

Microfabricated Sensors for Medical Applications

Ben Kloeck, Nicolaas F. de Rooij
Institute of Microtechnology, University of Neuchâtel,
2000 Neuchâtel, Switzerland

1. Introduction

Mainly because of their size, a typical application field for integrated sensors is the biomedical world, and more precisely the in-vivo determination of physical and physiological parameters. One important parameter is the pressure of body fluids. Piezoresistive pressure sensors are cheap to fabricate in mass and easy to read-out. Moreover the dimensions of piezoresistive sensors can be made very small. Therefore, the future of piezoresistive pressure sensors is in cheap disposable catheters for invasive measurements with external power supply. The first section of this paper shows how such a pressure sensor can be applied for that purpose by mounting it in a 6F heart catheter.

Two more applications are presented concerning catheters that contain pressure sensor chips which are based on the technology developed at the Institute of Microtechnology. The first is an 8F double-lumen catheter for the investigation of the esophageal function. A new sensor chip was designed for this application, using a double-side integration technique specially developed for this purpose, and the back-side contact technology. It consists of a pressure sensing part and a pII sensing part. The advantages of the sensor design with back-side contacts are outlined. In-vitro and preliminary in-vivo experiments are presented, which show satisfactory results for simultaneous pressure and pII measurements.

The second example is a 4F muscle catheter, developed to measure pressures and forces in the muscle tissue. Here the special feature is the very small lateral dimension of the sensor chip.

Another area where microfabrication of sensors can be successfully used for applications in the biomedical field is that of chemical sensors.

The fabrication technology for backside contacted ISFETs, similar to that used in the combined pII-pressure sensor, will be discussed in more detail. A micromachined flow cell for multi-ion sensing will be presented. The fabrication of this device is based on CMOS technology, combined with anodic bonding of machined glass as well as deposition on ion-selective polymeric membranes.

Finally, the fabrication, characteristics and application of a planar amperometric glucose microelectrode will be discussed.

2. Pressure sensor for heart catheter

Classical heart catheters are essentially tubes filled with a physiological solution that is in contact with the blood through a flexible membrane in the catheter tip. The pressure is measured externally at the other end of the catheter. This system works well for static pressures, but fast pressure changes are damped by the pliancy of the catheter walls. Evidently, this problem does not occur if the pressure is measured and transformed to an electrical signal, directly in the catheter tip [1-5].

The pressure sensor presented in this work was mounted in a 6F catheter (2 mm outer diameter) by Keller AG für Druckmesstechnik (Winterthur). The catheter tip was made of stainless steel and the tube of polyurethane. The piezoresistors are turned toward the inside of the catheter, and only the membrane cavity is exposed to the external environment.

The catheter has been tested in-vitro, dry and in physiological salt solutions. The stability was proven to be satisfactory; less than 1 mbar drift in 42 hours. So far the catheter has not been used for in-vivo experiments.

3. pII-pressure sensor for stomach catheter

3.1 Introduction

At present, esophageal catheters only allow the measurement of either pII (acidity) or pressure separately. For some studies and diagnoses however, the measurement of both simultaneously is felt as a need to obtain a more complete image of the physiological phenomena involved [6-8]. One important application is the investigation of the lower esophageal sphincter (the ring-shaped muscle that by contraction closes the access to the stomach), and in particular the reflux of stomach acid into the esophagus that occurs if this muscle is malfunctioning. Diagnosis is complicated by the fact that the symptoms are often intermittent and are triggered by stimuli like stress or temperature extremes. Another interesting application for medical and pharmacological research is the dynamic and chemical activity of certain medicines and drugs. The advantage of having a pressure sensor at the same time is that also informations about the movement of the esophageal tract are obtained.

Today's commercially available esophageal catheters for pII monitoring use either antimony or glass electrodes. Antimony electrodes have the advantages that they are small and very cheap, and thus suited for disposable use. On the other hand, however, they are inexact and suffer from ageing and hysteresis, since their electrode reaction is essentially a corrosion process. Moreover, at low pII values there is an accumulation of reaction products around the electrode, which causes false pII readings. Glass electrodes are exact to a tenth of a pII or better, and stable. The disadvantages are that they are fragile and that they have a high impedance. Still, for the moment the glass electrodes are the most reliable devices that are on the market, but if they have to be combined with pressure sensors, their size increases, causing thus a lot of discomfort for the patient who receives the catheter through his nose. Compared with these existing systems, the silicon based sensor has the advantages of small dimensions, good accuracy and stability, and above all, a vast flexibility to integrate two or more sensors on one chip and on more sites in the catheter. In this section, a silicon based pII-pressure catheter (double-lumen), with the possibility for the integration of a reference electrode in one lumen, is discussed. [9,10].

