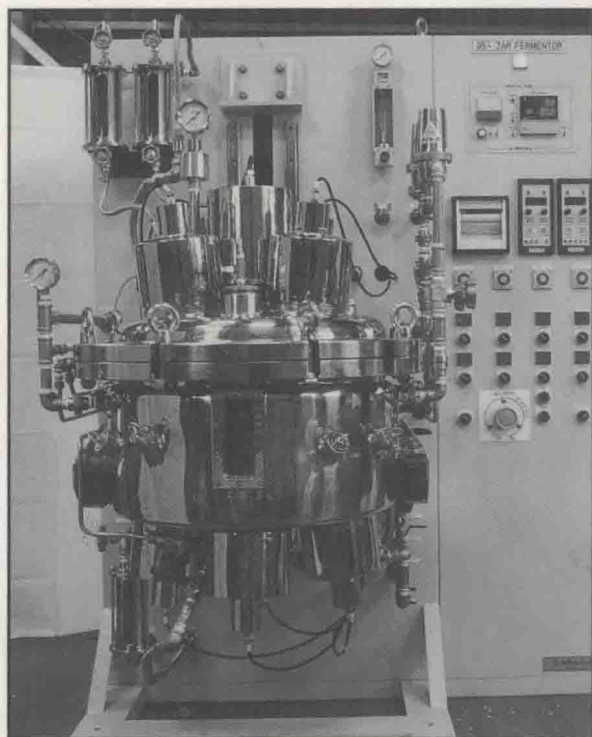


FERMENTATION AND BIOCHEMICAL ENGINEERING HANDBOOK

Principles, Process Design, and Equipment

SECOND EDITION



**Edited by
Henry C. Vogel and Celeste L. Todaro**

NOYES PUBLICATIONS

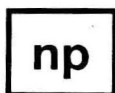
FERMENTATION AND BIOCHEMICAL ENGINEERING HANDBOOK

Principles, Process Design, and Equipment
Second Edition

Edited by
Henry C. Vogel
Consultant
Scotch Plains, New Jersey
and

江苏工业学院图书馆
藏书章

Celeste L. Todaro
Heinkel Filtering Systems, Inc.
Bridgeport, New Jersey



NOYES PUBLICATIONS
Westwood, New Jersey, U.S.A.

Copyright © 1997 by Noyes Publications

No part of this book may be reproduced or utilized
in any form or by any means, electronic or
mechanical, including photocopying, recording or
by any information storage and retrieval system,
without permission in writing from the Publisher.

Library of Congress Catalog Card Number: 96-29055

ISBN: 0-8155-1407-7

Printed in the United States

Published in the United States of America by

Noyes Publications

369 Fairview Avenue, Westwood, New Jersey 07675

10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

Fermentation and biochemical engineering handbook. -- 2nd ed. / edited
by Henry C. Vogel and Celeste L. Todaro.

p. cm.

Includes bibliographical references and index.

ISBN 0-8155-1407-7

1. Biochemical engineering--Handbooks, manuals, etc.

2. Fermentation--Handbooks, manuals, etc. I. Vogel, Henry C.

II. Todaro, Celeste L.

TP248.3.F74 1996

660'.28449--dc20

96-29055

CIP

DEDICATION

For my parents, Ernest and Charlotte Todaro,
whose pursuit of knowledge inspired me and
continues to do so.

Preface to the Second Edition

The second edition of the *Fermentation and Biochemical Engineering Handbook*, like the previous edition, is intended to assist the development, design and production engineer who is engaged in the fermentation industry. Particular emphasis is given to those unit operations most frequently encountered in the commercial production of chemicals and pharmaceuticals via fermentation, separation, and purification.

Some theory is included to provide the necessary insight into the unit operation but is not emphasized. Rather, the emphasis is placed on the practical aspects of development, design and operation—how one goes about collecting design data, what are the scale-up parameters, how to select the right piece of equipment, where operating problems arise, and how to troubleshoot.

The text is written from a practical and operating viewpoint, and all of the contributing authors have been chosen because of their industrial background and orientation. Several of the chapters which were in the first edition have been either deleted or replaced by other chapters which are more germane to current fermentation practice. Those chapters which were retained have been updated or have been rewritten to reflect current practice. Several new chapters were introduced to reflect current emphasis on cell cultures, nutritional requirements, statistical methods for fermentation optimization, cross-flow filtration, environmental concerns, and plant design

The editors wish to express their gratitude to Mrs. Connie Gaskill of Heinkel Filtering Systems, Inc., for the wordprocessing assistance she gave to this edition.

Scotch Plains, New Jersey
Bridgeport, New Jersey
September, 1996

Henry C. Vogel
Celeste L. Todaro

Preface to the First Edition

This book is intended to assist the development, design and production engineer who is engaged in the fermentation industry. Particular emphasis is given to those unit operations most frequently encountered in the commercial production of chemicals and pharmaceuticals via fermentation, separation, and purification.

