A PIEZOELECTRIC VALVE MANIFOLD WITH EMBEDDED SENSORS FOR MULTI-DRUG DELIVERY PROTOCOLS

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ABSTRACT

This paper describes a two-valve manifold for use in a dual chamber drug delivery device for pain therapy. The scalable manifold is hybrid assembled with piezoelectric stacks to actuate Si valve seats against a glass substrate. The substrate has two inlets and one outlet; a piezoresistive pressure sensor is embedded in the Si near each of these three ports. The sensors, which permit closed loop control and error monitoring of the flow rate, have a typical sensitivity of 647 ppm/kPa. The 1x1.5x3 cm^3 manifold provides modulation and mixing capabilities. In laboratory tests, flow of isopropyl alcohol was regulated from 1.77 mL/hr to 0.028 mL/hr. The manifold design achieves the desired dynamic range for intrathecal drug delivery and can also be used for gas modulation in other contexts.

KEYWORDS

Microvalve, drug delivery, liquid flow, manifold, piezoelectric.

INTRODUCTION

Chronic pain is a neuropathological condition that afflicts an estimated 19% of the population [1]. There are several echelons of treatment depending on the severity of the chronic pain [2-3]. The most difficult cases are often treated with an implantable intrathecal drug pump that delivers medication directly into the cerebrospinal fluid [4-6].

Implanted pump protocols that involve the modulation of multiple drugs are of emerging interest in anesthesiology, but traditional devices are unable to independently regulate delivery from multiple reservoirs [7-9]. In order to provide drug combinations, medications are currently mixed before being introduced into the pain pump. However, this requires the usage of a fixed ratio of drugs and does not permit the drugs to be multiplexed. These limitations can be addressed by using a drug delivery device that can independently regulate delivery from multiple reservoirs [10-12].

We previously reported a drug delivery device architecture that utilized isolated valves to independently regulate flow from multiple reservoirs [13]. There has been extensive work on microvalves and pumps [14-17]. The work described in this paper addresses specific functionality for an implantable intrathecal delivery device with multi-drug protocols.

DEVICE STRUCTURE

The manifold includes a micromachined silicon diaphragm with elevated valve seats that are bonded to a glass plate with perforations. The perforations are two inlets and a common outlet that are used to interface with other parts of the drug delivery system (Fig. 1). A piezoelectric stack actuator modulates the spacing between each valve seat and the glass to provide proportional flow control. Since piezoelectric actuation provides modest throw, the modulation is achieved by using an elongated valve seat that makes the flow channel extremely wide. A High Flow design has a starburst pattern with a 10 µm wide valve seat that is 315 mm long, where as a Normal Flow design has a 30 µm wide valve seat with a total length of 81 mm.

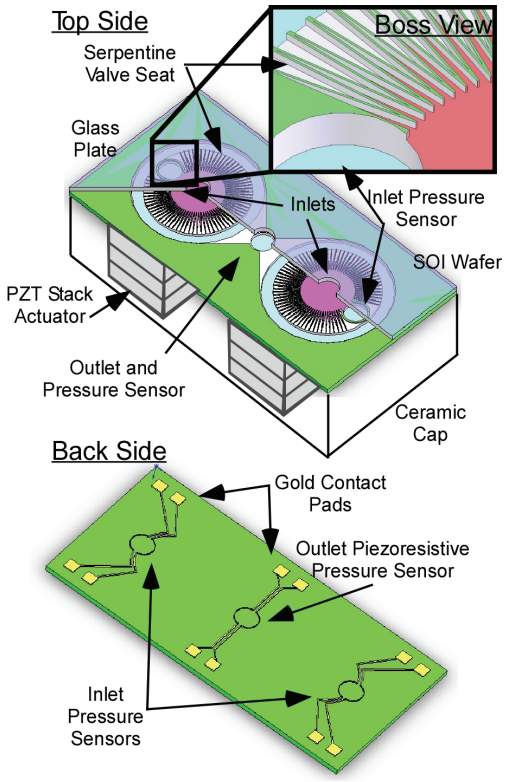

Fig. 1: On the top side of the Si wafer, which is the substrate side of an SOI wafer, there are two membranes with serpentine valve seats. Each one is located on a central boss that also houses a pressure sensor and presses against a glass plate that has two inlets and an outlet. The back side, which is the epitaxial side of the SOI, has boron doping and gold traces for the pressure sensors

The valves are designed to be partially open in the absence of applied voltage in order to prevent under-dosing and save power.

