Assay Qualification by Linear Mixed Models

Confidence, Prediction and Tolerance Intervals

Bernard G Francq
PSI Webinar, June 2022

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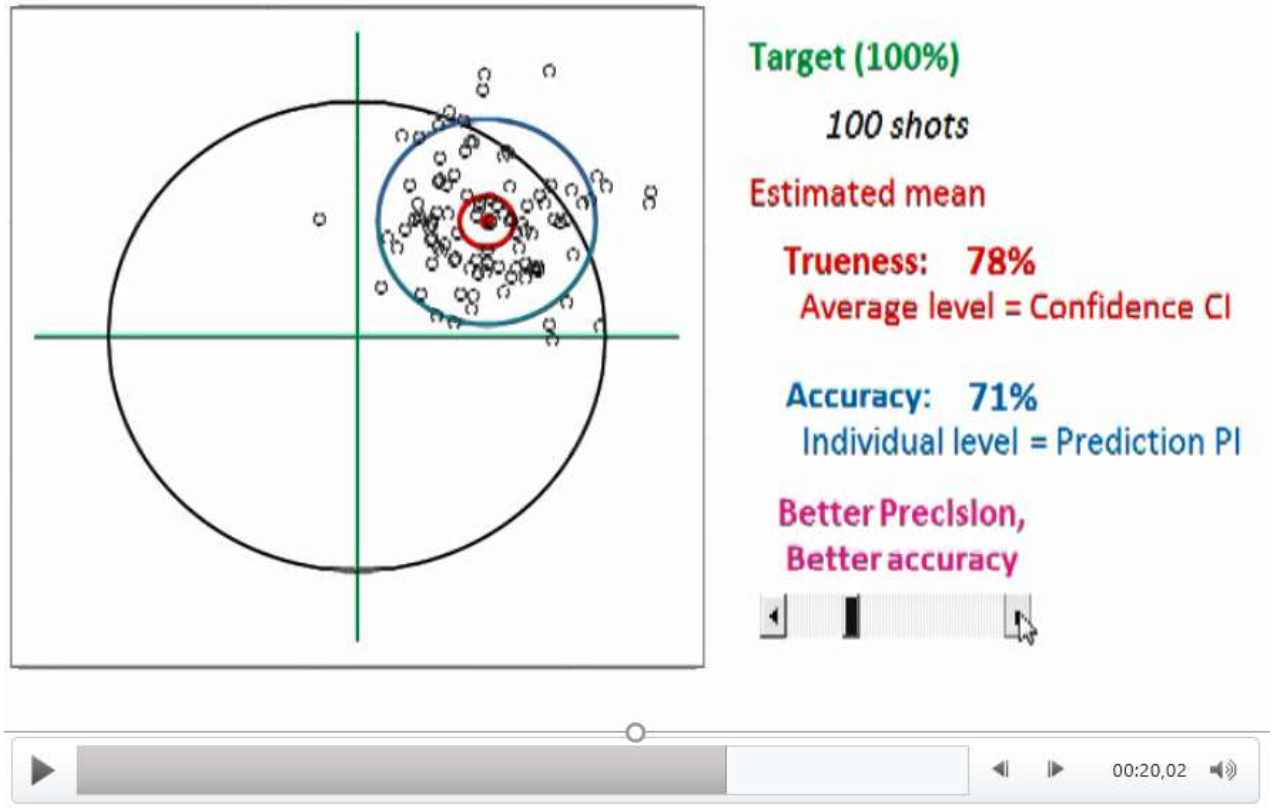
Assay Qualification: measurement accuracy

We expect a measure to be: Precise + True = Accurate



Assay Qualification: Introduction

Aim of qualification

- the analytical method is suitable for its intended use
- consequently to prove the reliability of the results obtained

Qualification statistics considered

- Precision
- Trueness
- Accuracy

Experimental design

- Multiple replicates per sample
- Multiple days / operators / sessions
- Series dilutions of a spiked-in sample or known concentrations

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Assay Qualification: Precision, Trueness, Accuracy

	Precision +	**Trueness** =	**Accuracy**
Meaning	Random error	Systematic Error	Total error
Related to	Method variability	Method bias	Total deviation from nominal value
Quantified by	**CV or STD**	**CI** Confidence Interval	**PI or TI** Prediction or Tolerance Interval

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Assay Qualification: Data Set

The study design is composed of:

- 2 different reagents (R1, R2)
- 4 operators (B, D, S, W): ..... *random* variable
- 3 days (D1, D2, D3): ..... *random* variable
- 2 replicates
- 4 nominal concentrations (25, 50, 75, 100) (µl): ..... *fixed* variable

Crossed Random Variables

\+

= Mixed Model

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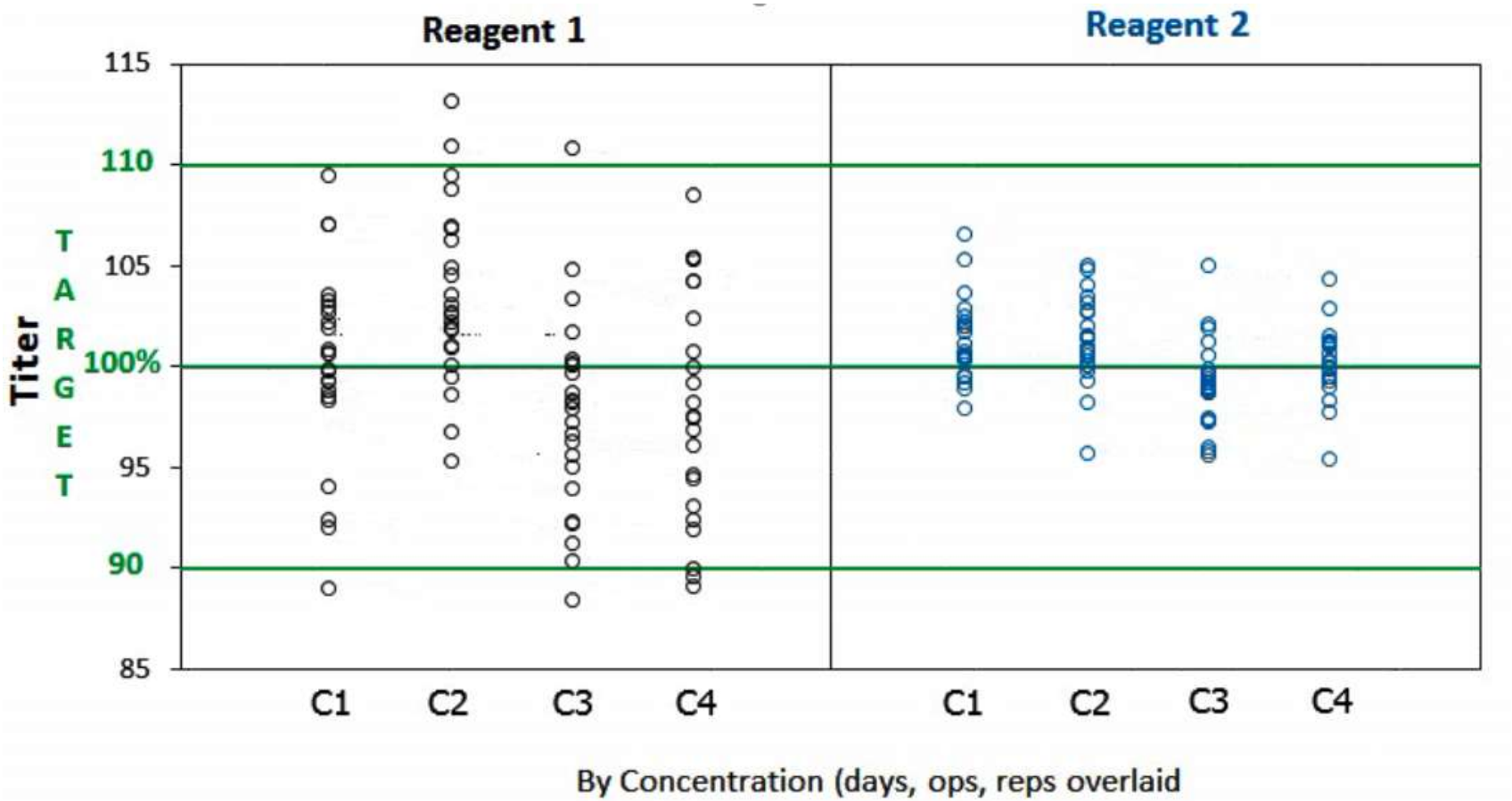
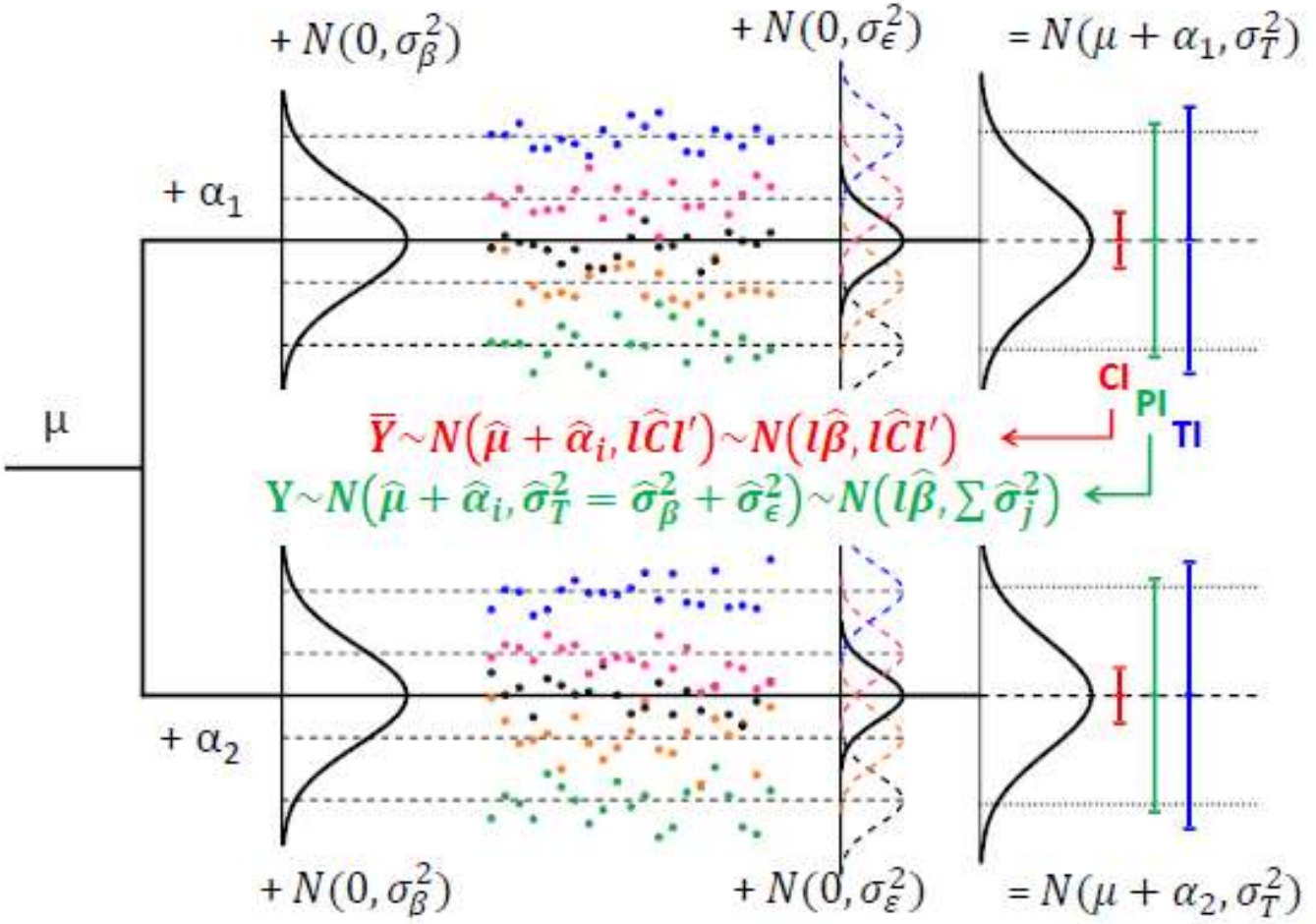
Assay Qualification: Data Set Visualisation



