

# Supplementary Material (S1)

## The Dynamic of Transcutaneous Sensing: A Closed Chamber Model

### Abstract

The aim of this document is to give the complete details and related calculations of a simplified transcutaneous carbon dioxide ( $\text{CO}_2$ ) sensor model using a closed chamber approach. The key results of this short study are presented in Section 4.2.3 of the main article.

## 1 The Model

The simplified model of the transcutaneous carbon dioxide ( $\text{CO}_2$ ) sensor under study is presented in Figure S1.

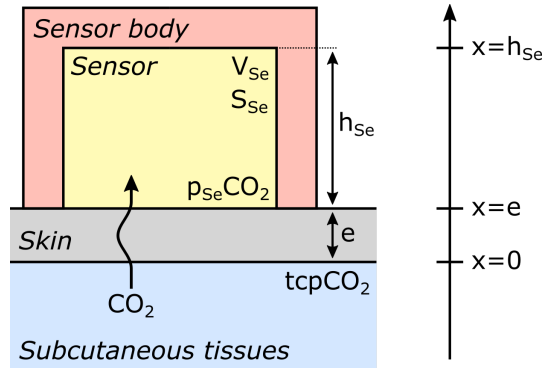


Figure S1: Sensor model.

In this model, the subcutaneous tissues are considered as a homogeneous, semi-infinite medium occupying the  $x \leq 0$  space volume. The subcutaneous tissues can be thought of as a  $\text{CO}_2$  reservoir with a constant partial  $\text{CO}_2$  pressure equal to  $\text{tcpCO}_2$ . Between  $x = 0$  and  $x = e$  is the skin membrane, of thickness  $e$  and diffusivity  $D$  ( $\text{m}^2.\text{s}^{-1}$ ) towards  $\text{CO}_2$ . In this skin model, the sub-cutaneous tissues and skin barrier are only used as a representation, and the skin barrier does not represent literally the stratum corneum. Consequently, the  $e$  and  $D$

parameters can hardly be measured experimentally since they are mere model parameters.

On top of these two layers is positioned a sensor consisting in an inner sensing medium of volume  $V_{Se}$ , surface in contact with the skin  $S_{Se}$  and height  $h_{Se} = V_{Se}/S_{Se}$ . This sensor is in turn surrounded by a gas-tight enclosure, preventing gaseous exchanges between the sensing medium and the outside—except for those with the skin surface, of course.

## 2 Inner Sensing Medium

In the following calculations, the inner sensing medium is considered as an homogenous air volume. While this assumption is more than justified in the case of Non Dispersive Infra-Red (NDIR) or (photo-)acoustic sensors, it seems more debatable in the case of conductometric or dye-based sensors. Yet, every sensing medium can be viewed as a potential  $\text{CO}_2$  reservoir through Henry's law, and thus be considered as an air volume.

For instance, if the sensing medium is water—*e.g.* in the case of a wet conductometric sensor—with a water volume  $V_{water}$  of height  $h_{water}$ , this latter water volume is equivalent to an air volume  $V_{air,eq}$  of height  $h_{air,eq}$  such that the amount of  $\text{CO}_2$  dissolved in the water volume  $n_{\text{CO}_2,water}$  (mol) is the same as that in the equivalent air volume  $n_{\text{CO}_2,air,eq}$  for a given  $p\text{CO}_2$ :

$$n_{\text{CO}_2,air,eq}(p\text{CO}_2) = n_{\text{CO}_2,water}(p\text{CO}_2) \quad (1)$$

with

$$\begin{aligned} n_{\text{CO}_2,air,eq} &= \frac{p\text{CO}_2 \cdot V_{air,eq}}{R \cdot T} \quad (\text{ideal gas law}) \\ \mathcal{C}_{\text{CO}_2,water} &= K_0 \cdot p\text{CO}_2 \quad (\text{Henry's law}) \\ n_{\text{CO}_2,water} &\triangleq V_{water} \cdot \mathcal{C}_{\text{CO}_2,water} \\ V_{water} &= S_{Se} \cdot h_{water} \quad \text{and} \quad V_{air,eq} = S_{Se} \cdot h_{air,eq} \end{aligned} \quad (2)$$

wherein  $R$  is the ideal gas constant ( $\text{J.K}^{-1}.\text{mol}^{-1}$ ),  $T$  the temperature (K) and  $K_0$  ( $\text{mol.m}^{-3}.\text{Pa}^{-1}$ ) is the solubility of  $\text{CO}_2$  in water as reported by Weiss[weiss1974]. Combining the above equations yields:

$$h_{air,eq} = h_{water} \cdot R \cdot T \cdot K_0 \quad (3)$$

Taking Weiss' value for  $K_0$  in pure water at 293 K under 1 atm yields:

$$h_{air,eq} \approx 0.952 \cdot h_W \quad (4)$$

and a similar train of thought can be applied to other media. Using Henry's law, it is thus always possible to convert from a given sensing medium into an equivalent air volume as is done above for water.

