Bioseparation Process Science

生物分离过程科学

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作　者：Antonio A. García　Matthew R. Bonen　Jaime　Ramírez-Vick
　　　　Mariam Sadaka　Anil Vuppu
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PREFACE

In this textbook, the word *bioseparations* is used in the context of biochemical engineering. In this context, the term refers to separation and purification methods for such biological products as biochemicals, proteins, polynucleic acids, and cells. The purpose of this text is to provide students and practitioners of engineering and science with a framework for decision making in the design of bioseparation processes.

Chapter 1 introduces some of the basic concepts central to understanding the remainder of the book. Part I of the text then moves on to discuss some illustrative biotechnology industrial processes and provides the reader with practical information on standard analytical methods. The two chapters that constitute Part I are important bookends covering the full industrial and analytical scale of bioseparations. Chapter 2 covers a broad range of important industrial bioseparation processes, stressing an overview of the arrangement of individual steps in the purification of the final product. Chapter 3 provides a useful discussion of analytical methods, a topic too often ignored in biochemical engineering texts. Process evaluation, however, cannot be carried out without analytical support and analytical methods, which are often emulated and redesigned for commercial-scale production.

Part II touches on several challenging subject areas, describing physical, chemical, and biological interactions with an eye toward exploiting these effects for bioseparations. Physical and chemical interactions are normally covered in some depth in engineering textbooks, and biological interactions are the focus of biochemistry texts. Within this section of the book, we present these different views simultaneously so as to give the student and the practitioner a more complete set of tools with which to design purification and separation processes.

Part III deals with commonly employed "unit" operations (that is, process steps). Its organization parallels the format used in many biochemical engineering textbooks, though we have made an effort to keep the number of symbols and parameters to a minimum so as to focus on the phenomena themselves. In addition, the use of differential calculus is primarily confined to standard first- and second-semester calculus topics, with the exception of the use of Laplace transforms (an orientation to Laplace transforms is provided in the appendices). Our goal in reducing the number of symbols and the level of math complexity is to lower the barriers erected by the use of excessive mathematical jargon and specialized techniques in the multidisciplinary environment of industrial biotechnology. Readers interested in more mathematical content are encouraged to review the specialized textbooks and references cited throughout this book.

Part IV, the final section of the text, covers several key topics necessary to begin the creative process of synthesizing a biological separation process flow diagram. One of the most important tools for designing such processes is computer software, which provides a built-in wealth of expert information. Part IV acknowledges the efficiency and effectiveness of using these tools by *not* subjecting the reader to pencil-and-paper methods that serve only to reinvent the capabilities of currently available software. Once the underlying principles and individual operation analyses of Parts II and III are covered, the practicing bioseparation process designer can learn to use the software design tools presented in Part IV, gaining an understanding of the underlying economics, process integration challenges, and final product formulation issues affecting bioseparations in the real world.

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CONTENTS

1

Introduction

Throughout this textbook, the reader will encounter the application of calculus, which is usually associated with the principle of conservation of mass. Traditionally, the use of calculus in textbooks signals that the book is directed toward readers who are studying engineering or who have an engineering background. The approach taken in this book, however, will be to apply useful mathematics to the analysis of bioseparation processes in such a way as to permit access by a wider scientific audience. Both this introductory chapter and Appendix A are designed to help bridge the so-called engineering–mathematics gap—that is, to make the coverage of these topics suitable for a reader who has completed one semester of calculus and physics. Moreover, we have kept the number of defined terms to a minimum whenever possible, and avoided the use of intricate mathematical methods so as to present a uniform and straightforward use of analysis tools.

This chapter deals with three analysis tools applicable to bioseparation processes:

- The principle of mass conservation as an accounting method
- The use of differentials and integrals to help answer important questions
- Chemical species accounting for processes involving diffusion, convection, or reaction

Appendix A introduces the use of Laplace transforms as a convenient method for solving the differential equations with which we model separation processes. The reader can skip this chapter if desired, returning to it as questions arise on the use of mathematics in our subsequent discussions of chromatography, solvent extraction, and crystallization.

1.1 MASS CONSERVATION AS AN ACCOUNTING METHOD

Science students will be familiar with the oft-quoted law of classical physics that states that "mass is neither created nor destroyed." This statement of mass conservation holds unless a nuclear reaction occurs, in which case Einstein's equation relating mass to energy must then be employed. For the purpose of bioseparations, this law holds true in every situation. Thus, in bioseparation process science, the law of mass conservation provides a basis for writing mathematical expressions to help predict the outcome for design variables based on the nature of the process.

The application of the law of mass conservation is entirely analogous to financial accounting or any other type of accounting. An anecdote will illustrate how to perform such mass accounting. Imagine that a professor brings a closed cardboard box and a basket of balls into class. She then requests that a student come to the front of the room to help in adding and removing balls to and from the box. The professor opens the box and allows the student to start by adding eight balls. Then she has him remove two balls. The rest of the class is charged with keeping track of the number of balls being added to and removed from the box.

