AUTOMATIC CONTROL OF BIOPROCESSES pdf

1: Automatic control of bioprocesses.

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Introduction In simple terms, we can define a fermentation process as the growth of microorganisms bacteria, yeasts, mushrooms, etc. Environmental conditions refer to physicochemical conditions pH, temperature, agitation, ventilation, etc. Techniques in the field of biotechnology can be roughly grouped into three major categories: 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. These approaches are obviously complementary to one another. This book discusses the matter within the context of the final approach. 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: 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; â€” 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 â€” where they exist â€” 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. 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. 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 What are the Challenges for the Control of Bioprocesses? Schematic representation of bioprocess control system of the process to date i. 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. Modeling and identification of bioprocesses: It is in fact on the basis of the time required for the development of the knowledge process that 14 Bioprocess Control 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. 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. 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. The material is divided between the two chapters on the basis of distinction between state variables i. 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. 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. 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. 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. However, it is important to note that these variations are nothing but a reflection of the inaccuracy or inadequacy of the selected model. 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: However, we should also mention other reference works worthy of interest: 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. 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: Bibliography [BAS 90] G. Modeling and Control, Springer, Berlin, Chapter 2 Dynamic Models of Biochemical Processes: Properties of Models 2. Introduction Modeling biochemical processes is a delicate exercise. As it is not possible to base them only on available and validated knowledge, it is very important to be able to characterize the reliability of the laws used in the construction of the model. This implies hierarchism in the construction of biochemical models. In this chapter, we will see how to organize knowledge in the model in order to distinguish a reliable part established on the basis of a mass balance, and a more fragile part which will describe the bacterial kinetics. The quality of the model and, above all, its structure must correspond to the objective for which the model was built. In fact, a model can be developed for very different purposes, which will have to be clearly identified from the beginning. Thus, the model could be used to: The modeling objectives will generally lead to a formalism for designing the model. If we want to explain spatial heterogenity in a fermentor, it will be necessary to resort to a spatialized model generally described by partial derivative equations. If the objective is

to improve the production of a metabolite during the transitional stages, it will be necessary to represent the dynamics of the system. Furthermore, within the limit of these objectives, the model will also have to be adapted to the data available. In fact, a complex model implying a great number of parameters will require a large quantity of data to be identified and validated. Finally, considering the lack of validated laws in biology, the key stage of modeling is the validation of the model. This will be the subject of a special section. It is in fact fundamental to be able to show, on the basis of experimental data, that the model correctly achieves the assigned goals; we invite the reader to refer to [PAV 94] for a thorough reflection on modeling. Description of biochemical processes 2. Micro-organisms and their use Microbial fermentation is a process in which a population of micro-organisms bacteria, yeasts, moulds, etc. It schematically corresponds to the transformation of substances generally carbonaceous substrates into products, resulting from the metabolic activity of cells. The main components of the reaction are as follows: These substrates generally contain a source of carbon glucose, ethanol, etc. Dynamic Models of Biochemical Processes: Properties of Models 19 Mineral salt and vitamins are added to these main components, which, although they seldom appear in the models, are essential for growth. Each type of micro-organism contains some characteristics related to its genetic inheritance and to its regulating systems and fermentation can have various uses: This is the case of fermentations aiming to produce baking yeast; â€" metabolic production: In this category, we will primarily find depollution processes biological treatment of wastewater, breakdown of specific pollutants, etc. This can, for example, be to better understand how the micro-organism develops in the natural environment. The majority of biotechnological processes developed at an industrial level use microbial cultures made up of a single species of micro-organism for the possible synthesis of a well defined product pure culture. However, in certain cases, several species can be made to grow simultaneously, but this is possible only if they are not too competitive. Types of bioreactors From the view point of mathematical modeling, biological reactors can be divided into two major classes [BAI 86]: In this chapter, we are interested only in the first class of stirred tank reactors, and any reader interested in the second class should see [JAC 96, DOC 94], etc. Three operating modes Operating modes of bioreactors are generally characterized by liquid exchanges, i. We can distinguish three main modes Figure 2. Discontinuous or batch mode All the nutritive elements necessary for biological growth are introduced at the beginning of the reaction. Neither supply nor removal except for some measurements

