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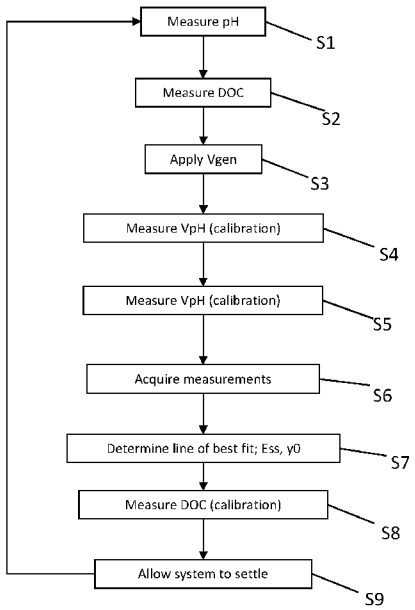

FIG. 11

(57) **Abstract:** A first aspect of the invention provides a pH sensor (10) for measuring pH levels within a measurement environment, the pH sensor comprising a reference electrode (40), a pH sensitive electrode (30), and a controller, for measuring the potential difference between the pH sensitive electrode (30) and the reference electrode (40), the measured potential difference being indicative of a pH level at the pH sensitive electrode (30), wherein the controller is operable to apply a voltage across first and second electrodes (50, 60) to control the pH level at the pH sensitive electrode (30) such that the pH level at the pH sensitive electrode (30) reaches a saturation level, and to perform a plurality of measurements of the potential difference between the pH sensitive electrode (30) and the reference electrode (40), at least one of the measurements taking place once the pH level at the pH sensitive electrode (30) has reached the saturation level, and at least one of the measurements taking place after the voltage has stopped being applied.

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SOLID-STATE PH SENSOR AND CALIBRATION METHOD

FIELD OF THE INVENTION

The present invention relates to a solid-state pH sensor and a calibration and/or recalibration method for the pH sensor, and to an implantable device comprising such a pH sensor. Embodiments of the present invention relate to a pH sensor for long-term, real-time, *in vivo* measurement of biophysical parameters in a human uterus, to a calibration method of calibrating the pH sensor (and optionally the dissolved oxygen sensor) *in situ*, and to a method to establish the value for pH within an electrolyte using the pH sensor.

BACKGROUND OF THE INVENTION

In a previous patent application by the present Applicant, PCT/GB2018/052612, an intra-uterine monitoring system and method for calibration are described. The system comprises an implantable device housing different sensors, including sensors for measuring pH levels and DO (dissolved oxygen) concentration, to aid in the diagnosis of sub-fertility.

A problem with sensors in this form of application, is that they become less accurate over time. Reasons for this inaccuracy include sensor drift, biofouling, surface changes and reference electrode instability. To maintain optimal performance recalibration is required. This is very challenging to achieve *in situ* in a remote environment such as the human body, or environmental measurements. Miniature solid state pH sensors such as ISFETs (ion-sensitive field effect transistors) and metal-oxide based sensors (Iridium Oxide, Platinum Oxide, Ruthenium etc.) can be implemented in small, remote, and low power sensing devices. Prior to measurements being taken, calibrations are carried out in solutions of known pH to achieve optimal performance. In applications where access to the sensor is not possible or undesirable, for example in implantable applications, these calibrations outside of the measurement environment are not possible during the course of the measurement.

Previous proposals for addressing such limitations include improving reference electrode stability (but this does not account for changes on the sensing electrode surface), the use of reference sensors (such as REFETs), but this is difficult to achieve in practice and not compatible with non-ISFET sensors, the use of drift prediction and

correction based on previously obtained data and recalibration using spectroscopic/optical techniques such as sensitive dyes *in situ*.

The present invention seeks to provide an alternative sensor and method to overcome these limitations.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a pH sensor for measuring pH levels within a measurement environment, the pH sensor comprising:

a reference electrode;

a pH sensitive electrode; and

a controller, for measuring the potential difference between the pH sensitive electrode and the reference electrode, the measured potential difference being indicative of a pH level at the pH sensitive electrode,

wherein the controller is operable:

to apply a voltage across first and second electrodes to control the pH level at the pH sensitive electrode such that the pH level at the pH sensitive electrode reaches a saturation level; and

to perform a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode, at least one of the measurements taking place once the pH level at the pH sensitive electrode has reached the saturation level, and at least one of the measurements taking place after the voltage has stopped being applied.

Saturation level is defined as the potential within a 10% range where the diffusion of the generated species has reached the pH sensitive electrode, creating a saturated state for a given species. The level of saturation is dependent on the injected current though, and distance between the first and/or second electrode and the pH sensitive electrode.

The first electrode can be the pH sensitive electrode. The second electrode can be an electrode other than the pH sensitive electrode and the reference electrode. The first and second electrodes may each be an electrode other than the pH sensitive electrode and the reference electrode.

The first and second electrodes may be referred to as first and second electrolysis electrodes, and herein are referred to as cathode/anode. The first and second electrodes may be disposed in the vicinity of the pH sensitive electrode (where they are distinct from the pH sensitive electrode).

The controller can be further operable, for example for re-calibration, to apply a voltage across first and second electrodes to control the pH level at the pH sensitive electrode, and to perform a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode, wherein the first and second electrodes can be separate from the pH sensitive electrode and the reference electrode.

This voltage can be the same or different to the initial voltage across first and second electrodes. The voltage can be a fixed or variable voltage and can be applied for long enough for the pH sensitive electrode to reach saturation of the pH level (or, of the electrode sites which interact with protons and/or hydroxide ions).

The plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode can be taken after the voltage has stopped being applied. This allows for reuse of the electrodes, i.e. the same electrodes can be used for applying the voltage and taking voltage measurements.

The pH sensor can be calibrated and/or recalibrated based on the measurements. The measurements being described above. The pH sensor can also be calibrated and/or recalibrated based on a rise time and/or relaxation curve arising from the measurements. The pH sensor can be further recalibrated based upon a change in the rise time and/or relaxation curve between successive applications of a voltage across first and second electrodes.

At least one of the measurements above can be taken at a set time point after the voltage has stopped being applied. This reduces power requirement of the device in comparison to taking multiple measurements.

Alternatively, the recalibration may take place externally of the pH sensor itself. The controller may be operable, while the DC recalibration voltage is being applied, to take a plurality of potential difference measurements over a time period, and be operable

subsequently to correlate the plurality of potential difference measurements with expected pH levels. The controller may be operable to determine the rise and relaxation curve upon application and removal of the DC recalibration potential, respectively. A line of best fit can be used to estimate the final value and obtain a calibration point. This process can be repeated using the opposite electrolysis potential:

1. To obtain a measurement of the pH value of a solution;
2. To obtain a two point calibration curve with a linear regression fit;
3. To derive the buffer capacity and/or pH value of the solution;
4. To derive a median value related to 1, and/or 2.

A plurality of measurements can be taken throughout the full time scale of relaxation from the saturation level to an equilibrium state after the voltage has stopped being applied.

The voltage is applied at a predetermined value and/or for a predetermined amount of time. The DC voltage can exceed the electrolysis potential of water, approximately 1.23V between the two electrolysis electrodes, to initiate the reaction generating the pH change. The rate of pH change will be dependent on the current passed.

The pH sensor can be an ISFET or metal oxide based sensor.

According to a second aspect of the invention, there is provided a multi-sensor device comprising the pH sensor according to the first aspect and a dissolved oxygen sensor, the dissolved oxygen sensor comprising the first and second electrodes, one of the first and second electrodes being used as the working electrode of the dissolved oxygen sensor.

The other one of the first and second electrodes can be used as a counter electrode of the dissolved oxygen sensor. The other one of the first and second electrodes can in addition be used as a reference electrodes of the dissolved oxygen sensor.

The reference electrode of the pH sensor can be a common reference electrode for use with the dissolved oxygen sensor.

The multi-sensor device can further contain a conductivity sensor. The dissolved oxygen and/or conductivity sensor can fulfil the function of the electrolysis electrode(s). The reference electrode of the pH sensor may be a common reference electrode for use with these sensors.

The pH sensitive electrode, the reference electrode and the first and second electrolysis electrodes may be fabricated on a substrate. The substrate can be any suitable material including glass, silicon etc. The pH sensitive electrode, the reference electrode and the first and second electrolysis electrodes may be disposed on the same side of the substrate. Alternatively, the pH sensitive electrode and the first electrolysis electrode may be disposed on a single side of the substrate and the reference electrode and the second electrolysis electrode may be disposed on the opposite, side of the substrate.

An electrolyte may be provided in a region bounded by the substrate and a semi-permeable membrane, the region containing at least the pH sensitive electrode and the first electrolysis electrode, diffusion of ions and molecules from the measurement environment into the electrolyte occurring via the semi-permeable membrane.

According to another aspect of the invention, there is provided an intra-uterine monitoring system comprising an implantable device having a pH sensor or a multi-sensor device according to the above, and an external receiver for receiving sensor data from the implantable device.

The pH sensor or the multi-sensor device can be within a human or animal body. More specifically, the measurement environment can be within a uterus. The pH sensor or the multi-sensor device can communicatively connect to an external receiver for receiving sensor data from the pH sensor or the multi-sensor device.

According to a third aspect of the invention, there is provided a method of calibrating or recalibrating a pH sensor, the pH sensor comprising a pH sensitive electrode and a reference electrode, the method comprising:

applying a voltage across first and second electrodes to control the pH level at the pH sensitive electrode such that the pH level at the pH sensitive electrode reaches a saturation level; and

performing a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode, at least one of the measurements taking place once the pH level at the pH sensitive electrode has reached the saturation level, and at least one of the measurements taking place after the voltage has stopped being applied.

The present method addresses the problem of sensor/reference electrode defects which occur during extended usage. By employing the method described herein, the current status of the sensor can be obtained with a zero-point reference created by the saturation of the pH sensitive electrode due to the induced pH change in its vicinity.

It will be appreciated therefore that the present method may provide either a measurement method and/or a calibration method for miniaturized solid-state pH sensors. Many commercial applications may be found for this technique, including the monitoring of pH in in vivo applications (e.g. implantable devices), monitoring of pH in environmental applications (e.g. at sea), or bench-top pH meters.

Optional features of the first and second aspects can be applied to the third aspects in an analogous manner.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described with reference to the accompanying drawings, in which:

Figure 1 schematically illustrates a pH sensor according to an embodiment of the invention;

Figure 2 schematically illustrates a side view of a combined pH and DO sensor behind a membrane;

Figure 3 schematically illustrates a top-down view of the sensor of Figure 2;

Figure 4 schematically illustrates a combined pH and DO sensor according to another embodiment of the invention;

Figure 5a schematically illustrates an alternative electrode structure according to another embodiment;

Figure 5b schematically illustrates a combined pH and DO sensor according to another embodiment of the invention;

Figure 6 schematically illustrates another electrode structure according to a further embodiment;

Figure 7 schematically illustrates a change in pH over time at a pH sensing electrode when a current is applied between a pair of electrolysis electrodes;

Figure 8a shows a graph of cyclical generation of Protons and Hydroxide sensed by the pH sensitive electrode;

Figure 8b shows an exponential fit with asymptote y0 of the relaxation curve from Protons and Hydroxide ions from Figure 8a;

Figure 9 shows a graph of the cyclical generation of Protons sensed by the pH sensitive electrode in different buffer solutions;

Figure 10a shows the repeated generation in phosphate buffered saline;

Figure 10b shows an exponential fit with asymptote y0 of the relaxation curve from Figure 10a;

Figure 11 is a schematic flow diagram illustrating a pH and DO sensor calibration method; and

Figure 12 is a schematic flow diagram illustrating a pH calibration method.

