

On Equivalence Criteria

Based on Multivariable Regression Models

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Outline

- 1 Introduction
 - Equivalence testing and motivation
 - Multiple linear regression model
- 2 Equivalence test for two unrelated samples adjusting for several covariates
 - Introducing auxiliary notations in the regression model
 - Confidence Interval Inclusion Principle
 - Testing procedures based on the non-central t-distribution
- 3 Example: Comparison of two formulations of Erythropoietin
 - Implementation in SAS

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Study Objectives

- The aim of the project is the development of equivalence criteria based on the parameters of (generalized) linear regression models.
- Using multivariable linear regression functions we try to establish the equivalence of two drugs or treatments.
- In addition to the target group variable, other variables will be incorporated in the models playing the role of covariables with respect to which one wants to adjust.
- After the selection of a function of the regression parameters yielding a reasonable measure of “distance” between the treatments under comparison, we derive the exact or asymptotic distribution of a suitable estimator for this parametric function.
- It will serve thereafter as the basis for the computation of a test statistic.

History

The development of equivalence tests received a decisive impulse in the late 60-ies, after the FDA established new regulations, which were supposed to govern the development of new generic drugs.

The statistical premises for the development of equivalence statistical tests were already created.

The preamble of the development of equivalence tests can be found in the works of Lehmann who in the 1959 wrote:

"One then sets up the (null) hypothesis that [the parameter] does not lie within the required limits so that an error of the first kind consists in declaring the parameter to be satisfactory when in fact it is not"

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Areas of Application

- Comparative bioequivalence trials
- Clinical trials involving an active control
- Tests for checking assumptions before carrying out other statistical tests (e.g. homoskedacity tests, goodness of fit tests)

Basic Equivalence Hypotheses.

We can then present the basic equivalence hypotheses, which were introduced to demonstrate bioequivalence, using e.g. one or more pharmacokinetic parameters (usually AUC , C_{max} or T_{max}):

$$H_0 : \frac{\mu_T}{\mu_R} \leq \delta_L \text{ or } \frac{\mu_T}{\mu_R} \geq \delta_U$$

versus

$$H_1 : \delta_L < \frac{\mu_T}{\mu_R} < \delta_U.$$

Here δ_L and δ_U are standards set by regulatory agencies (e.g. the EC proposed $\delta_L = 0.80$ and $\delta_U = 1.25$).

Basic Equivalence Hypotheses.

In most of the applications and motivated by FDA(EMEA) guidelines, logarithms are taken and the hypotheses are restated as follow:

$$H_0 : \eta_T - \eta_R \leq \theta_L \text{ or } \eta_T - \eta_R \geq \theta_U$$

versus

$$H_1 : \theta_L < \eta_T - \eta_R < \theta_U$$

Note that these tests could be seen as special cases of Intersection-Union tests, and therefore they could be decided at α level by combining two one sided α level tests.

In this introductory example the Intersection-Union tests is equivalent to the Confidence interval inclusion test.

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The Model

Consider the multiple linear regression model

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_p x_{ip} + u_i, \quad i = 1, 2, \dots, n$$

where

- 1 The u_i are mutually independent and identically distributed $E[u_i] = 0; V[u_i] = \sigma_u^2$.
- 2 The distributions of the u_i are independent,

$$E[Y] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_p X_p$$

and

$$V[Y] = \sigma_Y^2 = \sigma_u^2.$$

- 3 The unknown parameters $\beta_0, \beta_1, \beta_2, \dots, \beta_p$ are constant.

The Model

Using matrix notation this system of n equations can be written as

$$y = X\beta + u,$$

where

$$y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}_{n \times 1}; X = \begin{bmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1p} \\ 1 & x_{21} & x_{22} & \cdots & x_{2p} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & x_{n1} & x_{n2} & \cdots & x_{np} \end{bmatrix}_{n \times (p+1)}$$

$$\beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{bmatrix}_{(p+1) \times 1}; \text{ and } u = \begin{bmatrix} u_1 \\ u_2 \\ \vdots \\ u_n \end{bmatrix}_{n \times 1}.$$

Least Squares Estimations.

Given the observations in the sample y and the known matrix X , least squares estimations could be employed to estimate the parameter vector β . This procedure estimates that b vector that minimizes the observed sum of squares of the errors:

$$\zeta^2 = \sum_{i=1}^n (y_i - (\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_p x_{ip}))^2 = (y - X\beta)'(y - X\beta).$$

The solution can be calculated by solving the normal equations

$$X'y = X'X\beta.$$

If the matrix $X'X$ has full rank then the solution vector can be written as

$$b = (X'X)^{-1}X'y,$$

Least Squares Estimations.

