

Article

Analytical Solutions for Fungal Growth and Penicillin Production Dynamics with Simultaneous Product Hydrolysis in Batch Bioprocesses

Samuel C. Oliveira ^{1,*}  and Helenice O. Florentino ²¹ School of Pharmaceutical Sciences, São Paulo State University (UNESP), Araraquara 14800903, SP, Brazil² Institute of Biosciences, São Paulo State University (UNESP), Botucatu 18618689, SP, Brazil;
helenice.silva@unesp.br

* Correspondence: samuel.oliveira@unesp.br

Abstract

Few mathematical models describing the dynamics of cell growth, production formation and substrate consumption in batch and fed-batch bioprocesses have analytical solutions. In this study, analytical solutions for a mathematical model of a batch bioprocess of penicillin production based on the Logistic law for cell growth and on the Luedeking–Piret equation for antibiotic formation are obtained using classical methods of solving ordinary differential equations. The analytical solutions were validated by substitution into the differential equations themselves, as well as by comparison with numerical solutions obtained through the fourth-order Runge–Kutta–Gill integration method, using typical fungus inoculum concentrations ($X_0 = 0.25; 0.75\%$ DW) and kinetic parameters ($\mu_m = 0.5 \text{ h}^{-1}$, $X_m = 3.7\%$ DW, $\beta = 0.02 \text{ U}/(\text{mL} \cdot \text{h} \cdot \%) \text{ DW}$) and $k_t = 0.027 \text{ h}^{-1}$). The novelty in relation to the few studies published on the subject, which deal with the production of different metabolites, including other antibiotics, is that in the present study, the hydrolysis of penicillin is considered simultaneously with its production in the description of the dynamics of product formation. The main finding demonstrates that the hydrolysis reaction acts as a stabilizing factor, resulting in a system with two equilibrium points: an unstable point with no penicillin production, and a stable point in which a certain amount of antibiotic is produced.

Keywords: mathematical modeling; dynamic equation; analytical solution; cell growth; antibiotic production; penicillin hydrolysis; stability analysis



Academic Editor: Carlos Eduardo De Farias Silva

Received: 11 May 2026

Revised: 19 June 2026

Accepted: 27 June 2026

Published: 1 July 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

From an industrial perspective, penicillin remains a critical product of the global antibiotic market, accounting for a significant share of the global anti-infective landscape. Currently, the worldwide annual production of penicillin is estimated to be around 50,000 to 60,000 metric tons [1]. Despite the mature stage of this fermentation industry, global demand is not fully satisfied and faces critical bottlenecks. Recent clinical evaluations indicate that several regions face recurrent shortages of essential narrow-spectrum penicillins and broad-spectrum derivatives, such as amoxicillin. These supply deficits are primarily driven by fragile supply chains, low profit margins for Active Pharmaceutical Ingredients (APIs), sudden demand shocks from post-pandemic respiratory infections, and the centralization of bulk manufacturing. Consequently, enhancing the volumetric productivity of industrial penicillin fermentations remains highly relevant to stabilizing global supply and mitigating public health vulnerabilities [2,3].

Penicillin production on an industrial scale is a strict aerobic bioprocess carried out by filamentous fungi (*Penicillium chrysogenum*) in tank-type reactors under high stirring and aeration rates to increase the oxygenation of a fermentative medium and supply the oxygen required for cell respiration [4]. Several other antibiotics can be synthesized from the penicillin recovered from fermented media through the chemical modification of the original molecule, obtaining modified molecules with higher therapeutic and commercial values [5]. The biosynthetic pathway of penicillin in *P. chrysogenum* is practically understood and occurs after a fast cell growth phase (trophophase), when the activities of two key enzymes are accelerated, triggering the second phase (idiophase) [6,7]. One of these enzymes activates phenylacetic acid, a precursor that forms the side chain of penicillin. The other enzyme is the penicillin acyltransferase that links activated phenylacetate to 6-aminopenicillanic acid, forming the nucleus of the penicillin molecule [7].

Penicillin biosynthesis is subject to repression catabolite mainly by easily metabolizable sources of carbon (substrate), requiring a slow supply of these nutrients to minimize the repressive effects [5]. In this way, fed-batch processes have been preferably used for the industrial production of penicillin, although batch processes also are employed. These processes, when implemented on a commercial production scale—mainly those in the pharmaceutical industry—need strictly to follow a pre-specified manufacturing practice aimed at fermentation process reproducibility to ensure batch-to-batch product quality [8]. The determination of optimal profiles of temperature and substrate feed-rate in batch and fed-batch penicillin fermentation processes is a problem of optimization whose solution requires the use of phenomenological models and advanced mathematical methods such as those based on the Pontryagin Maximum/Minimum Principle (PMP) [9–11]. However, the PMP is not the only applicable approach for optimizing antibiotic production bioprocesses, since other optimization methodologies have been used, including Metaheuristic and Evolutionary Algorithms (Artificial Neural Networks coupled with Genetic Algorithms (ANN-GA)), Model Predictive Control (MPC), Response Surface Methodology (RSM) and Design of Experiments (DoE), Dynamic Programming (DP), and Machine Learning and Explainable AI (XAI) [12–17].

Based on a compromise between complexity and the applicability of a mathematical model, the most widely used approach to model penicillin production bioprocesses is the unsegregated–unstructured phenomenological one, according to which cells are considered homogeneous, with no distinction of cellular properties (age, size, activity and others) or variations in intracellular composition during successive cell divisions (balanced growth) [4,18,19]. Since the production of penicillin is generally carried out in homogeneous reactors, many of the mathematical models associated with this bioprocess were developed under isothermal conditions, consisting of ordinary differential equations that represent the mass balances of the main components considered in the modeling [4]. Energy balance equations are rarely included in descriptions, except when a temperature control law (proportional, proportional–integral, proportional–integral–derivative) is incorporated into the mathematical model of the bioprocess [20–22].

In these mass balance equations, kinetic equations are introduced to describe the substrate consumption, oxygen uptake, fungal growth and degradation, formation, and hydrolysis of the product during penicillin biosynthesis. Several equations have been proposed to describe these kinetics, most of them derived from the classical Monod equation, inserting additional terms referring to the main phenomena involved in the bioprocess of penicillin production by *P. chrysogenum* such as growth limitation by multiple substrates (carbon source and oxygen) and diffusion into fungal biomass, morphological differentiation, hyphal fragmentation, deactivation, autolysis, cell death, maintenance metabolism, penicillin production associated and not associated with cell growth, catabolite repres-

sion of product formation, and product hydrolysis [4,18]. Another equation that is also frequently used to represent various batch and fed-batch bioprocesses is the logistic law, according to which the specific rate of cell growth (μ_X) is determined by the carrying capacity of the system that includes nutrient availability and growth-inhibiting factors such as toxic product accumulation, shear and steric stresses, and contamination [4,23,24].

Once the mass balances of the components in the bioreactor are elaborated, the corresponding ordinary differential equations are solved in most cases—due to nonlinearities—by numerical integration from given initial conditions of the main modeled state variables (concentration of substrate, dissolved oxygen, cells, and product). However, depending on the bioreactor's operation mode (batch or fed-batch) and the structure of the adopted kinetic expressions, it is possible to obtain an analytical solution for the mass balance equations, allowing a comparison between both solutions.

