

Bioreaction Engineering Principles

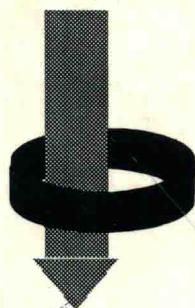


Primary eddies

Intermediate eddies

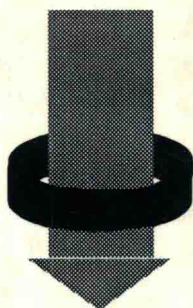
Terminal eddies

glucose



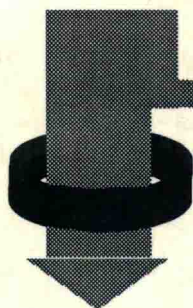
carbon dioxide

glucose



carbon dioxide

glucose



carbon dioxide

ethanol

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Bioreaction Engineering Principles

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Bioreaction Engineering Principles

Preface

There is something presumptuous in deciding to write a textbook. One invests the better part of two years finalizing the project, and then presses the result onto several generations of students and promotes it to colleagues in the industry. Do we, after all, have ideas that were not already conceived by others and described in sufficient clarity in existing textbooks with similar titles?

The authors of the present text are both relative newcomers to the field. One is young; the other has spent a lifetime in chemical engineering and mathematical modeling and is a fairly recent convert to the Society of Biotechnologists. The book is based on recent improvements in the quantitative treatment of bioreactions at the research center where we both work, as well as a service to meet the high standard Danish industry demands of candidates who, as future employees, are destined to realize the promises of modern biotechnology. We believe that a more or less unified treatment of the principles of Bioreaction Engineering is now in your hands; a text based on mathematical modeling, but with a deep respect for the wonderful complexity of microbial reactions. There are, as admitted, many books written with a similar purpose, and we have had occasion to profit from the experience of the authors of these texts, as well as from the results of numerous scientific papers published in recent years. We would not have been able to write the present text without a careful study of J. A. Roels, “Energetics and Kinetics in Biotechnology” (Elsevier, 1983) and J. E. Bailey and D. F. Ollis, “Biochemical Engineering Fundamentals” (2. ed.) (McGraw Hill, 1986).

To the abovementioned, our most sincere thanks for continuous inspiration. A special word of thanks to Dr. Martin Hjørtso of Louisiana State University who contributed most of the Problems in Chapter 6, and made many comments on the text of Chapter 6. Finally, we recognize the efforts of our graduate students and of a large number of undergraduate students at the Technical University of Denmark who suffered through the first versions of the many Problems that are now included at the end of each chapter.

Jens Nielsen and John Villadsen

Lynghy, Denmark

List of Symbols

Symbols that are defined and used only within a particular Example, Note, or Problem are not listed. A few symbols are used for different purposes, but only when no confusion is possible. In these cases both definitions are specified.

a	Cell age (hr)
a	Specific interfacial area (m^2 per m^3 of medium)
a_d	Specific interfacial area (m^2 per m^3 of gas–liquid dispersion)
a_{cell}	Specific cell surface area (m^2 per gram dry weight)
a_g	Genealogical cell age [used in Eq. (5.38)]
A	Total interfacial area in a gas–liquid dispersion
$\mathbf{A}, \mathbf{A}_s, \mathbf{A}_p$	Matrices of stoichiometric coefficients for intracellular substrates
$b(y)$	Breakage frequency (hr^{-1})
$\mathbf{B}, \mathbf{B}_s, \mathbf{B}_p$	Matrices of stoichiometric coefficients for intracellular products
Bi	Biot number, given by Eq. (7.68)
c_i	Concentration of the i th chemical compound (kg m^{-3})
c_i^*	Saturation concentration of the i th chemical compound (kg m^{-3})
\mathbf{c}	Vector of concentrations (kg m^{-3})
\mathbf{c}_e	Vector of concentrations in the efflux from the bioreactor (kg m^{-3})
\mathbf{c}_f	Vector of concentrations in the feed to the bioreactor (kg m^{-3})
C	Number of pathway intermediates in a metabolic model
C_{ij}	Concentration control coefficients with respect to the activity of the i th enzyme
C'_i	Flux control coefficient with respect to the activity of the i th enzyme
\mathbf{C}^*	Matrix containing the control coefficients [defined in Eq. (3.38)]
d_{cell}	Cell diameter (m)
d_b	Bubble diameter (m)
d_l	Thickness of liquid film (m)
d_{mean}	Mean bubble diameter (m)
d_{mem}	Lipid membrane thickness (m)
d_o	Orifice diameter (m)
d_s	Stirrer diameter (m)
d_{Sauter}	Mean Sauter bubble diameter, given by Eq. (7.18)
D	Dilution rate (hr^{-1})
D_{max}	Maximum dilution rate (hr^{-1})
D_{mem}	Diffusion coefficient in the lipid membrane ($\text{m}^2 \text{s}^{-1}$)
D_{eff}	Effective diffusion coefficient ($\text{m}^2 \text{s}^{-1}$)
D_i	Diffusion coefficient of the i th chemical compound ($\text{m}^2 \text{s}^{-1}$)
D_j	Energy dissipation to the surroundings in the j th reaction (kJ mole^{-1})
Da	Damköhler number, given by Eq. (7.45)

