Equivalence of regression curves

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Motivation

- An application: Populations of different geographic regions may bear differences in efficacy (or safety) dose response
  $\longrightarrow$ Objective: Ability to extrapolate study results
  $\longrightarrow$ Demonstrating similarity of curves becomes an issue
- Another application: Comparison of dose response relationships for two regimens
  $\longrightarrow$ For example, demonstrate that once-daily (o.d.) and twice-daily (b.i.d.) applications of a drug are similar over a given dose range
- Yet another application: Comparison of different drugs containing the same active substance in order to claim bioequivalence.
  $\longrightarrow$ Traditional approaches based on AUC or Cmax may be misleading
  $\longrightarrow$ Objective: Develop a test which takes the whole curve into account
- IDEAL project: Focus on small population clinical trials (e.g. rare diseases)
  $\longrightarrow$ Methodology should work for small sample sizes

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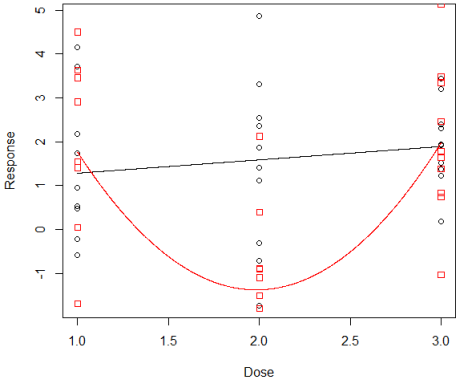
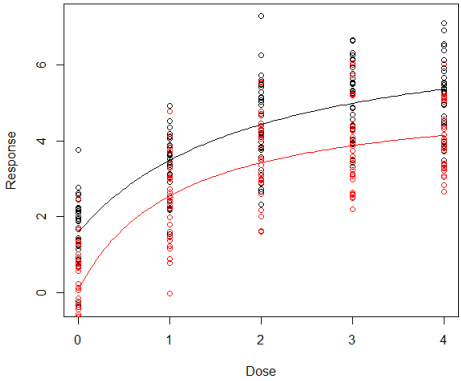
Comparing curves - The setting





Comparing curves - The setting II

- Two dose response curves (from two samples)

$$Y_{\ell,i,j} = m_\ell(x_{\ell,i}, \vartheta_\ell) + \varepsilon_{\ell,i,j} \quad (j = 1, \ldots, n_{\ell,i}; i = 1, \ldots, k_\ell; \ell = 1, 2)$$

  - $\varepsilon_{\ell,i,j}$ independent $\sim \mathcal{N}(0, \sigma_\ell^2)$ $\quad (\ell = 1, 2)$
  - $x_{\ell,i} \in \mathcal{X}$ (dose levels)
  - $\vartheta_\ell \in \mathbb{R}^{d_\ell}$ (parameter in model m_ℓ)

Problem: Are the dose response curves m_1 and m_2 similar?

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Problem: Are the dose response curves m_1 and m_2 similar?

Measures of similarity

- d: a *metric* measuring the distance between m_1 and m_2.
- Hypothesis of similarity:

$$H_0 : d(m_1, m_2) \geq \epsilon \quad \text{versus} \quad H_1 : d(m_1, m_2) < \epsilon$$

(here ϵ is a pre-specified constant).

- Examples
  - maximum absolute difference

$$d_\infty(m_1, m_2) = \max_{x \in \mathcal{X}} |m_1(x, \vartheta_1) - m_2(x, \vartheta_2)|$$

  - squared L_2-distance

$$d_2(m_1, m_2) = \int_{\mathcal{X}} (m_1(x, \vartheta_1) - m_2(x, \vartheta_2))^2 dx$$

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Efficient tests for similarity

Tests based on distances

Basic idea: Estimate the distance between m_1 and m_2 directly and decide for similarity for small values of the resulting estimate

- (parametric) estimates of m_1 and m_2:

$$\hat{m}_1 = m_1(\cdot, \hat{\vartheta}_1), \;\; \hat{m}_2 = m_2(\cdot, \hat{\vartheta}_2)$$

- estimate of the distance between m_1 and m_2:

$$\hat{\mathbf{d}} = d(\hat{m}_1, \hat{m}_2)$$

Tests based on distances

$\hat{\mathbf{d}}$: estimate the distance between m_1 and m_2

- Decide for similarity, i.e. reject the hypothesis

$$H_0 : d(m_1, m_2) \geq \epsilon$$

whenever

$$\hat{\mathbf{d}} = d(\hat{m}_1, \hat{m}_2) < q$$

- **Problem:** how do we find the critical value q?

