Vol. 21, No. 2(2022) Bio2701
Revista Mexicana de Ingeniería Química

Mathematical model to estimate volumetric oxygen transfer coefficient in bioreactors using conformable calculus

Modelo matemático para estimar el coeficiente volumétrico de transferencia de oxígeno en biorreactores usando cálculo conformal

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Received: January 13, 2021; Accepted: April 11, 2022

Abstract

The objective of this work was to propose a Convective Conformable Mass Transfer model (CCMT) to estimate mass transfer coefficients (k_La) in bioreactors. The model employs a conformable derivative order operator (α), which is a function of the electrode constant (k_P), and this constant changes with the use of the electrode and the operating conditions of the bioreactor. A complete mixed-level experimental design with two factors: agitation and the glycerol-buffer ratio was used to validate the model. The results showed that when the viscosity increases and the agitation decreases, α increases, and vice versa. Alpha is a parameter derived from the conformable calculus but could also have a physical meaning in the process. The CCMT model was compared with two conventional models, the correlation matrix of the experimental data and the three models studied, and the F-test ($p>0.05$) showed that the three models adequately describe the experimental data. Using the Akaike and Bayesian information criteria, they were determined that of the three compared models the CCMT model fits the experimental data more adequately according to the parameters of each model (72, 55, and 42%, respectively). This work proposes an additional alternative for the determination of k_La in bioprocesses.

Keywords: fractional calculus; conformable derivative; mathematical model; volumetric oxygen transfer coefficient; Akaike and Bayesian information criterion.

Resumen

El objetivo de este trabajo fue proponer un modelo de Transferencia de Masa Convectivo Conformal, (CCMT) para estimar coeficientes de transferencia de masa (k_La) en biorreactores. El modelo emplea un operador de orden de derivación conformal (α), que está en función de la constante del electrodo (k_P), y este último cambia con el uso del electrodo y las condiciones de operación del biorreactor. Se usó un diseño experimental completo de nivel mixto con dos factores: agitación y la relación glicerol-buffer para validar el modelo. Los resultados mostraron que cuando la viscosidad aumenta y la agitación disminuye, α aumenta, y viceversa. Alfa es un parámetro derivado del cálculo conformal pero también podría tener un significado físico en el proceso. El modelo CCMT se comparó con dos modelos convencionales, la matriz de correlación de los datos experimentales y los tres modelos estudiados y la F-test ($p>0.05$) demostraron que los tres modelos describen adecuadamente los datos experimentales. Mediante los criterios de información de Akaike y Bayesiano se determinó que de los tres modelos comparados el modelo CCMT describe más adecuadamente los datos experimentales en función de los parámetros de cada modelo (72, 55 y 42 % respectivamente). Este trabajo plantea una alternativa adicional para la determinación de k_La en bioprocesos.

Palabras clave: cálculo fraccional, derivada conformal, modelo matemático; coeficiente de transferencia volumétrico de oxígeno, criterio de información Akaike y Bayesiano.

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https://doi.org/10.24275/rmiq/Bio2701
ISSN:1665-2738, *issn-e*: 2395-8472

1 Introduction

Bioreactors are widely used for food and beverage production, bioremediation, and pharmaceuticals in industrial biotechnology. Aerated stirred tank reactors are used in the laboratory and industry due to their excellent operational flexibility and mixing capability (López-Taborda *et al*., 2022; Nauman, 2008). Oxygen is transferred from a gas to a liquid, and then is absorbed into a biocatalyst and consumed. In bioprocesses, controlling the dissolved oxygen (DO) in a liquid medium is critical for cell growth. Oxygen transfer is often considered a limiting factor in such aerobic processes, due to the low solubility of oxygen in the liquid medium (Suresh *et al*., 2009). The k_La of oxygen is an essential parameter to determine the efficiency of bioreactors and to obtain a successful scale-up (García-Cabrera *et al*., 2021; Sohail *et al*., 2008). It is important to mention when determining the k_La and when using this as a scaling criterion, it can have allowed error variations of up to 40% in totally aerobic systems (Linek and Vacek, 1981). However, there are processes where they cannot have dissolved oxygen concentrations above 10% in the bioreactor (Melgarejo-Torres *et al*., 2015a and 2015b) or other studies where mixing can have harmful effects on the biocatalyst causing cell rupture, therefore, the agitations are very low and there are deficiencies in the mass transfer (Palmerin-Carreño *et al*., 2016, Castillo-Araiza *et al*., 2017). Therefore, in these type of bioprocesses is imperative to accurately estimate and control the volumetric transfer coefficient (García-Ochoa *et al*., 2010).

In order to determine accurate and reliable values of k_La, it is necessary to use a suitable device. Commercially, there are various types of electrodes to measure the DO in bioreactors. The most common electrodes include electrochemical, optical, film thickness, and ultrasonic sensors (Zuluaga *et al*., 2018). Each device has advantages and disadvantages of cost, lifetime, whether they are sterilizable or not, and their range of applicability. In all of them, the time response (t_R) is an important parameter that directly affects the determination of a reliable value of k_La. The t_R is the time when the electrode reaches 63.2% of an initial value of 0 to 100% of the final DO reading, and is unique for each electrode. This is due to the fact that there are different types of electrodes with respect to their performance and that the t_R changes by the continuous use of the probe. For example, the t_R of an optical sensor is 1-4 s, while the other sensors range between 16 s and 100 s. The t_R generally depends on the characteristics of the membrane transport and the electrolyte that is used for the electrochemical reaction in the electrode's anode. In the case of optical sensors, another significant factor is the use of the electrode's light source. All electrodes increase their response-time with use, therefore, the k_La values obtained might not be accurate. Thus, it is necessary to consider the response time for k_La determinations in a bioreactor.

There are two widely used methods to obtain k_La values in bioprocesses: experimental determination and estimation, or prediction by mathematical models. The most commonly used methods for experimental determinations of k_La are the dynamic method (gassing out-gassing in) (García and Gómez, 2009), biotic dynamic methods (Mendes and Badino, 2015), and the sulfite method (Linek and Vacek, 1981). These methods have variations of up to 10-40% of error. Of these methods, the most commonly used is the gassing out-gassing method. This method is accurate and very simple to perform, while the sulfite method (Cooper's method) is a red-ox reaction in a slightly alkaline medium (the Cooper method is not viable for alkaline cultures) and the disadvantage is that the reaction is very fast, so the possible values of k_La may be oversized, in addition to the stoichiometric coefficients of the reaction rate of sodium sulfite with oxygen must be estimated (ASCE, 1991). Another approach uses the experimental data coupled to mathematical models to estimate a suitable k_La value (Fuchs *et al*., 1971; Ascanio *et al*., 2004; Li *et al*., 2012; Chen *et al*., 2013; Fang *et al*., 2017). Engineer's challenge relies on developing new dynamic mathematical models to predict macroscale behavior from microscale observations and measurements (Sun *et al*., 2018). Nowadays, fractional calculus is emerging as a new alternative to the mathematical modeling of various processes. Fractional calculus generalizes ordinary calculus, where derivatives and integrals of any order are defined. These fractional operators can model more efficiently certain real-world phenomena, especially when the dynamics are affected by constraints inherent to the system (Babakhani and Daftardar, 2002).

More recently in (Khalil *et al*., 2014), the first conformable calculus was introduced that is an alternative to conformal calculus, but with local operators, without memory. These conformable operators can improve the performance of conformal operators for example (see Meléndez-Vázquez *et al*., 2021; Reyes-Luis *et al*., 2021; Meléndez-Vázquez

et al., 2020), since these operators can introduce a function that conformal operators cannot, regardless of the non-integer order of these derivatives.

