Practical Flatness

Equivalence Approach
for Multi-Factor Robustness Evaluation
with Application in Vaccines Development

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Flatness as a Concept

- Quality-by-Design: Risk based, data driven decisions are key!
- Classification of process parameters into „**critical**" and „**non-critical**"
- To understand **relationship** between Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) and then estabish *„Design Space"* that *„have been demonstraded to provide assurance of quality"*.
- **Robustness** of a process is its property to stay within the specification limits (target $\pm\Delta$)

How far can we change

our experimental parameters

to stay within our target margin?

- **Flatness** describes this *desired* relationship between dependent and independent variables

Motivating Example

We want to evaluate robustness of a manufacturing process

- Continuous response
- Two factors, *Duration* and *Temperature*, refactored to a domain of $[-1, 1]$
- DoE: Central composite design, 6 reps at center point, else 2 reps
- Apply linear regression (e.g. response surface, etc.)

Significant Flatness

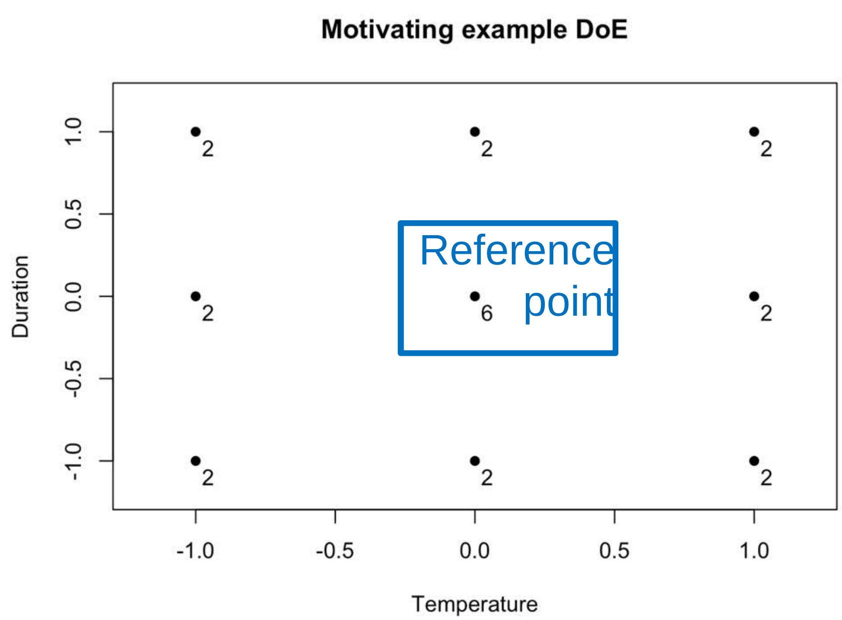
Do the mean responses differ?

→ e.g. t-Tests on differences

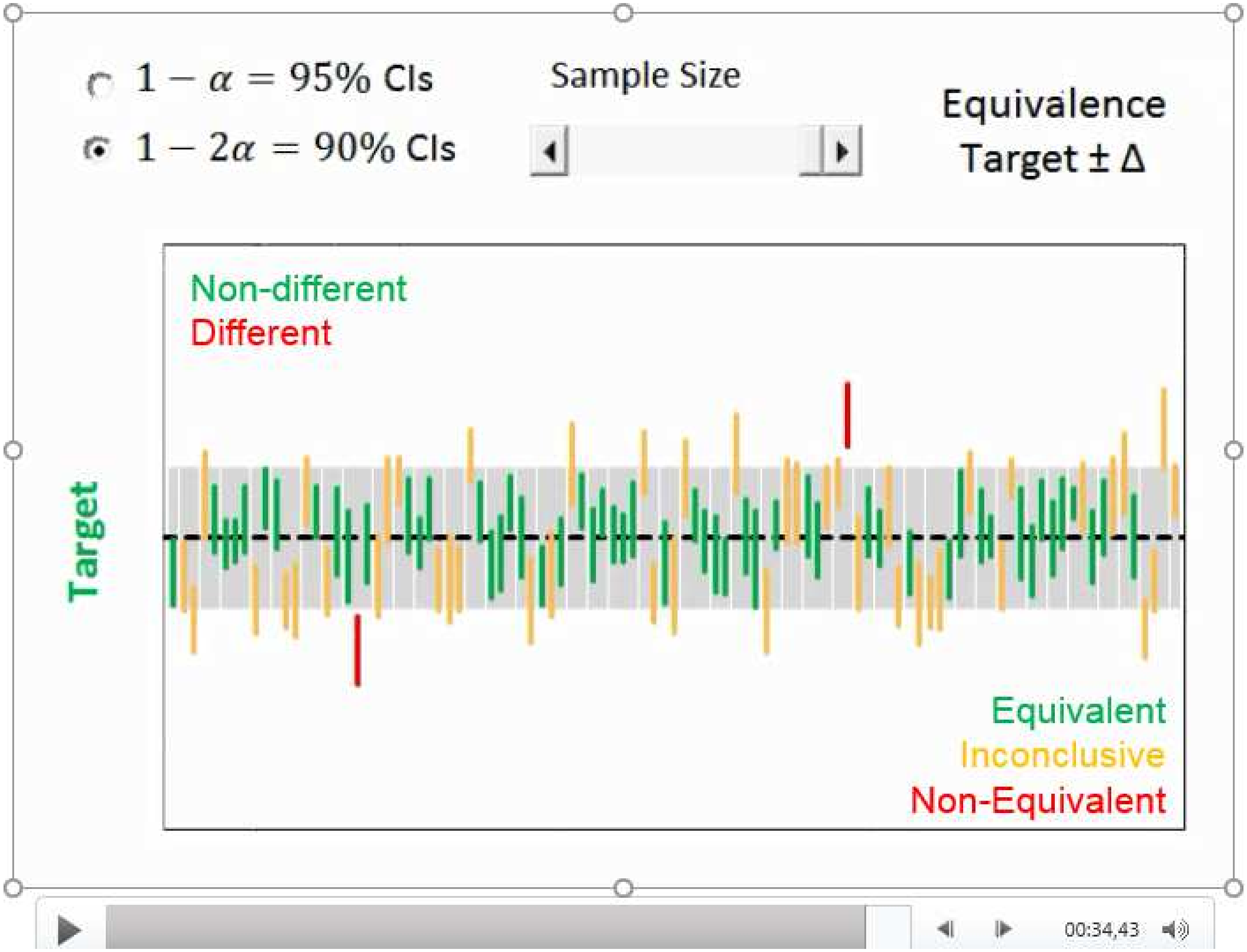
Practical Flatness

Are mean responses equivalent?

→ e.g. TOST



From Significance to Equivalence



Practical Flatness – TOST Procedure

Let $(Y_1, \dots, Y_{n_0}) \sim N(\mathbf{1}_{n_0}\mu_0, \sigma^2 \boldsymbol{I}_{n_0})$ and $(Y_{n_0+1}, \dots, Y_{n_0+n_1}) \sim N(\mathbf{1}_{n_1}\mu_1, \sigma^2 \boldsymbol{I}_{n_1})$ independent.

Are these two samples „equivalent“?

I.e.: is the difference of the means within a specified equivalence margin $(-\delta_L, \delta_U)$.

Schuirmann‘s TOST (Two one-sided tests):

$$H_0^L: \mu_0 - \mu_1 \leq -\delta_L \quad \text{vs.} \quad H_1^L: \mu_0 - \mu_1 > -\delta_L$$
$$H_0^U: \mu_0 - \mu_1 \geq \delta_U \quad \text{vs.} \quad H_1^U: \mu_0 - \mu_1 < \delta_U$$

Joint hypothesis (of „H_0^L or H_0^U“):

$$H_0: \mu_0 - \mu_1 \in (-\infty, -\delta_L] \cup [\delta_U, \infty) \text{ vs. } H_1: \mu_0 - \mu_1 \in (-\delta_L, \delta_U)$$

Usually checked via $(1 - 2\alpha)$-CIs → reject H_0 if the CI of the difference, if e.g.

$$\left[(\hat{\mu}_0 - \hat{\mu}_1) - t_{n_0+n_1-2,1-\alpha}\hat{\sigma}_{\mu_0-\mu_1}, (\hat{\mu}_0 - \hat{\mu}_1) + t_{n_0+n_1-2,1-\alpha}\hat{\sigma}_{\mu_0-\mu_1}\right],$$

is within equivalence margin.

Flatness in a DoE Setting

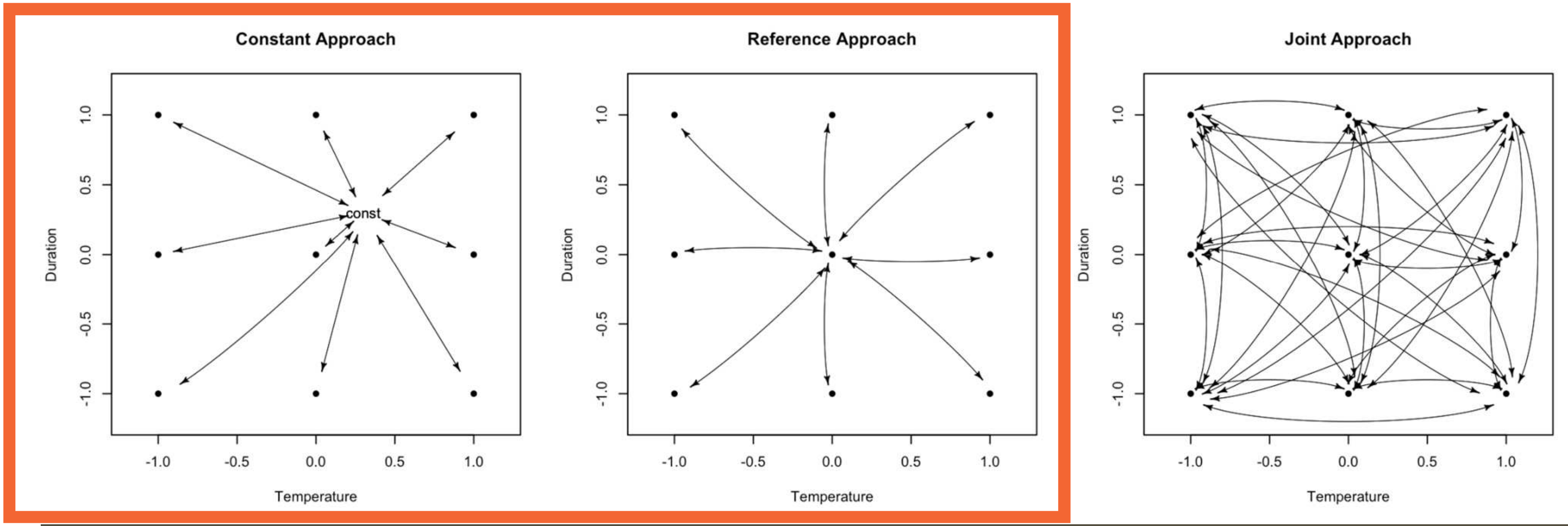
Back to our motivating example:

*How do we assess **flatness** among 9 design points?*

Constant Approach: Compare 9 design points to a given „textbook“ value

Reference Approach: Compare 8 design points to a *reference* (design) *point*

Many-to-many Approach: Pairwise comparison of all design points



Difference CI‘s and TOST Procedure

Problem Works in two-samples-settings.