Assay Qualification: Mixed Models Concept

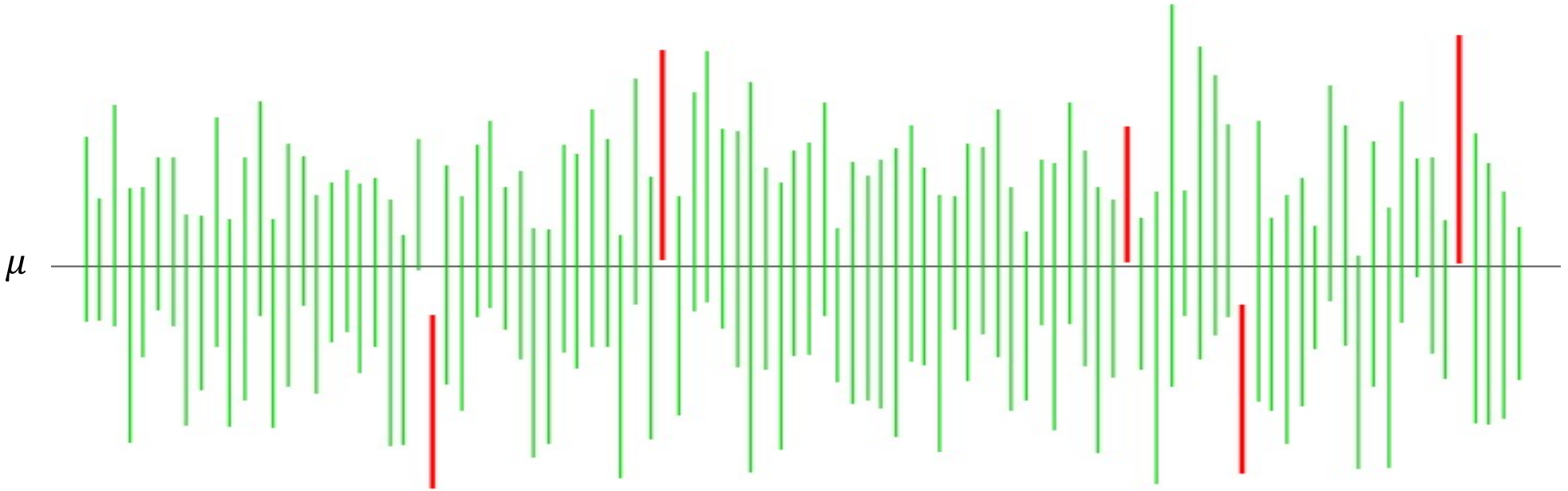


$$CV = \frac{\sigma_T}{\mu + \alpha_1}$$

$$CV = \frac{\sigma_T}{\mu + \alpha_2}$$

Confidence Interval concept

100 simulated 95% CI for the mean μ



→ The true value, μ, lies in 95% of the CIs

Note: in Bayesian statistics, credible intervals are usually used

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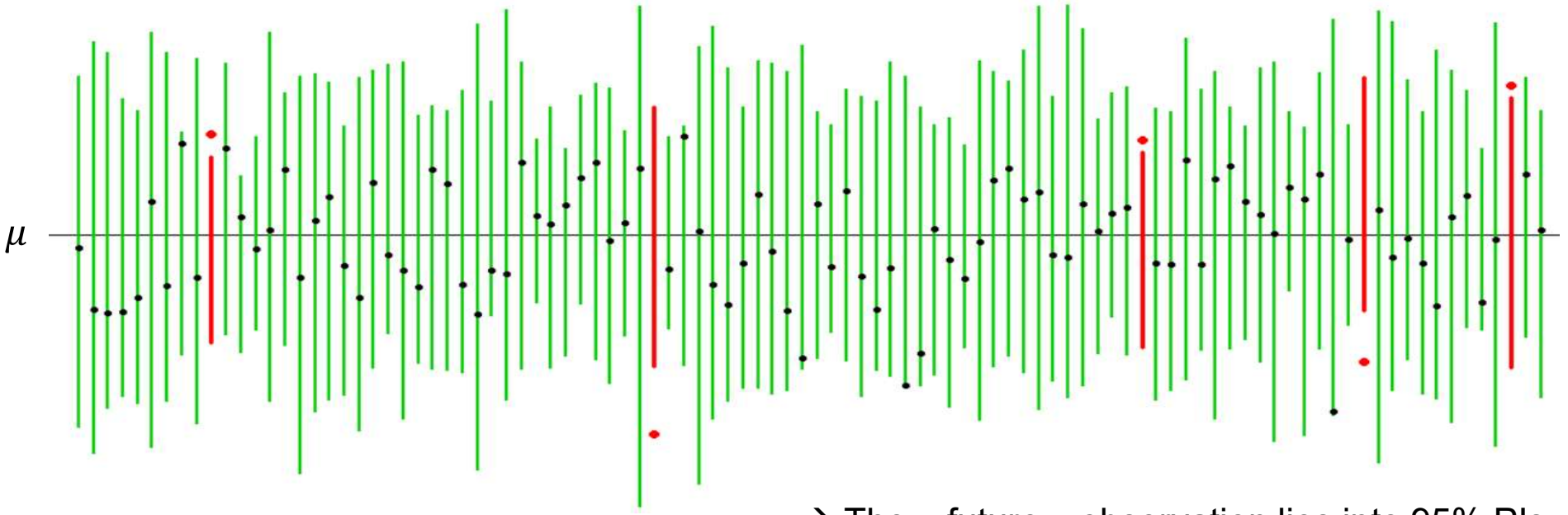
Prediction Interval concept

100 simulated 95% PI for a future observation



→ The « future » observation lies into 95% PIs

Note: in Bayesian statistics, PI can be obtained from the posterior distribution

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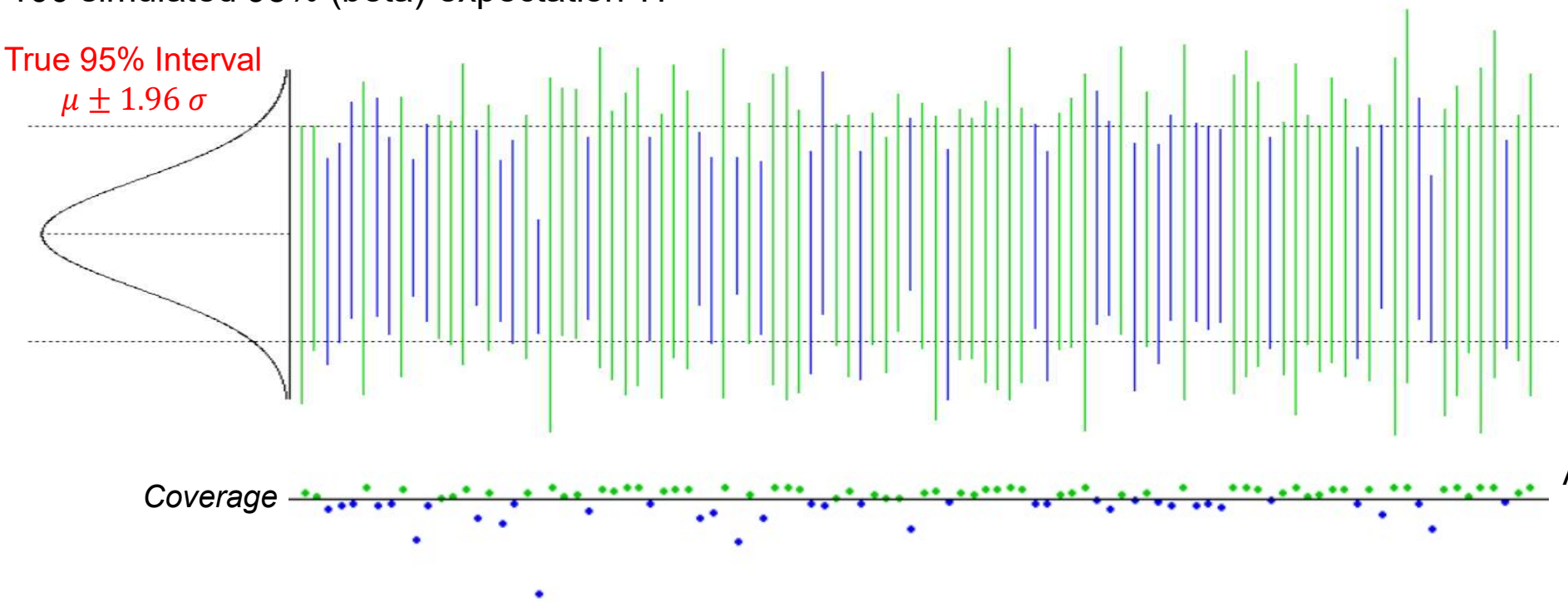
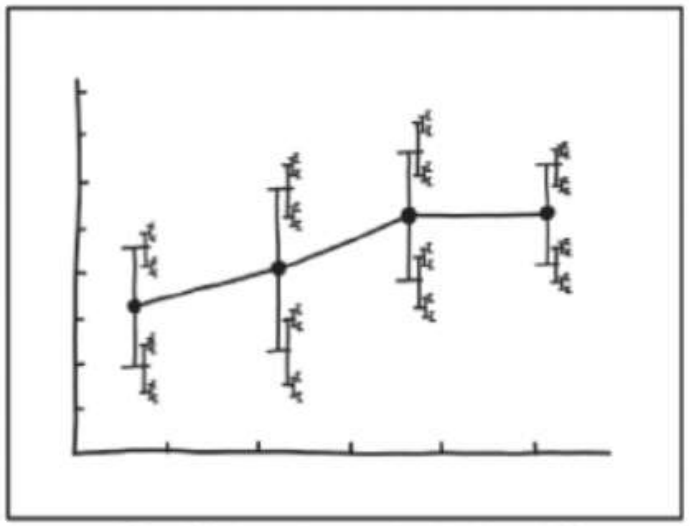
Expectation Tolerance Interval (type I) concept

100 simulated 95% (beta)-expectation TI



→ Expectation TI covers 95% of the population, on average

Confidence Interval of Confidence Interval



Errors Bars comic by Randall (2019)[36]

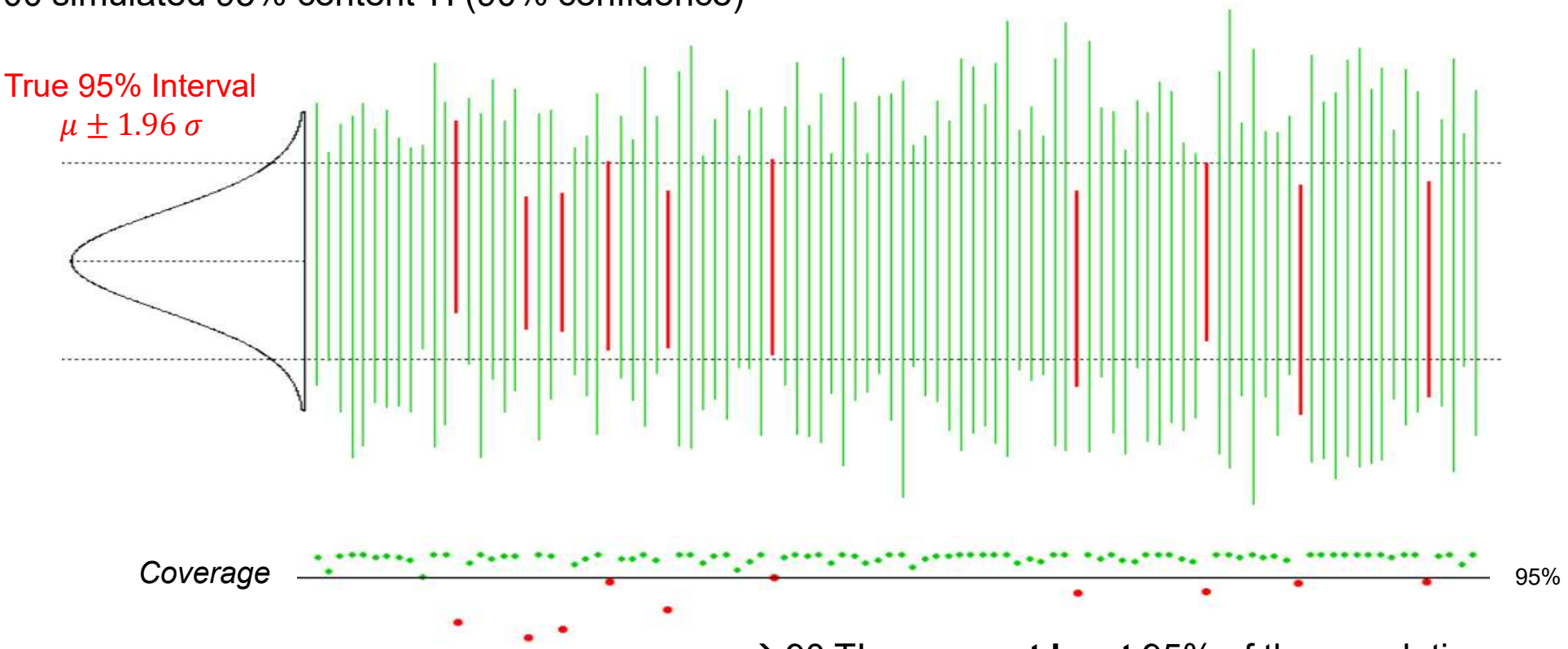
- The prediction interval is sometimes referred as “confidence interval for a future observation” (JMP)
- Will the PI contain less or more than 95% of future observations?

→ Some researchers calculate the 95% CI for each bound of the 95% PI

- (unfortunately) widely used in method comparison studies (bridging studies) with Bland-Altman plot
- This is awkward, confusing and misleading
- Use the Tolerance Interval type II

Content Tolerance Interval (type II) concept

100 simulated 95% content TI (90% confidence)



→ 90 TIs covers **at least** 95% of the population
→ 10 TIs covers **at most** 95% of the population

