

Bioprocess Engineering

Kinetics, Biosystems,
Sustainability, and Reactor Design

Shijie Liu



BIOPROCESS ENGINEERING

KINETICS, BIOSYSTEMS,
SUSTAINABILITY,
AND REACTOR DESIGN

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BIOPROCESS ENGINEERING

Preface

All I know is just what I read in the papers.
Will Rogers

The quote above is quite intriguing to me and reflective of this text. Everything in this text can be found either directly or with "extrapolation" or "deduction" from the books and papers one can find to date. The most influential books to this time are the *"Biochemical Engineering Fundamentals"* by J.E. Bailey and D.F. Ollis, *"Elements of Chemical Reaction Engineering"* by H.S. Fogler, *"The Engineering of Chemical Reactions"* by L.D. Schmidt, *"Chemical Reaction Engineering"* by O. Levenspiel, *"Bioprocess Engineering—Basic Concepts"* by M.L. Shuler and F. Kargi, and many others. All these texts and others have formed part of this text. In no intention this text is compiled to replace all these great textbooks of the time. A mere rearrangement and/or compiling is made in this text to give you the reader an opportunity to understand some of the basic principles of chemical and biological transformations in bioprocess engineering.

The computer age has truly revolutionized the literature, beyond the literature revolution brought about by the mass production or availability of paper and distribution of books via library. The explosion of the sheer amount of literature, birth of interdisciplines and disciplines or subject areas in the past decades has been phenomenal. Bioprocess Engineering is one that born of biotechnology and chemical engineering. With the maturing of Bioprocess Engineering as a discipline, it evolves from an interdisciplinary subject

area of Biology and Chemical Engineering, to a discipline that covers the engineering and engineering science aspects of biotechnology, green chemistry, and biomass or renewable resources engineering. As such, textbooks in the area are needed to cover the needs of educating the new generation of fine bioprocess engineers, not just by converting well-versed chemical engineers and engineering-savvy biologists to bioprocess engineers. I hope that this textbook can fill this gap and brings the maturity of bioprocess engineering. Yet, some of the materials in this text are deep in analyses that are suited for graduate work and/or research reference.

The key aspect that makes Bioprocess Engineering special is that Bioprocess Engineering as a discipline is centered around solving problems of transformation stemmed from cellular functions and biological and/or chemical conversions concerning the sustainable use of renewable biomass. The mechanism, rate, dynamic behavior, transformation performance and manipulations of bioprocess systems are the main topics of this text.

Chapter 1 is an introduction of bioprocess engineering profession including green chemistry, sustainability considerations and regulatory constraints. Chapter 2 is an overview of biological basics or cell chemistry including cells, viruses, stem cell, amino acids, proteins, carbohydrates and various biomass components, and fermentation media. In Chapter 3, a survey of chemical reaction analysis is introduced. The basic knowledge of reaction rates, conversion, yield, stoichiometry and energy regularity

for bioreactions are reviewed. The concepts of approximate and coupled reactions are introduced, providing the basis of understanding for the metabolic pathway representations later in the book. Mass and energy balances for reactor analyses, as well as the definitions of ideal reactors and commonly known bioreactors are introduced before an introduction to reactor system analyses. The biological basics and chemical reaction basics are followed by the reactor analysis basics in Chapters 4 and 5, including the effect of reaction kinetics, flow contact patterns and reactor system optimizations. Gasification (of coal and biomass) is also introduced in Chapter 5. How the ideal reactors are selected, what flow reactor to choose and what feed strategy to use are all covered in Chapter 5.

