



An Implantable Microsystem for Tonometric Blood Pressure Measurement

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Abstract. This paper presents an implantable microsystem for tonometric blood pressure measurement in small animals. The microsystem consists of four major components: (1) a titanium base for supporting a pressure sensor and an interface chip, (2) a micromachined capacitive pressure sensor array, (3) a switched-capacitor interface chip, and (4) a titanium cap. A new micromachining fabrication process has been developed to create capacitive pressure transducers with a flat surface necessary for tonometric pressure measurement. An array of three capacitive sensors is used to increase signal output and improve stability. A custom-designed switched-capacitor CMOS interface circuit is used to measure changes in capacitance. *In vitro* calibration tests have been performed on the complete cuff using a silastic tube to mimic a pliable blood vessel. A sensitivity of 2 mV/mmHg @ 100 mmHg and a resolution of 0.5 mmHg (based on 1 mV RMS interface chip noise floor) has been obtained. The dimensions of the cuff system $10(L) \times 6.5(W) \times 3(H) \text{ mm}^3$.

Key Words. implantable microsystems, tonometry, bioMEMS, biomedical microdevices, blood pressure measurement, biomedical transducers

1. Introduction

Chronic measurement of arterial blood pressure in small mammals is a cornerstone of basic research in hypertension and cardiovascular physiology [1]. A variety of implantable or external pressure measurement systems have been used for long-term monitoring of arterial blood pressure in various animal models [2]. External measurement systems can be classified as either direct or indirect. Direct techniques are more accurate and can provide a better frequency response but require catheterization and penetration of the blood vessel. Indirect measurements can be performed non-invasively (external cuff techniques) but are less accurate and incapable of providing adequate frequency response in more demanding applications (they only measure systolic and diastolic pressures). Implantable systems are advantageous for long-term monitoring due to their unobtrusiveness, higher accuracy, and extended frequency response. However, long-term baseline stability

has been a major requirement, and still poses many challenges to the successful deployment of implantable pressure sensors. An excessive baseline drift requires frequent calibrations which is time consuming and impractical when access to the animal is not possible.

Most commercially available implantable sensors are piezoresistive devices (e.g., Data Sciences International, Roseville, Minnesota [3], and Konigsberg Instruments Inc., Pasadena, California [4]), which either penetrate the vessel (Konigsberg), or connect to the vessel via an indwelling catheter (Data Sciences Int.). Both of these systems are invasive (i.e., blood vessel has to be penetrated) and carry the risk of creating blood clots. In addition, these sensors have a long-term baseline drift of $>5 \text{ mmHg/month}$, which is excessive for applications in low-pressure systems (e.g., venous and urogenital system) or experiments that require a few months of continuous monitoring. To overcome the aforementioned shortcomings, we have developed an implantable microsystem for tonometric blood pressure measurement. Arterial blood pressure measurement with this microsystem does not require penetration of the blood vessel, is highly accurate, provides adequate frequency response, and is less prone to long-term baseline drift. In Section 2, we discuss the tonometric measurement principle followed by the microsystem structure and design in Section 3. Section 4 presents the pressure sensor fabrication technology followed by a discussion of the measurement results on a prototype design in Section 5. Finally Section 6 draws some conclusions from the results of this work.

2. Tonometric Measurement Principle

Tonometry is a non-invasive technique for continuous measurement of pressure in closed vessels (blood vessels, uterus, bladder, intraocular, and brain pressure). This approach has been used quite successfully to measure intraocular pressure [5,6]. However, the application of tonometric technique to blood pressure measurement has had a limited success [7]. Figure 1