The pressure sensors are made by implanting boron into the epitaxial layer of an SOI wafer to define the piezoresistors (20 squares in length) in a Wheatstone bridge on the back side of a 20 µm thick membrane that is 2500 µm in diameter. The membranes are open to the flow channel at either the inlet or outlet of the device. Conductive paths from the pressure sensors located on the valve boss are arranged as radial traces across the actuation membrane to reduce the impact of actuation on sensor errors.

The manifolds are fabricated using a modification of the SOI process previously described in [3]. The process uses a glass wafer and an SOI wafer with an epitaxial layer of 20 µm for a controlled membrane height and reliable properties for piezoresistors (Fig. 2). Boron is implanted into the device layer and Ti/Pt is deposited to make ohmic contact to the piezoresistors. Gold is then deposited to form electrical connections from the resistors to contact pads at the perimeter of the device. Then, the bulk side of the SOI wafer is processed with two DRIE steps to define the valve and sensor membranes and the valve seat. A glass wafer is processed with HF to create perforations for the inlet and outlet and the two wafers are anodically bonded. The bonded wafer is diced to create individual manifolds.

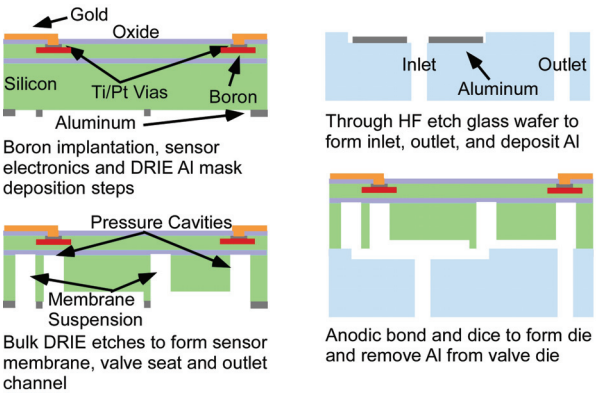

Fig. 2: The process utilizes an SOI wafer and a glass wafer. The back of the SOI wafer is processed for the pressure sensors, and two DRIE etches are used to define the valve seats and pressure sensor manifolds. Perforations in a glass wafer are made to act as inlets and the common outlet.

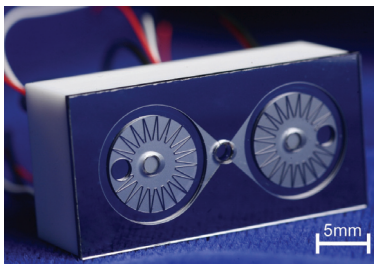

Fig. 3: A photograph of a valve manifold assembled with PZT actuators in a ceramic cap. Connections exit

The fabricated manifolds are assembled with PZT actuators in ceramic housings (Fig. 3). Actuation of the PZT during assembly at this point determines the unactuated state of each valve – open, closed, or partially open [14]. These are connected to ceramic headers for system integration; the total package volume is 4.5 cm^3.

EXPERIMENTAL RESULTS

Test Set-Up

The manifold was tested for both gas and liquid modulation (Fig. 4). Gas tests were conducted by routing pressurized nitrogen to each inlet of the manifold. Inlet pressure was monitored by an absolute pressure gauge. The output was connected to a volumetric flow meter calibrated for nitrogen. Liquid experiments utilized a gas/liquid interface to pressurize isopropyl alcohol (IPA) with nitrogen gas. The pressurized IPA was selectively introduced into the inlet ports of the manifold, and the output was driven through a 1 m long delivery catheter to mimic intrathecal applications. Air bubbles were introduced into the liquid flow, and the delivery rate was determined by monitoring the bubble travel rate with optical techniques. Pressure sensors were calibrated using the gas test technique. Instead of maintaining the outlet at atmosphere, the outlet was sealed to allow for pressure buildup from the inlet.

