

Statistical Methods in Analytical Chemistry

Second Edition

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Statistical Methods in Analytical Chemistry

CHEMICAL ANALYSIS

A SERIES OF MONOGRAPHS ON
ANALYTICAL CHEMISTRY AND ITS APPLICATIONS

Editor
J. D. WINEFORDNER

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Statistical Methods in Analytical Chemistry

Second Edition

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To our wives, Therese and Edith, respectively, who granted us the privilege of “book” time, and spurred us on when our motivation flagged.

To our children, Lukas and Irène, respectively, and Sabrina and Simona, who finally have their fathers back.

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PREFACE

This book focuses on statistical data evaluation, but does so in a fashion that integrates the question—plan—experiment—result—interpretation—answer cycle by offering a multitude of real-life examples and numerical simulations to show what information can, or cannot, be extracted from a given data set. This perspective covers both the daily experience of the lab supervisor and the worries of the project manager. Only the bare minimum of theory is presented, but is extensively referenced to educational articles in easily accessible journals.

The context of this work, at least superficially, is quality control in the chemical and pharmaceutical industries. The general principles apply to any form of (chemical) analysis, however, whether in an industrial setting or not. Other readers need only to replace some phrases, such as “Health Authority” with “discriminating customer” or “official requirements” with “market expectations,” to bridge the gap. The specifically chemical or pharmaceutical nomenclature is either explained or then sufficiently circumscribed so that the essentials can be understood by students of other disciplines.

The quality and reliability of generated data is either central to the work of a variety of operators, professionals, or managers, or is simply taken for granted. This book offers insights for all of them, whether they are mainly interested in applying statistics (cf. worked examples) or in getting a feeling for the connections and consequences (cf. the criminalistic examples). Some of the appended programs are strictly production-oriented (cf. *Histo*, *Similar*, *Data*, etc.), while others illustrate an idea (cf. *Pedigree*, *SimCal*, *OOS-Risk*, etc.).

When the first edition was being prepared in the late 1980s, both authors worked out of cubicles tucked into the corner of an analytical laboratory and were still very much engaged in hands-on detail work. In the intervening years, responsibilities grew, and the bigger the offices got, the larger became the distance from the work bench. Diminishing immediacy of experience may be something to bemoan, but compensation comes in the form of a wider view, i.e., how the origin and quality of the samples tie in with the product’s history and the company’s policies and interests.

Life at the project and/or line manager level sharpens awareness that

“quality” is something that is not declared, but designed into the product and the manufacturing process. Quality is an asset, something that needs management attention, particularly in large, multinational organizations. Laboratory instrumentation is largely computerized these days, a fact that certainly fosters standardization and method transfer across continents. The computational power makes child’s play of many an intricate procedure of yesteryear, and the excellent report-writing features generate marvels of GMP-compliant documentation (GMP = Good Manufacturing Practices). Taken at face value, one could gain the impression that analytical chemistry is easy, and results are inevitably reliable and not worthy of introspection. This history is reflected in the statistically oriented chemical literature: 10–15 years ago, basic math and its computer-implementation were at the forefront; today’s literature seeks ways to mine huge, multidimensional data sets. That numbers might be tainted by artifacts of nonideal chemistry or human imperfection is gradually being acknowledged; the more complex the algorithms, though, the more difficult it becomes to recognize, track, and convincingly discuss the ramifications. This is reason enough to ask for upfront quality checks using simple statistical tools before the individual numbers disappear in large data banks.

In a (laboratory) world increasingly dominated by specialization, the vendor knows what makes the instrument tick, the technician runs the samples, and the statistician crunches numbers. The all-arounder who is aware of how these elements interact, unfortunately, is an endangered species.

Health authorities have laid down a framework of regulations (“GMPs” in the pharmaceutical industry) that covers the basics and the most error-prone steps of the development and manufacturing process, for instance, analytical method validation. The interaction of elements is more difficult to legislate the higher the degree of intended integration, say, at the method, the laboratory, the factory levels, or at the sample, the batch, and the project perspectives. This second edition places even greater emphasis on these aspects and shows how to detect and interpret errors.

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PREFACE, First Edition

Both authors are analytical chemists. Our cooperation dates back to those happy days we spent getting educated and later instructing undergraduates and PhD candidates in Prof. W. Simon's laboratory at the Swiss Federal Institute of Technology in Zürich (ETH-Z). Interests ranged far beyond the mere mechanics of running and maintaining instruments. Designing experiments and interpreting the results in a wider context were primary motives, and the advent of computerized instrumentation added further dimensions. Masses of data awaiting efficient and thorough analysis on the one hand, and introductory courses in statistics slanted toward pure mathematics on the other, drove us to the autodidactic acquisition of the necessary tools. Mastery was slow in coming because texts geared to chemistry were rare, such important techniques as linear regression were relegated to the "advanced topics" page, and idiosyncratic nomenclatures confused the issues.