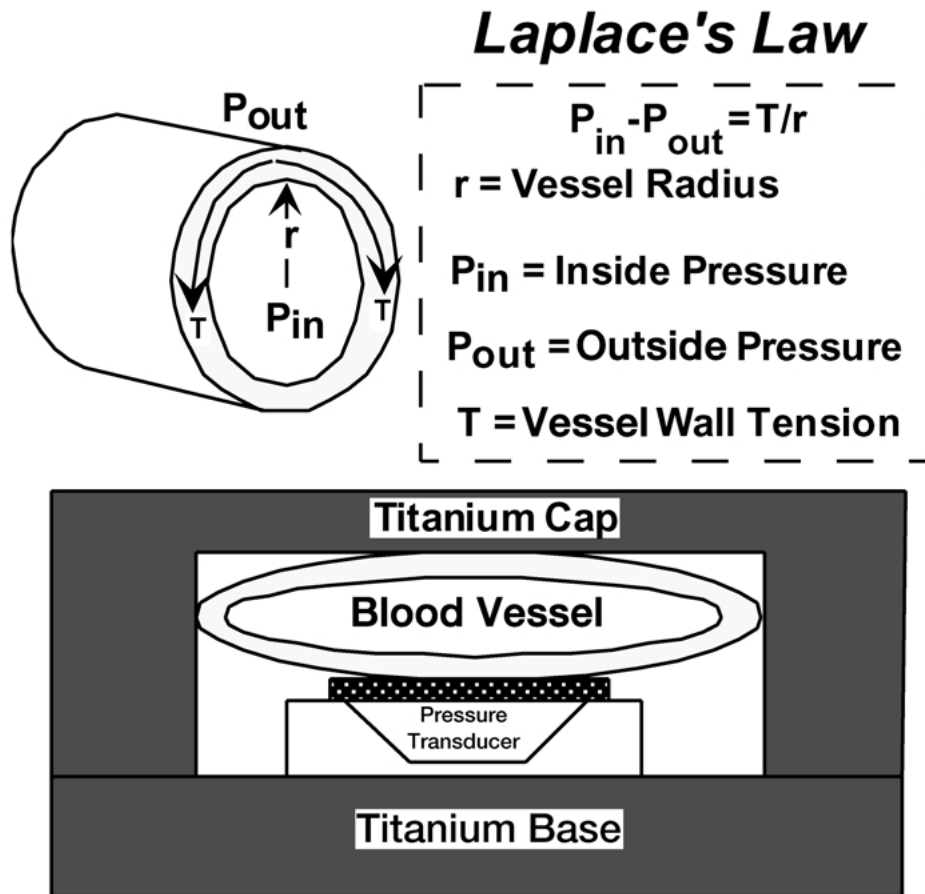


Fig. 1. Basic principle of tonometric blood pressure measurement.

illustrates the principle of tonometric blood pressure measurement [8]. The blood vessel is pressed flush against the sensor surface until appropriate flattening is achieved. According to the Laplace's law, pressure gradient across a thin-walled vessel is given [8] by:

$$P_{in} - P_{out} = \frac{T}{r} \tag{1}$$

where P_{out} and P_{in} are the pressures outside and inside the vessel (in Pa), respectively, T is the vessel wall tension (i.e., wall stress \times thickness, in N/m), and r is the vessel radius (in meter). This equation assumes that the wall thickness is much smaller than the vessel radius (by a factor of 10), which is correct for most blood vessels. As can be seen, if the vessel wall is completely flattened against a smooth sensor surface ($r \rightarrow \infty$), the measured pressure will be equal to the intra-luminal blood pressure ($\Delta P \rightarrow 0$). Three important requirements regarding this measurement technique are: (1) the hold down force should flatten the vessel wall without creating occlusion or significant hemodynamic disturbance, (2) the pressure

sensor diaphragm should be stiffer than the vessel wall, and (3) the pressure sensor active area (i.e., its membrane) should be smaller than the artery. The second requirement is to ensure appropriate flattening and prevent any excessive bending of the vessel wall during the measurement.

External arterial tonometers that are placed against the radial artery (wrist location) have not been commercially successful. Two major reasons for this failure have been the inaccuracies caused by imprecise positioning of the sensor and the degree of arterial flattening (excessive wrist movements can cause error in pressure measurements). Implantable tonometers are less prone to these sources of error due to their limited movements, which can be achieved by proper holding mechanisms. In addition, multiple element miniature sensors fabricated using micromachining technologies greatly reduce these placement inaccuracies [9]. Piezoresistive or capacitive transduction mechanisms can both be used for an implantable tonometric microsystem. In this work, we have chosen a capacitive sensing scheme due to their higher sensitivity, lower power consumption, and lower