1.1 Conformal-order calculus and conformable derivatives

Although fractional-order calculus (FOC) was introduced more than 300 years ago, nowadays FOC is an emerging field in mathematics, with applications in all related fields. Presently, FOC has been expanded to account for the complex dynamics of the real-world and is tested with real data (Sun *et al*., 2018). This application of FOC to the dynamics of complex phenomena is due to FOC?s capacity to provide a concise model to describe dynamic events that occur in heat and mass transfer (Babakhani and Daftardar, 2002; Podlubny, 1998; Oldham and Spanier, 1974). Many researchers have been trying to form new definitions of fractional derivatives, most of which include an integral form for fractional derivatives. Details of fractional calculus fundamentals can be found in several references (Khalil *et al*., 2014; Magin, 2010; Kilbas *et al*., 2006; Hilfer 2000; Gorenflo and Mainardi, 1997; Diethelm, 1997). A description of the fractional-order derivatives that have been most relevant in fractional calculus is shown below.

The conformal-order derivative $D^{\alpha} \equiv d^{\alpha}/dt^{\alpha}$ can be defined in different ways. Most of these definitions include integral form for conformal order derivatives. Two of the most popular definitions are (Kilbas *et al*., 2006; Oldham and Spanier, 1974; Podlubny, 1998):

i) Riemann-Liouville definition:

If n is a positive integer and $\alpha \in [n-1, n)$, α derivative of f is given by

$$D_a^{\alpha}(f)(t) = \frac{1}{\Gamma(n-a)} \frac{d^n}{dt^n} \int_a^t \frac{f(x)}{(t-x)^{\alpha-n+1}} dx \qquad (1)$$

ii) Caputo definition:

If n is a positive integer and $\alpha \in [n-1, n)$, α derivative of f is given by

$$D_a^{\alpha}(f)(t) = \frac{1}{\Gamma(n-a)} \int_a^t \frac{f^{(n)}(x)}{(t-x)^{\alpha-n+1}} dx \qquad (2)$$

In this paper we use the conformable derivative definition given by Khalil *et al*. (2014), where the authors consider a function defined as $f : [0, \infty) \to \mathbb{R}$ and $t > 0$, whose α^{th} order conformable conformal derivative, is given by:

$$T^{\alpha}(h)(t) = \lim_{\varepsilon \to 0} \frac{h(t + \varepsilon t^{1-\alpha}) - h(t)}{\varepsilon} \qquad (3)$$

for all $t > 0$, $\alpha \in (0, 1)$, if h is $\alpha-$differentiable in some $(0, a)$, $a > 0$, and $\lim_{t \to 0^+} T^{\alpha} h(t)$ exists, then define $T^{\alpha} h(0) = \lim_{t \to 0^+} T^{\alpha} h(t)$.

Almeida (2017) presents a definition of local conformal derivative using kernels. The author shows that some of the existent notions about local conformal derivatives are very closely related to the usual derivative function. In fact, the α-derivative of a function is equal to the first-order derivative, multiplied by a continuous function. The following definition is a modified definition from Almeida (2017).

Definition 1 (Almeida *et al*., 2016)

Let $f : [a, b] \to \tilde{}$ be a differentiable function and $t > a$. Then, f is $\alpha-$ differentiable at t and Eq. (3).

Also, if dh/dt is continuous $\partial^{\alpha} h(t)/\partial t^{\alpha} = f(t)^{1-\alpha} dh(t)/dt$, at $t = a$, then

$$\frac{\partial^{\alpha}}{\partial t^{\alpha}} h(a) = f(a)^{1-\alpha} \frac{d}{dt} h(a) \qquad (4)$$

However, there exist α-differentiable functions which are not differentiable in the usual sense.

This new definition 1 satisfies the properties given in the following Theorem (Fernández-Anaya, 2021):

Theorem 2. Let $\alpha \in (0, 1)$ and h, g be $\alpha-$differentiable at point $t > 0$, then:

a) $\frac{\partial^{\alpha}}{\partial t^{\alpha}}(ah + bg) = a \frac{\partial^{\alpha}}{\partial t^{\alpha}}(h) + b \frac{\partial^{\alpha}}{\partial t^{\alpha}}(g)$, for all $a, b \in R$.

b) $\frac{\partial^{\alpha}}{\partial t^{\alpha}}(t^p) = f(t)^{1-\alpha} p t^{p-1}$, for all $p \in R$.

c) $\frac{\partial^{\alpha}}{\partial t^{\alpha}}(\lambda) = 0$, for all constant function $h(t) = \lambda$.

d) $\frac{\partial^{\alpha}}{\partial t^{\alpha}}(hg) = h \frac{\partial^{\alpha}}{\partial t^{\alpha}}(g) + g \frac{\partial^{\alpha}}{\partial t^{\alpha}}(h)$.

e) $\frac{\partial^{\alpha}}{\partial t^{\alpha}}\left(\frac{h}{g}\right) = \frac{g \frac{\partial^{\alpha}}{\partial t^{\alpha}}(h) - h \frac{\partial^{\alpha}}{\partial t^{\alpha}}(g)}{g^2}$.

The main objective of this work was to develop a Convective Conformable Mass Transfer model (CCMT) using conformal calculus; to determine volumetric oxygen transfer coefficients ($k_L a$'s) in bioreactors and to analyze its performance concerning two other conventional models reported in the literature. The proposed model has a parameter derived from the conformal calculation (α). This parameter is a function of the electrode coefficient k_P. k_P measures the performance of the electrode depending on its use and bioreactor operating conditions such as agitation and viscosity. Performance of CCMT model was studied to different bioreactor operating conditions for in all cases, CCMT model adequately described the experimental data.

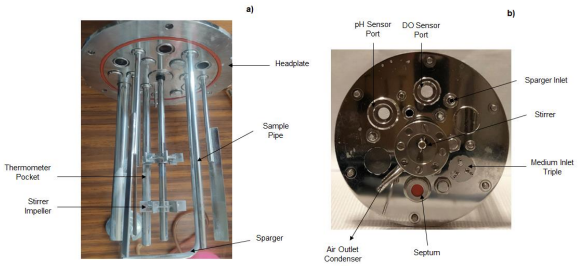

Figure 1. a) Applikon 3-Liter glass autoclavable biorreactor. b) Bioreactor head plate.

2 Materials and methods

2.1 Chemicals

The continuous aqueous phase used in all experiments was a potassium phosphate buffer solution 50 mM at pH 7 supplemented with glycerol (99% of purity) to different percentages according to the proposed experimental design (full mixed-level experimental design). The glycerol´s purpose was to validate the fractional calculus mathematical model under different homogenous conditions in the bioreactor and air was used as the gaseous phase.

2.2 Stirred tank bioreactor

A glass 3-L stirred tank bioreactor Model in-Control (Applikon, Delft, the Netherlands) was used for all hydrodynamic and mass transfer studies. The bioreactor had an internal diameter of 19 cm, and the operating volume was 2.1 L (H_L/D_T = 1.83). The bioreactor was equipped with a single six flat blade Rushton turbine, Di = 6.53 cm (D_T/D_i = 1.22), located at 4.53 cm from the vessel's flat base. The bioreactor was equipped with two central baffles of 1.0 cm to enhance liquid-liquid mixing (Figure 1).

