



# A wireless implantable micropump for chronic drug infusion against cancer



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## ABSTRACT

We present an implantable micropump with a miniature form factor and completely wireless operation that enables chronic drug administration intended for evaluation and development of cancer therapies in freely moving small research animals such as rodents. The low power electrolysis actuator avoids the need for heavy implantable batteries. The infusion system features a class E inductive powering system that provides on-demand activation of the pump as well as remote adjustment of the delivery regimen without animal handling. Micropump performance was demonstrated using a model anti-cancer application in which daily doses of 30  $\mu$ L were supplied for several weeks with less than 6% variation in flow rate within a single pump and less than 8% variation across different pumps. Pumping under different back pressure, viscosity, and temperature conditions were investigated; parameters were chosen so as to mimic *in vivo* conditions. In benchtop tests under simulated *in vivo* conditions, micropumps provided consistent and reliable performance over a period of 30 days with less than 4% flow rate variation. The demonstrated prototype has potential to provide a practical solution for remote chronic administration of drugs to ambulatory small animals for research as well as drug discovery and development applications.

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## 1. Introduction

Each year, approximately 8 million people around the world die from cancer. Research suggests that one-third of these deaths can be prevented with appropriate technologies and services [3]. Treatment typically involves surgery to remove cancerous tissues, followed by long-term chemotherapy or radiation therapy, among other types of therapies [28]. Chemotherapy and radiotherapy are used to initiate intrinsic apoptotic (cell death) pathways, but these type of treatments, when administered systemically, are non-specific and affect non-cancerous tissues as well as lead to severe side effects. Delivery to a specific tissue facilitates the goal of achieving therapeutic drug levels while reducing harmful side effects, the amount of drug needed, and the frequency of dosing

events [19]. Additionally, studies have shown that periodic biological fluctuations such as circadian rhythms may affect drug kinetics and dynamics [37]. Administration of chemotherapy at a specific time in a tumor cell cycle can increase treatment effectiveness while decreasing toxicity to healthy tissue [43]. A study of more than 30 anti-cancer drugs showed that the toxicity and efficacy of these drugs varied by more than 50% depending on the time of dosing [21]. Patient tolerance to medication and clinical outcome are also greatly affected by the dosing time [21]. Greater control over delivery rates allows tailored therapies and drug regimen changes during the course of therapy. Consequently, there is a great need for therapies combined with delivery methods to allow for long-term, localized, and patient tailored anti-cancer therapies.

In drug development for disease management, the scientific community relies heavily on animal studies to provide basis for human clinical trials [31]. The mouse genome has been completely sequenced allowing accurate comparisons to other mammal genomes such as humans and its physiologic, metabolic and pathologic processes have been well documented [24]. As such, human drug therapies are initially evaluated in small animal models; therefore, drug administration technologies for small laboratory animals are critically important for drug discovery and development. The most commonly used drug administration routes

**Abbreviations:** siRNA, small interfering ribonucleic acid; Pt, platinum; PBS, phosphate buffered saline; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; USP, United States Pharmacopeia; SL, stereolithography; EI, electrochemical impedance.

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for laboratory animals are oral, topical, or intravenous which require high drug dose concentration, leading to severe side effects, and frequent animal handling. In chronic studies, frequent animal handling or restraint induces stress, which can confound study results [17].

Current technologies for chronic dosing in laboratory animals include tethered infusion systems and vascular access ports. In tethered systems, the animal is connected to a precision infusion pump with a tether as shown in Fig. 1a [40]. The use of the external pump provides accurate dosing, but is impractical for chronic studies since restriction of movement by the tether induces stress. Vascular access ports are chronically implanted subcutaneously minimizing animal movement restrictions [41]. However, vascular ports require regular cleaning, maintenance, and appropriate protective measures to prevent infection or damage by the animal.

Implantable infusion pumps further minimize animal handling and permit natural movement after the initial healing period following implantation. The Med-e-Cell Infu-Disk is non-refillable, has a preset constant flow rate, and a maximum lifetime of 1 week [26]. This pump is only suitable for drug delivery in animal models larger than rats due to its large size. The Primetech iPrecio and the Alzet pumps are the only commercial pumps scaled for mice. The iPrecio peristaltic pump allows programmable infusion profiles, but is battery powered, only provides up to 52 days of operation, cannot be powered off, and is single use [16]. The Alzet osmotic pump provides a preset continuous flow rate, a drug payload of up to 6 weeks, and is non-refillable [1]. These technical limitations of current technology prohibit flexibility in designing administration regimens for drug discovery and development research. While commercially available pumps are not suitable for chronic drug infusion in small animals, recent advances in microelectromechanical systems (MEMS) technology have led to the miniaturization and improved efficacy of implantable drug delivery systems suitable for small laboratory animals [27]. Several ongoing efforts are being carried out in research laboratories to develop remotely activated drug delivery microsystems. Detailed descriptions of these efforts are available in [36,4].

