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Microfluidics for the treatment of the hydrocephalus

E. Morganti, G.U.Pignatel

Università degli Studi di Perugia, Via Duranti 93 06100 Perugia-Italy.
DIEI- Dept. of Electronic and Information Engineering
elisa.morganti@diei.unipg.it

Abstract

The aim of this work consists in investigating how micro fluidic systems realized with different micro-electro-mechanical (MEMS) technologies and telemetry sensors can be applied in the treatment of the human disease called hydrocephalus. In particular we will evaluate system performances in terms of maximum allowable flow-rate and valve efficiency.

Keywords: Hydrocephalus, microfluidic, telemetry sensor

1 Introduction

Hydrocephalus is a disease that can be congenital or acquired. It strikes 1 out of 500 children (in Italy) with lethal or invalidating consequences [1]. It manifests in an excessive accumulation of liquor in the brain. Liquor or cerebrospinal fluid (CSF) is a limpid, without colour liquid with density of 1005-1009 g/l. Its composition is similar to the blood plasma. The CSF is continuously produced in the ventricles, it flows in the cavity of the cranial base and finally it is absorbed. In the 24 hours the CSF is renewed three times.

For the hydrocephalus treatment, techniques of liquor derivations, called shunts, are used. They consists of a catheter placed in the brain, a valve that allows the fluid to flow only in one direction and a catheter that unloads the liquid in blood. This system has the drawback of not to react instantly and effectually to the variations of intra-cranium pressure. The solution to these limits can be found in a closed loop system constituted of an intracranial pressure sensor, a micropump that can move the liquor according to the data collected by the sensor and a control system. A complete shunt system like this has been presented in the framework of a research project from the University of Ajou, South Korea [2].

The particular application we are dealing with imposes several limits to the design of the system. These limits are mainly related to the compatibility with the human body and to the required performance. Liquid pressure is an important parameter to take into account. It must not go under 6 KPa in order to avoid air bubbles, and it should not exceed 1360 KPa so as do not damage internal organs. Maximum dimensions of the micropump must not exceed 3cm^2. The required flow rate should be 2ml/s (Table 1). In this work, we will present a panoramic view on the technologies and the materials that can be used in this particular application.

Table 1 Biomedical specifications

Feature	**Value**	**Comment**
Liquid pressure	Min 6 Kpa	No bubbles
INLET pressure	1360 Kpa	Inner body pressure
INLET tube	Diameter=1,2mm	Length=12cm
OUTLET tube	Diameter=5mm	Length=50cm
Flow-rate	2ml/s	Typical
Dimensions	1cm x 2-3cm	Max

2 CSF shunt system

2.1 Intracranial Pressure Sensor

A pressure sensor commonly used in the monitoring of intracranial pressure is supplied by Codman, an American Company specialized in the development of diagnostic and therapeutic products. The sensitive element consists in a silicon membrane in which piezo-resistors are inserted and connected in a Wheatstone bridge configuration. A nylon wire connects this transducer to an electronic interface.

The principal drawback of this kind of pressure monitoring is the presence of a connection wire, which makes the sensor not fully implantable.

A solution can be represented by the use of a telemetry wireless sensor, which could eventually be realized with a resonant LC circuit. An example of such kind of sensor is schematically represented in figure 1. It consists of a glass wafer on which a copper coil is deposited. A Cr/Au plate performs as electrode. The second electrode can be realized on a p+ silicon wafer. The method of pressure measurement is based on inductive coupling.

The capacitance between the coil and gold plate on the *p+* diaphragm depends on the diaphragm deflection caused by pressure variations. The sensor has a resonance frequency due to the coupling of his capacitance with the self inductance of the coil. An external loop antenna is feed with a VCO. When the resonance frequency of the magnetic field generated by the alternate current in the external coil, matches the resonance frequency of the sensor, the impedance of the external coil changes. Pressure variations are calculated by measuring the amplitude of the impedance peak at the resonant frequency, or the amplitude or the impedance peak at constant frequency or phase [3].

