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6

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Bioreaction Engineering Principles

(3rd Edition)

John Villadsen, Jens Nielsen and Gunnar Lidén

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Preface

In early 2009, we were approached by Springer Verlag, the company that had absorbed Kluwer Academic/Plenum Publishers. The second edition of our textbook "*Bioreaction Engineering Principles*" was now sold out, and we were asked to prepare a third edition.

With very little hesitation we accepted the offer.

Since 2003 the book has been used as course-book, in European universities and also in North and South America, in the Far East, and in Australia. We wished not only to revise the text, but also to write a book that would appeal to students at the best universities, at least until 2020. In short courses given at major Biotech companies we have also found that some of the material in the previous editions could be used right away to give the companies a better understanding of their processes and to propose better design of their reactors. This acceptance of the book by the industrial community prompted us to include even more examples relevant for design of processes and equipment in the industry. The changes that have been made since the second edition are outlined in the first, introductory chapter of the present edition.

Our initial enthusiasm to embark on a complete revision of the text was mollified by the duties imposed on two of us (J.N. and G.L.) in handling large research groups and with the concomitant administration. One of us (J.V.) had much more time available in his function as senior professor, and he became the main responsible person for the work during the almost 2 years since the start of the project. But we are all happy with the result of our common efforts – "*Tous pour un, un pour tous.*"

Some chapters have been read and commented by our colleagues. Special thanks are owed to Prof. John Woodley for commenting on Chaps. 2 and 3, and to Prof. Alvin Nienow for long discussions concerning the right way to present Chap. 11. The former Ph.D. students, Drs. Mikkel Nordkvist and Thomas Grotkjær have kindly given comments to many of the chapters.

We also thank Ph.D. student Saeed Sheykshoaie at Chalmers University who redrew many of the figures in the last rush before finishing the manuscript. Ph.D. student Jacob Brix at DTU has often assisted J.V. with his extensive knowledge of "how to handle the many tricks of Word."

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List of Symbols

Symbols that are defined and used only within a particular Example, Note, or Problem are not listed. It should be noted that a few symbols are used for different purposes in different chapters. For this reason, more than one definition may apply for a given symbol.

a	Cell age (h)
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)
$\mathbf{A}$	Matrix of stoichiometric coefficients for substrates, introduced in (7.2)
$b(y)$	Breakage frequency (h^{-1})
$\mathbf{B}$	Matrix of stoichiometric coefficients for metabolic products, introduced in (7.2)
c_i	Concentration of the ith chemical compound (kg m^{-3})
c_i^*	Saturation concentration of the ith chemical compound (kg m^{-3})
$\mathbf{c}$	Vector of concentrations (kg m^{-3})
C_{ij}	Concentration control coefficient of the jth intermediate with respect to the activity of the ith enzyme
C_i^J	Flux control coefficient with respect to the activity of the ith enzyme
$\mathbf{C}^*$	Matrix containing the control coefficients defined in (6.34)
d_b	Bubble diameter (m)
δ_f	Thickness of liquid film (m)
d_{mean}	Mean bubble diameter (m)
d_{mem}	Lipid membrane thickness (m)
d_s	Stirrer diameter (m)
d_{Sauter}	Mean Sauter bubble diameter (m), given by (10.18)
D	Dilution rate (h^{-1}), given by (3.1)
D_{max}	Maximum dilution rate (h^{-1})
D_{mem}	Diffusion coefficient in a lipid membrane (m^2 s^{-1})
D_{eff}	Effective diffusion coefficient (m^2 s^{-1})

