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Drug Delivery Micropump with Built-In Monitoring

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Abstract

We report on the fabrication of the first MEMS micropump including an integrated pressure sensor. The signal of this sensor allows direct insight into the pump's operating dynamics and enables real-time self-monitoring. We demonstrate the changes in the sensor signal under different pumping conditions, including the presence of air in the pumping chamber and a downstream occlusions. Deviations from normal operating conditions create clear and characteristic deviations from the normal signal. These deviations will be exploited to detect extraordinary or faulty pumping conditions during use.

Keywords: Micropump, pressure sensor, drug delivery, diabetes, self-monitoring.

1. Motivation

Today more than 240 million persons suffer from diabetes [1] and their numbers are increasing. The International Diabetes Federation estimates that already more than 8% of the adult population in Europe are diabetic. No cure is available until today, but therapies that allow the patients to live with their disease.

Persons suffering from diabetes type I have lost the ability to produce insulin and depend on its regular administration. Continuous injection of insulin into the subcutaneous tissue is the state of the art therapy for them [2]. Typically less than one milliliter of insulin is injected per day using an externally worn insulin pump. About half of the daily dose is injected continuously over 24 hours and the rest is injected in three to five doses before meals. Insulin is a very potent and potentially dangerous drug. Therefore the pump must provide not only excellent accuracy but also high reliability for a safe and efficient therapy.

Since patients wear their pumps continuously they have an understandable desire for a small and unobtrusive device. MEMS technology has the promise to shrink the size of insulin pumps considerably. Maillefer et al. [3] have previously demonstrated that a MEMS micropump can achieve the required flow rates and precision. We report here results of the first micropump including a pressure sensor. It enables the self-monitoring of the pump during use, a function essential to guaranteeing the safety of the therapy in real life conditions.

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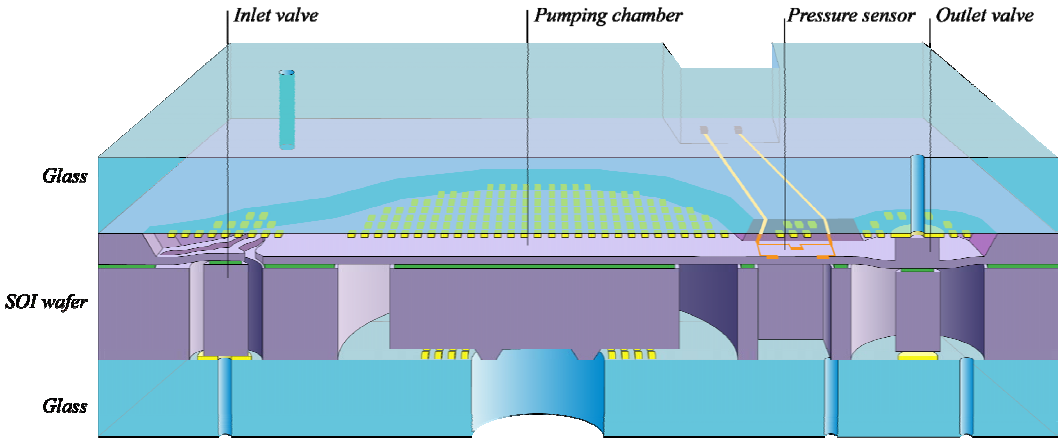

Fig. 1. Schematic cross section of the MEMS pump chip.

2. MEMS micropump

Debiotech's MEMS micropump is based on the membrane pump principle. Its schematic cross section is shown in figure 1.

2.1. Fabrication

The micropump chip is fabricated from two glass wafers and a silicon-on-insulator (SOI) wafer. In a first process sequence we form a shallow cavity on the SOI wafer using wet etching. This leaves a thin silicon membrane on the buried oxide (BOX). The cavity serves as the pumping chamber and the thin membrane will form all flexible elements of the pump. In the next sequence we define conductive regions in the membrane through ion implantation. We define the mobile elements of the pump and free the membrane with deep reactive ion etching from both sides of the wafer. The BOX layer is used as an etch stop for the DRIE and is removed afterwards where exposed.