Generally, analytical solutions, when they exist, are always preferred because they provide exact values for the response variable and can be used as references to evaluate the validity and accuracy of numerical solutions, given that these solutions, in being obtained by progressive methods of step-by-step integration, can provide wrong values depending on the method's order, integration-step size and numerical stiffness. Moreover, analytical solutions are more valuable as they explicitly show the relationship between dependent and independent variables and the influence of the parameters on such solutions [25].

Only a reduced number of cases allow analytical solutions to be obtained for batch bioprocess dynamics. Blanch and Clark [7], Bailey and Ollis [26], and Shuler and Kargi [27] developed analytical solutions for the cell growth and substrate consumption dynamics in batch cultures following Monod kinetics. In addition, Blanch and Clark [7] also solved the situation whereby the cell culture is inhibited by substrate, inserting a multiplicative inhibition factor $1/(1 + S/K_i)$ in the Monod equation, where S is the substrate concentration and K_i is the inhibition constant by the substrate, respectively. Advances in these studies were made by Garnier and Gaillet [28] when, in addition to the dynamics of cell growth and substrate consumption, they also included and analytically solved the dynamics of product formation, describing the production kinetics using the Luedeking–Piret equation [29], according to which product formation is partly associated and partly non-associated with cell growth. The Monod equation and the Andrews equation for substrate inhibition were used to describe the kinetics of cell growth, applying the same analytical procedure of problem resolution to both kinetic equations.

Using the logistic law to describe cell cultures, Blanch and Clark [7], Bailey and Ollis [26], Shuler and Kargi [27], and Najafpour [30] only presented solutions for the cell growth dynamics, since, in this case, it is only dependent on the cell concentration itself and on the time. However, the most frequent case is the one involving the combination of the cell growth Logistic law with the Luedeking–Piret kinetics for product formation, as listed in Table 1 [28,31–44], highlighting the studies by Dhavale et al. [32] and Bankar and Singhal [36], who presented a generalized and complete approach to the case under investigation.

The differences among the cases listed in Table 1 are related to two main aspects: (i) the form of describing the substrate consumption dynamics, whether through a mass balance equation or by the equation that defines the biomass yield coefficient from the substrate consumed ($Y_{X/S}$), and (ii) whether or not the substrate consumption kinetics takes into account the amount of substrate consumed separately for each cellular subprocess: growth, product formation, and maintenance [29].

Table 1. Cases reported in the literature on analytical solutions for dynamic equations of cell growth, product formation, and substrate consumption.

Case Reference	Bioprocess Related to the Case
Ali et al. [31]	Batch biomass and ethanol production from inulin by <i>Pichia caribbica</i>
Dhavale et al. [32]	Batch fermentation for glutathione production by <i>Saccharomyces cerevisiae</i>
Garnier and Gaillet [28]	General batch bioprocesses applied to fermentations for lactic acid production by <i>Lactobacillus delbrueckii</i> and xanthan production by <i>Xanthomonas campestris</i>
Zakeri et al. [33]	Batch fermentation for xanthan biopolymer production by <i>Xanthomonas campestris</i>
Vinayagam et al. [34]	Batch biomass and nattokinase production by <i>Bacillus subtilis</i>
Wu and Fan [35]	Batch ethanol production by an engineered <i>Escherichia coli</i> using a novel carbon source (sodium gluconate)
Bankar and Singhal [36]	Batch fermentation for poly- ϵ -lysine biosynthesis by <i>Streptomyces noursei</i>
Lu et al. [37]	Daptomycin batch fermentation by <i>Streptomyces roseosporus</i>
Uzir and Don [38]	General batch microbial growth and product formation
Kargi [39]	General batch microbial growth
Rao et al. [40]	Batch <i>Bacillus circulans</i> growth and alkaline protease production
Razvi et al. [41]	Batch fermentation by <i>Lactococcus lactis</i> under hemin-stimulated respirative condition
Kong et al. [42]	Batch butyric acid bioproduction by <i>Clostridium butyricum</i>
Dahanasekar and Viruthagiri [43]	Batch poly- β -hydroxy butyrate synthesis by <i>Azotobacter vinelandii</i> using different carbon sources
Elibol and Mavituna [44]	Batch fermentation for actinorhodin production by <i>Streptomyces coelicolor</i>

The popularity of the logistic equation is due to the fact that it is represented by a sigmoidal curve (S-shaped curve) with two kinetic parameters that can be adjusted in order to allow it to describe almost all phases of cell growth (lag, acceleration, exponential, deceleration, and stationary phases), with the exception of the decline phase.

Xu [45] developed analytical solutions for the dynamics of cell growth and substrate consumption in batch and continuous cultures following a hybrid cell growth kinetics, given by the Monod equation multiplied by the characteristic term of the logistic law ($1 - X/X_m$), where X is the cell concentration and X_m its maximum value, respectively.

The previous studies did not consider the kinetics of product degradation that, in the case of penicillin, occurs through alkaline hydrolysis, catalyzed by proteases produced by the fungus itself during antibiotic biosynthesis and leading to the formation of penicilloic acid. Penicillin hydrolysis is a first-order reaction that must be considered in the mathematical descriptions of production bioprocesses of this antibiotic [46].

This study is entirely theoretical and model-based, involving no laboratory experiments. The objective is to determine analytical solutions for the dynamic equations of cell growth and product formation during batch penicillin fermentations with the fungal growth and penicillin formation kinetics being given by the Logistic and Luedeking–Piret equations, respectively. In addition, penicillin hydrolysis is also considered, a case not yet reported in the literature. The analytical solutions are validated by substitution into the differential equations themselves, as well as by comparison with numerical solutions obtained through the fourth-order Runge–Kutta–Gill integration method [10,47]. While neglecting penicillin hydrolysis is standard for idealized, short-term fermentations, in-

corporating it into a bioprocess model becomes highly justified under specific industrial, operational, or downstream scenarios. A strong justification for including penicillin hydrolysis in a bioprocess model is to accurately predict real-world yield losses during prolonged batch cycles, extended downstream holding times, or unexpected bioreactor pH/temperature deviations.

2. Modeling Fungal Growth Dynamics and Penicillin Production in Batch Stirred-Tank Bioreactor (BSTR)

The growth description of the penicillin-producing fungus *Penicillium chrysogenum* is based on the logistic law of limited growth, a substrate-independent equation where microbial growth limitation is not explicitly described as a function of the limiting factors, but implicitly by introducing the term $(1 - X/X_m)$ in the growth rate equation (r_X). Since X increases, this term diminishes over time, becoming null in the stationary phase when X reaches the maximum value X_m .

The penicillin production rate (r_P) is given by the Luedeking–Piret equation ($r_P = \alpha r_X + \beta X$), where the parameters α and β represent the product formation associated and non-associated with fungus growth, respectively. At low specific rates of cell growth ($\mu_X < 0.015 \text{ h}^{-1}$), growth-associated penicillin formation occurs, while in the opposite condition ($\mu_X > 0.015 \text{ h}^{-1}$), non-growth-associated formation predominates [7]. Since penicillin is a product of secondary metabolism in fungus, produced mostly after the growth phase, it will be assumed, as a good first approximation, that $r_P = \beta X$. Moreover, to better describe the dynamics of penicillin production, it is considered that penicillin is hydrolyzed and that the hydrolysis rate (r_h) follows first-order kinetics with respect to own penicillin concentration ($r_h = k_h P$), where k_h is the reaction rate constant.

