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Mathematical Models for Microbial Kinetics in Solid-State Fermentation: A Review

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Context: In this review, we discuss empirical and stoichiometric models, which have been developed recently in SSF processes and the influence of environmental conditions on the variables of these models. Additionally, new studies on modeling of product formation are also mentioned.

Evidence Acquisition: Solid-state fermentation (SSF) is recognized as a cheap process for producing many valuable products like industrial enzymes and bioethanol. To develop, optimize, and scale-up this process, mathematical models are required. In this review, we collected all the papers regarding microbial growth and product formation modeling in SSF. The pros and cons of each model and confirmation with experimental data were also discussed. We discussed here the simple empirical growth kinetics models and the effect of environmental conditions on these models parameters, stoichiometric models and product formation models.

Results: Simple empirical models are used widely in the kinetic modeling of SSF processes due to their simplicity and ease of use. However, more studies should be done in this field to make them more accurate, especially; the effect of environmental conditions, like temperature and moisture, on key variables of the model must be considered. Robust modeling methods, like stoichiometric models, are in their early stages in SSF processes and require more studies. Developing models in which transport phenomena models are coupled with the growth kinetics models can help better SSF bioreactor designing. On the other hand, to use SSF for producing valuable products, product formation models, which are not developed well in SSF processes, are necessary.

Conclusions: To use SSF for producing valuable metabolites in large scales, more attention is required for modeling the SSF processes, especially for product formation models and using modern methods like stoichiometric models.

Keywords: Growth Kinetics; Mathematical Modeling; Product Formation Model; Solid-State Fermentation

1. Context

Solid-state fermentation (SSF) is a kind of fermentation, in which microorganisms grow on solid material in the absence (or near absence) of free water; however, sufficient moisture should exist in the solid material to support the growth and metabolism of the microorganisms (1). In this process the solid material may act as carbon/energy source or as an inert support (2). The inert support may also provide enough surface for microbial growth (3). SSF has some advantages over submerged fermentation such as cheaper substrate (usually agricultural wastes), lower energy requirements and investment cost, better volumetric yield and less wastewater production (which makes the downstream processes easier) (2, 4). Fungi and other microorganisms exhibit different physiologies in SSF that has been called physiology of solid medium. As a result of these different physiologies, enzymes and secondary metabolites are often produced at higher yields in SSF (5). According to studies on lovastatin production in SSF, the specific environment of SSF may induce higher transcription of the specific transcription factor.

On the other hand, some drawbacks cause difficulties in application and scale-up of SSF processes. For example, due to low heat conductivity of solid particles and lack of free water, heat removal is difficult in SSF processes, especially in large scales (6, 7). Additionally, due to the solid nature of the substrate, mixing is not effective in SSF. Thus, significant water and temperature gradients may appear in the solid bed. As a result of this heterogeneous composition of solid substrate, monitoring and controlling of the process parameters like temperature,

Implication for health policy/practice/research/medical education:
Solid state fermentation (SSF) is recognized as a cheap process for producing many valuable products like industrial enzymes and bioethanol. To develop, optimize and scale-up this process to industrial scales, mathematical models are required. In this review, the mathematical models on microbial growth and product formation in solid-state fermentation were discussed.

moisture, pH and biomass content is difficult in SSF processes (2, 4, 8).

The application of SSF in industrial processes was held back due to difficulties in monitoring and controlling different involved variables. To study the growth kinetics of the microorganisms and mathematically model the heat and mass transfer in SSF, measurement of biomass content, substrate and produced metabolite concentrations and other process parameters are required (8). Unfortunately, direct measurement of biomass content is difficult in SSF, because separating the microorganism from solid particles is difficult, especially for fermentations involving filamentous fungi, because the fungal hyphae penetrate into the substrate (9). Therefore, many researchers used indirect measurement methods such as production of primary metabolites (10), carbon dioxide and oxygen metabolism (11-15) and extracellular enzymes (16), protein content of biomass (17), variation in the electrical conductivity between biomass and solid substrate (18), changes in the color of the fermentation medium (19), measuring other compounds such as ergosterol, glocusamine (20), nucleic acids (21), quantification of antibody reactivity in the mycelium cell wall via enzyme-linked immunosorbent assays (22), using FT-NIR (Fourier transform near-infrared) spectroscopy, and support vector data description (23).

Like other processes, SSF requires mathematical models for optimization and scale-up. However, due to the above-mentioned reasons, modeling of the SSF processes is quite complicated, and many of the proposed models in SSF have been simple empirical models that are under developed (8).

As Mitchell et al. mentioned in their review article (8), SSF mathematical models consist of two sub-models: (1) models that use transport phenomena relations to describe the mass and heat transfer within and between various phases of the process and (2) models that describe the growth kinetic of the microorganisms. For evaluating the growth kinetic models, simple empirical equations or mechanistic models can be used. The latter is more difficult and is considered as the intraparticle phenomena that occur at the level of individual particles (8, 24). Since there were no recent developments in this field, we do not consider such models in this review, and instead, we review the kinetic sub-models, which have been developed recently.

In recent years, some new models were developed based on the interactions within cells. These models (Stoichiometric models) considered of the microbial metabolism, metabolic pathways and metabolism regulation (25). In these models, steady-state mass balances were written within the cell, as a result, extracellular phenomena like biomass formation rate, substrate uptake and product formation rates could be coupled with intracellular carbon and energy fluxes. This kind of modeling is rarely used in SSF processes and we have also considered these models in this review.

