1

BACKGROUND

1.1 INTRODUCTION

For some purposes, qualitative detection of a substance of interest may be sufficient; for example, is there melamine adulterant in milk [1] or ^{210}Po in an ex-spy [2]? In many cases, quantitation of the substance of interest, generally referred to as the analyte, is either desired or required. Three simple examples are as follows:

- What is the total organic content (TOC) in a drinking water specimen?
- What is the Cr^{3+} number density in a ruby laser rod?
- What is the pinene concentration in an air specimen collected in a pine forest?

In each of these cases, what matters is quantitative, since it is already known that all drinking water contains some organic content, every ruby has (and gets its color from) its Cr^{3+} content, and pinene contributes to the fragrance of a pine forest. What matters are the specific numerical concentrations, quantities, or amounts, that is, the quantitative analyte contents. In the drinking water example, unacceptable TOC levels should, politics and costs aside, trigger subsequent decisions and corrective actions.

In science fiction, it is common for instruments to be capable of scanning entire alien planets, and perfectly inventorying everything in them, perhaps in preparation for errorlessly teleporting up everything valuable. The real world is different: the laws of nature are always obeyed and experimental measurements are afflicted with measurement uncertainties. The immediate consequence of the latter is that only estimates of underlying true values may be obtained and these estimates, except by generally unknowable coincidence, do not equal the true values. These limits may be reduced further only if the relevant measurement uncertainties are reduced.

Limits of Detection in Chemical Analysis, First Edition. Edward Voigtman.

Companion Website: www.wiley.com/go/Voigtman/Limits_of_Detection_in_Chemical_Analysis

The elementary theory of detection limits in chemical measurement systems evolved over a century, through the dedicated efforts of many individuals. Based on their collective work, the next several chapters are devoted to the methodic and rigorous development of the concepts of decision level and limit of detection, with emphasis placed on understanding what they are and the purposes they serve. In Chapter 19, the concept of limit of quantitation is finally introduced, thereby completing the classic detection triptych.

1.2 A SHORT LIST OF DETECTION LIMIT REFERENCES

The refereed scientific literature contains hundreds of publications dealing with limits of detection. These attest to the fact that there was not a consensus understanding of chemical analysis detection power for many years. Although the large majority of early papers dealing with detection limits have few further insights to yield, those wishing to judge this for themselves have never had it easier, thanks to Internet availability of many publications and translation software for use with papers in some otherwise inaccessible languages. Accordingly, a lengthy list of early publications will not be presented, but references are provided to a few papers that contain such lists.

The review paper by Belter *et al*. [3] focuses on an historical overview of analytical detection and quantification capabilities and cites work back to 1911. Currie's 1987 book chapter [4] is also a valuable source of early references, as is his classic 1968 publication [5] and his paper in 1999 [6]. Additional papers containing especially relevant references include those of Gabriels [7], Kaiser [8–10], Boumans [11], Linnet and Kondratovich [12], Eksperiandova *et al*. [13], Mocak *et al*. [14], EPA document EPA-821-B-04-005 [15], and the Eurachem/CITAC Quantifying Uncertainty in Analytical Measurement (QUAM) Guide CG 4 (3rd Ed.) [16]. As well, there are maintained websites where useful lists of relevant publications may be found [17]. Additional references are provided throughout this text and in the Bibliography.

1.3 AN EXTREMELY BRIEF HISTORY OF LIMITS OF DETECTION

In 1947, Kaiser published what might be considered the first paper to deal explicitly with detection limit concepts as they apply to chemical analysis methods [18]. Others followed, including Altshuler and Pasternak [19], but it was the landmark 1968 publication by Currie [5] that marked the true beginning of the modern era of analytical chemistry detection limit theory. Subsequently, Currie tirelessly advocated for the basic precepts articulated in his heavily cited paper. His detection limit schema was based on classical Neyman–Pearson hypothesis testing principles, using standard frequentist statistical methodology. As a consequence, both false positives and false negatives must be taken into consideration. Neither Currie nor Kaiser was the first to recognize the value of considering both types of error: the prior development of receiver operating characteristics, briefly discussed in Chapter 6, clearly proves this. But Currie was the first highly regarded analytical chemist to clearly identify and discuss the issue, and bring it to the attention of practicing analysts.

Implicit in Currie's paper was his belief that a chemical measurement system possessed an underlying true limit of detection, temporarily denoted as L_D, and that this was the fundamental figure of merit that needed to be estimated with minimal, or even negligible, uncertainty. As shown in Chapter 15, it is easy to construct a simple experimental chemical measurement system that possesses an L_D, though this does not prove that every such system must possess an L_D. It does, however, definitively rule out general nonexistence of an L_D [20].

1.4 AN OBSTRUCTION

It might have been expected that Currie, or one of his contemporaries, would have rather quickly arrived at the results to be presented in subsequent chapters, for example, Chapters 7–14. Unfortunately, as every scientist knows only too well, scientific progress is far from a clean, linear progression. It actually evolves by creeps and jerks, many mistakes are made, and there is often no obvious way forward. Worse still, correcting mistakes may be a lengthy process even when the facts are incontrovertible. As it happened, a major problem arose only 2 years after Currie's paper: Hubaux and Vos [21] published an influential paper that effectively sidetracked Currie's program.