3.2 Sensor chip fabrication

The sensor chips are fabricated by standard microelectronic and micromachining processes on double-side polished, 3 inch wafers (boron-doped, 3-5 Ωcm , 380 μm thick). A very special feature of this chip is that components are integrated on both sides. This is because one of the major design goals was to locate all the contact pads on the back side of the chip, since it has to be mounted in a catheter. Therefore the pressure sensor is integrated on the back side and the pII ISFET, which must be exposed to the solution, on the front side, but with contact feed-throughs through the chip, as is shown schematically in Fig. 1. The dimensions of the chip are 1.5 mm by 4.0 mm.

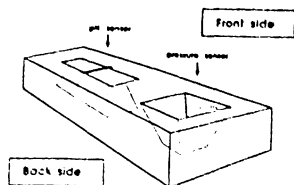


Fig. 1: Transparent scheme of the combined pH-pressure sensor

The pressure sensor consists of four boron-diffused piezoresistors at the edges of a thin membrane and connected in a Wheatstone bridge configuration. The output voltage is proportional to the pressure difference across the membrane and to the applied bridge voltage. The membrane is etched in potassium hydroxide from the front side of the wafer and its thickness is controlled by a four-electrode electrochemical etch-stop. A 10 μm thick epitaxial layer of n-type silicon is grown on a p-type silicon substrate. The p-type substrate is etched and etching is stopped at the epi-layer/substrate junction by applying a passivating potential to the epi-layer. The thickness of the remaining silicon membrane is thus defined exactly by the thickness of the epitaxial layer and not influenced by the taper of the wafer.

The pH-ISFET fabrication resembles the standard fabrication process [11] with one exception, i.e. the location of the drain and source contacts. Under the source and drain regions, holes are etched from the back side of the wafer, leaving a membrane of about 10 μm thick. A high phosphorous diffusion through this membrane, covered with aluminium establishes the electrical contacts to the source and drain from the back side of the chip. The process will be discussed in more detail in section 5.

3.3 Catheter encapsulation

The pH-pressure chip is mounted in a double lumen 8F catheter (2.7 mm diameter). Fig. 2 shows the important advantage of the back-side contacts: this approach allows the sensitive part to be almost at the same level as the outside surface of the catheter, avoiding thus the presence of a cavity in the tip, where local pH could differ from the effective pH in the stomach. The gate of the pH sensor and the back side of the pressure membrane are directly in contact with the solution. The catheter contains seven wires to contact the pressure sensor, two for the pH ISFET and one for possible integration of an Ag/AgCl reference electrode in the second lumen. The chips were mounted in the catheter by Keller AG für Druckmesstechnik (Winterthur).

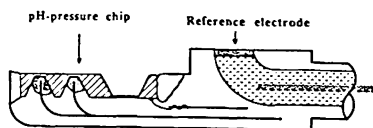


Fig. 2: Cross-section of the catheter tip, showing the chip encapsulation

3.4 Measurement set-up

For the in-vitro measurements the catheter was inserted in a vertical flexible tube that was consecutively filled with different pH buffer solutions. The upper liquid level was varied to yield pressure variations in the order of 100 mbar. Thus pressure and pH could be measured simultaneously. Merck pH buffer solutions were used. The pH was measured with an in-house built ISFET amplifier: a feedback control system that applies a constant V_{DS} , measures I_{DS} and adjusts V_{GS} through an Ag/AgCl reference electrode, in order to keep this I_{DS} constant. V_{GS} is then proportional to the pH of the

solution. The pressure was measured with a Wheatstone bridge amplifier supplied by Keller AG.

For the in-vivo measurements only battery powered equipment was used. A portable in-house built ISFET amplifier with skin reference electrode, a Keller DPM 80 Wheatstone bridge amplifier and MIC Gastrographs to obtain digital recordings of the measurements. The sensors were routinely calibrated before use.