e_i	Column vector of dimension i with all elements being 1
E_g	Activation energy of the growth process in Eq. (4.21)
$E(t)$	Residence time distribution
E	Elemental matrix for all compounds
E^*	Matrix given by Eq. (3.17)
E_c	Elemental matrix for calculated compounds
E_m	Elemental matrix for measured compounds
E_p	Elemental matrix for metabolic products
E_s	Elemental matrix for substrates
E_x	Elemental matrix for biomass components
$f(y)$	Distribution function for cells with property y in the population
F	Degrees of freedom
F	Variance-covariance matrix
g	Gravity ($m\ s^{-2}$)
G_i	Gibbs free energy for the i th reaction component ($kJ\ mole^{-1}$)
G_i^0	Gibbs free energy for the i th reaction component at standard conditions ($kJ\ mole^{-1}$)
ΔG_{ci}	Gibbs free energy of combustion of the i th reaction component ($kJ\ mole^{-1}$)
ΔG_{ci}^0	Gibbs free energy of combustion of the i th reaction component at standard conditions ($kJ\ mole^{-1}$)
$\Delta G_{c,j}$	Change in Gibbs free energy in the j th reaction ($kJ\ mole^{-1}$)
$\Delta G_{c,j}^0$	Change in standard free energy in the j th reaction ($kJ\ mole^{-1}$)
ΔG_d	Gibbs free energy change upon protein denaturation ($kJ\ mole^{-1}$)
Gr	Grashof number, given in Table 7.4
h	Test function given by Eq. (3.58)
$h(y)$	Net rate of formation of cells with property y upon cell division ($cells\ hr^{-1}$)
$h^+(y)$	Rate of formation of cells with property y upon cell division ($cells\ hr^{-1}$)
$h^-(y)$	Rate of disappearance of cells with property y upon cell division ($cells\ hr^{-1}$)
H_A	Henry's constant ($atm \cdot m^3\ kmole^{-1}$)
ΔH_{ci}^0	Heat of combustion of the i th reaction component ($kJ\ mole^{-1}$)
$\Delta H_{c,j}^0$	Change of enthalpy in the j th reaction ($kJ\ mole^{-1}$)
H	Community matrix for which the elements are given by Eq. (5.59)
I	Number of elements
I	Unity matrix (diagonal matrix with 1 in the diagonal)
J	Number of intracellular reactions
J_A	Mass flux of chemical compound A ($kg\ m^{-2}\ hr^{-1}$)
J	Jacobi matrix for which the elements are given by Eq. (8.93)
k_i	Rate constant ($kg\ kg^{-1}\ hr^{-1}$)
k_g	Mass transfer coefficient for gas film ($m\ s^{-1}$)
k_l	Mass transfer coefficient for a liquid film surrounding a gas bubble ($m\ s^{-1}$)
$k_{l,a}$	Volumetric mass transfer coefficient (s^{-1})
k_s	Mass transfer coefficient for a liquid film surrounding a solid particle ($m\ s^{-1}$)
K	Number of metamorphosis reactions
K_a	Acid dissociation constant ($moles\ m^{-3}$)
K_l	Overall mass transfer coefficient for gas-liquid mass transfer ($m\ s^{-1}$)
K_{par}	Partitioning coefficient
K_s	Saturation constant ($kg\ m^{-3}$)
K_i	Inhibition constant ($kg\ m^{-3}$)
K_j	Equilibrium constant for the j th reaction

