Statistical Tests of Agreement Based on Non-Standard Data

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Proving equivalence is increasingly important

- Testing is expensive & time consuming
- Newer methods and procedures are being developed
- Common goal: *assess agreement between two methods of measurement*

Applications to EPA problems

- Demonstrating equivalence between primary and secondary methods for measuring formaldehyde emissions from composite wood products
  - Large chamber test is expensive (single measurement)
  - Small chamber test is easier and less costly (multiple measurements)

- Prediction of Dioxin-Furan Congener (TEQ) toxicity in fresh-water fish based on fatty acid methyl ester (FAME) profiles
  - Equivalence between KVL and NERL labs for FAME
  - Equivalence between KVL & ECL labs for TEQ

Common methods for assessing agreement

- Hypothesis testing of the correlation coefficient
- Regression analysis
- Paired t-tests
- Least-squares analysis for intercept and slope
- Within-subject coefficient of variation

Mean, variance, covariance approach

- Some current tests are based only on the mean and standard deviation of the differences:

$$d_i = x_i - \bar{y}_i, i = 1, \ldots, n$$

- *Does not guarantee equivalence!!*

$$[(10, 22), (15, 12), (18, 10), (25, 17), (17, 25), (22, 18), (12, 15)]$$

$$\bar{d} = 0; s_x^2 = s_y^2 = 28; r_{xy} = -0.1012$$

- *Even high correlation, by itself, does not guarantee agreement!*

$$[(10, 15), (15, 25), (18, 25), (20, 26), (25, 30), (30, 36)]$$

$$r_{xy} = 0.965; \bar{d} = -6.5; s_x^2 = 50.67, s_y = 47.77$$

Assessing agreement

- Likelihood ratio test for combined hypothesis:

$$H_0 : \mu_x = \mu_y, \sigma_x = \sigma_y, \rho \geq \rho_0$$

(Yimprayoon et al., 2006)

- Interval hypothesis test

$$H_0 : |\mu_x - \mu_y| < \delta_1, \delta_2 < |\frac{\sigma_x}{\sigma_y}| < \delta_3, \rho \geq \rho_0$$

  - Extremely difficult and complicated test

- **Equivalence is not the same as equality!**

Nonstandard data problem

- Inference usually based on paired data *X* and *Y* (bivariate normal assumption)
  - Yinprayoon, Tiensuwan, and Sinha, 2006

- Generalize the LRT approach for **nonstandard** data

$$\left[\left(x_i, y_{i1}, \ldots, y_{i,m_i}\right), i = 1, \ldots, n\right]$$

  - Balanced case: $m_1 = \ldots = m_n = m$
  - Unbalanced case: $m_1 \neq \ldots \neq m_n$

Restricted dataset

$$[(x_i, \bar{y}_i), i = 1, \ldots, n]$$

- Likelihood function is based on marginal likelihood of *X* and conditional likelihood of *Y*

$$x_i \sim N\left[\mu_x, \sigma_x^2\right]$$

$$\bar{y}_i | x_i \sim N\left[\mu_y + \rho\frac{\sigma_y}{\sigma_x}(x_i - \mu_x), \frac{\sigma_y^2(1-\rho^2)}{m_i}\right]$$

Likelihood function

$$L(\mu_x, \mu_y, \sigma_x, \sigma_y, \rho | data) \sim (\sigma_x \sigma_y)^{-n} (1-\rho^2)^{-n/2} \times$$

$$exp\left[-\frac{1}{2}\sum_{i=1}^{n}\frac{(x_i-\mu_x)^2}{\sigma_x^2} - \frac{1}{2\sigma_y^2(1-\rho^2)}\sum_{i=1}^{n} m_i(\bar{y}_i - \mu_y - \rho\frac{\sigma_y}{\sigma_x}(x_i-\mu_x))^2\right]$$

$$A = \sum_{i=1}^{n}(x_i - \bar{x})^2, \qquad C = \sum_{i=1}^{n} m_i(x_i - \bar{\bar{x}})^2$$

$$D = \sum_{i=1}^{n} m_i(\bar{y}_i - \bar{\bar{y}})^2, \qquad E = \sum_{i=1}^{n} m_i(x_i - \bar{\bar{x}})(\bar{y}_i - \bar{\bar{y}})$$

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}, \qquad \bar{\bar{y}} = \frac{\sum m_i \bar{y}_i}{M}, \qquad \bar{\bar{x}} = \frac{\sum m_i x_i}{M}, \qquad M = \sum m_i$$

Unrestricted maximization

- Maximum likelihood estimates

$$\hat{\mu}_x = \bar{x}, \qquad \hat{\mu}_y = \bar{\bar{y}} + \frac{E}{C}(\bar{x} - \bar{\bar{x}})$$

$$\hat{\sigma}_x^2 = \frac{A}{n}, \quad \hat{\sigma}_y^2 = \frac{1}{n}[D + M\frac{AE^2}{nC^2} - \frac{E^2}{C}], \quad \hat{\rho}^2 = \frac{E^2\hat{\sigma}_x^2}{C^2\hat{\sigma}_y^2}$$

- Maximized likelihood

$$\left[\frac{C}{A(DC - E^2)}\right]^{n/2}$$

Restricted maximization

- Maximum likelihood estimates

$$\hat{\mu}_\rho = \frac{n\bar{x}(1+\rho) + M(\bar{\bar{y}} - \rho\bar{\bar{x}})}{M(1-\rho) + n(1+\rho)}$$

$$2n\hat{\sigma}^2_\rho = Q_1(\rho) = A + \frac{D + C\rho^2 - 2E\rho}{1-\rho^2} + \frac{nM\left[\bar{\bar{y}} - \bar{x} + \rho\left(\bar{x} - \bar{\bar{x}}\right)\right]^2}{(1-\rho)\left[M\left(1-\rho\right) + n\left(1-\rho\right)\right]}$$

