Published in final edited form as:

J Micromech Microeng. 2010 October 15; 20(11): 1–8. doi:10.1088/0960-1317/20/11/115020.

Microfluidic proportional flow controller

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Abstract

Precise flow control in microfluidic chips is important for many biochemical assays and experiments at microscale. While several technologies for controlling fluid flow have been implemented either on- or off-chip, these can provide either high-speed or high-precision control, but seldom could accomplish both at the same time. Here we describe a new on-chip, pneumatically activated flow controller that allows for fast and precise control of the flow rate through a microfluidic channel. Experimental results show that the new proportional flow controllers exhibited a response time of approximately 250 ms, while our numerical simulations suggest that faster actuation down to approximately 50 ms could be achieved with alternative actuation schemes.

Introduction

Microfluidics has become a useful tool for the advancement of biology research and surpassed many traditional assays by enabling both finer spatial and temporal control of the cellular microenvironment. Examples of powerful technologies for spatial control of local environment and substrate adhesion at single cell resolution include patterned cultures [1, 2], controlled co-cultures [3] and stable gradients for chemotaxis studies [4]. These technologies have advanced quickly due to the incorporation of microelectronic technologies [5] and new materials [6]. Meanwhile, technological advances in temporal control have been limited by several material-related and design challenges. For example, the material of choice in bio-microelectromechanical systems (BioMEMS) for its biological compatibility and optical transparency, namely polydimethylsiloxane (PDMS), is not directly compatible with methods of control using silicon or ceramics that have different mechanical, thermal and electrical properties. Consequently, transferring advances in flow control from microelectromechanical systems (MEMS) to BioMEMS remains a challenge and while in the field of MEMS, technology has existed for several decades to provide rapid, precise control over the volumetric flow rate of fluids through microfluidic devices [7], application of these technologies to the field of BioMEMS is not straightforward.

In the past few years, several on-chip designs for on/off valves in PDMS devices have been reported for rapid control [8–14]. For example, Lam *et al* developed a device that incorporates an array of leaky on/off valves for flow control. However, the precision of the control is limited by the number of valves in the array and involves a complicated off-chip actuation platform [15]. Different off-chip strategies have been developed as well to enable flow control [16, 17]. However, since these technologies have a relatively large dead volume between the off-chip valve and the on-chip point of control, their temporal precision is limited. Recently, technologies using the frequency-dependent response of passive deformable features have been reported to achieve control over the time-averaged flow rate

through a channel [18, 19]. Although the operation of this device is simple and allows for rapid control over the average flow rate, it is often desirable in biological systems to be able to control the instantaneous flow rate.

In this paper, we introduce a new design for on-chip, pneumatic valves, which allows for proportional control of the flow rate in a microfluidic channel. Using finite element modeling (FEM), we optimized the linear response of flow rate to the vacuum pressure applied to the flow controller and studied the steady-state and transient behavior of the flow controller. These simulations showed that the flow controller could exhibit a rapid response time, on the order of 50 ms, and identified the critical design parameters for the linear regime. We then implemented this flow controller design in a microfluidic device manufactured in PDMS and measured steady-state and transient responses of the flow controller comparable to the predictions from the model.

Materials and methods

We have designed a normally closed microfluidic valve, which takes advantage of existing MEMS principles to produce a pneumatically controlled proportional valve constructed in PDMS. The flow controller uses two-layer PDMS technology, with the bottom layer comprising the flow layer and the top layer comprising the pneumatic control layer. The flow controller itself consists of a microstructured membrane below a pneumatic control chamber. When an actuating vacuum pressure is applied to the control chamber, the upward deflection of the microstructured membrane results in a controlled opening of the normally closed valve. The finite element modeling software (Comsol) was used to investigate the optimization of various design parameters. Figure 1 provides a schematic of the working principle of the flow controller design. Panels (A)–(F) show the flow controller from different perspectives. When no vacuum pressure is applied to the control chamber, as in (A), (C) and (E), the valve sits on the glass surface blocking the fluid flow through the channel. When a vacuum pressure is applied to the control chamber, as in (B), (D) and (F), the micro-valve membrane is deformed upward pulling the valve off the glass surface, allowing fluid flow through the channel.

