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review

Unstructured Models for Lactic Acid Fermentation – A Review

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Summary

To describe a microbial process, two kinds of models can be developed, structured and unstructured models. Contrary to structured models, which take into account some basic aspects of cell structure, their function and composition, no physiological characterization of cells is considered in unstructured models, which only consider total cellular concentration. However, in spite of their simplicity, unstructured models have proven to accurately describe lactic acid fermentation in a wide range of experimental conditions and media. A partial link between cell growth and production, namely the Luedeking and Piret model, is mostly considered by the authors. Culture pH is the main parameter to be considered for model development. Acidic pH leads to inhibitory concentrations of undissociated lactic acid, the main inhibitory component, which causes cessation of growth and then production. On the other hand, pH control at optimal value for LAB growth allows to overcome product inhibition (by the total lactic acid produced or its undissociated part); hence nutritional limitations have to be considered for model development. Nitrogen is mainly involved in cessation of growth, owing to the fastidious nutritional requirements of LAB, while lactic acid production ceased when carbon was exhausted from the medium. The lack of substrate inhibition when usual concentrations of carbon substrate are used should be noted.

Key words: lactic acid bacteria, growth inhibition, unstructured models, nutritional limitations

Introduction

Kinetic models enable bioengineers to design and control microbial processes. Mathematical models, together with carefully designed experiments, allow the improvement of the evaluation and knowledge concerning system behaviour (*1*). To describe a microbial process, two kinds of models can be developed, structured and unstructured models. Structured models take into account some basic aspects of cell structure, their function and composition, and have been reported to accurately describe lactic acid fermentation (*1,2*), but they can seem complex. Only total cellular concentration is considered in unstructured models, and hence they do not involve any physiological characterization of the cells. However, they have proven to accurately describe lactic acid fermentation in a wide range of experimental conditions and media (*3–8*). An exhaustive review of the available

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unstructured models is therefore presented thereafter. The paper is divided into two main parts: models for growth kinetics are reviewed in the first part, followed by the available models for production kinetics in the second part.

Growth Kinetics

Some growth phases can be characterized by the examination of growth time-courses: the lag phase, the exponential growth phase, the deceleration growth phase, the stationary phase and the phase of exponential decay. The complexity of this biological phenomenon requires the use of nonlinear mathematical models to identify growth parameters. These models are described thereafter.

Bacterial growth can be described as follows:

$$\frac{dX}{dt} = \mu \cdot X \qquad /1/$$

where X is the concentration of biomass, μ is the specific growth rate and t is time.

Some authors (*9–14*) also took into account cell death in their growth kinetics model and considered an exponential decay for the decline phase:

$$\frac{dX}{dt} = \mu \cdot X - k_d \cdot X \qquad /2/$$

with k_d as the specific death rate.

Carbon limitation

The limitation by the carbon substrate (lack of inhibition by the product) is often described by the Monod model (*15*):

$$\mu = \mu_{max} \frac{S}{S + k_S} \qquad /3/$$

where S and k_S are the substrate concentration and substrate saturation constant, respectively.

Some authors added to the Monod model a term for inhibition by the carbon substrate (*16*), namely they considered the Haldane equation:

$$\mu = \mu_{max} \frac{S}{S + k_S + S^2/k_i} \qquad /4/$$

where k_i is the substrate inhibition constant.

An exponential substrate inhibition model (*17*) was also tested:

$$\mu = \mu_{max} \frac{S}{k_S + S} \exp\left(-\frac{S}{k_i}\right) \qquad /5/$$

However, according to Altiok *et al.* (*16*), a substrate inhibition term did not appear to be relevant to describe their experimental data. Regarding the carbon source (whey), substrate concentration was too low to be inhibitory, taking into consideration the high productivities reported for conventional batch cultures even at high initial glucose or lactose concentrations (above 100 g/L) (*18–20*).

Bâati *et al.* (*21*) proposed the following relation based on the Monod model (Eq. 3) and governing cell multiplication at low temperatures:

$$\mu = a \cdot q_p - b \frac{T_{max} - T}{c + (T_{max} - T)} \frac{S}{k_a + S} \qquad /6/$$

where q_p is the specific production rate, T is temperature and T_{max} a maximum temperature beyond which there is no more growth; the terms a (yield of biomass on lactate), b (maximal maintenance) and c (constant of affinity) are constants; and k_a is the substrate catabolic constant of affinity of the non-proliferating cells.