The complete model, incorporating two ordinary differential equations corresponding to the dynamics of cell growth and of penicillin production in BSTR, is given by Equations (1) and (2):

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

$$\frac{dP}{dt} = r_P - r_h = \beta X - k_h P \quad (2)$$

In Equations (1) and (2), t is the time (h), X is the cell concentration (% DW), P is the penicillin concentration (U/mL), r_X is the fungus growth rate (% DW/h), r_P is the penicillin production rate (U/(mL·h)), r_h is the product–hydrolysis rate in U/(mL·h), and μ_m , X_m , β , and k_h are the parameters of the model, according to the following meanings: μ_m is the maximum specific growth rate (h^{-1}), X_m is the attainable maximum cell concentration (% DW), β is the constant of product formation not associated with cell growth (U/(mL·h·% DW)), and k_h is the rate constant of the hydrolysis reaction (h^{-1}). The abbreviation DW stands for dry weight, and U is the international unit of measurement, equivalent to the activity of 0.6 µg of sodium salt of penicillin. Although expressing biomass concentration in mass-per-volume units (such as g/L) is the standard convention in modern bioprocess literature, the mathematical model formulated and simulated in this study was strictly built upon the fundamentals established by Constantinides et al. in their seminal papers [48,49]. In their original formulation, biomass concentration was explicitly expressed as percentage of dry weight (% DW). To ensure dimensional homogeneity, the notation was maintained. Additionally, da Paz et al. [50] recently developed a software architecture for penicillin fermentation modeling and used % DW as a unit to express cell concentration.

3. Results and Discussion

This section presents the analytical solutions for the dynamic equations of cell growth and product formation in batch bioprocesses of penicillin production, without and with antibiotic hydrolysis during its biosynthesis. The analytical solutions are then validated with numerical solutions, equilibrium points for the system are determined, and local stabilities are analyzed by using the first Lyapunov method.

3.1. Analytical Solutions

Fungal growth dynamics (Equation (1)) is independent or uncoupled of penicillin production dynamics (Equation (2)) and its solution is well known [51], which is given by Equation (3):

$$X(t) = \frac{X_0 e^{\mu_m t}}{1 + \left(\frac{X_0}{X_m}\right) (e^{\mu_m t} - 1)}; X_0 = X(0) \quad (3)$$

To solve Equation (2) (penicillin production dynamics), subject to the initial condition $P(0) = 0$, Equation (3) is inserted into Equation (2) and the cases below can be now analyzed.

3.1.1. Case 1: Bioprocess Without Product Hydrolysis ($k_h = 0$)

In this case, the solution of Equation (2) by using the method of separating variables provides Equation (3) as result (the step-by-step solution development is presented in Appendix A):

$$P(t) = \left(\frac{\beta X_m}{\mu_m}\right) \ln \left[1 + \left(\frac{X_0}{X_m}\right) (e^{\mu_m t} - 1)\right] \quad (4)$$

3.1.2. Case 2: Bioprocess with Product Hydrolysis ($k_h \neq 0$)

The solution for the dynamics of penicillin production when the hydrolysis of the product occurs is the main objective of the present study and was developed by using the integrating factor method [51], whose steps are described as follows.

Initially Equation (3) is inserted into Equation (2) and the result is manipulated to provide Equation (5):

$$\frac{dP}{dt} + k_h P = \beta \left[\frac{X_0 e^{\mu_m t}}{1 + \left(\frac{X_0}{X_m}\right) (e^{\mu_m t} - 1)} \right] \quad (5)$$

By multiplying both members of Equation (5) by the $e^{k_h t}$ integrating factor, one obtains:

$$\left(e^{k_h t}\right) \frac{dP}{dt} + k_h \left(e^{k_h t}\right) P = \beta \left(e^{k_h t}\right) \left[\frac{X_0 e^{\mu_m t}}{1 + \left(\frac{X_0}{X_m}\right) (e^{\mu_m t} - 1)} \right] \quad (6)$$

The two terms on the left member of Equation (6) represent the derivative of the product between them, so Equation (6) can be written as:

$$\frac{d}{dt} \left(e^{k_h t} P\right) = \beta \left[\frac{X_0 e^{(\mu_m + k_h)t}}{1 + \left(\frac{X_0}{X_m}\right) (e^{\mu_m t} - 1)} \right] \quad (7)$$

Separating the variables in Equation (7) and integrating results in Equation (8):

$$P(t) = e^{-k_h t} \left[\frac{\beta X_m X_0 e^{(\mu_m + k_h)t} {}_2F_1(1, \delta_1; \delta_2; \delta_3 e^{\mu_m t})}{(\mu_m + k_h) (X_m - X_0)} + C \right] \quad (8)$$

In Equation (8), ${}_2F_1(1, \delta_1; \delta_2; \delta_3 e^{\mu_m t})$ is the hypergeometric function of Gauss in time t , with parameters 1, δ_1 , δ_2 , and δ_3 , being $\delta_1 = (\mu_m + k_h)/\mu_m$, $\delta_2 = (2\mu_m + k_h)/\mu_m$, $\delta_3 = X_0/(X_0 - X_m)$, and C is the integration constant, which is determined from initial condition $P(0) = 0$, giving Equation (9):

$$C = - \left[\frac{\beta X_m X_0 {}_2F_1(1, \delta_1; \delta_2; \delta_3)}{(\mu_m + k_h)(X_m - X_0)} \right] \quad (9)$$

Inserting Equation (9) into Equation (8) and after algebraic manipulations, Equation (10) is obtained, which represents the temporal profile of product concentration.

$$P(t) = \frac{\beta X_m X_0}{(\mu_m + k_h)(X_m - X_0)} \left[{}_2F_1(1, \delta_1; \delta_2; \delta_3 e^{\mu_m t}) e^{\mu_m t} - {}_2F_1(1, \delta_1; \delta_2; \delta_3) e^{-k_h t} \right] \quad (10)$$

3.2. Validation of the Analytical Solution for Product Concentration

Appendix B shows that the solution obtained for $P(t)$ in Case 2 satisfies both the ordinary differential equation and the initial condition $P(0) = 0$. However, the analytical solution is, at times, a complex mathematical expression replete with composite functions, implicit terms, or integrals, making algebraic derivation a laborious task. In such cases, employing an independent, high-accuracy numerical method serves as a strict mathematical cross-verification tool. Upon observing perfect agreement between both simulated datasets, the mathematical verification of the analytical solution is proven, ensuring that it is ready for physical validation using experimental data. Analytical solutions have been validated using such a procedure, as performed by Shilsar et al. [52] when assessing the analytical solution for the pollutant transport equation obtained by the Laplace Transform technique. Analogously, Manitcharoen and Pimpunchat [53] validated an analytical solution to describe the pollutant concentration generated by uniform and exponentially increasing sources. In this context, numerical simulations were also performed in this study to validate the analytical solutions developed for the dynamic equations of fungal growth and penicillin production during fermentation processes subject to product hydrolysis. Thereby, the bioprocess was simulated using both the derived analytical solution and a numerical solution, under identical initial conditions and kinetic parameters.