On the two glass plates we first deposit and structure an isolating thin film called anti-bonding layer (ABL). Next, through holes are drilled in the glass. Finally the SOI wafer and the glass plates are anodically bonded together. The ABL locally prevents bond formation between the SOI wafer and the glass plates. The chip size is 6.5 mm by 9.5 mm.

2.2. Components

The MEMS micropump contains a pumping chamber with a flexible pumping membrane, two passive check valves and a pressure sensor. The inlet valve consists of a moveable silicon cylinder blocking the flow through a hole in the lower glass wafer. This cylinder is suspended on three flexible silicon cantilevers. The ABL forms the valve seat on the glass plate. It prevents bonding of the silicon cylinder to the glass plate and preloads the cantilevers. The valve is thus closed by default. Only if the pressure difference on the valve is sufficiently high, the cylinder is pushed away from the glass plate and the valve opens. The outlet valve has a very similar structure to the inlet valve with the cylinder suspended from a flexible silicon membrane.

The pumping chamber is a cavity formed between the central SOI wafer and the top glass plate. The SOI wafer is micromachined to form a flexible membrane with a central rigid boss on the backside. A piezo actuator (not shown) is attached to the boss through a hole in the lower glass plate. It drives the membrane upwards and downwards between the two mechanical stops: The upper glass plate limits the upward movement. The lower glass plate limits the downward movement. The piezo is dimensioned with sufficient force and deflection to reach both limiters under all specified working conditions. This double limiter design ensures a constant membrane stroke and for

incompressible fluids a constant displaced volume. The resulting precision and performance have been reported previously [3]. The micropumps presented here displace 200 nL per pumping cycle.

A pressure sensor is integrated between the pumping chamber and the outlet valve. It consists of a silicon membrane with an implanted piezo-resistive strain gauge in a Wheatstone bridge configuration. The membrane's front side is in direct contact with the pumped liquid, whereas the backside is communication with the ambient air. Thus the sensor measures the pressure inside the pumping chamber relative to the ambient. Its sensitivity is 0.3 mV V^{-1} kPa^{-1}.

3. Experimental results

The curve in figure 2 (a) shows the pressure sensor signal during a normal pumping cycle. It starts with the membrane flat, halfway between the two mechanical stops. At 0.1 seconds the actuator starts pushing the membrane towards the upper glass plate, compressing the fluid in the pumping chamber and thus increasing the pressure sharply. The increased pressure forces the outlet valve open and expels fluid. When the membrane comes to rest against the upper glass plate the pressure drops and the outlet valve closes. The pressure becomes stable. As soon as the actuator pulls the membrane towards the lower glass plate the pressure decreases sharply. The inlet valve opens and the pumping chamber refills. When the membrane settles on the lower glass plate the pressure recovers and the inlet valve closes. In the last phase the membrane returns to the initial position, again rising the pressure briefly and expelling fluid.

This pressure curve of a normal pumping cycle shows a number of characteristics that are indicative of the pump's behavior and its surrounding conditions. Among these are the timing and the shape of the three peaks and the level and slope of the three plateaus between the peaks.

3.1. Priming

Figure 2 (b) shows the pressure evolution during self-priming. Initially the pump is dry, liquid is contained in a reservoir upstream of the pump. At time 0 the actuator starts to drive the pump, with three cycles per second. Because the pumping cycles closely follow each other, the positive peak at the end of a cycle and the one at the beginning of the next merge into a single one. Initially the oscillation's amplitude is smaller than normal. Since the air in the pumping chamber is compressible and less viscous than the insulin, the pressure excursions are less pronounced. After a few strokes the amplitude increases and within three seconds stabilizes, indicating that the pump has been primed. From these results it is understood how the progress of the priming, that is, the expulsion of air from the pumping chamber, can be inferred from the pressure sensor signal.

3.2. Inlet pressure variation

Figure 3 (a) shows the sensor signal when different pressures are applied at the inlet of the micropump. We can observe that the plateau after the refilling phase is shifted downwards, proportional to the inlet pressure decrease.

