

**CAM**

Control Systems, Robotics and Manufacturing Series



# **Bioprocess Control**

**by Denis Dochain**

**ISTE**

 **WILEY**

## **Bioprocess Control**



# Bioprocess Control

Edited by  
Denis Dochain

ISTE

 WILEY

First published in France in 2001 by Hermes Science entitled "Automatique des bioprocédés"  
First published in Great Britain and the United States in 2008 by ISTE Ltd and John Wiley & Sons, Inc.

Apart from any fair dealing for the purposes of research or private study, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission in writing of the publishers, or in the case of reprographic reproduction in accordance with the terms and licenses issued by the CLA. Enquiries concerning reproduction outside these terms should be sent to the publishers at the undermentioned address:

ISTE Ltd  
6 Fitzroy Square  
London W1T 5DX  
UK  
www.iste.co.uk

John Wiley & Sons, Inc.  
111 River Street  
Hoboken, NJ 07030  
USA  
www.wiley.com

© ISTE Ltd, 2008  
© Hermes Science, 2001

The rights of Denis Dochain to be identified as the author of this work have been asserted by him in accordance with the Copyright, Designs and Patents Act 1988.

---

Library of Congress Cataloging-in-Publication Data

Automatique des bioprocédés. English.

Bioprocess control / edited by Denis Dochain.

p. ; cm.

Translation from French.

Includes bibliographical references and index.

ISBN: 978-1-84821-025-7

1. Biotechnological process control. 2. Biotechnological process monitoring. I. Dochain, D. (Denis), 1956- II. Title.  
[DNLM: 1. Biomedical Engineering. 2. Bioreactors. 3. Biotechnology. 4. Models, Biological. QT 36 A939 2008a]

TP248.25.M65A9813 2008

660.6--dc22

2007046923

---

British Library Cataloguing-in-Publication Data

A CIP record for this book is available from the British Library

ISBN: 978-1-84821-025-7

---

Printed and bound in Great Britain by CPI Antony Rowe, Chippenham, Wiltshire.



# Contents

<b>Chapter 1. What are the Challenges for the Control of Bioprocesses?</b> . . .	11
Denis DOCHAIN	
1.1. Introduction . . . . .	11
1.2. Specific problems of bioprocess control . . . . .	12
1.3. A schematic view of monitoring and control of a bioprocess . . . . .	12
1.4. Modeling and identification of bioprocesses: some key ideas . . . . .	13
1.5. Software sensors: tools for bioprocess monitoring . . . . .	14
1.6. Bioprocess control: basic concepts and advanced control . . . . .	15
1.7. Bioprocess monitoring: the central issue . . . . .	15
1.8. Conclusions . . . . .	16
1.9. Bibliography . . . . .	16
 <b>Chapter 2. Dynamic Models of Biochemical Processes: Properties of Models</b> . . . . .	17
Olivier BERNARD and Isabelle QUEINNEC	
2.1. Introduction . . . . .	17
2.2. Description of biochemical processes . . . . .	18
2.2.1. Micro-organisms and their use . . . . .	18
2.2.2. Types of bioreactors . . . . .	19
2.2.3. Three operating modes . . . . .	19
2.3. Mass balance modeling . . . . .	21
2.3.1. Introduction . . . . .	21
2.3.2. Reaction scheme . . . . .	21
2.3.3. Choice of reactions and variables . . . . .	23
2.3.4. Example 1 . . . . .	23
2.4. Mass balance models . . . . .	24
2.4.1. Introduction . . . . .	24
2.4.2. Example 2 . . . . .	24
2.4.3. Example 3 . . . . .	25

