Finite Sample Adjustments for Average Equivalence Testing

Younes Boulaguiem[1], Julie Quartier[2,3], Maria Lapteva[2,3], Yogeshvar N Kalia[2,3], Maria-Pia Victoria-Feser[1], Stéphane Guerrier[1,2,3] & Dominique-Laurent Couturier[4,5,*]

[1]Geneva School of Economics and Management, University of Geneva, Switzerland; [2]School of Pharmaceutical Sciences, University of Geneva, Switzerland; [3]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, Switzerland; [4]Medical Research Council Biostatistics Unit, University of Cambridge, England; [5]Cancer Research UK – Cambridge Institute, University of Cambridge, England; *Corresponding author: dominique.couturier@mrc-bsu.cam.ac.uk

Abstract: Average (bio)equivalence tests are used to assess if a parameter, like the mean difference in treatment response between two conditions for example, lies within a given equivalence interval, hence allowing to conclude that the conditions have 'equivalent' means. The two one-sided tests (TOST) procedure, consisting in testing whether the target parameter is respectively significantly greater and lower than some pre-defined lower and upper equivalence limits, is typically used in this context, usually by checking whether the confidence interval for the target parameter lies within the same limits. This intuitive and visual procedure is however known to be conservative, especially in the case of highly variable drugs, where it shows a rapid power loss, often reaching zero, hence making it impossible to conclude for equivalence when it is actually true. This motivated the development of more powerful procedures. Here, we propose a finite sample correction of the TOST procedure, the α-TOST, which consists in an adjustment of the level of the TOST allowing to guarantee a type-I error rate of α. This new procedure essentially corresponds to a finite sample and variability adjustment of the TOST procedure. We show that this procedure, also appealingly relying of the assessment of equivalence by means of confidence intervals, is uniformly more powerful than the TOST, easy to compute, and that its operating characteristics are better that the ones of its competitors. A case study about econazole nitrate deposition in porcine skin is used to illustrate the benefits of the proposed method and its advantages compared to other available procedures.

Keywords: similarity test, bioequivalence, scaled average bioequivalence, two one-sided test, interval inclusion principle.

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1. Introduction

Equivalence tests, also known as similarity or parity tests, have gained significant attention during the past two decades. They originated from the field of pharmacokinetics (Metzler, 1974; Westlake, 1976), where they are called bioequivalence tests and have numerous applications in both research and production (Pallmann and Jaki, 2017). They find their most common application in the manufacturing of generic medicinal drugs, where, by proving that the generic version has a similar bioavailability to its well-studied brand-name counterpart, the manufacturer can considerably shorten the approval process for the generic drug (for an overview, see e.g., Senn, 2021). Moreover, equivalence tests have attracted growing interest in other domains and for other types of purposes, such as in production when, for example, the mode of administration is altered or when the production site is changed (see e.g., Patterson and Jones, 2006), or in the social and behavioral sciences for the evaluation of replication results and corroborating risky predictions (Lakens, 2017). Very recent literature highlights the expanding use of equivalence tests across a growing range of domains. Examples include the investigation of the equivalence of virtual reality imaging measurements by feature (Sureshkumar et al., 2022), of cardiovascular responses to stimuli by sex (O'Brien and Kimmerly, 2022), of children neurodevelopment (Wehrle et al., 2022) or chemotherapy efficacy and safety (Sansone et al., 2022) by treatment, of post-stroke functional connectivity patterns by patient group (Branscheidt et al., 2022), of risk-taking choices by moral type (Feri et al., 2023), of 2020 US presidential election turnout by political advertising condition (Aggarwal et al., 2023). Review articles have also appeared, for example, in food sciences (Meyners, 2012), in psychology (Lakens et al., 2018) in sport sciences (Mazzolari et al., 2022), and in pharmaceutical sciences (Wang et al., 2022).

Equivalence testing implies defining an equivalence region within which the parameter of interest, such as the difference between outcome means measured under two conditions, would lie for these conditions to be considered as equivalent. When comparing two treatments, for example, deviations belonging to this region would typically be deemed irrelevant as they are too small to affect the similarity of their therapeutic effects. This is different from standard equality-of-means hypothesis tests in which the null and the alternative hypothesis are interchanged and the null hypothesis states that both means are equal rather than equivalent. Formally, a canonical form for the average equivalence problem consists of two independent random variables $\widehat{\theta}$ and $\widehat{\sigma}_\nu$ having the distributions

$$\widehat{\theta} \sim \mathcal{N}\left(\theta, \sigma_\nu^2\right), \quad \text{and} \quad \frac{\nu\widehat{\sigma}_\nu^2}{\sigma_\nu^2} \sim \chi_\nu^2, \tag{1}$$

where θ and σ_ν^2 respectively denote the target bioequivalence parameter and its variance, depending on the number of the degrees of freedom ν and thus function of the sample size and total number of parameters. This setting is very general. It covers cases where, for example, the bioequivalence parameter corresponds to the difference in means of the (logarithm of pharmacokinetic) responses between 2 experimental conditions in an independent or paired t-test, or to an element of the parameter vector of a (generalised) linear (mixed effect) model, like the shift in (tumour growth) increase between two conditions in a longitudinal study. The hypotheses of interest are given by

$$H_0: \ \theta \notin \Theta_1, \quad vs. \quad H_1: \ \theta \in \Theta_1 := (\theta_L, \theta_U), \tag{2}$$

where θ_L and θ_U are known constants. Without loss of generality it can be assumed that the equivalence limits are symmetrical around zero. In this case, $c := \theta_U = -\theta_L$ so that $\Theta_1 = (-c, c)$. Equivalence is typically investigated via the Two One-Sided Tests (TOST) procedure (Schuirmann, 1987), consisting in testing whether the target parameter is respectively significantly greater than $-c$ and lower than c, with the Type-I Error Rate (TIER), or test size, controlled at level α (see Berger, 1982), usually chosen as 5%. The most common way of assessing equivalence is to use the *Interval Inclusion Principle* (IIP) and check whether the 100(1 - 2α)% Confidence Interval (CI) for the target parameter falls within the equivalence margins $(-c, c)$ (see e.g., Muñoz et al., 2016; Pallmann and Jaki, 2017). This strategy has been shown to lead to the same test decision as the TOST procedure if the CI is equi-tailed (Hsu et al., 1994; Berger and Hsu, 1996).

However, it is well known that this procedure can be conservative as the TIER of the TOST can be considerably lower than the (specified) test level α. This induces a drop in power and therefore to a lower probability of detecting truly equivalent mean effects as such. This problem is particularly noticeable in cases where σ_ν is relatively large. Such situations may occur, for example, when the sample size is determined using an underestimated standard deviation value obtained from a prior experiment, or with studies involving highly variable drugs and in which the sample size that would be needed to achieve reasonable values for σ_ν are impossible to achieve. For that purpose, Anderson and Hauck (1983) proposed a test that has greater power than the TOST for situations where σ_ν is relatively large. This test, referred to here as the AH-test, can be liberal and therefore doesn't control the TIER either (see Berger and Hsu, 1996). In some cases, it can also lead to acceptance of equivalence when θ, the target parameter of interest, falls outside the equivalence interval (see Schuirmann, 1987). Brown et al. (1997) constructed an unbiased test that is uniformly more powerful than the TOST, however, it is computationally intensive and its rejection region may exhibit rather irregular shapes in some cases (see e.g. Berger and Hsu, 1996). Berger and Hsu (1996) therefore proposed a smoothed version. These three last tests do not require CIs and therefore do not rely on the IIP, and the last two are difficult to interpret due to polar coordinates (see e.g., Liu and Chow, 1996).