SSF was reported to be a favorable process for the production of enzymes. Using agricultural wastes as solid substrates makes SSF a cost-effective process for production of different metabolites. In addition to enzymes, there is an increasing interest for production of bioethanol using SSF as an economic process in recent years. To scale-up these researches to the industrial scale, we need product formation models. Like the biomass measurement, determination of the product formed in the SSF process is also complex. Consequently, many researchers have only reported the production of a specific metabolite in the SSF process and have not included product formation rate in their model. As a result, we can observe the lack of product formation models for the SSF processes. Here, we also mention some new product formation models.

The current work reviews both simple empirical microbial growth rate models that have been used in most bioreactor models and recently developed stoichiometric models. Additionally, some new models on product formation are also discussed.

2. Evidence Acquisition

2.1. Empirical Growth Kinetics Models

One of the most important models is growth kinetic models which are essential for controlling and modeling processes (8). To develop a suitable mathematical model for describing the SSF processes, a growth kinetic model should be developed first. In SSF processes, heterogeneous solid substrates and low heat conductivity of solid particles will cause significant gradients of temperature, moisture content, O_2, and other nutrient concentrations (1, 8, 26). Of course, mathematical modeling of such systems is more complicated and requires partial differential equations. Although mechanistic models can provide us with more accurate results (if developed well), the difficulties involved in this approach lead many researchers to use simple empirical models.

Linear, exponential, logistic, and two-phase models are the most important empirical growth rate models in SSF processes.

2.1.1. Logistic Growth Kinetics Model

The logistic model was first used by Okazaki et al. in SSF (10). This empirical model is used more frequently than other empirical models for studying the growth kinetics of SSF. The logistic model represents the growth limits and does not require transport phenomena relations (27). The logistic model is based on the fact that available surface area is limited in the SSF process and the rate of biomass growth depends on maximal biomass, X_m (8). The

other assumption of this model is that specific growth rate during the initial logarithmic growth phase, μ_m, is not dependent on substrate concentration. The differentiated and integrated forms of logistic model are as follows:

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

$$X = \frac{X_m}{1 + \left(\left(\frac{X_m}{X_0}\right) - 1\right)e^{-\mu t}} \quad [2]$$

where X_0 is the initial microbial biomass.

Growth kinetic models can be used to develop a bioreactor model in order to describe the environmental condition (like temperature, moisture, etc.) in the bioreactor as a function of time, and predict the changes in the behavior of microorganism in these conditions. Obviously, the two most important environmental variables in SSF bioreactor models are temperature and moisture content of the solid medium. Due to the heat generated from respiration of microorganisms, the temperature in the bioreactor bed increases. On the other hand, due to the lack of free water in the bioreactor bed and low heat conductivity of solid particles, this generated metabolic heat could not be removed from the bioreactor bed, and consequently, temperature gradients appear in the process. Mixing is rarely used in SSF for removing the gradients, because most of the fungi and solid particles cannot resist against the shear forces that result from mixing. Consequently, microorganisms' growth are a non-isothermal process in SSF bioreactors (28).

In addition to temperature, moisture gradients should also be considered in modeling SSF bioreactors. For removing the generated heat from the bed, forced aeration is usually used. However, low amounts of heat is removed from the bed by heat convection, and instead, evaporation has the main role in this regard (29). This phenomenon leads to large moisture losses, and thus, moisture gradients appear in the moist bed of SSF bioreactors. Therefore, the effect of moisture content and temperature on microbial growth should be considered in the models.

2.1.1.1. Effect of Environmental Conditions on Microbial Growth

The three parameters of the logistic model, x_0, x_m and μ_m may have dependency on temperature. The amount of inoculum at the beginning of the fermentation, x_0, is not temperature-dependent, but the lag phase period is temperature-dependent. Many researchers have investigated these dependencies (30). Many equations were developed for describing the effect of temperature on μ_m, like Esener (31), Rotkowsky model (32) and Arrhenius equation (30, 33) (Table 1). For the effect of temperature on the maximum amount of biomass x_m, polynomial equation (34) and an extended Ratkowsky model can be used (Table 1).

Table 1. Some Equations that Describe the Effect of Temperature on x m and μ m in the Logistic Model

Model	Equation	Parameters Definition	Ref.
Esener	$\mu_{max}(T) = \frac{A.\exp\left(-\frac{\Delta H_1}{RT}\right)}{1 + k.\exp\left(-\frac{\Delta H_2}{RT}\right)}$	μm: maximum growth rate, A, k: constants, $\Delta H1$ = activation enthalpy of limiting reaction, $\Delta H2$ = enthalpy change of the inactivation reaction, R: universal gas constant	(6, 31, 35)
Arrhenius	$\mu_{max}(T) = k_g^0.\exp\left(\frac{-E_g}{RT}\right) - k_g\left(\frac{-E_d}{RT}\right)$	kg^o: constant, Eg: growth activation energy, Ed: thermal deactivation energy	(30, 33)
Polynomials	$\mu_{max}(T) = -s_0 + s_1T - s_2T^2 + s_3T^3 - s_4T^4 + s_5T^5$ $\mu_{max}(T) = -b_0 + b_1T - b_2T^2$	$s0, \ldots, s5$: constants, $b0, b1, b2$: constants	(6, 36)
Ratkowsky	$\mu_{max}(T) = b.(T - T_{min}).\left[1 - \exp\left(c.(T - T_{max})\right)\right]^2$	$Tmin$: minimum growth temperature, $Tmax$: maximum growth temperature, b, c: constants	(32, 37)
Polynomial	$X_m(T) = -c_0 + c_1T - c_2T^2 + c_3T^3 - c_4T^4$	$c0, \ldots, c4$: constants	(6)
Saucedo-Castaneda	$\mu = \frac{2.964 \times 10^{11}\exp\left(\frac{-70225}{RT}\right)}{1 + 1.3 \times \exp\left(\frac{-283356}{RT}\right)}$ $X_m = -127.08 + 7.95(T - 273) - 0.016(T - 273)^2$ $4.03 \times 10^{-3}(T - 273)^3 + 4.73 \times 10^{-5}(T - 273)^4$		(6)