After several rounds of adding or removing balls from the box, the professor asks the class how many balls are in the box. Nearly everyone in the room answers the professor in unison. The professor, however, tells them that they are all wrong. After checking their tallies, the class members are even more firmly convinced that they have the right number. Yet the professor still claims that they are wrong. Finally, the class has become thoroughly incensed and accuses the professor of not being able to count. "Of course, you have the wrong answer," she exclaims. One student asks, "How can that be? We carefully tracked the number of balls that were added and subtracted, and then double-checked our answer." "But," says the professor, "you did not know that there were four balls in the box when I brought it into class."

This anecdote illustrates the importance of carefully and explicitly constructing an accounting procedure for mass. The proper way of dealing with accounting for the number of balls in the box at any time is to write a procedure, such as the following:

$$\begin{bmatrix}\text{Number of}\\\text{balls in box}\\\text{at any time}\end{bmatrix}=\begin{bmatrix}\text{number of}\\\text{balls in box}\\\text{initially } (t=0)\end{bmatrix}+\begin{bmatrix}\text{number of balls}\\\text{added since the}\\\text{beginning } (t>0)\end{bmatrix}-\begin{bmatrix}\text{number of balls}\\\text{removed since the}\\\text{beginning } (t>0)\end{bmatrix} \tag{1.1}$$

A mathematical equation can be created from Equation 1.1 when $b(t)$ is defined as the number of balls in the box at any time, $b(0)$ is the number of balls in the box initially, b_{in} is the number of balls put into the box, and b_{out} is the number of balls removed from the box. After substituting these expressions into Equation 1.1, we have the following equation:

$$b(t) = b(0) + b_{in} - b_{out} \tag{1.2}$$

In most cases, it is more useful to track rates than absolute numbers. For example, a person may want to know how fast his net worth is changing over time. This rate is especially important if the person wants to see whether bankruptcy is imminent or whether he is saving enough for retirement. In that case, one equation could satisfy this need:

$$\begin{bmatrix}\text{Rate of accumulation}\\\text{of dollars (\$/month)}\end{bmatrix}=\begin{bmatrix}\text{salary rate after}\\\text{taxes (\$/month)}\end{bmatrix}+\begin{bmatrix}\text{net rate of cash flow due}\\\text{to investments (\$/month)}\end{bmatrix}-\begin{bmatrix}\text{expense rate}\\\text{(\$/month)}\end{bmatrix} \tag{1.3}$$

For our simpler box problem, we can also change the accounting method to a rate:

$$\begin{bmatrix}\text{Rate of accumulation}\\\text{of balls (\#/minute)}\end{bmatrix}=\begin{bmatrix}\text{rate of balls into}\\\text{box (\#/minute)}\end{bmatrix}-\begin{bmatrix}\text{rate of balls out of}\\\text{box (\#/minute)}\end{bmatrix} \tag{1.4}$$

This expression can be written in terms of a differential equation,

$$\frac{db}{dt} = \dot{b}_{\text{in}} - \dot{b}_{\text{out}} \tag{1.5}$$

where the dots above the letter b refer to the rate. Note that we can integrate Equation 1.5 to obtain a solution when we know the number of balls that are in the box initially. In this case, we have the following equation:

$$\int_{b(0)}^{b(t_{\text{end}})} db = \int_{t=0}^{t=t_{\text{end}}} (\dot{b}_{\text{in}} - \dot{b}_{\text{out}})dt \tag{1.6}$$

Equation 1.6 can be greatly simplified if the rates at which balls are put into or taken out of the box are averaged over the time during which the class demonstration is performed:

$$b(t_{\text{end}}) - b(t = 0) = (\dot{b}_{\text{in}} - \dot{b}_{\text{out}})t_{\text{end}} \tag{1.7}$$

It may seem that this section began with the simple idea of counting balls going into and out of a box and ended in a rather complex equation. Equation 1.7, however, has general utility. The value in creating such generalized equations lies in our ability to then use them for design purposes. Although the design of boxes to hold balls might seem trivial, this knowledge would help the professor plan how many balls to take out and put in based on the number of balls she had initially. If one constraint is that the box can hold only 123 balls, Equation 1.7 can help her determine the acceptable average rates for adding and removing balls every minute. Also, this equation can help ensure that some balls are left in the box during the course of the demonstration.

In the next section, we discuss a more practical use of differential and integral calculus for analyzing data.

1.2 INTERPRETING DIFFERENTIALS AND INTEGRALS: WORLD POPULATION STATISTICS

The world population is a statistic that involves everyone. Figure 1.1 provides the most recent world population data (1), as well as historical data. Two important useful analyses can be conducted with these data using the definitions of derivatives and integrals. The analysis using derivatives draws attention to how the rate of population growth changes with time, while the analysis using integrals illustrates the cumulative impact of the world population on resources since 1 A.D.

To determine the rate of increase for the number of people per time, or dP_{pop}/dt where P_{pop} represents the world population, we can determine the slope of the curve at a particular date by using graphical methods. An easier solution, however, is to fit the data to an equation. Thomas Malthus, an English clergyman and political economist, predicted that the world's population would grow more rapidly than the food supply. Malthus' law, therefore, states that the rate of population growth is proportional to population:

$$\frac{dP_{\text{pop}}}{dt} = aP_{\text{pop}} \tag{1.8}$$