Due to the overly conservative TOST's TIER with highly variable drugs, i.e., for cases with relatively large σ_ν, regulatory authorities have recommended an alternative approach based on the linear scaling of the equivalence limits according to the value of the standard deviation σ_ν (within the reference group), called Scaled Average BioEquivalence (SABE), with the constraint that $\widehat{\theta}$ lies within the equivalence margins $(-c, c)$. These recommendations were issued by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (see e.g., Muñoz et al., 2016; Davit et al., 2012, for more details). The amount of expansion is limited by the authorities, and several recent publications have shown that the TIER can be larger than the nominal level α (see e.g., Wonnemann et al., 2015; Muñoz et al., 2016; Endrenyi and Tothfalusi, 2019; Molins et al., 2021; Schütz et al., 2022, and the references therein) and therefore have proposed different ways to correct for it (see also Labes and Schütz, 2016; Tothfalusi and Endrenyi, 2016; Ocaña and Muñoz, 2019; Deng and Zhou, 2020). These corrections not only ensure that the TIER is smaller than or equal to α, but also lead to acceptance regions that change more smoothly with σ_ν.

In this paper, as an alternative to previous methods, we propose a finite sample correction of the TOST procedure that simply consists in an adjustment the TOST's level that guarantees a TIER of exactly α when σ_ν is known. The *corrected level*, α^*, is straightforward to compute and allow to define 100(1 - 2α^*)% CIs used in the classical

TOST. Hence, the α-TOST essentially corresponds to a finite sample continuous variability adjustment of the TOST procedure, that leads to an increase probability of accepting equivalence when it is true for large values of σ_ν. Indeed, the α-TOST is shown to be uniformly more powerful than the TOST, and, for small to moderate values of σ_ν, to be nearly equivalent to the TOST with a comparable power as $\alpha^* \approx \alpha$ in such cases. This method also provides a more powerful test than the SABE with corrected level. Finally, since in practice σ_ν needs to be estimated from the data, a straightforward estimator for α^* is also proposed and it is shown, through simulations, that the estimator does not significantly alter the TIER of the α-TOST.

The paper is organized as follows. In Section 2, we consider a case study for which we apply the TOST and the α-TOST, as well as other available methods, in order to showcase the advantage of our proposed approach. The α-TOST is presented in Section 3 from a suitable formulation of the TOST. Its statistical properties as well as a simple algorithm to compute α^* are also provided. In particular, we provide a power comparison with alternative available methods. In Section 4, a simulation study is used for comparing the TIER and power of the α-TOST, to the TOST, the EMA implementation of the SABE, simple or corrected for the TIER. Finally, Section 5 discusses some potential extensions.

2. Evaluation of Bioequivalence for Econazole Nitrate Deposition in Porcine Skin

Quartier et al. (2019) study the cutaneous bioequivalence of two topical cream products: a reference medicinal product (RMP) and an approved generic containing econazole nitrate (ECZ), an antifungal medication used to treat skin infections. The evaluation of the putative bioequivalence is based on the determination of the cutaneous biodistribution profile of ECZ observed after application of the RMP and the generic product. This involves quantification of the amounts of ECZ present as a function of depth within the skin descending from the surface to a depth of 800 microns. It follows that the more similar the biodistribution profile, i.e. the more similar the amounts of drug present at each depth, the greater the likelihood of equivalent pharmacological effect. The dataset we analyse in this section consists in 17 pairs of comparable porcine skin samples on which measurements of ECZ deposition were collected using both creams. The data are presented in Figure 1. In order to assess bioequivalence of both topical treatments, the TOST and α-TOST procedures, based on a paired t-test statistic, are conducted using $c = \theta_U = -\theta_L = \log(1.25) \approx 0.223$. These equivalence limits correspond to the recommendation of regulatory agencies such as the Food and Drugs Administration (2001) and the European Medicine Agency (2010). Figure 2 shows the CIs corresponding to both approaches. The $100(1-2\alpha)\%$ TOST confidence interval for the mean of the paired differences in EZD levels equals $[-0.204, 0.250]$, given that $\widehat{\theta} = 0.023$, $\widehat{\sigma}_\nu = 0.130$, $\nu = 16$ and $\alpha = 5\%$. As its upper bound exceeds the upper equivalence limit, the classical TOST procedure doesn't allow to conclude that the topical products are (on average) equivalent. To reach a TIER of 5%, the α-TOST procedure uses, in this case, a type I error of $\widehat{\alpha}^* = 7.48\%$ leading to a confidence interval of $[-0.166, 0.211]$. This CI being strictly embedded within the $[-c, c]$ equivalence limits, the α-TOST procedure allows to accept bioequivalence, hence illustrating the increase in power induced by the reduced type I error level considered to reach a TIER of 5%. Note that in this case, given $\widehat{\sigma}_\nu^2$ and ν, the empirical power of the TOST is nil (regardless of $\widehat{\theta}$) as $t^{-1}_{16,0.05}\,\widehat{\sigma}_\nu^2 > c$, where $t^{-1}_{\nu,\alpha}$ denotes the upper quantile α of a t-distribution with ν degrees of freedom; see Section 3.3 for a detailed discussion. Since, as will be shown in Section 3.2, the α-TOST guaranties an adjusted level of α (for

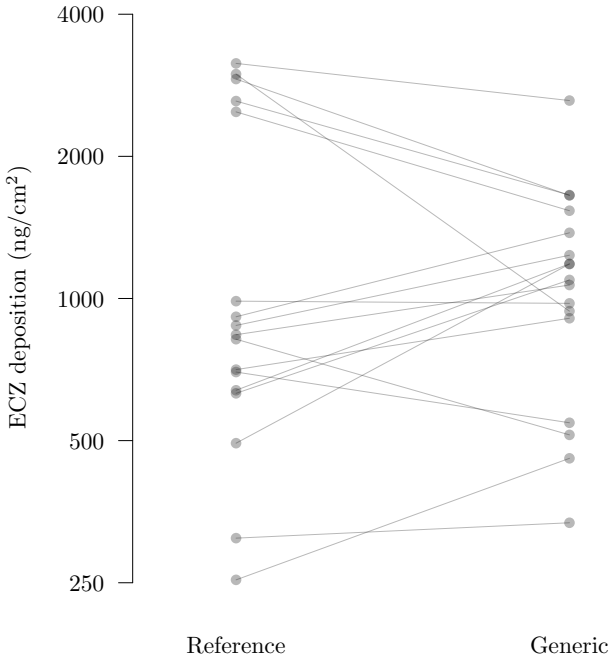

Figure 1: Econazole nitrate deposition levels (y-axis) measured using the reference and generic creams (x-axis) on 17 pairs of comparable porcine skin samples (lines).

all sample sizes), the conclusion brought in by the α-TOST is more trustworthy.

To gain additional insight of the benefits conferred by our approach, we also compare the characteristics and conclusion of the α-TOST to other available methods in Table 1 as well as their rejection region as a function of $\widehat{\theta}$ and $\widehat{\sigma}_\nu$ in Figure 3. We considered here the AH-test, the EMA implementation of the SABE (EMA), and the level-corrected version provided by Labes and Schütz (2016) (EMA corrected), together with the TOST and α-TOST. The AH-test does not satisfy the IIP, but represents a good proxy for the other tests without this property and is relatively easy to implement. The EMA is not α-level, so the decision is not trustworthy, and is mainly considered here for comparison with the EMA corrected. Note that, among the level α-tests, the α-TOST is the only one leading to the acceptance decision.

