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Article *in* Nuclear Instruments and Methods in Physics Research Section A Accelerators Spectrometers Detectors and Associated Equipment · June 2015

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Calculation of the detection limit in radiation measurements with systematic uncertainties

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ARTICLE INFO

Available online 12 January 2015

Keywords:
Detection limit
Characteristic limits
MDA
ISO 11929

ABSTRACT

The detection limit (L_D) or Minimum Detectable Activity (MDA) is an *a priori* evaluation of assay sensitivity intended to quantify the suitability of an instrument or measurement arrangement for the needs of a given application. Traditional approaches as pioneered by Currie rely on Gaussian approximations to yield simple, closed-form solutions, and neglect the effects of systematic uncertainties in the instrument calibration. These approximations are applicable over a wide range of applications, but are of limited use in low-count applications, when high confidence values are required, or when systematic uncertainties are significant. One proposed modification to the Currie formulation attempts account for systematic uncertainties within a Gaussian framework. We have previously shown that this approach results in an approximation formula that works best only for small values of the relative systematic uncertainty, for which the modification of Currie's method is the least necessary, and that it significantly overestimates the detection limit or gives infinite or otherwise non-physical results for larger systematic uncertainties where such a correction would be the most useful. We have developed an alternative approach for calculating detection limits based on realistic statistical modeling of the counting distributions which accurately represents statistical and systematic uncertainties. Instead of a closed form solution, numerical and iterative methods are used to evaluate the result. Accurate detection limits can be obtained by this method for the general case.

1. Introduction

The detection limit (L_D) or Minimum Detectable Activity (MDA) is an *a priori* estimate of measurement sensitivity. A well-established concept in the field of ionizing radiation measurements, it is based on straightforward principles of classical hypothesis testing as originally set out by L.A. Currie in his landmark 1968 paper on the subject [1]. In the past, calculations of the detection limit have almost universally relied on the asymptotic Gaussian approximation to Poisson counting statistics; they have also typically neglected to treat systematic uncertainties, such as those related to calibration parameters, which can nevertheless be significant components of the total measurement uncertainty and thus important contributors to an evaluation of measurement sensitivity.

One recent attempt to update the detection limit formalism was described in the ISO 11929:2010 standard [2], which sought to set the problem of detection limits on a rigorous Bayesian theoretical footing, while also extending the standard method to incorporate systematic uncertainties in calibration parameters. A shortcoming of that method is that it fails to make use of significant prior information available in the form of obvious physical constraints on the measurement problem. As a result inappropriate assumptions of Gaussian behavior are used to approximate the posterior distributions of the calibration parameters. The result is an approximation formula that works best only for small values of the relative systematic uncertainty, for which such a modification of Currie's method is the least necessary. For larger systematic uncertainties, for which such a correction would be the most useful, the ISO 11929 formula significantly overestimates the detection limit and can return infinite or otherwise non-physical results [3].

In contrast to that approach we have developed a method following from Currie's original hypothesis testing definition, which accurately accounts for systematic uncertainties of any magnitude through physically realistic statistical modeling of counting distributions and calibration parameter uncertainties. Bayesian inference is used to determine the forms of the probability distributions, utilizing relevant prior information including physical constraints and the explicitly Poisson nature of the counting experiment itself.

This new method provides the same improvements over the traditional Currie approach that were intended by the ISO 11929 standard, but avoids the problems of infinities and over-estimates that can be generated by the explicit formulas prescribed there.

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http://dx.doi.org/10.1016/j.nima.2015.01.005
0168-9002/

This makes the new method ideally suited for evaluating detection limits (or MDAs) for in vivo, in situ, waste disposition, or other similar applications where large relative calibration uncertainties are common. A detailed development of the calculational method is presented, and results are calculated and compared with both the traditional Currie approach and that of ISO 11929.