Another model for the kinetics of microbial growth that contains the influence of temperature variations in SSF

was developed by Dalsenter et al. (38). In this model, they used the level of an essential component within the biomass, F, in the logistic equation. It was assumed that the level of this component controls microbial growth. This component is dimensionless and varies between zero and one. When F = 1, there are normal levels of the component in healthy cells. It is assumed that this component is an auto-synthesized parameter and the rate of its auto-synthesis is a power-law version of the logistic equation. On the other hand, its thermal denaturation is assumed to be a first-order process (38). Consequently, the equation for the level of the component in the cell (F) is:

$$\frac{dF}{dt} = k_S F(1 - F^n) - k_D F \qquad [3]$$

Where n is the exponent in the power-law version of the logistic equation; t time, k_S and k_D are the rate coefficients of the synthesis and denaturation reactions, respectively. The temperature-dependency of rate coefficients of the synthesis and denaturation reactions of this component (k_S and k_D) are stated in the Arrhenius equation (38).

Consequently, by adding this component to the equation, the logistic model for the growth of the microorganism becomes:

$$\frac{dX}{dt} = \mu F X\left(1 - \frac{X}{X_m}\right) \qquad [4]$$

According to Eq. 3, by changing the temperature, the specific growth rate constant, μ, for a fully healthy cell does not change, instead, the level of essential component, F, can change. Therefore, temperature changes can affect the growth rate by affecting the level of essential component, F (8, 38). To prove the model by experimental results, Dalsenter et al. (38) compared their model results to the literature data for the growth of *Rhizopus oligosporus*. They observed that the model predictions have reasonable agreement with all the experimental results. This model by considering the effect of temperature, made the logistic model more accurate, but more attempts should be done for better understanding of the effect of temperature and moisture on the parameters.

In all of the models mentioned above, only the present values of environmental conditions were considered to affect growth. Subsequently, some researchers suggested that the growth conditions experienced in the past should also be considered in the models (8). For instance, Bovill et al. developed one such model, in which, the parameter Q, was added to the logistic model for modifying the equation (8, 39).

$$\frac{dX}{dt} = \mu X\left(1 - \frac{X}{X_m}\right)\left(\frac{Q}{1+Q}\right) \qquad [5]$$

This parameter (Q) represents the physiological state of the cell. The past environmental conditions could affect parameter Q, in result; the past conditions could affect the current microbial rate through this parameter. The effect of environmental condition on the physiological parameter can be expressed by a differential equation. Although it is possible to assume that Q might be the intracellular enzymes, much more studies are required to accurately define the nature of this parameter. Predictions of this model reasonably agreed with experimental results obtained from the growth of *L. monocytogenes* in pasteurized milk and chicken liver pate and *Salmonella* in pasteurized milk and minced chicken. The deviations of predictions from measurements were mainly due to less accurate lag predictions than growth rate predictions, and inhibition by the natural flora (39).

In another study, Fanaei and Vaziri developed these two previously-mentioned ideas for the growth kinetics of *A. niger* on wheat bran (40). They took into account both the impact of past temperature and current temperature on growth rate. Their kinetic model equation is as follows:

$$\frac{dX}{dt} = \mu\phi X\left(1 - \frac{X}{X_m}\right) \qquad [6]$$

where X, X_m and φ are the biomass concentration, the maximum biomass concentration and level of physiological factor, respectively. In fact, the level of physiological factor (φ) is a dimensionless value and is responsible for its own synthesis similar to the variable F in Dalsenter's model. Thermal denaturation and rate of auto-synthesis of this factor can be expressed in the same way as variable F:

$$\frac{d\phi}{dt} = \gamma_S\phi(1 - \phi^\alpha) = \gamma_D\phi \qquad [7]$$

where α is the exponent in the power-law version of the logistic equation, and γ_S and γ_D are the rate coefficients of the synthesis and denaturation reactions, respectively. These rate coefficients were stated as functions of temperature with the Arrhenius equation.

