

Electronic Supplementary Information

Wireless implantable chip with integrated Nitinol-based pump for radio-controlled local drug delivery

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Fabrication process

Microfluidic chip of the drug delivery device

Fig. S1 outlines the fabrication process flow for the microfluidic chip in which the Nitinol LC-tank actuator is integrated. First, a piece of 127- μm -thick polyimide film (Fralock, CA, USA) is cut out and cleaned with acetone and isopropyl alcohol (IPA). Next, 3 μm of Parylene C is deposited onto both sides of the substrate using a commercial deposition system (PDS 2010 Labcoter 2, Specialty Coating Systems, IN, USA) (Fig. S1(a)). Then a thick positive photoresist (SPR220-7.0, Rohm and Haas, PA, USA) is spun on, exposed using a mask aligner through a mask containing patterns of a valve (Parylene) layer, and developed in a developer (MF-24A, Rohm and Haas, PA, USA). The sample is then subjected to an oxygen plasma etch to pattern the Parylene layer with the photoresist mask (Fig. S1(b)). After all the remaining SPR220 is stripped with acetone, 1.5 μm of positive photoresist (S1813, Rohm and Haas, PA, USA) is spun on the top side, over the patterned Parylene features. The sample is exposed and then developed in a developer (MF-319, Shipley, MA, USA) (Fig. S1(c)). This layer of photoresist is used as a spacer to prevent the valve disc on one Parylene layer from bonding with the valve seat on the other layer. The surface of the sample is descummed in an oxygen plasma for 30 seconds and another 3 μm of Parylene C is deposited on (the edges of the sample are sealed to a wafer to prevent any deposition of the Parylene onto the sample's backside). The second layer of Parylene C is patterned in the same manner as the first; photolithography is performed using SPR220 to form an etch mask, the Parylene layer was etched through using oxygen plasma (Fig. S1(d)), and the remaining accessible photoresist is dissolved to complete the fabrication of the valves.

Next, the sample was flipped over and the Parylene on the backside was patterned to form another etch mask (Fig. S1(e)). This mask defines where on the substrate the polyimide etchant reacts with to form the microfluidic channels and the through holes to the reservoir and the valves. The sample is flipped over again to continue processing the top side. The next step is to form a $\sim 200\text{-}\mu\text{m}$ -thick sacrificial layer for the pump chamber. Although a thick layer of photoresist (160-180 μm) can be attained by spinning on several coats of SPR220 at low speed for a short duration, the resultant film becomes too opaque and does not allow proper alignment of the mask in the next step. To avoid the issue, a small amount of SPR220 is manually applied on the area where the pump chamber is created. The sample is then baked on the hot plate at 75 $^{\circ}\text{C}$ for 3 hours, followed by gradual cooling. Photo-patterning of the thick SPR220 is performed through a mask with the pump chamber's pattern. This patterning requires a long exposure time due to the large thickness of the layer, which leads to thermal damage (bubbling) of the photoresist; to circumvent such issue, it is repeatedly exposed with shorter times and developed until all the exposed photoresist is removed. After the photoresist is fully patterned into a $1.75 \times 2.94 \text{ mm}^2$ block, the top side of the sample is descummed and deposited with another 5 μm of Parylene while preventing the coating on the backside in the same manner as before. At this point, Parylene covers the entire substrate except for the channel patterns on the backside (Fig.

S1(f)). The sample is then immersed in a polyimide etchant (40% KOH and 20% ethanolamine mixed aqueous solution heated to 87 °C)¹ to wet etch the channels leading from the reservoir to the inlet valve and from the outlet valve to the exterior of the chip. This step is performed in an ultrasonic bath to assist the etching process, followed by thorough cleaning. Removal of the sacrificial layer is performed with acetone through these etched polyimide channels (refer to Fig. 3(a)). Once all the photoresist is dissolved out of the pump chamber, IPA followed by hot water is pumped through it to remove the organic solvents (Fig. S1(g)). Fig. S2 shows the fabricated valves and pump chamber.

