

A Valved Responsive Hydrogel Microdispensing Device With Integrated Pressure Source

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Abstract—Stimulus responsive hydrogels provide the actuation pressure required for both valving and dispensing functions in the device presented. The microdispensing device uses an array of responsive hydrogels to deform a flexible membrane above a fluid reservoir chamber. When the microvalve is open, the deformation of the membrane reduces the volume of the reservoir chamber and pushes fluid through the microvalve. When the microvalve is closed, the expanding hydrogel array generates a storable pressure source that will result in fluid dispensing once the microvalve is opened. Experiments determined the pressure generated by this device to be 35 kPa. The device has a stroke volume of 45 μL , and is able to hold the pressure for over 24 h. [1162]

Index Terms—Dispensing device, hydrogel, microfluidic, polydimethylsiloxane (PDMS), pressure source.

I. INTRODUCTION

THE handling and analysis of small volumes of fluid in a controlled manner, not currently available through bench top equipment provides a motivation for the development of microfluidic systems. Specifically, microfluidics offers potential advantages over larger systems when the price of reagent is expensive, the volume infused is very small or when multiple tasks can be integrated into a single device. Some applications of microfluidics research include gene chips [1]–[5], analytical/diagnostic chips [6]–[9], and drug delivery devices [10].

In the above microfluidic devices, the control of fluid movement remains a critical parameter in device design. Optimizing micropumps has been an area of active research for some time and many clever schemes spawn from these efforts. Examples of micropumps generally reside in two main categories: membrane displacement micropumps and nonmechanical micropumps. Membrane displacement micropumps are actuated by a variety of methods including piezoelectric [11], shape memory alloys [12], and magnetic stimulus [13]. Nonmechanical micropumps include the electrohydrodynamic pump [14], ac magnetohydrodynamic micropump [15], osmotic micropumps [16], [17], ferrofluidic micropumps [18], passive micropumps [19], and bubble micropumps [20], [21].

Despite the large array of micropumps currently being developed, no specific micropump design has gained widespread use. Because each design has its own set of advantages and limitations, it is unlikely that a single design will be appropriate over a wide range of applications. Rather the application will

drive the selection of the pump design. This paper presents a device requiring no electronic controls and is able to precisely deliver a given amount of fluid over a specified time. The device is designed to perform these functions as part of a constant rate drug infusion system. The number of protein therapeutics under development continues to rise, while small molecule drugs developed is beginning to wane [22]. These protein therapeutics are not generally suitable for oral or subcutaneous delivery, but rather must be administered via injection. Thus, the development of new cost effective drug delivery technologies is paramount if protein drugs are to become more widely used and personalized medicine is to become a reality [23], [24]. The approach outlined in this paper involves developing a membrane micropump using hydrogel actuators to provide the actuation pressure for subcutaneous infusion. There is a large body of research investigating implantable drug loaded hydrogels to achieve zero-order infusion [25], [26]. As the hydrogel would expand (or degrade) the drug would be released from the hydrogel matrix. However, in this paper, we use a different approach. Specifically, the volume expansion of the hydrogel actuator is coupled to deform a flexible membrane to create pressure for infusion.

Several attributes of hydrogel actuators warrant their use for this application. The direct transduction of chemical energy to mechanical work eliminates the need for the integration of electronic controls and circuitry. Also, since the hydrogel expansion is driven by diffusion of the chemical stimulus into the hydrogel matrix, the expansion rate can be tailored to fit the application.

II. RESPONSIVE HYDROGEL ACTUATORS

Hydrogels consist of a broad range of polymers with high water content. Within this class of materials, exist stimulus-responsive hydrogels able to undergo volumetric changes in response to local environmental changes. Responsive hydrogel materials allow the combination of multiple functions (e.g., sensing and actuation) in a single component. In addition, they make use of efficient energy conversion (e.g., chemical to mechanical) without needing complicated control systems or power supplies. This paper describes the use of an anionic hydrogel coupled to flexible membranes to valve a microdevice and create a storable pressure source.

Kuhn first demonstrated volume transitions in hydrogels and realized their potential by dubbing them “chemical muscles” [27], and more recently hydrogels have been found to control fluid transport in the xylem of plants [28], [29]. For the anionic hydrogel used in this device (crosslinked acrylic acid-2-hydroxymethylmethacrylate copolymer), the mechanism behind the reversible volume transition arises from the reversible ionization

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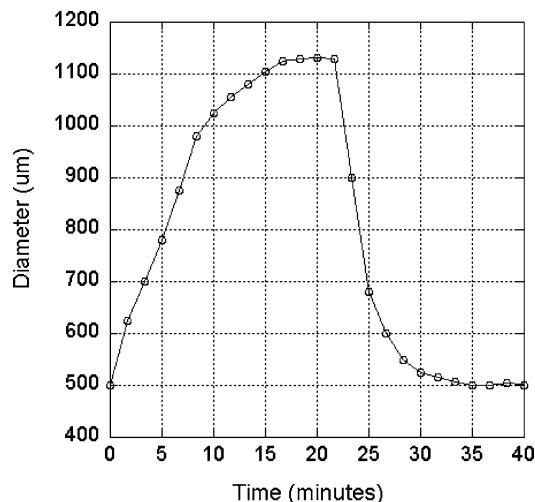


Fig. 1. Plot showing the volume expansion and contraction of a 500 μm diameter hydrogel post. Buffer at pH 12 was introduced at time zero to initiate volume expansion and buffer at pH 2 was introduced at 65 min to induce hydrogel contraction.

