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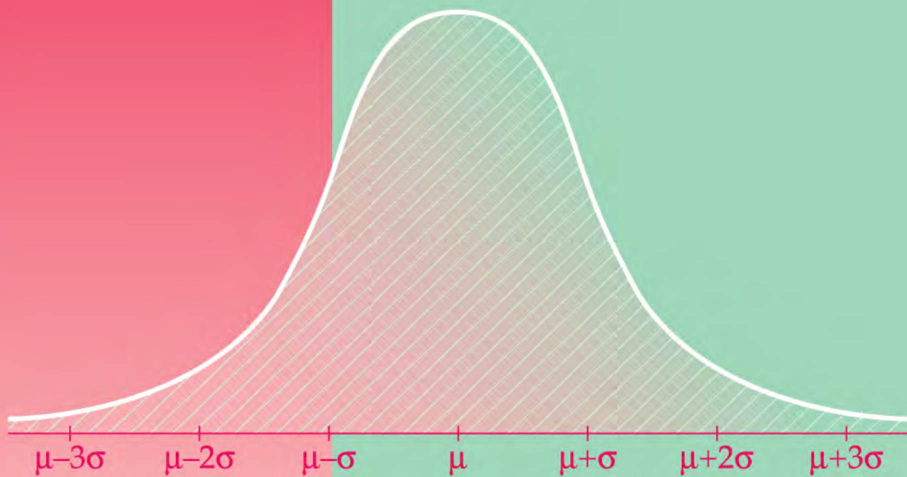

statistics for the quality control chemistry laboratory

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advancing the chemical sciences

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Preface

This book is intended to be a simple, though not simplistic, introduction to the statistical methods that are routinely applied in analytical chemistry Quality Control laboratories. While it is strongly influenced by my experiences of teaching short courses to laboratory scientists in pharmaceutical companies, the ideas are quite general and would find application in virtually every type of analytical chemistry laboratory. I have included data from different application areas, based on a wide range of analytical techniques. I hope, therefore, that the book will have a broad appeal and serve the needs of a large laboratory audience.

The book is oriented towards the needs of analysts working in QC laboratories rather than towards a wider research-oriented readership. Accordingly, it focuses on a small number of statistical ideas and methods and explores their uses in the analytical laboratory. The selected methods are important aids in method development, method validation and trouble-shooting. The book strongly emphasises simple graphical methods of data analysis, such as control charts, which are a key tool in Internal Laboratory Quality Control and which are a fundamental requirement in laboratory accreditation. A large part of the book is concerned with the design and analysis of laboratory experiments. The coverage ranges from the simplest studies, requiring a single system parameter change, to robustness/ruggedness studies, involving simultaneous changes to many system parameters as an integral part of the method validation process. The approach taken focuses on the statistical ideas rather than on the underlying mathematics. Practical case studies are used throughout to illustrate the ideas in action. A short introduction to the eight chapters is given below.

Chapter 1 establishes the statistical terminology which is basic to the description of the quality of analytical results. It introduces the idea of a statistical model (the Normal distribution) as a basis for thinking about analytical data and describes some of the more commonly used measures of analytical precision, which are related to this model.

Chapter 2 is mainly about control charts. The chapter focuses entirely on Shewhart charts, because these are the most widely used and most easily understood charts. Interested readers will be able to develop their knowledge of other charting techniques, having established a sound understanding of the basic material covered here. This approach characterizes the book as a whole. I have chosen to provide an extended discussion, including a detailed case study, of the use of one type of chart, rather than to provide succinct introductions to several different types of chart. The chapter also contains a short introduction to proficiency tests.

Chapter 3 is an introduction to some of the ideas of statistical inference. It covers three main areas: statistical tests, confidence intervals and the determination of sample size. These ideas are fundamental and are developed in various ways in the remaining chapters.

