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Microfluidic diafiltration-on-chip using an integrated magnetic peristaltic micropump

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Abstract

Diafiltration is a membrane filtration technique that rapidly removes permeable molecules from a solution by controlling the tangential and orthogonal flows over a membrane and by replenishing the permeate with an equivalent amount of replacement buffer. However, its application to the purification of many key biomaterials and nanomaterials has been limited by the large dead volume (>10 mL) that is required to automate the process. To address this challenge, we have developed a diafiltration-on-a-chip device that can process low-volume samples (50 μ L). The key innovation of this device is a magnetically-driven on-chip peristaltic pump that is able to continuously drive fluid flow at rates as high as 50 mL/hr with minimal external instrumentation and a dead volume of <50 μ L. To demonstrate the utility of this device, we purified microbeads from dye with >99% purity and >96% retention within two hours. We additionally showed that cells could be purified from microbeads with >97% purity and >97% retention in two hours. Because our approach requires minimal instrumentation, it is well suited for on-chip parallelization, which was demonstrated by incorporating four complete diafiltration systems onto a single credit card-sized chip.

Graphical abstract

A novel magnetically-driven peristaltic pump can be used to drive cyclic on-chip flow for small volume (50uL) diafiltration.

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Conflicts of Interest: There are no conflicts of interest to declare.

Introduction

Diafiltration is a membrane filtration technique^{1–3} that can achieve high purification with low loss^{1,4}. Unlike dialysis, which relies on a concentration gradient to remove waste, diafiltration uses a pressure gradient to push fluid across a porous membrane, reducing purification times from days to hours⁴ or less³. Like other size-based purification strategies, the goal of diafiltration is to filter small waste particles from the sample input into the permeate while retaining large objects in the retentate³. During the purification process, fluid from the input is pushed into the permeate through multiple cycles of tangential flow over the membrane filter, and the volume lost from the retentate is continuously replenished by clean buffer solution to maintain a constant total volume². Alternatively, more sample can be used in place of clean buffer to yield a retentate volume that is smaller than the sample input volume to concentrate the sample⁵. In contrast to single-pass cross-flow filtration^{6–8}, the sample passes over the filter many times until the desired purity is reached^{1,3,5}. This feature allows the flux through the filter to be adjusted to find the desired balance between maximizing purification rate and minimizing retentate loss or clogging of the filtration membrane⁹. Unfortunately, despite its advantages, diafiltration is currently limited to samples with volumes >10 mL⁵ because of the large dead volume inherent to the pumps and tubing required for its implementation. This requirement for large sample volumes currently precludes its use for many nanomaterial purification applications where small, precious samples need to be processed^{10–12}.

To address this challenge, we have developed a microfluidic approach that incorporates all of the components of a diafiltration system into a chip-based format. By miniaturizing the entire system, the minimum sample volume can be reduced to 50 μL , a 200 $\times$ improvement over conventional systems. In a conventional diafiltration system, fluid flow is driven by a peristaltic pump; a filter membrane is used to separate the retentate from the permeate; and a constriction in the fluid channel is used to control the pressure across the membrane³ (Fig. 1a). Our chip incorporates all of these components onto a single microfluidic device roughly the size of a credit card ($75 \times 50 \times 0.25 \text{ mm}^3$) (Fig. 1b).

The key innovation of this work is the incorporation of a magnetically driven peristaltic pump to achieve continuous recirculating flow (Fig. 2a). This pump is implemented using a three-dimensional microfluidic architecture, wherein magnetic material (iron filings) is incorporated into a layer above a flow channel that is separated from the flow channel by a thin layer of PDMS (Fig. 2b). This geometry is simple to fabricate with conventional soft lithography, and the physical separation of the magnetic material from the sample simplifies use and avoids potential contamination of the sample. When a fixed magnet is placed below the flow channel, separated from the sample by a glass slide, the iron filings are pulled downward in response to the magnetic field, deforming the PDMS membrane and compressing the flow channel (Fig. 2b). As the external magnet is moved in-plane along the length of the flow channel, the site of this compression in the channel moves with the magnet and forces the fluid to move in the direction of the magnet's motion, similar to a peristaltic pump. The on-chip magnetic pump drives flow continuously past a permeable membrane and through a high resistance microfluidic pinch channel. The flux across the

membrane is controlled by the relative resistances of the pinch channel and the membrane (Fig. 2c).

