Biosensors **2** (1986) 15–33

The Development and Application of FET-based Biosensors*

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(Received 8 July, 1985; accepted 27 September, 1985)

ABSTRACT

After having considered the general definition of biosensors, the specifications of one type are discussed here in more detail, namely the pH-sensitive ISFET, which is at present being clinically investigated for intravascular blood pH recording. Results, advantages and possible improvements will be discussed, as well as a prediction with respect to future developments of FET-based biosensors.

Key words: Biosensor, ISFET, CHEMFET, blood pH, BIOFET.

1. INTRODUCTION

The subject of biosensors is relatively new, and it will be worthwhile to first of all present a definition of what they really are.

Very recently, various papers have appeared concerning the subject of biosensors, not always containing, however, the same or even similar definitions. In the author's opinion this is also the reason that the editors of

*This paper was originally presented at the IVA Biosensor Symposium in Stockholm on March 21, 1985. IVA has edited the symposium proceedings, complete with all contributions, and this is available from the Royal Swedish Academy of Sciences, Box 5073, S-102, 42 Stockholm, Sweden.

this journal do not define in their editorial introduction precisely whic field they will cover (*Biosensors*, **1** (1) (1985)). They propose a rathe broad field involving the interfaces between biology, chemistry an physics in order to improve medical diagnosis as well as the control o biotechnological processes.

In other recent papers the biosensor concept is limited to the inter facing between biochemistry and micro-electronics, in such a way that i will enable biochemical and chemical analyses to be done on a microscal suitable for *in situ* measurements. A proposal which goes one step furthe is the development of biochips, where micro-electronic circuitry nowadays mostly consisting of a silicon chip, has also acquired a biochemical nature (Tucker, 1984).

Personally, the author would like to compare biosensors with th natural type of biosensors, which are as old as the living organisms o earth, namely the bioreceptors (Stieve, 1983). Bioreceptors are natura transducers which convert all types of chemical and physical signals fro the environment into electrical signals, resulting in action potentia which can be processed by the natural computer consisting of nerve o brain tissue. Note that the presence of bioreceptors is not limited to ou organs of sense but that they appear in widely varying locations fo controlling all kinds of physical, chemical and biochemical processes i living organisms and cells.

Because our industrial computers need electrical signals which ar carried by electrons, the artificial bioreceptors we are at presen developing will in addition have to contain a conversion to an electron signal. This conversion can be direct or indirect. Examples of a direc conversion are the potentiometric and amperometric mode of senso operation, while the use of an intermediate optical signal line is a example of an indirect conversion.

The use of a direct or indirect signal conversion depends mainly on th presence of observed sensing effects or is imposed by external condition as, for instance, safety requirements. Nevertheless, if biosensors ar defined as analogues of bioreceptors, it will be clear that the technolog by which these sensors are produced is of minor importance. In principle every effect which can be made useful for a desired signal conversion is a suitable choice for application in biosensor development. It is known however, that the contact between living systems and non-living materia is very difficult to achieve, especially if the conditions are not wel

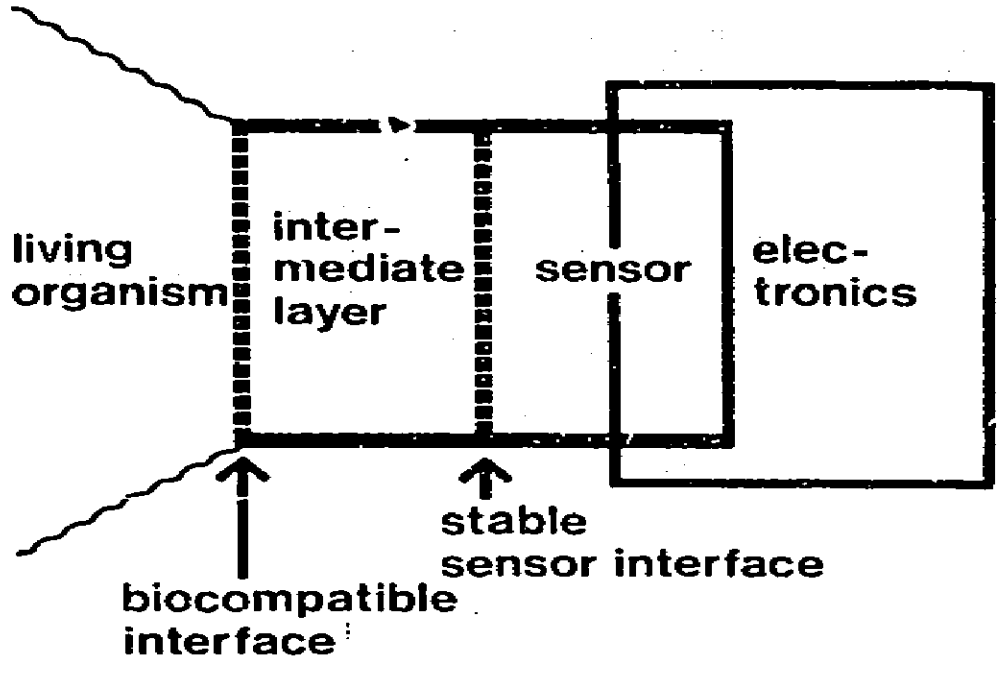

Fig. 1. Schematic representation of biosensor concept with design requirements.

established. This means that the development of biosensors has been sought in the use of an intermediate layer, the operational conditions of which can be controlled and stabilized in such a way that contact with both sides fulfils the corresponding requirements. One side should be biocompatible with the living surroundings, while the other side should be compatible with the attached sensor. This situation is shown schematically in Fig. 1.

Let us consider, as an example, the use of a catheter tip blood pressure sensor. The sensor itself always consists of a membrane, the displacement of which is converted into an electrical signal. To make the sensor suitable for bioapplications the membrane has to be covered by a biocompatible layer which prevents thrombogenic reactions but does not influence the characteristics of the pressure sensor. It should form a very good attachment to the sensor membrane but should not change its mechanical properties.

An example from the chemical sensing field is an enzymatically controlled sensor for measuring a certain substrate S. An enzymatic reaction converts the substrate S into a product P which can be measured by a P sensor. These reactions are mostly influenced by the chemical surroundings, including unwanted by-products of the enzymatic reaction. In order to remove this effect, which disturbs the measurement and limits the lifetime of the system, the intermediate layer shown in Fig. 1 should contain the enzyme in a chemically stable condition. Only the substrate S to be measured may enter the intermediate layer, for instance, through a

specific membrane covering this layer, while the by-products produced during the reaction should be neutralized. Unfortunately, such sensors have not yet been produced, but special attention is being paid to research efforts in this direction. Progress in solid-state sensor technology as well as in biotechnology will certainly stimulate development of this class of biosensors.

