Design and Rapid Fabrication of a Microfluidic Fraction Collector

Bozhi Yang[1], George C. Lopez[2], Alan J. Rosenbloom[3], Qiao Lin[1]
[1]Department of Mechanical Engineering, Carnegie Mellon University, Pittsburgh, PA 15213
[2]Robotics institute, School of Computer Science, Carnegie Mellon University, Pittsburgh, PA 15213
[3]Department of Critical Care Medicine and Medical Center, University of Pittsburgh, Pittsburgh, PA 15213
Email: qlin@andrew.cmu.edu Phone: 412-268-3641

Abstract

This paper presents a novel microfluidic fraction collector that directs a liquid to fill a set of collection chambers in a predetermined sequence. All microfluidic channels and liquid chambers are fabricated on a flat PDMS sheet. The device exploits surface tension effects at the microscale and uses no moving parts. The filling process can be completed with low driving pressures, which are below 1400 Pa for a constant flow rate of 1 μl/min. Cross-diffusion between the individual collection chambers during the filling process is also estimated for various device geometries using typical parameters, and is shown to be generally negligible.

Keywords: Fraction collector, hydrophobic surface, laser engraving, microfluidics, surface tension.

INTRODUCTION

A fraction collector is one of the key devices used for microdialysis. Microdialysis is a sampling method for studying localized *in vivo* metabolic events by monitoring the chemistry of the extracellular space in living tissue. The technique involves using a small polymeric catheter with a semipermeable membrane at the end of the probe. Small molecules and proteins diffuse across the size-selective membrane and are carried out by a circulating buffer fluid. The outflowing fluid, called the dialysate, is collected in a fraction collector for analysis [1]. In traditional fraction collectors, a series of tubes are sequentially filled with the dialysate. Fraction collection by such an approach is bulky, expensive, and not portable.

This paper presents an innovative microfabricated fraction collector that overcomes the limitations of conventional devices. All collection chambers along with associated microchannels are fabricated on a single polydimethylsiloxane (PDMS) chip. As the channel surfaces are hydrophobic, surface tension effects can be employed to direct the dialysate into microfabricated collection chambers in the desired sequence. This fraction collector is inexpensive and disposable, has excellent reliability and portability, and can maintain continuous operation without power.

Surface tension is the tangential force that keeps a fluid together at the air/fluid interface. It is the intermolecular force of attraction between adjacent molecules. At the microscale, surface tension has dominant effects. These effects are exploited in micro devices to enable unique functionalities not seen in the macro world [2]. In particular, surface tension has been used as passive microfluidic valves, as those used by Ahn et al [3] in their structurally programmable microfluidic systems and by McNeely et al. for sample processing in hydrophobic microchannels [4]. Here we also use such passive hydrophobic valves to enable fraction collection on a microchip. The microchip fraction collector is fabricated from PDMS, which offers advantages such as hydrophobicity and low fabrication cost. PDMS is widely used in microfluidic systems [5][6].

The microchip fraction collector reported here is intended for use in microdialysis, but can also be useful in many other applications (e.g. chromatography). Further, the collection chambers can be further integrated with micro sensors for detection of target molecules, allowing truly integrated biomedical diagnostics and monitoring microsystems.

PRINCIPLE

The microfluidic fraction collector exploits the dominance of the microscale surface tension. When an aqueous buffer flows through a hydrophobic microchannel, the liquid front will assume a ellipsoidal shape centered on the liquid side, and a pressure difference is generated across the liquid-air interface as shown in Figure 1. This pressure difference is provided by the Young-Laplace equation [5]:

$$\Delta p = p_1 - p_2 = -2\gamma \cos\theta \cdot (\frac{1}{W} + \frac{1}{H})$$

where γ is the surface tension of the liquid/air interface, θ is the liquid contact angle on channel wall, H and W (not shown) are the height and width of the channel. Since the pressure on the liquid side is higher than that on the air side, there is a pressure barrier that must be overcome to drive the fluid flow. These pressure barriers can be used to direct the flow in fraction collection.

