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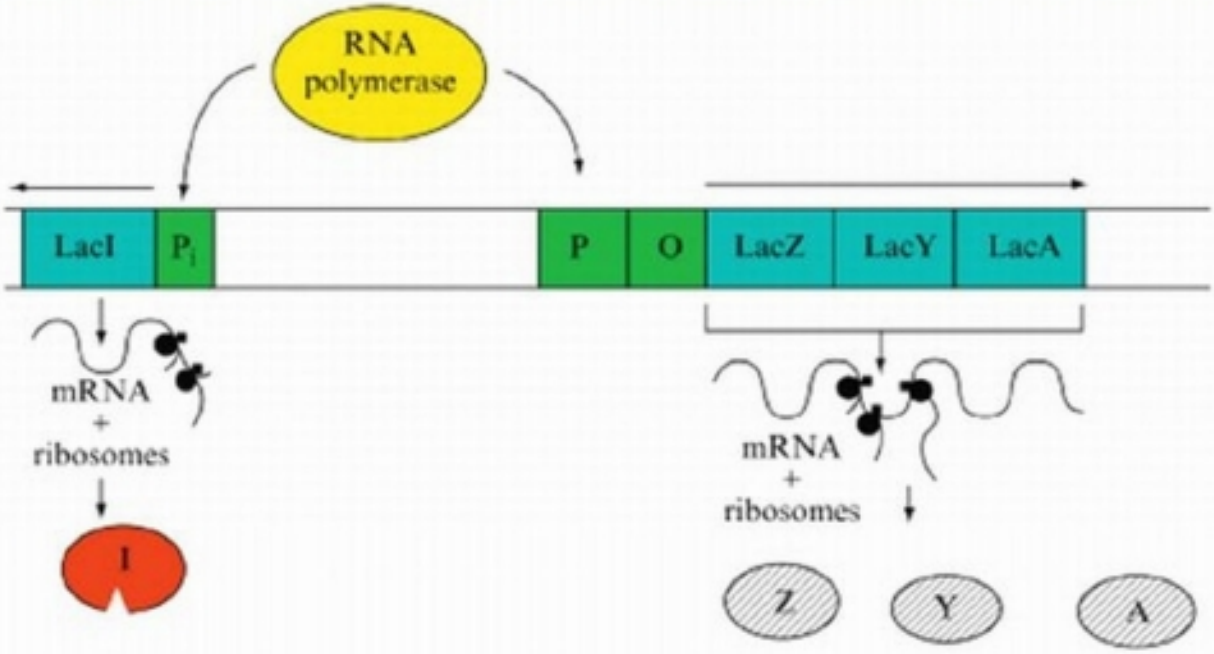

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Essential Numerical Computer Methods

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30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA
32 Jamestown Road, London NW1 7BY, UK
Linacre House, Jordan Hill, Oxford OX2 8DP, UK

Material in the work originally appeared in Volumes 210, 240, 321, 383, 384, 454, and 467 of *Methods in Enzymology* (1992, 1994, 2000, 2004, 2009, Elsevier Inc.)

ISBN: 978-0-12-384997-7

For information on all Academic Press publications
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Printed and bound in USA

10 11 12 10 9 8 7 6 5 4 3 2 1

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PREFACE

Many of the chapters within this volume were first published almost two decades ago. Since then, these basic algorithms have not changed. However, what has changed is the huge increase in computer speed and ease of use along with the corresponding decrease in the costs. The increase in computer speed has made the use of some algorithms common that were almost never used in biochemistry laboratories two decades ago. During the past two decades, the training of the majority of senior M.D.s and Ph.D.s in clinical or basic disciplines at academic research and medical centers has not kept pace with advanced coursework in mathematics, numerical analysis, statistics, or computer science.

Nevertheless, the use of computers and computational methods has become ubiquitous in biological and biomedical research. One primary reason is the emphasis being placed on computers and computational methods within the National Institutes of Health (NIH) Roadmap. Another factor is the increased level of mathematical and computational sophistication among researchers, particularly among junior scientists, students, journal reviewers and NIH Study Section members. Yet another is the rapid advances in computer hardware and software that make these methods far more accessible to the rank-and-file members of the research community.

There exists a general perception that the applications of computers and computer methods in biological and biomedical research are either basic statistical analysis or the searching of DNA sequence data bases. While these are important applications, they only scratch the surface of the current and potential applications of computers and computer methods in biomedical research. The various chapters within this volume include a wide variety of applications that extend far beyond this limited perception. The chapters within this volume are basically in chronological order of original publication in Methods in Enzymology volumes 210, 240, 321, 383, 384, 454, and 467. This chronological order also provides a general progression from basic numerical methods to more specific biochemical and biomedical applications.

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CHAPTER 1

Use of Least-Squares Techniques in Biochemistry[1]

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I. Update
II. Introduction
III. Nonlinear Least-Squares
IV. Why Use NLLS Analysis Procedures?
V. When to Use NLLS Analysis Procedures
  A. Assumption 1: No Experimental Uncertainty
  B. Assumption 2: Gaussian Uncertainties
  C. Assumption 3: Independent Observations
  D. Assumption 4: Large Number of Data Points
VI. What Confidence Can Be Assigned to Results of NLLS Analysis?
VII. Conclusions
References

I. Update

This chapter was originally published (Johnson, 1992) under the title "Why, When, and How Biochemists Should Use Least-Squares" and this descriptive title clearly states the purpose of this chapter. This chapter emphasizes the underlying assumptions and philosophy of least-squares fitting of nonlinear equations to experimental data.