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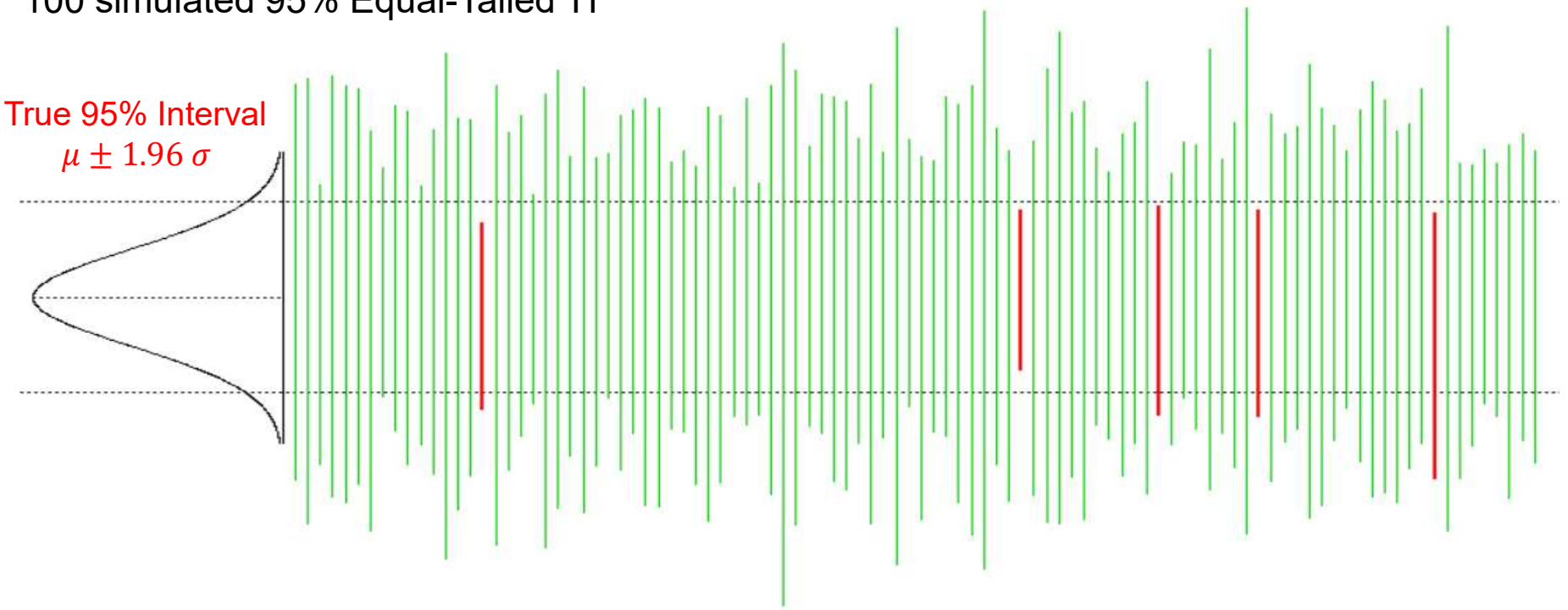
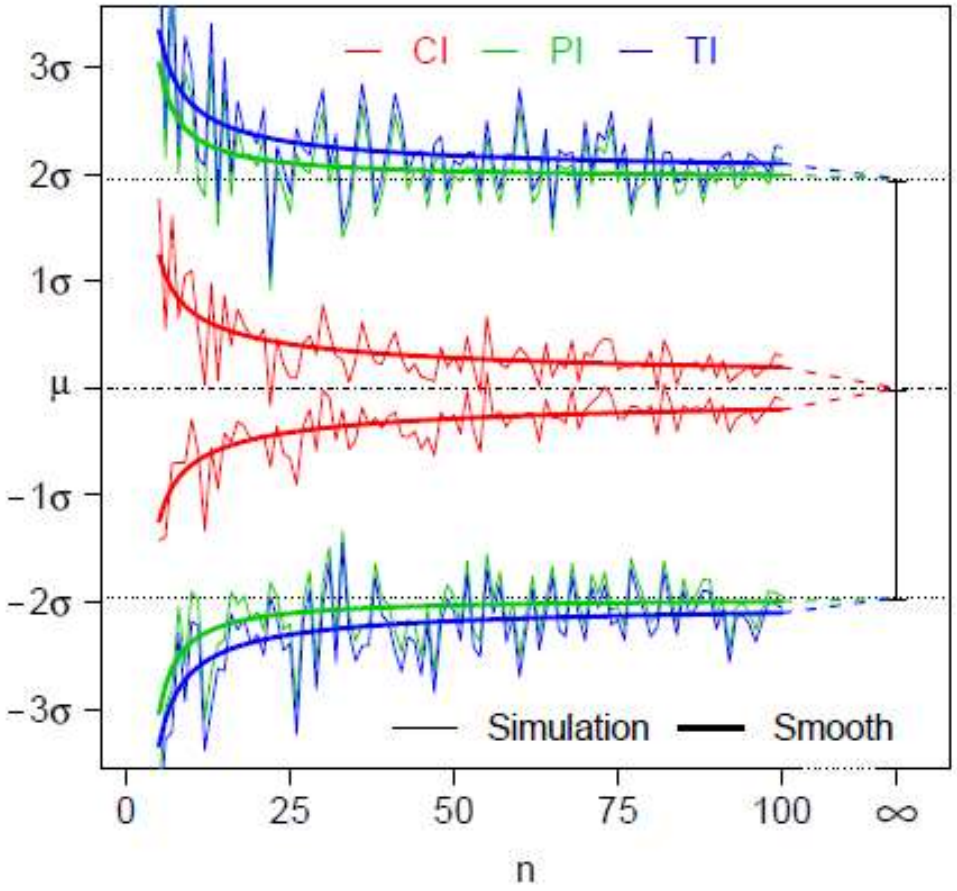
Equal-Tailed Tolerance Interval (type III) concept

100 simulated 95% Equal-Tailed TI



→ 95% Equal-Tailed TI includes both quantiles 2.5% and 97.5%

Confidence, Prediction, Tolerance



When the sample size increases

- CIs collapse to the point estimate
- PIs and TIs move closer to the true quantiles

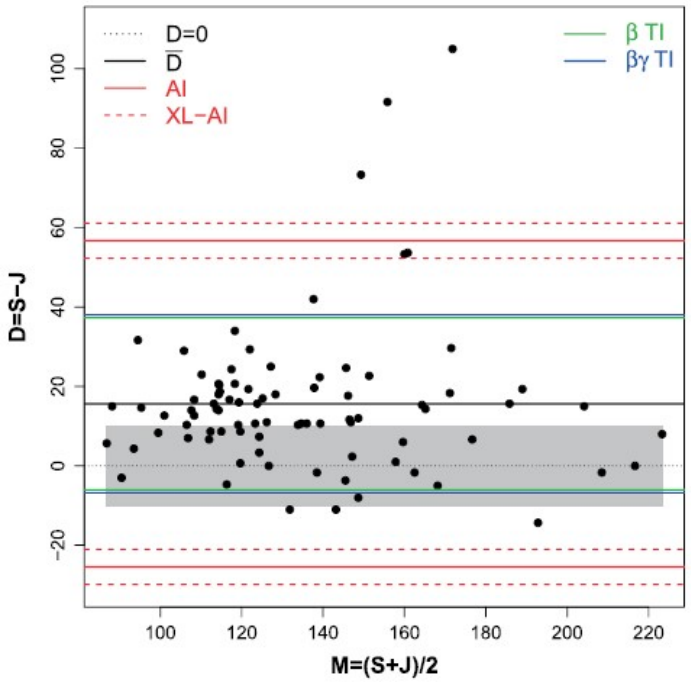
A Tutorial on Tolerance Intervals

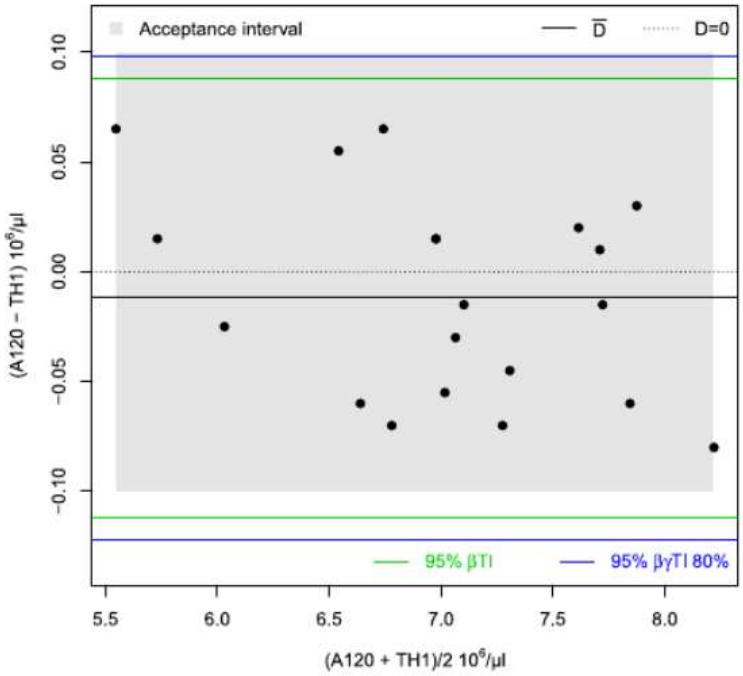
TUTORIAL IN BIOSTATISTICS

To tolerate or to agree: A tutorial on tolerance intervals in method comparison studies with BivRegBLS R Package

Bernard G Francq, Marion Berger, Charles Boachie

Statistics in Medicine, 2020.





Assay Qualification: Confidence, Prediction, Tolerance

Confidence intervals are used to assess the trueness

- The degrees of freedom are typically calculated by Kenward-Roger (KR) method
- A plot can be displayed with the CIs calculated at the different level of concentrations

Prediction Intervals (PIs) are used to assess the accuracy

- The uncertainty of the prediction is the sum of the total variance and the uncertainty on the 'mean': systematic error (Trueness) + random error (Precision)
- An accuracy profile can be displayed with the PIs calculated at the different level of concentrations

Remarks: PIs in mixed models are not implemented in most of stat software

- SAS: pred and predm options are confidence intervals, no option for PI
- JMP: no explicit option, but "save prediction" option (in fit model) uses KR
- R: no direct analytical solution, not implemented in varComp, lmer, …
- Practitioners usually perform bootstrap (but is time-consuming)
- Bayesian approach

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Mixed Model Maximum Likelihood (REML)

How to compute the variance-covariance matrix of:

- Fixed effects (β)
- Random effects (γ)
- Variance components (θ)

Summary

Variance - Covariance matrix of (β, γ, θ)

$$= \begin{pmatrix} \begin{pmatrix} \hat{C}_{11} & \hat{C}'_{21} \\ \hat{C}_{21} & \hat{C}_{22} \end{pmatrix} & \begin{matrix} 0 \\ 0 \end{matrix} \\ \begin{matrix} 0 & 0 \end{matrix} & 2H^{-1} \end{pmatrix}$$ *where H is the Hessian matrix*

What is the difference between the univariate and the mixed models to calculate a prediction interval (accuracy)?

(nearly) none! Except the degrees of freedom

Prediction Interval in Linear Mixed Model

Mee R. β-Expectation and γ-Content Tolerance Limits for Balanced One-Way ANOVA Random Model. *Technometrics* 1984; 26: 251-254.

The most commonly used formula for the PI (or Expectation TI) is given for a 1-random factor model

$$\hat{\mu} \pm t_{1-\psi/2,r'} \hat{\sigma}_T \sqrt{1 + 1/N_e}$$

- where $\hat{\mu}$ is the intercept
- Ne is the 'effective sample size'
- $\hat{\sigma}_T^2$ the total variance
- The degrees of freedom are calculated with the Satterthwaite approximation on the mean squares

Improvement

- We need a generalized formula for a wide variety of designs
- One random factor, nested and crossed designs for multiple random factors, balanced or unbalanced designs

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Prediction Interval in Linear Mixed Model

We propose to calculate the PI (or β-expectation TI) for a given linear combination of fixed effects as :

$$\hat{Y}_{\boldsymbol{l\beta},n+1} \pm t_{1-\psi/2,r}\sqrt{\boldsymbol{l}\hat{\boldsymbol{C}}_{\mathbf{11}}\boldsymbol{l}' + \hat{\sigma}_T^2} \qquad r = 2\frac{\hat{\sigma}_T^4}{\mathrm{Var}(\hat{\sigma}_T^2)}$$

- the degrees of freedom, r, are calculated with the generalized Satterthwaite method
- The variance of the total variance is obtained from the Hessian matrix

$$\widehat{\mathrm{Var}}(\hat{\sigma}_T^2) = \sum_{r=1}^{q}\sum_{s=1}^{q}\hat{\vartheta}_{rs}$$

Our generalized formula includes (is equivalent to) the specific 1-random model PI

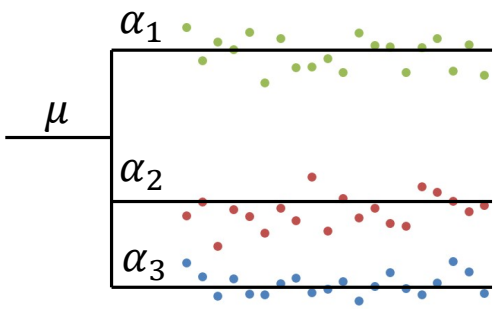
Parametrization in Linear Mixed Model for PI

Fixed effects

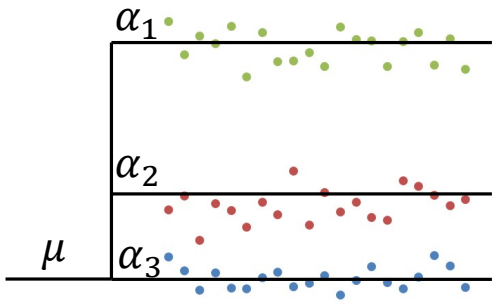
- Cell means model (no intercept)
- Combine all fixed effects into 1 variable

Random effects

- Reflect the actual design of experiments (no simplification)
- Omitting or combining random effects can underestimate the total variance

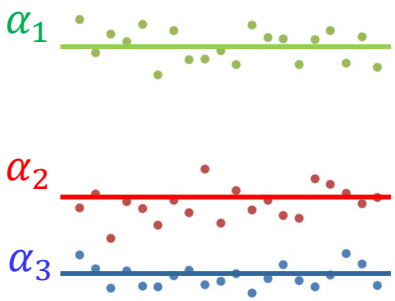


Reference level
= overall (unweighted) mean
→ JMP

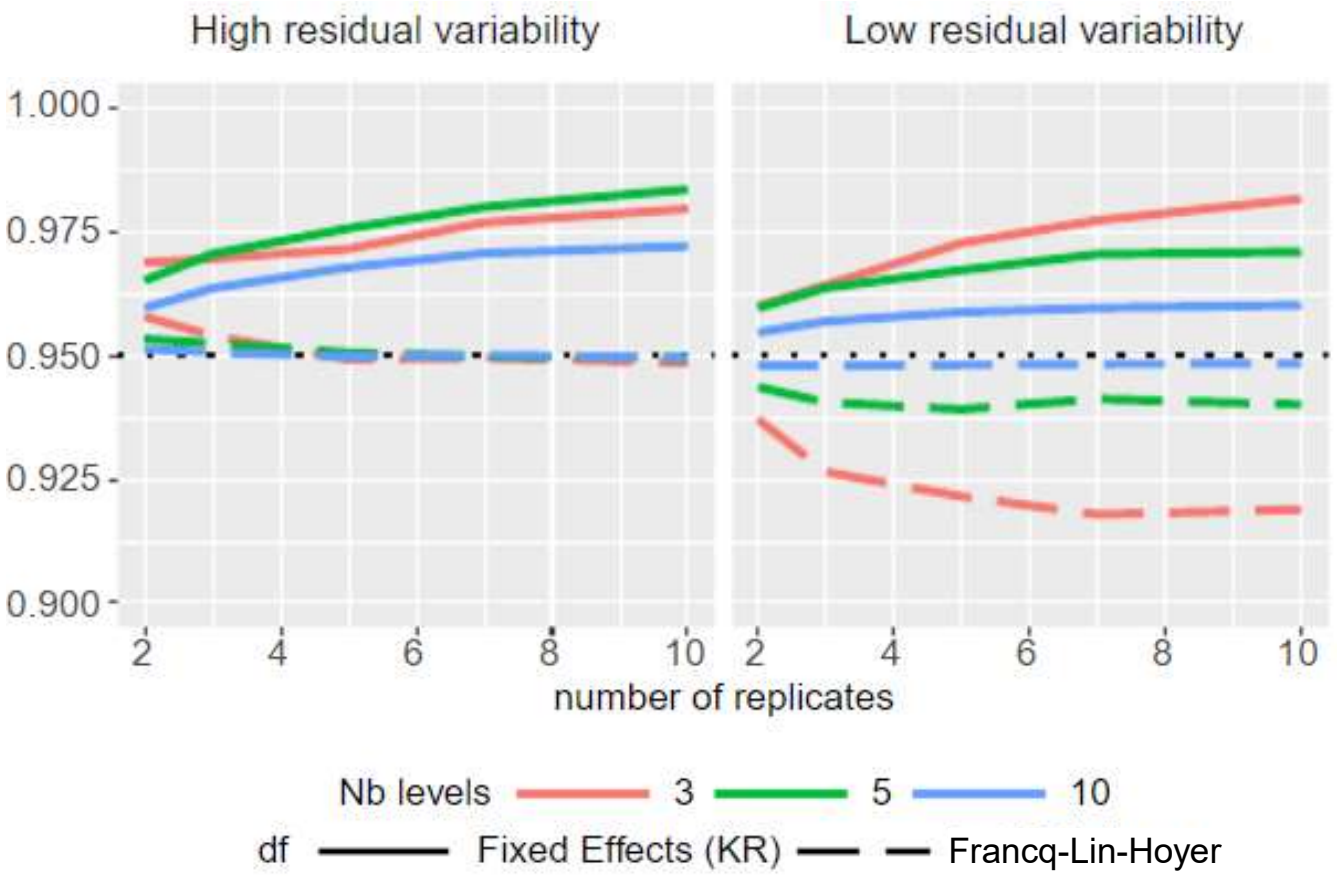


Reference level
= a given level fixed effect
→ SAS, R,…

Cell means model
(no intercept)



Accuracy – 1 random variable - Coverage Probabilities 95% PI



Coverage probabilities closer to the target with the DF obtained by Francq et al.