DETAILED DESCRIPTION OF EMBODIMENT(S)

In an embodiment there is provided a smart sensor which is capable of determining pH and DO content within a measurement environment, such as a uterus or other organ of a human or animal body. Such a smart sensor may also be used in other remote environments, such as long-term environmental monitoring (for example in the ocean). The high-level structure and operation of each of a solid-state pH sensor and DO sensor will now be described:

<u>pH sensor</u>

A solid-state pH sensor comprises a pH sensitive electrode and a reference electrode provided within an electrolyte. Different kinds of micro-scale solid state pH sensors have been developed, including a metal oxide-based pH sensor, which has good pH measurement capabilities, a simple structure and can be micro-fabricated. A wide variety of metal oxides have been characterised and iridium oxide (IrOx) and Ruthenium oxide (RuOx) are commonly used. A typical IrOx pH sensor is made from a thin IrOx film (IROF) deposited onto an electrode. A simple structure enables simple

fabrication. The use of a relatively simple processing circuit and small size is beneficial to monitoring applications.

Such a solid-state pH sensor includes a pH sensing electrode (formed of IrOx) and a reference electrode, formed of Ag/AgCl. The electrode potential of the pH sensing electrode has a linear relationship with the pH of a solution according to the Nernst-equation, as will be discussed below. The open circuit potential (OCP) (versus the reference electrode) can be used to measure the electrode potential across the pH sensitive electrode and the reference electrode from which the pH value can be determined in accordance with the known relationship/expression. This relationship is predetermined and requires calibration to be accurate. Given the linear response of the electrode potential with respect to pH, the calibration involves determining the offset $E^{0'}$ and the slope of the Nernst equation:

$$E = E^{0'} - \frac{2.303RT}{nF}\log[H^+] \qquad \text{(Equ 1)}$$

E is the electrode potential, R is the gas constant, T is temperature in Kelvin, n is the number of electrons, and F is Faraday's constant. H^+ is the activity of the hydrogen ions in the solution.

However, during long-term continuous operation, drift in the pH sensitive electrode and/or the reference electrode cause errors in the measurement. In this situation a recalibration is required to obtain the up-to-date status of the pH sensor. In practice, it is the $E^{0\prime}$ term of the linear regression fit which varies most over time, and it is the sensitivity that remains mostly constant.

Over recent decades, numerous materials have been investigated for use in pH sensing applications. One material of particular interest is Iridium Oxide (IrOx). This, in fact, is a metal oxide-metal oxide based system, having a response (variation in electrode potential as a function of pH) which is determined by the reaction occurring between its oxidation states. The IrOx pH sensor holds the following advantages: a linear response, low temperature coefficient, applicable in harsh environments, low impedance. Additionally, its simplicity of fabrication and biocompatibility make it a promising candidate for *in vivo* biomedical studies.

The working principle of these pH sensors relies on the formation of insoluble hydroxide groups on the metal oxide surface when placed in solution. This formation allows for proton displacement to occur between the hydroxyl sites in which protons from the electrode surface are exchanged with the bulk solution, resulting in an electron transfer reaction. In simple terms, the interaction between the surface of the metal oxide and the pH of the solution causes a change in surface potential.

The underlying mechanism for metal-oxides pH sensitive electrodes is described next for iridium oxide films (IROF), the possible REDOX reactions are listed in Equ 2 and 3.

$$IrO_2 + H^+ + e^- \leftrightarrow IrO \cdot OH \qquad \text{(Equ 2)}$$

$$2Ir0_2 + 2H^+ + 2e^- \leftrightarrow Ir_2O_3 + 2H_2O \qquad \text{(Equ 3)}$$

When immersed in an electrolyte, hydroxide groups are formed on the surface. These groups are capable of interacting with the protons in solution. Since the pH equals the negative log of the proton activity, the change in potential at the pH sensitive electrode can thus be related to the pH within the electrolyte.

For Hydrated IROF the equation takes the form of Equation 4:

$$2[IrO_2(OH)_{2-x}\,(2+x)\cdot H_2O]^{(2-x)^-} + (3-2x)H^+ + 2e^- \rightleftarrows [Ir_2O_3(OH)_3 \cdot 3H_2O] + 3H_2O \qquad \text{(Equ 4)}$$

It will be understood that Ir_2O_3 represents an Ir^{3+} oxidation state and that IrO_2 represents an Ir^{4+} oxidation state. This can be substituted into the Nernst equation which yields Equation 5 and shows the dependence of the slope on pH and the offset $E^{0\prime}$ on the ratio between the oxidation states within the metal-oxide.

$$E = \left(E^0 + 2.303\frac{RT}{nF}log\left(\frac{Ir^{4+}}{Ir^{3+}}\right)\right) - 2.303\frac{RT}{nF}pH \qquad \text{(Equ 5)}$$

Note that $pH = -log(H^+)$.

In equation 3, E is the electrode potential of the pH sensitive electrode, E^0 is the standard reduction potential. $E^{0\prime}$ is the complete formal potential, which can be seen to be a function of both E^0, and the ratio of activity of the Ir^{4+} and Ir^{3+} states. R is the

gas constant, T is temperature in Kelvin, n is the number of electrons and F is Faraday's constant. H^+ is the activity of the hydrogen ions in the solution. Activity (of the H+, Ir^{4+} and Ir^{3+} states) is a measure of the effective concentration of the respective species under non-ideal (e.g. concentrated) conditions, as would be understood by a person skilled in the art. Reviewing the Nernst-equation 5, it can be seen that two factors would influence the stability of the pH sensor: sensitivity factor (the rate of change of electrode potential as a function of pH change, that is, the slope of the equation) and formal potential. For a long term implantable system, the potential needs to remain stable at fixed pH. The resulting potential from the IrOx sensor can be rewritten in terms of the activity of its two active oxides and the proton activity, as shown in equation 5. As can be seen, a redox system consisting of the Ir^{4+} and Ir^{3+} is present. The amount of each species will determine the response of the fabricated sensor and is dependent on the method of deposition. Furthermore, the degree of hydration within the film i.e. the amount of hydroxide sites available will determine the stability of $E^{0'}$.

Most of the problems related to IrOx sensors are due to drift of the formal potential. In contrast, the sensitivity is less prone to change. When the formal potential drift has shifted too much by either a drifting reference electrode or a change in the IrOx ratio and its degree of hydration recalibration is required.

DO Sensor

An electrochemical DO sensor uses the electrochemical reduction of dissolved oxygen (DO) at a microelectrode. The micro electrodes may be readily fabricated onto silicon substrates with micro-fabrication technologies and can be constructed out of different materials including platinum, gold and carbon. The most common electrochemical DO sensor is of the Clark type, in which the electrode is situated behind a gas permeable membrane. Electrochemical DO sensors utilize a two or three electrode system, comprising a working electrode and a reference electrode/counter electrode (separate in a three electrode system). The working electrode is made from an inert metal, such as platinum or gold, and the electrochemical reactions of interest occur on its surface. The reference electrode is a non-polarizable electrode, and has a stable and well-known electrode potential. For example, a widely used reference electrode for electrochemical purposes is Ag/AgCl electrode.

The electrochemical DO sensor is immersed in an electrolyte. When a negative voltage is applied to the working electrode against the reference electrode, dissolved oxygen in the electrolyte is consumed according to the following chemical reactions.

$$O_2 + 4e^- + 2H_2O \leftrightarrow 4OH^- \quad \text{(Equ 6)}$$

$$O_2 + 42 + 2H_2O \leftrightarrow H_2O_2 + 2OH^- \quad \text{(Equ 7)}$$

$$H_2O_2 + 2e^- \leftrightarrow 2OH^- \quad \text{(Equ 8)}$$

These reactions produce an electrical current through the working electrode which can be measured by an electronic circuit. In the case of a two-electrode system, this current flows through the working electrode and the reference electrode. In the case of a two-electrode system, this current flows through the working electrode and the counter electrode. Following the theory of oxygen reduction, upon sweeping the voltage between working electrode and reference electrode toward the potential of oxygen reduction an initial increase in current is observed. After a given period of time the current reaches a limit; its steady-state or saturated state. This value is limited by the diffusion of oxygen to the working electrode surface. The magnitude of the observed current varies with dissolved oxygen content.

For low-power applications, prolonged operation of the DO circuitry is undesirable. Instead, a transiently operated DO measurement can be employed. Here, a rest voltage, defined as the voltage applied to the electrodes without any oxygen reduction resulting in zero current is applied prior to measurement. Next a measurement voltage, defined as the optimal voltage to achieve oxygen reduction is applied. By applying this step wave form, a transient current response is observed. When the measurement voltage is applied to the working electrode, the dissolved oxygen around the electrode is consumed. A current spike occurs at the beginning because of the fast potential change. Over time the current decreases rapidly due to oxygen consumption. At the same time, an oxygen concentration gradient is formed around the electrode. This oxygen concentration gradient causes oxygen molecules to diffuse to the working electrode from the bulk. Here, the oxygen reduction current approaches its steady-state value limited by oxygen diffusion. By taking fixed points on the transient profile a calibration curve can be obtained. Overall, the time taken for this type of measurement

is in the millisecond range. Hence, the power consumption of the system is significantly reduced.

Over time, the reference electrode suffers from fouling and/or degradation. This results in a varying potential between working electrode and reference electrode shifting the optimal potential for both rest and measurement voltage.

Calibration of a dissolved oxygen sensor, in terms of setting the relationship between oxygen reduction current and dissolved oxygen concentration, may be achieved by operating the dissolved oxygen sensor in the presence of a known (and preferably high) dissolved oxygen concentration at the working electrode.

pH sensor with calibration function

Referring to Figure 1, a pH sensor 10 is shown. The sensor 10 comprises a substrate 20 on which is formed a pH sensitive electrode 30. The substrate 20 may be a glass substrate, which is impermeable to the electrolyte and measurement solution. A reference electrode 40 is provided, which may be formed of Ag/AgCl. The pH sensitive electrode 30 and the reference electrode 40 are connected to a sensor read-out (not shown) which measures a potential (voltage) difference between the pH sensitive electrode 30 and the reference electrode 40. The sensor read-out may be part of a controller (control circuitry) which serves to measure voltage and/or current levels across and through the various electrodes. As discussed above, the potential difference is related to the pH at the pH sensitive electrode. The sensor 10 also comprises an anode (or cathode) 50 and a cathode (or anode) 60, forming a pair of electrolysis electrodes, which are connected to a DC source (not shown) able to supply a constant current as part of a recalibration process. The anode (or cathode) 50 is proximate the pH sensitive electrode 30. By applying a DC potential difference (at constant current) between the anode (or cathode) 50 and the cathode (or anode) 60, an electrolysis reaction is initiated.

The electrolysis of water generates products according to the following reaction:

$$2H_2O \leftrightarrow O_2 + 4H^+ + 4e^- \quad \text{(anode)} \quad \text{(Equ 9)}$$

$$2e^- + 2H_2O \leftrightarrow H_2 + 2OH^- \quad \text{(cathode)} \quad \text{(Equ 10)}$$

The above reactions at the anode and cathode (equations 9 and 10 respectively) can be initiated at electrode surfaces by applying a DC potential difference between the electrodes 50, 60 of at least 1.23V. By doing so, a local change in pH to either more acidic or more alkaline, dependent on the polarisation of the potential difference, is generated. If the distance between the pH sensing electrode 30 and generating electrode 50 is known, the change in pH at the pH sensing electrode 30 can be estimated based on the diffusion of H^+ and OH^-. These estimations over time can then be used to obtain a calibration curve (curve in this context may include a straight line). The estimations can be based on the generated pH changes measured with pH sensitive electrode. From this, the new state of the sensor is determined and more accurate values of pH levels can be obtained, omitting drift in said pH sensor and the incorporated reference electrode.