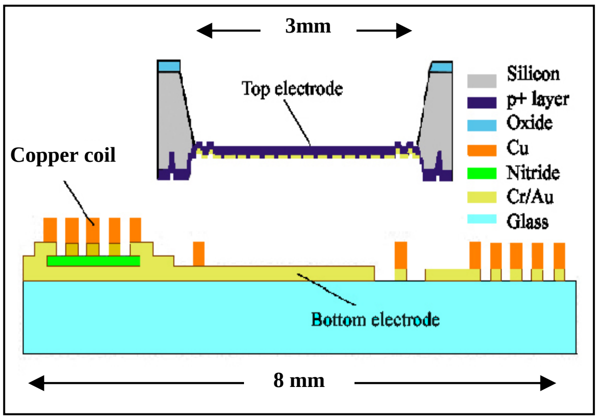


Figure 1 Telemetry sensor (electrodes not to scale). The total size of the sensor is 7.8mmx8mm. The gap between the two electrodes is 10μm

2.1.1 Micropumps

Microsystems are more and more diffused in different application fields, from automotive to medicine. And the micropumps cover a fundamental role in the microfluidic systems. Usually the micropumps are composed by an actuator, a mobile membrane that moves the fluid inside a pumping chamber and a certain number of inlet and outlet valves. The micropump performance can be modified to fulfil the required specifications, by choosing accurately the actuation method and the dimensions of the several parts that constitute the entire structure. Until today the research in the micropump field concentrates mostly on the project of microsystems able to manipulate smaller and smaller volumes, of the order of few picoliters. Micropumps are used in the so called lab-on-chip (μTAS) or for reagent and drug delivery as, for example, in case of the insulin for diabetic patients. Very few studies focus on the search of high flow-rate micropumps, as required by our application.

There are several methods to actuate a membrane micropump; however we focused our attention on a) piezoelectric; b) thermopneumatic; c) electromagnetic actuations because they yield higher flow-rates.

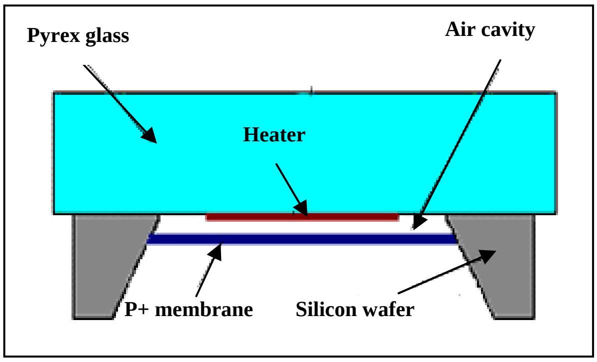
a) a piezoelectric actuator is a ceramic disc that deforms when a voltage is applied to its faces. The resonance frequency of a piezoelectric disc attached to a silicon membrane together with its maximum deflection can be calculated by means of a Finite Elements Method (FEM) program (like Ansys). For example, we have estimated that a silicon square membrane, whose dimensions are 2.3mmx2.3mmx23 μm coupled with a commercially available piezoelectric crystal (PZT-5H), gives a deflection of about 1μm at 22KHz at an applied voltage of 190V. At the resonance frequency the current density on the piezoelectric disc is about 10mA/m^2.

In the framework of a Multi-Project-Wafer we have designed a piezoelectric micropump, whose dimensions are reported in table 2. First prototype of this microsystem is currently being processed at SensoNor, Norway. Spice simulations of the equivalent electric circuit of the designed micropump are reported in ref. [4]. The micropump exhibits a theoretical maximum flow-rate of 25.5μl/s at 170Hz.

