BIOLOGICAL REACTION ENGINEERING

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Biological Reaction Engineering

Principles, Applications and Modelling with PC Simulation

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The included diskette contains the ISIM simulation language as well as simulation examples. It can be run on all DOS-PC's.

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Preface

Our goal in this textbook is to teach, through modelling and simulation, the quantitative description of bioreaction processes to scientists and engineers. In working through the forty-five simulation examples on the accompanying diskette, you, the reader, will learn to apply mass and energy balances to describe a variety of dynamic bioreactor systems. For your efforts, you will be rewarded with a greater understanding of biological rate processes. The many example applications will help you to gain confidence in modelling, and you will find that the included simulation language, ISIM, is a powerful tool for developing your own simulation models. Your new abilities will be valuable for designing experiments, for extracting kinetic data from experiments, in designing and optimizing biological reaction systems, and for developing bioreactor control strategies.

This book is based on part of our successful course, "Biological Reaction Engineering", which has been held annually in the Swiss mountain resort of Braunwald over the past eleven years and which is now known, throughout European biotechnology circles as the "Braunwald Course". The framework for the course and for this book has developed as a result of over fifteen years experience in research and teaching in biochemical engineering, combined with a strong interest in modelling and simulation. The first course, held in 1981, was the very first occasion that a continuing education course had been offered with the specific intention of familiarizing biological scientists with the basic principles of chemical engineering modelling methodology. Its approach in teaching biochemical engineering fundamentals is still unique, particularly in its use of computers. Although the course and this book were designed with the non-engineer in mind, we have found that the majority of the course participants have been engineers. Apparently our course offers something that has been missing in the educational backgrounds of many biotechnologists, and we hope this book captures the essence of our approach. The advertisement in the back describes our course in more detail.

Modelling is often unfamiliar to biologists and chemists, who nevertheless need modelling techniques in their work. The general field of biochemical reaction engineering is one that requires a very close interdisciplinary interaction between applied microbiologists, biochemists, biochemical engineers, engineers and managers: a large degree of collaboration and mutual understanding is therefore important. Professional microbiologists and biochemists often lack the formal training needed to analyze laboratory kinetic data in its most meaningful sense.

and they may sometimes experience difficulty in participating in engineering design decisions and in communicating with engineers. These are just the very types of activity required in the multi-disciplinary field of biotechnology. Chemical engineering's greatest strength is its well-developed modelling concepts, based on mass and energy balances, combined with rate processes. The realization that this important contribution to biotechnology was not being taught to biological scientists led to the inception of the course and later to the idea for this book.

Biochemical engineering is a discipline closely related to conventional chemical engineering, in that it attempts to apply physical principles to the solution of biological problems. This approach may be applied to the measurement and interpretation of laboratory kinetic data or as well to the design of large scale fermentation, enzymatic or waste treatment processes. The necessary interdisciplinary cooperation requires the biological scientists and chemical engineers involved to have at least a partial understanding of each other's field. The purpose of this book is to provide the mathematical tools necessary for the quantitative analysis of biological kinetics and other biological process phenomena. More generally, the mathematical modelling methods presented here are intended to lead to a greater understanding of how the biological reaction systems are influenced by process situations.

Engineering science depends heavily on the use of applied theory, quantitative correlations and mathematics, and it is often difficult for all of us (not only the biological scientist) to surmount the mathematical barrier, which is posed by engineering. A mistake, often made, is to confuse "mathematics" with the engineering modelling approach. In modelling, an attempt is made to analyze a real and possibly very complex situation into a simplified and understandable physical analog. This physical model may contain many subsystems, all of which still make physical sense, but which now can be formulated as mathematical equations. These equations have to be solved, but much of the former mathematics is now replaced by numerical solution and can be handled automatically by the computer. Thus the engineer and the biologist are freed from the difficulties of mathematical solution and can tackle complex problems which were impossible before. Also the computer has become much easier to use. The modern approach to solution, using desktop computers with easy-to-program software, thus helps considerably in making modelling far more attractive for the non-specialist than it has been in the past. One aim of this book is to introduce the reader-modeller to the wonders of modern computing.

Models, however, still have to be formulated and one of the most important tools of the biochemical engineer, in this operation, is the use of material balance equations. Though it may not be easy for the microbiologist to fully appreciate the importance of differential equations, mass balance equations are not so difficult to understand, since the first law of conservation, namely that matter can neither be created nor destroyed, is fundamental to all science. Mass balances, when combined with kinetic rate equations, to form simple mathematical models, can be used with very great effect as a means of planning, conducting and analyzing experiments. Models are especially important as a means of obtaining a better understanding of process phenomena. A rational approach to experimentation and design requires a considerable knowledge of the system, which can really only be achieved by means of a mathematical model. This book attempts to demonstrate this by way of the many detailed examples.