However, this relies on the accuracy of the models and their prediction on pH. Therefore, knowledge on the solution is required to a greater extent. In this invention this limitation is omitted. More particularly, during calibration, a fixed voltage and constant current are applied across the electrodes 50, 60. The resulting electrolysis reaction will start to generate H^+ (H_3O^+) or OH^- ions at the electrode 50, near the pH electrode 30, depending on the polarity of the applied voltage. This will cause the pH to either rise, or fall, again depending on polarity. The pH will therefore change over time, and the potential difference between the pH electrode 30 and the reference electrode 40 will therefore also change over time. The pH generated by the electrolysis reaction proximate the pH sensitive electrode at any given time during the calibration process is predetermined (that is, an expected value of pH given the amount of time over which the voltage has been applied across the electrodes 50, 60 is known). Accordingly, it is possible to map the voltage measured at the pH electrode 30 to a pH level known to be present at the electrode 30 at the time the voltage was measured. It will be appreciated that the magnitude of the pH changes caused by the electrolysis reaction will dominate over any fluctuations in pH present in the electrolyte itself prior to calibration, and so such fluctuations should not have a significant material effect on the calibration process.

This type of calibration can be performed either with the pH sensor 10 in direct contact with the measurement solution or through separation of the sensor by an internal (an)ion conductive electrolyte and membrane. In the latter case, the sensed pH

change is dependent on the diffusion of the products within the internal electrolyte, preventing natural convection to take effect, and keeping out interfering species.

In Figure 1, a pair of electrolysis electrodes are used in combination with the pH sensitive electrode and reference electrode of a solid-state pH sensor. The electrolysis electrodes are shown to be dedicated electrolysis electrodes (anode and cathode) separate from the pH electrode and the reference electrode. They are dedicated in the sense that they serve no purpose other than recalibration.

In one alternative implementation, the first electrode of the pair of electrolysis electrode is the pH sensitive electrode itself. The second electrode is separate from the pH sensitive electrode and the reference electrode. In this case, the pH sensor with calibration function can be achieved with three electrodes rather than four. However, as the pH measurement cannot be taken at the same time as a DC reference voltage is applied across the pH measurement electrode (acting as the first electrode) and the second electrode, the application of the DC reference voltage will need to be discontinued for a short time while the pH measurement is made. The discontinuation of the DC reference voltage (and thus the taking of the pH measurement) would take place after a predetermined duration of application of the DC reference voltage – at which time the pH level at the pH measurement electrode could be expected to be a first known value. Once the pH measurement has been taken, the DC reference voltage can be applied again for a further predetermined duration before another pH measurement is taken (at a time at which the pH level at the pH measurement electrode could be expected to be a second known value). This process can be continued until sufficient pH data points have been obtained to enable an accurate recalibration.

In another alternative implementation, the first electrode of the pair of electrolysis electrodes is the pH sensitive electrode itself, and the second electrode of the pair of electrolysis electrodes is the reference electrode. In this case, the pH sensor with calibration function can be achieved with two electrodes rather than three or four, but the issues associated with the three-electrode implementation also arise, and in addition this may place constraints on the type of reference electrode which can be used. In particular, this implementation is only viable if the reference electrode is capable of passing the current required to cause the electrolysis reaction. An Ag/AgCl reference electrode would not survive this, but a platinum electrode for example can

pass it but is in other senses less effective as a reference electrode. Other reference electrodes can also be used such as graphene/carbon.

Figure 2 extends the implementation of Figure 1 by recognising that the pair of electrolysis electrodes could be implemented as the working electrode and counter electrode of a three-electrode dissolved oxygen sensor, thus permitting a combined pH and DO sensor to be provided with pH calibration (and also, as will be discussed below, DO calibration) without adding any further electrodes beyond those already required for pH and DO sensing (or pH sensing with calibration).

Referring to Figure 2, a cross sectional view though a combined sensor 100 shows a substrate 110 upon which the various electrodes of the sensor are formed, side walls 120 and a semi-permeable membrane 130. The substrate 110, side walls 120 and membrane 130 define a substantially sealed unit which can be placed into a solution/sample which is to be measured. Within the sealed unit an electrolyte solution 140, in this case Chloride Cl-, is provided. The electrolyte solution 140 may be a gel, or liquid. The electrolyte is therefore separated from the measurement solution by the membrane 130, which permits transmission of ions (H+/OH-) and other chemicals (for example dissolved oxygen, in the form H2O) via diffusion through the membrane 130. As discussed above, dissolved oxygen (for example) diffuses across the membrane 130 at a rate proportional to the pressure of oxygen within the measurement solution. Similarly, the pH within the measurement solution will cause pH changes within the electrolyte by diffusion of ions through the membrane 130.

Upon the substrate, several electrodes are provided. In particular, a pH sensitive electrode 160, a first generating electrode 170, a second generating electrode 180 and a reference electrode 190. The pH sensitive electrode 160 corresponds to the pH sensitive electrode 30 of Figure 1. The reference electrode 190 corresponds to the reference electrode 40 of Figure 1, and also serves as a reference electrode of the DO sensing part of the combined sensor 100. The first generating electrode 170 corresponds to the electrode 50 of Figure 1, but also serves a working electrode of the DO sensing part of the combined sensor 100. The second generating electrode 180 corresponds to the electrode 60 of Figure 1, but also serves as a counter electrode of the DO sensing part of the combined sensor 100. The pH sensitive electrode 160, the first generating electrode 170, the second generating electrode 180 and the reference electrode 190 are all electrically connected to a controller 195. The controller 195

comprises circuitry for measuring the potential difference across the pH sensitive electrode 160 and the reference electrode 190 during a pH measurement process. The controller 195 also comprises circuitry for applying a potential difference across the reference electrode 190 and the first generating electrode 170 and measuring a resulting current flow through the first generating electrode 170 (and thus the second generating electrode 180) in order to measure the dissolved oxygen concentration at the first generating electrode 170. The controller 195 also comprises circuitry for applying a DC recalibration voltage across the first generating electrode 170 and the second generating electrode 180 in order to modify the pH in the vicinity of the pH sensitive electrode 160, and as will be discussed subsequently to increase the dissolved oxygen concentration at the first generating electrode 170. The electrical circuitry within the controller 195 required to implement the above would be well known and understood by the skilled person.

During measurement operations, a potential difference between the pH sensitive electrode 160 and the reference electrode 190 are used to determine the pH of the electrolyte 140, and thereby the pH of the measurement solution outside the sensor. Similarly, during measurement operations, a small first voltage (insufficient to cause electrolysis) is applied between the first generating (working) electrode 170 and the second generating (counter) electrode 180, and a resulting current proportional to the dissolved oxygen level in the electrolyte is measured and used to identify the dissolved oxygen level.

During pH calibration, a second voltage, greater than the first voltage, is applied between the first generating electrode 170 and the second generating electrode 180, causing the above-discussed electrolysis reactions to occur. In particular, it can be seen that the electrolysis reaction of equation 9 takes place at the first generating electrode 170 and the electrolysis reaction of equation 10 takes place at the second generating electrode 180. This results in the local pH at the first generating electrode 170 reducing (becoming more acidic), since the first generating electrode 170 is in this case the anode. The opposite change in pH can be achieved by reversing the polarity of the voltage applied between the first and second generating electrodes 170, 180. The first generating electrode 170 is proximate to the pH sensitive electrode 160, and so local changes in pH at the first generating electrode 170 will be experienced at the pH sensitive electrode. The second voltage is applied as a fixed voltage, and with a constant current. The potential difference between the pH sensitive electrode 160 and

the reference electrode 190 (which is relatively distant from both the first generating electrode 170 and the second generating electrode 180 and will therefore not experience the effects of the electrolysis reactions) is periodically or continuously measured over time, and used to calibrate the pH sensor in the manner described above.

When the first generating electrode 170 is used as the anode, the electrolysis reaction (equation 9) which takes place generates oxygen as a by-product. As discussed previously, calibration of a dissolved oxygen sensor can be achieved by taking measurements at a high DO concentration. Accordingly, when the pH calibration has been complete, the oxygen concentration at the first generating electrode 170 can be expected to be high. Accordingly, by discontinuing the application of the second (higher) voltage at a constant current across the first and second generating electrodes 170, 180 and instead applying the first (lower) voltage across the first and second generating electrodes 170, 180 and measuring the resulting current, a calibration measurement at a high oxygen concentration can be obtained. In other words, the electrode structure and configuration of Figure 2 permits (a) pH measurement, (b) DO measurement, (c) pH calibration and (d) DO calibration without the need for additional components, and as part of an integrated sensing and calibration procedure. The method described here can be used in a single on-chip electrode system when the pH sensor is used in combination with a dissolved oxygen (DO) sensor.

To summarise, the sensor, consisting of a platinum or gold working electrode, counter electrode and a reference electrode, can be configured electronically to form the anode and cathode to facilitate the generation of ions to calibrate the pH sensor. In this manner, the pH change is generated at the surface of the dissolved oxygen sensor. By adding the pH sensor in close proximity, the current status of the pH sensor is determined. In particular, a zero-crossing point (E0' in equation 1) and a slope (remainder of expression in equation 1) can be determined by determining a line of best fit to the sampled voltages. Additionally, the anodic reaction generates oxygen as a product of the electrolysis. By performing a transient dissolved oxygen measurement shortly after generating of H_3O^+ and O_2 a single point calibration at a high DO concentration value can be obtained and used to assess the state of the DO sensor. This smart-sensor is able to measure both pH and DO accurately on a single system without the need for additional electrodes outside of the sensor package.

It will be understood that the electrolysis reaction could be carried out any number of times in any direction of polarisation, as to increase the pH from its base level and measure the resulting voltage changes, and to decrease the pH from its base level and measure the resulting voltage changes. In practice, since the relationship between voltage and pH is linear, this may not be required to identify the slope and zero crossing point of the sensor. Furthermore, in order to change the polarity of the applied voltage, a switching circuit will be required, thereby increasing complexity and size. It is preferable for the anode (rather than the cathode) of the electrolysis electrodes to be proximate/adjacent the pH sensitive electrode, since it is only the electrolysis reaction which takes place at the anode which generates the oxygen which also permits calibration of the DO sensor.

It will be appreciated that the calibration process artificially raises DO and pH levels, and that actual measurements of DO and pH levels of the measurement environment cannot be made until the levels in the electrolyte solution have returned to normal.

Referring to Figure 3, this shows a top view of the electrode structure of Figure 2. Like reference numerals are used to identify like components. It can be seen that the pH sensitive electrode 160 comprises a disk-like area 162, while the first generating electrode 170 comprises a ring area 172 which substantially surrounds the disk-like area 162 of the pH sensitive electrode 160. This places the disk-like area 162 and the ring area 172 in close proximity to strongly influence the ion and oxygen concentration at the pH sensitive electrode 160 during electrolysis. It will be appreciated that this arrangement could be reversed such that the pH sensitive electrode surrounds the first generating electrode. The distance between the pH sensitive electrode and the first generating electrode influences the time that would be required for the measurement to reach a desired pH value. A separation of 50 to 100μm has been found to obtain a suitable pH shift within seconds. The time taken is also dependent on the current passed through the electrolysis electrodes. In particular, the higher the (constant) current which is applied, the faster the desired pH shift is achieved.