D_i	Diffusion coefficient of the ith chemical compound ($m^2\ s^{-1}$)
e_0	Enzyme concentration (g enzyme L^{-1})
E_g	Activation energy of the growth process in (7.28)
E	Mixing efficiency, defined in (11.1)
$\mathbf{E}$	Elemental matrix for all compounds
$\mathbf{E}_c$	Elemental matrix for calculated compounds
$\mathbf{E}_m$	Elemental matrix for measured compounds
$f(\mathbf{y},t)$	Distribution function for cells with property $\mathbf{y}$ in the population (8.1)
$\mathbf{F}$	Variance–covariance matrix
g	Gravity ($m\ s^{-2}$)
G	Gibbs free energy ($kJ\ mol^{-1}$)
G^0	Gibbs free energy at standard conditions ($kJ\ mol^{-1}$)
ΔG_{ci}	Gibbs free energy of combustion of the ith reaction component ($kJ\ mol^{-1}$)
ΔG_d	Gibbs free energy of denaturation ($kJ\ mol^{-1}$) (7.29)
ΔG^0_{ci}	Gibbs free energy of combustion of the ith reaction component at standard conditions ($kJ\ mol^{-1}$)
ΔG^0_f	Gibbs free energy of formation at standard conditions ($kJ\ mol^{-1}$)
Gr	Grashof number, defined in Table 10.6
h	Test function, given by (3.54)
$h(y)$	Net rate of formation of cells with property y upon cell division (cells h^{-1})
$h^+(y)$	Rate of formation of cells with property y upon cell division (cells h^{-1})
$h^-(y)$	Rate of disappearance of cells with property y upon cell division (cells h^{-1})
H_A	Henry's constant for compound A (atm L mol^{-1})
ΔH_{ci}	Enthalpy of combustion of the ith reaction component ($kJ\ mol^{-1}$)
ΔH^0_f	Enthalpy of formation ($kJ\ mol^{-1}$)
$\mathbf{I}$	Identity matrix (diagonal matrix with 1 in the diagonal)
$\mathbf{J}$	Jacobian matrix (9.102)
k_0	Enzyme activity (g substrate [g enzyme]$^{-1}$ h^{-1})
k_i	Rate constant (e.g., kg $kg^{-1}\ h^{-1}$)
k_g	Mass transfer coefficient for gas film (e.g., mol $atm^{-1}\ s^{-1}\ m^{-2}$)
k_l	Mass transfer coefficient for a liquid film surrounding a gas bubble ($m\ s^{-1}$)
k_la	Volumetric mass transfer coefficient (s^{-1})
k_s	Mass transfer coefficient for a liquid film surrounding a solid particle ($m\ s^{-1}$)
K_a	Acid dissociation constant ($mol\ L^{-1}$)
K_l	Overall mass transfer coefficient for gas–liquid mass transfer ($m\ s^{-1}$)
K	Partition coefficient
K_{eq}	Equilibrium constant
K_m	Michaelis constant ($g\ L^{-1}$) (6.1)
m	Amount of biomass (kg)

m_{ATP}	Maintenance-associated ATP consumption (moles ATP [kg DW]$^{-1}$ h^{-1})
m_s	Maintenance-associated specific substrate consumption (kg [kg DW]$^{-1}$ h^{-1})
$M_n(t)$	The nth moment of a one-dimensional distribution function, given by (8.9)
n	Number of cells per unit volume (cells m^{-3}) (8.1)
N	Stirring speed (s^{-1})
N_A	Aeration number, defined in (11.14)
N_f	Flow number, defined in (11.6)
N_p	Power number, defined in (11.10)
p	Extracellular metabolic product concentration (kg m^{-3})
p_A	Partial pressure of compound A (e.g., atm.)
$p(y,y^*,t)$	Partitioning function (8.5)
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)
$\mathbf{P}$	Variance–covariance matrix for the residuals, given by (3.48)
Pe	Peclet number, defined in Table 10.6
q_A^t	Volumetric rate of transfer of A from gas to liquid (mol L^{-1} h^{-1})
q_x	Volumetric rate of formation of biomass (kg DW m^{-3} h^{-1})
$\mathbf{q}$	Volumetric rate vector (kg m^{-3} h^{-1})
$\mathbf{q}^t$	Vector of volumetric mass transfer rates (kg m^{-3} h^{-1})
Q	Number of morphological forms
Q	Heat of reaction (kJ mol^{-1})
Q_t	Fraction of repressor-free operators, given by (7.47)
Q_2	Fraction of promotors being activated, given by (7.53)
Q_3	Fraction of promoters, which form complexes with RNA polymerase, in (7.55)
r_i	Specific reaction rate for species i (kg [kg DW]$^{-1}$ h^{-1})
r	Enzymatic reaction rate (Chap. 6) (g substrate L^{-1} h^{-1})
r_{ATP}	Specific ATP synthesis rate (moles of ATP [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}$	Specific reaction rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_s$	Specific substrate formation rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_p$	Specific product formation rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_x$	Specific formation rate vector of biomass constituents (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}(\mathbf{y},t)$	Vector containing the rates of change of properties, in (8.2)
R	Gas constant (=8.314 J K^{-1} mol^{-1})
R	Recirculation factor (Sect. 9.1.4)
$\mathbf{R}$	Redundancy matrix, given by (3.41)
$\mathbf{R}_r$	Reduced redundancy matrix

