CLARIFICATIONS AND CORRECTIONS TO:

A Modular Simulation Package for Fed-Batch Fermentation: Penicillin Production

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Table 1: Cross reference of equations in the paper and the book

Paper	Book
1	2.11
3	2.48
5,6	none
9	2.49
10	2.50
11	2.51
12	2.52
13	2.53
14	2.54
15	none
16	2.55
17	2.56
18	2.57

A few typographical errors in the paper are listed below and the model equations of the fermentor are cross referenced (Table 1) to those in the book titled *Batch Fermentation: Modeling, Monitoring and Control*, A. Cinar, S. J. Parulekar, C.Ündey, and G. Birol, Marcel Dekker, 2003.

For the users of the book, Equations (5), (6) and (15) of the paper are listed below to complete the model:

Equation (5):

$$\frac{d[H^+]}{dt} = \gamma \left(\mu X - \frac{FX}{V} \right) + \left[\frac{-B + \sqrt{(B^2 + 4 \times 10^{-14})}}{2} - [H^+] \right] \frac{1}{\Delta t}$$

where B is defined in Eq. (6) of the paper as

$$B = \frac{\left[\frac{10^{-14}}{[H^+]} - [H^+] \right] V - C_{a/b} \left(F_a + F_b \right) \Delta t}{V + \left(F_a + F_b \right) \Delta t}.$$

F_a and F_b represent acid and base flow rates in L/h, respectively where the concentrations in both solutions are assumed equal as $C_{a/b} = 3M$. The contribution of [H$^+$] change due to

penicillin or any other metabolite concentration variation is not included in Eq. (5) due to lack of experimental data of this nature.

Equation (15):

$$F_{loss} = V\lambda(e^{5(\frac{T-T_0}{T_v-T_0})} - 1)$$

where T_0 and T_v are the freezing and boiling temperatures of the culture medium that were assumed to have the same properties as water, respectively. We have assumed that the evaporation rate will tend to infinity at the boiling point, and for engineering purposes the exponent 5 is large enough to represent this. λ is arranged to give an evaporation rate of 2.5×10^{-4} L.h^{-1} at the operation temperature (25^oC). This expression suggests including an evaporative loss term in volume due to temperature rather than proposing a mechanism. Since we do not base our F_{loss} term on experimental findings, this should be treated as a *heuristic* since as a general tendency, the temperature increase favors evaporative loss. A more accurate relationship can be developed by carrying out a set of experiments at different temperatures and measuring the corresponding humidity of the inlet/exit gas and the volume of the culture broth with respect to time.

- As stated on page 1559, simultaneous solution of Equations (1), (2), (9-18) is necessary for simulating the penicillin fermentor. Equation (5) (H^+ concentration change) should be included in this set of equations. Equation (4) is already embedded into Equation (3) and should not be included in the set.

- C_L^* is the saturation value of dissolved oxygen concentration at 30^oC and is $1.16 mmol/L$ (Table 2)

- The Contois saturation constant K_x is dimensionless (Table 2)

- Equation (3) as published in the paper is correct. The corresponding equation in the book (2.48) should have additional brackets.

$$\mu = \left[\frac{\mu_x}{1 + \frac{K_1}{[H^+]} + \frac{[H^+]}{K_2}}\right] \frac{S}{K_x X + S} \frac{C_L}{K_{ox} X + C_L} \left[k_g exp\left(-\frac{E_g}{RT}\right)\right] - \left[k_d exp\left(-\frac{E_d}{RT}\right)\right].$$

- Equation (8) consists of two equations:

$$\begin{aligned} \Delta MV_N &= K_c \left(E_N - E_{N-1} + \frac{\Delta t}{\tau_I} E_N - \frac{\tau_d}{\Delta t} \left(CV_N - 2CV_{N-1} + CV_{N-2}\right)\right) \\ MV_N &= MV_{N-1} + \Delta MV_N \end{aligned}$$

- The units of oxygen limitation constant K_{op} (Equation 10) are $mmol^p/gbiomassL^{p-1}$ where the constant $p = 3$
- The units of dissolved oxygen concentration C_L are $mmol/L$
- Specific rate of penicillin production is shown as μ_p in the paper (Eq. 10) and ϵ_p in the book (Eq. 2.50), both are equal to 0.005 h^{-1}
- The mass unit in all terms of Equation (11) is g as listed in the updated Table 2 and derived from Equation (10)
- The constants α and β in Equation (13) are dimensionless (Table 2)
- Equation (16) in the paper is correct, while the corresponding equation in the book (2.55) has a typo. The correct equation is:

$$\frac{dQ_{rxn}}{dt} = r_{q_1}\frac{dX}{dt}V + r_{q_2}XV$$

where r_{q_1} is assumed to be constant treated as a yield coefficient and r_{q_2} is calculated and tabulated in Table 2.

