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Kinetic models and parameters estimation study of biomass and ethanol production from inulin by *Pichia caribbica* (KC977491)

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The growth kinetics and modeling of ethanol production from inulin by *Pichia caribbica* (KC977491) were studied in a batch system. Unstructured models were proposed using the *logistic equation* for growth, the *Luedeking-Piret* equation for ethanol production and modified *Leudeking-Piret* model for substrate consumption. Kinetic parameters (X_0, μ_m, m, n, p and q) were determined by nonlinear regression, using Levenberg-Marquart method implemented in a Mathcad program. Since the production of ethanol was associated with *P. caribbica* cell growth, a good agreement between model predictions and experimental data was obtained. Indeed, significant R^2 values of 0.91, 0.96, and 0.95 were observed for biomass, ethanol production and substrate consumption, respectively. Furthermore, analysis of variance (ANOVA) was also used to validate the proposed models. According to the obtained results, the predicted kinetic values and experimental data agreed well. Finally, it is possible to predict the development of *P. caribbica* using these models.

Key words: *Pichia caribbica*, inulin, bioethanol, numerical simulation.

INTRODUCTION

Bio-ethanol being a clean, safe and renewable resource has been considered as a potential alternative to the ever-decreasing fossil fuels (Martin et al., 2002; Wyman, 1994). Various substrates are available for the ethanol production but their choice depends on the cost and the production process profitability (Quintero et al., 2015). Most of the industrial processes are currently based on hexose carbohydrates from starch or sucrose-containing biomass (Kumari and Pramanik, 2012; Duhan et al., 2013). Among these substrates, inulin has received a major interest since it is present as a carbohydrate reserve in a large variety of plant roots and tubers such

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as Jerusalem artichoke (*Helianthus tuberosus*), chicory (*Cichorium intibus*), dahlia (*Dahlia pintana*) and dandelion (*Taraxacum officinal*) (Cabezas et al., 2002; Singh and Bhermi, 2008).

The bioconversion of biomass to ethanol is executed following two steps: hydrolysis of solid substrate to reducing sugars and the fermentation by yeast or bacteria to convert fermentable sugars to ethanol (Torget et al., 1991; Kara Ali et al., 2013). The bioprocess which involves microbial cells is complex in nature and is a critical step for better yield achievement (Mahajan et al., 2010). Behavior of the microbial system can be evaluated by the development of kinetic models and experimental designs (Voll et al., 2011; Xu et al., 2011). The use of kinetic models is interesting to reduce the number of experiments needed to assess the extreme operation conditions and for optimization and control (Lin and Tanaka, 2006). Two different categories of mathematical model; the structured and unstructured models, can be considered for modeling a microbial process (Nielsen et al., 1991; Gadjil and Venkatesh, 1997; Murat and Ferda, 1999; Lei et al., 2001). Structured models take into account some basic aspects of cell structure, function and composition. By contrast, in unstructured models, only a global parameter such as cell mass is employed to describe the biological system, cell growth or product formation. Usually, theoretical models have been proposed and used for the elucidation of metabolic steps and for the calculation of kinetic parameters (Ghosh et al., 2012). To our knowledge, this is the first report to study *Pichia caribbica* (KC977491) growth kinetics and the modeling of ethanol production from inulin by this yeast strain. The main objectives were to: (I) Produce biomass and ethanol by *P. caribbica* (KC977491) in a batch system; (II) Propose unstructured models for growth and ethanol production to predict a process of fermentation by *P. caribbica* (KC977491); (III) Validate the obtained results between the theoretical unstructured models and experimental data.

MATERIALS AND METHODS

Yeast and culture media

The yeast *P. caribbica* (KC977491) used in this work was isolated from arid soil area and identified previously (Kara Ali et al., 2013). This strain was grown in a medium containing 100 ml of YPD (yeast extract, 10 g/L; peptone, 20 g/L; glucose, 20 g/L), incubated at 30°C for 24 h under agitation of 150 rpm. Cells (11 ml/ DO_{600} = 9) were further transferred into flasks containing 100 ml of the fermentation medium composed of (g/L): inulin 30, yeast extract 4, peptone 4 and initial pH 5. The culture was incubated at 37°C under agitation of 150 rpm for 5 days.

