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 $\pi(\theta_0, \sigma^2) = \mathbb{P}\big(R \mid \theta_0, \sigma^2\big)$, 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 paramteres 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 $\mathbb{E}\left(\pi_{\theta_0\cdot}(\sigma^2)\right)$, 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 distribtuion $N(\hat{\theta}_0, \frac{\sigma^2}{\lambda})$, where $\lambda = \left(\frac{\sigma}{\widehat{\text{sem}}_m}\right)^2$ and $\widehat{\text{sem}}_m$ denotes the observed standard error of the difference of means from the historical trial, see [2, Example 6.26]. Note that in case of no missing data (and balanced sequences/groups) we have $\frac{\sigma^2}{\lambda} = \frac{\text{bk}\cdot\sigma^2}{m}$, where m is the total sample size of the historical trial.

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 $\mathbb{E}\left(\pi_{\cdot\cdot}(\theta_0, \sigma^2)\right)$ 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 $\mu = \hat{\theta}_0$, $\lambda = \left(\frac{\hat{\sigma}}{\widehat{\text{sem}}_m}\right)^2$, $\alpha = \frac{\hat{\nu}_m}{2}$, $\beta = \frac{\hat{\nu}_m}{\hat{\sigma}^2}$ 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.

4 Implementation details

4.1 Uncertainty with respect to σ^2

We need to evaluate the integral

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

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

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

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::adaptIntegrate` with maximum tolerance of 10^{-4}.

References

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