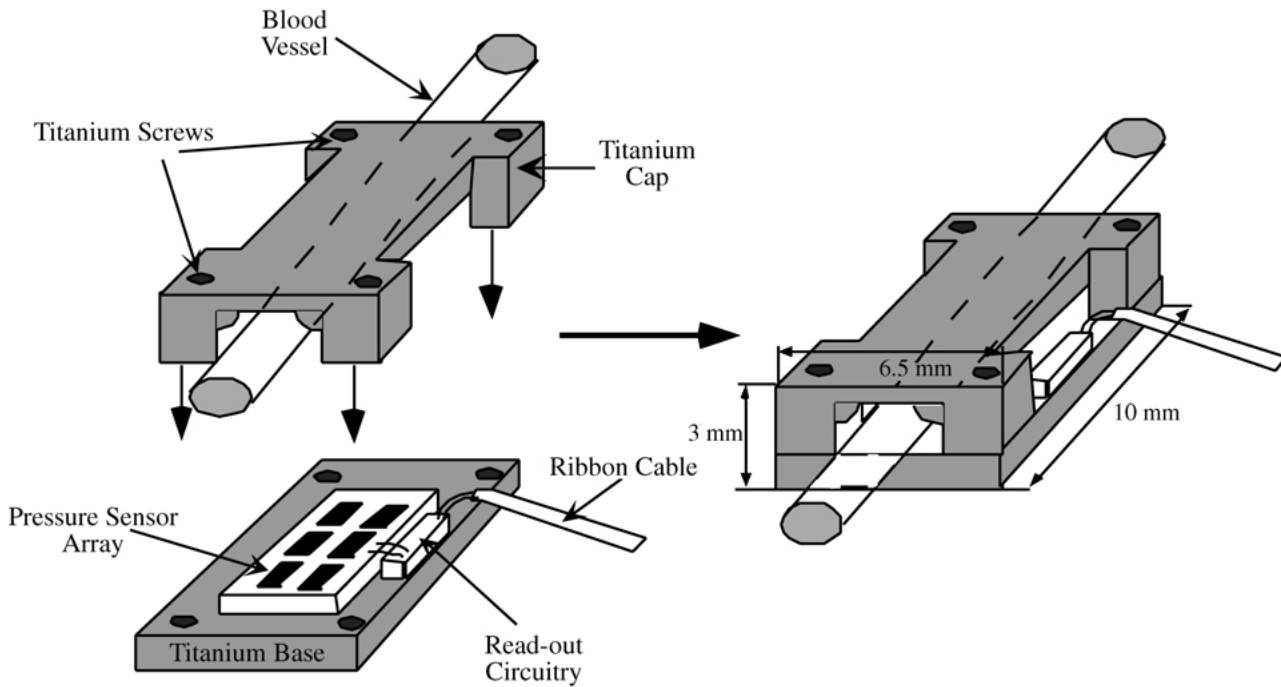


Fig. 2. Pressure sensor cuff microsystem for tonometric blood pressure measurement.

baseline drift [10]. However, capacitance variations in micromachined pressure transducers are small (in the femto-farad) and a read-out circuitry located close to the sensor is needed to achieve the required accuracy in the presence of large parasitic capacitances.

3. Microsystem Structure and Design

Figure 2 shows the implantable microsystem developed for tonometric blood pressure measurement. The microsystem consists of four major components: (1) a titanium base for supporting the pressure sensor and interface chip, (2) a micromachined capacitive pressure sensor array, (3) a switched-capacitor interface chip, and (4) a titanium cap.

3.1. Pressure sensor design

The micromachined capacitive pressure sensor was designed to measure arterial blood pressure in small mammals. The measurement site was chosen to be a rat's descending aorta (1.5–2 mm in diameter, 0.1 mm wall thickness). This location provides sufficient space to fit the pressure sensor cuff without exerting pressure on vital organs. Table 1 summarizes design parameters for the pressure transducer. An array of three pressure sensors ($0.4 \times 1.4 \text{ mm}^2$ each, with a 1.5 mm spacing) is located underneath the vessel to increase signal output and improve stability. In order to increase the sensitivity,

a long rectangular diaphragm was designed. The central deflection of a rectangular diaphragm under applied pressure is greater than a circular or a square diaphragm (assuming a width equal to the diameter, or side, of the circular or square diaphragm), and under large deflections, is given [11] by:

$$\frac{Pa^4}{Eh^4} = \frac{1}{\alpha(1-\nu^2)} \left(\frac{y}{h}\right) + \frac{1}{A^3} \left(\frac{y}{h}\right)^3 + \frac{\sigma a^2}{\beta Eh^2} \left(\frac{y}{h}\right) \quad (2)$$

where P is the applied pressure, y is the central deflection, a and h are the diaphragm width and thickness, E and ν are Young's modulus and Poisson's ratio, respectively, of the diaphragm material (170 GPa and 0.006 for P^{++} silicon [12]), σ is the internal stress (40 MPa tensile for P^{++} silicon [12]), and finally, γ , β , and A are geometrical constants depending on the diaphragm length to width ratio [11]. For the designed

Table 1. Design parameters for the pressure transducer

Pressure range	0–300 mmHg
Resolution	1 mmHg
Base-line drift	< 1 mmHg/month
Frequency response	0–50 Hz

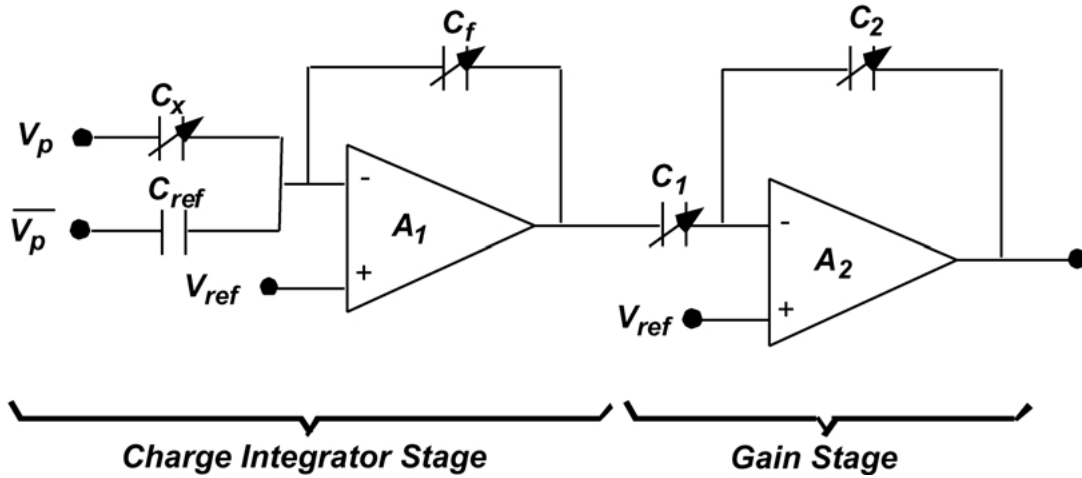


Fig. 3. Block diagram of the interface readout circuitry.

diaphragm a pressure of 100 mmHg yields a central deflection of $\sim 2 \mu\text{m}$. An initial (zero differential pressure) gap of $4 \mu\text{m}$ between the electrodes was chosen for the pressure sensor to achieve enough sensitivity ($\sim 3 \text{ fF/mmHg @ } 100 \text{ mmHg}$) while providing the required bandwidth ($\sim 50 \text{ Hz}$).

3.2. Interface circuit design

A CMOS custom-made switched-capacitor interface chip was designed to readout the sensor output. CMOS switched-capacitor circuits can be designed for low power consumption, are very tolerant of input parasitic capacitance, and are amenable to complete integration (unlike LC techniques) [13]. Figure 3 shows the schematic diagram of the interface chip. The first OpAmp stage is a charge integrator and is used to produce an output voltage proportional to the difference between the sensor capacitance (C_x) and an on-chip

reference capacitor (C_{ref}). By driving the input nodes by a non-overlapping clock voltage (V_p), the first stage output voltage is given by equation (3).

$$V_{\text{out}} = V_p \frac{C_x - C_{\text{ref}}}{C_f} \tag{3}$$

The first stage gain and offset can be adjusted by laser trimming the on-chip capacitors. The second stage serves as a voltage amplifier to provide additional gain ($\text{Gain} = C_1/C_2$) and programming flexibility (through an array of on-chip capacitors). Figure 4 shows a photograph of a MOSIS fabricated switched capacitor read-out circuit. Table 2 summarizes important characteristics of the interface chip.

