Analytical method transfer: proposals for the location-scale approach and tolerance intervals

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The method transfer

Procedure

- an analytical method is established in laboratory a (*sender*)
- method shall be transferred to another laboratory b (*receiver*)
- Aim: to prove similarity of both laboratories. Hence:
- samples $i = 1, \ldots, n$ for analysis are created; each sample is split in two subsamples
- subsamples are analyzed in lab j, where $j = a, b$
- observations are denoted as x_{ij}

The method transfer

Data

- paired data
- method comparison: different data scales possible
  method transfer: same data scales
- range of method should cover all future incoming samples
- here: no repeated measurements (sample with a specific concentration not repeated)

In general

- correlation > 50%
- location test is not robust to a systematic proportional difference - however, this is not expected in an analytical method transfer

Example

Lipase activity of 51 different product batches was measured in two laboratories over a time period of approximately 2 years (collaborative trial).

total data consists of $2n$ ($n = 51$)
paired observations

lab a (Ph.Eur.-u/g)	**lab b (Ph.Eur.-u/g)**
59017	55943
138940	120628
31992	31496
61741	62585
65451	67979
80447	67923
108324	95589
58359	54479
23250	21903
30627	30454
...	...

Statistical guidelines for method transfer

- FDA Guidance for Industry: Protocols for the Conduct of Method Transfer Study for Type C Medicated Feed Assay Methods
- EMEA Validation of Bioanalytical Method
- FDA Guidance for Industry: Bioanalytical Method Validation

Trueness and precision should be lower than 15%.

→ trueness and precision can be interpreteded as location and scale
→ margin of 15% is multiplicative - therefore we suggest ratios

Selection of current statistical approaches

Typically, similarity of two laboratories is transferred to equivalence of the laboratories

- *test on equivalence for trueness and precision*
  location and scale usually combined with IUT (Choudhary et al., 2005)
  or one single test for location and scale (Bradley et al., 1989)
- *tolerance/predication intervals*
  test for limits of tolerance intervals (Zhong et al., 2008)
  total error approaches (Hoffman et al., 2007, Rozet et al., 2009)
  prediction intervals (Carstensen et al., 2010)

→ single test for location and scale: interpretation is difficult (especially when transfer has failed)
→ of interest: separate confidence intervals for location and scale - separate and post-hoc interpretation possible

Two-sided $100(1-\alpha)\%$ tolerance interval (TI)

… which contains at least a proportion p of the population

Parametric TI for differences (Hahn and Meeker, 1991)

$TI_p^{diff} = \bar{d} \pm k_{1-\alpha;p,n} s_d,$

where $k_{1-\alpha;p,n}$ is tabulated in e.g. Hahn and Meeker (1991)

Nonparametric TI for differences (Hahn and Meeker, 1991)

$TI_{np}^{diff} = [d_{lower}; d_{upper}]$

Sort d_i in ascending order: $d_{(1)} \leq d_{(i)} \leq d_{(n)}$.
Cut off smallest and largest values, where number of values to be removed are tabulated in Hahn and Meeker (1991)

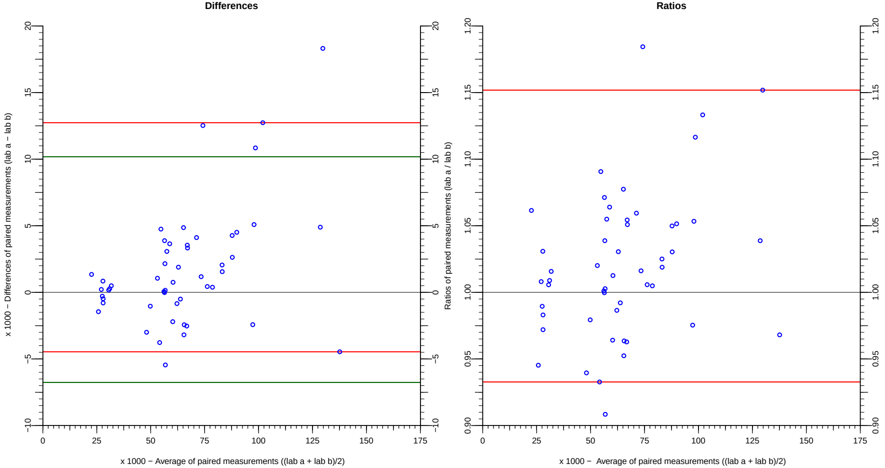
Modification: nonparametric TI for ratios

$TI_{np}^{ratio} = [r_{lower}; r_{upper}]$

Sort r_i in ascending order: $r_{(1)} \leq r_{(i)} \leq r_{(n)}$.
Cut off smallest and largest values, where number of values to be removed are tabulated in Hahn and Meeker (1991).