Referring to Figure 4, this shows an alternative structure in which a pH sensitive electrode 160' and a first generating electrode 170' are provided on an upper side of the substrate 110, while a second generating electrode 180' and a reference electrode 190' are provided on a lower (opposite) side of the substrate 110. This has the added benefit that the OH- generated on the cathode does not interfere with the generated

H3O+ which would otherwise cancel out the pH change if the distance between the two is too small.

Referring to Figure 5a, an alternative embodiment is schematically illustrated in which a substrate 510 comprises a recessed well 515 within which a pH electrode 560 and first generating electrode 570 are formed (on the base of the well). As the recalibration voltage is applied between the first and second generating electrodes, a pH change at the first generating electrode 570 will fill the well 515 allowing the solution within the proximity of the pH sensor 560 to reach a particular (known) pH value more quickly than with the above-described embodiments. Typically, the depth of the well 515 will be in the micro-meter range. The reference electrode and second generating electrode (neither of which are shown in Figure 5) are placed outside of and preferably away from the well. For example, the reference electrode and second generating electrode may be provided to the other side of the substrate 510 in a similar manner to Figure 4. The shape of the well 515 when viewed from above (in plan view) preferably substantially follows the perimeter of the first generating electrode 570, to be substantially circular in the present example. The well 515 may be formed as a ridge extending substantially around the pH electrode 560 and first generating electrode 570. In Figure 5, the pH electrode 560 is substantially surrounded by the first generating electrode 570 in like manner to Figure 3. However, the first generating electrode 570 and the pH sensor 560 can be reversed, such that the pH electrode surrounds the first generating electrode.

Referring to Figure 5b, this shows a pH sensitive electrode 560' and a first generating electrode 570' are provided on an upper side of the substrate 510', while a second generating electrode 580' and a reference electrode 590' are provided on a lower (opposite) side of the substrate 510'. This structure also incorporates a well 515' similar to the well of Figure 5a. For this design the recessed electrode in the well can also be used as an oxygen sensor. There is also a photoresist material 525 applied onto the upper side of the substrate 510'. The photoresist material 525 defines the electrode geometry; in this example a disk or a ring/band.

Referring to Figure 6, another alternative embodiment is schematically illustrated in which a substrate 610 comprises a recessed well 615 within which a pH electrode 660 is formed (on, and substantially covering, the base of the well 615). As with Figure 5, the well 615 may be formed as a ridge extending substantially around (in this case) the

pH electrode 660. A first generating electrode 670 is formed on top of the ridge of the well 615. In this case, a pH change in the solution at the first generating electrode 670 will progress from the corners of the first generating electrode 670 into the well 615. As with Figure 5, the second generating electrode and the reference electrode are disposed outside of and preferably away from the well, for example to the other side of the substrate 510 in a similar manner to Figure 4. As with Figure 5, the structure of Figure 6 can be expected to allow the pH level in the vicinity of the pH electrode 660 to change more quickly due to the shelter provided by the well 615 and provides an environment that is insensitive to convective forces.

Referring to Figure 7, an example change in pH (y axis) with respect to time (x axis) is illustrated when a constant current of 200μA is applied across the first and second generating electrodes 170, 180 (at a fixed voltage of 1.23V and 50uA cm-2 current density). It can be seen that the pH rapidly reduces during the first few seconds but then the rate of reduction slows due to the diffusion rate in water. It will be appreciated that the voltage measurements taken at various times during the electrolysis reaction can be mapped to the expected pH levels at those times (represented illustratively by the graph of Figure 7) to calibrate the pH sensor.

The method for recalibrating the pH sensor may use either a two or three electrode electrolysis set-up. With a two-electrode set up, only the working electrode 170 and the counter electrode 180 are used, in the manner described above, but applying a constant voltage and current across them. The electrolysis electrodes 170, 180 in this case are ungrounded, which means that the absolute voltage at the first generating/working electrode 170 is unknown. With a three-electrode set up, the reference electrode 190 is used as a ground. In particular, an absolute voltage at the working electrode 170 is achieved by grounding the counter electrode 180 to the reference electrode 190. The three-electrode set up is particularly useful for variable environments, which with a two-electrode setup might result in an unpredictable absolute voltage being applied at the working electrode.

However, the method of applying the DC reference voltage for a further predetermined duration and then taking a pH measurement in order to calibrate the pH sensor relies on the accuracy of the models and their prediction on pH. Therefore, knowledge of the solution is required. In order to overcome this problem another calibration method will now be discussed.

Furthermore, this relies on the accuracy of the models and their prediction on pH. Therefore, knowledge on the solution is required to a greater extent. In this invention this limitation is omitted. During either measurement, calibration, and/or re-calibration, a fixed voltage and constant current are applied across the electrolysis electrodes 170, 180. The resulting electrolysis reaction will start to generate H^+ or OH^- ions at the cathode or anode, near the pH electrode 160, depending on the polarity of the applied voltage. This will cause the pH to either rise, or fall, again depending on polarity. The pH will therefore change over time, and the potential difference between the pH electrode 160 and the reference electrode 190 will therefore also change over time. The pH generated by the electrolysis reaction in proximity to the pH sensitive electrode 160 at any given time during the calibration process is predetermined (that is, an expected value of pH given the amount of time over which the voltage has been applied across the electrodes, is known). The potential is applied constantly, resulting in an increased acidification or alkalinisation at the pH sensitive electrode 160 due to the diffusion of the generated ionic species i.e. H^+ or OH^-, measureable as a potential difference between the pH sensitive electrode 160 and the reference electrode 190. A rise and fall, as shown in Figure 8 can thus be observed.

Figure 8 shows the result of oscillating the voltage (positive to negative) across the first and second generating electrodes 170, 180 on the measured potential 710 across the pH sensitive electrode 160 and the reference electrode 190. Put another way Figure 8 shows the cyclical generation of Protons and Hydroxide sensed by the pH sensitive electrode. At 100 seconds a potential is generated across the first and second generating electrodes 170, 180, this causes the generation of Protons (H^+). Here, the potential rises in a rise curve until all the sites on the metal-oxide (which interact with the Protons in the solution) are saturated at the saturated state potential (Ess). The potential across the first and second generated electrodes 170, 180 is then removed at 125 seconds, the measured potential 710 is shown to relax with a relaxation curve to an asymptote y0. At 200 seconds the potential generated across the first and second generating electrodes 170, 180 is reversed, this causes the generation of Hydroxide ions (OH^-). Again the metal-oxide saturates (although this time with Hydroxide ions) to the saturated state (Ess). This potential equals the lowest and/or highest pH possible for which the solid-state pH sensor can give a reading and thus can be seen as a zero-point. The value of the pH at Ess can be determined either through measurement or through calculation and/or simulation. The voltage across the first and second

generating electrodes 170, 180 is shown to continue to oscillate, further showing that the values of Ess are highly reproducible if the time duration of voltage generation is chosen adequately.

When the DC potential is switched off, the relaxation curve tends towards an asymptote y0 which is representative of the locally generated pH change re-equalising with the solution due to the solutions buffering capacity, diffusion and convection. A theoretical curve can be fitted to the relaxation curve and/or rise curve and a value for the asymptote y0 i.e. the predicted potential within the solution coming from the zero-point i.e. saturated state, can be made.

Figure 9 shows the result of oscillating the voltage (positive to neutral) across the first and second generating electrodes 170, 180 on the measured potential 710 across the pH sensitive electrode 160 and the reference electrode 190 in three different pH buffers (pH 4, pH 7, pH 9). Put another way Figure 9 shows the cyclical generation of Protons sensed by the pH sensitive electrode at pH 4, pH7, and pH 9.

The state of these changes is again highly reproducible, in particular after several electrolysis cycles as shown in Figure 9. Thus, there is a relationship between the predicted value for the asymptote y0 and the pH within the solution and its buffering capacity. Because the sensitivity in metal-oxide based sensors is unchanging over time, the difference in potential divided-by the sensitivity equals the change in pH caused by the solution.

As an example, Figure 10a shows the repeated generation in phosphate buffered saline. As can be denoted at time 0-15 min, the measured potential 810 is in equilibrium with the solution. However, the state of the pH sensor is unknown. At t = 15 an electrolysis potential (a voltage across the first and second generating electrodes 170, 180) initiates the generation of protons, and the potential between the pH sensitive electrode 160 and the reference electrode 190 starts to rise. A value for Ess is obtained at t = 17 min. As the electrolysis potential is switched off the measured potential 810 starts to drop reaching a new equilibrium at t = 20 min. The new equilibrium differs from the original equilibrium position because the pH sensing mechanism described in equations 2-5 is dependent on the oxy-hydroxides within the pH sensitive film. As the generated protons and/or hydroxide ions reach the surface of the pH sensitive electrode all oxy-hydroxide sites are occupied by the respective species providing a

reproducible "zero-state". When the electrolysis potential is switched off a new equilibrium is established, dependent on the roughness and porosity of the pH sensitive film.

The drop in measured potential 810 produces a relaxation curve which can be mathematically described and a line fitted to obtain asymptote y0 as shown in Figure 10b. Repeated cycles show a high degree of reproducibility and thus can give an indication of the pH value. The extracted results are listed in Table 1.

Table 1: Example measurement of pH based on Ess and ΔpH

	y_0 (mV)	E_{ss} (mV)	ΔpH	pH_{sim}+ ΔpH	Error
For figure 8	596.0	943.1	4.85	7.55	0.14
	610.4	946.4	4.70	7.40	0.01
	602.9	949.5	4.85	7.55	0.14
	613.6	950.4	4.71	7.41	0.00
	607.3	955.3	4.87	7.57	0.16
For figure 10a	554.3	941.9	5.19	7.95	0.18
	559.6	944.3	5.15	7.91	0.14
	562.5	955.4	5.26	8.02	0.25
	568.3	960.6	5.25	8.01	0.24
	561.2	947.1	5.17	7.92	0.16

Other electrodes within the system can fulfil the purpose of anode/cathode this includes but is not limited to a dissolved oxygen sensor and a conductivity sensor. It will be apparent that the electrolysis reaction could be carried out twice, once to increase the pH from its base level and measure the resulting voltage changes, and once to decrease the pH from its base level and measure the resulting voltage changes. In which case a median value for y0 can be obtained. Furthermore, the zero-point can also be used as a single point calibration for which the sensitivity is assumed constant.

Referring to Figure 11, a high-level flow diagram is provided to explain the overall operation of a combined pH and DO sensor with built in calibration. At a step S1, the potential VpH at the pH sensitive electrode 160 with respect to the reference electrode 190 potential is measured over time. The measured potential is related to the current pH value of the electrolyte solution. At a step S2, a dissolved oxygen concentration is measured by applying a small fixed voltage versus the reference electrode and measuring the current between the first and second generating electrodes of which

one functions as the working electrode for the DO sensor 170, 180. The current is related to the DO concentration in the electrolyte solution. The steps S1 and S2 can be carried out in parallel, or can be interleaved. At a step S3, a calibration process is triggered, and in particular a higher fixed voltage (Vgen) at a constant current is applied between the first and second generating electrodes 170, 180. A local pH change is thereby generated over time at the surfaces of the first generating electrode 170 and the second generating electrode 180. As time progresses, the boundary of the pH change in the electrolyte solution starts to cover the pH sensitive electrode 160 resulting in a change in VpH until a saturation level is reached. Where the majority of the pH sensitive sites are occupied by the generated species and the potential of the pH sensitive electrode has reached a stable level. At a step S4, the voltage VpH is repeatedly sampled over the rise time (for Proton generation or Hydroxide ion generation). At a step S5, the voltage Vgen is switched off and the voltage VpH is further repeatedly sampled over the full time scale of relaxation (i.e. until the measurement solution has fully re-equilibrated). Alternatively, the voltage can be sampled until a certain time has elapsed, which may not correspond with the full time scale of relaxation. At a step S6, at least two points of VpH at registered times are acquired (at least one at the saturation level, and at least one over the relaxation time), and are set to correspond with simulated, measured or calculated values of the generated pH change across the pH sensor surface (that is, for example, the graph of Figure 7). At a step S7, a linear fit is performed on the acquired points to obtain a new calibration curve/relationship between voltage and pH. At a step S8, a smaller voltage applied in order to measure the current through the working electrode 170 and counter electrode 180 at the high oxygen concentration resulting from the electrolysis reaction at the anode (first generating electrode 170). This serves to calibrate the DO sensor. At a step S9, the system is allowed to re-equilibrate with the measurement solution. Measurement at the steps S1 and S2 can then continue.