Note that the first example described above (the blood pressure sensor) is designed for *in vivo* measurements. The living organism mentioned in Fig. 1 is in this case the blood inside a human body. The second example (the enzyme sensor) is not necessarily limited to the field of medical care. In this case the living organism and the intermediate layer in Fig. 1 can be integrated, e.g. enzymes or cells which are immobilized in a polymeric matrix. The application could be useful in biotechnology and other fields.

The use of an intermediate layer which contains biologically active material is the reason that some authors denote these sensors as biosensors, but it will be clear that it limits the definition of a biosensor as an artificial bioreceptor and does not include the sensors for measuring biophysical parameters such as blood pressure, blood flow, etc. Because these sensors can be distinguished from their industrial counter parts precisely by the biomedical application with its specific requirements, the author prefers to include them in the definition of biosensors; this is in complete agreement with the comprehension of bioreceptors.

With respect to the medical application of these biosensors it will be clear that in the first place they will be used for diagnostic purposes, especially if measurements by means of a sampling technique and off-line analysis show an unallowable deficiency and therefore a continuous on-line measurement is necessary, e.g. to monitor fast transients of important parameters. A further application will be the use of implantable sensors for controlling, for instance, the functioning of artificial organs such as a pacemaker or an insulin delivery system. It will be clear that the requirements for biocompatibility, accuracy, stability, reliability, etc., will be much greater for implantable sensors than for monitoring sensors. The latter can be of a disposable type.

A sensor concept which is strongly favoured for the development of these biosensors is the ion-sensitive field effect transistor (ISFET) (Bergveld & de Rooij, 1981). This device is based on a direct conversion of the concentration of chemical species into an electronic signal. The measurement does not influence the chemical composition of the intermediate layer (Fig. 1) due to its capacitive nature.

To date the ISFET has been mainly developed for pH measurements

but research efforts are progressing and other ions and molecules will certainly be measurable by means of modified ISFETs in the near future.

Because of these high expectations it will be useful to first explain the basic operation of the device, then show the present state of clinical applications, including a discussion of the measurement results, and finally discuss the problems which still have to be solved. Based on this knowledge we can consider further the future possibilities of FET-based biosensors.

2. THE ISFET OPERATION

A very short description of the operation of an ISFET can be made by comparing it with its purely electronic analogue, the MOSFET (metal oxide semiconductor field effect transistor) (Bergveld & de Rooij, 1981). Figure 2 illustrates the similarities and differences between this well-

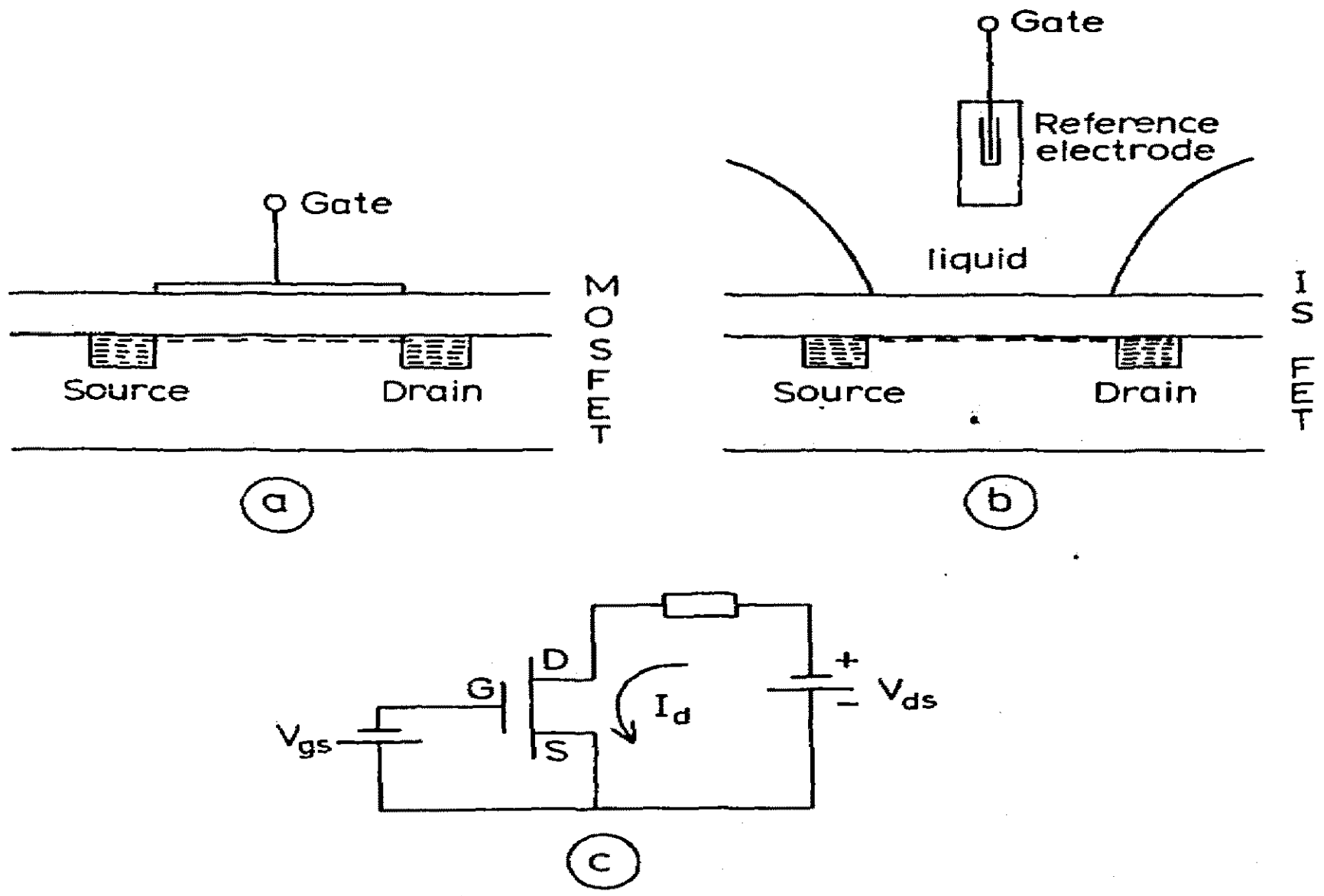

Fig. 2. (a) Schematic diagram of MOSFET; (b) schematic diagram of ISFET; (c) schematic electrical diagram for both MOSFET and ISFET.

known MOSFET and the ISFET. The metal gate of the MOSFET of Fig. 2(a) is replaced by the metal of a reference electrode, while the liquid in which this electrode is present makes contact with the original gate insulator (Fig. 2(b)). Both devices have the same electrical equivalent circuit, which is symbolized in Fig. 2(c).