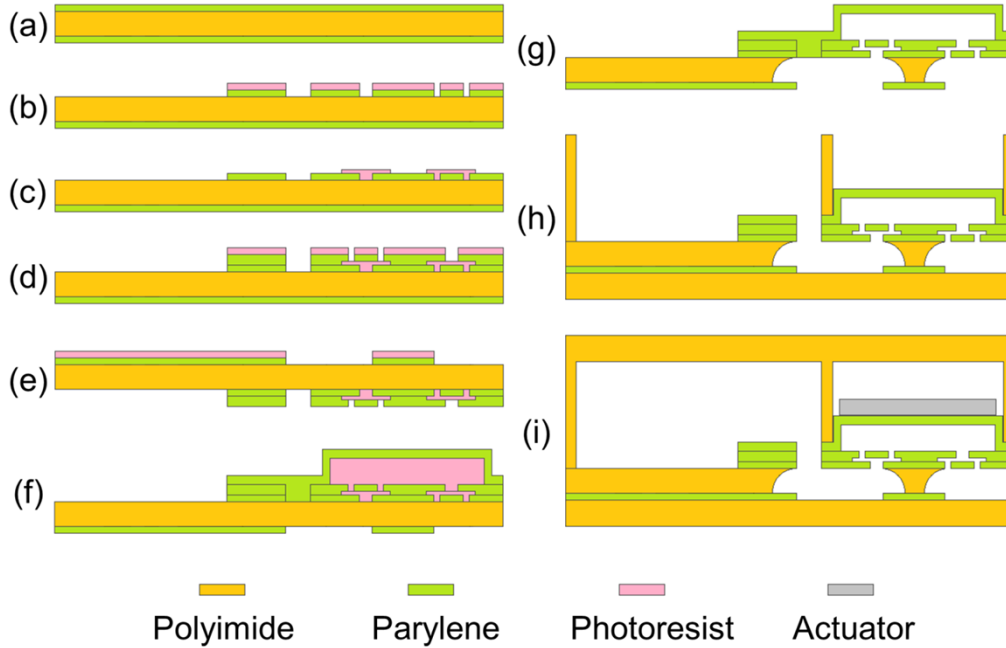


Fig. S1 Fabrication process flow (not to scale): (a) Deposit Parylene C onto both sides of the polyimide; (b) pattern top Parylene; (c) pattern spacers; (d) deposit Parylene onto top side and pattern; (e) pattern bottom Parylene; (f) deposit thick sacrificial layer and deposit Parylene onto top side; (g) etch channels into polyimide and dissolve out sacrificial layer; (h) bond on walls; (i) bond on actuator and cover.

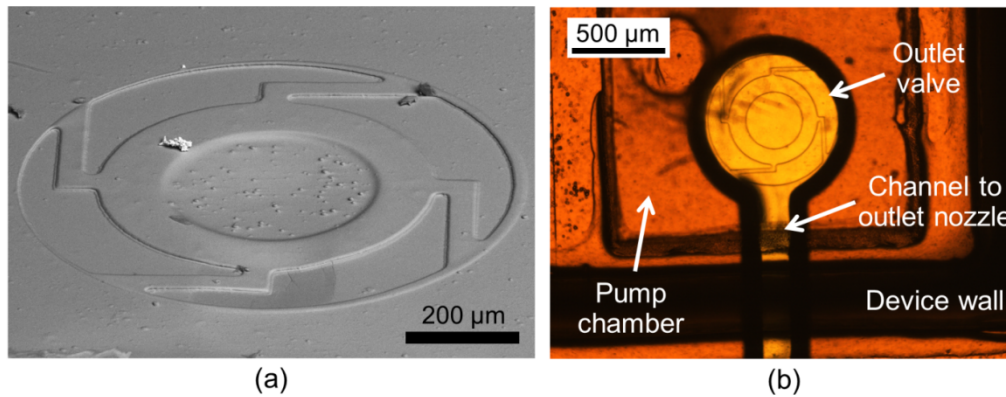


Fig. S2 (a) SEM image of a fabricated inlet valve and (b) optical image of a fabricated Parylene pump chamber and an outlet valve visible through the chamber wall. (Note that the tether design is different from that used in the valves discussed in the paper.)