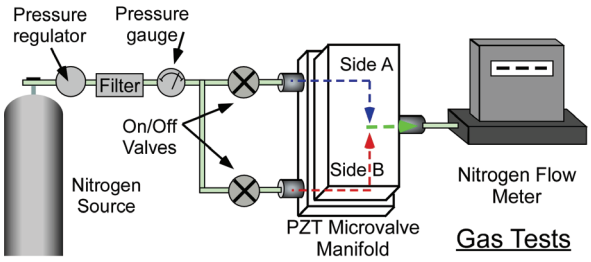

Fig. 4a: Gas tests were conducted by routing nitrogen to both inlets of the manifold. The regulated flow rates were monitored by the flow meter at the output.

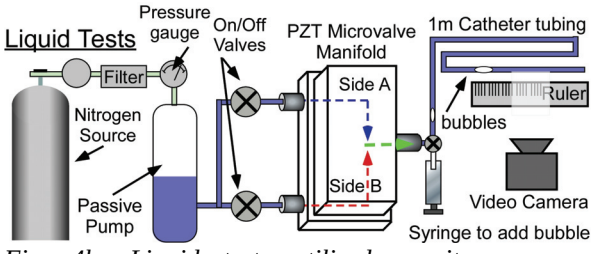

Fig. 4b: Liquid tests utilized a nitrogen gas pressurized liquid that was independently routed to each side of the manifold. A video camera recorded travel of bubbles through a 1 m long catheter tube to detect flow rate.

Results

Gas Modulation: Within the preferred actuation

voltage range of 0 - 80 V, at 14 kPa, Normal Flow valves modulated from 100% to 64% of the open gas flow rate while, High Flow valves provided a dynamic range of 100% to 12% (Fig. 5).

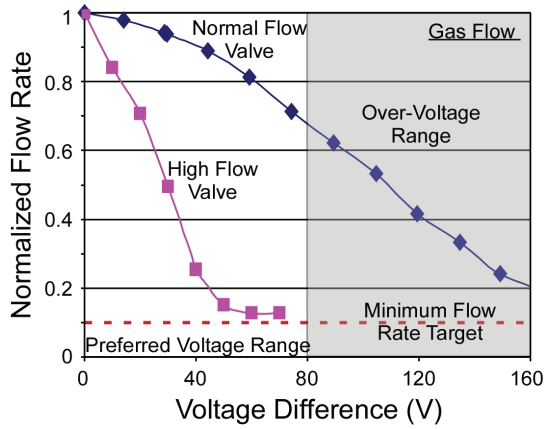

Fig. 5: Normal and High Flow valve performance at 14 kPa. High Flow valves provide greater dynamic range in the preferred voltage range for system design.

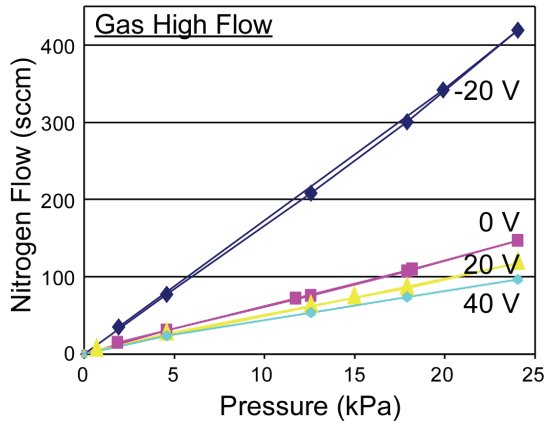

Fig. 6: Flow rates in a High Flow valve manifold assembled at 60 V actuation during encapsulation for operating voltages ranging from -20 to 40 V.

