(54) Title: VOLTAMMETRIC SENSOR

(55) Abstract: A voltammetric sensor has a working electrode and a counter electrode, each for making contact with an analyte. The porosity of the counter electrode accessible to the analyte is higher than the porosity of the working electrode accessible to the analyte. This increases the capacitance between the counter electrode and the analyte (or electrolyte in which the analyte is received). This capacitance increase results in reduced voltage drop at the electrode interface, thereby reducing or eliminating electrochemical reactions at the counter electrode.
Voltammetric sensor

FIELD OF THE INVENTION

The invention relates to voltammetric sensors.

BACKGROUND OF THE INVENTION

Voltammetric sensors are a class of electrochemical sensor that determine the concentration of chemical and biochemical species by measuring the voltage-current relationship of an electrochemical cell.

In cyclic sweep mode, the voltage is scanned linearly up and down repeatedly, then the height of the peak current quantifies the concentration of the species. In amperometric mode a fixed voltage is applied, and current is proportional to the redox reaction rate which depends on the concentration of the species.

Conventional electrochemical cells consist of three electrodes:
- a working electrode (WE), that possesses the interface to the sample of interest to be studied;
- a counter electrode (CE), that serves to collect the current to complete the electrochemical circuit; and
- a reference electrode (RE), that serves as a stable and well-known potential without passing current.

The voltage-current relationship of the electrochemical cell is measured with a potentiostat. This electronic circuit maintains the potential of the working electrode with respect to the reference electrode by adjusting the current through the counter electrode.

For in-vivo measurements of biochemical species the voltammetric sensor can be miniaturized to fit at the tip of a catheter. For example, such a three-electrode (WE, CE, RE) voltammetric sensor is known for lactate analysis on the tip of a micro-catheter, used for early diagnosis of bacterial meningitis caused by the ventricular drain.

There are various biochemical parameters that can be detected by voltammetric sensors. A non-exhaustive list, with possible applications, is given below:
- pH of tissue, e.g. to discriminate tumour tissue from healthy tissue;
- partial oxygen pressure $pO_2$ in blood, e.g. to signal depressed respiration or pulmonary embolism;
- partial carbon dioxide pressure $pCO_2$ in blood, e.g. to signal high bicarbonate level due to use of medication;
- nitric oxide in blood, e.g. to signal atherosclerosis or stroke;
- nitric oxide in tissue, e.g. to discriminate tumour tissue from healthy tissue;
- glucose in blood, e.g. to identify hypo/hyperglycemia;
- cholesterol in blood, e.g. to signal coronary heart disease, arteriosclerosis, myocardial infarction, brain thrombosis, lipid metabolism dysfunction, hypertension;
- uric acid in blood, e.g. to signal kidney disease or heart disease;
- lactic acid in blood, e.g. to signal hypoxia, lactic acidosis and some acute heart diseases;
- creatinine in blood, e.g. to signal renal, muscular and thyroid dysfunctions.

It is widely recognised that the main issue that hampers application of miniaturised voltammetric sensors integrated into catheters is reliability.

In conventional electrochemical cells there is a desired redox reaction at the working electrode. However, simultaneously, there occurs an interfering redox reaction at the counter electrode. This undesired reaction affects the voltage drop over the counter electrode-electrolyte interface, which is the motivation for the common use of a third electrode (the reference electrode).

However, the voltage drop over the reference electrode-electrolyte interface is also not constant, but depends on the concentration of redox species (given by the Nernst equation). In practice this limits the stability and reliability of voltammetric sensors.

For example, commonly an Ag/AgCl reference electrode is used, consisting of a silver wire coated with silver chloride, immersed in an electrolyte containing chloride ions. The reference electrode interface voltage can vary due to variations in chloride concentration resulting from reactions at the working and/or counter electrodes, and exposure to body fluids. In addition, the AgCl coating may dissolve or react, which also affects the interface voltage.

SUMMARY OF THE INVENTION

The invention is defined by the claims.
According to the invention, there is provided a voltammetric sensor comprising a working electrode and a counter electrode, each for making contact with an analyte,

wherein the analyte accessible porosity of the counter electrode is higher than the analyte accessible porosity of the working electrode. In the context of the present invention, the porosity of the electrode is defined as the fraction of the volume of the voids inside the electrode over the total volume of the electrode. For the present invention, only the voids that are accessible to the analyte are taken into account. The (relatively) large porosity of the counter electrode of the invention effectively behaves as a super-capacitor. The large asymmetry in porosity between the working electrode and the counter electrode ensures that the voltage drop over the counter electrode-electrolyte interface is minimized. Thereby, redox reactions at the counter electrode are minimised or avoided, while at the same time the required substrate size can remain small, allowing for example for integration in the tip of a catheter. In addition, the use of a reference electrode and potentiostat controlling electronics is no longer required. Thus, preferably the sensor comprises the two electrodes and no other electrodes for contact with the analyte.