The micropump presented in this work was actuated using electrolysis which offers low power consumption, large driving force, low heat generation, on-demand activation, and post-implantation flow rate control through the applied current [33]. Wired implantable MEMS micropumps scaled for use in small laboratory animals (e.g., mice) were previously demonstrated [10,8]. Preliminary *in vivo* studies with this wired system demonstrated the potential of using micropumps to combat radiation resistance of tumors in mice by improving the exposure of siRNA through sustained localized delivery compared to needle injections [10,8,25]. However, the use of transcutaneous wires for powering the pump required animals to be restrained during dosing, prohibited chronic studies, and placed restrictions on experimental throughput. Also, the lack of reliable, small form factor check valves resulted in a slow diffusion of drug from the reservoir into the animal and thereby limited the accuracy of delivery. The absence of a reliable check valve could also lead to fluid to flow back through the delivery catheter to the reservoir as a result of the reverse pressure gradient created during recombination of electrolysis gases.

Here, we present a redesigned implantable micropump that incorporates wireless power telemetry and an integrated miniature check valve, suitable for chronic drug delivery in untethered, freely moving small laboratory animals such as mice (Fig. 1b, Table 1). This wireless drug administration method can eliminate the induced stress from animal handling or tethered and wired drug administration systems that could potentially confound interpretation of data [17]. Wireless operation was facilitated by improving electrolysis actuation efficiency which further reduced actuator power consumption (1 mW from 3 mW). A miniature check valve with

**Table 1**

Primary differences between the previous generation refillable implantable micropump system (RIMS) and our current implantable micropump for drug delivery in small animals.

	RIMS Pump [8]	Current Pump
Operation	Wired, external constant current power supply	Wireless power telemetry
One way valve specifications	Bridge-type membrane valve 0.515 × 1.23 mm, L × OD 1.31 kPa cracking pressure	Duckbill valve 3 × 2 mm, L × OD 0.69 kPa cracking pressure
Height	10 mm	8.1 mm
Footprint	21 mm OD	20 × 15 mm, L × W
Dead volume	1087 µL	96 µL
Power consumption	3 mW	1 mW

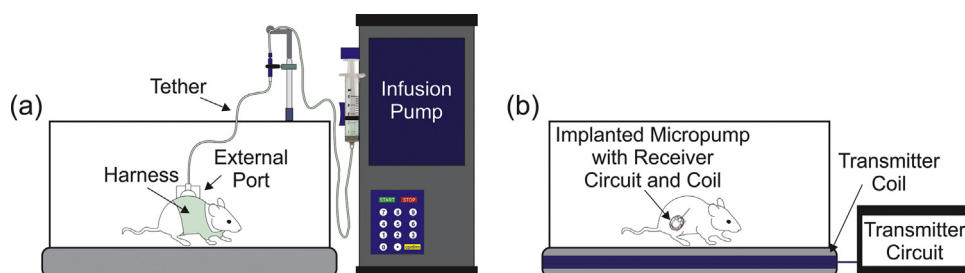
small form factor and improved performance enabled appropriate flow regulation during pumping and resting states. The check valve contributes to accurate dosing and prevents drug contamination with biological fluids during the recombination reaction between electrolysis actuation cycles [33]. Acute characterization of pump performance was previously presented [5]. For this work, the pump performance characterization was extended to simulate *in vivo* chronic conditions, including those relevant to future studies to deliver agents to combat radiation resistance in a mouse xenograft cancer model. A redesigned drug reservoir achieved a more compact footprint by reducing dead volume (inaccessible drug) by nearly 91% and check valve dimensions, which were essential to accommodate the addition of wireless circuitry. Integrated refill ports allow long term use of the micropump for chronic studies.