Solution Compare several differences, and accept *global* flatness iff individual comparisons are considered flat.

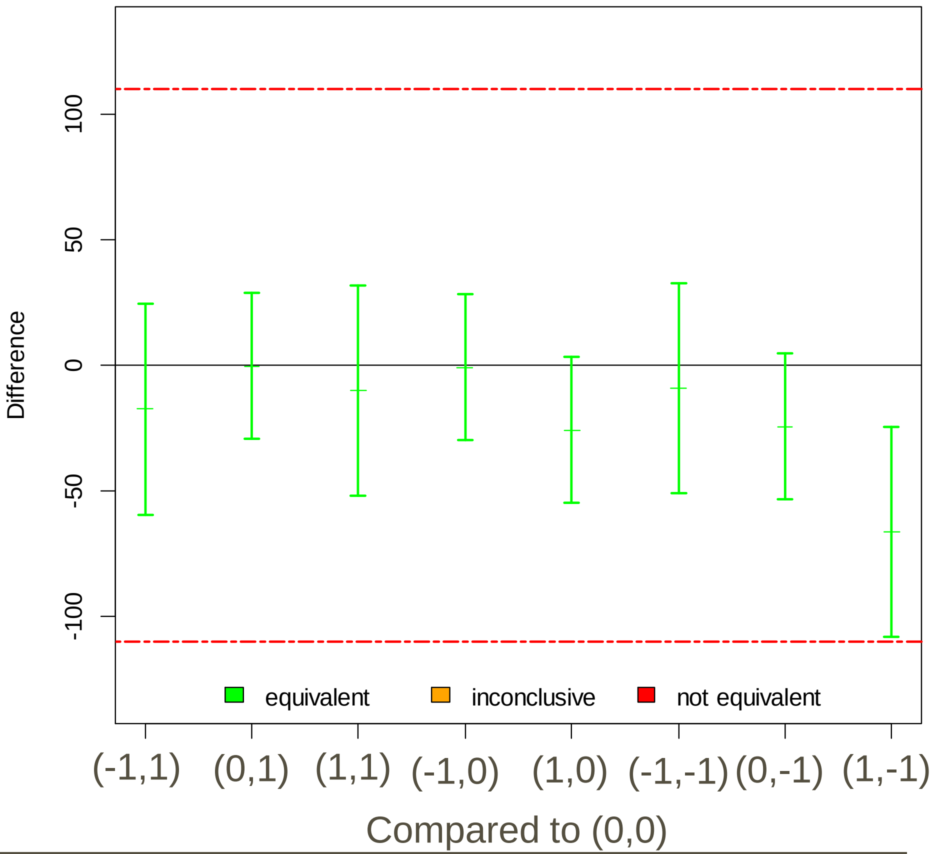
***Significant flatness* decision rule:**

Assume flatness when all $(\mathbf{1}-\boldsymbol{\alpha})$-CI‘s of the difference cover 0!

***Practical flatness* decision rule:**

Assume flatness when all $(\mathbf{1}-\mathbf{2}\boldsymbol{\alpha})$-TOST CI‘s lie within the equivalence margin!

Unadjusted 90% CIs (contrasts)



Simulation & Multiplicity Issue in contrasts for Reference Approach

Coverage Simulation

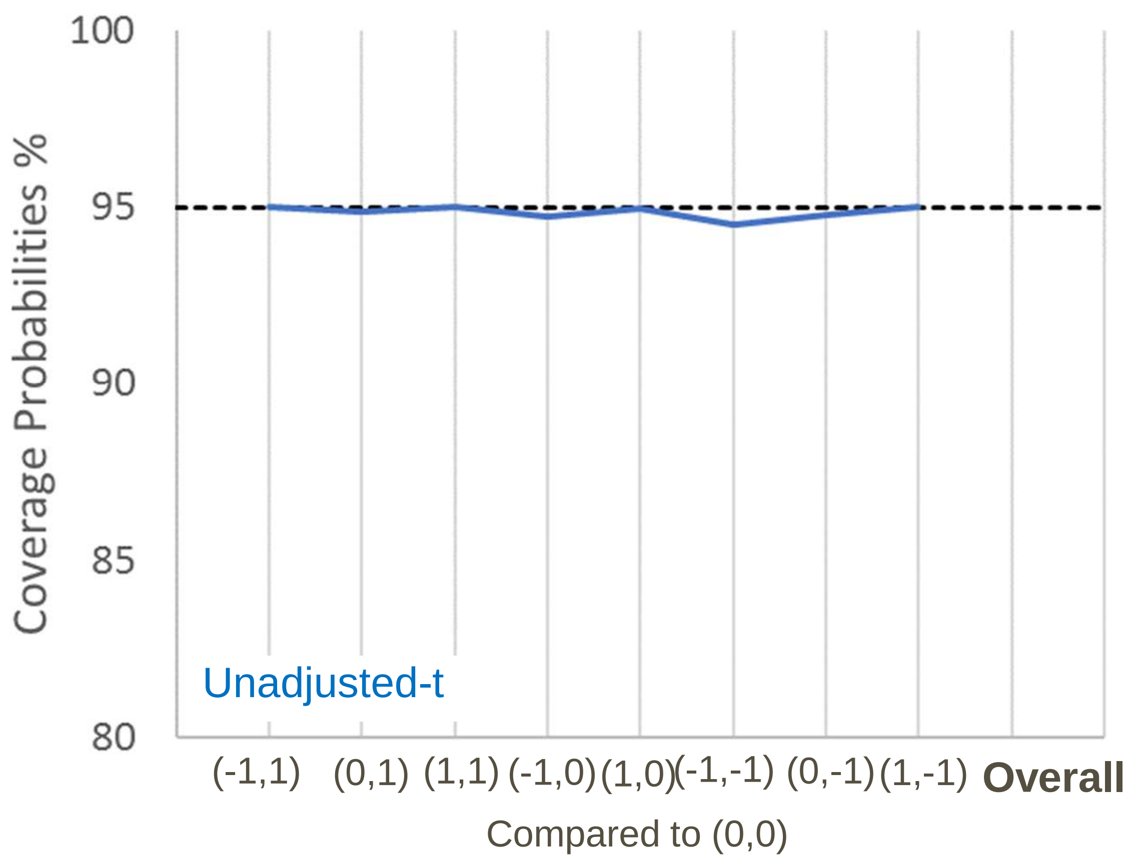
- 10^5 simulated DoE's
- $n = 6$, one per design point
- Number of Parameters $p = 6$

Problem

8 Comparisons:
Multiple Comparisons…

Solution

Use adjustments,
e.g. Bonferroni, Šidák,
Tukey, Dunnett, etc.



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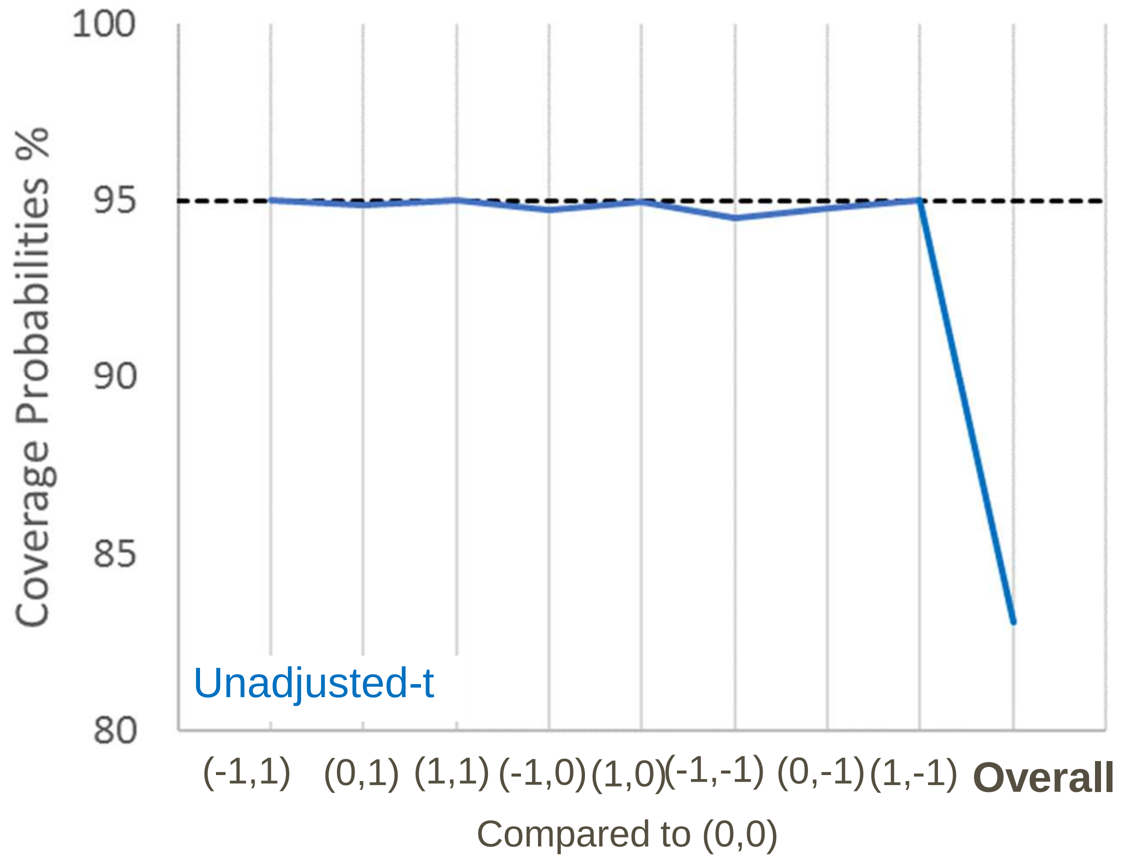