Some theory is included to provide the necessary insight into the unit operation but is not emphasized. Rather, the emphasis is placed on the practical aspects of development, design and operation—how one goes about collecting design data, what are the scale-up parameters, how to select the right piece of equipment, where operating problems arise and how to troubleshoot.

The text is written from a practical and operating viewpoint, and all of the contributing authors have been chosen because of their industrial background and orientation. Since the handbook concerns fermentation and often the engineers involved in fermentation are not versed in microbiology, it was thought advisable to introduce this subject at the beginning of the book. Similarly, since much of fermentation deals with the production of antibiotics, it was deemed advisable to include some chapters specifically oriented to the production of sterile products.

The engineering using this handbook may wish that other unit operations or different pieces of equipment had been included other than those

selected. The selection was based on the individual contributors and my own experience, over many years of work in the field, with unit operations and pieces of equipment that have been the backbone and workhorses of the industry.

The editor wished to express his thanks to Mr. Stanley Grossel of Hoffmann-La Roche and Mr. John Carney of Davy McKee Corporation for reviewing and editing the draft copies. He also thanks Miss Mary Watson of Davy McKee Corporation for typing assistance, and Mr. Michael Garze of Davy McKee Corporation for his help in producing many of the graphs and illustrations. Dr. Sol Barer, the author of the microbiology chapter acknowledges the valuable input to the Celanese Biotechnology Department, and especially thanks Miss Maria Guerra for her patience in typing and retyping the manuscript.

Berkeley Heights, New Jersey
June 1983

Henry C. Vogel

Contributors

Michael J. Akers
Eli Lilly and Company
Indianapolis, IN

Giovanni Bellini
3V Cogem S.P.A.
Dalmine, Italy

Ramesh R. Bhave
U.S. Filter Corporation
Warrendale, PA

Frederick J. Dechow
Biocryst Pharmaceuticals Inc.
Birmingham, AL

Barry Fox
Niro Inc.
Columbia, MD

Howard L. Freese
Allvac
Monroe, NC

Edwin O. Geiger
Pfizer Inc.
Groton, CT

Stephen M. Glasgow
Union Carbide Chemical and
Plastics Co., Inc.
South Charleston, WV

Elliott Goldberg
Consultant
Fort Lee, NJ

Yujiro Harada
K. F. Engineering Co., Ltd.
Tokyo, Japan

Willem Kampen
Louisiana State University
Agriculture Center
Baton Rouge, LA

Mark Keyashian
CENTEON
Kankakee, IL

John P. King
Foxboro Company
Rahway, NJ

Maung K. Min
Gemini Management Consultants
New York, NY

James Y. Oldshue
Mixing Equipment Co., Inc.
Rochester, NY

Laura Pellegrini
Politecnico di Milano
Milano, Italy

Russell T. Roane
Bechtel Engineering
San Francisco, CA

Kuniaki Sakato
Kyowa Hakko Kogyo Co., Ltd.
Tokyo, Japan

Seiji Sato
Kyowa Medex Co., Ltd.
Sunto-gun, Shizuoka Pref., Japan

Allan C. Soderberg
Fort Collins, CO

Curtis S. Strother
Eli Lilly Company
Indianapolis, IN

Shinsaku Takayama
Tokai University
Numazu, Shizuoka Pref., Japan

Celeste L. Todaro
Heinkel Filtering Systems, Inc.
Bridgeport, NJ

David B. Todd
Todd Engineering
Princeton, NJ

Henry C. Vogel
Consultant
Scotch Plains, NJ

Mark R. Walden
Eli Lilly Company
Indianapolis, IN

NOTICE

To the best of our knowledge the information in this publication is accurate; however the Publisher does not assume any responsibility or liability for the accuracy or completeness of, or consequences arising from, such information. This book is intended for informational purposes only. Mention of trade names or commercial products does not constitute endorsement or recommendation for use by the Publisher. Final determination of the suitability of any information or product for use contemplated by any user, and the manner of that use, is the sole responsibility of the user. We recommend that anyone intending to rely on any recommendation of materials or procedures mentioned in this publication should satisfy himself as to such suitability, and that he can meet all applicable safety and health standards.