Table 2 – Dimensions of the designed micropump

Elements	Value
Membrane length	2,3 mm
Membrane thickness	23 μm
Actuator length	2 mm
Pump chamber depth	400 μm
Valves length	1 mm
Minimum valves section	250μmx250μm
Valves aperture angle	10°

b) thermopneumatic actuation takes place thanks to the heating of the air inside a cavity over the membrane. When the air heats, the pressure that it exercises on the membrane increases, causing the membrane to deflect. A Cr/Au layer can be deposited on a glass substrate and it performs as the heater. The glass is then bonded to a silicon wafer. Figure 2 shows the working principle of a thermo pneumatic



actuation.

Figure 2 Thermopneumatic actuation. Actual dimensions are: thickness = 900μm and length = 4cm.

It is reported that, using a 4mmx4mm silicon membrane, the max deflection experienced is 37.5µm, if a voltage of 6V is applied for 3s [5]. The heating and cooling time is 0.75s. So, the working frequency can't be high. Driving the micropump with 4Hz, one can obtain a flow-rate of about 14µl/min.

c) an electromagnetic actuator may consist on a permanent magnet embedded in a suitable chamber (figure 3). A copper coil can be deposited on top of a parylene membrane. As reported in ref. [2], the permanent magnet is commercial rare-earth neodymium (NdFeB). In that case, if a current of 380mA is forced in the coil, a membrane deflection of 143µm occurs at a resonance frequency of 35Hz, without considering the presence of the fluid. When the pumping chamber is filled with an aqueous solution and the valves are inserted, an applied voltage of 5V produces a flow-rate of 230µl/min at 2.5Hz.

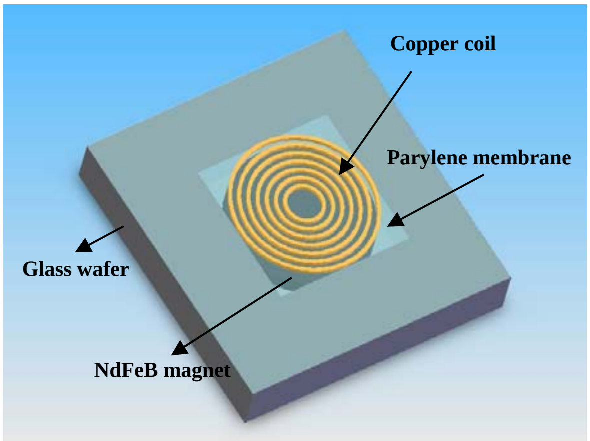


Figure 3 Electromagnetic actuator. Side=2mm

In the design presented in ref. [2], the micropump is fed trough golden electrodes connected to an external source. In principle, such sort of structure can be wireless actuated with an external antenna coil or with a rotary magnet.

2.2 Other solutions

A solution similar to the one described above has been reported by the Ecole Polytechnique Fédérale of Lausanne (EPFL) [6]. In that case the micropump is made of two glass wafers bonded together in which a pump chamber and two valves are etched. The valves have a ball inside which allows the flow only in one direction. The membrane is made in a PDMS (poly - dimethyl siloxane) polymer and a composite magnet made of NdFeB magnetic powder is integrated on it. The actuation takes place thanks to an external coil with a resistance of 230Ohm. For a sinusoidal current of 100mA a flow-rate of 6ml/min is achieved at 20-30Hz.

Another PDMS micropump with ball valves has been designed at the Minnesota University. In this case a flow-rate of 1ml/min at 6Hz with a power consumption of 13mW was obtained [7].

For what concern the pressure sensor, a batteryless telemetric sensor has been developed by the Integrated Sensing System, Ypsilanti USA (ISSYS). Such sensor can measure the pressure with high accuracy and rapidity. It has been positively tested on animals and it can wireless communicate until a distance of 15 cm [8].

3 Micropump performances

3.1 Actuator

Three parameters act a fundamental role in the membrane actuators' performance: the volume stroke (Vs), the working frequency (f) and the power consumption (Pw). The product between Vs and f directly determines the pumping rate (Q). The electromagnetic and the piezoelectric actuation give a higher pumping rate than the thermopneumatic one. The piezoelectric actuator needs a high voltage to vibrate and the maximum deformation is limited by the crystal oscillations amplitude.