Chapters 6, 7, 8, 9, 10 and 11 are studies on bioprocess kinetics. In Chapter 6, you will learn the collision theory for reaction kinetics and approximations commonly employed to arrive at simple reaction rate relations. Kinetics of acid hydrolysis, of an important unit operation in biomass conversion, is introduced as a case study. In Chapter 7, we turn to discuss the techniques for estimating kinetic parameters from experimental data, breaking away from the traditional straight line approaches developed before the computer age. You can learn how to use modern tools to extract kinetic parameters reliably and quickly without complex manipulation of the data. In Chapters 8 and 9, we discuss the application of kinetic theory to catalytic systems. Enzymes, enzymatic reactions and application of enzymes are examined in Chapter 8, while adsorption and solid catalysis are discussed in Chapter 9. The derivation of simplified reaction rate relations, such as the Michaelis–Menten equation for enzymatic reaction and LHHW for solid catalysis, is demonstrated. The applicability of these simple kinetic relations

is discussed. In Chapter 9, you will learn both ideal and non-ideal adsorption kinetics and adsorption isotherms. Is multilayer adsorption the trademark for physisorption? The heterogeneous kinetic analysis theory is applied to reactions involving woody biomass where the solid phase is not catalytic in §9.5. Chapter 10 discusses the cellular genetics and metabolism. The replication of genetic information, protein production, substrate uptake, and major metabolic pathways are discussed, hinting at the application of kinetic theory in complicated systems. In Chapter 11, you will learn how cell grows: cellular material quantifications, batch growth pattern, cell maintenance and endogenous needs, medium and environmental conditions, and kinetic models. Reactor analyses are also presented in Chapters 8 and 11.

In Chapters 12 and 13, we discuss the controlled cell cultivation. Continuous culture and wastewater treatment are discussed in Chapter 12. Exponential growth is realized in continuous culturing. An emphasis is placed on the reactor performance analyses, using mostly Monod growth model in examples, in both Chapters. Chapter 13 introduces fed-batch operations and their analyses. Fed batch can mimic exponential growth in a controlled manner as opposed to the batch operations where no control (on growth) is asserted besides environmental conditions.

Chapter 14 discusses the evolution and genetic engineering, with an emphasis on biotechnological applications. You will learn how cells transform, how cells are manipulated, and what some of the applications of cellular transformation and recombinant cells are. Chapter 15 introduces the sustainability perspectives. Bioprocess engineering principles are applied to examine the sustainability of biomass economy and atmospheric CO₂. Is geothermal energy a sustainable or renewable energy source? Chapter 16

discusses the stability of catalysts: activity of chemical catalyst, genetic stability of cells and mixed cultures, as well as the stability of reactor systems. Sustainability and stability of bioprocess operations are discussed. A stable process is sustainable. Multiple steady states, approach to steady state, conditions for stable operations and predator–prey interactions are discussed. Continuous culture is challenged by stability of cell biomass. In ecological applications, sustainability of a bioprocess is desirable. For industrial applications, the ability of the bioprocess system to return to the previous set point after a minor disturbance is an expectation. In Chapter 17, the effect of

mass transfer on the reactor performance, in particular with biocatalysis, is discussed. Both external mass transfer, e.g. suspended media, and internal mass transfer, e.g. immobilized systems are discussed, as well as temperature effects. The detailed numerical solutions can be avoided or greatly simplified by following directly from the examples. It is recommended that examples be covered in classroom, rather than the reading material. Chapter 18 discusses the reactor design and operation. Reactor selection, mixing scheme, scale-up, and sterilization and aseptic operations are discussed.