2.4.4. Matrix representation . . . . .	25
2.4.4.1. Example 2 (continuation) . . . . .	26
2.4.4.2. Example 1 (continuation) . . . . .	26
2.4.5. Gaseous flow . . . . .	27
2.4.6. Electroneutrality and affinity constants . . . . .	27
2.4.7. Example 1 (continuation) . . . . .	28
2.4.8. Conclusion . . . . .	29
2.5. Kinetics . . . . .	30
2.5.1. Introduction . . . . .	30
2.5.2. Mathematical constraints . . . . .	30
2.5.2.1. Positivity of variables . . . . .	30
2.5.2.2. Variables necessary for the reaction . . . . .	31
2.5.2.3. Example 1 (continuation) . . . . .	31
2.5.2.4. Phenomenological knowledge . . . . .	31
2.5.3. Specific growth rate . . . . .	32
2.5.4. Representation of kinetics by means of a neural network . . . . .	34
2.6. Validation of the model . . . . .	35
2.6.1. Introduction . . . . .	35
2.6.2. Validation of the reaction scheme . . . . .	35
2.6.2.1. Mathematical principle . . . . .	35
2.6.2.2. Example 4 . . . . .	36
2.6.3. Qualitative validation of model . . . . .	37
2.6.4. Global validation of the model . . . . .	39
2.7. Properties of the models . . . . .	39
2.7.1. Boundedness and positivity of variables . . . . .	39
2.7.2. Equilibrium points and local behavior . . . . .	40
2.7.2.1. Introduction . . . . .	40
2.8. Conclusion . . . . .	42
2.9. Bibliography . . . . .	43
<b>Chapter 3. Identification of Bioprocess Models . . . . .</b>	<b>47</b>
Denis DOCHAIN and Peter VANROLLEGHEM	
3.1. Introduction . . . . .	47
3.2. Structural identifiability . . . . .	48
3.2.1. Development in Taylor series . . . . .	49
3.2.2. Generating series . . . . .	50
3.2.3. Examples for the application of the methods of development in series . . . . .	50
3.2.4. Some observations on the methods for testing structural identifiability . . . . .	51
3.3. Practical identifiability . . . . .	52
3.3.1. Theoretical framework . . . . .	52
3.3.2. Confidence interval of the estimated parameters . . . . .	54

3.3.3. Sensitivity functions . . . . .	55
3.4. Optimum experiment design for parameter estimation (OED/PE) . . . .	57
3.4.1. Introduction . . . . .	57
3.4.2. Theoretical basis for the OED/PE . . . . .	59
3.4.3. Examples . . . . .	61
3.5. Estimation algorithms . . . . .	63
3.5.1. Choice of two datasets . . . . .	63
3.5.2. Elements of parameter estimation: least squares estimation in the linear case . . . . .	64
3.5.3. Overview of the parameter estimation algorithms . . . . .	65
3.6. A case study: identification of parameters for a process modeled for anaerobic digestion . . . . .	68
3.6.1. The model . . . . .	69
3.6.2. Experiment design . . . . .	70
3.6.3. Choice of data for calibration and validation . . . . .	70
3.6.4. Parameter identification . . . . .	71
3.6.5. Analysis of the results . . . . .	75
3.7. Bibliography . . . . .	75

## **Chapter 4. State Estimation for Bioprocesses . . . . . 79**

Olivier BERNARD and Jean-Luc GOUZÉ

4.1. Introduction . . . . .	79
4.2. Notions on system observability . . . . .	80
4.2.1. System observability: definitions . . . . .	80
4.2.2. General definition of an observer . . . . .	81
4.2.3. How to manage the uncertainties in the model or in the output . .	83
4.3. Observers for linear systems . . . . .	84
4.3.1. Luenberger observer . . . . .	85
4.3.2. The linear case up to an output injection . . . . .	86
4.3.3. Local observation of a nonlinear system around an equilibrium point . . . . .	86
4.3.4. PI observer . . . . .	87
4.3.5. Kalman filter . . . . .	87
4.3.6. The extended Kalman filter . . . . .	89
4.4. High gain observers . . . . .	89
4.4.1. Definitions, hypotheses . . . . .	89
4.4.2. Change of variable . . . . .	90
4.4.3. Fixed gain observer . . . . .	91
4.4.4. Variable gain observers (Kalman-like observer) . . . . .	91
4.4.5. Example: growth of micro-algae . . . . .	92
4.5. Observers for mass balance-based systems . . . . .	94
4.5.1. Introduction . . . . .	94
4.5.2. Definitions, hypotheses . . . . .	96



