Equivalence of dose-response curves

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Motivation I

Three examples:

- 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 equivalence of curves becomes an issue

- Another application: Comparison of dose response relationships for two regimens
  $\longrightarrow$ For example, demonstrate that once-daily and twice-daily applications of a drug are similar over a given dose range

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  $\longrightarrow$ Traditional approaches based on AUC or Cmax may be misleading
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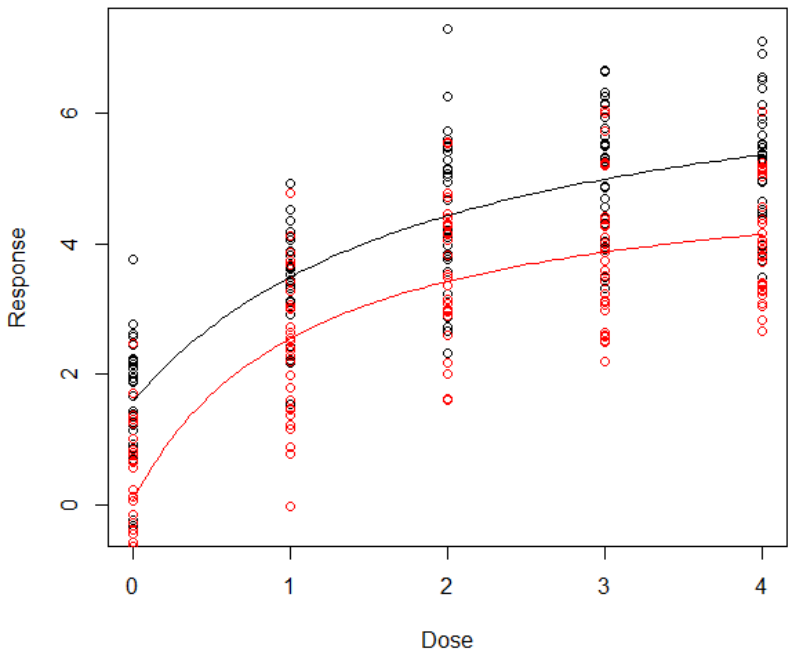
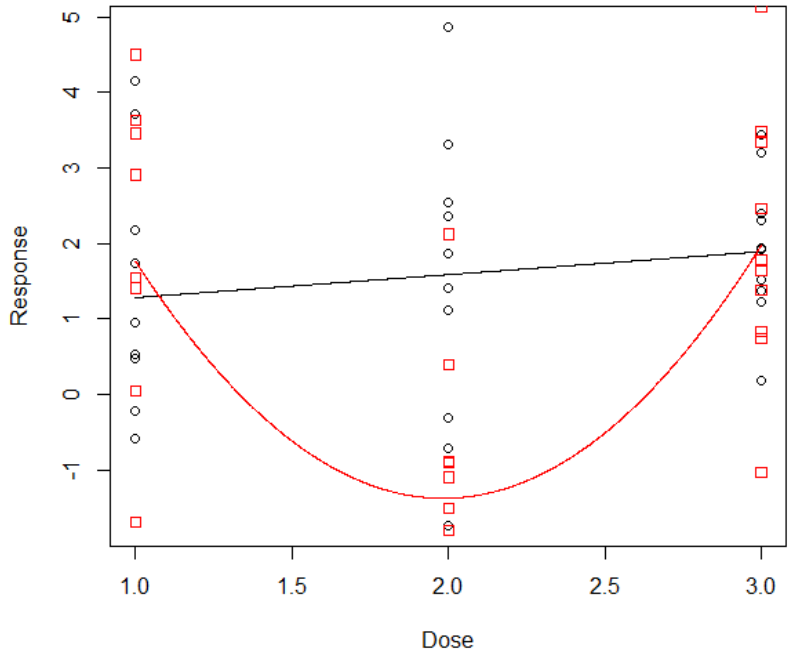
Comparing curves - The setting

Two dose response profiles from different populations. For example:

