

A Prototype towards a Test Bench for Noninvasive Transcutaneous Carbon Dioxide Monitoring Devices

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Abstract— Dioxygen and carbon dioxide arterial partial pressures are important clinical parameters that enable to assess the respiratory status of a patient. That is why they are continuously monitored in intensive care units, where large and expensive bedside devices are used. To grant access to continuous monitoring of these parameters to a larger portion of patients, smaller and noninvasive medical devices were developed to measure transcutaneous dioxygen and carbon dioxide concentrations. They accurately estimate the partial pressures of those gases based on measurements made at the level of the skin. These devices are validated through clinical trials, which require long and expensive procedures. Developing advanced test benches mimicking human physiology is an interesting alternative to mature medical devices before submitting them to clinical trials. This work presents, to the best of our knowledge, a first-of-its-kind test bench prototype that mimics blood and skin for testing transcutaneous carbon dioxide monitoring medical devices. We also propose a proof-of-concept method to monitor dissolved carbon dioxide using common chemistry laboratory sensors. A similar test bench for transcutaneous dioxygen is currently under development.

Keywords- test bench; transcutaneous gas monitoring; carbon dioxide partial pressure.

I. INTRODUCTION

Blood gas analysis enables to detect and interpret respiratory, circulatory and metabolic disorders [1]. It is a common diagnostic tool for critically ill patients in intensive care departments. The reference method to analyze blood gases requires arterial sampling, an invasive and painful method. As an alternative, medical devices for transcutaneous gas monitoring were conceived in a noninvasive approach [2][3]. Developing and validating such devices require clinical trials, at the cost of a long and expensive procedure. An interesting option is to develop these devices using test benches that mimic human

physiology up to a certain level of maturity before validating them in clinical trials [3].

Such test benches would require generating a gaseous partial pressure starting from a liquid phase. Therefore, monitoring the concentration in the aqueous phase is necessary for an accurate test bench. The blood gases of interest are dioxygen O_2 and carbon dioxide CO_2 and this work focuses on the latter. The classical principle exploited by reference sensors for measuring dissolved CO_2 concentration is diffusion through a selective hydrophobic membrane to get CO_2 molecules in a gaseous phase inside the sensor. The gas concentration is then measured using an optical method, typically based on infrared absorption. Such sensors suffer from a slow response due to the diffusion phenomenon in the sensor chamber, leading to a slow response time: a 10 min $Tr_{99\%}$ response in the case of AquaMS sensor [4], the cost of which is around 10 k€. PreSens [5] offers a quicker sensor, delivering results in a few seconds, with a principle based on optical quenching using selective photosensible spots directly in the solution, getting rid of the diffusion part, but for a higher price around 15k€.

The work described in Section II aims to offer an alternative to these sensors by measuring dissolved carbon dioxide indirectly, using common chemistry laboratory devices. Section III presents a test bench prototype that mimics transcutaneous carbon dioxide at the level of the forearm. We conclude our work in Section IV.

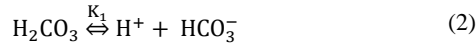
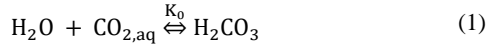
II. A METHOD TO MEASURE DISSOLVED CARBON DIOXIDE IN A CONTROLLED ENVIRONMENT

The controlled environment of interest is the liquid phase that is used to simulate blood in the test bench (see Section III). A physiological solution is a possible option. In this study, an aqueous solution of sodium chloride NaCl at 0.9% is used. It allows to monitor the pH and salinity of the liquid phase without any chemical reaction between chloride or sodium ions and the carbon dioxide CO_2 or the ions resulting

from its dissolution in water. Therefore, the dissolution of CO_2 in an aqueous solution of NaCl follows the same steps as in water.

A. Theory

Carbon dioxide CO_2 , after dissolution in water, leads to the formation of carbonic acid H_2CO_3 , a weak acid that dissociates into bicarbonate ions HCO_3^- then to carbonate ions CO_3^{2-} in cascade reactions [4][5] :