## 2. Design

Our micropump system utilizes a low power electrolysis actuation mechanism. The electrochemical actuator consists of an electrolyte (water) encased by a Parylene bellows and a pair of interdigitated platinum (Pt) electrodes supported on a rigid glass substrate. An applied electrical current to the electrodes dissociates liquid water into oxygen and hydrogen gas and induces an increase in pressure. This deflects the bellows, activates a one-way check valve, and displaces the surrounding fluid out of the rigid reservoir through the outlet catheter to the delivery site. The gases recombine to water once the current is turned off, allowing the bellows to return to the original rest position.

The interdigitated electrode design reduces the solution resistance path resulting in improved electrolysis reaction [23]. Pt was selected as the electrode material due to its biocompatibility, good corrosion and oxidation resistance, and ability to catalyze recombination [15,14]. Electrolysis efficiency was further improved by coating the electrodes with Nafion®, a solid polymer electrolyte that provides higher solubility of oxygen and hydrogen gases than water [33]. Nafion®-coated electrodes also provided faster and more repeatable recombination, decreased electrode delamination or damage at high current operation, and increased flow rate [34].

Bellows possess the ability to achieve large deflection with low applied pressure compared to corrugated or flat diaphragms [23]. Parylene C was selected as the bellows material due to its low Young's modulus, biocompatibility, inertness and low permeability [22,23,12]. The bellows consisted of two convolutions each having a 6 mm inner diameter, 9.5 mm outer diameter, 0.4 mm height and 13.5 µm thickness. This bellows can safely displace 185 µL of fluid contained within the adjacent drug reservoir without experiencing plastic deformation [7].



**Fig. 1.** Schematic diagram of *in vivo* testing setup for small animal research with (a) commercial tethered infusion system, and (b) wireless implantable drug delivery pump.

The micropump design achieves compact footprint by reducing dead volume between the reservoir wall and bellows. The reservoir inner diameter was reduced by 46% resulting in a substantial reduction in dead volume from approximately 1100 to 100  $\mu\text{L}$  compared to previous micropump prototypes [9]; this new volume combined with the capability for refill is adequate for most small animal drug delivery applications. The reduction in reservoir footprint allowed incorporation of the wireless components while maintaining a total device mass of approximately 10% of the weight of the animal (typically adult mice are 30 g) to allow free, unhindered movement [39].

The pump is normally off until wirelessly activated by a class E inductive powering system (Fig. 2). Inductive transmission is most suitable for transcutaneous powering compared to other forms of wireless powering (radiation, conductive, and capacitive) [20]. For this system the power transmission frequency was chosen to minimize heat generation [13]. It relies on magnetic field coupling and transmission frequency can be chosen to minimize power dissipation. The class E inductive powering transmitter is placed underneath the rodent cage. A current regulator on the subcutaneously implanted receiver controls the application of current to the electrolysis actuator; here, a single constant current magnitude was supplied corresponding to a single flow rate. The volume delivered is controlled by the duration of pump activation. Heat generation from the wireless system is negligible in part due to chosen operation frequency [36]. High efficiency off the shelf components were chosen to minimize power dissipation [42].

### 3. Fabrication

#### 3.1. Electrolysis actuator

The actuator's interdigitated electrodes (100  $\mu\text{m}$  wide elements separated by 100  $\mu\text{m}$  gaps, 8 mm diameter footprint, 300  $\text{\AA}$ /2000  $\text{\AA}$  Ti/Pt) were fabricated on a Borofloat 33 glass substrate (University Wafer, Boston, MA) by liftoff following e-beam deposition of the thin film metal using a previous method described in [8,34]. The electrodes were potentiostatically cleaned at  $\pm 0.5\text{ V}$  (Gamry Reference 600 Potentiostat, Warminster, PA) in  $1\times$  phosphate buffered saline (PBS). The electrodes were then dip coated in Nafion<sup>®</sup> (Dupont DE521 Solution, Ion Power, Inc., New Castle, DE). Kynar<sup>™</sup> nickel plated copper wires (30 AWG, Jameco Electronics, Belmont, CA) were soldered to the electrode contact pads. The joint was reinforced and insulated with nonconductive marine epoxy (Loctite, Westlake, OH) [34].

Parylene bellows were fabricated using a lost-wax two-part molding process previously described in [7]. Polydimethylsiloxane (PDMS, Sylgard 184; Dow Corning Corp., Midland, MI) sheets (0.4 mm thick) were perforated with 6 mm and 9.5 mm holes to mold the inner and outer diameters of the bellows, respectively. The sheets were visually aligned and stacked together on glass slides to form mold modules. These modules were filled with molten (50  $^{\circ}\text{C}$ ) polyethylene glycol (PEG; 1000 Mn, Sigma–Aldrich, St. Louis, MO).