Assay techniques

Fructose and ethanol analysis

After the fermentation period, the biomass was separated from medium using centrifugation technique at 5,000 rpm and 4°C for 5 min. The supernatant were cleaned by cellulose acetate membrane (0.2 µm, Minisart Sartorius), then, the fructose consumption and ethanol production were investigated by HPLC under subsequent conditions following the CWBI protocol: Agilent 1110 series (HP Chemstation software) with a Supelcogel C-610H column preceded by a Supelguard H pre-column (oven temperature 40°C). 0.1% H_3PO_4 solution (in milliQ water) was used as the isocratic mobile phase at a flow rate of 0.5 ml $min^{-}1$ and a differential refractive index detector (RID) was heated at 35°C. The process lasted for 35 min at a maximum pressure of 60 bars. The standard curves were prepared using the different concentrations of fructose and ethanol (from 0.125 to 4 g/l) for both of them.

Cell mass analysis

The biomass concentration of *P. caribbica* was determined by the dry weight method (Buono and Erickson, 1985). The cells obtained as mentioned previously were washed twice with water and dried by incubation at 105°C until constant weight.

Mathematical approach

Kinetic models

A mathematical model is a collection of mathematical relationships which describe a process. Practically in each model, a simplification of the real process is made. Mathematical models have proven to be very useful in gaining insight in processes (Philippidis et al.,1992; Santos et al., 2012) for instance by comparing different models and their ability to describe experimental data (Auer and Thyrion, 2002; Amribt et al., 2013). Furthermore, models have been successfully used for optimization or control of processes (Yip and Marlin, 2004). Different types of models can be distinguished for the different goals and depending on the available information. Some characteristics which are of interest for modeling bioprocesses are illustrated in Table 1.

Microbial growth kinetics

The logistic equation is a very common unstructured model in macroscopic description of cell growth processes (Parente and Hill, 1992). It accounts for the inhibition of growth which occurs in many batch processes (Benkortbi et al., 2007). In this study, the logistic equation was adapted to investigate *P. caribbica* (KC977491) growth. It can be described as follows:

$$\frac{dX}{dt} = \mu_m X\left(1 - \frac{X}{X_m}\right) \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where X is the biomass concentration (g/L), X_m is the maximum biomass concentration (g/L), μ_m is the maximum growth rate (h^{-1}) and t is the time (h). The integration of the biomass production rate with the use of the initial condition (at t = 0, X = X_0) gives a sigmoidal variation of X as a function of t which may represent both an exponential and a stationary phase (Equation 2):

$$X = \frac{X_0 e^{\mu m t}}{\{1-(X_0/X_m)(1-e^{\mu m t})\}} \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

Ethanol production kinetics

The kinetic of product formation was based on the *Luedeking-Piret* model, initially developed for the fermentation of gluconic acid by different types of microorganisms (Luedeking and Piret, 1959). It is

Table 1. Some growth models reported in the literature.

Kinetic models	Symbols used	Authors
$\mu = \mu_{max}\frac{S}{K_S + S + S^2/K_i}$	**μ**: is the specific growth rate (h^{-1}) **μ_{max}:** is the maximum specific growth rate (h^{-1}) **S**: is the substrate concentration (g/L) **K_S**: is the Substrate saturation constant (g/L) **K_i**: is the substrate inhibition constant (g/L)	Jackson and Edwards (1975)
$\mu = \mu_{max}\frac{S^n}{S^n + K_S}$	**n**=Constant of the process	Moser (1983)
$\mu = \mu_{max}\frac{S}{S + K_S}\{1 - \frac{S}{S_m}\}^n$	**S_m** : is the maximum substrate concentration above which growth is completely inhibited (g/L) **n:** is an empirical constant	Luong (1987)
$\mu = \mu_{max}\frac{S}{K_m + \left(1 + \frac{P}{K_p}\right)S}$	**K_m**: is the Michaelis constant **K_p**: is the lactate inhibition constant for cell growth (g/L) **P** : is the product concentration (g/L)	Ishizaki and Ohta (1989)
$\mu = \mu_{max}\left(\frac{S}{S + K_S}\right).\left(\frac{K_i}{S + K_i}\right).(1 + \frac{P - K_i}{P_m - P_i})$	**K_i** : is the substrate inhibition constant (g/L) **P_m**: is the maximum inhibitory lactate concentration (g/L) **P_i** : is the threshold level of lactate before an inhibitory effect (g/L)	Boonmee et al. (2003)
$\mu = \mu_{max}\left(1 - \frac{X}{X_{max}}\right)^f.\left(1 - \frac{P}{P_{max}}\right)^h$	**f**: is a parameter related to the toxic power for biomass **h**: is a parameter related to the inhibitory product	Altiok et al. (2006)

an unstructured model, which combines growth and non-growth associated contribution towards product formation. Thus, the product formation depends upon the growth rate (dX/dt) and instantaneous biomass concentration (X) (Equation 3).