of specific side chains within the gel. Under basic conditions, H^+ ions come off the acidic side chains and combine with an OH^- ion to form H_2O . Charge neutrality is maintained by cations entering the gel with OH^- ions. The increased cation concentration yields an osmotic pressure that causes the gel to swell. Ionic gels also swell from the tendency of the polymer network to mix with the solution, but normally, the osmotic force dominates the mixing force. Equilibrium is reached when the elastic restoring force balances the osmotic forces [30], [31]. By altering the chemistry at the end groups, different hydrogels have been developed to respond to a wide variety of stimuli including pH [32], temperature [32], [33], light [34], glucose [35]–[38], antigens [34], electric field [39], and magnetic field [40]. However, the relatively long response times (e.g., hours to days at the millimeter scale) limits their widespread use in macroscale systems. Since diffusion of chemical signals into the gel matrix limits the time response of hydrogel expansion, decreasing the size of the hydrogel will decrease the response time response of the gel [41]. The improved time response facilitates the use of responsive hydrogel actuators in many practical applications including microvalves [41]–[49], pH regulation systems [50], and drug delivery devices [51]. The kinetics of volume expansion for the hydrogel used in this system is shown in Fig. 1.

III. FABRICATION

The fabrication of the microdispensing device involves two distinct stages. First, a polydimethylsiloxane (PDMS) micromolding procedure is employed to create the three-dimensional (3-D) microfluidic network. Next, the hydrogel actuators are assembled inside the microfluidic network via *in situ* photopolymerization.

PDMS is used due to its optical clarity, compliant properties, and most importantly, its ability to pattern a relief structure off a mold master. PDMS is also relatively inexpensive, permeable to oxygen and carbon dioxide, and considered to be biocompatible [52]. The actuators for the valve and pump consist

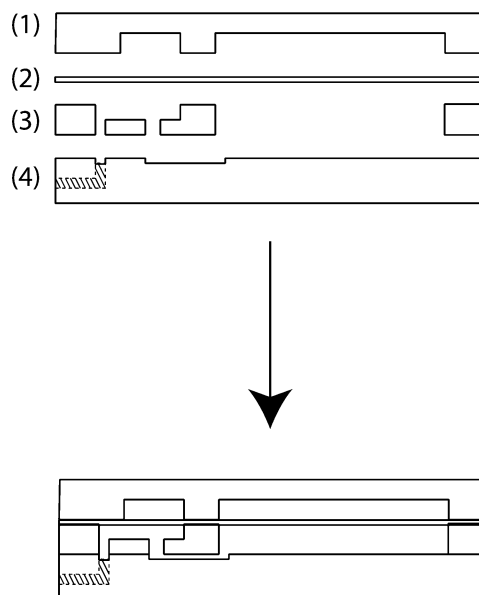


Fig. 2. Schematic cross section of a device depicting the multilayered micromolding procedure used to fabricate devices. All four layers are fabricated separately and permanently bonded sequentially using an oxygen plasma.

of a crosslinked poly[acrylic acid-2-hydroxyethyl methacrylate] (pAA-HEMA) copolymer. This hydrogel expands in high pH and contracts in low pH due to the protonation and deprotonation of the carboxylic acid end groups which causes salt binding, an osmotic pressure gradient, and water influx or outflux.

A. Microfluidic Network Fabrication

The 3-D microfluidic network is created by stacking several planar PDMS sheets onto a thicker PDMS base as shown in Fig. 2 [53]. The device's four layers are all fabricated in a slightly different ways, but all are made from PDMS (Sylgard 184, Dow) mixed in an 11:1 prepolymer to hardener ratio and cured at 85°C for 140 min. The thick base (layer 4) is fabricated by molding PDMS inside a Petri dish on a SU-8 EPON mold master. Layer 3 is fabricated by first pouring 5 mL of PDMS prepolymer mixture onto a bilayer SU-8 EPON mold master. Next, a transparency is placed onto the PDMS prepolymer mixture to facilitate removal from the compression weights. A 3" Pyrex wafer is then placed onto the transparency to ensure a uniform pressure distribution over the mold master. Finally, three pounds of compression weights are placed onto the Pyrex wafer. The 30 μm flexible membrane (layer 2) is fabricated by spin coating PDMS onto a 3" silicon wafer at 3500 rpm for 20 s. The top layer (layer 1) is fabricated by pouring 10 mL of PDMS onto a mold master inside a Petri dish and allowed to cover the surface of the wafer completely. A 10-mL drop of PDMS will spread to be 2 mm thick inside a 3" Petri dish. The top layer needs to be thick enough to provide a rigid support for the hydrogel actuators to push against, but thin enough to allow polymerization of the hydrogels through the top layer. Experiments reveal a 2 mm height is rigid enough to resist deformation by the hydrogels but thin enough to minimize diffraction of UV light during photopolymerization of the hydrogel actuators. After the four layers are fabricated, they are sequentially stacked together after

exposure to oxygen plasma, which activates the surfaces and results in a permanent bond when two active surfaces are brought together. Connections are attached to the device through holes cored out of the thick base layer (layer 4) with a 12-gauge syringe needle prior to bonding.

B. Hydrogel Actuator Fabrication

Once the microfluidic network is fabricated the hydrogel actuators can be polymerized *in situ*. The hydrogels are introduced into the system in two steps as shown in Fig. 3. First, the hydrogel valve is photopolymerized followed by photopolymerization of the actuation array. Both the hydrogel valve and actuation array consist of hydrogels fabricated from a liquid prepolymer containing 2-hydroxyethyl methacrylate and acrylic acid (in a 4:1 weight ratio), ethylene glycol dimethacrylate (1 wt%), and Irgacure 651 (3 wt%). The ethylene glycol dimethacrylate is a crosslinking agent and the Irgacure 651 is a photoinitiator.