This estimator is well known to be the best linear unbiased, which means that among those estimators of β , which are both unbiased and linear functions of y , the elements of b are the estimators with the smallest variances.

The variances of the estimator b could be summarized in the covariance matrix

$$E[(b - \beta)(b - \beta)'] = \begin{bmatrix} V(b_0) & C(b_0, b_1) & \cdots & C(b_0, b_p) \\ C(b_0, b_1) & V(b_1) & \cdots & C(b_0, b_p) \\ \vdots & \vdots & \ddots & \vdots \\ C(b_0, b_p) & C(b_0, b_p) & \cdots & V(b_p) \end{bmatrix}.$$

That matrix can be more concisely written as

$$\sigma_u^2(X'X)^{-1} =: \sigma_u^2 C.$$

Least Squares Estimations.

The elements on the diagonal of that matrix are just the estimates of the variances of the elements of the vector b .

An unbiased estimator of σ_u^2 is given by

$$s^2 = (y - Xb)'(y - Xb)/(n - p - 1).$$

Therefore an unbiased estimator of the variance of b_j is given by $s^2 c_{jj}$.

Inferences for the Regression Coefficients

For the individual regression coefficient β_j inferences can be made using the statistic

$$(b_j - \beta_j)/(s^2 c_{jj})^{1/2}.$$

It is a well known result that this statistic has a central t distribution with $n - p - 1$ degrees of freedom.

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Motivation

- Now let us consider a retrospective study, where our aim is to assess the equivalence of two drugs, e.g. the gold standard drug and a generic drug.
- In the study the patients in both cohorts could have very dissimilar demographical or other baseline characteristics. In such comparisons adjustment for those covariates is a necessity.
- Thus we could use a multiple linear regression model where we describe the outcome variable of interest as a function of the group variable, while adjusting for those covariables.

Notations in the Linear Regression Model.

As in the general multiple linear regression model we consider now the model

$$y = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_{p-1} x_{ip-1} + \nu g_i + u_i, \quad i = 1, 2, \dots, n.$$

Where now ν is the regression coefficient belonging to the group identifier G . We could as before write

$$y = X\beta + u,$$

Notations in the Linear Regression Model.

where

$$y = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}_{n \times 1} ; X = \begin{bmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1(p-1)} & g_1 \\ 1 & x_{21} & x_{22} & \cdots & x_{2(p-1)} & g_2 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 1 & x_{n1} & x_{n2} & \cdots & x_{n(p-1)} & g_n \end{bmatrix}_{n \times (p+1)}$$

$$\beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_{p-1} \\ v \end{bmatrix}_{(p+1) \times 1} ; u = \begin{bmatrix} u_1 \\ u_2 \\ \vdots \\ u_n \end{bmatrix}_{n \times 1} .$$

with c_g being the element in the diagonal of $C = (X'X)^{-1}$ associated to the group indicator.

Our Goal

Using this model, by calculating the parameter corresponding to the group variable, we will not only be able to get an estimate of the groups mean average difference, but also we will adjust the observed difference for the relevant covariates.

We could now use the coefficient estimate of the group variable for testing equivalence between groups effects by evaluating

$H_0 : \nu \leq -\varepsilon_1 \text{ or } \nu \geq \varepsilon_2$ versus $H_1 : -\varepsilon_1 < \nu < \varepsilon_2$.

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CIIC - Introduction

One of the most frequently used methods for the evaluation of equivalence tests is based on the confidence interval inclusion principle.

We will use that principle to evaluate the equivalence problem 5.

An appropriate statistic is constructed, which estimates the parameter of interest. Using the distribution of that statistic we then proceed calculating a confidence interval (L_l, L_u) around the parameter estimate obtained by evaluating the statistic with the observed sample. L_u and L_l are thus the lower and upper confidence limits for the one sided confidence levels.

The test based on the interval inclusion principle rejects H_0 if

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Application to Equivalence Testing of the Regression Parameter

For the coefficient ν of the group variable in the multiple linear regression model the $100(1 - \alpha)\%$ one sided confidence limits are equal to

$$b_g \pm t_{\alpha;(n-p-1)} \sigma_g,$$

plugging the σ_g estimator $sc_g^{\frac{1}{2}}$ we get

$$b_g \pm t_{\alpha;(n-p-1)} sc_g^{\frac{1}{2}},$$

where now b_g is the parameter estimate for the coefficient ν and c_g is the element on the diagonal of C , which is associated to the group identifier.

