Hi dear,

I am so sorry that I did not complete the task of Q9 because I am rushing my graduation thesis.

Since my background is not very strong, I need to read enough papers to supplement my understanding of the black-box model. Unfortunately, my time is not enough to complete such a task.

I have attached another article below that I have submitted to a journal. I hope it could help you find out my writing, reading and information searchability.

Kind regards

Shiying Guo

(Please find the attached paper on the next page)

Which model? Comparing kinetic expressions for cream cheese production

Shiying Guo[1,2], Bing Li[1,2*], Wei Yu[1,2*], David I. Wilson[2,3], Brent R. Young[1,2]

1Department of Chemical & Materials Engineering, The University of Auckland, New Zealand

[2]Industrial Information and Control Centre, University of Auckland, Auckland 1023, New Zealand

[3]Electrical and Electronic Engineering Department, Auckland University of Technology, New Zealand

* bing.li@auckland.ac.nz, w.yu@auckland.ac.nz

ABSTRACT

Knowledge of the time-varying concentrations of biomass, lactose, and lactic acid is crucial for the optimal production of cream cheese. This paper reviews the various different kinetic models historically proposed for the cream cheese fermentation process. The performance of several kinetic growth rate models is evaluated by cross-validation, Akaike information criterion and the coefficient of determination using previous lab data. The product inhibition model- Boulton Model gives the best prediction. This model is a valuable instrument for cream cheese research.

Keywords: Cheese fermentation, mathematic model, Monod kinetics, model comparison

1. INTRODUCTION

Cheese is one of the most popular foods all over the world. The average amount of cheese consumed every year was 5.4 million tonnes from 2008 to 2012, and it also had an average increase of 4.6% every year. The average annual export value of cheese was US $26.7 billion during this period.[1] According to another report conducted by Imarc, the total market value of cheese worldwide was US $69.7 billion in 2019.[2] It is projected to grow steadily to US $112.8 billion by 2025, with a compound annual growth rate of 8.4% from 2020 to 2025. As a critical part of the cheese market, global cream cheese market is expected to reach about US $8.3 billion by 2026. Due to the great potential of the cheese market, there is a steady increase in the amount of research on cheese published per year (Figure 1).
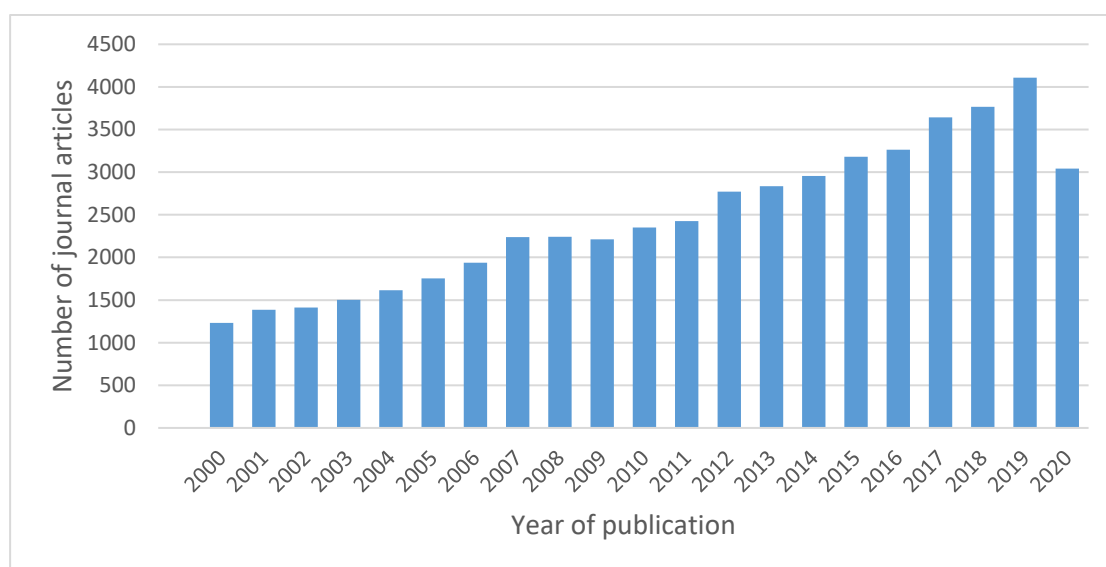

Figure 1:The amount of research on cheese published in recent 20 years (Web of Science)

Fermentation is a crucial part of cream cheese production because bacteria will consume lactose and produce lactic acid in this step. In the cream cheese industry, the mixture containing cream and milk goes through homogenization, pasteurization, inoculation, and fermentation, step by step. In this process, there is a gradual decrease in the mixture's pH to about 4.5.[3] The by-product, cheese whey, could be separated by centrifuges or membrane processes. Then cream cheese is ready for packaging.

Milk as the raw material of cream cheese is crucial in fermentation. It contains about 85% water, which provides solvents for other components like fat, lactose, lactic acid, and protein. About 5% of milk is lactose, which is vital to produce cream cheese because lactic acid

bacteria consume lactose to produce lactic acid during the fermentation. Although fat is only a small part of milk, it has a deep connection with cream cheese texture and flavour. 80% of milk protein is caseins, and the remaining 20% is whey proteins. Both of them play essential roles in coagulation.[4]

As many factors such as temperature, bacteria types, and milk composition affect the fermentation, it is not easy to determine the relationship between factors and fermentation. As a result, it is hard to optimize the fermentation process simply by the design of experiments (DoE). Compared with the DoE method, a deterministic fermentation model not only clearly reveals the impact of related factors, like temperature and pH, but also can be used for optimizing product quality and production rate.[5–8] Thus, modelling could provide constructive guidance for optimizing the fermentation process. For example, pH prediction is vital in the cheese industry as it shows the degree of fermentation, which means it will impact the operational schedule. However, it is not easy to calculate the fermentation end time because the variation of milk feed composition may significantly impact the fermentation process and cheese product consistency. Building a fermentation model could be one solution to solve this problem.[9] Furthermore, modelling also could improve product yield directly. A fermentation model with an embedded control strategy was able to increase the product yield by 14.2%, cell growth by 72.0%, and reduce the residual substrate by 84.8%.[10]

This paper aims to clearly provide a model with considerable potential by reviewing different types of models and comprehensively evaluating the performance of different kinetic growth rate models based on cream cheese fermentation data collected from laboratory data for a specific case. The model having the best prediction is a reliable instrument for cream cheese research at least for kinetic models conditions considered. Section 2 summarizes different categories of models available for cream cheese fermentation modelling. Section 3 evaluates the different deterministic models' performance with cross-validation, the Akaike information criterion (AIC) and the coefficient of determination (R^2). Those models could be suitable or not suitable for cream cheese fermentation modelling. By analyzing our experimental data, we have proposed a robust model that not only requires fewer parameters, but also has high prediction accuracy. Section 4 discusses the performance of different white-box models. Section 5 points out the conclusions. This paper also provides researchers with a comprehensive evaluation model method.