Lipase data: Bland-Altman plot

Bland-Altman plot (Bland et al., 1986) extended with 90% tolerance interval to contain 90% of the population



Location-scale approach

Basic idea

Similarity of laboratories = equivalence of location AND non-inferiority of scale by means of confidence intervals.
All intervals are marginal due to intersection union principle.

Hypotheses

Based on differences:
$H_0 : \{|\mu_a - \mu_b| \geq \delta\} \cup \{\sigma_a - \sigma_b \leq \varepsilon\}$ vs. $H_1 : \{|\mu_a - \mu_b| < \delta\} \cap \{\sigma_a - \sigma_b > \varepsilon\}$

Based on ratios:
$H_0 : \frac{\mu_a}{\mu_b} \leq \theta^{-1} \cup \frac{\mu_a}{\mu_b} \geq \theta \cup \frac{\sigma_a}{\sigma_b} \leq \lambda$ vs. $H_1 : \theta^{-1} < \frac{\mu_a}{\mu_b} < \theta \cap \frac{\sigma_a}{\sigma_b} > \lambda$

Note

Similarity thresholds: $\delta > 0, \varepsilon < 0, \theta > 1, \lambda < 1$.

Note: location: (1-2α)-confidence interval,
for scale: (1-α) lower confidence bound

Parametric CI's for difference

$(1-2\alpha)$ CI for the difference of means (Altman, 1990)

$$CI_{\bar{d}} = \bar{d} \pm t_{n-1,1-2\alpha}\sqrt{\frac{1}{n}}s_d,$$

where $t_{n-1,1-2\alpha}$ denotes the $(1-2\alpha)$-quantile of the t-distribution with $n-1$ d.o.f.

$(1-\alpha)$ lower confidence bound for difference of variances

$$CI_{s^2} = \left[s_a^2 - s_b^2 - \frac{2}{\sqrt{n-2}}\sqrt{s_a^2 s_b^2 - cov_{ab}^2}\, t_{n-2,1-\alpha}; +\infty\right),$$

where $cov_{ab} = \frac{\sum_{i=1}^n x_{ia}x_{ib} - \sum_{i=1}^n x_{ia}\sum_{i=1}^n x_{ib}/n}{n-1}$

Parametric CI's for ratios

$(1-2\alpha)$ CI for ratio of means (Ogawa, 1982)

$$CI_{\bar{x}_a/\bar{x}_b} = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A},$$

with

$$A = n(n-1)\bar{x}_b^2 - t^2_{n-1,1-2\alpha} \sum_{i=1}^{n} (x_{ib} - \bar{x}_b)^2$$

$$B = -2[n(n-1)\bar{x}_a\bar{x}_b - t^2_{n-1,1-2\alpha} \sum_{i=1}^{n} (x_{ia} - \bar{x}_a)(x_{ib} - \bar{x}_b)]$$

$$C = n(n-1)\bar{x}_a^2 - t^2_{n-1,1-2\alpha} \sum_{i=1}^{n} (x_{ia} - \bar{x}_a)^2$$

and the side condition of significant denominator $n(n-1)\frac{\bar{x}_b^2}{\Sigma(x_{ib} - \bar{x}_b^2)} > t^2_{n-1,1-\alpha}$.

$(1-\alpha)$ lower confidence bound for ratio of variances (Bonett, 2006)

$$CI_{s_a^2/s_b^2} = \left[\frac{s_a^2}{s_b^2}\{g - (g^2 - 1)^{0.5}\}; +\infty\right),$$

where $g = 1 + \{2(1-\hat{\rho}^2)t^2_{n-2,1-\alpha}\}/(n-2)$

This is the inversion of the Pitman-Morgan test.