3.5 Results and discussion

In-vitro measurements have shown that the pressure sensor had good linearity and a sensitivity of 8 mV/Vbar. The pH sensor had a sensitivity of 56 mV/pH and a stability better than 0.2 mV/h. Preliminary in-vivo measurements were carried out at the Insel Spital in Bern, in the stomach of a normal volunteer. A typical simultaneous recording of pressure and pH is shown in Fig. 3. At the same time a glass pH-electrode (Ingold) was inserted in the stomach and the readings were observed to be parallel, with only slight differences between both electrodes caused by their different position in the stomach. One of the advantages of the pressure recording is that the moment when the catheter passes through the sphincter can be determined exactly.

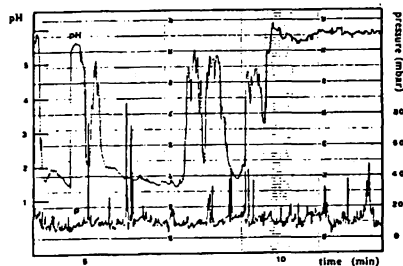


Fig. 3: Simultaneous recording of pressure and pH in the stomach of a normal volunteer

3.6 Conclusion

The in-vitro characteristics of the pH-pressure sensor are comparable to equivalent single transducers. The integration of pH and pressure sensors on one chip with back-side contacts enables an easy catheter mounting and adequate encapsulation. To obtain better spatial information, more measuring sites in the catheter are feasible. The integration of a reference electrode has been tested in vitro. The first in-vivo tests with skin electrodes showed a good response for both pH and pressure recordings.

4. Force sensor for muscle catheter

4.1 Introduction

The activity of muscles can be investigated by inserting a thin catheter longitudinally into the muscle bundle. A force sensor in the side-wall of the catheter gives information on the lateral action of the muscle. A sensor chip was designed to replace an older system where minuscule strain gauges were glued on a beam. Its fabrication involved individual assembling of each sensor and laborious handling of the microscopic parts. Evidently this application is a typical challenge for integrated sensor technology. This section presents a first generation of this type of sensors, to show the feasibility of fabricating silicon integrated force sensors with very small lateral dimensions.

4.2 Chip fabrication

The chip had to be designed to be mounted in a 4F catheter (1.3 mm outer diameter). Its dimensions were limited at maximum 0.6 mm width and 6 mm length. A mesa was required on one end of the chip, to touch the thin membrane in the catheter opening, as shown schematically in Fig. 4. The chip thickness was 0.2 mm, and the total thickness of the chip and the mesa was 0.4 mm. The operational range was 40 mN and the maximum allowed deflection of the beam 0.05 mm. If the beam deflects too much, then the muscle tissue presses on the border of the catheter opening, and not on the mesa anymore. To increase the force sensitivity, a cavity was etched

under the resistors. It is easily calculated that the sensitivity is proportional to the inverse of the square of the remaining thickness. The only restriction is the deflection at maximum force. It was calculated that a thickness of 100 μm would give a beam deflection at 40 mN of less than 50 μm .

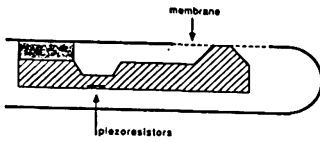


Fig. 4: Cross-section of the force sensor and the catheter encapsulation

The sensors were fabricated on three-inch phosphorous doped silicon wafers of (100) orientation. The nominal thickness was 381 μm and the resistivity 1-10 $\Omega\text{ cm}$. The fabrication sequence was similar to that of the pressure sensors, with the exception of the doping concentration of the piezoresistors. Since no Wheatstone bridge configuration was used for these sensors, the doping concentration was chosen high, $2 \times 10^{20}\text{ cm}^{-3}$ at the surface, in order to reduce the temperature dependence of the piezoresistance coefficients. The sheet resistivity was 20 Ω per square. After fabrication of the piezoresistors, the wafers were etched in 40% potassium hydroxide at 60°C, to obtain the chip profile that is illustrated in Fig. 4. The etching was done in two steps: first the aforementioned cavity was etched, and then the oxide mask was removed, except on the mesas, to etch the chip to the required thickness of 200 μm . Finally the wafers were diced into individual sensors. Fig. 5 shows the design of two sensor types that were realized; one was 0.6 mm wide and the second only 0.3 mm.