Once the PEG solidified, PDMS sheets were peeled. The modules were stacked and fused together by moistening connecting interfaces with water. Completed PEG molds were coated with 13.5  $\mu\text{m}$  United States Pharmacopeia (USP) class VI Parylene C (Specialty Coating Systems, Indianapolis, IN), followed by soaking in deionized water at room temperature to remove sacrificial PEG.

The Parylene C bellows were filled with double deionized water and attached to the electrode using double-sided pressure sensitive adhesive film (Tape 415, 3M, St. Paul, MN). The joint was then reinforced with marine epoxy.

#### 3.2. Check valve

A one-way duckbill valve made of medical grade silicone (2.0 mm duckbill; Minivalve, Cleveland, OH) with a measured cracking pressure of less than 0.69 kPa (5.17 mmHg) was selected. Valves were prescreened for proper closure and then incorporated into the pump by attaching the base of the valves to the reservoir housing output path using biocompatible epoxy (EPO-TEK<sup>®</sup> 730 unfilled, Epoxy Technologies, Billerica, MA).

#### 3.3. Wireless powering system

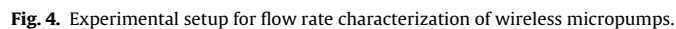
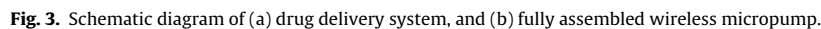
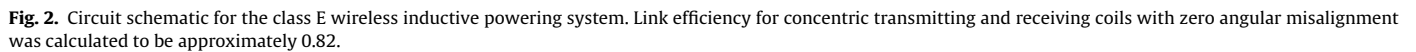
A 2 MHz clock oscillator (ECS-2100, ECS International, Olathe, KS) was used to create the power signal from a 9 V power supply (0.3 W). The generated signal was then amplified in two stages before being applied to a tuned transmitting coil (8 turns of 20 AWG single strand wire, size: 310 mm  $\times$  140 mm). Litz wire (6 turns, 50/54 SPN/SN Litz Wire, Wiretron, Volcano, CA) was used for the receiving coil ( $\varnothing$  17 mm). The received alternating signal was fully rectified using two Schottky diodes (BAT54A and BAT54C, Fairchild Semiconductor, San Jose, CA). A resistor was used to set the output current on a 3-terminal adjustable current source (LM334, Texas Instruments, Dallas, TX) to 0.33 mA for driving the pump.

#### 3.4. System packaging and assembly

The reservoir domes and bases were produced using stereolithography (SL) in USP class VI DSM Somos<sup>®</sup> WaterShed XC 11122 material (FineLine Prototyping, Inc., Raleigh, NC). This material is optically clear, durable, water resistant, and rigid [38,6].

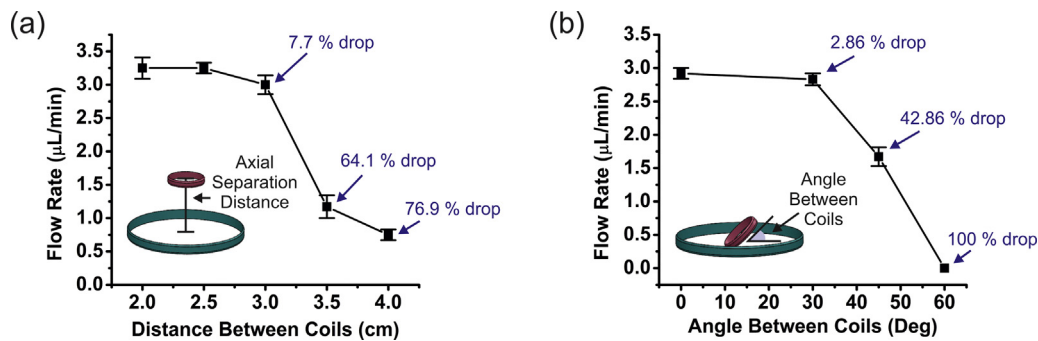
Medical grade silicone rubber septa (10:1 base-to-curing agent ratio USP class VI MDX-4 4210; Factor II, Lakeside, AZ) were fabricated based on results of a leak puncture test allowing for at least one dozen punctures with a maximum applied pressure within the dome of 775 mmHg (15 psi). The septa were then inserted into the refill ports of the SL dome and the perimeters reinforced with marine epoxy. This assembly was encapsulated with 5  $\mu\text{m}$  Parylene C to further improve biocompatibility and barrier properties. Then the electrolysis actuator was situated in the reservoir assembly and secured with biocompatible epoxy.