The hydrogel actuator for the valve is introduced into the system by first injecting the liquid prepolymer into the channel and allowing it to rest for 5 min to ensure no fluid flow during photopolymerization. Next, a photomask with a 300- μm circular hole is placed over the device with the circular hole positioned above the center of the hydrogel valve. The time for polymerization is 120 s under 15 mW of 365 nm UV light. Once the hydrogel is polymerized, the remaining prepolymer solution is flushed out with methanol. After the hydrogel valve is fabricated, a simple flow test is performed to ensure proper valving performance. The flow test consists of monitoring the flow through the reservoir network. The inlet to the reservoir is connected to a pressure head and the outlet is connected to a collection tube. When the valve is open, water flows unrestricted through the reservoir network. When the valve's hydrogel actuator is expanded with a high pH phosphate buffer, the outlet to the reservoir is occluded and the flow stops. It is important to verify the valve's performance if an unexpected variables prevents the valve from operating properly including membrane collapse, tears in the membrane, or particulates blocking the membrane from completely deforming.

Once the valve is completed the hydrogel actuation array is fabricated *in situ*. The conditions for polymerization are similar to the hydrogel valve. The only exception is the photomask now contains an array of 2000, 400- μm circles spaced evenly 500 μm apart. The mask is aligned over the device with alignment marks as aids. One of the advantages of using soft hydrogels as actuators is they do not require precise alignment. If the actuation array is slightly misaligned, the device will still function properly since the hydrogels are not anchored to the flexible membrane and are free to move within the support structures they are fabricated within. Once the hydrogel array is polymerized the remaining prepolymer is flushed away with methanol. Careful consideration is paid to minimize bubble introduction into the hydrogel actuation array. Bubbles would create voids of prepolymer which would therefore create voids of actuators after photopolymerization of the actuation array. The most common scenario of accidental bubble introduction occurs when the buffers are changed. To minimize bubble introduction, the buffers were switched out as quickly as possible

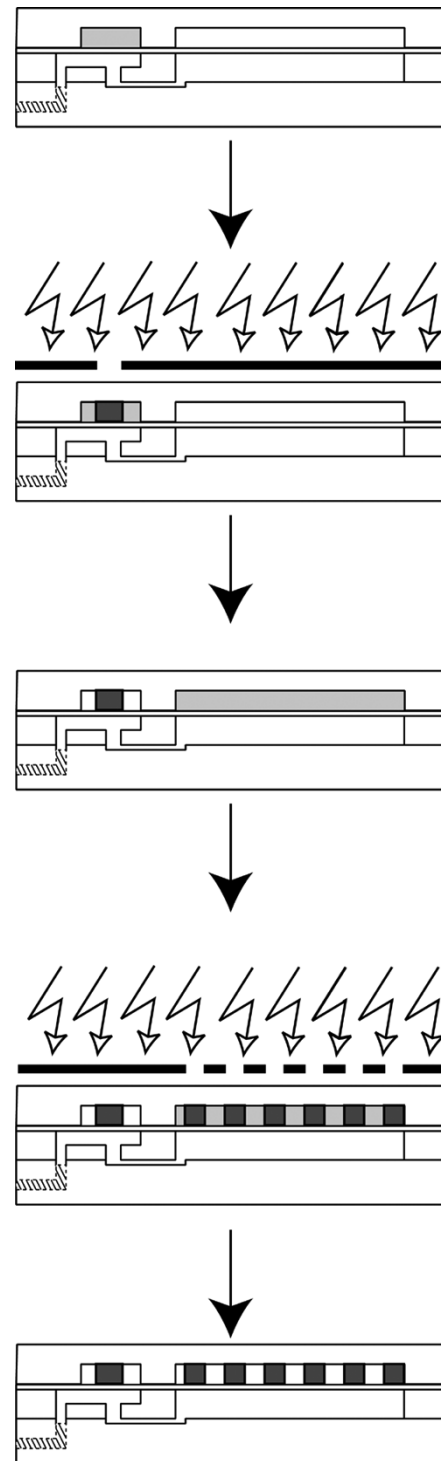


Fig. 3. Schematic cross section of the *in situ* photopolymerization procedure for making both the valve actuator and actuation array. First, the valve chamber is filled with liquid prepolymer and exposed to UV light. Next, the actuation array is filled with liquid prepolymer and exposed to UV light.

and this would ensure that no air was injected into the system between buffer switching.

IV. RESULTS AND DISCUSSION

The device as shown in Fig. 4 can be used as both a dispensing device and a storable pressure source. Whether it acts as a pressure source or a dispensing device depends on the state of the

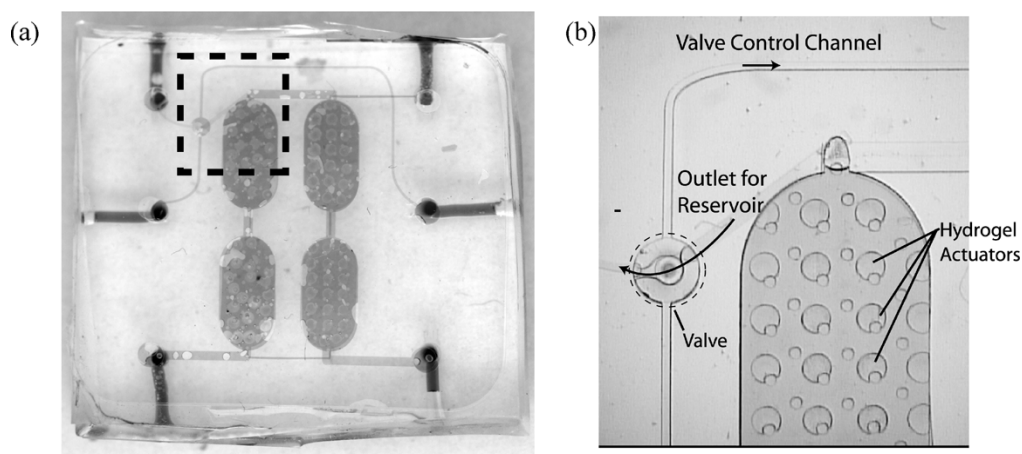


Fig. 4. Top view image of the device with various layers highlighted for clarity (a) all three layers are highlighted to show the complete microfluidic network. (b) The actuation array and valve channel are highlighted. (c) The reservoir channel is highlighted. Notice how the outlet of the reservoir channel passes through the valve.