Growth kinetics on multiple substrates was also described. Nancib (*13*) examined the effect of both glucose (G) and fructose (F) concentrations during batch cultures of *Lactobacillus casei* ssp. *rhamnosus* on date juice for lactic acid production and took into account cell death in their model:

$$\frac{dX}{dt} = \left[\mu_{maxG} \frac{G}{k_G + G} - k_{dG}\right] X_G + \left[\mu_{maxF} \frac{F}{k_F + F} - k_{dF}\right] X_F \qquad /7/$$

where G and F are the glucose and fructose concentrations, respectively.

Bajpai-Dikshit *et al.* (*22*) proposed the following model which involved the intracellular enzyme level to describe the growth of *Lactobacillus rhamnosus* on multiple substrates:

$$\mu_i = \frac{\mu_{max,i}\left(\frac{e_i}{e_{max,i}} S_i\right)}{k_{Si} + S_i} \qquad /8/$$

where $\mu_{max,i}$ is the maximum specific growth rate on the substrate S_i, $\frac{e_i}{e_{max,i}}$ is the specific relative growth enzyme levels inside the cell and k_{Si} is the substrate saturation constant of the substrate S_i. The net specific growth rate μ on a medium containing two substrates in terms of individual growth rates can be defined as:

$$\mu_i = \alpha_1 \mu_1 + \alpha_2 \mu_2 \qquad /9/$$

where μ_i is the specific growth on the substrate i, α_1 and α_2 are the control coefficients corresponding to the genetic and metabolic regulations inside the cell, respectively. According to these authors, the developed kinetic model can be used for the design and operation of batch and continuous reactors, such as fed-batch and chemostat reactors.

However, a carbon substrate limitation model (Monod) is only recorded in case of a high nitrogen supplementation of culture media (*23,24*); while in the general case, cessation of growth can be attributed to the deficiency in peptide sources (*25,26*) or in growth factors (*27,28*).

Product inhibition

Inhibition by the total lactic acid formed

Luedeking and Piret (*3*) proposed a linear relation between the inhibitory end-product and the specific growth rate:

$$\mu = \mu_{max} - \delta \cdot P \qquad /10/$$

This relation where δ is a constant and P is the lactic acid concentration matched the results recorded for *Lactobacillus delbrueckii* grown on glucose (*3*). Belhocine (*29*)

showed that the results obtained in continuous culture of *Lactobacillus helveticus* grown on lactose depend on the proportional inhibition (Eq. 10) rather than on substrate limitation (Eq. 3) and/or a non-competitive inhibition by the product, which were considered by many authors as discussed below.

Several authors held into account in their growth model an inhibition by the formed product. If this production is non-competitive, the specific growth rate becomes (*30–33*):

$$\mu=\mu_{max}\frac{S}{S+k_S}\frac{k_P}{P+k_P} \qquad /11/$$

where P and k_P are the product concentration and product inhibition constant, respectively.

Owing to the low k_S values (some tens of mg/L), which appear negligible in comparison with the experimental residual lactose concentration (1 or 2 g/L), a substrate limitation model (Eq. 3) may lead to the following simplified expression:

$$\mu=\mu_{max}\frac{S}{S+k_S}\approx\mu_{max} \qquad /12/$$

while the specific growth rate remains constant only during the exponential growth phase. Tayeb *et al.* (*34*), as well as Ajbar and Fakeeha (*35*) considered therefore only the product inhibition, without considering the carbon substrate limitation:

$$\mu=\mu_{max}\frac{k_P}{P+k_P} \qquad /13/$$

Rogers *et al.* (*4*) attempted to describe experimental data on batch culture using *Streptococcus cremoris* HP[1] various growth models, including the Kendall model (*36*):

$$\mu=k_1\left(1-\frac{X}{k_2}\right) \qquad /14/$$

the Monod model (Eq. 3) (*15*); a non-competitive inhibition, with (Eq. 11) or without (Eq. 13) substrate limitation (*34,37*), or a modified non-competitive inhibition:

$$\mu=k_1\left(\frac{S}{k_S+S}\right)\left(\frac{k_P}{k_P+P}\right)-k_3 \qquad /15/$$

as well as the Edwards model (*38*), which was only a modified non-competitive inhibition with an additional term to account for a possible substrate inhibition:

$$\mu=k_1\left(\frac{S}{k_S+S}\right)\left(\frac{k_P}{k_P+P}\right)\left(\frac{k_i}{k_i+S}\right) \qquad /16/$$

According to Rogers *et al.* (*4*), if compared to Eq. 11, Eqs. 15 and 16 did not improve growth fitting, so the simplest non-competitive inhibition (Eq. 11) should be preferred. These authors reported that lactose limitation and lactic acid inhibition had a significant effect on the growth, while initial substrate concentration and cell mortality did not affect growth significantly.

