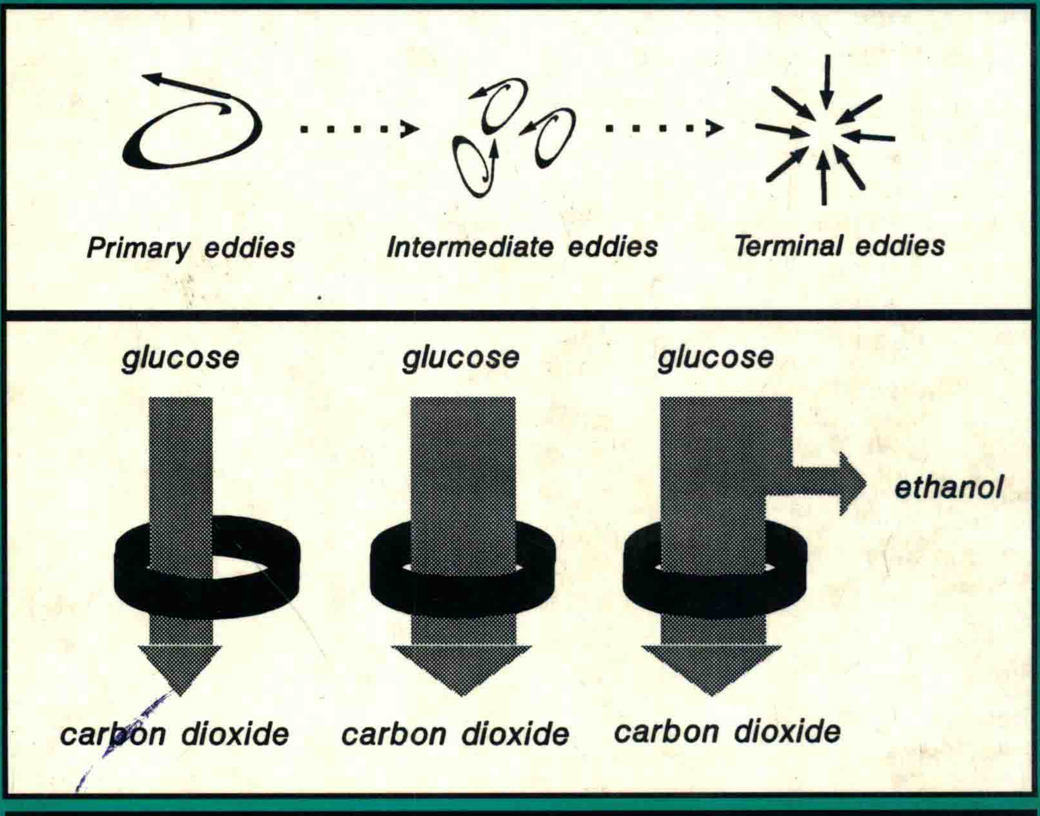
Bioreaction Engineering Principles



Jens Nielsen
and
John Villadsen

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Jens Nielsen and John Villadsen
Technical University of Denmark
Lyngby, Denmark

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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 Hjortsø of Lousiana 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

Lyngby, 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
$\mathbf{A}$, $\mathbf{A}_\mathrm{s}$, $\mathbf{A}_\mathrm{p}$	Matrices of stoichiometric coefficients for intracellular substrates
$b(y)$	Breakage frequency (hr^{-1})
$\mathbf{B}$, $\mathbf{B}_\mathrm{s}$, $\mathbf{B}_\mathrm{p}$	Matrices of stoichiometric coefficients for intracellular products
Bi	Biot number, given by Eq. (7.68)
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})
$\mathbf{c}_\mathrm{e}$	Vector of concentrations in the efflux from the bioreactor (kg m^{-3})
$\mathbf{c}_\mathrm{f}$	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 ith enzyme
C_i^r	Flux control coefficient with respect to the activity of the ith 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 (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})
D_j	Energy dissipation to the surroundings in the jth reaction (kJ mole^{-1})
Da	Damköhler number, given by Eq. (7.45)