Application to Equivalence Testing of the Regression Parameter

Using therefore the interval inclusion principle, we reject the null hypothesis of inequivalence if

$$(b_g - t_{\alpha;(n-p-1)}sc_g^{\frac{1}{2}}; b_g + t_{\alpha;(n-p-1)}sc_g^{\frac{1}{2}}) \subset (-\varepsilon_1, \varepsilon_2).$$

Power Calculations

As seen before we reject the null hypothesis if

$$-\varepsilon_1 < b_g - t_{\alpha;(n-p-1)}\sigma_g$$

and

$$b_g + t_{\alpha;(n-p-1)}\sigma_g < \varepsilon_2$$

After a simple linear transformation of the regression parameter associated to the group variable, we could simplify the interval inclusion test to the case $\varepsilon_0 = \varepsilon_1 = \varepsilon_2$.

Then the test rejects if

$$|b_g| < \varepsilon_0 - t_{\alpha;(n-p-1)}\sigma_g$$

Power Calculations

The power of the interval inclusion test against an arbitrary fix alternative $-\varepsilon_0 < \varepsilon < \varepsilon_0$ can be calculated as

$$\begin{aligned}
 POW_{\varepsilon}(\varepsilon_0) &= P_{\varepsilon}(|b_g| < \varepsilon_0 - t_{\alpha;(n-p-1)}\sigma_g) = \\
 &= \int_0^{v(\varepsilon_0/\sigma_g;n-p-1,\alpha)} \left[\Phi\left(\frac{\varepsilon_0 - \varepsilon_1}{\sigma_g} - vt_{\alpha}^*\right) - \Phi\left(\frac{\varepsilon_0 - \varepsilon_1}{\sigma_g} + vt_{\alpha}^*\right) \right] \\
 &\quad \sqrt{n-p-1} \cdot g_{n-p-1}(\sqrt{n-p-1}v) dv
 \end{aligned}$$

Power Calculations

where

$$t_{\alpha}^* = t_{\alpha;(n-p-1)}, v(\varepsilon_0/\sigma_g; n-p-1, \alpha) = (\varepsilon_0/\sigma_g)/t_{\alpha}^*$$

and $g_{n-p-1}(\cdot)$ stands for the density function of the χ -distribution with $n-p-1$ degrees of freedom. Explicitly to [4]

$$g_n(u) = 2^{1-n/2} e^{-u^2/2} u^{n-1} / \Gamma(n/2).$$

Using that formula the power of the interval inclusion test can be carried out by slightly modifying a SAS macro found at http://www.zi-mannheim.de/wktsheq/pow_abe.

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The Decision Test

Another approach we could use to investigate the groups equivalence using the linear regression model could be done by formulating another testing problem, namely

$H_0 : |\nu|/\sigma \leq -\varepsilon_1$ or $|\nu|/\sigma \geq \varepsilon_2$ versus $H_1 : -\varepsilon_1 < |\nu|/\sigma < \varepsilon_2$,
where as before ν is the regression coefficient of the group identifier and σ is the standard deviation of the residual.

Introducing the Test Statistic

First, let us consider the following statistic $|b_g|/s$. This statistic is an estimator of the parameter of interest. After some elementary transformations we can see that

$$|b_g|/s = \left| c_g^{\frac{1}{2}} \cdot \frac{\frac{b_g - v}{\sigma_g} + \frac{v}{\sigma_g}}{\frac{\sqrt{n-p-1} s c_g^{\frac{1}{2}}}{\sigma_g}} \right|. \quad (1)$$

Introducing the Test Statistic

Now referring to Hogg and Craig (1978) b_g has normal distribution and thus

$$Z = \frac{b_g - v}{\sigma_g}$$

has a $N(0,1)$ distribution. On the other hand

$$(n - p - 1) \frac{s^2 c_g}{\sigma_g^2}$$

has a χ^2 distribution with $f = n - p - 1$ degrees of freedom and is statistically independent from Z , ...