For both devices the following equation is valid for the non-saturated region (below pinch-off):

$$I_d = \beta(V_{gs} - V_T - 1/2V_{ds})V_{ds} \tag{1}$$

in which β is a parameter, determined by the mobility of the electrons in the inversion layer, the gate insulator capacitance per unit area C_{ox}, and the width to length ratio of the channel W/L.

$$\beta = \mu C_{ox} W/L \tag{2}$$

Besides differences in the performance of the two devices, there is a difference in the value of the threshold voltage V_T, which is constant in the case of a MOSFET but is a function of the pH of the liquid for the ISFET, according to eqns (3) and (4):

$$V_T = V_{FB} - Q_B/C_{ox} + 2\phi_F \tag{3}$$

$$V_{FB} = E_{REF} - \psi_0 + \chi^{sol} - \frac{1}{q}\Phi_{si} - (Q_{ss} + Q_{ox})/C_{ox} \tag{4}$$

Here V_{FB} is the flat band voltage, Q_B is the depletion charge in the silicon, ϕ_F the Fermi-potential, E_{REF} the reference electrode potential relative to vacuum, χ^{sol} the surface dipole potential of the solution, Φ_{si} the silicon work function, Q_{ss} the surface state density at the silicon surface and Q_{ox} the fixed oxide charge. The potential drop in the electrolyte at the oxide–electrolyte interface, ψ_0, is the parameter which makes the flat band voltage a function of the pH, resulting in the ion sensitivity of the device. Therefore this parameter has to be investigated in more detail (Bousse *et al.*, 1983).

3. THE SITE-DISSOCIATION MODEL

The theory which describes the interaction between an inorganic insulator and an adjacent electrolyte is based on the assumption that the

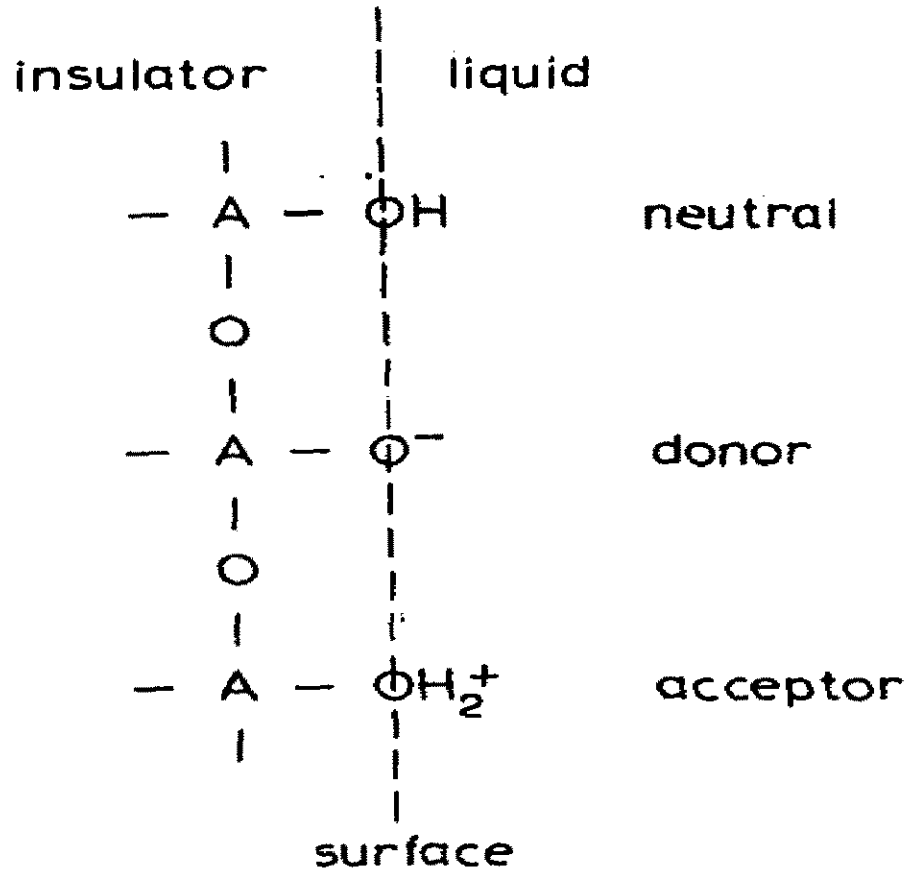

Fig. 3. Schematic representation of site–dissociation model.

surface contains a discrete number of surface sites which may dissociate. Therefore an expression for ψ_0 will be derived on the basis of the site-dissociation model.

Insulators which are widely used in ISFET process technology are SiO_2, Al_2O_3 and Ta_2O_5. The surfaces of these oxides contain hydroxyl groups which act as discrete sites for chemical reactions of the surface when it is brought into contact with an electrolyte solution. It is usually considered that only one type of site is present, with an amphoteric character. This means that each surface site can be neutral, act as a proton donor (acidic reactions) or as a proton acceptor (basic reactions). This surface property is schematically represented in Fig. 3.

The corresponding acidic and basic reactions are characterized by their equilibrium constants, K_a and K_b.

The resulting surface potential, ψ_0, can be calculated from the total number of surface sites, N_s, which will be partly charged to a surface charge, σ_0, depending on the pH as determined by the equilibrium constants K_a and K_b:

$$\psi_0 = 2{\cdot}3\frac{kT}{q}\frac{\beta}{\beta+1}(\mathrm{pH}_{pzc} - \mathrm{pH}) \tag{5}$$

where

$$pH_{pzc} = -\log\left[\frac{K_a}{K_b}\right]^{1/2}$$

being the pH at the point of zero charge (pzc), thus the pH for which $\psi_0 = 0$ and $\sigma_0 = 0$, and

$$\beta = \frac{2q^2 N_s (K_a K_b)^{1/2}}{kT C_{DL}}$$

being a surface reactivity parameter in which $C_{DL} = \sigma_0/\psi_0$, the double-layer capacitance.

Substitution of eqn (5) into eqns (4), (3) and (1), respectively, results in a fixed relation between the drain current of an ISFET and the pH of the measuring solution.