4.3 Measurement set-up

For in-vitro measurement, the sensors were glued on a PCB in a way that allowed vertical deflection of the beam. A special measurement set-up was developed to measure simultaneously the force applied on the mesa, the deflection of the beam and the resistor change. For this purpose, an I-DIM displacement sensor (Cary Compar, Le Locle) was mounted vertically on a support. In the sensor head, an inductive stylus was suspended on two horizontal spring blades with a precisely known spring constant. The I-DIM head could move vertically, and a second displacement sensor allowed to measure its movement. When the stylus just touched the beam, the applied force was zero and the reading of the displacement of the stylus (caused by its own weight) was set to zero. When the I-DIM head was moved down, the applied force and the stylus displacement were read from the display. The deflection of the beam was the difference of the readings of the I-DIM and the second displacement sensor. In this way increasing forces were applied and the corresponding resistance changes and deflections were measured.

For the temperature characterization, the PCB-mounted force sensors were placed in a furnace. The sensitivity was measured by a two-point calibration, using a known weight.

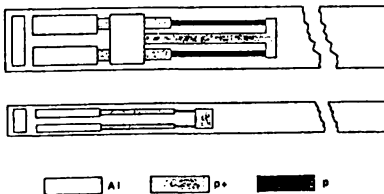


Fig. 5: Two designs of the force sensor: one with a chip width of 0.6 mm (upper), and one of 0.3 (lower)

4.4 Results and discussion

This paragraph summarizes the results of the measurements on four sensors. No functional differences were observed between the two sensor types (0.6 mm and 0.3 mm). Fig. 6 shows a typical recording of the resistance change and the deflection of the beam as a function of applied force. The sensitivity was 0.5 $\Omega/\text{k}\Omega$ mN. For a range of 40 mN, this results in a full scale resistance change of 20 $\Omega/\text{k}\Omega$. The deflection at 40 mN was 34 μm , which is within the required specification limit of 50 μm . It is noted that the sensitivity could be increased by taking a lower doping concentration for the resistors. For the used concentration the longitudinal piezoresistance coefficient in the $\langle 110 \rangle$ direction was $30 \times 10^{-11}\text{ Pa}^{-1}$, as opposed to e.g. $50 \times 10^{-11}\text{ Pa}^{-1}$ for doping concentration of 10^{19} cm^{-3} . However, that would be at the expense of a higher temperature coefficient. In the interval from room temperature to 70°C, the temperature coefficient of the resistor (TCR) was measured to be 1400 ppm/°C and of the sensitivity (TCS) 1700 ppm/°C.

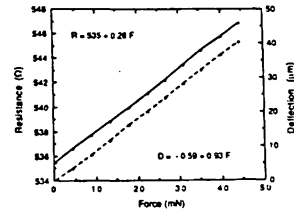


Fig. 6: Resistance change (—) and beam deflection (----) as a function of applied force.

4.5 Conclusion

The chip presented in this section was mainly a feasibility study as a first step towards a more sophisticated device. In particular temperature compensation was completely lacking on this chip. Because of the small dimensions (especially for the 0.3 mm chip), it is hardly possible to integrate two supplementary transverse piezoresistors and build a Wheatstone bridge. A full bridge would require the two transverse resistors to be placed on one line and besides the longitudinal ones, in order to sense the same mechanical tensions.

A valuable solution of this problem that requires only longitudinal resistors and still includes temperature compensation is proposed here. If two identical pairs of longitudinal resistors are integrated on both sides of the chip, as schematically shown in Fig. 7, then deflection of the chip causes the two resistors on one side to increase and the two on the other side to decrease. As for the pressure sensors, the four resistors can be connected in a Wheatstone bridge configuration, and temperature changes will in first order be a common mode effect and will not appear at the differential output of the bridge. Using the double-side integration and back-side contact technologies which were developed for the pH-pressure chip, such a force sensor can easily be fabricated with very small lateral dimensions. To decrease the size of the contact feed-throughs, very thin wafers should be used (100 to 150 μm thick).

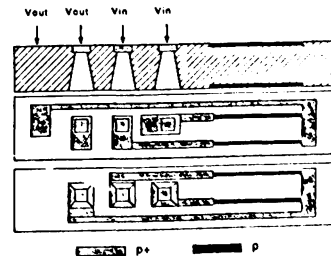


Fig. 7: Design proposition for a very narrow force sensor, using double-side integration and back-side contact technologies (the figure does not show the Al contact pads).