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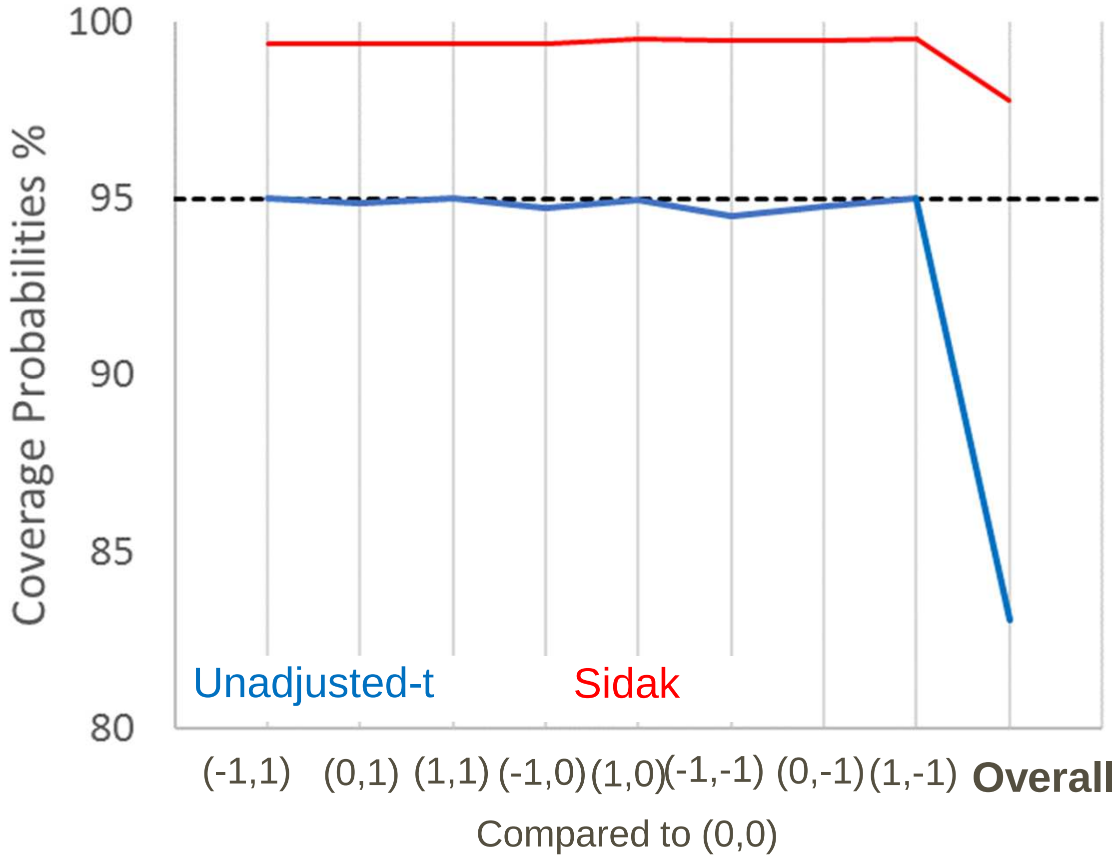
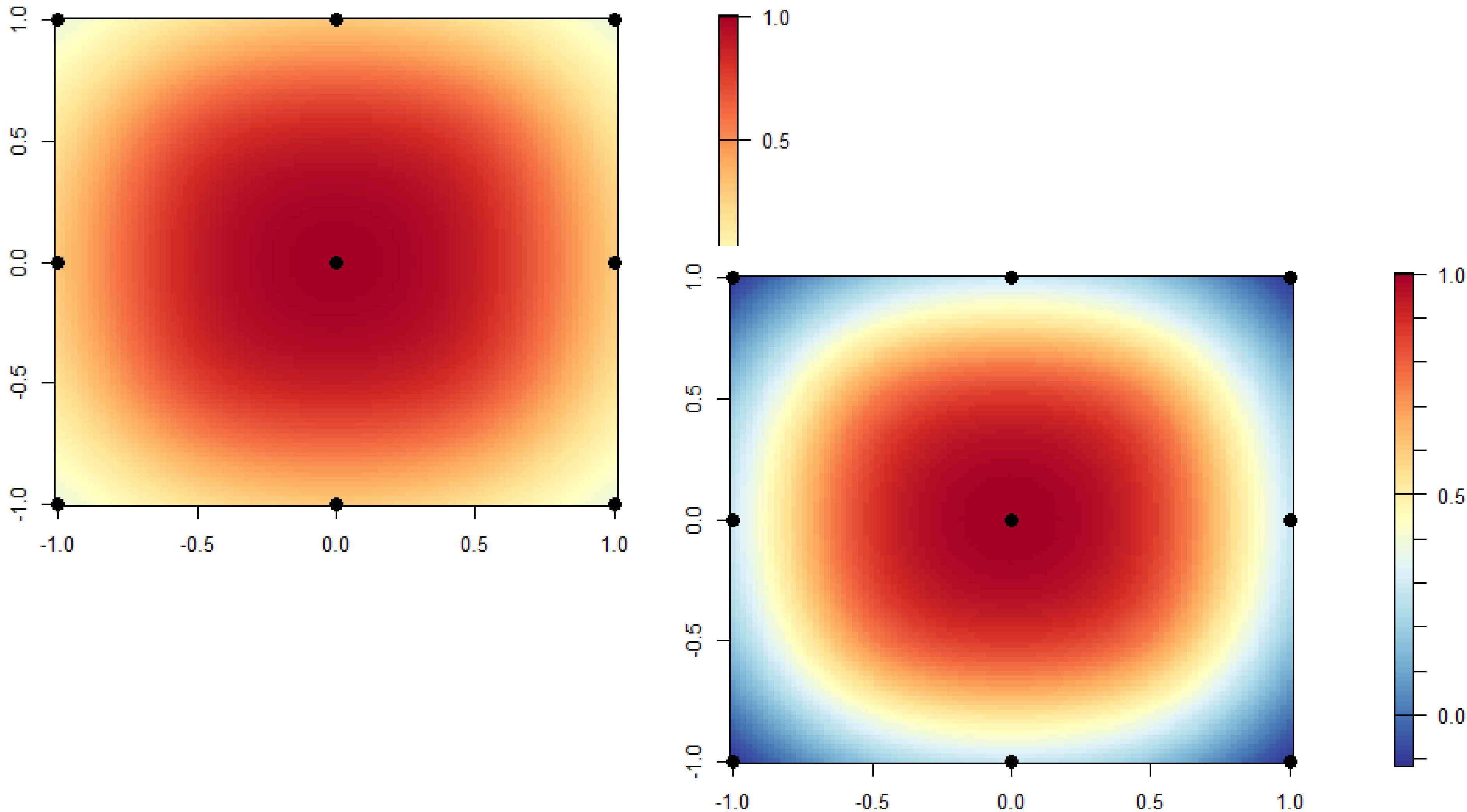
Why the actual coverage of unadjusted or Šidák are not equal to 95% (or 66.34% for unadjusted)?



„Spatial“ Correlation Issue: correlation to the center point



„Spatial“ Correlation Issue

Problem Comparisons are correlated!

Solution Multivariate t-distribution

Distribution of the comparison vector:

$$\tilde{Y} \sim N(\tilde{X}\beta, \sigma^2 \tilde{X}(X'X)^{-1}\tilde{X}')$$

and

$$\frac{\hat{\sigma}^2}{\sigma^2} \sim \chi^2_{n-p}.$$

Hence the standardized comparisons vector follows a central multivariate t-distribution:

$$\frac{\tilde{Y} - \tilde{X}\beta}{\hat{\sigma}} \sim t_{n-p}(0_k, \tilde{X}(X'X)^{-1}\tilde{X}')$$

→ Now: Calculate CI‘s using MVt and Corr.

(in R e.g. `mvtnorm::qmvt`)

Reference Approach

Mean response at 'selected points' at $\hat{Y}_0 = (\hat{Y}_1, \dots, \hat{Y}_{k+1})$ and corresponding matrix $X_0 = (x_1, \dots, x_{k+1})'$

We obtain k comparisons to reference point $\hat{Y}_r$:

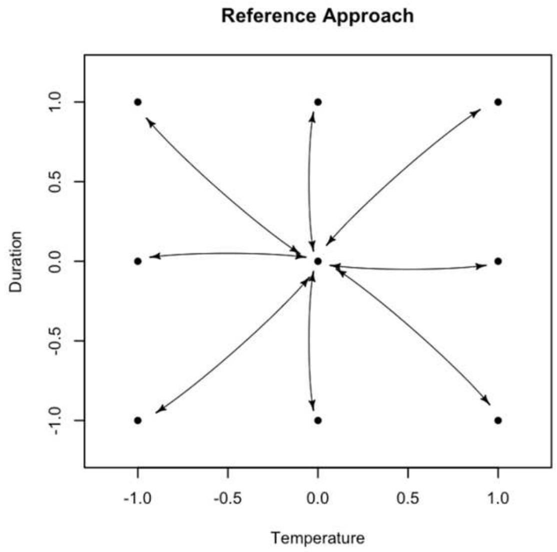
$$\tilde{Y} = \begin{pmatrix} \tilde{Y}_1 \\ \vdots \\ \tilde{Y}_k \end{pmatrix} := \begin{pmatrix} \hat{Y}_1 - \hat{Y}_r \\ \vdots \\ \hat{Y}_{k+1} - \hat{Y}_r \end{pmatrix}$$

Assume k comparisons of PIO points to reference point $\hat{Y}_r$, then

$$\mathrm{E}\left(\hat{Y}_i - \hat{Y}_r\right) = (x_i - x_r)'\beta$$

$$\mathrm{Var}(\hat{Y}_i - \hat{Y}_r) = \mathrm{Var}\left(\hat{Y}_i\right) + \mathrm{Var}\left(\hat{Y}_r\right) - 2\mathrm{Cov}(\hat{Y}_i, \hat{Y}_r)$$

with $i \neq r$.