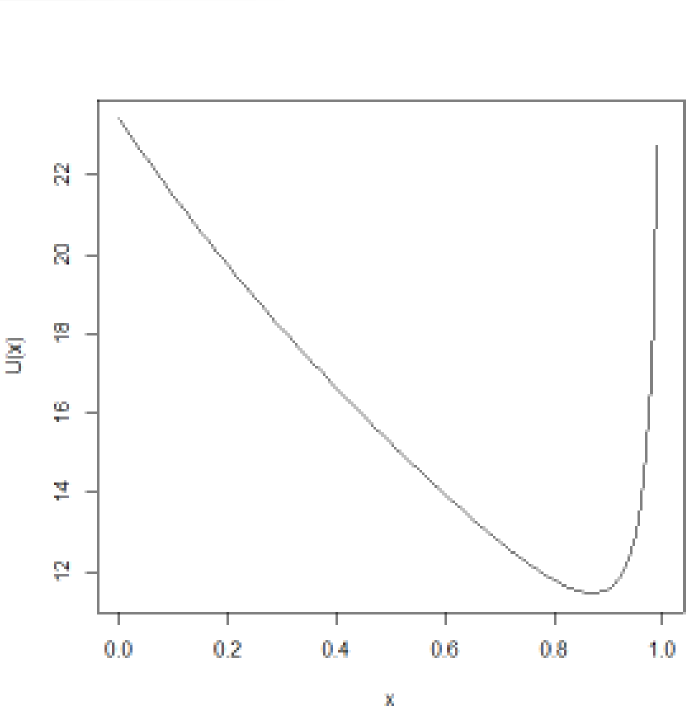
- Likelihood function, maximized wrt μ and σ^2

$$L_1\left(\rho \middle| \, \text{data}\right) \sim \left[\left(1-\rho^2\right)^{\frac{1}{2}} \times Q_1\left(\rho\right)\right]^{-n}$$

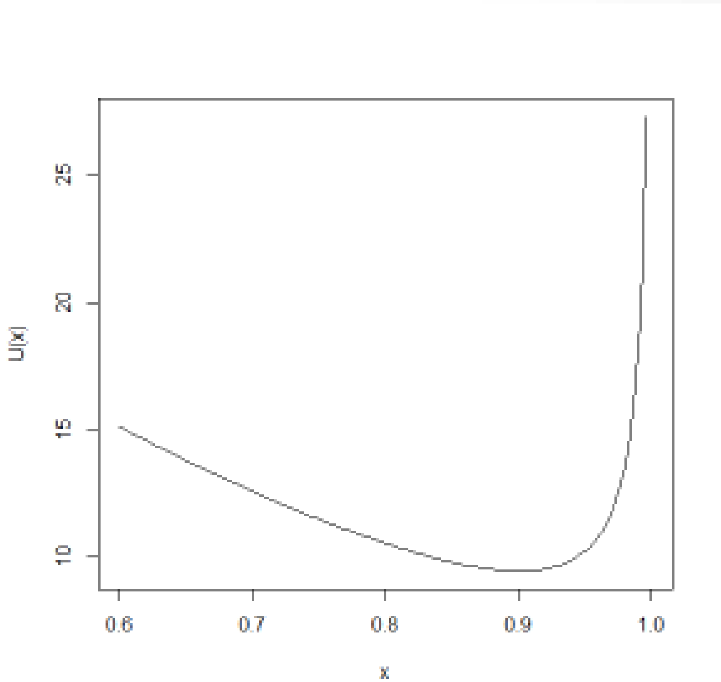
- To maximize the likelihood, minimize wrt ρ

$$U_1\left(\rho\right) = \left[\left(1-\rho^2\right)^{\frac{1}{2}} \times Q_1\left(\rho\right)\right]$$

Images of U_1



$\rho = 0.9, \rho_0 = 0.9, n = 15, m = 1$



$\rho = 0.9, \rho_0 = 0.9, n = 15, m = 3$

Likelihood ratio test statistic

- Test statistic

$$\lambda = \frac{\sup_{H_0} L(\mu_x, \mu_y, \sigma_x^2, \sigma_y^2, \rho_{xy} | \text{ data })}{\sup_{\text{unrestricted}} L(\mu_x, \mu_y, \sigma_x^2, \sigma_y^2, \rho_{xy} | \text{data})}$$

- Reject H0 for large values of T_1

$$T_1 = \left[\min_{\rho \geq \rho_0} U_1(\rho)\right] \times \left[\frac{C}{A(DC - E^2)}\right]^{\frac{1}{2}}$$

- Select cutoff d_1 so that

$$\alpha = P\left[T_1 > d_1 | H_0 : \mu_x = \mu_y, \sigma_x = \sigma_y, \rho = \rho_0\right]$$

Remarks

- T_1 is location and scale invariant
- Composite null hypothesis: determine the cutoff value d1 under $\rho = \rho_0$ and verify size is less than or equal to alpha for $\rho > \rho_0$
- Simulations: different correlation, means, variances, and combinations thereof to get an idea of power

Unrestricted dataset

$$\left[x_i, \left(y_{i1}, \ldots, y_{im_i}\right), i = 1, \ldots, n\right]$$

- Likelihood function:

$$L(\mu_x, \mu_y, \sigma_x, \sigma_y, \rho | data) \sim (\sigma_x)^{-n}[\sigma_y^2(1-\rho^2)]^{-M/2} \times$$

$$exp\left[-\frac{1}{2}\sum_{i=1}^{n}\frac{(x_i-\mu_x)^2}{\sigma_x^2} - \frac{1}{2\sigma_y^2(1-\rho^2)}\{\sum_{i=1}^{n} m_i(\bar{y}_i - \mu_y - \rho\frac{\sigma_y}{\sigma_x}(x_i-\mu_x))^2 + W_y\}\right]$$

$$W_y = \sum_{i=1}^{n}\sum_{j=1}^{m_i}(y_{ij}-\bar{y}_i)^2 : \text{ additional term}$$