2. Models USED FOR CREAM CHEESE FERMENTATION

2. 1 Basic modelling approach

There are two broad approaches to modelling: first-principles modelling, and empirical modelling, which correspond to white-box models (WBMs) and black-box models (BBMs), respectively. Grey-box models (GBMs) combine both first-principle modelling and empirical modelling. A WBM is built on a clear understanding of the system.[11] For example, to research the relationship in simple systems, a WBM could have a good prediction whose coefficient of determination is larger than 0.85 and only requires a small amount of data for model calibration.[12–15] However, a cream cheese WBM needs more measurements, such as bacteria, lactic acid, lactose concentration. The complexity of a WBM will grow with the addition of potential influence factors like pH and volume change during fermentation. As the fermentation process is complicated, it is not practical to use a WBM to predict pH change. A BBM is based on data from the experiment, which is also known as an empirical model. For BBM, not only data volume is important, but another more important criteria is the data quality, specifically on the excitation of the process. The data should include multiple conditions or different states of the process. However, most industrial data contains little variation since the industry wants to maintain the process as steady as possible. BBMs have been applied to measure the physical properties of cheese, food quality and predict moisture in cheese.[16–19]

In summary, good quality data for BBMs is vital but not always available from the industry. Although BBM could be built with less or even zero mechanism-understanding than WBMs, a huge amount of data is required to train BBMs, which may sometimes not be available from industries. GBMs combine advantages from empirical BBMs and mechanistic WBMs.[11] GBM users believe that system-related knowledge from other sources is likely to optimize modelling process outcomes.[20] Figure 2 shows a classic structure of an ANN GBM. The inputs are historical pH data from time "t" to time "t-N" where "N" is the feedback delay size.[21] There are "j" neurons to capture the pH change. The output layer can predict the pH value at time "$t+1$". GBMs have been used to predict pH change in cheese fermentation and simulate the production of ethanol from "ricotta cheese whey".[9,22] The structure of GBMs' case and BBMs' case are shown in Figure 3 and Figure 4, respectively. Figure 3 shows the

structure of Li's GBM.[23] The kinetic model will feed back the corresponding predicted concentration (X_i, S_i, P_i) by inputting the initial biomass (X_0), lactose(S_0), lactic acid (P_0)concentration. After receiving the predicted concentration, the Long Short-Term Memory (LSTM) network will output the predicted pH change. In Figure 4, the initial fermentation condition (lactose concentration), and operational conditions (temperature, pH, reactor stirring rate, and reaction time) were used as inputs to an artificial neural network (ANN). The kinetic parameter was obtained as output. The kinetic parameter was then fed to a logic gate in order to reduce the error propagation caused by the purely BBM. Finally, the filtered kinetic parameter was applied to calculate the current concentration (biomass, lactose, lactic acid) based on mass balance. Table 1 summarizes the advantages and disadvantages of WBMs, BBMs, and GBMs
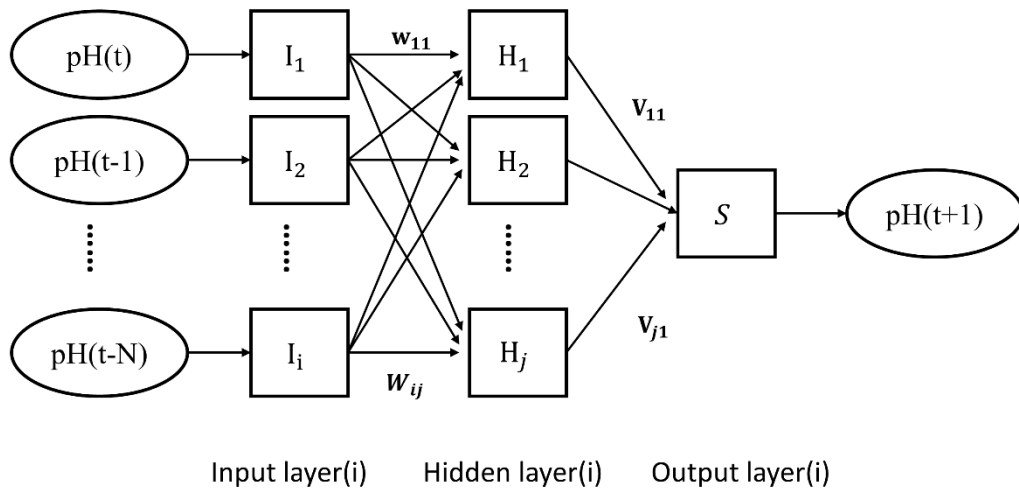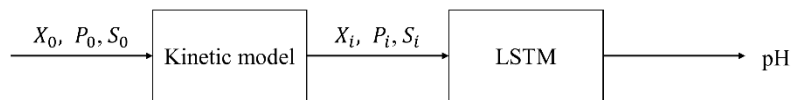

Figure 2: An ANN black-box model's structure [21]
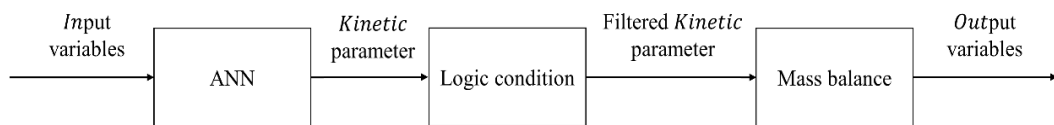

Figure 3: A Grey-box model's structure [23]

Figure 4: A Grey-box model's structure [22]

Table 1: Advantages and disadvantages of WBMs, BBMs, and GBMs

Model types	Advantages	Disadvantages
WBMs	A small amount of data required for model calibration	Need mechanism understanding
BBMs	No mechanism understanding required Generic structure	Need plenty of data to train a model
GBMs	Great estimation accuracy Good extrapolation properties	Need mechanism understanding Need plenty of data to train a model

2. 2 Development of fermentation models

The majority of fermentation models are based on unstructured WBMs which describe the bacterial growth model, product generation model, and substrate consumption. Of these three terms, the bacterial growth expression is the most important.[11] The first, and most famous, bacterial growth model is known as the Monod model.[24] Most industries use a full-batch model in the fermentation process where at the beginning of fermentation, the reactions begin with an excess of carbon source.[25] With the growth of bacteria and product formation, the amount of carbon source will decrease. Once most carbon sources are consumed, more carbon sources will be added to support the generation of biomass and product formation.[26]

In recent years, there has been significant development of the standard parametric kinetic models focused on fermentation as shown in Figure 5 with further details given in the reference list.
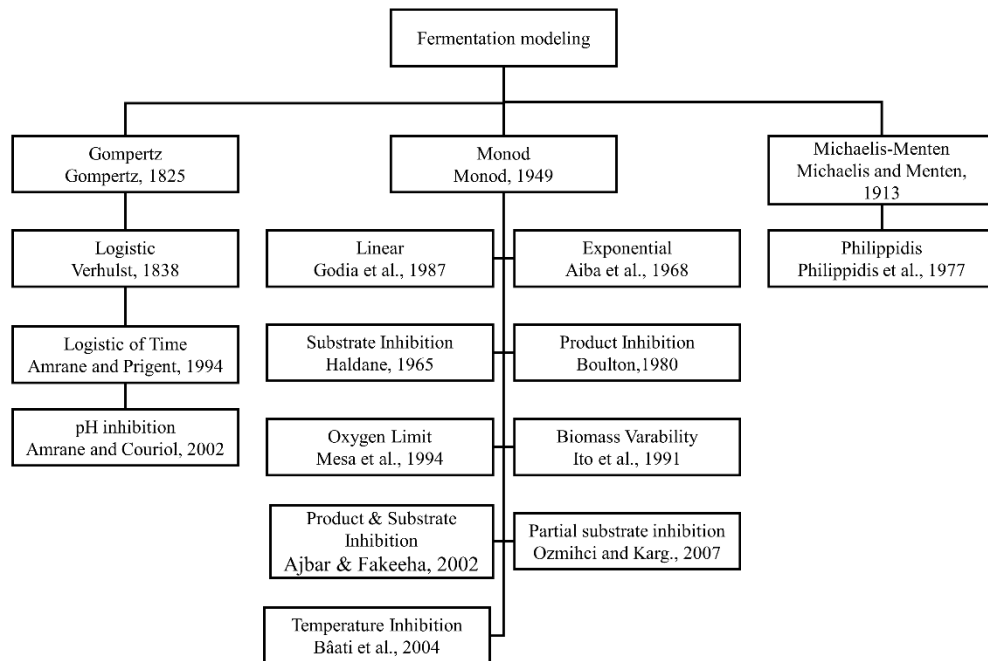
Figure 5: Family tree of fermentation modelling