l_{hgu}	Hyphal growth unit length in Eq. (5.47) (m tip^{-1})
L	Number of intracellular biomass components
m	Amount of biomass (kg)
m	Degree of mixing
m_{ATP}	Maintenance-associated ATP consumption (moles of ATP per kg dry weight per hr)
$m_{\text{ATP}}^{\text{true}}$	The true maintenance-associated ATP consumption (moles of ATP per kg dry weight per hr)
m_{hgu}	Hyphal growth unit mass, given by Eq. (5.47) (kg dry weight per tip)
m_s	Maintenance-associated specific substrate consumption (kg per kg dry weight per hr)
m_p	Maintenance-associated specific metabolic product formation (kg per kg dry weight per hr)
M	Number of metabolic products
M_n	The n th moment of a one-dimensional distribution function, given by Eq. (6.9)
M_w	Molar mass (kg mole^{-1})
\mathbf{M}	Matrix with the specific growth rates of morphological forms in the diagonal
n	Number of cells per unit volume (cells m^{-3})
N	Number of substrates
N	Stirring speed (s^{-1})
N_A	Aeration number, given by Eq. (9.21)
N_f	Flow number, appearing in Eq. (9.22)
N_p	Power number, appearing in Eq. (9.18)
p	Extracellular metabolic product concentration (kg m^{-3})
p_A	Partial pressure of compound A (atm)
$p(y, y^*)$	Partitioning function, used in Eq. (6.5)
\mathbf{p}	Extracellular metabolic product concentration vector (kg m^{-3})
P_i	Productivity of species i in a chemostat ($\text{kg m}^{-3} \text{hr}^{-1}$)
P	Dimensionless metabolic product concentration
P	Permeability coefficient (m s^{-1})
P	Power input to a bioreactor (W)
P_g	Power input to a bioreactor at gassed conditions (W)
\mathbf{P}	Intracellular metabolic product concentration vector (kg per kg dry weight)
\mathbf{P}	Variance-covariance matrix for the residuals, given by Eq. (3.52)
\mathbf{P}_q	Intracellular metabolic product concentration vector for the q th morphological form (kg per kg of q th morphological form)
Pe	Peclet number, given by Eq. (7.35)
q_{Λ}^{mt}	Volumetric rate of transfer of A from gas to liquid ($\text{kg m}^{-3} \text{hr}^{-1}$)
$q_{\Lambda, \text{obs}}$	Observed reaction rate, given by Eq. (7.61)
q_s	Volumetric rate of formation of biomass (kg dry weight per m^3 per hr)
q_Q	Volumetric rate of heat generation ($\text{kJ m}^{-3} \text{hr}^{-1}$)
\mathbf{q}	Volumetric rate vector ($\text{kg m}^{-3} \text{hr}^{-1}$)
\mathbf{q}^*	Vector where q_Q is added as the last element to \mathbf{q}
\mathbf{q}^{mt}	Vector of volumetric mass transfer rates (kg dry weight per m^3 per hr)
\mathbf{q}_c	Volumetric rate vector of formation of calculated compounds ($\text{kg m}^{-3} \text{hr}^{-1}$)
\mathbf{q}_m	Volumetric rate vector of formation of measured compounds ($\text{kg m}^{-3} \text{hr}^{-1}$)
\mathbf{q}_p	Volumetric rate vector of formation of metabolic products ($\text{kg m}^{-3} \text{hr}^{-1}$)
\mathbf{q}_s	Volumetric rate vector of formation of substrates ($\text{kg m}^{-3} \text{hr}^{-1}$)