4.5.3. The asymptotic observer . . . . .	96
4.5.4. Example . . . . .	98
4.5.5. Improvements . . . . .	99
4.6. Interval observers . . . . .	101
4.6.1. Principle . . . . .	102
4.6.2. The linear case up to an output injection . . . . .	103
4.6.3. Interval estimator for an activated sludge process . . . . .	105
4.6.4. Bundle of observers . . . . .	107
4.7. Conclusion . . . . .	110
4.8. Appendix: a comparison theorem . . . . .	111
4.9. Bibliography . . . . .	112
<b>Chapter 5. Recursive Parameter Estimation . . . . .</b>	<b>115</b>
Denis DOCHAIN	
5.1. Introduction . . . . .	115
5.2. Parameter estimation based on the structure of the observer . . . . .	116
5.2.1. Example: culture of animal cells . . . . .	116
5.2.2. Estimator based on the structure of the observer . . . . .	117
5.2.3. Example: culture of animal cells (continued) . . . . .	119
5.2.4. Calibration of the estimator based on the structure of the observer: theory . . . . .	119
5.2.5. Calibration of the estimator based on the structure of the observer: application to the culture of animal cells . . . . .	124
5.2.6. Experimental results . . . . .	127
5.3. Recursive least squares estimator . . . . .	129
5.4. Adaptive state observer . . . . .	133
5.4.1. Generalization . . . . .	138
5.5. Conclusions . . . . .	140
5.6. Bibliography . . . . .	141
<b>Chapter 6. Basic Concepts of Bioprocess Control . . . . .</b>	<b>143</b>
Denis DOCHAIN and Jérôme HARMAND	
6.1. Introduction . . . . .	143
6.2. Bioprocess control: basic concepts . . . . .	144
6.2.1. Biological system dynamics . . . . .	144
6.2.2. Sources of uncertainties and disturbances of biological systems . . . . .	146
6.3. Stability of biological processes . . . . .	147
6.3.1. Basic concept of the stability of a dynamic system . . . . .	147
6.3.2. Equilibrium point . . . . .	148
6.3.3. Stability analysis . . . . .	149
6.4. Basic concepts of biological process control . . . . .	150
6.4.1. Regulation and tracking control . . . . .	150
6.4.2. Strategy selection: direct and indirect control . . . . .	151

6.4.3. Selection of synthesis method . . . . .	152
6.5. Synthesis of biological process control laws . . . . .	153
6.5.1. Representation of systems . . . . .	153
6.5.2. Structure of control laws . . . . .	154
6.6. Advanced control laws . . . . .	160
6.6.1. A nonlinear PI controller . . . . .	160
6.6.2. Robust control . . . . .	162
6.7. Specific approaches . . . . .	165
6.7.1. Pulse control: a dialog with bacteria . . . . .	165
6.7.2. Overall process optimization: towards integrating the control objectives in the initial stage of bioprocess design . . . . .	167
6.8. Conclusions and perspectives . . . . .	170
6.9. Bibliography . . . . .	170

## **Chapter 7. Adaptive Linearizing Control and Extremum-Seeking Control of Bioprocesses . . . . .**

Denis DOCHAIN, Martin GUAY, Michel PERRIER and Mariana TITICA

7.1. Introduction . . . . .	173
7.2. Adaptive linearizing control of bioprocesses . . . . .	174
7.2.1. Design of the adaptive linearizing controller . . . . .	174
7.2.2. Example 1: anaerobic digestion . . . . .	176
7.2.2.1. Model order reduction . . . . .	177
7.2.2.2. Adaptive linearizing control design . . . . .	179
7.2.3. Example 2: activated sludge process . . . . .	183
7.3. Adaptive extremum-seeking control of bioprocesses . . . . .	188
7.3.1. Fed-batch reactor model . . . . .	189
7.3.2. Estimation and controller design . . . . .	191
7.3.2.1. Estimation equation for the gaseous outflow rate $y$ . . . . .	191
7.3.2.2. Design of the adaptive extremum-seeking controller . . . . .	192
7.3.2.3. Stability and convergence analysis . . . . .	195
7.3.2.4. A note on dither signal design . . . . .	196
7.3.3. Simulation results . . . . .	197
7.4. Appendix: analysis of the parameter convergence . . . . .	202
7.5. Bibliography . . . . .	207

## **Chapter 8. Tools for Fault Detection and Diagnosis . . . . .**

Jean-Philippe STEYER, Antoine GÉNOVÉSI and Jérôme HARMAND

8.1. Introduction . . . . .	211
8.2. General definitions . . . . .	212
8.2.1. Terminology . . . . .	212
8.2.2. Fault types . . . . .	213
8.3. Fault detection and diagnosis . . . . .	214
8.3.1. Methods based directly on signals . . . . .	215

