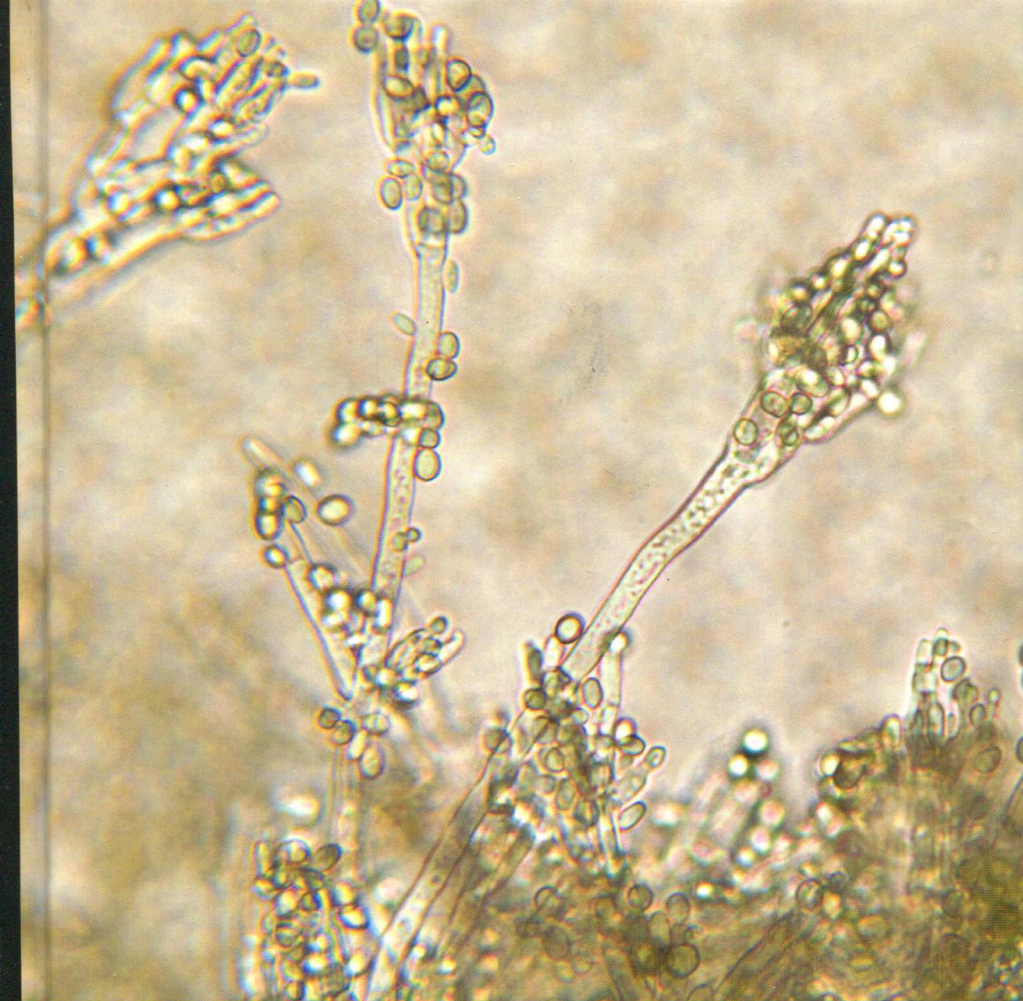


VOLUME 2



# UPSTREAM INDUSTRIAL BIOTECHNOLOGY

*Equipment, Process Design, Sensing, Control,  
and cGMP Operations*

MICHAEL C. FLICKINGER, EDITOR

 WILEY

# **UPSTREAM INDUSTRIAL BIOTECHNOLOGY**

---

**Equipment, Process Design, Sensing, Control,  
and cGMP Operations**

**Volume 2**

**Edited By**

**MICHAEL C. FLICKINGER**

Golden LEAF Biomanufacturing Training and Education Center (BTEC)  
Department of Chemical and Biomolecular Engineering  
North Carolina State University, Raleigh  
North Carolina, USA



A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2013 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey  
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at [www.copyright.com](http://www.copyright.com). Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

**Limit of Liability/Disclaimer of Warranty:** While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at [www.wiley.com](http://www.wiley.com).

***Library of Congress Cataloging-in-Publication Data:***

Upstream industrial biotechnology / edited by Michael C. Flickinger.

v. cm

Includes bibliographical references and index.

Contents: volume 1. Expression Systems and Process Development—volume 2. Equipment, Process Design, Sensing, Control and cGMP Operations. ISBN 978-1-118-13123-7 (set : hardback) 1. Biotechnology. I. Flickinger, Michael C., editor of compilation. II. Encyclopedia of industrial biotechnology. Selections.