This empirical equation was used to express the effect of temperature on the specific growth rate:

$$\mu = \left(\frac{s + (T_{max} - T_{opt})}{T_{max} - T_{opt}}\right)\left(\frac{\mu_{opt}(T_{max} - T)}{s + (T_{max} - T)}\right) \qquad [8]$$

Where s is the sensitivity of the specific growth rate to increases in temperature. T_{max} and opt are the maximum and optimum temperatures for growth, respectively, and μ_{opt} is the optimum specific growth rate constant. When φ =1, it means that there are normal levels of the physiological factor within a fully healthy cell. Surprisingly, even when there is no growth in the system, the physi-

ological factor can increase. The physiological factor is denatured when temperature rises, but it takes time for this phenomenon to happen. On the other hand, it also takes time for the physiological factor to be re-established when the temperature falls from harmful values to optimum values. Therefore, the role of the factor φ is to postpone the effects of temperature changes (40). Since the physiological factor has an important role on determination of growth rate, and high temperatures can denature this factor, physiological factor could be possibly intracellular enzymes or ribosomes (8, 40). The predicted results of this model were compared with data from the literature for the growth of *Aspergillus niger* on wheat bran and agreed reasonably with experimental results (40). Although analyses have been done for a particular microorganism and substrate, this modeling approach can be used for other microorganisms and substrates if the appropriate parameters are available.

In addition to temperature, another important environmental condition which has not been extensively studied in SSF modeling is moisture content (28). In the literatures, the effects of temperature and moisture on microbial growth were reported separately (30-37, 41-43). Recently, Hamidi-Esfahani et al. (28) studied the simultaneous influence of temperature and moisture on the growth of *A. niger* on wheat bran . To achieve this aim, they used the logistic model for calculating the growth parameters at different temperatures and moistures. X_m and μ_m were calculated by fitting the logistic equation to the experimental data at different initial moisture contents and temperatures. According to their results, μ_m depends on both temperature and moisture. Meanwhile, X_m is not temperature-dependent and only depends on moisture content. They used the Ratkowsky equation for temperature dependency and polynomial equation for moisture content dependency. They proposed the following equation for the effect of temperature and moisture content on μ_m (28):

$$\mu_m = \left(\left(a_1(T - T_{min})^2\left(1 - \exp\left(a_2(T - T_{max})\right)\right)\right)\right) \times (b_0 + b_1 Y + b_2 Y^2) \quad [9]$$

Where Y is the moisture content, a_1 and a_2 are constants of correlation of specific growth rate and temperature and b_0, b_1 and b_2 are constants of correlation of specific growth rate and water content, respectively. Furthermore, for X_m, which only depends on moisture content, the following quadratic polynomial can express the influence of moisture content on X_m:

$$X_m = c_0 + c_1 Y + c_2 Y^2 \quad [10]$$

Their results had a good agreement with experimental results of *A. niger* growth on wheat bran (28). Since this model is one of the rare models, which considers both the temperature and moisture in the model, it could be a promising and useful model in practical studies and can be used in heat and mass transfer studies of SSF processes. However, this model is a modification of the logistic model and still suffers from the disadvantages of the logistic model.

2.1.2. Two-Phase Kinetic Models

Actually, the real growth profile in SSF consists of two periods: a short period of rapid acceleration followed by a long period of slow growth deceleration. However, the logistic model does not predict such behavior and it is symmetric around the inflection point (8, 28, 44). This means that in the logistic model the acceleration and deceleration rates are the same. Consequently, the logistic model cannot describe the entire growth profile accurately, especially during early stages of growth.

We can explain the sudden growth deceleration at the end of the exponential phase by considering the microscopic phenomena. When hyphae from different expanding colonies meet each other, their extending tips may not remain active. This sudden decrease in the number of active hyphae tips can lead to sudden growth deceleration at the end of the exponential phase. Mitchell et al. proposed that the accumulation of inhibitory metabolites, draining of utilizable nutrients and the beginning of oxygen limitation might be the reasons for the deceleration of fungal growth in SSF.

These disadvantages led to the development of models with greater accuracy. One such model was the two-phase model developed by Ikasari and Mitchell (45). In this model, the growth curve has two phases: (1) an exponential phase, (2) a deceleration phase, and each phase has its own kinetic equation. In the first phase, an exponential equation, Eq. 11, was used and for the deceleration phase, Equitation 12 was developed, assuming first-order decay in the number of tips. In Equitation 12, the specific growth rate during the deceleration phase appears in square brackets and decreases as a result of two factors. One of these two factors is parameter L, which represents the ratio of the specific growth rate at the start of the deceleration phase to the specific growth rate during the previous exponential phase. The other factor is parameter k, a first-order rate constant of the exponential term in Equitation 12. This exponential term describes an exponential decay in specific growth rate throughout the deceleration phase (45):

$$\frac{dX}{dt} = \mu X, t < t_a \quad [11]$$

$$\frac{dX}{dt} = \left[\mu L \exp\left(-k(t - t_a)\right)\right]X, t \geq t_a \quad [12]$$

t_a is the transition time between the two phases, when the exponential phase finishes and the deceleration phase begins (45).

$$If\ t < t_a \quad r_{O1} = r_{x1}Y_{Ox} + mx \quad [13]$$

$$else \qquad r_{O2} = r_{x2}Y_{Ox} + mx$$

However, this model still suffers from some weak points, where the exponential phase is short and biomass concentration is low in this period. Consequently, a few data points could be gathered during this phase, therefore, it makes the determination of the parameters of the exponential phase difficult to determine and generates large error. Additionally, due to the use of specific growth rate of the exponential phase (μ) in the analysis of deceleration phase, errors could also be found in the deceleration phase (8, 44). The model was used to describe the growth profile of *Rhizopus oligosporus* in membrane cultures and had a reasonably good agreement (45).

The two-phase growth model is very simple to use. However, the simplicity of the model does limit its applicability. To have a useful model describing bioreactor performance, the model parameters need to be expressed as functions of the key environmental variables, especially temperature.