$$\frac{dP}{dt} = m\frac{dX}{dt} + nX \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

Where "P" is the product concentration (g/L), "m" (g/g) and "n" (1/h) are the *Luedeking-Piret* equation parameters for growth and non-growth associated product formation respectively. A carbon substrate is used to form cellular material and metabolic products as well as for the cellular maintenance.

The product formation rate equation (Equation 4) can be expressed by integrating Equation 3 using Equation 2 with the initial conditions P = 0 at t = 0:

$$p = mX_0\left\{\frac{e^{\mu m t}}{\left\{1-\left(\frac{X_0}{X_m}\right)(1-e^{\mu m t})\right\}}\right\} + n\frac{X_m}{\mu_m}\ln\{1 - \frac{X_0}{X_m}(1 - e^{\mu_m t}) \quad \ldots\ldots \quad (4)$$

Substrate consumption kinetics

Kinetics substrate consumption can be described as follows:

$$-\frac{dS}{dt} = p\frac{dX}{dt} + qX \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

Where, p= $1/Y_{X/S}$ (g/g) and q is maintenance coefficient (1/h). Equation (5) is rearranged as follows:

$$-dS = p\,dX + q\int X(t)\,dt \quad \ldots\ldots\ldots\ldots\ldots \quad (6)$$

Substituting Equation 2 in Equation 6 and integrating with initial conditions ($S = S_0$; t = 0) give the following equation:

$$S = S_0 - pX_0\left\{\frac{e^{\mu m t}}{\left\{1-\left(\frac{X_0}{X_m}\right)(1-e^{\mu m t})\right\}} - 1\right\} - q\frac{X_m}{\mu_m}\ln\{1 - \frac{X_0}{X_m}(1 - e^{\mu_m t}) \quad (7)$$

Model of parameters estimation

Kinetic models which describe the microbial process on a particular substrate are nonlinear which in turn makes parameter estimation relatively difficult. Though few models can be linear, their utilization is limited because of the error associated with the transformation of dependent variable and therefore resulted in inaccurate parameter estimations. Hence, the nonlinear least-squares regression is often used to estimate kinetic parameters from nonlinear expressions. The parameter estimation obtained from the linear kinetics expressions can be used as initial estimation in the iterative nonlinear least-squares regression using the least square curve fit in order to fit the models developed and to estimate the parameters (substrate consumption, biomass and product formation).

Fitting procedures and parametric estimations calculated from the results were carried out by minimization of the sum of quadratic differences between experimental and model-predicted values, using the nonlinear least-squares Levenberg-Marquardt method (Marquardt, 1961) with a developed Mathcad program. The coefficient of determination R^2 was estimated to assess the accuracy of the estimated parameters achieved by fitting the experimental values to the proposed mathematical models. If R^2 approximate to 1, this coefficient justifies an excellent consistency of these equations (Annuar et al., 2008). Furthermore, the ANOVA

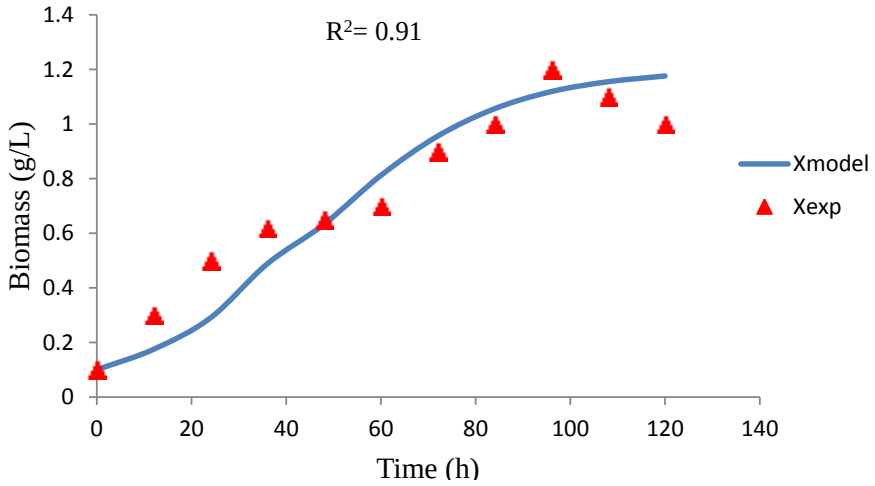

Figure 1. Comparison between predicted and experimental growth kinetics.