Contents

1 Fermentation Pilot Plant 1

Yujiro Harada, Kuniaki Sakata, Seiji Sato and Shinsaku Takayama

PROLOGUE (by Yujiro Harada)	1
1.0 MICROBIAL FERMENTATION (by Kuniaki Sakato)	2
1.1 Fermentation Pilot Plant	3
1.2 Bioreactors and Culture Techniques for Microbial Processes	3
1.3 Application of Computer Control and Sensing Technologies for Fermentation Process	8
1.4 Scale-Up	19
1.5 Bioreactors for Recombinant DNA Technology	22
References (Section 1)	24
2.0 MAMMALIAN CELL CULTURE SYSTEM (by Seiji Sato)	25
2.1 Introduction	25
2.2 Culture Media	25
2.3 Microcarrier Culture and General Control Parameters	26
2.4 Perfusion Culture Systems as a New High Density Culture Technology	31
2.5 Sedimentation Column Perfusion Systems	33
2.6 High Density Culture Using a Perfusion Culture System with Sedimentation Column	34
2.7 Acknowledgment	35
References and Bibliography (Section 2)	38

3.0 BIOREACTORS FOR PLANT CELL TISSUE AND ORGAN CULTURES (by Shinsaku Takayama)	41
3.1 Background of the Technique—Historical Overview	41
3.2 Media Formulations	43
3.3 General Applications	45
3.4 Bioreactors—Hardware Configuration	46
3.5 Bioreactor Size	54
3.6 Culture Period	54
3.7 Aeration and Agitation	55
3.8 Microbial Contamination	56
3.9 Characteristics	56
3.10 Manipulation	58
3.11 Scale-up Problems	61
3.12 Bioprocess Measurement and Control	62
References (Section 3)	64
2 Fermentation Design	67
<i>Allan C. Soderberg</i>	
1.0 INTRODUCTION	67
2.0 FERMENTATION DEPARTMENT, EQUIPMENT AND SPACE REQUIREMENTS	68
2.1 The Microbiological Laboratories	68
2.2 Analytical Support Laboratories	70
2.3 Production: Raw Material Storage	71
2.4 Media Preparation or Batching Area	72
2.5 The Seed Fermenter Layout	73
2.6 The Main Fermenter Layout	74
2.7 Nutrient Feed Tanks	74
2.8 Sterile Filters	75
2.9 Air Compressors	76
2.10 Valves (To Maintain Sterility)	77
2.11 Pumps	78
2.12 Cooling Equipment	78
2.13 Environmental Control	79
3.0 GENERAL DESIGN DATA	79
4.0 CONTINUOUS STERILIZERS	81
4.1 A Justification for Continuous Sterilization	81
4.2 Support Equipment for a Sterilizer	82
4.3 The Sterilizing Section	89
4.4 The Cooling Section	89
5.0 FERMENTER COOLING	94

6.0 THE DESIGN OF LARGE FERMENTERS (BASED ON AERATION)	99
6.1 Agitator Effectiveness	99
6.2 Fermenter Height	100
6.3 Mixing Horsepower by Aeration	101
6.4 Air Sparger Design	107
6.5 Comparison of Shear of Air Bubbles by Agitators and Jets	107
6.6 The Effect of Shear on Microorganisms	109
6.7 Other Examples of Jet Air/Liquid Mixing	109
6.8 Mechanical Versus Non-mechanical Agitation	110
7.0 TROUBLE SHOOTING IN A FERMENTATION PLANT	111
8.0 GENERAL COMMENTS	119
REFERENCES	120

3 Nutritional Requirements in Fermentation Processes 122

Willem H. Kampen

1.0 INTRODUCTION	122
2.0 NUTRITIONAL REQUIREMENTS OF THE CELL	125
3.0 THE CARBON SOURCE	128
4.0 THE NITROGEN AND SULFUR SOURCE	135
5.0 THE SOURCE OF TRACE AND ESSENTIAL ELEMENTS	136
6.0 THE VITAMIN SOURCE AND OTHER GROWTH FACTORS	144
7.0 PHYSICAL AND IONIC REQUIREMENTS	147
8.0 MEDIA DEVELOPMENT	149
9.0 EFFECT OF NUTRIENT CONCENTRATION ON GROWTH RATE	155
REFERENCES	159

4 Statistical Methods For Fermentation Optimization 161

Edwin O. Geiger

1.0 INTRODUCTION	161
2.0 TRADITIONAL ONE-VARIABLE-AT-A-TIME METHOD	161
3.0 EVOLUTIONARY OPTIMIZATION	162
4.0 RESPONSE SURFACE METHODOLOGY	166

5.0 ADVANTAGES OF RSM	168
5.1 Maximum Information from Experiments	169
5.2 Forces One To Plan	170
5.3 Know How Long Project Will Take	170
5.4 Interaction Between Variables	170
5.5 Multiple Responses	171
5.6 Design Data	171
6.0 DISADVANTAGES OF RSM	174
7.0 POTENTIAL DIFFICULTIES WITH RSM	174
7.1 Correlation Coefficient	176
7.2 Regression Coefficients	176
7.3 Standard Error of the Regression Coefficient	176
7.4 Computed T Value	177
7.5 Standard Error of the Estimate	177
7.6 Analysis of Variance	177
8.0 METHODS TO IMPROVE THE RSM MODEL	178
9.0 SUMMARY	179
REFERENCES	179

