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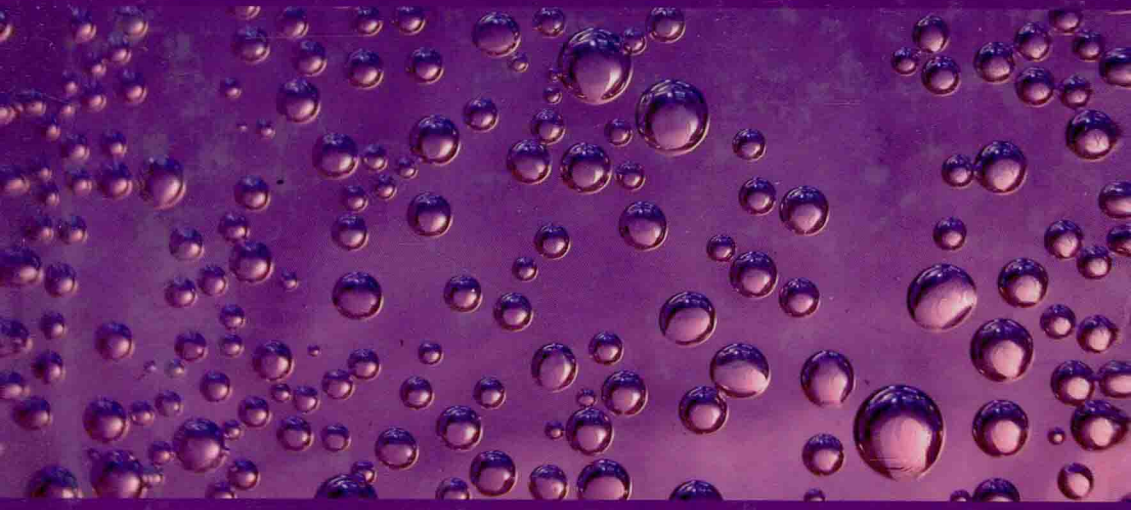

# Bioprocess Control

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# Contents

# 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

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Chapter written by Denis DOCHAIN.

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

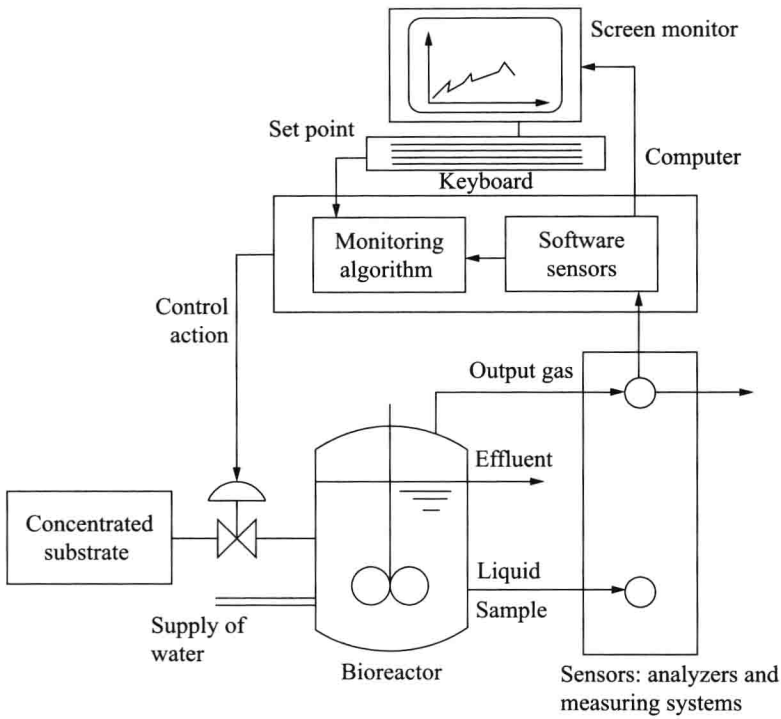


**Figure 1.1.** *Schematic representation of bioprocess control system*

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)[1]. 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.

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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].

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