4. PRACTICAL ISFET APPLICATION

In order to obtain a stable ISFET operation, the ISFET is always applied in a feedback circuit (Bergveld, 1981). This will always result in an operation mode where the drain–source voltage has a constant preset value and the feedback control also ensures a constant drain current. This will result in a gate–source voltage that is adapted to the value of ψ_0. As the gate voltage is actually the voltage of the reference electrode, which is usually the ground connection of the feedback amplifier, it means that the source voltage with respect to ground exactly follows the pH-dependent surface potential, ψ_0, as given in eqn (5).

Figure 4 shows the result of a measurement with an Al_2O_3-ISFET. where V_{out} is the output voltage of the amplifier, equal to the source voltage with respect to ground and where the amplifier offset control is set to 0 V for pH = 7. This result shows that an Al_2O_3-ISFET behaves almost linearly in a wide pH-range around its $pH_{pzc} = 7{\cdot}9$ with a sensitivity of 53 mV/pH.

For biomedical application the ISFET chips, usually 2 or 3 mm long and 1 or 1·5 mm wide, are encapsulated as an integral part of a catheter or hypodermic needle, in order to be able to insert them into a blood vessel or directly into tissue.

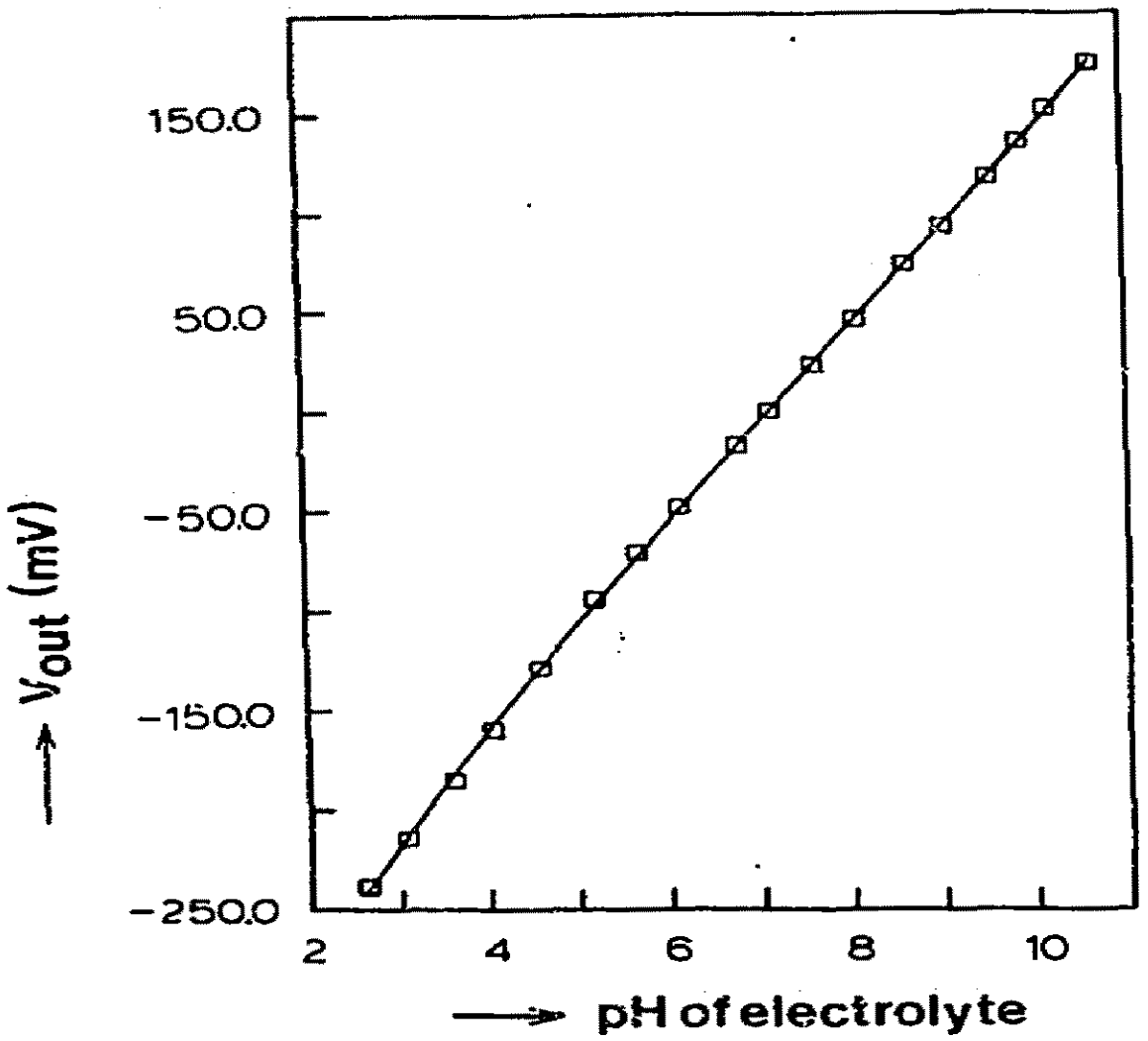

Fig. 4. Output voltage, V_{out}, of ISFET amplifier as function of pH.

5. THE PRESENT STATE OF *IN-VIVO* ISFET USE

The Sentron company (Roden, The Netherlands) has developed, especially for use in intravascular measurements, a catheter tip pH ISFET sensor, based on the original work at the Twente University of Technology. This sensor is at present under clinical investigation.

The use of Al_2O_3 as inorganic gate material is essential, because it combines a rather large pH-sensitivity with excellent biocompatibility. The 6F catheter has a built-in reference electrode of the Margules type (Margules *et al.*, 1983) and an additional lumen for taking blood samples. Each ISFET is factory-tested *in vitro* before sterilization, and the essential parameters, which will be dealt with below, are stored in a PROM (programmable read only memory) which is an integral part of the ISFET connector. Experience obtained from animal as well as clinical experiments has shown that the *in vitro* characterization is also valid for the *in vivo* use of the devices. Therefore, the data stored in the PROM connector also have an *in vivo* valuation and are used by the floating signal conditioner to transfer the ISFET output signal to the blood pH.