European: $m_1(d, \theta_1)$
Japanese: $m_2(d, \theta_2)$





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Measures of equivalence

- We need a **measure** for the equivalence of m_1 and m_2. Here we use the **maximum deviation between the curves:**

$$\mathbf{d} = \max_{d \in \mathcal{D}} |m_1(d, \theta_1) - m(d, \theta_2)|$$

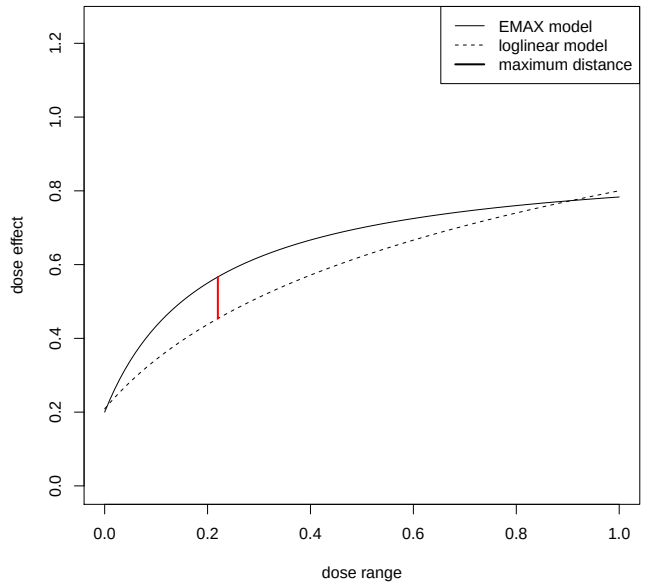
- Hypothesis of equivalence:

$$H_0 : \mathbf{d} \geq \Delta \quad \text{versus} \quad H_1 : \mathbf{d} < \Delta$$

(here Δ is a pre-specified constant depending on the particular application).

Example: maximal deviation

- EMAX and Log-linear model



Improvements obtained during IDEAL funding

- **New tests for the hypothesis of equivalence**
  - Bretz, Dette, Liu, Möllenhoff, Trampisch (2017) Assessing the equivalence of dose response and target doses in two non-overlapping subgroups. (to appear in *Statistics in Medicine*)
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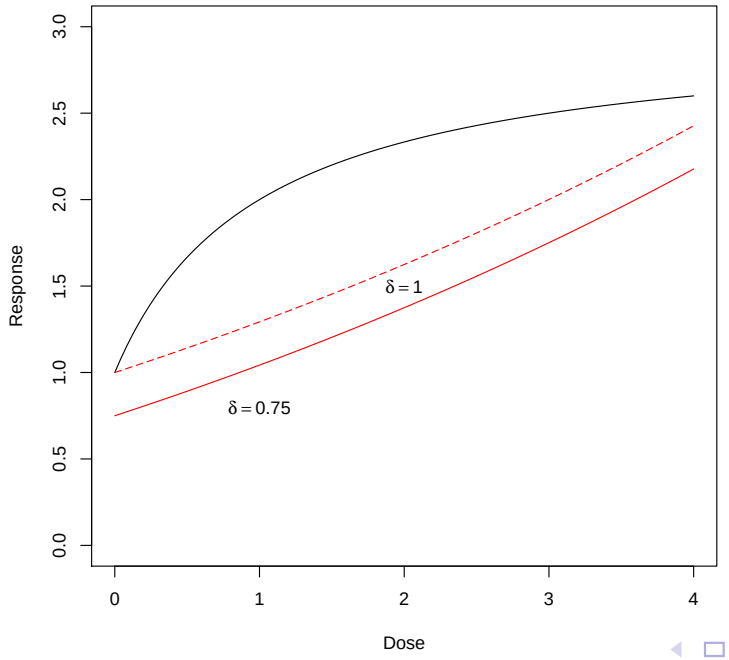
Example: EMAX and an exponential model

- EMAX model : $m_1(d, \theta_1) = 1 + \frac{2d}{1+d}$
- Exponential model: $m_2(d, \theta_2) = \delta + 2.2 \cdot (\exp(\frac{d}{8}) - 1),$
- Dose range $\mathcal{D} = [0, 4]$, five dose levels
- Hypotheses: $H_0 : \mathbf{d} \geq 1$ versus $H_1 : \mathbf{d} < 1$



Simulated level

- Hypotheses $H_0 : \mathbf{d} \geq 1$ versus $H_1 : \mathbf{d} < 1$

		$\alpha = 0.05$			$\alpha = 0.1$		
		(σ_1^2, σ_2^2)			(σ_1^2, σ_2^2)		
(n_1, n_2)	**d**	(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)	1.5	0.001 (0.000)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	0.004 (0.000)	0.000 (0.000)
(10, 10)	1.25	0.005 (0.000)	0.011 (0.000)	0.006 (0.000)	0.013 (0.000)	0.030 (0.000)	0.020 (0.000)
(10, 10)	1	0.045 (0.007)	0.037 (0.000)	0.036 (0.001)	0.102 (0.021)	0.086 (0.002)	0.090 (0.007)
(10, 20)	1.5	0.000 (0.000)	0.002 (0.000)	0.000 (0.000)	0.000 (0.000)	0.002 (0.000)	0.000 (0.000)
(10, 20)	1.25	0.004 (0.000)	0.013 (0.000)	0.005 (0.000)	0.015 (0.000)	0.025 (0.000)	0.009 (0.000)
(10, 20)	1	0.045 (0.017)	0.046 (0.002)	0.028 (0.004)	0.099 (0.042)	0.104 (0.011)	0.079 (0.017)