Figure 3 shows the combinations of values of $\widehat{\theta}$ and $\widehat{\sigma}_\nu$ leading to accepting equivalence in the setting of the porcine skin dataset, i.e., with $c = \log(1.25)$ and $\nu = 16$. Note that the rejection regions of the different methods almost perfectly overlap for values of $\widehat{\sigma}_\nu$ below 0.09 and that their operating characteristics then differ. Regardless of $\widehat{\sigma}_\nu$, The TOST and EMA corrected methods can't accept bioequivalence for large values of $\widehat{\sigma}_\nu$ (greater than ~ 0.15 here) while the α-TOST and AH-test can, with the rejection rejection of the α-TOST embedded in the too liberal one of the AH-test. The EMA method shows an atypical rejection area leading to paradoxical cases where, for a given value of $\widehat{\theta}$ and two (reasonable) values of $\widehat{\sigma}_\nu$, $\widehat{\sigma}_\nu^{(a)}$ and $\widehat{\sigma}_\nu^{(b)}$, with $\widehat{\sigma}_\nu^{(a)} > \widehat{\sigma}_\nu^{(b)}$, non-equivalence is rejected with $\widehat{\sigma}_\nu^{(a)}$ but not with $\widehat{\sigma}_\nu^{(b)}$. Such irregular rejection regions were also noted for other tests briefly mentioned above (see e.g., the Figures 1 of Berger and Hsu (1996), Brown et al. (1997) and Cao and Mathew (2008)). In Figure 3, the symbol $\times$ shows the values of $\widehat{\theta}$ and $\widehat{\sigma}_\nu$ obtained in the porcine skin dataset. Note that these coordinates lead to the acceptance of bioequivalence of the two topical products with the EMA (not corrected), AH-test and α-TOST procedures among

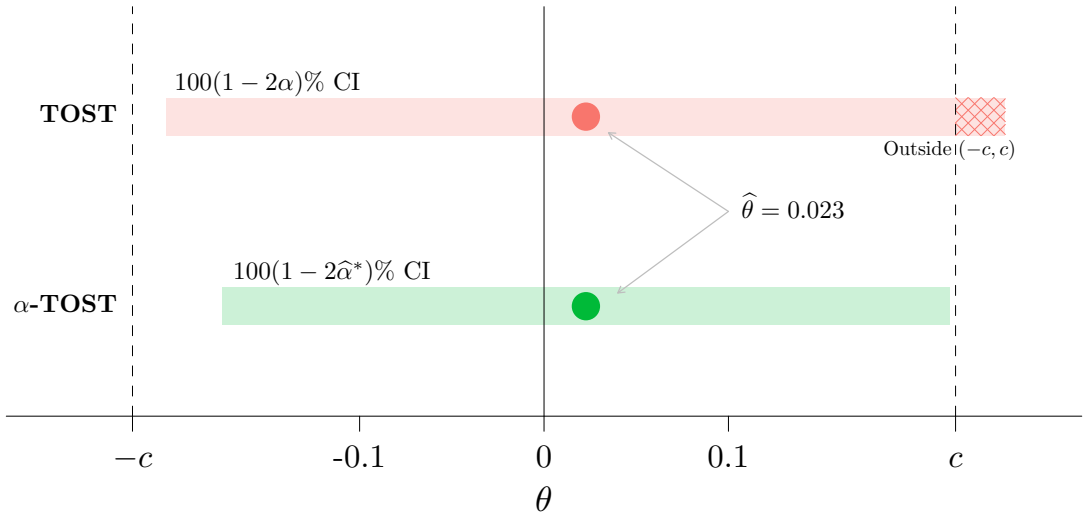

Figure 2: $100(1-2\alpha)\%$ and $100(1-2\widehat{\alpha}^*)\%$ confidence intervals of the TOST and α-TOST procedures for the mean of the paired differences in EZD levels obtained with the reference and generic creams with $\alpha = 5\%$ and $\widehat{\alpha}^* = 7.48\%$. The dashed vertical lines correspond to the used lower and upper equivalence limits with $c = \log(1.25)$. Comparison of the CI of each approach to the bioequivalence limits lead to the acceptance of equivalence for the $\alpha-$TOST procedure and not for the classic TOST approach due to its CI upper limit exceeding c (hatched area).

Method	IIP	Level α	TIER α	Decision
AH-test	no	no	no	Accept
EMA	yes	no	no	Accept
EMA corrected	yes	yes*	no	Reject
TOST	yes	yes	no	Reject
α-TOST	yes	yes*	yes*	Accept

Table 1: Bioequivalence acceptance/rejection (Decision) for the econazole nitrate deposition in porcine skin data using the AH-test, EMA implementation of the SABE (EMA), level-corrected EMA implementation of the SABE (EMA corrected) of Labes and Schütz (2016), TOST and α-TOST. The parameters' values are $\widehat{\sigma}_\nu = 0.130$, $\nu = 16$, $\widehat{\theta} = 0.0227$ and $\alpha = 5\%$. The columns IIP, Level and TIER α respectively indicate if each method satisfies the Interval Inclusion Principle (IIP), has a level α (the TIER is bounded by α) and if its TIER is exactly α. The symbol * specifies that the property is valid when the standard error σ_ν is known.

which only the α-TOST is level α.

A more comprehensive description of the power of selected methods is provided in Section 3.3, and a simulation study comparing the respective TIER and finite sample power is given in Section 4.