2. Definitions

Following Currie, we define the detection limit as "the 'true' net signal level which may be *a priori* expected to lead to detection" [1]. Signal detection is here defined in terms of a traditional hypothesis testing problem: the null hypothesis, H_0, describes the possibility that there is no signal present in our future measurement and that all counts observed will be due only to a background process. It is assumed that some estimate $\hat{\mu}_b$ of the mean of the background process and an uncertainty $\sigma(\hat{\mu}_b)$ in that estimate have previously been obtained, or will be obtained directly from the future measurement itself.

The manner in which the background estimate and its uncertainty are obtained can vary depending on the type of measurement under consideration. In single-channel measurements, as are often done in alpha and beta counting applications, a non-radioactive "blank" count is often performed for this purpose prior to the sample assay. In multichannel spectroscopic measurements, it is common to specify "sidecar" regions on either side of the photopeak region of interest (ROI) which can be used to estimate the continuum counts beneath the peak. Because the count times of blank and sample measurements may differ (or analogously the widths of the peak and the combined sidecar regions may differ) a scale factor may be applied to estimate the sample background, with the result that the pure Poisson relationship $\sigma^2(\hat{\mu}_b)=\hat{\mu}_b$ does not hold. More complicated techniques such as spectral unfolding are also common, and will also tend to violate assumptions of purely Poisson statistical behavior.

To help decide whether or not a detection has occurred, the critical level L_C is defined as the smallest number of counts m such that the probability of obtaining m or fewer counts the experiment is greater than or equal to $(1-\alpha)$ if H_0 is true; α is the probability of a Type I error (i.e. a false detection). We can express this in mathematical form as

$$\tilde{L}_C \equiv \min\left\{ m : (1-\alpha) \le \sum_{b=0}^{m} \Pr(b|H_0) \right\} \tag{1}$$

where $\Pr(b|H_0)$ is the *a priori* distribution of the number of background counts b according to the null hypothesis. Detection occurs when the observed count equals or exceeds the critical level. The quantity $(1-\alpha)$ is called the significance of the detection test. The standard deviation of the *a priori* background distribution is denoted as σ_0; we expect it to encompass both the uncertainty in the true mean background and the usual Poisson counting fluctuations about that mean.

Here we have differed slightly from Currie's convention by defining the critical level in terms of the total counts observed; Currie defined it in terms of the net count observed after subtracting the expected (mean) background. This notational difference simplifies the mathematics somewhat for the general non-Gaussian case which we address in later sections.

The second hypothesis is the test or alternate hypothesis, H_1, which describes the possibility that the observed counts are due to a combination of the background process and some signal process which is the goal of the experiment to detect. The *a priori* probability distribution for observing g gross counts under the alternate hypothesis we denote as $\Pr(g|H_1,\mu_s)$, where we have made explicit that the mean of the signal process, μ_s, is one of the parameters of the distribution. The detection limit is then defined as the value of the mean of the signal process such that the probability under H_1 of obtaining gross counts g less than critical level is equal to some value β, the probability of a Type II error (i.e. a false negative result):

$$L_D \equiv \mu_s : \beta = \sum_{g=0}^{\tilde{L}_C} \Pr(g|H_1,\mu_s). \tag{2}$$

The quantity $(1-\beta)$ describes the confidence of detection under H_1.

For Currie, the detection limit and the critical level are both defined in terms of counts at the detector. The critical level is thus properly restricted to take on only non-negative integer values. The detection limit, since it is represents the mean count rather than an observed value, may take real values but must still be non-negative. Both the background and gross counting distributions are discrete, and must be normalized on the interval from zero to infinity. Eqs. (1) and (2) completely define the detection limit problem, in the most general way possible consistent with both Currie's original formulation and the obvious natural constraints of the radiation measurement problem. Evaluating the detection limit is in principle a simple matter of selecting the correct value of the mean signal necessary to satisfy Eq. (2).