2.3 Electrode response time determination

A dissolved oxygen electrode AppliSens Z010023525, 235 mm length, (Applikon, Delft, The Netherlands) was used. The response time is related to the diffusion of oxygen from the liquid phase (where it is dissolved) to the anode electrode (where the measurement occurs), crossing the electrode membrane and the sensor electrolyte solution. Each step of this diffusion path is associated with a resistance to the oxygen flux. To determine the response time of the electrode, it was previously calibrated to 0 and 100% of DO, and it was submerged in distilled water without oxygen using nitrogen gas. When the electrode had a 0% measurement, it was put quickly in distilled water saturated with oxygen using an airflow of 1 vvm. Measurements were collected each 10 s until reaching 100% oxygen using the Lucullus Lite® software (Applikon, Delft, The Netherlands). The response time was defined when the electrode reached 63.2% of DO (Hadjiev *et al*., 2006).

2.4 Full mixed-level experimental design

To determine the experimental k_La in different operating conditions, a full mixed-level experimental design was proposed. The experimental design had two independent factors: the percentage ratio glycerol-buffer and agitation. Glycerol had levels 0, 10, 20, 30, 40 and 50% and the agitation 300, 600, and 900 rpm. The design consisted of a total of 21 runs (Montgomery D., 2013), and all runs were carried out in triplicate at 30 °C. For the experimental design and data analysis, the "Fusion Pro" D of E software was used.

2.5 Oxygen mass transfer coefficient (k_La) determination

A dissolved oxygen electrode AppliSens Z010023525, 235 mm length, (Applikon, Delft, The Netherlands) was used for k_La determination. The oxygen electrode was coupled to an ADI 1010 Bio controller (Applikon, Delft, The Netherlands). Dissolved oxygen concentrations during dynamic gassing out experiments were measured every 5 seconds. The mass transfer coefficient was calculated according to Koizumi and Aiba method (Koizumi and Aiba, 1984; Aiba *et al*., 1973).

2.6 Viscosity measurement

The viscosities as a function of the percentage ratio between the glycerol and the medium for the 21 runs of the experimental design were measured using a Physica MCR 300 (Physica Messtechnic GmbH, Stuttgart, Germany) modular compact rheometer. The objective of measuring glycerol-medium viscosity was to obtain an average viscosity between the different percentages of glycerol and aqueous phase, and to study the parameter α in the mathematical model proposed in this work at different viscosities. The temperature was controlled with a Peltier (TEK 150

PC, USA), and all measurements were carried out in triplicate at 30 °C.

2.7 Densities determination

The densities of glycerol-medium were measured on an Anton Paar 500 vibrating tube densimeter. The densimeter was calibrated with deionized water (Millipore SuperQ) and dry air. The measurements were carried in triplicate for all 21 runs of the experimental design at 30 °C.

2.8 Mathematical model proposed

There are two conventional models that can be used to estimate k_La values from experimental data. The first model estimates by means of a mass balance Eq. (5) and subsequently resolving and re-arranged Eq (6):

$$\frac{dC(t)}{dt} = k_La[C^* - C(t)] \tag{5}$$

$$\ln\left(\frac{C^* - Co}{C^* - C(t)}\right) = k_La t \tag{6}$$

where $C(t)$ is the concentration of DO at any time, C^* is the concentration of DO in the saturation in the medium, Co is the initial concentration of DO (0%), and the slope of the Eq. (6) is the k_La value. This model could be used only when the response time of the electrode is less than 10 s (Fuchs *et al*., 1971).

The other model also commonly used was proposed by Fuchs *et al*., (1971). This model is more robust and considers the constant of the electrode (k_P) where it is defined as:

$$k_p = \frac{1}{t_R} \tag{7}$$

The authors modified the equation for oxygen transfer and superposing in function of the electrode response, expressed in two dimensionless equations. Equation 8 and 9 are dissolved oxygen in the bioreactor and for the oxygen detected by the electrode, respectively:

$$\frac{dY_M}{dt} = -k_La Y_M \tag{8}$$

$$\frac{dY_p}{dt} = k_p(Y_M - Y_p) \tag{9}$$

where Y_M and Y_p are dimensionless concentrations of dissolved oxygen in the bioreactor and in the electrode, respectively and are defined as:

$$Y_M = \frac{C_M^* - C_M}{C_M^* - C_{Mo}} \tag{10a}$$

$$Y_P = \frac{C_P^* - C_P}{C_P^* - C_{Po}} \tag{10b}$$

Where C_M^* is the saturation concentration in the liquid, C_M is the DO concentration at any time, and C_{Mo} is the DO concentration at $t = 0$, in the same way for C_P^*, C_P and C_{Po} but at the electrode membrane.

Simultaneously solving the equations 8 and 9:

$$Y_M = \frac{k_p \exp(-k_La t) - k_La \exp(-k_p t)}{k_p - k_La} \tag{11}$$

Now, this work proposes that the temporal derivative in the Eq. (5) to be replaced by the fractional order derivative to obtain the (CCMT) equation:

$$\frac{d^\alpha C(t)}{dt^\alpha} = k_La[C^* - C(t)] \tag{12}$$

where α is the anomalous convective coefficient. This model allows estimate the volumetric oxygen transfer coefficients from the experimental data.

The conformal derivative definitions, used in above equation, are non-local time memory conditions in nature, that is, that take into account a long-time interval to perform the calculation of the conformal order derivative, and physically considers the effects that occur in that time interval. For this reason, its main characteristic is that to perform the calculation it consumes many computational resources (Khalil *et al*., 2014), while the conformable derivative is an instantaneous calculation. Considering this, the definition of local conformal order derivatives proposed by Definition 1 is used in this paper to obtain the (CCMT) model, Eq (13):

$$\frac{dC(t)}{dt} = \frac{k_La[C^* - C(t)]}{f(t)^{1-\alpha}} \tag{13}$$

The Eq (14) kept the properties of ordinary derivatives. This CCMT equation considers that there exists an α differentiable function to be able to obtain its solution. In this work, the function $f(t)$ is defined as:

$$f(t) = k_p t \tag{14}$$

This function involves the electrode constant at any time when the DO is measured. Inserting Eq (14) into Eq (13) result in Eq (15)

$$\frac{dC(t)}{dt} = \frac{k_La[C^* - C(t)]}{(k_p t)^{1-\alpha}} \tag{15}$$

This equation allows us to investigate the electrode constant effect over the calculated value of the volumetric oxygen transfer coefficient using CCMT equation based on derivatives of fractional order with the help of conformable derivative definition.

The proposed model has some important considerations that should be mentioned:

a) Glycerol and buffer behave as a completely homogeneous phase.

b) Mass transfer from gas to liquid phase. ensures saturation concentration in the liquid

c) The model is based solely on a two-phase gas-liquid system.

d) The model is for an abiotic system.

2.9 Analysis of the mathematical model

The proposed mathematical model was solved by integrating a set of differential equations (ODEs) with the Runge Kutta Fehlberg method. The model contains two parameters (k_La and α), which were estimated by the weighted least-squares of the residuals (RSS) between the calculated and experimental dissolved oxygen concentrations according to the following minimized weighted objective function (OF), Eq. (16):

$$OF(b) = \sum_{j}^{n_{exp}} \sum_{l}^{n_{resp}} W_{jl}(\tilde{y}_{ij} - y_{ij})(\tilde{y}_{il} - y_{il})^{b_1,b_2} \rightarrow \min \tag{16}$$

The responses used in the regression are the concentration of dissolved oxygen through time. In Eq. (16), $\tilde{y}_{ij}$ denotes the calculated value and y_{ij} denotes the observed oxygen concentration in experiment j; b_j is the parameter vector (k_La and α) to be estimated; n_{exp} is the number of independent experiments; n_{resp} is the number of the model response variables; and W_{ij} is the weighting factor that can be used to give greater importance to some portion of the response variable (DO). The parameters k_La and α were estimated by a software program (ODRPACK 2.01, FORCE Ver. 2.0 USA) using multi-response non-linear regression and the Levenberg-Marquardt method with a 95% confidence interval.