3.3. Titanium cuff design and packaging

The titanium cuff consists of two parts: (1) a titanium base for supporting the pressure sensor and the interface

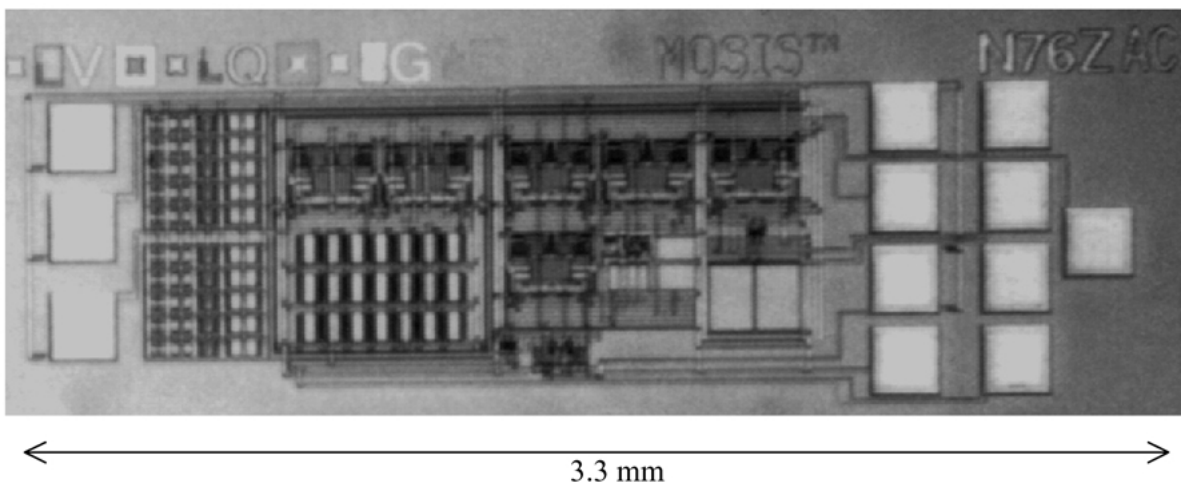


Fig. 4. Photograph of an interface capacitive readout chip.

Table 2. Important characteristics of the interface chip

Clock frequency	1 kHz
Supply voltage	3 V
Power consumption	120 μ W
Trimmable offset cap.	6.6 pF in 1,10,100,500 fF steps
Trimmable gain	1-7
Resolution	1.4 fF
Die area	3.3 mm \times 0.64 mm

chip, and (2) a titanium cap which is attached to the base using miniature screws (see Figure 2). The two components are machined from a cylindrical titanium stock and their dimensions are designed according to the anatomical location of the implant (this determines the overall dimensions) and the diameter of the blood vessel (this sets the recess diameter). A rectangular recess is milled in the base to house the pressure sensor array and