A commonly used quantity closely related to the detection limit is the Minimum Detectable Activity (MDA), which is defined in terms of activity A present in the sample. The equivalent equation to (2) for defining the MDA can be written as

$$\mathrm{MDA} \equiv \left\{ A : \beta = \sum_{g=0}^{\tilde{L}_C} \Pr(g|H_1,A) \right\} \tag{3}$$

which can be evaluated by recognizing that the mean net signal is related to the activity by a calibration factor ν:

$$\mu_s = \nu A. \tag{4}$$

The calculation of the calibration factor and its uncertainty will differ by application. As an example, consider the case of a simple spectroscopic measurement in which the activity A is determined from a measured net peak area N, a previously measured detection efficiency ε at the energy of interest, the assay counting time T, and a branching ratio or gamma-ray yield Y which is usually obtained from published nuclear data tables:

$$A = \frac{N}{\varepsilon T Y}. \tag{5}$$

The calibration factor in this case is the quantity $\nu=\varepsilon TY$, and its relative uncertainty is typically evaluated as

$$\frac{\sigma^2(\nu)}{\nu} = \frac{\sigma^2(\varepsilon)}{\varepsilon} + \frac{\sigma^2(Y)}{Y} \tag{6}$$

where is has been assumed, as is most often the case, that the uncertainty in the count time is so small that it can be ignored.

It is worth noting that the ISO standard 11929(2010) [2] conflates the concepts of detection limit and MDA by calculating the detection limit directly in units of activity present in the sample. We find it preferable to maintain the distinction between the two.

3. Solutions in the Gaussian limit

Approximate solutions to the detection limit or MDA are readily obtained by representing both the background and gross counting distributions described above with Gaussian distributions. The conditions defined by (1) and (2) or (3) are diagrammed for the Gaussian limit in Fig. 1.

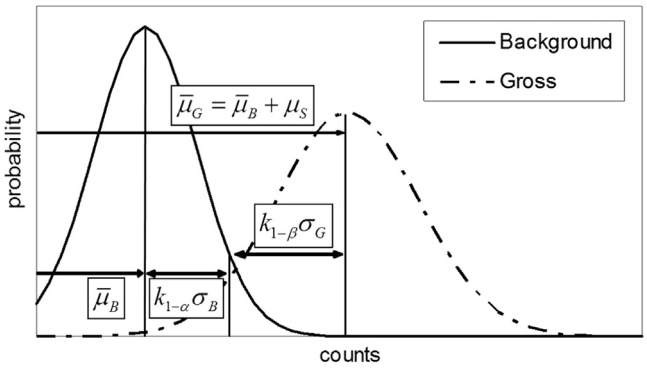

Fig. 1. Hypothesis testing relationships in Gaussian approximation.

As detailed in [3], in the Gaussian limit these conditions describe a quadratic equation for the MDA having the solution:

$$\mathrm{MDA} = \frac{-b+\sqrt{b^2-4ac}}{2a}, \tag{7}$$

where the parameters are

$$a = \left(1 - k_{1-\beta}\frac{\sigma_\nu^2}{\nu^2}\right) \tag{8}$$

$$b = -\left(2k_{1-\alpha}\sigma_0 - k_{1-\beta}^2\right)\nu \tag{9}$$

$$c = \left(k_{1-\beta}^2 - k_{1-\alpha}^2\right)\sigma_0^2\nu^2. \tag{10}$$

In these expressions,

- $\sigma_0 = \sqrt{\hat{\mu}_b + \sigma^2(\hat{\mu}_b)}$ is the standard deviation of the *a priori* background distribution,
- $\hat{\mu}_b$ is a previous estimate of the mean background,
- $\sigma(\hat{\mu}_b)$ is the uncertainty in the estimate of the mean background.

This is the general form of the solution obtained by the ISO 11929 method. If the uncertainty on the calibration factor in these equations is taken to be zero, then this is identical to the traditional Currie MDA. Setting the calibration factor to unity, with zero uncertainty, gives the Currie detection limit in counts. For the general ISO 11929 case, we observe that the quadratic parameter a goes to zero when the relative uncertainty in the calibration factor is equal to $1/k_{1-\beta}$, producing a non-physical pole in the calculated MDA, which is shown in Fig. 4.