2.10 Statistical analysis

To determine the statistical significance of the parameters, the t-test was used, while the F- test was used to obtain the regression significance. The covariance matrix was used to obtain the correlation matrix between the experimental data and the three proposed models. An analysis of variance was used to determine if there was a significant difference between the experimental data and the mathematical models studied.

2.11 Akaike and Bayesian information criterion

The Akaike and Bayesian information criteria were used for the selection and comparison of the three models studied. These criteria are widely used for model selection in health, biological and bioprocess research. Some researchers and fields of study routinely use one or the other, often without clear justification. Others attempt to compare models using multiple criteria, but encounter the ambiguity that different criteria lead to substantially different answers, leading to the question of which criterion is best. In this work, both criteria were employed with the aim of comparing the information criteria obtained and determine which model adequately fits the experimental data (Diziak *et al.*, 2020). The Akaike Information Criterion (AIC) was developed by Akaike in 1973 and is widely used in modeling of biological systems to decide between different models (Akaike, 1973). For models with the same number of adjustable parameters, it selects the model with the best least-squares fit. Models with more parameters typically fit better, but the addition of more parameters may not be statistically justifiable (Ingdal *et al.*, 2019). For this reason, the three models studied were analyzed by means of AIC. According to this type of analysis:

$$AIC = -2\ln(L) + 2k \tag{17}$$

where AIC is the Akaike information criterion, L is the likelihood estimator which for normally distributed errors is maximized when the residual sum of squares is minimized, and can be considered as $L = \sigma^2$ where σ^2 is the variance between the model regression and the experimental data and k is the number of parameters to estimate plus the error term ($k = q + 1$). However, for AIC analyses where the number of observations is small ($n_{obs}/k < 40$) a correction of Eq. (17) can be made, giving more precise information about the fit of the models as a function of sample size.

$$AICc = -2\ln(L) + 2k + \frac{2k^2 + 2k}{n_{obs} - k - 1} \tag{18}$$

To determine the probability of which model best fits the experimental data, the term of Akaike weights is

used for each of the models studied and is defined as follows:

$$wAIC = \frac{\exp\left(-\frac{1}{2}\Delta AICc\right)}{\sum_{k=1}^{k}\exp\left(-\frac{1}{2}\Delta AICc\right)} \tag{19}$$

where ΔAIC is defined as the difference between the minimum $AICc$ value obtained minus each of the $AICc$ of the models studied. $\Delta AIC = AICc_{min} - AICc_i$

Bayesian Information Criterion (BIC) is based on the log likelihood function ($\hat{L}$) and is closely related to the Akaike information criterion. As in AIC, BIC introduces a penalty term for the number of parameters in the model (Kass and Raftery, 1995).

In general, BIC is defined as:

$$BIC = 2k + 2\ln(\hat{L}) \tag{20}$$

$$\hat{L} = \frac{\sum RSS}{n} = \frac{\sum(y_i - \hat{y}_i)^2}{n} \tag{21}$$

Rearranging Eq. (20)

$$BIC = k\log(n) + n\log\left(\frac{\sum RSS}{n}\right) \tag{22}$$

Where k is the number of model parameters, n is the number of experimental observations and $\sum RSS$ is the residual sum of squares between the model prediction ($\hat{y}_i$) and the experimental data (y_i).

2.12 *Parametric sensitivity analysis*

Parametric sensitivity analysis can be defined as the change in an output variable as a function of a change in one or more input variables or factors of a mathematical model describing a process (Pianosi *et al.*, 2014 Melgarejo *et al.*, 2015b). Parametric sensitivity analysis can be applied to analyze how model performance changes when it departs from some optimal or reference parameter, to support model calibration, verification, diagnostic evaluation or simplification, to analyze the dominant controls of a system, to support important decision making in a specific process (Anderson *et al.*, 2014; Butler *et al.*, 2014). For this work the electrode constant k_P, is a relevant input parameter that modifies the output variable (k_La) of the proposed model, which was modified with values of 15, 17, 20, and 25 s^{-1}.

3 Results and discussions

3.1 *Electrode response time*

The response time was determined when the DO reached 63.2% from 0 to 100% (Hadjiev *et al.*, 2006). The response time is related to the diffusion of oxygen from the liquid phase (where it is dissolved) to the probe anode (where the measurement occurs), crossing the probe membrane and the sensor electrolyte solution. This liquid thickness is determined by the liquid viscosity and the operating conditions. Higher viscosity and operating conditions at low rpm result in increased thickness of the stagnant liquid film (Cerri *et al.*, 2016). It is clear that the electrode had good stability in ratio to the measurement of oxygen dissolved. This is due to the electrode being new and having little previous use. According to the manufacturer, this type of electrode has a response time of 15 seconds when they are new. Response time was measured in triplicate. Figure 2a) shows the dissolved oxygen profiles with respect to time at different percentage ratios of glycerol and buffer solution. (0, 10, 20, 30, 40 and 50 % glycerol). It can be seen that as the percentage of glycerol increases, the viscosity of the medium increases, therefore the transfer of oxygen from the liquid phase in the reactor to the electrode membrane present a higher resistance, thus increasing the response time of the electrode. Figure 2b) shows the linear zone of the DO profiles where 63.2 % is reached for all conditions studied in Figure 2a). The colored arrows on the abscissa axis indicate how the response time increased at different fluid viscosities as a function of the percentage of glycerol. An analysis of variance and the Student-Newman-Keuls (SNK) test were performed, which showed that there is no significant difference between the response times for 10, 20 and 30 % glycerol (16.2, 16.6 and 16.8 s, respectively), while for 0, 40 and 50 % there is a statistically significant difference between these times (15.2, 19.3 and 27.1 s, respectively).

3.2 *Volumetric oxygen transfer coefficient (k_La) experimental determination*

The present study used the statistical analysis of the proposed experimental design (Fusion Pro D of E Ver. 6.7 program) to compare the similarity of the k_La values obtained with the three models as a function of the factors and levels of the experimental design

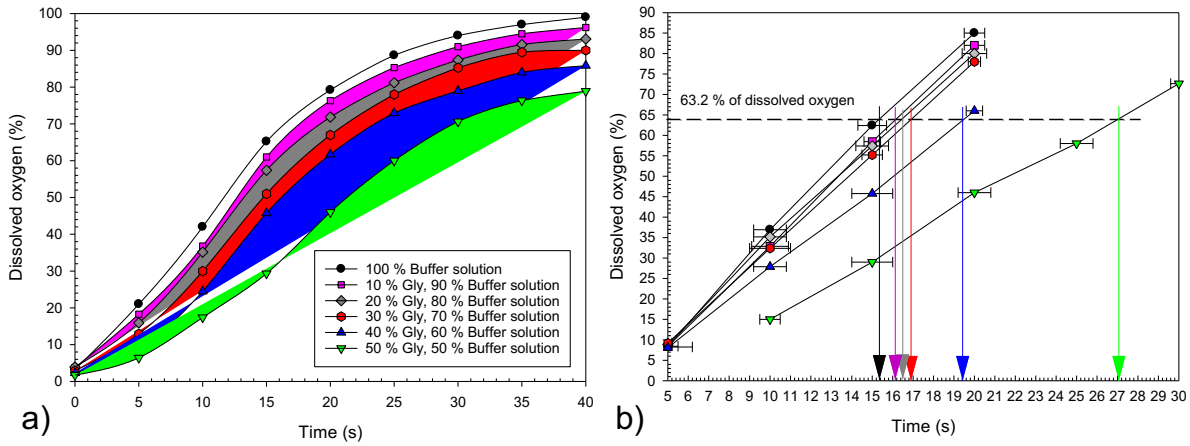

Figure 2. a) Concentration of DO profile of the electrode. b) linear section of the DO measurement by the electrode when it was reached at 63.2% to different percentage ratios of glycerol - buffer solution.