Ben Youssef *et al.* (*12*) modified the non-competitive inhibition by adding a term to account for the effect of a critical lactic acid concentration P_c:

$$\mu=\mu_{max}\left(\frac{S}{k_S+S}\right)\left(\frac{k_P}{k_P+P}\right)\left(1-\frac{P}{P_c}\right) \qquad /17/$$

Some authors (*39,40*) added product inhibition term to the Monod relation:

$$\mu=\mu_{max}\frac{S}{k_S+S}\left(1-\frac{P}{P_{inh}}\right) \qquad /18/$$

where P_{inh} is the product concentration above which bacteria do not grow.

Amongst the several models tested by Burgos-Rubio *et al.* (*41*), a simplified expression of the above relation was proposed:

$$\mu=\mu_{max}\left(1-\frac{P}{P_{inh}}\right) \qquad /19/$$

The above expression was also considered by Mercier *et al.* (*42*) and Moldes *et al.* (*43*), who considered the maximum lactic acid concentration, P_{max}, instead of the inhibitory concentration, P_{inh}.

Kumar Dutta *et al.* (*7*), as well as Kwon *et al.* (*20*), modified the above expression by considering the addition of a toxic power for the product n:

$$\mu=\mu_{max}\frac{S}{k_S+S}\left(1-\frac{P}{P_{max}}\right)^n \qquad /20/$$

Boonmee *et al.* (*8*) considered substrate limitation and inhibition, as well as product inhibition, and hence proposed the following model:

$$\mu=\mu_{max}\left(\frac{S}{k_S+S}\right)\left(\frac{k_i}{k_i+S}\right)\left(1+\frac{P-P_i}{P_m-P_i}\right) \qquad /21/$$

where P_m and P_i are the maximum inhibitory lactate concentration and the threshold level of lactate before an inhibitory effect, respectively.

Nandasana and Kumar (*14*) modified the above model by considering an exponential decay for product inhibition:

$$\mu=\mu_{max}\left(\frac{S}{k_S+S}\right)\left(\frac{k_i}{k_i+S}\right)\exp\left(-\frac{P}{k_P}\right) \qquad /22/$$

It should be observed that lactose can only be inhibitory at high concentration levels (above 100 g/L) (*18–20*), which is obviously not the case with whey, the usual substrate used for lactic acid production. Consequently, Pinelli *et al.* (*33*) did not consider the substrate inhibition term in their model:

$$\mu=\mu_{max}\left(\frac{S}{k_S+S}\right)\exp\left(-\frac{P}{k_P}\right) \qquad /23/$$

In agreement with Gonçalves *et al.* (*44*), who considered both substrate and product inhibitions, Åkerberg *et al.* (*45*) added a product inhibition term to the substrate inhibition relation of Briggs-Haldane (*46*):

$$\mu=\mu_{max}\frac{S}{k_S+S+S^2/k_i}\left(1-K_{pH}\cdot P\right)^n \qquad /24/$$

With the following expressions, the pH dependence of the parameters is described:

$$\mu_{max}=\frac{\mu_m}{1+\left(k_{\mu1}/[H^+]\right)+\left(k_{\mu2}[H^+]\right)} \qquad /25/$$

$$K_{pH}=\frac{K_{pm}}{1+\left(k_{p1}/[H^+]\right)+\left(k_{p2}[H^+]\right)} \qquad /26/$$

where K_{pH} is the parameter representing the pH dependence of product inhibition, and μ_m, k_μ, K_{pm} and k_p are kinetic parameters that describe the effect of the pH on μ_{max} and K_{pH}.