→ Calculate Comparisons CI's of $\tilde{Y}_i$ for Difference or Equivalence Settings

Simulation & Multiplicity Issue in contrasts for Reference Approach

Coverage Simulation

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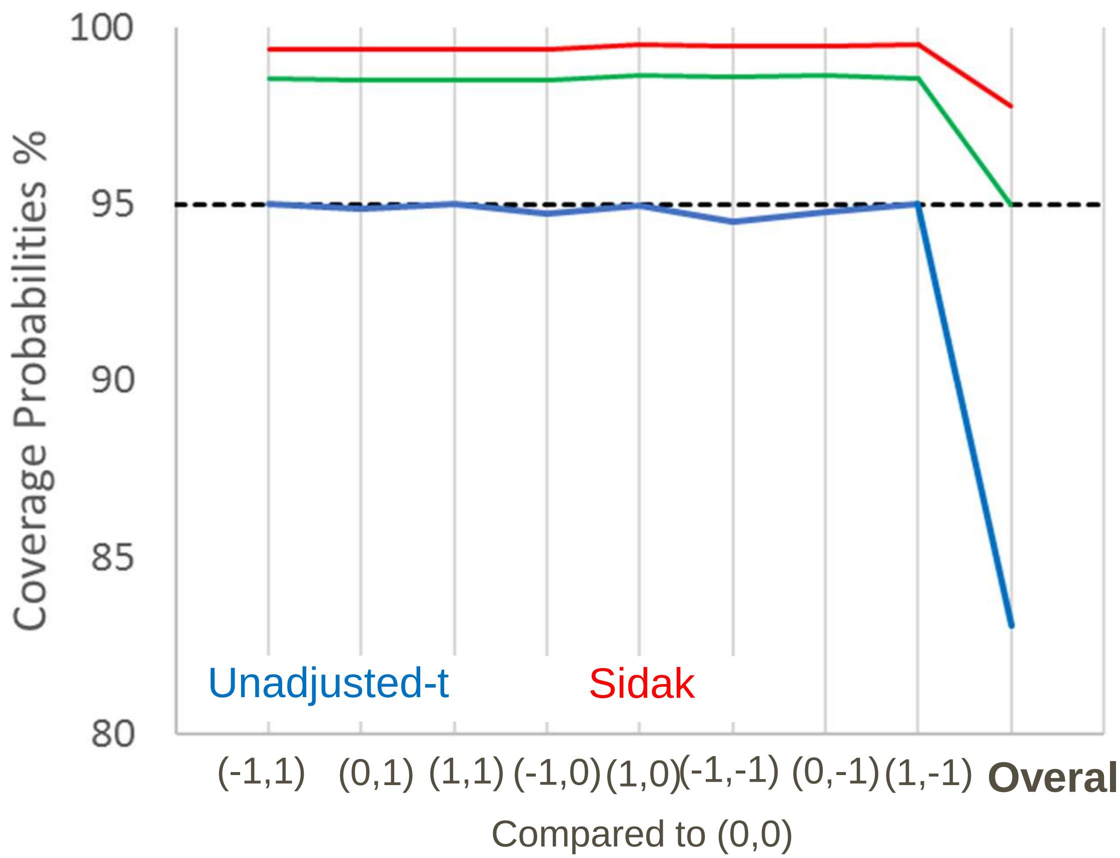
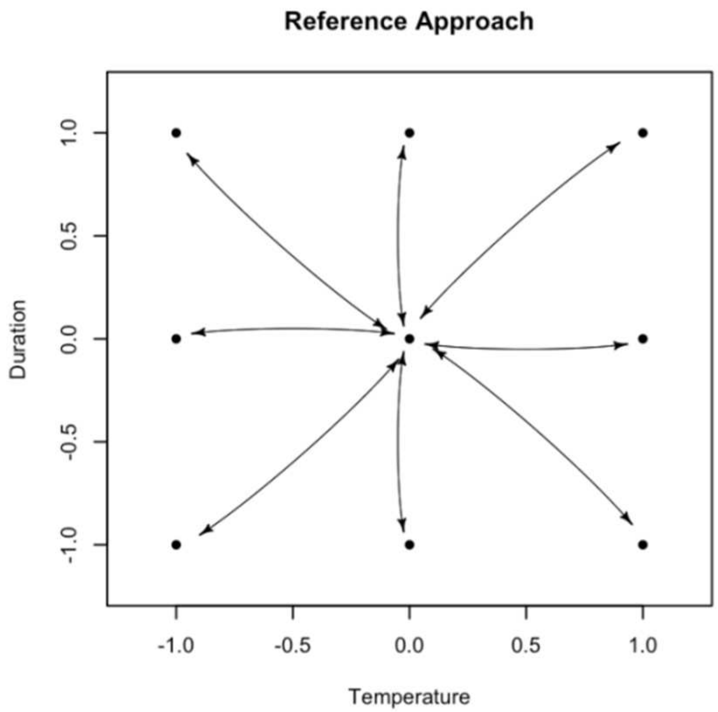


Solution for overall contrasts:

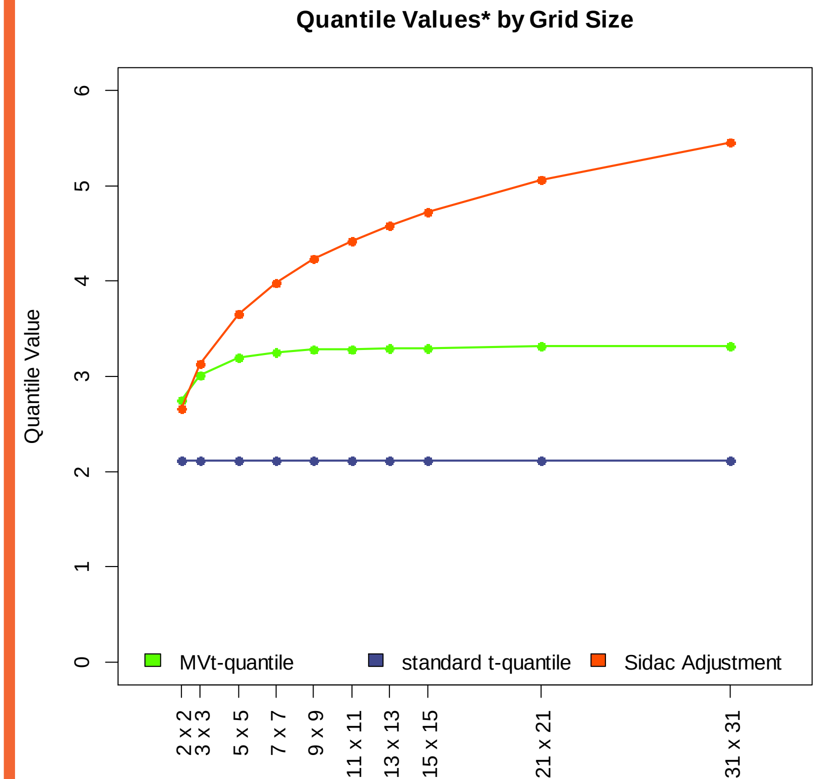
Multi-t is your friend ☺

Simulation & Quantiles for Reference Approach



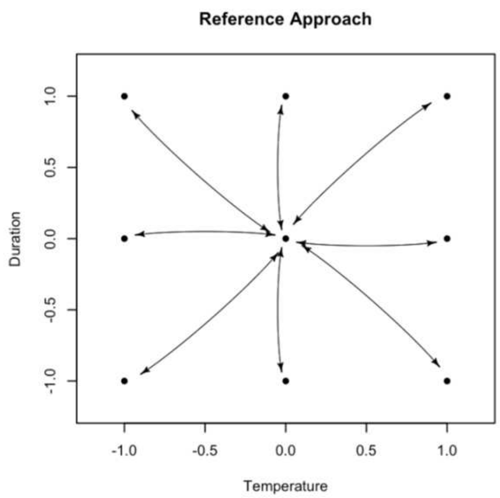
Motivating Example – Quantiles

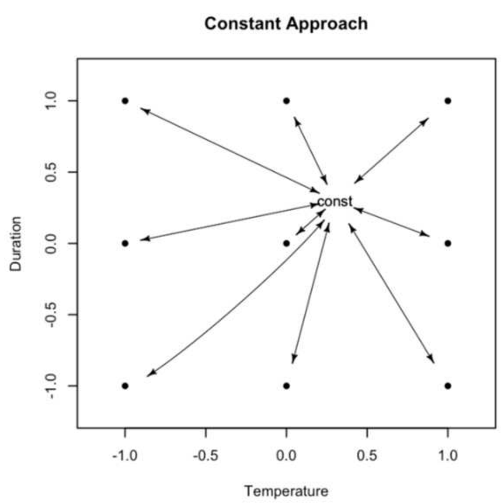
$$n = 22, p = 6, df = 16, \ \alpha = 0.05$$