Figure 1 shows the cell (X) and product (P) concentration profiles simulated by the analytical solutions (Equations (3) and (10)) and by numerical integration of Equations (1) and (2) using the fourth-order Runge–Kutta–Gill method [10,47]. For these simulations, the following characteristic values of parameters for penicillin fermentations were extracted from the literature [4,10] and used in the mathematical model of the bioprocess: $\mu_m = 0.5 \text{ h}^{-1}$, $X_m = 3.7\% \text{ DW}$, $\beta = 0.02 \text{ U}/(\text{mL} \cdot \text{h} \cdot \% \text{ DW})$ and $k_h = 0.027 \text{ h}^{-1}$.

As can be seen in Figure 1, the agreement between the two solutions is quasi total, which means that the analytical solution obtained is correct and the numerical solution is precise. In fact, the fourth-order Runge–Kutta–Gill algorithm for numerical integration of ordinary differential equations has a small local truncation error of order h^4 and a total truncation error of h^3 , where h is the integration step size whose value adopted in this study was 10^{-5} h . Both solutions involve numerical calculations with an intermediate degree of complexity; the analytical solution to evaluate the value of the hypergeometric function of Gauss, which is given by an infinite series, and the numerical solution to integrate the ordinary differential equations representative of the bioprocess mathematical model. As all points from the numerical solution coincide with the respective points of the curves from the analytical solution, any of the solutions can be used to simulate the batch bioprocess of penicillin production.

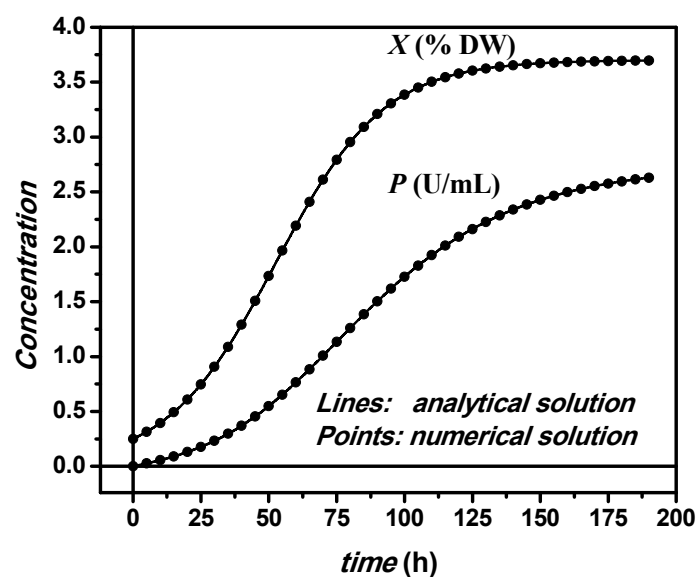


Figure 1. Comparison between the analytical and numerical solutions.

The observed product plateau, rather than a maximum followed by a decline, is a direct consequence of the model's behavior. Because the specific antibiotic production rate is a constant (β) not limited by substrate depletion in this simplified model, the production term (βX) never drops below the degradation term ($k_h P$) at high process times. Instead, it asymptotically matches it, resulting in $dP/dt = 0$. This prevents a drop in product concentration and forces the system to achieve a steady-state plateau ($P_{plateau}$) rather than a peak, given by $P_{plateau} = \beta X_m / k_h$.

Figure 2 shows the temporal profiles of the simulated state variables with the analytical solution for two different concentrations of fungus inoculum ($X_0 = 0.25$ and 0.75% DW), suggesting that the higher the inoculum concentration, the faster the bioprocess, although the final plateau reached is the same.

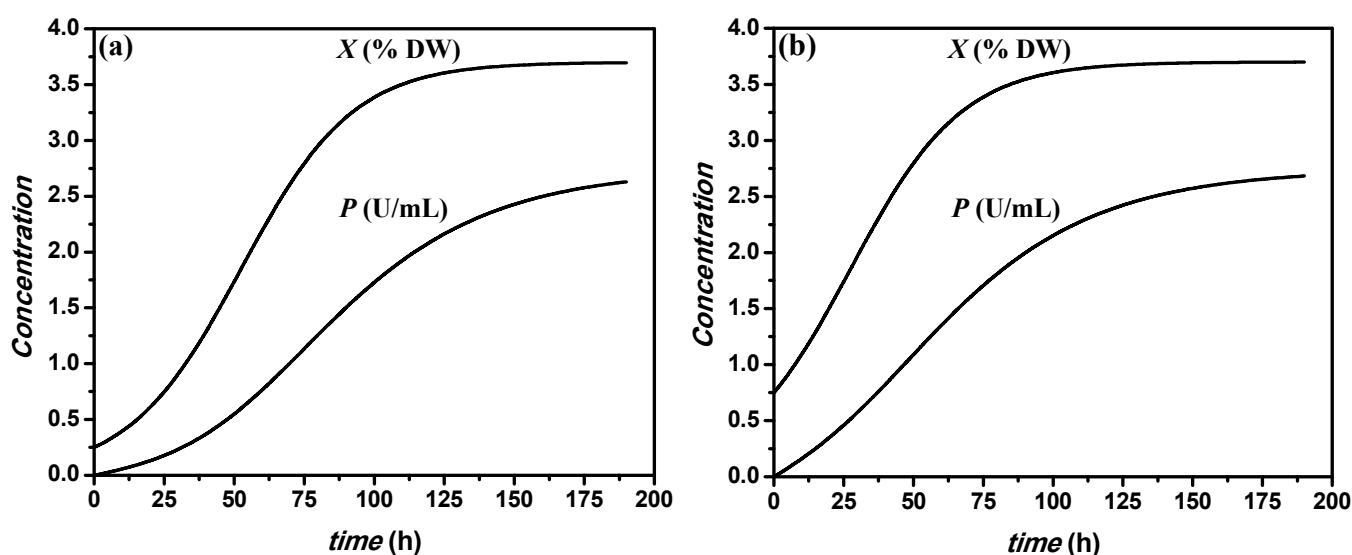


Figure 2. Simulation of the influence of inoculum concentration on the batch bioprocess of penicillin production (analytical solution): (a) $X_0 = 0.25\%$ DW; (b) $X_0 = 0.75\%$ DW.

3.3. Equilibrium Points and Stability Analysis

As can be seen in Figure 2, the hydrolysis reaction acts as a stabilizing factor in the dynamics of product formation and makes the penicillin concentration reach a plateau after

a certain processing time corresponding to one of the multiple equilibrium points possibly existing for the system, $E_i(X_i^*, P_i^*)$, which are analytically determined as follows.

Starting from Equations (1) and (2) and considering that $dX/dt = 0$ and $dP/dt = 0$ at the equilibrium points, Equations (11) and (12) can be obtained:

$$\mu_m X^* \left(1 - \frac{X^*}{X_m}\right) = 0 \quad (11)$$

$$\beta X^* - k_h P^* = 0 \quad (12)$$

Since Equation (11) is quadratic in X^* , it has two roots given by $X_1^* = 0$ and $X_2^* = X_m$. From these roots, the corresponding roots in P of Equation (14) are $P_1^* = 0$ and $P_2^* = \beta X_m / k_h$. Therefore, the dynamical system represented by Equations (1) and (2) has two equilibrium points given by $E_1(0, 0)$ and $E_2(X_m, \beta X_m / k_h)$, whose local stability for small perturbations will be analyzed later using the first Lyapunov method [7,54,55].