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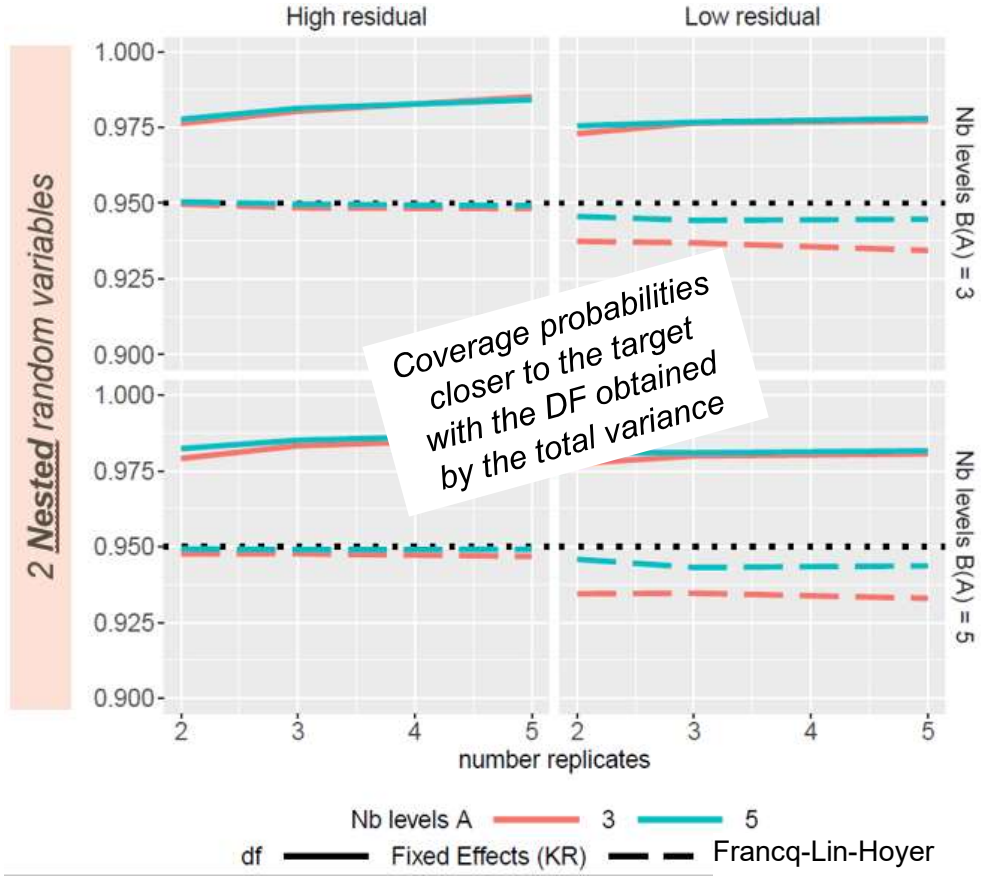
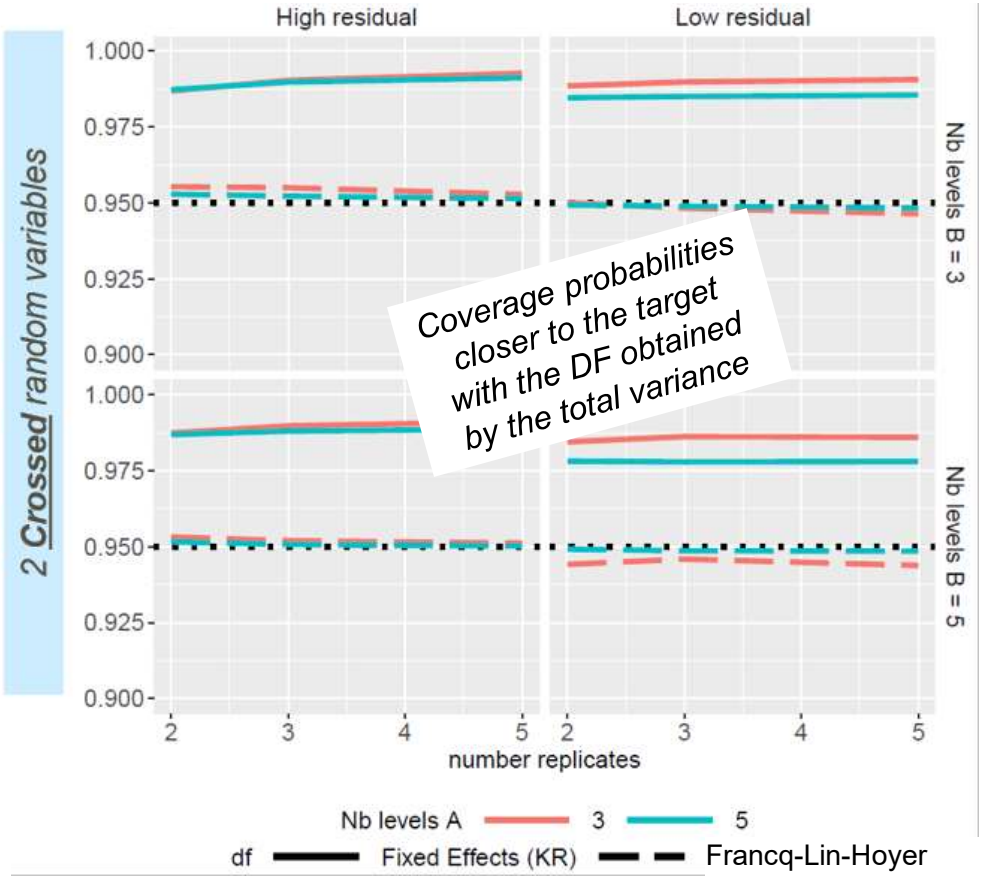
Accuracy – 2 random variables - Coverage Probabilities 95% PI





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Tolerance Interval in linear mixed model

The (content) TI for a given level of fixed effects is obtained by the MLS (Modified Large Sample) method

TWO-SIDED TOLERANCE INTERVALS FOR BALANCED AND UNBALANCED RANDOM EFFECTS MODELS

David Hoffman and Robert Kringle

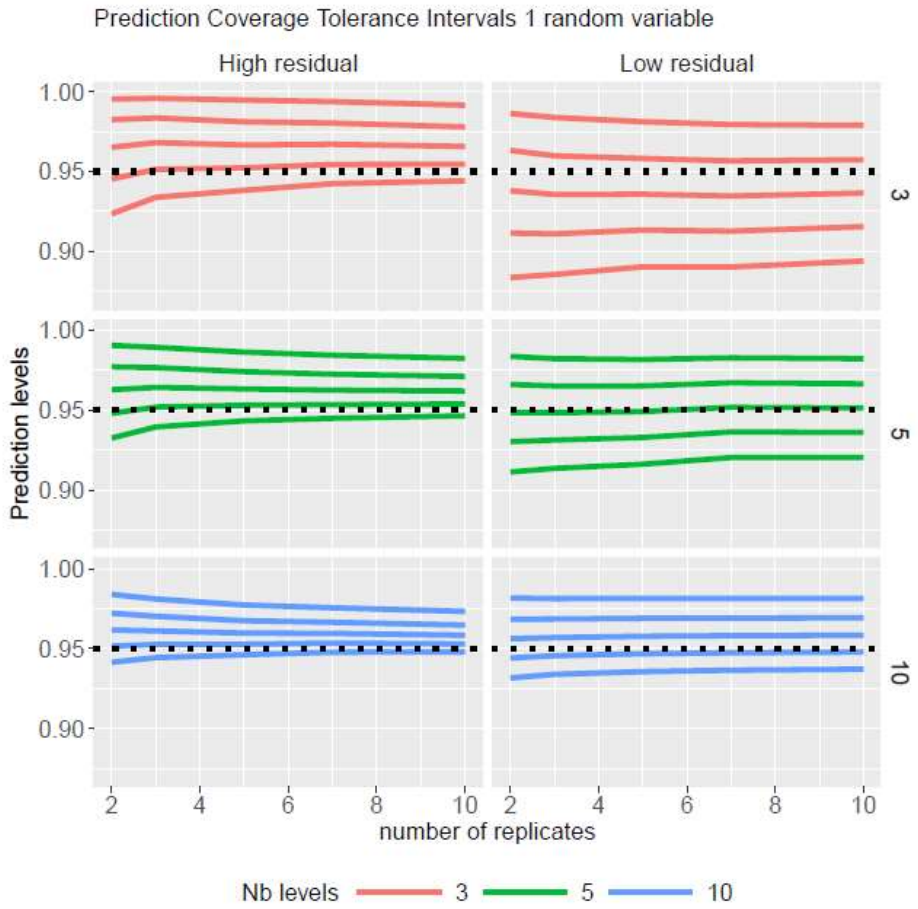
Journal of Biopharmaceutical Statistics, 15: 283–293, 2005

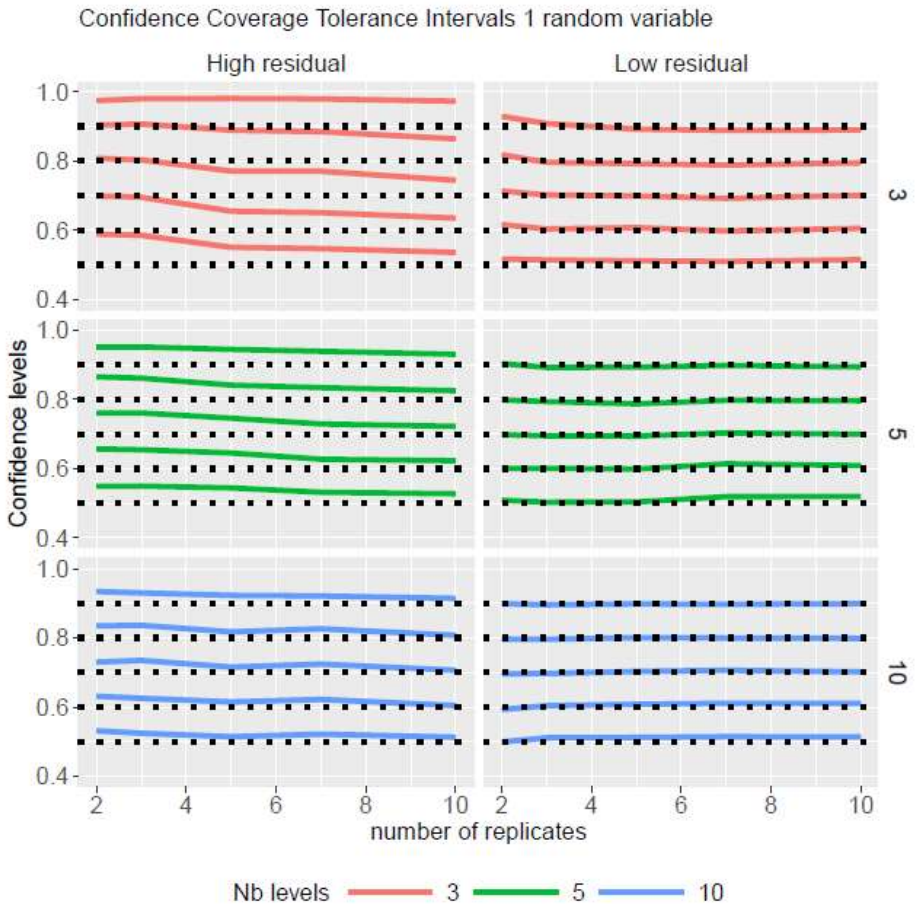
$$\hat{Y}_{l\beta,n+1} \pm z_{1-\psi/2}\sqrt{l\hat{C}_{11}l' + \hat{\sigma}_T^2}\sqrt{1 + \frac{1}{\hat{\sigma}_T^2}\sqrt{\sum_{j=1}^{q} H_j^2 k_j^2 \mathrm{EMS}_j^2}}$$