Unrestricted maximization

- Maximum likelihood estimates

$$\hat{\mu}_x = \bar{x}, \quad \hat{\mu}_y = \bar{\bar{y}} + \frac{E}{C}(\bar{x} - \bar{\bar{x}}), \quad \hat{\sigma}_x^2 = \frac{A}{n}$$

$$\hat{\sigma}_y^2 = \frac{1}{M}[W_y + D + \frac{MAE^2}{nC^2} - \frac{E^2}{C}], \quad \hat{\rho} = \frac{E\hat{\sigma}_x}{C\hat{\sigma}_y}$$

- Maximized likelihood

$$\frac{1}{A^{\frac{n}{2}} \times [D - \frac{E^2}{C} + W_y]^{\frac{M}{2}}}$$

Restricted maximization

- Maximum likelihood estimates

$$\hat{\mu}_\rho = \frac{n\bar{x}(1+\rho) + M(\bar{\bar{y}} - \rho\bar{\bar{x}})}{M(1-\rho) + n(1+\rho)} \qquad \hat{\sigma}^2_\rho = \frac{1}{n+M} Q_2(\rho)$$

$$Q_2(\rho) = A + \frac{D + C\rho^2 - 2E\rho + W_y}{1-\rho^2} + \frac{nM[\bar{\bar{y}} - \bar{x} + \rho(\bar{x} - \bar{\bar{x}})]^2}{(1-\rho)[M(1-\rho) + n(1+\rho)]}$$

- Likelihood maximized wrt μ and σ²

$$L_2(\rho|\,\mathrm{data}) \sim \left[\left(1-\rho^2\right)^{\frac{M}{2}} \times Q_2(\rho)^{\frac{n+M}{2}}\right]^{-1}$$

- To maximize likelihood, minimize

$$U_2(\rho) = \left[\left(1-\rho^2\right) \times Q_2(\rho)^{1+\frac{n}{M}}\right]$$

Likelihood ratio test statistic

- Test statistic

$$\lambda = \frac{\sup_{H_0} L(\mu_x, \mu_y, \sigma_x^2, \sigma_y^2, \rho_{xy} | \text{ data })}{\sup_{\text{unrestricted}} L(\mu_x, \mu_y, \sigma_x^2, \sigma_y^2, \rho_{xy} | \text{data})}$$

- Reject H0 for large values of T_2

$$T_2 = \frac{1}{A} \times \left[\frac{\min_{\rho \geq \rho_0} U_2(\rho)}{D - \frac{E^2}{C} + W_y} \right]^{\frac{M}{n}}$$

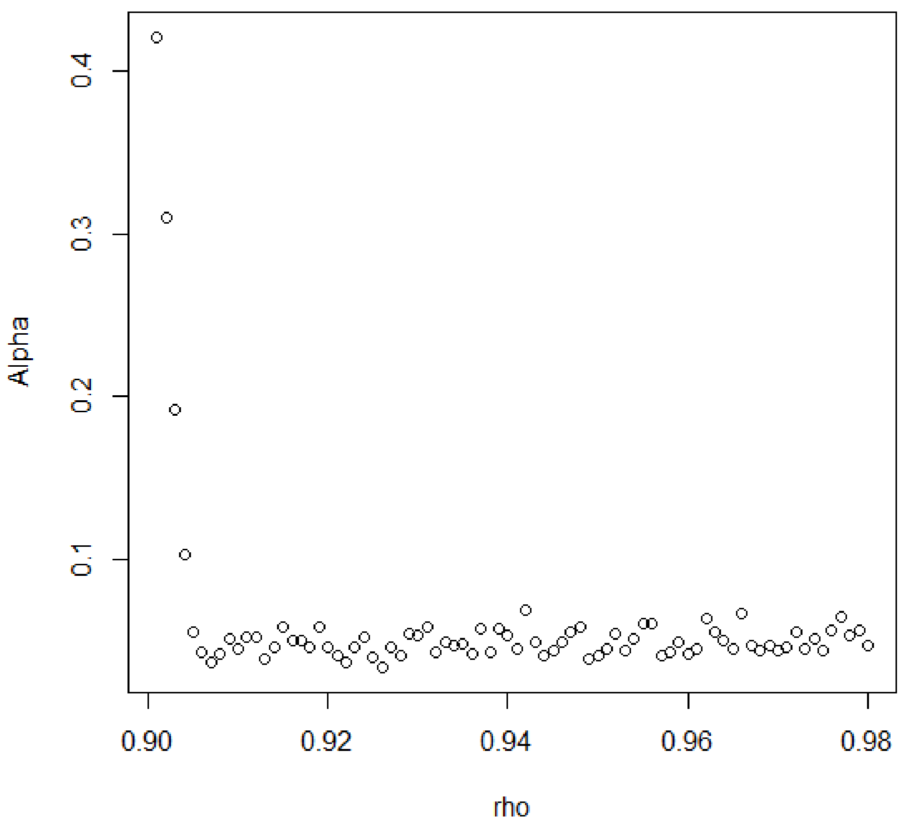
- Select cutoff d_2 so that

$$\alpha = P\left[T_2 > d_2 | H_0 : \mu_x = \mu_y, \sigma_x = \sigma_y, \rho = \rho_0\right]$$