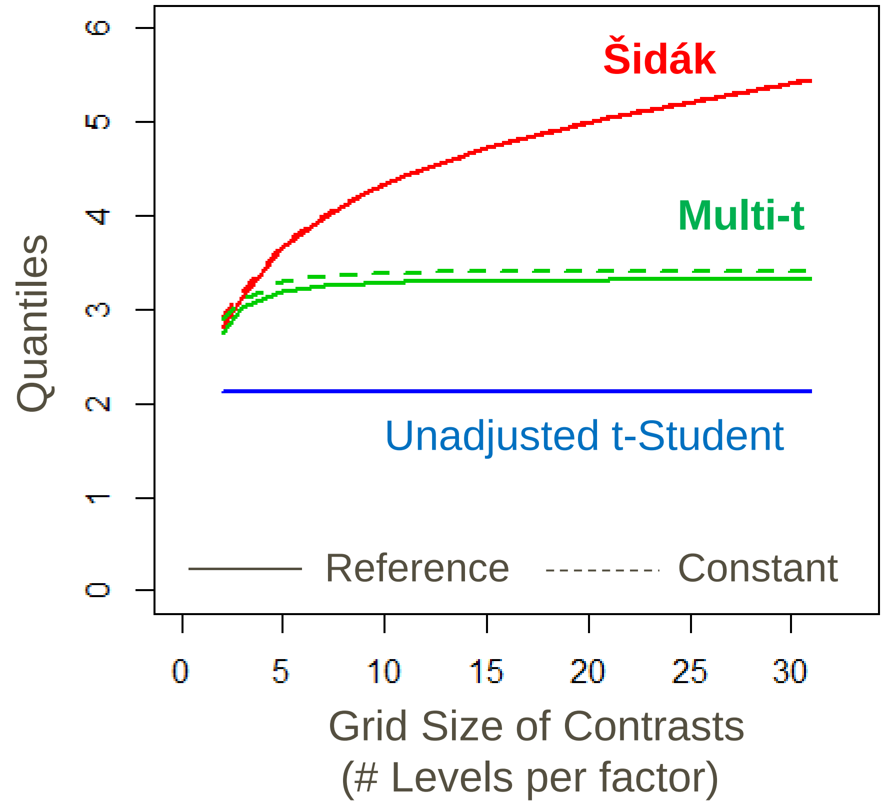


* quantiles calculated for both-sided 95%-CI's and 16 degrees of freedom

Constant versus Reference approach: quantile



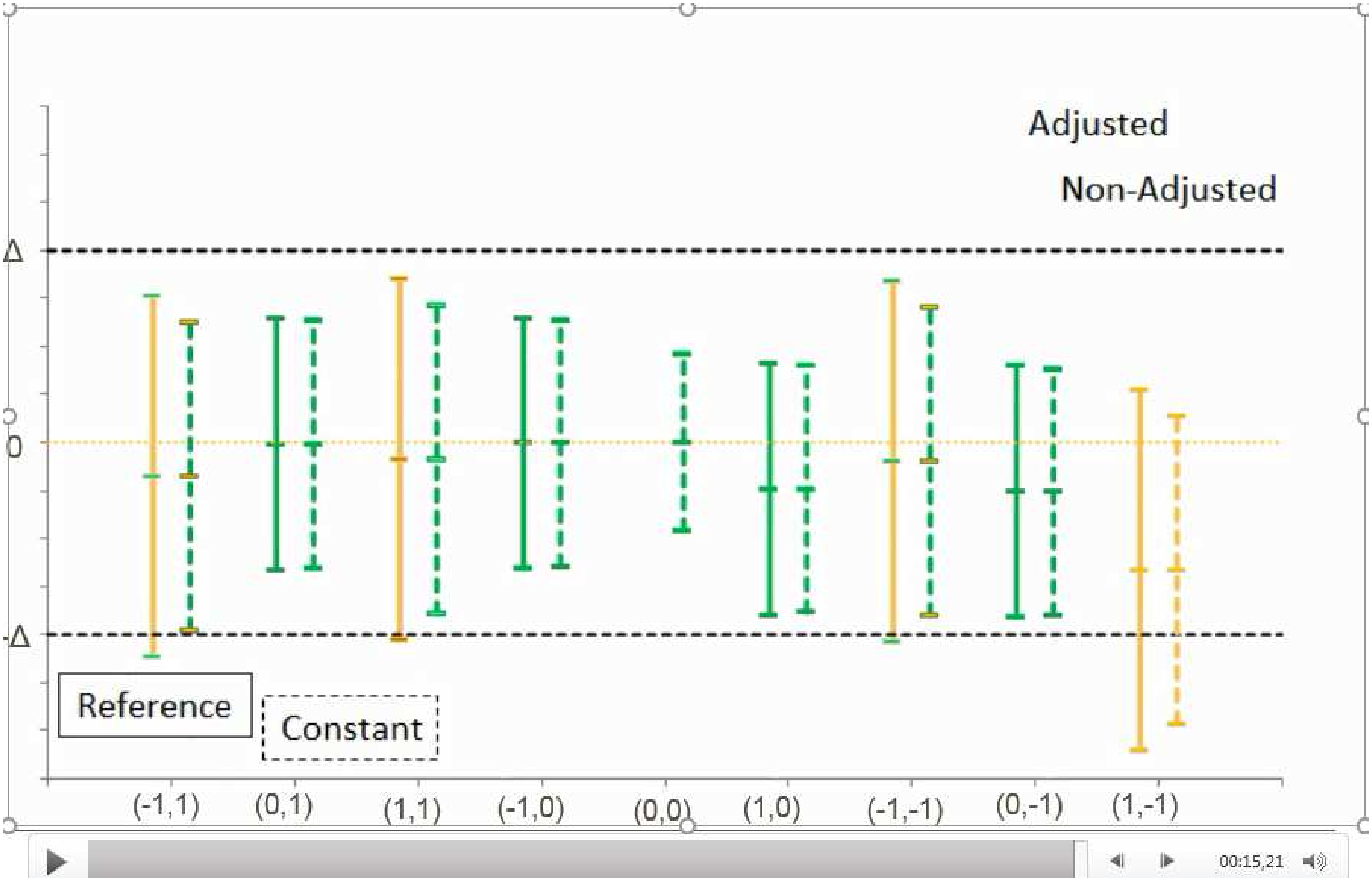




There is not so much difference
in contrasting to a reference a point,
or in comparing predictions to a constant value

But what about the CIs?

Constant versus Reference approach: CIs



Application / Case Study

Run experiment* for our motivating example

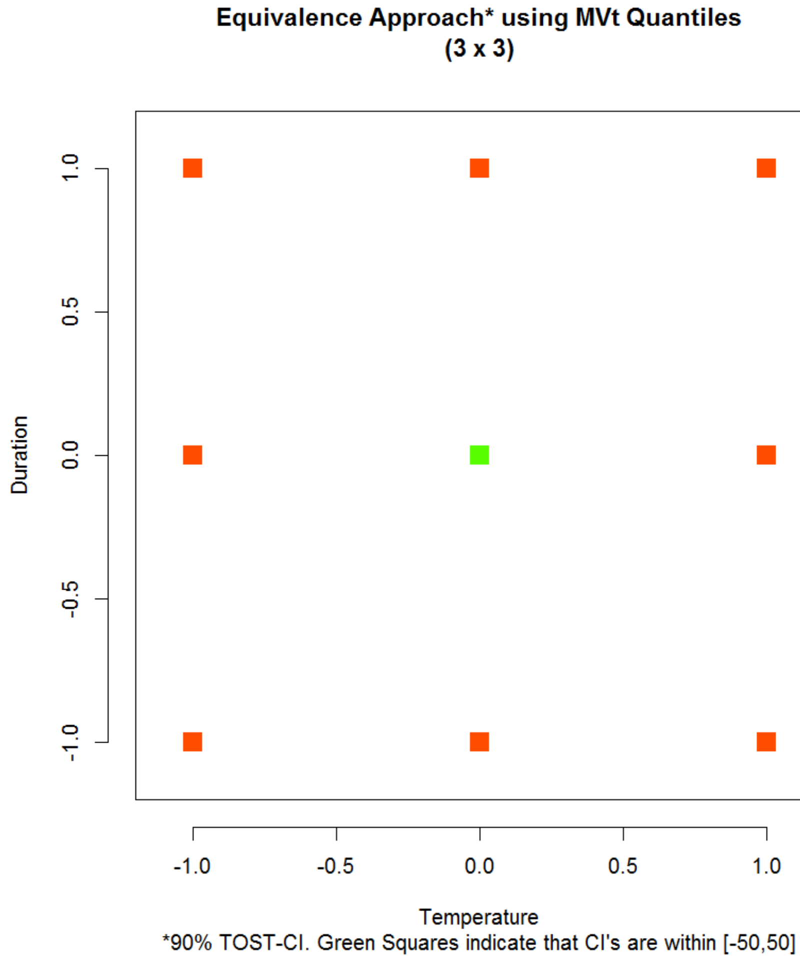
- Cell count Y
- Duration D
- Temperature T

$$Y = \beta_0 + \beta_1 T + \beta_2 D + \beta_3 DT$$
$$+ \beta_4 D^2 + \beta_5 T^2 + \varepsilon$$

*Check **practical flatness** when comparing to the center point as a reference (contrast)!*

* Simulated data

Application / Case Study



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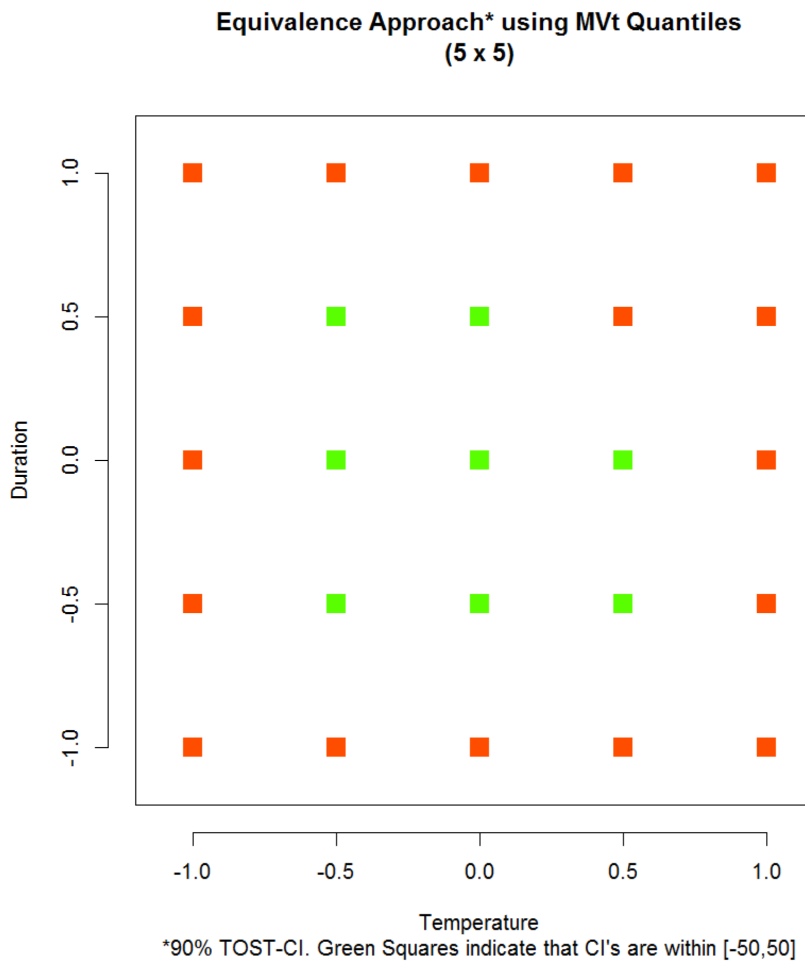