TP248.2.U675 2013

660.6—dc23

2012030697

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

# CONTENTS

## VOLUME I: EXPRESSION SYSTEMS & PROCESS DEVELOPMENT

---

<b>PREFACE</b>	<b>xi</b>
<b>CONTRIBUTORS</b>	<b>xiii</b>
<b>PART I INTRODUCTION</b>	<b>3</b>
<b>PART II INDUSTRIAL CELL GROWTH AND GENE EXPRESSION SYSTEMS</b>	<b>7</b>
<b>1 Animal Cells, Suspension Culture</b> <i>John R. Birch</i>	<b>9</b>
<b>2 Baculovirus Expression Systems</b> <i>Robert D. Possee, Richard B. Hitchman, and Linda A. King</i>	<b>19</b>
<b>3 Baculovirus Kinetics, Insect Culture</b> <i>Leslie Chan, Steve Reid, and Lars Keld Nielsen</i>	<b>33</b>
<b>4 Cell Culture, Aseptic Techniques</b> <i>John M. Davis and Kevin L. Shade</i>	<b>49</b>
<b>5 Cell Cycle in Bioprocesses</b> <i>Mariam Naciri and Mohamed Al-rubeai</i>	<b>71</b>
<b>6 Cell Growth and Protein Expression Kinetics</b> <i>Dhinakar S. Kompala</i>	<b>85</b>

vi CONTENTS

<b>7</b>	<b>Cell Viability Measurement</b>	<b>97</b>
	<i>Ning Wei and Benjamin Sommer</i>	
<b>8</b>	<b>Contamination Detection in Animal Cell Culture</b>	<b>105</b>
	<i>Carol Mclean and Colin Harbour</i>	
<b>9</b>	<b>Culture Collections and Biological Resource Centers (BRCs)</b>	<b>131</b>
	<i>David Smith</i>	
<b>10</b>	<b>Culture Preservation</b>	<b>153</b>
	<i>Robert L. Gherna</i>	
<b>11</b>	<b>Expression and Secretion of Heterologous Proteins, <i>Bacillus</i> and Other Gram-Positive Bacteria</b>	<b>163</b>
	<i>Boyke Bunk, Rebekka Biedendieck, Dieter Jahn, and Patricia S. Vary</i>	
<b>12</b>	<b>Gene Expression in Human Cells</b>	<b>181</b>
	<i>Marco A. Cacciuttolo, Gene Lee, John Chon, and John Lewis</i>	
<b>13</b>	<b>Gene expression in <i>Pichia</i> and other methylotroph yeast</b>	<b>195</b>
	<i>Koti Sreekrishna</i>	
<b>14</b>	<b>Gene Expression in Recombinant Animal Cells and Transgenic Animals</b>	<b>213</b>
	<i>Richard M. Twyman and Bruce Whitelaw</i>	
<b>15</b>	<b>Inoculum Expansion Methods, Animal Cell Lines</b>	<b>297</b>
	<i>Claudia Kloth, Glenn MacIsaac, Haile Ghebremariam, and Alahari Arunakumari</i>	
<b>16</b>	<b>Insect Cell Culture</b>	<b>311</b>
	<i>Someet Narang, Erik M. Whiteley, Sunyia Hussain, and Michael J. Betenbaugh</i>	
<b>17</b>	<b>Kinetics of Microbial Growth</b>	<b>331</b>
	<i>Nicolai S. Panikov</i>	
<b>18</b>	<b>Microalgae, Mass Culture Methods</b>	<b>371</b>
	<i>Emilio Molina Grima, Jose María Fernández Sevilla, and Francisco Gabriel Acién Fernández</i>	
<b>19</b>	<b>Microbial Growth Measurement</b>	<b>399</b>
	<i>Arthur L. Koch</i>	
<b>20</b>	<b>Microbial Media Composition</b>	<b>413</b>
	<i>Rosalie J. Cote</i>	
<b>21</b>	<b>Microscopic Characterization of Cells</b>	<b>437</b>
	<i>Erwin Huebner</i>	
<b>22</b>	<b>Mycoplasma Contamination of Cell Cultures</b>	<b>467</b>
	<i>Cord C. Uphoff and Hans G. Drexler</i>	

