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Decision rules based on the estimate of a proportion of measurements

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1 Introduction

The purpose of validation of analytical methods, for each laboratory, is to demonstrate that the method is suited for its intended purpose. Validation is not only required by regulatory authorities [10], [14] but it is also the ultimate phase before the routine use of the method. Analytical method validation must bring confidence for the laboratories in the results that will be produced since they are used to make critical decision.

1.1 Objective of the pre-study validation phase

Before an analytical method is used on unknown samples, it is required to perform a set of experiments to evaluate whether the method will be able to meet a criteria. This set is usually called “pre-study validation”.

The aim of the pre-study validation phase is to generate enough information to have guarantees that the analytical method will provide, in routine use, measurements close to the true value without being affected by other elements present in the sample, assuming everything else remains reasonably similar. In other words, the validation phase will contribute to estimate the probability π described in the following equation

$$\pi = \mathbb{P}[|X - \mu_T| \leq \lambda] = \mathbb{P}[-\lambda + \mu_T \leq X \leq \lambda + \mu_T] = \Phi\left(\frac{\lambda - \delta}{\sigma}\right) - \Phi\left(\frac{-\lambda - \delta}{\sigma}\right), \quad (1)$$

where X is the measurement or observation, μ_T is the “true value” of the test sample, λ is predefined acceptance limit, $\delta = \mu - \mu_T$ is the systematic error (bias), σ is the random error (standard deviation or precision) [8], [9] and Φ stands for the cumulative distribution function of the standard normal distribution.

Remark 1: The classical assumption of normality for the measurement results is, of course, used here. We will work without this assumption in an other paper.

Remark 2: The acceptance limit λ can be different depending on the objective of the analytical procedure. This objective is linked to the requirements usually admitted by the practice, for example 5% on drug products, 15% for biological samples,...

The quantity π is purely theoretical because the true values of these performance parameters (δ, σ) are unknown but will be estimated based on the validation experiments. The reliability of these estimates depends on the adequacy of these experiments as for example the design of the experiment or the size of the samples. Hence, the conditions used during the pre-study validation must be representative of the future routine application of the analytical method, for instance in terms of days, operators, laboratories and equipment.

So, the one objective of the pre-study validation phase is to evaluate whether, given the estimates of bias and standard deviation, the expected proportion of measurements that will fall within the acceptance limits.

1.2 Our aims

One burning issue that commonly arises in official quality laboratories is the estimation of the proportion of experimental results that lie within two limits, as we mentioned in the paragraph 1.1. The literature is rather well furnished on this subject: let's cite among all these works [5], [12] and [1] for further details. Assume that a sequence of experimental results that follow a normal distribution with unknown mean μ and unknown variance $\sigma^2 > 0$ and that the proportion of experimental results that lie within the limits of the interval $[L, U]$, where L stands for Lower and U for Upper, denoted by π , is the parameter of interest. For instance, in official quality laboratories, $[L, U]$ is the the range of the acceptable values and then π is the proportion of valid units.

The purpose of the present paper is to study decision rules for moderate sample sizes based on the estimate of a proportion of measurements derived from the use of small sample asymptotics [6].

2 Theory

Let $\{X_i : 1 \leq i \leq n\}$, where $n \geq 2$, be a sequence of experimental results that follow a normal distribution with mean μ and variance $\sigma^2 > 0$. We denote the sample mean and the sample variance respectively by

$$\bar{X} = \frac{1}{n} \sum_{i=1}^n X_i \quad s_c^2 = \frac{1}{n-1} \sum_{i=1}^n (X_i - \bar{X})^2.$$

We recall the proportion π defined by:

$$\pi := \pi(\mu, \sigma^2) = \mathbb{P}[L \leq X \leq U] = \Phi\left(\frac{U - \mu}{\sigma}\right) - \Phi\left(\frac{L - \mu}{\sigma}\right), \quad (2)$$

where Φ stands for the cumulative distribution function of the standard normal distribution, U and L , with $L < U$, are the "limits of acceptance", whose values depend on the active regulatory norm.

