MICROSENSORS FOR MULTIPLE-PARAMETER MEDICAL MEASUREMENTS

D. Tanase, J.F.L. Goosen, A. Firouzian, P.J. French
TU Delft, DIMES, ET/EWI, Mekelweg 4, 2628 CD, Delft, The Netherlands
TU Delft, OCP, Mekelweg 2, 2628 CD, Delft, The Netherlands

ABSTRACT

Often in medical applications a single measurement does not give sufficient information to the clinicians. IC technology allows the combination of several sensors in a small volume for instantaneous multi-measurements at a single location. This paper presents two multi-parameter sensors for catheter applications, with initial experimental results, along with the packaging issue – an important aspect for biomedical sensors.

INTRODUCTION

Over the past years the world of biomedical engineering has extended significantly into a broad field consisting of biomechanics, prosthetic devices and artificial organs, medical imaging, biomaterials, biotechnology, tissue engineering, neural engineering, biomedical instrumentation, bionanotechnology, physiological modelling, rehabilitation engineering, medical bioinformatics, clinical engineering, medical and biological analysis and biosensors. In almost all of these medical fields, biomedical sensors are routinely used in-vivo to perform invasive and non-invasive monitoring of physiological variables as well as in-vitro to aid clinicians in various diagnostic procedures (1).

In minimal-invasive medical interventions, in which small incision sites are used to insert the medical tools in the human body, the use of sensors becomes even more important, as the visual and tactile controls in the operating theatre are reduced, or lost. Clinicians have to be experienced to manoeuvre instruments such as laparoscopes and endoscopes in the abdominal cavity, navigate guide wires and catheters through the maze of blood vessels or use ventriculoscopes to explore the cavities of the brain.

Adding sensors to these tools increases their functionality by rendering additional relevant information to the clinical staff and improves the traditional way of performing the interventions. For example, by placing ultrasound sensors on a laparoscopic tool, it becomes possible to determine the position and orientation of the tip of the laparoscope with respect to the anatomical structures of the abdominal cavity (Figure 1) and to indicate this location on the monitors (2). In this way, the 2D images are augmented with depth information and the time to perform the intervention is shortened, as the instruments do not need to be retracted and reinserted every time a hidden corner is encountered. The complete system consists of pairs of...
ultrasound transmitters (Quantelec) and it uses the time-of-flight principle for the detection of the position and orientation. The error is 200 µm, far better than the requirements for this medical application (2). The system has been developed at the TU Delft and has not yet been tested in a clinical environment.

Similar to the ultrasound-based system, a magnetic-based system (Figure 2) for guide wires uses a magnetic sensor at the tip of the medical tool in combination with a magnetic source (external to the patient) to navigate the instrument to the place of interest (3). Using this system, a reduction of 55% of the total radiation dose employed for this kind of interventions can be achieved. In this way, not only the navigation process can be improved, but also the health risk associated with a high radiation dose can be minimised. Similar to the previous system, this one has also been developed at the TU Delft and not yet tested in the clinical setting.

![Figure 1. Ultrasound-based system for laparoscopic tools](image1)

![Figure 2. Magnetic-based system for guide wires and/or catheters](image2)

The combination of a number of sensors on the same chip gives even more functionality to the medical tool, allowing the detection of additional parameters. The present work focuses on two types of multi-parameter sensor-systems. Both systems are intended for continuous, in-vivo measurements in the vascular system. One consists of a flow-velocity sensor, a differential-pressure sensor, four electrodes and
four intravascular ultrasound sensors. This sensor combination is used to determine the cardiac output in intensive-care units. The other system integrates a blood-pressure sensor, a blood flow-velocity sensor and an oxygen-saturation sensor, for regular measurements in interventional radiology. While the first sensor system is to be placed in the pulmonary artery (with a diameter varying from 5mm to 1.5 cm), the second system was designed for use in blood vessels through which a catheter with a diameter of 1.67 mm (5 French) can be navigated.

The first part of the paper presents the system that is being developed for cardiac-output measurements, while in the second part, a number of aspects regarding the sensor-system for interventional radiology will be given. Packaging issues are addressed at the end of the paper, as they play an important role for both sensor systems.

**CARDIAC-OUTPUT MEASUREMENTS**

An important parameter monitored in intensive-care units is the cardiac output, which represents the quantity of blood delivered by either ventricle per unit time (litres/minute). A number of methods and techniques have been developed over the years to measure cardiac output. From all methods, the most important ones are thermodilution, continuous thermodilution, Fick method, bolus indicator dilution and Doppler ultrasound (esophageal and transthoracical) (4).

Thermodilution is the method commonly used in the IC although it is a rather imprecise technique (5), it introduces extra intravenous volume and measurements are labour-intensive (6). On the other hand, continuous thermodilution alleviates some of these disadvantages, but the costs of existing systems are high (7). The Fick method is too complex for clinical applications and therefore it is not widely used in clinical practice despite its accuracy (8). One of the problems using bolus indicator dilution is the recirculation of the marker (4). Although Doppler ultrasound is a minimal-invasive technique, it is prone to errors during surgical manipulation and therefore frequent probe repositioning is necessary (4). Nevertheless, when compared to thermodilution, this method is more accurate. In order to avoid the problems with existing systems, we investigate the use of three techniques for the assessment of the cardiac output.