(300, 600, 900 rpm, and 0, 10, 20, 30, 40 and 50% glycerol). Glycerol was added to demonstrate that the CCMT model proposed was accurate in a wide range of culture media, depending on their density, and the viscosity of the culture media. The glycerol had a viscosity of 1.5 N.s.m^{-2} which means it is 1500 times more viscous than water (1×10^{-3} N.s.m^{-2}), and the densities were 1261 Kg.m^{-3} and 999 Kg.m^{-3}, respectively. With this culture medium as a model, it was possible to study the behavior of k_La with the two classical models and the CCMT model. To obtain the response surfaces in Figure 3, the DO in the bioreactor was experimentally quantified to the different operating conditions proposed by the experimental design (21 runs) and with this dynamic data the k_La values were estimated for each of the three mathematical models studied, to subsequently generate the response surfaces and the statistical analysis using Fusion Pro Ver. 6.7 program. Figure 3 shows that the three models have a similar trend. The linear model obtained k_La values of 37 to 142 h^{-1}. This model did not consider the response time of the electrode (Figure 3a). The model of Fuchs *et al*., 1971 has k_La values of 41.55 to 119.81 h^{-1}. Fuchs? model presented a better linear fit compared to the other two models (Figure 3b), while the CCMT model had k_La values of 37.29 to 131.35 h^{-1} (Figure 3c), similar to k_La values obtained by the first model (Figure 3a). The last two models considered the response time of the DO electrode. In all three cases, the more influential independent variable affecting k_La values was the agitation. For the glycerol-buffer ratio, it is observed in the three cases that the k_La decreases as the percentage of glycerol increases. This makes sense because the viscosity of the medium increases and therefore mass transfer decreases. Analyzing the Pareto chart (figure not shown) in the statistical analysis of the response surfaces it was obtained that agitation has a positive effect, while the increase of glycerol has a negative effect on the k_La. Of these two factors, agitation has a major influence on k_La while glycerol has a minor influence on k_La. The k_La values of Fuchs *et al*., 1971 and CCMT models were below those of the linear model (117 and 131 h^{-1} respectively); While the linear model estimated maximum k_La values of 143 h^{-1}. The standard deviation of the estimated k_La values among the three models was 13 h^{-1} equivalent to a variation of ±10 %. This 10 % variation can be considered acceptable. It is important to mention that the electrode used is relatively new and its measurement is accurate according to the manufacturer (AppliSens Z010023525, 235, Delft, The Netherlands). In section (3.8.) a parametric sensitivity analysis study was carried out to simulate what happens when the electrode begins to lose sensitivity due to wear and tear from continuous use.

3.3 Analysis of mathematical models

For the analysis of the three models studied, nonlinear regressions were performed and the k_La values for each model with their respective parameters were fitted to the experimental data. Figure 4 shows the operating conditions where the medium is more viscous at low agitation and vice versa. Figure a1) shows the experimental data vs. the three models

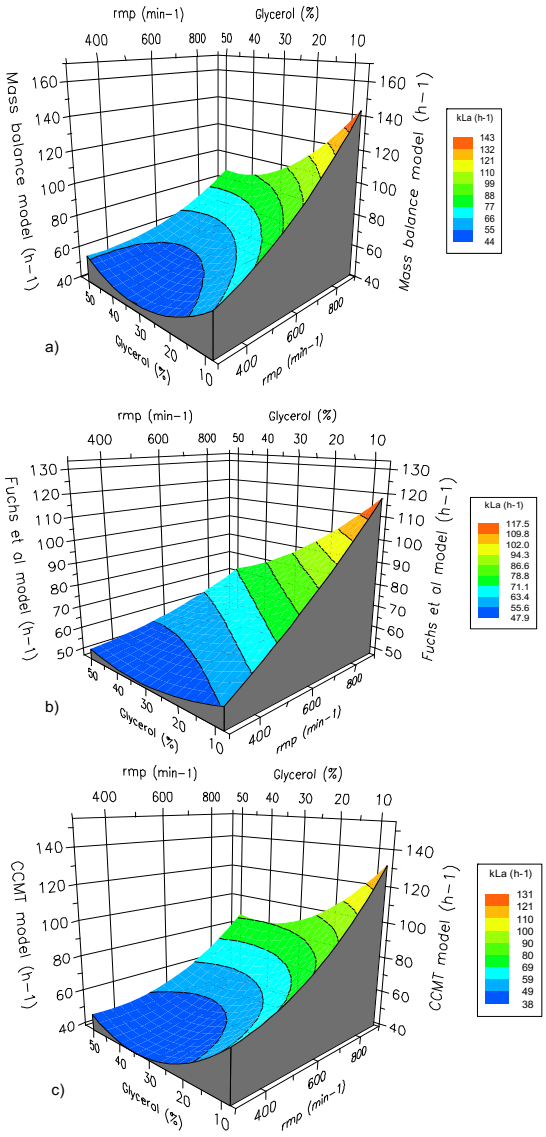

Figure 3. Experimental k_La values analyzed with the three mathematical models; a) mass balance model, b) model proposed by Fuchs *et al.* (1)971, c) CCMT model.

studied (300 rpm and 50% glycerol), while Figure a2) shows the conditions at 300 rpm and 0 % glycerol. Figure b1) shows data at 600 rpm and 50% glycerol. The data shown in Fig b2) is for 600 rpm and 0% glycerol. And the fit of the three models vs. experimental data at high agitation. Figure c1) shows data at 900 rpm and 50% glycerol. Similarly, the data in Figure c2) are for 900 rpm and 0% glycerol (there are culture media where only minimal amounts of glycerol are required, Melgarejo *et al.*, 2015). For the three cases in the operating conditions shown with Figures a), b) and c) the CCMT model (solid red line) was the best fit to the experimental data. It is worth mentioning that for all cases the non-linear regression of the three models were statistically significant, similar to the experimental data ($p>0.05$). However, the CCMT model had the highest correlation index with the experimental data $R^2 > 0.98$, while the other two models were between the interval of $0.98< R^2 <0.99$. According to t-tests, the parameters (k_La and α) showed statistical significance within the 95% confidence interval when using the CCMT model. In other words, the parameter α has two functions: on the one hand it has a mathematical memory that takes into account the last data to restart the estimation of k_La and the fit to the experimental data (Fang *et al.*, 2017), and on the other hand it takes into account the functional state of the electrode. This parameter α could explain a real phenomenon of this convective mass transfer mechanism as a function of the functional state of the probe (k_P). The results obtained show that the proposed CCMT model has the ability to fit well a wide range of different operating conditions to experimental data and a better estimation of mass transfer coefficients than the other conventional models.