Chapter 4 is an introduction to the statistical aspects of experimental design. First, it builds on the methods introduced in Chapter 3 by showing how statistical tests and the associated confidence intervals may be used to analyze the data generated by designed experiments – the studies are of the simplest type, involving a change to a single aspect of the analytical system. Next it discusses how sample sizes appropriate for such studies can be determined in advance. It then discusses design aspects such as randomization, pairing and appropriate measures of precision. Throughout, there is a focus on validating the assumptions of the simple statistical models that underlie the tests and confidence intervals. Residual plots and tests for Normality are key tools in doing so.

Chapter 5 develops the arguments of Chapter 4 to discuss how complex systems may be investigated using two-level factorial designs. These designs are important tools for method development, method validation and trouble-shooting. Full factorial designs for investigating relatively small numbers of system parameters are discussed in detail. The fractional factorial designs that form the basis of the designs commonly used for robustness/ruggedness testing are then discussed.

Chapter 6 is concerned with the use of regression analysis for modelling relationships between variables. The technique is introduced in the context of stability testing of pharmaceutical products – a case study concerned with the establishment of the shelf life of a drug is described. The application of regression analysis to calibration is then discussed. The use of residual analysis for validating the statistical models is emphasized. Examples are shown of how the commonly encountered problems of non-linearity and changing variability may be detected. Methods for dealing with these problems are then introduced:

weighted least squares to allow for changing response variability and multiple regression to model non-linearity. A short introduction to the fitting of response surfaces is also given.

Chapter 7 extends the discussion of experimental designs. It introduces (fixed effects) Analysis of Variance (ANOVA), which is used to analyze multi-level factorial designs – these are a simple extension of the two-level designs of Chapter 5. In this context, the idea of blocking is discussed–this is an extension of the discussion of paired comparisons, introduced in Chapter 4. Nested or hierarchical designs are then introduced. These designs implicitly underlie the discussion of control charts in Chapter 2 and are also key to the estimation of the various measures of precision discussed in Chapter 1.

Chapter 8 discusses quantitative measures of the quality of measurements produced by a laboratory. The long-standing approach of estimating the repeatability and reproducibility standard deviations of a method by conducting a collaborative inter-laboratory trial is discussed first. This is followed by an introduction to the statistical ideas used in estimating 'measurement uncertainty'. The use of collaborative trial data in the estimation of measurement uncertainty is then discussed. The final section reviews many of the ideas discussed earlier in the book using the framework of a hierarchical statistical model of the measurement process. Sophisticated readers may find this section a useful introductory overview of some of the important issues discussed in the book. Novices would probably find it abstract and unhelpful. Careful study of the rest of the book will, I hope, change this.

I have assumed that virtually everyone working in a technical environment will have access to computers. All the calculations required for this book may be implemented in a spreadsheet, though I would recommend, in preference, use of a validated statistics package. Accordingly, while formulae suitable for hand calculations are presented, the book assumes that calculations will be carried out using a computer, and focuses on the interpretation of the results. The data analyses in the book were carried out using Minitab, but any statistical package might be used for the purpose – the book is not intended to teach Minitab, *per se*.

The book is not a comprehensive account of all the statistical methods that are likely to be of value in the analytical laboratory. If it is successful, it will give the reader a strong grasp of the concept of statistical variation in laboratory data and of the value of simple statistical ideas and methods in thinking about and manipulating such data. I have deliberately limited the range to include only those topics that I have encountered in use in the laboratories with which I have had dealings. Of course, this means that experienced readers will find that topics they consider important are absent, but a line had to be drawn and this seemed a reasonable decision criterion. For some, the omission of any discussion of multivariate statistical methods (chemometrics) will be notable. However, a good understanding of the simple ideas discussed in this book is, in my opinion, a minimum requirement before the more sophisticated methods are likely to be used confidently or correctly. Accordingly, I have preferred to focus the discussion on the simpler ideas.