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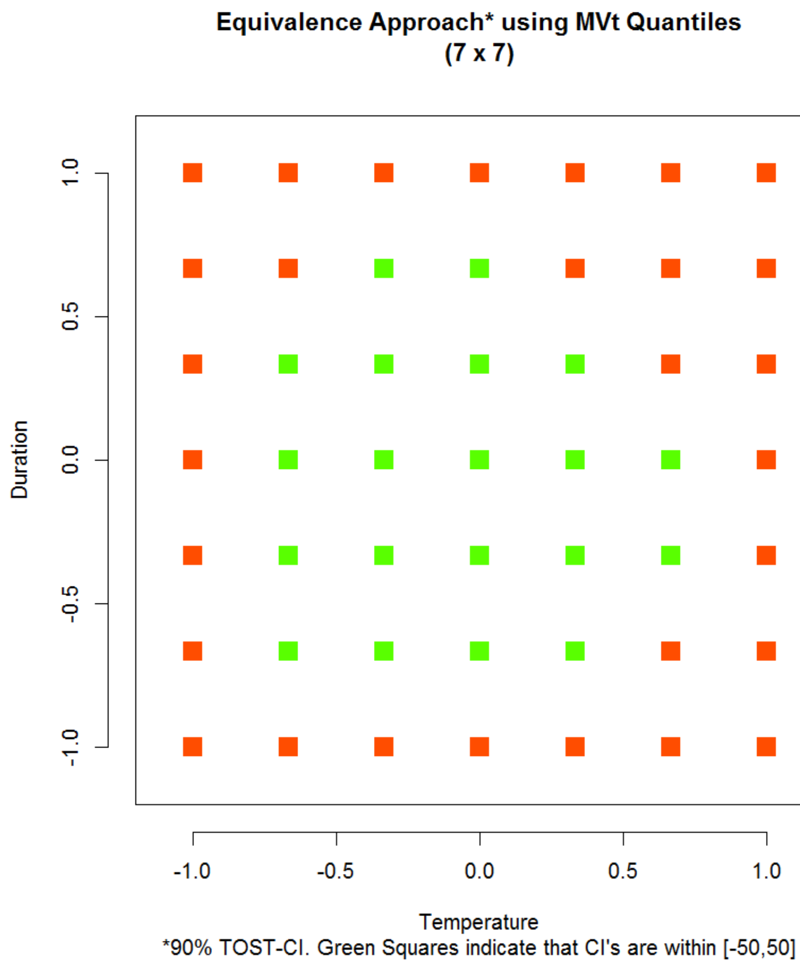

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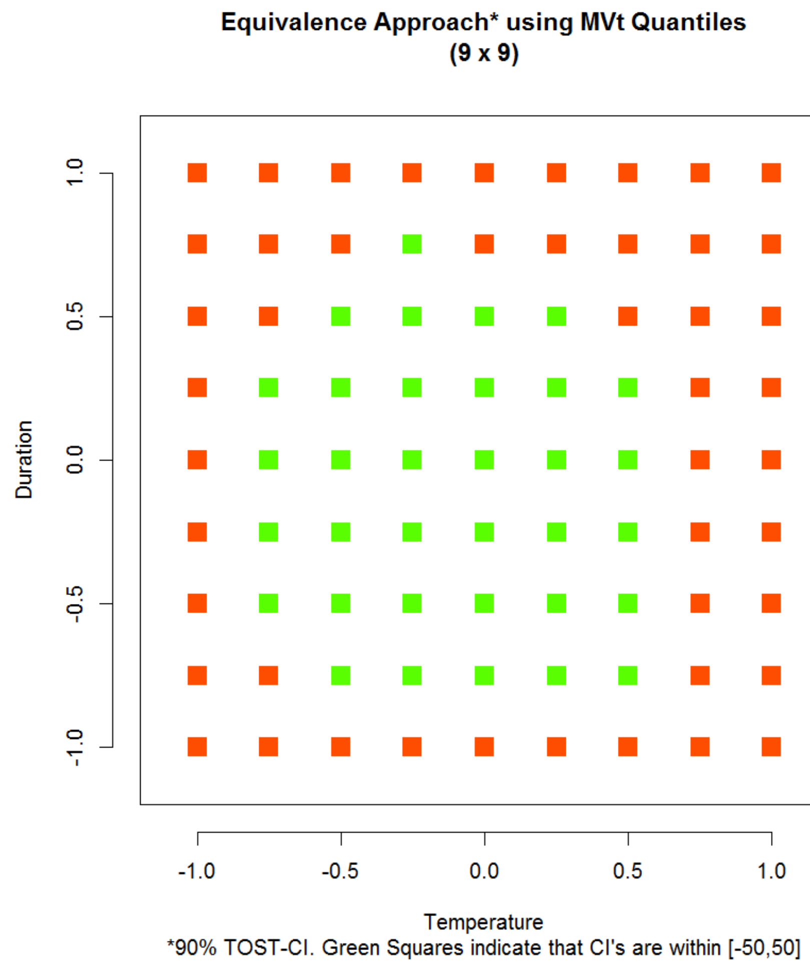

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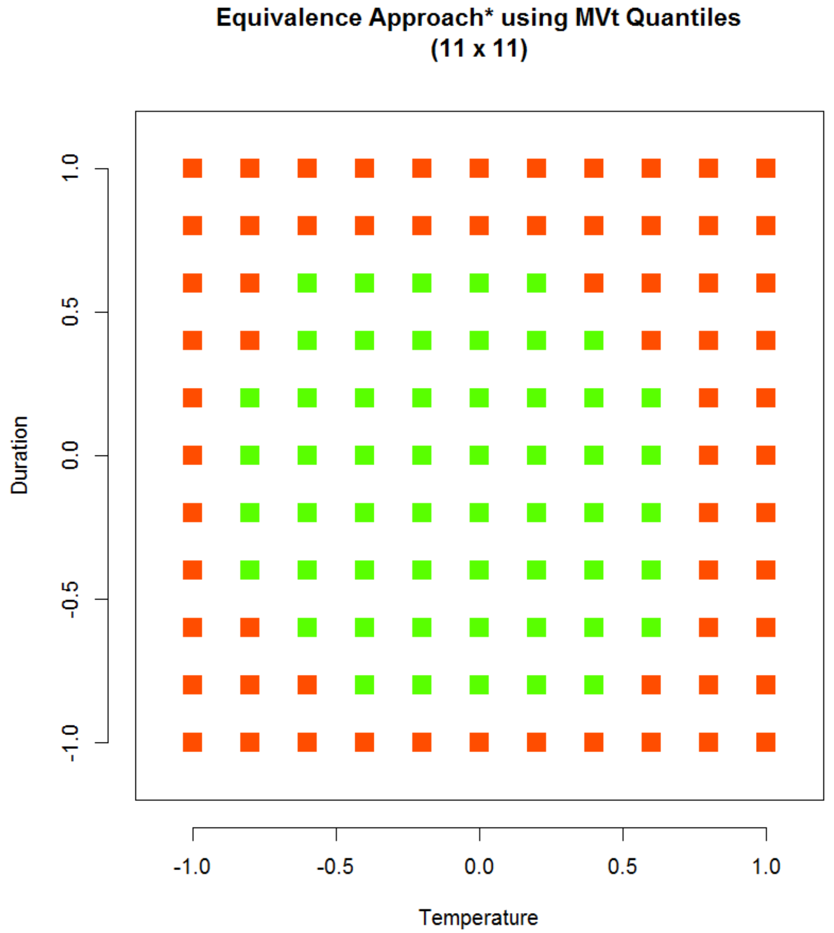
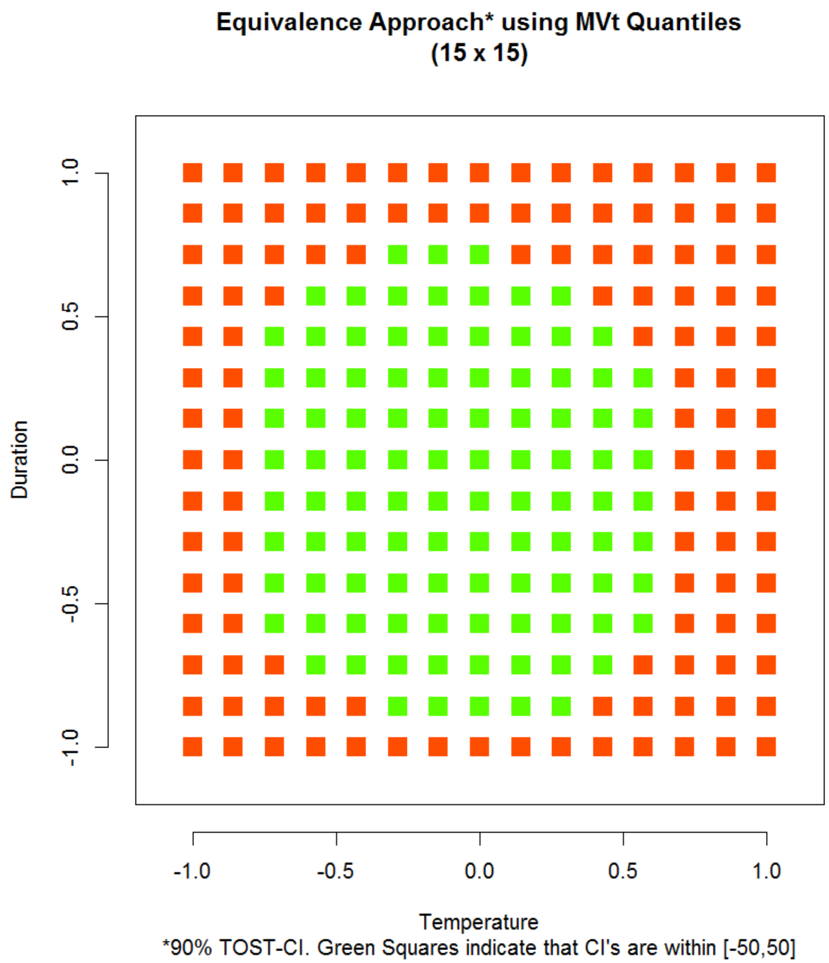