To improve the two-phase model, Hamidi-Esfahani et al. (44) developed a new two-phase kinetic model. In this new two-phase kinetic model, like the Ikasari-Mitchell model, the first phase is the exponential phase, but in contrast, the second phase is a logistic model. Their model parameters were temperature-dependent and were determined from the oxygen consumption rate (OUR) of *A. niger* during cultivation on wheat bran. Measuring the OUR has two advantages: first, it has a fast response time and, second, it is directly linked to metabolism of the microorganism (44, 46). The equations for the first phase of this new two-phase model (exponential phase) is as follows:

$$r_{x1} = \mu_1 x_1 \quad [14]$$

$$x_1 = x_{01} exp(\mu_1 t) \quad [15]$$

where rx_1, μ_1 , x_1 and x_{01} are the growth rate, specific growth rate, biomass concentration and initial biomass concentration in the exponential phase, respectively.

The oxygen consumption rate was expressed with a linear-growth model, which depends on maintenance activity of the fungal biomass:

$$r_{O1} = Y_{OX} r_{x1} + m x_1 \quad [16]$$

Where r_{O1} is the OUR in the exponential model, Y_{OX} is the yield coefficient and m is the maintenance coefficient.

At the second phase, the logistic model is used for describing the growth of the microorganism:

$$r_{X2} = \mu_{m2} x_2 \left(1 - \frac{x_2}{x_m}\right) \quad [17]$$

Where r_{x2}, μ_{m2}, x_2 and x_m are the growth rate, maximum specific growth rate, biomass concentration and maximum biomass concentration in the logistic model, respectively.

By assuming the same maintenance coefficient for both phases, OUR for the logistic phase can be written as:

$$r_{O2} = Y_{OX} r_{x2} + m x_2 \quad [18]$$

For transition from exponential to logistic phase, the following assumption was used instead of t_a:

$$If\ \ r_{x1} < r_{x2}\ \ r_x = r_{x1} \quad [19]$$

$$else \qquad r_x = r_{x2}$$

The parameters x_{01}, m, Y_{ox} and x_{max} are assumed to be temperature-independent and the parameters μ_1, μ_{m2} and x_{02} are temperature-dependent. The unknown parameters of the model were calculated from O_2 consumption rates at various temperatures. A good correlation between the experimental results and model predictions for the new two-phase kinetic model was reported by Hamidi-Esfahani et al. in their original paper (44).

Comparing the results of the new two-phase model with the logistic model, Hamidi-Esfahani et al. observed that the logistic model does not fit the experimental results (the growth of *A. niger* on wheat bran) very well (44). The results predicted by the logistic model have a sharper peak than the experimental results. In addition, at the early stages of the growth curve, the results predicted by the logistic model for oxygen uptake are different from the experimental data. Meanwhile, the new two-phase model has better predictions in comparison to the logistic model predictions. Hamidi-Esfahani et al. (44) declared that by using x_2 as the value of biomass during the second phase of the growth, they can overcome the limitations of the logistic model.

Hamidi-Esfahani et al. (44) also compared their new two-phase model with Ikasari-Mitchel two-phase model. They observed that the Ikasari-Mitchell predictions are as accurate as the new two-phase model predictions at the early stages of growth. However, after the first phase finishes, differences between the predictions of the two models can be observed at the second phase of growth. The Ikasari-Mitchell predictions had a positive deviation at the deceleration phase, especially at low temperatures. One of the reasons for the better predictions of the new

two-phase model is the assumption made for the transition from the first phase to the second phase. In the new two-phase model, the fungal growth rate is used as a condition for transition from the exponential phase to the deceleration phase, instead of t_a, and it seems to be a better and more accurate assumption. Furthermore, Hamidi-Esfahani et al. (44) considered the temperature dependencies of the parameters in their model and this makes their model more accurate than the Ikasari-Mitchell model. They believed that the new two-phase kinetic model combined with the mass and energy balances of the packed bed bioreactors model can predict microorganisms' growth and other parameters such as temperature and moisture content adequately. Furthermore, the new two-phase model also precisely describes the growth rate of *Aspergillus oryzae* on wheat.

2.2. Models Based on the Metabolic Pathways

As previously mentioned in the introduction, modeling microbial processes based on the metabolic pathways is one of the most advanced approaches. Such models focus on metabolic pathways and metabolic regulations. In this type of modeling, intracellular interactions and extracellular phenomena are considered (47). This robust approach has been used for studying phenomena that occur in submerged fermentations (48, 49), but there are rare reports about the application of this method for modeling SSF processes (25). This may be due to the heterogeneity of the SSF medium that makes it difficult to measure the required data for modeling.

Recently, Mazutti et al. (25) investigated the growth of *Kluyveromyces marxianus* in SSF within a packed-bed bioreactor. Their study is one of the first reports, which uses metabolic pathway models in SSF processes. They developed a mathematical model based on an artificial neural network (ANN) to predict the microbial rates as a function of fermentation time, initial total reducing sugar concentration, and inlet and outlet temperatures. The models responses were the cell mass, metabolic heat, CO_2, metabolic water and ethanol production, and the total reducing sugar and oxygen consumptions.