Reaction 1 represents the CO_2 hydration equation, and has a low equilibrium constant $K_0 \approx 10^{-7}$ [6], which means that $\text{CO}_{2,\text{aq}}$ concentration exceeds greatly H_2CO_3 concentration. The concentration of all dissolved CO_2 will be referred to as the concentration of $\text{CO}_{2,\text{aq}}$ and the thermodynamic equilibrium between a gaseous phase and the aqueous phase is described by Henry's law:

$$[\text{CO}_{2,\text{aq}}] = \alpha P_{\text{CO}_2} \quad (4)$$

where $[\text{CO}_{2,\text{aq}}]$ (mol L^{-1}) is the concentration in the aqueous phase, P_{CO_2} (Pa) is the partial pressure in the gaseous phase and $\alpha = K_0 K_{\text{CO}_{2,0}}$ with $K_{\text{CO}_{2,0}}$ the molar solubility of carbon dioxide in the aqueous solution, which depends on pressure, temperature, salinity, ionic strength and dissolved organic matter [4][6]. This study is conducted at ambient pressure, and the variables are the temperature T (K) and salinity S (ppt). Therefore, the solubility is computed as follows [6]:

$$\ln(K_{\text{CO}_{2,0}}) = -58.09 + 90.05 \left(\frac{T_0}{T}\right) + 22.29 \ln\left(\frac{T}{T_0}\right) + S \left[-0.68 + 0.40 \left(\frac{T}{T_0}\right) - 0.06 \left(\frac{T}{T_0}\right)^2 \right] \quad (5)$$

with $T_0 = 100$ K. The equilibrium constants K_1 and K_2 of reactions 2 and 3 are defined as follows:

$$K_1 = \frac{[\text{H}^+][\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3] C_0} \quad (6)$$

$$K_2 = \frac{[\text{H}^+][\text{CO}_3^{2-}]}{[\text{HCO}_3^-] C_0} \quad (7)$$

where $[X]$ represents the molar concentration of species X , and $C_0 = 1 \text{ mol L}^{-1}$.

The electrical conductivity of the solution is a necessary parameter for the computation. The Kohlrausch law applied to the studied system results in the following equation:

$$\sigma = \lambda_{\text{HCO}_3^-} [\text{HCO}_3^-] + 2\lambda_{\text{CO}_3^{2-}} [\text{CO}_3^{2-}] + \lambda_{\text{H}^+} [\text{H}^+] + \lambda_{\text{OH}^-} [\text{OH}^-] + \lambda_{\text{Na}^+} [\text{Na}^+] + \lambda_{\text{Cl}^-} [\text{Cl}^-] \quad (8)$$

where σ (S m^{-1}) is the electrical conductivity of the solution and λ_X ($\text{S m}^{-1} \text{ mol}^{-1} \text{ L}$) is the molar conductivity of ion X .

The ionic product of water K_w is defined as follows [9]:

$$K_w = \frac{[\text{H}^+][\text{OH}^-]}{C_0^2} \quad (9)$$

B. Method proposed to measure dissolved carbon dioxide

The concentration of CO_2 can be computed by combining (6), (7), (8) and (9):

$$[\text{CO}_{2,\text{aq}}] = \frac{\sigma - \lambda_{\text{H}^+} [\text{H}^+] - \lambda_{\text{OH}^-} \frac{K_w}{[\text{H}^+]} - \lambda_{\text{Na}^+} [\text{Na}^+] - \lambda_{\text{Cl}^-} [\text{Cl}^-]}{\frac{\lambda_{\text{HCO}_3^-} K_1}{[\text{H}^+]} + \frac{2\lambda_{\text{CO}_3^{2-}} K_1 K_2}{[\text{H}^+]^2}} \quad (10)$$

Equation (10) shows that measuring the pH and the conductivity allows to compute the concentration of dissolved CO_2 in an aqueous solution of known NaCl concentration. The measurement of temperature is also necessary, as the constants used in (10) are temperature-dependent thermodynamic parameters. The evolution of the equilibrium constants with respect to the temperature is the following:

$$\text{p}K_1 = \frac{T_1}{T} + \frac{T}{T_2} - 14.84 \quad (11)$$

where $K_1 = 10^{-\text{p}K_1}$, $T_1 = 3404.71$ K and $T_2 = 30.49$ K [10].

$$\text{p}K_2 = \frac{T_3}{T} + \frac{T}{T_4} - 6.49 \quad (12)$$

where $K_2 = 10^{-\text{p}K_2}$, $T_3 = 2902.39$ K and $T_4 = 42.03$ K [11].

$$\ln(K_w) = 148.98 - \frac{T_5}{T} - 23.6521 \ln\left(100 \frac{T}{T_0}\right) \quad (13)$$

where $T_5 = 13847.26$ K and $T_0 = 100$ K [9].

The evolution of the molar conductivity λ_X of the ions of interest with respect to the temperature was not found in the literature. Hence, it was extracted from the Nernst-Einstein equation [12]:

$$\lambda_X = \frac{D_X Z_X F^2}{RT} \quad (14)$$

where D_X ($\text{m}^2 \text{ s}^{-1}$) is the binary diffusion coefficient of ion X in water and Z_X its charge, F (C mol^{-1}) the Faraday constant, R ($\text{J mol}^{-1} \text{ K}^{-1}$) the ideal gas constant, T (K) the temperature.