$$H_j = r_j / \chi^2_{\alpha, r_j} - 1$$

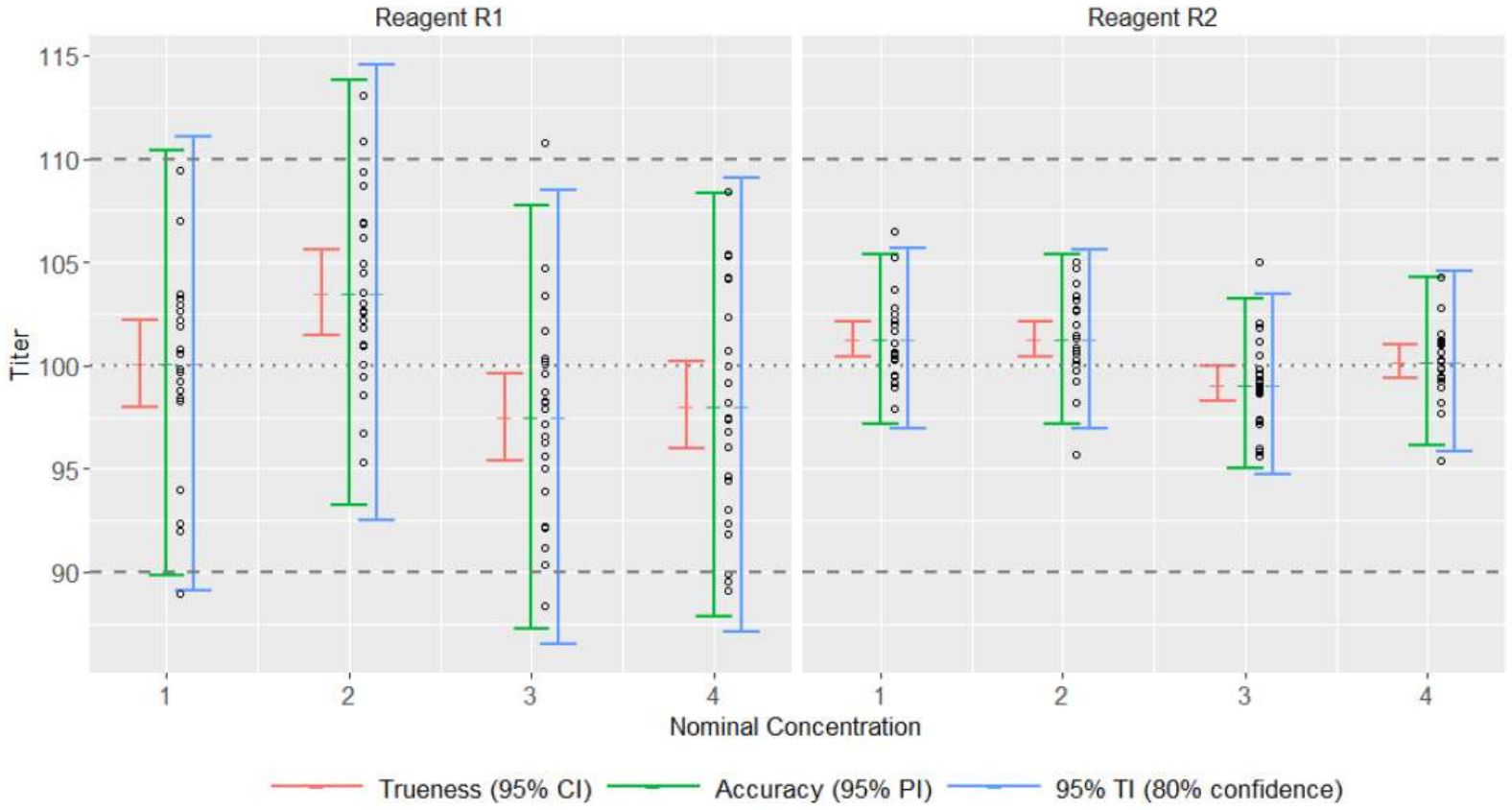
- *Estimate (e.g., cell mean)*
- *Prediction (coverage) level (e.g., 95%)*
- *Variance of fixed effect (collapse with big sample size)*
- *Total variance (e.g., sum of variance components)*
- *Confidence level (e.g., 80 to 95%)*

Tolerance Interval – 1 random variable - Coverage Probabilities





Assay Qualification - Results



Assay Qualification - Interpretation

Recovery	95% CI		95% PI		95% TI (90% conf.)	
	Lower	Upper	Lower	Upper	Lower	Upper
Reagent 2, Conc 1	100.5	102.1	97.2	105.4	96.9	105.6

Target recovery = 100%

Confidence Interval = CI

- The interpretation is usually confusing and holds only for the average

Prediction Interval = PI

- The future (next) measure is expected to deviate between 97.2 and 105.4 (with 95% confidence)

Expectation Tolerance Interval = TI type I

- 95% of the future measurements are expected to deviate between 97.2 and 105.4 (on average)

Content Tolerance Interval = TI type II

- At least 95% of the future measurements will deviate between 96.9 and 105.6 (with 90% confidence)

Remarks

- The interpretation of PI and TI is similar in frequentist or Bayesian
- Their interpretation remains identical with/without the log transformation

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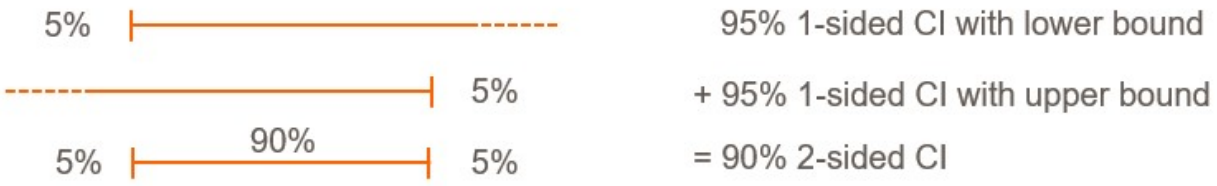
Tolerance Intervals, Quantiles, 1 + 1 = 2 ?

Few remarks:

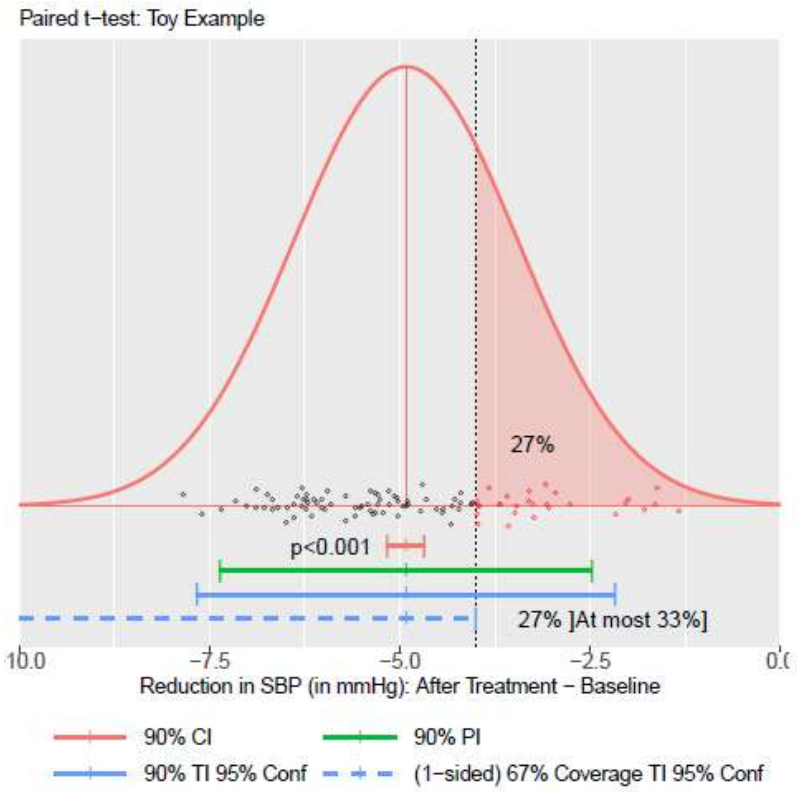
- 2 ‘1-sided’ and 1 ‘2-sided’ TI are not the same !
- 90% 1-sided TI 95% coverage = 90% CI for the quantile 95%
- Content 2-sided TI ≠ Estimation of 2 quantiles
- Equal-tailed 2-sided TI = Estimation of 2 quantiles with an overall 95% Confidence level



Tolerance Intervals and Out-Of-Specification

Few remarks:

- The Probability of out-of-specification (POOS) estimation is identical to TI
- The POOS is its upper bound is more straightforward to calculate in mixed models



Bayesian Mixed Models

Bayesian analyses have many advantages

- Prior knowledge
- Get posterior distribution
- Straightforward for “complex” statistics

Examples

- Bayesian Tolerance Intervals

See courses “Introduction to computational Bayesian methods for CMC”
by José G. Ramírez (AMGEN) and Fang Chen (SAS). IQ pharma (2021)

- Coefficient of Variation

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Frequentist Mixed Models: CV (Coefficients of Variation)

CVs are used to assess the precision

- Frequentist 95% CI are calculated from an adaptation of the modified McKay formula

In mixed models

- The CV is calculated per variance components
- Total variance = Intermediate Precision
- The mean is replaced by the fixed effects estimate (i.e., intercept)

Under normality assumption

$$CV_T = \frac{\sigma_T}{l\beta} \text{ estimated by } \frac{\hat{\sigma}_T}{l\hat{\beta}}$$

CI for CV (from McKay formula)

$$\frac{CV}{\left(\frac{\chi^2_{K,r}}{r+1}-1\right)CV^2+\frac{\chi^2_{K,r}}{r}}$$

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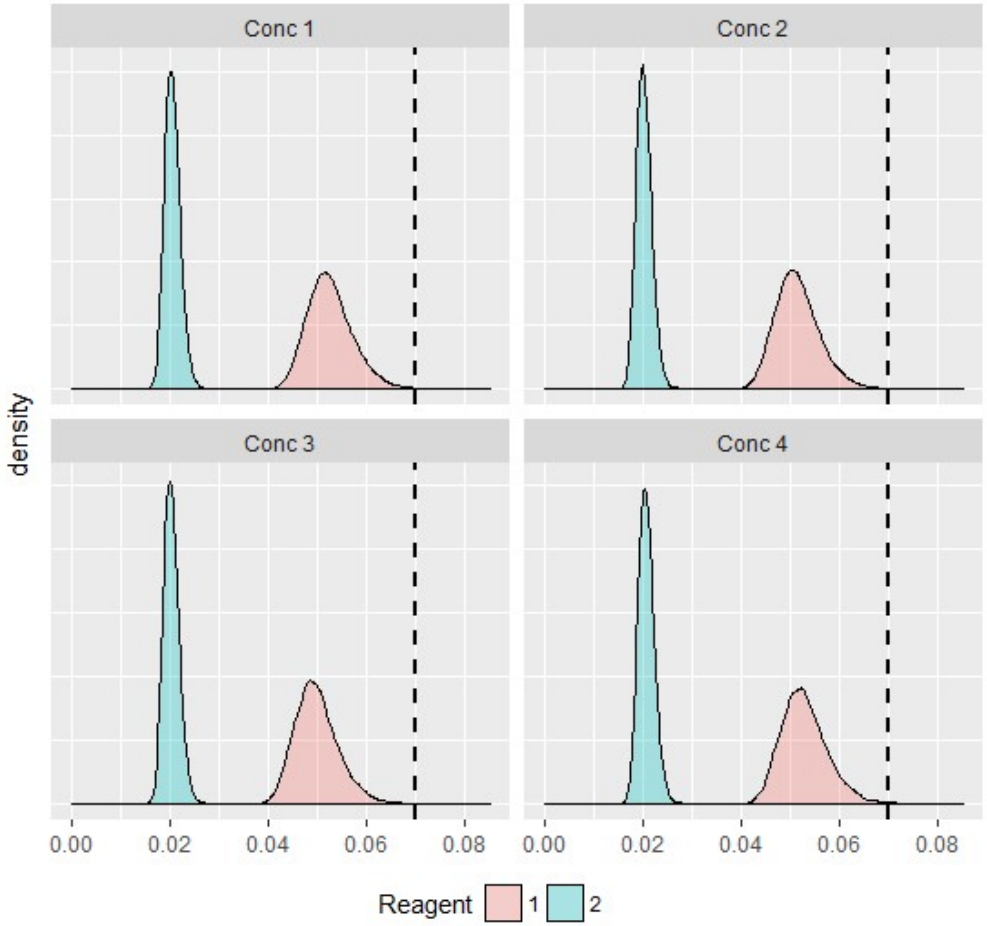
Bayesian Mixed Models: CV (Coefficients of Variation)

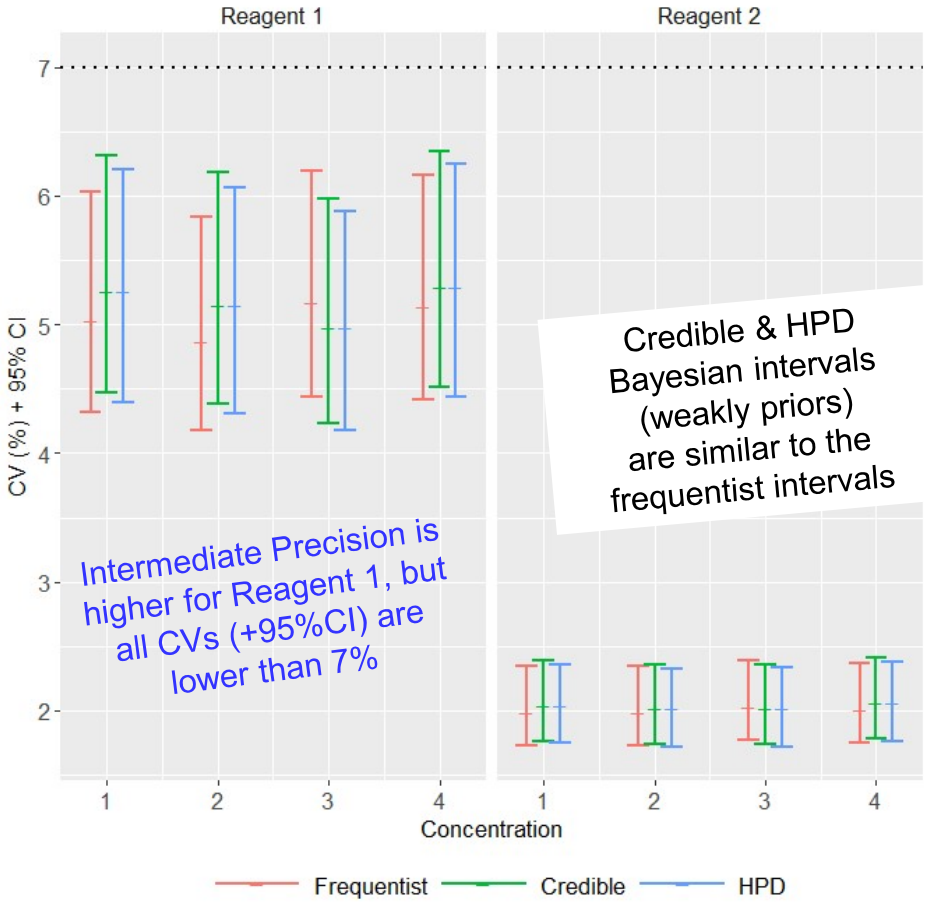
In Bayesian mixed models, the CV can be obtained from the posterior distribution with MCMC simulations, by 95% credible or HPD intervals