They considered this general stoichiometry for aerobic microbial growth of *Kluyveromyces marxianus* with ethanol formation (25):

$$\alpha C_6H_{12}O_6 + \beta NH_4 + \lambda O_2 \rightarrow CH_{1.94}O_{0.76}N_{0.17} + \gamma CO_2 + \delta H_2O + \sigma C_2H_6O \quad [20]$$

where α, β, λ, δ and σ are stoichiometric coefficients on the basis of the C-mol of biomass. The C, H, O, and N balances and the experimental measurements of CO_2 and total reducing sugars could compute these coefficients. In this stoichiometry, the metabolism of yeast was considered aerobic and it was assumed that oxygen is not limited inside the bioreactor. Subsequently, by measuring the CO_2 in the outlet air stream of the bioreactor, the oxygen concentration in the outlet air stream, the global metabolic water and ethanol production in the moist solid bed of the bioreactor could be calculated according to the above stoichiometry (25). Mazutti et al. used the following equation (previously developed by Brand et al. (50)) for calculating microbial growth expressed in terms of mass of cells considering oxygen uptake rate:

$$X_n = \frac{Y_{X/O}.\Delta t\left[\frac{1}{2}\left(\frac{dO_2}{dt}_{t=0} + \frac{dO_2}{dt}_{t=n}\right) + \Sigma_{i=1}^{n-1}\frac{dO_2}{dt}_{t=i}\right] + \left(1-\frac{a}{2}\right).X_0 - a.\Sigma_{i=1}^{n-1}X_i}{1+\frac{a}{2}} \quad [21]$$

where

$$a = m.Y_{X/O}.\Delta t \quad [22]$$

The model, which was developed in this way, was reported to show good performance during both training and validation steps of the ANN procedure. Mazutti et al. (25) expressed that this approach was capable of correlating complex metabolic rates involved in the fermentation of microorganisms in SSF processes. The results of the model can properly predict the growth of *Kluyveromyces marxianus*.

Mazutti et al. used artificial neural network (ANN) to develop their model. The artificial neural network can be used to model complex phenomena like microbial growth in SSF processes. The ANN method is capable of describing multivariable systems, especially highly nonlinear dynamic systems like SSF processes. ANN shows the real capabilities of a real system: parallel processing, classification, learning and pattern recognition (51). Using these capabilities, ANNs can detect complicated relations between inputs and outputs, understand the patterns and re-create the behavior of the system after a training step with gathered data. This technique only uses knowledge obtained from experimental inputs and outputs of the system to predict performance without any background information about the details of phenomena happening during the process and solves

complex equations ruling the system. In fact, one of the advantages of the ANN method is that no great deal of knowledge about the process under investigation is required. Consequently, the ANN methods are accepted as a modeling method for scientific and industrial applications (25). The capability of learning from experimental data and simplicity of performance are the other advantages of ANNs over other mathematical modeling methods. Additionally, developments in computer sciences and advanced computer programs with high ability to calculate mathematical procedures encourage researchers to use ANN for modeling systems. On the other hand, to obtain good results, neural network requires a large amount of data for training, and of course, it is difficult to obtain such a large quantity of data in some processes, like SSF processes. In ANN steps, the researcher has to choose the proper network parameters, and the selection of network parameters needs experience and knowledge about the process (52). These kinds of modeling, especially in SSF systems, are still at the beginning of their way to become a useful model, but according to their accurate basis and robust computer programs, a brilliant future can be predicted for them. However, using such models is much more difficult than empirical models.

2. 3. Product Formation Models

Growth of a microorganism is accompanied by the consumption of oxygen and nutrients and the production of metabolic heat, water, CO_2, and various products. By using a low cost substrate, SSF has gained attention for the production of different products. It has been mentioned that SSF is a very good process for enzyme production (53, 54). Nowadays, many researchers use SSF for producing other valuable products like bioethanol due to its cheap and available substrate. Agricultural products like sweet sorghum (55), sugar beet pomaces (56, 57), mahula flowers (58), carob pods (3, 59), arrowroots (60), and many other low cost materials have been used for bioethanol production in SSF. For optimization and scale-up of such processes, mathematical models for product formation are essential. Because of the difficulties involved in separating the product from the fermentation medium, there are a few product formation models for SSF processes.

One of the common approaches for modeling the formation of products in biological processes is to assume growth-associated and non-growth associated components (8). The general equation for a product (P) is therefore:

$$\frac{dP}{dt} = Y_{PX}\frac{dX}{dt} + m_P X \qquad [23]$$

Where Y_{PX} is the stoichiometric coefficient and m_P is the maintenance coefficient. If the product is a secondary metabolite, the changes in both active biomass and limiting substrates should be described (61). In the case of modeling the production of secondary metabolites, the logistic model cannot be used, because as mentioned before, it cannot completely predict the microorganism's behavior during the death phase. In this section, we discuss some of the product formation models.

One of these few product formation models is the simple differential equation model developed by Gelmi et al. used to express the growth and production of a secondary metabolite in SSF under conditions of limited nitrogen (61). Applying mass balances in SSF, they developed a lumped parameter differential equation model, leading to eight differential equations (Eqs. 24-31). As an experimental case, they studied the growth of filamentous fungus *Gibberella fujikuroi* and the production of gibberellic acid (GA3). In this model, it was assumed that oxygen transfer resistance is negligible; the nitrogen source is the limiting substrate; the carbon source is not limiting and temperature, moisture and model parameters remain constant during cultivation (61).