The exterior and partitioning (between the reservoir and the actuator space) walls of the chip are prepared by mechanically micromachining a 1.52-mm-thick piece of polyimide (Fralock, CA, USA). A liquid polyimide (HD-3007, HD Microsystems, NJ, USA), serving as an adhesive, is spun onto a piece of 127- μm -thick polyimide and baked on a hotplate at 100 °C for 5 seconds. The microfluidic substrate containing the pump chamber is carefully placed on top of the polyimide piece to prevent the liquid polyimide from filling in the channels. The polyimide walls are fixed on the microfluidic substrate using HD-3007 as well. The combination is baked at 100 °C for 30 minutes with a pressure of ~ 40 KPa applied to it to solidify the adhesive and complete the bonding of the chip component (Fig. S1(h)). The 5- μm -thick Parylene layer on the through-hole region is punctured to connect the reservoir to the underlying channel. Two small pieces of 305- μm -thick polyimide (Fralock, CA, USA) are prepared and bonded onto the bottom side of the Nitinol actuator (refer to the next section). One piece is bonded at the capacitor end and another piece at the free end using HD-3007. The piece at the free end is used as a thermal barrier between the actuator and the pump chamber. The other piece is to raise the fixed end by an identical height. Additional HD-3007 is applied to the bottom side of the polyimide spacers, after which the actuator is placed in its designated spot above the pump chamber on the chip (Fig. S1(i)). The actuator is bonded in place by heating the entire device at 100 °C for 10 minutes, fixing the capacitor end of the actuator to the base of the chip and the free end to the top of the pump chamber. After cutting away the excess polyimide substrate protruding past the chip walls, a 305- μm -thick polyimide piece, shaped the same size as the chip and with an $800 \times 800 \mu\text{m}^2$ refill hole created in it, is finally bonded to the chip as the top cover to complete the chip fabrication.

Wireless LC-tank cantilever actuator

Actuator fabrication starts with thinning of an original sheet of Nitinol with 200- μm thickness (Alloy M, austenitic temperature (T_a) = 65 °C, Memry, CT, USA) down to 100 μm using a wet etchant (10% hydrofluoric acid and 30% nitric acid mixed in distilled water). Through a plasma-enhanced chemical vapor deposition process, 2 μm of SiO_2 is coated onto both sides of the Nitinol sample (Fig. S3(a)). To pattern each SiO_2 layer independently using the wet etchant, a layer of photoresist (SPR220-7.0, Rohm and Haas Co., PA, USA) is spin coated on a glass substrate and the Nitinol sample is placed onto it; the sample is then hard baked to adhere it and protect the SiO_2 on the underside from the etchant. A positive photoresist (S1813, Rohm and Haas, PA, USA) is then spun on and photo-patterned using a mask with the SiO_2 layer pattern. After developing the exposed photoresist, the SiO_2 is wet etched and patterned by immersing the sample in buffered oxide etchant (Fig. S3(b)), followed by dissolving the remaining photoresist. The sample is flipped over and bonded onto another glass substrate using SPR220 again to protect the patterned oxide and to keep the sample flat. The photoresist baking temperature is adjusted to be higher than T_a so that the Nitinol maintains its memorized flat shape while the photoresist solidifies. The SiO_2 layer on the backside (now facing up) is patterned in the same manner as the top side SiO_2 (Fig. S3(c)). Flipping the sample over again (top side facing up), a liquid polyimide (HD-3007, HD Microsystems, NJ, USA) is spun on as a dielectric layer for the capacitor (whose shape is defined by masking) and cured at 300 °C. After adhering the sample to another glass substrate, 15 nm of titanium followed by 150 nm of copper are evaporated through a patterned layer of S1813 to define the shape of the top capacitor electrode and the interconnect between the electrode and the coil's inner end (Fig. S3(d)). Then a dry-film negative photoresist (PM240, DuPont, DE, USA) with 37- μm thickness is applied on the sample using a hot-roll

laminator. The laminated photoresist layer is patterned to form an electroplating mold, after which 30-40 μm of copper is electroplated in the mold to thicken the top capacitor electrode as well as form the interconnect bridge (Fig. S3(e)). The excess areas of evaporated metal (with no electroplated structures) are lifted off by stripping all the photoresist. The sample is flipped over and bonded onto a glass substrate one last time (Fig. S3(f)); with the copper bridge on the underside, the Nitinol is finally micromachined into the designed rectangular spiral coil using a micro-electro-discharge machining (μEDM) system (EM203, SmalTec International, IL, USA) and then released from the substrate for final cleaning (Fig. S3(g)). A sample of the fabricated wireless actuator and its measured resonance are shown in Figs. S4(a) and S4(b), respectively.