To demonstrate the capability of this chip, we purified $d = 1\ \mu\text{m}$ beads from sulforhodamine B using a 100 nm pore-sized track etched membrane filter. Additionally, we purified Jurkat cells ($d \sim 10\ \mu\text{m}$) from $d = 1\ \mu\text{m}$ beads using a 3 μm pore-sized track etched membrane filter. For both applications, sample volumes as small as 50 μL could be processed. To demonstrate the advantage of using magnetically driven pumps, we incorporated four complete diafiltration systems, including peristaltic pump, pinch channel, and membrane filter, onto a single chip that could be run using a single external magnet.

Methods

Device Design

The diafiltration chip was fabricated using a combination of soft lithography¹³ and laser micromachining of laminate sheet microfluidics¹⁴ (Fig. 3a). The portion of the chip that contains the magnetic peristaltic pump and the pinch channel consisted of three soft lithography layers: a PDMS layer containing a semicircle shaped cut-out for iron filings to drive the magnetic pump, fabricated using an $\sim 1/8''$ thick acrylic mold (Layer 1); a thin 240 μm PDMS film, fabricated by spin coating PDMS on a 135 μm tall SU-8/silicon wafer mold (Layer 2); and a PDMS sample layer (Layer 3) containing a 2 mm wide $\times$ 135 μm high channel in the shape of a U (Fig. 3b) with a 70 μm wide pinch channel near one end (Fig. 3c) to generate the pressure gradient for purification. The resistance of the pinch channel was controlled by varying the length of the channel. The PDMS layers were permanently bonded by plasma treatment. Input holes and air outlet holes were cut into the PDMS channels on either side of the pinch channel using a 1.5 mm biopsy punch (Integra).

The purification portion of the chip, which contains the membrane filter, was fabricated using three layers of micromachined laminate sheet microfluidics¹⁴. The use of laminate sheet microfluidics enables a variety of membrane filters to be easily incorporated into the device for high pressure, leak-free use. Because glass can be plasma bonded to PDMS and adhered to the laser cut Mylar, but PDMS is not easily adhered to Mylar, we used glass as an interface between the PDMS portion of the device and the Mylar portion of the device. For this transition layer, we used a $75 \times 50 \times 1\ \text{mm}^3$ glass slide (Fisher) with 0.6 mm diameter through-holes micromachined using a 1 mW CO_2 laser (Universal Laser Systems) (Layer 4). The microchannels in the purification section of the chip were laser cut from 75 μm adhesive Mylar (3M) to make the purification layer (Layer 5), and 250 μm adhesive Mylar (McMaster Carr) to make the waste channel (Layer 7). The membrane filter (Layer 6) was sandwiched between the purification layer and the waste layer. In this study, two different membrane filters were used: a 100 nm diameter pore polycarbonate track etched (PCTE) membrane (Sterlitech) to separate beads from dye, and a 3 μm diameter pore PCTE membrane (Sterlitech) to purify beads from cells. A final PDMS waste output layer was prepared with two outlet holes that were created using a 1.5 mm biopsy punch (Layer 8). Because the bond between the waste channel (Layer 7) and the waste output (Layer 8) is not subject to high pressures, there is no need for an additional glass transition layer between the waste channel and waste output. The devices were pre-treated with 1% Pluronic F-127 (Sigma) to diminish

loss of retentate though adherence to the channel walls. After device assembly, the magnetic pump region was completed by loading the space above the 240 μm PDMS membrane with 325 mesh iron filings (Sigma). The iron filings were sealed into the space using clear tape. Fluid flow in the device was driven by a pair of $1/8'' \times 1/8'' \times 1/16''$ NdFeB magnets (KJ Magnetics) mounted on an acrylic plate rotated by a DC motor (Pololu). Using COMSOL Multiphysics software, we simulated the magnetic field gradient from each magnet. Each magnet generates a field of 0.2 T and a gradient of 3.1 T/mm at a distance of 1.375 mm away from the surface of the magnet, equivalent to the distance between the magnet surface and the bottom of the iron filing layer (Fig. S1). Though the field drops to <0.05 T and the gradient drops to <0.5 T/mm at a distance of 4.55 mm, corresponding to the top of the iron filings layer (Fig. S1), we continued to use a $1/8''$ thick iron layer for ease of fabrication.