The balance for total biomass (without lysis) leading to:

$$\frac{dX_{total}}{dt} = \mu X \qquad [24]$$

Where X is the active biomass. The change in active biomass was described by:

$$\frac{dX}{dt} = \mu X - k_d X \qquad [25]$$

Where kd is the death rate coefficient. The consumption rate of the urea (the nitrogen source) is:

$$\frac{dU}{dt} = -k \qquad [26]$$

Where U is the concentration of urea, and k is the conversion rate from urea to available nitrogen for the microorganism (N_i). N_i can be directly converted into active biomass. The change in available nitrogen during fermentation is given by:

$$\frac{dN_1}{dt} = 0.47k - \mu\left(\frac{X}{Y_{X/N_1}}\right) \qquad [27]$$

Where 0.47 represents the nitrogen content of the urea. The consumption rate of the carbon source (soluble starch) can be written as:

$$\frac{dS}{dt} = -\frac{\mu X}{Y_{X/S}} - m_s X \qquad [28]$$

The production rate of GA3 is proportional to the concentration of active biomass, because it is a secondary metabolite. To represent GA3 degradation, an additional term is required:

$$\frac{dGA_3}{dt} = \beta X - k_p GA_3 \quad [29]$$

These two equations also represent CO_2 production and O_2 consumption:

$$\frac{dCO_2}{dt} = \mu\left(\frac{X}{Y_{X/CO_2}}\right) + m_{CO_2}X \quad [30]$$

$$\frac{dO_2}{dt} = \mu\left(\frac{X}{Y_{X/O_2}}\right) + m_{O_2}X \quad [31]$$

After guessing the initial amounts of key parameters, a non-linear optimization routine was used to obtain the least square fit for the model. It was observed that this mathematical model could reproduce measured variables like biomass, urea, starch, CO_2, O_2 and GA3 (61).

Mass balances have also been used to develop the product formation models. In a recent study, Hashemi et al. used this approach to model different phases of bacterial growth curve and the production of α-amylase by *Bacillus sp*. in the SSF process (62). They assumed that the changes in total dry fermenting medium weight (W) corresponds to substrate consumption rate (dS/dt), biomass growth rate (dB/dt) and product formation rate (dP/dt).

$$\frac{dW}{dt} = \frac{dS}{dt} + \frac{dB}{dt} + \frac{dP}{dt} \quad [32]$$

On the other hand, substrate consumption rate can be explained by three equations: the equation for biomass growth ((dS/dt) g) and the yield coefficient for biomass (Yg), the equation for product formation ((dS/dt) p) and its yield coefficient (Yp) and equation for maintenance ((dS/dt) m):

$$\frac{dS}{dt} = \left(\frac{dS}{dt}\right)_g + \left(\frac{dS}{dt}\right)_p + \left(\frac{dS}{dt}\right)_m \quad [33]$$

where

$$\left(\frac{dS}{dt}\right) = -\frac{1}{Y_g}\frac{dB}{dt} \quad [34]$$

$$\left(\frac{dS}{dt}\right)_p = -\frac{1}{Y_p}\frac{dP}{dt} \quad [35]$$

$$\left(\frac{dS}{dt}\right)_m = -K_m B \quad [36]$$

For the kinetics of α-amylase production, Hashemi et al. used the Luedeking-Piret equation (63), in which the product formation rate depends on both biomass concentration (B) and growth rate (dB/dt):

$$\frac{dP}{dt} = \alpha B + \beta\frac{dB}{dt} \quad [37]$$

Where α and β are empirical constants that may vary with fermentation conditions. Since each growth kinetic curve of microorganisms may be divided into three phases (exponential growth, stationary and death), Hashemi et al. presented the dry weight variation into three terms that indicate those three phases:

$$\frac{dW}{dt} = \left(\frac{dW}{dt}\right)_{growth} + \left(\frac{dW}{dt}\right)_{statinary} + \left(\frac{dW}{dt}\right)_{death} \quad [38]$$

The final equations for each phase are provided in Table 2. Readers wishing to understand the details of the equations derivation should refer to the original paper (62). According to their results, it can be observed that bacterial growth and the production of α-amylase on wheat bran substrate could successfully be modeled based on variations in solid substrate weight. This model was validated by experimental data collected from a series of batch fermentations. The authors suggested their model for the development of growth, and α-amylase production in SSF processes (62).

Similar to growth kinetic models, stoichiometric models can also be used for product formation models. Mazutti et al. used the same procedure they had used before for modeling the growth kinetics to model inulinase production in SSF packed-bed bioreactor (64).

In general, product formation models in SSF process are not advanced enough to be used on practical and industrial scales, and to be able to use this cost-effective technology for producing different valuable products, more attempts should be done in this field.

3. Results

Simple empirical models are widely used in SSF, and although some improvements (like two-phase models) were made in these models, there is still much to do in this field. Since there are many experimental difficulties in SSF processes, modeling of this process is improving slowly. Nevertheless, many researchers have attempted to develop advanced models for SSF bioreactors. One of

the most important issues that should be studied more in the field of SSF processes modeling is the effect of environmental conditions, especially temperature and moisture, on key variables of the model.

It seems that stoichiometric models, focusing on microbial pathways, can predict the behavior of microorganisms well and can be a good substitution for simple empirical models in SSF processes. These models can be better coupled with heat and mass transfer models compared to empirical models. However, more studies must be done on these kinds of models in SSF.