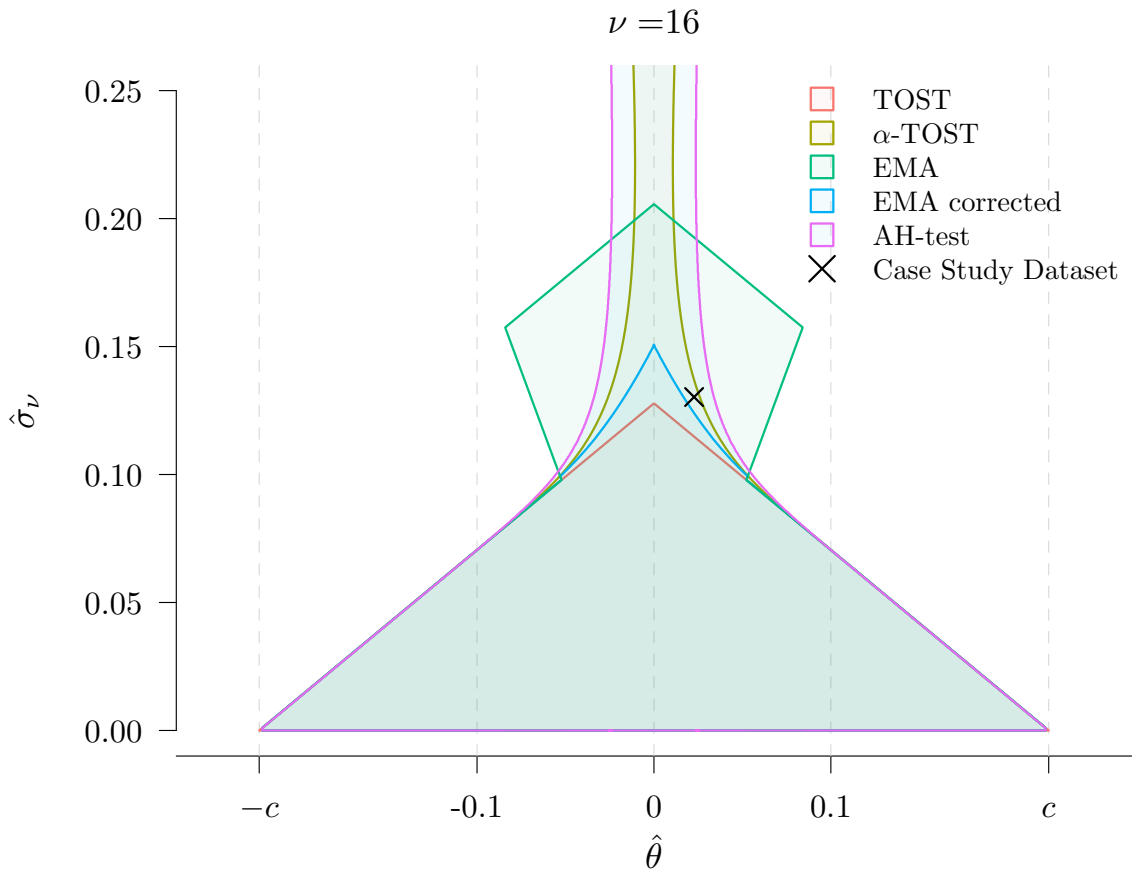

Figure 3: Equivalence test rejection regions as a function of $\widehat{\theta}$ (x-axis) and $\widehat{\sigma}_\nu$ (y-axis) per method considered in Table 1 (coloured areas) showing combinations of values of $\widehat{\theta}$ and $\widehat{\sigma}_\nu$ leading to accepting equivalence in the setting of the porcine skin dataset, i.e., with $c = \log(1.25)$ and $\nu = 16$. Note that the rejection regions of the different methods almost perfectly overlap for values of $\widehat{\sigma}_\nu$ below 0.09 and that their operating characteristics then differ. Regardless of $\widehat{\sigma}_\nu$, the TOST and EMA corrected methods can't accept bioequivalence for large values of $\widehat{\sigma}_\nu$ (greater than ~ 0.15 here) while the α-TOST and AH-test can, with the rejection rejection of the α-TOST embedded in the too liberal one of the AH-test. The EMA method has an atypical rejection area. The symbol $\times$ represents the analysed data set in the acceptance/rejection regions where $\widehat{\theta} = 0.023$ and $\widehat{\sigma}_\nu = 0.130$.

3. Equivalence Testing

In this section, we present the methodology for deriving a level-adjusted statistical equivalence test. We first present the TOST and its properties. We then define the α-TOST procedure through a natural adjustment of the TOST, derive its statistical properties, propose an iterative procedure to compute the corrected level α^* and show that this procedure is exponentially fast. We also show that the α-TOST is uniformly more powerful than the TOST and the level-adjusted versions of the SABE.

3.1. The TOST Procedure

For testing the hypotheses in (2), the TOST uses the two following test statistics:

$$Z_L := \frac{\widehat{\theta} + c}{\widehat{\sigma}_\nu}, \quad \text{and} \quad Z_U := \frac{\widehat{\theta} - c}{\widehat{\sigma}_\nu},$$

where Z_L tests for $\mathrm{H}_{01} : \theta \leqslant -c$ versus $\mathrm{H}_{11} : \theta > -c$, and Z_U tests for $\mathrm{H}_{02} : \theta \geqslant c$ versus $\mathrm{H}_{12} : \theta < c$. At a significance level α, the TOST therefore rejects $\mathrm{H}_0 := \mathrm{H}_{01} \cup \mathrm{H}_{02} = \theta \notin \Theta_1$ in favor of $\mathrm{H}_1 := \mathrm{H}_{11} \cap \mathrm{H}_{12} = \theta \in \Theta_1$ if both tests simultaneously reject their marginal null hypotheses, that is, if

$$Z_L \geqslant t_{\alpha,\nu}, \quad \text{and} \quad Z_U \leqslant -t_{\alpha,\nu},$$

where $t_{\alpha,\nu}$ denotes the upper α quantile of a t distribution with ν degrees of freedom. The corresponding rejection region of the TOST, for any σ_ν, is given by

$$C_1(\sigma_\nu) := \left\{ \theta \in \mathbb{R},\, \sigma_\nu \in \mathbb{R}_+ \,\middle|\, c \geqslant |\theta| + t_{\alpha,\nu}\sigma_\nu \right\}. \tag{3}$$

Consequently and as noted in Figure 3, equivalence cannot be accepted with the TOST for all $\sigma_\nu > \sigma_{\max} := c/t_{\alpha,\nu}$, even for $\widehat{\theta} = 0$.

With respect to the TOST's TIER, given α, θ, σ_ν, ν and c, the probability that equivalence is accepted can be expressed as follows (see also Phillips, 1990):

$$\begin{aligned} p(\alpha, \theta, \sigma_\nu, \nu, c) :=& \Pr\left(Z_L \geqslant t_{\alpha,\nu} \text{ and } Z_U \leqslant -t_{\alpha,\nu}, \,\middle|\, \alpha, \theta, \sigma_\nu, \nu, c\right) \\ =& Q_\nu\left(-t_{\alpha,\nu}, \frac{\theta - c}{\sigma_\nu}, \lambda\right) - Q_\nu\left(t_{\alpha,\nu}, \frac{\theta + c}{\sigma_\nu}, \lambda\right), \end{aligned} \tag{4}$$

where $\lambda := \frac{c\sqrt{\nu}}{\sigma_\nu t_{\alpha,\nu}}$ and $Q_\nu(t, y, z)$ corresponds to a special case of Owen's Q-function (Owen, 1965), a bivariate non-central Student distribution, defined as

$$Q_\nu(t, y, z) := \frac{\sqrt{2\pi}}{\Gamma\left(\frac{1}{2}\nu\right) 2^{\frac{1}{2}(\nu-2)}} \int_0^z G\left(\frac{tx}{\sqrt{\nu}} - y\right) x^{\nu-1} G'(x) dx,$$

where

$$G'(x) := \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{1}{2}x^2\right), \quad \text{and} \quad G(x) := \int_{-\infty}^{x} G'(t)dt.$$

Then, for given values of α, σ_ν and ν, the TOST's TIER is defined as the supremum of (4) (see e.g., Lehmann, 1986), and is given by

$$\omega(\alpha, c, \sigma_\nu, \nu) := \sup_{\theta \notin \Theta_1} p(\alpha, \theta, \sigma_\nu, \nu, c) = p(\alpha, c, \sigma_\nu, \nu, c) = Q_\nu\left(-t_{\alpha,\nu},\, 0,\, \lambda\right) - Q_\nu\left(t_{\alpha,\nu},\, \frac{2c}{\sigma_\nu},\, \lambda\right). \tag{5}$$