Microfabricated flow controller

The microfluidic device was fabricated as described before [10] by casting the PDMS (Dow Corning, Midland, MI) polymer on two separate resist-structured silicon wafers to produce two separate layers of PDMS. Structures in SU-8 resist (MicroChem, Newton, MA) were produced according to the supplier's recipe using standard lithographic techniques. The PDMS was thoroughly mixed (10:1, w/w) with a cross linker, poured on top of the silicon wafer, degassed and cured at 65° C for at least 6 h. For the bottom layer, degassed PDMS was poured on the wafer, which was then spun at 800 rpm, to produce a membrane layer of PDMS. The PDMS with the replicated channels was peeled off from the master and channel access holes were punched with a 25-gauge needle. The first, a fluidic network layer and second, a control layer of PDMS were first irreversibly bonded together, with the control layer on top, and then the fluidic network layer was bonded on a glass slide via oxygen plasma. Access tubing (Tygon; Small Parts, Miami Lakes, FL) of diameter slightly larger than that of the holes was press fitted into the holes.

Flow experiments

Experimental testing of the manufactured microfluidic device was performed in two steps: steady-state and transient analysis.

Steady-state characterization of the flow controller—For the steady-state experiments, a device was used which consisted of three channels, each containing a flow controller (figures 2(A)–(D)). The flow controllers were pneumatically activated using a house vacuum pump. The pressure was mechanically adjusted using a regulator and a digital gauge was used to determine the vacuum pressure applied to the flow controller. The three channels joined into one channel downstream from the flow controllers. This resulted in three separate streams in the one large channel.

Fluid was flowed through the device at a constant pressure via a siphon from three independent fluid reservoirs with a height difference corresponding to a driving pressure of 436.1 Pa. The two outer streams contained water, while the inner stream contained a solution of fluorescein sodium salt (Sigma-Aldrich, St. Louis, MO) in a phosphate buffered saline solution (Fisher Scientific, Suwanee, GA). A Qimaging Retiga 2000R Fast 1394 CCD camera (Qimaging, Surrey, BC, Canada) was used to capture the fluorescent images.

ImageJ was then used to determine the location, in the channel, of the interfaces between the three streams. The interface locations depend only on the relative flow rates in the three streams. Thus, using a polynomial fit for the velocity profile in the channel using laminar flow calculations, the relative flow rate in each stream was calculated from the measured interface locations. To determine the absolute flow rate for each actuation pressure, a single initial measurement of the total flow rate was made by determining the amount of fluid captured from the outlet for 15 min. From observations of the stream interfaces, the flow rate remained constant during this time period. The measured total flow rate was then used to calculate the flow rate in the middle fluorescent stream, which was kept constant throughout the experiment.

Transient response of the flow controller—To analyze the transient behavior of the flow controller, a symmetrical network of channels was employed. One main channel is split into two branches, and flow controllers are positioned on each of the branches which merge together farther downstream (figures 2(E)–(H)). The two flow controllers were actuated in anti-phase relative to each other. This resulted in the total volumetric flow rate through the device remaining constant and minimizes the inertial effects of the flowing fluid, thus minimizing the delay caused by the compliance of the device and the inlet/outlet tubing to only the portion of the device containing the branches.

Fluid flow was established in the device via siphons from two separate reservoirs, one containing a saline buffer solution and other containing a concentrated solution of fluorescein dye. The pneumatics were controlled by outputting an analog voltage signal from Labview to a low-flow precision digital regulator (Kelly Pneumatics, Costa Mesa, CA), which adjusted the vacuum pressure, provided by a mechanical pump. Our own program written in Labview was used to capture the images, determine the stream width and control the pneumatics of the flow controllers. Labview VI's provided by Qimaging were used to control the CCD camera. Images were then processed later using Matlab to calculate the relative flow rate in the streams based on the width of the two streams.