Table 2. Final Equations for α-amylase Production for Each Phase of the Growth Curve in Hashemi et al. Model (62)

Phase		Product Equation
Growth phase	$B = B_0 e^{\mu t}$ and $dW/dt = \epsilon\mu e^{\mu t}$	$P = C(e^{\mu t} - 1)$ $C = \left(\alpha - \frac{\gamma}{\delta}\right)\frac{B_o}{\mu} + \frac{\beta\epsilon}{\delta}$
Stationary phase	$B = B_s$ and $dB/dt = 0$	$P = C_1 \int \frac{dW}{dt} dt$ $C_1 = \frac{\alpha}{\gamma}$
Death phase	$B = B_s e^{-k_d t_d}$ and $dW/dt = k_d \vartheta e^{-k_d t_d}$	$P = C_2 e^{-k_d t_d} + C_3$ $C_2 = \left(\alpha - \frac{\gamma}{\delta}\right)\frac{B_s}{-k_d} - \frac{B\vartheta}{\delta}$ $C_3 = \left[\frac{\beta\vartheta}{\delta} - \left(\alpha - \frac{\gamma}{\delta}\right)\frac{B_s}{-k_d}\right] e^{-k_d t}$
where		
$\gamma = \alpha\left(1 - \frac{1}{Y_P}\right) - K_m$	$\delta = 1 - \frac{1}{Y_g} + \beta\left(1 - \frac{1}{Y_P}\right)$	
$\epsilon = \frac{B_0(\gamma + \delta\mu)}{\mu}$	$\vartheta = \frac{B_0 e^{\mu t_2}(k_d\delta - \gamma)}{K_d}$	

Using very cheap substrates like agricultural wastes, SSF could be an economical process for producing many valuable metabolites such as industrial enzymes and bioethanol. For this purpose, more robust product formation models are required. So far, difficulties in separating the product from the solid medium prevent the development of product formation models. As a result, more studies should be done on the modeling of products to make the SSF process, an industrial and economical process for producing valuable compounds in the future.

To use SSF for producing valuable metabolites in large scales, more attention is required for modeling the SSF processes, especially for product formation models. Robust modeling methods like stoichiometric models and coupling the kinetic models with heat and mass transfer models should be considered more in SSF bioreactor models.

Developing more accurate models and combining them with mass and energy balance models for better controlling bioreactors, using modern methods like stoichiometric models, focusing on product formation models, and performing more studies on measuring the important parameters of SSF system during the process are the future challenges of SSF modeling.

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Authors' Contribution

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مروری بر مدل های ریاضی سینتیک میکروبی در فرآیند تخمیر حالت جامد

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خلاصه مقاله

زمینه: در این مقاله مروری به مدل های سینتیک میکروبی تجربی و اثر عوامل مختلف محیطی بر روی ضرایب این معادلات، مدل های بر اساس روش نوین استوکیومتری و نیز مدل های تولید محصول در فرآیند تخمیر حالت جامد پرداخته شده است.

شواهد: از آنجا که روش تخمیر حالت جامد فرآیندی ارزان برای تولید بسیاری از محصولات تخمیری مانند آنزیم ها است، برای استفاده از این فرآیند در مقیاس صنعتی و بزرگنمایی و طراحی بیوراکتورهای آن به مدل های ریاضی دقیق نیاز است. در این مقاله مروری، پژوهش های مرتبط با این موضوع جمع آوری و تحلیل شده و مزایا و کاستی های هر مدل، و میزان تطابق آن با داده های آزمایشگاهی مورد بحث قرار گرفته است. در این راستا مدل های ساده تجربی سینتیک رشد و اثر عوامل محیطی مانند دما و رطوبت بر ضرایب این مدل ها مورد بحث قرار گرفته و سپس مدل های نوین رشد به روش استوکیومتری در فرآیند تخمیر حالت جامد معرفی و تحلیل شده است. در پایان مدل های بر پایه تولید محصول و افق آینده و مشکلات پیش رو در زمینه مدل سازی فرآیند تخمیر حالت جامد ارائه شده است.

یافته ها: مدل های تجربی علیرغم سادگی برای مدل سازی فرایند تخمیر حالت جامد بسیار مورد استفاده قرار می گیرند. برای بهبود این مدل ها باید تلاش بیشتری به خصوص در مورد بررسی اثر عوامل مختلف بر روی ضرایب معادلات صورت گیرد. مدل های پیشرفته تر مانند مدل های استوکیومتری در فرایند تخمیر حالت جامد هنوز در ابتدای راه خود قرار دارند و بایستی مطالعات بیشتری برای توسعه آنها انجام شود. برای استفاده از مدل های رشد میکروبی در طراحی بیوراکتورهای صنعتی، بایستی این معادلات با معادلات انتقال حرارت و جرم تجمیع شوند، که در این زمینه نیاز به تلاش فراوانی وجود دارد. مدل های تولید محصول نیز یکی از جنبه هایی هستند که بسیار کم در فرایند تخمیر حالت جامد مورد توجه قرار گرفته اند و برای به کارگیری فرایند تخمیر حالت جامد برای تولید محصولات ارزشمند به این نوع مدل ها نیاز است.

نتیجه گیری: به کارگیری فرآیند تخمیر حالت جامد در مقیاس صنعتی و برای تولید محصولات با ارزش نیاز به توسعه بیشتر مدل های ریاضی بخصوص مدل های تولید محصول و استفاده از مدل های نوین دارد.

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کاربرد در زمینه سیاست‌های بهداشت و درمان/ پژوهش و آموزش پزشکی:
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