The three approaches that are being considered are: the investigation of the applicability of Poiseuille’s law to cardiovascular flow, the detection of the differential pressure in the pulmonary artery as a measure of the flow and the use of the flow-area relationship to determine the flow volume. Considering the pulmonary artery a long tube, the Hagen-Poiseuille equation [1] expresses the volume-flow rate \( Q \) as a function of the pressure difference \( \Delta p \), the radius of the blood vessel \( r \), the viscosity of blood \( \eta \) and the length of the blood vessel \( L \) over which the pressure difference is measured.

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Q = \frac{r^4 \pi \Delta p}{8L\eta} \quad [1]
\]
To determine all parameters of interest for the three approaches, a medical-probe prototype was fabricated and will be used together with four intravascular ultrasound transducers to be placed around a catheter as shown in Figure 3.

The final goal is to place the sensor system on a Swan-Ganz catheter. This is a standard medical tool, which is routinely introduced in the right atrium and further advanced into the pulmonary artery for different purposes, such as the administration of medication, the measurement of cardiac output using the thermodilution method, or the measurement of the wedge pressure. By adding the sensor system to the Swan-Ganz catheter it becomes possible to continuously monitor the cardiac output and avoid the problems posed by the current methods.

![Figure 3. Schematic of the medical probe](image)

**Pressure sensor**

For the detection of the differential pressure, two absolute-pressure sensors are used, each of them consisting of a membrane over a sealed cavity (Figure 4). The membrane deflects as a result of the pressure difference between the blood pressure and the reference pressure in the cavity. The deformation of the membrane is measured using piezo-resistors connected in a Wheatstone bridge configuration. The change in the output voltage of the bridge is a measure for the blood pressure.

The 4µm thick epitaxial polysilicon membrane has diameters of 180 µm, 200µm and 400µm. The small cavity underneath (700nm) serves as an overpressure protection, an important safety issue in this medical application.

![Figure 4. Schematic of the pressure sensor](image)
To characterise the fabricated devices, initial pressure measurements were performed using a pressure chamber, but tests still have to be performed in liquids.

**Flow sensor**

For the detection of the blood-flow velocity the thermotransfer principle is used. A heater placed between two thermopiles (Figure 5) heats the blood locally and due to the blood flow, the output voltage on the two thermopiles will change.

The sensor structure is placed on a similar epitaxial polysilicon membrane as the pressure sensor, but the silicon-oxide layer beneath the membrane is in this case left in place, for thermal insulation. The thermopile lengths are 470µm, 1.47mm and 2.48mm, while the chip lengths are 1mm, 3mm and 5mm, respectively. The distance between the heater and the thermopiles is 15µm.

![Flow-velocity sensor schematic](image)

**Figure 5. Schematic of the flow-velocity sensor**

Initially, the flow sensors were tested in air, using a wind tunnel with different airflow velocities and a reference sensor. The heater was provided with a current varying in steps, from 0.5-2.5mA, while the output of the thermopiles was measured. The measurement results shown in Figure 6 were obtained for a heater current of 2.5mA.

![Measurement results](image)

**Figure 6. Measurement results when the flow-velocity sensor was in air**

At a later stage, flow measurements were performed in demineralised water and therefore, the sensors had to be completely sealed in order to avoid shortcuts between the electrical connections. The test set-up consisted of a closed-loop system with pipes of different diameters in which the flow sensors were placed.
For this medical application, the average for normal flow velocities is in the range 15-80cm/sec and the flow is pulsatile. The results that were obtained in demineralised water, showed a good sensitivity for the low flow range, as presented in Figure 7, but saturated below the average flows currently measured in the pulmonary artery.

In order to increase the sensitivity of the sensor to larger flow rates, new sensor structures have been designed and are presently being fabricated. These sensor structures have different thermopile lengths and the distance between the thermopile and heater varies from 5-100µm. For some sensors, the thermopiles are still symmetric to the heater, for other sensors, the thermopiles are asymmetric (depending on the flow direction) to the heater or even one single thermopile is used on top of the heater.

![Figure 7. Measurement results when the flow-velocity sensor was tested in demineralised water](image)

Apart from the measurements performed in air and water, the sensor was also placed in a pulsatile-flow measurement system (1-2Hz), to estimate its reaction time to low volume-flow rates. The volume-flow rate was 1mL/sec, which is far below the average normal rates in the intensive care. Although not yet quantitative, the tests showed that the sensor can respond to the required frequencies.