\mathbf{q}_k	Volumetric rate vector of formation of biomass components ($\text{kg m}^{-3} \text{hr}^{-1}$)
Q	Number of morphological forms
Q_j	Heat generated by the j th reaction (kJ mole^{-1})
Q_1	Fraction of repressor-free operators, given by Eq. (4.44)
Q_2	Fraction of promoters being activated, given by Eq. (4.50)
Q_3	Fraction of promoters which form complexes with RNA polymerase
\mathbf{Q}	Vector containing the heat of combustion of all compounds (kJ mole^{-1})
r	Specific reaction rate ($\text{kg per kg dry weight per hr}$)
r_{ATP}	Specific ATP synthesis rate (moles of ATP per kg dry weight hr)
r_Q	Specific rate of heat generation in all cellular reactions ($\text{kJ per g dry weight per hr}$)
\mathbf{r}	Specific reaction rate vector ($\text{kg per kg dry weight per hr}$)
$\mathbf{r}(y)$	Vector containing the rates of change of properties, in Eq. (6.2)
\mathbf{r}_p	Specific metabolic product formation rate vector ($\text{kg per kg dry weight per hr}$)
$\mathbf{r}_{p,q}$	Specific metabolic product formation rate vector for the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
\mathbf{r}_q	Specific reaction rate vector for the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
\mathbf{r}_s	Specific substrate uptake rate vector ($\text{kg per kg dry weight per hr}$)
$\mathbf{r}_{s,q}$	Specific substrate uptake rate vector for the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
R	Gas constant ($=8.314 \text{ J K}^{-1} \text{ mole}^{-1}$)
R	Recirculation factor
\mathbf{R}	Vector of net rates for the formation of intracellular components ($\text{kg per kg dry weight per hr}$)
\mathbf{R}	Redundancy matrix, given by Eq. (3.45)
\mathbf{R}_q	Vector of net rates for the formation of intracellular components in the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
\mathbf{R}_r	Reduced redundancy matrix
\mathbf{R}_s	Vector of net rates for the formation of intracellular substrates ($\text{kg per kg dry weight per hr}$)
$\mathbf{R}_{s,q}$	Vector of net rates for the formation of intracellular substrates in the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
\mathbf{R}_p	Vector of net rates for the formation of intracellular metabolic products ($\text{kg per kg dry weight per hr}$)
$\mathbf{R}_{p,q}$	Vector of net rates for the formation of intracellular metabolic products in the q th morphological form ($\text{kg per kg of } q\text{th morphological form per hr}$)
Re	Reynolds number, given in Table 7.4
s	Extracellular substrate concentration (kg m^{-3})
\mathbf{s}	Extracellular substrate concentration vector (kg m^{-3})
s_f	Substrate concentration in the feed to the bioreactor (kg m^{-3})
S	Dimensionless substrate concentration
$\Delta S_{c,j}^0$	Entropy change in the j th reaction ($\text{kJ mole}^{-1} \text{ K}^{-1}$)
\mathbf{S}	Intracellular substrate concentration vector ($\text{kg per kg dry weight}$)
\mathbf{S}_q	Intracellular substrate concentration vector for the q th morphological form ($\text{kg per kg of } q\text{th morphological form}$)
Sc	Schmidt number, given in Table 7.4
Sh	Sherwood number, given in Table 7.4
t	Time (hr)