The wireless receiver was mounted on the micropump body and encapsulated with 5  $\mu\text{m}$  Parylene C, followed by a thin coating of

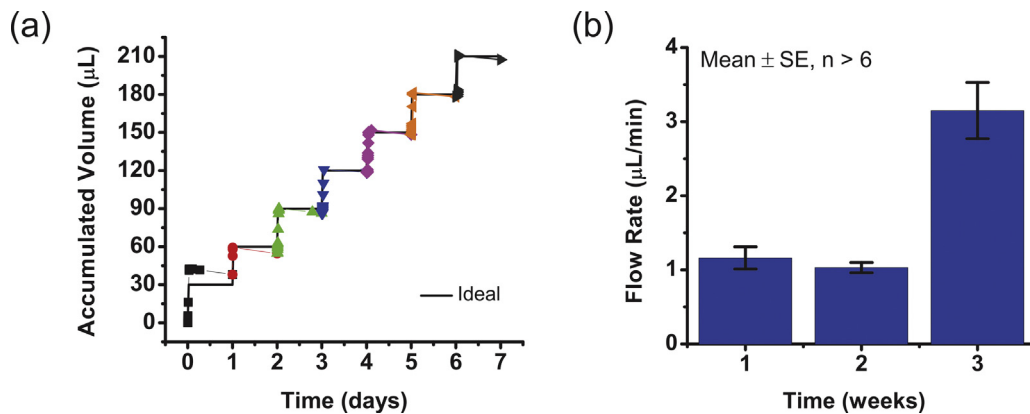


Flow rate measurements were taken on a single micropump with five different wireless receivers. Flow rate was calculated by measuring fluid front displacement in a 100  $\mu\text{L}$  calibrated micropipette (VWR International, Radnor, PA) connected to the catheter outlet as shown in Fig. 4. The axial separation distance (parallel coils, 2–4 cm, 0.5 cm steps) and angular misalignment (0, 30, 45, and 60°) between concentric transmitter and receiver coils (2 cm distance between coils) was varied to study the effects on pump flow rate performance.





**Fig. 5.** The effects of (a) axial separation distance between concentric transmitter and receiver coils, and (b) angular misalignment between concentric coils on pump performance (at 0.33 mA constant current).



**Fig. 6.** Representative data from one stationary micropump wirelessly operated. (a) Bolus delivery from a micropump operated once a day during week two (at 0.33 mA constant current) and (b) flow rates for the three weeks dosing.

#### 4.2. Daily dosing

Successful dose delivery of six stationary (2 cm distance and  $0^\circ$  angular misalignment between concentric coils) micropumps over a period of one week was obtained. Here, two of the previous micropumps were operated daily for an additional week to simulate the two week dosing regimen planned for the anti-cancer application. Daily dosing regimen over a period of three weeks was studied in one of said micropumps. A constant current of 0.33 mA was supplied to the actuator wirelessly for a duration that allowed 30  $\mu\text{L}$  of double deionized water to be delivered daily. The pumps were only refilled once per week and the duration of applied current was increased with each successive dosing event. The micropump catheter was connected to a calibrated micropipette for flow rate measurements as previously described. The fluid front position was recorded several times during each delivery at discrete time points. Reverse leakage between dosing events, if any, was recorded. To avoid confounding results from evaporation, the fluid front being tracked was followed by a small air pocket (10 mm), followed by a column of water resulting in negligible evaporation between dosing events.

#### 4.3. Room temperature versus body temperature

In implantable drug delivery devices, the device will be operated at body temperature. Three fully assembled and encapsulated micropumps were filled with double deionized water, flush of any air bubbles and soaked in a room ( $23^\circ\text{C}$ ) or body temperature ( $37^\circ\text{C}$ ) deionized water bath for 30 minutes. Flow rate test was performed while the pump was submerged in a

temperature-controlled water bath. The flow rate was determined as previously described during four cycles each lasting 5 minutes after valve opening.