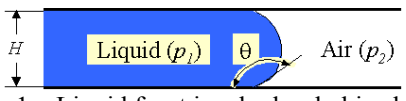

Figure 1. Liquid front in a hydrophobic channel

While we have made fraction collector designs with a variety of configurations, we will focus on the configuration schematically shown in Figure 2. Constricted channels (channel 3 shown in figure) with smaller hydraulic diameters are designed at chamber B, D, and F's entrance. Cross sections 2, 3 and 4 are designed so that they are decreasing in the $WH/(W+H)$ value**,** hence have increasing pressure barriers. Thus, Chamber A will first be filled then followed by chamber B, which is in turn followed by the liquid flowing through cross section 4, that is immediately next to the inlets of chambers A and B. The filling process for chambers C and D, and chamber E and F follows a similar process. Thus, the chambers will be filled in the predetermined sequence {A, B, C, D, E, F}.

This surface tension based passive valving principle allows for a fraction collector with no moving parts. The fraction collector will have excellent reliability and portability, and can maintain continuous operation without power. In addition, the fraction collector is inexpensive, can be made disposable, and can be further integrated with on-chip biosensing capabilities.

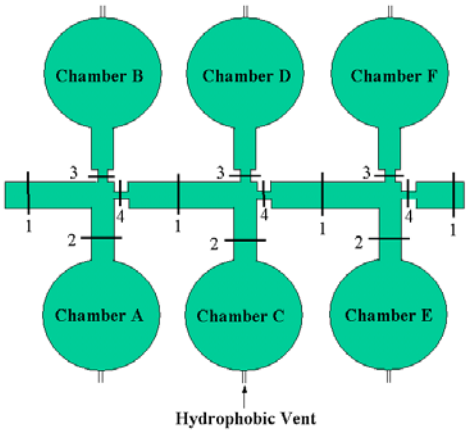

Figure 2. Schematic of the microchip fraction collector

DESIGN

In the design shown in Figure 2, there are six collection chambers of 240 µl in volume each. The diameter and depth of these chambers are 12.36 mm and 2 mm, respectively. The fraction collection flow rate is expected to be a few microliters per minute. For example, at a flow rate of 1µl/min, it takes 4 hours to fill each chamber. Thus, this six-chamber device can be potentially used for fraction collection in a 24-hour period.

The cross-sections of the hydrophobic microchannels are designed to have dimensions such that both their widths and depths decrease with the cross section number, i.e., $w_1 > w_2 > w_3 > w_4$ and $h_1 > h_2 > h_3 > h_4$. These dimensions, as well as the associated pressure barriers, are shown in Table 1. In all the pressure calculations, the material properties of water and PDMS (γ=0.0728 N/m and θ=110°) are used. The main channels, with cross section 1, have lengths ranging from 8 mm to 15 mm. The inlet channels leading to the chambers (with cross section 2) are approximately 3 mm in length. The constricted channels (with cross sections 3 and 4), which determine the chamber filling sequence, have the same length of 500 µm. Overall, the fraction collector microchip is 75 mm long, 60 mm wide, and 5.5 mm thick (see Figure 3).

Table 1. Cross section dimensions and corresponding pressure barriers.

Cross Section	Width W (µm)	Height H (µm)	Δp (Pa)
1	600	300	249
2	500	200	349
3	300	75	830
4	150	50	1328

In the design, hydrophobic air vents for the six liquid chambers are designed as microchannels on the base PDMS slab. They have the minimum channel cross section (with channel width of 100 µm and depth of 30 µm). Therefore they have the largest pressure barrier (2157 Pa) and thus will not leak during the chamber filling process.

The microchannels of this fraction collector have relatively large cross sections and are short in length. It can be shown that the pressure loss due to wall friction over the flow paths is very small (less than 30 Pa) because of the low flow rate (1 µm/min). Therefore the pressure loss due to friction is negligible compared with the surface tension induced pressure difference.