To compute the molar conductivity at different temperatures, a Taylor expansion to the first order is applied to (14) around $T_6 = 298.15$ K, the temperature at which the values of molar conductivity are given in the literature. D_X is also a temperature-dependent thermodynamic parameter. However, it will be considered constant and its value is taken at $T = T_6$:

$$\lambda_X(T) = \lambda_X(T_6) + \frac{D_X Z_X F^2}{R} \times \left(\frac{1}{T} - \frac{1}{T_6}\right) \quad (15)$$

In conclusion, we show that injecting the measurements of pH, conductivity and temperature in (10) and (15) allows to compute the concentration of dissolved carbon dioxide.

III. TEST BENCH CONCEPTION

The test bench aims to generate carbon dioxide to test a noninvasive transcutaneous CO_2 gas sensor that is yet to be developed. The bench has the specifications of the measurement site, which is the forearm. The end goal is to generate the same carbon dioxide partial pressure P_{CO_2} and flux Φ_{CO_2} . A liquid phase is used to simulate the blood and a membrane to simulate the skin, as shown in Figure 1. A liquid phase was chosen instead of a gaseous phase to mimic the kinetics of diffusion in the aqueous phase and through the membrane. Transcutaneous gas measurement devices can heat the skin up to 42°C , hence the test bench parameters are determined at both 37 and 42°C .

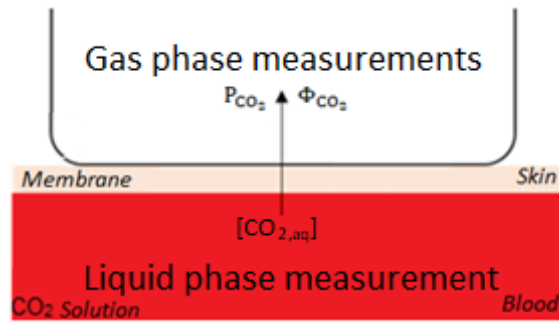


Figure 1. Test bench schematic diagram

A. Test bench conception

P_{CO_2} varies between 2.66 and 13.33 kPa (20 and 100 mmHg) [13]. At 42°C , using (4) and (5), the corresponding $[\text{CO}_{2,\text{aq}}]$ ranges from 0.6 to 3 mmol L^{-1} . In order to mimic the kinetics of carbon dioxide diffusion in blood, the bench has to generate a CO_2 flux of $7.54 \cdot 10^{-7} \text{ mol m}^{-2} \text{ s}^{-1}$ as it is the case at the level of the forearm [14]. To be able to do so, simulations at our lab show that the depth of the liquid in the tank (see Figure 2 right) has to be 3 and 12 mm for a 37 and 42°C temperature, respectively.

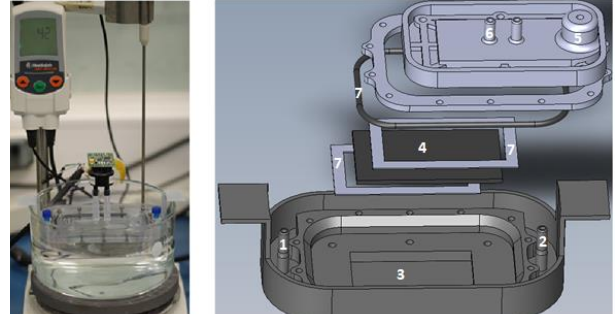
The skin is represented by a polymer membrane that exhibits similar carbon dioxide diffusion properties as human skin at the level of the forearm. The selection was made on the basis of the permeability, defined by Krogh's diffusion constant:

$$K_r = \frac{k \cdot x}{P_{\text{air}}} \quad (16)$$

where K_r is the Krogh coefficient ($\text{m}^2 \text{ s}^{-1} \text{ Pa}^{-1}$), k the mass transfer coefficient (m s^{-1}), x the thickness (m) of the membrane and P_{air} the total air pressure (Pa) at the membrane temperature. A polydimethylsiloxane membrane (PDMS) of thickness 4.3 and 2.8 mm can mimic the skin [15] at 37 and 42°C , respectively.

B. Experimental setup and results

To create a liquid phase with the mentioned concentrations, CO_2 stock solutions Standard Hanna HI



1: inlet, 2: outlet, 3: tank, 4: membrane, 5: vent, 6: CO_2 sensor connection, 7: seals

Figure 2. Left: test bench. Right: architecture of the test bench

4005-01 at 0.1 mol L^{-1} and Reagecon SC026C at 6 g L^{-1} were diluted in an Otec sodium chloride 0.9% sterile pyrogen-free solution.