Device Characterization

To characterize the scaling of our miniaturized magnetic pump with the geometry of the microfluidic device, we first measured the tangential flow rate ($\varphi_{\parallel,s}$) in mL/hr for channel widths of 1-4 mm on simplified devices containing only the magnetic pump portion of the final device and no pinch channel. The input to the device was water, and the output of the device was collected in a 20 mL glass vial. Flow rate was calculated by measuring the volume of water in the output vial at the end of 10 minutes.

For each channel width, the flow rate $\varphi_{\parallel,s}$ initially increased linearly with the motor rotation speed f , but plateaued at a critical motor rate f_{ss} (Fig. 4a). To better understand this behavior, we plotted $\varphi_{\parallel,s}/f$ (slope of the linear regime) *versus* channel width w and found these two variables to be directly proportional (Fig. 4b). The critical frequency f_{ss} above which the flow rate plateaued, calculated by interpolating the RPM at which flow rate reached 90% of its maximum, was found to be inversely proportional to channel width, $f_{ss} \propto w^{-1}$ (Fig. 4c). The magnetic pump was able to achieve flow rates of greater than 50 mL/hr in a channel with cross sectional dimensions of $2 \text{ mm} \times 135 \mu\text{m}$, corresponding to a flow velocity of 5.1 cm/s. This flow rate is on par with rates achieved by typical syringe pumps used in the field, and $10\times$ faster than other microfluidic pump systems^{15,16}. Other studies have shown that iron microparticles can respond at frequencies much greater than the 10 Hz rotation speeds used here¹⁷; hence, we believe that the flow rate at high frequencies is limited by the mechanics of the membrane, rather than by the response time of the iron filings.

To characterize the device's capability to balance the orthogonal ($\varphi_{\perp}$) and tangential ($\varphi_{\parallel}$) flow rates, we measured the orthogonal and tangential flow rates in devices with various pinch channel lengths l_p with and without a membrane filter, respectively. The capability to balance these flow rates allows the flux through the filter to be adjusted, as there is a trade-off between increasing purification rate and minimizing retentate loss and clogging of the filtration membrane.

Previous work has shown that high pressure can severely limit fluid flow in pump systems¹⁵. Therefore, we wished to understand the effect of the high resistance pinch channel on flow behavior in our device. To this end, we measured tangential flow rate $\varphi_{\parallel}$ in mL/hr within devices that contained pinch channels of four different lengths l_p (0 mm, 2.5 mm, 5 mm, and 7.5 mm) with no orthogonal flow (Fig. 5c). As the length of the pinch channel increased, the

tangential flow rate through the device decreased across all motor spin speeds (Fig. 5a). Furthermore, at $f = 500$ RPM, the tangential flow rate was inversely proportional to pinch channel length, $\varphi_{\parallel} \propto l_p^{-1}$ (Fig. 5b), consistent with the known inverse linear relationship between flow rate and hydrodynamic resistance at a given pressure in microfluidic channels¹⁸.

Next, to understand how the pinch channel could be used to drive orthogonal flow, we quantified the orthogonal flow rate by measuring the volume of flow through the waste output in a device containing both the pinch channel and a filtration membrane (Fig. 5f). We performed these characterization experiments using diafiltration-on-chip devices with pinch channel lengths l_p of 0 mm, 2.5 mm, 5 mm, and 7.5 mm and a 100 nm PCTE membrane. We found that the orthogonal flow rate $\varphi_{\perp}$ increased with the length of the pinch channel l_p and with motor spin speed f (Fig. 5d). At $f = 500$ RPM, the orthogonal flow rate $\varphi_{\perp}$ was found to be directly proportional to the length of the pinch channel l_p , $\varphi_{\perp} \propto l_p$ (Fig. 5e).