The signal conditioner applies the ISFET in the constant drain current mode, with constant source–drain voltage, V_{ds}, resulting in a gate–source voltage, V_{gs}, which directly reflects the pH-sensitive interfacial potential at the gate surface. If no temperature sensitivity and time drift occur, the equation handled by the signal conditioner would be simply:

$$\mathrm{pH} = \mathrm{pH}_{\mathrm{cal}} + \frac{V_{gs}}{S} \tag{6}$$

where $\mathrm{pH}_{\mathrm{cal}}$ is the pH of a calibration liquid at 37°C (T_{cal}), V_{gs} the electrical output signal of the ISFET amplifier circuit and S the pH sensitivity (mV/pH) of the particular ISFET, stored in the memory. Although the ISFET is roughly applied at the temperature-insensitive bias point, it appears that a temperature sensitivity of V_{gs} as well as S still occurs, which has to be corrected. Furthermore it appears that, after an initial drift, the time drift of the Al_2O_3-ISFET can be approximated to be linear for a certain time. Therefore a linear time drift correction is necessary (de Rooij & Haemmerli, 1984). This correction (DC in mV/h) as well as the temperature coefficient TC (in mV/°C) and the temperature dependence of S, $\mathrm{d}S/\mathrm{d}T$ (in mV/pH/°C), are also determined *in vitro* and stored in the ISFET–PROM connector. These data are used for the exact pH determination by the signal conditioner according to:

$$\mathrm{pH} = \mathrm{pH}_{\mathrm{cal}} + \frac{\Delta V_{gs} + DC\Delta t + (TC - S \times 0{\cdot}0147)\Delta T}{S + \dfrac{\mathrm{d}S}{\mathrm{d}T}\Delta T} \tag{7}$$

where Δt is the time after calibration with $\mathrm{pH}_{\mathrm{cal}}$ and ΔT is the difference of the temperature with respect to $T_{\mathrm{cal}} = 37$°C; in addition a factor $S \times 0{\cdot}0147$, which is the same for all ISFETs, is taken into account for correction of the temperature sensitivity of the blood pH itself.

In order to measure the actual blood temperature necessary to solve eqn (7), the ISFET chip contains a temperature-sensitive resistor, which is also characterized beforehand; the data from the resistor are also stored in the PROM connector.

Equation (7) expresses the essential procedure as developed and patented by Sentron (formerly Cordis). In this way the present ISFETs can be applied with well-defined accuracy, despite their intrinsic drift phenomenon and temperature dependency. The complete ISFET catheter assembly is shown in Fig. 5.

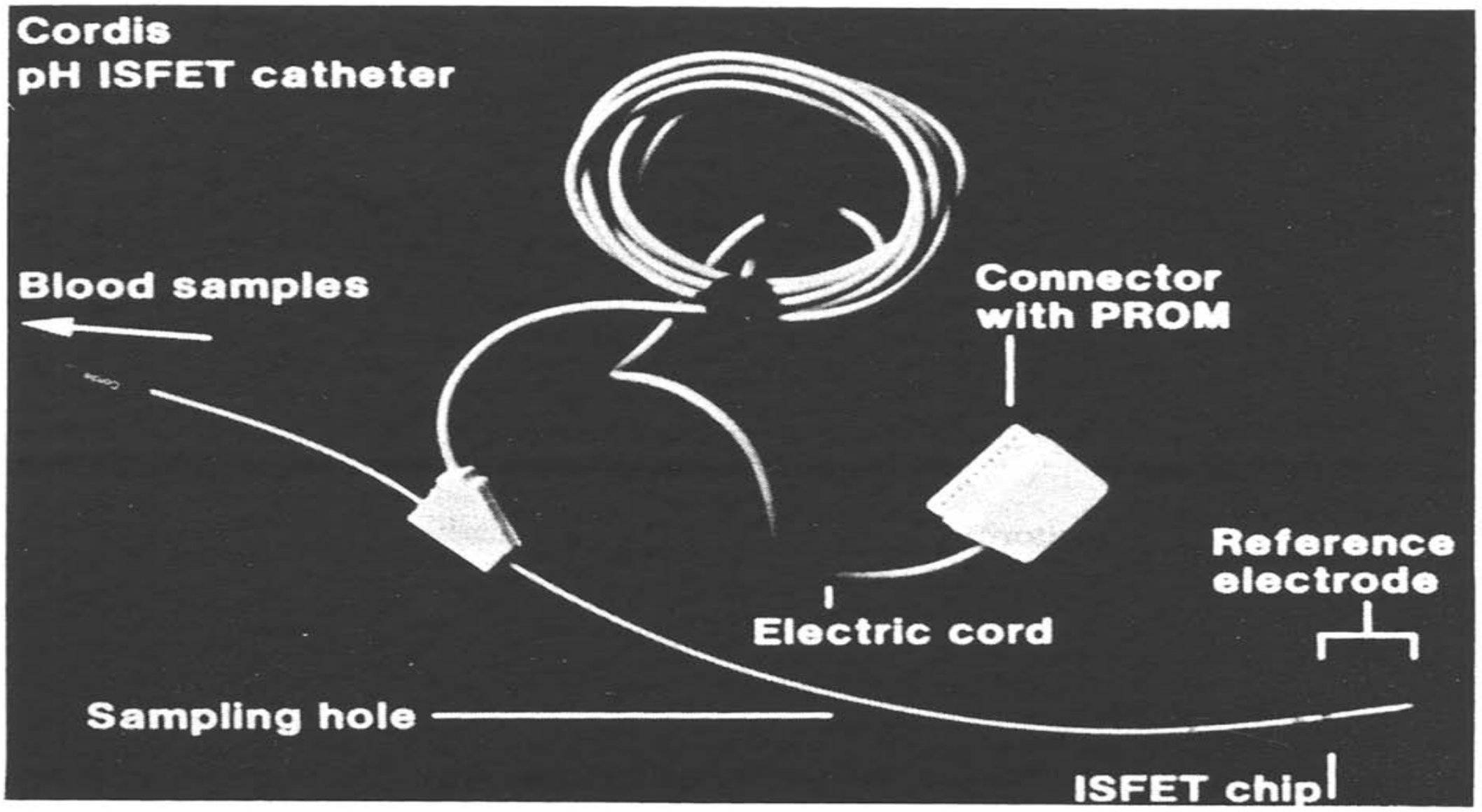

Fig. 5. Complete Cordix ISFET catheter assembly. (Photograph courtesy of Sentron v.o.f., Roden, The Netherlands.)

The ISFETs are protected against electrostatic damage. The sterilized catheters are stored with the ISFET chip in a dry environment, while the tip, containing the reference electrode, is kept in a wet environment. When making a recording the ISFET and the reference electrode have to be brought into contact with the calibration liquid or with blood for at least half an hour, before the signal conditioner can handle eqn (7) correctly. If the ISFET is in contact with blood during this conditioning period, the calibration is achieved by means of a blood sample, the pH of which has to be determined by pH laboratory equipment.