The Gompertz model is a sigmoid black-box model widely used to describe the growth rate of bacteria.[27,28] In a similar vein, the *logistic* model also describes the rate of bacteria growth.[29] One of the most critical differences between these two 'S'-curve models is symmetry; the logistic growth curve is symmetric, while the Gompertz model is asymmetric.[30]

A slightly different variant is the Michaelis–Menten model, popular for fermentation reactions involving enzymes.[31,32] To include the effects of product inhibition, Philippidis *et al.* added an inhibition constant.[33]

To date, the Monod kinetic is the most popular model to describe the bacteria growth rate.[34] Compared with the Michaelis–Menten model, the Monod constant has no specific fundamental meaning, whereas the Michaelis–Menten constant is the concentration of substrate when the activity of enzyme reaches half of the maximum activity. On the other hand, the Michaelis–Menten model is based on theoretical derivation. However, the Monod model is an empirical formula.[35] Maiorella et al. and Aiba et al. proposed a linear model and an exponential model, respectively, based on Monod model.[36,37] Haldane improved the Monod model by adding a toxic substrate constant to handle the substrate inhibition.[38] However, these models above could be unsuitable to describe product inhibition.

Jerusalimsky and Neronova generalized the Monod by introducing the product inhibition constant.[39] Similarly, Levenspiel added the toxic power parameter to explain the inhibition caused by toxic products.[40] In some fermentations, there could be both substrate and product inhibition in the reaction, so a combination of these two types of kinetic models will deliver a better performance. Ajbar found that the growth rate could have the following rate, $\mu(s,p) = \mu_1 s \cdot \mu_2 p$ where $\mu(s,p)$ is the growth rate related to product inhibition and substrate inhibition, $\mu_1 s$ means the kinetic equation related to substrate inhibition and $\mu_2 p$ means the kinetic equation related to the product inhibition.[41] Therefore, the number of models has increased because it is not difficult to combine models and generate a new model, like Haldane and Boulton model.[42]

2.3 Variations of the Monod kinetic model

The original Monod model is defined as Equations 1-3.

$$\frac{dX}{dt} = \mu X \qquad\qquad (1)$$

$$\frac{dS}{dt} = -(\frac{1}{Y_{xs}} + \frac{1}{Y_{ps}})\mu X - m_s X \qquad\qquad (2)$$

$$\frac{dP}{dt} = \alpha\, Y_{ps}\mu X + \beta X \qquad\qquad (3)$$

where Y_{xs} is the biomass yield coefficient, Y_{ps} is the product yield coefficient. α is the growth-associated product formation coefficient, β is the non-growth-associated product formation coefficient, m_s is the maintenance coefficient, and μ is the specific growth rate. However, by adjusting expressions for the critical parameter, μ, different models within this family have been postulated as listed in Table 2. Further details on the incentives behind these modifications are given in Section 4.

Table 2: Some Monod-based models used for fermentation modelling

Category	Models	Notes	Reference
Basic model	$\mu = \mu_{max} \dfrac{S}{S + K_s}$	most commonly used	[24]
Substrate inhibition	$\mu = \mu_{max} \dfrac{S}{S + K_s + \dfrac{S^2}{K_i}}$	introduce substrate inhibition constant.	[38]
Substrate inhibition	$\mu = \mu_{max} \dfrac{S}{S + K_s} - K(S - S_{crit})$	for linear growth rate	[43]
Substrate inhibition	$\mu = \mu_{max} \left(\dfrac{S}{S + K_s}\right)^{-\frac{S}{K_i}}$	for Exponential growth rate	[37]
Substrate inhibition	$\mu = \mu_{max} \dfrac{S^n}{K_s + S^n}$	introduce substrate inhibition constant.	[44]
Product inhibition	$\mu = \mu_{max} \left(\dfrac{S}{S + K_s}\right)\left(\dfrac{K_p}{K_p + P}\right)$	classical model	[39]
Product inhibition	$\mu = \mu_{max} \dfrac{K_p}{K_p + P}$	introduce product inhibition term	[45]
Product inhibition	$\mu = \mu_{max} \dfrac{S}{S + K_s}\left(1 - \dfrac{P}{P_m}\right)^n$	more flexible, including a limiting concentration of inhibitory products	[40]
Substrate and product inhibition	$\mu = \mu_{max} \left(\dfrac{S}{S + K_s + \dfrac{S^2}{K_i}}\right)\left(\dfrac{K_p}{K_p + P}\right)$	combine Haldane and Boulton models	
Substrate and product inhibition	$\mu = \mu_{max} \dfrac{S}{S + K_s + \dfrac{S^2}{K_i}}\left(1 - \dfrac{P}{P_m}\right)^n$	combine Haldane and Levespiel models	
pH	$\mu = \mu_{max}\, e^{-\frac{[HL]}{[HL]_C}} - \mu_0$	the influence of undissociated lactic acid concentrations	[46]

Not every model, however, is suitable for cheese fermentation. This paper uses experimental data to analyze and compare several different types of models. It shows the advantages and disadvantages of different models and gives some directions to build cheese fermentation

models. Due to the diverse experimental starting conditions, these models could also be easily applied to a wide range of situations.

3. CASE STUDY

Of the 11 parameterized kinetic models given in Table 2, this study aims to establish the best model for a given set of fermentation data. The significance of this paper is that the reader can use the efficient model validation approach described for their own experimental data to establish which model, and model family is appropriate.

3.1 Experimental procedure

The experimental data is previously published [9].

The cheese culture containing *Lactococcus lactis subsp. cremoris* and *Lactococcus lactis subsp. lactic* was bought from Mad millie NZ (Cheese culture-Mesophilic culture sachets). The media was M.R.S Agar from Thermo Fisher.

1.5L commercial Achor Blue Top milk and 0.5L Countdown Cream was added to the fermenter BioFlo 3000 and heated to 37℃ with stirring at 150rpm. After that, one sachet of culture was added to the fermenter. Samples were taken every 1.5 hours to measure the concentration of biomass, lactose, and lactic acid. The pH was recorded every 0.15s in software. In the cream cheese industry, the fermentation process will stop once the mixture's pH reaches 4.6. For this reason, this fermentation experiment only recorded data before the pH reaches 4.6.

In total four experiments were undertaken. The first experiment, termed 'base Case', uses a nominal starting condition, while the other 3 experiments used differing initial conditions as shown in Table 3.

