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Comparison of ANN & RSM Approaches for Optimum Production of γ-Decalactone

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Abstract**:** γ-Decalactone is an important flavor compound widely used in food, diary and fragrances. Previously it was produced from fruits through chemical synthesis. Due to increase in demand for natural products by consumers, it has gained interest for its production through biotechnological way. The present study focusses on fermentation variables optimization for the production of γ-decalactone using *Sporidiobolus salmonicolor* via Response surface methodologies (RSM) and Artificial neural networks (ANN) using castor oil as substrate. The prediction abilities of RSM and ANN were compared based on error parameters namely Mean absolute error (MAE), Root mean square error (RMSE), chi-square (χ^2) and correlation coefficient (R^2) to suggest the best approach for modeling. The response variable (γ-decalactone production) was modelled and optimized as a function of four input variables (castor oil percentage, pH, incubation time and temperature). Training of ANN network was performed using a multilayer feed forward architecture with same experimental datasets used in RSM. Model predictions of both approaches were compared with the experimental values and reported that these are in good close agreement. The highest production of γ-decalactone 72.73 mg/l obtained at an optimum conditions of castor oil -29.68 %, pH -5.32, incubation time -99.89 h and temperature -23.22^{0}C. Hence, results were beneficial in using appropriately trained ANN over RSM for nonlinear fermentation systems.

Keywords**:** RSM, ANN, Fermentation, γ-decalactone and *Sporidiobolus salmonicolor*

γ-Decalactone is an important industrial flavour compound with a peachy aroma. It is approved as a food additive by FDA (Hamideh et al 2013). It has been widely used in dairy products, food, fragrances and beverages (Adelaide et al 2016, Jung-Ung et al 2013) and was produced from fruits through chemical synthesis, however, due to the increase in demand for natural flavors and has gained interest in producing through biotechnological processes using microorganisms (Dayana et al 2017). It is highly toxic for the microorganisms used for its production and accumulation in the medium depends on the difference between the formation and consumption rates by the yeast cells since lactones are toxic to the producing cells. In the last two decades, researchers have focused on the selection of suitable yeast strains, substrates, preliminary optimization of fermentation conditions, β-oxidation metabolic pathways, use of different mutant strains and mode of fermenter operation to enhance growth and production of γ-decalactone (Dayana et al 2017, Jolanta et al 2020, Eko et al 2020). However, there are few reports on the statistical optimization of fermentation conditions for γ-decalactone production. The aim of this work is to enhance γ-decalactone production and optimization of fermentation variables using statistical methods.

Castor oil is one of the main substrates used to produce γ-decalactone and it contains 86% of ricinoleic acid (Cao et al 2014, Dayana et al 2017). The ricinoleic acid transforms into γ-decalactone by yeast cells through the β-oxidation pathway (Adelaide et al 2016). The main limitation of industrial process development is lactone toxicity towards growing yeast cells. After a few hours of batch fermentation, yeast cells consume decalactone as a carbon source when a substrate is completely exhausted. Thus, results in a lower yield of γ-decalactone. One factor at a time (OFAT) method is laborious, time taken, unable to predict interaction effects and rarely guaranties the estimation of optimum conditions. The limitations of OFAT can overcome with the help of empirical methods, namely, RSM and ANN, in which levels of all desired factors can be varied simultaneously. RSM has been widely used in the medium optimization for fermentation systems (Suganthi et al 2015, Taswar et al 2017). RSM is a combination of several statistical techniques applied for model development, experimental design, determination of the influence of factors, and finding optimum values (Kalil et al 2000). The output responses in RSM are fitted according to second order polynomial equations. Thus, RSM can be considered to be the best choice for fermentation systems optimization. Recently, ANN has also been developed as an effective method for modeling of

nonlinear systems due to its ability to learn from historical data and genetic structure (Kiran et al 2005). ANN does not need a predefined fitting function. It has the characteristics of universal approximation (Kiran et al 2008). Moreover, ANN provides better sensitivity analysis than RSM. The major objective of the present study was to maximize γ-decalactone production by *Sporidiobolus salmonicolor* using castor oil as substrate and to analyze modelling efficiencies of RSM and ANN for optimum production of γ-decalactone.