1-way random (operator) model

```
PROC MCMC DATA = Set3 NBI = 10000 NMC = 10000 STATISTICS = Intervals;
    PARMS B0 S2;
    PARMS S2op 1;
    PRIOR B0  ~ normal(0, var=1e6);
    PRIOR S2 ~ igamma(0.01, scale = 0.01);   or half-Cauchy distribution
    prior S2op ~ igamma(0.01, scale = 0.01);   or half-Cauchy distribution
    random Gamma ~ normal(0, var = S2op) subject = op;
    Mu = B0 + Gamma;
    S2tot = S2op + S2;
    cvtot = sqrt (S2 + S2op) / B0;
    MODEL resp ~ normal(Mu, var = S2);
RUN;
```

Bayesian Mixed Models: CV (Coefficients of Variation)





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USP: concatenate the random effects

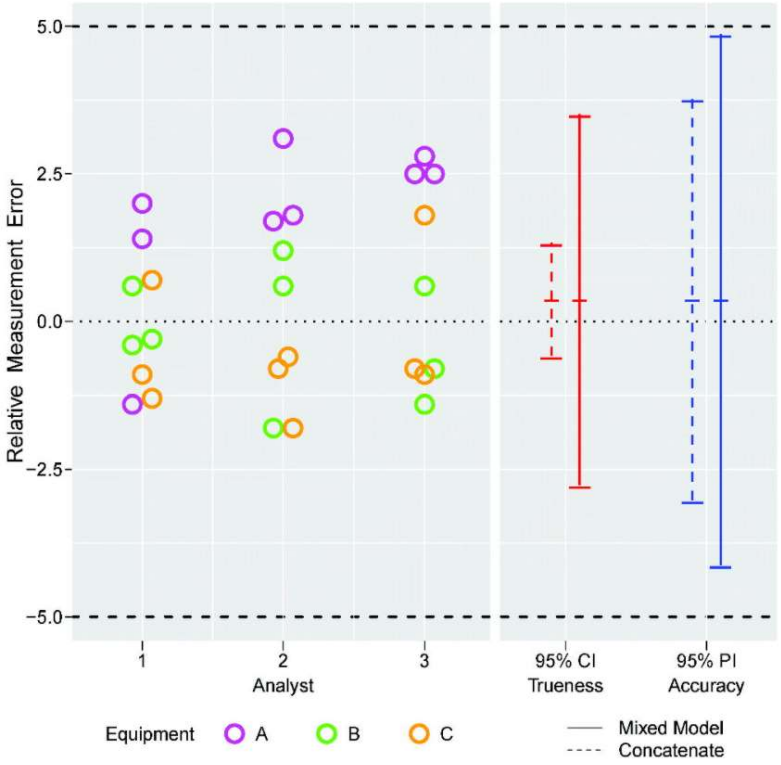
Burdick RK, LeBlond DJ, Sandell D, Yang H, Committee USE. Statistical Methods for Validation of Procedure Accuracy and Precision. ; 39(3).

Mixed Model (crossed or nested)

One random variable

Y	Day	Op	Rep	Run
Y_{111}	Day1	Op1	1	Day1Op1
Y_{112}	Day1	Op1	2	Day1Op1
...	...	...	...	...
Y_{331}	Day3	Op3	1	Day3Op3
Y_{332}	Day3	Op3	2	Day3Op3

Concatenate the random effects



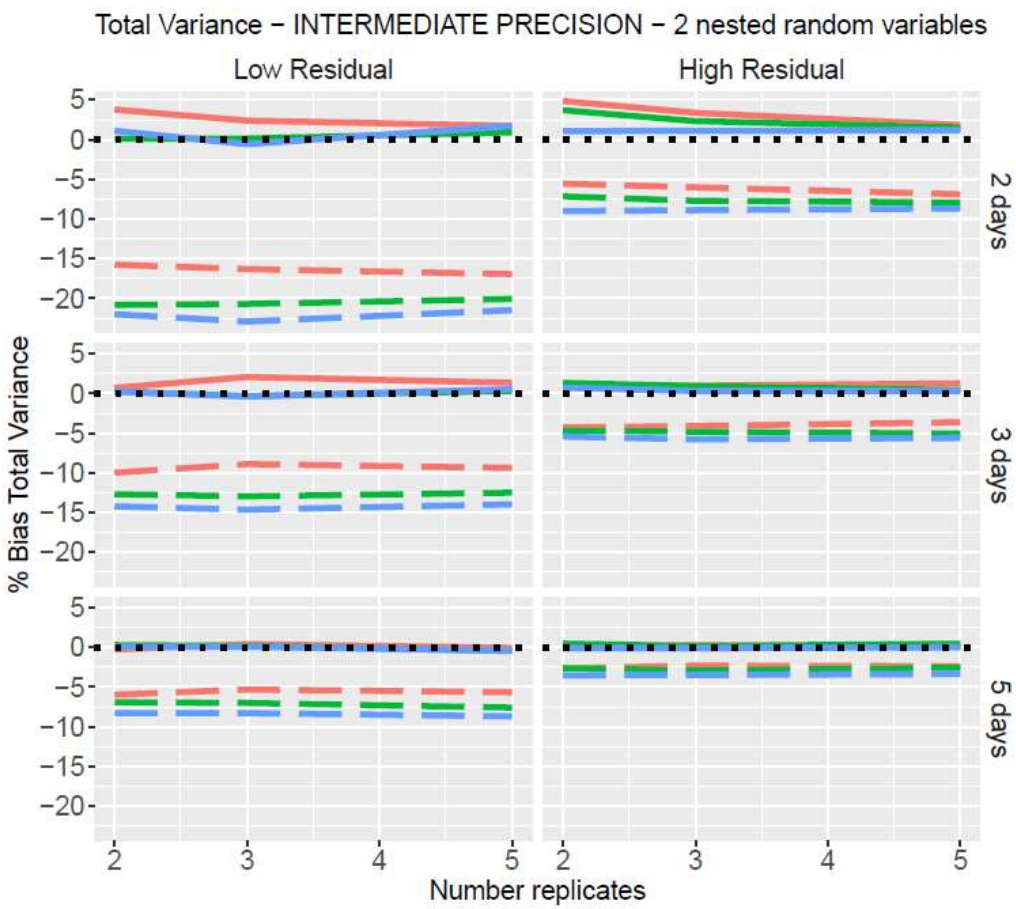
STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2020, VOL. 12, NO. 3, 262-272

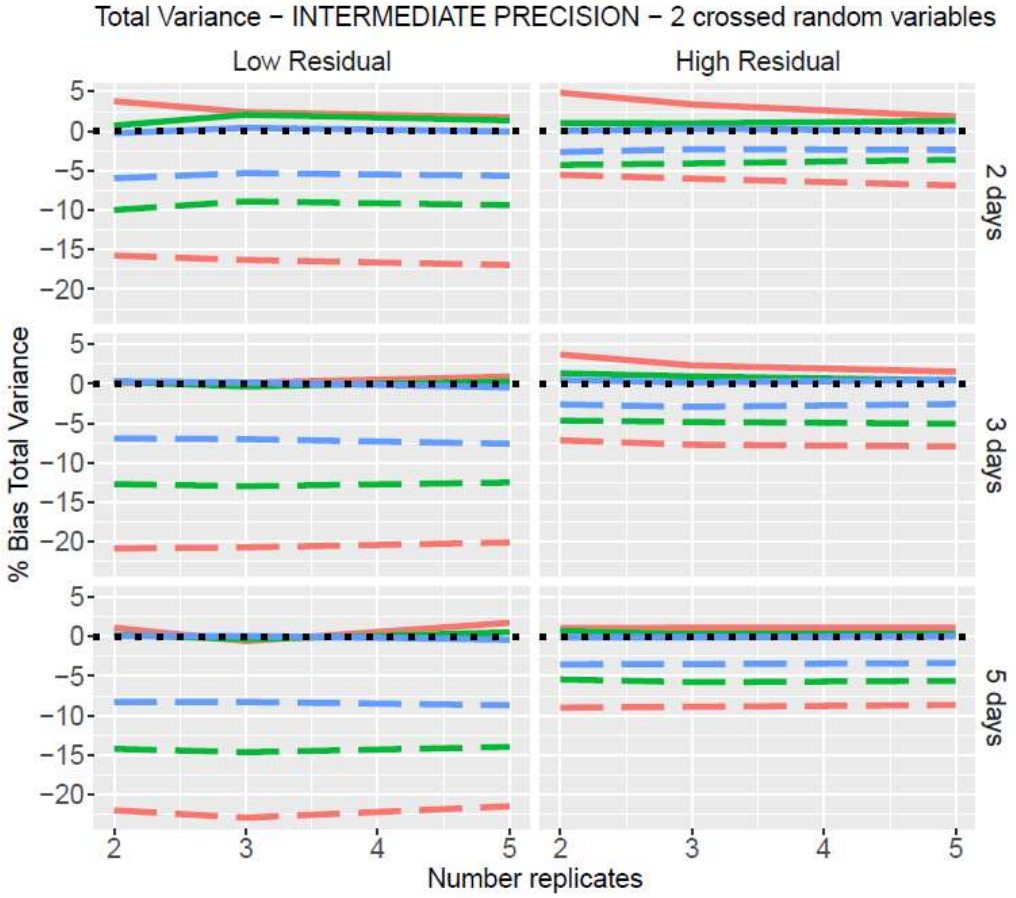
Confidence and Prediction in Linear Mixed Models: Do Not Concatenate the Random Effects. Application in an Assay Qualification Study

Bernard G Francq, Dan Lin, Walter Hoyer

In the pharmaceutical industry, all analytical methods must be shown to deliver unbiased and precise results. In an assay qualification or validation study, the trueness, accuracy, and intermediate precision are usually assessed by comparing the measured concentrations to their nominal levels. Trueness is assessed by using Confidence Intervals (CIs) of mean measured concentration, accuracy by Prediction Intervals (PIs) for a future measured concentration, and the intermediate precision by the total variance.

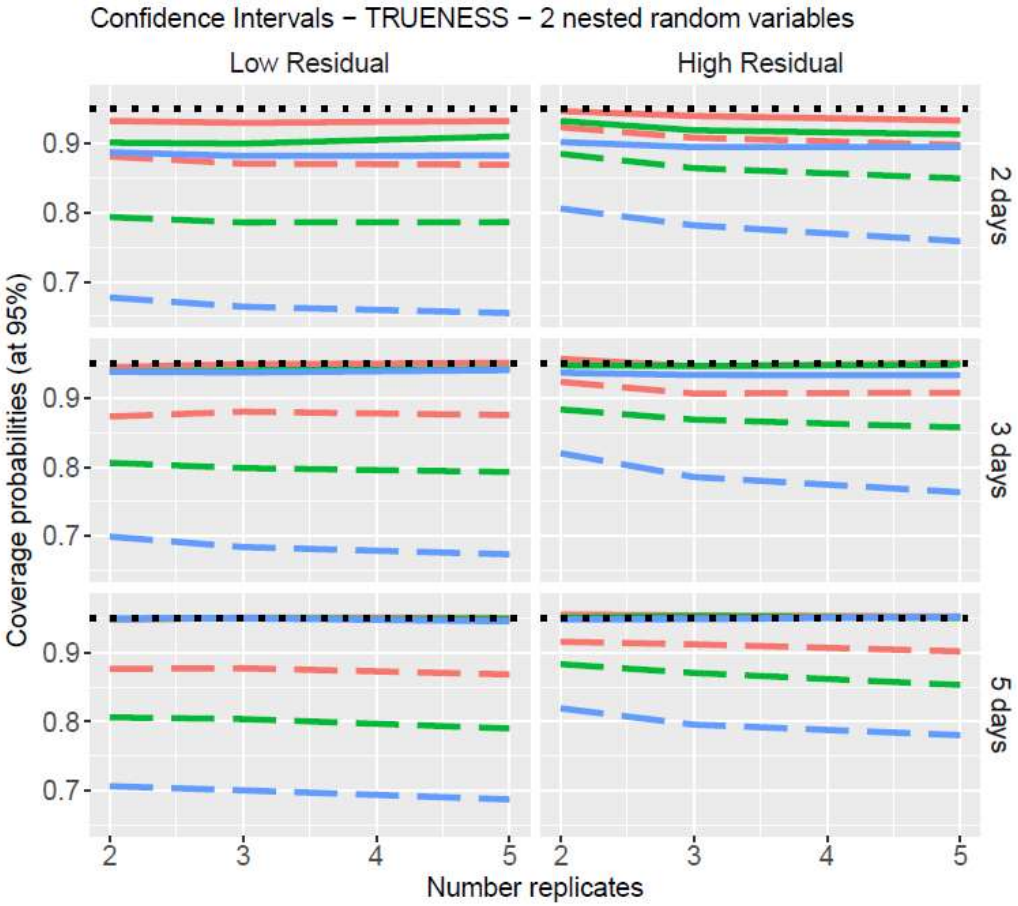
Total Variance (Intermediate Precision): simulations

