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A note on the calculation of reference change values for two consecutive normally distributed laboratory results

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ABSTRACT

Population reference limits are inadequate for personalized analyses of medical laboratory results. Reference change values have been recommended as a valid alternative in assessing individual changes across sequential measurements. In this paper, we investigate the accuracy (type I error) and power (complement of type II error) of reference change values under three different statistical modeling scenarios and show that oversimplified hypotheses lead to misinterpretation of laboratory results. The power is strongly affected by the statistical modeling assumptions: it is shown that positive shifts in the individual average health condition are difficult to detect, while it is much easier to identify negative shifts.

1. Introduction

Medical laboratory results are traditionally compared with normal reference limits, i.e. ranges of values that are expected for healthy persons. They are typically defined by the lower and upper 5% quantiles of a reference group, i.e. subjects for which no morbidity is assessed [7]. These population-based reference ranges are mere cut-off values and can lead to false positives and false negatives. The classification of a normal measurement does not guarantee that the value is normal for the specific patient and alternatively an abnormal measurement does not necessarily imply disease alert, in particular when the value is close to the critical threshold. The reason is that measurements in individuals are affected by true condition's shifts, but also by some other inherent causes, such as pre-analytical, analytical, between- and within-subject biological variations [5]. Population-based reference ranges do not separate these sources of variation.

The considerations above have led to the development of alternative methods for the interpretation of medical laboratory results, in particular recently with an increased interest in personalized medicine. Modern methods aim at understanding changes in individuals, rather than comparing results with respect to population-based references. Reference change values (RCV) or critical differences are a popular method for the assessment of laboratory results, introduced by Ref. [6]. Several manuscripts can be found in this field, for example [3,9–11]. The approach defines criteria for normal variation in two sequential measurements, which mathematically are often defined as

$$\mathrm{RCV} = \pm z_\alpha \sqrt{2(\sigma_A^2 + \sigma_I^2)}, \tag{1}$$

with σ_A^2 the analytical variability, σ_I^2 the intra-individual variability, and z_α a quantile from the standard normal distribution. Typical values for z_α are 1.645 for $\alpha = 0.05$, 1.960 for $\alpha = 0.025$ or even 2.58 for $\alpha = 0.005$. A good review on the subject is given by Ref. [4].

The calculation of RCVs for many different laboratory outcomes is quite simple since all laboratories know approximately the analytical and intra-individual variabilities for medical laboratory results from samples from the healthy population. A possible disadvantage of the RCVs in (1) is that the analytical variation is assumed to be independent of the health status, an assumption which might be incorrect, as raised by Refs. [8] and [1]. To overcome this [8], proposed a modification of the traditional RCV to an RCV that changes with the level of the quantity it tries to measure, assuming a constant coefficient of variation. However, the work of [8] lacks mathematical rigor, does not specify the statistical assumptions, and does not discuss the consequences of the simplified hypotheses on the detection of possible shifts in the health status between two sequential measurements.

In this paper, we give a rigorous formulation of the reference change values under various statistical hypotheses, and demonstrate that the result of [8] is a special case of our general framework. We also show that

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the power to detect true health changes is counterintuitive when the analytical variability depends on the health state. In Section 2 we introduce the modeling framework and provide a general definition of the reference change values. We consider three different scenarios, corresponding to diverse dependencies of the variances. In Section 3 we discuss how the model can be generalized to allow for a real non-physiological change in the health status and study the power of reference change values in detecting real changes. We end the paper with a discussion.