Restricted dataset Simulations: Type I Error rates

ρ	ρ_0	n	m	α
0.92	0.9	5	1	0.0439
0.92	0.9	10	1	0.0396
0.92	0.9	15	1	0.0371
0.92	0.9	5	3	0.0452
0.92	0.9	10	3	0.0409
0.92	0.9	15	3	0.0335
0.95	0.9	5	1	0.033
0.95	0.9	10	1	0.0299
0.95	0.9	15	1	0.0274
0.95	0.9	5	3	0.0374
0.95	0.9	10	3	0.0305
0.95	0.9	15	3	0.0237
0.99	0.9	5	1	0.0299
0.99	0.9	10	1	0.0254
0.99	0.9	15	1	0.0253
0.99	0.9	5	3	0.0309
0.99	0.9	10	3	0.0277
0.99	0.9	15	3	0.0266

Type I Error rates



Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.5	0.9	0	1	5	1	0.05	0.2458
0.5	0.9	0	1	10	1	0.05	0.642
0.5	0.9	0	1	15	1	0.05	0.8527
0.5	0.9	0	1	5	3	0.05	0.4265
0.5	0.9	0	1	10	3	0.05	0.8875
0.5	0.9	0	1	15	3	0.05	0.9723

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.9	0.9	1	1	5	1	0.05	0.8815
0.9	0.9	1	1	10	1	0.05	0.9999
0.9	0.9	1	1	15	1	0.05	1
0.9	0.9	1	1	5	3	0.05	0.9996
0.9	0.9	1	1	10	3	0.05	1
0.9	0.9	1	1	15	3	0.05	1

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.9	0.9	0	4	5	1	0.05	0.5481
0.9	0.9	0	4	10	1	0.05	0.961
0.9	0.9	0	4	15	1	0.05	0.9984
0.9	0.9	0	4	5	3	0.05	0.9096
0.9	0.9	0	4	10	3	0.05	0.9996
0.9	0.9	0	4	15	3	0.05	1

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.9	0.9	1	4	5	1	0.05	0.8197
0.9	0.9	1	4	10	1	0.05	0.9976
0.9	0.9	1	4	15	1	0.05	1
0.9	0.9	1	4	5	3	0.05	0.9885
0.9	0.9	1	4	10	3	0.05	1
0.9	0.9	1	4	15	3	0.05	1

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.5	0.9	1	1	5	1	0.05	0.6795
0.5	0.9	1	1	10	1	0.05	0.9836
0.5	0.9	1	1	15	1	0.05	0.9988
0.5	0.9	1	1	5	3	0.05	0.9515
0.5	0.9	1	1	10	3	0.05	1
0.5	0.9	1	1	15	3	0.05	1

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.5	0.9	0	4	5	1	0.05	0.5043
0.5	0.9	0	4	10	1	0.05	0.9442
0.5	0.9	0	4	15	1	0.05	0.9955
0.5	0.9	0	4	5	3	0.05	0.5077
0.5	0.9	0	4	10	3	0.05	0.9486
0.5	0.9	0	4	15	3	0.05	0.9888

Simulations

ρ	ρ_0	μ_y	σ_y^2	n	m	α	$1-\beta$
0.5	0.9	1	4	5	1	0.05	0.6653
0.5	0.9	1	4	10	1	0.05	0.9862
0.5	0.9	1	4	15	1	0.05	0.9995
0.5	0.9	1	4	5	3	0.05	0.8536
0.5	0.9	1	4	10	3	0.05	0.9978
0.5	0.9	1	4	15	3	0.05	0.9998

- Test is most powerful when means are different
- Least powerful when only variances are different

Tests based on combinations of P-values

- Consider the composite hypothesis test

$$H_{01} : \mu_x = \mu_y; H_{02} : \sigma_x^2 = \sigma_y^2; H_{03} : \rho \geq \rho_0$$

$$\text{versus}$$

$$H_{11} : \mu_x \neq \mu_y; H_{12} : \sigma_x^2 \neq \sigma_y^2; H_{13} : \rho < \rho_0$$

- We consider three separate tests for H_{01}, H_{02}, and H_{03}, and combine the resulting P-values to derive an overall test.

Testing H01

- Paired t-test:

$$x_i - \bar{y}_i = d_i \sim N\left[\mu_x - \mu_y, (\sigma_x - \rho\sigma_y)^2 + \frac{\sigma_y^2\left(1-\rho^2\right)}{m_i}\right]$$

  - Assumption: $m_1 = \cdots = m_n = m$

- Reject the null for large values of $|t_d| = \left|\frac{\sqrt{n}\bar{d}}{s_d}\right|$

$$d_i = x_i - \bar{y}_i, \bar{d} = \frac{\sum_{i=1}^n d_i}{n}, s_d^2 = \frac{\sum_{i=1}^n (d_i - \bar{d})^2}{n-1}$$

- P-value $p_1 = Pr\left(|t_{n-1}| > |t_d|\right)$

Testing H02

- Modified Pittman-Morgan

$$u_i = x_i + \bar{y}_i \left(\frac{m_i}{1 + (m_i - 1)\rho_0^2} \right)^{\frac{1}{2}}, \qquad v_i = x_i - \bar{y}_i \left(\frac{m_i}{1 + (m_i - 1)\rho_0^2} \right)^{\frac{1}{2}}$$

$$H_{02} \equiv H_{02}^* : \rho_{uv} = 0 \qquad t_{uv} = \frac{r_{uv}(n-2)^{\frac{1}{2}}}{(1 - r_{uv}^2)^{\frac{1}{2}}}$$

- P-value $p_2 = Pr\left(|t_{n-2}| > |t_{uv}|\right)$

Testing H03

- assume $m_1 = \cdots = m_n = m$

$$\rho_{x\bar{y}} = \left(\frac{m\rho^2}{1 + (m-1)\rho^2} \right) = \rho^*$$

$$z^* = \frac{1}{2} \ln \frac{1 + r^*}{1 - r^*}; \zeta^* = \frac{1}{2} \ln \frac{1 + \rho_0^*}{1 - \rho_0^*} \text{ with } \rho_0^* = \left(\frac{m\rho_0^2}{1 + (m-1)\rho_0^2} \right)$$