An actual ISFET registration during spontaneous breathing is shown in Fig. 6. The ISFET was calibrated using a blood sample, after an initial conditioning period of half an hour, with the catheter tip in the iliac artery. The two dots are blood sample pH values for comparison with the ISFET recording. The registration shows that the ISFET measures with an accuracy within the values that can be obtained with the usual intermittent sampling technique. Furthermore, we may conclude, from

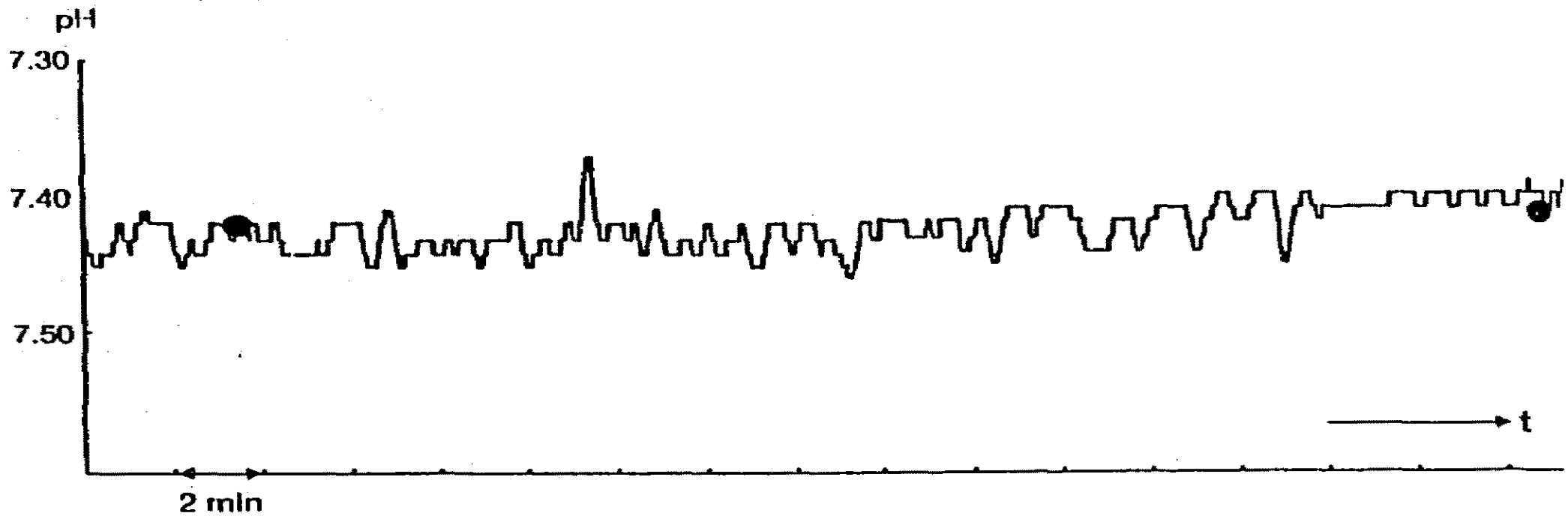

Fig. 6. Result of pH monitoring with the Cordis pH ISFET catheter and signal conditioner during spontaneous breathing. (By permission of Sentron v.o.f., Roden, The Netherlands.)

this registration and from others not given here, that during spontaneous breathing the blood pH may vary by at least 0·06 pH units; this indicates that the pH determination of an arbitrary blood sample within an accuracy of 0·001 pH unit, as is possible with the modern pH–blood gas analysers, is physiologically insignificant.

The real value of a continuous on-line pH measurement will be clear from observation of the registrations in Figs 7(a) and (b). Again the dots refer to the pH value of blood samples, taken for comparison.

Figure 7(a) shows the result of successful weaning after a period of mechanical ventilation. The patient was put on a pH value of 7·4 and took control of his own acid–base balance after starting weaning from the mechanical ventilation (at ↓) within a few minutes at a slightly lower pH value. The registration shown in Fig. 7(b) shows an unsuccessful weaning at point a, which is the reason for the anaesthetist deciding to restart the mechanical ventilation at point b.

It will be clear that such a very important and relatively fast phenomenon can hardly be observed with a sampling technique needing further time-consuming off-line analysis and especially not on a routine basis. More details concerning the medical significance of these measurements can be found (Van de Starre *et al.*, 1986).

In conclusion it can be stated that it is possible to perform on-line continuous pH recording, which makes the ISFET a worthwhile tool. It provides the physician with the facility to monitor pH trends, enabling the