FABRICATION

The microfluidic fraction collector is fabricated by laser engraving using an M-300 Laser Platform (Universal Laser Systems, Inc.) from a layout generated with CorelDraw and AutoCAD. The M-300 system uses RF driven, sealed CO_2 laser, and have a minimum light spot size of 75 µm with a 1.5" lens. The fabrication process was accomplished in three steps. The first step involves the molding flat PDMS sheets. A curing agent and PDMS prepolymer (Sylgard 184 Silicone Elastomer Kit, Dow Corning) were thoroughly mixed in a 1:10 weight ratio. After degassing for 1 hour, the mixture was poured onto a molding kit, which has a silicon wafer as the molding plate to ensure the smoothness of the resulting PDMS surface. A transparent film was carefully lowered onto the prepolymer mixture to prevent bubbles from forming at the interface. It also allows easy removal of the cover plate from the PDMS molds after curing. The silicon wafer/prepolymer/transparent film stack was then clamped between two thick acrylic plates and cured for 3 hours at 100 ℃. After curing a flat and elastomeric PDMS sheet resulted, which was peeled off from the silicon wafer [7]. In the second fabrication step, the microfluidic features were generated by etching the PDMS sheet with the laser engraver. Adjustment of the laser power and laser cartridge speed allowed generation of the varying feature depths as desired. The last fabrication step involves surface cleaning

and bonding of PDMS. The etched PDMS sheet was cleaned with ultrasonic agitation in methanol, and then bonded to a cover sheet that was also made of PDMS. The bonding is based on reversible self-adhesion between two PDMS surfaces and no adhesives were used for the bonding. This will allow the microchip to be opened and resealed for purposes of priming, cleaning, and liquid removal. A fabricated fraction collector chip is shown in Figure 3.

PDMS fabrication has been traditionally based on replica molding by photoresist molds generated with photolithography [7]. In comparison, laser engraving allows further simplification of the fabrication process, allowing rapid and inexpensive generation of microfluidic prototypes. In addition, laser engraving readily allows features of different depths to be generated, which is difficult with replica molding techniques. It has also been reported that laser engraving increases the hydrophobicity of PDMS [8], which is desirable for our applications. The main limitation of laser engraving techniques, though, is relatively large feature size (75 μm in our work).

RESULTS AND DISCUSSION

Testing Results. During testing, the microfluidic fraction collector is connected to a micro syringe pump (CMA/102 Microdialysis Pump, CMA Microdialysis, Sweden). Tygon tubing is used to connect the chip to the syringe pump. One end of an auxiliary polymide tubing with a smaller outer diameter is inserted in a hole punctured in the PDMS cover sheet. The other end of the polymide tubing is inserted into the Tygon tubing, whose end surface is sealed onto the PDMS cover sheet by epoxy. Water with added non-staining blue dye was used as the filling liquid for ease of visualization. The syringe pump was set to a constant flow rate of 1 μm/min throughout the filling operation. During testing, the chambers were filled with the liquid in the predetermined sequence as desired.

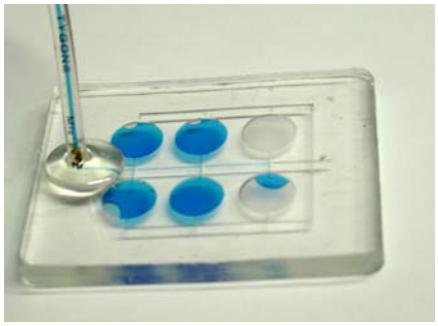

Figure 3. A fabricated fraction collector chip in the chamber filling process. The fluidic interconnect tubing is also shown.

We observed during testing that some of the chambers were not completely filled. This was likely caused by the limited air venting capabilities of the chambers since there was only one hydrophobic vent for each chamber. As the liquid reached a vent before the associated chamber is completely filled, it will effectively seal the chamber and trap the air that remained in this chamber at that time. This can be readily addressed by incorporating more hydrophobic vents for each chamber in the design.

Pressure at the Collector Chip Inlet. It is important to consider the pressure at the fraction collector inlet. This pressure determines the pressure at the microdialysis membrane, and should be kept sufficiently low so as not to hinder the diffusion of biomolecules across the membrane from the tissue. Our estimate shows an acceptable range of a few thousand Pascals for such pressures. To evaluate the applicability of our fraction collector chip to microdialysis, we estimated the time history of the pressure at the chip inlet during the filling process, which is shown in Figure 4. Since it takes only a short time interval for the liquid front to travel through the constricted channels but an extended period of time to fill the chambers, the time intervals are not shown to the scale in the figure. As a chamber is being filled, the pressure at the chip inlet is mainly due to viscous friction and is estimated to not exceed 25 Pa. This inlet pressure associated with chamber filling is thus neglected in the figure. From Figure 4, we see that the estimated maximum pressure in the fraction collection process is only about 1328 Pa. In addition, relatively high pressures only occur in short time intervals and therefore will have little influence on trans-membrane diffusion. Thus we conclude that the chip inlet pressure is acceptable for microdialysis applications.