Introducing the Test Statistic

... therefore the statistic between absolute value symbols in the second factor of the equation [1]

$$T_{n-p-1}\left(\frac{v}{\sigma_g}\right) = \frac{\frac{b_g - v}{\sigma_g} + \frac{v}{\sigma_g}}{\frac{\sqrt{n-p-1}sc_g^{\frac{1}{2}}}{\frac{\sigma_g}{\sqrt{n-p-1}}}}$$

has a non central t-distribution with f degrees of freedom and a non-centrality parameter

$$\frac{v}{\sigma_g} = \frac{v}{\sigma c_g}.$$

The Decision Test

On the boundaries of the 0-hypothesis the centrality parameter equals

$$-\frac{\varepsilon_1}{c_g} \left(\frac{\varepsilon_2}{c_g} \right).$$

Therefore $T_{n-p-1}^2 \left(\frac{v}{\sigma c_g} \right)$ has a “singly non central F-distribution” with 1, $n-p-1$ degrees of freedom and non centrality parameter $\left(\frac{v}{\sigma c_g} \right)^2$. Therefore on the boundaries of the 0-hypothesis the centrality parameter equals

$$\left(-\frac{\varepsilon_1}{c_g} \right)^2 = \left(\frac{\varepsilon_1}{c_g} \right)^2 \text{ or } \left(\frac{\varepsilon_2}{c_g} \right)^2.$$

We could therefore use the of the percentiles of the non central F-distribution for evaluating the null hypothesis above.

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Motivation

- The methods will be used for providing an answer to the question whether an EPO alpha being available in Latin American countries is comparable in efficacy and/or in safety to EPO alpha formulations produced in Europe.
- The study was a retrospective study, where we examined the efficacy of erythropoietin in patients treated with EPO in FME dialysis centers in Argentina compared to those in Europe.

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Motivation

- Erythropoetin, is a glycoprotein hormone that controls erythropoiesis, or red blood cell production, which is often used by hemodialysis (HD) patients.
- These drugs are effective for increasing the hemoglobin levels in any individual and particularly in patients treated with HD, as renal anemia is a frequent and primary complication in patients with kidney failure undergoing HD.

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SAS Code

Suppose an investigator consider a drop or gain in Hb within 1mg/dL as evidence of equivalence. We model the change in Hb level in both treatment group(defined by the continent). Using PROC MIXED in SAS:

```
proc mixed data=data_regr;
  title1 '6.3.2 EPO efficacy';
  title 'EPO efficacy with change in Hb level as response variable';
  class continent gender DIAB_21 EPOroute_21 va_21;
  model Hb_change=age_21 Hb_21 ferritin_21 DIAB_21 va_21
        EPOroute_21 IV_iron_dose_21 continent gender / solution covB;
  /*ods output ParameterEstimates=glmparms
        InvXPX=glmpxi;*/
run;
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Proc Mixed Output

Parameter Estimates and Covariance Matrix

Using the options solution and covB in the model statement we get the parameter estimates and the covariance matrix

The Mixed Procedure								
Covariance Matrix for Fixed Effects								
Row	Effect	continent	Gender	diab_21	EPOroute_21	va_21	Col11	Col12
1	Intercept						-0.00004	0.01035
2	age_21						-2.63E-8	-7.25E-6
3	Hb_21						2.059E-7	-0.00104
4	ferritin_21						2.242E-8	1.184E-7
5	diab_21			0			-1.31E-6	0.000173
6	diab_21			1				
7	va_21					1	1.879E-6	-0.00117
8	va_21					2		
9	EPOroute_21				1		-6.65E-6	-0.01263
10	EPOroute_21				2			
11	IV_iron_dose_21						7.622E-7	-1.46E-6
12	continent	1					-1.46E-6	0.01618
13	continent	2						
14	GENDER		1				-2.29E-6	0.000113
15	GENDER		2					

We have then $b_g = 0.457$, $(sc_g^{\frac{1}{2}})^2 = 0.01618$.

The resulting confidence interval around b_g is then

$(0.248, 0.666) \subset (-1, 1)$, and thus we reject inequivalence.

Summary

- The interval inclusion criteria was adapted for testing equivalence between two groups in a linear regression model.
- Power calculations were showed for the IIC for an equivalence test on a regression coefficient, including the practical implementation.
- An additional test based on noncentral F-distribution was derived for testing equivalence between two groups in a linear regression model.
- Outlook
 - Derive tests of equivalence when the X are not treated as a known matrix, but X is a random matrix.
 - Specify appropriate boundaries for the new equivalence tests.






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