outlet valve. The actuation chamber for both the hydrogel array and hydrogel valve are separated from the reservoir and outlet of the device by a fluid impermeable flexible membrane. Therefore, the chemistry of the fluid being dispensed will not be affected by the chemistry of the hydrogel actuators or the buffers used to initiate volume expansion in the hydrogels. Also, the fluidic channels of the valve and actuation array are separated so each can be triggered independently from one another.

The device works as shown in Fig. 5. An actuation chamber consists of an array of responsive hydrogels positioned above a 30- μm -thick PDMS membrane with PDMS isolation structures localizing individual hydrogel actuators in a given region. Below the actuation chamber is the reservoir chamber which is similar to the actuation layer minus the hydrogels, membrane, and isolation structures. One outlet of the reservoir chamber passes through a gate valve with a hydrogel actuator fluidically isolated from both the reservoir and actuation chamber. The valve consists of a 600- μm diameter hydrogel post positioned above a 30- μm -thick PDMS membrane in a 1500 μm diameter circular chamber. Below the membrane is another 1500 μm diameter circular chamber with a 200- μm -diameter circular orifice in the center. When the hydrogel post in the valve chamber expands, the membrane is deflected down and occludes the orifice to prevent flow. The flexible membrane and hydrogel actuator of the valve are compliant enough to seal around minor imperfections in the valve, but stiff enough to gate a pressure up to 1.5 MPa, as found from previous experiments [47]. The valve effectively gates the reservoir chamber because the outlet of the reservoir chamber passes through the circular orifice.

If the valve is open before the actuation array is triggered, the fluid reservoir will empty at an average flow rate of 2.0 $\mu\text{L}/\text{min}$ as shown in Fig. 6(a). The hydrogel does not expand linearly, however, a small window of the hydrogel expansion approximates linear expansion and the device can be tailored to operate within this window. However, if the outlet valve is closed prior to actuation array expansion, the hydrogels will expand, but the fluid in the reservoir will not empty due to the outlet valve gating the flow. Once the outlet valve is opened, the fluid reservoir empties at an average flowrate of 540 $\mu\text{L}/\text{min}$ as shown in Fig. 6(b).

The pressure generated from the hydrogels takes roughly 60 min to fully develop as shown in Fig. 7, which shows the pressure being held for 120 min followed by opening the valve to release the pressure in steps. The pressure profile arises from a combination of the viscoelastic response of the elastomeric flexible membrane and the kinetics of hydrogel expansion. Resistance to deformation in elastomers under tension is initially low, but as the elastomer extends, the resistance to deformation increases. Also, the kinetics of hydrogel expansion involve a fast initial swelling, followed by a tapering off of expansion as described previously [30].

Further experiments determined the pressure source to remain stable for more than 24 h with no leakage after the maximum pressure was achieved. The time required for maximum pressure buildup is a function of hydrogel diameter which can be altered to tailor fit the desired application. One application for the device might require a slow and steady hydrogel expansion to achieve a slow and steady infusion rate (e.g., larger gel structures), while another application might require a quick bolus to be infused (e.g., smaller gel structures).

The volume of the reservoir chamber is 50 μL and the stroke volume of the device is 45 μL corresponding to a 10% dead volume in the device. The dead volume is due to the flexible membrane not completely deforming near the walls of the reservoir chamber. A reduction in dead volume could be achieved via modifications to the chamber diameter. The maximum pressure the actuation array can develop is 35 kPa and is well within the range of pressure the hydrogel valve can gate (1.5 MPa). The maximum pressure is measured by connecting one outlet of the reservoir chamber to a pressure transducer (162PC01D, OMEGA) and the other outlet occluded by the hydrogel valve. The high pH phosphate buffer that swells the hydrogel array is then injected into the actuation chamber using a 10-kPa pressure head. After the high pH buffer fills the actuation chambers, it is disconnected from the system and both outlets of the actuation chamber are left open to atmosphere. This ensures the data collected by the pressure transducer are the pressures being built up by the hydrogel array and not an artifact of the system.