Alternatively, at steps S4 and S5 only two samples are taken (in total) which are used in step S6. The second of the two samples can be taken at a set time point after the voltage has stopped being applied.

It is understood that due to the simulated or calculated values, or characterised reference measurements of pH as a result of the generated pH change across the pH sensor surface, all that is necessary to establish a known pH is the saturation level measurement, and at least one measurement on the relaxation curve. This is because

for each saturation level, and equilibrium point (e.g. asymptote, y0) a known relaxation curve exists. Thus knowing two of these three values allows for the calculation of the missing value.

After the initial calibration it may be necessary to re-calibrate the device to compensate for sensor drift. Referring to Figures 12 a possible pH calibration method using the present technique is described. The method of Figure 12 is effective where the pH of the environment in which the pH sensor is disposed at the time of calibration is known, or is unknown but constant, but is also effective where the pH of the environment in which the pH sensor is disposed at the time of calibration is neither known, nor can be assumed to be constant.

In Figure 12, at a step V1, a recalibration voltage/current is applied to the pair of electrolysis electrodes for a period of time (a rise time) until a first steady-state pH at the pH sensitive electrode is achieved. The period of time required to achieve this, and the pH value reached, is generally known because of the electrode geometry, the applied voltage and current are all known and predetermined, however voltage measurements are taken successively until a saturated state is reached. At a step V2, a voltage reading is taken while the pH is at the first steady state, and is associated with the known, steady state, pH value, to provide a first calibration point. At a step V3, the recalibration voltage/current is switched off. At a step V4, the pH value will then start to relax back to its equilibrium point, and after a set point time (before the equilibrium point is reached) another voltage reading is taken, to provide a second calibration point. At a step V5, the recalibration voltage is applied for a second time (the polarity can be reversed). Here, the recalibration voltage is applied for a further period of time (a rise time) (which may be the same as that of the step V1 if the pH level at the pH sensitive electrode has already settled, or may be of greater duration if the pH change arising from the step V1 first needs to be reversed), again, until a saturated state pH is achieved. At a step V6, a voltage reading is taken while the pH is at the second saturated state, and is associated with the known, steady state, pH value, to provide a further calibration point. At a step V7, the recalibration voltage/current is switched off. At a step V8, the pH value will again start to relax back to its equilibrium point, and after a set point time (before the equilibrium point is reached) another voltage reading is taken, to provide a further calibration point. At a step V9, the pH sensor is recalibrated based upon a change in the rise time and/or relaxation curve between the successive applications of a voltage across the first and

second electrodes. This recalibration can obtain the formal potential of the Nernst equation and changes to the sensitivity. These will then be used during future operation of the pH sensor, in mapping a read voltage to a particular pH value.

The DC recalibration voltage should exceed the electrolysis potential of water, approximately 1.23V between the two electrolysis electrodes, to initiate the reaction generating the pH change. The rate of pH change will be dependent on the current passed and distance between the generating electrodes and the pH sensitive electrode.

Alternatively, successive measurements are taken of the relaxation curve instead of measuring after the set point time (as described above), and a point along the curve is selected which can represent the curve or the time from the start of the relaxation curve to the approximate equilibrium point (y0) is used for recalibration.

Alternatively, the voltage applied to the pair of electrolysis electrodes is applied for a predetermined period of time. This predetermined period of time is long enough so that a saturation state would have been reached irrespective of the starting pH value, for example by simulating or determining the diffusion time over the distance between the electrolysis electrode and the pH sensitive electrode for a value of the injected current. Thus, only one measurement needs to be taken during the rise time (which can be used as a calibration point).

It will be understood that the techniques and structures described herein could be applied to intrauterine monitoring (by implementing a combined pH and DO sensor in an implantable sensor device), to other body-cavity monitoring, such as within a vagina, bladder or digestive tract of a human or animal body. Furthermore, the pH sensor and calibration method (optionally with a DO and conductivity sensor) could be used in other applications such as remote environmental modelling or laboratory instrumentations. The present technique is relevant in any application in which long term remote monitoring of a pH level is required, since the long term use requires recalibration to compensate for (for example) drift, while the remote use means that such recalibration must be carried out in situ rather than by removing the sensor from the measurement environment. In addition to the structures described above, a sensor device containing a pH sensor and optionally a DO sensor can be expected to comprise components such as an antenna and transmitter/receiver circuitry for communicating

sensor readings to an external device, and optionally for receiving control signals for controlling the sensor device. Such transmitter/receiver circuitry would be interfaced with, or part of, the controller 195 described above, or equivalent controllers applied to the other embodiments of the invention described herein.

The present invention is not limited to a specific pH sensitive material. Suitable materials could include (but are not limited to) different metal oxides, ISFETS, or hydrogels. Further, various fabrication aspects of the system such as the separation distance between electrodes and electrode materials can be varied in dependence on the application, requirements and materials used. Moreover, various different types of electrode lay-out can be used, for example disks, rings and interdigitated electrodes.

It will be appreciated that the calibration could take place on-chip (that is, within the sensor itself), or alternatively the sensor may simply apply voltages and measure voltages and currents for transmission externally of the sensor, Awith the calibration being applied to the voltage and current measurements being output by the sensor by a device in receipt of such voltage and/or current measurements. Similarly, the sensor may itself fully control the calibration process of triggering electrolysis, or may alternatively be responsive to a received instruction from outside the sensor to trigger the electrolysis reaction.

Although the invention has been described above with reference to one or more preferred embodiments, it will be appreciated that various changes or modifications may be made without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. A pH sensor for measuring pH levels within a measurement environment, the pH sensor comprising:

a reference electrode;

a pH sensitive electrode; and

a controller, for measuring the potential difference between the pH sensitive electrode and the reference electrode, the measured potential difference being indicative of a pH level at the pH sensitive electrode,

wherein the controller is operable:

to apply a voltage across first and second electrodes to control the pH level at the pH sensitive electrode such that the pH level at the pH sensitive electrode reaches a saturation level; and

to perform a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode, at least one of the measurements taking place once the pH level at the pH sensitive electrode has reached the saturation level, and at least one of the measurements taking place after the voltage has stopped being applied, wherein the pH sensor is calibrated and/or recalibrated based on the measurements..

2. A pH sensor according to claim 1, wherein the first electrode is the pH sensitive electrode.

3. A pH sensor according to claim 1 or claim 2, wherein the second electrode is an electrode other than the pH sensitive electrode and the reference electrode.

4. A pH sensor according to claim 1, wherein

the first and second electrodes are separate from the pH sensitive electrode and the reference electrode.

5. A pH sensor according to any preceding claim, wherein a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode are taken after the voltage has stopped being applied.

6. A pH sensor according to any preceding claim, wherein the pH sensor is calibrated and/or recalibrated based on a rise time and/or relaxation curve arising from the measurements.

7. A pH sensor according to claim 6, wherein the pH sensor is recalibrated based upon a change in the rise time and/or relaxation curve between successive applications of a voltage across first and second electrodes.

8. A pH sensor according to any preceding claim, wherein at least one of the measurements is taken at a set time point after the voltage has stopped being applied.

9. A pH sensor according to any preceding claim, wherein a plurality of measurements are taken throughout the full time scale of relaxation from the saturation level to an equilibrium state after the voltage has stopped being applied.

10. A pH sensor according to any preceding claim, wherein the voltage is applied at a predetermined value and/or for a predetermined amount of time.

11. A pH sensor according to any preceding claim, wherein the pH sensor is an ISFET or metal oxide based sensor.

12. A pH sensor according to any preceding claim, wherein the measurement environment is within a human or animal body.

13. A pH sensor according to claim 12, wherein the measurement environment is within a uterus.

14. A multi-sensor device comprising the pH sensor according to any preceding claim and a dissolved oxygen sensor, the dissolved oxygen sensor comprising the first and second electrodes, one of the first and second electrodes being used as the working electrode of the dissolved oxygen sensor.

15. A multi-sensor device according to claim 14, wherein the other one of the first and second electrodes is used as a counter electrode of the dissolved oxygen sensor.

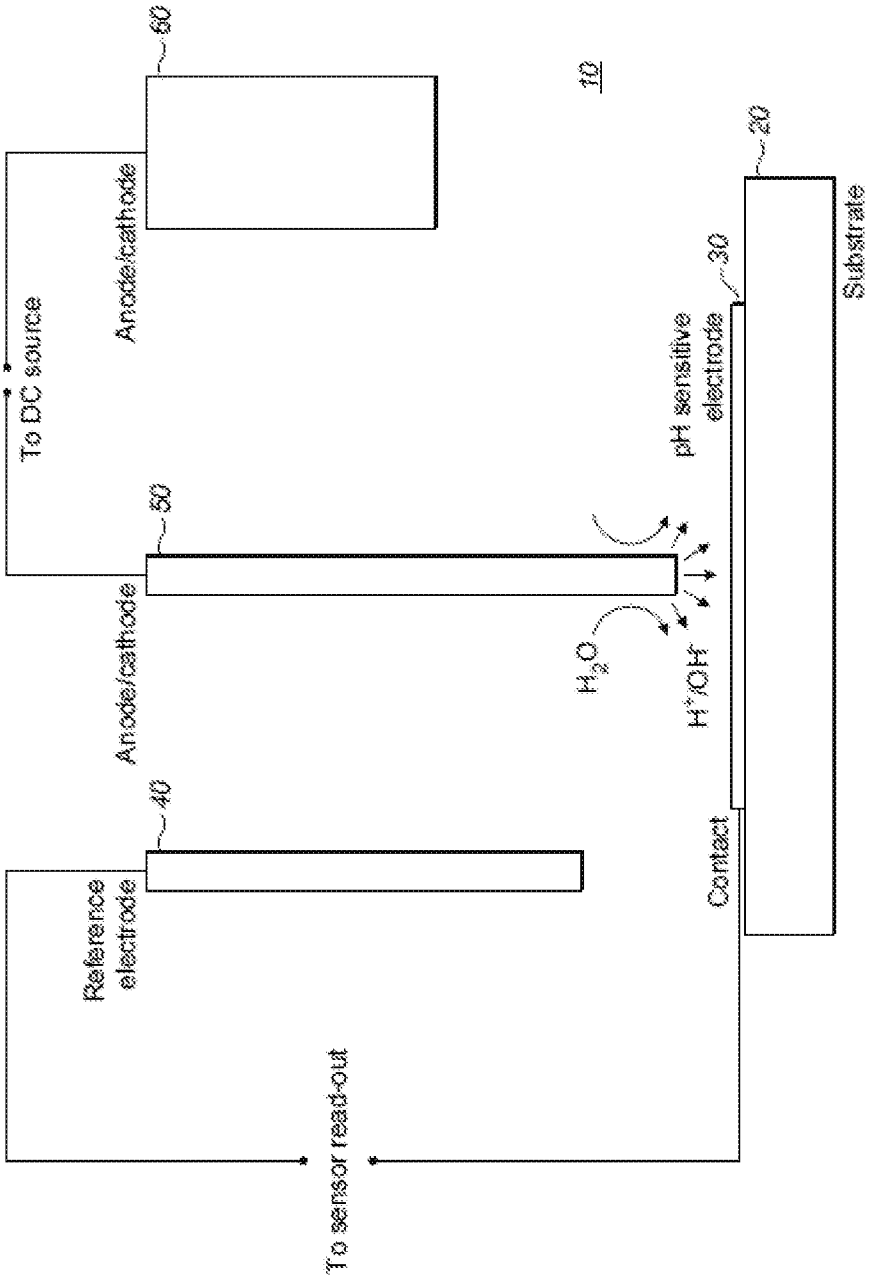
16. A multi-sensor device according to claim 15, wherein the other one of the first and second electrodes is used as a reference electrodes of the dissolved oxygen sensor.