Nonparametric CI's for ratios (location)

$(1-2\alpha)$ confidence interval for the ratio of means (Bennett, 1965)

Assume: x_{ia}, x_{ib} with $E(x_a) = \mu(>0)$ and $E(x_b) = \kappa\mu$

Wilcoxon signed rank sum statistic $U^+(\kappa) = U^+ = u_1 + u_2 + \cdots + u_n$,
where $u_i = i$ if $z_i > 0$, 0 otherwise and $z_i = z_i(\kappa) = x_{ib} - \kappa x_{ia}$

Estimates $CI_\kappa = [\hat{\kappa}^-; \hat{\kappa}^+]$ are values of κ^-, κ^+ for which $U^+(\kappa)$ is closest to C_{k^-}, C_{k^+}:

$$|U^+(\hat{\kappa}^-) - C_{\kappa^-}| = \inf_\kappa |U^+(\kappa) - C_{\kappa^-}|, \quad |U^+(\hat{\kappa}^+) - C_{\kappa^+}| = \inf_\kappa |U^+(\kappa) - C_{\kappa^+}|,$$

where C_{κ^-} and C_{κ^+} are computed as $C_{\kappa^-}, C_{\kappa^+} \approx \frac{n(n+1)}{4} \pm z_{1-2\alpha} \left\{ \frac{n(n+1)(2n+1)}{24} \right\}^{0.5}$

$\rightarrow$ exact approach exists

Nonparametric CI's for ratios (scale)

$(1-\alpha)$ lower confidence bound for the ratio of the mean absolute deviation of median (Bonett and Seier, 2003)

- Estimate is ratio of mean absolute deviation from the median (MAD) of samples. MAD of sample j is defined as: $\hat{\tau}_j = \sum_{i=1}^{n} |x_{ij} - \tilde{x}_j|/n$
- Lower (1-α) confidence bound for large samples:

$$CI_{\tau_a/\tau_b} = \left[\exp([\log(\frac{\hat{\tau}_a}{\hat{\tau}_b}) - z_\alpha \{var[\log(\hat{\tau}_a/\hat{\tau}_b)]\}^{0.5}]); +\infty\right)$$

- $var[\log(\hat{\tau}_j)] = (s_j^2/\hat{\tau}_j^2 + ((\bar{x}_j - \tilde{x}_j)/\hat{\tau}_j)^2 - 1)/n$
- $var[\log(\hat{\tau}_a/\hat{\tau}_b)] =$ $var[\log(\hat{\tau}_a)] + var[\log(\hat{\tau}_b)] - 2\hat{\rho}_d\{var[\log(\hat{\tau}_a)]var[\log(\hat{\tau}_b)]\}^{0.5}$
- Pearson correlation $\hat{\rho}_d$ based on squared deviation scores $d_{ia} = |x_{ia} - \tilde{x}_a|$ and $d_{ib} = |x_{ib} - \tilde{x}_b|$

Example for location-scale approach

Lipase example with $n = 51$ paired observations
Transfer successful, if trueness $<$ 10% and receiver's precision is non-inferior to a margin of 1/1.1)
The Bland-Altman plot shows no evidence for a systematic proportional difference

Intervals for the difference (sender-receiver)

	location		scale	
type	estimate	95% confidence limits	point estimate	95% lower limit
param.	1,709.3	(673.0; 2,745.7)	104,504,740	(53,403,531; $+\infty$)

Intervals for the ratio (sender/receiver)

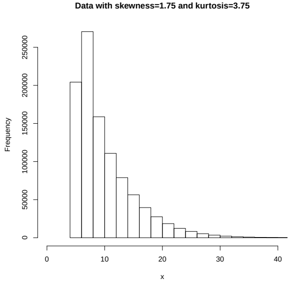
	location		scale	
type	estimate	95% confidence limits	point estimate	95% lower limit
param.	1.027	(1.011; 1.042)	1.075	(1.046; $+\infty$)
nonparam.	1.019	(1.007; 1.033)	1.081	(1.028; $+\infty$)

- a-priori or even a-posteriori definition of absolute scale-variant thresholds of similarity is difficult (especially for precision)
- trueness less than 5% (param ratio: 1.042) and receiver is more precise (nonparam. ratio 1.028)
- transfer is successful