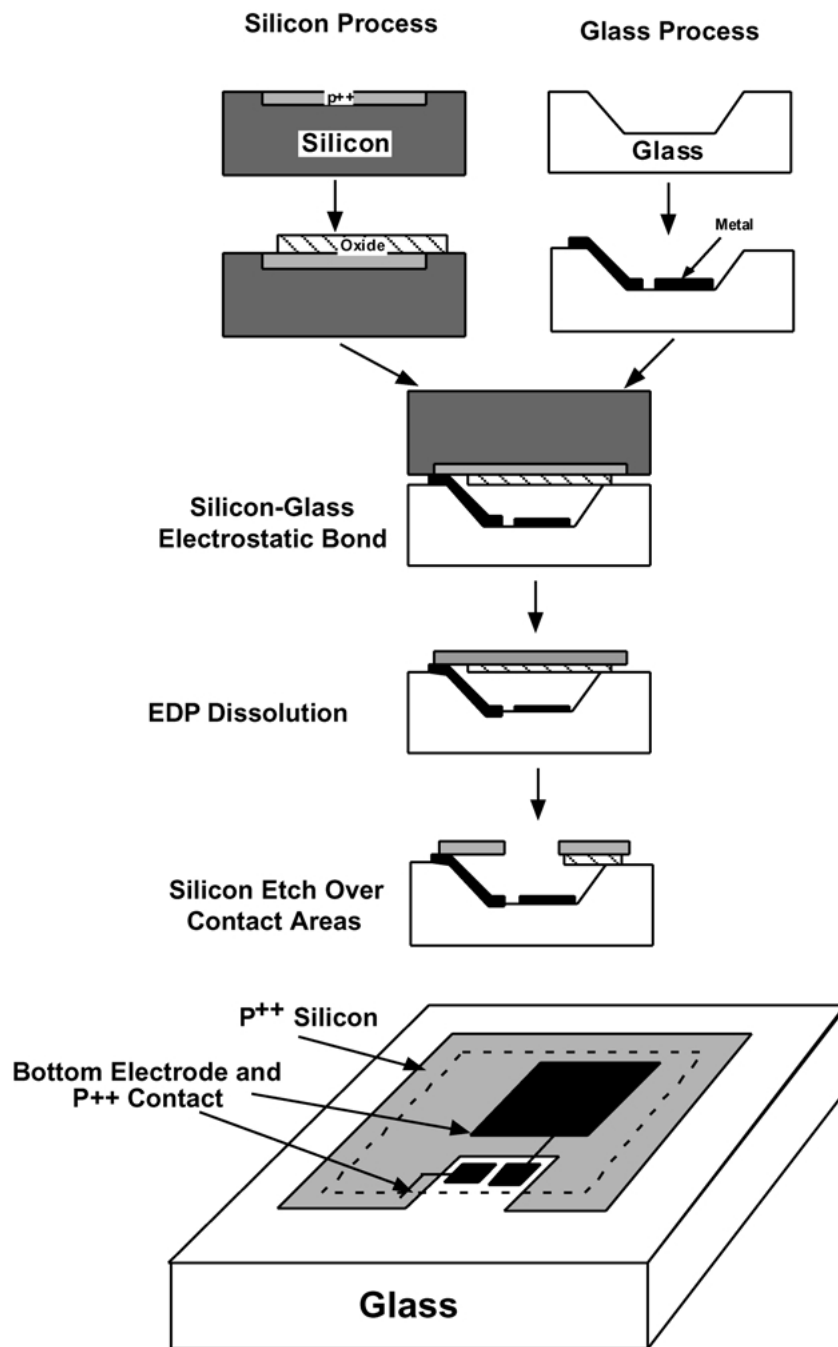


Fig. 5. Fabrication process flow for tonometric blood pressure transducer.

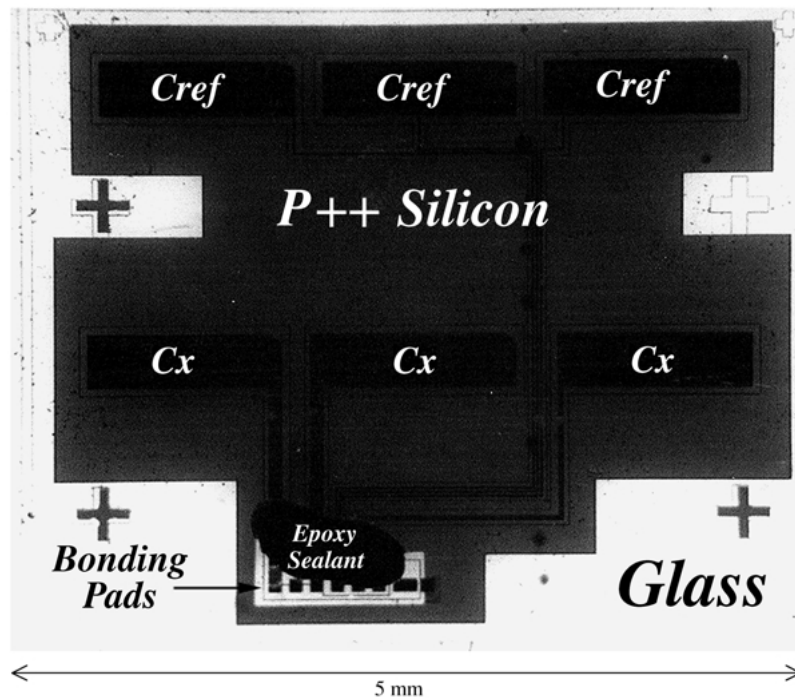


Fig. 6. Photograph of a fabricated pressure sensor array.