17. A multi-sensor device according to any one of claims 14-16, wherein the reference electrode of the pH sensor is a common reference electrode for use with the dissolved oxygen sensor.

18. A method of calibrating or recalibrating a pH sensor, the pH sensor comprising a pH sensitive electrode and a reference electrode, the method comprising:

applying a voltage across first and second electrodes to control the pH level at the pH sensitive electrode such that the pH level at the pH sensitive electrode reaches a saturation level; and

performing a plurality of measurements of the potential difference between the pH sensitive electrode and the reference electrode, at least one of the measurements taking place once the pH level at the pH sensitive electrode has reached the saturation level, and at least one of the measurements taking place after the voltage has stopped being applied.


10
60
Anode/cathode
To DC source
50
Anode/cathode
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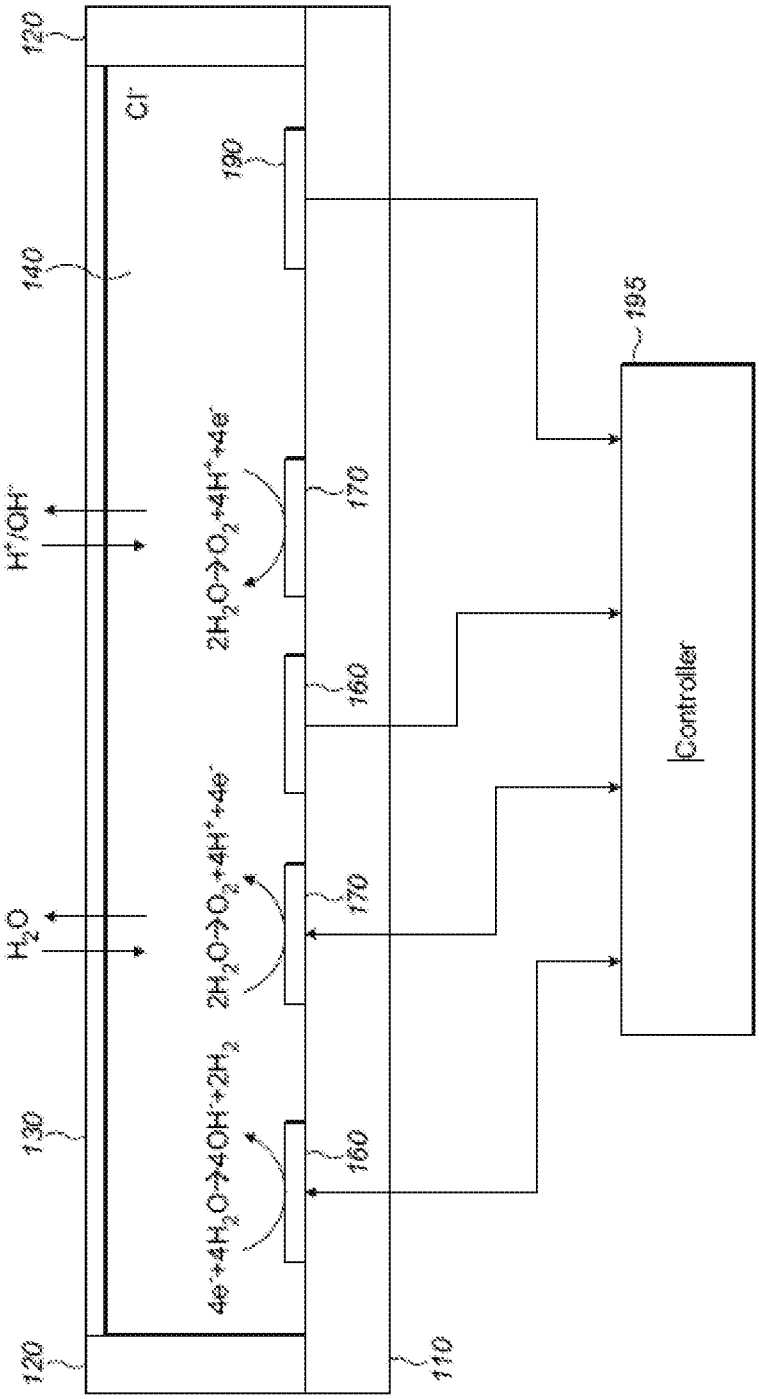
Reference electrode
To sensor read-out
H_2O
H^+/OH^-
30
pH sensitive electrode
20
Substrate
Contact

FIG. 1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Cl⁻
190
140
195
H⁺/OH⁻
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170
160
H2O
2H2O→O2+4H⁺+4e⁻
170
130
4e⁻+4H2O→4OH⁻+2H2
160
120
110
Controller

FIG. 2

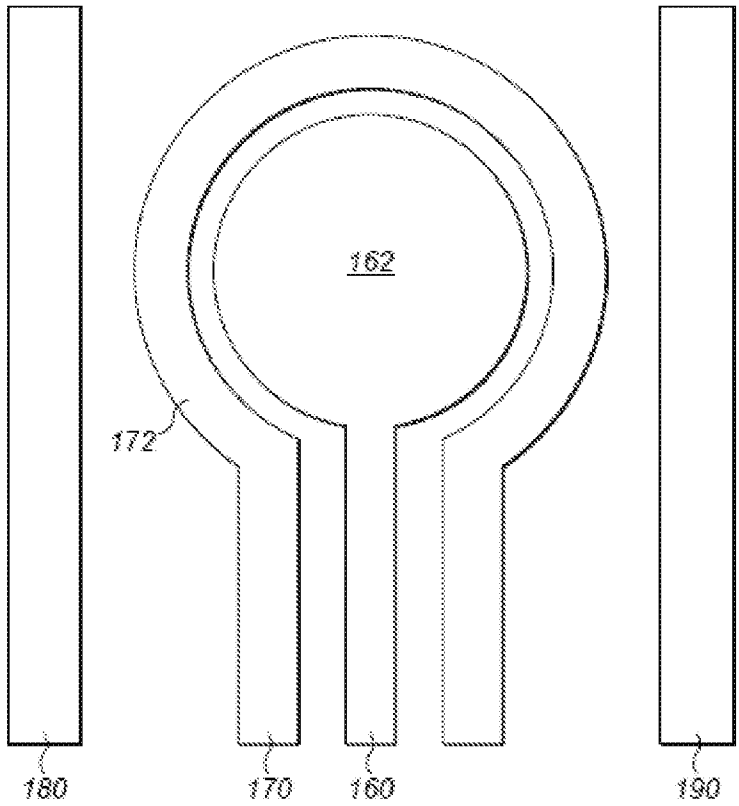
162
172
180
170
160
190

FIG. 3

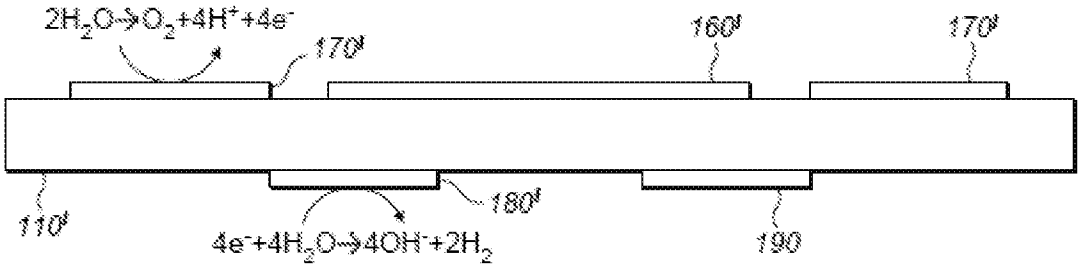
2H2O→O2+4H++4e-
170'
160'
170'
110'
180'
4e-+4H2O→4OH-+2H2
190

FIG. 4

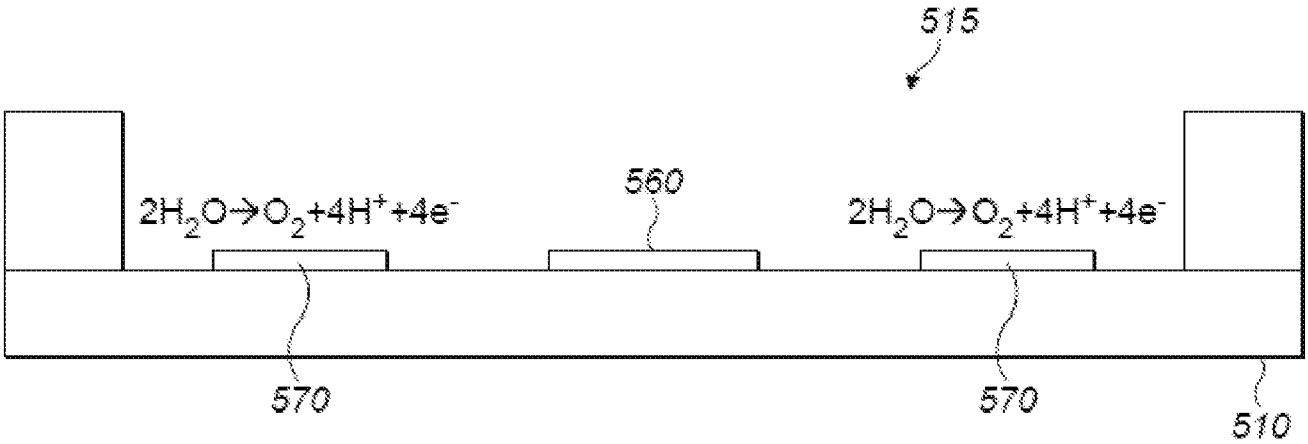
515
$2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
560
$2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
570
570
510

FIG. 5a

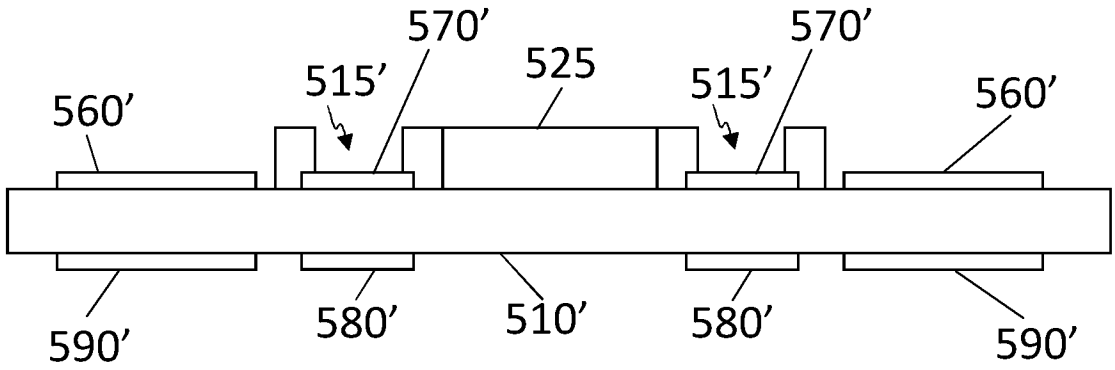
570'
525
570'
515'
515'
560'
560'
590'
580'
510'
580'
590'