8.3.1.1. Hardware redundancy . . . . .	215
8.3.1.2. Specific sensors . . . . .	216
8.3.1.3. Comparison of thresholds . . . . .	217
8.3.1.4. Spectral analysis . . . . .	217
8.3.1.5. Statistical approaches . . . . .	218
8.3.2. Model-based methods . . . . .	218
8.3.2.1. Parity space . . . . .	219
8.3.2.2. Observers . . . . .	220
8.3.2.3. Parametric estimation . . . . .	221
8.3.3. Methods based on expertise . . . . .	222
8.3.3.1. AI models . . . . .	223
8.3.3.2. Artificial neural networks . . . . .	224
8.3.3.3. Fuzzy inference systems . . . . .	225
8.3.4. Choice and combined use of diverse methods . . . . .	227
8.4. Application to biological processes . . . . .	227
8.4.1. “Simple” biological processes . . . . .	228
8.4.2. Wastewater treatment processes . . . . .	229
8.5. Conclusion . . . . .	231
8.6. Bibliography . . . . .	232
<b>List of Authors . . . . .</b>	<b>239</b>
<b>Index . . . . .</b>	<b>241</b>

## Chapter 1

# What are the Challenges for the Control of Bioprocesses?

### 1.1. Introduction

In simple terms, we can define a fermentation process as the growth of microorganisms (bacteria, yeasts, mushrooms, etc.) resulting from the consumption of substrates or nutrients (sources of carbon, oxygen, nitrogen, phosphorus, etc.). This growth is possible only when favorable “environmental” conditions are present. Environmental conditions refer to physicochemical conditions (pH, temperature, agitation, ventilation, etc.) necessary for good microbial activity.

Techniques in the field of biotechnology can be roughly grouped into three major categories:

1. microbiology and genetic engineering;
2. bioprocess engineering;
3. bioprocess control.

Microbiology and genetic engineering aim to develop microorganisms, which allow for the production of new products, or aim to choose the best microbial strains so as to obtain certain desired products or product quality. Process engineering chooses the best operating modes or develops processes and/or reactors, which change and improve the output and/or the productivity of bioprocesses. Automatic control aims to increase the output and/or productivity by developing methods of monitoring

and control, enabling real-time optimization of the bioprocess operation. These approaches are obviously complementary to one another. This book discusses the matter within the context of the final approach.

## 1.2. Specific problems of bioprocess control

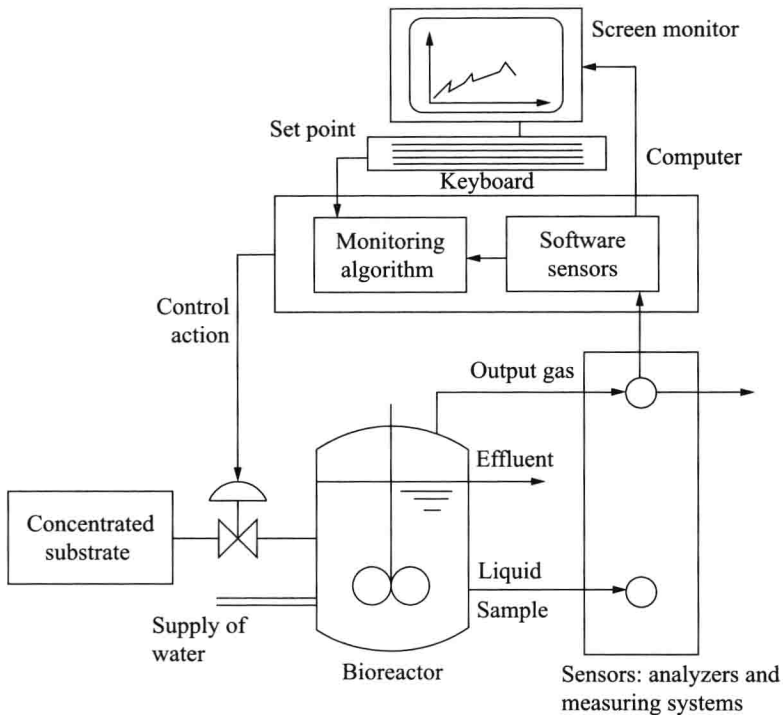
Over the past several decades, biotechnological processes have been increasingly used industrially, which is attributed to several reasons (improvement of profitability and quality in production industries, new legislative standards in processing industries, etc.). The problems arising from this industrialization are generally the same as those encountered in any processing industry and we face, in the field of bioprocessing, almost all of the problems that are being tackled in automatic control. Thus, system requirements for supervision, control and monitoring of the processes in order to optimize operation or detect malfunctions are on the increase. However, in reality, very few installations are provided with such systems. Two principal reasons explain this situation:

- first of all, biological processes are complex processes involving living organisms whose characteristics are, by nature, very difficult to apprehend. In fact, the modeling of these systems faces two major difficulties. On the one hand, lack of reproducibility of experiments and inaccuracy of measurements result not only in one or several difficulties related to selection of model structure but also in difficulties related to the concepts of structural and practical identifiability at the time of identification of a set of given parameters. On the other hand, difficulties also occur at the time of the validation phase of these models whose sets of parameters could have precisely evolved over course of time. These variations can be the consequence of metabolic changes of biomass or even genetic modifications that could not be foreseen and observed from a macroscopic point of view;

- the second major difficulty is the almost systematic absence of sensors providing access to measurements necessary to know the internal functioning of biological processes. The majority of the key variables associated with these systems (concentration of biomass, substrates and products) can be measured only using analyzers on a laboratory scale – where they exist – which are generally very expensive and often require heavy and expensive maintenance. Thus, the majority of the control strategies used in industries are very often limited to indirect control of fermentation processes by control loops of the environmental variables such as dissolved oxygen concentration, temperature, pH, etc.

## 1.3. A schematic view of monitoring and control of a bioprocess

Use of a computer to monitor and control a biological process is represented schematically in Figure 1.1. In the situation outlined, the actuator is the feed rate of the reactor. Its value is the output of the control algorithm, which uses the information of the available process. This information regroups, on the one hand, the state



**Figure 1.1.** Schematic representation of bioprocess control system

of the process to date (i.e. measurements) and, on the other hand, available *a priori* knowledge (for example, in the form of a “material balance” model type) relative to a dynamic biological process and mutual interactions of different process variables. In certain cases – and in particular, when control objectives directly use variables that could not be measured (certain concentrations of biomass, substrates and/or products) or key parameters of the biological process (growth rate or more generally production rate, yield coefficients, transfer parameters) – information resulting from “in-line” measurements and *a priori* knowledge will be combined to synthesize “software sensors” or “observers,” whose principles and methods will be presented in Chapters 4 and 5. Thus, according to the available process knowledge and control objectives specified by the user, we will be able to develop and implement more or less complex control algorithms.

#### 1.4. Modeling and identification of bioprocesses: some key ideas

The dynamic model concept plays a central role in automatic control. It is in fact on the basis of the time required for the development of the knowledge process that

the total design, analysis and implementation of monitoring and control methods are carried out. Within the framework of bioprocesses, the most natural way to determine the models that will enable the characterization of the process dynamics is to consider the material balance (and possibly energy) of major components of the process. It is this approach that we will consider in this work (although certain elements of hybrid modeling, which combines balance equations and neural networks, will be addressed in the chapter on modeling). One of the important aspects of the balance models is that they consist of two types of terms representing, respectively, conversion (i.e. kinetics of various biochemical reactions of the process and conversion yields of various substrates in terms of biomass and products) and the dynamics of transport (which regroups transit of matter within the process in solid, liquid or gaseous form and the transfer phenomena between phases). These models have various properties, which can prove to be interesting for the design of monitoring and control algorithms for bioprocesses, and which will, thus, be reviewed in Chapter 2. Moreover, we will introduce in Chapter 4 on state observers a state transformation that makes it possible to write part of the bioprocess equations in a form independent of the process kinetics. This transformation is largely related to the concept of reaction invariants, which are well known in the literature in chemistry and chemical engineering.

An important stage of modeling consists not only of choosing a model suitable and appropriate for describing the bioprocess dynamics studied but also of calibrating the parameters of this model. This stage is far from being understood and therefore no solution has been obtained, given the complexity of models as well as the (frequent) lack of sufficiently numerous and reliable experimental data. Chapter 3 will attempt to introduce the problem of identification of the parameters of the models of the bioprocess (in dealing with questions of structural and practical identifiability as well as experiment design for its identification) and suitable methods to carry out this identification.

### **1.5. Software sensors: tools for bioprocess monitoring**

As noted above, sometimes many important variables of the process are not accessible to be measured online. Similarly, many parameters remain unclear and/or are likely to vary with time. There is, thus, a fundamental need to develop a model, which makes it possible to carry out a real-time follow-up of variables and key parameters of the bioprocess. Thus, Chapters 4 and 5 will attempt, respectively, to develop software tools to rebuild the evolution of these parameters and variables in the course of time. Insofar as their design gives reliable values to these parameters and variables, they play the role of sensors and will thus be called “software sensors”. The material is divided between the two chapters on the basis of distinction between state variables (i.e. primarily, component concentrations) whose evolution in time is described by differential equations and parameters (kinetic, conversion and transfer parameters), which are either the functions of process variables (as is typically the case for kinetic parameters

such as specific growth rates) or constants (output parameters, transfer parameters)<sup>1</sup>. For state variables, we will proceed with the design of “software sensors” called state observers (Chapter 4), whereas for estimating the unknown or unclear parameters online, parameter estimators will be used (Chapter 5). Due to space considerations, Chapter 5 will deal exclusively with the estimation of kinetic parameters, which proves to be a more crucial problem to be solved. However, the methods which are developed are also applicable to other parameters.