- P-value $p_3 = Pr\left(N(0,1) < z^*(n-3)^{\frac{1}{2}} \right)$

Tests based on P-values

1. Tippett's test:

$$\text{Reject } H_0 \text{ when } min(p_1, p_2, p_3) < c_1$$

2. Fisher's test:

$$\text{Reject } H_0 \text{ when } \; -2\left[\ln p_1 + \ln p_2 + \ln p_3\right] > c_2$$

3. Stouffer's test:

$$\text{Reject } H_0 \text{ when } \; \left[\Phi^{-1}(p_1) + \Phi^{-1}(p_2) + \Phi^{-1}(p_3)\right] < c_3$$

Tests based on P-values

Simulations: Type I Error rates

ρ	ρ_0	n	m	Tippett	Fisher	Stouffer
0.92	0.9	5	1	0.0498	0.0481	0.0358
0.92	0.9	10	1	0.0468	0.0439	0.0327
0.92	0.9	15	1	0.0409	0.0343	0.0248
0.92	0.9	5	3	0.0484	0.0448	0.0349
0.92	0.9	10	3	0.0416	0.0354	0.0271
0.92	0.9	15	3	0.0412	0.0402	0.0271
0.95	0.9	5	1	0.0457	0.0402	0.0183
0.95	0.9	10	1	0.0388	0.0314	0.0092
0.95	0.9	15	1	0.039	0.025	0.0053
0.95	0.9	5	3	0.0474	0.0442	0.0172
0.95	0.9	10	3	0.0473	0.0421	0.0116
0.95	0.9	15	3	0.0551	0.0427	0.0088
0.99	0.9	5	1	0.0399	0.0309	0.0007
0.99	0.9	10	1	0.0386	0.0262	0
0.99	0.9	15	1	0.0388	0.023	0
0.99	0.9	5	3	0.1112	0.1067	0.0018
0.99	0.9	10	3	0.3148	0.2344	0.0001
0.99	0.9	15	3	0.5378	0.4211	0

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.5	0.9	0	1	5	1	0.2151	0.2762	0.3224
0.5	0.9	0	1	10	1	0.6453	0.6981	0.5593
0.5	0.9	0	1	15	1	0.8661	0.8714	0.6836
0.5	0.9	0	1	5	3	0.2984	0.3835	0.4372
0.5	0.9	0	1	10	3	0.8323	0.8956	0.7832
0.5	0.9	0	1	15	3	0.9764	0.9898	0.9391

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.9	0.9	1	1	5	1	0.8507	0.8843	0.6941
0.9	0.9	1	1	10	1	0.9998	0.9998	0.9243
0.9	0.9	1	1	15	1	1	1	0.9796
0.9	0.9	1	1	5	3	0.9981	0.9984	0.8461
0.9	0.9	1	1	10	3	1	1	0.9781
0.9	0.9	1	1	15	3	1	1	0.9987

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.9	0.9	0	4	5	1	0.403	0.4249	0.3596
0.9	0.9	0	4	10	1	0.9154	0.9615	0.754
0.9	0.9	0	4	15	1	0.994	0.9984	0.9189
0.9	0.9	0	4	5	3	0.6942	0.7543	0.5457
0.9	0.9	0	4	10	3	0.9971	0.9994	0.916
0.9	0.9	0	4	15	3	1	1	0.9925

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.9	0.9	1	4	5	1	0.5252	0.7668	0.7903
0.9	0.9	1	4	10	1	0.9759	0.9979	0.9904
0.9	0.9	1	4	15	1	0.9991	0.9999	0.9993
0.9	0.9	1	4	5	3	0.823	0.9734	0.9505
0.9	0.9	1	4	10	3	1	1	0.9994
0.9	0.9	1	4	15	3	1	1	1

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.5	0.9	1	1	5	1	0.4099	0.6822	0.7232
0.5	0.9	1	1	10	1	0.9163	0.9835	0.9622
0.5	0.9	1	1	15	1	0.9957	0.9997	0.9963
0.5	0.9	1	1	5	3	0.6486	0.9415	0.9381
0.5	0.9	1	1	10	3	0.995	0.9999	0.9993
0.5	0.9	1	1	15	3	1	1	1

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.5	0.9	0	4	5	1	0.3051	0.5042	0.5782
0.5	0.9	0	4	10	1	0.8448	0.9602	0.9209
0.5	0.9	0	4	15	1	0.9982	0.9969	0.9846
0.5	0.9	0	4	5	3	0.3223	0.458	0.5203
0.5	0.9	0	4	10	3	0.8789	0.9489	0.8779
0.5	0.9	0	4	15	3	0.9886	0.9962	0.9783

Simulations: Power

ρ	ρ_0	μ_y	σ_y^2	n	m	Tippett	Fisher	Stouffer
0.5	0.9	1	4	5	1	0.3575	0.6788	0.7638
0.5	0.9	1	4	10	1	0.8987	0.9887	0.979
0.5	0.9	1	4	15	1	0.9929	0.9995	0.9984
0.5	0.9	1	4	5	3	0.5109	0.852	0.8831
0.5	0.9	1	4	10	3	0.9796	0.9987	0.9964
0.5	0.9	1	4	15	3	0.9999	1	0.9998

- Stouffer’s test has the lowest Type I Error rates (of all tests, including LRT)

- LRT and Fisher’s tests have similar power
  - Fisher’s test has the highest power of the combined P-value tests in almost every case
  - Stouffer’s has a higher power in some small sample size (n=5) cases