3.4 *Statistical analysis*

The covariance matrix was used to obtain the correlation matrix between the experimental data and the three models studied. The reactor operating conditions were 300, 600 and 900 rpm to 50% glycerol, respectively. The correlation matrix shows that in the operating conditions studied the three models fit the experimental data accurately (correlation coefficients r above 0.98). Analysis of variance for the three case studies showed that there are no significant differences between the three models with respect to the experimental data ($p > 0.05$), therefore no post hoc tests were performed. Table 1 shows the F-test values for each case studied. The analysis of covariance and the F-test show that statistically the three models studied fit the experimental data adequately to the conditions studied. However, these results may be partial. Indeed, the criteria in the following section 3.6. allowed to discern which of the three models may be better from the number of parameters that each model has.

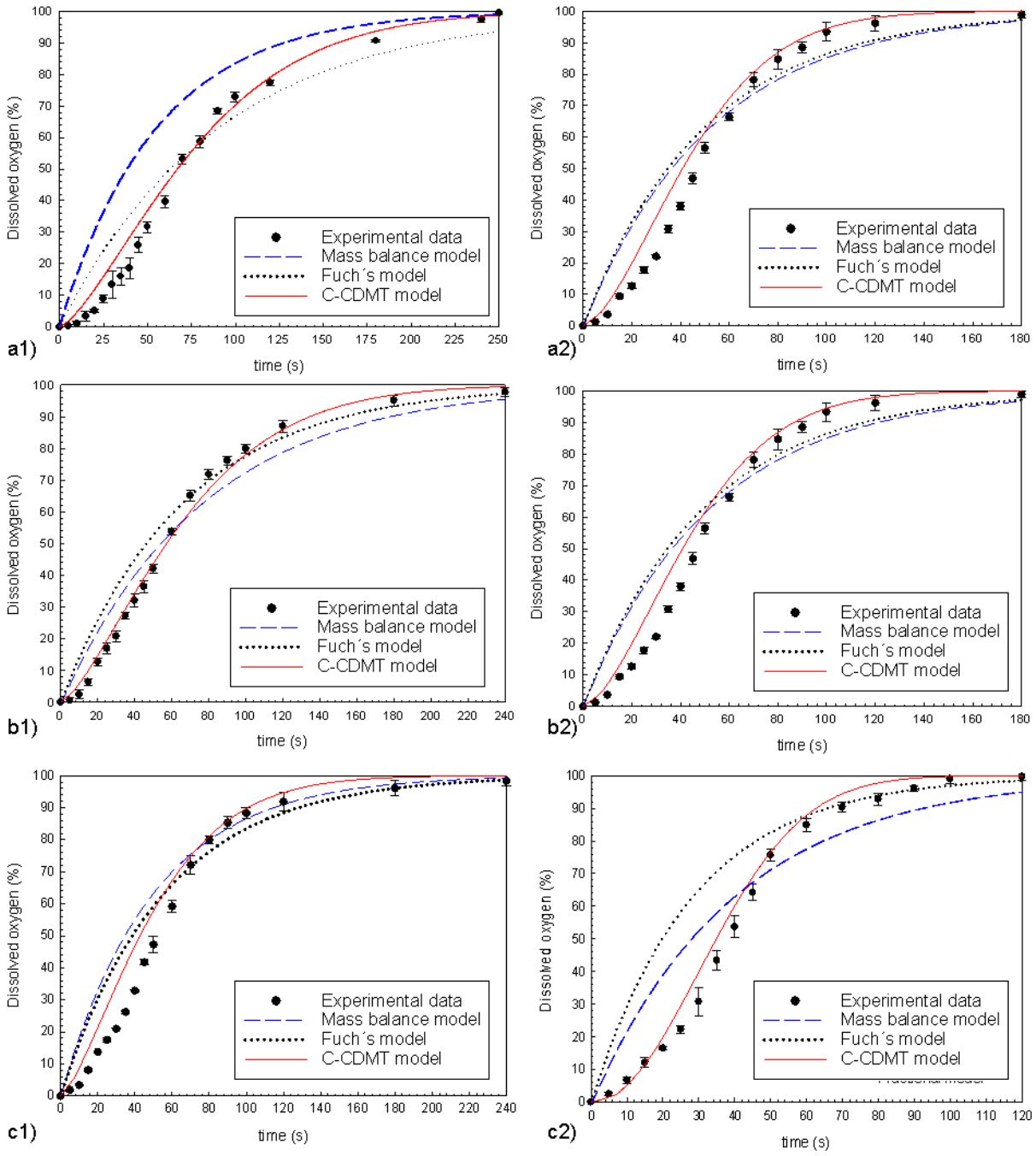

Figure 4 a1) Fit of the mathematical models studied with the experimental data by nonlinear regression at 300 rpm and 50 % of glycerol. a2) at 300 rpm and 0% of glycerol. The same form is for b1) 600 rpm and 50% of glycerol. b2) 600 rpm and 0% of glycerol. c1) by operating conditions to 900 rpm and 50% of glycerol and c2) 900 rpm and 0% of glycerol.

Table 1. Correlation matrix and F-test of the three models studied and experimental data to different operating conditions.

Operating conditions		
300 rpm and 50% glycerol	600 rpm and 50% glycerol	900 rpm and 50% glycerol
$\begin{array}{c} \\ ED \\ Mass \\ Fuchs \\ CCMT \end{array}\begin{array}{c} \begin{array}{cccc} ED & Mass & Fuchs & CCMT \end{array} \\ \begin{bmatrix} 1.00 & 0.986 & 0.997 & 0.996 \\ 0.986 & 1.00 & 0.994 & 0.988 \\ 0.997 & 0.994 & 1.00 & 0.995 \\ 0.997 & 0.998 & 0.995 & 1.00 \end{bmatrix} \end{array}$	$\begin{array}{c} \\ ED \\ Mass \\ Fuchs \\ CCMT \end{array}\begin{array}{c} \begin{array}{cccc} ED & Mass & Fuchs & CCMT \end{array} \\ \begin{bmatrix} 1.00 & 0.984 & 0.998 & 0.998 \\ 0.984 & 1.00 & 0.984 & 0.988 \\ 0.998 & 0.984 & 1.00 & 0.997 \\ 0.998 & 0.988 & 0.997 & 1.00 \end{bmatrix} \end{array}$	$\begin{array}{c} \\ ED \\ Mass \\ Fuchs \\ CCMT \end{array}\begin{array}{c} \begin{array}{cccc} ED & Mass & Fuchs & CCMT \end{array} \\ \begin{bmatrix} 1.00 & 0.972 & 0.990 & 0.997 \\ 0.972 & 1.00 & 0.992 & 0.980 \\ 0.990 & 0.971 & 1.00 & 0.993 \\ 0.997 & 0.980 & 0.993 & 1.00 \end{bmatrix} \end{array}$
F- test = 0.0305 $F_{0.05,20,20} = 2.12$ for $1-\alpha = 0.95$	F- test = 0.108 $F_{0.05,19,19} = 2.16$ for $1-\alpha = 0.95$	F- test = 0.371 $F_{0.05,18,18} = 2.27$ for $1-\alpha = 0.95$

ED: Experimental data
Mass: Mass transfer model
Fuchs: Fuchs *et al*., 1971 model
CCMT: Conformable Convective Mass Transfer Model

Table 2 Bayesian information criterion for the three models studied to 300, 600 and 900 rpm and 50 % glycerol respectively.