*90% TOST-CI. Green Squares indicate that CI's are within [-50,50]

Application / Case Study



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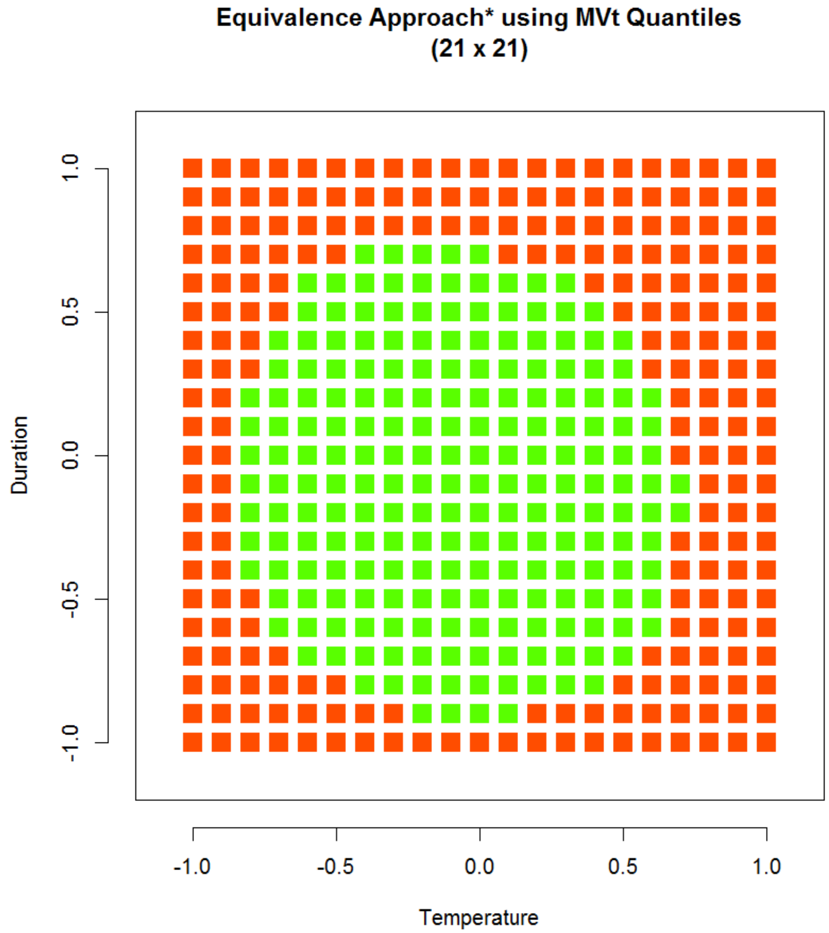

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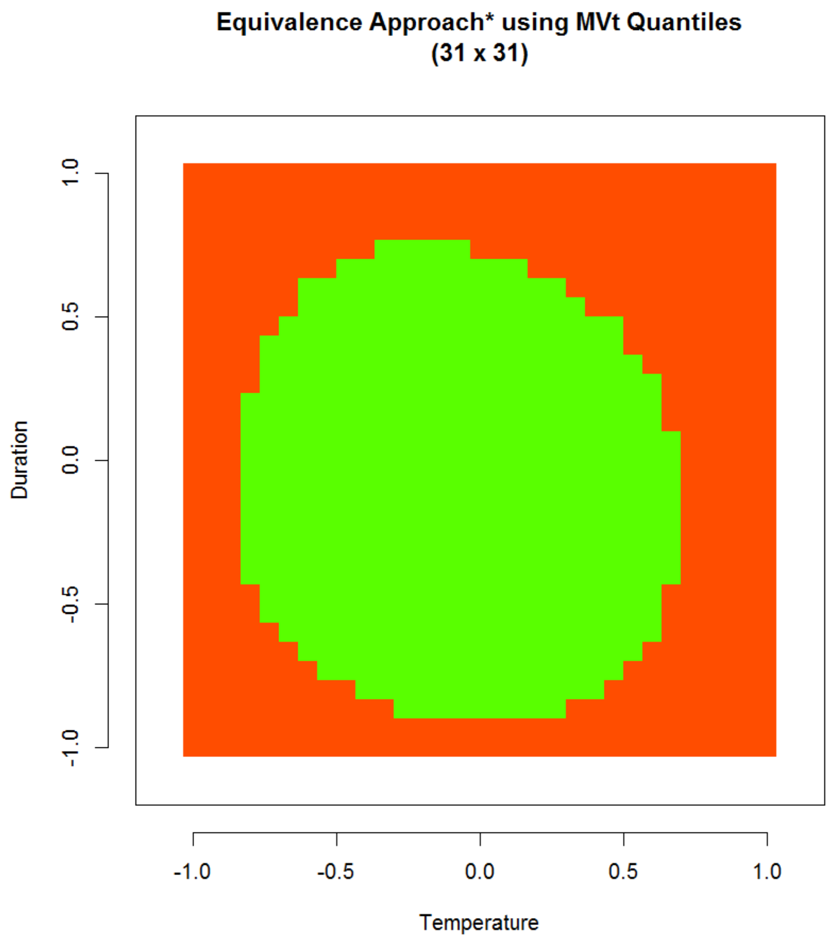

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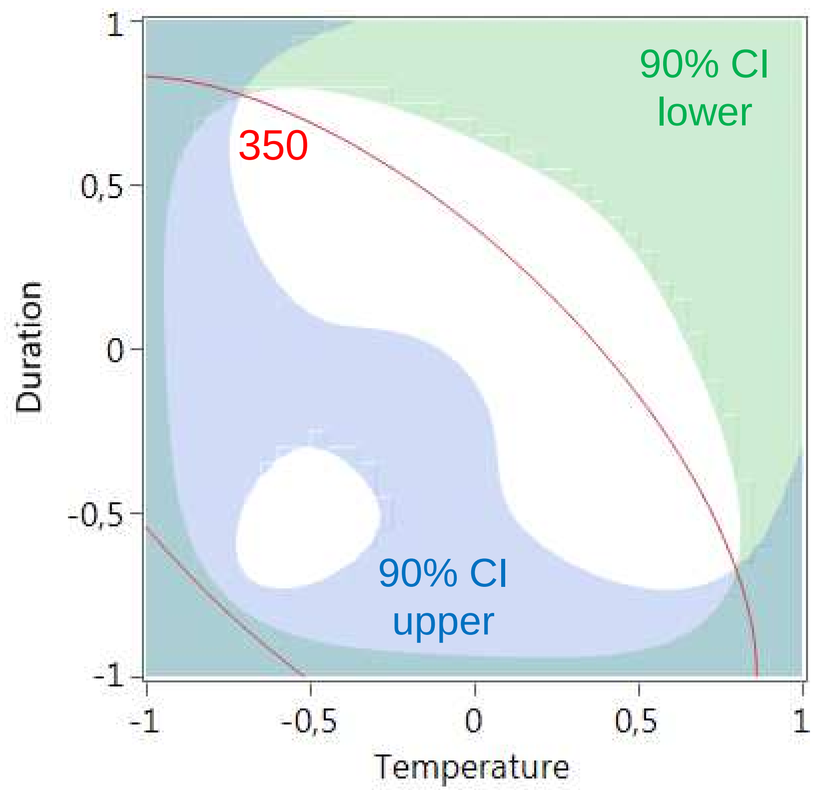
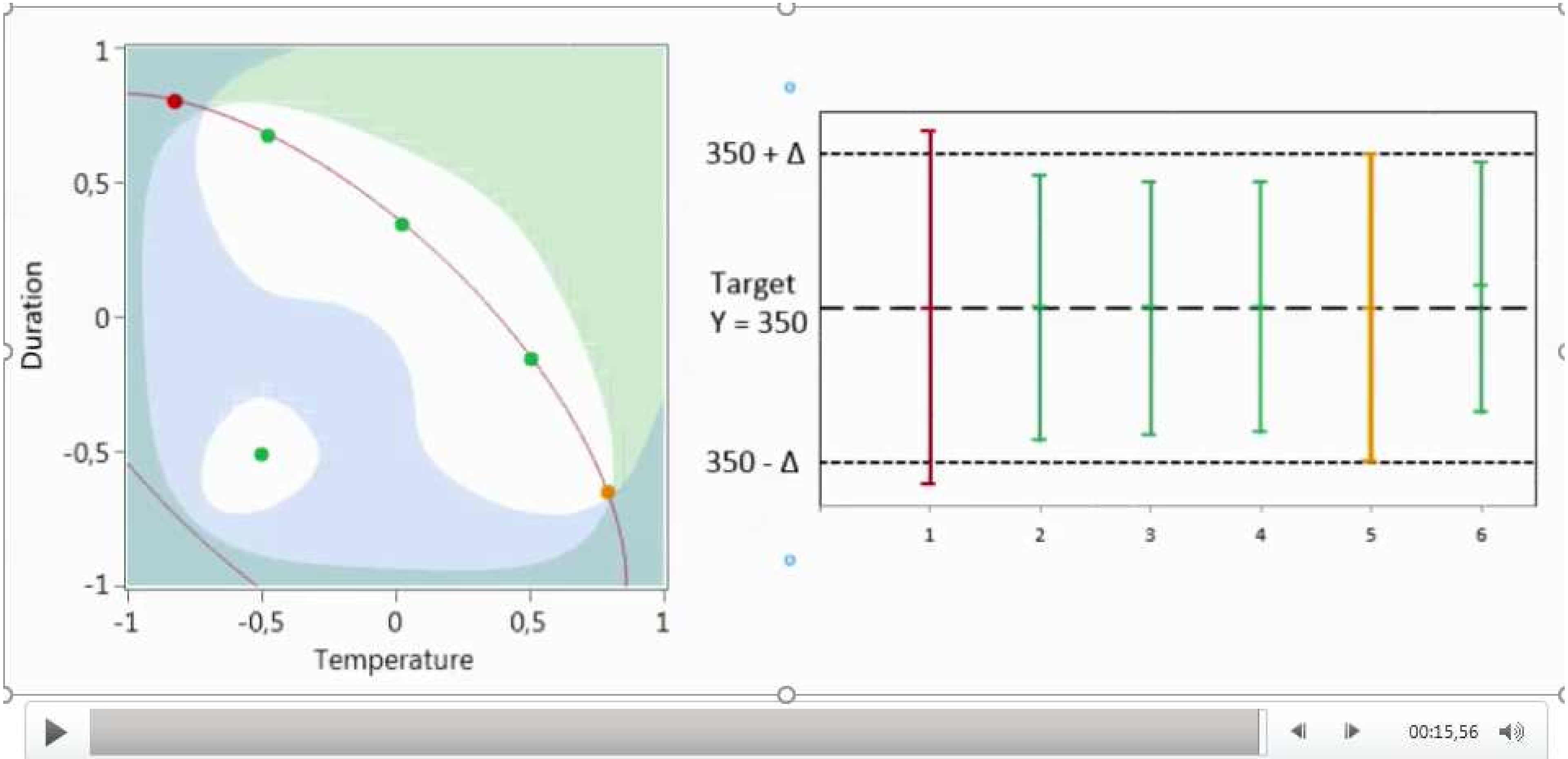
Application with a given constant approach → Smooth it