MATERIAL AND METHODS

Inoculum and culture conditions : *Sporidiobolus salmonicolor* (MTCC No. 485) was obtained from IMTECH, Chandigarh, India. It was rejuvenated on YM agar media at 30^{0}C for 2 days. A 3 ml of grown suspension was taken aseptically to a Erlenmeyer flask (250 ml) consists of 100 ml fermentation medium (castor oil-30 %, NH_4Cl-3 g/l, $CaCl_2.2H_2O$-1 g/l, KH_2PO_4-2 g/l, Tween 80-1 g/l, $FeSO_4.7H_2O$-0.5 g/l and $MgSO_4.7H_2O$-1 g/l) and incubated in rotating shaker at 180 rpm and 30^{0}C for 18–19 h until the cells enter the late exponential phase to obtain 10^6-10^7 cells/ml.

Biomass estimation: The biomass concentration was determined with the help of Neubauer's improved counting chamber method (Recombigen Laboratories, New Delhi) (Mather and Roberts 1998). The methylene blue method was used for estimating the viability of cells (Angelo and Donatella 1982).

Extraction and analysis of γ-decalactone: To estimate the lactones in the grown culture followed the method described by (Nelma et al 2011) after centrifugation, 2 mL of supernatant was taken and pH was varied to 2 with 1 N HCl. The lactone extraction was done with 2 ml of diethyl ether through sixty gentle shakings. After the partition of liquid phases, the diethyl ether phase was isolated and examined by gas chromatography (Analytical Technologies Limited, Baroda, India; model: GC2979 Plus) with a capillary column (300mmx280mmx270mm) using a helium carrier gas. The temperatures of the split injector and detector were set as 250^{0}C and 300^{0}C, respectively. The oven temperature varied from 60^{0}C to 145^{0}C at a rate of 5^{0}C/min and 145^{0}C to 180^{0}C at 2^{0}C/min.

RSM modeling: In previous studies, Plackett-Burman experimental design was performed to screen influential parameters on γ-decalactone production. Among eleven factors screened, five factors such as castor oil percentage, pH, incubation time, inoculum size and temperature had shown most influential effect on γ-decalactone production (Venkata Narayana et al 2019). However, inoculum size was eliminated due to a high p-value and less standard effect. Thus, the remaining four factors were considered for further optimization using RSM and ANN in this study. RSM based central composite design was adopted to determine the optimum values of screened parameters for γ-decalactone production. The parameters were designated as castor oil percentage (X_1), pH (X_2), incubation time (X_3) and temperature (X_4) (Table 1). The central values allocated for screened parameters based on preliminary experiments of OFAT were castor oil 30 %, pH 5, incubation time 100 h, and temperature 22.5^{0}C. In CCD, design of experiments was planned with four variables and each in five levels (-2, -1, 0, 1, 2) (Table 2). A total of thirty triplicate experimental runs were conducted in a randomized order, of which sixteen cube, eight axial and six center points as per CCD. The input variables were coded as per the equation (1) (Jamil et al 2018)

$$x_i = \frac{X_i - X_0}{\Delta X_i} \qquad (1)$$

where x_i denotes the coded form of input variable X_i and X_0 is the real value of input variable at the center and ΔX_i is the increment.

The process efficiency was estimated by analyzing the output response variable (Y) in relation to the input variables as represented by equation (2) (Jamil et al 2018)

$$Y = f(X_1, X_2, ... X_K) + e \qquad (2)$$

Where $X_1, X_2, ...X_K$ are input variables and e is the error.

Experimental data was fitted with second order polynomial equation and model terms were evaluated with Design Expert 8.0.7.1 software. Quadratic model equation is represented as per equation (3) (Jamil et al 2018)

$$Y = \beta_0 + \sum_{i=1}^{K} \beta_i X_i + \sum_{i=1}^{K} \beta_{ii} X_{ii}^2 + \sum_{i=1}^{K-1} \sum_{j=2}^{K} \beta_{ij} X_i X_j + e \quad (3)$$

Where Y is the response (γ-decalactone production), X_i

Table 1. Independent parameters (input variables) levels and ranges used in DOE

Independent parameters	Symbol	Levels and range				
		-2	-1	0	+1	+2
Castor oil (%)	X_1	10	20	30	40	50
pH	X_2	7	6	5	4	3
Incubation time (hr)	X_3	80	90	100	110	120
Temperature (^{0}C)	X_4	17.5	20	22.5	25	27.5

and X_j are coded input variables, β_0 is intercept & β_i, β_{ii}, β_{ij} are linear, square and interactive coefficients, respectively; k represents number of factors and *e* is the error, which is the difference of measured and observed values.

Quadratic model performance was examined with reference to R^2, predicted R^2 and adjusted R^2. The significance of model terms was confirmed with ANOVA. Factors interaction on the response was predicted from contour plots generated from regression models.