prevent its displacement during operation. The major source of base-line drift in implantable pressure transducers is the package-induced stress, which can be transferred to the transducer diaphragm. Therefore, the assembly and packaging of the complete system is critical in reducing drift. The assembly process starts with mounting the pressure sensor array and the interface chip on the titanium. The pressure transducer is attached in the rectangular recess on the base using a medical grade silicone rubber (NuSil Silicone Technologies, Carpinteria, CA). By using a compliant silicone rubber to attach the sensor to the package and isolating the sensor from the rest of the assembly, we anticipate to achieve a rather low base-line drift. The blood vessel is subsequently laid on top of the sensor, and the titanium cap is then clamped to the base using four miniature screws (Walter Lorenz Surgical, Jacksonville, Florida), thus pressing the blood vessel flat against the silicon diaphragm.

4. Pressure Sensor Fabrication Process

To form a flat sensor surface required by tonometric measurement technique, we have developed a new structure and fabrication process (Figure 5), based on the dissolved-wafer process [10]. The capacitive air gap ($\sim 4\ \mu\text{m}$) is formed by etching a recess in a glass substrate using $\text{HF}/\text{HNO}_3/\text{DI}$ (7:3:10, etch rate

$\sim 2.2\ \mu\text{m}/\text{min}$). The glass substrate also supports Ti/Pt/Au (200/200/1000Å) lines to form the bottom capacitor plate and interconnect lines. A silicon wafer is patterned for a shallow boron diffusion step using an oxide mask (7500Å). A $2.5\ \mu\text{m}$ P^{++} diffusion is performed to create the pressure sensor diaphragms and bonding areas. This is followed by a thin oxide isolation layer (1000Å) deposition and patterning over the diaphragm areas. The silicon wafer is then electrostatically bonded to the glass wafer and the undoped silicon is dissolved away in EDP to form pressure sensors wherever there is a recess. This technique creates a perfect flat surface, and sealed cavities to prevent fluid accumulation and stiction during the silicon etch. However, since electrical contacts (bonding pads) to the top and bottom plates are located inside the sealed cavities, openings need to be formed in the top plate in order to access these electrodes. This is done in the final step through the reactive ion etching of silicon membrane ($\text{NF}_3 = 10\ \text{sccm}$, $\text{O}_2 = 15\ \text{sccm}$, 200 mT, 100 W, etch rate $\sim 3000\ \text{Å}/\text{min}$). Figure 6 shows a fabricated sensor array (dimensions $\sim 4.8 \times 5.7\ \text{mm}^2$).

5. Test Results

In vitro tests have been performed on a complete cuff microsystem using a silastic tube (Scientific Products, Deerfield, Illinois) to mimic a pliable blood vessel. The

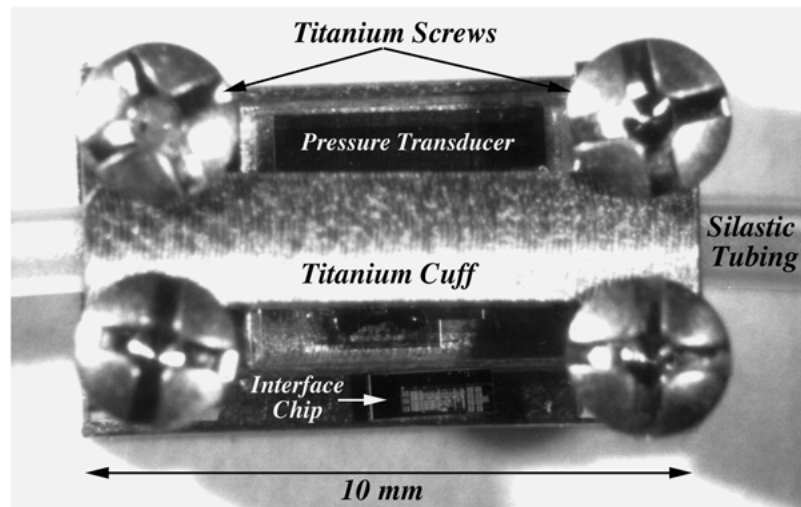


Fig. 7. Photograph of an assembled unit showing various components of the microsystem.