Re	Reynolds number, defined in Table 10.6
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
ΔS	Entropy change (kJ mol^{-1} K^{-1})
Sc	Schmidt number, defined in Table 10.6
Sh	Sherwood number, defined in Table 10.6
t	Time (h)
t_c	Circulation time (s) (11.7)
t_m	Mixing time (s) (11.3)
T	Temperature (K)
$\mathbf{T}$	Matrix in (5.11). $\mathbf{T}^T$, the transform of $\mathbf{T}$, is the stoichiometric matrix
$\mathbf{T}_1$	Matrix corresponding to calculated fluxes (5.12)
$\mathbf{T}_2$	Matrix corresponding to measured rates (5.12)
u_b	Bubble rise velocity (m s^{-1})
u_i	Cybernetic variable, given by (7.36)
u_s	Superficial gas velocity (m s^{-1})
$\mathbf{u}$	Vector containing the specific rates of the metamorphosis reaction (kg kg^{-1} h^{-1})
v	Liquid flow (m^3 h^{-1})
v_e	Liquid effluent flow from the reactor (m^3 h^{-1})
v_f	Liquid feed to the reactor (m^3 h^{-1})
v_g	Gas flow (m^3 h^{-1})
v_i	Flux of internal reaction i in metabolic network (kg [kg DW]$^{-1}$ h^{-1})
v_{pump}	Impeller induced flow (m^3 s^{-1}) (11.6)
$\mathbf{v}$	Flux vector, i.e., vector of specific intracellular reaction rates (kg [kg DW]$^{-1}$ h^{-1})
V	Volume (m^3)
V_d	Total volume of gas–liquid dispersion (m^3) (10.16)
V_g	Dispersed gas volume (m^3) (10.16)
V_l	Liquid volume (m^3)
V_y	Total property space (8.2)
w_i	Cybernetic variable, given by (7.47)
x	Biomass concentration (kg m^{-3})
X	Dimensionless biomass concentration
X_i	Concentration of the ith intracellular component (kg [kg DW]$^{-1}$)
$\mathbf{X}$	Vector of concentrations of intracellular biomass components (kg [kg DW]$^{-1}$)
$\mathbf{y}$	Property state vector
Y_{ij}	Yield coefficient of j from i (kg j per kg of i or C-mol of j per kg of i)
Y_{xATP}	ATP consumption for biomass formation (moles of ATP [kg DW]$^{-1}$)
Z_i	Concentration of the ith morphological form (kg [kg DW]$^{-1}$)

Greek Letters

α_{ji}	Stoichiometric coefficients for substrate i in intracellular reaction j
β_{ji}	Stoichiometric coefficient for metabolic product i in intracellular reaction j
$\dot{\gamma}$	Shear rate (s^{-1})
γ_{ji}	Stoichiometric coefficient for intracellular component i in intracellular reaction j
$\dot{\gamma}$	Shear rate (s^{-1}), defined in (11.24)
Γ	Matrices containing the stoichiometric coefficients for intracellular biomass components
$\boldsymbol{\delta}$	Vector of measurement errors in (3.43)
Δ	Matrix for stoichiometric coefficients for morphological forms
ε	Gas holdup (m^3 of gas per m^3 of gas–liquid dispersion)
ε	Porosity of a pellet
ε_{ji}	Elasticity coefficients, defined in (6.27)
$\boldsymbol{\varepsilon}$	Vector of residuals in (3.46)
$\mathbf{E}$	Matrix containing the elasticity coefficients
η	Dynamic viscosity (kg m^{-1} s^{-1})
η	Internal effectiveness factor, defined in (9) of Note 6.2
π_i	Partial pressure of compound i (atm)
θ	Dimensionless time
κ_i	Degree of reduction of the ith compound
μ	Specific growth rate of biomass (h^{-1})
μ_{max}	Maximum specific growth rate (h^{-1})
μ_q	Specific growth rate for the qth morphological form (kg DW [kg DW]$^{-1}$ h^{-1})
ρ_{cell}	Cell density (kg wet biomass [m^{-3} cell])
ρ_l	Liquid density (kg m^{-3})
σ	Surface tension (N m^{-1})
σ^2	Variance
τ	Space time in reactor (h)
τ	Shear stress (N m^{-2}), defined in (11.25)
τ_p	Tortousity factor, used in (6.23)
Φ_n	Thiele modulus for reaction of order n (2) and (5) in Note 6.2
Φ_{gen}	Generalized Thiele modulus, Note 6.2
$\psi(X)$	Distribution function of cells (8.8)

Abbreviations

AcCoA	Acetyl co-enzyme A
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
CoA	Coenzyme A
DHAP	Dihydroxy acetone phosphate
DNA	Deoxyribonucleic acid
E_c	Energy charge
EMP	Embden–Meyerhof–Parnas
FAD	Flavin adenine dinucleotide (oxidized form)
FADH	Flavin adenine dinucleotide (reduced form)
FDA	Food and Drug Administration
F6P	Fructose-6-phosphate
F1,6P	Fructose 1,6 diphosphate
GAP	Glyceraldehyde triphosphate
2 PG	2-phosphoglycerate
3 PG	3-phosphoglycerate
1,3 DPG	1,3 diphosphoglycerate
GTP	Guanosine triphosphate
G6P	Glucose-6-phosphate
HAc	Acetic acid
HLac	Lactic acid
LAB	Lactic acid bacteria
MCA	Metabolic control analysis
MFA	Metabolic Flux 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
TCA	Tricarboxylic acid
UQ	Ubiquinone

Contents