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In batch bioprocessing, material flow is discrete, with a hold step between two unit operations, and product is harvested only once for each unit operation. Batch processes have been studied extensively and optimized through numerous advancements in experimental design 1, 2 , monitoring 3â€”5 , measurement techniques 6â€”9 , and control strategies 10â€” However, such processes require large facility footprints for equipment 13 as well as sterilization, load, and harvest steps between individual batches, which in turn decreases their overall spaceâ€”time yield STY Furthermore, many traditional batch processes have shown inconsistent performance in productivity and critical quality attributes CQAs. Therefore, companies increasingly turn to alternative operation modes for overcoming those process bottlenecks associated with batch culture. With the introduction of single-use systems, continuous processing offers an attractive alternative to batch processing in terms of facility footprint for lean manufacturing and STY. This approach already has been implemented in both the food and chemical industries. Both the US Food and Drug Administration FDA and the European Medicines Agency EMA have defined batches in terms of material quantities rather than mode of operation 15, 16 , which could pave the way for accelerated implementation of continuous processing. The biopharmaceutical industry is beginning to move from batch and fed-batch processing toward continuous processing: The main advantages of continuous processing are low production costs, constant product recovery, and increased manufacturing flexibility However, this mode has several disadvantages of its own, from process variability to long development times. CPPs can change throughout a culture and therefore necessitate different control strategies for reducing process variability. In recent decades, advances in process analytical technology PAT and quality by design QbD approaches have reduced process development times significantly 19â€” Even though a number of approaches to overcoming process variability do exist, fully continuous processing has yet to be realized in industrial bioprocesses. That is mainly attributable to bottlenecks associated with process variability, infrastructure, and technology transfer. Tackling process variability through identification, monitoring, and control We postulated the following queries describing what we considered to be the primary obstacles to overcome in an attempt to realize continuous processing in the biopharmaceutical industry: Process models are available to identify variability but seldom are used in industrial scenarios. Why are modeling approaches still not transferable to industrial bioprocesses? Continuous bioprocessing requires real-time monitoring of process states to ensure robust productivity. Where is the bottleneck to achieving real-time process monitoring? Biological variations and time effects should be controlled during continuous processing. How can we effectively control or counteract them? Below, we discuss different modeling approaches, monitoring techniques, and control strategies as enablers to overcoming process variability. Figure 1 is a schematic representation of tackling process variability using different tools. Overcoming Process Variability Identification: Variability in KPIs e. But identifying variability in KPIs and controlling it is cumbersome and requires model-based methods. Mechanistic models can be used to describe KPI variability based on process data and mechanistic links e. Such links usually are based on first-order principles or kinetic equations that describe the general relationships among process parameters e. In recent decades, organizations have made available huge libraries of mechanistic linkages for establishing mechanistic models The main problem with developing such models is that they are nontransferable, which hinders the use of modeling techniques in bioprocess development. A article described a self-iterative development workflow that identifies and validates mechanistic links for establishing a mechanistic model That workflow includes determining whether mechanistic links from process information can be identified with process data using sensitivity analyses â€” and if not, it indicates the need for gathering more process data to describe the mechanistic linkages in a process. Such workflows can be used directly at the time of process development for developing a model for bioindustrial scenarios. This workflow has been used to establish a mechanistic model in Chinese hamster ovary CHO cell bioprocesses, for which the state of