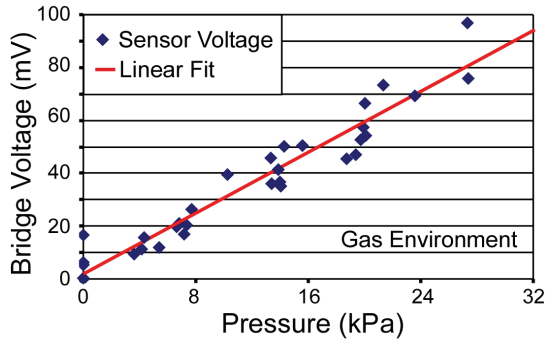

Fig. 7: Characterization of pressure sensors with nitrogen gas. Typical differential voltage from a piezoresitive pressure sensor Wheatstone bridge in a manifold. Sensitivity is 647 ppm/kPa.

A High-Flow manifold was actuated from -20 to 40 V across pressures up to 24 kPa and yielded flow rates up to 419 mL/min (Fig. 6). These flow rates are five times greater than those previously reported for a valve with the same volume actuated with the same voltage [13].

The piezoresistive pressure sensors were tested using gas pressures up to 30 kPa (Fig. 7). Several pressure sensors were tested over several days and remained consistent to with 1 %. Typical sensitivity for a 5 V supply was 647 ppm/kPa

Liquid Modulation: The dynamic range of Normal Flow valves was 100% to 4% of peak flow. Liquid tests for each valve in the manifold were conducted with IPA pressurized at 14 kPa (Fig. 8). The individual valves that comprise the manifold regulated flow with actuation voltages within an 80 V operating range. As previously noted, the operating voltage range can be adjusted by changing the actuation during assembly [14].

Flow from valve A varied from 1.77 mL/hr to 0.028 mL/hr and valve B varied from 2.12 mL/hr to 0.38 mL/hr with actuation voltages varying from -40 to 60 V (Fig. 9). These represent typical intrathecal drug delivery flow rates. When both valve A and B were open together, flow rates combined from each valve fell within two separate regimes. At high flow rates, the catheter resistance dominated flow. At lower flow rates, valve resistance dominated, and the combined flow rates were close to the individual flow rates of each valve added together. The flow patterns represent the expected response for a variable resistance regulation mechanism.

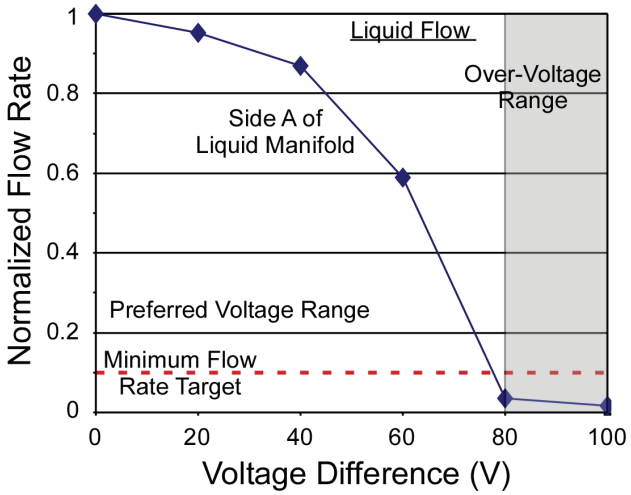

Fig. 8: Normalized flow rate in a single normal flow valve into a 1 m catheter at 14 kPa differential pressure for varying actuation voltage. The target dynamic range is realized in an 80 volt operating range.

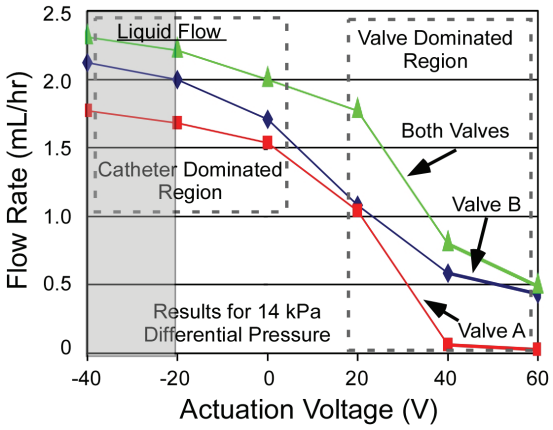

Fig. 9: Flow rate of alcohol through individual and combined valves in a manifold at 14 kPa. Catheter resistance is greater than valve resistance at low voltages outside preferred operating region. This results in reduced modulation. Mixing functions as expected.