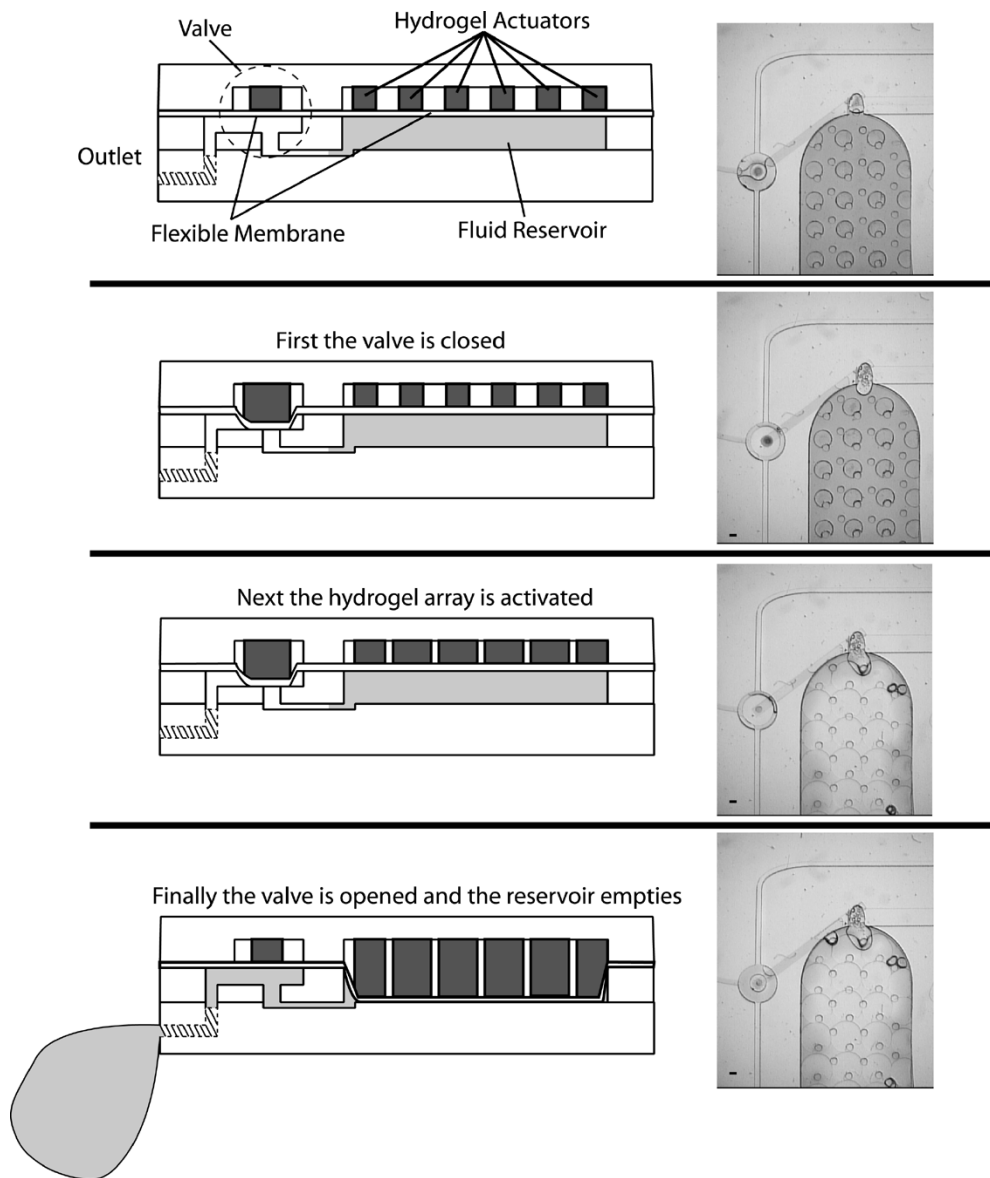


Fig. 5. Schematic cross section of the device (left) and top view images (right) of the device under the various stages of operation. (a) Depicts the device before the fluid is dispensed, the important features of the device are identified. (b) First, the hydrogel valve is expanded to seal off the outlet of the reservoir. (c) Next, the hydrogel array is expanded and a pressure is generated. (d) Finally, the pressure is released when the valve is opened.

The flow rate was measured by monitoring the amount of fluid displaced through a 0.5-mm diameter collection tube at the outlet of the reservoir chamber with data collected every minute. The flow rate of the device when the valve is open prior to actuation array expansion is shown in Fig. 6. The stroke volume was determined by monitoring the total amount of fluid displaced through the collection tube during flow rate experiments.

As shown by Fig. 4 the current device design contains four actuation and reservoir chambers. The stroke volume of the device could be increased by increasing the number of actuation and reservoir chambers per device. Four segmented chambers are used instead of one large chamber to prevent the flexible membrane from collapsing under its own weight. The shape of the chambers was optimized to maximize chamber area while maintaining a stable flexible membrane through a device iteration process. The height of the reservoir chamber is $100\ \mu\text{m}$ and was chosen to maximize membrane deflection and mini-

mize dead volume in the reservoir chamber. Simply increasing the height of the reservoir chamber would not increase the stroke volume of the device since the hydrogel actuators are fully expanded $100\ \mu\text{m}$ into the reservoir chamber under the current device design. However, by increasing the height of the actuation chamber, the maximum pressure could be increased. Another way to increase the maximum pressure the device generates is by decreasing the force needed to deform the flexible membrane. This could be accomplished by either increasing the compliance of the flexible membrane or by decreasing the thickness of the membrane.

There are several approaches to gel array activation. As the device stands now, a bolus of high pH phosphate buffer is manually injected into the system. Therefore, the device requires fluid to be pumped into the system for the device to pump fluid out. However, once the bolus of high pH buffer is injected into the system, the device can deliver a constant flow rate for an