Table 3：Initial concentrations of *X*, *S*, and *P* in g/L

	Base	Double biomass	High lactose	High lactic
$X(t=0)$	0.035	0.123	0.038	0.053
$S(t=0)$	40.346	40.937	43.164	38.523
$P(t=0)$	0.012	0.024	0.026	0.472

3.2Analytical Methods

All kinetic models are simulated in the Matlab rapid prototyping environment. The concentration of biomass, lactose, and lactic are used to verify the accuracy of the model. In order to assess if the more complex Monod-type models are appropriate, we need to both assess the predictive power of the models, cognizant of the fact that a model with a higher number of fitted parameters will typically fit any given finite data set better. In order to mitigate against the bias-variance tradeoff, we need to first estimate parameters and then cross-validate the models using data not previously used for the fitting. However, given the paucity of the data, in this case, we use a leave-one-out cross-validation strategy.

The parameter estimation process is shown in Algorithm 1.

The cross-validation process is shown in Algorithm 2.

Algorithm 1: Basic parameter fitting

Step 1: Use optimizer to find the optimum parameters (θ_1) with minimum weighted SSE for all 4 data sets.

Step 2: Report the optimum parameters (θ_1) and R^2.

Algorithm 2: Cross validation

Step 1: Select a data point randomly from each group of data as the validation set. Other data are used as the fit-only data sets. Unless the initial condition (X_0, P_0, S_0) is identified, the first data point needs to be excluded from the validation data because the first data point is used as the initial condition for the ODE integrator.

Step 2: Use θ_1 as the initial estimate of the parameters. Then repeat Step 1 only using the fit-only data sets. Report the optimum parameter (θ_2).

Step 3: Calculate the validation $\text{SSE}_k(\theta_2)$ using the validation set.

Step 4: Repeat Step 1,2,3 around ten times. Report the average validation $\text{SSE}=\sum_{K=1}^{10}\text{SSE}_k/10$, and AIC.

Step 5: Calculate the AIC value for the specific model.

Note:

The final parameters are θ_1 from one iteration generated by Algorithm 1. And then θ_1 is evaluated by Algorithm 2.

Equation 4 describes the weighted sum of squared estimate of errors (SSE) function:

$$\text{SSE} = \Sigma w_x \, (X_{e,i} - X_{p,i})^2 + \Sigma w_s \, (S_{e,i} - S_{p,i})^2 + \Sigma w_p \, (P_{e,i} - P_{p,i})^2 \qquad (4)$$

where w_x, w_s, and w_p, are the weights for biomass concentration, lactose concentration, and lactic acid concentration, respectively, *X is* the biomass concentration in g/L, *S* is the substrate concentration (lactose) in g/L, *P is* the product concentration (lactic acid) in g/L, *e* is the experiment data, and *p* is the prediction data, and *i* is a different data point. As the accuracy of *X* is less than *P* and *S*, the weights for them are set at 1,5,5, respectively.

Equation 5 describes the AIC function used to penalize those models with an excessive number of parameters [47]:

$$\text{AIC} = 2k + n\ln(\text{SSE}) \qquad (5)$$

where *k* is the number of parameters, *n* is the sample size.

The coefficient of determination （R^2） is defined as Equation 6:

$$R^2 = 1 - \frac{\Sigma_i (y_i - f_i)^2}{\Sigma_i (y_i - y_{mean})^2} \qquad (6)$$

Where *i* is the different data point, y_{mean} is the mean of experimental data, y_i is the experimental data, f_i the prediction data.

The standard deviation (SD) is used to measure the amount of dispersion of each parameter. It is defined as Equation 7, where *N* is the sample size, x_i is different sample, and $\bar{x}$ is the mean of all samples.

$$\text{SD} = \sqrt{\frac{1}{N} \Sigma_{i=1}^{N} (x_i - \bar{x})} \qquad （7）$$

A good model should have a small average validation SSE and AIC value and its' R^2 should close to 1. The AIC value will be used to compare across different models.

4. RESULT

The prediction results of the first set of data from Table 3 for different models are shown in Figure 6.
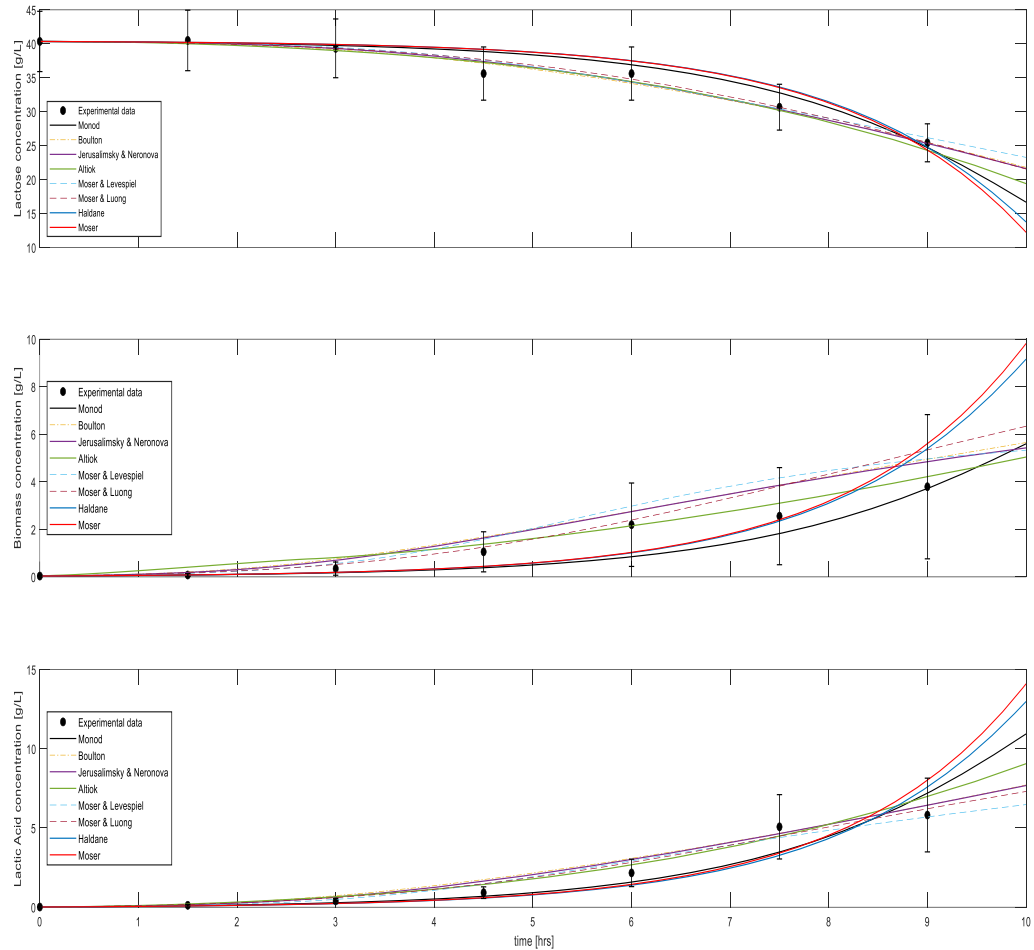

Figure 6: Predictions for the first set of data

The prediction results of the remaining three sets from Table 3 are very similar to the base case, most probably because the initial conditions are not different. Their R^2 values will be used for evaluating each model prediction reliability in the following section. All the parameters are described in Table 4.