In the last two decades, the basic algorithms have not changed. Most are based on the Gauss-Newton algorithm. However, what has changed is the huge increase

[1] This article was originally published as "Why, When, and How Biochemists Should Use Least Squares" in *Analytical Biochemistry*, Volume 206 (1992). Reprinted with permission from Academic Press.

DOI: 10.1016/B978-0-12-384997-7.00001-7

in computer speed and ease of use along with the corresponding orders of magnitude decrease in cost. These factors have combined to make the least-squares fitting of nonlinear equations to experimental data a common task in all modern research laboratories. Many of the available software packages will perform the required least-squares fits, but fail to address subjects such as goodness-of-fit, joint confidence intervals, and correlation within the estimated parameters. This chapter provides an introduction to these subjects.

The increase in computer speed has made some algorithms possible that were almost never used in biochemistry laboratories two decades ago. One such algorithm is the use of bootstraps (Chernick, 1999) for the determination of parameter confidence intervals. If this chapter were being written today (Johnson, 2008), I would have stressed their use.

II. Introduction

There are relatively few methods available for the analysis of experimental data in the biochemical laboratory. Graphical methods and least-squares (regression) methods are by far the most common. Unfortunately, both classes of analysis methods are commonly misused. The purpose of this chapter is to explain why, when, and how a biochemist should use least-squares techniques and what confidence can be assigned to the resulting estimated parameters.

One classic group of biochemical experiments involves measuring the response of a system to an external perturbation. Temperature-jump experiments perturb the chemical equilibrium of a solution by rapidly increasing the temperature of the solution and subsequently monitoring an observable, like absorbance, as a function of time. Here, the absorbance is the observable (i.e., the variable) that is dependent on the experiment, and time is the variable that can be independently controlled by the experimental protocol.

Another example of this general class is the ligand-binding titration experiment. The investigator measures the amount of a ligand bound (the dependent variable) by fluorescence, absorbance, or radioactive counting. To do so, the investigator titrates the ligand concentration (the independent variable). Note that the ligand concentrations might be either the total or the free ligand concentration, depending on the experimental protocol.

In these examples, and all others of this class, the investigator has measured a response caused by a perturbation of the system. The next step is to obtain the parameters of the system that characterize the chemical processes by ''analyzing'' the data. In the above examples, these parameters, the desired answers, might be the relaxation half-lives or macroscopic binding constants. Alternatively, the desired parameters might be the microscopic forward and reverse reaction rates of the biochemical system.

Analysis of these data requires that the biochemist assume a mathematical relationship between the observed quantities, the dependent variables, and the

independent variables. This relationship is the fitting function. In the past, analysis of relaxation experiments, such as temperature jump, assumed that the mathematical relationship was a single exponential decay. Based on this assumption, the investigator would commonly perform a logarithmic transformation of the dependent variable and create a graph of, for example, the logarithm of absorbance as a function of time. If the original assumption of a single exponential process is correct, then the graph will be a straight line with a slope related to the relaxation rate of the chemical process. A single class of binding sites is a common assumption for ligand binding experiments. This, in turn, implied that the mathematical relationship for the amount bound as a function of free, or unbound, ligand was a rectangular hyperbola. A consequence of this mathematical relationship is that various transformations of the data, such as a Scatchard plot, will yield a straight line with a slope related to the binding affinity. It was quickly realized that the assumption of a single biochemical process was generally not valid. Generalizations of these graphical procedures for consideration of multiple processes were attempted but with generally poor results.

The desired result of the analysis of any experimental data is to obtain the set of parameters of the biochemical reaction with the maximum likelihood (ML), highest probability, of being correct. This is the most critical lesson of this review. We do not care what the slope of a log plot is; we want the relaxation rate constants with the ML of being correct. We do not care what the slope of a Scatchard plot is; we want the ligand binding constants with the highest probability of being correct.

Does a Scatchard plot, or a logarithmic plot, yield parameter values with the ML of being correct? Generally, they do not (Johnson and Frasier, 2010). These methods are mathematically correct if the experimental data contain no experimental uncertainties. They fail because they do not correctly consider the experimental uncertainties present in all experimental data. Why then were these graphical methods developed and commonly reported? The evaluation of the parameters with the ML of being correct requires a high-speed digital computer to perform the calculations, but the development of the graphical methods occurred before high-speed digital computers were commonly available to the biochemical researcher. At that stage graphical methods were the only practical ones for the analysis of the experimental data. Should these methods still be used? They may aid the investigator in visualizing the data, but the methods should not be used for determining parameter values.

The most common alternative to graphical analysis in use in the biochemical laboratory today is nonlinear least-squares (NLLS). To use a NLLS method, an investigator must assume a functional form for the mathematical relationship between the dependent and independent variables of the experiments in terms of a series of desired parameters. This functional form is not restricted to a form that can be transformed into a straight line, as with the graphical procedures. NLLS is a process of ''fitting'' the experimental data to almost any functional form by evaluating an optimal set of parameters for the fitting function.

Does a NLLS method yield parameter values with the highest probability of being correct? It may, if the NLLS analysis procedure is correctly formulated and