t_c	Circulation time (s)
t_m	Mixing time (s)
T	Temperature (K)
\mathbf{T}	Total stoichiometric matrix
$\mathbf{T}_1, \dots, \mathbf{T}_7$	Partitioning of \mathbf{T}^T
u_b	Bubble rise velocity (m s^{-1})
u_i	Cybernetic variable, given by Eq. (4.52)
u_k	Specific rate of the k th metamorphosis reaction ($\text{kg kg}^{-1} \text{hr}^{-1}$)
u_s	Superficial gas velocity (m s^{-1})
\mathbf{u}	Vector containing the specific reaction rates of the metamorphosis reactions ($\text{kg kg}^{-1} \text{hr}^{-1}$)
U_q	Net rate of formation of the q th morphological form ($\text{kg kg}^{-1} \text{hr}^{-1}$)
\mathbf{U}	Vector of net rates for the formation of morphological forms (kg per kg dry weight per hr^{-1})
v	Liquid flow ($\text{m}^3 \text{hr}^{-1}$)
v_c	Liquid effluent flow from the bioreactor ($\text{m}^3 \text{hr}^{-1}$)
v_f	Liquid feed flow to the bioreactor ($\text{m}^3 \text{hr}^{-1}$)
v_g	Gas flow ($\text{m}^3 \text{hr}^{-1}$)
v_i	Cybernetic variable, given by Eq. (4.53)
v_{pump}	Impeller induced flow ($\text{m}^3 \text{hr}^{-1}$)
V	Medium volume (m^3)
V_d	Total volume of gas-liquid dispersion (m^3)
V_g	Dispersed gas volume (m^3)
V_l	Liquid volume (m^3)
V_{hgu}	Hyphal growth unit volume, in Eq. (5.47) ($\text{m}^3 \text{cells tip}^{-1}$)
V_y	Total property space
w	Water content of the biomass (kg of water per kg of biomass)
x	Biomass concentration (kg m^{-3})
x_c	Biomass concentration in the effluent from the bioreactor (kg m^{-3})
x_f	Biomass concentration in the feed to the bioreactor (kg m^{-3})
x_R	Biomass concentration in the recirculation stream (kg m^{-3})
X	Dimensionless biomass concentration
X_{ci}	Activity of the i th enzyme in a pathway
X_i	Concentration of the i th intracellular component (kg per kg dry weight)
\mathbf{X}	Vector of concentrations of intracellular biomass components (kg per kg dry weight)
\mathbf{X}_q	Vector of concentrations of intracellular biomass components in the q th morphological form (kg per kg of q th morphological form)
\mathbf{y}	Property state vector
Y_{ij}	Yield coefficient of j from i (kg j per kg of i)
Y_{xATP}	ATP consumption for biomass formation (moles of ATP per kg dry weight)
$Y_{\text{ATP}}^{\text{true}}$	The true ATP consumption for biomass formation (moles of ATP per kg dry weight)
Z_i	Concentration of the i th morphological form (kg per kg dry weight)
\mathbf{Z}	Vector of concentrations of morphological forms (kg q per kg dry weight)

Greek Letters

α_{ji}	Stoichiometric coefficients for substrate i in intracellular reaction j
$\alpha_{s,ji}$	Stoichiometric coefficient for substrate i in the uptake of the j th substrate

$\alpha_{p,ji}$	Stoichiometric coefficient for substrate i in excretion of the j th metabolic product
$\mathbf{A}, \mathbf{A}_s, \mathbf{A}_p$	Matrices containing the stoichiometric coefficients for substrates
$\mathbf{A}_q, \mathbf{A}_{s,q}, \mathbf{A}_{p,q}$	Matrices containing the stoichiometric coefficients for substrates in the q th morphological form
β_{ji}	Stoichiometric coefficient for metabolic product i in intracellular reaction j
$\beta_{s,ji}$	Stoichiometric coefficient for metabolic product i in the uptake of the j th substrate
$\beta_{p,ji}$	Stoichiometric coefficient for metabolic product i in excretion of the j th metabolic product
$\mathbf{B}, \mathbf{B}_s, \mathbf{B}_p$	Matrices containing the stoichiometric coefficients for metabolic products
$\mathbf{B}_q, \mathbf{B}_{s,q}, \mathbf{B}_{p,q}$	Matrices containing the stoichiometric coefficients for substrates in the q th morphological form
$\dot{\gamma}$	Shear rate (s^{-1})
γ_{ji}	Stoichiometric coefficient for intracellular component i in intracellular reaction j
γ_{ji}^*	Stoichiometric coefficient for reduction equivalents of H_2 in the j th reaction
$\gamma_{s,ji}$	Stoichiometric coefficient for intracellular component i in the uptake of the j th substrate
$\gamma_{p,ji}$	Stoichiometric coefficient for intracellular component i in excretion of the j th metabolic product
$\Gamma, \Gamma_s, \Gamma_p$	Matrices containing the stoichiometric coefficients for intracellular biomass components
$\Gamma_q, \Gamma_{s,q}, \Gamma_{p,q}$	Matrices containing the stoichiometric coefficients for intracellular biomass components in the q th morphological form
δ	Vector of measurement errors in Eq. (3.47)
δ_{kq}	Stoichiometric coefficient for morphological form q in the k th metamorphosis reaction
Δ	Matrix for stoichiometric coefficients for morphological forms
Δ^+	Matrix of positive elements in Δ
Δ^-	Matrix of negative elements in Δ
ε	Gas holdup (m^3 of gas per m^3 of gas-liquid dispersion)
ε	Porosity of a pellet
ε_{ji}	Elasticity coefficients
ε	Vector of residuals in Eq. (3.50)
\mathbf{E}	Matrix containing the elasticity coefficients
η	Viscosity ($\text{kg m}^{-1} \text{s}^{-1}$)
η_{eff}	Efficiency factor
η_{th}	Thermodynamic efficiency
η_{tr}	Overall transcription efficiency of a gene
θ	Dimensionless time
κ_i	Generalized degree of reduction of the i th compound
κ_i^*	Generalized degree of reduction of the i th compound with N_2 as the nitrogen source
\mathbf{K}	Vector containing the generalized degree of reduction of all compounds
\mathbf{K}_p	Vector containing the generalized degree of reduction of metabolic products
\mathbf{K}_s	Vector containing the generalized degree of reduction of substrates