**Electrodes for viscosity measurements**

On the same chip with the pressure and flow sensor are the electrodes for blood viscosity measurements. In (9, 10), the authors showed that blood electrical impedance matches the whole-blood viscosity. Blood is a suspension of red cells, white cells and platelets in plasma. The concentration of red blood cells is called hematocrit (Ht) and in the equivalent electrical model of blood (Figure 8) it is represented by the plasma resistance, $R_p$. The cell interior resistance is represented by $R_c$, while $C_m$ is a measure for the cell membrane capacitance and is considered to be in good correlation with the whole-blood viscosity. The total complex impedance measured by the sensor involves also the polarisation effect of the electrodes, $Z_e$ (10, 11).

Apart from blood rheology, there are a number of factors that influence the whole-blood viscosity as well: shear rate (velocity gradient), hematocrit, temperature, plasma viscosity, acute-phase protein concentration, the deformability of red blood cells and their aggregation (Rouleaux formation). Hence, the continuous monitoring of whole-blood viscosity is a complex and uneasy task. Moreover, blood has a frequency-dependent behaviour and one should consider carefully the impedance-measurement principle when performing a blood electrical characterization.
Figure 8. The electrical model of blood (\(R_p\)=plasma resistance, \(R_i\)=internal cell resistance, \(C_m\)=cell membrane capacitance, \(Z_e\)=electrode polarisation impedance)

Initial measurements were conducted in saline solution using the four-electrode measurement technique and the measurement frequency between 20kHz and 40kHz (11). The aim of these tests was to investigate the electrical-field distribution (Figure 9a). Further tests were performed to better understand the effect of the vessel wall on the measured impedance. In this respect, simulations were performed to analyse the electrical-field distribution around the sensor. The obtained results were compared with the experimentally obtained data (Figure 9b).

Figure 9. a.) Electrical-field distribution limited by the vessel wall
b.) Experiments and simulations showing the influence of the vessel wall on the measurements

Considering the electrode-polarisation effect and the effect of the vessel wall on the measurement results, a number of planar-electrode configurations were designed and are being fabricated. Simulations of the newly designed sensor structures together
with the experiments should indicate the best sensor configuration for this medical application.

**Intravascular ultrasound (IVUS) sensors**

The role of the four ultrasound sensors on the catheter is to determine the radius of the blood vessel, necessary for the calculation of the cardiac output. Using the time-of-flight principle and sequentially exciting the sensors, the four distances D1-D4 (Figure 3) can be determined. From these data, the radius of the vessel can be calculated, irrespective of the location of the catheter in the blood vessel. Highly accurate ultrasound transducers (12) are available and will be used in combination with the sensor chip for these measurements.

**MULTI-SENSOR FOR INTERVENTIONAL RADIOLOGY**

Apart from the cardiac-output measurements, another sensor system (Figure 10) was developed for interventional radiology (13). The sensing principles for the pressure and flow sensor are the same as for the previously presented sensor system, therefore, in this section, the oxygen-saturation sensor will be described. Using the combination of pressure, flow and oxygen saturation (single time/single point measurement), the clinician has a better picture of the blood vessel condition (e.g. blood vessel compliance).

![Multi-parameter sensor](image)

Figure 10. Chip photograph and schematic of the multi-parameter sensor consisting of an oxygen-saturation sensor, a blood-pressure sensor and a flow sensor

**Oxygen saturation**

The oxygen saturation of blood is defined as the ratio between the amount of the oxygen bound to hemoglobin (oxyhemoglobin) and the oxygen-carrying capacity of hemoglobin. The normal range for arterial oxygen saturation in healthy subjects varies between 94 and 100%.

The sensor for oxygen saturation uses the difference in light absorption between oxyhemoglobin and hemoglobin (Figure 11a), a method called oximetry. In fact, the sensor consists of two stacked photodiodes and it uses two wavelengths (660nm and 800nm) for optical detection. The results shown in Figure 11b were obtained from animal tests using a heart-lung machine.
PACKAGING

Along with the issues on biocompatibility, sterilisation and patient safety, packaging is an important aspect that should be taken into account when designing a biomedical sensor. All sensors presented in this paper will come in direct contact with blood, therefore, the traditional wire bonding (Figure 13) will only complicate the packaging and will disrupt the correct functioning of certain sensors (e.g. flow), due to the protruding wires and the sealant on top of them. Moreover, sealing the bond wires is a time-consuming process, which is not always successful, as some wires might break due to stress.

As an alternative to this standard, through-wafer interconnects are proposed. All new sensor structures being developed for this application make use of this packaging
technique. As shown in Figure 14, the electrical connections are sent to the backside of the chip from where contact is made with a PCB, using the flip-chip technique. The cavity between the PCB and the chip is later filled with the so-called “underfill”, ensuring the sealing of the sensor system and leaving only those parts open, which have to be in contact with blood. At the moment tests are being performed to optimise the through-wafer interconnect process.

![Figure 14. Through-wafer interconnects, with electrodes as the sensor example](image)

**CONCLUSIONS**

This paper has shown how integration of different sensors on the same chip can offer more information to the clinicians than single measurements. Two multi-parameter sensors have been described along with some initial measurements. Work is continuing with more measurements and improved packaging.

**REFERENCES**