Using (2) one can put forward two point estimators of π : the first, denoted by $\hat{\pi}$ and defined by the following equation:

$$\hat{\pi} := \hat{\pi}\left(\bar{X}, \frac{s_c^2}{w^2}\right) = \Phi\left(w \frac{U - \bar{X}}{s_c}\right) - \Phi\left(w \frac{L - \bar{X}}{s_c}\right) = g_{ML}\left(\bar{X}, \frac{s_c^2}{w^2}\right), \quad (3)$$

where $w^2 = n/(n-1)$, is based on the maximum likelihood theory (ML) and the second, denoted by $\tilde{\pi}$ and defined by the following equation (see [11] for more details)

$$\tilde{\pi} := \tilde{\pi}\left(\bar{X}, \frac{s_c^2}{w^2}\right) = (\tilde{\pi}_1 - \tilde{\pi}_2)\left(\bar{X}, \frac{s_c^2}{w^2}\right) = g_{MVUE}\left(\bar{X}, \frac{s_c^2}{w^2}\right), \quad (4)$$

where

$$\tilde{\pi}_i\left(\bar{X}, \frac{s_c^2}{w^2}\right) = \begin{cases} 0 & \text{if } b_i \leq 0 \\ 1 & \text{if } b_i \geq 1 \\ B_{b_i}\left(\frac{n-2}{2}, \frac{n-2}{2}\right) & \text{else,} \end{cases}$$

and where

$$B_{b_i}\left(\frac{n-2}{2}, \frac{n-2}{2}\right) = \frac{\Gamma(n-2)}{\Gamma\left(\frac{n-2}{2}\right)\Gamma\left(\frac{n-2}{2}\right)} \int_0^{b_i} u^{\frac{n-4}{2}} (1-u)^{\frac{n-4}{2}} du,$$

$$b_1 = \frac{1}{2} \left(1 + w \frac{\bar{X} - L}{s_c \sqrt{n-1}}\right) \quad \text{and} \quad b_2 = \frac{1}{2} \left(1 + w \frac{\bar{X} - U}{s_c \sqrt{n-1}}\right),$$

is unbiased with minimal variance (MVUE).

The asymptotic properties of the two estimators $\hat{\pi}$ and $\tilde{\pi}$ were studied in [1]: $\hat{\pi} - \pi$ and $\tilde{\pi} - \pi$ renormalized by \sqrt{n} are asymptotically normal statistics, whose variances are equal.

If we only consider a single tail proportions π_i , then the lower limit (respectively upper limit) of an exact $100(1 - \alpha)$ %-level confidence interval, denoted by P_L (respectively P_U), can be easily derived, see [12], thanks to the following formula:

$$\mathbb{P} [T (\sqrt{n}z_{1-P_L}) \leq \sqrt{n}k_{\text{obs}}] = \alpha \quad (5)$$

$$\text{(respectively } \mathbb{P} [T (\sqrt{n}z_{1-P_U}) \leq \sqrt{n}k_{\text{obs}}] = 1 - \alpha) \quad (6)$$

where $k_1 = (\bar{X} - L)/s_c$, $k_2 = (U - \bar{X})/s_c$, $k_{\text{obs}} = k_{i,\text{obs}}$, $k_{i,\text{obs}}$ is the sample value of de k_i and z_α the 100α percentile of a standard normal distribution and the distribution of $T(\Theta)$ is a noncentral Student distribution with Θ as noncentrality parameter and $(n - 1)$ degrees of freedom.

3 Material and methods

We aim to derive accurate decision rules using confidence intervals for a proportion of measurements. These rules are based on one-sided confidence intervals and therefore we use second-order Cornish-Fisher expansions to improve their accuracy. To state a Cornish-Fisher expansion one needs to derive first the Edgeworth expansions or the involved statistics. Even though computing the Edgeworth expansions of $\hat{\pi}$ and $\tilde{\pi}$ is a fairly long task, even trickier for $\tilde{\pi}$ than for $\hat{\pi}$, this work was completed in [1] and is thoroughly detailed in the preprint [2]. The Theorem 4.1 states the Edgeworth expansions of the estimator $\hat{\pi}$.