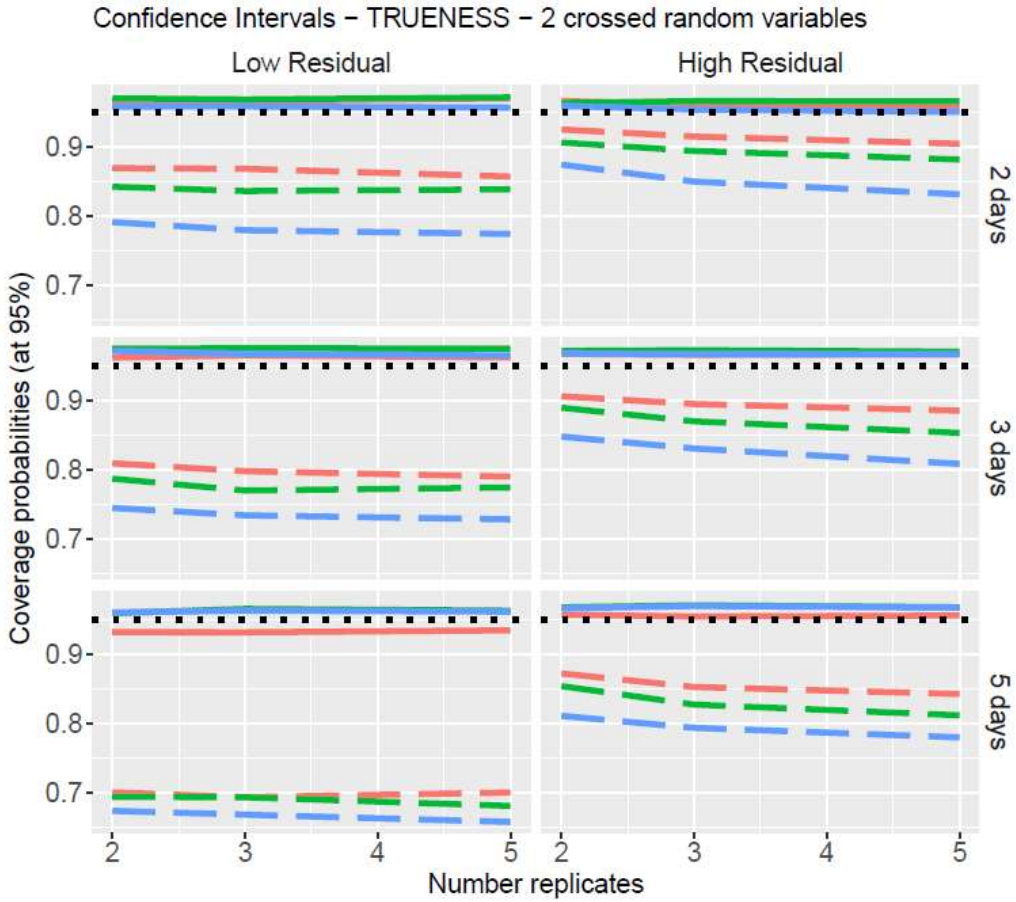




Operator (day) 2 3 5
Method Mixed Model Concatenate

Trueness (Confidence Intervals): simulations

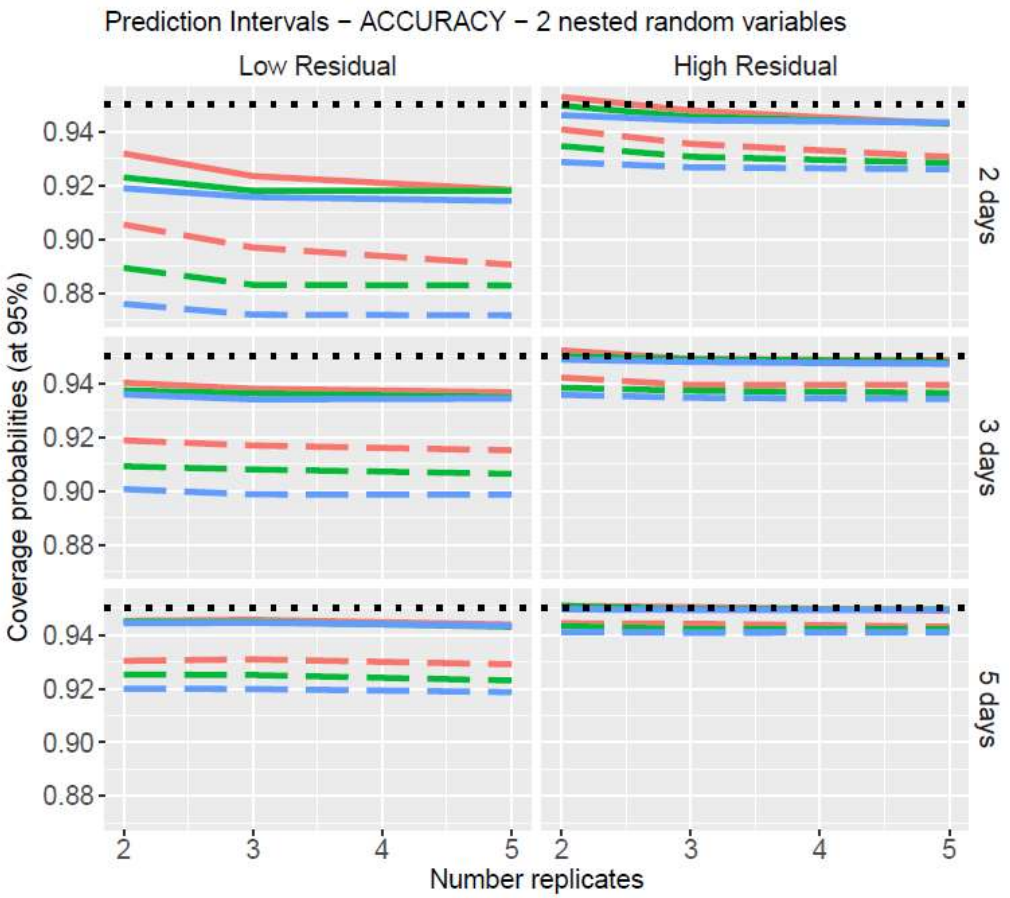


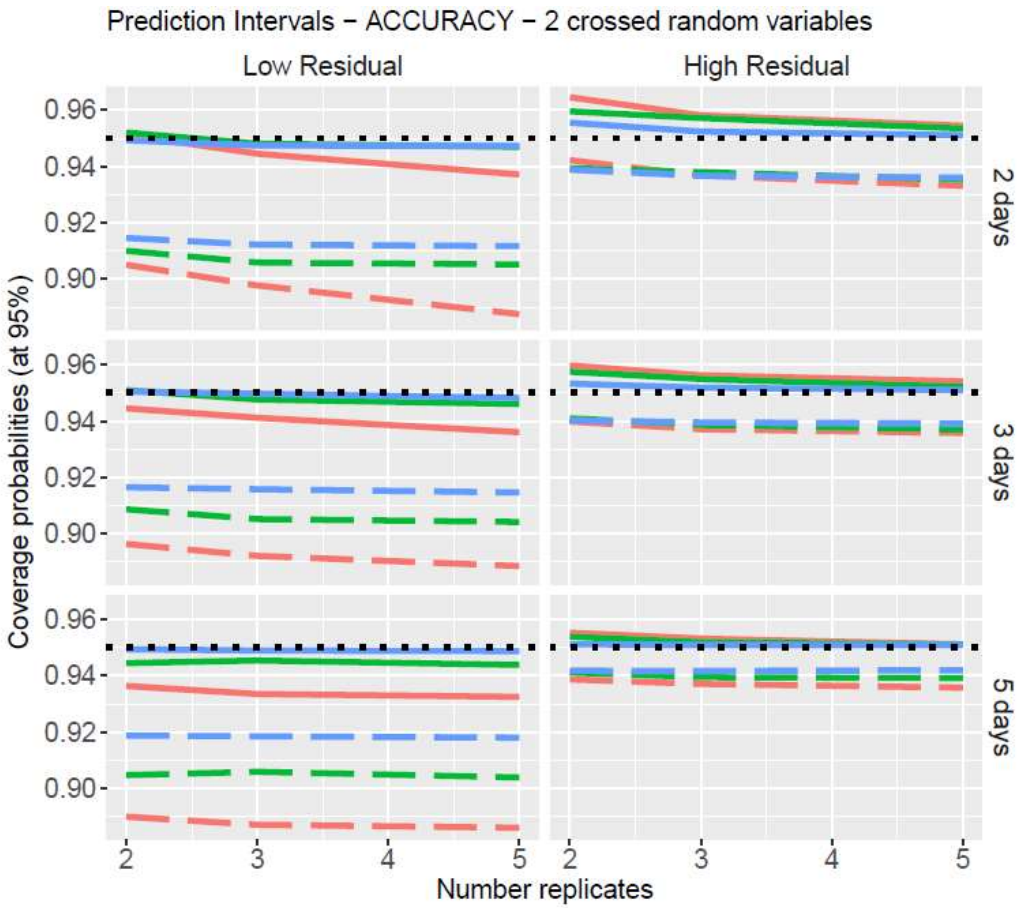


Operator (day) 2 3 5

Method Mixed Model Concatenate

Accuracy (Prediction Intervals): simulations





Operator (day) 2 3 5
Method Mixed Model Concatenate

Concatenate or not ?

When the random variables are concatenated

- the **bias** of the total variance **soar** and may **exceeds 20% bias**
- the **trueness** (95% CI) **collapse** and **drop** to **70%**
- the **accuracy** (95% CI) **collapse** and **drop** lower than **the nominal level**

→ The power will be over-optimistic when designing a new qualification study by concatenating the random variables

USP example revisited

Assay qualification study

- 2 crossed random effects model
- 3 analysts
- 3 equipments
- 3 measures
- 27 total number of experiments

- Y = relative measurement error expressed as a percentage of introduced concentration
- ± 5% for Trueness
- ± 10% for Accuracy

- Guidelines recommend to concatenate the random effects, and obtain then 9 ‘treatments’

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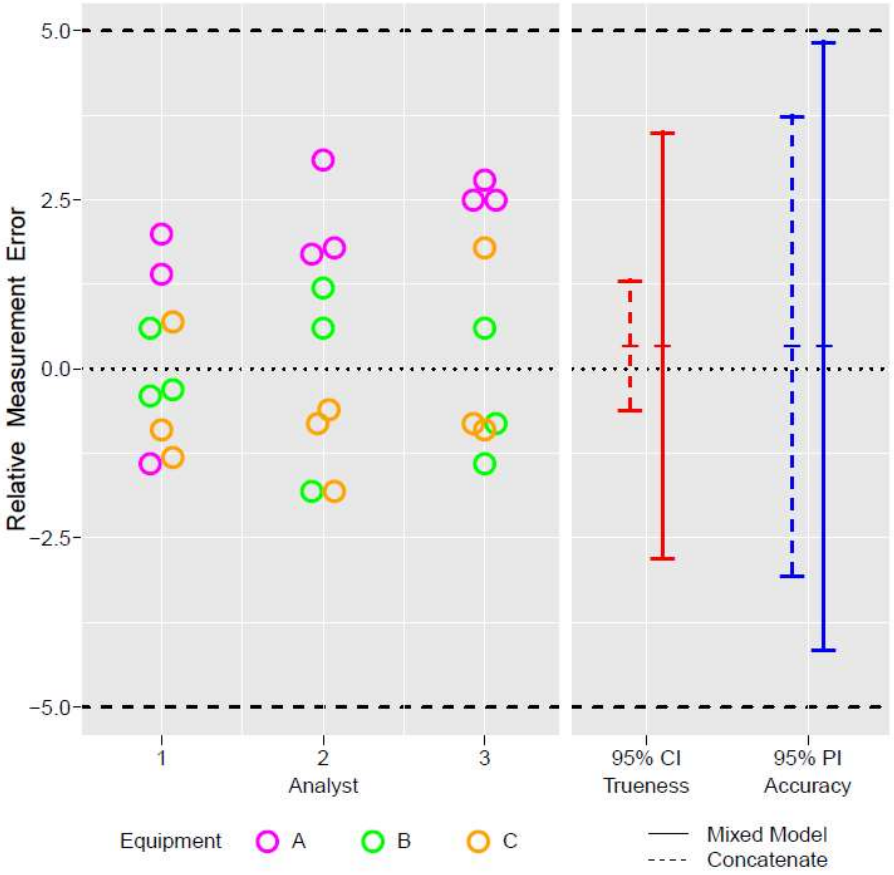
USP example revisited



		95% CI (Trueness)			95% PI (Accuracy)		
Method	$\hat{\mu}$	DF	Lower	Upper	DF	Lower	Upper
Concatenate	0.374	8	-0.585	1.333	17.027	-3.025	3.773
Mixed Model	0.374	2	-2.767	3.515	5.795	-4.120	4.868

The intermediate precision is under-estimated by 13%
Biased estimate = 2.423 versus unbiased = 2.783

Widths CI and PI = 1.918 and 6.798 versus 6.282 and 8.988
→ CI is 3.3-fold narrower
→ PI is 1.3-fold narrower

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USP example revisited: the V matrix

Correct V matrix

	A1E1	A1E2	A1E3	A2E1	A2E2	A2E3	A3E1	A3E2	A3E3
A1E1	ρ_{AE}	ρ_A	ρ_A	ρ_E	0	0	ρ_E	0	0
A1E2	ρ_A	ρ_{AE}	ρ_A	0	ρ_E	0	0	ρ_E	0
A1E3	ρ_A	ρ_A	ρ_{AE}	0	0	ρ_E	0	0	ρ_E
A2E1	ρ_E	0	0	ρ_{AE}					
A2E2	0	ρ_E	0	ρ_A					
A2E3	0	0	ρ_E	ρ_A					
A3E1	ρ_E	0	0	ρ_E					
A3E2	0	ρ_E	0	0					
A3E3	0	0	ρ_E	0					

Estimated V matrix

	A1E1	A1E2	A1E3	A2E1	A2E2	A2E3	A3E1	A3E2	A3E3
A1E1	0.53	0	0	0.52	0	0	0.52	0	0
A1E2	0	0.53	0	0	0.52	0	0	0.52	0
A1E3	0	0	0.53	0	0	0.52	0		
A2E1	0.52	0	0	0.53	0	0	0.5		
A2E2	0	0.52	0	0	0.53	0	0		
A2E3	0	0	0.52	0	0	0.53	0		
A3E1	0.52	0	0	0.52	0	0	0.5		
A3E2	0	0.52	0	0	0.52	0	0		
A3E3	0	0	0.52	0	0	0.52	0		

USP V matrix

By concatenating

the random variables

	T1	T2	T3	T4	T5	T6	T7	T8	T9
T1	0.46	0	0	0	0	0	0	0	0
T2	0	0.46	0	0	0	0	0	0	0
T3	0	0	0.46	0	0	0	0	0	0
T4	0	0	0	0.46	0	0	0	0	0
T5	0	0	0	0	0.46	0	0	0	0
T6	0	0	0	0	0	0.46	0	0	0
T7	0	0	0	0	0	0	0.46	0	0
T8	0	0	0	0	0	0	0	0.46	0
T9	0	0	0	0	0	0	0	0	0.46