5. Microfabricated chemical sensors

5.1 pH-ISFETs

Ion-concentration or ion-activity sensors using field effect transistors are known since almost twenty years and denoted as ion-sensitive Field Effect Transistors or ISFETs. Despite their promising perspectives, a number of problems related to encapsulation and drift are still not solved and hamper a wide spread use. In order to improve the encapsulation we developed pH-ISFETs with back-side contacts. [12]

To fabricate feed-throughs in a silicon wafer, several techniques can be utilized. A rather simple method which can be used on wafer level, is the anisotropic etching of the silicon substrate with e.g. potassium hydroxide to form holes in the substrate leaving a thin membrane the thickness of which can be controlled. Electrical contacts to the source and drain regions on the topside of the chip, can be made by diffusion of drain/source dopant through this thin silicon membrane. On a double side polished wafer (p-type 3-5 Ωcm , thickness 380 μm) an oxide layer of about 1.5 μm is grown as masking layer for the potassium hydroxide etching. Then the openings for the drain and source back-side contacts are made. The holes in the silicon are etched in a 40 % potassium hydroxide solution at 60 °C. The wafer is etched until less than 10 μm of silicon is left leaving a diaphragm of about 80 μm x 80 μm at the bottom

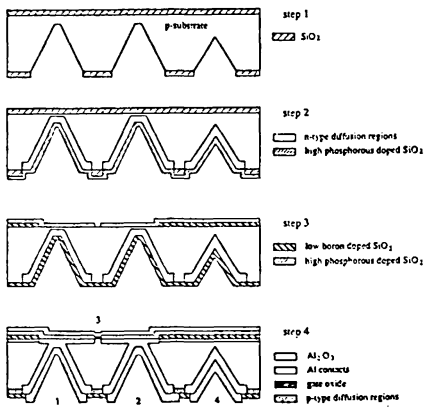


Fig. 8: Fabrication sequence of back-side pH-ISFETs

The back-side openings are now enlarged to enable the deposition of a phosphorous doped silicon oxide layer by chemical vapour deposition (CVD). After the diffusion of the phosphorous into the silicon all oxide layers are etched away and a boron doped silicon oxide layer is deposited on both sides of the wafer. Then the drain and source areas are opened and a phosphorous doped silicon oxide layer is grown (typically 900 Å) and at the same time the drain and source areas are formed together with the channel stop at both sides of the wafer. Alumina is then deposited by CVD as pH-sensitive layer (600 Å). After opening the contact windows on the back-side, aluminium contacts are formed by lift-off and the source and the substrate are directly connected. Furthermore some MOSFETs are made for on wafer testing. A diagram of the sensor fabrication is shown in Fig. 8.

The characteristics of the pH sensor are the following: drift less than 0.5 mV/h and pH sensitivity of about 56 mV/pH.

A carbon dioxide electrode based on the Severinghaus principle has been developed using the back-side contacted pH-ISFETs (Fig. 9). The pH-ISFET is used as the internal pH-sensing element and a temperature sensitive diode is integrated on the same chip [13].

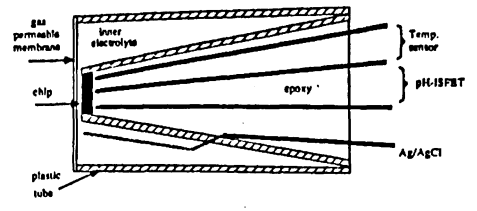


Fig. 9: Schematic diagram of the CO₂-sensor

5.2 Multi-ion sensors

In order to realize FET-based sensors sensitive to other ions than H⁺-ions, polymeric membranes with ionophores can be applied. However, the fixation of this type of membranes to the basic sensor structure is a problem. Glass encapsulations based on anodic bonding can solve both the problem of membrane fixation and packaging. The types of glass commonly used for this process are known to be highly resistant against chemical attack. Prior to the bonding process, holes are drilled through the glass in order to have access to the sensing area as well as to the electrical contacts. The glass hole provides excellent physical fixation of the membrane. Additional treatment of the glass before membrane deposition can further improve the adhesion of the membrane to the sensor [14].

The basic design of our structure is shown schematically in Fig. 10. It consists of a silicon substrate into which a field effect transistor has been realized. The gate of the transistor consists of a silver thin film, using a titanium adhesion layer. On top of the silicon substrate, the glass plate is applied by anodic bonding on an intermediate polysilicon layer. After the anodic bonding procedure, the silver layer (gate) is partially converted into a silverchloride layer in order to provide a stable electrochemical interface with the covering membrane.