The porosity of the counter electrode accessible to the analyte can be at least 10%, more preferably at least 25%, and even more preferably at least 50%.

The working electrode preferably has a planar electrode surface for contact with the analyte. This presents the lowest possible porosity. The counter electrode has a non-planar electrode surface for contact with the analyte, therefore presenting an increased porosity. The counter electrode surface can comprise:

- active carbon electrodes;
- a nanotube array; or
- an array of trenches.

The sensor can further comprise a controller for controlling the voltage applied between the working electrode and counter electrode, and a current monitor for monitoring the current flowing, wherein the controller is adapted to operate a cyclic voltammetric sweep mode.

By using a cyclic voltammetric sweep mode, the high capacitance counter electrode is prevented from becoming saturated with adsorbed ions.

The sensor preferably further comprises an electrolyte chamber within which the working electrode and counter electrode are housed, the chamber being defined by a
membrane which allows the passage of analyte molecules into the electrolyte chamber. The electrolyte chamber can contain a fluid, gel or dry polymer electrolyte.

The sensor can be:
- a pH sensor;
- a partial oxygen pressure sensor;
- a partial carbon dioxide pressure sensor;
- a nitric oxide sensor;
- a glucose sensor;
- a cholesterol sensor;
- a uric acid sensor;
- a lactic acid sensor; or
- a creatinine sensor.

BRIEF DESCRIPTION OF THE DRAWINGS

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

Figure 1 shows the known three electrode configuration for a voltammetric sensor;

Figure 2 shows the two electrode configuration for an example of voltammetric sensor in accordance with the invention;

Figure 3 shows how an encapsulated electrolyte region can be defined by a membrane; and

Figure 4 shows possible examples of how to implement the high porosity counter electrode used in the sensor of the invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

The invention provides a voltammetric sensor which has a working electrode and a counter electrode, each for making contact with an analyte. The analyte accessible porosity of the counter electrode is higher than the analyte accessible porosity of the working electrode. This increases the capacitance between the counter electrode and the analyte (or electrolyte in which the analyte is received) relative to the capacitance between the working electrode and the analyte. This capacitance increase results in reduced voltage variations at the counter electrode, thereby reducing or eliminating electrochemical reactions at the counter electrode.
Figure 1 shows the known three electrode configuration for a voltammetric sensor. The sensor comprises an electrolyte 10 which contains the analyte molecules to be detected by the voltammetric experiment. The sensor has a working electrode 12, counter electrode 14 and a reference electrode 15.

The working electrode applies the desired potential in a controlled way and enables transfer of charge to and from the analyte. The counter electrode functions as the other half of a cell, and the voltammetry analysis essentially involves determining the half cell reactivity of the analyte. The counter electrode needs to have a known potential with which to gauge the potential of the working electrode and to balance the charge added or removed by the working electrode. However, it is difficult for the counter electrode to maintain a constant voltage while passing a current to counter the redox events at the working electrode.

To address this problem, the roles of supplying electrons and providing a reference potential are divided between the counter electrode 14 and the reference electrode 15. The role of the reference electrode is to provide a reference in controlling the working electrode potential and it does not pass any current.

Figure 2 shows the two electrode configuration for an example of voltammetric sensor in accordance with the invention.

The sensor has only the working electrode 12 and counter electrode 14.

Figure 2 additionally shows in schematic form the controller 20 for receiving the current measurement data, and for controlling the applied potential.

By way of example, the working electrode can consist of gold, platinum, or carbon, or other materials known to those skilled in the art.

In accordance with the invention, the counter electrode 14 has a higher porosity accessible to the electrolyte than the working electrode, in particular at least 10%, against a porosity of less than 1% for the working electrode. This is shown schematically in Figure 2.

The voltage change at the electrical double layer (Stern layer) interfacing the electrolyte and counter electrode 14 in response to the adsorbed ions at this interface (as result of current flow and ion transport) is derived simply from:

$$\Delta V_{\text{Stern}} = \frac{Q_{\text{adsorbed}}}{C_{\text{Stern}}}$$
From this equation, it can be seen that by increasing the Stern layer interfacial capacitance $C_{\text{Stern}}$ between the analyte and the electrode the voltage drop over this interface can be suppressed, and thereby electrochemical redox reactions at this interface avoided.

A conductive interface is present between the analyte and the electrode.

Preferably, the analyte accessible porosity of the counter electrode is 50% or more. This can for example be realized by using active carbon electrodes, or a (carbon) nanotube array, or deep-reactive-ion etched trenches inside a conductive material or coated with a conductive material.