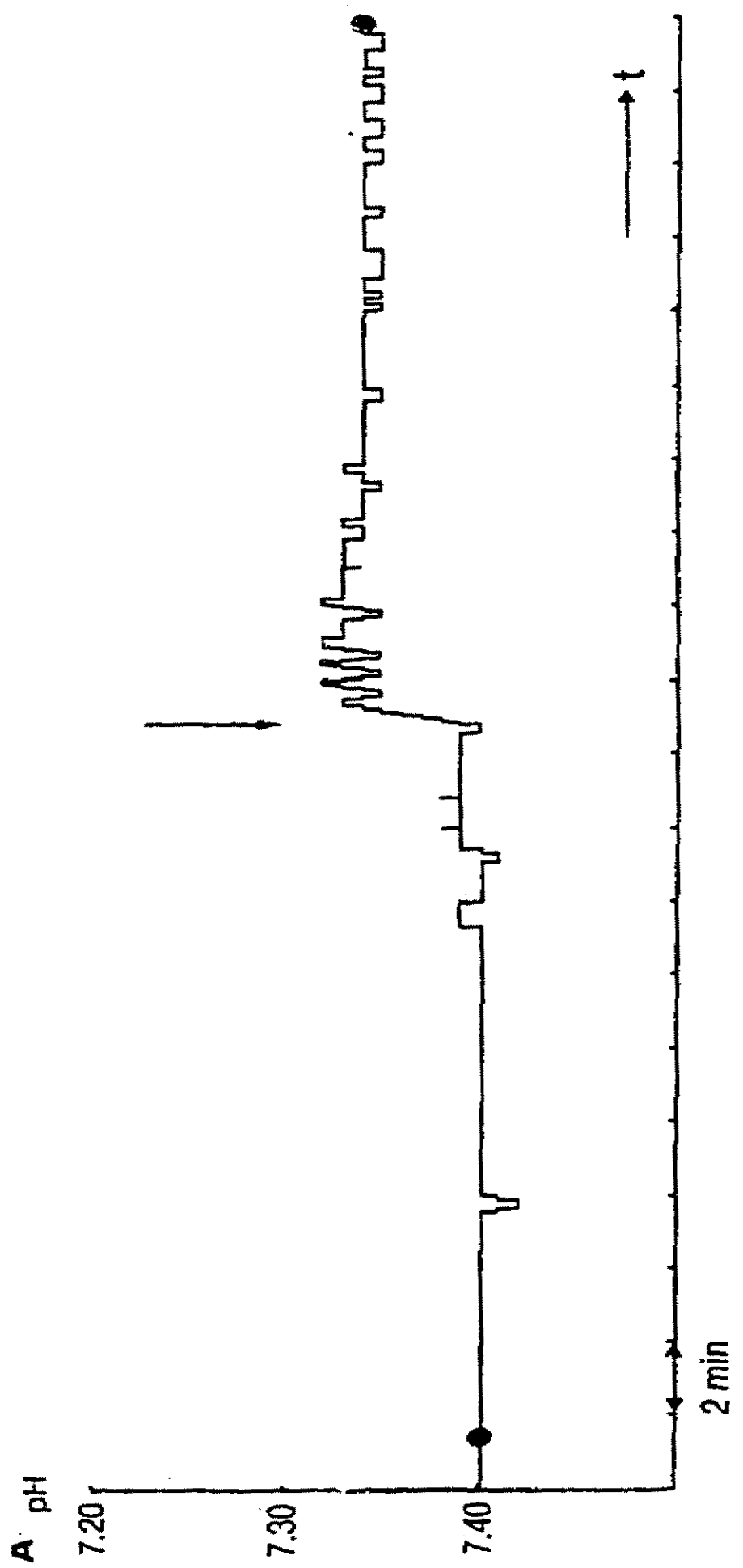

Fig. 7. Result of pH monitoring with the Sentron pH ISFET catheter and signal conditioner in a post-operative patient with (A) successful weaning and (B) unsuccessful weaning from mechanical ventilation. (By permission of Sentron v.o.f., Roden, The Netherlands.)

necessary rapid decisions to be made, and thus improving the clinical treatment of the patient.

6. FUTURE DEVELOPMENTS

Now that it is clear that the use of ISFETs is a reality, even under clinical conditions, the question arises as to which improvements have to be implemented to make them a commonly accepted biomedical tool, and which modifications and extensions can be expected in the near future to make them suitable for the measurement of other chemical species.

With respect to desired improvements of the present type of catheter tip pH ISFET, it will be clear that a system with *in vivo* calibration possibilities would greatly enhance the measurement time, which is now limited to the predictable behaviour time of the ISFET, or in other words as long as the various parameters stored in the accessory PROM are constant. In particular, it will be clear that *in vivo* calibration facilities will be an absolute necessity for ISFETs implanted for very long periods.

An approach, at present under investigation at the Twente University of Technology, is the integration of a micro-coulometric cell with the ISFET chip. This cell contains a working electrode around the ISFET gate and a counter electrode at a certain distance from the gate, applying a current pulse. A known ΔpH can now be induced very locally at certain time intervals, resulting in an ISFET response from which the pH sensitivity can be determined. A future development for implantable sensors with on-board calibration facilities is schematically drawn in Fig. 8. A further improvement of the present ISFET, especially with respect to its production costs, would be its integration with a solid-state reference electrode. Up to now the reference electrodes in use are of the salt-bridge type. An Ag/AgCl electrode is immersed in a KCl liquid or gel which makes contact with the solution to be measured by means of a porous plug. Production technology of such a device is completely incompatible with the planar ISFET technology. It will be obvious that a completely solid-state reference electrode, made using planar technology as an integral part of the sensor chip, would be preferable, but surprisingly, up to now, at least in the literature, little attention has been paid to this point.

The most promising approach, described in the literature by various authors but not yet put into practice, is the development of a so-called

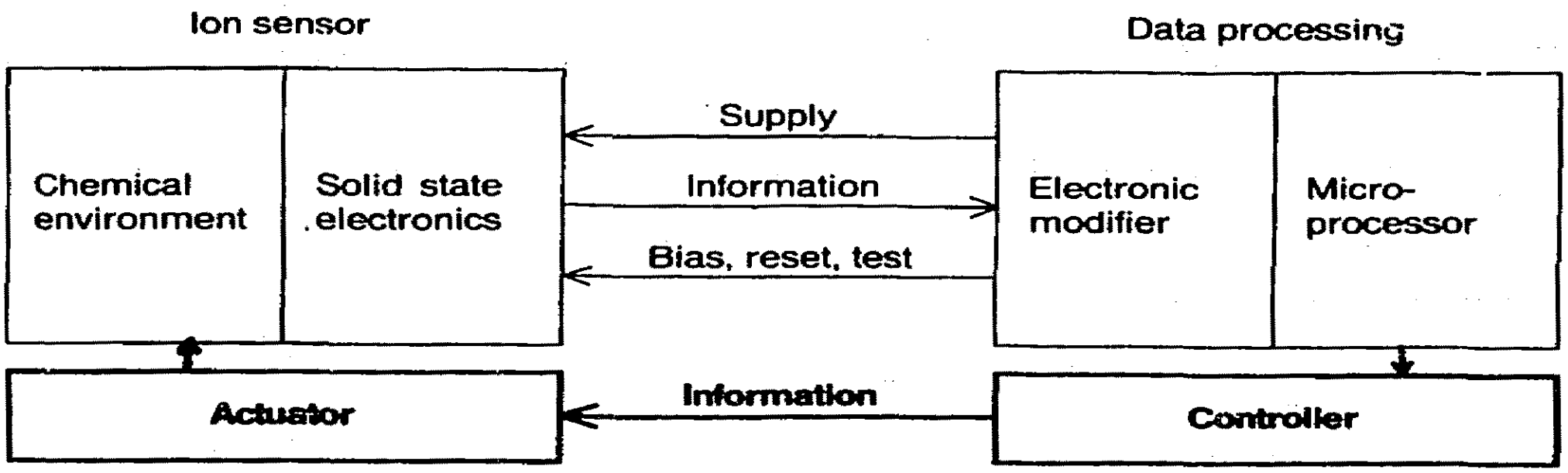

Fig. 8. Schematic representation of sensor–actuator system.