From the values adopted for the kinetic parameters, the analysis obtains $X_2^* = 3.7\%$ DW and $P_2^* = 2.74$ U/mL. The final cell and penicillin concentrations at the specified simulation time (190 h) reached values above 95% of the equilibrium values. Processing times longer than specified are prohibitive because they negatively impact on the overall productivity of the bioprocess, which incorporates the amount of antibiotic produced, production volume and processing time.

The stability for a given equilibrium point $E_i(X_i^*, P_i^*)$ depends on the sign and on the real or imaginary form of the eigenvalues (λ_j) of the characteristic matrix of the system, given by $C = \lambda I - J$, where I and J are the identity and Jacobian matrices, respectively, which, in the present case, are as follows:

$$I = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \quad (13)$$

$$J = \begin{bmatrix} \left(\frac{\partial f_1}{\partial X}\right)_{X_i^*, P_i^*} & \left(\frac{\partial f_1}{\partial P}\right)_{X_i^*, P_i^*} \\ \left(\frac{\partial f_2}{\partial X}\right)_{X_i^*, P_i^*} & \left(\frac{\partial f_2}{\partial P}\right)_{X_i^*, P_i^*} \end{bmatrix} \quad (14)$$

$$f_1 = \mu_m X \left(1 - \frac{X}{X_m}\right) \quad (15)$$

$$f_2 = \beta X - k_h P \quad (16)$$

To determine the eigenvalues (λ_j), the determinant of matrix C is set equal to zero as shown in Equation (17):

$$\det \begin{bmatrix} \lambda - \left(\frac{\partial f_1}{\partial X}\right)_{X_i^*, P_i^*} & -\left(\frac{\partial f_1}{\partial P}\right)_{X_i^*, P_i^*} \\ -\left(\frac{\partial f_2}{\partial X}\right)_{X_i^*, P_i^*} & \lambda - \left(\frac{\partial f_2}{\partial P}\right)_{X_i^*, P_i^*} \end{bmatrix} = 0 \quad (17)$$

Subsequently, the partial derivatives indicated in Equation (17) are developed and the determinant is calculated, resulting in Equation (18):

$$\left(\lambda - \mu_m + \frac{2\mu_m X_i^*}{X_m}\right)(\lambda + k_h) = 0 \quad (18)$$

At the equilibrium point $E_1(0, 0)$, Equation (18) becomes $(\lambda - \mu_m)(\lambda + k_h) = 0$, whose roots are $\lambda_1 = \mu_m$ and $\lambda_2 = -k_h$. Since $\mu_m > 0$ and $k_h > 0$, then $\lambda_1 > 0$ and $\lambda_2 < 0$, which characterizes the equilibrium point $E_1(0, 0)$ as locally unstable without penicillin production, but it is possible to change it, for example, by inoculating a small amount of fungus in the medium, leading to some antibiotic production. Conversely, at the equilibrium point $E_2(X_m, \beta X_m/k_h)$, Equation (18) becomes $(\lambda + \mu_m)(\lambda + k_h) = 0$ and the eigenvalues are $\lambda_3 = -\mu_m$ and $\lambda_4 = -k_h$. As $\lambda_3 < 0$ and $\lambda_4 < 0$, the equilibrium point $E_2(X_m, \beta X_m/k_h)$ is characterized as locally stable, making this equilibrium point desirable for the bioprocess as it corresponds to the maximum antibiotic production possible to be reached.

The stability/instability of the equilibrium points was confirmed by 200 h simulations of the temporal response of the dependent variables under small perturbations in their initial values, as shown in Figure 3. In simulation (a), a perturbation of +5% was performed in the value of X_2^* . Consequently, $dX/dt < 0$ in Equation (1) and the fungus concentration decreases until it reaches the equilibrium value again. In response to the increase in fungus concentration triggered by the perturbation, the concentration of penicillin initially increases because $dP/dt > 0$ in Equation (2) and later continuously decreases until it returns to the original equilibrium value. An analogous analysis can be made for simulation (b), in which a perturbation of −5% was performed in the value of X_2^* . In simulation (c), a perturbation of +5% was performed in the value of P_2^* . Since the fungal growth dynamics is uncoupled to that of penicillin formation, the fungus concentration remains constant at X_2^* and $dP/dt < 0$. Thus, the concentration of penicillin gradually decreases, returning to its original equilibrium value P_2^* . A similar discussion can be developed for simulation (d), in which a perturbation of −5% was performed in the value of P_2^* . These first four simulations confirm the stability predicted for the equilibrium point E_2 .

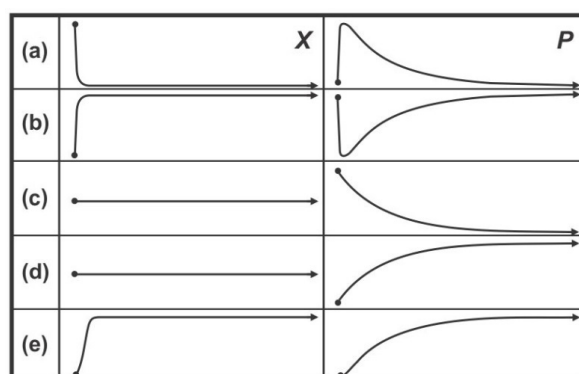


Figure 3. Stability analysis for the equilibrium points: (a) +5% perturbation in X_2^* ; (b) −5% perturbation in X_2^* ; (c) +5% perturbation in P_2^* ; (d) −5% perturbation in P_2^* ; (e) change in X_1^* to 0.05%.

The instability of equilibrium point E_1 is demonstrated by simulation (e). Since the E_1 equilibrium state corresponds to null concentrations of fungus and penicillin, negative perturbations are not feasible because negative values of concentration have no phenomenological significance, as would as any simulation performed without considering the presence of fungus because, in this condition, there would be no cellular activity on the medium. Therefore, in simulation (e), the value of X_1^* was changed to 0.05% DW and, according to Equation (1), $dX/dt > 0$. The fungus concentration progressively increases until it reaches the equilibrium value X_2^* , without returning to its original equilibrium value. According to Equation (2), with the progressive increase in the fungus concentration, the rate of penicillin formation exceeds that of its hydrolysis, inducing a gradual rise in the concentration of penicillin until reaching a plateau in which the rates of penicillin

formation and hydrolysis become equal and $P = P_2^*$, also without returning to its original equilibrium value.

4. Conclusions

Based on the results of this study, the following conclusions can be made:

- By using classical analytical methods for solving ordinary differential equations (variable-separating and integrating-factor methods), it was possible to analytically solve the dynamic equations referring to fungal growth and penicillin production, with the specific rates of cell growth and product formation described by the equations logistic and Luedeking–Piret, respectively, in addition to considering the hydrolysis of the product.
- Both solutions involve numerical calculations of intermediate complexity.
- The agreement between analytical and numerical solutions is quasi complete, and any one of them can be used for simulation, optimization and bioprocess control purposes.
- Stability analysis using the first Lyapunov method revealed that the system has two equilibrium points, one locally unstable (undesirable point) and the other locally stable (desirable point), two relevant dynamic features that are fully captured by the mathematical model, as shown by the performed simulations.