Then, it should be emphasised that only the equivalent height  $h_{Se}$  of the sensor really matters. Indeed, no matter what the actual inner volume of the sensor looks like, only its volume to surface ratio matters, as is detailed below.

Finally, one should bear in mind that the CO<sub>2</sub> diffusion process into the sensing medium is also neglected. Indeed, it is assumed in the remainder of this article that as soon as CO<sub>2</sub> crosses the skin barrier and reaches the sensor itself, it readily diffuses into it. Thus the pCO<sub>2</sub> inside the sensing medium is considered to be homogenous and only a function of the amount of CO<sub>2</sub> diffusing through the skin. This assumption is more than justified in first approximation when considering the response times of the different sensing techniques presented in Section 2 of the review article. Indeed, most of them easily reach response times below 1 min, which is far below the response times of the simple model presented here for thicknesses  $h_{Se}$  above 100  $\mu\text{m}$ , as is presented below—see Section 4.

### 3 Diffusion Through the Skin

The CO<sub>2</sub> diffusion across the skin barrier can be studied using Fick's first law of diffusion:

$$J_S = -D \cdot \frac{d\mathcal{C}_{CO_2}(x)}{dx} \quad (5)$$

wherein  $J_S$  is the CO<sub>2</sub> diffusion flux per unit area ( $\text{mol} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$ ),  $D$  the diffusivity of skin toward CO<sub>2</sub> ( $\text{m}^2 \cdot \text{s}^{-1}$ ), and  $\mathcal{C}_{CO_2}$  the CO<sub>2</sub> concentration ( $\text{mol} \cdot \text{m}^{-3}$ ) inside the membrane. With the hypothesis ( $\mathcal{H}_1$ ) that there is no CO<sub>2</sub> accumulation inside the skin itself—*i.e.* that the capacitive effect of the skin is negligible compared to that of the sensing medium— $J_S$  can be considered constant along the  $x$  axis, leading to:

$$J_S = \frac{D}{e} \cdot (\mathcal{C}_{CO_2}(x=0) - \mathcal{C}_{CO_2}(x=e)) \quad (6)$$

Since  $x=0$  corresponds to the subcutaneous tissues wherein  $\text{pCO}_2 = \text{tcpCO}_2$  and  $x=e$  corresponds to the inner sensing medium wherein  $\text{pCO}_2 = p_{Se}\text{CO}_2$ :

$$\begin{cases} \mathcal{C}_{CO_2}(x=0) = K_{skin,CO_2} \cdot \text{tcpCO}_2 \\ \mathcal{C}_{CO_2}(x=e) = K_{skin,CO_2} \cdot p_{Se}\text{CO}_2 \end{cases} \quad (7)$$

with  $K_{skin,CO_2}$  the solubility of CO<sub>2</sub> into the skin ( $\text{mol} \cdot \text{m}^{-3} \cdot \text{Pa}^{-1}$ ). Besides, under ( $\mathcal{H}_1$ ):

$$\frac{dn_{CO_2,Se}}{dt} = S_{Se} \cdot J_S \quad (8)$$

wherein  $n_{CO_2,Se}$  is the amount of CO<sub>2</sub> in the inner sensing medium (mol), given by:

$$n_{CO_2,Se} = \frac{p_{Se}\text{CO}_2 \cdot V_{Se}}{R \cdot T} \quad (\text{ideal gas law}) \quad (9)$$

Equations 6–9 yields:

$$\frac{dp_{Se}\text{CO}_2}{dt} = \frac{D}{e \cdot h_{Se}} \cdot R \cdot T \cdot K_{skin,CO_2} \cdot (\text{tcpCO}_2 - p_{Se}\text{CO}_2) \quad (10)$$

Additionally,  $K_{skin,CO_2}$  can be estimated from the solubility of  $CO_2$  in various biological tissues [wright1934, nichols1957, scheuplein1976, gill1988] leading to a  $R \cdot T \cdot K_{skin,CO_2}$  factor in the 0.6–1.0 range. Close to these values, Scheuplein *et al.* [scheuplein1976] present a  $R \cdot T \cdot K_{skin,CO_2}$  near 1.5 for the stratum corneum. Again though, the skin membrane of our model does not necessarily represent the stratum corneum alone, but is only a model for the different skin layers that may hinder  $CO_2$  diffusion. Consequently, we chose to take the  $R \cdot T \cdot K_{skin,CO_2}$  product equal to 1 in the following developments. Another possibility would be to simply integrate it inside the  $e/D$  ratio, leading to identical conclusions in the end, at the cost of an additional complexity in the writing. Thus, we can reasonably discard it, leading to the following simplified differential equation:

$$\frac{dp_{Se}CO_2}{dt} = \frac{D}{e \cdot h_{Se}} \cdot (tcpCO_2 - p_{Se}CO_2) \quad (11)$$

which—considering the initial condition  $p_{Se}CO_2(t=0) = 0$ —has a unique solution:

$$p_{Se}CO_2(t) = tcpCO_2 \cdot \left(1 - \exp\left(-\frac{t}{\tau}\right)\right), \quad \text{with } \tau = h_{Se} \cdot \frac{e}{D} \quad (12)$$

This formulation is essentially the same as that found by Chatterjee *et al.* [chatterjee2015], although they used a more sophisticated model taking into account the  $CO_2$  production inside the skin, leading to an additional  $\beta/\alpha$  factor in Equation (6) of their work.