Table 4: Parameters' notation

Parameter	Notation
μ_{max}	maximum specific growth rate (1/h)
K_s	Monod constant (dim)
X_m	inhibitory biomass concentration (g/L)
P_m	inhibitory lactic acid concentration (g/L)
Y_{xs}	biomass yield coefficient (dim)
Y_{ps}	product yield coefficient (dim)
α	growth-associated product formation coefficient (dim)
β	non-growth-associated product formation coefficient (dim)
m	product inhibition constant (dim)
n	substrate inhibition constant (dim)
$[HL]$	undissociated lactic acid concentrations (g/L)
$[HL]_C$	constants coefficients in the inhibition relation (dim)

4.1 The original Monod Model

The original Monod model uses the following expression for growth rate (μ).

$$\mu = \mu_{max} \frac{S}{S+K_s} \qquad (8)$$

where K_s is known as the Monod constant, and μ_{max} is the maximum growth rate. The original Monod model has 7 parameters. This equation represents an exponential growth rate of bacteria under ideal conditions.

The results are shown in Figure 7 and Table 5-6, where the model is fitted using the blue data points, and validated only on the red data points.
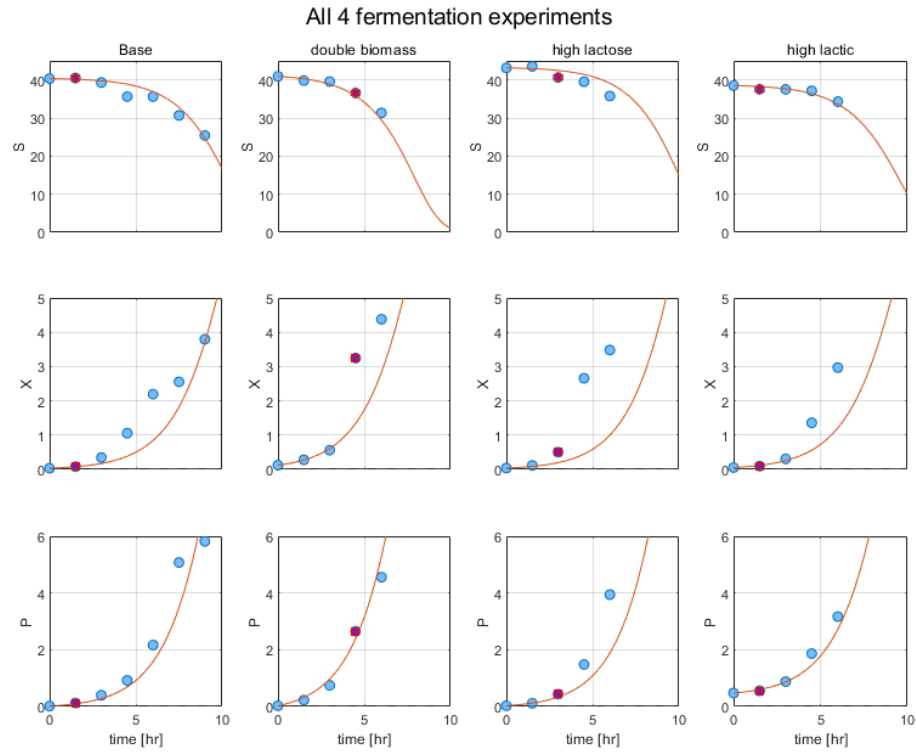
Figure 7: Cross-validation results for Monod model

(Red dots are validation set, blue dots are fit-only data set and orange curve the model.)

The average validation SSE: SSE = 174.2803

The Akaike information criterion: AIC = 75.9280

Table 5: The R^2 value for the Monod model

	Base	Double biomass	High lactose	High lactic
X	0.7731	0.6084	0.0031	0.3961
S	0.8627	0.9544	0.5649	0.9288
P	0.9067	0.9171	0.5356	0.8486
Ave		0.6839		

Table 6: Optimized parameters for Monod model

Parameter	Value	SD
μ_{max}	0.7975	0.0555
K_s	19.6314	0.0867
α	2.5942	0.5402
β	0.0872	0.0277
Y_{xs}	0.3838	0.1282
Y_{ps}	0.6838	0.0836
m_s	0.0856	0.0093

The advantage of the Monod model is that there are only 7 parameters. However, it is only suitable to describe the growth rate in low substrate concentration.[11]

4.2 The Haldane Model (substrate inhibition Model 1)

The following equation defines the Haldane Model:

$$\mu = \mu_{max} \frac{S}{K_s + S + \frac{S^2}{K_i}} \qquad (9)$$

where K_i is an introduced inhibition constant. The Haldane model has 8 parameters.

It is a popular extension to the Monod model used to describe the growth rate of bacteria with substrate inhibition. The Haldane model solves several defects of the Monod model. It could be applied at high or low substrate concentration with, or without, substrate inhibition. Therefore we expect it to perform better than the basic Monod model, especially in the latter data sets.

The results are shown by SSE, AIC, and R^2 and in Table 7-8.

The average validation SSE: SSE = 104.1174

The Akaike information criterion: AIC = 71.7462

Table 7: The R^2 value for the Haldane model

	Base	Double biomass	High lactose	High lactic
X	0.6478	0.7654	0.0062	0.5886
S	0.7981	0.9665	0.4004	0.8730
P	0.8615	0.9890	0.2943	0.9174
Ave		0.6736		

Table 8: Optimized parameters for the Haldane model

Parameter	Value	SD
μ_{max}	0.6835	0.0048
K_s	4.6372	0.0033
α	0.5931	0.0005
β	0.2017	0.0001
Y_{xs}	0.5293	0.0056
Y_{ps}	1.7721	0.0031
m_s	0.2502	0.0009
K_i	400.5746	0.0000

4.3 The Moser Model (substrate inhibition Model 2)

In an effort to fit experimental data better, Moser introduced a new parameter (n), which is an adjustable parameter in the Monod equation. This term can provide a better description of substrate inhibition dynamic behaviour. The Moser model could describe the lag phase in high substrate concentration. However, it can not simulate the death phase [48].

The Moser model is defined as

$$\mu = \mu_{max} \frac{S^n}{K_s + S^n} \qquad (10)$$

The Moser model has 8 parameters.

The results are shown by SSE, AIC, and R^2 and in Table 9-10.

The average validation SSE: SSE = 128.0679

The Akaike information criterion: AIC = 74.2307

Table 9: The R^2 value for the Moser model

	Base	Double biomass	High lactose	High lactic
X	0.5977	0.7773	0.0013	0.6056
S	0.7668	0.9608	0.4276	0.8979
P	0.8614	0.9875	0.2988	0.9157
Ave		0.6741		

Table 10: Optimized parameters for Moser model

Parameter	Value	SD
μ_{max}	0.5654	0.0037
K_s	8.4996	0.0000
α	0.6067	0.0002
β	0.5889	0.0005
Y_{xs}	3.5735	0.0000
Y_{ps}	0.6502	0.0004
m_s	0.5943	0.0002
n	2.5248	0.0000

4.4 The Boulton Model (Production inhibition Model 1)

The Boulton model is one typical product inhibition model. With the introduction of K_p, the Boulton model could handle production inhibition. Both the Boulton model's advantages and disadvantages are evident as the form of the Boulton equation is very similar to the Monod equation. It is simple to apply because of the low number of parameters. However, it can not describe the growth rate with substrate inhibition.

The Boulton model is defined by the following equation.

$$\mu = \mu_{max}\frac{K_p}{K_p+P} \qquad (11)$$

where K_p is the product inhibition term. The Boulton model has 7 parameters.