4. The statistical modeling solution: a robust method for the general case

The use of the Gaussian approximation in the ISO 11929 MDA is valid when the uncertainties of all the relevant parameters are small compared to their estimated values, but strictly speaking it violates key physical constraints of the measurement problem under consideration: it permits non-zero probabilities for observing negative counts, as well as non-zero probabilities for negative values of the calibration factor. This becomes problematic when parameter uncertainties are significant.

To avoid these difficulties, we construct probability distributions based on true Poisson counting behavior and plausible modeling of the uncertainties in imperfectly known model parameters. Once the distributions are obtained, the MDA can be evaluated numerically in software. The implementation is straightforward: according to Eq. (1), the background distribution is summed up to the desired significance level to locate L_C. The activity A is then numerically optimized to solve Eq. (3), for example using Newton's method.

4.1. The background distribution

The *a priori* background distribution represents future counts from a Poisson process for which we have an estimate $\hat{\mu}_b$ of the mean, with some uncertainty $\sigma(\hat{\mu}_b)$. This distribution is constructed as a Poisson distribution averaged over all possible values of the true mean, weighted by a suitable likelihood function for the true mean value given our estimate and its uncertainty:

$$\Pr(b\,|\,\hat{\mu}_b, \sigma(\hat{\mu}_b)) = \int_{\mu_b=0}^{\infty} \frac{\mu_b^b}{b!} e^{-\mu_b} \Pr(\mu_b\,|\,\hat{\mu}_b, \sigma(\hat{\mu}_b))\, \mathrm{d}\mu_b. \tag{11}$$

The appropriate weighting function is given by the Bayesian posterior distribution for the inferred mean of a Poisson distribution, assuming a uniform prior, which is the Gamma distribution:

$$\Pr(\mu_b\,|\,\hat{\mu}_b, \sigma(\hat{\mu}_b)) = T\frac{(\mu_b T)^n}{\Gamma(n+1)} e^{-\mu_b T}. \tag{12}$$

The parameters n and T are related to the estimated mean and its uncertainty by

$$n = \frac{\hat{\mu}_b^2}{\sigma^2(\hat{\mu}_b)} + 1 \tag{13}$$

and

$$T = \frac{\hat{\mu}_b}{\sigma^2(\hat{\mu}_b)}. \tag{14}$$

Using (12), the integral over the unknown true mean background in (11) evaluates to

$$\Pr(b\,|\,\hat{\mu}_b, \sigma(\hat{\mu}_b)) = \frac{1}{(1+T)^b}\left(\frac{T}{1+T}\right)^{n-1} \frac{\Gamma(b+n-1)}{\Gamma(b+1)\Gamma(n-1)}. \tag{15}$$

The standard deviation of this distribution has the expected form of Currie's σ_0:

$$\sigma(b) = \sqrt{\hat{\mu}_b + \sigma^2(\hat{\mu}_b)} = \sigma_0. \tag{16}$$

The derivation of these formulas can be found in [4] for a specific application of spectroscopic ROI analysis, where they were expressed in terms of raw sidecar-region counts and scaling factors. They have been reparametrized for generality here in terms of the estimated background and its uncertainty.

Some examples of the *a priori* background distribution (15) are shown in Fig. 2.

