Expected Power for the TOST Procedure

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The following elaboration is based on [1], [2], [4] and [5].

1 Motivation

For some fixed $\theta_0 \in \mathbb{R}$, $\sigma^2 \in \mathbb{R}_{>0}$, let π denote the power function $\pi(\theta_0, \sigma^2) = \mathbb{P}\big(R \,|\, \theta_0, \sigma^2\big)$, where the event R denotes the rejection of the null hypothesis of non-equivalence. We assume that the parameters are specified on the additive scale. The function $\pi = \pi(\theta_0, \sigma^2)$ is the same as in equation (I) in the short cursory excerpt on BE within inst/doc/.

This power function is conditional on the unknown (true) values θ_0 and σ^2. That is, it is assumed that those parameters are given as known entities. Therefore, this probability only reflects the probability of trial success if θ_0 and σ^2 are known with absolute certainty. This assumption may however not be valid in practice. The concept of the *expected power* (or *assurance*) aims at defining the power without conditioning on those parameters.

2 Expected power

For some parameter of interest $\boldsymbol{\theta}$, the expected power is the (weighted) average power over all possible values of $\boldsymbol{\theta}$. The weights are chosen according to the likelihood of an outcome to occur. More precisely, the expected power is defined as $\mathbb{E}(\pi(\boldsymbol{\theta}))$, where the expectation is taken with respect to the probability distribution of $\boldsymbol{\theta}$. It can therefore be seen as unconditional probability of success. In other words, the expected power does not assume that the parameter $\boldsymbol{\theta}$ is known but is estimated from a prior study and hence is associated with some uncertainty. It therefore provides a measure to deal with uncertainty regarding $\boldsymbol{\theta}$. Depending on the setting we can consider $\boldsymbol{\theta}$ being σ^2, θ_0 or (θ_0, σ^2) and therefore deal with uncertainty with respect to either one of these choices.

How should the distribution for $\boldsymbol{\theta}$ be chosen? We define a prior distribution with respect to some pilot trial from which information on the treatment effect θ_0 and/or variability σ^2 may be obtained. After observing the parameter of interest, the distribution will be updated to give a posterior distribution which is then used in the definition of the expected power (it is considered a prior distribution with respect to the trial to be planned).

3 Application to bioequivalence trials

3.1 Uncertainty with respect to σ^2

We first deal with the case where uncertainty with respect to σ^2 only should be accounted for. Consider the function $\pi_{\theta_0 \cdot} : \mathbb{R}_{>0} \to [0,1]$, $v \mapsto \pi(\theta_0, v)$, where $\theta_0 \in \mathbb{R}$ is some fixed value. We need to derive $\mathbb{E}\big(\pi_{\theta_0 \cdot}(\sigma^2)\big)$, i.e. the expected value with respect to σ^2. As prior distribution of σ^2 we choose Jeffreys' prior as in [1] and [2, Example 6.26]. Thus, given the observed information $\hat{\sigma}^2$ from the historical trial, the posterior distribution of σ^2 is given by the inverse gamma distribution with shape and scale parameters $\frac{\hat{\nu}_m}{2}$ and $\frac{\hat{\nu}_m}{2} \cdot \hat{\sigma}^2$, respectively, where $\hat{\sigma}^2$ and $\hat{\nu}_m$ denote the observed residual variance and degrees of freedom from the historical trial, respectively. Note that for this case Julious and Owen [3] provide an approximate formula for the expected power.

3.2 Uncertainty with respect to θ_0

Now consider the case where uncertainty with respect to only θ_0 should be dealt with. We consider the function $\pi_{\cdot \sigma^2} : \mathbb{R} \to [0,1]$, $t \mapsto \pi(t, \sigma^2)$, where $\sigma^2 \in \mathbb{R}_{>0}$ is some fixed value. In order to derive $\mathbb{E}(\pi_{\cdot \sigma^2}(\theta_0))$ we use Jeffreys' prior for θ_0 (with σ^2 known) which leads to the posterior distribution $N(\hat{\theta}_0, \frac{\sigma^2}{\lambda})$, where $\lambda = \frac{m}{\mathrm{bk}}$, m is the total sample size of the historical trial and bk is the design specific constant (= 2 for non-replicated trials). More generally, λ may be re-written using the standard error of the difference of means from the historical trial: $\lambda = \left(\frac{\sigma}{\mathrm{sem}_m}\right)^2$ (which coincides with the previous definition for the case of no missing data and balanced groups). See for example [2, Example 6.25 and 6.26].

3.3 Uncertainty with respect to σ^2 and θ_0

Finally, if uncertainty with respect to both parameters should be accounted for, consider the function $\pi_{\cdot\cdot} : \mathbb{R} \times \mathbb{R}_{>0} \to [0,1]$, $(t, v) \mapsto \pi(t, v)$. For the expected power $\mathbb{E}\big(\pi_{\cdot\cdot}(\theta_0, \sigma^2)\big)$ we use the reference prior $d(\boldsymbol{\theta}) \propto \sigma^{-2}$ for $\boldsymbol{\theta} = (\theta_0, \sigma^2)$ which leads to the normal-inverse-gamma distribution with parameters $\mu = \hat{\theta}_0$, $\lambda = \frac{m}{\mathrm{bk}}$ (or $\left(\frac{\hat{\sigma}}{\hat{\mathrm{sem}}_m}\right)^2$), $\alpha = \frac{\hat{\nu}_m}{2}$, $\beta = \frac{\hat{\nu}_m}{2} \cdot \hat{\sigma}^2$ as posterior distribution, [2, Example 6.26].