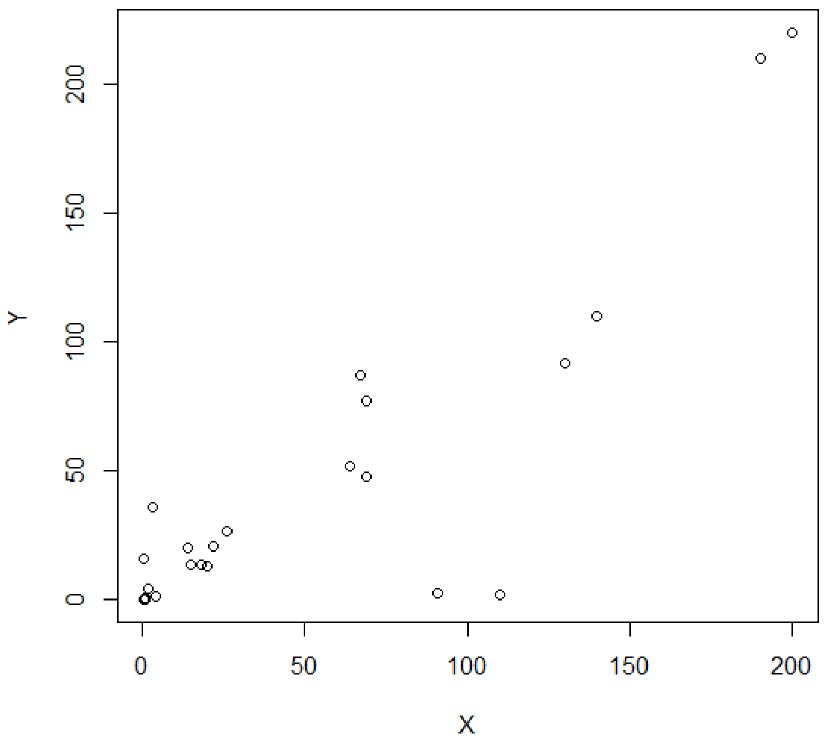
Applications

- Application to EPA data: measuring concentrations of pollutants in groundwater
  - Conventional purging methods i.e. low-flow sampling methods
    - A pump slowly collects groundwater so that the sample is not contaminated by water at different levels
  - New HydraSleeve method
    - A tube is lowered into the well and left there long enough for sediment etc. to settle, then water is collected as the tube is pulled upwards
- Focus: specific pollutants

Results

- TCE

$$H_0 : \mu_x = \mu_y, \sigma_x = \sigma_y, \rho \geq 0.9$$



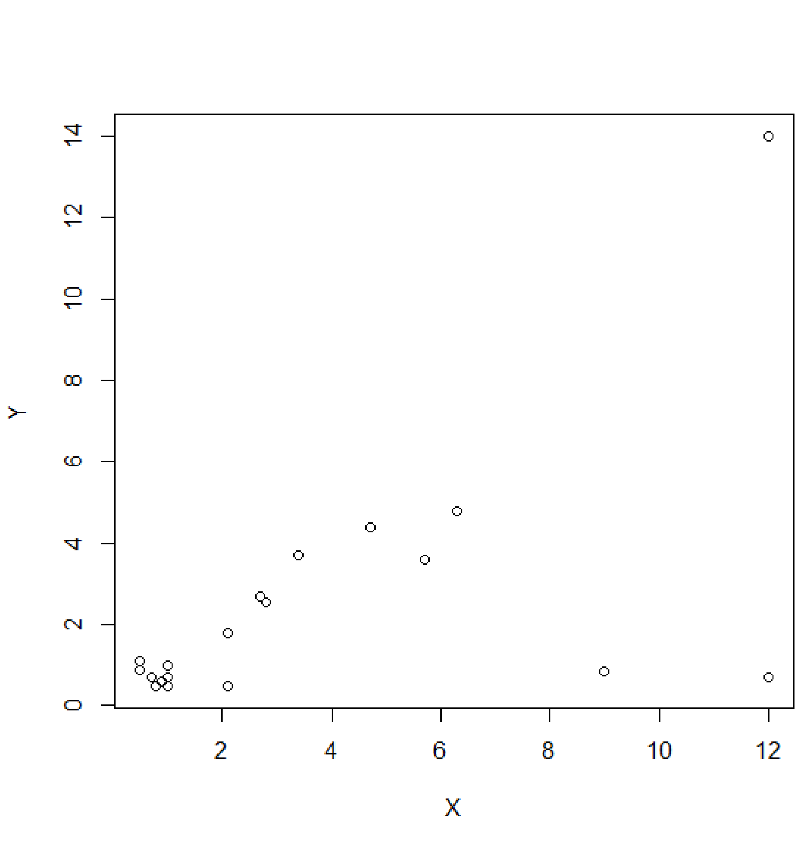
Test	Cutoff	Test Statistic	Conclusion
LRT	2.37547	2.206056	Do not reject
Tippett	0.01803122	0.2217555	Do not reject
Fisher	11.74769	5.849823	Do not reject
Souffer	-2.473122	0.4399887	Do not reject

$$n = 23$$

Results

- DCA

$$H_0 : \mu_x = \mu_y, \sigma_x = \sigma_y, \rho \geq 0.9$$



Test	Cutoff	Test Statistic	Conclusion
LRT	2.462177	3.641468	Reject
Tippett	0.01858661	0.0007817254	Reject
Fisher	11.65932	20.72726	Reject
Souffer	-2.418705	-4.703667	Reject

$$n = 19$$

Strong resemblance to bioequivalence testing

- In an equivalence trial, the aim is to show that two treatments are not too different in characteristics
- **Not too different** is defined in a clinical manner
- Called **bioequivalence testing**
- Nature of the data for bioequivalence testing
  - Same patients
  - Washout period
  - Crossover designs