Results

To characterize our chip's capability to purify samples, we quantified the purification of two model systems: (i) Purification of $d = 1 \mu\text{m}$ beads from sulforhodamine B using a 100 nm pore-sized PCTE filter; and (ii) Purification of Jurkat cells ($d \sim 10 \mu\text{m}$) from $d = 1 \mu\text{m}$ beads using a $3 \mu\text{m}$ pore sized PCTE filter. Prior to purification, each device was initialized by flowing phosphate buffered saline (Invitrogen) into the inlet behind the pinch channel. During this initialization step, the outlet on the other side of the pinch channel was left open for air to leave the channel. After initialization, the sample was loaded into the inlet tube while the outlet was maintained open. After sample loading into the inlet tube, the outlet was blocked with a PDMS-filled tube to ensure that any further fluid either travelled across the pinch channel or across the purification membrane (Fig. 2a). All samples were purified for 2 hours with motor speed $f = 105$ RPM and pinch channel length $l_p = 0.2$ mm. This pinch channel length was chosen empirically to balance the tangential flow and orthogonal flow, to optimize for the desired purity and retention. As the pinched channel was lengthened, the retentate was more prone to stick to the membrane filter or be pushed through the filter and thus be lost. However, as the pinch channel was shortened, loss was reduced but purification times were increased. We quantified purification using on-chip fluorescence microscopy and an off-chip plate fluorimeter (Tecan).

For bead vs. dye separation, $1 \mu\text{m}$ yellow fluorescent beads (Life Technologies) and sulforhodamine B (Sigma) were used as received. For cell vs. bead separation, Jurkat cells (ATCC) were harvested and labeled with red CellTracker stain (Thermo Fisher) during their logarithmic growth phase. Purity was calculated as $(I_{w, post} - I_{bg}) / (I_{w, pre} - I_{bg})$ and retention was calculated as $(I_{r, post} - I_{bg}) / (I_{r, pre} - I_{bg})$, where the signal intensity I is differentiated by subscripts w for waste in the sample; r for retentate; $post$ for post-purification; pre for pre-purification; and bg for background.

We first characterized the separation of yellow fluorescent $d = 1 \mu\text{m}$ beads from free sulforhodamine B dye using a 100 nm PCTE membrane. While the amount of free dye within the sample channel decreased exponentially in time, the beads were retained (Fig.

6a). When using microscopy to measure purification, we observed that the concentration of the sulforhodamine B dye began to fall below the noise floor after approximately 1.5 hours (Fig. 6a, **solid line**). We extrapolated the exponential purification beyond the noise floor of the microscope (Fig. 6a, **dotted line**), and confirmed this extrapolation using off-chip fluorescence measurements. After 2 hours, the sample was $99.6 \pm 0.21\%$ pure, while $96.7 \pm 4.5\%$ of the beads could be recovered (Fig. 6b). To validate that this approach could be applied to other biological samples, we purified Jurkat cells ($d \sim 10 \mu\text{m}$) from $1 \mu\text{m}$ yellow beads using a $3 \mu\text{m}$ diameter pore PCTE membrane. After 2 hours, the sample was $97.2 \pm 2.1\%$ pure, and $97.6 \pm 4.4\%$ of the cells were recovered (Fig. 6b).

To demonstrate the ability of the diafiltration-on-chip device to purify multiple samples in parallel, we built a chip that incorporated four fully self-contained dialiltration systems on a $50 \text{ mm} \times 75 \text{ mm}$ glass slide with 100 nm PCTE size-based filters. By arranging these devices in a circular array, we were able to use a single motor to simultaneously drive the magnetic pump in all four devices. In this implementation, two magnets were used to drive four devices so that at any given time, the fluid channel in two of the devices was in the peristaltic compression phase while the other two devices were in the peristaltic recovery phase. Using water dyed with food coloring, we were able to show that this multi-device chip could purify four samples in parallel within 15 minutes (Fig. 7).