The results are shown in Figure 8 and Table 11-12. Note that in this case, in a similar fashion to the basic Monod model in Figure 7, this model does not capture the 'S' curve in the *X(t)* profile, especially evident in the base case.
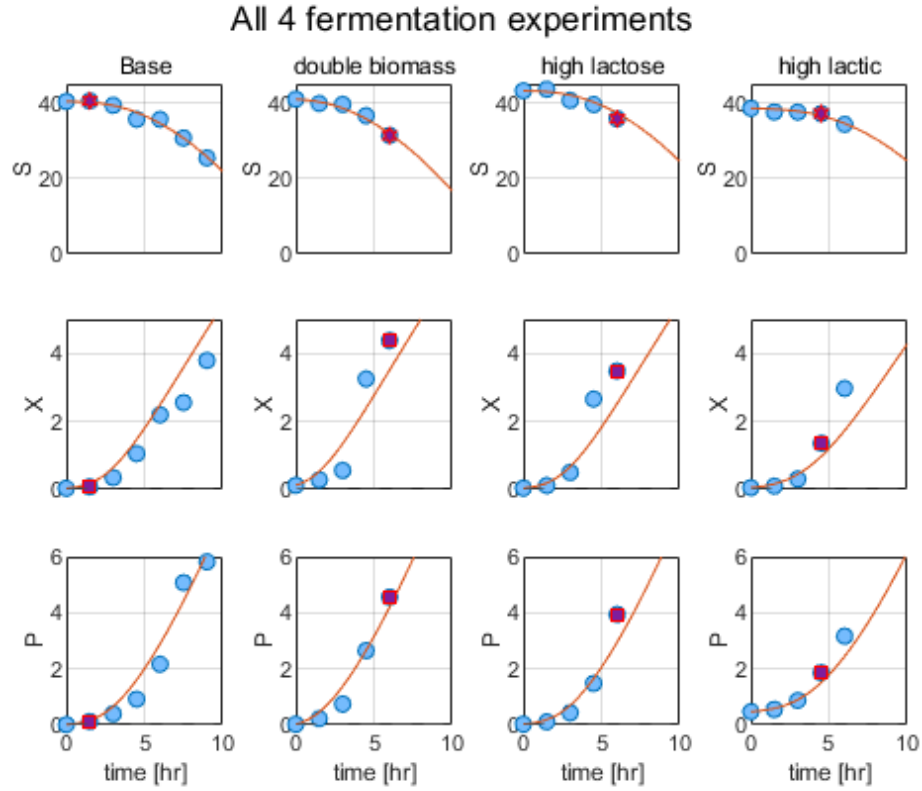
Figure 8: Cross-validation results for Boulton model

(Red dots are validation set, blue dots are fit-only data set and orange curve the model.)

The average validation SSE: SSE = 18.3896

The Akaike information criterion: AIC = 48.9414

Table 11: The R^2 value for the Boulton model

	Base	Double biomass	High lactose	High lactic
X	0.6860	0.8807	0.8531	0.7720
S	0.9386	0.9599	0.9181	0.8871
P	0.9745	0.9555	0.9115	0.8984
Ave		0.8863		

Table 12: Optimized parameters for the Boulton model

Parameter	Value	SD
μ_{max}	1.2886	0.0618
K_p	0.8079	0.0739
α	0.5205	0.0276
β	0.1300	0.0171
Y_{xs}	2.2393	0.2358
Y_{ps}	1.6218	0.0550
m_s	0.5514	0.0483

4. 5 The Jerusalimsky and Neronova Model (Production inhibition Model 2)

Jerusalimsky and Neronova combined the Monod equation Equation 8 and Boulton equation Equation 11 to fit experimental data better with

$$\mu = \mu_{max}(\frac{S}{S+K_S}) \, (\frac{K_p}{K_p+P}) \qquad (12)$$

This model has 8 parameters.

The cross-validation result is shown by SSE, AIC, and R^2 in Figure 9 and Table 13-14.
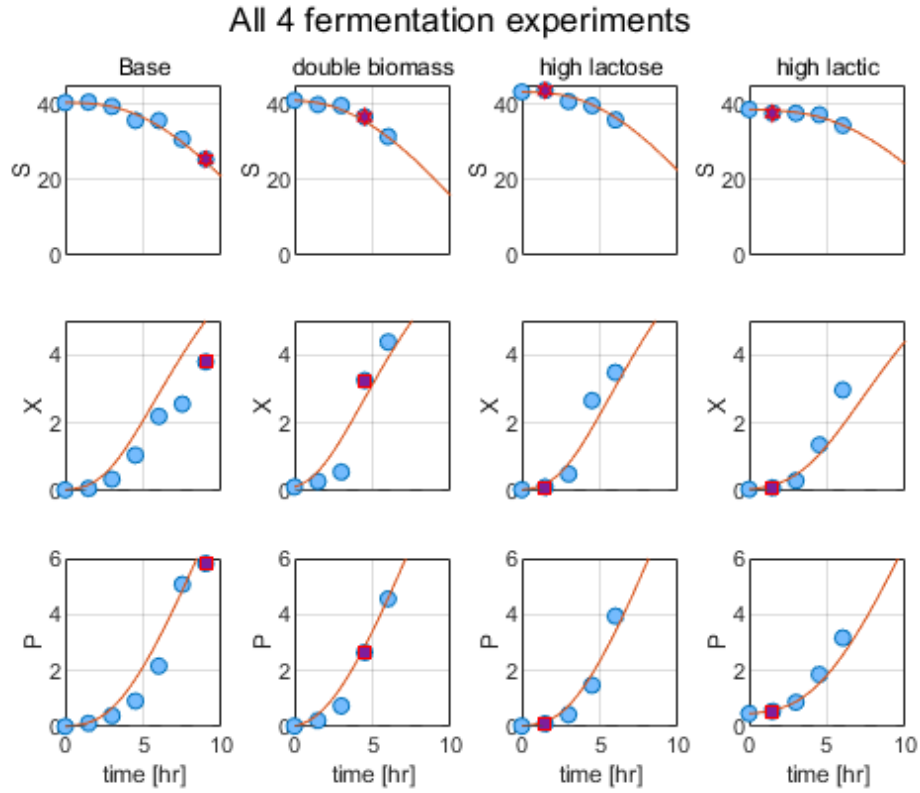
Figure 9: Cross-validation results for Jerusalimsky and Neronova model

(Red dots are validation set, blue dots are fit-only data set and orange curve the model.)

The average validation SSE: SSE = 21.0126

The Akaike information criterion: AIC = 52.5415

Table 13: The R^2 value for the Jerusalimsky and Neronova model

	Base	Double biomass	High lactose	High lactic
X	0.7141	0.8931	0.8871	0.7730
S	0.9475	0.9676	0.9385	0.8962
P	0.9734	0.9636	0.9148	0.8999
Ave		0.8957		

Table 14: Optimized parameters for the Jerusalimsky and Neronova model

Parameter	Value	SD
μ_{max}	2.1855	0.0564
K_s	33.9141	0.1159
K_p	1.0074	0.0973
α	0.5965	0.0366
β	0.1550	0.0411
Y_{xs}	10.4610	0.0514
Y_{ps}	1.3061	0.1038
m_s	0.6296	0.0657

4.6 The Altıok Model (Production inhibition Model 3)

Altıok did not change the equation of growth rate but changed other 3 ODEs to introduce the production inhibition parameters, defined as per Equations 13-16.

$$\mu = \mu_{max}\frac{S}{S+K_s} \qquad (13)$$

$$\frac{dX}{dt} = \mu \left(1 - \frac{X}{X_m}\right)^f \left(1 - \frac{P}{P_m}\right)^h \qquad (14)$$

$$\frac{dS}{dt} = -\frac{1}{Y_{ps}}\frac{dP}{dt} - m_s X \qquad (15)$$

$$\frac{dP}{dt} = \alpha\frac{dX}{dt} + \beta X \qquad (16)$$

where X_m is the inhibitory biomass concentration, P_m is the maximum product concentration, and *f*, *h* are the toxic power for biomass and product inhibition, respectively. If X is more than X_m or P is more than P_m, the bacteria will not grow.