A product inhibition term was also added to the Briggs-Haldane relation by Ajbar and Fakeeha (*35*):

$$\mu=\mu_{max}\frac{S}{k_S+S+S^2/k_i}\left(1-\frac{P}{P_{max}}\right)^n \qquad /27/$$

Ishizaki and Ohta (*47*) examined the fermentation of L-lactate in batch culture of *Streptococcus* sp. IO-1 at various carbon substrate concentrations. They reported uncompetitive inhibition, and hence proposed the following relationship:

$$\mu=\mu_{max}\frac{S}{K_m+\left(1+P/k_p\right)S} \qquad /28/$$

where K_m and k_p are the Michaelis constant and the lactate inhibition constant for cell growth, respectively.

Some authors used a complex model to validate their experimental results; Biazar *et al.* (*48*) tried to solve the equation related to the growth kinetics of *Lactobacillus helveticus* using an Adomian decomposition method (*49, 50*):

$$\mu=\mu_{max}\frac{S}{k_S+S}\exp\left(-\frac{S}{K_{iS}}\right)^{n_1}\exp\left(-\frac{P}{K_{iP}}\right)^{n_2}-k_d \qquad /29/$$

where K_{iS} is the substrate concentration at which the substrate inhibition factor is: $e^{-(S/K_{iS})^{n_1}}=0.368$; and K_{iP} is the lactic acid inhibition concentration at which the product inhibition factor is: $e^{-(P/K_{iP})^{n_2}}=0.368$.

Peeva and Peev (*51*) considered only the inhibitory effect by the product and hence proposed the following model:

$$\mu=\mu_{max}\left(1-k_pP^\alpha\right)-k_d \qquad /30/$$

$$\alpha=6.13\cdot P_{max}-0.056 \qquad /31/$$

where k_d is the cell death rate, k_p is a coefficient for product inhibition and P_{max} is the theoretical lactic acid concentration obtained after total substrate consumption.

Growth inhibition by lactic acid is only observed in experiments carried out at acidic pH (*52,53*) or in the absence of pH control (*54*), therefore pH control is needed at its optimal value for lactic acid production (5.9) (*55,56*) during culturing to overcome this inhibition. Moreover, the lack of product inhibition during culturing at usual carbon substrate concentrations, like the lactose content of whey, has been clearly demonstrated (*57*). This constitutes one of the main drawbacks of the above models.

Inhibition by undissociated lactic acid

It is now recognised that the main inhibitory component is the undissociated form of lactic acid. Inhibition by weak organic acids is related to the solubility of the undissociated form within the cytoplasmic membrane and the insolubility of the ionised acid form (*54,58*); the result is an acidification of the cytoplasm and the collapse of the motive force, causing an inhibition of nutrient transport (*59,60*). It should be observed that in case of pH control at its optimal value for lactic acid production (5.9), the final free lactic acid concentration during culture on whey (approx. 0.3 g/L) is below the inhibitory threshold (*54*), leading to the absence of inhibitory effect (*61,62*).

Yeh *et al.* (*63*) assumed a non-competitive inhibition:

$$\mu=\mu_{max}\frac{S}{S+k_S}\left(\frac{K_{HL}}{[HL]+K_{HL}}\right) \qquad /32/$$

with $[HL]$ as the undissociated lactic acid concentration.

Some authors (*9,11,64*) added to the Monod model a term to account for the inhibition by the lactate ion L and an exponential decay to account for the inhibitory effect of the undissociated lactic acid HL:

$$\mu=\mu_{max}\frac{S}{k_S+S}\left(1-\frac{[L]}{[L]_{max}}\right)\exp\left(-\frac{[HL]}{[HL_{max}]}\right) \qquad /33/$$

where L_{max} and HL_{max} are the dissociated and undissociated lactic acid inhibition constants, respectively.

Leroy and De Vuyst (*65*) also added to the Monod model an inhibitory term involving the concentration of undissociated lactic acid with a toxic power n:

$$\mu=\mu_{max}\frac{S}{k_S+S}\left(1-\frac{[HL]}{[HL]_{max}}\right)^n\gamma_N \qquad /34/$$

where γ_N is the remaining self-inhibition coefficient ascribed to the limited availability of nutrients.

A drawback of the above models is their development to describe cultures carried out at pH controlled at the optimal value, namely close to 6, leading to a final free lactic acid concentration below the inhibitory threshold (*54*). However, such models can be useful to describe cultures carried out at acidic pH or without pH control. With this aim, Amrane and Couriol (*66*) noted that the specific growth rate decreased when undissociated lactic acid concentrations increase, and consequently proposed the following logistic equation to describe cultures carried out without pH control:

$$\mu=\mu_{max}\exp\left(-\frac{[HL]}{[HL]_C}\right)-\mu_0 \qquad /35/$$

where μ_0 and $[HL]_C$ are the constants.