Modeling

COMSOL Multiphysics was used to perform finite element modeling (FEM) simulations of the device. Two different sizes of valves were modeled: one with a maximum channel width of 1000 μm and one with a width of 500 μm . The pre-defined fluid-structure interaction application found in the MEMS module was used to model the physics of the device. This application couples the fluid dynamics to the structural mechanics by using the moving mesh application, with the mesh deformation determined by the x , y and z displacements calculated from the structural deformations. The structural mechanics of the system is

coupled to the fluid dynamics by calculating the deformation of the solid due to the pressure applied by the fluid.

The in-built CAD function of COMSOL was used to create a two dimensional cross-section in the x - y plane, which was extruded in the z -direction. The extrusions were performed in three steps to create three separate, interfacing layers. The first extruded layer consisted solely of a fluid subdomain, while the top layer consisted solely of a solid subdomain. For the middle layer, the triangular valve region (figures 1(C), (D)) was set to be a solid domain, while the other two regions were defined as fluid. As can be seen from figure 1, this creates a volume of fluid that is blocked by a valve, which can be opened by deforming the top membrane of the device upward.

For both sizes of valves, the bottom layer was chosen to have a thickness of $5\text{ }\mu\text{m}$, while the middle layer was chosen to have a thickness of $45\text{ }\mu\text{m}$. The thickness of the top layer was chosen to be $70\text{ }\mu\text{m}$ for the smaller valve and $30\text{ }\mu\text{m}$ for the larger valve. These dimensions were chosen to correspond to the dimensions of microfluidic devices that were manufactured.

The physical properties of the fluid domain were set to those of water (density of 1000 kg m^{-3} and viscosity of 0.001 Pa s). In order to properly model the material properties of the highly elastic PDMS silicone rubber used in the manufactured devices a hyper-elastic neo-Hookean model was chosen. The bulk modulus was chosen to be $7.5 \times 10^5\text{ Pa}$ and the density was chosen to be 920 kg m^{-3} , based on material properties found in the literature [20]. The fluid was driven through the device by a pressure difference from inlet to outlet of 436.1 Pa . The boundaries at the fluid-structure interface were modeled so that the velocity of the fluid was equal to the structural velocity calculated by the structural mechanics module. All other external boundaries were chosen to be 'no-slip'. The boundary conditions for the structural mechanics module were chosen such that an external pressure was applied to the top surface of the valve upward in the z -direction. The external boundaries on the side of the solid domain were chosen to be fixed in place to simulate the presence of the additional volume of PDMS surrounding the device. The boundaries at the solid-fluid interface were allowed to deform freely.

Results and discussion

We have developed a microfluidic proportional flow controller that allows for both linear control of the flow rate through a microfluidic channel in relation to an applied actuation pressure and a rapid response of the flow rate to changes in the flow controller actuation pressure.

Steady-state characterization of the flow controller

Using the FEM simulations, we first tested the steady-state flow rate through the flow controller for increasing levels of actuation vacuum pressure applied. It was found that the device exhibited a working range of 0 to $\sim 0.15\text{ psi}$ (0 to $1 \times 10^3\text{ Pa}$) and 0 to $\sim 6\text{ psi}$ (0 to $4 \times 10^3\text{ Pa}$), for the $1000\text{ }\mu\text{m}$ and $500\text{ }\mu\text{m}$ valve designs, respectively. Both flow controllers exhibited a linear relationship ($R^2 > 0.997$) between flow rate and actuation pressure for a large range of the working pressure, namely 0 to 0.1 psi (0 to $7 \times 10^2\text{ Pa}$) and 2.1 to 6 psi (1.5 to $4 \times 10^4\text{ Pa}$) for the $1000\text{ }\mu\text{m}$ and $500\text{ }\mu\text{m}$ valves, respectively.