The Altıok model has 10 parameters.

The results are shown by SSE, AIC, and R^2 in Table 15-16.

The average validation SSE: SSE = 33.4968

The Akaike information criterion: AIC = 62.1374

Table 15: The R^2 value for the Altıok model

	Base	Double biomass	High lactose	High lactic
X	0.9284	0.5625	0.6481	0.8359
S	0.9357	0.8168	0.8459	0.9671
P	0.9698	0.8814	0.8892	0.7319
Ave		0.8344		

Table 16: Optimized parameters for the Altıok model

Parameter	Value	SD
μ_{max}	0.2447	0.0616
K_s	0.3420	8.2407
X_m	0.0677	0.0130
P_m	0.5743	0.1597
f	0.1850	0.0912
h	0.1799	0.0203
α	0.1595	0.1675
β	0.4241	0.0548
Y_{ps}	6.2629	0.8892
m_s	1.0023	0.0342

4.7 The Moser and Levespiel Model (S&P inhibition Model 1)

The Moser and Levespiel Model is an application of Ajbar's result [41] to fit experimental data better. The combinations of the Moser Equation 10 and Levespiel Model, The Moser and Levespiel Model, is defined as Equation 17.

$$\mu = \mu_{max} \frac{S^n}{S^n + K_s} \left(1 - \frac{P}{K_p}\right)^m \qquad (17)$$

This model has 10 parameters.

The results are shown by SSE, AIC, and R^2:

The average validation SSE: SSE = 21.4861

The Akaike information criterion: AIC = 56.8089

The performance is shown in Table 17-18.

Table 17: The R^2 value for the Moser and Levespiel model

	Base	Double biomass	High lactose	High lactic
X	0.6056	0.9317	0.8821	0.9476
S	0.9615	0.9725	0.9181	0.9779
P	0.9668	0.9533	0.8767	0.7773
Ave		0.8976		

Table 18: Optimized parameters for the Moser and Levespiel model

Parameter	Value	SD
μ_{max}	0.9622	0.1769
K_s	-0.0223	0.0795
K_p	23.1818	15.0266
α	0.0950	0.0897
β	0.0945	0.0412
Y_{xs}	1.0022	1.9602
Y_{ps}	8.5346	9.2487
m_s	0.4857	0.0411
m	8.6831	6.4975
n	0.0267	0.1795

4.8 The Moser and Luong Model (S&P inhibition Model 2)

The Moser and Luong Model is another application of Ajbar's result [41] to fit experimental data. The combinations of the Moser and Luong Model is defined as Equation 18.

$$\mu = \mu_{max} \frac{S^n}{S^n + K_s} \left(1 - \left(\frac{P}{P_m}\right)^m\right) \qquad (18)$$

This model has 10 parameters.

The results are shown by SSE, AIC, and R^2:

The average validation SSE: SSE = 23.5024

The Akaike information criterion: AIC = 57.8852

The performance is shown in Table 19-20.

Table 19: The R^2 value for the Moser and Moser and Luong model

	Base	Double biomass	High lactose	High lactic
X	0.6726	0.9095	0.8899	0.6405
S	0.9632	0.9702	0.9551	0.8101
P	0.9729	0.9647	0.9513	0.8879
Ave		0.8823		

Table 20: Optimized parameters for the Moser and Moser and Luong model

Parameter	Value	SD
μ_{max}	0.9173	0.1826
K_s	-0.3709	0.0098
K_p	47.0343	25.9756
α	5.8944	27.2984
β	1.7268	0.6204
Y_{xs}	-0.0256	0.1023
Y_{ps}	0.7217	0.4722
m_s	0.4101	0.1480
m	-0.2340	0.0088
n	0.0218	0.0075

5. DISCUSSION

Typically, the accuracy of model prediction will increase by introducing more parameters. However, the paper shows a different result. Some of the more complex models are not as good as they first appear. The addition of parameter does not necessarily lead to better prediction results. For example, the Haldane Model and the Moser Model have more parameters than the Boulton model. However, the Boulton model has a better prediction result than them. The cross-validation results for different models are shown in Table 21.

Table 21: The cross-validation results for different models

Category	Model	Number of parameters	R^2	SSE	AIC
Basic model	Monod	7	0.68	174.280	75.93
Substrate inhibition	Haldane	8	0.67	104.117	71.75
Substrate inhibition	Moser Model	8	0.67	128.068	74.23
Production inhibition	**Boulton**	**7**	**0.89**	**18.390**	**48.94**
Production inhibition	Jerusalimsky and Neronova	8	0.90	21.013	52.54
Production inhibition	Altıok	10	0.83	33.497	62.14
S&P inhibition	Moser and Levespiel	10	0.90	21.486	56.81
S&P inhibition	Moser and Luong	10	0.88	23.502	57.89

Overall, the product inhibition models and S&P inhibition models have a better description than basic and substrate inhibition models based on Lin's data. The R^2 values of all production inhibition models and S&P inhibition models are over 0.83. The substrate inhibition models have the worst R^2 value. This result is similar to the SSE validation result. The SSE validation value of production inhibition models and S&P inhibition models are smaller than that of substrate inhibition models and the Monod model. The AIC value, integrating the effects of SSE and the number of parameters, is the most important indicator to evaluate those models. Although S&P inhibition models have a good performance on SSE validation, their AIC results are not very good because the number of parameters is 10, whereas that of some production inhibition models is only 7. Of all models above, the Boulton model has the smallest AIC and SSE validation value. It also has an R^2 of 0.8863, extremely close to the best R^2 value, 0.8976. The product inhibition models and S&P inhibition models have a better prediction of biomass concentration, lactose concentration, and lactic acid concentration because of the lactic acid inhibition. During the cream cheese fermentation, the pH value decreases from about 6.6 to 4.6. The concentration of lactic acid inhibits the growth of those lactic acid bacteria. There is a decrease in lactose concentration from 44 g/L to 35 g/L, which means lactose is excess during the whole fermentation process. That could explain why the Monod model and substrate inhibition models do not have an ideal prediction. As for these

combined S&P models, the result is very close to the best model, the Boulton model. The slight gap may be caused by the negative effects of the substrate inhibition parameter. The prediction of biomass concentration is not as accurate as that of lactose and lactic acid concentration.

The inaccuracy of biomass concentration could cause this problem. As the mixture is not homogenized, the uncertainty will increase with the number of dilutions.

