NONLINEAR REGRESSION AS A TOOL FOR PARAMETER ESTIMATION OF A MATHEMATICAL MODEL FOR OXYGEN TRANSFER IN BIOREACTORS

Rayrine T. L. Andrade[1*], Leonardo G. M. Mendes[2] & Guilherme Y. Rodriguez [1]

[1] *Bioprocess Engineering, Federal University of Itajubá, Natural Resources Institute, Itajubá, Brazil.*
[2] *Chemical Engineering, Federal University of Itajubá, Natural Resources Institute, Itajubá, Brazil.*

* *Corresponding author: rayrine@unifei.edu.br*

ABSTRACT

Oxygen transfer is one of the main performance parameters used as criteria in bioreactor analysis, quantified by the volumetric oxygen transfer coefficient (k_La). The aim of this work was to develop an Excel spreadsheet that automates the estimation of parameters of an empirical mathematical model used to calculate k_La from experimental data using air and water as fluids. The mathematical model consists of a multivariable function with two inputs (agitation and aeration) and three adjustable empirical parameters (α, β and γ.). The primary methodology used was the nonlinear regression of the aforementioned mathematical model to experimental data inputted by the user. It was concluded that automating nonlinear regression in a spreadsheet makes the process more accessible and immediate, although the complexity of the mathematical model may lead to convergence problems of the numerical method.

Keywords: Bioreactors. Excel. K_La. Oxygen transfer. Nonlinear regression.

1 INTRODUCTION

Bioreactors are equipment developed to provide a favorable environment, with adequate physical-chemical conditions, to conduct a fermentative or enzymatic bioprocess. Variables such as temperature, pH, agitation and aeration are essential in bioprocesses, and they are maintained or changed by the controller coupled to the bioreactor (RODRIGUEZ et al., 2015).

Oxygen transfer is one of the essential variables to analys the performance of bioreactors, as it is related to the availability of gas for cell growth and maintenance, which in turn relates to the production of desired biomolecules. Proper aeration contributes to the efficiency of the process and the transfer of mass and heat in bioreactors (CERRI et al., 2005).

The volumetric oxygen transfer coefficient, known by the acronym k_La, is one of the main performance parameters of bioreactors, as it is related to how favorable the oxygen transfer within the system is. This coefficient represents the rate at which oxygen is transferred from gas to liquid, per unit volume and time, under specific operating conditions of the bioreactor (CERRI et al., 2005).

Several studies have been dedicated to estimating k_La in bioreactors and understanding its relationship with other operational and design variables. Research, such as that conducted by Thomasi (2010), has investigated the influences of parameters such as agitation, aeration, bioreactor geometry, and properties of the culture medium on the value of k_La.

Modeling these relationships often requires the use of advanced nonlinear regression techniques. This approach is essential for capturing effects in the relationships between variables that cannot be adequately described by simple linear models (ZEVIANI, 2013). This flexibility is crucial when dealing with complex systems, where the behavior of k_La can be highly dependent on multiple operational and environmental factors.

Industry 4.0, with its premise of automating and connecting equipment and processes in a network, constantly demands the automation of engineering procedures and calculations (MOTA et al., 2021). In this context, the development of automation of calculations in MS Excel® for processing laboratory data involving nonlinear regression is proposed, as well as enabling the calculation of k_La. The automation of calculations through spreadsheets has proven to be an effective tool for simplifying and expediting analyses. It's possible to integrate k_La values with other relevant variables such as agitation and aeration, thereby facilitating decision-making and experiment planning.

This work aimed to automate the estimation of the k_La in agitated and aerated bioreactors, operating with water and air. It was used an Excel spreadsheet containing a nonlinear regression of a k_La empirical model on experimental data of agitation and aeration obtained from Thomasi (2010). It was intended to provide computational resources on these complex relationships and facilitating the estimation of parameters in bioprocesses.

2 MATERIAL & METHODS

This work presents an approach to calculate the oxygen mass transfer coefficient (k_La) in agitated and aerated bioreactors. For this purpose, na empirical mathematical model that calculates k_La from agitation (N) and aeration (ϕ) was adapted from Thomasi (2010) and it is represented by Equation (1). Experimental data was also an adaption from Thomasi (2010) values. The implementation of this model was carried out using Excel® software, ran on a DESKTOP-MV6KTP1 model notebook equipped with an Intel(R) Celeron(R) CPU N3060 1.60GHz processor and 4.00 GB of RAM.

$$k_La = \alpha . \phi^{\beta} . N^{\gamma} \tag{1}$$

Nonlinear regression, as demonstrated in Equation 2, requires more specialized computational resources and longer processing time. This is because, unlike linear regression, which has direct analytical solutions, nonlinear regression typically requires the use of iterative algorithms to estimate model parameters. These algorithms can be more complex and require a specific comptacional routine. The omega (Ω) function in Equation 2 must be minimized in order to achieve the empirical parameters α, β and γ.

$$\Omega = \sum_{i=1}^{N} (kLa_{EXP,i} - kLa_{MOD,i})^2 \tag{2}$$

3 RESULTS & DISCUSSION

The Figure 1 below shows the spreadsheet containing the start of the calculation. All the three values of α, β and γ are initial guesses.