Next, we tested the sensitivity of the observed linear relationship to various design features, both geometrical and physical. FEM simulations were performed as before, while varying several parameters. The parameters we tested were the following: (1) the distance the inlet channel extends into the chamber ($130, 140, 150, 160, 170\text{ }\mu\text{m}$), (2) the stiffness of the

material ($5.625, 6.75, 7.5, 8.25, 9.375 \times 10^5$ Pa), (3) the distance from the center of the chamber to the tip of the triangular flap ($0, 30, 90, 130, 180 \mu\text{m}$), (4) the width of the base of the valve ($150, 200, 250, 375, 550 \mu\text{m}$), (5) the shape of the end of the input channel (scaling factor— $0.05, 0.3, 0.45, 0.6, 0.9$ — 0.05 corresponds to a flat end, 0.45 to a round end, 0.9 to an elongated end) and (6) the thickness of the membrane ($50, 75, 100, 125, 150 \mu\text{m}$). Results of this sensitivity analysis show the highest dependence on the thickness of the membrane (figure 3(A)). The instantaneous slope of the flow rate pressure relationship also depends on the membrane thickness (figure 3(B)). From figure 3(A), we can see that there are several design parameters that could be varied to achieve flow controllers that are either more sensitive to the actuation pressure or provide for finer control of the flow rate.

To experimentally test the behavior of the flow controller we incorporated few of the simulated designs into microfluidic devices with three independent flow controllers (figures 2(A)–(D)). The control chamber of each flow controller was connected to a vacuum line, controlled individually by a manual regulator. Measurements of the flow rate through the flow controller were made as described above. Figures 4(A)–(D) shows the results of the steady-state measurements for both the $500 \mu\text{m}$ and the $1000 \mu\text{m}$ valve both simulated (A, C) and from the experimental setup (B, D). These results show that the flow controllers in the experimental setup exhibit very similar working ranges (0 – 4 psi (0 – 2.8×10^4 Pa) and 0 – 0.35 psi (0 – 2.5×10^3 Pa), for the $500 \mu\text{m}$ and $1000 \mu\text{m}$ valve, respectively) as compared to the numerical simulations. The slightly larger working range for the experimental $1000 \mu\text{m}$ valve could result from a slightly thicker membrane than was used in the simulation.

These results suggest that our valve design provides for better flow control for two primary reasons. First, the channel extending into the valve structure provides for a more extended cross-sectional area. Previous membrane barrier valve designs are only able to change the cross-sectional area of the channel along one dimension, the vertical [10, 21, 22]. Our valve design allows for adjustment of the cross-sectional flow area along two dimensions, a wider range of deformations result in a significant change in the fluidic resistance. Second, traditional MEMS valves are designed in silicon, which is roughly seven orders of magnitude stiffer than PDMS. Thus, for MEMS valves, one can use high actuation pressures, which result in small deformations of the valve, while for the most PDMS valves, even small pressures result in a significant deformation [7]. Our valve design effectively increases the stiffness of the valve membrane, while still allowing for significant deformation of the valve structure. As a result, a larger increase in actuation pressure is needed to produce the same membrane deformation, allowing for finer control of the flow. These two features combined give our valve design finer flow control than previous PDMS valve designs.

Transient response of the flow controller

To probe the transient responses of the proportional flow controllers, we run simulations in which the vacuum pressure applied to the flow controller was varied over time according to both a sine wave and a square wave. The calculated flow rates showed that the flow controller had an extremely fast response time, on the order of few milliseconds (data not shown). We also tested the response of the flow controller to a sinusoidal actuation pressure of varying frequencies and equal amplitudes. Figure 4(E) shows that significant attenuation of the output flow rate amplitude relative to the actuation pressure amplitude occurs for frequencies greater than roughly 20 Hz.

