane S159-500, Fisher Scientific). We inserted the hydraulic liquid at the free end of a tube and allowed it to flow by gravity until it emerged from the displacement chambers through the bleeding ports, at which instance, the bleeding screw was tightened to seal off the chamber's outlet and to facilitate bubble-free operation. The other end of the tube was immersed in an oil bath. When, in an earlier design, an oil bath was not used and the free end of the tube was sealed, we occasionally observed cavitation right behind the moving roller during the squeezing process. The use of an oil bath eliminated this problem.

For the purpose of the demonstration experiments, the valve manifold was attached to a microfluidic chip with double-sided adhesive tape (Fig. 2B). Alternatively, the bottom polycarbonate layer of the valve manifold can be designed to be a part of the microfluidic chip. In the latter case, it may be desirable to decouple the top piece containing the pressure chamber and the bottom piece containing the valve chamber as discussed earlier in the paper.

Results and discussion

The performance of the hydraulic valve was evaluated with dyed DI water as the working fluid. During the experiments, the inlet pressure was set, and the flow rate was measured as a function of the roller's distance from the "ground" zone's leading edge. Fig. 3 depicts the flow rate as a function of roller position when the inlet pressure is 15.5 kPa (circles), 31.0 kPa (upright triangles), 46.4 kPa (squares), and 61.9 kPa (diamonds). The solid lines correspond to best-fit straight lines. The "squeezing length" corresponds to the oil volume that was needed to compensate for the increase in the pressure chamber's volume due to valve deformation and the increase in the tubing volume downstream of the roller due to pressure-induced expansion. The squeezing length can be reduced by reducing the valve's chamber volume, tubing length, and tubing elasticity. The flow rate decreased nearly linearly as the "squeezing length" increased until it ceased altogether. As the line pressure increased, so did the "squeezing length" needed to completely shut the valve. Although not pursued here, the data suggests that these valves can operate as proportional valves, *i.e.*, one can control the flow rate by appropriate deformation of the membrane.

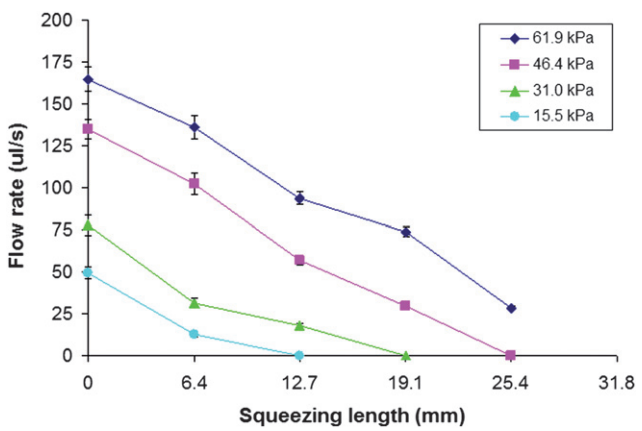

Fig. 3 The flow rate through the valve as a function of the roller's distance from the ground state's leading edge at various valve inlet pressures.

To demonstrate the effectiveness of the valve control, we controlled four valves with a single carriage. The microfluidic chip used in this experiment is depicted in Fig. 2B. Valve 1 (V1) was kept open throughout the experiment to accept liquid (dye) from the flow line while the other valves (V2, V3 and V4) alternated, in a pre-programmed sequence, between "open" and "closed" states. Each valve's state was determined by the position of the roller corresponding to the particular valve (Fig. 2A). Each track was divided into four zones labeled 1, 2, 3, and 4 (Fig. 2A). The corresponding tracks' patterns are documented in Table 1, where R stands for recess (open valve) and G for ground (closed valve). For example, as roller 3 moved from zone 1 to zone 4, valve 3 went from closed to open to closed. The dye lines in Fig. 4 show the results of the three-way control. Fig. 4A corresponds to the roller carriage stationed in zone 1, V1 open, V2 open, V3 closed, and V4 closed, and the fluid going from port V1 to port V2. Fig. 4B corresponds to zone 2, V1 open, V2 closed, V3 open, and V4 closed, and the fluid going from port 1 to port 3. Fig. 4C corresponds to zone 3, V1 open, V2 closed, V3 closed, and V4 open, and the fluid going from port 1 to port 4. When the roller carriage is in zone 4, all four valves are closed and the microfluidic chip is sealed.

As another demonstration of the utility of the valve controller, we tested the feasibility of using the valves for PCR amplification. The microfluidic chip (Fig. 2B) was modified to include a 10 μL cavity at its center (not shown), enabling the chip to hold 15 μL of liquid. The chip was filled with a PCR mix while all the valves were open. Subsequent to filling, all the valves were closed and the chip was brought into contact with a Peltier-based in-house heater[17] for PCR thermal cycling.