First, we introduce the function $F_{0,ML}$ (respectively the Studentized function $F_{s,ML}$) defined by:

$$F_{0,ML} : (x, y) \in \mathbb{R}^2 \mapsto \widetilde{g}_{ML}(x, y)/\sigma_{ML} \in \mathbb{R} , \quad (7)$$

$$F_{s,ML} : (x, y, z, t) \in \mathbb{R}^4 \mapsto \widetilde{g}_{ML}(x, y) / \sqrt{\widehat{\sigma}_{ML}^2(x, y, z, t)} \in \mathbb{R} \quad (8)$$

where $\widetilde{g}_{ML}(x, y) = g_{ML}(x, y - x^2) - \pi(\mu, \sigma^2)$ and, with \mathbf{x} standing for (x, y, z, t) ,

$$\begin{aligned} \widehat{\sigma}_{ML}^2(\mathbf{x}) &= \xi(\mathbf{x}, L) + \xi(\mathbf{x}, U) + \left[\psi(\mathbf{x}, L) + \psi(\mathbf{x}, U) + \frac{1}{8\pi(-y + x^2)^3} \times \right. \\ &\quad \left. (-8x^4 + 16yx^2 - 8xz - 2y^2 + 2t)LU \right] e^{\frac{(-L+x)^2 + (-U+x)^2}{(-y+x^2)}} \end{aligned} \quad (9)$$

and where $\xi(\mathbf{x}, b) = ((-t + y^2 - 8yx^2 + 4xz + 4x^4)b^2 + (-4x^2z + 2xt - 4zy + 10xy^2 - 4x^3y)b + (4xyz - x^2t + x^2y^2 - 4y^3)) \frac{e^{(-b+x)^2/(-y+x^2)}}{8\pi(-y + x^2)^3}$ and $\psi(x, y, z, t, b) = \frac{1}{8\pi(-y + x^2)^3} (4x^2z - 10xy^2 + 4x^3y - 2xt + 4zy)b$.

One can easily check that the value of $\widehat{\sigma}_{ML}^2(\mathbf{x})$ for $\mathbf{x} = (0, 1, 0, 3)$ is equal to σ_{ML}^2 , the asymptotic variance of $\sqrt{n}(\hat{\pi} - \pi)$, given by Mee in [12] and hence to σ_{MVUE}^2 , the asymptotic variance of $\sqrt{n}(\tilde{\pi} - \pi)$:

$$\widehat{\sigma}_{ML}^2(0, 1, 0, 3) = \frac{1}{2\pi} \left(\left(e^{-U^2/2} - e^{-L^2/2} \right)^2 + \frac{1}{2} \left(Ue^{-U^2/2} - Le^{-L^2/2} \right)^2 \right). \quad (10)$$

Definition 3.1 *An analytical method is considered as valid or able to achieve its objective if for each unknown sample to quantify it is very likely that the result obtained will fall within the acceptance limits. This is formally express by:*

$$\pi := \pi(\mu, \sigma^2) = \mathbb{P} [|X - \mu_T| \leq \lambda] \geq \pi_{\text{min}}. \quad (11)$$

Remark: The value of π_{min} , called the quality level, will be equal to 80% for example.

Since the true values of the parameters (μ, σ^2) are unknown, this problem cannot be solved exactly. The lower limit, denoted by $I_{\hat{\pi}}^{\infty}$, of an asymptotic confidence interval of π , computed using the delta method and the estimator $\hat{\pi}$, was derived in [4] and is equal to:

$$I_{\hat{\pi}}^{\infty} = \Phi\left(w \frac{U - \bar{X}}{s_c}\right) - \Phi\left(w \frac{L - \bar{X}}{s_c}\right) - \frac{z_{1-\alpha}}{\sqrt{n}} \sqrt{\widehat{\sigma}_{ML}^2(\widehat{\mu}, \widehat{\sigma}^2, 0, 3)}. \quad (12)$$

The decision rule based on this estimator is: the analytical method is then declared valid if $I_{\hat{\pi}}^{\infty} > \pi_{min}$.

4 Results and discussion

To simplify the expression of the quantities stated below, we deal, in this section, with a symmetric acceptance interval and assume, without loss of generality that $\mu = 0$ and $\sigma = 1$. Therefore the two acceptance limits, L and U , are opposite numbers: $U = \lambda = -L$.