2. Reference change values

Let Y_{ij} be a measured medical laboratory quantity for subject $i = 1, 2, \ldots, n$ at two consecutive moments in time $j = 1, 2$. We will assume, possibly after a suitable mathematical transformation (e.g. logarithm), that these laboratory results can be described by an additive structure such as

$$Y_{ij} = \mu_i + V_{ij} + E_{ij}, \tag{2}$$

where μ_i is the true mean of subject i, V_{ij} is the random intra-subject variability and E_{ij} is the random analytical variability. The subject-specific mean μ_i should be considered random for population reference change values, but it can be assumed deterministic when the focus is on detecting changes within a subject. The random variable V_{ij} is assumed normally distributed with zero mean and variance σ_i^2. Thus

$$X_{ij} = \mu_i + V_{ij}, \tag{3}$$

representing the true value (without analytical variation) for subject i at time point j, follows a normal distribution $\mathcal{N}(\mu_i, \sigma_i^2)$. The error term E_{ij} is normally distributed with zero mean and variance τ_{ij}^2, conditionally on V_{ij}. Furthermore, the two measurements are assumed to be distant enough in time, such that (V_{i2}, E_{i2}) can be assumed independent of (V_{i1}, E_{i1}).

To include variability that depends on the true health condition, we will assume that the variances σ_i^2 and τ_{ij}^2 may depend on the true health values μ_i and X_{ij},

$$\begin{aligned} \sigma_i^2 &= \sigma^2(\mu_i), \\ \tau_{ij}^2 &= \tau^2\left(\mu_i, V_{ij}\right) \end{aligned} \tag{4}$$

Note that the intra-subject variability may depend on the mean health state only, but the analytical variation may also be affected by the levels of V_{ij}. This general formulation implies that the difference $Y_{i2} - Y_{i1}$ is no longer normally distributed if τ_{ij} depends on V_{ij}. The cumulative distribution function of the difference $Y_{i2} - Y_{i1}$ is

$$\mathbb{P}(Y_{i2} - Y_{i1} \le y) = \mathbb{E}\left[\Phi\left(\frac{y - (V_{i2} - V_{i1})}{\sqrt{\tau^2(\mu_i, V_{i1}) + \tau^2(\mu_i, V_{i2})}}\right)\right], \tag{5}$$

where Φ is the cumulative distribution of a standard normal variable, and the expectation is with respect to V_{i1} and V_{i2} (see Appendix A.1 for the derivation). The mean of the difference is zero and the variance is given by

$$\mathrm{Var}(Y_{i2} - Y_{i1}) = 2\left(\sigma^2(\mu_i) + \mathbb{E}\left[\tau^2\left(\mu_i, V_{ij}\right)\right]\right), \tag{6}$$

with $V_{ij} \sim \mathcal{N}(0, \sigma^2(\mu_i))$. Based on this variance and the definition in (1), a first approximation for the reference change values becomes

$$\begin{aligned} L_\alpha &= -z_\alpha\sqrt{2\left(\sigma^2(\mu_i) + \mathbb{E}\left[\tau^2\left(\mu_i, V_{ij}\right)\right]\right)}, \\ U_\alpha &= z_\alpha\sqrt{2\left(\sigma^2(\mu_i) + \mathbb{E}\left[\tau^2\left(\mu_i, V_{ij}\right)\right]\right)} \end{aligned} \tag{7}$$

where z_α denotes again the upper α-quantile of the standard normal distribution. A more precise RCV would be determined by two reference change values L_α and U_α such that

$$\mathbb{P}(Y_{i2} - Y_{i1} \le L_\alpha) = 1 - \mathbb{P}(Y_{i2} - Y_{i1} \le U_\alpha) = \alpha, \tag{8}$$

but the boundaries L_α and U_α may still depend on the unknown parameter μ_i through $\sigma(\mu_i)$ and $\tau(\mu_i, \nu_{ij})$. A possible alternative is to use the first observation Y_{i1} in the lower and upper bounds, i.e. $L_\alpha(Y_{i1})$ and $U_\alpha(Y_{i1})$, such that

$$\mathbb{P}(Y_{i2} - Y_{i1} \le L_\alpha(Y_{i1})) = 1 - \mathbb{P}(Y_{i2} - Y_{i1} \le U_\alpha(Y_{i1})) = \alpha. \tag{9}$$

The inclusion of Y_{i1} in the RCV may help eliminate the parameter μ_i and in a way it is used as an estimator of μ_i. The following cases provide the boundaries under certain assumptions on $\sigma(\mu_i)$ and $\tau(\mu_i, \nu_{ij})$.