ANN modeling: The ANN feed forward architecture was employed to develop a nonlinear model between the output variable (γ-decalactone production) and four input variables (castor oil percentage, pH, incubation time and temperature) for the same data sets used in RSM. The input player consists of four neurons (input variables), while the output layer contains one neuron (response variable). The training of ANN network was performed with TRAIN tool using MATLAB 9.2 R2017a version. The process of data occurs in the forward direction from input to the output layers. The input data were scaled up by input neurons and then transferred to hidden layer through several weights. The weighted inputs are summed up via hidden layer neurons together with bias

Table 2. CCD DOE experimental runs along with experimental and predicted values of RSM and ANN for γ-decalactone production by S*poridiobolus salmonicolor*

Run No.	Castor oil % (X_1)	pH (X_2)	Incubation time (hr) (X_3)	Temperature (°C) (X_4)	Experimental γ-decalactone production (mg/L)	Predicted γ-decalactone production (mg/L)	
						RSM	ANN
1	30	5	120	22.5	47.38	46.60	46.98
2	20	6	90	20	34.29	34.96	34.32
3	40	6	110	25	44.67	45.15	44.81
4	30	5	100	27.5	50.36	50.28	50.42
5	20	6	90	25	43.58	43.16	43.52
6	30	3	100	22.5	38.95	39.61	38.73
7	40	6	110	20	28.94	29.03	28.99
8	20	6	110	25	47.29	47.49	47.01
9	30	5	100	22.5	73.23	71.74	72.67
10	40	4	90	25	35.68	34.59	36.70
11	30	5	100	22.5	69.83	71.74	71.27
12	30	5	100	22.5	71.68	71.74	71.48
13	40	6	90	25	50.27	51.17	50.27
14	50	5	100	22.5	8.25	8.28	8.26
15	30	5	80	22.5	46.74	47.10	46.92
16	20	4	110	25	38.35	38.77	38.44
17	20	4	110	20	42.75	42.27	44.96
18	20	6	110	20	37.74	38.83	37.92
19	30	5	100	22.5	70.23	71.74	71.23
20	30	5	100	22.5	72.64	71.74	73.79
21	40	4	90	20	30.85	31.08	30.92
22	30	5	100	22.5	72.83	71.74	71.92
23	10	5	100	22.5	16.73	16.28	17.86
24	40	6	90	20	35.93	35.51	35.72
25	30	7	100	22.5	53.83	52.75	53.52
26	30	5	100	17.5	38.46	38.11	38.36
27	20	4	90	20	37.23	36.75	37.12
28	40	4	110	25	30.47	30.22	30.10
29	20	4	90	25	32.46	32.79	32.62
30	40	4	110	20	25.83	26.25	25.97

as per equation (4) (Kiran et al 2008)

$$SUM = \sum X_i W_{ij} + \theta_j \qquad (4)$$

Where X_i is the input parameter, θ_j is bias and W_{ij} is connection weight.

The output-weighted sum is transferred to an activation function f (sum) as per equation (5) (Kiran et al 2008)

$$f(sum) = \frac{1}{1 + \exp(-sum)} \qquad (5)$$

In ANN training, predefined error in minimized by controlling the weights. The root-mean-squared error (RSME) is calculated as per the equation (6) (Kalil et al 2000)

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}\sum_{n=1}^{M}(y_n^i - \widehat{y_n^i})^2}{MN}} \qquad (6)$$

Here 'i' is the pattern index, N is the no. of patterns, M is the output nodes number and y^i_n & y^i_n are the target and predicted responses of n^{th} node, respectively.

Comparison of ANN and RSM model abilities: The prediction capabilities and fitness of experimental data for both models were estimated by calculating RMSE (Kiran et al 2008), MAE (Youssefi et al 2009), χ^2 (Abuzer and Faruk, 2011) and R^2 (Rajendra et al 2009) as per the equations (6) – (9). In addition, the responses generated by ANN and RSM were represented in graphs against experiments as shown in Figure 2.

$$MAE = \frac{i}{n}\sum_{i=1}^{n}\left|Y_{i,e} - Y_{i,p}\right| \qquad (7)$$

$$\chi^2 = \sum_{i=1}^{n}\frac{(Y_{i,e} - Y_{i,p})^2}{Y_{i,p}} \qquad (8)$$

$$R^2 = \frac{\sum_{i=1}^{n}(Y_{i,p} - Y_{i,e})}{\sum_{i=1}^{n}(Y_{i,p} - Y_{i,e})^2} \qquad (9)$$

Where 'n' is no. of experiments, $Y_{i,e}$ is response for i^{th} experiment, $Y_{i,p}$ is predicted response for i^{th} experiment and Y_e is experimental average.