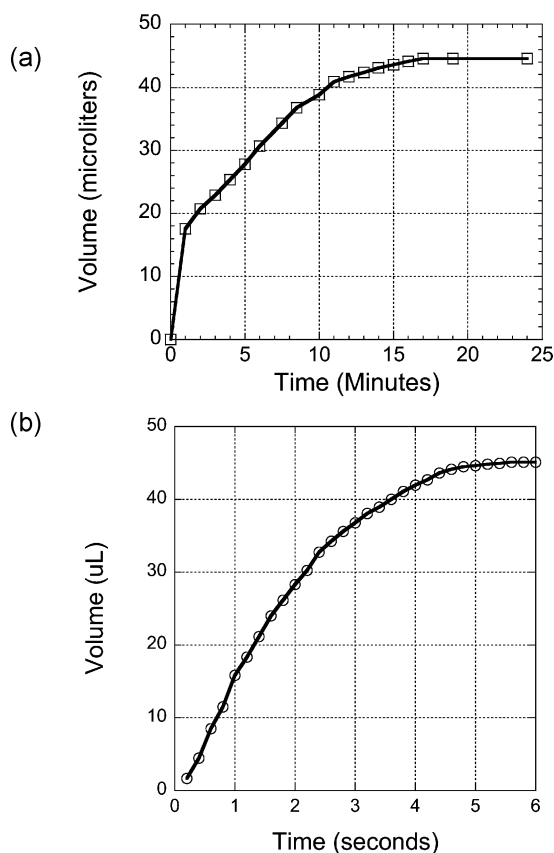


Fig. 6. (a) Plot of the infusion rate of the device with the valve opened prior to actuation array expansion. (b) Plot of the infusion rate of the device with the valve closed prior to actuation array expansion.

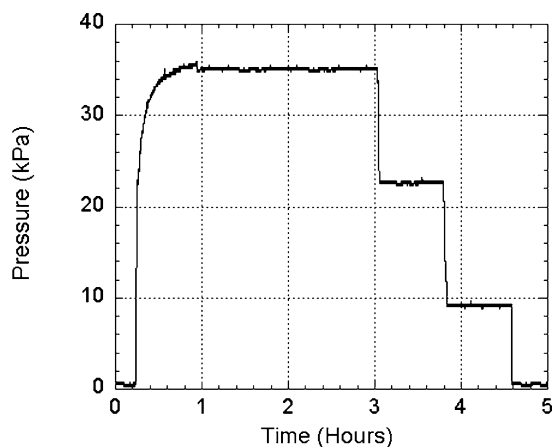


Fig. 7. Plot of the pressure the device builds up when one outlet of the device is sealed with the valve and the other is connected to a pressure transducer. The device builds up a maximum pressure of 35 kPa and can hold this for an extended period of time. The pressure was released in steps by contracting the valve to release pressure, then expanding the hydrogel in the valve to hold the pressure again to demonstrate the functionality of the device.

extended period of time without the use of external power or controls. Once the fluid reservoir is emptied, the device can be reused if the reservoir is refilled and low pH buffer is injected into the actuation array to contract the hydrogel actuation array. Alternatively, the actuation array could be triggered electronically, thereby allowing for simpler reversal of gel size and

converting the dispensing device into a micropump. The use of electric stimulus to actuate hydrogels is not new [39], and there has been recent work applying these principles to hydrogels at the microscale [54]. In addition, other stimuli such as light or thermal energy could be used to activate the gel array.

One application for the valved dispensing device is drug delivery. The experiments described in this paper lay the foundation for the integration of the device into a closed-loop infusion system (e.g. insulin delivery). Such a closed-loop system would require increasing the reservoir volume to accommodate a day's supply of insulin, modifying the outlet valve to respond to interstitial glucose concentration, incorporating a delivery needle, and incorporating a method to transport interstitial fluid into the outlet valve [55]. Substituting a glucose sensitive hydrogel for the pH sensitive hydrogel will allow the device to regulate the outlet infusion rate based upon interstitial glucose concentration. The chemistry for developing such a hydrogel is not trivial, but is currently being investigated. It is also uncertain if 35 kPa is enough pressure to drive infusion into the subcutaneous tissue. Further experiments will investigate this specific parameter, along with testing the various modifications needed to modify the system into the closed-loop insulin infusion system.

V. CONCLUSION

A device has been developed that can act as both a microdispensing device and a storable pressure source depending on the desired end application. The device incorporates a responsive hydrogel valve fluidically isolated from the rest of the device and controlled independently. An array of responsive hydrogel actuators swell to provide the driving pressure to power the dispensing device and pressure source. Responsive hydrogels have the unique ability to directly transduce a chemical signal into mechanical work and therefore are advantageous for applications where bulky power supplies and controls would impede device performance, such as biomedical applications. Future work will focus on developing the valved microdispensing device into a closed-loop insulin infusion system.

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REFERENCES

- [1] A. T. Wooley and R. A. Mathies, "Ultra-high-speed DNA fragment separations using microfabricated capillary array electrophoresis chips," in *Proc. Nat. Acad. Sci.*, vol. 1994, 1994, pp. 11 348–11 352.
- [2] M. Burns, C. Mastrangelo, T. Sammarco, F. Man, J. Webster, B. Johnson, B. Foerster, D. Jones, Y. Fields, A. Kaiser, and D. Burke, "Microfabricated structures for integrated dna analysis," in *Proc. Nat. Acad. Sci.*, vol. 93, 1996, pp. 5556–5561.
- [3] M. U. Kopp, A. J. deMello, and A. Manz, "Chemical amplification: continuous-flow PCR on a chip," *Science*, vol. 280, pp. 1046–1049, 1998.
- [4] Z. Ronai, C. Barta, M. Sasvari-Szekely, and A. Guttman, "DNA analysis on electrophoretic microchips: effect of operational variables," *Electrophoresis*, vol. 22, pp. 294–299, 2001.
- [5] J. Khandurina, T. E. McKnight, S. C. Jacobson, L. C. Waters, R. S. Foote, and J. M. Ramsey, "Integrated system for rapid PCR-based DNA analysis in microfluidic devices," *Anal. Chem.*, vol. 72, pp. 2995–3000, 2000.