FIG. 5b

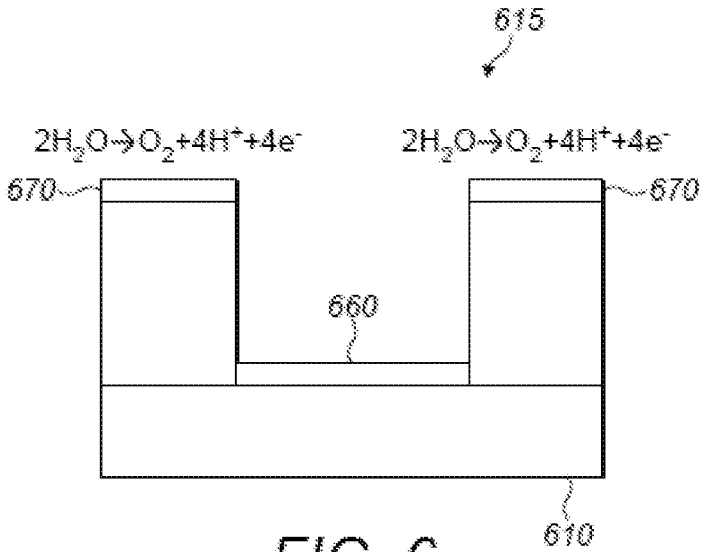
615
2H2O→O2+4H++4e-
2H2O→O2+4H++4e-
670
670
660
610

FIG. 6

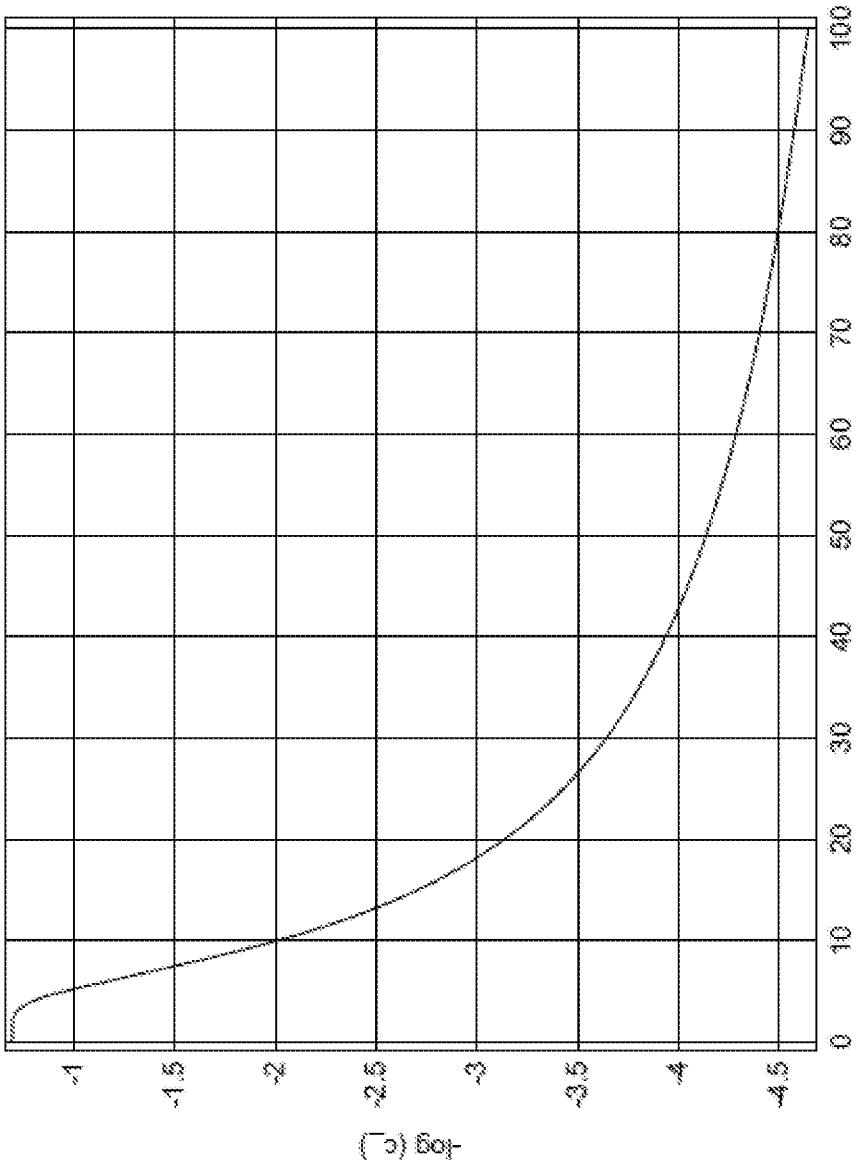

FIG. 7

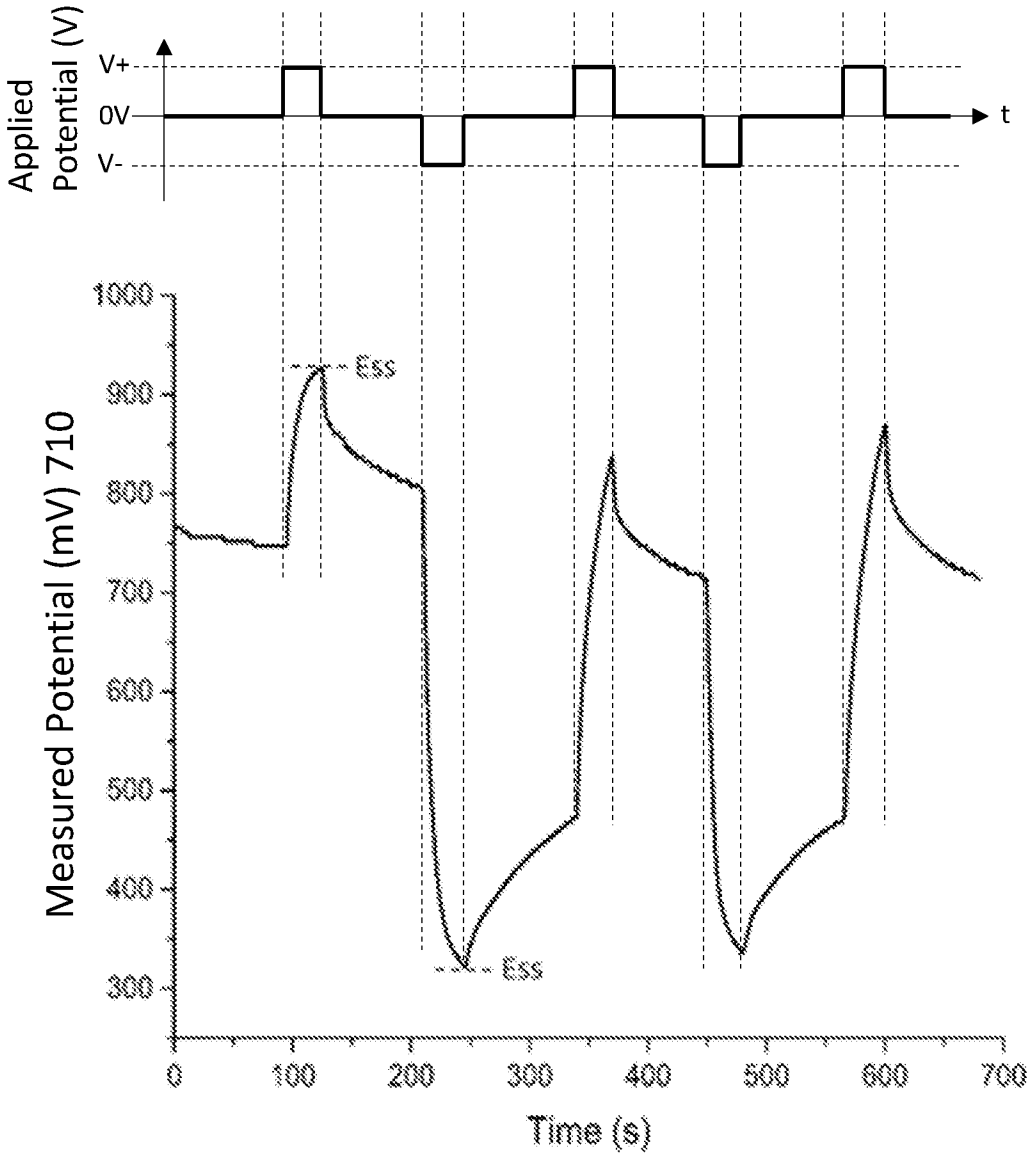
Applied Potential (V)
V+
0V
V-
t
Measured Potential (mV) 710
1000
900
800
700
600
500
400
300
Ess
Ess
0
100
200
300
400
500
600
700
Time (s)

FIG. 8a

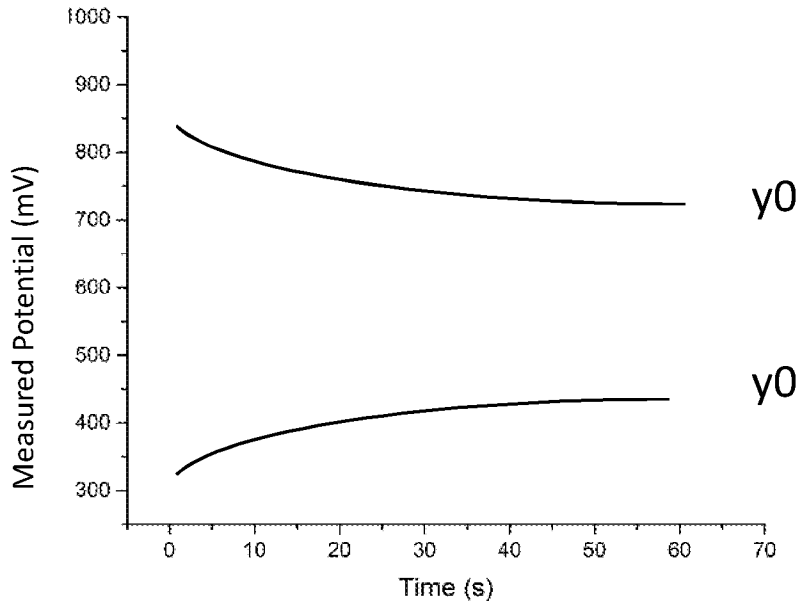
Measured Potential (mV)
1000
900
800
700
600
500
400
300
y0
y0
0
10
20
30
40
50
60
70
Time (s)