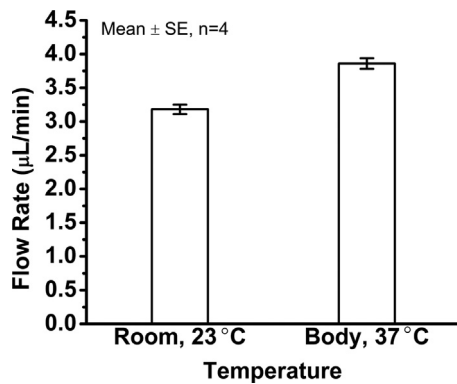
#### 4.4. Physiological environment simulation

System performance in simulated *in vivo* conditions was investigated to verify that Parylene C and silicone rubber encapsulation layers provide adequate protection for the electronics for the duration of the anticipated *in vivo* study. Three fully assembled and encapsulated micropumps were soaked in  $1\times$  PBS at body temperature ( $37^\circ\text{C}$ ). Periodically, the micropumps were removed from the bath, refilled with double deionized water, and subjected to flow rate testing. Valve opening times were recorded and flow rate measurements were taken for 5 minutes after valve opening.

### 5. Experimental results

#### 5.1. Wireless testing

Benchtop testing of a single micropump with five different receivers resulted on an average flow rate of  $2.66 \pm 0.16 \mu\text{L}/\text{min}$  (mean  $\pm$  SE,  $n=5$ ), a 6% variation between receivers. The results from changing the axial separation distance between coils and angular misalignment between transmitter and receiver showed a drop in flow rate by 64.1% and 42.86% for a 3.5 cm separation distance between coils and for  $45^\circ$  angular misalignment between transmitter and receiver, respectively as shown on Fig. 5.



**Fig. 7.** Representative data from one wireless micropump flow rate performance when increasing the environmental temperature from room (23 °C) to body temperature (37 °C) (at 0.33 mA constant current).

## 5.2. Daily dosing

Two wirelessly operated micropumps consistently delivered 30 μL doses daily over the course of two weeks as required by the anti-cancer application. These micropumps showed similar flow rate performance during the two week testing with less than 8% variation. Fig. 6a shows representative results from the daily dosing regimen of one micropump for one week. The data is presented as accumulated volume to study the effects of increasing pressure build up within the reservoir during recombination periods. Similar data was obtained for all pumps tested. The shown micropump delivered 30 μL doses daily for three consecutive weeks. Mean flow rates during the first two weeks are not significantly different as confirmed by statistical analysis (ANOVA,  $p > 0.05$ ) (Fig. 6b). Valve performance varied across the micropumps, but it consistently limited back flow to a maximum of 10 μL when the pump was turned off. The slight volume drop seen before each dosing event correlates to the back flow allowed by the valve. Some valves showed improved sealing performance in each consecutive week of testing.

## 5.3. Room temperature versus body temperature

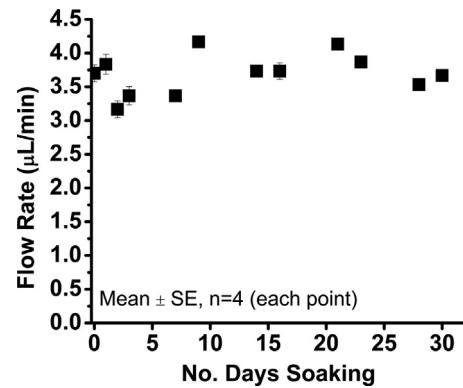
Fig. 7 shows representative results of the flow rate performance at room temperature (23 °C) and body temperature (37 °C) for one micropump (mean  $\pm$  SE,  $n = 4$ ). As expected, an increase in flow rate was apparent at body temperature. For two micropumps, changes in temperature resulted in significant flow rate differences as confirmed by performing a one way analysis of variance (ANOVA,  $p < 0.05$ ).

## 5.4. Physiological environment simulation

A 30 day trial with three fully encapsulated and packaged pumps immersed in a 1 × PBS bath at body temperature (37 °C), showed continued accurate and reliable flow rate performance with a standard error of less than 4% for each pump. Fig. 8 shows representative results of the flow rate performance for one micropump (mean  $\pm$  SE,  $n = 4$ ). This micropump was previously used for the three week daily dosing study, but has a new receiver. Mean flow rates between weeks for each pump are not significantly different as confirmed by statistical analysis (ANOVA,  $p > 0.05$ ).