$\mathbf{e}_i$	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
$\mathbf{E}$	Elemental matrix for all compounds
$\mathbf{E}^*$	Matrix given by Eq. (3.17)
$\mathbf{E}_c$	Elemental matrix for calculated compounds
$\mathbf{E}_m$	Elemental matrix for measured compounds
$\mathbf{E}_p$	Elemental matrix for metabolic products
$\mathbf{E}_s$	Elemental matrix for substrates
$\mathbf{E}_x$	Elemental matrix for biomass components
$f(y)$	Distribution function for cells with property y in the population
F	Degrees of freedom
$\mathbf{F}$	Variance–covariance matrix
g	Gravity (m s^{-2})
G_i	Gibbs free energy for the ith reaction component (kJ mole^{-1})
G_i^0	Gibbs free energy for the ith reaction component at standard conditions (kJ mole^{-1})
ΔG_{ci}	Gibbs free energy of combustion of the ith reaction component (kJ mole^{-1})
ΔG_{ci}^0	Gibbs free energy of combustion of the ith reaction component at standard conditions (kJ mole^{-1})
$\Delta G_{c,j}$	Change in Gibbs free energy in the jth reaction (kJ mole^{-1})
$\Delta G_{c,j}^0$	Change in standard free energy in the jth 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 uponcell division (cells hr^{-1})
H_A	Henry's constant (atm · m^3 kmole^{-1})
ΔH_{ci}^0	Heat of combustion of the ith reaction component (kJ mole^{-1})
$\Delta H_{c,j}^0$	Change of enthalpy in the jth reaction (kJ mole^{-1})
$\mathbf{H}$	Community matrix for which the elements are given by Eq. (5.59)
I	Number of elements
$\mathbf{I}$	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})
$\mathbf{J}$	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 jth 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)
$m_{\mathrm{ATP}}^{\mathrm{true}}$	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 (kg m^{-3} 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)
$\mathbf{P}_{\mathrm{q}}$	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)
$q_{\mathrm{A}}^{\mathrm{mt}}$	Volumetric rate of transfer of A from gas to liquid (kg m^{-3} hr^{-1})
$q_{\mathrm{A,obs}}$	Observed reaction rate, given by Eq. (7.61)
q_{x}	Volumetric rate of formation of biomass (kg dry weight per m^3 per hr)
q_{Q}	Volumetric rate of heat generation (kJ m^{-3} hr^{-1})
$\mathbf{q}$	Volumetric rate vector (kg m^{-3} hr^{-1})
$\mathbf{q}^*$	Vector where q_{Q} is added as the last element to $\mathbf{q}$
$\mathbf{q}^{\mathrm{mt}}$	Vector of volumetric mass transfer rates (kg dry weight per m^3 per hr)
$\mathbf{q}_{\mathrm{c}}$	Volumetric rate vector of formation of calculated compounds (kg m^{-3} hr^{-1})
$\mathbf{q}_{\mathrm{m}}$	Volumetric rate vector of formation of measuredcompounds (kg m^{-3} hr^{-1})
$\mathbf{q}_{\mathrm{p}}$	Volumetric rate vector of formation of metabolic products (kg m^{-3} hr^{-1})
$\mathbf{q}_{\mathrm{s}}$	Volumetric rate vector of formation of substrates (kg m^{-3} hr^{-1})

$\mathbf{q}_\mathrm{x}$	Volumetric rate vector of formation of biomass components (kg m^{-3} hr^{-1})
Q	Number of morphological forms
Q_j	Heat generated by the jth reaction (kJ mole^{-1})
Q_1	Fraction of repressor-free operators, given by Eq. (4.44)
Q_2	Fraction of promotors being activated, given by Eq. (4.50)
Q_3	Fraction of promotors which form complexes with RNA polymerase
$\mathbf{Q}$	Vector containing the heat of combustion of all compounds (kJ mole^{-1})
r	Specific reaction rate (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 (kJ per g dry weight per hr)
$\mathbf{r}$	Specific reaction rate vector (kg per kg dry weight per hr)
$\mathbf{r}(y)$	Vector containing the rates of change of properties, in Eq. (6.2)
$\mathbf{r}_\mathrm{p}$	Specific metabolic product formation rate vector (kg per kg dry weight per hr)
$\mathbf{r}_\mathrm{p,q}$	Specific metabolic product formation rate vector for the qth morphological form (kg per kg of qth morphological form per hr)
$\mathbf{r}_\mathrm{q}$	Specific reaction rate vector for the qth morphological form (kg per kg of qth morphological form per hr)
$\mathbf{r}_\mathrm{s}$	Specific substrate uptake rate vector (kg per kg dry weight per hr)
$\mathbf{r}_\mathrm{s,q}$	Specific substrate uptake rate vector for the qth morphological form (kg per kg of qth morphological form per hr)
R	Gas constant ($=8.314$ J K^{-1} mole^{-1})
R	Recirculation factor
$\mathbf{R}$	Vector of net rates for the formation of intracellular components (kg per kg dry weight per hr)
$\mathbf{R}$	Redundancy matrix, given by Eq. (3.45)
$\mathbf{R}_\mathrm{q}$	Vector of net rates for the formation of intracellular components in the qth morphological form (kg per kg of qth morphological form per hr)
$\mathbf{R}_\mathrm{r}$	Reduced redundancy matrix
$\mathbf{R}_\mathrm{s}$	Vector of net rates for the formation of intracellular substrates (kg per kg dry weight per hr)
$\mathbf{R}_\mathrm{s,q}$	Vector of net rates for the formation of intracellular substrates in the qth morphological form (kg per kg of qth morphological form per hr)
$\mathbf{R}_\mathrm{p}$	Vector of net rates for the formation of intracellular metabolic products (kg per kg dry weight per hr)
$\mathbf{R}_\mathrm{p,q}$	Vector of net rates for the formation of intracellular metabolic products in the qth morphological form (kg per kg of qth 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
$\Delta S^0_{\mathrm{c},j}$	Entropy change in the jth reaction (kJ mole^{-1} K^{-1})
$\mathbf{S}$	Intracellular substrate concentration vector (kg per kg dry weight)
$\mathbf{S}_\mathrm{q}$	Intracellular substrate concentration vector for the qth morphological form (kg per kg of qth 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
$\mathbf{T}_1, \ldots, \mathbf{T}_7$	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 kth metamorphosis reaction (kg kg^{-1} hr^{-1})
u_{s}	Superficial gas velocity (m s^{-1})
$\mathbf{u}$	Vector containing the specific reaction rates of the metamorphosis reactions (kg kg^{-1} hr^{-1})
U_q	Net rate of formation of the qth morphological form (kg kg^{-1} 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 (m^3 hr^{-1})
v_{e}	Liquid effluent flow from the bioreactor (m^3 hr^{-1})
v_{f}	Liquid feed flow to the bioreactor (m^3 hr^{-1})
v_{g}	Gas flow (m^3 hr^{-1})
v_i	Cybernetic variable, given by Eq. (4.53)
v_{pump}	Impeller induced flow (m^3 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) (m^3 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_{e}	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
$X_{\mathrm{e}i}$	Activity of the ith enzyme in a pathway
X_i	Concentration of the ith intracellular component (kg per kg dry weight)
$\mathbf{X}$	Vector of concentrations of intracellular biomass components (kg per kg dry weight)
$\mathbf{X}_{\mathrm{q}}$	Vector of concentrations of intracellular biomass components in the qth morphological form (kg per kg of qth 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)
$Y_{\mathrm{ATP}}^{\mathrm{true}}$	The true ATP consumption for biomass formation (moles of ATP per kg dry weight)
Z_i	Concentration of the ith 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
$\alpha_{\mathrm{s},ji}$	Stoichiometric coefficient for substrate i in the uptake of the jth substrate