To experimentally test the transient response of the flow controller, we used the parallel, anti-phase arrangement of the proportional flow controllers in the microfluidic setup described above (figures 2(E)–(H)). A Labview program was used to apply both sinusoidal and square-wave time-varying vacuum pressures to the control chamber of the flow

controller. Frequencies varying from 0.1 to 20 Hz were tested. Figure 4(F) shows the frequency dependence of the output-to-input ratio for the experimental setup. As can be seen, significant attenuation of the output signal of the experimental setup occurs at a frequency roughly an order of magnitude lower than that observed for the numerical simulations. We believe that this difference can be accounted for by the fact that the simulations only take into account the mechanics of the valve structure, while the experiments include additional components, each with their own frequency dependence.

To further probe into the dynamics response of the proportional flow controller, we measured the amplitude of the flow rate versus amplitude of the voltage used to control the digital regulators, at a driving frequency of 0.1 Hz (figure 5(A)). This plot shows that at this frequency there is a small, albeit detectable difference in phase between the input voltage and output flow rate. The observed hysteresis is most likely due to nonlinear behavior of the flow controller when it is nearly fully closed or fully opened. Furthermore, panel D shows the response of the microfluidic setup to a square wave pulse of frequency 0.5 Hz. As can be seen from the lower plot, the response time of the flow controller is roughly 250 ms for the step down and 100 ms for the step up. This asymmetry in response times is likely a result of the different forces acting when the valve is being opened versus being closed. When a vacuum pressure is applied, the force driving the membrane to deform upward is the applied vacuum itself, while the elasticity of the membrane resists this force. In contrast, when the valve closes, the elasticity of the membrane is the force driving the closing, while the resistance is provided by the volume of fluid that must be expelled from the valve chamber.

The data we present here, both from simulation and experiment, show we have developed an on-chip proportional flow controller, which provides both a high level of control over the flow rate in a channel and a rapid response time. Although both on-chip and off-chip technologies for temporal control of the fluid flow have been developed, most provide either high resolution control or a rapid response, and not both, while others are limited by the complexity of the control mechanism, and thus are difficult to scale-up to provide control of multiple channels. In contrast, due to the simplicity of the flow controller control mechanism, our design would be easily scaled to provide independent, high-resolution, rapid control of multiple channels. Finally, there are actuation schemes that could prove to be faster than pneumatic control.

Conclusions

In conclusion, we have successfully developed a micro-scale proportional flow controller which allows for rapid, precise adjustments of the flow rate through a microfluidic channel. The characterization of the system shows that several parameters can be changed to optimize the device for applications which require either even higher precision or even faster response. The numerical simulations we developed can also be used as a valuable tool for further optimization and design of the flow controller.

Acknowledgments

We thank Octavio Hurtado for valuable assistance with microfabrication, Dr Aman Russom for his assistance in performing the simulations and Dr Jagesh Shah for his help in producing this manuscript. This work was supported in part by the National Institutes of Health grants (P41EB002503 and R21AI076760).

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Figure 1.

Diagram of the flow controller demonstrating the mechanics involved to control the flow rate. (A) and (B) show the flow controller viewed from the side looking perpendicular to the direction of fluid flow through the device. As a vacuum pressure is applied to the control chamber above the valve, the valve membrane deflects upward, increasing the area of the fluid flow cross-section, which is shown in (B). (C) and (D) show the flow controller as viewed from above. As the membrane deflects upward, the tip of the triangular flap (darker gray) deflects upward more than the rest of the valve, causing the valve to controllably 'peel' off the glass surface, as shown in (D). A small relief channel ($\sim 2 \mu\text{m}$ high, $\sim 10 \mu\text{m}$ wide) was included to minimize hysteresis effects of the fluid surface tension. Thus, even in the closed position, there was a small amount of flow through the valve. (E) and (F) are images exported from the Comsol simulations of the closed and open valves, respectively, to provide a more realistic representation of the amount of deflection observed.

Figure 2.