Estimating the distance between two curves – the squared L_2-distance

- Define an estimate by

$$\hat{\mathbf{d}}_{\mathbf{2}} = d_2(\hat{m}_1, \hat{m}_2) = \int_{\mathcal{X}} (m_1(x, \hat{\vartheta}_1) - m_2(x, \hat{\vartheta}_2))^2 dx$$

- Empirical process theory: $\left\{ m_1(x, \hat{\vartheta}_1) - m_2(x, \hat{\vartheta}_2) - (m_1(x, \vartheta_1) - m_2(x, \vartheta_2)) \right\}_{x \in \mathcal{X}}$ converges weakly to a centered Gaussian process (as $n_1, n_2 \to \infty$)

$$\longrightarrow d_2(\hat{m}_1, \hat{m}_2) - d_2(m_1, m_2) \overset{a}{\sim} \mathcal{N}\Big(0, \frac{\tau^2}{n_1 + n_2}\Big)$$

where

$$\tau^2 = \int_{\mathcal{X} \times \mathcal{X}} (m_1(x, \vartheta_1) - m_2(x, \vartheta_2)) \cdot (m_1(y, \vartheta_1) - m_2(y, \vartheta_2)) k(x, y) dx\, dy$$

Estimating the distance between two curves – the squared L_2-distance II

An asymptotic test for similarity of two dose response curves:

- If $\hat{\tau}^2$ is an estimate of τ^2, then

$$H_0 : d_2(m_1, m_2) \geq \epsilon_2$$

is rejected, whenever

$$d_2(\hat{m}_1, \hat{m}_2) < \epsilon_2 + \frac{\hat{\tau}}{\sqrt{n_1 + n_2}} u_\alpha$$

- **It is very difficult to estimate τ^2, especially for small sample sizes**

Estimating the distance between two curves – the maximum distance

- Define an estimate by

$$\hat{\mathbf{d}}_\infty = d_\infty(\hat{m}_1, \hat{m}_2) = \max_{x \in \mathcal{X}} |m_1(x, \hat{\vartheta}_1) - m_2(x, \hat{\vartheta}_2)|$$

- If the true absolute difference curve has only one extremal point, we have

$$d_\infty(\hat{m}_1, \hat{m}_2) - d_\infty(m_1, m_2) \overset{a}{\sim} \mathcal{N}\Big(0, \frac{\sigma^2_{d_\infty}}{n_1 + n_2}\Big),$$

  where $\sigma^2_{d_\infty}$ depends on the location of the extremal point
- Otherwise $d_\infty(\hat{m}_1, \hat{m}_2)$ is not asymptotically normal distributed
- **An asymptotic test is not always available!**

Bootstrap test for similarity

Generate data under the **null hypothesis**

- Estimate ϑ_1, ϑ_2 under the restriction of the null hypothesis, that is the estimates fulfill $d(m_1, m_2) = \epsilon$

  $\rightsquigarrow$ **constrained** estimates $\hat{\hat{\vartheta}}_1, \hat{\hat{\vartheta}}_2$

  e.g. for $d = d_2$, $\hat{\hat{\vartheta}}_1, \hat{\hat{\vartheta}}_2$ satisfy $\int_{\mathcal{X}} (m_1(x, \hat{\hat{\vartheta}}_1) - m_2(x, \hat{\hat{\vartheta}}_2))^2 dx = \epsilon_2$
- Generate bootstrap data (parametric bootstrap)

$$Y^*_{\ell,i,j} = m_\ell(x_{\ell,i}, \hat{\hat{\vartheta}}_\ell) + \hat{\sigma}_\ell \varepsilon^*_{\ell,i,j}$$

where $\varepsilon^*_{\ell,i,j}$ are i.i.d. $\sim \mathcal{N}(0,1)$

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Bootstrap test for similarity II

Bootstrap test:

- Calculate $\hat{\vartheta}_1^*, \hat{\vartheta}_2^*$ from the bootstrap data $Y_{\ell,i,j}^*$
- Calculate $\hat{d}^* = d(\hat{m}_1^*, \hat{m}_2^*)$, for $d = d_2$ that is

$$\hat{\mathbf{d}}_2^* = \int_{\mathcal{X}} (m_1(x, \hat{\vartheta}_1^*) - m_2(x, \hat{\vartheta}_2^*))^2 dx$$

- Repeat this procedure B times
- If $\hat{\mathbf{d}}^{*(\mathbf{1})}, \ldots, \hat{\mathbf{d}}^{*(\mathbf{B})}$ denote the ordered bootstrap replicates the hypothesis

$$H_0 : d(m_1, m_2) \geq \epsilon$$

is rejected, whenever

$$\hat{\mathbf{d}} < \hat{\mathbf{d}}^{*(\lfloor \mathbf{B}\alpha \rfloor)}$$

Bootstrap test for similarity III

- Theoretical properties:
  - the bootstrap test has asymptotic level α
  - the bootstrap test is consistent
- More precisely: for increasing sample sizes $n_1, n_2 \to \infty$

$$\begin{aligned} d(m_1, m_2) = \epsilon &\rightsquigarrow \quad \mathbb{P}(\text{“rejection”}) \to \alpha \\ d(m_1, m_2) > \epsilon &\rightsquigarrow \quad \mathbb{P}(\text{“rejection”}) \to 0 \\ d(m_1, m_2) < \epsilon &\rightsquigarrow \quad \mathbb{P}(\text{“rejection”}) \to 1 \end{aligned}$$