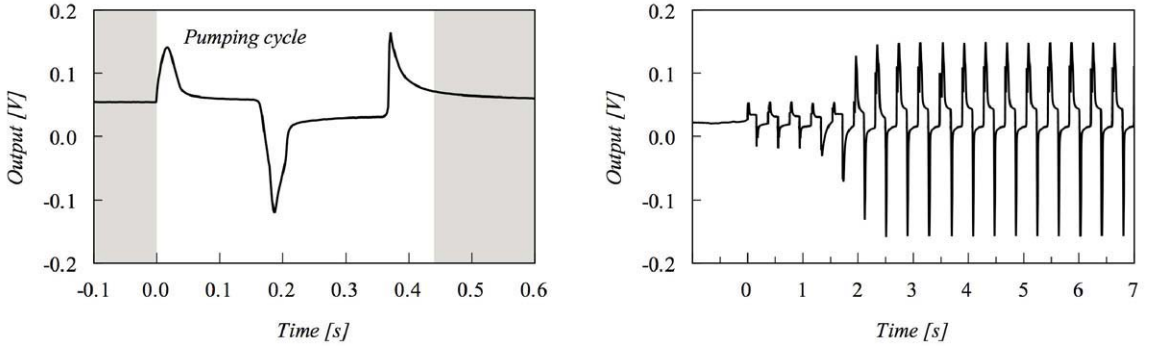

Fig. 2 (a) Pressure curve during a normal actuation cycle; (b) Pressure curve during initial pump priming.

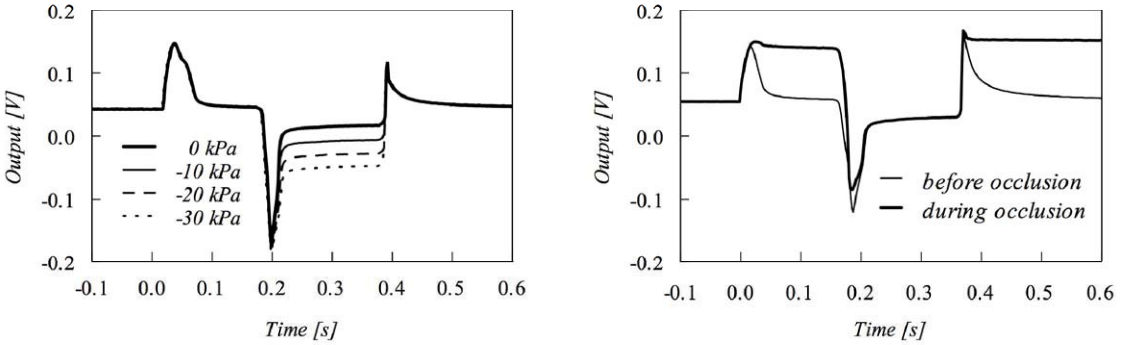

Fig. 3. (a) Pressure curves with different pressures applied at the pump's inlet; (b) Pressure curves of the last cycle before and the first cycle during a downstream occlusion.

3.3. Occlusion detection

A commercially available insulin infusion set (length 1.09 m, volume app. 100 µL) was connected to the micropump and primed. The pump was set to perform a cycle every twelve seconds, resulting in a flow rate of 60 µL/h. After some normal pump cycles the outlet of the infusion set was blocked creating a downstream occlusion. Figure 3 (b) shows the sensor signals of the last cycle before and the first cycle during the occlusion. We observe that the first and third plateaus are clearly higher during the occlusion than before. This demonstrates that an occlusion can be detected during the first pumping cycle, within less than one minute. Current insulin pumps, all based on syringe drive mechanisms, would require typically more than two hours to detect a similar occlusion.

4. Summary and outlook

We have reported on the fabrication of a first MEMS micropump including a pressure sensor. We have demonstrated that the signal of this pressure sensor allows direct insight into the dynamics of the membrane pump. We have further demonstrated how different working conditions clearly and characteristically change the sensor signal. We conclude that this unique pressure sensor will be a valuable means to determine the pump's condition during use. We expect that this MEMS enabled, real-time self-monitoring, will provide unmatched safety features to future insulin pumps.

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