RESULTS AND DISCUSSION

RSM modelling: In this study, RSM modeling determines the influence of four input variables (castor oil %, pH, incubation time, and temperature) on γ-decalactone production. Thirty experimental runs were conducted using CCD, of which 16 cube points, 8 axial points and 6 central points. Model abilities were evaluated in terms of degrees of freedom, mean squares and sum of squares. RSM based CCD models were analyzed through the second-order polynomial regression equation and represented as follows

$Y = -1315.866 + 8.8486X_1 + 39.3135X_2 + 13.3129X_3 + 42.017X_4 + 0.1554X_1X_2 - 0.0258X_1X_3 + 0.0746X_1X_4 - 0.0413X_2X_3 + 1.2152X_2X_4 + 4.575E - 003X_3X_4 - 0.1486X^2_1 + 6.3906X^2_2 - 0.0622X^2_3 - 1.101X^2_4$ (10)

Where Y is the response (γ-decalactone production), while X_1, X_2, X_3 and X_4 are castor oil %, pH, incubation time, and temperature, respectively. Equation (10) was represented in terms of coded factors and is used to compare relative influence of factors with coefficient of factors (Busra et al 2020). In this case, temperature (X_4) was the most effective factor and followed by pH (X_2), incubation time (X_3) and castor oil (X_1). Castor oil was the least influential factor.

The fitness of quadratic model was analyzed, adjusted R^2 and the coefficient of determination (R^2). The model is significant and ensures good goodness of fit. The R^2 value of 0.9978 indicates that the model explains more than 99% of data variability. The predicted R^2 of 0.9927 is in reasonably good agreement with adjusted R^2 of 0.9958 and shows the model's high significance. The significance of model terms was determined based on p-values. A Lower p-value (<0.05) refers to the greater significance of respective parameters (Busra et al 2020), X_1 (castor oil %), X_2 (pH), X_4 (temperature), X_1X_2 (interaction of castor oil % and pH), X_1X_4 (interaction of castor oil % and temperature) and X_2X_4 (interaction of pH and temperature) had shown significant effects on production of γ-decalactone. The interaction effects of input variables on the response were shown with contour plots. The oval shape represents the significant interaction between a pair of input variables. The γ-decalactone production rises as castor oil percentage varies from 20 % to 29.68%, beyond which the production decreased as an increase in the percentage of castor oil (Fig. 1) and it might be due to growth inhibition of yeast cells at high percentage of castor oil (Dayana et al 2017). As pH rises from 4.0 to 5.3, γ-decalactone production also increases up to optimum value beyond which production reduced (Dayana et al 2017). Other two variables also followed same pattern as incubation time reaches to 99.8 hr obtained highest production beyond which production decreased (Dayana et al 2017). Thus, the maximum γ-decalactone production predicted by the RSM model is 72.73 mg/L at optimum values (castor oil % -29.68, pH-5.32, incubation time-99.89 hr, and temperature-23.22^{0}C).

ANN modeling: A multilayer perception with feed forward architecture ANN model was generated, which consists of four input nodes (castor oil %, pH, incubation time, and temperature) and one output node (γ-decalactone production). The RSM DOE data and the corresponding experimental response were used to train the ANN model network. Over parameterization is avoided by grading data into training, validation and testing. ANN model was optimized to minimize the error. Training of data was performed by varying neurons in the hidden layer for different

ANN parameters combination. The optimum number of hidden layers obtained was one. The transfer function generated was shown in equation (Dufosse et al 1999). The error was minimized based on trial-and-error method during the training of network. The ability of ANN model was proved by choosing parameter weights results in minimum value of RMSE. The correlation coefficient of 0.999 was obtained for γ-decalactone production.