	Operating conditions		
Model	300 rpm	600 rpm	900 rpm
Mass balance	41.8	40.88	44.68
Fuchs *et al*., 1971	27.07	22.16	36.07
CCMT	25.54	16.6	20.91

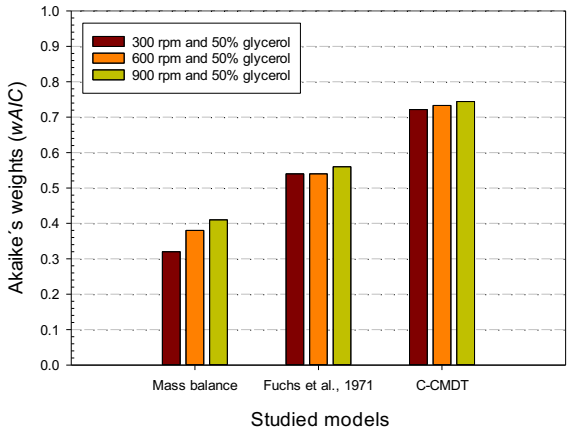

Figure 5. Analysis of the Akaike information criterion represented in a Pareto chart of the three models studied.

3.5 Akaike and Bayesian information criterion analysis

From the data required for the analysis of the Akaike information criterion (Ingdal *et al*., 2019; Akaike H, 1973), the Pareto chart was obtained, it shows how from the wAIC the CCMT model obtained the highest percentage fraction (close to 70 %) to describe the experimental data (300, 600 and 900 rpm and 50% glycerol respectively), while the Fuchs *et al*. model, 1971 described about 50 % and the mass balance model was the least descriptive of the experimental data with approximate percentage fractions of 30 to 40 % (Figure 5). With these results the Akaike information criterion indicates that the model that best fits the experimental data is the one proposed in this work (CCMT model).

There are several reports that use *AIC* and *BIC* as criteria for the selection of a mathematical model (Diziak *et al*., 2020). In this work, both criteria were used to analyze which of the three models studied described the experimental data more adequately. Table 2 shows the values obtained for the Bayesian information criterion at the same reactor operating conditions used for the *AIC* analysis. It is observed that the *BIC* values obtained for the CCMT model are the lowest compared to the mass balance models and Fuchs *et al*., 1971, for the three operating conditions studied. The criterion applied to determine the most adequate model to describe the experimental data is the lowest *BIC* value obtained among all the models analyzed (Burnham and Anderson, 2004). It is observed that the CCMT has the lowest value of *BIC* than the other two models, therefore the *BIC*

analysis also showed that the CCMT model is the one that best describes the experimental data. The AIC and *BIC* analyses are based for the selection of the appropriate model on the number of parameters it has to describe the experimental data. The CCMT model has three parameters (k_La, k_P and α) while the model of Fuchs *et al*., 1971 has two parameters (k_La and k_P) and the mass balance model has only one (k_La). The additional parameter α of the CCMT model comes from the definition of the fractional calculation, α allows more flexibility in the description of the experimental data, compared to the other two models. However, it is pertinent to mention that the statistical analysis ($p>0.05$) showed that the three models are statistically equal to the experimental data.

3.6 Alpha parameter analysis

The CCMT model has an additional parameter α, estimated according to Eq. (14). This parameter is a function of the constant of the electrode k_P. It was studied that factors modify the value of the α to give a physical interpretation to this parameter. The indirect association of this parameter is associated with the different viscosities and turbulence of the flow in the bioreactor medium through the k_P. The association with the different characteristics of the medium was demonstrated through a statistical analysis using the Pareto chart (Figure 6a). The Pareto chart shows that the main independent variables that influenced the parameter α were the agitation and percentage of glycerol as first and second influence, respectively. The third effect was the agitation square, that is to say that α parameter behaves parabolically as a function of agitation squared. The last effect was the interaction of glycerol-buffer - agitation. Figure 6b analyzes the behavior of parameter α as a function of the operating conditions studied. The values obtained for α were 0.21 (for high agitation and low viscosity) and a maximum value of 1 (for high viscosity and low agitation). It is observed that the parameter α increases with increasing fluid viscosity (% glycerol) and decreasing agitation, this suggests that α is not only an additional parameter of the mathematical model but also suggests that it may be intrinsically related to the system studied, as a function of fluid properties such as viscosity and bioreactor operations (agitation). Alpha also takes into account oxygen probe membrane wear, i.e. as the probe loses sensitivity due to continuous use, due to α parameter which is also a function of k_P. Therefore, the CCMT model allows a more adequate estimation of k_La in the reactor. The authors propose future studies to obtain a correlation through dimensional analysis of the k_P value and the mechanisms of mass transfer and hydrodynamics, as well as the validation of this correlation with experimental data.

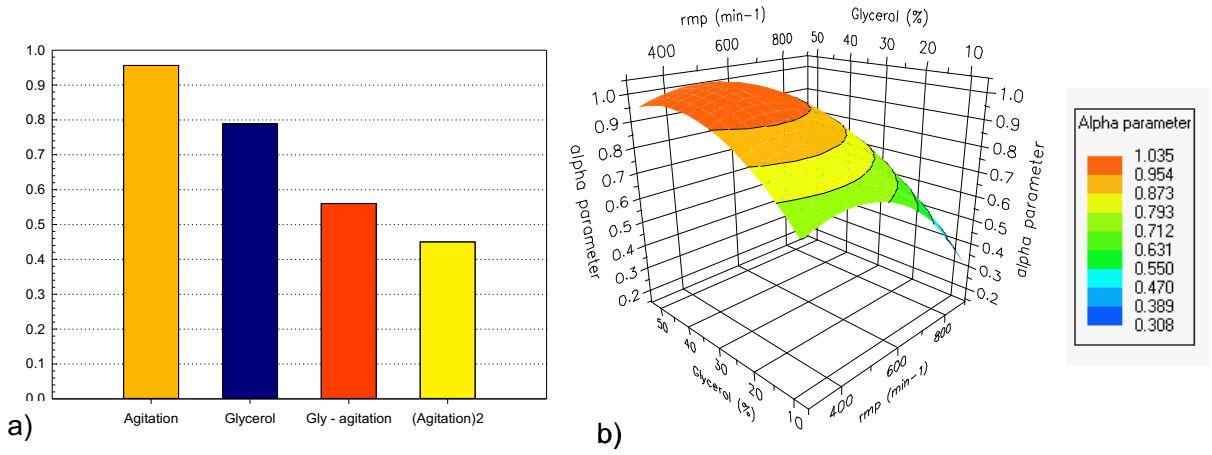

Figure 6. a) Pareto chart showing the factors and the interactions between them that affect the α parameter; b) Behavior of the α parameter as a function of the bioreactor operating conditions (percentage of glycerol and agitation).