The contribution made to biotechnology by the biochemical engineering modelling approach is especially important because the basic procedure can be developed from a few fundamental principles. An aim of this book is to demonstrate that you do not have to be an engineer to learn modelling and simulation. The basic concepts of the material balance, combined with biological and enzyme kinetics, are easily applied to describe the behavior of well-stirred tank and tubular fermenters, mixed culture dynamics, interphase gas-liquid mass transfer and internal biofilm diffusional limitations, as demonstrated in the computer examples supplied with this book. Such models, when solved interactively by computer simulation, become much more understandable to non-engineers.

Modern simulation languages are now available that provide the possibility of carrying out the interactive simulation of complex problems at one's own desk. For DOS compatible systems, several types of languages are currently available. The ISIM simulation language, provided with this book, is also the language we have used during the last five years for our continuing education course. It is especially suitable because of its sophisticated computing power, interactive facility and ease of programming. The use of this PC-based, digital simulation programming language makes it possible for the reader, student and teacher to experiment directly with the model, in the classroom or at the desk. In this way it is possible to immediately determine the influence of changing various operating parameters on the bioreactor performance – a real learning experience.

The simulation examples serve to enforce the learning process in a very effective manner and also provide hands-on confidence in the use of a simulation language. The readers can program their own examples, by formulating new mass balance equations or by modifying an existing example to a new set of circumstances. Thus by working directly at the PC, the no-longer-passive reader is able to experiment directly on the bioreaction system in a very interactive way by changing parameters and learning about their probable influence in a real situation. A true degree of interaction is possible with ISIM because at the stroke of a few keys a simulation run is stopped, parameters are changed, and the run is restarted from the point of interruption. Plotting the variables in any configuration is easy at any time during a run. Runs can be repeated with new parameters, and the results from multiple runs can be plotted together for comparison.

The solution technique, based on the use of a simulation language, is particularly beneficial because it permits easy programming, easily comprehensible program listings, a rapid and efficient solution of the model equations, interactive variation of the model parameters, and a convenient graphical output of the computed results. In our experience, digital simulation has proven itself to be absolutely the most effective way of introducing and reinforcing new concepts which involve multiple interactions. The thinking process is ultimately stimulated to the point of solid understanding.

Organization of the Book

The book is divided into two parts: a presentation of the background theory in Part I and the computer simulation exercises in Part II. The function of the text in Part I is to provide the basic theory required to fully understand and to make full use of the computer examples and simulation exercises. Numerous case studies provide illustration to the theory. Part II constitutes the main part of this book, where the simulation examples provide an excellent instructional and self-learning tool. Each of the forty-five examples is self-contained, including a model description, model equations, exercises, computer program listing, nomenclature and references. The exercises range from simple parameter-changing investigations to suggestions for writing a new program. The combined book thus represents a synthesis of basic theory and computer-based simulation examples. The aim of this approach is to provide an opportunity to learn by actually working on the computer examples oneself and represents a major innovation in biochemical engineering education.

Quite apart from the educational value of the text, the provision of the ISIM master program with the book provides the reader with the considerable practical advantage of a desktop differential equation solution package. A condensed manual with all the ISIM commands is found in the last chapter.

Part I: "Principles of Bioreactor Modelling" covers the basic theory necessary for understanding the computer simulation examples. This section presents the basic concepts of mass balancing, and their combination with kinetic relationships, to establish simple biological reactor models, carefully presented in a way which should be understandable to biologists. In fact, engineers may also find this rigorous presentation of balancing to be valuable. In order to achieve this aim, the main emphasis of the text is placed on an understanding of the physical meaning and significance of each term in the model equations. The aim in presenting the relevant theory is thus not to be exhaustive, but simply to provide a basic introduction to the theory, required for a proper understanding of the modelling methodology.

The presentation is thus slightly different to that of other well-established texts, where further amplification of the relevant theory can be found, but where balances are often not so carefully developed. In our book the emphasis is on the application of theory to modelling, because we believe that a deeper understanding of the theory can be obtained by actually working with the computer simulations.

Chapter 1 deals with the basic concepts of modelling, the basic principles, development and significance of differential balances and the formulation of mass and energy balance relationships. Emphasis is given to physical understanding. The text is accompanied by example cases to illustrate the application of the material.

Chapter 2 serves to introduce the varied operational characteristics of the various types of bioreactors and their differing modes of operation, with the aim of giving a qualitative insight into the quantitative behavior of the computer simulation examples.

Chapter 3 provides an introduction to enzyme and microbial kinetics. A particular feature of the kinetic treatment is the emphasis on the use of more complex structured models. Such models require much more consideration to be given to the biology of the system during the modelling procedure, but despite their added complexity can nevertheless also be solved with relative ease. They serve as a reminder that biological reactions are really infinitely complex.

Chapter 4 is used to derive general mass balance equations, covering all types of fermentation tank reactors. These generalized equations are then simplified to show their application to the differing modes of stirred tank bioreactor operation, discussed previously and which are illustrated by the simulation examples.