Schematic of the operation of the microfluidic devices for the (A) steady-state and (E) transient experiments. For the steady-state experiments, three separate reservoirs were used, with the middle containing a fluorescent dye. The flow from each reservoir was controlled using the new flow controller design, downstream of which the separate streams joined in one channel. Panels (B)–(D) show the state of the three streams in the channel for the flow controller controlling the left stream being completely closed (B), partially open (C) and completely open (D). For the transient experiments, two reservoirs were used, with the left one containing a fluorescent dye. The flow from each reservoir joined together in a large channel, then split into two symmetric channels, each of which contained a flow controller. These two flow controllers were operated in anti-phase relative to each other. Panels (F)–(H) show the state of the flow in the two streams for the left flow controller open at a minimum (F), halfway open (G) and open to a maximum (H).

Figure 3.

Sensitivity analysis of the simulated flow controller behavior for various design parameters. (A) Relationship between the flow rate and geometrical design parameters of the valve. The nominal flow rate was considered for a valve of diameter $500\ \mu\text{m}$, at an applied vacuum pressure of 4 psi ($2.75 \times 10^4\ \text{Pa}$), for values of the following geometrical and physical properties (nominal value $\pm$ variation): (1) length of the inlet channel into the chamber ($150 \pm 20\ \mu\text{m}$), (2) initial stiffness ($7.5 \pm 1.8 \times 10^5\ \text{Pa}$), (3) length of the valve structure ($90 \pm 90\ \mu\text{m}$), (4) width of the valve structure ($250\text{--}100\text{--}300\ \mu\text{m}$), (5) roundedness of the end of the inlet channel (0.45 ± 0.45) and (6) membrane thickness ($100 \pm 50\ \mu\text{m}$). The vertical axis shows the relative change in flow rate for the changes of geometrical and physical parameters tested. For all parameters, except the inlet channel length, the larger values resulted in lower flow rates. (B) Detailed analysis of the relationship between linearity of the flow controller response and membrane thickness. The vertical axis shows the derivative of the flow rate through the controller with respect to the pressure applied to the valve membrane for values of the membrane thickness varying between 50 and $150\ \mu\text{m}$ (1 psi = $6894.7\ \text{Pa}$). *The membrane stiffness (2) and membrane thickness (6) parameters cannot be shown schematically on the pictured valve cross-section.

Figure 4.

Results from the analysis of the steady-state and transient behavior of the flow controller from both simulations (A), (C), (E) and experiments (B), (D), (F). Panels (A)–(D) show the relationship between steady-state flow rate through the flow controller and vacuum-pressure applied to the valve membrane, for valve chamber diameters of 500 (A), (B) and 1000 μm (C), (D). Both simulation and experimental results demonstrate a linear relationship between the pressure applied to the valve membrane and the flow rate through the controller. The relationship could be described by a linear function over a range >70% of the working range of pressures with a residual $R^2 > 0.997$. Panels (E) and (F) show the frequency response of the flow controller to sine wave signals, as measured by both simulation (E) and experiment (F). In (E), the gain is calculated as the ratio of the amplitude of the flow rate through the controller in microliters per minute to the amplitude of the applied pressure (1 psi = 6894.7 Pa). Meanwhile, in (F), the output response is defined as the ratio of the amplitude of the width of the fluorescent stream in pixels to the amplitude of the voltage applied to the digital regulators. Vacuum pressure is reported as the gauge pressure below atmospheric pressure.

Figure 5.

Flow controller response to dynamically varying signals. (A) Plot showing the time response of the flow controller for a sinusoidal voltage signal of frequency 0.1 Hz. The vertical axis of the phase plot shows the flow rate in the fluorescent stream relative to the total flow rate in the microfluidic device, while the horizontal plot shows the input voltage given to the vacuum regulators. (B) and (C) show the individual waveforms for the channel flow rate and input control voltage, respectively. (D) Time response of the microfluidic flow controller to an applied square wave voltage pulse of 1 Hz. The top plot shows the voltage signal, which had amplitude of 2 V and offset of 1 V. The bottom plot shows the width of the fluorescent stream relative to the width of the channel.