Bioequivalence testing

- Often data are collected from healthy volunteers

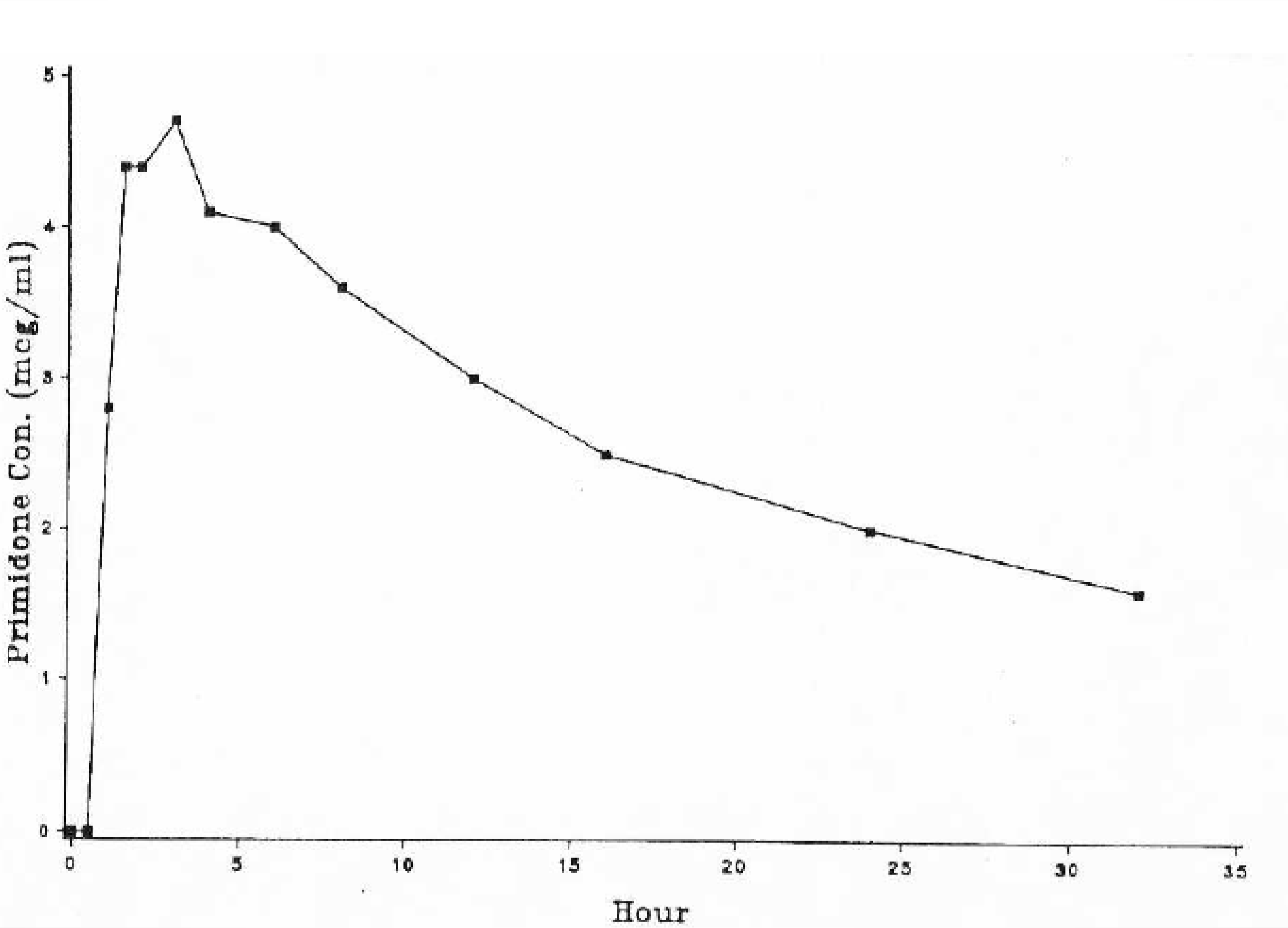
- If two drug products perform the same in healthy volunteers, the assumption is made that they will perform the same in patients with the disease

- Data obtained on three patient characteristics
  - Area under the curve (AUC)
  - Maximum blood concentration C_{max}
  - Time to reach the maximum concentration T_{max}

Bioequivalence testing

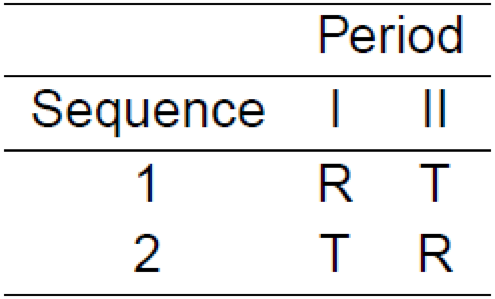
- Two drug products are *bioequivalent* if they have similar rate and extent of absorption into the blood.
- Two drug products are *therapeutically equivalent* if they provide similar therapeutic effects.
- **Fundamental bioequivalence assumption**: If two drug products are bioequivalent, they are also therapeutically equivalent

Data for bioequivalence testing



Experimental designs

- Reference drug (R)
- Test drug (T)
- Each subject receives both R and T, separated by a washout period
- Crossover designs are used
- A two sequence–two period crossover design:



	Period	
Sequence	I	II
1	R	T
2	T	R

Average bioequivalence

- Let μ_T, μ_R: average responses among the population of patients who will take the test drug, and the reference drug, respectively.

- The response is usually AUC, after log-transformation (could be C_{max} or T_{max}).

- Average bioequivalence holds if μ_T and μ_R are equivalent, i.e., they are "close"

Average bioequivalence

- μ_T and μ_R are considered equivalent if $|\mu_T - \mu_R| < \ln(1.25)$.
- Hypothesis to be tested:

$$H_0 : |\mu_T - \mu_R| \geq \ln(1.25) \text{ versus } H_1 : |\mu_T - \mu_R| < \ln(1.25)$$

- Conclude average bioequivalence if H0 is rejected after a statistical test based on the log-transformed AUC data.