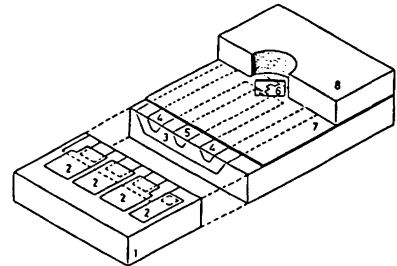


Fig. 10: Diagram of the glass-encapsulated pH-sensitive ISFET 1) n-type substrate, 2) contact pads, 3) p-well, 4) drain and source (n-type), 5) conductor (n-type) (forms diode with well) with at the end a Pt/Al electrode (black triangle connected during the anodic bonding with a metal layer to the gate), 6) gate area, exposed to the solution after the anodic bonding, 7) polysilicon layer, 8) glass (only partly shown but covers completely the polysilicon layer)

The sensitivity of these sensors to chloride ions was 58.5 ± 1 mV/pCl at 25 °C. The observed drift was less than 10 μV per hour at 25 °C in a 0.1 M KCl solution. The pH characteristics of a glass encapsulated ISFET without the Ag/AgCl gate is comparable to those mentioned above.

A flow-through cell based on the above described technology has been realized. It allows simultaneous measurement of H⁺, K⁺ and Ca⁺⁺-ion activities [15] For the K⁺-ion activity and Ca⁺⁺-ion activity measurement solvent polymeric membranes are used. As reference electrode a pH-ISFET with a retarded pH-response was developed thereby creating the possibility to operate this ISFET as an ion-insensitive FET over short periods of time (pseudo-REFET). The multi-ion sensor consisting of the pH-ISFET, pK-ISFET and pCa-ISFET together with the pseudo-REFET shows a high precision in combination with a high-sample frequency.

The cell, with an internal volume as small as 12 μ l, is evaluated in connection with a FIAstar® flow injection analysis system. The system's performance is illustrated in Fig. 11. Into the carrier stream respectively samples of different pH, different pK and different pCa were injected. Subsequently, a sample was measured in which the concentration of all three species was changed. As can be seen from the width of the peaks, the response is very fast and up to at least 200 samples per hour can be analyzed. The small pH-peaks at the injection of the higher calcium ion concentration are caused by an actual decrease in pH and not by interference, and thus it can be concluded that the cross-talk between the sensors is negligible.

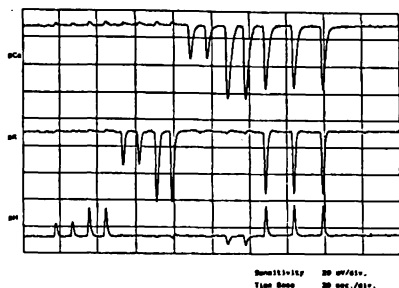


Fig. 11: Typical output registration of the flow-through cell in connection with an FIA system

5.3 Planar glucose sensor

An amperometric glucose sensor (dimensions: 0.8 mm by 3 mm) consisting of a planar three-electrode cell, an enzyme membrane and an outer polyurethane membrane, has been developed in our laboratory [16,17].

The sensor is realized using thin-film deposition and lift-off techniques and consists of two Pt electrodes (working and counter) and an Ag/AgCl reference electrode. It is coupled with an immobilized glucose oxidase membrane and the amount of H_2O_2 produced is measured at 0.7 V. In order to render the sensor response less dependent of the dissolved oxygen concentration a polyurethane membrane is applied by dip-coating. The sensor response, measured at 37 °C in a Ringer solution (pH 7.5) saturated with 5 % O_2 , is linear up to 40 mM glucose with a sensitivity of 1.8 ± 0.2 nA/mM. The operational lifetime, defined as the period during which the sensitivity remains constant, is approximately one week. The storage lifetime is more than one month. Recently the lift-off technique has been used for patterning enzymatic membranes on wafer level [18]. Sensors with on wafer deposited enzymatic membranes (without the polyurethane membrane) show a linear response to 1.5 mM glucose and respond to about 6 mM with a good uniformity amongst the sensors.

6. Conclusions

Many classical systems for medical diagnosis can be miniaturized effectively by the introduction of silicon integrated sensors. Moreover, the performance of the sensors is often better than that of the classical devices, and even new possibilities are created. This has been shown in this paper by examples of sensors that were mounted in catheters for invasive use in the human body. Also with sensors for ex vivo use, such as the multi-ion sensing flow through cell, the small dimension are of great advantage to minimize the sample volume.

