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A fiberoptic sensor for tissue carbon dioxide monitoring

John J. Davenport, Michelle Hickey, Justin P. Phillips, Member, IEEE, Panicos A. Kyriacou, Senior Member, IEEE

Abstract—We present a new fiberoptic carbon dioxide sensor for transcutaneous and mucosa (indwelling) blood gas monitoring. The sensor is based on optical fluorescence of molecules sensitive to pH changes associated with dissolved CO$_2$. A three layer chemical coating was dip-coated onto the distal tip of an optical fiber (600 μm core radius). It contained the 50mg/ml ‘polym H7’, a coating polymer bonded to a fluorescence indicator dye, along with 125mg/ml of the transfer agent tetraoctylammonium hydroxide (TONOH). Light from a blue (460 nm) LED was launched into the fiber to excite the sensing film. The sensing film fluoresced green (530 nm), the intensity of which decreased in the presence of CO$_2$. The sensor was tested in vitro, finding a correlation between change in fluorescence (in AU) and aqueous CO$_2$ concentration with a minimum detection threshold of 40%. The sensor is being developed for medical applications where its small size and ability to continuously monitor the partial pressure of CO$_2$ (PCO$_2$) will make it an extremely useful diagnostic tool.

I. INTRODUCTION

In vitro blood gas analysis has become a vital component of care for critically ill patients, providing diagnostic information about oxygenation, respiratory function and homeostasis [1, 2]. Routine monitoring of respiratory gases, particularly carbon dioxide concentration, in exhaled air can also provide additional information regarding ventilation, cardiac output and metabolic rate [3, 4]. In addition to these routine measurements, more specialized measurements of carbon dioxide partial pressure in body tissue (PCO$_2$) can reveal a mismatch between metabolic demand and tissue blood flow.

Transcutaneous CO$_2$ monitoring is used in observational sleep studies for detection of sleep apnea syndromes [5] and utilizes an electrochemical cell type sensor placed on the skin surface. Gastric tonometry was in routine use in intensive care units for several decades to monitor PCO$_2$ in the wall of the gut [6]. The technique involves injecting saline or other liquid into a gas permeable balloon placed in the stomach or small intestine for several minutes to allow equilibration of carbon dioxide from the gut wall into the saline [7].

A significant difference between PCO$_2$ in the withdrawn saline and arterial blood PCO$_2$ (the ‘CO$_2$ gap’) reveals poor gut circulation, a precursor to serious conditions such as sepsis, septic shock, and in more serious cases, multiple organ dysfunction syndrome and death [4]. The technique is rarely used in clinical practice now due to the need for significant user intervention to obtain a single non-continuous reading.

Fluorescence based PCO$_2$ sensors show a lot of potential for clinical applications and have been the focus of many recent studies [6, 8, 9, 10]. Their advantages include electrical isolation, the ability to operate in aqueous or gaseous environments and the possibility of being miniaturized. Sensing layers can also be made and applied cheaply, giving the possibility of single use, disposable sensors [8].

Coating the fluorescent sensitive layers onto the tips of optical also presents significant advantages and all electronic components such as LEDs and spectrometers can be kept well away from the sensing sight [10]. This has the combined advantages of decreasing noise from electrical interference, and avoiding any danger to a patient from electrocution.

Probes can be made small with optical fiber diameters typically between 600 μm or less [7], allowing them to be inserted into patients with minimum invasiveness or discomfort. Once inserted they can be used for continuous monitoring, allowing changes in the patient’s condition to be easily identified. Fiberoptic probes can be made simple and disposable, decreasing costs for hospitals and reducing the risk of cross-infection.

A PCO$_2$ sensing film was developed by Contreras-Gutierrez et al [8]. It was based on optical fluorescence of the pH change caused by CO$_2$ and incorporated a fluorescence indicator, a phase transfer agent and a matrix forming polymer.

Cross-sensitivity was also considered. Contreras-Gutierrez et al [8] compared the fluorescence response of Poly H7 to CO$_2$ to that of humidity levels, O$_2$, NO$_2$ and CO. Only NO$_2$ showed any cross sensitivity. The cross-sensitivity of pH levels has not yet been ascertained, which may be an issue with patients with conditions such as acid reflux causing variation in the pH of the lower esophagus.

This study builds on the work of Contreras-Gutierrez et al, developing a method of applying the sensing film on the distal tip of an optical fiber. This will allow the sensor to be used for minimally invasive monitoring of PCO$_2$ in the clinical environment, regions such as the lower esophagus.

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J. J. Davenport is with the School of Computer Science, Mathematics and Engineering, City University London, EC1V 0HB, UK (e-mail: john.davenport.1@city.ac.uk)

M. Hickey is with the School of Computer Science, Mathematics and Engineering, City University London, EC1V 0HB, UK (e-mail: michelle.hickey.1@city.ac.uk)

J. P. Phillips is with the School of Computer Science, Mathematics and Engineering, City University London, EC1V 0HB, UK (e-mail: justin.phillips.1@city.ac.uk)

P. A. Kyriacou is with the School of Computer Science, Mathematics and Engineering, City University London, EC1V 0HB, UK (e-mail: p.kyriacou@city.ac.uk)
II. THEORY

Fluorescence occurs when a molecule, referred to as a fluorophore, is excited by light of one wavelength and then emits light of another. This occurs when a photon is absorbed by the fluorophore, transferring energy and exciting an electron to a higher energy state. The fluorophore can then decay to a lower energy state and emit another photon.