A canonical form

- Under an appropriate model for the log-transformed data, a canonical form is

$$D \sim N\left(\mu_T - \mu_R, c^2\sigma^2\right) \qquad \nu\frac{S^2}{\sigma^2} \sim \chi^2_\nu$$

$$H_0 : |\mu_T - \mu_R| \geq \ln(1.25) \text{ versus } H_1 : |\mu_T - \mu_R| < \ln(1.25)$$

- Rewrite as

$$H_{01} : \mu_T - \mu_R \leq -\ln(1.25) \text{ vs. } H_{11} : \mu_T - \mu_R > -\ln(1.25)$$

$$H_{02} : \mu_T - \mu_R \geq \ln(1.25) \text{ vs. } H_{12} : \mu_T - \mu_R < \ln(1.25)$$

- Average bioequivalence is concluded if both H_{01} and H_{02} are rejected.

Assessing bioequivalence

- Carry out t-tests: conclude average bioequivalence at significance level a if

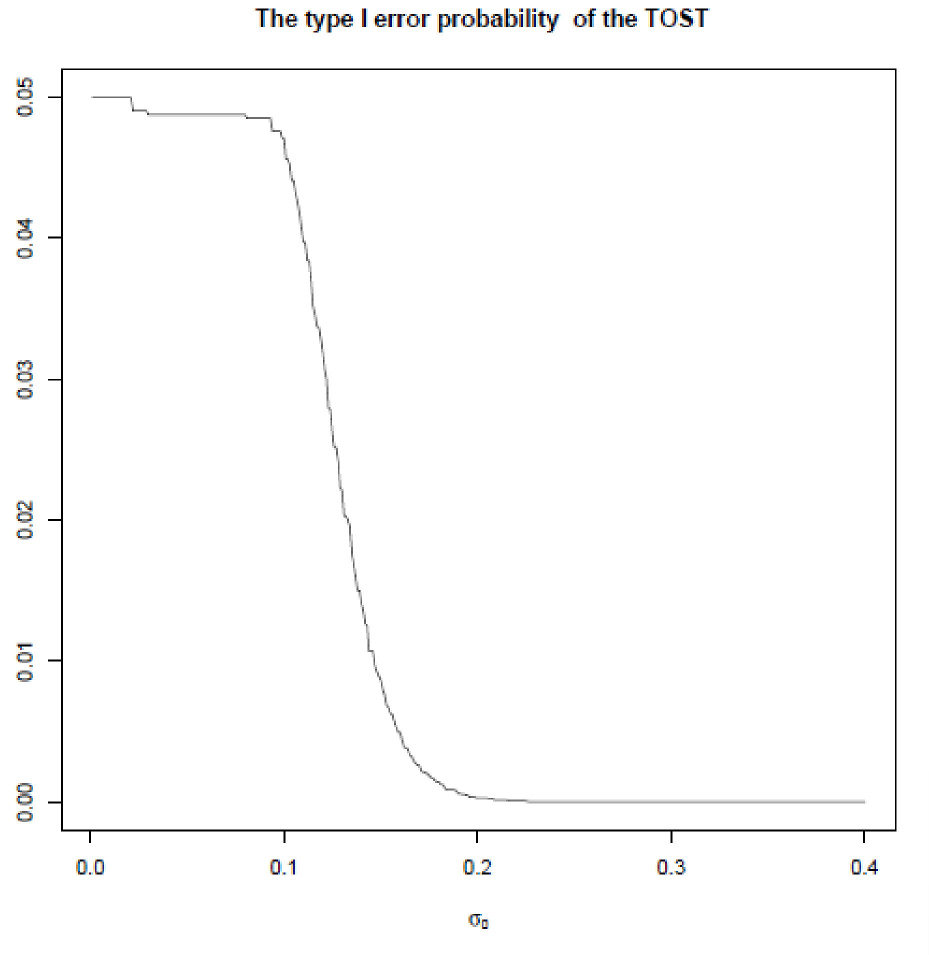
$$\frac{D+\ln(1.25)}{cS} > t_{\nu}(\alpha) \text{ and } \frac{D-\ln(1.25)}{cS} < -t_{\nu}(\alpha)$$

- Equivalently, if $\dfrac{|D|-\ln(1.25)}{cS} < -t_{\nu}(\alpha)$

- Two one-sided t-test (TOST)
  - Schuirmann (1981), *Biometrics*
  - Schuirmann (1987), *Journal of Pharmacokinetics and Biopharmaceutics*

- Main drawback: <u>not</u> scale invariant
  - Performance depends on unknown σ

Type I Error rate: TOST



Improvements on TOST

- The TOST can be quite conservative as σ gets large

- Improved tests due to:
  - Anderson and Hauck (1983), *Communications in Statistics*
  - Munk (1993), *Biometrics*
  - Berger and Hsu (1996), *Statistical Science*
  - Brown, Hwang and Munk (1997), *Annals of Statistics*
  - Munk, Brown and Hwang (2000), *Biometrical Journal*
  - Cao and Mathew (2008), *Biometrical Journal*

- Improvement in power at values of σ that are unlikely.

Criterion for equivalence

$$X : \text{ measurements made by the standard device (SD)}$$
$$Y : \text{ measurements made by the alternative device (AD)}$$

- If the probability that Y/X is around 1 is large, conclude that the standard device and the alternative device are equivalent.
- Let $\theta = P\left(1 - \delta \leq \frac{Y}{X} \leq 1 + \delta\right)$

  for small δ.
- If θ is large, conclude that the standard device and the alternative device are equivalent.

Criterion for equivalence

- A usual choice is δ= 0.25

$$\theta = P\left(0.75 \leq \frac{Y}{X} \leq 1.25\right)$$

- Use the data to test

$$H_0 : \theta \leq 0.90 \text{ versus } H_1 : \theta \geq 0.90$$

- Accept equivalence if H_0 is rejected, i.e., if θ ≥ 0.90 is concluded.

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