Author Contributions: Conceptualization: S.C.O. and H.O.F.; methodology: S.C.O. and H.O.F.; software: S.C.O. and H.O.F.; validation: S.C.O. and H.O.F.; formal analysis: S.C.O. and H.O.F.; investigation: S.C.O. and H.O.F.; resources: S.C.O. and H.O.F.; data curation: S.C.O. and H.O.F.; writing—original draft preparation: S.C.O.; writing—review and editing: S.C.O. and H.O.F.; visualization: S.C.O. and H.O.F.; supervision: H.O.F.; project administration: S.C.O. and H.O.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

In this appendix, the step-by-step development of the solution to the dynamic equation of product formation without considering the product hydrolysis is presented. Therefore, making $k_d = 0$ in Equation (2), one obtains Equation (A1):

$$\frac{dP}{dt} = \beta X \quad (\text{A1})$$

Substituting Equation (3) into Equation (A1) gives:

$$\frac{dP}{dt} = \beta X_0 \left[\frac{e^{\mu_m t}}{1 + \left(\frac{X_0}{X_m} \right) (e^{\mu_m t} - 1)} \right] \quad (\text{A2})$$

By separating the variables in Equation (A2) and integrating them, Equation (A3) is obtained:

$$\int dP = \beta X_0 \int \left[\frac{e^{\mu_m t}}{1 + \left(\frac{X_0}{X_m} \right) (e^{\mu_m t} - 1)} \right] dt \quad (\text{A3})$$

Making $u = 1 + \left(\frac{X_0}{X_m}\right)(e^{\mu_m t} - 1)$, one obtains $du = \mu_m \left(\frac{X_0}{X_m}\right) e^{\mu_m t} dt$ and $e^{\mu_m t} dt = \frac{1}{\mu_m} \left(\frac{X_m}{X_0}\right) du$. Substituting these relationships into Equation (A3) results in:

$$\int dP = \left(\frac{\beta X_m}{\mu_m}\right) \int \left(\frac{1}{u}\right) du \quad (\text{A4})$$

Performing the integrals indicated in Equation (A4), one obtains:

$$P(t) = \left(\frac{\beta X_m}{\mu_m}\right) \ln|u| + C = \left(\frac{\beta X_m}{\mu_m}\right) \ln \left| 1 + \left(\frac{X_0}{X_m}\right)(e^{\mu_m t} - 1) \right| + C \quad (\text{A5})$$

To determine the integration constant C , the initial condition $P(0) = 0$ is applied in Equation (A5), giving $C = 0$. Therefore, making $C = 0$ in Equation (A5) gives:

$$P(t) = \left(\frac{\beta X_m}{\mu_m}\right) \ln \left| 1 + \left(\frac{X_0}{X_m}\right)(e^{\mu_m t} - 1) \right| \quad (\text{A6})$$

As $e^{\mu_m t} \geq 1$, then $1 + \left(\frac{X_0}{X_m}\right)(e^{\mu_m t} - 1) > 0$ and the modulus operator can be removed from the Equation (A6), providing the final equation:

$$P(t) = \left(\frac{\beta X_m}{\mu_m}\right) \ln \left[1 + \left(\frac{X_0}{X_m}\right)(e^{\mu_m t} - 1) \right]$$

Appendix B

This appendix demonstrates that the solution obtained for $P(t)$ in Case 2 satisfies both the ordinary differential equation and the initial condition $P(0) = 0$. It will be shown first that the solution satisfies the ODE and, secondly, that it satisfies the IC (Initial Condition).

To simplify the notation of Equation (10), the following relations can be established:

$$K = \frac{\beta X_m X_0}{(\mu_m + k_h)(X_m - X_0)} \quad (\text{A7})$$

$$A(t) = {}_2F_1(1, \delta_1; \delta_2; \delta_3 e^{\mu_m t}) e^{\mu_m t} \quad (\text{A8})$$

$$B(t) = {}_2F_1(1, \delta_1; \delta_2; \delta_3) e^{-k_h t} \quad (\text{A9})$$

The simplified form of Equation (10) becomes:

$$P(t) = K[A(t) - B(t)] \quad (\text{A10})$$

Thus:

$$\frac{dP}{dt} = K \left[\frac{dA}{dt} - \frac{dB}{dt} \right] \quad (\text{A11})$$

To differentiate the term $A(t)$ with respect to t , it is necessary to use the recurrence relation [56]:

$$z \left(\frac{a}{b}\right) {}_2F_1(a+1, b+1; c+1; z) = (c-1)[{}_2F_1(a, b; c-1; z) - {}_2F_1(a, b; c; z)] \quad (\text{A12})$$

Considering that, in Equation (A12), $a = 1$, $b = \delta_1$, $c = \delta_2$, and $z = \delta_3 e^{\mu_m t}$, the expression for dA/dt is developed as follows:

$$\frac{dA}{dt} = \mu_m (\delta_2 - 1) [{}_2F_1(1, \delta_1; \delta_1; z) - {}_2F_1(1, \delta_1; \delta_2; z)] e^{\mu_m t} + \mu_m A(t) \quad (\text{A13})$$

Since ${}_2F_1(1, \delta_1; \delta_1; z) = (1 - z)^{-1}$ and $\delta_2 - 1 = \delta_1$, the derivative becomes:

$$\frac{dA}{dt} = \mu_m \delta_1 (1 - z)^{-1} e^{\mu_m t} - \mu_m \delta_1 A(t) + \mu_m A(t) \quad (\text{A14})$$

By substituting $\delta_1 = \frac{\mu_m + k_h}{\mu_m}$, one obtains:

$$\frac{dA}{dt} = (\mu_m + k_h) \frac{e^{\mu_m t}}{1 - \delta_3 e^{\mu_m t}} - k_h A(t) \quad (\text{A15})$$

Developing dB/dt :

$$\frac{dB}{dt} = \frac{d}{dt} \left({}_2F_1(1, \delta_1; \delta_2; \delta_3) e^{-k_h t} \right) \quad (\text{A16})$$

Since ${}_2F_1(1, \delta_1; \delta_2; \delta_3)$ is independent of t , it follows that:

$$\frac{dB}{dt} = -k_h {}_2F_1(1, \delta_1; \delta_2; \delta_3) e^{-k_h t} = -k_h B(t) \quad (\text{A17})$$

Substituting the expressions for dA/dt and dB/dt into Equation (A11) gives:

$$\frac{dP}{dt} = K \left[(\mu_m + k_h) \frac{e^{\mu_m t}}{1 - \delta_3 e^{\mu_m t}} - k_h A(t) + k_h B(t) \right] \quad (\text{A18})$$

Inserting the expressions for $A(t)$ and $B(t)$ into Equation (A18), followed by some algebraic manipulation, gives Equation (A19), which is the original ODE, thus validating the obtained solution.

$$\frac{dP}{dt} = \beta \left[\frac{X_0 e^{\mu_m t}}{1 + \frac{X_0}{X_m} (e^{\mu_m t} - 1)} \right] - k_h P = \beta X - k_h P \quad (\text{A19})$$

To show that the solution also satisfies the initial condition, i.e., $P(0) = 0$, it is only necessary to substitute $t = 0$ into Equation (A10). Since $A(0) = 0$ and $B(0) = 0$, it follows that $P(0)$ is also zero, thus satisfying the initial condition.