<b>23 Protein Glycosylation: Analysis, Characterization, and Engineering</b>	<b>489</b>
<i>Mikael R. Andersen, Jong Hyun Nam, and Susan T. Sharfstein</i>	
<b>24 Secretion of Heterologous Proteins, Gram Positive Bacteria</b>	<b>543</b>
<i>Eric Morello, Isabelle Poquet, Philippe Langella</i>	
<b>25 Soluble Protein Expression in Bacteria</b>	<b>557</b>
<i>Catherine H. Schein</i>	
<b>PART III MEDIA, CELL LINES AND PROCESS DEVELOPMENT</b>	<b>579</b>
<b>26 Animal Cell Culture Media</b>	<b>581</b>
<i>Natarajan Vijayasankaran, Jincal Li, Robert Shawley, Aaron Chen, Masaru Shiratori, Martin Gawlitzek, Feng Li, Robert Kiss, and Ashraf Amanullah</i>	
<b>27 Animal Cell Culture, Effects of Osmolality and Temperature</b>	<b>599</b>
<i>James C. Warren and Shyamsundar Subramanian</i>	
<b>28 Animal Cell Stability</b>	<b>617</b>
<i>Martin S. Sinacore, Timothy S. Charlebois, Denis Drapeau, Mark Leonard, Scott Harrison, and S. Robert Adamson</i>	
<b>29 Animal Cell Types, Hybridomas</b>	<b>635</b>
<i>K. Heilmann and B. Micheel</i>	
<b>30 Antibody Production, Human Recombinant</b>	<b>645</b>
<i>Stefan Dübel</i>	
<b>31 Antifoams and Pluronic Polyols, Cell Protection</b>	<b>663</b>
<i>David W. Murhammer</i>	
<b>32 Biominiaturization of Bioreactors</b>	<b>669</b>
<i>Michael A. Hanson and Govind Rao</i>	
<b>33 Inoculum Preparation</b>	<b>699</b>
<i>Craig J.L. Gershater</i>	
<b>34 Microcarrier Culture</b>	<b>711</b>
<i>Susan T. Sharfstein and Christian Kaisermayer</i>	
<b>35 Monoclonal Antibody Production, Cell Lines</b>	<b>733</b>
<i>Julia F. Markusen and David K. Robinson</i>	
<b>36 Plant Cell Culture, Laboratory Techniques</b>	<b>747</b>
<i>Mark Richard Fowler</i>	
<b>37 Scale-Up of Biotechnological Processes</b>	<b>759</b>
<i>Marko Zlokarnik</i>	

**VOLUME II: EQUIPMENT, PROCESS DESIGN, SENSING,  
CONTROL, AND cGMP OPERATIONS**

---

<b>PREFACE</b>	<b>ix</b>
<b>CONTRIBUTORS</b>	<b>xi</b>
<b>PART IV BIOREACTOR DESIGN, ENGINEERING, PROCESS SENSING AND CONTROL</b>	<b>789</b>
<b>38 Aeration, Mixing, and Hydrodynamics in Animal Cell Bioreactors</b> <i>Ruben Godoy-Silva, Claudia Berdugo, and Jeffrey J. Chalmers</i>	<b>791</b>
<b>39 Biocatalytic Membrane Reactors</b> <i>Lidietta Giorno and Enrico Drioli</i>	<b>821</b>
<b>40 Bioreactor Scale-Down</b> <i>Laura A. Palomares, Alvaro R. Lara, and Octavio T. Ramírez</i>	<b>847</b>
<b>41 Bioreactor Scale-Up</b> <i>Laura A. Palomares and Octavio T. Ramírez</i>	<b>863</b>
<b>42 Bioreactors: Airlift Reactors</b> <i>J.C. Merchuk and F. Garcia Camacho</i>	<b>887</b>
<b>43 Bioreactors, Continuous Culture of Plant Cells</b> <i>H.J.G. Ten Hoopen</i>	<b>955</b>
<b>44 Bioreactors, Fluidized-Bed</b> <i>Winfried Storch</i>	<b>963</b>
<b>45 Bioreactors, Gas-Treatment</b> <i>Graham Andrews and William Apel</i>	<b>979</b>
<b>46 Bioreactors, Perfusion</b> <i>Wei Wen Su</i>	<b>995</b>
<b>47 Bioreactors: Rotating Biological Contactors</b> <i>Susana Cortez, Pilar Teixeira, Rosário Oliveira, and Manuel Mota</i>	<b>1013</b>
<b>48 Bioreactors, Stirred Tank for Culture of Plant Cells</b> <i>Pauline M. Doran</i>	<b>1031</b>
<b>49 Cell Immobilization, Engineering Aspects</b> <i>Ronnie Willaert</i>	<b>1069</b>
<b>50 Fermenter/Bioreactor Design</b> <i>Marvin Charles and Jack Wilson</i>	<b>1101</b>
<b>51 Gas-Holdup in Bioreactors</b> <i>Christian Sieblist and Andreas Lübbert</i>	<b>1137</b>