Discussion

In this work, we have engineered a diafiltration-on-chip device driven by a cyclic magnetic pump for purification of low-volume, biologically relevant samples. The magnetic pump, fabricated using conventional soft lithography, is able to drive fluid flows of $>50 \text{ mL/hr}$, is easily multiplexed, and requires minimal instrumentation to operate.

Conventional diafiltration is an extremely effective method of purification, but is difficult to implement for small volumes, preventing its use with microfluidic devices as well as in many biological assays¹⁹. A critical component of diafiltration systems is a peristaltic pump^{3,5}; however, current methods of adapting a peristaltic pump to an on-chip cyclic pump for microfluidics are limited. Here, we have developed a self-contained, on-chip peristaltic pump using iron filings and PDMS that is driven by magnets and a motor. We have used this magnetic pump to build a diafiltration-on-chip system that can be used to rapidly purify biologically-relevant samples, including small molecules from beads^{20–22} and beads from cells^{23,24}. However, by replacing the membrane filter, the use of the diafiltration-on-chip device may also be extended to include size-based purification of other samples such as extracellular vesicles²⁵, proteins²⁶, and nanoparticles³.

In contrast to the more commonly used on-chip pneumatically controlled pumps, which rely on pressure generated by gas deformation of a membrane^{15,19,27,28} or gas permeation across a thin membrane²⁹, magnetic pumps have the advantage that they do not require cumbersome external instrumentation such as compressed gas and regulators that make pneumatically driven systems challenging to miniaturize and multiplex. Prior work in using magnets to actuate on-chip pumps include a magnetic pump system that uses an immiscible hydrophobic ferrofluid in the flow channel³⁰ or precisely embedded small magnetic blocks

combined with one-way valves¹⁶ to drive flow. While these systems are self-contained and miniaturizable, using an immiscible ferrofluid requires careful initialization of the device to incorporate the fluid and risks sample contamination with the organic material. Meanwhile, the precise placement of magnetic blocks near valves complicates the fabrication process, making the incorporation of many pumps onto a single chip for multiplexing unfeasible. To address these challenges, our on-chip magnetic pump uses a simple-to-fabricate three dimensional architecture that physically separates the iron filings used to actuate the magnetic pump from the sample to prevent contamination.

One of the main advantages of our approach is its ability to run many devices in parallel on a single chip. To this end, we showed that we could parallelize the diafiltration-on-chip device. Here, we have purified four samples; however, the incorporation of more parallel devices could be achieved by fabricating concentric rings of devices. Alternatively, while the devices in this work are driven by a magnet moving on a rotating track for simplicity, this is not a requirement for the function of the magnetic pump; in fact, preliminary experiments to test the concept were done by using a linear pump channel. Therefore, an array of magnets aligned below an array of devices and moving in a rectangular or circular pattern could be used to drive many more devices (>10) simultaneously without significantly adding to the external instrumentation.

Though we have focused on diafiltration in this paper, we believe that the use of this magnetic pump can be extended to other applications. Adaptation of cyclic biological processes such as PCR to on-chip formats has been limited by challenges in achieving on-chip cyclic flow^{31,32}. Our magnetic pump removes the necessity of using an off-chip external pump, which minimizes working sample volume. Other on-chip flow systems are already in use for single cell analysis³³, mixing³⁴, and protein assays³⁵ at low volumes. A self-contained magnetic pump could be used to further parallelize or minimize the instrumentation of these and similar applications. Future work will also focus on further miniaturizing the magnetic pump, expanding multiplexing, and incorporating additional magnetically actuated components such as valves³⁶. Therefore, we believe that diverse applications beyond diafiltration are possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Microchip diafiltration for small volume purification

(a) In conventional diafiltration, a peristaltic pump repeatedly cycles >10 mL of sample over a size-based membrane under pressure to drive small waste particles into the permeate. The lost volume is replaced drop for drop by clean buffer solution or additional sample. (b) In the on-chip system, $50\ \mu\text{L}$ of sample can be cycled through the device using a microfabricated magnetic pump. Pressure is generated using a long thin pinch channel, encouraging waste to flow across the purification membrane as permeate.