Having been through despiriting experiences, we happily accepted, at the suggestion of Dr. Simon, an offer to submit a manuscript. We were guided in this present enterprise by the wish to combine the cookbook approach with the timely use of PCs and programmable calculators. Furthermore, the when-and-how of tests would be explained in both simple and complex examples of the type a chemist understands. Because many analysts are involved in quality-control work, we felt that the consequences statistics have for the accept/reject decision would have to be spelled out. The formalization that the analyst's habitual quest for high-quality results has undergone—the keywords being GMP and ISO 9000—is increasingly forcing the use of statistics.

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September 1992*

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INTRODUCTION

Modern instrumental analysis is an outgrowth of the technological advances made in physics and electronics since the middle of this century. Statistics have been with us somewhat longer, but were impractical until the advent of powerful electronic data processing equipment in the late 1960s and early 1970s, and even then remained bottled up in the central computer department.

Chemistry may be a forbidding environment for many nonchemists: there are few rules that link basic physics with the observable world, and typical molecules sport so many degrees of freedom that predictions of any kind inevitably involve gross simplifications. So, analytical chemistry thrives on very reproducible measurements that just scratch the phenomenological surface and are only indirectly linked to whatever one should determine. A case in point: what is perceived as off-white color in a bulk powder can be due to any form of weak absorption in the VIS(ible) range ($\lambda \approx 400\text{--}800\text{ nm}$), but typically just one wavelength is monitored.

For these reasons, the application of statistics in an analytical setting will first demand chemical experience, full appreciation of what happens between start of sampling[§] and the instrument's dumping numbers on the screen, and an understanding of which theories might apply, before one can even think of crunching numbers. This book was written to tie together these aspects, to demonstrate how every-day problems can be solved, and how quality is recognized and poor practices are exposed.

Analytical chemistry can be viewed from two perspectives: the insider sees the subject as a science in its own right, where applied physics, math, and chemistry join hands to make measurements happen in a reliable and representative way; the outsider might see the service maid that without further effort yields accurate results that will bring glory to some higher project.

The first perspective, taken here, revolves around calibration, finding reasons for numbers that are remarkable or out of line in some way, and validation. The examples given in this book are straight from the world of routine quality control and the workhorse instruments found there: gas chromatography (GC), high-pressure liquid chromatography (HPLC), acidity (pH) meters, and the like. Whether we like it or not, this represents analytical "ground truth." The employed statistical techniques will be of the simpler type. No statistical theory can straighten out slips in manufacturing

or sampling. Those lucky enough to have access to high-profile, one-of-a-kind instruments in special settings are a minority that is overrepresented in the literature, which conveys the wrong picture.

The second perspective might be that of the leader of some large project where chemical analyses are just a side issue, where sample numbers are large and chemical niceties might be completely swamped by, say, biological variability; here a statistician will be necessary to make sense of the results in the context of a very complex model. Chemistry is a bit harder to relate to than many other industries in that the measured quantities are often abstract, invisible, and only indirectly linked to what one wants to control.

This book, written by two passionate analysts, treats the application of statistics to analytical chemistry^{1,2} in a very practical manner. A minimum of tools is explained and then applied to everyday, that is, complex situations. The examples should be illuminating to both beginners and specialists from other fields in their quest to evaluate data and make decisions.

What are the circumstances of this decision process? The scheme in Table 1 might serve as an illustration. Every step is fraught with uncertainties and is subject to artifacts.³² Sampling,^{3,6} a weak point for various reasons, is the hinge on which everything else depends: carelessness in this area makes the best intentions meaningless. Lack of maintenance and instrument calibration endangers the relevance of the decisions made. Note that statistics are only part of the picture; the decision process has to be viewed as a coherent whole; a decision can only be passed by taking into account the complex interrelations among the chemical species being consumed and formed, and the legal, economic, scientific, and environmental characteristics of the analytical process.

The sensor only incompletely maps physicochemical reality into an electrical signal that is then subject to signal-conditioning hardware, and the instrument again transforms the individual measurements into time averages, signal areas,¹⁷ or other user-oriented information. Just filtering out noise, strictly speaking, already constitutes an adulteration. The instrument configuration (hard- and software) is to be regarded as just one element that the analyst has to put to use without exceeding its inherent limitations (not necessarily the design specifications quoted in the prospectus!).¹⁵

Thus, one can be far from the ideal world often assumed by statisticians: tidy models, theoretical distribution functions, and independent, essentially uncorrupted measured values with just a bit of measurement noise superimposed. Furthermore, because of the costs associated with obtaining and analyzing samples, small sample numbers are the rule. On the other hand, linear ranges upwards of 1 : 100 and relative standard deviations of usually 2% and less compensate for the lack of data points.

The authors have found the tests and procedures described in Chapters 1