- In case of $d = d_\infty$ and the true difference curve having more than one extremal point the bootstrap test is still valid but more conservative

Finite sample properties

- $m_1(x, \vartheta_1) = \delta + \frac{5x}{x+1}, \qquad m_2(x, \vartheta_2) = \frac{5x}{1+x}, \qquad \mathcal{X} = [0, 4]$

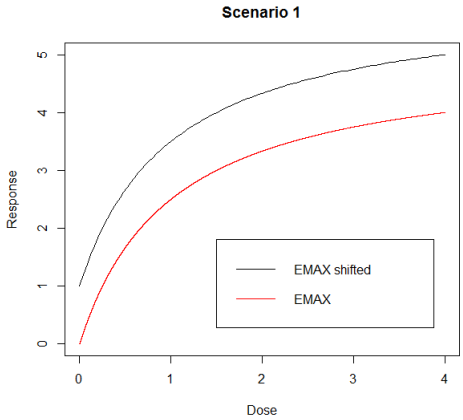

Figure: Two shifted EMAX models.

The d_2 bootstrap test – simulation of Type I error rates

- $m_1(x, \vartheta_1) = \delta + \frac{5x}{x+1}, \qquad m_2(x, \vartheta_2) = \frac{5x}{1+x}, \qquad \mathcal{X} = [0, 4]$
- $H_0 : d_2(m_1, m_2) \geq 1$ versus $H_1 : d_2(m_1, m_2) < 1$

			$\alpha = 0.05$			$\alpha = 0.1$		
			(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	δ	d_2	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
$(10, 10)$	1	4	0.000	0.000	0.000	0.000	0.000	0.000
$(10, 10)$	0.75	2.25	0.004	0.002	0.001	0.000	0.002	0.000
$(10, 10)$	0.5	1	0.051	0.064	0.052	0.101	0.120	0.118
$(20, 20)$	1	4	0.000	0.000	0.000	0.000	0.000	0.000
$(20, 20)$	0.75	2.25	0.001	0.002	0.000	0.004	0.005	0.001
$(20, 20)$	0.5	1	0.057	0.058	0.050	0.125	0.107	0.097
$(50, 50)$	1	4	0.000	0.000	0.000	0.000	0.000	0.000
$(50, 50)$	0.75	2.25	0.001	0.000	0.000	0.002	0.000	0.000
$(50, 50)$	0.5	1	0.057	0.048	0.054	0.097	0.114	0.093

Table: Simulated Type I error rates of the d_2-bootstrap test (1000 simulations, $B = 300$).

The d_2 bootstrap test – simulation of Type I error rates

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- $H_0 : d_2(m_1, m_2) \geq 1$ versus $H_1 : d_2(m_1, m_2) < 1$

			$\alpha = 0.05$			$\alpha = 0.1$		
			(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	δ	d_2	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
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The d_2 bootstrap test – simulation of power

			$\alpha = 0.05$			$\alpha = 0.1$		
			(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	δ	d_2	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
$(10, 10)$	0.25	0.25	0.210	0.118	0.134	0.300	0.212	0.256
$(10, 10)$	0.1	0.04	0.294	0.132	0.186	0.427	0.250	0.312
$(10, 10)$	0	0	0.351	0.145	0.176	0.467	0.286	0.340
$(20, 20)$	0.25	0.25	0.392	0.171	0.225	0.534	0.302	0.382
$(20, 20)$	0.1	0.04	0.560	0.308	0.418	0.720	0.460	0.562
$(20, 20)$	0	0	0.610	0.314	0.390	0.757	0.462	0.555
$(50, 50)$	0.25	0.25	0.724	0.460	0.554	0.825	0.595	0.825
$(50, 50)$	0.1	0.04	0.961	0.691	0.821	0.982	0.824	0.973
$(50, 50)$	0	0	0.984	0.734	0.865	0.998	0.861	0.999

Table: Simulated power of the d_2-bootstrap test (1000 simulations, $B = 300$).