References

1. Fierro, F.; Vaca, I.; Castillo, N.I.; García-Rico, R.O.; Chávez, R. *Penicillium chrysogenum*, a Vintage Model with a Cutting-Edge Profile in Biotechnology. *Microorganisms* **2022**, *10*, 573. [CrossRef] [PubMed]
2. Lőrinczy, L.; Turbucz, B.; Hankó, B.; Zekó, R. Managing Antibiotic Shortages in Inpatient Care—A Review of Recent Years in Comparison with the Hungarian Status. *Antibiotics* **2023**, *12*, 1704. [CrossRef] [PubMed]
3. Pagano, F.; De Marco, G.; Trojano, B.; Amato, C.; Micillo, M.; Cecere, G.; Guarino, A.; Lo Vecchio, A. Impact of Amoxicillin Shortage on Pediatric Antibiotic Prescriptions in Primary Care. *Antibiotics* **2025**, *14*, 313. [CrossRef] [PubMed]
4. Oliveira, S.C. Mathematical Modeling of Batch Antibiotic Production: Comparative Analysis between Phenomenological and Empirical Approaches. *J. Bioprocess. Biotech.* **2017**, *7*, 298.
5. Menezes, J.C.; Alves, T.P.; Cardoso, J.P. *Biotechnologia microbiana: A produção de penicilina*. In *Biotechnologia: Fundamentos e Aplicações*; Lima, N., Mota, M., Eds.; DIFEL: Lisboa, Portugal, 2000; pp. 267–282.
6. Nielsen, J.; Jørgensen, H.S. A Kinetic Model for the Penicillin Biosynthetic Pathway in *Penicillium chrysogenum*. In *IFAC Proceedings Volumes*; Elsevier: Amsterdam, The Netherlands, 1995; Volume 28, pp. 136–141.
7. Blanch, H.W.; Clark, D.S. *Biochemical Engineering*; Taylor & Francis: Boca Raton, FL, USA, 1997; 702p.
8. Grigs, O.; Galvanauskas, V.; Dubencovs, K.; Vanags, J.; Suleiko, A.; Berzins, T.; Kunga, L. Model Predictive Feeding Rate Control in Conventional and Single-use Lab-scale Bioreactors: A Study on Practical Application. *Chem. Biochem. Eng. Q.* **2016**, *30*, 47.
9. Lim, H.C.; Lee, K.S. Process control and optimization. In *Bioprocess Monitoring and Control*; Pons, M.N., Ed.; Hanser Publishers: Munich, Germany, 1992; pp. 159–222.
10. Constantinides, A.; Mostoufi, N. *Numerical Methods for Chemical Engineers with MATLAB Applications*; Prentice Hall PTR: Upper Saddle River, NJ, USA, 1999; 560p.

11. Oliveira, S.C. Model-based evolutionary operation design for batch and fed-batch antibiotic production bioprocess. In *Design of Experiments Applied to Industrial Chemical Processes*; Silva, V., Ed.; IntechOpen: Rijeka, Portugal, 2018; pp. 43–63.
12. Yu, Z.; Fu, H.; Wang, J. Modeling and Optimization of the Culture Medium for Efficient 4'-N-Demethyl-Vicenistatin Production by *Streptomyces parvus* Using Response Surface Methodology and Artificial-Neural-Network-Genetic-Algorithm. *Fermentation* **2024**, *10*, 154. [\[CrossRef\]](#)
13. Bolmanis, E.; Dubencovs, K.; Suleiko, A.; Vanags, J. Model Predictive Control—A Stand Out among Competitors for Fed-Batch Fermentation Improvement. *Fermentation* **2023**, *9*, 206. [\[CrossRef\]](#)
14. Rathore, A.S.; Mishra, S.; Nikita, S.; Priyanka, P. Bioprocess Control: Current Progress and Future Perspectives. *Life* **2021**, *11*, 557. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Hu, L.; Sun, Y.; Jia, R.; Dong, X.; Shen, X.; Wang, Y. Enhancement of Mycelial Growth and Antifungal Activity by Combining Fermentation Optimization and Genetic Engineering in *Streptomyces pratensis* S10. *Microorganisms* **2025**, *13*, 1943. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Cuthbertson, A.B.; Rodman, A.D.; Diab, S.; Gerogiorgis, D.I. Dynamic Modelling and Optimisation of the Batch Enzymatic Synthesis of Amoxicillin. *Processes* **2019**, *7*, 318. [\[CrossRef\]](#)
17. Boudza, R.; Bounou, S.; Segura-Garcia, J.; Moukadiri, I.; Maicas, S. Artificial Intelligence as a Catalyst for Antimicrobial Discovery: From Predictive Models to De Novo Design. *Microorganisms* **2026**, *14*, 394. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Menezes, J.C.; Alves, S.S.; Lemos, J.M.; Azevedo, S.F. Mathematical modelling of industrial pilot-plant penicillin-G fed-batch fermentations. *J. Chem. Tech. Biotechnol.* **1994**, *61*, 123.
19. Saraceno, A.; Sansonetti, S.; Calabrò, V.; Iorio, G.; Curcio, S. A Comparison Between Different Modeling Techniques for the Production of Bio-ethanol from Dairy Industry Wastes. *Chem. Biochem. Eng. Q.* **2011**, *25*, 461.
20. Birol, G.; Undey, C.; Cinar, A. A modular simulation package for fed-batch fermentation: Penicillin production. *Comput. Chem. Eng.* **2002**, *26*, 1553. [\[CrossRef\]](#)
21. Cinar, A.; Parulekar, S.J.; Ündey, C.; Birol, G. *Batch Fermentation: Modeling, Monitoring, and Control*; Marcel Dekker: New York, NY, USA, 2003; 606p.
22. Ahmad, A.; Fazli, N.A.; Samad, A.; Wei, C.A. Mathematical Modelling and Analysis of Dynamic Behaviour of a Fed-Batch Penicillin G Fermentation Process. In *Proceedings of the International Conference on Chemical and Bioprocess Engineering*; Universiti Malaysia Sabah: Kota Kinabalu, Malaysia, 2003; pp. 387–394.
23. Vlaev, S.D.; Pavlova, K.; Rusinova-Videva, S.; Georgieva, K.; Georgiev, D. Agitation Effects and Kinetic Constants of Exoglucan Production by Antarctic Yeast Strain in a Stirred Tank Bioreactor. *Chem. Biochem. Eng. Q.* **2016**, *30*, 393.
24. Novak, M.; Koller, M.; Braunnegg, G.; Horvata, P. Mathematical Modelling as a Tool for Optimized PHA Production. *Chem. Biochem. Eng. Q.* **2015**, *29*, 183. [\[CrossRef\]](#)
25. Rice, R.G.; Do, D.D. *Applied Mathematics and Modeling for Chemical Engineers*; John Wiley & Sons: New York, NY, USA, 1995; 719p.
26. Bailey, J.E.; Ollis, D.F. *Biochemical Engineering Fundamentals*, 2nd ed.; McGraw-Hill: New York, NY, USA, 1986; 984p.
27. Shuler, M.L.; Kargi, F. *Bioprocess Engineering: Basic Concepts*, 2nd ed.; Prentice Hall PTR: Upper Saddle River, NJ, USA, 2002; 553p.
28. Garnier, A.; Gaillet, B. Analytical solution of Luedeking-Piret equation for a batch fermentation obeying Monod growth kinetics. *Biotechnol. Bioeng.* **2015**, *112*, 2468. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Sinclair, C.G.; Kristiansen, B. *Fermentation Kinetics and Modeling*; Open University Press: Milton Keynes, UK, 1987; 113p.
30. Najafpour, G.D. *Biochemical Engineering and Biotechnology*; Elsevier: Amsterdam, The Netherlands, 2007; 421p.
31. Ali, M.K.; Hilgsmann, S.; Outili, N.; Cherfia, R.; Chaouche, N.K. Kinetic models and parameters estimation study of biomass and ethanol production from inulin by *Pichia caribbica* (KC977491). *Afr. J. Biotechnol.* **2017**, *16*, 124. [\[CrossRef\]](#)
32. Dhavale, A.; Vhanmarathi, A.; Deshmukh, S.; Dabeer, S. Unstructured Kinetic Modeling of Glutathione Production by *Saccharomyces cerevisiae* NCIM 3345. In *Biotechnology and Biochemical Engineering*; Prasanna, B.D., Gummadi, S.N., Vadlani, P.V., Eds.; Springer: Singapore, 2016; pp. 11–20. [\[CrossRef\]](#)
33. Zakeri, A.; Pazouki, M.; Vossougi, M. Kinetics investigation of cell growth, xanthan production and sugar cane molasses consumption by *Xanthomonas campestris*. *Iranian J. Chem. Eng.* **2015**, *12*, 84.
34. Vinayagam, R.; Vytla, R.M.; Chandrasekaran, M. Development of a Simple Kinetic Model and Parameter Estimation for Biomass and Nattokinase Production by *Bacillus subtilis* 1A752. *Austin J. Biotechnol. Bioeng.* **2015**, *2*, 1036.
35. Wu, W.; Fan, Z. A general inhibition kinetics model for ethanol production using a novel carbon source: *Sodium gluconate*. *Bioprocess. Biosyst. Eng.* **2013**, *36*, 1631. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Bankar, S.B.; Singhal, R.S. Fermentation kinetics makeover in poly- ϵ -lysine biosynthesis by *Streptomyces noursei* NRRL 5126. *J. Biochem. Tech.* **2012**, *3*, 312.
37. Lu, W.; Fan, J.; Wen, J.; Xia, Z.; Caiyin, Q. Kinetic Analysis and Modeling of Daptomycin Batch Fermentation by *Streptomyces roseosporus*. *Appl. Biochem. Biotechnol.* **2011**, *163*, 453. [\[CrossRef\]](#) [\[PubMed\]](#)

