Fieller’s Theorem

Fieller’s theorem is used in finding a confidence set for a ratio of parameters, $\rho = \theta_1/\theta_2$. This problem arises in a variety of biostatistical problems including inverse dose estimation in quantal bioassay (see Quantal Response Models) [estimation of the LD50 (or median effective dose) is a special case], estimation of relative potency in slope-ratio and parallel-line bioassays (see [2]), and the assessment of bioequivalence. Other applications include inverse prediction in linear calibration and estimation of the point of intersection of two linear regressions or the point of extremum in a quadratic regression (see Polynomial Regression).

In general there are two statistics, $\hat{\theta}_1$ and $\hat{\theta}_2$, which estimate $\theta_1$ and $\theta_2$, respectively. It is assumed that $(\hat{\theta}_1, \hat{\theta}_2)$ follows either exactly or approximately a bivariate normal distribution with mean $(\theta_1, \theta_2)$ with $\sigma_{11} = \text{var}(\hat{\theta}_1)$, $\sigma_{22} = \text{var}(\hat{\theta}_2)$, and $\sigma_{12} = \text{cov}(\hat{\theta}_1, \hat{\theta}_2)$. An estimate of the covariance matrix is available with $\hat{\sigma}_{ij}$ denoting the estimate of $\sigma_{ij}$. In the original, exact form of Fieller’s theorem [1] $(\hat{\theta}_1, \hat{\theta}_2)$ is exactly normally distributed with $\sigma_{ij} = \sigma^2 v_{ij}$, where the $v_{ij}$ are known constants, and there is a $\hat{\sigma}$, independent of $(\hat{\theta}_1, \hat{\theta}_2)$, such that $d\hat{\sigma}^2/\sigma^2$ follows a chi-square distribution with $d$ degrees of freedom. This leads to

$$H(\rho) = \frac{(\hat{\theta}_1 - \rho \hat{\theta}_2)}{(\sigma_{11}^2 - 2\rho \sigma_{12} + \rho^2 \sigma_{22})^{1/2}}$$

following exactly a Student’s $t$ distribution with $d$ degrees of freedom. This arises when estimating a ratio of linear combinations in a normal linear model; see [5]. In other contexts $(\hat{\theta}_1, \hat{\theta}_2)$ is only approximately normal and the $\hat{\sigma}_{ij}$s are consistent estimators of the $\sigma_{ij}$s leading to $H(\rho)$ being approximately $t$ distributed with $d$ degrees of freedom; where $d = \infty$ designates a standard normal distribution.

With $t_{1-a/2}(d)$ denoting the 100$(1 - \alpha/2)$th percentile of the $t$ distribution with $d$ degrees of freedom,

$$P[H(\rho)^2 \leq t_{1-a/2}(d)^2] = 1 - \alpha.$$

This holds exactly or approximately according to whether $H(\rho)$ follows exactly or approximately a $t$ distribution, and the resulting confidence set is exact or approximate accordingly. Eq. (1) can be rewritten as $P(\hat{Q}(\rho) \leq 0) = 1 - \alpha$, where $\hat{Q}(\rho) = f_0 - 2f_1\rho + f_2\rho^2$ is a quadratic function of $\rho$, with $f_0 = \hat{\theta}_1^2 - t_{1-a/2}(d)^2\hat{\sigma}_{11}$, $f_1 = \hat{\theta}_1 \hat{\theta}_2 - t_{1-a/2}(d)^2\hat{\sigma}_{12}$, and $f_2 = \hat{\theta}_2^2 - t_{1-a/2}(d)^2\hat{\sigma}_{22}$. A confidence set for $\rho$ with confidence coefficient 1 $- \alpha$ is given by the set of values $\rho$ satisfying $\hat{Q}(\rho) \leq 0$. Defining $D = f_1^2 - f_0f_2$, $r_1 = (f_1 - D^{1/2}/f_2$, and $r_2 = (f_1 + D^{1/2}/f_2$, the confidence set for $\rho$ is:

Case 1. A finite interval $[r_1, r_2]$, if $D \geq 0$ and $f_2 \geq 0$.

Case 2. The complement of a finite interval, $(-\infty, r_2] \cup [r_1, \infty)$, if $D \geq 0$ and $f_2 < 0$.

Case 3. $(-\infty, \infty)$ if $D < 0$ and $f_2 < 0$.

It is known that $D < 0$ and $f_2 \geq 0$ cannot occur together; see [4]. Hence we get a finite interval if and only if $f_2 \geq 0$ or equivalently $|\hat{\theta}_2/\hat{\sigma}_{22}| \geq t_{1-a/2}(d)$, which means rejecting $H_0 : \theta_2 = 0$ (see Hypothesis Testing). When $f_2 < 0$ we do not reject $H_0 : \theta_2 = 0$ and the confidence set is infinite (Cases 2 and 3). Note that if $\theta_2 = 0$, then $\rho$ is ill defined. While such confidence sets have often been dismissed as uninformative or worse (Miller [3] calls them “absurdities”) they can have a reasonable interpretation. Fortunately, a finite interval usually results in practice.

One alternative confidence interval uses

$$\hat{\rho} \pm t_{1-a/2}(d) \sqrt{\frac{\hat{\sigma}_{11} - 2\hat{\rho} \hat{\sigma}_{12} + \hat{\rho}^2 \hat{\sigma}_{22}}{\hat{\sigma}^2}}^{1/2},$$

where $\hat{\rho} = \hat{\theta}_1/\hat{\theta}_2$. This results from a delta method approximation to the variance of $\hat{\rho}$. While this interval (which is close to $[r_1, r_2]$ from Fieller’s theorem for many data sets) is sometimes suitable it can perform badly in terms of achieving the desired confidence coefficient of 1 $- \alpha$.

References


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(See also Biological Assay, Overview)

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