Models validation: Model predictions of RSM and ANN were confirmed by conducting experiments in thrice at

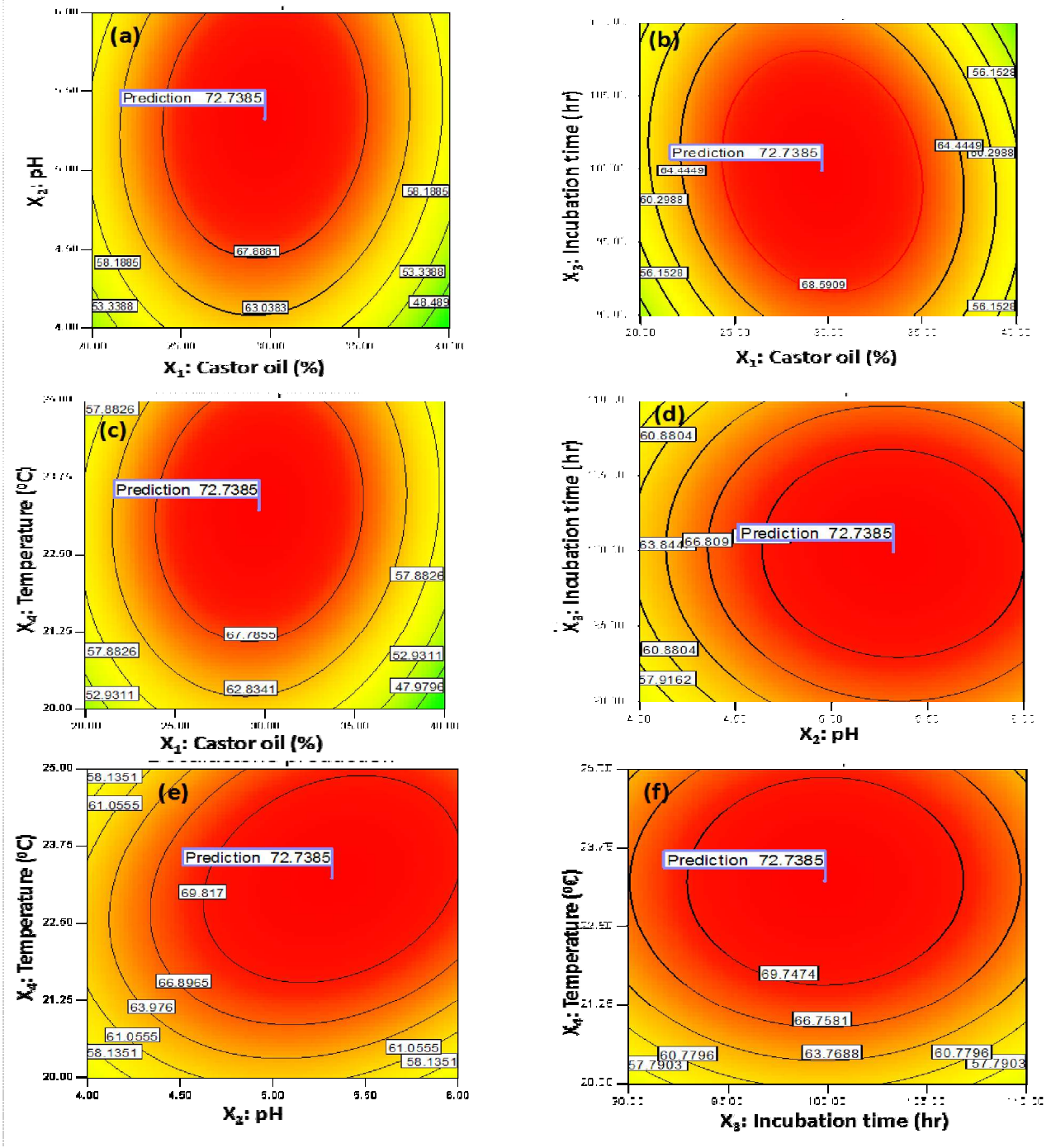

Fig. 1. Contour plots depicting interaction effect of input variables on γ-decalactone production by *Sporidiobolus salmonicolor*: Interaction effects of pH and castor oil (%) (a); incubation time and castor oil (%) (b); temperature and castor oil (%) (c); pH and incubation time (d); pH and temperature (e); incubation time and temperature (f)

optimum conditions. The predicted values of γ-decalactone production by RSM and ANN were 72.73 and 66.14 mg/L, respectively. The optimum input conditions predicted by RSM were castor oil-29.68 %, pH-5.32, incubation time-99.89 hr and temperature-23.22^{0}C with the desirability of 0.992 for γ-decalactone production. The average of triplicate experiments for γ-decalactone production was 73.25 mg/L and it was reasonably close agreement with the response values predicted by models. The outstanding correlation coefficient of RSM and ANN confirms the validity of the models.