Simuated power

- Hypotheses $H_0 : \mathbf{d} \geq 1 \quad$ versus $H_1 : \mathbf{d} < 1$

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(n_1, n_2)	**d**	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$	$(0.25, 0.25)$	$(0.5, 0.5)$	$(0.25, 0.5)$
$(10, 10)$	0.75	0.160 (0.026)	0.093 (0.004)	0.125 (0.007)	0.297 (0.083)	0.225 (0.007)	0.229 (0.033)
$(10, 10)$	0.5	0.237 (0.037)	0.133 (0.003)	0.164 (0.009)	0.383 (0.117)	0.231 (0.018)	0.309 (0.029)
$(10, 20)$	0.75	0.185 (0.084)	0.123 (0.006)	0.159 (0.025)	0.320 (0.162)	0.226 (0.035)	0.283 (0.089)
$(10, 20)$	0.5	0.300 (0.087)	0.175 (0.005)	0.269 (0.035)	0.457 (0.190)	0.305 (0.043)	0.414 (0.120)

Conclusions and future research

- **New powerful tests for the equivalence of curves**
  - estimate the distance directly
  - generate quantiles by parametric bootstrap (non standard - constrained estimation)
  - applicable for small sample sizes
  - Software is available: `R` package `TestingSimilarity`

- **Once again:** methodology is applicable, whenever curves have to be compared

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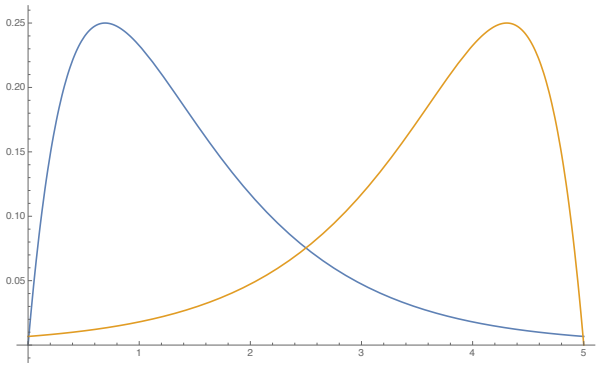
Bioequivalence

Collaboration with FDA (jointly with F. Mentré)

- **Traditional bioequivalence studies focus on AUC and Cmax**



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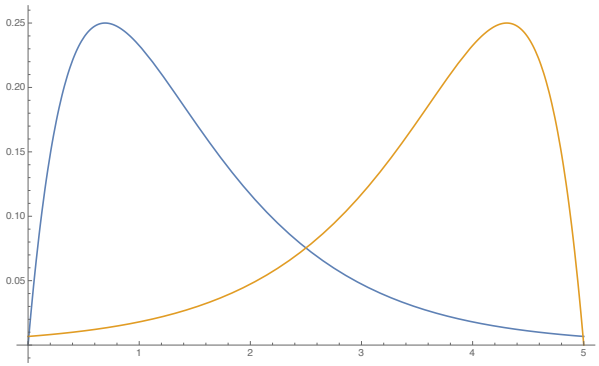

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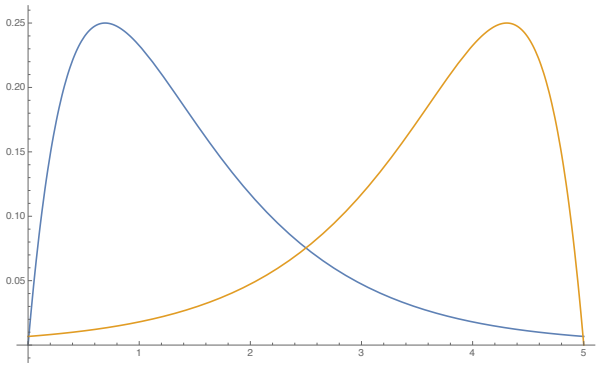

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Comparison of dissolution profiles

Collaboration with O. Collignon and E. Kotzagiorgis (EMA)

- *In vitro* dissolution profile comparison of two formulations (test vs. reference product) in order to demonstrate bioequivalence
- Figure: twelve tablets per product, each measured at six time points