To prepare the PCR mix, we used an Illustra PuRe Taq Ready-To-Go™ PCR bead (GE Healthcare, Piscataway, NJ) containing 2.5 units of DNA polymerase, 10 mM Tris-HCl, 50 mM KCl, 1.5 mM $MgCl_2$, 200 μM dNTPs, carbohydrate stabilizers, and BSA. For a 15 μL reaction volume, one PCR bead was dissolved in water along with 0.5 μl of PEG 8000 (Sigma Aldrich) and the primer Mixture-A (20 μM each). Proof of concept experiments were carried out with 10 pg, 48 kb lambda DNA (Takara Bio, Inc., Shiga, Japan) dissolved in

Table 1 The table documents each valve's state as a function of the roller's position (zone). The various zones are cross-referenced with Fig. 2A. "R" and "G" denote, respectively, recess (open) and ground (closed)

Zone	V1	V2	V3	V4
1	R	R	G	G
2	R	G	R	G
3	R	G	G	R
4	G	G	G	G

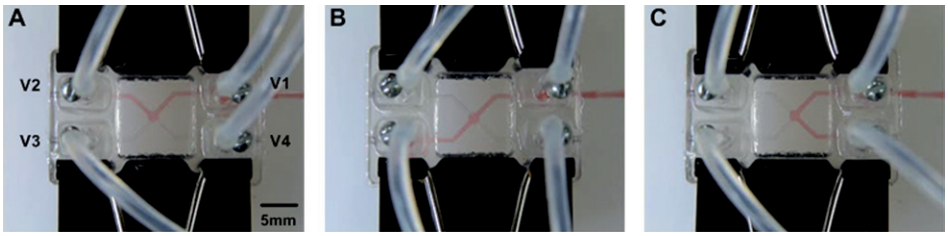

Fig. 4 Images of the flow path in the microfluidic chip as a function of the valves' positions. Valve 1 is open to accept the red dye, and the other valves are either open or closed according to the programmed sequence listed in Table 1.

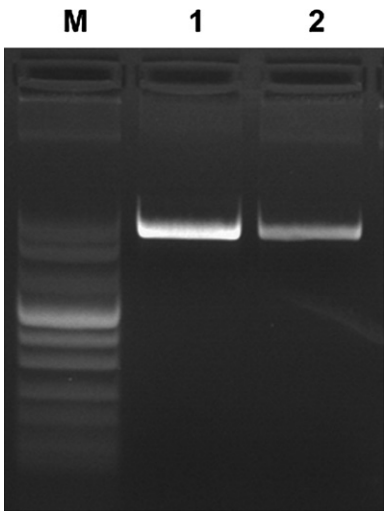

Fig. 5 An agarose gel image of PCR products amplified from a 10 pg lambda DNA template. Lane M is a marker VIII ladder. Lanes 1 and 2 correspond, respectively, to the control (benchtop PCR amplification) and the product of the PCR chip sealed with the hydraulic valves.

water. The amplicon was approximately 1 kb. A control test was carried out in a standard bench-top PCR thermocycler (Techne Incorporated, Princeton, NJ) using the same PCR mix.

About 15 μL of the PCR mix was loaded *via* V1 of the PCR chip. Then the roller carriage was moved to zone 4 (Fig. 2) to close all the valves. The thermal cycling was performed by an initial denaturation step at 94 °C for 1 min followed by 25 cycles (denaturation: 94 °C, 20 s; annealing: 60 °C, 20 s; extension: 72 °C, 40 s), with a final extension at 72 °C for 3 min.

There were neither visible leaks nor bubble formation during the thermal cycling. The products of the positive control (bench-top PCR) and the PCR chip were subjected to gel (agarose 1.5%) electrophoresis (Fig. 5). The products from the PCR chip yielded a visible band, suggesting that our valves can, indeed, seal the PCR reactor without significant leakage or bubble formation. Significant bubble formation during PCR would displace the PCR reagents and suppress amplification.

Conclusions

We developed a simple, inexpensive, robust, hydraulic, automated, pre-programmed, multiplexed actuation system for valves in lab-on-a-chip applications. The system uses rollers that travel along patterned tracks and squeeze/relax flexible tubes containing hydraulic fluid. When the roller travels over a level ("ground") surface, it squeezes and pressurizes the flexible tube, pressurizing the hydraulic fluid, and, in turn, effectuating the deflection of one or more flexible membranes and the closing of the valves connected to this particular tube. When the roller moves to a recessed region of the track, the pressure is released, and the valves return to their normal, open positions. By judicious patterning of the tracks, one can effectuate a pre-programmed sequence of multiple valves' closings and openings.

Many rollers can be combined into a single carriage for concurrent actuation to facilitate the control of multiple groups of valves, each group executing a different sequence of operations. Our design eliminates the need for multiple external pressure sources such as may be needed in the case of pneumatic actuators.

The linear-type track described here could be replaced with a rotary actuator in which the carriage rotates against a stationary base disk with patterned tracks. The rotor carriage could be driven either manually or with a motor. Manual operation may be useful when portability is desired or in resource-poor regions where cost is a major factor and electrical power supply is limited.

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