2.1. Case I. $\sigma(\mu_i) = \sigma_0$ and $\tau(\mu_i, \nu_{ij}) = \tau_0$

This is the traditional setting for computing reference change values. Under the stated normal distributional and independence assumptions, the RCVs are directly determined by (1) and (6),

$$L_\alpha = -z_\alpha\sqrt{2(\sigma_0^2 + \tau_0^2)} \text{ and } \; U_\alpha = z_\alpha\sqrt{2(\sigma_0^2 + \tau_0^2)}. \tag{10}$$

This case may seem trivial, and in a way it is, but it can include the cases of distributions other than normal. If for instance the original data $\tilde{Y}_{ij}$ follows a log-normal distribution, it is possible to compute reference change values for the measurements in the logarithmic scale, i.e. $Y_{i2} - Y_{i1} = \log(\tilde{Y}_{i2}) - \log(\tilde{Y}_{i1})$. These limits can be transformed back to the limits for the ratio $\tilde{Y}_{i2}/\tilde{Y}_{i1}$ in the original scale. In fact, when introducing model (2), we have considered the additive normal structure possibly after some transformations of the original data, and that can include more general distributions.

2.2. Case II. $\sigma(\mu_i) = c_s\mu_i$ and $\tau(\mu_i, \nu_{ij}) = c_m\mu_i$

Let $c_s > 0$ and $c_m > 0$ denote the intra-subject and measurement coefficients of variation respectively, expressed as fractions. Since the variance of the measurement error τ_{ij}^2 is still independent of the random term V_{ij}, the difference $Y_{i2} - Y_{i1}$ is normally distributed with variance $\mathrm{Var}(Y_{i2} - Y_{i1}) = 2c_t^2\mu_i^2$, where $c_t = \sqrt{c_s^2 + c_m^2}$ denotes the total coefficient of variation. Thus the reference change values, without using Y_{i1} in the computation, would be given by $\pm z_\alpha\sqrt{2c_t^2\mu_i^2}$. While the total coefficient of variation of laboratory results is usually known from experimental studies, the individual mean μ_i is unknown. Instead, we propose the limits $L_\alpha(Y_{i1}) = \sqrt{2}c_t L_\alpha^0 Y_{i1}$ and $U_\alpha(Y_{i1}) = \sqrt{2}c_t U_\alpha^0 Y_{i1}$, where $L_\alpha^0 < 0$ and $U_\alpha^0 > 0$ are constants chosen such that the equalities (9) hold. In this case L_α^0 and U_α^0 can be determined in closed-form expression

$$\begin{aligned} L_\alpha^0 &= -\frac{\sqrt{2}}{2}z_\alpha\frac{\sqrt{2 - z_\alpha^2c_t^2} - z_\alpha c_t}{1 - z_\alpha^2c_t^2} \text{ and} \\ U_\alpha^0 &= \frac{\sqrt{2}}{2}z_\alpha\frac{\sqrt{2 - z_\alpha^2c_t^2} + z_\alpha c_t}{1 - z_\alpha^2c_t^2}, \end{aligned} \tag{11}$$

with restrictions $c_t \le \sqrt{2}z_\alpha^{-1}$ for the lower bound and $c_t < z_\alpha^{-1}$ for the upper bound. Note that the lower bound L_α^0 for $c_t = z_\alpha^{-1}$ is defined by its continuity extension, since the limit exists and is finite,

$$\lim_{c_t \to z_\alpha^{-1}} L_\alpha^0 = -z_\alpha\frac{\sqrt{2}}{2}, \tag{12}$$

while the upper bound diverges to infinity when c_t approaches z_α^{-1}. See Appendix A.2 for the derivation of the bounds (11) and Appendix A.3 for