CONCLUSION

A piezoelectric valve manifold has been designed and fabricated to regulate liquid flow from multiple sources for use in an implantable drug delivery device. Manifolds were fabricated and assembled with PZT actuators inside a ceramic cap with a total system volume of 4.5 cm^3. The manifolds were used to regulate gas flows of up to 419 mL/min at pressures from 0 – 23.5 kPa. Embedded differential pressure sensors were tested and exhibited an average sensitivity of 647 ppm/kPa. Liquid tests with IPA pressurized at 14 kPa demonstrated flow modulation from 2.30 mL/hr to 0.51 mL/hr in the 80 V operating range. Both sides of manifolds were regulated together to demonstrate flow combination where either catheter resistance or valve resistance dominates. The manifold shows promise for use in an implantable drug delivery device for the treatment of chronic pain.

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REFERENCES

[1] L. Visser, "Epidural Anaesthesia," *Update in Anesthesia*, Issue 13, Article 11, 2001, pp. 1-4

[2] K. H. Knight, F. M. Brand, A. S. Mchaourab, G. Veneziano, "Implantable Intrathecal Pumps for Chronic Pain: Highlights and Updates." *Croatian Medical Journal* 48(1): 22-34.

[3] V.C. Anderson, K.J. Burchiel, "A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain," *Neurosurgery*, 44, 2 (1999)

[4] ASHP guidelines on quality assurance for pharmacy-prepared sterile products. American Society of Health System Pharmacists, *Am J Health Syst Pharm*, 57, 12 (2000)

[5] D.W. Coombs, N. Fine, "Spinal anesthesia using subcutaneously implanted pumps for intrathecal drug infusion," *Anesth Analg*, 73, 2 (1991)

[6] J.S. Crawford, "Site of action of intrathecal morphine," *Br Med J*, 281, 6248 (1980)

[7] T. Grabow, D. Derdzinski, P. Staats, "Spinal drug delivery," *Curr Pain Headache Rep*, 5, 6 (2001)

[8] S.J. Hassenbusch, R.K. Portenoy, "Current practices in intraspinal therapy--a survey of clinical trends and decision making," *J Pain Symptom Manage*, 20, 2 (2000)

[9] Joint Committee on Accrediation of Healthcare Organizations, "New standards to assess and manage pain," *Jt Comm Perspect*, 19, 5 (1999)

[10] N.G. Rainov, V. Heidecke, "Management of chronic back and leg pain by intrathecal drug delivery," *Acta Neurochir Suppl*, 97, 1 (2007)

[11] R.L. Rauck, D. Cherry, M.F. Boyer, P. Kosek, J. Dunn, K. Alo, "Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain," *J Pain*, 4, 8 (2003)

[12] S.J. Hassenbusch, et al., "Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery-- report of an expert panel," *J Pain Symptom Manage*, 27, 6 (2004)

[13] A.T. Evans, J. M. Park, et al., "A Low Power, Microvalve-Regulated Drug Delivery System using a Si Micro-Spring Pressurized Balloon Reservoir." *Transducers '07*, Lyon, France.

[14] J.M. Park, A.T. Evans, K. Rasmussen, T.R. Brosten, G.F. Nellis, S.A. Klein, and Y.B. Gianchandani, "A Microvalve with Integrated Sensors and Customizable Normal State for Low Temperature Operation," *IEEE/ASME J. Microelectromechanical Systems*, 18(4), pp. 868-879, August 2009

[15] D.J. Laser, J.G. Santiago, "A Review of Micropumps," *J. of Mic. and Microengineering*, vol. 14(6), 2004, pp. R35-R64.

[16] S.K. Sia, G.M. Whitesides, "Microfluidic Devices Fabricated in Poly(dimethylsiloxane) for biological studies," *Electrophoresis*, vol. 24, 2003, 3563-76.

[17] M. Esashi, S. Shoji, A. Nakano, "Normally Closed Microvalve and Micropump Fabricated on a Silicon Wafer," *Sensors and Actuators*, 20, 1-2 (1989)