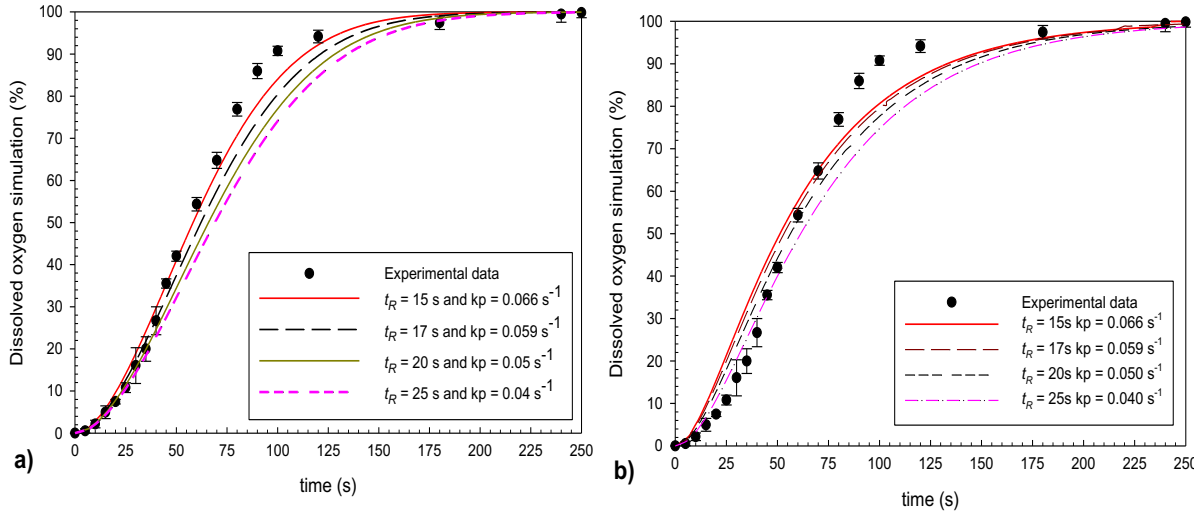

Figure 7. Parametric sensitivity analysis of dissolved oxygen concentration at different electrode response times a) CCMT model and b) Fuchs model.

Table 3 Constants and their electrode response times with the k_La predicted in the sensitivity analysis using the mass balance, Fuchs *et al*., 1971, and CCMT models.

Electrode constant, k_p (s^{-1})	Response time, t_R (s)	Mass balance model	Fuchs *et al*. model k_La (h^{-1})	CCMT model k_La (h^{-1})
0.066	15	62	63	64
0.059	17	58	61	62
0.05	20	52	58	58
0.04	55	50	56	57

3.7 Parametric sensitivity analysis

The electrode constant k_P is defined as the inverse of the response time (Eq. 7). k_P changes according to the daily use of the electrode and also due to the effect of the viscosity of the medium. In order to analyze how the electrode response would be, given the loss of sensitivity due to its use in the DO measurement a parametric sensitivity analysis was performed with the Fuchs *et al*., 1971 and CCMT models by varying only the k_P as parameter. Figure 7a shows the parametric sensitivity analysis of the CCMT model vs. experimental data. For this analysis, only a viscosity was considered and the sensitivity analysis consisted of several simulations varying the change of the electrode constant due to the use of the electrode. The operating and experimental conditions are a) 300 rpm, 1 vvm and 10% glycerol and Figure 7b shows the parametric sensitivity analysis for the Fuchs *et al*., 1971 model at the same conditions. For both parametric sensitivity analyses, the response time was varied starting from the experimentally calculated (15 s) up to 25 s: the response time increased up to 66 %, and it can be observed that the increase of the electrode constant does not cause a loss of sensitivity in both models. When estimating the values of k_La for both models with respect to different k_P only vary a percentage for the Fuchs *et al*., 1971 model of 13 % while for the CCMT it was 11 %.

Table 3 shows the k_P values used for this sensitivity analysis with their respective electrode response times and the k_La values predicted by Mass Balance, Fuchs *et al*., 1971 and CCMT models and it is pertinent to mention that the Mass Balance model does not have the k_P parameter, yet it was studied to compare what happens with the determination of the k_La for this model. The parametric sensitivity analysis (Figure 7) and the data in Table 3 shows that regardless of the increase of k_P up to 66 % the estimation calculated k_La in both models can have a measurement accuracy of up to 87 % and 89 % for the Fuchs *et al*., 1971 and the CCMT models respectively and the mass balance model without the

k_P term varies in the estimation of k_La by up to 79 %. That is why it is imperative to consider the use of electrodes in the measurement of k_La's in order to have the optimal performance of the bioprocess. It is known that there are several bioprocesses where, when there are 5 to 10 % of DO in the bioreactor, the biocatalyst can suffer oxidative stress or, on the contrary, that the deficiency of oxygen with those same percentages can make the biocatalyst not have adequate performance (Palmerín-Carreño *et al*., 2016; Melgarejo-Torres *et al*., 2014). The CCMT model, by its mathematical properties and the operator α which allows to fit the model adequately to the experimental data also is a function of the electrode k_P. The CCMT permits the predictions and accurate calculation of k_La values under different operating conditions of the bioreactor, and also takes into consideration the functional condition of the electrode.

Conclusions

A Convective Conformable Convective Mass Transfer mathematical model (CCMT) was proposed as an alternative to estimate volumetric oxygen transfer coefficients (k_La) in bioreactors. The CCMT model is simple and is a function of the electrode constant, therefore the CCMT model estimates k_La's based on electrode performance. The operator α of the CCMT model opens the possibility to studies that this operator is a physical interpretation of the process and is not just a mathematical operator coming from the conformable derivative order. The CCMT model fits the experimental data adequately as well as two conventional models reported, however, the Bayesian and Akaike information criteria showed that due to the α parameter it allows a much better fit than the other two models. It is proposed to do more studies on the parameter α, to determine if it can have a physical meaning in the process. Although the conformable calculus has already been studied in mass and heat transfer problems, there are few reports of its use in bioprocesses. This work proposes to continue using the conformable calculus in mathematical models to open new doubts, ideas, studies, applications and to have other alternatives to the conventional ones to study and describe a wide range of mechanisms that occur in biological processes.

Acknowledgments

We thank all those researchers in the world who, from their trenches, never stopped working to make a better world, despite this global pandemic.

The third author acknowledge the financial support from the National Strategic Project No. 212602 (AZTLAN Platform) as part of the Sectorial Fund for Energetic Sustainability CONACYT-SENER.

Nomenclature

C	oxygen concentration at any time in the bioreactor (%)
C^*	oxygen saturation concentration in the bioreactor (%)
C_f	final oxygen concentration in the bioreactor (%)
Co	initial oxygen concentration in the bioreactor (%)
C_p	oxygen concentration at any time in the electrode (%)
C_p^*	oxygen saturation concentration in the electrode (%)
C_{po}	initial oxygen concentration in the bioreactor (%)
D_i	impeller diameter (m)
D_T	tank diameter (m)
DO	dissolved oxygen (%)
H_L	height of the liquid in the bioreactor (m)
k_La	overall mass transfer coefficient of oxygen (s^{-1} or h^{-1})
k_P	electrode constant (s^{-1})
N	tip speed of impeller (s^{-1})
N_{Re}	Reynolds number in the bioreactor (dimensionless)
rpm	revolution per minute (min^{-1})
t	measurement time of dissolved oxygen in the bioreactor (s)
t_r	response time of the electrode (s)
x	fraction of the glycerol or buffer in the bioreactor (dimensionless)
Y_M	dimensionless concentration in the bioreactor of the model proposed by Fuchs *et al*. [6]
Y_P	dimensionless concentration in the electrode of the model proposed by Fuchs *et al*. [6]
Greek letters	
α	parameter that corresponds to the mathematical model of fractional order (dimensionless)

ρ density of the glycerol or buffer or apparent phase of the system (Kg m^{-3})

μ viscosity of aqueous or apparent phase of the system (N s m^{-2})

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