<b>52 Immobilization of Proteins and Enzymes, Mesoporous Supports</b>	<b>1147</b>
<i>Martin Hartmann and Dirk Jung</i>	
<b>53 Immobilized Cells</b>	<b>1179</b>
<i>Manojlović Verica, Bugarski Branko, and Nedović Viktor</i>	
<b>54 Immobilized Enzymes</b>	<b>1201</b>
<i>Jose M. Guisan, Lorena Betancor, and Gloria Fernandez-Lorente</i>	
<b>55 Impeller Selection, Animal Cell Culture</b>	<b>1219</b>
<i>Alvin W. Nienow</i>	
<b>56 Mammalian Cell Bioreactors</b>	<b>1233</b>
<i>Weichang Zhou, Gargi Seth, Maria J. Guardia, and Wei-Shou Hu</i>	
<b>57 Mammalian Cell Culture Reactors, Scale-Up</b>	<b>1245</b>
<i>J. Bryan Griffiths</i>	
<b>58 Mass Transfer</b>	<b>1261</b>
<i>Yusuf Chisti</i>	
<b>59 Oxygen Transfer Rate Determination Methods</b>	<b>1303</b>
<i>Felix Garcia-Ochoa and Emilio Gomez</i>	
<b>60 Photobioreactors</b>	<b>1327</b>
<i>Mario R. Tredici, Graziella Chini Zittelli and Liliana Rodolfi</i>	
<b>61 Rheological Behavior of Fermentation Fluids</b>	<b>1347</b>
<i>Colin R. Thomas and Grainne L. Riley</i>	
<b>62 Rheology of Filamentous Microorganisms, Submerged Culture</b>	<b>1359</b>
<i>Maria Papagianni</i>	
<b>63 Sampling and Sample Handling for Process Control</b>	<b>1377</b>
<i>Bo Mattiasson and Martin Hedström</i>	
<b>64 Solid State Fermentation, Kinetics</b>	<b>1387</b>
<i>David A. Mitchell, Deidre M. Stuart, and Robert D. Tanner</i>	
<b>65 Solid Substrate Fermentation, Automation</b>	<b>1413</b>
<i>Mario Fernández-fernández and J. Ricardo Pérez-correa</i>	
<b>66 Stainless Steels</b>	<b>1427</b>
<i>C.P. Dillon</i>	
<b>67 Static Mixing, Fermentation Processes</b>	<b>1435</b>
<i>Radu Z. Tudose and Maria Gavrilescu</i>	
<b>68 Transfer Phenomena in Multiphase Systems</b>	<b>1451</b>
<i>Rodica-Viorica Roman</i>	



<b>PART V PROCESS ANALYTICAL TECHNOLOGIES (PAT)</b>	<b>1469</b>
<b>69 Bioprocess and Fermentation Monitoring</b>	<b>1471</b>
<i>Michael Pohlscheidt, Salim Charaniya, Marco Jenzsch, Christopher Bork, Tim L. Noetzel, and Andreas Luebbert</i>	
<b>70 Flow Injection Analysis in Industrial Biotechnology</b>	<b>1493</b>
<i>Elo Harald Hansen and Manuel Miró</i>	
<b>71 Fluorescence Techniques for Bioprocess Monitoring</b>	<b>1511</b>
<i>Fabienne Anton, Carsten Lindemann, Bernd Hitzmann, Kenneth F. Reardon, and Thomas Scheper</i>	
<b>72 Off-Line Analysis in Animal Cell Culture</b>	<b>1523</b>
<i>Heino Büntemeyer</i>	
<b>73 Process Analytical Technology: Strategies for Biopharmaceuticals</b>	<b>1543</b>
<i>Anurag S. Rathore and Gautam Kapoor</i>	
<b>74 Vent Gas Analysis</b>	<b>1567</b>
<i>David Pollard and Jens Christensen</i>	
<b>PART VI UPSTREAM cGMP OPERATIONS</b>	<b>1585</b>
<b>75 Antibody Manufacture, Disposable Systems</b>	<b>1587</b>
<i>Regine Eibl and Dieter Eibl</i>	
<b>76 Bioreactor Operations</b>	<b>1595</b>
<i>David R. Gray</i>	
<b>77 Bioreactors, Cell Culture, Commercial Production</b>	<b>1635</b>
<i>Tan-Che Zhou, Wen-Wen Zhou, Weiwei Hu, and Jian-Jiang Zhong</i>	
<b>78 Biotransformation, Process Optimization</b>	<b>1665</b>
<i>Lutz Hilterhaus, Andreas Liese, and Udo Kragl</i>	
<b>79 Foam Formation and Control in Bioreactors</b>	<b>1679</b>
<i>Frank Delvigne and Jean-Paul Lecomte</i>	
<b>80 Pilot Plants, Design and Operation</b>	<b>1695</b>
<i>Beth H. Junker</i>	
<b>81 Shear Sensitivity</b>	<b>1719</b>
<i>Yusuf Chisti</i>	
<b>82 Sterilization and Decontamination, Bioprocess Equipment</b>	<b>1763</b>
<i>Peter L. Roberts</i>	
<b>INDEX</b>	<b>1781</b>