cavity of the pressure sensor was sealed using a high viscosity, low outgassing epoxy (Master Bond, EP51ND) at atmospheric pressure. The sensor was then attached to the titanium base and a silastic tube (2 mm in diameter) was subsequently laid on top of the diaphragm and the titanium cap was screwed to the base. Figure 7 shows the photograph of an assembled unit, which measures $10 \times 6.5 \times 3 \text{ mm}^3$. The silastic tube was pressurized (0–200 mmHg) with air using a handheld manometer pump and the output voltage was monitored using an oscilloscope and a digital multimeter. Figure 8 shows the measured output voltage as a function of pressure in the

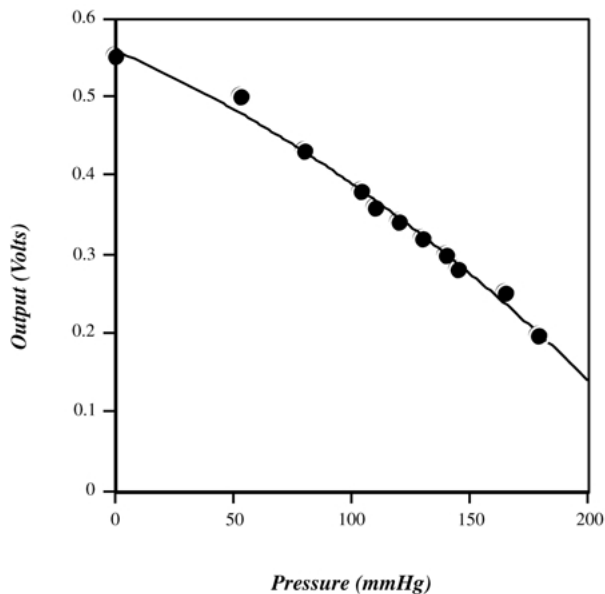


Fig. 8. Pressure sensor calibration curve in the arterial blood pressure range with lowest gain setting.

silastic tube. A sensitivity of $2.0 \text{ mV/mmHg @ 100 mmHg}$ and a resolution of 0.5 mmHg were obtained using the lowest gain setting of the read-out electronics. The resolution is set by the output noise of the read-out electronics which has a RMS value $\sim 0.5 \text{ mV}$ (peak-peak $\sim 4 \text{ mV}$). Table 3 summarizes important measurement results on the pressure sensor cuff microsystem. To test the base-line stability, the pressure sensor output has to be monitored at a fixed temperature and pressure. This requires a controlled test setup to ensure a minimum interference from these variables. We are planning a controlled long term stability test and will report on our results in the future.

6. Conclusion

A biomedical microsystem for tonometric blood pressure measurement using micromachining techniques has been developed. This system is the smallest implantable pressure cuff that includes an integrated package, a completely planar capacitive sensor, and an on-board interface circuit (dimensions $\sim 3 \times 6.5 \times 10 \text{ mm}^3$). A titanium base supports a planar pressure transducer and a custom-made switched-capacitor interface chip. The blood vessel is positioned on top of the sensor and a

Table 3. Important characteristics of the pressure sensor cuff

C_o	1.5 pF
$\Delta C/\Delta P @ 100 \text{ mmHg}$	2.8 fF/mmHg
$\Delta V/\Delta P @ 100 \text{ mmHg}$	2.0 mV/mmHg
Interface chip noise	1 mV, RMS
Resolution	0.5 mmHg
Sensor chip dimensions	4.8 mm \times 5.7 mm
Ti cuff dimensions (H \times W \times L)	3 mm \times 6.5 mm \times 10 mm

titanium cap is screwed to the base to clamp the vessel. *In vitro* tests have shown a sensitivity and resolution of 2.0 mV/mmHg and 0.5 mmHg at 100 mmHg, respectively. Long term base-line stability tests under controlled environment are planned.

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