Optimum conditions and production of γ-decalactone: The input conditions for γ-decalactone production were optimized using RSM and ANN. The model predictions were validated with experiments. The final yield of γ-decalactone production was 72.73 mg/L at optimum conditions of castor oil-29.68%, pH-5.32, incubation time-99.89 hr and temperature-23.22^{0}C. Earlier reports on the production of γ-decalactone revealed that a maximum production capacity of 131.8 mg/l with immobilized cells and 107.5 mg/l for free cells by *Sporidiobolus salmonicolor* CCRC 2195 after five days of cultivation and indicated that alginate immobilized cells are less susceptible to toxic effects than free cells (Shiow-Ling et al 1998). Gilles et al (1997) reported the production of γ-decalactone 1.8 ± 0.03 g/l with wild strain *Yarrowia lipolyitca* W29 and 5.5 g/l with mutant strain MTLY40-2p after 7 days of biotransformation. They revealed that mutant strain did not show any ability to degrade γ-decalactone.

Nama et al (2016) revealed that the γ-decalactone production of 62.2 mg/l with the same wild type strain used in this study and 81.9 mg/l with mutant strain UV3 after 96 h of fermentation and showed a 33% increase in production compared to wild type strain. Eko et al (2020) observed that γ-decalactone production of 282 mg/l through engineered oleaginous yeast *Yarrowia lipolyitca* from oleic acid in fed-batch fermenter. The yields of γ-decalactone reported above are slightly more compared to the current study. It is mainly due to the toxicity of lactone to producing cells and not genetically engineered strain. However, the fermentation conditions reported for γ-decalactone production in this study are in close agreement with (Dayana et al 2017) in which reported pH-5.0 and castor oil-30% using yeast *L. saturnus* CCMA 0243.

RSM and ANN models comparison: ANN and RSM models were evaluated for predictive abilities by taking the production of γ-decalactone as a case study. These models were compared based on error generated (RMSE, MAE, chi-square (χ^2) and R^2 from the predicted and experimental responses, as shown in Table 3. Thus, results revealed that ANN has good prediction ability compared to RSM for γ-decalactone production due to low error values of ANN and high correlation coefficient. Additionally, responses (γ-decalactone production) predicted by ANN in close agreement with experimental values than that of RSM (Table 2 & Fig. 2). The better prediction of ANN is mainly due to ANN can attribute to the universal approximation, while RSM is limited to a quadratic regression (Kiran et al 2008). ANN has better optimization and prediction abilities compared to RSM. ANN suitable for nonlinear systems for interactions higher than quadratic, whereas RSM is recommended for modeling new processes. Earlier studies reported a better prediction ability of ANN than RSM (Runni et al 2019, Hui-Chuan et al 2019). Thus, ANN proved to be a better prediction and optimization tool.

Table 3. ANN and RSM models comparison based on error parameters

Parameter	γ-decalactone production	
	RSM	ANN
Root mean squared error (RMSE)	0.777	0.617
Mean absolute error (MAE)	0.624	0.426
Chi-square (χ^2)	0.345	0.304
Coefficient of determination (R^2)	0.992	0.999

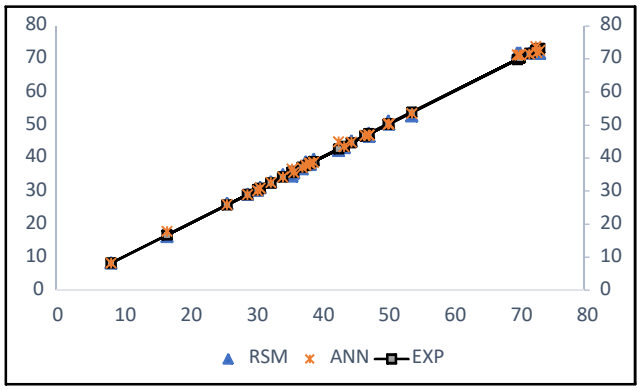

Fig. 2. Comparison of experimental values with the predicted data from ANN and RSM for γ-decalactone production

CONCLUSIONS

In this work modeling approaches of ANN and RSM were assessed for their predictive abilities by taking fermentative production of γ-decalactone as a case study. Optimized the input conditions for maximum γ-decalactone production by S*poridiobolus salmonicolor* and validated model predictions against experiments. The maximum obtained production of γ-decalactone was 72.73 mg/L at optimum conditions of castor oil -29.68 %, pH -5.32, incubation time -99.89 h and temperature -23.22^{0}C. ANN showed less error parameters and more predictive ability than RSM. Thus, it is showed that

ANN can be considered as alternative for RSM. And also, microbial strain S*poridiobolus salmonicolor* can be used as commercial strain for industrial production of γ-decalactone.

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