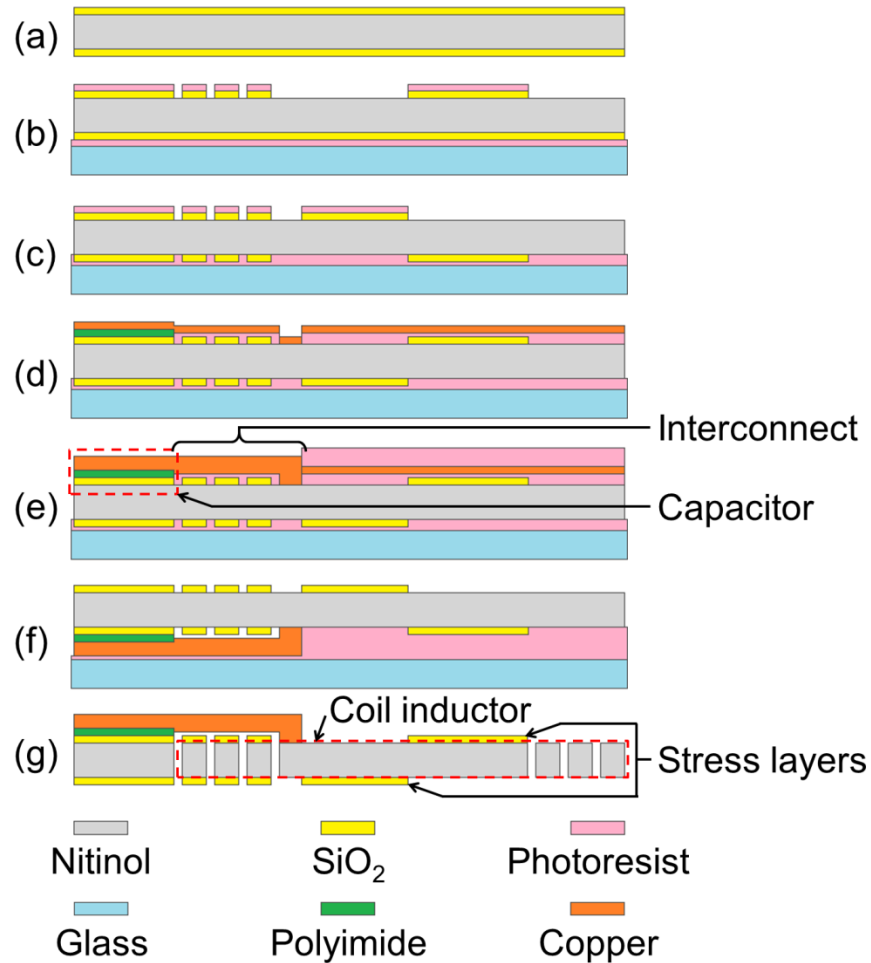


Fig. S3 Fabrication process flow (not to scale): (a) Deposit SiO₂ onto both sides of the Nitinol; (b) pattern top SiO₂; (c) pattern bottom SiO₂; (d) deposit polyimide and titanium/copper seed layer; (e) electroplate copper; (f) flip sample over and bond onto a glass substrate; (g) μEDM rectangular-coil in the Nitinol layer.