The use of an electromagnetic actuator requires more power, but in the other hand, it can be wireless driven with telemetric techniques. Moreover the large deflection obtained with this kind of actuation results in a high-compression ratio of the chamber and makes the micropump self priming. However, silicon based micropumps have a reduced stroke volume due to the elevate Young modulus. The use of PDMS or other polymers reduces this limitation, resulting in best performances. In addiction, materials chemical inertness and biocompatibility are relevant aspects for implantable devices.

3.2 Valves

The working frequency and the general performances of the whole micropump are greatly dependent on the valve design. For the specific application of hydrocephalus, it would be better using valves without moving part. In fact suspended particles in the CSF could obstacle the correct functioning of mobile part as membrane or cantilever.

For that reason, the use of nozzle/diffuser, and tesla [1] valves should be preferable.

Nozzle and diffuser valves have a very simple structure, consisting essentially in a properly shaped duct. However, the drawback of these valves is their low efficiency. The efficiency E can be defined as (1):

$$E = \frac{\left|\phi_{div} - \phi_{conv0}\right|}{\phi_{div}} \qquad (1)$$

where Φ_{div} and Φ_{con} are the flow in the divergent and convergent versus of the valves side walls, respectively. Valves with a small aperture's angle (diffuser) may have an efficiency of about 0.4. The efficiency decreases for higher aperture's angle until 0.2-0.3. An efficiency close to 1 means that the valve presents very low leakage flow and a great level of one way directionality. This feature must is desirable to have better performance and to avoid dangerous reflux.

A Tesla valve performs as a diode with efficiency up to 0.8. In the case of a Tesla valve, the efficiency is defined as (2):

$$E = \frac{\left|\phi_{backward} - \phi_{forward}\right|}{\phi_{backward}} \qquad (2)$$

where $\Phi_{backward}$ and $\Phi_{forward}$ are the flow rate in the backward and in the forward direction respectively. A Tesla valve has a bifurcated channel that re-enters the main flow channel perpendicularly when the flow is in the reverse direction, decreasing the net flow in that direction. The final results are a good one way directionality and low pressure losses. Figure 4 and 5 show a FEM static simulation of a valve with two bifurcations that presents an efficiency of 0.65 if a pressure of 6KPa is applied.

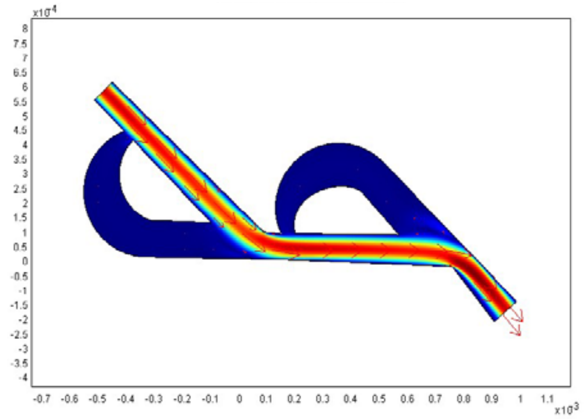


Figure 4 Velocity field of a tesla valve in the forward direction with an applied pressure of 6KPa. X, Y dimensions are in meters.

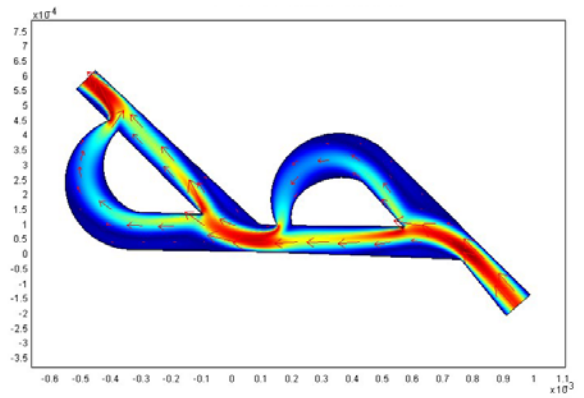


Figure 5 Velocity field of a tesla valve in backward direction with an applied pressure of 6KPa. X, Y dimensions are in meters.