Equation (1) shows the general case for the excitation of a fluorophore by a photon.

\[ h\nu_e + S_0 = S_1 \]  

(1)

Here, \( S_0 \) is the ground (unexcited) state of the fluorophore and \( S_1 \) is the excited state of the fluorophore. \( h \) is Planck’s constant (equal to \( 6.63 \times 10^{-34} \)Js) and \( \nu_e \) is the frequency of the exciting photon. The general case of a fluorophor decaying and emitting a photon is shown in equation (2):

\[ S_4 = S_0 + h\nu_e + E_{\text{other}} \]  

(2)

where \( \nu_{em} \) is the frequency of the fluorescent photon. \( E_{\text{other}} \) represents other forms of energy such as heat or additional photons. In general, the energy of the emitting photon is smaller than that of the exciting photon, leading to a lower frequency and longer wavelength. Excitation and emission wavelengths are dependent on electron shell structure of the molecule and are specific to the fluorophore.

The \( PCO_2 \) sensor is based on fluorescence indication of pH changes associated with dissolved \( CO_2 \). The fluorescence indicator can absorb light of 460 nm and re-emit light of 530 nm. In the presence of \( CO_2 \) and a transfer agent, the intensity of fluorescent light decreases [8]. The concentration of \( CO_2 \) can be found from the intensity of the emitted light.

The interaction between the fluorophore, TONOH and dissolved \( CO_2 \) is shown in Scheme 1 [9]. Here, DH is the protonated form of the fluorophore and D is the deprotonated form.

\[ \underset{\text{TONOH}}{U} + T \rightarrow xH_2O \rightleftharpoons U^\ddagger \cdot xH_2O + H_2O \]
\[ CO_2 + T \rightarrow xH_2O \rightleftharpoons H + O_2T \cdot xH_2O \]
\[ L^\ddagger \cdot N^\ddagger \cdot xH_2O + H \rightarrow L^\ddagger \cdot N^\ddagger \cdot xH_2O \]
\[ \rightleftharpoons C \cdot \frac{1}{2} L^\ddagger \cdot N^\ddagger (T \cdot xH_2O) \cdot 2xH_2O + U \]

Scheme 1. Chemical interaction between the fluorophore, TONOH and dissolved \( CO_2 \).

The first line shows the interaction between the TONOH and the fluorophore before the sensor is exposed to the sample. The second line shows the interaction between \( CO_2 \) and TONOH. The third line shows the interaction between the reaction products of the first two lines. Therefore, when TONOH is abundant, the ratio of DH to D is dependent on the quantity of \( CO_2 \) [9]. When excited, DH fluoresces green (530 nm). Measuring the intensity of fluorescent light allows the concentration of \( CO_2 \) to be found.

III. SENSOR FABRICATION AND SETUP

A. The sensor

The \( PCO_2 \) sensors were made by dip coating a layer of \( PCO_2 \) sensitive material onto the distal tip of an optical fiber. The tip was then placed in contact with a sample. The interaction between the sensing layer and \( CO_2 \) in the sample allowed the \( CO_2 \) partial pressure to be measured.

Figure 1 shows a diagram of the distal tip of the probe. The sensing layer contains Polym H7, a matrix forming polymer bonded to fluorescent molecules, as well as the transfer agent TONOH. Blue (460 nm) LED light was shone down the length of the optical fiber to excite the fluorescent indicator molecules, which fluoresced green (530 nm) depending on the concentration of \( CO_2 \).

![Diagram of the distal tip of the \( PCO_2 \) optical fiber sensor.](image)

B. Preparation and application of the sensing films

The chemical cocktails used for coating were prepared by mixing 50mg/ml of Polym H7 (supplied by nanoMyp, Spain) with 125mg/ml of TONOH (supplied in 2% \( CO_2 \) by Sigma Aldrich, USA) using methanol as a solvent (Sigma Aldrich, USA). All chemicals were used as received.

The sensing layer was applied to a 600 m multi-mode fiber using a precision dip coater (Qualitech QPI-168, USA). It was set to lower the tip of the optical fiber into a 6ml vial of coating solution and then withdraw it at a rate of 1mm/s. Three coats were applied. At least two minutes were allowed between dips for the solvent to evaporate and the coatings to dry. Throughout the testing the immersion time was kept to 1s, the minimum setting of the dip coater, to minimize solvent damage to previously applied coatings.

C. System setup

Sensors were mechanically spliced to an optical fiber splitter (bifurcated borosilicate fiber, 600 m diameter multimode core, BIFBORO-600-2 supplied by Ocean Optics) connected to an LED (460 nm, Wurth Elektronik, 151033BS03000, RS Components, UK) and a spectrometer
(Ocean optics HR4000) [11]. Figure 2 shows a diagram of the optical layout of the system.