Theorem 4.1 *For the symmetric case, the second-order Edgeworth expansion of the non-studentized statistic, $F_{0,ML}$, is:*

$$\begin{aligned} \mathbb{P}\left[\sqrt{n}F_{0,ML}\left(\bar{X}, \frac{s_c^2}{w^2}\right) \leq x\right] &= \Phi(x) + \frac{1}{6\sqrt{2n}}((-5 + 3\lambda^2)x^2 - 4)\phi(x) + \frac{1}{n}\left[\left(-\frac{25}{144} + \frac{5}{24}\lambda^2 - \right.\right. \\ &\quad \left.\left.\frac{1}{16}\lambda^4\right)x^5 + \left(\frac{1}{9} - \frac{1}{6}\lambda^2 + \frac{1}{6}\lambda^4\right)x^3 - \frac{1}{6}x\right]\phi(x) + O\left(\frac{1}{n^{3/2}}\right) \end{aligned} \quad (13)$$

uniformly in $x \in \mathbb{R}$.

For the symmetric case, the second-order Edgeworth expansion of the studentized statistic, $F_{s,ML}$, is:

$$\begin{aligned} \mathbb{P}\left[\sqrt{n}F_{s,ML}\left(\bar{X}, \frac{s_c^2}{w^2}\right) \leq x\right] &= \Phi(x) + \frac{1}{6\sqrt{2n}}((19 - 3\lambda^2)x^2 - 4)\phi(x) + \frac{1}{n}\left[\left(-\frac{361}{144} + \frac{19}{24}\lambda^2 - \right.\right. \\ &\quad \left.\left.\frac{1}{16}\lambda^4\right)x^5 + \left(\frac{137}{18} - \frac{35}{12}\lambda^2 + \frac{1}{6}\lambda^4\right)x^3 - \frac{1}{6}x\right]\phi(x) + O\left(\frac{1}{n^{3/2}}\right) \end{aligned} \quad (14)$$

uniformly in $x \in \mathbb{R}$.

These results lead to Cornish-Fisher expansions of the quantiles of the estimator $\hat{\pi}$ given by the following equation:

$$\begin{aligned} w_{\alpha}^{0,ML} &= \left(-\frac{7}{18} + \frac{1}{3}\lambda^2 - \frac{1}{6}\lambda^4\right)z_{\alpha}^3 + \frac{19}{18}z_{\alpha} + \frac{1}{6\sqrt{2n}}((5 - 3\lambda^2)z_{\alpha}^2 + 4) + \frac{z_{\alpha}}{36n}((-5 + 3\lambda^2)^2z_{\alpha}^2 + \\ &\quad (20 - 12\lambda^2)) + O\left(\frac{1}{n^{3/2}}\right), \end{aligned} \quad (15)$$

$$\begin{aligned} w_{\alpha}^{s,ML} &= \left(-\frac{59}{19} + \frac{11}{4}\lambda^2 - \frac{1}{6}\lambda^4\right)z_{\alpha}^3 + \frac{19}{18}z_{\alpha} - \frac{1}{6\sqrt{2n}}((19 - 3\lambda^2)z_{\alpha}^2 - 4) + \frac{z_{\alpha}}{36n}((-19 + 3\lambda^2)^2z_{\alpha}^2 + \\ &\quad (-76 + 12\lambda^2)) + O\left(\frac{1}{n^{3/2}}\right), \end{aligned} \quad (16)$$

where z_{α} is the α -level standard normal quantile.

One can now use these quantiles to compute the lower limit of a $100(1 - \alpha)$ confidence interval for π and check whether it is greater than the quality level π_{min} or not. Yet the true values of the parameters μ and σ of the normal distribution, whose values are required to use the Cornish-Fisher expansions derived for a standard normal distribution in (15) and (16), are unknown. Bootstrap techniques can be used to solve that issue, see [3].

A similar result holds for $\tilde{\pi}$. Unfortunately due to length limitations, we cannot state it here. Yet the accuracy of Cornish-Fisher expansions of the quantiles of the non-studentized and studentized statistics based on this estimator will be compared to those of $\hat{\pi}$.

5 Conclusion

From a theoretical point of view, this work provides second-order accurate one-sided confidence intervals whose lower limit will be used in the decision rule. Even if Cornish-Fisher expansions are asymptotic ones, they often work well with moderate sample sizes, see [7] for example. This should result in an improvement of the correctness of the decision rule and reduce both consumer and laboratory risks.

Simulations will be provided to compare the decision rules based on the Cornish-Fisher expansions of the two estimators $\hat{\pi}$ and $\tilde{\pi}$ with well known methods such as the one based on the asymptotic confidence interval lower limit $I_{\hat{\pi}}^{\infty}$, defined by (12), β -expectation or β -content tolerance limits, whose definition may be found in [13].

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