## 6. Discussion

The pump components were redesigned to optimize pump performance and ease of use. The new reservoir dome features two refill ports as oppose to one to facilitate filling and flushing of the reservoir. The refill ports are robust enough to prevent leaks



**Fig. 8.** Representative flow rate performance results for a micropump under simulated in vivo conditions for 30 days (at 0.33 mA constant current).

after a high number of punctures under high reservoir pressure. The new redesigned rigid reservoir significantly decreased device footprint by decreasing dead volume by 91%. The total filled encapsulated device mass including wireless power components was 3.8 g, slightly exceeding the mass requirements for a mouse experiment (3 g or approximately 10% of an adult mouse weight of 30 g). The encapsulation was identified as the heaviest component. Therefore, the pump mass can be reduced by eliminating the encapsulation material and instead using a low density polymer outer casing to enclose the current system.

Fully integrated wireless stationary micropumps successfully delivered 30 μL daily boluses at low flow rates ( $\sim$ μL/min) for several weeks, a regimen relevant for the administration of siRNA therapy to a radiation resistance cancer. The 2.8 fold increase in flow rate observed during the third week of the daily dosing study was attributed to a faulty receiver. Due to this systematic error, flow rate variation was calculated after the receiver was replaced (4%). Since we previously demonstrated consistent actuator performance [33], slight variations in mean flow rate were attributed to variations due to manual assembly of the packaging and receiver coils and inconsistent performance in the commercially produced valves. Also, valves permitted up to 33% of dose volume in back flow when the pump was turned off. Some delay in forward flow during current application was present in all micropumps tested and is due to the low current application [29], and valve cracking pressure. This delay was further increased in daily dosing regimens where the reservoir was not refilled and higher pressure build up was required in order to deliver the same dose volume [33]. As discussed in [11], the forward flow delay prior to refill follows a predictable pattern and can be accounted for by increasing the current application time, thus our flow rate variation of 4% does not include the forward flow delay. The forward flow delay in our previous prototypes was minimized by replacing the compliant reservoir material with a rigid material and utilizing higher efficiency electrolysis electrodes [34]. The dosing regimen can be altered depending on the intended application. A diverse assortment of liquid drug formulations can be delivered within a wide dynamic range of dose volumes (nL–μL) and flow rates (0.33–141.9 μL/min) [33]. The bellows can safely deliver 180 μL. Once this volume is reached the actuator should be allowed to fully recombine prior to the next dosing event. Full recombination is achieved within several hours [35]. While the pump can store medication for long term, it is important for the drug to be stable when stored at body temperature between refill events.

Previous prototypes of this pump included commercial valves with high sealing pressures [8] that showed significant reverse flow during recombination. For *in vivo* studies, reverse flow needs to be avoided in order to obtain safe and accurate dosing. The check valve

incorporated into this system was the only small commercial valve with low sealing pressure and cracking pressure. Unfortunately, the valve manufacturing process leads to variability and inconsistency in valve performance. Thus, valves were screened before incorporation into the pump and only 50% of the valves passed screening (reverse leakage <20% of dose volume). Variable and inconsistent performances of the valve resulted in additional variability among pump performance. Therefore, high quality valves with repeatable performance are now being developed.

A class D wireless power system was developed to power an electrochemical actuator in Sheybani et al. [8]. While it was simple in design and provided large currents, this class D system had several drawbacks including difficulty in fine tuning the amplifier and inability to generate the required power without overheating the transmitter circuit components. A class E system combines the advantages of the class D system with its series-tuned output and parallel-tuned amplifier tanks. Class E systems can cope with the rigorous demands of weakly coupled links, produce smooth signals, be insensitive to low switching time, and operate over several tens of MHz. This pump was powered with a class E powering system, which allows higher efficacy when a considerable amount of power is to be transferred [30]. Pump flow rate is linearly dependent on applied current to the actuator [34]. A current regulator was chosen as part of the implanted receiver circuit to ensure the current applied to the actuator to be relatively constant (within certain limits of distance and angular misalignment between the transmitting and receiving coils) regardless of slight changes in the power. Current regulators are inherently lossy components, as such, power efficiency is partially sacrificed to ensure proper pump operation. Flow rate performance for an individual pump varied when it was powered with different receivers. Variations in flow rate remained within less than 6%. This slight variation in performance can be attributed to the manual assembly of receiver coils, but can be alleviated by calibrating each pump prior to *in vivo* studies. As expected, a decrease in power transferred due to increased axial separation distance and angular misalignment between concentric transmitter and receiver coils resulted in decreased in flow rate. Pump flow rate stability can be further improved by increasing the transmitted power [20]. The addition of multiple coils at either the transmitter or receiver side can improve power transfer to mitigate angle misalignment. Another potential solution is to move the external receiving coil along with the moving animal by tracking the movement of the internal transmitting coil with a similar setup to the one proposed by Kilinc et al. [18].