Table 2. Analysis of variance for the growth model.

Source of variation	Sum of squares (SS)	Degree of freedom (DF)	Mean square (MS)	F-value	Critical F value (Fcrit)
Regression	1.68333955	1	1.68333955	**101.694608**	**5.11735501**
Error	0.148976	9	0.01655289		
Total	1.83231555	10	0.18323155		

test was also carried out to evaluate the accuracy of the models. The two basic data measures of variation sources are: Variation due to the regression and variation due to residuals. The statistical F-value is a ratio of the relative regression variation/relative residual variation. Thus, if F value is significantly greater than critical F value, this indicates that the regression model is accepted.

RESULTS AND DISCUSSION

Many researchers have attempted to model yeast fermentation and different approaches have been considered (Aiba et al., 1968; Ghose and Tyagi, 1979; Hoppe and Hansford, 1982). However, it is not easy to choose a single best fitting. In order to choose the best model it is important to consider how well it describes the transition from exponential to stationary phase of the process model (Kostov et al., 2012).

Microbial growth

The logistic equation of biomass growth (Equation 2) is used to fit the batch fermentation growth data. Figure 1 compares the predictive model related to cell growth with the experimental data recorded during batch fermentation of *P. caribbica* (KC977491). The maximum biomass concentration (1.2 g/L) was obtained after 96 h of fermentation and a complete depletion of fructose in the medium. In addition, a Levenberg-Maquardt method is used in Mathcad to obtain μ_{max} by minimizing the difference between experimental growth and calculated one using Equation 2. The program gives the value of μ_{max} = 0.052 h^{-1}. This value is relatively low compared to those reported in several studies. Indeed, the μ_{max} value from *Saccharomyces diastaticus* (strain LORRE316) was in the interval of 0.1 and 2 h^{-1} with optimum of 0.9 h^{-1} (Wang and Sheu, 2000). Otherwise, the production of ethanol using *Saccharomyces cerevisiae* (ATCC4126) has showed a μ_{max} of 0.28 h^{-1} (Bazua and Wilke, 1977). Moreover, the μ_{max} related to *S. cerevisiae* ITD00196 reached 0.58 h^{-1} in a batch system (Jiménez-Islas et al., 2014). The variation of this parameter may be explained by the type of microorganisms, the substrate consumption and the environmental conditions.

The analysis of Figure 1 shows that there is an adequacy between the experimental data and those predicted (R^2 = 0.91). Also, the analysis of variance (ANOVA) results for the growth model are presented in the Table 2. F-value (101.694608) is greater than critical F value (5.11735501), which proved the acceptance of this test. On the basis of the obtained results, a good correlation coefficient (R^2 = 0.91) and a significant ANOVA test shows that the proposed logistic model is adequate to explain the sigmoidal profile of the yeast growth. According to the literature, the study proposed by Dodic et al. (2012), was carried out used logistic