The d_∞ bootstrap test – simulation of Type I error rates

		$\alpha = 0.05$			$\alpha = 0.1$		
		(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	$d = d_\infty$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
$(10, 10)$	1	0.000	0.004	0.001	0.007	0.019	0.010
$(10, 10)$	0.75	0.000	0.008	0.006	0.013	0.041	0.020
$(10, 10)$	0.5	0.015	0.040	0.016	0.050	0.104	0.054
$(20, 20)$	1	0.000	0.000	0.000	0.000	0.004	0.006
$(20, 20)$	0.75	0.000	0.002	0.000	0.003	0.010	0.002
$(20, 20)$	0.5	0.006	0.019	0.016	0.027	0.051	0.046
$(50, 50)$	1	0.000	0.000	0.000	0.000	0.000	0.001
$(50, 50)$	0.75	0.006	0.000	0.000	0.004	0.007	0.002
$(50, 50)$	0.5	0.003	0.005	0.004	0.018	0.027	0.034

Table: Simulated Type I error rates of the d_∞-bootstrap test for $\epsilon_\infty = 0.5$ (1000 simulations, $B = 300$).

The d_∞ bootstrap test – simulation of power

		$\alpha = 0.05$			$\alpha = 0.1$		
		(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	$d = d_\infty$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
$(10, 10)$	0.25	0.062	0.050	0.053	0.147	0.118	0.118
$(10, 10)$	0.1	0.100	0.070	0.099	0.195	0.137	0.190
$(10, 10)$	0	0.109	0.090	0.092	0.216	0.143	0.176
$(20, 20)$	0.25	0.085	0.060	0.076	0.171	0.134	0.162
$(20, 20)$	0.1	0.158	0.090	0.112	0.309	0.184	0.220
$(20, 20)$	0	0.178	0.108	0.120	0.324	0.209	0.219
$(50, 50)$	0.25	0.162	0.086	0.098	0.283	0.178	0.218
$(50, 50)$	0.1	0.390	0.212	0.232	0.568	0.349	0.398
$(50, 50)$	0	0.457	0.211	0.266	0.630	0.363	0.438

Table: Simulated power of the d_∞-bootstrap test for $\epsilon_\infty = 0.5$ (1000 simulations, $B = 300$).

A case study – IBS data set

- Biesheuvel, E. and Hothorn, L. A. : Female and male patients with Irritable Bowel Syndrome (IBS), $n = 369$
- randomized to one of the five doses 0 (placebo), 1, 2, 3, and 4
- larger values corresponding to a better treatment effect
- fitted models
  - male: $m_1(x, \beta_1) = 0.398 + 0.043x$
  - female: $m_2(x, \beta_2) = 0.220 + 0.517 \frac{x}{1.396+x}$
- maximum distance: 0.1784

A case study – IBS data set II

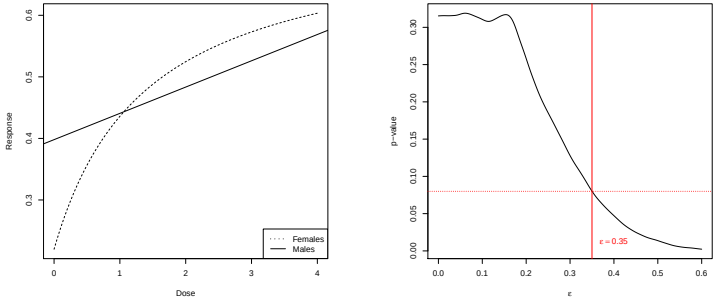

Figure: Left: Fitted dose response curves for male (linear model) and female (Emax model) patients. Right: p-values of the d_∞- bootstrap test for different values of the threshold ϵ_∞.

- the p-value corresponding to the choice $\epsilon_\infty = 0.35$ is given by 0.078

Further results and extensions

- the bootstrap d_∞-test was implemented in the `R` package `TestingSimilarity`
- we investigated the performance of all tests under the assumption of model misspecification and observed a robust performance
- the proposed tests were adapted to
  - the case of multiple curve comparison
  - dependent data
  - models with common parameters
- especially the adaption to dependent data offers a variety of new applications, e.g. the demonstration of bioequivalence

Further results and extensions II

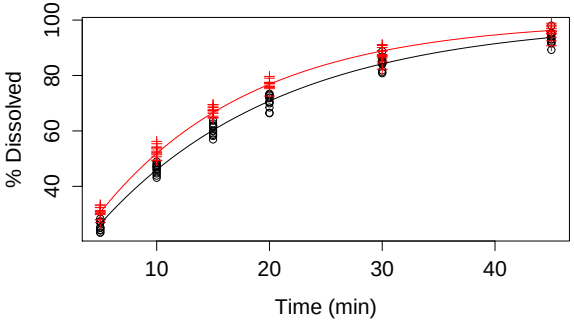

Figure: *Comparison of concentration profiles.*

Conclusions

- Two powerful tests have been proposed by
  - estimating the distance and the variance of the test statistic directly (asymptotic approach)
  - generating quantiles by a parametric bootstrap
- the bootstrap approach can be applied to any metric without deriving the asympotic distribution
- the tests are robust against misspecification of the functional form and can also be applied to dependent data

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Acknowledgments

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