We want a cell count = 350
or equivalently inside 350 ± 55

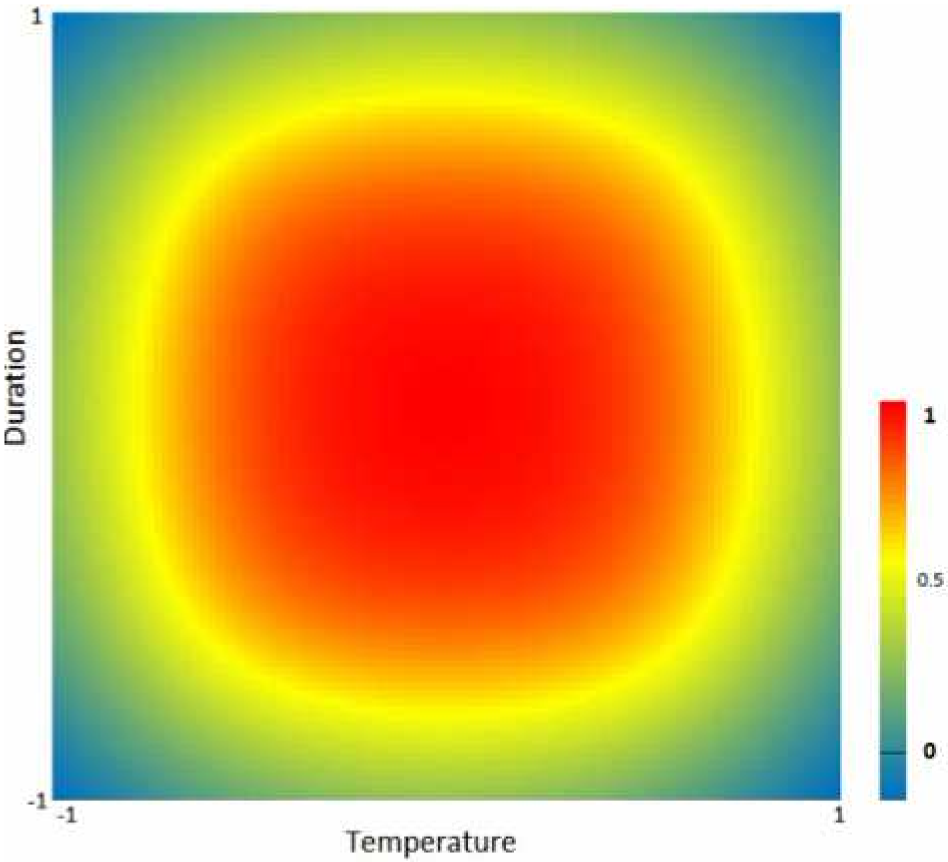
→ 'Design Space'
= Area where 90% CIs (with multi-t)
lie between 295 and 405



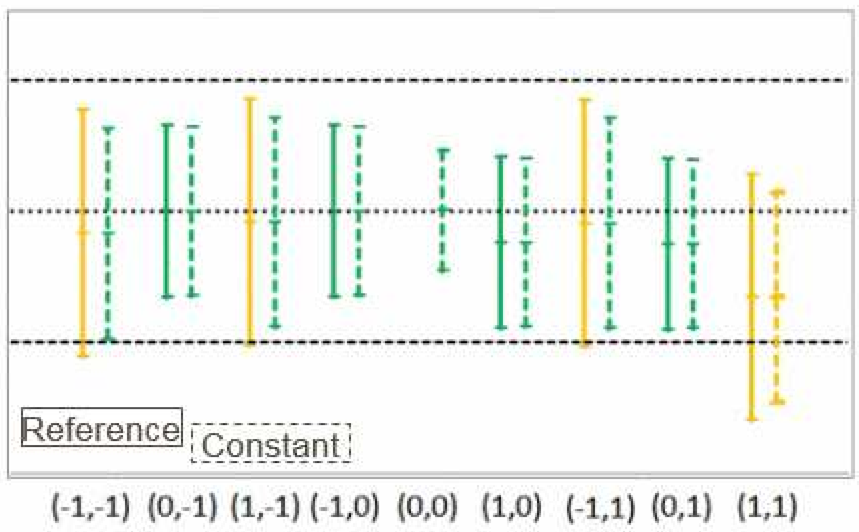
Application with Constant approach → Pick some points



Last Question: what if intercept model ?



From RSM to Intercept Model



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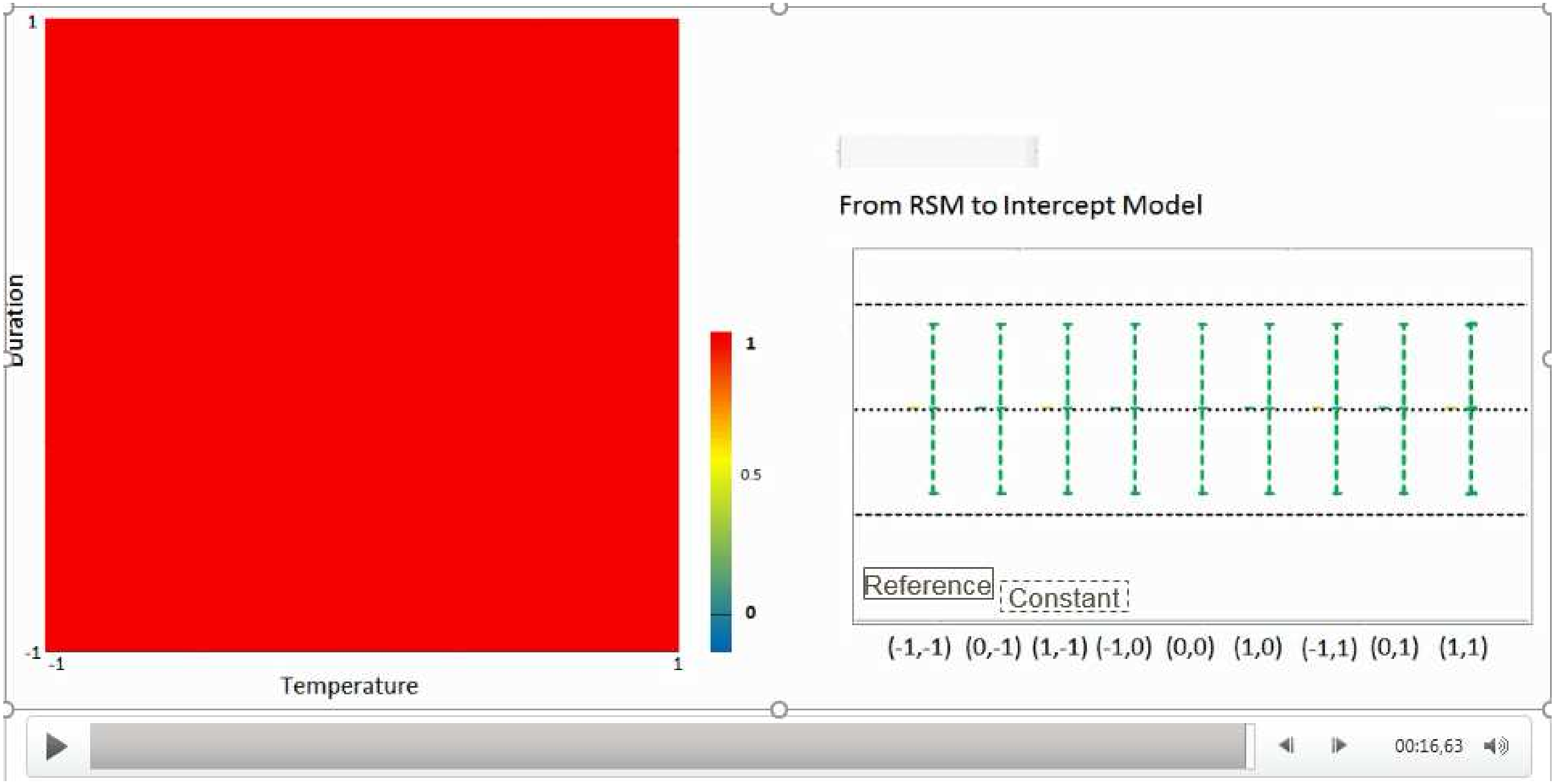

CIs for reference approach (contrast) collapse! CIs for constant approach converge to the classical univariate CI for a mean

Conclusion: Flatness Concept Summary

Significantly flat	Practically flat
Difference Approach	Equivalence Approach
H_0: $\mu_i - \mu_j = 0$ for all $i \neq j$	H_0: $\lvert\mu_i - \mu_j\rvert \notin [-\delta_l, \delta_u]$
H_1: at least one true difference is not 0.	H_1: all true differences within $[-\delta_l, \delta_u]$
Assume strict flatness if all CI's cover 0	Assume practical flatness, if the equivalence margin contains all CI's
• With $n \to \infty$, will detect any difference!	• Heavily depends on the width of equivalence margin • There is a "saturated" / max. sample size for detecting flatness
Both depend on the underlying regression model!	

Acknowledgement & Conflict of Interest

Acknowledgement

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- Mathieu Vasselle
- Sylvie Scolas

Conflict of Interest

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