Vereecken and Van Impe (*67*) also proposed an exponential decay, which involved the undissociated lactic acid concentration and pH (or hydrogen ion concentration $[H^+]$:

$$\mu=\mu_{max}\exp\left(-k_\mu\left([HL]-[HL]_{min}\right)\right) \qquad /36/$$

$$k_\mu=a+\frac{b}{[H^+]^2} \qquad /37/$$

where $[HL]_{min}$ is the minimum inhibitory concentration of undissociated lactic acid, while a and b are constants.

To describe *Lactobacillus plantarum* growth in cucumber juice (vegetable fermentation), Passos *et al.* (*10,68*) took into account NaCl and undissociated acetic acid concentrations, $[HA]$, added to the juice, in addition to a carbon substrate limitation (Monod model), an inhibitory pH (hydrogen ion) effect and an undissociated lactic acid concentration effect:

$$\mu=\mu_0\left(\frac{[S]}{0.056+[S]}\right)\left(1-\frac{[H^+]}{[H^+]_{max}}\right)^{2.6}\left(1-\frac{[HL]}{69}\right)^{2.0} \qquad /38/$$

$$\mu_0 = 0.35\left(1+\frac{1.5[HA]}{5.8+[HA]}\right)\left(1-\frac{[HA]}{150}\right)^{1.7} \cdot \left(1+\frac{1.6[\mathrm{NaCl}]}{4.47+[\mathrm{NaCl}]}\right)\left(1-\frac{[\mathrm{NaCl}]}{11.8}\right) \quad /39/$$

pH inhibitory effect

In addition to the undissociated lactic acid concentration (*54*), pH also plays a significant role in the inhibitory effect (*69*). Moreover, according to Fu and Mathews (*70*), the inhibitory effect of acidic product resulted mainly from the action of the proton ions, and hence pH can be used as a basic parameter in kinetic models based on the Monod model with μ_{max} and k_S functions of the pH:

$$\mu = \mu_{max}(\mathrm{pH})\frac{S}{k_S(\mathrm{pH})+S} \quad /40/$$

where the optimal parameter sets are correlated with pH through the following empirical equations (4≤pH≤7) (*70*):

$$\mu_{max} = 0.523\exp\left(-0.16(\mathrm{pH}-5.0)^2\right) - \frac{0.265}{0.614(\mathrm{pH}-4.0)} \quad /41/$$

and $$k_S = 0.605\exp\left(0.85(\mathrm{pH}-5.0)^2\right) + \frac{106.4}{0.65+(\mathrm{pH}-4.0)} \quad /42/$$

Nitrogen limitation

The above models involved only the carbon substrate limitation, mainly through the Monod model, as well as product inhibition, through the total concentration of the produced acid or its undissociated form, or the consequence of this production, a pH decrease. However, it is not the general feature recorded during lactic acid fermentation. Growth inhibition by lactic acid is observed in experiments carried out at acidic pH (*52,53*) or in the absence of pH control (*54*), which is why pH control is needed at its optimal value for lactic acid production (5.9) (*55,56*) to overcome this inhibition. Moreover, the complex substrates containing peptidic nitrogen and growth factors (*71–73*) added to the culture media are major contributors to the production cost of the final product (*74, 75*), and hence nitrogen limitations are usually observed instead of carbon limitation of growth.

Amrane and Prigent (*6,76*) proposed a logistic function (Eq. 13) to describe experimental data:

$$\mu = \mu_{max}\frac{1}{1+\frac{c\cdot\exp(d\cdot t)}{\mu_{max}-c}} \quad /43/$$

where c and d are constants.

Growth time-course was accurately fitted by means of the above model; however, it was not completely satisfactory from a cognitive point of view. Indeed, all growth parameters did not have an obvious biological meaning (*6*).

Consequently, the Verlhust model (*77–79*), which was successfully applied to describe LAB growth (*52,53,61, 62,80–84*) may be preferred to the above model, since this logistic expression involves only growth parameters:

$$\mu = \mu_{max}\left(1-\frac{X}{X_{max}}\right) \quad /44/$$

where X_{max} is the maximum biomass concentration.

