# A Disposable Microfluidic Chip for Nanoliter Drug Injection
**(Invited)**

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## Introducton

Sample injection is essential function required in most micro chemical analysis systems including single-cell monitoring system which require accurate injection rate of infinitely small amount of drug or stimulant chemicals. In this paper, we report a disposable microfluidic chip which perform nanoliter drug injection for single-cell monitoring system, a micropump to control the sample liquid with low power consumption and low operation voltage, and a micromixer for fast and accurate mixing of chemical reagents.

## Micropump

Previously, a number of micropumps have been developed using various actuation methods. However, most of them require either high voltages (electrostatic, piezo actuation) or high powers (thermal, magnetic actuation). In recent years, Lee *et al.* reported the surface-tension-driven microactuation based on CEW with low power (10-30μW) and low voltage (1-3V) [1]. We have applied this actuation mechanism to build up the pressure to deflect pumping membranes by the mercury movement in a microchannel.

Fig.1 shows the structure of the proposed micropump illustrated with the principle of pump actuation. In step 1, with a positive applied voltage to the electrode, the mercury drop moves toward the outlet chamber and the membrane moves downward opening the valve in the inlet chamber while closing the valve in the outlet chamber. In step 2, the polarity of the applied voltage is reversed to make the mercury drop moves toward the inlet chamber and the actions in the two chambers are reversed. From a consequence of mercury motion due to alternating applied signals, the liquid flows

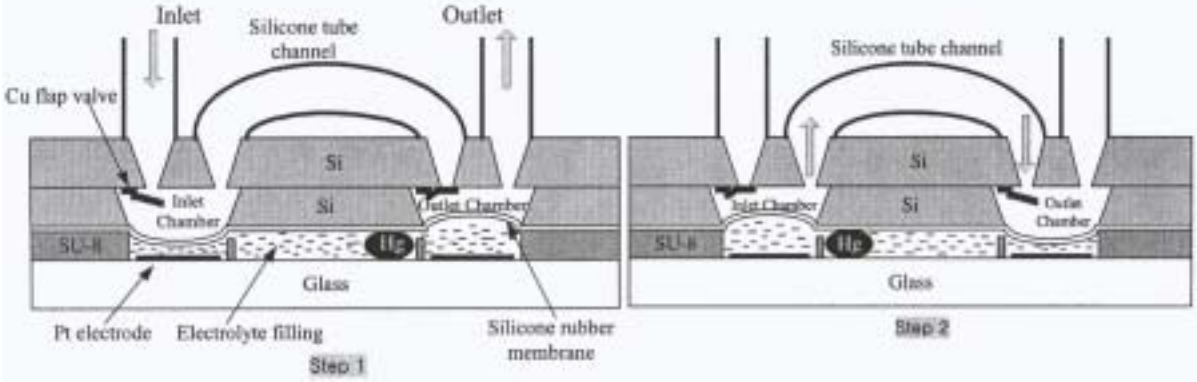


**Fig. 1:** Schematic view of proposed micropump and the principle of pump actuation.

from the inlet to the outlet.

The micropump is composed of three parts – CEW actuator, silicone rubber pumping membranes and copper flap check valves. The detailed processes have been reported on previous publication [2]. Fig. 2 shows the photograph of the mercury-placed actuator part. Fig. 3 shows the measured flow rates of the micropump using the silicone rubber membrane when the square wave voltages are applied. The maximum flow rate is measured as 70μl/min at frequency of 25Hz with applied voltage of 2.3Vpp. These experimental data demonstrate that the continuous electrowetting can be applied to micropump actuation with low voltage (<2.3Vpp) and low power (<170μW).