## 1.6. Bioprocess control: basic concepts and advanced control

An important aspect of bioprocess control is to lay down a stable real time operation, less susceptible to various disturbances, close to a certain state or desired profile compatible with an optimal operating condition. Chapter 6 will attempt to develop the basic concepts of automatic control applied to bioprocesses, particularly the concepts of control and setpoint tracking, feedback, feedforward control and proportional and integral actions. We can also initiate certain control methods specific to bioprocesses. The following chapter will concentrate on the development of more sophisticated control methods with the objective of guaranteeing the best possible bioprocess operation while accounting, in particular, for disturbances and modeling uncertainties. Emphasis will be placed, particularly, on optimal control and adaptive control methods based on the balance model as developed in the chapter on modeling. The objective is clearly to obtain control laws, which seek the best compromise between what is well known in bioprocess dynamics (for example, the reaction scheme and the material balance) and what is less understood (for example, the kinetics).

## 1.7. Bioprocess monitoring: the central issue

With the exception of real-time monitoring of state variables and parameters, there has been little consideration of bioprocess monitoring. In particular, how to manage bioprocesses with respect to various operation problems, which are about malfunctioning or broken down sensors, actuators (valves, pumps, agitators, etc.), or even more basically malfunction of the bioprocess itself, if it starts to deviate from the nominal state (let us not forget that the process implements living organisms, which can possibly undergo certain, at least partial, transformations or changes, which are likely to bring the process to a different state from that expected). This issue is obviously important and cannot be ignored if we wish to guarantee a good real time process operation. This problem calls for all the process information (which is obtained from modeling, physical and software sensors or control). This will be covered in the final chapter.

---

1. The models used in practice are often so simplified with respect to reality that these parameters can “apparently” undergo certain variations with time. However, it is important to note that these variations are nothing but a reflection of the inaccuracy or inadequacy of the selected model.



## 1.8. Conclusions

A certain number of works exist in the literature, which deal with the application of automatic control in bioprocesses. This book is largely based on the following books: [BAS 90, VAN 98]. However, we should also mention other reference works worthy of interest: [MOS 88, PAV 94, PON 92, SCH 00]. Due to lack of space, we have not considered certain topics, which could, however, legitimately have had a place in this book. Initially, the informed reader would have noted that there is no chapter on instrumentation, which is, however, an essential link in monitoring and control. Fortunately, the reader will be able to complement the reading of this work with that (in French) of Boudrant, Corrieu, and Coulet [BOU 94] or that (in English) of Pons [PON 92]. In addition, we did not have the space for approaches such as metabolic engineering, a type of approach, which is already playing a growing role in bioprocess control. We suggest the reader consult the following book on metabolic engineering: [STE 98].

## 1.9. Bibliography

- [BAS 90] G. BASTIN and D. DOCHAIN, *On-line Estimation and Adaptive Control of Bioreactors*, Elsevier, Amsterdam, 1990.
- [BOU 94] J. BOUDRANT, G. CORRIEU and P. COULET, *Capteurs et Mesures en Biotechnologie*, Lavoisier, Paris, 1994.
- [MOS 88] A. MOSER, *Bioprocess Technology. Kinetics and Reactors*, Springer Verlag, New York, 1988.
- [PAV 94] A. PAVÉ, *Modélisation en Biologie et en Ecologie*, Aléas, Lyon, 1994.
- [PON 92] M.N. PONS, *Bioprocess Monitoring and Control*, Hanser, Munich, 1992.
- [SCH 00] K. SCHÜGERL and K.H. BELLGARDT, *Bioreaction Engineering. Modeling and Control*, Springer, Berlin, 2000.
- [STE 98] G. STEPHANOPOULOS, J. NIELSEN and A. ARISTIDOU, *Metabolic Engineering*, Academic Press, Boston, 1998.
- [VAN 98] J. VAN IMPE, P. VANROLLEGHEM and D. ISERENTANT, *Advanced Instrumentation, Data Interpretation and Control of Biotechnological Processes*, Kluwer, Amsterdam, 1998.