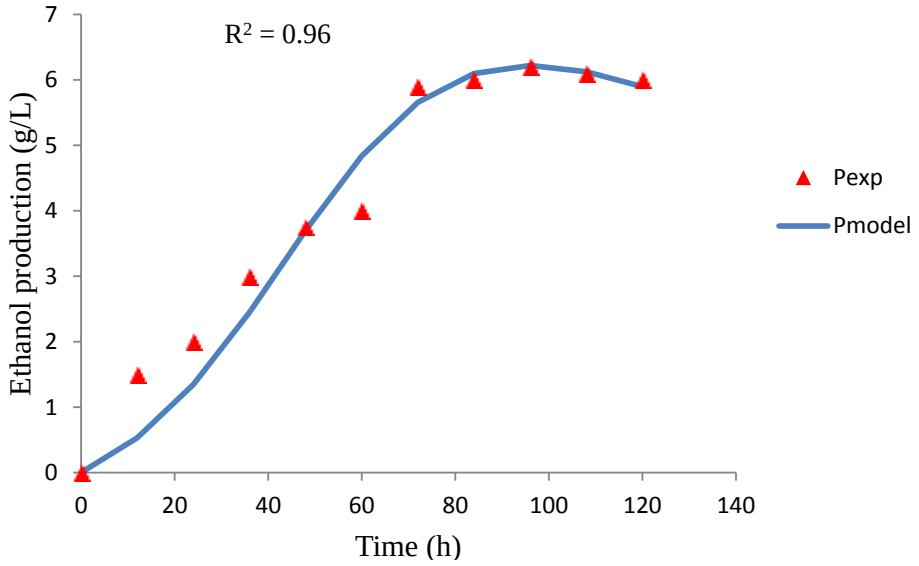

Figure 2. Comparison between predicted and experimental ethanol formation kinetics.

empirical kinetic model to describe batch fermentation of raw juice. The results show a good agreement with experimental data (R^2 = 0.99), thus, the logistic equation was found to be an appropriate kinetic model for successfully describing yeast cell growth in batch fermentation of raw juice system.

Ethanol production

The Equation 4 is applied to simulate the product formation, thus, Figure 2 shows the comparison of predicted model and experimental data for ethanol production by *P. caribbica*. The ethanol concentration reached its highest values in 96 h (6.2 g/L) from experimental data. Using the same procedure as above, the programs returns the values of 7.725 g/g for the growth associated rate constant 'm' and - 0.088 1/h for the non-growth associated rate constant 'n'.

These results show that the degree of growth associated constant rate 'm' is much greater than the non-growth associated rate constant 'n'. Similar results were achieved by Jiménez-islas et al. (2014). The simultaneous cell growth and ethanol production suggest that it is a growth-associated product. This result is in accordance with that of Thatipamala et al. (1992) who found that when using glucose as substrate, ethanol and biomass were produced simultaneously. In contrast, Ahmad et al. (2011) performed a series of experiments to show that ethanol batch fermentation is a non-growth-associated process that uses glucose. However, these authors used a forced aeration of 0.075 vvm in the culture medium and an agitation speed of 75 rpm, whereas, in our experiments, air was only transferred naturally from air phase to liquid phase. This discrepancy can be explained by the fact that when oxygen is absent, *S. cerevisiae* produces ethanol in order to reoxidize $NADH^+$ to NAD^+; however, in presence of oxygen, it acts as a final electron acceptor.

Moreover, the analysis of Figure 2 shows that there is a good agreement between model predictions and experimental data, effectively a correlation coefficient (R^2) value for ethanol production was 0.96. The analysis of variance (ANOVA) results for the ethanol production model are presented in the Table 3.

ANOVA of the regression model (Table 3) demonstrates the fitness of this model due to the F-value of 95.485816 greater than critical F value (4.4589701).

A good R^2 (0.96) for ethanol production and a significant ANOVA test confirmed that the model provides the relevant prediction The same results were obtained in several researches using the same model (Annuar et al., 2008). In addition, Jiménez-Islas et al. (2014) found the effects of pH and temperature on ethanol production from red beet juice by two strains: *S. cerevisiae* ITD00196 and *S. cerevisiae* ATCC 9763. This study was predicted by using the *Luedeking-Piret* model for ethanol production and validated only by a correlation coefficient (R^2). The authors concluded that this model was found to describe quantitatively this study due to a high level of correlation (R^2 = 0.97).

Substrate consumption

In this study, Equation 7 is applied to predict the consumption of the fructose substrate. However, *P. caribbica* is able to convert inulin to fructose, which was converted, after that, to ethanol. The hydrolysis of inulin in fructose by inulinase enzyme secreted by this yeast

Table 3. Analysis of variance (ANOVA) for the ethanol production model.