Each curve shown has an estimated mean of 20 counts, with uncertainties on the estimated mean varying from 0% (pure Poisson) to 50%. The deviation from Gaussian behavior for a poorly known background is evident in the asymmetry and elevated tails of the

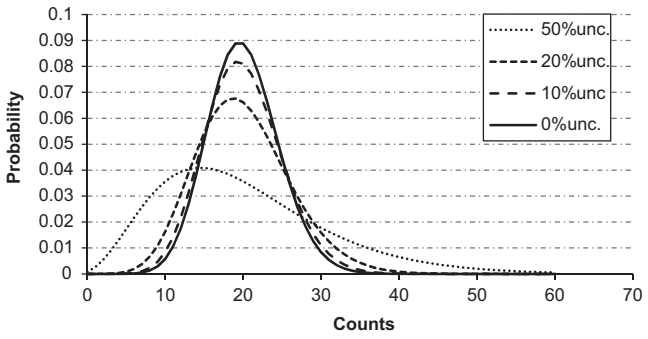

Fig. 2. Examples of the *a priori* background distribution with different uncertainties in the estimated mean value.

distributions, and in the fact that even at 50% uncertainty on the mean, there is no probability of negative counts.

4.2. The gross count distribution

The *a priori* distribution of gross counts in a future measurement under the alternate hypothesis is given by the sum of all possible ways to obtain g counts from the combination of the background and the signal processes:

$$\Pr(g|H_1) = \sum_{b=0}^{g} \Pr(b|H_0) \times \Pr(s = g - b|H_1). \quad (17)$$

The background distribution $\Pr(b|H_0)$ here is the same given in (15).

We model the signal process by a Poisson distribution with mean $\mu_s = \nu A$. The calibration factor ν is imperfectly known, so that we have only an estimate $\hat{\nu}$ with uncertainty $\sigma(\hat{\nu})$ and we must average over all possible true values as before:

$$\Pr(s|A, \hat{\nu}, \sigma(\hat{\nu})) = \int_{\nu=0}^{\nu_f} \frac{(\nu A)^s}{s!} e^{-\nu A} \Pr(\nu|\hat{\nu}, \sigma(\hat{\nu}))\, d\nu. \quad (18)$$

Here we include an upper limit of integration, ν_f, since in some cases the calibration factor may be constrained, for example to values between zero and unity. If there is no upper constraint, we let $\nu_f \to \infty$.

Unlike the background distribution, there is no one obviously correct weighting distribution to use to model the uncertainty in the calibration factor. Plausible arguments could be made for a number of different choices, depending on the factors contributing to the uncertainty. We consider a few of these.

- The Beta distribution, the Bayesian posterior for the mean of a binomial distribution, is a reasonable choice if the detection efficiency is expected to dominate the calibration uncertainty since detection efficiency is fundamentally a binomial process:

$$\Pr(\nu|\hat{\nu}, \sigma(\hat{\nu})) = \frac{\Gamma(m+2)}{\Gamma(n+1)\Gamma(m-n+1)} \nu^n (1-\nu)^{m-n}. \quad (19)$$

  The parameters n and m are related to the mean and uncertainty of the calibration factor by

$$m = \frac{\hat{\nu} - \hat{\nu}^2}{\sigma^2(\hat{\nu})} - 3 \quad (20)$$

  and

$$n = \frac{\hat{\nu}^2 - \hat{\nu}^3}{\sigma^2(\hat{\nu})} - (\hat{\nu} + 1). \quad (21)$$

  The Beta distribution is appropriate if there are upper as well as lower bounds on the calibration factor (e.g. the efficiency must be a number between zero and one). Note that the Beta distribution places limits on the possible values of the mean and uncertainty, F such that $m \geq n \geq 0$. If the estimated calibration factor and its uncertainty violate these conditions, another distribution must be used.
- The Gamma distribution, given in Eq. (12), is a convenient two-parameter distribution with a lower bound at zero but no upper bound. Since the Gamma distribution is the Bayesian posterior distribution for the mean of a Poisson distribution, it is not a physically unreasonable choice to represent a general uncertainty in the mean of a Poisson process in the absence of a more specific model. With this choice the integral in (18) evaluates to obtain essentially the same form as (15). This is convenient for implementation in software as it significantly reduces the number of intermediate numerical integrations necessary to solve (3) for the MDA.
- The maximum entropy distribution, obtained by maximizing the Shannon–Jaynes entropy of a distribution with known mean and standard deviation and with lower and possibly upper limits, is a truncated Gaussian distribution. The maximum entropy (MaxEnt) distribution is theoretically the preferred distribution in the absence of any physical model of the uncertainty since it imposes the least bias on the solution given the available information [5]. Calculating the Gaussian parameters to achieve the desired mean and standard deviation on the bounded interval is not trivial in the general case, so from an implementation point of view this is less preferable than the previous two options.