## 4 Response Time

As mentioned in Section 1, the  $e$  and  $D$  parameters cannot be measured experimentally since they are only model parameters. However, the  $e/D$  fraction can be estimated from the  $CO_2$  exhalation rate through the skin— $Q_S$  ( $m^3 \cdot m^{-2} \cdot s^{-1}$ )—defined as:

$$Q_S = \frac{1}{S_{Se}} \cdot \frac{dV_{CO_2,Se}}{dt} \quad (13)$$

wherein  $V_{CO_2,Se}$  is the volume that would occupy the  $CO_2$  contained inside the sensing medium if considered as pure  $CO_2$  under total ambient pressure  $p_0$ , given by:

$$\frac{V_{CO_2,Se}}{V_{Se}} = \frac{p_{Se}CO_2}{p_0} \quad (14)$$

yielding:

$$Q_S = \frac{h_{Se}}{p_0} \cdot \frac{dp_{Se}CO_2}{dt} \quad (15)$$

Taking the first derivative of  $p_{Se}CO_2$ —see Equation 12—with respect to time, and evaluating it at  $t = 0$  leads to:

$$\tau = \frac{h_{Se}}{Q_S} \cdot \frac{tcpCO_2}{p_0} \quad \text{or} \quad \frac{e}{D} = \frac{tcpCO_2}{Q_S \cdot p_0} \quad (16)$$

Several works on the determination of  $Q_S$  for  $CO_2$  across human skin can be found in the literature—see Table 2 in the review article—and a value of  $100 \text{ cm}^3 \cdot \text{m}^{-2} \cdot \text{h}^{-1}$  can reasonably be assumed. Since most subjects in the aforementioned works were healthy, we can also assume a normal capnia of 5.3 kPa (or 40 mmHg)[nunns]. In these conditions, and  $p_0 = 1 \text{ atm}$ :

$$\frac{e}{D} \approx 1.90 \times 10^6 \text{ s} \cdot \text{m}^{-1} \quad (17)$$

In other words, if the sensor has a height of 1 mm,  $\tau$  will be near 1900 s, or about 32 min, and a 95% response will be achieved after 1 h 35 min—or  $3 \cdot \tau$ . These calculations are summarised in Figure S2.

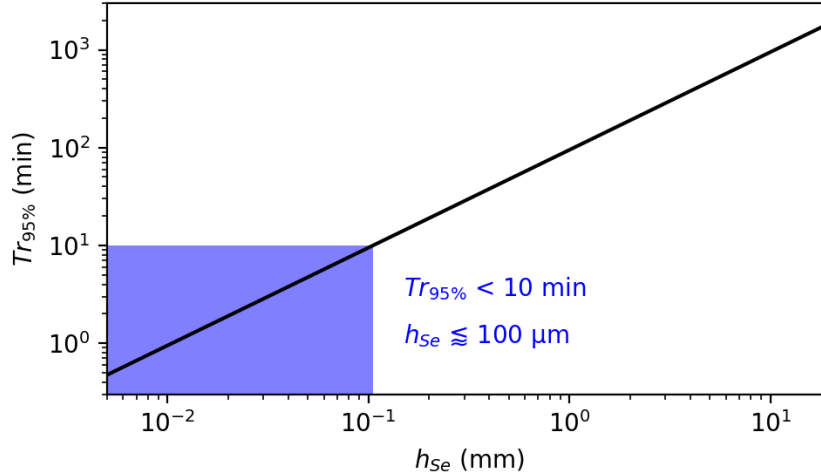


Figure S2: 95% response time ( $Tr_{95\%} \approx 3 \cdot \tau$ ) for a sensor of height  $h_{Se}$ . The blue area underlines the portion of the line with a response time below 10 min, which corresponds to a sensor height below approximately 100  $\mu\text{m}$ .

**Note:**  $Q_S$  is of course time-dependent, especially during transcutaneous monitoring with the presented closed-chamber sensor model—as it will decrease with a diminishing  $tcpCO_2 / p_{Se}CO_2$  gradient. However, since only its value at  $t = 0$  has been used in the end, and since it is also the only one reported in the literature, the  $Q_S(t)$  notation has been dropped.