4 Fabrication techniques

Silicon micropump can be made with conventional techniques used in MEMS fabrication like thin films deposition, wet and dry etching, lithography, anodic bonding, and deep reactive ion etching (DRIE).

Newest technologies as micro erosion with powder blasting, photo-selective etching [10], Advanced Deep Reactive Ion Etching (ADRIE) [11] allows valves and channel to be etched with high aspect ratio also in amorphous materials as, for example, glass.

Polymers are more and more attractive materials because they are cheap, flexible and they can be easily and quickly molded. Moreover polymers are biocompatible and integrable into hybrid devices. There are several technologies for their fabrication as Soft-Lithography, Injection Molding, Hot embossing, Micro contact printing, Photo-polymerization [12] . Figure 6 shows a schematic representation of four examples of soft-Lithography techniques, i.e. Replica Molding, micro Transfer Molding, micromolding in capillaries and solvent assisted micromolding. The most attractive feature of these techniques consists in the possibility to fabricate nano-structures with dimensions down to 30nm.

The most used polymer in microfluidics is PDMS which is transparent and can be made hydro repellent with an exposure to Oxygen Plasma.

The SU-8 is a polymer commonly used in the construction of mold and as structural support for high aspect ratio micro-channels. It is also used as thick photo resist in photolithography.

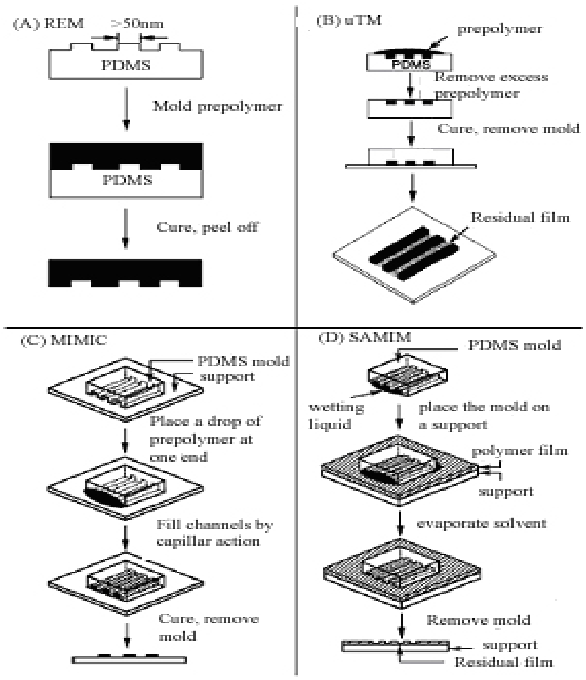


Figure 6 Schematic illustration of Replica Molding (REM), Microtransfer Molding (μTM), micromolding in capillaries (MMIC), and solvent assisted micromolding (SAMIM) techniques.

5 Conclusions

In this work we have examined the influence of micro valves, micro actuators and fabrication technologies in the realization of high flow-rate micropumps. In table 3 a comparison between the three different kinds of actuation methods introduced in section 3.1 is presented. From the evaluation of the data reported in the table, piezoelectric actuation seems to be the best choice in order to obtain a high flow-rate. However, piezoelectric discs need an elevate voltage to operate and this is difficult to be obtained wireless.

Table 3 - Comparison Table

Actuation technology	**Flow-rate (μl/s)**	**Freq. (Hz)**	**Dimensions (mm^3)**
Piezoelectric	25.5	170	6x6x1.5
Thermopneumatic	0.23	4	6x6x1.5
Electromagnetic	3.8	2.5	14x9x6

In conclusion, according with the considerations made so far, we can assert that the most suitable combination of materials, technology and design for obtaining a fully implantable micropump with high flow rate, seems to be: i) electromagnetic actuation ii) polymeric membranes (PDMS), iii) tesla valves.

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