Figure 2. Diagram of the optical layout of the probe. The fiber splitter allows light from the LED to reach the sensing layer and excite the fluorophores, and fluorescent light to pass back to the spectrometer.

Blue light (460 nm) was introduced to the optical fiber using an LED, which then passed through the fiber splitter to the sensing layer. The sensing layer fluoresced green (530 nm), the intensity of which decreased in the presence of CO$_2$. Some of the fluorescent light from the sensing layer returned along the optical fiber. The fiber splitter delivered this light to the spectrometer. By measuring the intensity of green light, the partial pressure of CO$_2$ could be ascertained.

### IV. IN-VITRO TESTING

The probes were tested in-vitro. Figure 4. The probe was inserted into a conical flask containing liquid water in order to measure the PCO$_2$. The partial pressure was controlled by bubbling gas through the water and allowing at least five minutes to reach equilibrium. The gas input was made by combining flow from a 100 % nitrogen cylinder and a 100 % CO$_2$ cylinder (supplied by BOC, USA).

A total flow rate of 1 l/min was delivered from the two cylinders. Flow rates were measured and controlled using a two mass flow controllers (FMA-A2406-SS-(N$_2$) mass flow controller, supplied by Omega Engineering, US). PCO$_2$ was varied by varying the proportion of flow from the CO$_2$ cylinder between 0 and 100 %.

CO$_2$ flow rates were calculated using a scaling factor of 0.74 as given by the system manual [12]. The maximum flow rate of the mass flow controllers was 1.025 l/min calibrated for N$_2$. This gave a maximum CO$_2$ flow rate of 759 ml/min. Details of the flow rates used are given in Table 1.

### Table I. PCO$_2$ VARIATION DETERMINED BY FLOW RATES OF CO$_2$ AND N$_2$

<table>
<thead>
<tr>
<th>CO$_2$ flow rate (ml/min)</th>
<th>N$_2$ flow rate (ml/min)</th>
<th>CO$_2$ Percentage (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1000</td>
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<td>200</td>
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<td>759</td>
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<td>100</td>
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Figure 3 shows examples of the spectrum of light reaching the spectrometer at various CO$_2$ levels. The peak at approximately 460 nm is light from the LED reflected from the distal tip of the fiber. It is largely independent of PCO$_2$. The peak at approximately 530 nm is the fluorescence signal from the sensing layer and can be seen to decrease in intensity with increasing PCO$_2$.

Figure 4 shows how the intensity of the 530 nm peak varies with increasing PCO$_2$. Errors predominantly come from accuracy in determining the intensity of the LED used as for reference calculations as well as accuracy of gas flow rates. A clear correlation can be seen between the two, indicating that the sensing layer is responding to CO$_2$ as expected. The minimum detectable concentration was around 40 %.
gives the sensor potential for M. Cajlakovic and V. R. A. Bizzarri, "Luminescence lifetime, potentially combined with other A2400's Massflow Controllers vol. 112, no. 4, pp. 1035.


Ocean Optics HR4000 Data Sheet, Technical Data Sheet, Ocean Optics, Dunedin, Florida, USA, 2011.


Figure 4. Graph showing the correlation between PCO2 and fluorescence peak intensity as measured by the spectrometer, normalized for 0 % CO2, given in counts. A line of best fit is included using a least squares regression between 40 and 100 %.

V. CONCLUSION

The intention of this work was to develop, optimize and test a fiberoptic sensor for minimally invasive PCO2 monitoring. The sensor was fabricated by dip coating three layers of a PCO2 sensitive material onto the tip of an optical fiber. PCO2 sensitive material combined a matrix forming polymer bonded to a fluorescence indicator (Polym H7) with TONOH as a phase transfer reagent.

The sensor tip was excited by blue (460 nm) light from an LED causing it to fluoresce green (530 nm). CO2 molecules interacted with the sensor layer, decreasing the intensity of green light. By measuring the intensity of the green fluorescent light with a spectrometer, the PCO2 level of the sample could be calculated.

The sensor was tested in vitro by bubbling various concentrations of CO2 in nitrogen trough a sample of water. The gas dissolved into the water, thereby controlling the PCO2. The results showed a strong correlation between the PCO2 and change in fluorescence signal recorded by the spectrometer. The minimum detectable concentration of around 40 % CO2.

Typical PCO2 concentrations in human blood are around 5 % so improvement in sensitivity will be required before this sensor is usable for medical applications. Potential options include detailed optimization of chemical concentrations, optical fiber radii, coating thickness as well as reduction in noise such as temperature control of the excitation LED. Further study is likely to be required into these areas.

They sensor has advantages including small size and physical isolation between the sensing site and the electronic components. The optical fiber gives the sensor potential for use as an indwelling probe, allowing minimally invasive monitoring of PCO2 in the clinical environment. Future work will include encapsulating the sensor in a protective, biocompatible sheath and carrying out in-vivo investigations with intensive care patients, potentially combined with other sensors currently in development. A proposed encapsulation material is silicone as it is, biocompatible, gas permeable and can dip-coated onto the tip of the probe.

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VI. REFERENCES