We can then deduce that the TOST is α-level, by noting that, for $\sigma_\nu > 0$, we have

$$\begin{aligned} \omega(\alpha, c, \sigma_\nu, \nu) < Q_\nu\left(-t_{\alpha,\nu},\, 0,\, \lambda\right) &= \frac{\sqrt{2\pi}}{\Gamma\left(\frac{1}{2}\nu\right) 2^{\frac{1}{2}(\nu-2)}} \int_0^{\lambda} G\left(-\frac{t_{\alpha,\nu}x}{\sqrt{\nu}}\right) x^{\nu-1} G'(x)dx \\ &< \frac{\sqrt{2\pi}}{\Gamma\left(\frac{1}{2}\nu\right) 2^{\frac{1}{2}(\nu-2)}} \int_0^{\infty} G\left(-\frac{t_{\alpha,\nu}x}{\sqrt{\nu}}\right) x^{\nu-1} G'(x)dx = \Pr\left(T_\nu \leqslant -t_{\alpha,\nu}\right) = \alpha, \end{aligned} \tag{6}$$

where T_ν denotes a random variable following a t-distribution with ν degrees of freedom, so that

$$\lim_{\sigma_\nu \to 0} \omega(\alpha, c, \sigma_\nu, \nu) = \alpha.$$

Thus, while the TOST's TIER is indeed α-level, it actually never achieves a level of α, except in the theoretical case of $\sigma_\nu = 0$, as already highlighted by several authors (see e.g., Deng and Zhou, 2020, and the references therein). When $\widehat{\sigma}_\nu$ is small, the difference between the TIER and α is marginal, but as $\widehat{\sigma}_\nu$ approaches or exceeds $c/t_{\alpha,\nu}$, this difference increases, leading to a high probability of the TOST failing to detect equivalence when it exists. As a solution to this issue, we suggest an alternative approach, the α-TOST, that corrects the TIER of the TOST for any value of $\widehat{\sigma}_\nu$ and still allows to assess equivalence by means of confidence intervals, as depicted in Figure 2.

3.2. Adjusted α-TOST

A corrected level version of the TOST can, theoretically, be constructed by adjusting the test level and using α^* instead of α in the standard TOST procedure, where

$$\alpha^* := \alpha^*(\sigma_\nu) = \underset{\gamma \in [\alpha, 0.5)}{\text{argzero}} \left[\omega(\gamma, c, \sigma_\nu, \nu) - \alpha\right], \tag{7}$$

with $\omega(\gamma, c, \sigma_\nu, \nu)$ defined in (5). The dependence of α^* on α and ν is omitted from the notation as these quantities are known. A similar type of correction was also used to amend the level of the SABE procedure by Labes and Schütz (2016) and Ocaña and Muñoz (2019) (see also Palmes et al., 2022, for power adjustment), but, in these cases, the adjusted level was reduced (instead of increased like in (7)) so that the TIER does not exceed the nominal level of α, thus the aim of these adjustments is not the same as the one proposed here. Furthermore, the TIER of the α-TOST is guarantied to be exactly α when σ_ν is known, which is not the case for these competing methods.

The conditions under which α^* exists are explained in Appendix A. In particular, they can be translated into a maximal value for the estimated standard error $\widehat{\sigma}_\nu$, that is $\widehat{\sigma}_\nu < \frac{2c}{\Phi^{-1}(\alpha+0.5)}$. As explained in Section 3.3, this bound

allows the α-TOST to have a non nil power for larger values of σ_ν, compared to other methods satisfying the IIP.

Since, $\alpha^*(\sigma_\nu)$ is a population level quantity as it depends on the unknown quantity σ_ν, a natural estimator for its sample value is given by

$$\widehat{\alpha}^* := \alpha^*(\widehat{\sigma}_\nu) = \underset{\gamma \in [\alpha, 0.5)}{\text{argzero}} \left[\omega(\gamma, c, \widehat{\sigma}_\nu, \nu) - \alpha\right]. \tag{8}$$

Hence, in practice, based on the (estimated) corrected level $\widehat{\alpha}^*$, the α-TOST procedure rejects the non-equivalence null hypothesis in favour of the equivalence one at the level α, if $Z_L > t_{1-\widehat{\alpha}^*,\nu}$ and $Z_U < -t_{1-\widehat{\alpha}^*,\nu}$. In Section 4, we compare, in a simulation study, the TIER and power of different methods, when σ_ν needs to be estimated and show that α-TOST keeps a relatively good TIER, at least compared to other available methods.

The corrected level $\widehat{\alpha}^*$ can easily be computed using the following iterative approach. At iteration k, with $k \in \mathbb{N}$, we define

$$\alpha^{*(k+1)} = \alpha + \alpha^{*(k)} - \omega\left(\alpha^{*(k)}, c, \widehat{\sigma}_\nu, \nu\right), \tag{9}$$

with $\omega(\ldots)$ given in (5) and where the procedure is initialized at $\alpha^{(0)} = \alpha$. This simple iterative approach converges exponentially fast to $\widehat{\alpha}^*$ as it can be shown that

$$\left|\alpha^{*(k+1)} - \alpha^*\right| < \frac{1}{2}\exp(-bk),$$

for some positive constant b (see Appendix B for more details).

3.3. Power Analysis

Since, compared to the TOST, the acceptance of equivalence with the α-TOST approach is evaluated using an interval computed by considering a smaller value of $t_{\alpha,\nu}$, as $\alpha^* > \alpha$, the α-TOST rejection interval is necessarily larger than its TOST counterpart. This implies that the α-TOST is uniformly more powerful than the TOST, and explains cases like the ones encountered in the porcine skin case study presented in Section 2, in which equivalence is accepted using the α-TOST but not with the TOST (which has an empirical power of 0 given $\widehat{\sigma}_\nu$).

Figure 4 compares the rejection regions of the TOST, α-TOST and of the level-corrected EMA implementation of the SABE of Labes and Schütz (2016) for different values of ν ranging from $\nu = 12$ to $\nu = 36$. The EMA corrected approach was selected here as it it respects the IIP, guaranties a TIER of α. The implementation and correction of the FDA procedure (see e.g., Muñoz et al., 2016) would lead to the same conclusions. We can see that, for all values of ν and $\widehat{\sigma}_\nu$ considered here, the rejection regions of the TOST and EMA corrected approaches are embedded in the α-TOST one, meaning that our approach is uniformly more powerful than both methods. The comparison of the rejection regions of α-TOST and EMA corrected approaches shows that the difference in power decreases with increasing values of ν and that the α-TOST maintains a power that is not nil for larger values of $\widehat{\sigma}_\nu$, namely up to $\frac{2c}{\Phi^{-1}(\alpha+0.5)} \approx 3.55$ (see Appendix A). It should be noted that allowing a testing procedure to accept for equivalence when the standard error is allowed to take very large values might be questionable (see also the discussion in Choi et al., 2008). We believe that the definition of an acceptable range of standard errors goes beyond a simple statistical rationale and ultimately relies on the discretion of practitioners and/or regulatory authorities.