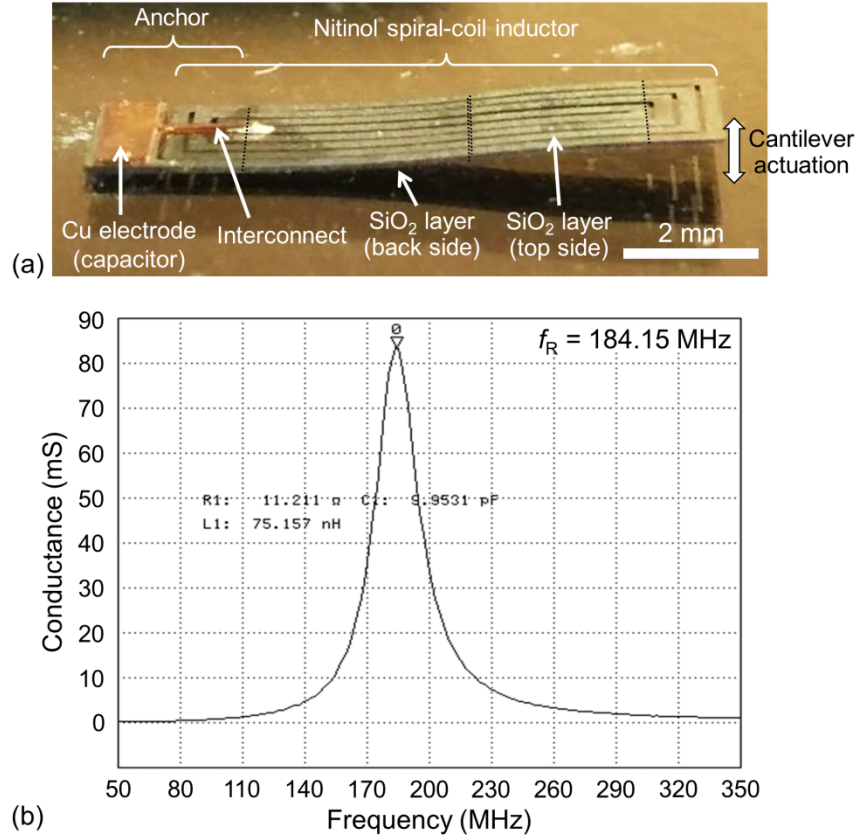


Fig. S4 (a) Fabricated Nitinol *LC*-tank actuator prior to integration with the microfluidic chip, showing its cantilever-like geometry with a displacement at its free end at room temperature. (b) Conductance of the tank resonator measured as a function of frequency showing the resonant frequency of ~ 184 MHz along with other electrical parameters. The conductance peaks at resonance because the reactance of the resonator becomes zero at this condition, maximizing the electromotive force wirelessly produced in the Nitinol inductive coil and hence the heat generation. This makes the Nitinol coil strongly dependent on the operation frequency for heating and actuation.

Conversion of ambient conductivity to released molar amount and volume

The concentration of the released chemical in the water ambient can be calculated using an formula found by interpolating the relevant data.² For example, in the case of saline, the following linear formula shows an excellent fit with the data (within 0.95% error for the conductivity range involved in the current study):

$$G = 21304C_w + 0.0904 \quad (1)$$

where G is the conductivity in $\mu\text{S}/\text{cm}$ and C_w is the concentration in %. The molar amount of the released chemical, m , can be calculated from the obtained concentration using:

$$m = \frac{C_w V_w}{M} \quad (2)$$

where V_w is the volume of the surrounding water and M is the chemical's molar mass. Assuming that the concentration of the chemical supplied to the pump chamber is constant, the volume of the agent ejected out of the device per pump, V_s , can be determined with:

$$V_s = \frac{(C_f - C_i)V_w}{C} \quad (3)$$

where C_f is the concentration after the reading stabilized, C_i is the concentration before pumping started, and C is the concentration of the agent in the reservoir. When backflow is present, the concentration of the agent in the pump chamber is reduced, consequently affecting the volume calculation. Knowing the molar change with each pump (quantified with the recorded conductivity data), the volume calculation can be compensated to estimate the actual volume of ejection. By comparing the molar amount of the agent ejected from one pump with the prior pump (Fig. 8(c)), the average decrease per pump was found to be $\sim 5\%$. Then each pump's volume was corrected by a factor of $1.05^{(n-1)}$ where n is the pump number.

References

1. V. Sridhar and K. Takahata, *Sens. Actuators A*, 2009, **155**, 58–65.
2. Conductivity Ordering Guide,
<http://myweb.wit.edu/sandinic/Research/conductivity%20v%20concentration.pdf>, (accessed October 2014).