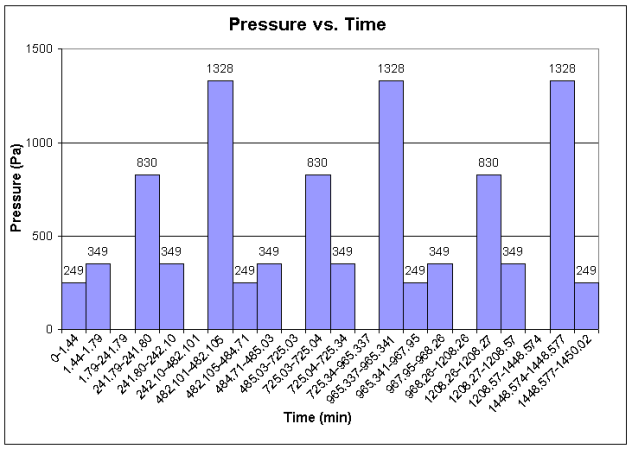

Figure 4. Estimated pressure at the fraction collector inlet relative to the atmosphere throughout the filling process.

Cross-Diffusion. Since the fraction collection process takes an extended time, diffusion of analytes could be significant. Molecules could cross-contaminate among the individual collection chambers. Here we approximately estimate the potential cross contamination between a chamber and the main channel (with cross section 1 in Figure 2). This provides an estimate of the cross-diffusion among individual chambers.

Assume that the concentration of the molecule is C_1 in the chamber and C_2 in the channel. For simplicity also assume that C_1 and C_2 are both constant throughout the

fraction collection process. Since the liquid flow rate is low, we ignore effects of convection. Diffusion between the chamber and the main channel occurs across the inlet that leads into the chamber. Since the length L of the channel is much larger than the dimensions of the channel's cross section (with width W and height H), we assume that diffusion is one dimensional along the length of the chamber inlet channel. It follows that flux per unit cross-sectional area of the molecules in the chamber inlet channel due to diffusion is given by $J = D(C_1 - C_2)/L$, where D is the diffusivity of the molecule. The sign of the equation's right-hand-side is chosen such that J gives the diffusion from the chamber to the main channel. The total amount of molecules diffused, in time t, into the main channel from the chamber is thus

$$Q_d = D(C_1 - C_2)WHt/L$$

Note that we assume the chamber inlet channel has a uniform cross section and neglect effects of the constriction for a conservative estimate. The extent of cross contamination can be evaluated by the ratio Q_d/Q, where $Q = C_1 V$ is the total amount of the molecule in the chamber and V is the chamber's volume. Thus, we have

$$Q_d / Q = \frac{D(C_1 - C_2)WHt}{C_1 VL}$$

Table 2 shows the estimated values of this ratio for different chamber inlet dimensions. To generate the table, we note that $V = 240$ mm^3 and $t = 24$ hours. We also assume that diffusivity to be $D = 4\times10^{-9}$ m^2/s, and set the concentration of the molecule in the main channel to zero ($C_2 = 0$). From the table, we can see that the cross contamination is very small relative to the amount of molecules in the chamber and can therefore be neglected for practical purposes.

Table 2. Estimates of cross contamination.

Channel	W (μm)	H (μm)	L (mm)	Q_d / Q
1	300	200	3	0.0288
2	200	100	3	0.0096
3	100	50	3	0.0024

CONCLUSION

An innovative PDMS-based microfluidic fraction collector has been designed and fabricated by laser engraving. The fraction collector exploits the dominance of surface tension in hydrophobic channels to direct a liquid into collection chambers in a predetermined sequence. The laser engraving technique allows rapid and flexible fabrication of fraction collector prototypes. Based on this passive fluid direction principle, the fraction collector has excellent reliability and operates continuously without power. It is also estimated that the fraction collector induces only a small back pressure at the chip inlet, and has minimal cross contamination between liquid chambers.

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