$\alpha_{\mathrm{p},ji}$	Stoichiometric coefficient for substrate i in excretion of the jth metabolic product
$\mathbf{A}$, $\mathbf{A}_{\mathrm{s}}$, $\mathbf{A}_{\mathrm{p}}$	Matrices containing the stoichiometric coefficients for substrates
$\mathbf{A}_{\mathrm{q}}$, $\mathbf{A}_{\mathrm{s,q}}$, $\mathbf{A}_{\mathrm{p,q}}$	Matrices containing the stoichiometric coefficients for substrates in the qth morphological form
β_{ji}	Stoichiometric coefficient for metabolic product i in intracellular reaction j
$\beta_{\mathrm{s},ji}$	Stoichiometric coefficient for metabolic product i in the uptake of the jth substrate
$\beta_{\mathrm{p},ji}$	Stoichiometric coefficient for metabolic product i in excretion of the jth metabolic product
$\mathbf{B}$, $\mathbf{B}_{\mathrm{s}}$, $\mathbf{B}_{\mathrm{p}}$	Matrices containing the stoichiometric coefficients for metabolic products
$\mathbf{B}_{\mathrm{q}}$, $\mathbf{B}_{\mathrm{s,q}}$, $\mathbf{B}_{\mathrm{p,q}}$	Matrices containing the stoichiometric coefficients for substrates in the qth 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 jth reaction
$\gamma_{\mathrm{s},ji}$	Stoichiometric coefficient for intracellular component i in the uptake of the jth substrate
$\gamma_{\mathrm{p},ji}$	Stoichiometric coefficient for intracellular component i in excretion of the jth metabolic product
Γ, Γ_{s}, Γ_{p}	Matrices containing the stoichiometric coefficients for intracellular biomass components
Γ_{q}, $\Gamma_{\mathrm{s,q}}$, $\Gamma_{\mathrm{p,q}}$	Matrices containing the stoichiometric coefficients for intracellular biomass components in the qth morphological form
δ	Vector of measurement errors in Eq. (3.47)
δ_{kq}	Stoichiometric coefficient for morphological form q in the kth 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)
E	Matrix containing the elasticity coefficients
η	Viscosity ($\mathrm{kg\,m^{-1}\,s^{-1}}$)
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 ith compound
κ_i^{*}	Generalized degree of reduction of the ith compound with N_2 as the nitrogen source
$\mathbf{K}$	Vector containing the generalized degree of reduction of all compounds
$\mathbf{K}_{\mathrm{p}}$	Vector containing the generalized degree of reduction of metabolic products
$\mathbf{K}_{\mathrm{s}}$	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 qth 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

Contents

List of Examples

Chapter 2

Chapter 3