\mathbf{K}_x	Vector containing the generalized degree of reduction of biomass components
Λ	Vector of multiplication factors in Eq. (2.31)
μ	The specific growth rate of biomass (kg dry weight per kg dry weight per hr)
$\mu(X)$	The specific growth rate of cells with composition X (kg dry weight per kg dry weight per hr)
μ_{\max}	The maximum specific growth rate (kg dry weight per kg dry weight per hr)
μ_q	The specific growth rate for the q th morphological form (kg dry weight per kg dry weight per hr)
ρ_{cell}	Cell density (kg of wet biomass per m^3 of cell)
ρ_l	Liquid density (kg m^{-3})
ρ_g	Gas density (kg m^{-3})
σ	Surface tension (N m^{-1})
σ^2	Variance
τ	Space time in a bioreactor (hr)
τ_s	Shear stress (N m^{-2})
τ_t	Tortuous factor, used in Eq. (7.65)
ϕ	Branching frequency (tips formed per g dry weight per hr)
$\phi(y)$	Normalized distribution function of number of cells
Φ	Thiele modulus, given by Eq. (7.60)
Φ_{gen}	Generalized Thiele modulus, given by Eq. (7.65)
$\psi(X)$	Normalized distribution function of morphological forms

Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
Arc	Anabolic reductive charge
ATP	Adenosine triphosphate
BST	Biochemical systems theory
CoA	Coenzyme A
Crc	Catabolic reductive charge
DNA	Deoxyribonucleic acid
Ec	Energy charge
EMP	Embden–Meyerhof–Parnas
FAD	Flavin adenine dinucleotide (oxidized form)
FADH ₂	Flavin adenine dinucleotide (reduced form)
F6P	Fructose-6-phosphate
Glc	Glucose
GTP	Guanosine triphosphate
G6P	Glucose-6-phosphate
MCA	Metabolic control analysis
NAD ⁺	Nicotinamide adenine dinucleotide (oxidized form)
NADH	Nicotinamide adenine dinucleotide (reduced form)
NADP ⁺	Nicotinamide adenine dinucleotide phosphate (oxidized form)
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
PEP	Phosphoenol pyruvate

PP	Pentose phosphate
PSS	Protein synthesizing system
PTS	Phosphotransferase system
PYR	Pyruvate
P/O ratio	Number of molecules of ATP formed per atom of oxygen used in the oxidative phosphorylation
RNA	Ribonucleic acid
mRNA	Messenger RNA
rRNA	Ribosomal RNA
tRNA	Transfer RNA
RQ	Respiratory quotient
R5P	Ribose-5-phosphate
SCP	Single cell protein
TCA	Tricarboxylic acid

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