Aeration - ϕ (min^{-1})	Agitation - N (rpm)	k_La_{exp} (s^{-1})	k_La_{mod} (s^{-1})	$(k_La_{exp} - k_La_{mod})^2$
0,2	600	0,0312	5,4772	29,66
0,4	600	0,0380	7,7460	59,41
0,8	600	0,0453	10,9545	119,01
0,2	800	0,0502	6,3246	39,37
0,4	800	0,0555	8,9443	79,01
0,8	800	0,0636	12,6491	158,40
0,2	1000	0,0641	7,0711	49,10
0,4	1000	0,0657	10,0000	98,69
0,8	1000	0,0729	14,1421	197,94

$$k_La = \alpha . \phi^{\beta} . N^{\gamma}$$

Empirical parameters	
α	0,5
β	0,5
γ	0,5

Sum of squares of residuals (Ω)
830,59

R^2	0,44

Figure 1 Interface of the spreadsheet for Kla calculation

The mathematical model in Excel for calculating k_La operates iteractively, allowing the user to input initial guesses for the parameters α, β and γ . Additionally, it offers the flexibility to adjust experimental data as needed. Afterward, the user can use Excel's Solver, whose interface is shown in Figure 2, to initiate the optimization process for the nonlinear regression.

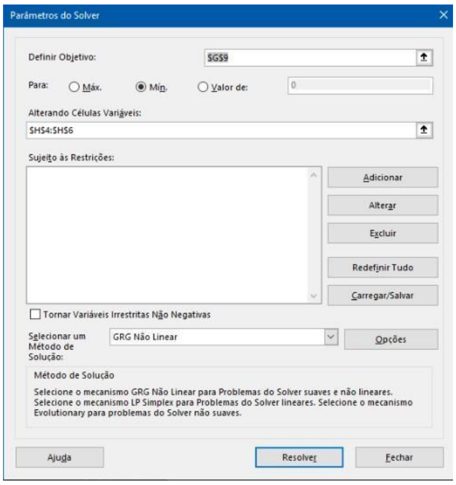

Figure 2 Solver graphical interface

The Solver employes multivariate parametric optimization algorithms, specifically the Generalized Reduced Gradient (GRG) method. It seeks the values of α, β, and γ that minimize the value of the function Ω, as defined in Equation 2. The solution should provide a reasonable coefficient of determination R^2 (above 0.9), indicating that the nonlinear model, with these parameter values, can be used for estimating k_La within a reasonable range of agitation and aeration values.

The results of the k_La calculation on Excel are presented in Figure 3. As stated before, the adjusted values of the parameters α, β, and γ were obtained by minimizing the function omega, as defined in Equation 2. The coefficient of determination R^2 is greater than 0.96. This high R^2 value demonstrates an excellent fit of the model on the experimental data, confirming the nonlinear model's ability to accurately predict k_La values for different agitation and aeration conditions.

It is worth noting that the model developed to estimate the k_La value can be employed in operational conditions not included in the original experimental data. For example, the model can be applied to predict k_La under specific situations, such as agitation at 500 rpm and aeration at 0.6 min^{-1}. These results highlight the robustness and effectiveness of the proposed model, providing a useful tool for k_La prediction in a variety of operational scenarios in research and industry. Due to the fact that the model is nonlinear with several local minima of the omega objective function, the Solver needed to be activated several times to obtain the global minimum.

Aeration - ϕ (min^{-1})	Agitation - N (rpm)	k_La_{exp} (s^{-1})	k_La_{mod} (s^{-1})	$(k_La_{exp} - k_La_{mod})^2$
0,2	600	0,0312	0,0373	0,00
0,4	600	0,0380	0,0411	0,00
0,8	600	0,0453	0,0452	0,00
0,2	800	0,0502	0,0490	0,00
0,4	800	0,0555	0,0539	0,00
0,8	800	0,0636	0,0594	0,00
0,2	1000	0,0641	0,0605	0,00
0,4	1000	0,0657	0,0666	0,00
0,8	1000	0,0729	0,0734	0,00

$$k_La = \alpha . \phi^{\beta} . N^{\gamma}$$

Empirical parameters	
α	0,00010852
β	0,13923719
γ	0,94783812

Sum of squares of residuals (Ω)
0,00

R^2	0,96

Figure 3 Graphical interface of the spreadsheet for kLa calculation

4 CONCLUSION

This work aimed to automate the estimation of k_La in bioreactors using an Excel spreadsheet. A mathematical model, with two input variables (agitation and aeration) and three adjustable parameters (α, β, and γ), is applied through nonlinear regression to the provided experimental data. The automation simplifies the process, although the complexity of the model may cause convergence issues.

In summary, the detailed analysis conducted during the spreadsheet development demonstrated that the process in question is significantly optimized and effective. Simply activating the Solver after inputting the initial values for α, β, and γ provides an efficient approach. However, it is crucial to note that the convergence of the system may be affected by the chosen initial values, as reflected by a coefficient of determination (R^2) below 0.9. It's prudent to be aware of the possibility of requiring multiple Solver executions to achieve a satisfactory solution.

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