Source of variation	Sum of squares(SS)	Degree of freedom (DF)	Mean square (MS)	F-value	Critical F value (Fcrit)
Regression	58.5522127	2	29.2761064	**95.485816**	**4.45897011**
Error	2.452813	8	0.30660163		
Total	61.0050257	10	6.10050257		

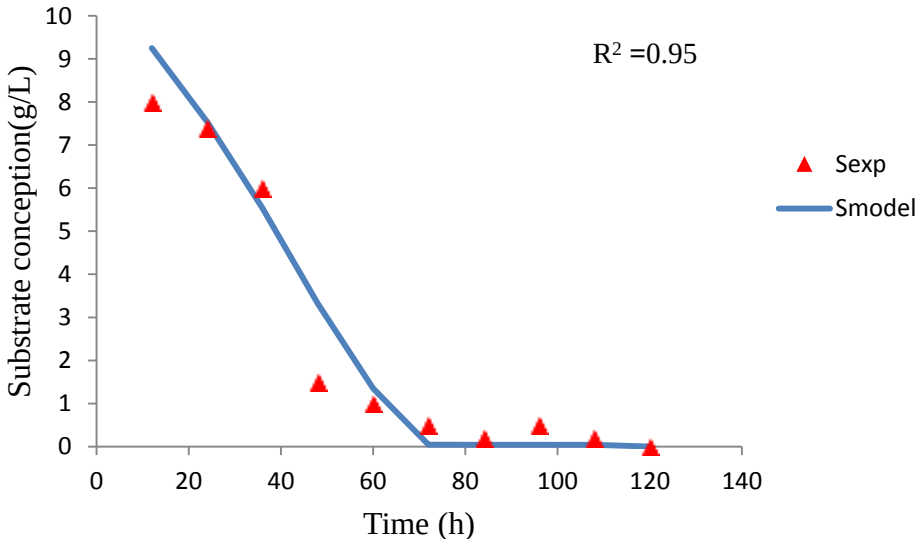

Figure 3. Comparison between predicted and experimental fructose consumption kinetics.

Table 4. Analysis of variance (ANOVA) for the substrate consumption model.

Source of variation	Sum of squares (SS)	Degree of freedom (DF)	Mean square (MS)	F-value	Critical F value (Fcrit)
Regression	159.57095	2	79.7854749	**91.2945575**	**4.45897011**
Error	6.991477	8	0.87393463		
Total	166.562427	10	16.6562427		

was previously studied using two medium containing separately pure chicory inulin and artichoke extract (Kara Ali et al., 2016).

The comparison of predicted model and experimental data for substrate consumption modeling during batch fermentation by *P. caribbica* is shown in Figure 3.

In the beginning, the initial fructose concentration was 8 g/L after 12 h (conversion inulin into fructose by *P. caribbica*). Biomass concentration and ethanol production (Figures 1 and 2) increased with a decrease in the fructose level (Figure 3). Fructose consumption had been gradually reduced from the beginning of the fermentation until t_{120h} when it ran out. In addition, the program used in this study, gives the values of p =14.735 g/g and q = -0.077 1/h, these values were calculated in another kinetic study (Pazouki et al., 2008). Thus, the bio-decolorization of distillery effluent in a batch culture was conducted using *Aspergillus fumigatus*. A simple model was proposed using the *Leudeking-Piret* kinetics for substrate utilization, the equation coefficients calculated were p = 1.41 (g/g) and q = 0.0007 (1/h). The difference between these values may be explained by the types of microorganism, fermentation period and the rate of substrate consumption to obtain the energy necessary for the maintenance of the cells in stationary phase.

It can be observed from Figure 3 that there is a good adequacy between model prediction and experimental data (R^2 = 0.95). The analysis of variance (ANOVA) results for the ethanol production model are presented in the Table 4. The F value (91.2945575) is larger than critical F value (4.45897011); this result clearly shown that, this model was applicable to this particular system (a good correlation coefficient R^2 and a significant ANOVA test). The experimental data reported by Oghome and

Kamalu (2012), using modified Leudeking-Piret model, were also studied; the correlation coefficients, R^2 and adjusted R^2 are 0.6849 and 0.9827 respectively, which indicates that this model fits the experimental data very well.

Conclusion

Microbial fermentation is complex and it is quite difficult to understand the complete details process. The model proposed in this study appears relevant to describe the biomass, ethanol production and substrate consumption versus fermentation time. The growth pattern followed the logistic model and the parameters were proved. Ethanol production was represented by *Luedeking-Piret* model; it was noticed that ethanol production by *P. caribbica* (KC977491) was growth associated. High significance of coefficient of determination (R^2) was observed with the experimental and predicted results. The statistical analyses using ANOVA were done by means of statistical F-value test which indicates the sufficiency of the regression models. Therefore, the models developed may be useful for controlling the growth, ethanol production and substrate consumption kinetics at large fermentation scale using this strain.

Conflict of Interests

The authors have not declared any conflict of interests.

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