5 Agitation 181

James Y. Oldshue

1.0 THEORY AND CONCEPTS	181
2.0 PUMPING CAPACITY AND FLUID SHEAR RATES	182
3.0 MIXERS AND IMPELLERS	183
3.1 Fluidfoil Impellers	191
4.0 BAFFLES	201
5.0 FLUID SHEAR RATES	203
5.1 Particles	206
5.2 Impeller Power Consumption	207
5.3 Mass Transfer Characteristics of Fluidfoil Impellers	217
6.0 FULL-SCALE PLANT DESIGN	219
6.1 Some General Relationships in Large Scale Mixers Compared to Small Scale Mixers	219
6.2 Scale-Up Based on Data from Existing Production Plant	220
6.3 Data Based on Pilot Plant Work	223
6.4 Sulfite Oxidation Data	226
6.5 Oxygen Uptake Rate in the Broth	227
6.6 Some General Concepts	227
6.7 Reverse Rotation Dual Power Impellers	228
7.0 FULL SCALE PROCESS EXAMPLE	229
8.0 THE ROLE OF CELL CONCENTRATION ON MASS TRANSFER RATE	231

9.0 SOME OTHER MASS TRANSFER CONSIDERATIONS	235
10.0 DESIGN PROBLEMS IN BIOCHEMICAL ENGINEERING	236
11.0 SOLUTION—FERMENTATION PROBLEMS	238
LIST OF ABBREVIATIONS	240
REFERENCES	241

6 Filtration 242

Celeste L. Todaro

1.0 INTRODUCTION	242
1.1 Depth Filtration	243
2.0 CAKE FILTRATION	243
3.0 THEORY	243
3.1 Flow Theory	243
3.2 Cake Compressibility	244
4.0 PARTICLE SIZE DISTRIBUTION	245
5.0 OPTIMAL CAKE THICKNESS	246
6.0 FILTER AID	247
7.0 FILTER MEDIA	248
8.0 EQUIPMENT SELECTION	250
8.1 Pilot Testing	250
9.0 CONTINUOUS vs. BATCH FILTRATION	251
10.0 ROTARY VACUUM DRUM FILTER	251
10.1 Operation and Applications	251
10.2 Optimization	258
11.0 NUTSCHES	258
11.1 Applications	258
11.2 Operation	260
11.3 Maintenance	264
12.0 HP-HYBRID FILTER PRESS	266
12.1 Applications	266
12.2 Operation	267
12.3 Maintenance	269
13.0 MANUFACTURERS	269
Rotary Drum Vacuum Filters	269
Nutsches	269
Hybrid Filter Press	270
REFERENCES	270

7 Cross-Flow Filtration 271

Ramesh R. Bhawe

1.0 INTRODUCTION	271
------------------------	-----

2.0 CROSS-FLOW vs. DEAD END FILTRATION	273
3.0 COMPARISON OF CROSS-FLOW WITH OTHER COMPETING TECHNOLOGIES	277
4.1 Polymeric Microfilters and Ultrafilters	281
4.2 Inorganic Microfilters and Ultrafilters	285
5.0 OPERATING CONFIGURATIONS	289
5.1 Batch System	289
5.2 Feed and Bleed	292
5.3 Single vs. Multistage Continuous System	297
6.0 PROCESS DESIGN ASPECTS	297
6.1 Minimization of Flux Decline With Backpulse or Backwash	297
6.2 Uniform Transmembrane Pressure Filtration	300
6.3 Effect of Operating Parameters on Filter Performance ..	305
6.4 Membrane Cleaning	314
6.5 Pilot Scale Data and Scaleup	316
6.6 Troubleshooting	318
6.7 Capital and Operating Cost	318
6.8 Safety and Environmental Considerations	322
7.0 APPLICATIONS OVERVIEW	322
7.1 Clarification of Fermentation Broths	323
7.2 Purification and Concentration of Enzymes	323
7.3 Microfiltration for Removal of Microorganisms or Cell Debris	324
7.4 Production of Bacteria-free Water	329
7.5 Production of Pyrogen-free Water	331
8.0 GLOSSARY OF TERMS	333
ACKNOWLEDGMENT	337
APPENDIX: LIST OF MEMBRANE MANUFACTURERS (MICROFILTRATION AND ULTRAFILTRATION)	338
REFERENCES	343
 8 Solvent Extraction	 348
<i>David B. Todd</i>	
1.0 EXTRACTION CONCEPTS	348
1.1 Theoretical Stage	350
2.0 DISTRIBUTION DATA	352
3.0 SOLVENT SELECTION	354
4.0 CALCULATION PROCEDURES	355
4.1 Simplified Solution	358
4.2 Sample Stage Calculation	360
5.0 DROP MECHANICS	363