The term $\left(1-\frac{X}{X_{max}}\right)$ was taken in a global way for an increasing lack of nutrients, namely for nitrogen limitation (*23,24,78*).

According to Lan *et al.* (*85*), growth kinetics can be satisfactorily described by a modified Verlhust model, which indirectly takes into account the inhibitory effect of the product through an exponent m (*86*):

$$\mu = k\left(1-\frac{X}{X_{max}}\right)^m \quad /45/$$

where k is an empirical constant related to the maximum specific growth rate.

In addition to nutritional limitations through the Verlhust model, Altiok and *et al.* (*16*) also considered an inhibition by the produced lactic acid:

$$\mu = \mu_{max}\left(1-\frac{X}{X_{max}}\right)^f\left(1-\frac{P}{P_{max}}\right)^h \quad /46/$$

where f and h are parameters related to the 'toxic power' for biomass and the inhibitory product, respectively. These authors showed that the inhibitory effects on both biomass and product increased with the increase of h and f toxic power values.

However, since the main inhibitor of growth is the undissociated form of lactic acid (*54,60*), Bouguettoucha *et al.* (*62*) replaced the total lactic acid concentration by its undissociated form in the inhibition term:

$$\mu = \mu_{max}\left(1-\frac{X}{X_{max}}\right)\left(1-\frac{[HL]}{[HL]_{inh}}\right) \quad /47/$$

where $[HL]_{inh}$ is the undissociated lactic acid inhibitory threshold value, 8.5 g/L (*69*).

Owing to the fastidious nutritional requirements of lactic acid bacteria (especially those concerning nitrogen) (*87–89*), it appears difficult to include these limitations in a growth model, and the available literature lacks in models involving nutritional limitations in 'a direct way'. Leh and Charles (*5*) tried to solve this difficulty, since they considered carbon and nitrogen substrate limitations in their model. To account for both limitations, the following modification of the Monod relation (Eq. 3) was considered:

$$\mu = \mu_{max}\cdot\frac{1}{1+\frac{k_{pr}}{pr}+\frac{k_S}{S}+\frac{k_S}{S}\cdot\frac{k_{pr}}{pr}} \quad /48/$$

In this relation, pr and k_{pr} are the concentration and the saturation constant of 'usable proteins', respectively. The difficulties encountered in the use of this model come from the definition of the 'usable proteins'.

If the carbon substrate saturation constant k_S is neglected during growth when compared to the carbon substrate concentration S (*90*), the above equation (Eq. 48) can be simplified, leading to the Monod equation modified to account for a nitrogen substrate limitation:

$$\mu = \mu_{max}\cdot\frac{pr}{pr+k_{pr}} \quad /49/$$

By adding the product inhibition term to Eq. 48, the specific growth rate becomes:

$$\mu=\mu_{max}\cdot\frac{pr}{pr+\left(\frac{P}{k_{pr}+1}\right)^2\cdot k_{pr}} \qquad /50/$$

The above model can only be 'usable' if a clear definition and a relevant method for the determination of the really 'usable nitrogen' by bacteria is given (*91*), which is not at all obvious.

Schepers *et al.* (*92*) assumed that the specific growth rate was a function of the carbon and nitrogen substrates, the product and the pH, and proposed the following complex relation:

$$\mu=\underbrace{\left(\mu_{max}+\underbrace{\beta\cdot pH_c\cdot WP_c}_{A}\right)\frac{S}{S+k_S}\cdot\frac{Z}{Z+k_z}}_{B}\cdot \underbrace{\left(\frac{\exp\left(-k_{[HL]}\frac{P}{1+10^{(pH-pKa)}}\right)}{1+\exp\left(k_{[L^-]}\left(\frac{P}{1+10^{(pKa-pH)}}-k_{[L^-]}\right)\right)}\right)}_{C}\cdot \underbrace{e\left(\frac{\left(\left|pH_{opt}-pH\right|\right)_n}{\sigma^2}\right)}_{D} \qquad /51/$$

The above equation is the combination of four parts: the first one (A) characterizes a strong interaction between pH and whey permeate, WP, for maximum specific growth rate deduced from multifactor kinetic analysis, leading to its involvement in the growth model through coded factors, pH_c and WP_c (*93*); Monod substrate limitations were assumed for carbon and nitrogen substrate effects (part B); exponential inhibition by the undissociated lactic acid and logistic inhibition by lactate were taken into account through the third part (C); and the last part (D) corresponds to the pH effect (combination of Gaussian pH effect).