cells and KPIs are determined using an iterative cycle of validation Process modeling is necessary to identify variations in early stages of process development. Consequently, developers must use automated workflows that generate models in a structured frame, then implement those models to identify sources of process variability. Workflows such as those described above can be integrated throughout an entire product life cycle to generate mechanistic models and easily identify process variability at early stages. Furthermore, modeling workflows are the solution to accelerating technology transfer and vastly reducing development times. Modeling approaches require real-time data for identifying and monitoring process variations. Real-time monitoring requires timely data collection, transmission, and analysis to capture process variability and predict process performance. Therefore, it is important that a technological and information infrastructure be available for processing data in real time for monitoring process variability. Measuring, monitoring, modeling, and control M3C methodology are the cornerstones of robust bioprocesses. The term soft sensor refers to models that extrapolate process information from indirect measurements Soft sensors for monitoring biomass subpopulations in CHO bioprocesses were reported last year For example, an online microscope can be used to determine variations in biomass populations e. Changes in state variables such as cell lysis during CHO bioprocesses have been analyzed for their impact on cell count, growth kinetics, and productivity In continuous bioprocessing, real-time monitoring of process variability is prerequisite to identifying process deviations and ensuring consistent performance. Observer algorithm for determining the state variable using measurement and modeling Based on modeling techniques and prior knowledge about the state of cells in culture, future predictions of state variables can be made. Hardware sensors estimate the current state of a variable to monitor it, then the model is used to predict the future states of that variable at set time points. The observer algorithm is used to correct for changes in the state variable. With integrated hardware sensors and models, the entire analysis is facilitated by real-time architecture such as process management systems. Figure 2 shows the observer algorithm for determining the state variable x e. Architecture for performing real-time process monitoring has been developed and implemented in some production bioprocesses. However, to extract the maximum amount of useful information, advanced PAT tools need to be combined with real-time architecture to achieve real-time process monitoring. A recent study combined mechanistic modeling and Raman spectroscopy for real-time monitoring of unmeasurable states in an industrial fed-batch bioprocess Similar approaches have been taken to define the optimal time point of process termination 30, 31 and to monitor the onset of cell lysis 5, 32 for ensuring continuous bioprocessing. Advanced PAT tools necessarily facilitate data acquisition for modeling approaches, real-time analysis, and feedback of process information, as well as for reduction of error-prone offline measurements. To exploit such tools, real-time architecture for data processing and modeling will be needed. Information from different modeling approaches and PAT tools can be fed back into a process model for real-time monitoring of process variability, thereby enabling continuous processing. Such systems can be integrated directly into early stages of process development, making them highly beneficial for product lifecycle management and technology transfer. Mechanistic relationship between glucose and lactose uptake rates for tuning between growth and production in an Escherichia coli DE3 bioprocess; dashed line represents the switch between production and growth. Bioprocesses are dynamic by nature, with constant changes in process conditions and parameters. Biological time effects cause the most variability inside process design spaces. Although that is well known and different approaches have been developed to negate biological time effects, such negation has yet to be realized. Advances in molecular biology pave the way for robust promoter systems that can be used to tune productivity 33, 34 and prevent process variations. Tunable promoter systems have been developed recently and used for removing biological time effects and ensuring robust productivity. Such systems can help maintain cultured cells in a productive state for long durations and render consistent product quality. Figure 3 exemplifies mechanistic relations among substrate uptake rates in a tunable promoter system of Escherichia coli. The ultimate goal of continuous processing is to keep a production culture healthy over long periods of time and thus lessen or eliminate process variation. Combining tunable promoter systems with model-based approaches can help a system attain constant productivity. Simultaneous control of different feeds for sophisticated strategies has been implemented Furthermore, monitoring specific productivity can be used to determine the optimal time

point for harvest to ensure product quality and reduce downstream complications. One mechanistic model has been used for concomitant feed-control strategies to curb process variability 34, Tunable promoter systems and control strategies can be used to maintain cells in a productive state for the longest possible time and to control consistent product quality, thereby enabling continuous processing. Furthermore, Monte Carlo techniques can be used to simulate process performance within a defined design space and thus enable process engineers to determine the effects of CPP variability on desired product quality. Based on those simulations, control charts can be created to prevent unwanted process deviations and help control process variability within a narrow range. To overcome such complexities and understand process variability, bioprocess engineers need a complete knowledge of process parameters and raw material attributes and their effects on quality attributes. We propose the use of modeling workflows, advanced PAT tools, and tunable promoter systems to reduce process variability. To overcome it for continuous processing, we can answer the questions raised above: Modeling workflows will be the enabler to generate process models quickly for direct transfer and testing in industrial processes. We envision the use of advanced PAT tools â€" for example, using genetic fingerprinting methods and CQA analysis â€" and real-time architecture as enablers for real-time process monitoring. How can we effectively control or counteract biological time effects and variations? Tunable promoter systems are enablers to effectively counteract biological time effects, thereby curbing process variability and providing the essential step toward continuous upstream processing. Combining all three enablers modeling, monitoring, and control to curb process variability will be needed to ensure robust continuous bioprocessing. A cystic fibrosis drug has been produced using a continuous upstream process Thanks to the available tools and advances, we envision intense incorporation of continuous processing in the biopharmaceutical industry within the coming decades. References 1 Lim M, et al. A Novel Toolbox for E. Sensors Switzerland 15 5 Heterogeneity in Pure Microbial Systems: Experimental Measurements and Modeling. Automatic Control of Bioprocesses. A Changing Processing Paradigm. The Future of Industrial Bioprocessing: Title 21, Part US Food and Drug Administration: Rockville, MD, ; www. London, UK, 29 April

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Automatic control of bioprocesses. Stanke M(1), Hitzmann B. Author information: (1)Process Analytics and Cereal Technology, Institute of Food Science and Biotechnology, University of Hohenheim, Garbenstr. 23, , Stuttgart, Germany.

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