FIG. 8b

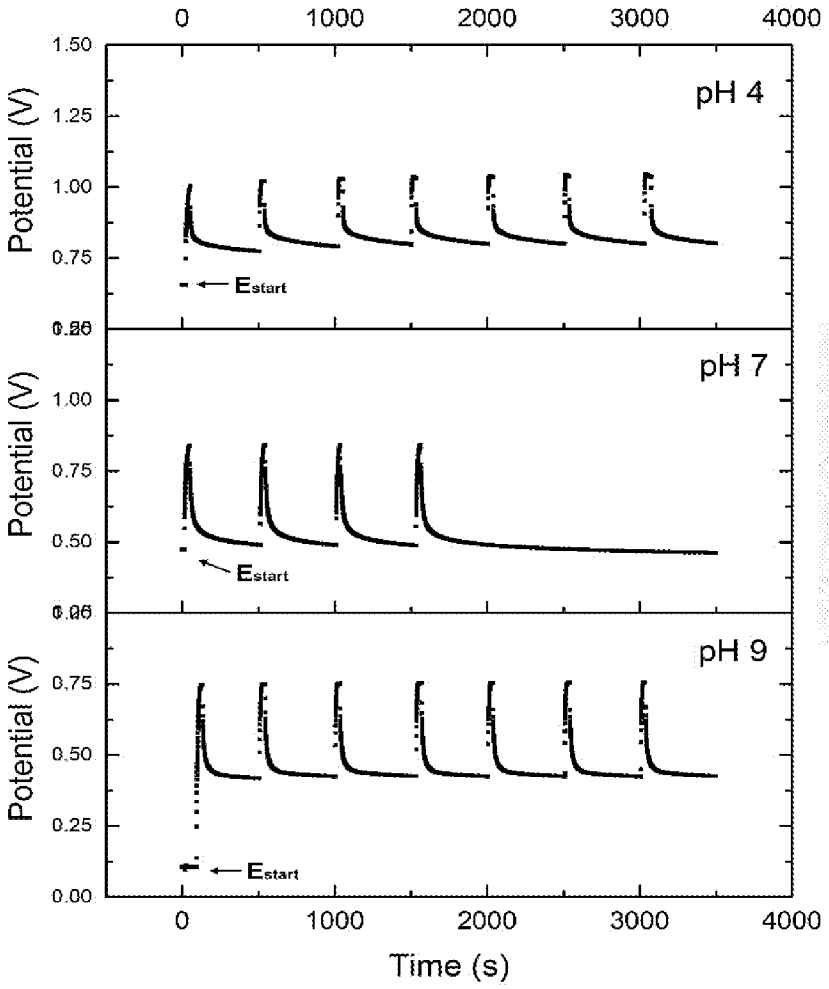
0
1000
2000
3000
4000
1.50
1.25
1.00
0.75
pH 4
Potential (V)
Estart
pH 7
1.00
0.75
0.50
Potential (V)
Estart
pH 9
0.75
0.50
0.25
0.00
Potential (V)
Estart
Time (s)

FIG. 9

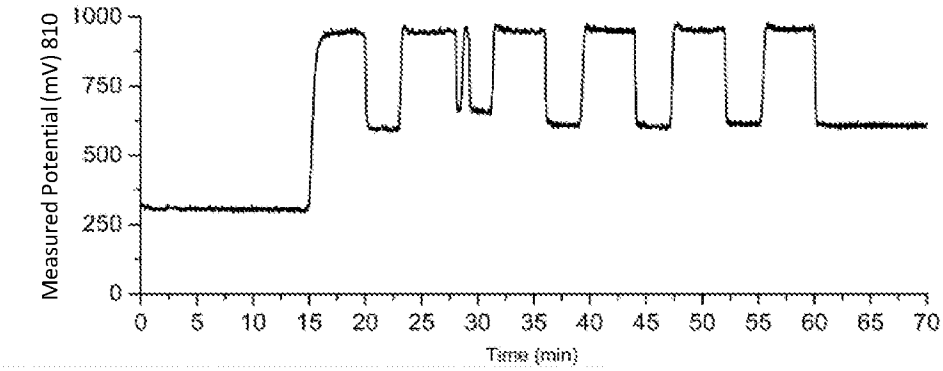

FIG. 10a

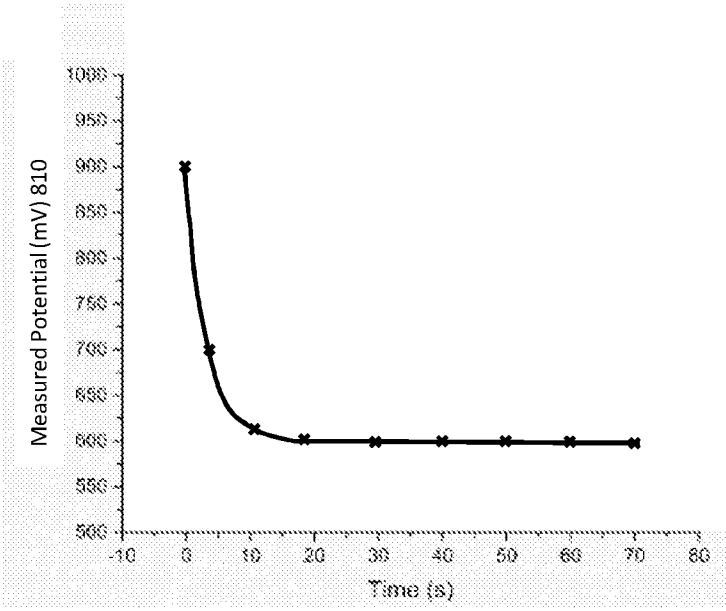

FIG. 10b

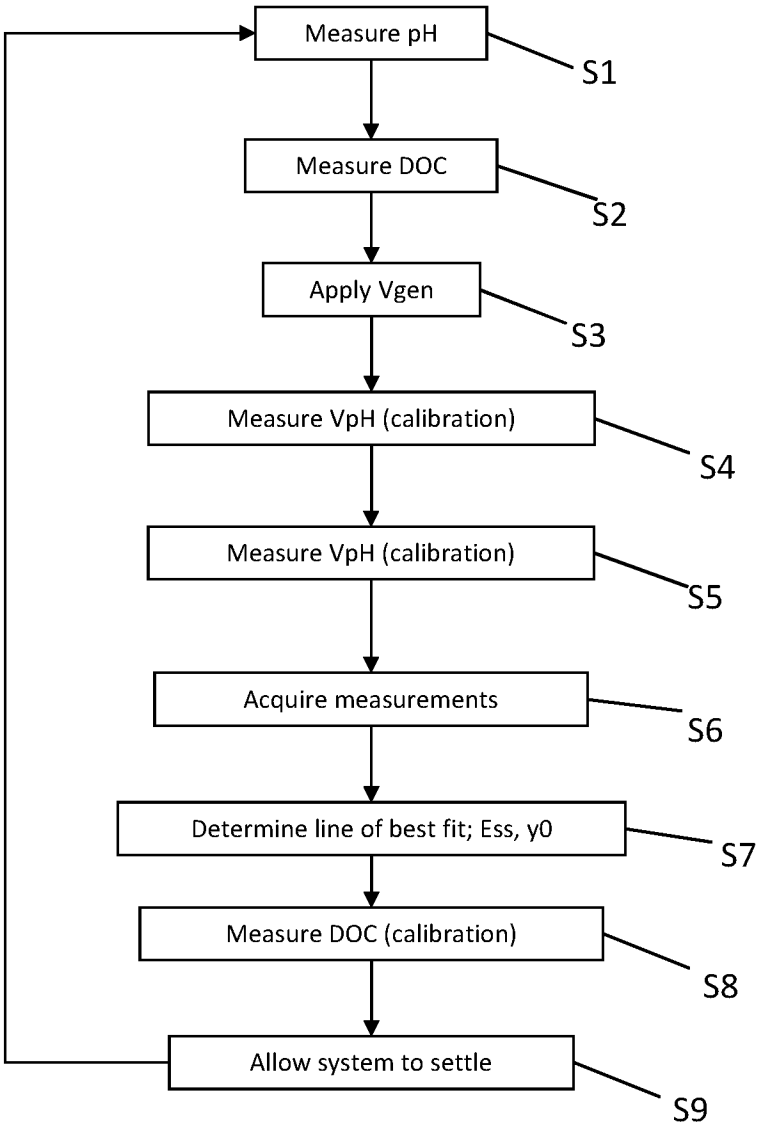
Measure pH
S1
Measure DOC
S2
Apply Vgen
S3
Measure VpH (calibration)
S4
Measure VpH (calibration)
S5
Acquire measurements
S6
Determine line of best fit; Ess, y0
S7
Measure DOC (calibration)
S8
Allow system to settle
S9

FIG. 11

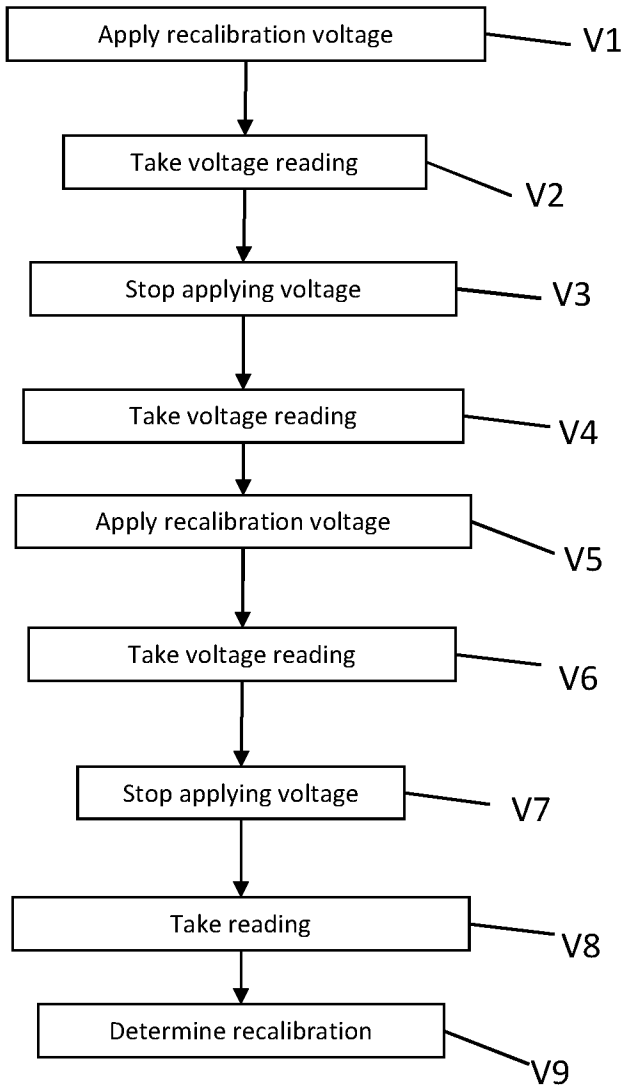
Apply recalibration voltage
V1
Take voltage reading
V2
Stop applying voltage
V3
Take voltage reading
V4
Apply recalibration voltage
V5
Take voltage reading
V6
Stop applying voltage
V7
Take reading
V8
Determine recalibration
V9

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/050633

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N27/416 A61B5/145 G01N27/404
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 046 028 A (BRYAN AVRON I [US] ET AL) 3 September 1991 (1991-09-03)	1-13,18
Y	abstract figures column 1, line 10 - line 14 column 1, line 57 - line 66 column 4, line 6 - column 6, line 26	14-17
Y	US 5 098 547 A (BRYAN AVRON I [US] ET AL) 24 March 1992 (1992-03-24) abstract figures column 4, line 12 - column 5, line 20	14-17
X	US 2010/268078 A1 (SCARANTINO CHARLES W [US] ET AL) 21 October 2010 (2010-10-21) abstract figures 20-22 paragraphs [0152] - [0167]	1,18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2020	26/06/2020

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2020/050633

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2010268078 A1	21-10-2010
		WO 0122874 A1	05-04-2001