- [6] A. Y. Fu, C. Spence, A. Scherer, F. H. Arnold, and S. R. Quake, "A microfabricated fluorescence-activated cell sorter," *Nature Biotechnol.*, vol. 17, pp. 1109–1111, 1999.
- [7] J. Kruger, K. Singh, A. O'Neil, C. Jackson, A. Morrison, and P. O'Brian, "Development of a microfluidic device for fluorescence activated cell sorting," *J. Microelectromech. Syst.*, vol. 12, pp. 486–494, 2002.
- [8] S. Gawad, L. Schild, and P. Renaud, "Micromachined impedance spectroscopy flow cytometer for cell analysis and particle sizing," *Lab on a Chip*, vol. 1, pp. 76–82, 2001.
- [9] L. Nihlen and H. Capps, "Nanolaser microfluidic biochip for realtime tumor pathology," *Biomed. Microdev.*, vol. 2, pp. 111–122, 1999.
- [10] J. T. Santini, A. C. Richards, R. Scheidt, M. J. Cima, and R. Langer, "Microchips as controlled drug-delivery devices," *Angewandte Chemie*, vol. 39, pp. 2396–2407, 2000.
- [11] E. Stemme and G. Stemme, "A valveless diffuser/nozzle based fluid pump," *Sens. Actuators A*, vol. 39, pp. 159–167, 1993.
- [12] W. L. Benard, H. Kahn, A. H. Heuer, and M. A. Huff, "Thin-film shape-memory alloy actuated micropumps," *J. Microelectromech. Syst.*, vol. 7, pp. 245–251, 1998.
- [13] M. Khoo and C. Liu, "Micro magnetic silicone elastomer membrane actuator," *Sens. Actuators A*, vol. 89, pp. 259–266, 2001.
- [14] S. F. Bart, M. Mehregany, and J. H. Lang, "Microfabricated electrohydrodynamic pumps," *Sens. Actuators A*, vol. 21, pp. 193–197, 1990.
- [15] A. Lemoff and A. Lee, "An AC magnetohydrodynamic micropump," *Sens. Actuators B*, vol. 63, pp. 178–185, 2000.
- [16] Y. C. Su, L. W. Lin, and A. P. Pisano, "A water-powered osmotic microactuator," *J. Microelectromech. Syst.*, vol. 11, pp. 736–742, 2002.
- [17] C. H. Chen and J. G. Santiago, "A planar electroosmotic micropump," *J. Microelectromech. Syst.*, vol. 11, pp. 672–683, 2002.
- [18] A. Hatch, A. E. Kamholz, G. Holman, P. Yager, and K. F. Bohringer, "A ferrofluidic magnetic micropump," *J. Microelectromech. Syst.*, vol. 10, pp. 215–221, 2001.
- [19] G. Walker and D. Beebe, "A passive pumping method for microfluidic devices," *Lab on a Chip*, vol. 1, pp. 131–134, 2002.
- [20] J. H. Tsai and L. Lin, "A thermal-bubble-actuated micronozzle-diffuser pump," *J. Microelectromech. Syst.*, vol. 11, pp. 665–671, 2002.
- [21] X. Geng, H. Yuan, H. N. Oguz, and A. Prosperetti, "Bubble-based micropump for electrically conducting liquids," *J. Microelectromech. Syst.*, vol. 11, pp. 270–276, 2001.
- [22] J. M. Reichert, "Trends in development and approval times for new therapeutics in the United States," *Nature Rev. Drug Disc.*, vol. 2, pp. 695–702, 2003.
- [23] A. Pandey and M. Mann, "Proteomics to study genes and genomes," *Nature*, vol. 405, pp. 837–846, 2000.
- [24] L. M. Gelbert and R. E. Gregg, "Will genetics really revolutionize the drug discovery process?," *Current Opinion in Biotechnol.*, vol. 8, pp. 669–674, 1997.
- [25] S. Sershen and J. West, "Implantable, polymeric systems for modulated drug delivery," *Adv. Drug Deliv. Rev.*, vol. 54, pp. 1225–1235, 2002.
- [26] G. P. Misra and R. A. Siegel, "New mode of drug delivery: long term autonomous rhythmic hormone release across a hydrogel membrane," *J. Controlled Release*, vol. 81, pp. 1–6, 2002.
- [27] W. Kuhn, B. Hargitay, A. Katchalsky, and H. Eisenberg, "Reversible dilation and contraction by changing the state of ionization of high-polymer acid networks," *Nature*, vol. 165, pp. 514–516, 1950.
- [28] M. A. Zwieniecki, P. J. Melcher, and N. M. Holbrook, "Hydrogel controls of xylem hydraulic resistance in plants," *Science*, vol. 291, pp. 1059–1062, 2001.
- [29] —, "Hydraulic properties of individual xylem vessels of *Fraxinus americana*," *J. Experiment. Botany*, vol. 52, pp. 257–264, 2001.
- [30] S. K. De, N. R. Aluru, B. Johnson, W. C. Crone, D. J. Beebe, and J. Moore, "Equilibrium swelling and kinetics of pH-responsive hydrogels: models, experiments, and simulations," *J. Microelectromech. Syst.*, vol. 11, pp. 544–555, 2002.
- [31] H. J. van der Linden, S. Herber, W. Olthuis, and P. Bergveld, "Stimulus-sensitive hydrogels and their applications in chemical (micro) analysis," *Analyst*, vol. 128, pp. 325–331, 2003.
- [32] T. Tanaka, D. Fillmore, S. Sun, I. Nishio, G. Swislow, and A. Shah, "Phase transitions in ionic gels," *Phys. Rev. Lett.*, vol. 45, pp. 1636–1639, 1980.
- [33] J. Hoffman, M. Plotner, D. Kuckling, and W. Fischer, "Photopatterning of thermally sensitive hydrogels useful for microactuators," *Sens. Actuators B*, vol. 77, pp. 139–144, 1999.