Hubaux and Vos' method obtained detection limit estimates by employing standard calibration curves, processed via ordinary least squares, with the customary prediction limit hyperbolas. The statistical methodology they employed was both familiar and entirely conventional. Not surprisingly, this led to a long period where very little progress was made because, with the notable exception of Currie, the experts at the time thought the matter was largely settled. A perfect example was provided in 1978 by Boumans, who confidently declared, as the lead sentence in his detection limit tutorial [22]: "Are there any problems left to be solved in defining, determining and interpreting detection limits?" His immediate answer was "Fundamentally most problems have been adequately discussed in the literature." It is now known that his answer was incorrect and that the Hubaux and Vos method, discussed in Appendix E, was an inadvertent obstruction. But this was not at all obvious at the time and there appeared to be no reason to doubt Boumans' expert opinion.

1.5 AN EVEN BIGGER OBSTRUCTION

Early in 1988, Currie published a lengthy book chapter [4] in which he came close to solving the problem of how to instantiate his 1968 detection limits schema. Tellingly, the Hubaux and Vos paper and method, which had absolutely no need for either true underlying detection limits or explicit hypothesis testing, was neither mentioned in Currie's book chapter nor listed in the references at its end. However, a more important event preceded Currie's book chapter by a few months: Clayton *et al*. published their highly influential detection limits paper [23]. Their work was based on the "statistical power" of the t test and used critical values of the noncentrality parameter, δ, of the noncentral t distribution. These critical values are specific numerical values of the δ parameter, and, for brevity below, they are generically denoted by δ_{critical}.

Currie adopted the δ_{critical} method and promoted it as the underlying basis of the analytical detection limits methodology currently sanctioned by various standards organizations, for example, the International Standards Organization (ISO) and the International Union of Pure and Applied Chemistry (IUPAC). Currie apparently felt that the δ_{critical} method was the key to correctly bringing to fruition his 1968 detection limits schema, but an insurmountable problem eventually surfaced: in 2008, the δ_{critical} method was proven to be irrelevant to detection limits [24, 25].

This quite unexpected finding is discussed in detail in Chapter 17, which, among other things, shows how to perform simple *Mathematica*® simulations to verify the result. Unlike German standard DIN 32645 [26], the ISO and IUPAC official detection limit protocols are directly based upon the δ_{critical} method, thereby rendering them irrelevant. Accordingly, it is the primary purpose of this book to demonstrate the rigorous theory upon which Currie's detection limit schema is correctly founded and to demonstrate, via both properly designed experiments and comprehensive computer simulations, that it works as predicted.

1.6 WHAT WENT WRONG?

As will be seen in progressing through the chapters, several unfortunate mistakes were made between 1987 and 2008. First, what many found irresistibly appealing about the δ_{critical} method was that it appeared to circumvent the problem of true detection limits, which are errorless, being unobtainable from experimental data. In contrast, with reference to the Hubaux and Vos method, Currie stated [27, p. 163]

> The major drawback with the method is that it produces 'detection limits' that are *random variables*, as acknowledged in the original publication of the method ([27], p. 850), different results being obtained for each realization of the calibration curve, even though the underlying measurement process is fixed. N.B.: The italics and single quotation marks are those of Currie [27] and [27] in the quotation is [21] here.

In this, Currie was incorrect: the Hubaux and Vos method cannot legitimately be criticized for producing experimental detection limits, that is, estimates, from experimental data. The method can, however, be found to be disadvantageous for other reasons, as per Appendix E.

The second mistake was the assumption that the δ_{critical} method's true theoretical detection limit was unique. In fact, there is *another* true underlying detection limit, known long before 1987, that is always fundamentally superior. Currie knew this at least as far back as 1968: with suitable definition of "k," it is simply his eqn 5b [5]. Failure to recognize that there could be two true underlying detection limits was ultimately due to the baseless assumption that there was only one possible hypothesis applicable to the testing of false negatives. Indeed, Clayton *et al*. explicitly state two hypotheses applicable to testing false positives, yet, with regard to false negatives, they state [23, p. 2507].

> Other techniques involving similar assumptions, such as those cited previously, purport to provide fixed type I and type II error rates but avoid the use of noncentral *t* probabilities. As pointed out by Burrows, the derivation of such methods must include some type of logical or mathematical fallacy;

In the quotation, both Burrows and Clayton *et al*. were incorrect: the current problem of irrelevant officially sanctioned detection limit methodology could have been entirely avoided if the two relevant false negative hypotheses had been carefully formulated, articulated, and then tested. This is demonstrated in Chapter 17.

The third mistake involved the failure to properly test the δ_{critical} method. Indeed, it is still quite common to encounter just the opposite, that is, experimental "validation" via overly complicated experiments having only marginal demonstrated compliance with the assumptions upon which the theory was predicated. Even the experiments reported by Clayton *et al*. [23] were not in compliance with their proposed method, as discussed in Chapter 17.

At minimum, any posited detection limit theory should be rigorously tested via both real experiments, which are properly designed and instantiated, and via comprehensive computer simulations. Yet, in the two decades between 1987 and 2008, detection limit computer simulations were rarely performed. In Chapter 17, computer simulations demonstrate that the δ_{critical} method is a red herring and an opportunity is provided to verify this result for oneself.

The above trio of missteps seriously obstructed progress in correctly instantiating Currie's 1968 detection limits schema. Given the typically long time constant required for science to self-correct, it is unknown when matters may be set straight, but it is hoped that this book will accelerate the process. Otherwise, Azoulay *et al*. [28] may be proven correct.

1.7 CHAPTER HIGHLIGHTS

This chapter began by briefly stating the obvious case for making quantitative measurements. Then a few of the relevant older literature references were provided, followed by an extremely concise history of analytical detection limit progress, stagnation, and obstructions, with a short discussion of how the obstructions arose.

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