38. Uzir, M.H.; Don, M.M. *Biochemical Engineering: A Concise Introduction*, School of Chemical Engineering; Universiti Sains Malaysia: Nibong Tebal, Malaysia, 2007; 109p. Available online: https://chemical.eng.usm.my/notes/HEKARL/notes/ekc471_notes.pdf (accessed on 26 June 2025).
39. Kargi, F. Re-interpretation of the logistic equation for batch microbial growth in relation to Monod kinetics. *Lett. Appl. Microbiol.* **2009**, *48*, 398. [[CrossRef](#)] [[PubMed](#)]
40. Rao, C.S.; Sathish, T.; Brahmaiah, P.; Kumar, T.P.; Prakashama, R.S. Development of a mathematical model for *Bacillus circulans* growth and alkaline protease production kinetics. *J. Chem. Technol. Biotechnol.* **2009**, *84*, 302. [[CrossRef](#)]
41. Razvi, A.; Zhang, Z.; Lan, C.Q. Effects of Glucose and Nitrogen Source Concentration on Batch Fermentation Kinetics of *Lactococcus lactis* under Hemin-Stimulated Respirative Condition. *Biotechnol. Prog.* **2008**, *24*, 852. [[CrossRef](#)] [[PubMed](#)]
42. Kong, Q.; He, G.Q.; Chen, F.; Ruan, H. Studies on a kinetic model for butyric acid bioproduction by *Clostridium butyricum*. *Lett. Appl. Microbiol.* **2006**, *43*, 71. [[CrossRef](#)] [[PubMed](#)]
43. Dhanasekar, R.; Viruthagiri, T. Batch kinetics and modeling of poly- β -hydroxy butyrate synthesis from *Azotobacter vinelandii* using different carbon sources. *Indian J. Chem. Technol.* **2005**, *12*, 322.
44. Elibol, A.; Mavituna, F. A kinetic model for actinorhodin production by *Streptomyces coelicolor* A3(2). *Process Biochem.* **1999**, *34*, 625. [[CrossRef](#)]
45. Xu, P. Analytical solution for a hybrid Logistic-Monod cell growth model in batch and continuous stirred tank reactor culture. *Biotechnol. Bioeng.* **2020**, *117*, 873. [[CrossRef](#)] [[PubMed](#)]
46. Pirt, S.J. Penicillin hydrolysis rate: Its effect on the kinetics of penicillin fermentation. *J. Ferment. Bioeng.* **1990**, *69*, 259. [[CrossRef](#)]
47. Ramirez, W.F. *Computational Methods for Process Simulation*; Butterworth Publishers: Stoneham, MA, USA, 1989; 461p.
48. Constantinides, A.; Spencer, J.L.; Gaden, E.L., Jr. Optimization of Batch Fermentation Processes. I. Development of Mathematical Models for Batch Penicillin Fermentations. *Biotechnol. Bioeng.* **1970**, *12*, 803–830. [[CrossRef](#)] [[PubMed](#)]
49. Constantinides, A.; Spencer, J.L.; Gaden, E.L., Jr. Optimization of Batch Fermentation Processes. II. Optimum Temperature Profiles for Batch Penicillin Fermentations. *Biotechnol. Bioeng.* **1970**, *12*, 1081–1098. [[CrossRef](#)] [[PubMed](#)]
50. da Paz, P.M.; Nakama, C.S.M.; Le Roux, G.A.C. Development of a Software Architecture for Bioprocess Modeling. *Dig. Chem. Eng.* **2025**, *14*, 100210.
51. Zill, D.G. *A First Course in Differential Equations with Modeling Applications*, 10th ed.; Cengage Learning: Boston, MA, USA, 2012; 384p.
52. Shilsar, M.J.F.; Mazaheri, M.; Samani, J.M.V. Analytical solution of the pollution transport equation with variable coefficients in river using the Laplace Transform. *J. Water Irrig. Manag.* **2022**, *11*, 683. [[CrossRef](#)]
53. Manitcharoen, N.; Pimpunchat, B. Analytical and Numerical Solutions of Pollution Concentration with Uniformly and Exponentially Increasing Forms of Sources. *J. Appl. Math.* **2020**, *2020*, 1. [[CrossRef](#)]
54. Comberbach, D.M.; Ghommidh, C.; Bu'Lock, J.D. Steady-state stability and dynamic behavior of continuous ethanol fermentation at high cell densities. *Enzyme Microb. Technol.* **1987**, *9*, 676. [[CrossRef](#)]
55. Widowati, W.; Nurhayati, N.; Sutimin, S.; Laylatussyaarifah, L. Dynamic Analysis of Ethanol, Glucose, and *Saccharomyces* for Batch Fermentation. In *Proceedings of 6th SEAMS-UGM Conference 2011*; Department of Mathematics, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada: Yogyakarta, India, 2012; pp. 561–570.
56. Abramowitz, M.; Stegun, I.A. *Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables*; National Bureau of Standards: Washington, DC, USA, 1965; Chapter 15.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.