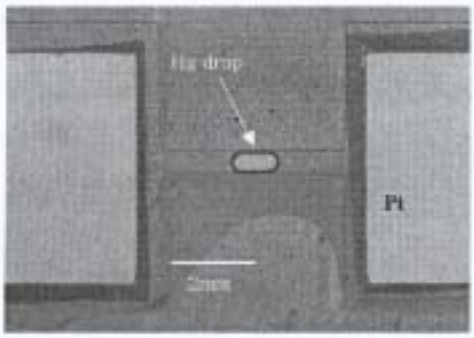


**Fig. 2:** Photographs of mercury-placed actuator

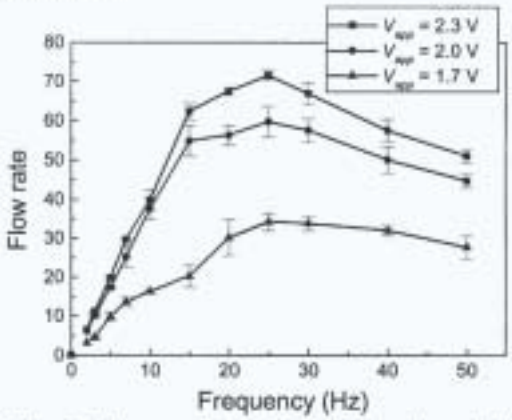


**Fig. 3:** The pumping rates as a function of the actuation frequency.

## Micromixer

Rapid mixing is essential in many of the microfluidic systems targeted for use in biochemistry analysis, drug delivery, and sequencing or synthesis of nucleic acids [3]. Biological processes such as cell activation, enzyme reactions, and protein folding often involves reactions that require mixing of reactants for initiation. Mixing is also necessary in many microfabricated chemical systems that carry out complex chemical synthesis.

Fig. 4 shows the schematic diagram of the proposed micromixer and photograph of the fabricated micromixer which has been fabricated using polydimethylsiloxane (PDMS) and SU-8 [4]. The mixer consists of two-layer channels and the mixing occurs in a two-step process. The first step is segmentation where a heterogeneous mixture of two fluids is formed by convection and the second step is the inter-diffusion of molecules between domains. The proposed mixer has a separated serpentine flow path in order to increase the chaotic advection as well as has the repeated segments to increase the interfacial area.

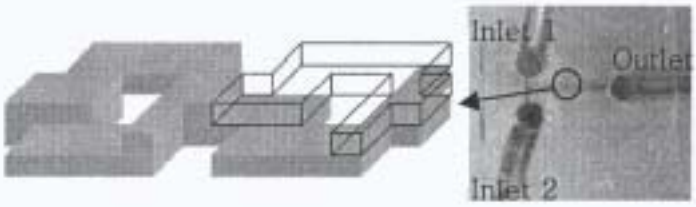


**Fig. 4:** Photograph of the schematic diagram of the proposed micromixer and fabricated micromixer.

We have tested the mixer using phenolphthalein, a pH indicator that changes from colorless to red

for pH values greater than eight. Fig. 5 shows the mixing of 0.1 mol/L phenolphthalein and 0.3mol/L NaOH in the microchannel connected in series. Fig. 6 shows the normalized average optical intensity in each stage of the fabricated mixer. After five or six mixing sections two streams were fully mixed.

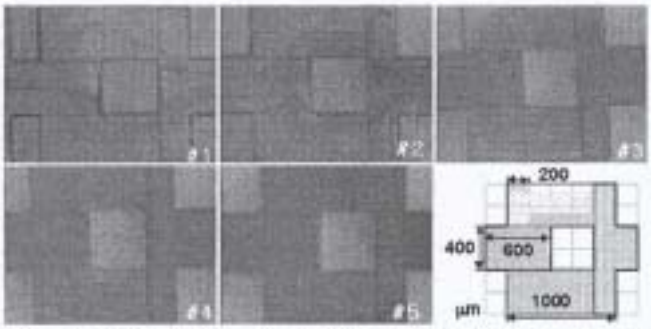


**Fig. 5:** Photographs of reacted phenolphthalein in the fabricated mixer (at flow rate 2mL/min).

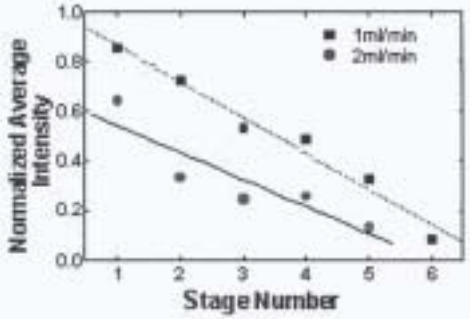


**Fig. 6:** Normalized average intensity in each stage of the mixer.

## Nanoliter Drug Injection

In micro total analysis systems (micro TAS), it is required to accurately control the infinitely small amount of reagents in the range of nano-, pico- and furthermore femto-liter chemical solution. The single-cell monitoring chips previously reported also require nanoliter drug injection onto the target cell to monitor the cellular response of the chemical stimulation [5].

The schematic view of the proposed cell-monitoring chip is shown in Fig. 7. The cell suspension media is introduced into the inlet by external pressure and single cell is positioned on each cell-positioning site. The drug or other chemicals can be injected on each captured cell through the corresponding injection channels and the resulting cell secretions may be monitored. The hydrophobic region is formed to prevent the cell suspension media from flowing into injection channel and allows the air to leak out during drug introduction.