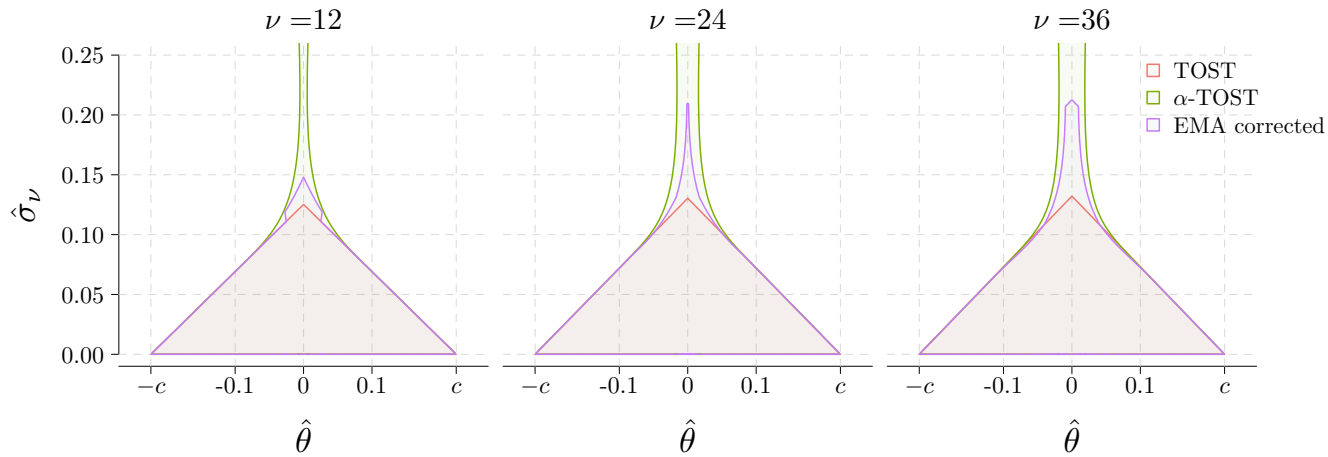

Figure 4: Equivalence test rejection regions of 3 methods, the TOST (red), the α-TOST (green) and the level-corrected EMA implementation of the SABE of Labes and Schütz (2016) (EMA corrected, purple), as a function of $\widehat{\theta}$ (x-axis), $\widehat{\sigma}_\nu$ (y-axis) and ν (plots) with $c = \log(1.25)$ and $\alpha = 5\%$. For all values of ν and $\widehat{\sigma}_\nu$ considered here, the rejection regions of the TOST and EMA corrected approaches are embedded in the α-TOST one, meaning that our approach is more powerful.

Finally, note that the idea of correcting the CI length by adjusting the critical values is not new, and has been used, for example, by Cao and Mathew (2008) who proposed an adjustment depending on the standard error and obtained by linear interpolation. Their Table 1 thus proposes adjusted critical values that evolve with piecewise values of $\widehat{\sigma}_\nu$. The lower plot of Figure 7 of appendix C compares the critical values obtained with the method of Cao and Mathew (2008) to the ones obtained by the α-TOST for different values of $\widehat{\sigma}_\nu$ and ν. We can note that, for all values of ν considered here and for values of $\widehat{\sigma}_\nu$ above 0.1, the critical values of Cao and Mathew (2008) correspond to a piecewise version of the critical values of the α-TOST obtained when ν is large. Therefore, their correction appears to be an approximation of the α-TOST, evaluated asymptotically, i.e., at $\nu \to \infty$.

4. Simulation Study: Comparing the TIER and Power of Different Methods

The analyses shown in Section 3.3 were performed using the (unknown) true values for σ_ν and θ. In practice, however, these must be estimated. In this section, we conduct a Monte Carlo simulation study to assess the TIER and power operating characteristics of different procedures when σ_ν and θ are estimated. We selected the same methods as considered in Section 3.3 to which we added the (non-corrected) EMA to showcase that its TIER can be well above the level α. For given values of $\theta, c, \nu, \sigma_\nu$ and α, the simulation process to evaluate the TIER and power of the α-TOST can be described using the following steps for each Monte Carlo sample $b = 1, \ldots, B$:

1. simulate two values for $\widehat{\theta}$, namely $\widehat{\theta}_{b,0}$ and $\widehat{\theta}_{b,c}$, using (1), with $\theta = 0$ for the power and $\theta = c$ for the TIER,
2. simulate one value for $t = \frac{\nu\widehat{\sigma}_\nu^2}{\sigma_\nu^2}$ using (1) and set $\widehat{\sigma}_{\nu,b} = \sqrt{t \cdot \sigma_\nu^2/\nu}$,
3. compute $\widehat{\alpha}^*$ using (the algorithm associated to) (7) with $\widehat{\sigma}_{\nu,b}$ instead of σ_ν,
4. compute $t_{\widehat{\alpha}*,\nu,b}$.

The finite sample TIER is then obtained as

$$\frac{1}{B}\sum_{b=1}^{B}\eta\left(c \geqslant |\widehat{\theta}_{b,c}| + t_{\widehat{\alpha}*,\nu,b}\widehat{\sigma}_{\nu,b}\right)$$

and the finite sample power as

$$\frac{1}{B}\sum_{b=1}^{B}\eta\left(c \geqslant |\widehat{\theta}_{b,0}| + t_{\widehat{\alpha}*,\nu,b}\widehat{\sigma}_{\nu,b}\right),$$

where $\eta(\cdot)$ is the indicator function with $\eta(A) = 1$ if A is true and 0 otherwise. For the other methods, Steps 1 and 2 are the same, and the following ones are adapted to the specific methods. The parameters' values for the Monte Carlo simulation are presented below.

Simulation 1: Parameters' values for the simulation study.

- $c = \log(1.25)$,
- $\nu = 20, 30, 40$,
- $\sigma_\nu = 0.01, 0.012, \ldots, 0.6$,
- $\alpha = 5\%$,
- $B = 10^4$, the number of Monte Carlo simulations per parameters combination.

Figure 5 shows the Monte Carlo finite sample TIER estimates as a function of σ_ν and ν for the different methods of interest. We can note that, as expected, the EMA procedure can have a TIER well above the $\alpha = 5\%$ nominal level, while the other three methods successfully guaranty a TIER of at most 5%. Under all scenarios considered here, the α-TOST is the method allowing to maintain the highest non-liberal TIER, especially when the number of degrees of freedom is large. Both the TOST and the EMA corrected approaches have a TIER that becomes nil for relatively small values of σ_ν (around 0.274).

The behaviour of the TIER has a direct consequence on the power, as can be seen in Figure 6 showing the Monte Carlo finite sample power estimates as a function of σ_ν and ν for the different methods of interest. Indeed, for the TOST and EMA corrected, the power is zero when the TIER is zero, which is achieved at values of σ_ν around 0.274. The seemingly large power of the EMA is a consequence of its TIER being well above the level α. When its TIER stops being liberal with growing values of σ_ν, its power is dominated by the one of the α-TOST. The power of the α-TOST non-only remains above the one of its competitors with non-liberal TIER under all configurations of Simulation 1, it is also greater than 0 for all values of σ_ν considered here.