Production Kinetics

The model of Luedeking and Piret (*3,94*) is the most widely used concerning the kinetics of production. Amongst others, Kumar Dutta *et al.* (*7*), Boonmee *et al.* (*8*), Altiok *et al.* (*16*), Tayeb *et al.* (*34*), Keller and Gerhardt (*39*), Burgos-Rubio *et al.* (*41*), Åkerberg *et al.* (*45*), Biazar *et al.* (*48*), Roy *et al.* (*52*), Wang *et al.* (*64*), Vázquez and Murado (*83,84*), Bibal *et al.* (*95*), Ye *et al.* (*96*), Ha *et al.* (*97*) are authors who have shown that lactic acid production is partially associated with growth and then proposed the following relation:

$$q_P=\frac{dP}{X dt}=A\cdot\mu+B \qquad /52/$$

In this relation, q_p is the specific productivity rate, A and B are coefficients for growth- and non-growth-associated production, respectively.

Total link between growth and production has been considered by some authors (*13,98*), leading to the following simplified Luedeking and Piret expression:

$$q_p=A\cdot\mu \qquad /53/$$

However, this particular case is only recorded for media supplemented with high concentrations of nitrogen.

During lactic acid production by *L. casei*, Peeva and Peev (*51*) found that acid production was mainly non-growth associated, and hence proposed the following relationship:

$$q_p=\beta\left(1-k_p P^{\alpha}\right) \qquad /54/$$

where β is the biomass productivity coefficient.

Amrane and Prigent (*6,76*) noted that the beginning of the production is accurately described by Luedeking and Piret relation, namely for significant values of the specific growth rate. However, almost half of the lactic acid is produced during the deceleration and the stationary growth phases, whereas the specific growth rate tends towards the zero value. This part of production is not satisfactorily described by the Luedeking and Piret relation, which cannot account for the decrease of the specific production rate at low specific growth rates. The Luedeking and Piret model was therefore modified by introducing an additive term:

$$q_p=A\cdot\mu+B\left[1-\exp\left(-H\cdot\mu\right)\right] \qquad /55/$$

where H is a constant.

Rogers *et al.* (*4*) tested two substrate-dependent models, in addition to the Luedeking-Piret model, and obtained the following relation:

$$q_p=A\cdot\mu+B\cdot S \qquad /56/$$

which was improved by Jørgensen and Nikolajsen (*99*):

$$q_p=A\cdot\mu+B-C\cdot S \qquad /57/$$

where C is a constant.

Rogers *et al.* (*4*) also tested a substrate limitation model which described more accurately their experiment with *S. cremoris*:

$$q_p=A\cdot\mu+B\left(\frac{S}{k_S+S}\right) \qquad /58/$$

The above substrate limitation model was also considered by Berry *et al.* (*11*), as well as by Ben Youssef *et al.* (*12*), who replaced the substrate saturation constant k_S by the affinity constant of the resting cells for glucose $\overline{k}_S^{rc}$, which is the function of k_S.

In addition to substrate limitation, Boonmee *et al.* (*8*) took into account substrate inhibition, as well as possible limitation and inhibition by the lactate in their model:

$$q_p=A\cdot\mu+q_{pmax}\cdot B\left(\frac{S}{k_S+S}\right)\left(\frac{k_i}{k_i+S}\right)\left(1+\frac{P-P_i}{P_m-P_i}\right) \qquad /59/$$

where P_m and P_i are maximum and inhibitory threshold of lactic acid concentrations for lactic acid production, respectively.

Similarly to the growth (Eq. 22), Nandasana and Kumar (*14*) modified the model by Boonmee *et al.* (*8*) by considering an exponential decay for product inhibition:

$$q_p=A\cdot\mu+q_{pmax}B\left(\frac{S}{k_S+S}\right)\left(\frac{k_i}{k_i+S}\right)\exp\left(-\frac{P}{k_P}\right) \qquad /60/$$

The model was found to provide good predictions of experimental lactic acid production data.