Acknowledgements

My principal debt is obviously to those who developed the statistical ideas discussed in the book. Next, I am indebted to those who taught me these ideas – both in the classroom and through their writing. Of these, the first group is composed of colleagues and former colleagues in Trinity College, Dublin. In particular, I want to single out Professor Gordon Foster, who set up the Department of Statistics, and from whom I learned so much over many years of interaction. I would find it difficult to produce a list of the statistical writing that has most influenced me, though some books are given in the references. However, the writings of Professor George Box would undoubtedly be at the top of any such list. The references in the text list papers from which I learned much about the application of statistical methods to analytical chemistry data. I am conscious of how often the statistical sub-committee of the Analytical Methods Committee of the RSC is listed and, in particular, of the number of times I have made reference to the work of its Chairman, Professor Michael Thompson and his co-workers. Readers will find it profitable to follow-up these references.

This book arises directly out of my teaching in-house short courses in industry. These have covered a wide range of industries and statistical topics and have involved teaching both manufacturing engineers and chemists, and laboratory scientists. All the courses have helped to shape the current book, since the statistical ideas are essentially the same whether the objective is to evaluate, monitor, trouble-shoot or optimize either a manufacturing or an analytical system. Accordingly, I am indebted first to those who commissioned the courses and then to the attendees. I doubt if I have ever taught a short course without learning something from the participants. It would be impossible though to thank by name all those who have influenced me in this way. However, some people who have very directly influenced the book must be thanked.

I am indebted to the following friends, clients and colleagues who have either commissioned courses, provided me with data, or who have clarified analytical chemistry ideas for me. To some I am heavily indebted, but I am grateful to all of them for what they have given me: Jill Ahearne, Norman Allott, Norah Blount, John Bohan, John Buckley, Dorothy Claffey, Margaret Connolly, Marion Cullinane, Martin Danaher, Tom Dempsey, Robert Dunne, Mary English, Lynn Feery, Marion Finn, Jacintha Griffin, Rosemary Hayden, Denise Heneghan, Arlene Hynes, Fintan Keegan, Jim Kelly, Kevin Kinnane, Des McAteer, Ger McCann, Ken McCartney, Kevin McNamara, Michael Metzler, Liam Murphy, John O'Connor, Michael O'Dea, Tom O'Hara, Michael O'Keeffe, Marie O'Rourke, John Prendergast, Joe Rowley, Colette Ryan, Eva Ryan, Tom Ryan, Kevin Shelly and Sarah Tait. Andrew Mullins and Paul McNicholas provided research assistance for which I am grateful. I remember with pleasure many conversations on topics relevant to the book with my former MSc student Joe Vale. My colleague Myra O'Regan, by taking on the headship of the Department of Statistics in Trinity College for six months, allowed me to take sabbatical leave in order to concentrate on finishing the book – I am grateful for her generosity in doing so.

I would like to thank Janet Freshwater, Katrina Turner and the editorial and production staff of the Royal Society of Chemistry for turning what was undoubtedly a difficult typescript into the finished book you are now holding. The book is heavily dependent on data extracted from two analytical chemistry journals, The Analyst and The Journal of the Association of Official Analytical Chemists – I am grateful to the editors for permission to reproduce the data extracted from the articles cited in the references. I am grateful to Martin Danaher and Michael O'Keeffe of the Irish Food Centre for providing me with a copy of Figure 6.29 and to Dr A. Lamberty of the Institute for Reference Materials and Measurements, Belgium, for providing a copy of Figure 1.2. I am grateful to Pearson Education for permission to reproduce Figure 3.15 from the book Statistics for the Life Sciences by Professor Myra L. Samuels.

Two friends deserve special thanks. Jack Doyle of the Irish State Laboratory has been a constant source of information on matters related to analytical chemistry, over many years. He also provided valuable comments on the first draft of Chapter 8. Michael Stuart, as a teacher, colleague and friend has had more influence than anyone else on my thinking about statistics. He read earlier drafts of all the chapters and provided detailed criticisms and helpful suggestions. It is certainly a better book than it would otherwise have been without his many contributions.

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Eamonn Mullins

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