Simulation of the IUT: Set-up

simulated data

- bivariate normal or correlated, nonnormal data with skewness=1.75 and kurtosis=3.75
- $\mu_a = \mu_b = 10$ ($\mu_b = 11.5$ for α)
- $\sigma_a^2 = \sigma_b^2 = 25$ ($\sigma_b^2 = 28.75$ for α)
- $n = 50$ or $n = 500$
- varying correlation from 0 to 0.9



other parameters

- equivalence bounds: $\delta = 0.15, \varepsilon = -0.15, \theta = 1.15, \lambda = 1/1.15$
- $\alpha = 0.05$
- simulations runs: 1,000 for power, 10,000 for α (except nonparametric approach)

Simulation: type I error of IUT

bivariate normal

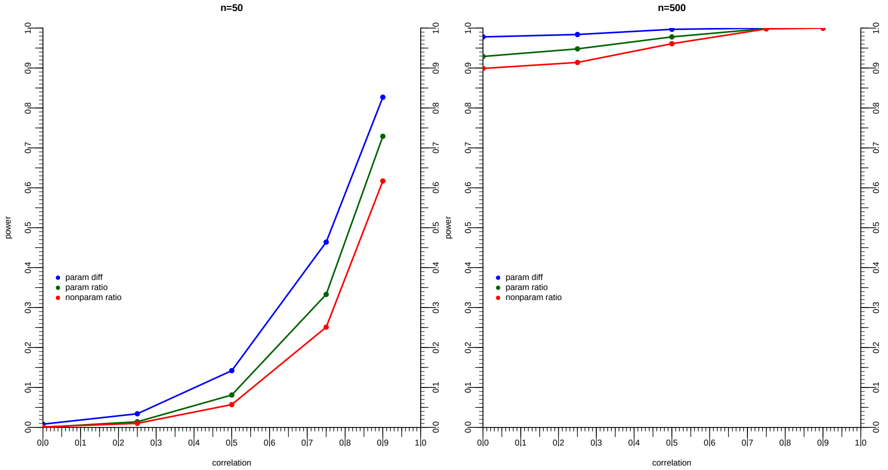
- paired t-test: marginally liberal when $\rho > 0$ in combination with large n

correlated nonnormal

parametric approaches

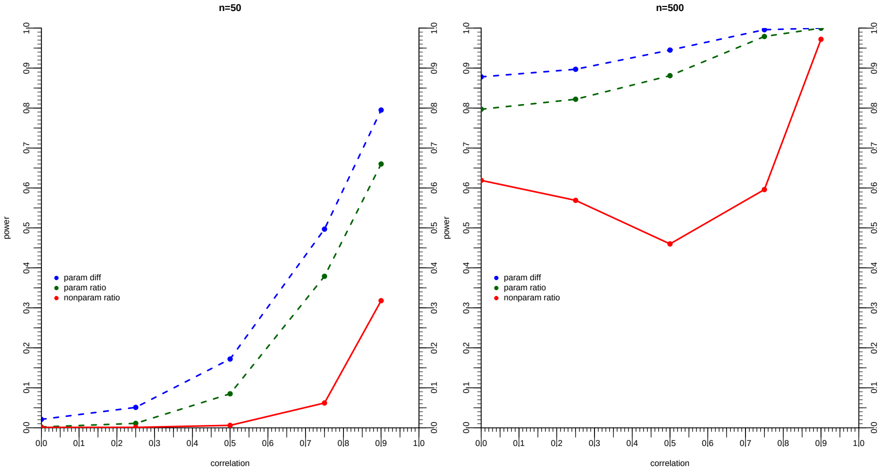
- both location and scale tests:
  increasing α up to 11%-20% with decreasing n and $|\rho|$
- marginal confidence intervals are biased
- IUT still not liberal

Simulation of IUT: normal distributed data



Simulation of IUT: nonnormal distributed data

skewness=1.75 and kurtosis=3.75



Summary and conclusions

- Bland-Altman plot should be routinely used, here for diagnostic of systematic proportional difference
- Bland-Altman plots can be extended with parametric/nonparametric tolerance intervals
- Similarity should be transferred to equivalence for location and non-inferiority for scale
- Margins are assay-specific; if margins cannot be achieved a-priori, post-hoc interpretation is possible with marginal confidence intervals
- Ratios are interpretable and approaches based on ratios are available
- The power of the IUT decreases for smaller variance thresholds more than for smaller location thresholds, i.e. commonly we have to tolerate larger variance confidence intervals for a transfer
- On the other side: if we tolerate a larger variance confidence interval, then the nonparametric test for location can be biased
- R-Code is available on request - a package is planned

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Thank you very much for your attention!