Notes

- The distribution used in the first case (uncertainty with respect to σ^2) coincides with the conditional distribution $\sigma^2 \mid \theta_0 = \hat{\theta}_0$ from the joint posterior distribution (normal-inverse-gamma) from the last case (uncertainty with respect to both σ^2 and θ_0).
- Similarly, in the second case the relevant distribution is the conditional distribution $\theta_0 \mid \sigma^2 = \hat{\sigma}^2$.
- While it is often the case that the expected power value is smaller than the classical conditional power value (for fixed sample size), this is in general not true.
- Moreover, the expected power may be bounded above by a value less than 1, see e.g. [5].

4 Implementation details

4.1 Uncertainty with respect to σ^2

We need to evaluate the integral

$$\mathbb{E}\left(\pi_{\theta_0 \cdot}(\sigma^2)\right) = \int_0^\infty \pi_{\theta_0 \cdot}(v) f(v)\,\mathrm{d}v = \int_0^\infty \pi(\theta_0, v) f(v)\,\mathrm{d}v,$$

where π is the classical conditional power function as a function in v, θ_0 is some fixed real number and f is the densitiy of the inverse gamma distribution with parameters as described in section 3.1. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via change of variables using the transformation $v = \frac{u}{1-u}$ so that

$$\mathbb{E}\left(\pi_{\theta_0 \cdot}(\sigma^2)\right) = \int_0^1 \pi\left(\theta_0, \frac{u}{1-u}\right) f\left(\frac{u}{1-u}\right) \cdot \frac{1}{(1-u)^2}\,\mathrm{d}u\,.$$

The expected power is then calculated according to the right hand side using `stats::integrate` with relative error tolerance of 10^{-5}.

4.2 Uncertainty with respect to θ_0

We need to evaluate the integral

$$\mathbb{E}(\pi_{\cdot\sigma^2}(\theta_0)) = \int_{-\infty}^{\infty} \pi_{\cdot\sigma^2}(t) f(t)\,\mathrm{d}t = \int_{-\infty}^{\infty} \pi(t,\sigma^2) f(t)\,\mathrm{d}t,$$

where π is the classical conditional power function as a function in t, σ^2 is some fixed positive number and f is the densitiy of the normal distribution with parameters as described in section 3.2. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via change of variables using the transformation $t = \frac{u}{1-u^2}$ so that

$$\mathbb{E}(\pi_{\cdot\sigma^2}(\theta_0)) = \int_{-1}^{1} \pi\left(\frac{u}{1-u^2},\sigma^2\right) f\left(\frac{u}{1-u^2}\right) \cdot \frac{1+u^2}{(1-u^2)^2}\,\mathrm{d}t\,.$$

The expected power is then calculated according to the right hand side using `stats::integrate` with relative error tolerance of 10^{-5}.

4.3 Uncertainty with respect to σ^2 and θ_0

We need to evaluate the integral

$$\begin{aligned}
\mathbb{E}\big(\pi_{\cdot\cdot}(\theta_0,\sigma^2)\big) &= \int_{(-\infty,\infty)\times(0,\infty)} \pi_{\cdot\cdot}(t,v) f(t,v)\,\mathrm{d}(t,v) \\
&= \int_{-\infty}^{\infty}\int_{0}^{\infty} \pi_{\cdot\cdot}(t,v) f(t,v)\,\mathrm{d}v\,\mathrm{d}t \\
&= \int_{-\infty}^{\infty}\int_{0}^{\infty} \pi(t,v) f(t,v)\,\mathrm{d}v\,\mathrm{d}t,
\end{aligned}$$

where π is the classical conditional power as a function in (t,v) and f is the density of the normal-inverse-gamma distribution with parameters as described in section 3.3. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via repeated change of variables using the transformation $t = \frac{u}{1-u^2}$ and $v = \frac{w}{1-w}$ so that

$$\mathbb{E}\big(\pi_{\cdot\cdot}(\theta_0,\sigma^2)\big) = \int_{-1}^{1}\int_{0}^{1} \pi\left(\frac{u}{1-u^2},\frac{w}{1-w}\right) f\left(\frac{u}{1-u^2},\frac{w}{1-w}\right) \cdot \left|\frac{1}{(1-w)^2}\cdot\frac{1+u^2}{(1-u^2)^2}\right| \mathrm{d}w\,\mathrm{d}u\,.$$

The expected power is then calculated according to the right hand side using `cubature::hcubature` with maximum tolerance of 10^{-4}.

References

[1] A. Bertsche, G. Nehmiz, J. Beyersmann, and A P. Grieve. The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials. *Biometrical Journal*, 58(4):797–809, 2016. doi: 10.1002/bimj.201500245.

[2] L. Held and D. Sabanés Bové. *Applied Statistical Inference. Likelihood and Bayes*. Springer, 2014. doi: 10.1007/978-3-642-37887-4.

[3] S. A. Julious and R. J. Owen. Sample size calculations for clinical studies allowing for uncertainty in variance. *Pharmaceutical Statistics*, 5(1):29–37, 2006.

[4] A. O'Hagan, J. W. Stevens, and M. J. Campbell. Assurance in clinical trial design. *Pharmaceutical Statistics*, 4(3):187–201, 2005. doi: 10.1002/pst.175.

[5] M. L. Zierhut, P. Bycott, M. A. Gibbs, B. P. Smith, and P Vicini. Ignorance is not bliss: Statistical power is not probability of trial success. *Clinical Pharmacology and Therapeutics*, 99(4):356–359, 2016.