The effects of environmental factors on pump performance were investigated. Changing the environmental temperature from room temperature (23 °C) to body temperature (37 °C) for our wireless micropumps resulted in increased flow rate. Improved electrolysis efficiency can be attributed to the increased permeability of Nafion® to hydrogen and oxygen when the ambient temperature is increased [2]. This is in agreement with [33], which found slight increase in flow rate at body temperature for electrochemical actuators. Physiological environmental simulation test showed that all three pumps were functioning consistently and as expected after 30 days of soaking in 1× PBS at body temperature (37 °C) exceeding the intended *in vivo* study duration by 100%. This verifies that the Parylene C and silicone rubber encapsulation layers provide adequate protection for the electronics for the duration of the anticipated *in vivo* study. This packaging scheme may also be suitable for longer term *in vivo* studies beyond 30 days.

## 7. Conclusion

We demonstrated the characterization of a fully implantable wireless infusion micropump for use in chronic drug delivery

therapies in small research animals. Wireless control of operation permits a user to select the desired delivery regimen in a freely moving animal. Wireless powering of the actuator with a class E inductive powering system allowed repeatable delivery with less than 6% variation in flow rate. Pump performance was affected by increased axial separation distance and angular misalignment between concentric transmitter and receiver coils. If necessary, this can be alleviated by increasing the power transmitted and inclusion of a second receiver coil [20]. Wireless powering with an implantable device requires inductive coupling link through the skin and biological tissue. As such, it is essential to characterize device performance *in vivo*. Future work will include characterization of system operation in simulated tissue material to mimic device operation in animals.

Stationary micropumps successfully delivered a single bolus daily for several weeks and achieved flow rates on the order of  $\mu\text{L}/\text{min}$ , an experimental regimen relevant for an anti-cancer drug delivery application. Valves significantly decreased reverse flow compared to a valve less system. We demonstrated that flow rate was not significantly affected by back pressures of up to 20 mmHg (when delivering solutions of 1 cP) or delivering solutions with viscosities of up to 6 cP (data shown in [5]). As expected, micropump flow rate increased with increased environmental temperatures. Consistent micropump performance was also demonstrated in simulated physiological environmental conditions with less than 4% flow rate variation.

Drug delivery micropumps need to incorporate closed-loop feedback systems to enable pump performance monitoring, and increase effectiveness of therapies. Control over delivery profile can be achieved through the incorporation of physical sensors that provide information on pressure, flow rate, delivered volumes, forward flow delay and real-time state of the pump. A variety of sensing techniques are available for MEMS flow sensors, such as electrical, nuclear, thermal, mechanical, optical, and acoustic. We are currently developing an electrochemical impedance (EI) dose tracking system capable of tracking accidental release of reservoir content, blockage and refill detection or lack of delivery in real time [32].

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E. M. has a significant interest in Fluid Synchrony LLC (CA, USA).

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## Biographies



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**Heidi Tu** received her B.S. in Biomedical Engineering and B.A. in German from The University of Texas at Austin. Heidi has a Ph.D. in Biomedical Engineering from the University of Southern California, where she developed an implantable drug delivery pump. She is currently a Product Design Engineer at a private healthcare technology company in the San Francisco Bay Area. Her professional goal is to develop medical technology to enable better treatment and care for patients.



**Ellis Meng** received her B.S. degree in engineering and applied science and her M.S. and Ph.D. degrees in electrical engineering from the California Institute of Technology (Caltech), Pasadena, in 1997, 1998, and 2003, respectively. She is a Professor of Biomedical Engineering and Electrical Engineering at the University of Southern California, Los Angeles where she has been since 2004. She directs the Biomedical Microsystems Laboratory which specializes in biomicroelectromechanical systems, implantable biomedical microdevices, neural interfaces, and microfluidics. She is a recipient of the NSF CAREER, the Wallace H. Coulter Foundation Early Career Translational Research, and the ASEE Curtis W. McGraw Research Awards. In 2009, she was recognized as one of the TR35 Technology Review Young Innovators under 35. E. M. has a significant financial interest in Fluid Synchrony LLC (CA, USA).