- [34] A. Suzuki and T. Tanaka, "Phase transition in polymer gels induced by visible light," *Nature*, vol. 346, pp. 345–347, 1990.
- [35] K. Ishihara, M. Kobayashi, N. Ishimura, and I. Shinohara, "Glucose induced permeation control of insulin through a complex membrane consisting of immobilized glucose oxidase," *Polymer J.*, vol. 16, pp. 625–631, 1984.
- [36] D. Shiino, Y. Murata, K. Katakoka, Y. Koyama, M. Yokoyama, T. Okano, and Y. Sakurai, "Preparation and characterization of a glucose-responsive insulin-releasing polymer device," *Biomaterials*, vol. 15, pp. 121–128, 1994.
- [37] T. Miyata, A. Jikihara, and K. Nakamae, "Preparation of poly(2-glucosyloxyethyl methacrylate)-concanavalin A complex hydrogel and its glucose sensitivity," *Macromolec. Chem. Phys.*, vol. 197, pp. 1135–1146, 1996.
- [38] K. Kataoka, H. Miyazaki, M. Bunya, T. Okano, and Y. Sakurai, "Totally synthetic polymer gels responding to external glucose concentration: their preparation and application to on-off regulation of insulin release," *J. Amer. Chem. Soc.*, vol. 120, pp. 12 694–12 695, 1998.
- [39] T. Tanaka, S. Sun, I. Nishio, and S. Ueno-Nishio, "Collapse of gels in an electric field," *Science*, vol. 218, pp. 467–469, 1982.
- [40] N. Kato, F. Takahashi, and S. Yamanobe, "Property of magneto-driven poly(N-isopropylacrylamide) gel containing iron oxide in NaCl solution as a chemomechanical device," *Mater. Sci. Eng. C: Biomimetic Mater., Sens. Syst.*, vol. C5, pp. 141–147, 1997.
- [41] D. Beebe, J. Moore, J. Bauer, Q. Yu, R. Liu, C. Devadoss, and B.-H. Jo, "Functional hydrogel structures for autonomous flow control inside microfluidic channels," *Nature*, vol. 404, pp. 588–590, 2000.
- [42] M. E. Harmon, M. Tang, and C. W. Frank, "A microfluidic actuator based on thermoresponsive hydrogels," *Polymer*, vol. 44, pp. 4547–4556, 2003.
- [43] C. Yu, S. Mutlu, P. Selvaganapathy, C. H. Mastrangelo, F. Svec, and J. M. J. Frechet, "Flow control valves for analytical microfluidic chips without mechanical parts based on thermally responsive monolithic polymers," *Anal. Chem.*, vol. 75, pp. 1958–1961, 2003.
- [44] A. Baldi, Y. Gu, P. E. Loftness, R. A. Siegel, and B. Ziaie, "A hydrogel-actuated environmentally sensitive microvalve for active flow control," *J. Microelectromech. Syst.*, vol. 12, pp. 613–621, 2003.
- [45] L. M. Low, S. Seetharaman, K. Q. He, and M. J. Madou, "Microactuators toward microwaves for responsive controlled drug delivery," *Sens. Actuators B-Chem.*, vol. 67, pp. 149–160, 2000.
- [46] A. Richter, D. Kuckling, S. Howitz, T. Gehring, and K. F. Arndt, "Electronically controllable microvalves based on smart hydrogels: magnitudes and potential applications," *J. Microelectromech. Syst.*, vol. 12, pp. 748–753, 2003.
- [47] R. H. Liu, Q. Yu, and D. Beebe, "Fabrication and characterization of hydrogel-based microvalves," *J. Microelectromech. Syst.*, vol. 11, pp. 45–53, 2001.
- [48] Q. Yu, J. M. Bauer, J. S. Moore, and D. J. Beebe, "Responsive biomimetic hydrogel valve for microfluidics," *Appl. Phys. Lett.*, vol. 78, pp. 2589–2591, 2001.
- [49] Y. Gu, A. Baldi, B. Ziaie, and R. A. Siegel, "Modulation of drug delivery rate by hydrogel incorporating MEMS devices," in *2nd Int. IEEE-EMBS Special Topic Conf. Microtechnologies in Medicine and Biology*, Madison, WI, 2002.
- [50] D. T. Eddington, R. H. Liu, D. J. Beebe, and J. S. Moore, "An organic self-regulating microfluidic system," *Lab on a Chip*, vol. 1, pp. 96–99, 2001.
- [51] X. Cao, S. Lai, and L. J. Lee, "Design of a self-regulated drug delivery device," *Biomed. Microdev.*, vol. 3, pp. 109–118, 2001.
- [52] J. McDonald, D. Duffy, J. Anderson, D. Chiu, H. Wu, O. Schueller, and G. Whitesides, "Fabrication of microfluidic systems in poly(dimethylsiloxane)," *Electrophoresis*, vol. 21, pp. 27–40, 2000.
- [53] B. H. Jo, L. Vanderberghe, K. Motsegood, and D. J. Beebe, "Three-dimensional micro-channel fabrication in polydimethylsiloxane (PDMS) elastomer," *J. Microelectromech. Syst.*, vol. 9, pp. 76–81, 2000.
- [54] M. J. Bassetti and D. J. Beebe, "Demonstration of hydrogel volume control using pulse width modulation," in *Micro Total Analysis Syst. 2002*, Nara, Japan, 2002.
- [55] H. Suzuki, T. Tokuda, T. Miyagishi, H. Yoshida, and N. Honda, "A disposable on-line microsystem for continuous sampling and monitoring of glucose," *Sens. Actuators B*, vol. 97, pp. 90–97, 2004.



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