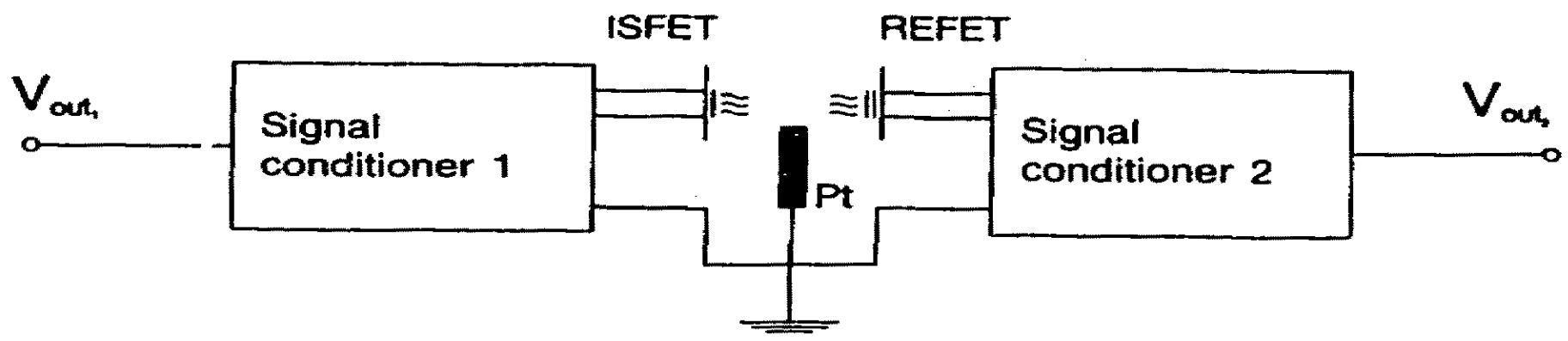

Fig. 9. Schematic representation of ISFET/REFET system with common platinum (pseudo) reference electrode.

REFET (Tahara *et al.*, 1982). A REFET is essentially an ISFET, the surface of which is made insensitive to ions. The REFET should be applied, together with an ISFET, in a differential mode, while the common lead of the amplifier is connected to a simple platinum electrode, evaporated on the chip, which also contains the REFET as well as the ISFET. This approach is shown schematically in Fig. 9.

Although the platinum electrolyte interface is not reversible and thus generates an unstable voltage, this voltage is measured by the differential ISFET/REFET pair as a common mode voltage and will therefore not result in an output voltage. A change in the pH of the liquid will, however, be measured as a differential signal between the ISFET and the REFET.

The problem with such a system is that a good suppression of the common mode voltages can only be accomplished if the CMRR of the amplification system is high. A high CMRR can, however, only be achieved if the ISFET and the REFET have the same sensitivity for electrical potentials. A REFET/ISFET pair consisting essentially of two equal ISFETs, one of which is coated with an additional insulating layer, will, however, always have very different electrical sensitivities.

A solution to this problem is not to use an ISFET and a REFET, but two electrically equal ISFETs, which differ, however, in their chemical sensitivity. This approach was shown to be valid by Kuisl (Kuisl & Klein, 1982), who exploited the different chemical sensitivities of a Si_3N_4 and a SiO_2 ISFET. Both ISFETs were applied in a constant drain-current mode. The difference between the output voltages of both signal conditioners only reflected a change in pH and was not sensitive to common mode signals up to 500 mV.

In summary, the ISFET/REFET or dual ISFET approach will probably be the best solution for the implantable use of ISFETs, because no salt bridge with an inherent low lifetime is necessary.

7. OTHER FET-BASED BIOSENSORS

The ISFETs realized up to now, and which have been developed to the point where they can be actually used in clinical practice as described in Section 5, are all inorganic gate ISFETs and thus explicitly sensitive to pH.

ISFETs described in the literature for the measurement of other ions make use of additional membranes which cover the gate area and which are sensitive to other ions (Sibbald, 1983). In principle, the same membranes as those used for the more conventional solid-state ion-sensitive electrodes can be applied, such as coated wire electrodes. ISFETs have the advantage that they also accept insulating materials as a coating, e.g. photoresist, which may contain specific ion-carrier ligands. Up to now all ISFETs which are modified in this way suffer from a limited lifetime. This is mainly caused by the poor attachment of the specific membranes to the original inorganic gate materials, which consists of a physical bond. It would be more convenient to modify the inorganic gate material of the ISFET chemically, in such a way that the hydroxyl groups

react with certain groups of the membrane material whose outside surface is sensitive to ions other than H^+. Such surface modification processes are already known from metal ion chromatography, where crown ethers are chemically bound to silica gel. We have recently started to investigate whether these processes can also be implemented in planar ISFET technology. This is very promising because it is known that a large variety of crown ethers can be synthesized, each type having a very specific affinity for one type of ion. The same concept of chemical surface modification can also be used to develop REFETs as mentioned in the previous section.

FET-based sensors are also discussed in the literature on biosensors coated with a bioactive material. An example is the enzyme FET (Niyahara *et al.*, 1983). In this case the ISFET is coated with a gel membrane which contains immobilized enzymes. These enzymes control very specific chemical reactions, resulting in chemical products which can be measured by the underlying ISFET.

In this way urea can be measured by means of the enzyme urease, immobilized in a membrane which covers an ISFET, due to a local pH change resulting from the reaction:

$$(NH_2)_2CO + 2H_2O + H^+ \xrightarrow{\text{urease}} 2NH_4^+ + HCO_3^-$$

The development of ENFETs is, however, faced with the same problem of membrane fixation as mentioned above with respect to membrane-covered ISFETs. In addition, ENFETs suffer from the same problem as found in the more conventional enzyme sensors, namely the limited lifetime of the immobilized enzymes.

A further example of FET-based biosensors is the Immuno FET, of which even less has been announced in the literature than for ENFETs (Schenck, 1978). The development of an IMFET is based on the knowledge that ISFETs appear to be very sensitive for any electrical interaction at the surface. It is therefore expected that if it is possible to adsorb or covalently bond a layer of antibodies or antigens to the ISFET surface as with the ELISA technique (enzyme linked immunosorbent assay), reaction with the corresponding antigen or antibody would result in a change of the surface potential of the ISFET and thus in the drain current. However, this effect has still to be proved possible under realistic conditions.

8. CONCLUSIONS

In conclusion it can be stated that the existence of ISFETs, particularly the pH-sensitive ISFET, is a fact. They are out of the laboratory and in clinical use. The measurement results are of important physiological significance, mainly because of the continuous nature of the application.

Improvements are desirable with respect to the character of the reference electrode or reference system, as well as to the *in vivo* calibration possibilities, especially those concerning the implantable application.

All other FET-based biosensors, including the chemically sensitive sensors as well as the biochemical types, are still under investigation. At present they all exist as laboratory prototypes.

ACKNOWLEDGEMENTS

The original ISFET research started at the Twente University of Technology, where various basic research projects are still continuing. The development towards a real clinical product was carried out by the sensor research group of Cordis, which at present operates as the Sentron Company. This paper could not have been written without close co-operation between the author and the Sentron scientists, including their clinical co-operators.

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