Figure 2. Magnetically-driven fluid flow

(a) As the motor rotates, the magnets move along the bottom of the magnetic pump region of the device. During device initialization, sample is introduced into the inlet (green) with the air outlet (red) left open. After initialization, the outlet is sealed with a PDMS-filled tube.

(b) The cyclic magnetic pump comprises magnetic iron filings that deform a flexible PDMS membrane to drive fluid flow in response to a magnet moving along the bottom of the channel.

(c) Sample filtration is driven by a pressure drop across the size-based filter.

Figure 3. Combined soft lithography and laser micromachining fabrication

(a) The magnetic pump region of the device is fabricated using PDMS on an SU-8/silicon wafer mold. The purification region is laser cut from Mylar plastic. A glass slide serves as a transition between the PDMS and plastic layers to form pressure resistant bonds. **(b)** Iron filings fill the space above a 240 μm flexible PDMS membrane. The iron filings deform the membrane upon exposure to a magnetic field, driving fluid flow in the 135 μm high channel below. **(c)** Backpressure to drive fluid flow across the size-based filter is generated using a high resistance 70 μm wide pinch channel.

Figure 4. Magnetically-driven pump for fluid flow

(a) The tangential flow rate ($\phi_{l,s}$) initially increases linearly with motor speed f , but plateaus for high speeds exceeding the response time of the device. Data shown are for representative devices with channel widths $w = 1$ mm, 1.5 mm, and 2 mm. (b) As the width w of the channel increases, $\phi_{l,s}/f$ increases linearly ($\phi_{l,s}/f = 0.11w - 0.09$, $r^2 = 0.96$). (c) However, as w increases, the plateau point (f_{ss}) of the device decreases as w^{-1} ($f_{ss} = 678w^{-1.1}$, $r^2 = 0.94$). For all measurements, $n = 3$.

Figure 5. Effect of pinch channel on tangential and orthogonal flow rates

(a) As pinch channel length increases, the tangential flow rate $\phi_{\parallel}$ decreases across all motor speeds. (b) Tangential flow rate at 500 RPM is inversely proportional to the length of the pinch channel l_p , consistent with Darcy's law ($\phi_{\parallel}^{-1} = 0.05l_p + 0.008$, $r^2 = 0.98$). (c) Schematic of device used for characterization of $\phi_{\parallel}$. (d) As the length of the pinch channel increases, orthogonal flow rate $\phi_{\perp}$ across the membrane increases. (e) Orthogonal flow rate across the filter at 500 RPM is directly proportional to l_p ($\phi_{\perp} = 0.60l_p + 0.095$, $r^2 = 0.95$). (f) Schematic of device used for characterization of $\phi_{\perp}$.

Figure 6. Purification using diafiltration-on-chip device

(a) Bead purification from free dye can be visualized by fluorescence imaging. While the dye concentration within the device decreases exponentially, the bead concentration is constant. As the dye concentration decreases, the fluorescence measurement begins to be affected by the noise floor of the microscope (solid blue line). However, extrapolating from the linear regime of the purification curve (dashed black line) indicates that purity should be $\sim 99.7\%$ after 2 hours. This is consistent with off-chip measurements ($n=3$) of purity and retention (b).

Figure 7. Parallelized diafiltration-on-chip for simultaneous purification of multiple samples Four samples can be purified on a single chip over 15 minutes. Magnets pass under the magnetic pump region of each device as the motor rotates (**schematic, top**). Each device is initialized with inputs and outputs open to remove air (**1, 2**). After initialization, the initialization output is blocked with a PDMS-filled tube to close the system (**2**). Each device contains a magnetic pump region comprising iron filings above a flexible PDMS membrane (**3**) and a sample purification region (**4**). Here, motor rotation is clockwise and the pinch channel is visible between the inlets and blocked outlets.