Shijie Liu

Nomenclature

<i>a</i>	Catalyst activity	<i>D</i>	Diffusivity, m ² /s
<i>a</i>	Specific surface or interfacial area, m ² /m ³	<i>D</i>	Dilution rate, s ⁻¹
<i>a</i>	Thermodynamic activity	<i>D</i> —	Chirality or optical isomers: right-hand rule applies
<i>a_d</i>	Dimensionless dispersion coefficient	<i>DO</i>	Concentration of dissolved oxygen, g/L
<i>a</i>	Constant	<i>DNA</i>	Deoxyribonucleic acid
<i>A</i>	Chemical species	<i>e</i>	electron
<i>A</i>	Adenine	<i>E</i>	Enzyme
<i>A</i>	Constant	<i>E</i>	Energy, kJ/mol
<i>A</i>	Heat transfer area, m ²	<i>EMP</i>	Embden-Meyerhof-Parnas
<i>Ac</i>	Acetyl	<i>f</i>	Fractional conversion
<i>ADP</i>	Adenosine diphosphate	<i>f</i>	Fanning friction factor
<i>AMP</i>	Adenosine monophosphate	<i>F</i>	Flow rate, kg/s or kmol/s
<i>ATP</i>	Adenosine triphosphate	<i>F</i>	Farady constant
<i>B</i>	Chemical species	<i>FAD</i>	Flavin adenine dinucleotide in oxidized form
<i>B</i>	Constant	<i>FADH</i>	Flavin adenine dinucleotide in reduced form
<i>BOD</i>	Biological oxygen demand	<i>FDA</i>	Food and Drug administration
<i>BOD₅</i>	Biological oxygen demand measured for 5 days	<i>FES</i>	Fast equilibrium step (hypothesis)
<i>c</i>	constant	<i>g</i>	Gravitational acceleration, 9.80665 m ² /s
<i>C</i>	Chemical species	<i>G</i>	Gibbs free energy, kJ/mol
<i>C</i>	Concentration, mol/L or kg/m ³	<i>G</i>	Guanine
<i>C</i>	Constant	<i>GRAS</i>	Generally regarded as safe
<i>C</i>	Cytosine	<i>GMP</i>	Good manufacture practice
<i>C_p</i>	Heat capacity, J/(mol·K), or kJ/(kg·K)	<i>GTP</i>	Guanosine triphosphate
<i>CoA</i>	Coenzyme A	<i>h</i>	height or length
<i>CHO</i>	Chinese hamster ovary cell	<i>H</i>	Enthalpy, kJ/mol or kJ/kg
<i>COD</i>	Chemical oxygen demand	<i>H_C</i>	Harvesting cost
<i>CSTR</i>	Continuously stirred tank reactor	<i>HMP</i>	Hexose Monophosphate (pathway)
<i>d</i>	Diameter, m	<i>J</i>	Total transfer flux, kmol/s or kg/s
<i>D</i>	Diameter, m		

J	Transfer flux, $\text{kmol}/(\text{m}^2 \cdot \text{s})$ or $\text{kg}/(\text{m}^2 \cdot \text{s})$	P_X	Productivity or production rate of biomass
k	Kinetic rate constant	P_0	Probability of the vanishing of the entire population
k	Mass transfer coefficient, m/s	P_1	Probability of the entire population not vanishing
K	Thermodynamic equilibrium constant	PCR	Polymerase chain reaction
K	Saturation constant, mol/L or kg/L	PEP	Phosphoenol pyruvate
K_L	Overall mass transfer coefficient (from gas to liquid)	PFR	Plug flow reactor
L	Length	PP	Pentose phosphate (pathway)
L -	Chirality or optical isomers: left hand rule applies	PSSH	Pseudo-steady-state hypothesis
m	Amount of mass, kg	P/O	ATP formation per oxygen consumption
\dot{m}	Mass flow rate, kg/s	q	Thermal flux, J/s or W
m_S	Maintenance coefficient	Q	Volumetric flow rate, m^3/s
M	Molecular weight, Dalton (D) or kg/kmol	\dot{Q}	Thermal energy transfer rate into the system
MC	Molar (or mass) consumption rate	r	Radial direction
MG	Mass generation rate	r	Rate of reaction, $\text{mol}/(\text{m}^3 \cdot \text{s})$ or $\text{kg}/(\text{L} \cdot \text{s})$
MR	Mass removal rate	R	Correlation coefficient
MS	Molar or Mass supply rate	R	Ideal gas constant, $8.314 \text{ J}/(\text{mol} \cdot \text{K})$
MSS	Multiple steady state	R	Product, or product concentration
n	Total matters in number of moles	R	Recycle ratio
N	Mass transfer rate, $\text{kJ}/(\text{m}^2 \cdot \text{s})$ or $\text{kg}/(\text{m}^2 \cdot \text{s})$	Re	Reynolds number
N	Number of species	RNA	Ribonucleic acid
NAD	Nicotinamide adenine dinucleotide	s	Selectivity
NADP	Nicotinamide adenine dinucleotide phosphate	S	Entropy
O_R	Order of reaction	S	Overall selectivity
OTR	Oxygen transfer rate	S	Substrate (or reactant)
OUR	Oxygen utilization rate	S	Substrate concentration, g/L
p	Pressure	S	Surface area, m^2
P	Probability	Sh	Sherwood number
P	Pressure	SMG	Specific mass generation rate
P	Product, or Product concentration, kg/m^3 , or g/L , or mol/L	SMR	Specific mass removal rate
P	Power (of stirrer input)	t	Time, s
		T	Temperature, K
		T	Thymine