The working electrode can have a planar electrode surface for contact with the analyte, whereas the counter electrode has a non-planar electrode surface for contact with the analyte.

Figure 3 shows that the sensor can have an electrolyte chamber within which the working electrode 12 and counter electrode 14 are housed, the chamber being defined by a membrane 16 which allows the passage of analyte molecules into the electrolyte chamber. The electrolyte chamber contains a fluid, gel or dry polymer electrolyte 10.

Figure 4a shows that the counter electrode surface can comprise active carbon electrodes. Figure 4b shows that the counter electrode surface can comprise a nanotube array. and Figure 4c shows that the counter electrode surface can comprise an array of trenches. These structures are known themselves in supercapacitor applications.

As shown in Figure 2, a controller is used for controlling the voltage applied between the working electrode and counter electrode, and a current monitor is used for monitoring the current flowing. The controller is preferably adapted to operate a cyclic voltammetric sweep mode. This sweep mode enables prolonged operation, by ensuring that the ions are alternatively adsorbed and desorbed from the high capacitance counter electrode.

The sensor of the invention can be applied to all known uses of the voltammetric sensing, and enables simplification of the structure and control, by avoiding the need for the reference electrode. For example, the sensor can be:

- a pH sensor;
- a partial oxygen pressure sensor;
- a partial carbon dioxide pressure sensor;
- a nitric oxide sensor;
- a glucose sensor;
- a cholesterol sensor;
- a uric acid sensor;
- a lactic acid sensor; or
- a creatinine sensor.

The specificity of the sensor is determined by the composition of the electrolyte or by the properties of the membrane. Two examples are given below:

(i) pO2 sensor.

As an example of a sensor where the membrane determines the specificity, an oxygen sensor will be presented in more detail. This could be used to measure the oxygen concentration in for instance blood.

Electrolyte (added to water):

3mol/L potassium chloride KCl
1mol/L tris (hydroxymethyl) aminomethane buffer, pH 8.5. pH adjusted with hydrochloric acid. Supplier: Teknova Inc

20wt% Polyvinylpyrrolidone (PVP) polymer

Membrane: oxygen specific permeable membrane (Room Temperature Vulcanizing (RTV)silicone, tradename: Shinetsu KE-3475T)

Reaction:

\[ \text{O}_2 + 2\text{H}_2\text{O} + 4e^- \rightarrow 4\text{OH}^- \]

At a given applied voltage, the above reaction gives a current proportional to the oxygen concentration. By measuring the electrical current, the oxygen concentration can be determined. By sweeping the voltage periodically up and down, it can be avoided that the counter electrode becomes saturated with absorbed ions.

(ii) Glucose sensor.

As an example of a sensor where the electrolyte determines the specificity, a glucose sensor will be presented in more detail.

Electrolyte: glucose oxidase enzyme (GOx) immobilized in polyacrylamide Membrane: nafion (optional).
The membrane in this case is optional because it does not provide selectivity to the sensor as this is already provided by the GOx electrolyte. The membrane enhances the robustness of the sensor, and protects against fouling.

Reaction:

\[
\text{D-Glucose + } \text{H}_2\text{O + O}_2 \xrightarrow{\text{Glucose Oxidase}} \text{D-Gluconic acid + H}_2\text{O}_2 \\
\text{H}_2\text{O}_2 \rightarrow 2\text{H}^+ + \text{O}_2 + 2\text{e}^-
\]

The glucose oxidase enzyme specifically forms hydrogen peroxide proportionally to the concentration of glucose. In a second step, electrical current can be measured proportionally to the concentration of hydrogen peroxide.

The invention is of interest for healthcare applications as voltammetric biosensors for inclusion in catheters, implantables, syringes or stents. In addition, for consumer applications in household appliances, for instance to detect formaldehyde gas in air purifiers, or the caffeine level in coffee makers.

The invention thus provides a voltammetric biosensor that is simple and robust, and may be integrated into a catheter for in-vivo measurements of analytes such as oxygen, carbon dioxide, nitric oxide, glucose, cholesterol, and others.

The required increase in surface area can be realized by e.g. active carbon, a carbon nanotube array or RIE etched trenches. The large asymmetry in porosity minimizes the voltage drop over the counter electrode-electrolyte interface, thereby ensuring that electrochemical reactions occur only at working electrode and not at the counter electrode.

The example of the invention above makes use of a controller. The controller can be implemented in numerous ways, with software and/or hardware, to perform the various functions required. A processor is one example of a controller which employs one or more microprocessors that may be programmed using software (e.g., microcode) to perform the required functions. A controller may however be implemented with or without employing a processor, and also may be implemented as a combination of dedicated hardware to perform some functions and a processor (e.g., one or more programmed microprocessors and associated circuitry) to perform other functions.