In addition to a substrate limitation, Bâati *et al.* (*21*) also considered an exponential decay for product inhibition:

$$q_P = q_{Pmax} \frac{S}{S+k_S} \exp(-k_P \cdot P) \qquad /61/$$

where q_{pmax} is the maximum specific lactic acid production rate, which was given by the following expression:

$$q_{Pmax} = \left(K_b \cdot T - K_c\right)^2 \qquad /62/$$

where K_b and K_c are constants.

Similarly to the relation proposed for growth (Eq. 19), Moldes *et al*. (*43*) proposed a logistic relation for the production rate:

$$\frac{dP}{dt} = P_0^{'}\left(1 - \frac{P}{P_{max}}\right)P \qquad /63/$$

This relation can be helpful to describe experimental data, but its biological meaning is not at all obvious, owing to the absence of involvement of the biomass.

Monteagudo *et al*. (*40*) also considered a logistic term for the lactic acid inhibition, which was added to the Luedeking-Piret relation:

$$q_p = \left(A \cdot \mu + B\right)\left(1 - \frac{P}{P^{'}_{max}}\right) \qquad /64/$$

where P'_{max} is the concentration greater than P_{max}, above which bacteria do not produce lactic acid.

Since the undissociated form of lactic acid is the main growth inhibitor (*54,60*), Balannec *et al.* (*82*) considered the undissociated form of the product instead of its total amount. The inhibitory term was added to the non-growth-associated part of the production, to account for cessation of production in case of culture without pH control or at acidic pH:

$$q_p = A \cdot \mu + B\left(1 - \frac{[HL]}{[HL]_{inh}}\right) \qquad /65/$$

On the other hand, during culturing at pH controlled at 5.9, the exhaustion of the carbon substrate caused cessation of production; a corrective term was therefore introduced to account for this behaviour (*100*):

$$q_p = A \cdot \mu + B\left(1 - \frac{S_{res}}{S}\right) \qquad /66/$$

The parameter S_{lim}, which corresponds to the limiting lactose concentration (3 g/L), deduced from several runs on whey supplemented with various yeast extract concentrations (*24,91*), has recently been introduced in the above relation in place of the residual lactose concentration S_{res}:

$$q_p = A \cdot \mu + B\left(1 - \frac{S_{lim}}{S}\right) \qquad /67/$$

To avoid the use of two expressions for production rate (Eqs. 61 and 63), depending on culture conditions, both above expressions were merged, leading to a unique expression taking into account both effects, a nutritional limitation effect and an inhibitory effect:

$$q_p = A \cdot \mu + \left(1 - \frac{S_{lim}}{S}\right)\left(1 - \frac{[HL]}{[HL]_{inh}}\right) \qquad /68/$$

Conclusion

Nutritional limitations (carbon and nitrogen) and product inhibition are mainly considered to account for cessation of growth. However, analysis of lactic acid bacteria culture shows that pH is the main factor to be considered for model development. The undissociated form of lactic acid is the main inhibitor, whose concentration increased at acidic pH, and thus in addition to the pH effect caused the cessation of growth. Some authors take into account the inhibitory effect of the undissociated lactic acid in their growth model, and hence also involve the pH through the Henderson–Hasselbach equation. To overcome inhibitory effects, pH is usually controlled at its optimal value (close to 6). Under these conditions and the usual culture conditions, the lack of lactic acid inhibition, as well as carbon substrate inhibition, is clearly demonstrated. Therefore, nutritional limitations cause the cessation of growth. Complex substrates containing peptidic nitrogen and growth factors are generally added to culture media, owing to the fastidious nutritional requirements of lactic acid bacteria, and hence nitrogen limitation is usually observed instead of carbon limitation of growth. However, there is a lack of models involving nutritional limitations in 'a direct way' in the available literature, owing to the difficulty to characterize the 'usable nitrogen'. However, some models are available, involving nitrogen limitations in 'a direct way' or indirectly through the Verlhust expression, for instance.

The Luedeking and Piret model, involving a partial link between growth and production, is the most widely used to describe production kinetics. As for the growth, pH is the main parameter to be considered for model development. At acidic pH, cessation of production resulted from both inhibitory effects of the undissociated part of lactic acid and pH, and has been considered by some authors. On the other hand, the control of pH at its optimal culture value leads to cessation of production due to carbon exhaustion from the medium, since LAB are unable to use the carbon components released by autolysis of dead cells; the Monod model is mainly considered to account for this behaviour.

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