TCA	Tricarboxylic acid	β	Chirality or optical isomers: two chiral centers with the same hand gestures
u	superficial velocity, m/s		
U	Average velocity or volumetric flux	χ	Fraction
U	Internal energy	γ	Thermodynamic activity coefficient
U	Overall heat transfer coefficient, kJ/m^2	γ	Activation energy parameter
U	Uracil	γ_{DR}	Degree of reduction
CoQ _n	Co-Enzyme ubiquinone	δ	Thickness or distance
v	Molar volume, m^3/kmol	Δ	Difference
V	Volume, m^3	ε	Void ratio
\dot{W}	Rate of work input to the system	ϕ	Thiele modulus
\dot{W}_s	Rate of shaft work done by the system	η	Effectiveness factor
x	Variable	θ	Fractional coverage (on available active sites)
x	Axial direction	μ	Specific rate of formation, or rate of reaction normalized by the catalyst or cell biomass concentration, s^{-1} or $\text{g} \cdot \text{g}^{-1} \cdot \text{s}^{-1}$
X	Cell or biomass	μ	Specific biomass growth rate, s^{-1} or $\text{g} \cdot \text{g}^{-1} \cdot \text{s}^{-1}$
X	Cell biomass concentration, L^{-1} , or g/L	μ_f	Dynamic viscosity of fluid, $\text{Pa} \cdot \text{s}$
X_{SU}	Biomass storage for managed forest	ν	Stoichiometric coefficient
X_{SU}	Biomass storage for undisturbed unmanaged forest	ν_f	Kinematic viscosity of fluid or medium, m^2/s
y	Mole fraction	ρ	Density, kg/m^3
y	Variable	σ	Active site
Y	Yields	σ	Variance
YF	Yield factor, or ratio of stoichiometric coefficients	τ	Space time, s
z	Vertical direction	ω	Mass fraction
z	Variable	ω	Rotational speed
Z	Collision frequency	ω	Weighting factor
Z	Valence of ionic species		

Greek Symbols

α	Constant
α	Chirality or optical isomers: two chiral centers with different hand gestures
β	Heat of reaction parameter
β	Constant

Subscript

ads	Adsorption
app	Apparent
A	Species A
b	reverse reaction
B	Batch
c	Combustion

cat	Catalyst
C	Species C
C	Cold stream
C	Concentration based
C	Calculated based on model
d	Death
d	Doubling
des	Desorption
D	Diffusion coefficient related
e	Endogenous (growth needs)
e	External (mass transfer)
e	In effluent stream
eq	Equilibrium
eff	Effective
f	Final or at end
f	Fluid or medium
f	Formation
f	Forward reaction
F	In feed stream
G	Growth
H	Heat of reaction
H	Hot stream
i	Reaction i
i	Initial
i	Impeller
in	Inlet
I	Inhibition
j	Species j
m	Maximum
max	Maximum
net	Net
OPT	Optimum

obs	Observed
out	Outlet
p	Particle
P	Product
P	Preparation
R	Reaction; Reactor
R	Reference; Reduced
s	Solid
S	Sterilization
S	Saturation
S	Substrate
S	Surface
S	Total species
t	Tube, or reactor
T	Tube
T	Total
U	Unloading
0	Initial
0	In feed
0	Pre-exponential
+	Plasmid-containing
—	Plasmid-free
∞	maximum or at far field
Σ	Total or sum