- Equation (17) is missing a term as printed in the paper and the book (2.56). The term s_f should also be replaced with V. The units of F (Feed flow rate of substrate) is g/Lh (Table 2). The correct form of Eq. (17) is

$$\frac{dT}{dt} = \frac{F}{V}(T_f - T) + \frac{1}{V\rho c_p}\left[Q_{rxn} - \frac{aF_c^{b+1}}{F_c + \frac{aF_c^b}{2\rho_c c_{pc}}}[T - qT_h - (1-q)T_c]\right]$$

where q is a flag and $q = 1$ for when hot water is used for heating and $q = 0$ when cold water is used for cooling.

- The simulator is written in Matlab. We have not used any Simulink function. The controller gains used are roughly tuned values, fine tuning may be required for better controller performance: Kc=8E-4 for pH controller (with base solution), Kc=1E-4 for pH controller (with acid solution), Kc=70 for temperature controller (with coolant), Kc=5 for temperature controller (with hot water).

Table 2: Initial conditions, kinetic and controller parameters for nominal operation

Time: t (h)	
Initial Conditions	**Value**
Substrate concentration: S (g/L)	15
Dissolved oxygen concentration: C_L (= C_L^* at saturation) (mmol/L)	1.16
Biomass concentration: X (g/L)	0.1
Penicillin concentration: P (g/L)	0
Culture volume: V (L)	100
Carbon dioxide concentration: CO_2 (mmole/L)	0.5
Hydrogen ion concentration: $[H^+]$ (mole/L)	$10^{-5.1}$
Temperature: T (K)	297
Heat generation: Q_{rxn} (cal)	0
Kinetic Parameters and Variables	
Feed substrate concentration: s_f (g/L)	600
Feed flow rate of substrate: F (L/h)	
Feed temperature of substrate: T_f (K)	298
Yield constant: $Y_{x/s}$ (g biomass/g glucose)	0.45
Yield constant: $Y_{x/o}$ (g biomass/g oxygen)	0.04
Yield constant: $Y_{p/s}$ (g penicillin/g glucose)	0.90
Yield constant: $Y_{p/o}$ (g penicillin/g oxygen)	0.20
Constant: K_1 (mole /L)	10^{-10}
Constant: K_2 (mole /L)	7×10^{-5}
Maintenance coefficient on substrate: m_x (h^{-1})	0.014
Maintenance coefficient on oxygen: m_o (h^{-1})	0.467
Constant relating CO_2 to growth: α_1 (mmole CO_2/ g biomass)	0.143
Constant relating CO_2 to maintenance energy: α_2 (mmole CO_2/ g biomass h)	4×10^{-7}
Constant relating CO_2 to penicillin production: α_3 (mmole CO_2/ L h)	10^{-4}
Maximum specific growth rate: μ_x (h^{-1})	0.092
Contois saturation constant: K_x	0.15
Oxygen limitation constant: K_{ox}, K_{op} (no limitation)	0
Oxygen limitation constant: K_{ox}, K_{op} (with limitation) $mmol^p/g$ biomass L^{p-1}	2×10^{-2}, 5×10^{-4}
Specific rate of penicillin production: μ_p (h^{-1})	0.005
Inhibition constant: K_p (g/L)	0.0002
Inhibition constant for product formation: K_I (g/L)	0.10
Constant: p	3
Penicillin hydrolysis rate constant: K (h^{-1})	0.04
Arrhenius constant for growth: k_g	7×10^3
Activation energy for growth: E_g (cal/mole)	5100
Arrhenius constant for cell death: k_d	10^{33}
Activation energy for cell death: E_d (cal/mole)	50000
Density × heat capacity of medium: $\rho\ C_p$ (cal/L^oC)	1500
Density × heat capacity of cooling liquid: $\rho_c C_{pc}$ (cal/L^oC)	1000
Yield of heat generation: r_{q1} (cal/g biomass)	60
Constant in heat generation: r_{q2} (cal/g biomass.h)	1.6783×10^{-4}
Heat transfer coefficient of cooling/heating liquid: a (cal/h^oC)	1000
Cooling water flow rate: F_c (L/h)	
Constant: b	0.60
Constants in K_{la}: α, β	70, 0.4
Constant in F_{loss}: λ (h^{-1})	2.5×10^{-4}
Proportionality constant: γ (mole $[H^+]$/g biomass)	10^{-5}
Controller Parameters (**PID**)	
pH : (Base)K_c,τ_I:(h),τ_d:(h)	8×10^{-4}, 4.2, 0.2625
(Acid)K_c,τ_I:(h),τ_d:(h)	1×10^{-4}, 8.4, 0.125
Temperature: (Cooling)K_c,τ_I:(h),τ_d:(h)	70, 0.5, 1.6
(Heating)K_c,τ_I:(h),τ_d:(h)	5, 0.8, 0.05