6. CONCLUSIONS

In this paper, the Boulton model evaluated by cross-validation, AIC, and R^2, turned out to be a valuable tool for the simulation of cream cheese fermentation process and analysis. It can well describe the relationship between lactose, lactic acid, and biomass concentration in cream cheese fermentation process based on previous lab data. What is more, to find the optimal kinetic model for cream cheese fermentation, choosing the model that is biased toward product inhibition could be easier to get satisfactory results. The product inhibition model-Boulton model only required seven parameters, which is also crucial for the industry's practical applications. Future development of this work could combine with WBMs to research the effect of more influencing factors. For example, the combination of WBMs and BBMs could be used to research the effect of stirring rate, milk filling rate, and the temperature during the cheese fermentation process. Those GBMs may also explain the relationship between initial concentration (biomass, lactose, lactic acid) and cheese structure. Furthermore, combining with soft sensors to realize online data measurement makes it possible to upgrade the factory's ability from predicting data like fermentation time or cheese structure to control them.

References

[1]   B. Vlahovic, A. Popovic-Vranjes, I. Mugoša, *Econ. Insights – Trends Challenges* **2014**, 66.1.

[2]   IMARC, Cheese Market: Global Industry Trends, Share, Size, Growth, Opportunity and Forecast 2021-2026, **2020**, https://www.imarcgroup.com/cheese-manufacturing-plant.

[3]   R. C. Chandan, "CHEESES | Soft and Special Varieties," *Encyclopedia of Food Sciences and Nutrition*, Elsevier **2003**, p. 1093.

[4]   P. S. Kindstedt, "The Basics of Cheesemaking," *Cheese and Microbes*, American Society of Microbiology **2014**, p. 17.

[5]   L. Bâati, G. Roux, B. Dahhou, J.-L. Uribelarrea, *Math. Comput. Simul.* **2004**, *65*, 137.

[6]   A. Amrane, Y. Prigent, *J. Chem. Technol. Biotechnol.* **1999**, *74*, 33.

[7]   A. Souza, M. Mousaviraad, K. Mapoka, K. Rosentrater, *Bioengineering* **2018**, *5*, 34.

[8]   E. Ccopa Rivera, C. K. Yamakawa, M. B. W. Saad, D. I. P. Atala, W. B. Ambrosio, A. Bonomi, J. Nolasco Junior, C. E. V. Rossell, *Biochem. Eng. J.* **2017**, *119*, 42.

[9]   Y. Lin, *Res. Auckl.* **2018**.

[10] N. F. Abunde, N. Y. Asiedu, A. Addo, *Int. J. Ind. Chem.* **2019**, *10*, 67.

[11] C. González-Figueredo, R. Alejandro Flores-Estrella, O. A. Rojas-Rejón, "Fermentation: Metabolism, Kinetic Models, and Bioprocessing," *Current Topics in Biochemical Engineering*, IntechOpen **2019**, p. 1.

[12] F. Ardestani, *Iran. J. Energy Environ.* **2014**, *5*, 8.

[13] J. Krishnan, A. A. Kishore, A. Suresh, A. K. Murali, J. Vasudevan, M. June, M. June, *Res. J. Pharm. Biol. Chem. Sci.* **2017**, 365.

[14] A. Abdussamad, M. Abdullahi, D. Shehu, Y. Murtala, B. Abba, S. Abubakar, I. Hadiza, S. Usman, M. Ferdaus, I. Salihu, *J. Appl. Sci. Environ. Manag.* **2017**, *21*, 1085.

[15] K. Dutta, *Chem. Biochem. Eng. Q.* **2015**, *29*, 437.

[16] S. A. Jimenez-Marquez, J. Thibault, C. Lacroix, *Int. Dairy J.* **2005**, *15*, 1156.

[17] B. Cho, J. Irudayaraj, M. C. Bhardwaj, *Trans. ASAE* **2001**, *44*.

[18] C. Du, D. Sun, *J. Food Eng.* **2006**, *72*, 39.

[19] H. Zheng, S. Fang, H. Lou, Y. Chen, L. Jiang, H. Lu, *Expert Syst. Appl.* **2011**, *38*, 5591.

[20] P. Sadegh, H. Melgaard, H. Madsen, J. Holst, *IFAC Proc. Vol.* **1994**, *27*, 1181.

[21] M. Ebrahimpour, W. Yu, B. Young, *Food Bioprod. Process.* **2021**, *126*, 81.

[22] A. Saraceno, S. Curcio, V. Calabrò, G. Iorio, *Comput. Chem. Eng.* **2010**, *34*, 1590.

[23] B. Li, Y. Lin, W. Yu, D. I. Wilson, B. R. Young, *J. Chem. Technol. Biotechnol.* **2021**, *96*, 125.

[24] J. Monod, *Annu. Rev. Microbiol.* **1949**, *3*, 371.

[25] L. Bodizs, M. Titica, N. Faria, B. Srinivasan, D. Dochain, D. Bonvin, *J. Process Control* **2007**, *17*, 595.

[26] L. Mears, S. M. Stocks, G. Sin, K. V. Gernaey, *J. Biotechnol.* **2017**, *245*, 34.

[27] K. M. C. Tjørve, E. Tjørve, *PLoS One* **2017**, *12*, e0178691.

[28] B. Gompertz, *Philos. Trans. R. Soc. London* **1825**.

[29] P. F. Verhulst, *Corresp. Mathématique Phys.* **1838**, *10*, 113.

[30] P. H. Franses, *Technol. Forecast. Soc. Change* **1994**, *46*, 45.

[31]   K. A. Johnson, R. S. Goody, *Biochemistry* **2011**, *50*, 8264.

[32]   L. Michaelis, M. L. Menten, R. S. Goody, K. A. Johnson, *Biochemistry* **1913**.

[33]   G. P. Philippidis, T. K. Smith, C. E. Wyman, *Biotechnol. Bioeng.* **1993**, *41*, 846.

[34]   M. Muloiwa, S. Nyende-Byakika, M. Dinka, *South African J. Chem. Eng.* **2020**, *33*, 141.

[35]   E. I. Canela, G. Navarro, J. L. Beltrán, R. Franco, The Michaelis-Menten paradox: Km is not an equilibrium constant but a steady-state constant. *bioRxiv* **2019**.

[36]   B. Maiorella, H. W. Blanch, C. R. Wilke, *Biotechnol. Bioeng.* **1983**, *25*, 103.

[37]   S. Aiba, M. Shoda, M. Nagatani, *Biotechnol. Bioeng.* **1968**, *10*, 845.

[38]   J. Haldane, *Enzymes, 1930*, MIT, Cambridge, **1965**.

[39]   N. Jerusalimsky, N. Neronova, *Dokl. Akad. Nauk SSSR* **1965**, 1437.

[40]   O. Levenspiel, *Biotechnol. Bioeng.* **1980**, *22*, 1671.

[41]   A. Ajbar, A. Fakeeha. *Bioprocess Biosyst. Eng.* **2002**, *25*, 21.

[42]   M. Arellano-Plaza, E. J. Herrera-López, D. M. Díaz-Montaño, A. Moran, J. J. Ramírez-Córdova, *Int. J. Mahematics Comput. Simul.* **2007**, *1*, 1.

[43]   M. M. Tseng, M. Wayman, *Can. J. Microbiol.* **1975**, *21*, 994.

[44]   H. Moser, *Cold Spring Harb. Symp. Quant. Biol.* **1957**.

[45]   R. Boulton, *Am. J. Enol. Vitic.* **1980**.

[46]   A. Amrane, C. Couriol, *J. Chem. Technol. Biotechnol.* **2002**, *77*, 950.

[47]   F. S. Guthery, K. P. Burnham, D. R. Anderson, *J. Wildl. Manage.* **2003**, *67*, 655.

[48]   J. D. Kong, **2017**, University of Alberta.