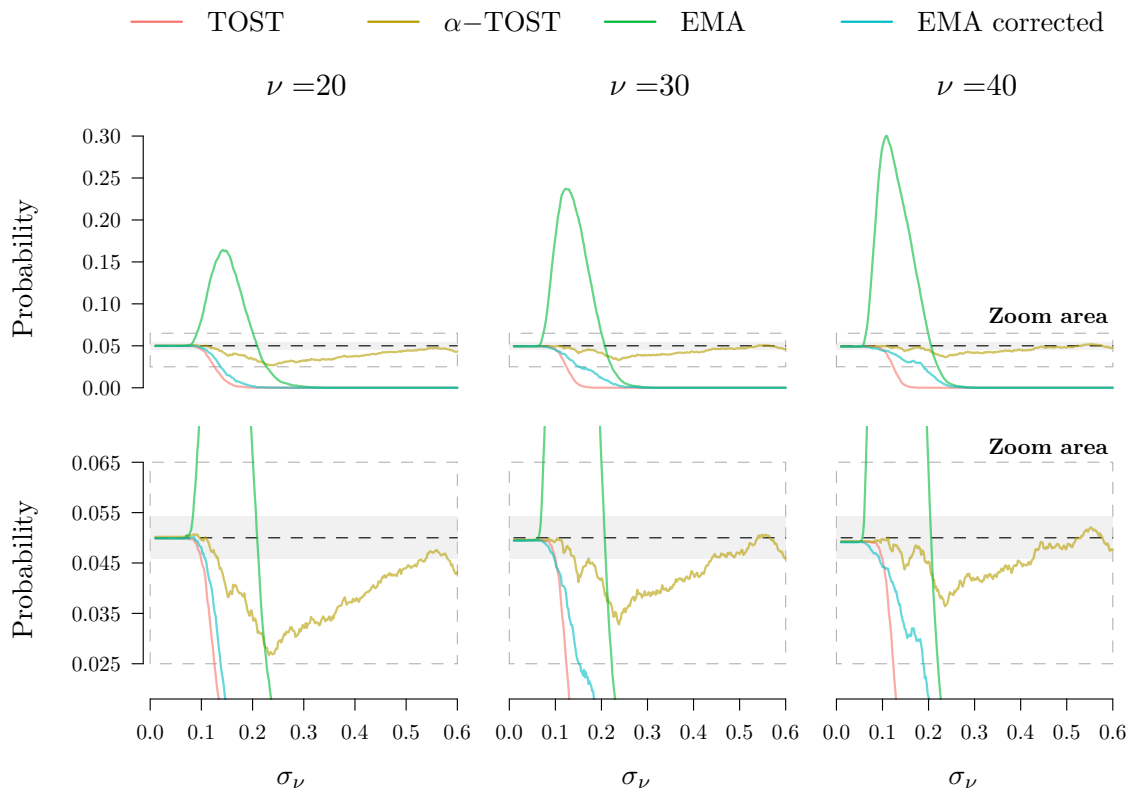

Figure 5: Finite sample TIER (y-axes) computed using the simulation setting in Simulation 1 as a function of σ_ν (x-axes), and ν (columns) for the different methods of interest (colours). Top panels: complete results. Bottom panels: TIER truncated outside $(0.025; 0.065)$. The shaded gray areas correspond to the pointwise 95% Monte Carlo tolerance band. We can note that the TIER of the TOST and EMA corrected approaches tend to be overly conservative for values of $\sigma_\nu > 0.1$, with a slight advantage of the EMA corrected approach compared to the TOST for values of σ_ν below 0.2, especially when ν is large. As expected the original EMA approach is overly liberal for some range of σ_ν. Under all scenarios considered here, the α-TOST is the method allowing to maintain the highest non-liberal TIER.

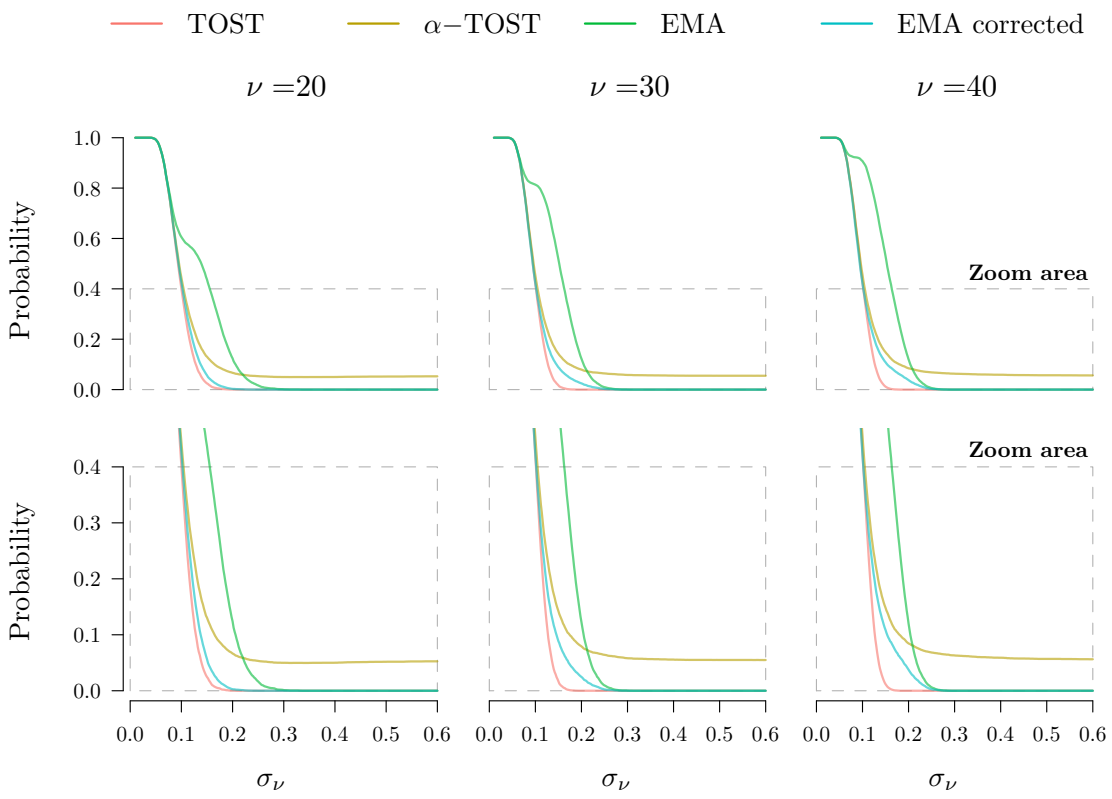

Figure 6: Finite sample power (y-axes) computed using the simulation setting in Simulation 1 as a function of σ_ν (x-axes), and ν (columns) for the different methods of interest (colours). Top panels: complete results. Bottom panels: power truncated below 0.4. The power of the α-TOST non-only remains above the one of its competitors with non-liberal TIER under all configurations of Simulation 1, it is also greater than 0 for all values of σ_ν considered here.

5. Discussion

The canonical framework treated in this paper is given in (1) and therefore concerns differences that can be assumed to be normally distributed (in finite samples), with a known finite sample distribution for $\widehat{\sigma}_\nu$. This framework covers a quite large spectrum of data settings, such as typically the standard two-period crossover experimental design (see e.g., Kenward MG, 2015), and could be extended to include covariates to possibly reduce residual variance. Extensions to non-linear cases, such are for example binary outcomes (see e.g., Dunnett and Gent, 1977; Tu, 1998; Schouten and Kester, 2010; Lui and Chang, 2011; Ostrovski, 2022, and the references therein), would follow the same logic, but would require a specific treatment which is due to the nature of the responses and also the associate function that is used (e.g., ratio of proportions, odds ratios). These extensions also deserve some attention but are left for further research.

For the sample size calculation, one could, in principle, proceed as with the TOST, but with the value of α^* obtained in (7), for given values of c, θ and σ_ν. However, when considering high levels of power, as shown in Section 4, the correction is negligible and we have $\alpha^* \approx \alpha$, so that computing the sample size can be done using the TOST, as implemented in standard packages.