Examples of controller components that may be employed in various embodiments of the present disclosure include, but are not limited to, conventional
microprocessors, application specific integrated circuits (ASICs), and field-programmable gate arrays (FPGAs).

In various implementations, a processor or controller may be associated with one or more storage media such as volatile and non-volatile computer memory such as RAM, PROM, EPROM, and EEPROM. The storage media may be encoded with one or more programs that, when executed on one or more processors and/or controllers, perform at the required functions. Various storage media may be fixed within a processor or controller or may be transportable, such that the one or more programs stored thereon can be loaded into a processor or controller.

Other variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measured cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.
CLAIMS:

1. A voltammetric sensor comprising a working electrode (12) and a counter electrode (14), each for making contact with an analyte, wherein the analyte accessible porosity of the counter electrode (14) is higher than the analyte accessible porosity of the working electrode (12).

2. A sensor as claimed in claim 1, wherein the analyte accessible porosity of the counter electrode (14) is at least 10%, more preferably at least 25%, and even more preferably at least 50%.

3. A sensor as claimed in claim 1 or 2, wherein the sensor comprises the two electrodes (12, 14) and no other electrodes for contact with the analyte.

4. A sensor as claimed in any preceding claim, wherein the working electrode (12) has a planar electrode surface for contact with the analyte.

5. A sensor as claimed in any preceding claim, wherein the counter electrode (14) has a non-planar electrode surface for contact with the analyte.

6. A sensor as claimed in any preceding claim, wherein the counter electrode (14) surface comprises active carbon electrodes.

7. A sensor as claimed in any preceding claim, wherein the counter electrode (14) surface comprises a nanotube array.

8. A sensor as claimed in any preceding claim, wherein the counter electrode (14) surface comprises an array of trenches.

9. A sensor as claimed in any preceding claim, further comprising a controller (20) for controlling the voltage applied between the working electrode and counter electrode,
and a current monitor for monitoring the current flowing, wherein the controller is adapted to operate a cyclic voltammetric sweep mode.

10. A sensor as claimed in any preceding claim, further comprising an electrolyte chamber within which the working electrode and counter electrode are housed, the chamber being defined by a membrane (16) which allows the passage of analyte molecules into the electrolyte chamber.

11. A sensor as claimed in claim 10, wherein the electrolyte chamber contains a fluid, gel or dry polymer electrolyte (10).

12. A sensor as claimed in any preceding claim, comprising:
   - a pH sensor;
   - a partial oxygen pressure sensor;
   - a partial carbon dioxide pressure sensor;
   - a nitric oxide sensor;
   - a glucose sensor;
   - a cholesterol sensor;
   - a uric acid sensor;
   - a lactic acid sensor; or
   - a creatinine sensor.

13. A sensor as claimed in any preceding claim, wherein the analyte accessible porosity of the working electrode (12) is less than 1%.
FIG. 1

$V_{ref} = E^0 - \frac{kT}{e} \ln \left( \frac{R_{\text{red}}}{R_{\text{ox}}} \right)$

$W_{\text{red}} \rightarrow W_{\text{ox}}^+ + e^-$
$C_{\text{red}} = C_{\text{ox}} + e^-$

FIG. 2

$W_{\text{red}} \rightarrow W_{\text{ox}}^+ + e^-$

$\mu\text{C}$

ion$^+$
ion$^-$
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N27/48
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 H01G

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, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>claim 89; figures 1-12 paragraphs [0047], [0053], [0108], [0110], [0118], [0208] ----- -/-/-</td>
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search
7 November 2014

Date of mailing of the international search report
14/11/2014

Name and mailing address of the ISA/
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Gangl, Martin
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<td>WO 92/19961 A1 (MASSACHUSETTS INST TECHNOLOGY [US]; HARVARD COLLEGE [US]) 12 November 1992 (1992-11-12) figures 1-6 page 1, line 7 page 2, paragraph 2 page 4, paragraph 6 page 6, paragraph 1 page 9, paragraph 2 page 10, paragraph 2 page 11, paragraph 2 page 12, paragraph 2 - paragraph 3</td>
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<td>US 5 958 214 A (NIKOLSKAJA ELENA J [RU]) 28 September 1999 (1999-09-28) claim 14; figures 1,2 column 2, line 60 - line 63 column 3, line 1 - line 7 column 5, line 59 - line 66 column 6, line 49 - line 50</td>
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<td>SU 600 426 A1 (PISAREVSKIJI ALEKSANDR M [SU]; POLOZOVA IZABELLA P; KRUNCHAK VLADIMIR G) 30 March 1978 (1978-03-30) abstract; figures 1,2 column 4, line 4 - line 5</td>
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