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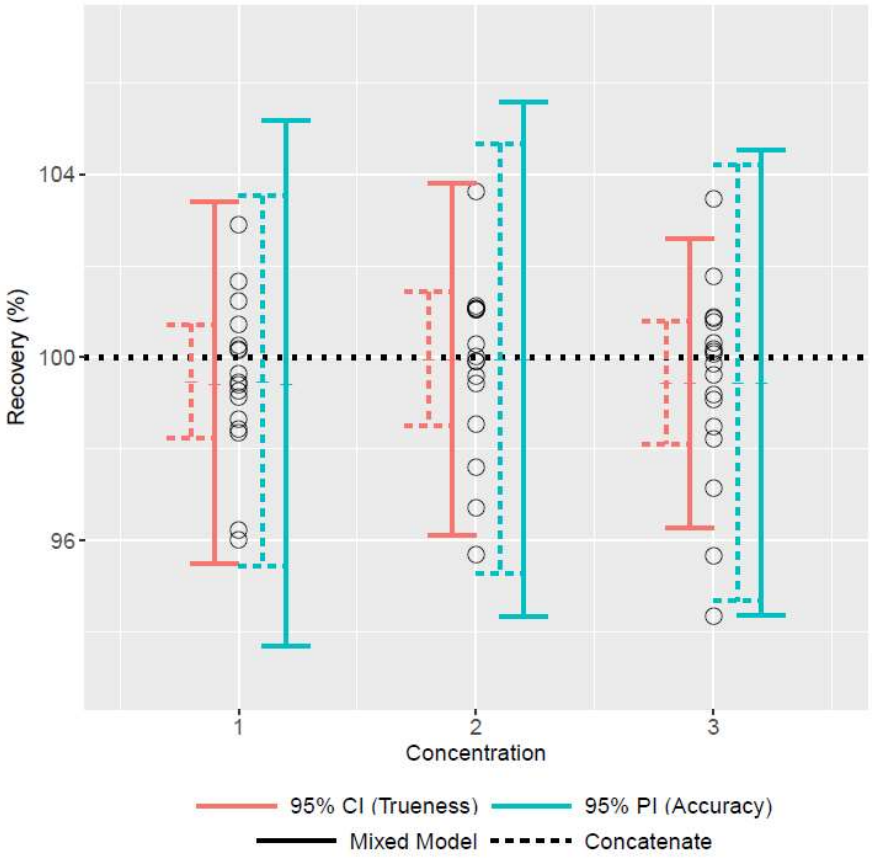
GSK example

Assay qualification study

- 2 nested random effects model on assay validation - Unbalanced
- 9 analyst (3 per day)
- 3 days
- 3 concentrations
- 2 measures
- 54 – 3 = 51 total number of experiments

- ± 7% for Accuracy

GSK example



	Mixed Model				Concatenated			
	$\hat{Y}$	DF	Lower	Upper	$\hat{Y}$	DF	Lower	Upper
Conc.	95% CI (Trueness) - Recovery							
1	99.4	1.97	95.5	103.4	99.5	8.17	98.2	100.7
2	100.0	2.01	96.1	103.8	100.0	7.24	98.5	101.4
3	99.4	2	96.3	102.6	99.4	8	98.1	100.8
	95% PI (Accuracy) - Recovery							
1	99.4	4.29	93.7	105.2	99.5	10.98	95.4	103.5
2	100.0	5.91	94.3	105.6	100.0	10.26	95.3	104.7
3	99.4	11.58	94.4	104.5	99.4	15.00	94.7	104.2

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The V matrix

Estimated V matrix

	D1O1	D1O2	D1O3	D2O4	D2O5	D2O6	D3O7	D3O8	D3O9	
	0.72	0.57	0.57	0	0	0	0	0	0	D1O1
	0.57	0.72	0.57	0	0	0	0	0	0	D1O2
	0.57	0.57	0.72	0	0	0	0	0	0	D1O3
	0	0	0	0.72	0.57	0.57	0	0	0	D2O4
	0	0	0	0.57	0.72	0.57	0	0	0	D2O5
	0	0	0	0.57	0.57	0.72	0	0	0	D2O6
	0	0	0	0	0	0	0.72	0.57	0.57	D3O7
	0	0	0	0	0	0	0.57	0.72	0.57	D3O8
	0	0	0	0	0	0	0.57	0.57	0.72	D3O8

	T1	T2	T3	T4	T5	T6	T7	T8	T9	
	0.66	0	0	0	0	0	0	0	0	T1
	0	0.66	0	0	0	0	0	0	0	T2
	0	0	0.66	0	0	0	0	0	0	T3
	0	0	0	0.66	0	0	0	0	0	T4
	0	0	0	0	0.66	0	0	0	0	T5
	0	0	0	0	0	0.66	0	0	0	T6
	0	0	0	0	0	0	0.66	0	0	T7
	0	0	0	0	0	0	0	0.66	0	T8
	0	0	0	0	0	0	0	0	0.66	T9

USP V matrix

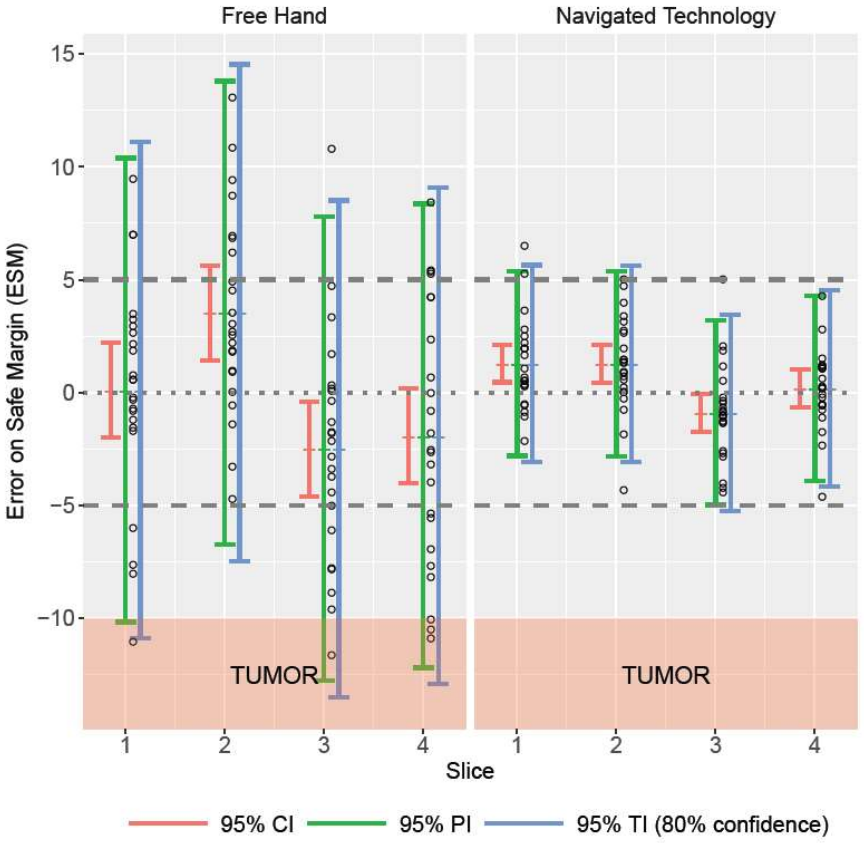
By concatenating

the random variables

Correct V matrix

	D1O1	D1O2	D1O3	D2O4	D2O5	D2O6	D3O7	D3O8	D3O9	
	ρ_{OD}	ρ_D	ρ_D	0	0	0	0	0	0	D1O1
	ρ_D	ρ_{OD}	ρ_D	0	0	0	0	0	0	D1O2
	ρ_D	ρ_D	ρ_{OD}	0	0	0	0	0	0	D1O3
	0	0	0	ρ_{OD}	ρ_D	ρ_D	0	0	0	D2O4
	0	0	0	ρ_D	ρ_{OD}	ρ_D	0	0	0	D2O5
	0	0	0	ρ_D	ρ_D	ρ_{OD}	0	0	0	D2O6
	0	0	0	0	0	0	ρ_{OD}	ρ_D	ρ_D	D3O7
	0	0	0	0	0	0	ρ_D	ρ_{OD}	ρ_D	D3O8
	0	0	0	0	0	0	ρ_D	ρ_D	ρ_{OD}	D3O9

Confidence, Prediction, Tolerance in Linear Mixed Models



RESEARCH ARTICLE

Confidence, Prediction, and Tolerance in Linear Mixed Models

Bernard G Francq, Dan Lin, Walter Hoyer
Statistics in Medicine, 2019.

The literature about Prediction Interval (PI) and Tolerance Interval (TI) in linear mixed models is usually developed for specific designs, which is a main limitation to their use.

This paper proposes to reformulate the two-sided PI to be generalizable under a wide variety of designs (one random factor, nested and crossed designs for multiple random factors, and balanced or unbalanced designs).

Finally, these CIs, PIs, and TIs are applied to two real data sets: one from orthopedic surgery study (intralesional resection risk) and the other from assay validation study during vaccine development.

R versus SAS

```
library(varComp)              # Archived

model = varComp(data = qualification, fixed = as.formula("resp ~ fixed -1"), random = as.formula("~ Surgeon"))
summary(model)

# Variance components and their covariance matrix:
var.comp = model$varComp
var.res = model$sigma2
cov.matrix = vcov(model, what = "random")

# Total variance and its variance:
var.tot = var.comp + var.res
var.var.tot = sum(cov.matrix)
```

```
PROC MIXED DATA=qualification ASYCOV NOPROFILE;
 CLASS operator day ;
 MODEL resp = &fixed / SOLUTION CL  DDFM=KR &NOINT ALPHA = 0.05;
 RANDOM operator day operator*day;
 BY concentration;
RUN;
```

R versus SAS: comparison and validation

In pharma, every in-house application (in R) must be validated to guarantee the reliability and correctness of its results.
A key part of the validation is to verify results against well-established software like SAS which ideally should show identical results.

Some very basic statistics
are not calculated
with the same algorithm
between R and SAS…

Example: median, quantile,…

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R versus SAS: comparison and validation

“

Perhaps I can try again to explain why I do not take the "obviously correct" approach of attempting to reproduce the results provided by SAS.

Although there are those who feel that the purpose of the R Project - indeed the purpose of any statistical computing whatsoever - is to reproduce SAS, I am not a member of that group.

If those people feel that I am a heretic for even suggesting that a result provided by SAS could be other than absolute truth and that I should be made to suffer a slow, painful death by being burned at the stake for my heresy ...

“

Douglas Bates (lme4)

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R versus SAS: comparison and validation

> *“ I don’t see the point to provide variance of variance*
>
> (covariance matrix of variance components)*…* *“*
>
> *Douglas Bates (lme4)*

Well… variance of variance are very useful, especially in pharma industry

- Intermediate Precision
- Prediction Interval
- OOS
- …

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R versus SAS: comparison and validation

See Ben Bolker attempt solution few years later

https://stackoverflow.com/questions/31694812/standard-error-of-variance-component-from-the-output-of-lmer

Standard Error of variance component from the output of lmer

Asked 4 years, 8 months ago Active 4 years, 8 months ago Viewed 6k times

3

I need to extract the `standard error` of variance component from the output of `lmer` .

```
library(lme4)
model <- lmer(Reaction ~ Days + (1|Subject), sleepstudy)
```

The following produces estimates of variance component :

```
s2 <- VarCorr(model)$Subject[1]
```

It is **NOT** the standard error of the variance. And I want the standard error . How can I have it ?

can you post the data for this example? It would also help to know what you're going to use the standard errors for (as I point out below, standard errors of variance estimates are unreliable uncertainty metrics -- profile intervals will be better) – Ben Bolker Jul 29 '15 at 15:43

Why do you want standard errors for a parameter that is not symmetrically distributed. You should reframe the question you ask. Don't imitate the SAS mistake. If you want hypo test then use anove function. If you want CI, use profile or bootstrap CI. There are reasons why lmer does not give the number you ask for. Although Ben tells you how you might get it. Don't let fact that SAS or Stata report that influence you. – pauljohn32 Oct 10 '18 at 10:15

I think you are looking for the Wald standard error of the variance estimates. Please note that these (as often pointed out by Doug Bates) the Wald standard errors are often **very poor** estimates of the uncertainty of variances, because the likelihood profiles are often far from quadratic on the variance scale ... I'm assuming you know what you're doing and have some good use for these numbers ...

R versus SAS: comparison and validation

In Mixed Models:

The fixed effects are the easiest part to estimate
→ *We should always get the same in all software with very high precision*

The variance components and their covariance are really the tricky part!
→ *More likely to obtain (slightly) different results from different software*

The nightmare is the degree of freedom for fixed effects ! (by Kenward-Roger)
→ M*ore likely to obtain different results from different software*

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R versus SAS: comparison and validation

Using a few real data sets
Provides only very limited evidence that no difference will be encountered in a future analysis.

Using thousands of simulated data sets (per design)
Analysed with both software packages, allows to spot many differences that could be traced back

Compare the results between SAS and R
→ Proc Compare in SAS is your best friend

```
proc compare base = MeansSAS_Twocrossed compare = MeansR
            LISTEQUALVAR METHOD=PERCENT CRITERION = 0.5001;
 title 'Compare SAS and R - One random variable - Means, Accuracy, Trueness';
run;

proc compare base = VarsSAS_Twocrossed compare = VarsR
            LISTEQUALVAR METHOD=PERCENT CRITERION = 0.5001;
title 'Compare SAS and R - One random variable - Variances';
run;
```

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R versus SAS: comparison and validation

DF, trueness and statistical intervals

Variables with All Equal Values

Variable	Type	Len	MaxCrit
simul	NUM	8	0
DF	NUM	8	0.00004
dfvartot	NUM	8	0.039
trueness	NUM	8	607E-13
CI_lower_trueness	NUM	8	0.00078
CI_upper_trueness	NUM	8	0.00059
PI_lower_accuracy	NUM	8	0.0096
PI_upper_accuracy	NUM	8	0.0026

Variance components, DF and CV

Variables with All Equal Values

Variable	Type	Len1	Len2	MaxCrit
simul	NUM	8	8	0
CovParm	CHAR	9	10	
Estimate	NUM	8	8	0.019
dfvar	NUM	8	8	0.039
std_up	NUM	8	8	0.034
cv	NUM	8	8	0.0096
cv_upper	NUM	8	8	0.034

Last but not least

References

- Francq, Lin, Hoyer, Cartiaux, Kenett: Individual Success Probability: Beyond the t-test and p-values. (2022) (under review)
- Francq, Berger, Boachie: To Tolerate or To Agree: A Tutorial on Tolerance Intervals in Method Comparison Studies with BivRegBLS R Package. Statistics in Medicine (2020)
- Francq, Lin, Hoyer: Confidence and Prediction in Linear Mixed Models: Do Not Concatenate the Random Effects. Application in an Assay Qualification Study. Statistics in Biopharmaceutical research (2020)
- Francq, Lin, Hoyer. Confidence, Prediction and Tolerance in Linear Mixed Models. Statistics in Medicine (2019)
- Francq B, Cartiaux O. Delta Method and Bootstrap in Linear Mixed Models to Estimate a Proportion When no Event is Observed: Application to Intralesional Resection in Bone Tumor Surgery. Statistics in Medicine (2016)

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Conflict of interest

This work was sponsored by GlaxoSmithKline Biologicals SA.
BG Francq is employee of the GSK group of companies.

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Thanks!