Superscript

0	(Thermodynamic) Standard conditions
*	Equilibrium
*	Based on transitional state
'	Catalyst mass based
'	Variant

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Introduction

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1.1. BIOLOGICAL CYCLE

Figure 1.1 illustrates the natural biological processes occurring on Earth. Living systems consist of plants, animals and microorganisms. Sunlight is used by plants to convert CO_2 and H_2O into carbohydrates and other organic matter, releasing O_2 . Animals consume plant matter, converting plant materials into animal cells, and using the chemical energy from oxidizing plant matter into CO_2 and H_2O (H_2O also serves as a key substrate for animals), finishing the cycle. Microorganisms further convert dead animal and/or plant biomass into other form of organic substances fertilizing the growth of plants, releasing CO_2 and H_2O , and the cycle is repeated. Energy from the Sun is used to form molecules and organisms that we call life. Materials or matter participating in the biological cycle are renewable so long as the cycle is maintained. Bioprocess engineers manipulate and make use of this cycle by designing processes to make desired products, either by training microorganisms, plants, and animals or via direct chemical conversions.

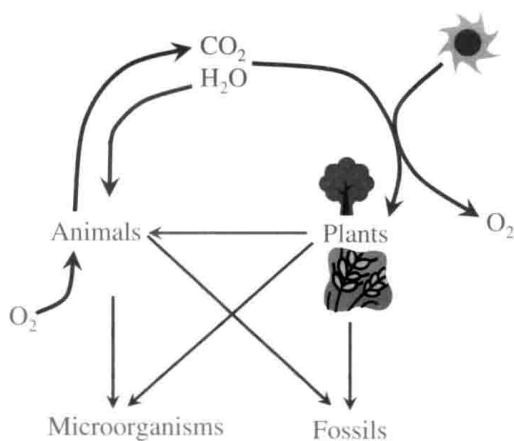


FIGURE 1.1 The natural biological processes.

The reactor is the heart of any chemical and/or biochemical processes. With reactors, bioprocesses turn inexpensive sustainably renewable chemicals, such as carbohydrates, into valuable ones that humans need. As such, bioprocesses are chemical processes that use biological substrates and/or catalysts. While not limited to such, we tend to refer to bioprocesses as 1) biologically converting inexpensive “chemicals” or materials into valuable chemicals or materials and 2) manipulating biological organisms to serve as “catalyst” for conversion or production of products that human need. Bioprocess engineers are the only people technically trained to understand, design, and efficiently handle bioreactors. Bioprocess engineering ensures that a favorable sustainable state or predictable outcome of a bioprocess is achieved. This is equivalent to saying that bioprocess engineers are engineers with, differentiating from other engineers, training in biological sciences, especially quantitative and analytical biological sciences and green chemistry.

If one thinks of science as a dream, engineering is making the dream a reality. The maturing of Chemical Engineering to a major discipline and as one of the very few well-defined disciplines in the 1950s has led to the ease in the mass production of commodity chemicals and completely changed the economics or value structure of materials and chemicals, thanks to the vastly available what were then “waste” and “toxic” materials: fossil resources. Food and materials can be manufactured from the cheap fossil materials. Our living standards improved significantly. Today, chemical reactors and chemical processes are not built by *trial-and-error* but by design. The performance of a chemical reactor can be predicted, not just found to happen that way; the differences between large and small reactors are largely solved. Once a dream for the visional pioneers, it can now be achieved at ease. Fossil chemical and energy sources have provided much of our needs for advancing and maintaining the living standards of today. With the dwindling of fossil resources, we are facing yet another value structure change. The dream has been shifted to realizing a society that is built upon renewable and sustainable resources. Fossil sources will no longer be abundant for human use. Sustainability becomes the primary concern. Who is going to make this dream come true?