The test bench is a closed chamber designed using SolidWorks (Figure 2 right) and crafted in non-permeable materials to carbon dioxide. It includes a circulatory system composed of the inlet, the tank and the outlet in order to mimic blood circulation. On top of the liquid phase, sits the membrane that represents the skin and finally the connection with the carbon dioxide sensor. The test bench is maintained at 42°C using a bain-marie, heated by a temperature-regulated stirrer. The carbon dioxide generated by the test bench was measured using a SprintIR-WP20 gas sensor (Figure 2 left).

Equation (10) requires the measurement of the pH, the conductivity and the temperature of the solution in order to compute its concentration in carbon dioxide. In this work, bench-top measuring instrument Orion™ Versa Star Pro™ VSTAR 52 was used. Using an extra conductivity module, this device allows to measure the salinity also. These measurements were made inside the glass reactor that supplies the bench test tank through a peristaltic pump.

The $[\text{CO}_{2,\text{aq}}]$ range has been explored through five measurement points: starting from a solution of 3 mmol L^{-1} and diluting up to 0.6 mmol L^{-1} . The intermediary concentrations at which measurements were made are 1.2, 1.8 and 2.4 mmol L^{-1} , they are referred to as measurement points. At each point, conductivity, pH and temperature were measured to compute $\text{CO}_{2,\text{aq}}$ concentration using (10). Each measurement was repeated five times to create five-fold measurement points and assess the stability and reproducibility of the experiment. Five minutes separated each dilution to allow the solution to reach equilibrium.

Equation (10) shows a linear relationship between $[\text{CO}_{2,\text{aq}}]$ and conductivity, and between $[\text{CO}_{2,\text{aq}}]$ logarithm and pH. Therefore, three values of each five-fold measurement point were randomly chosen to create a linear regression learning batch. The resulting linear regression ‘‘Predicted value’’ was

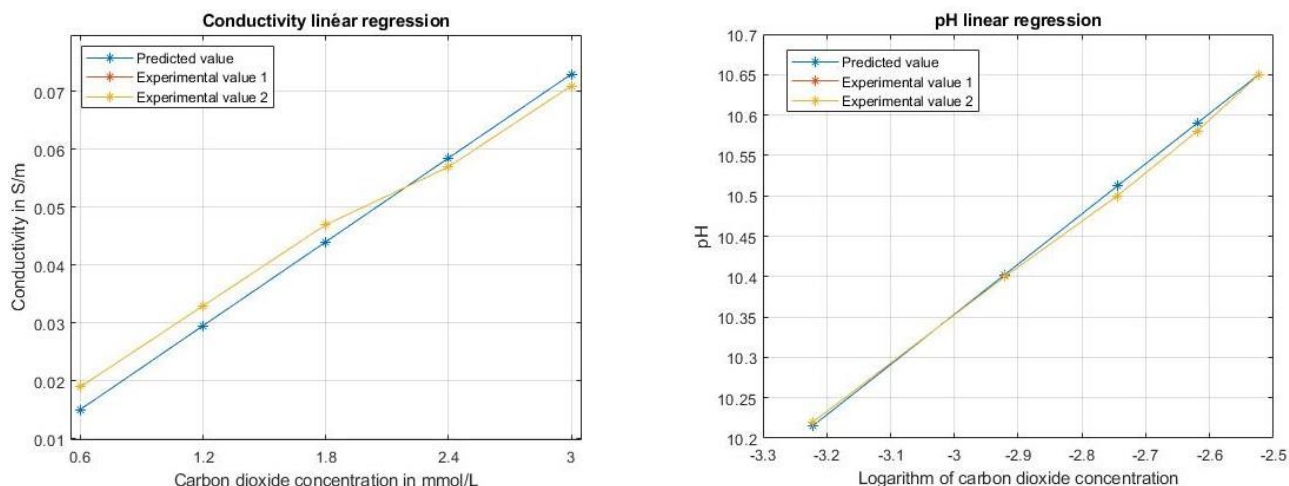


Figure 3. Left: Conductivity linear regression. Right: pH linear regression

plotted against the experimental values “Experimental value 1” and “Experimental value 2”.

Figure 3 shows that the experimental results validate the proposed method based on (10). It also proves the reproducibility of the experiments and the stability of the measurements.

IV. DISCUSSION AND CONCLUSION

The results obtained so far from of this ongoing work show that it is possible to compute $[CO_{2,aq}]$ from the measurement of pH and conductivity. This indirect measurement is also valid for the dynamic regime and not only at equilibrium as Figure 3 was obtained by consecutive dilutions. The devices used in this approach have a few seconds time response, allowing real-time monitoring of $[CO_{2,aq}]$ using the method proposed in Section II.B. The aim is to be able to control the partial pressure in the gaseous phase above the membrane by adjusting the concentration in the aqueous phase. A previous study worked on developing a model describing the relationship between these two physical quantities [16].

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