Gross counting distributions with net signal means distributed by each of the three methods discussed above are shown in Fig. 3, along with the background distribution for comparison.

The MDA is seen to be fairly insensitive to reasonable choices of calibration uncertainty model: the difference in final MDA value between the three choices is under 0.5%, in the example shown. Because of this, and for ease of calculation, we consider the Gamma distribution to be the first choice for general use in most applications.

The MDA results of our method are compared to those of ISO 11929 and Currie in Fig. 4. For low values of the uncertainty, all methods are in good agreement. At moderate uncertainties the ISO 11929 result significantly exceeds the MDA calculated by our model. At higher uncertainty values the ISO 11929 MDA is clearly shown to be in error by the infinite and non-physical negative

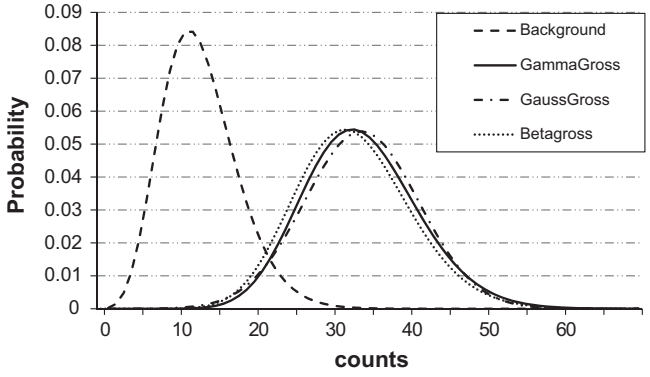

Fig. 3. Background and gross counting distributions. The mean background is 12 ± 3.46 counts. The gross distribution is calculated for signals distributed according to each of the Gamma, Beta, and Gaussian (MaxEnt) distributions with a calibration uncertainty of 15%. The variation in MDAs is $< 0.5\%$ between the three methods.

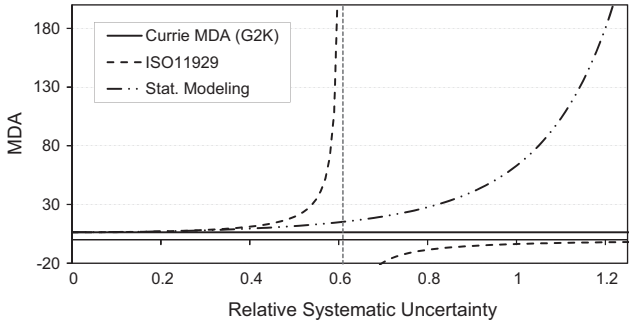

Fig. 4. Comparison of Currie, ISO 11929, and statistical modeling MDA values as a function of relative systematic uncertainty. The position of the pole in the ISO 11929 MDA is indicated by the dashed line.

results it returns, while our method continues to yield consistent values.

5. Conclusions

We have developed a numerical approach to calculating MDA values for radiation measurements which uses realistic statistical modeling to account for the effects of systematic uncertainties in the instrument calibration factors. We believe that this approach provides a universal solution that is suitable for the calculation of MDAs in any number radiation measurement applications, regardless of the size of the systematic uncertainties. However, it is of particular use for in vivo, in situ, waste disposition, and other measurement applications where significant systematic uncertainties are commonplace and unavoidable, as it offers a reliable alternative for accurate evaluations of assay sensitivity that is consistent with both the historical definition of detection limits originally formulated by Currie and with the intended aims of the ISO 11929 standard.

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