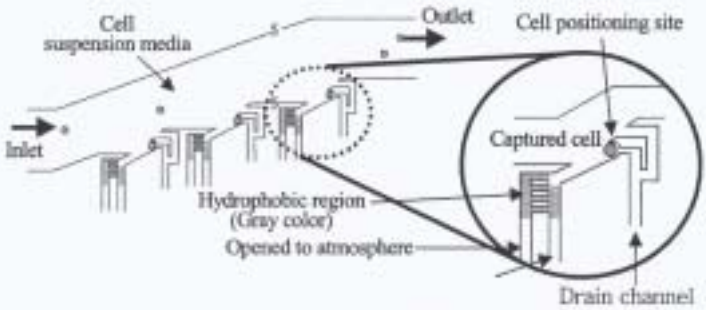


**Fig. 7:** Schematic view of the proposed cell-monitoring and nanoliter drug injection chip.

The device consists of a grooved PDMS and silicon substrate bonded together. The PDMS structure is formed by replica molding method using 20 μm-thick SU-8 molds. For the silicon structure, the silicon substrate is etched using RIE and the PECVD silicon nitride is deposited. Next, for the preparation of hydrophobic region, fluorocarbon (FC) film is spin coated [6] and patterned using lift-off process. Finally the PDMS surface is modified to hydrophilic surface using $O_2$ plasma treatment and bonded with silicon substrate. Fig. 8 shows the photograph of the fabricated device.

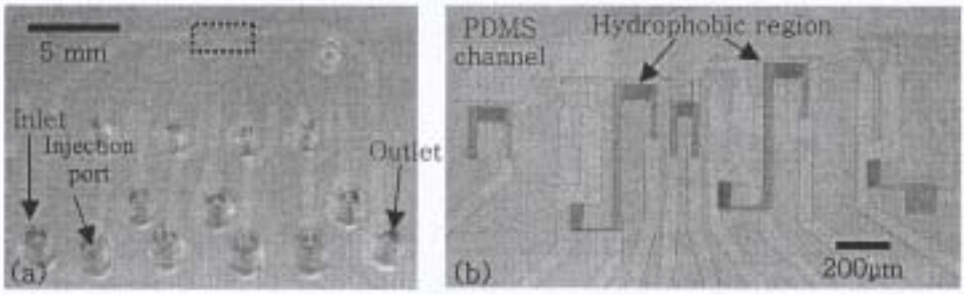


**Fig. 8:** (a) Photograph of fabricated device. (b) Detailed view of dotted region in (a).

Fig. 9 shows a sequence of drug injection. First a polystyrene bead (15 μm in diameter) is exactly placed on a cell-positioning site from the pre-determined flow stream as shown in Fig. 9(a). Next the blue ink is introduced from the injection channel (Fig. 9(b), 9(c)) and subsequently injected into the captured bead (Fig. 9(d)). During the ink injection, air in the injection channel can leak out through hydrophobic vent ports. Fig. 9(d) shows that the excess ink stream is drained out through the buffer drain channel located above the main drain channel, demonstrating the injected drug (in this experiment the injected ink) does not flow into other captured cells.

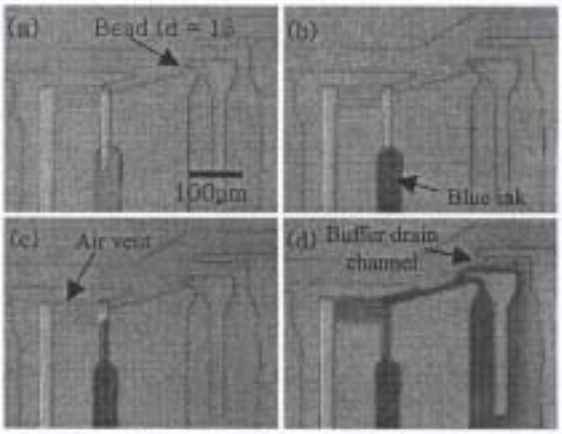


**Fig. 9:** Series of pictures during the drug injection(a) capturing a bead. (b) introducing blue ink (drug) from the injection channel. (c) overcoming the capillary force with increased injection pressure. (d) ink (drug) injection onto the captured bead.

## Conclusions

In this paper we have presented the structure of nanoliter drug injection for single-cell monitoring system and successfully demonstrated the nanoliter injection onto single micro-bead or cell. Also the surface-tension-driven micropump for low power consumption and low voltage operation and new 3-dimensional micromixer has been fabricated and successfully demonstrated.

## References

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