7. Acknowledgements

The author would like to thank his coworkers of the Microelectronics Sensor Technology Group of the Institute of Microtechnology of the University of Neuchâtel as well as his colleagues of the Swiss Center for Electronics and Microtechnology Inc. (CSEM) for the many discussions, designs, skillful fabrication and characterization of the sensors discussed in this paper.

8. References

- [1] Samaun, K.D. Wise and J.B. Angel, An IC Piezoresistive Pressure Sensor for Biomedical Instrumentation, IEEE Transactions on Biomedical Engineering, BME-20 (2), pp., 101-109 (1973)
- [2] W.H.Ko, J.Hynecek and S.F. Boetcher, Development of a Miniature Pressure Transducer for Biomedical Applications, IEEE Transactions on Electron Devices, ED-26 (12 pp). 1869-1905 (1979)
- [3] M. Esashi, Fabrication of Catheter-Tip and Sidewall Miniature Pressure Sensors, IEEE Transactions on Electron Devices, ED-29 (1) pp. 57-63 (1982).
- [4] X.-P. Wu, M.-H. Bao and W.-X. Ding, An Integrated Pressure Transducer for Biomedical Applications, Sensors and Actuators, 2 pp. 309-320 (1982).
- [5] J. Bryzek, R. Mayer and Ph. Barth, Disposable Blood Pressure Sensors with Digital On-Chip Laser trimming, Technical Digest of the IEEE Solid-State Sensor and Actuator Workshop, Hilton Head Island, South Carolina, June 1988, pp. 121-122.
- [6] M.B. Orringer, R. Lee and H. Sloan, A combined manometric-pH recording catheter for esophageal function tests, Ann. thoracic. Surg., 26 p. 581 (1978).
- [7] P. Ask, G. Edwall and G. Tibbling, Combined pH and pressure measurements for oesophageal investigations, Medical & Biological Engineering & Computing, 19 pp. 443-446 (1981).
- [8] J.C.-M. Huang and K.D. Wise, A monolithic pressure-pH sensor for esophageal studies, International Electron Devices Meeting, Technical Digest, San Francisco, USA, pp. 316-319 (1982).
- [9] B. Kloeck, H.H. Van den Vlekkert, N.F. de Rooij, M. Muntwyler and K. Anagnostopoulos, A Combined pH Pressure Catheter for Gastro-Enterological Applications, Sensors and Actuators, 17, pp. 541-545 (1989)
- [10] H.H. Van den Vlekkert, B. Koleck, D. Prongue, J. Berthoud, B. Iju, N.F. de Rooij, E. Gilli, Ph. de Crouzaz, A pH-ISFET and an integrated pH-pressure sensor with back side contacts, Sensors and Actuators, 14 pp. 165-176 (1988).
- [11] P. Bergveld, N.F. de Rooij, Nederland Tijdschrift voor Natuurkunde, A 46-1 (1980)
- [12] H.H. van den Vlekkert, Some fundamental and practical aspects of CHEMFETS, Ph.D. Thesis. University of Neuchâtel, Switzerland, 1988.
- [13] B. Iju, H.H. van den Vlekkert, N.F. de Rooij, Carbon dioxide gas-sensing electrode based on a pH-ISFET with back-side contact, Sensors and Actuators, 17 (1989) 275-278.
- [14] Hans van den Vlekkert, Colin Francis, Alain Grisel, Nico de Rooij, Solvent Polymeric Membranes combined with chemical Solid State Sensors, Analyst, 113 (1988).
- [15] H.H. van den Vlekkert, A. van den Berg, A. Grisel, N.F. de Rooij, "Multi-ion sensing system based on glass-encapsulated pH-ISFETs and a pseudo-REFET", Sensors and Actuators, B1 (1990) 395-400.
- [16] S. Gernet, M. Koudelka, N.F. de Rooij, Fabrication and characterisation of a planar electrochemical cell and its application as a glucose sensor, Sensors and Actuators 18 (1989) 59-70.

- [17] M. Koudelka, S. Gernet, N.F. de Rooij, Planar amperometric enzyme-based glucose microelectrode Sensors and Actuators 18 (1989) 157-163.
- [18] S. Gernet, M. Koudelka, N.F. de Rooij, A planar glucose enzyme electrode, Sensors and Actuators 17 (1989) 537-540.