FED-BATCH CULTURES

Many, if not most, industrially important fermentation and bioreactor operations are carried out in fed-batch mode, producing a wide variety of products. Despite this, until now, no single book has dealt with fed-batch operations. This is the first book that puts together all the necessary background material regarding the what, why, and how of optimal and suboptimal fed-batch operations. Numerous examples are provided to illustrate the application of optimal fed-batch cultures. This unique book, by world experts with decades of research and industrial experience, is a must for researchers and industrial practitioners of fed-batch processes (modeling, control, and optimization) in the biotechnology, fermentation, food, pharmaceutical, and waste treatment industries.

Henry C. Lim gained industrial experience by working for Pfizer for five years in reaction engineering and separation and purification. He taught for 21 years at Purdue University and initiated biochemical engineering research in 1970. He was recruited to the University of California, Irvine, where he was founding chair of biochemical engineering and chemical engineering for 10 years and taught for 22 years. He has extensive consulting experience with Leeds and Northrup, Novo Enzyme Corporation, Pharmacontrol Inc., Eli Lilly, Merck, Monsanto, LG Biotech Inc., CJ Biotechnology, and Zander Renewable Systems, LLC. He has studied bioreactions and bioreactor engineering, modeling, optimization and control of bioreactors, cellular regulation, recombinant DNA technology, and bioremediation. Dr. Lim has supervised more than 50 PhD dissertations and has published more than 160 journal articles, as well as two books. He received the Food, Pharmaceutical, and Bioengineering Division Award of the AIChE for his work on bioreactor and enzyme engineering.

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Fed-Batch Cultures

PRINCIPLES AND APPLICATIONS OF SEMI-BATCH BIOREACTORS

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To my wife, Sun Boo Lim; children, David, Carol, Michael, Tom, and Melia; and grandchildren, Natalie and Lanie

and

To my parents, Mr. and Mrs. Shin; wife, Jung Hye Hyun; and children, Alyssa and Claire

Contents

Preface

Fed-batch operations are semi-batch operations in which one or more streams of feed containing nutrient sources, precursors, inducers, and mineral sources are fed either continuously or intermittently during the course of otherwise batch operations. The culture content is harvested either fully or partially at the end of the run and is used as the inoculum for the next cycle. By regulating the feed rates, it is possible to regulate the bioreactor environment to maximize the total rate of production, the reactor productivity, or the product yield.

Many industrially important bioreactor operations involving microbial and animal cells are carried out in fed-batch mode. These so-called fed-batch cultures have been found to be particularly effective for fermentation processes and cell cultures in which it is desirable to overcome such common phenomena as substrate inhibition, catabolite repression, product inhibition, and glucose effects to achieve high cell density for efficient fermentation, to minimize high viscosity effects, and to take advantage of auxotrophic mutants. Products produced by fed-batch cultures include amino acids, antibiotics, enzymes, microbial cells, organic chemicals, polysaccharides, proteins, tissue culture products, and various recombinant DNA products.

Despite the long history of the industrial use of fed-batch cultures, only recently have we gained a thorough understanding of them, and industrial practices have tended to be empirical in nature and most often based on experiences gained through bench, pilot plant, or production-level operations. Theoretical analyses and experimental studies of fed-batch operation have received considerable attention in the past 10 years. A better understanding of principles and applications of modern optimal control theory and geometric interpretation has opened the door for improving the performance of fed-batch fermentation processes and cell cultures. As a result of the surge in research activity, an abundance of information can now be effectively utilized in improving the performance of industrial fed-batch processes. Until now, however, no single book or monograph has been fully devoted to fed-batch processes, and therefore, the information has remained largely scattered and untapped. Textbooks dealing with biochemical engineering principles provide at best either very little coverage of fed-batch operations or unconventional treatments. Therefore, there was a strong need for a book that would put together all principles, guide the reader through the up-to-date theoretical developments in fed-batch processes, and describe step-by-step procedures leading to the optimization of fed-batch processes.

Such a book, dealing with the what, why, and how of fed-batch operation, would provide basic principles of fed-batch cultures in the simplest terms and practical means for optimizing the processes.

This book is a first attempt to provide all the necessary background materials regarding the what, why, and how of fed-batch operations. A simple conception of a fed-batch operation is a one-bioreactor operation mimicking a two-bioreactor operation, a continuous-stirred tank reactor followed by a batch reactor (a temporal equivalence of a tubular reactor) that maximizes the overall reaction rate, the product yield, or a combination of the two.

The systematic coverage presented in this work is an attempt to include elementary principles, theoretical developments in optimization and control, and practical implementation of optimal strategies for fed-batch processes. This book can be used fully or partially as a textbook and/or reference by advanced undergraduate and graduate students in biochemical engineering, environmental engineering, chemical engineering, biotechnology, and other related areas. It is also useful as a reference or guide for practitioners and research and development personnel in biotechnology, fermentation, food, pharmaceuticals, and industrial waste treatment.

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We wish to thank Cambridge University Press, especially Peter Gordon, for his patience in extending a number of deadlines so that we could finish the book – it has taken much more time than we anticipated. We also express our appreciation to Purdue University and the University of California, Irvine, for the opportunity to initiate and complete this book.