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Appendices

A. Existence of α^*

In this section, we state the conditions for α^*, defined in (7), to be a singleton. Fixing α, c, $\widehat{\sigma}_\nu$, and ν, we simplify our notation so that $\omega(\gamma) := \omega(\gamma, c, \widehat{\sigma}_\nu, \nu)$ and let

$$\mathcal{A} := \left\{ x \in [\alpha,\, 0.5) \,\middle|\, \omega(\gamma) > 0 \right\}.$$

The function $\omega(\gamma)$, defined in (5), is continuous differentiable and strictly increasing in γ in $\mathcal{A}$. From (6), we have that $\alpha \geqslant \omega(\alpha)$. Thus, it is sufficient to show that $\alpha < \alpha_{\max} := \lim_{\alpha \to 0.5^-} \omega(\alpha)$, where $\alpha \to 0.5^-$ denotes the limit from below 0.5, to ensure that α^* is a singleton. Let $T_{\nu,\delta}$ denote a random variable following a non-central t-distribution with ν degrees of freedom and noncentrality parameter δ, $\Phi(x)$ denote the cumulative distribution function of the standard normal distribution, and $\delta := 2c/\sigma_\nu$. Then, we have

$$\begin{aligned}\alpha_{\max} &= \lim_{\gamma \to 0.5^-} \omega(\gamma) = \lim_{\gamma \to 0.5^-} \left\{ Q_\nu\left(-t_{\gamma,\nu},\, 0,\, \frac{c\sqrt{\nu}}{\sigma_\nu t_{\gamma,\nu}}\right) - Q_\nu\left(t_{\gamma,\nu},\, \delta,\, \frac{c\sqrt{\nu}}{\sigma_\nu t_{\gamma,\nu}}\right) \right\} \\ &= \Pr\left(T_{\nu,0} \leqslant 0\right) - \Pr\left(T_{\nu,\delta} \leqslant 0\right) = 0.5 - \Pr\left(T_{\nu,\delta} \leqslant 0\right) = 0.5 - \Phi(-\delta) = \Phi(\delta) - 0.5.\end{aligned}$$

Thus, the condition $\alpha < \alpha_{\max}$ can expressed as follows

$$\Phi(\delta) - 0.5 > \alpha \quad \Longleftrightarrow \quad \frac{2c}{\sigma_\nu} > \Phi^{-1}(\alpha + 0.5) \quad \Longleftrightarrow \quad \sigma_\nu < \frac{2c}{\Phi^{-1}(\alpha + 0.5)}.$$

Therefore, the condition $\sigma_\nu < \frac{2c}{\Phi^{-1}(\alpha+0.5)}$ implies that $\alpha < \alpha_{\max}$ and, consequently that α^* is a singleton

B. Convergence Rate of the Iterative Approach for α^*

Using the notation of Appendix A and for $\gamma \in \mathcal{A}$, we have that $\omega(\gamma)$ is continuously differentiable and such that $0 < \dot{\omega}(\gamma) < 2$, where

$$\dot{\omega}(\gamma) := \left.\frac{\partial}{\partial x}\omega(x)\right|_{x=\gamma}.$$

Next, we define

$$T(\gamma) := \alpha + \gamma - \omega(\gamma).$$

For all $\alpha_1, \alpha_2 \in \mathcal{A}$, we have the mean value theorem stating that

$$T(\alpha_1) - T(\alpha_2) = \alpha_1 - \alpha_2 - \omega(\alpha_1) + \omega(\alpha_2) = \alpha_1 - \alpha_2 + \dot{\omega}(\alpha^*)(\alpha_2 - \alpha_1),$$

where $\alpha^* = \tau\alpha_1 + (1-\tau)\alpha_2$ for some $\tau \in [0,1]$. Thus, we obtain

$$\left|T(\alpha_1) - T(\alpha_2)\right| = \left|\left\{1 - \dot{\omega}(\alpha^*)\right\}(\alpha_1 - \alpha_2)\right| = \left|1 - \dot{\omega}(\alpha^*)\right| \left|\alpha_1 - \alpha_2\right| < \left|\alpha_1 - \alpha_2\right|.$$

Then, using Kirszbraun theorem (see Federer, 2014), we can extend the function $T(\gamma)$ with respect to $\gamma \in \mathcal{A}$ to a contraction map from $\mathbb{R}$ to $\mathbb{R}$. Thus, Banach fixed point theorem ensures that $T\left(\alpha^{*(k)}\right)$ converges as $k \to \infty$. We then define the limit of the sequence $\left(\alpha^{*(k+1)}\right)_{k\in\mathbb{N}}$ as α^*, which is the unique fixed point of the function $T(\gamma)$. Indeed, we have

$$\alpha^* = T\left(\alpha^*\right) = \alpha + \alpha^* - \omega\left(\alpha^*\right).$$

By rearranging terms, we have

$$\alpha^* = \underset{\gamma\in\mathcal{A}}{\text{argzero}}\ \omega\left(\gamma\right) - \alpha = \underset{\gamma\in[\alpha,0.5)}{\text{argzero}}\ \omega\left(\gamma\right) - \alpha,$$

concluding the convergence of the sequence $\left(\alpha^{*(k+1)}\right)_{k\in\mathbb{N}}$. As a result, there exists some $0 < \epsilon < 1$ such that for $k \in \mathbb{N}$ we have

$$\left|\alpha^{*(k+1)} - \alpha^*\right| < \epsilon^k \left|\alpha^* - \alpha\right| < \frac{1}{2}\exp(-bk),$$

for some positive constant b.

C. Comparison of the α-TOST with Cao and Mathew (2008) Method

In Figure 7, the critical values for different values of ν, obtained by Cao and Mathew (2008) (Table 1) and the ones obtained using the α-TOST, are compared. One can see that the method of Cao and Mathew (2008) appears to be an approximation of the α-TOST, evaluated asymptotically, i.e., at $\nu \to \infty$.

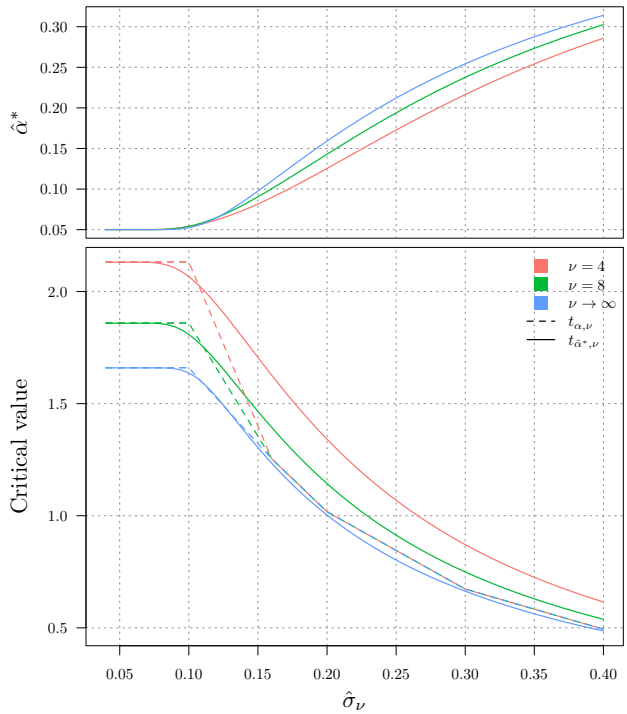

Figure 7: Upper panel: values of $\widehat{\alpha}^*$ of the α-TOST (y-axis) as a function of $\widehat{\sigma}_\nu$ (x-axis) for different values of ν (coloured lines). Lower panel: Comparison of the critical values (y-axis) obtained by the method of Cao and Mathew (2008)(dashed lines showing $t_{\tilde{\alpha},\nu}$) and of the α-TOST (solid lines showing $t_{\widehat{\alpha}*,\nu}$)as a function of $\widehat{\sigma}_\nu$ (x-axis) for different values of ν (coloured lines). Note that for all values of ν considered here and for values of $\widehat{\sigma}_\nu$ above 0.1, the critical values of Cao and Mathew (2008) correspond to a piece-wise version of the critical values of the α-TOST obtained when ν is large. Therefore, their correction appears to be an approximation of the α-TOST, evaluated asymptotically, i.e., at $\nu \to \infty$.