Chapter 5 explains the basic theory of interfacial mass transfer as applied to fermentation systems and shows how equations for rates of mass transfer can be combined with mass balances, for both liquid and gas phases. A particular extension of this approach is the combination of transfer rate and material balance equations to models of increased geometrical complexity, as represented by large scale airlift and multiple impeller fermenters.

Chapter 6 treats the cases of external diffusion to a solid surface and internal diffusion combined with biochemical reaction, with practical application to immobilized biocatalyst and biofilm systems. Emphasized here is the conceptual ease of handling a complex reaction in a solid biocatalyst matrix. The resulting sets of tractable differential-difference equations are solved by simulation techniques in several examples.

Chapter 7 describes the importance of control and summarizes control strategies used for bioreaction processes. Here the fundamentals of feedback control systems and their characteristic responses are discussed. This material forms the basis for performing the many recommended control exercises in the simulation examples. It also will allow the reader-simulator to develop his own control models and simulation programs.

Part II: "Dynamic Bioprocess Simulation Examples and the ISIM Simulation Language" comprises Chapter 8, with the computer simulation examples as found on the ISIM diskette, and Chapter 9, which gives the instructions for using ISIM. Each example in Chapter 8 includes a description of its physical system, the model equations, which were developed in Part I, and a list of suggested exercises. These example exercises can be carried out in order to explore the model system in detail, and it is suggested that work on the computer exercises be done in close reference to the model equations and their physical meaning, as described in the text. The exercises, however, are provided simply as an idea for what might be done and are by no means mandatory or restrictive. Working through a particular example will often suggest an interesting variation, such as a control loop, which can then be programmed and inserted. The examples cover a wide range of application and can easily be extended by reference to the literature. They are robust and are well tested by a variety of undergraduate and graduate students and by also the 250 participants, or so, who have previously attended the Braunwald course. In tackling the exercises, we hope you will soon come to share our conviction that, besides being very useful, computer simulation is also fun to do.

Our book has a number of special characteristics. It will be obvious, in reading it through, that we concentrate only on those topics of biological reaction engineering that lend themselves to modelling and simulation and do not attempt to cover the area completely. Our own research work is used to illustrate theoretical points and from it many simulation examples are drawn. A list of suggested books for supplementary reading is found at the end of Chapter 6, together with the list of cited references. The diversity of the simulation examples made it necessary to use separate nomenclature for each. The symbols used in Chapters 1 - 6 are defined at the end of Part I. The authors' four nationalities and three mother tongues, made it difficult to settle on American or British spelling. Somehow we like modelling better than modeling.

We are confident that the book will be useful to all life scientists wishing to obtain an understanding of biochemical engineering and also to those chemical and biochemical engineers wanting to sharpen their modelling skills and wishing to gain a better understanding of biochemical process phenomena. We hope that teachers with an interest in modelling will find this to be a useful textbook for undergraduate and graduate biochemical engineering and biotechnological courses.

ISIM Simulation Software

This software is made available only for the purposes described in the book "Biological Reaction Engineering" and its features are restricted to these examples. Users wishing to purchase the full ISIM or ESL software should contact ISIM Simulation directly. User manuals for ISIM may also be purchased for £ 40 from ISIM Simulation.

ISIM Simulation, A Division of Salford University Business Services Ltd. Technology House, Lissadel Street, Salford M6 6AP, England (Tel.: +44 (0) 6 17 45 74 44; Fax.: +44 (0) 6 17 37 77 00).

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Many years ago, one of us was involved in teaching two courses with Professor Russell, in which modelling and mass balancing were presented in a lucid way to members of the chemical industry. Here it was ably demonstrated that chemical engineering modelling can be an important and teachable contribution to other fields. These were the first modelling courses held in Braunwald and can reasonably be acknowledged as having had an important influence on this book.

We are especially grateful to all past participants of the Braunwald course, for their assistance in the continuing development of the course and of the material presented in this book. Continual stimulus and assistance has also been given by a sequence of doctoral candidates in the Chemical Engineering Department, ETH-Zurich, as noted throughout the references.

Our grateful thanks are due to Dr. John L. Hay of the Department of Electrical Engineering, University of Salford, for his agreement to release, in conjunction with this book, the use of the ISIM digital simulation programming language. We hope that this book will be useful in drawing attention to his advanced simulation language, ESL, for which we are happy to include a programmed example and an advertisement at the back of the book.

It is hard to imagine writing a book without an Apple Macintosh, on which the text was done with MS Word. Special thanks are due to Priska Brülhart and Albert Ochsner, who were geniuses at word processing and making drawings. Dr. Jonathan B. Snape and Hermann Stockinger put the simulation examples in final shape and produced the graphical outputs. Our publisher, VCH, known for its production of well-designed books, was a helpful and pleasant partner, and for this we are thankful.

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