Homogeneity within an individual tablet

Leveraging NIR technology to study within tablet location effects

04/10/2018 Nonclinical Statistics Conference 2018

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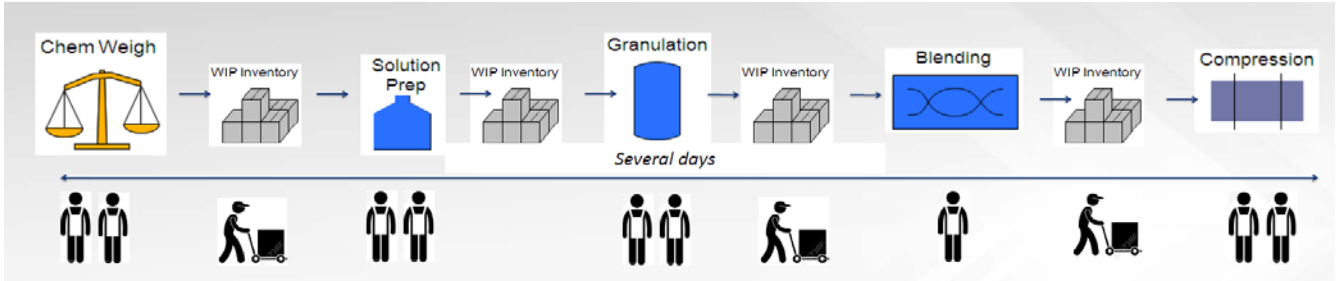
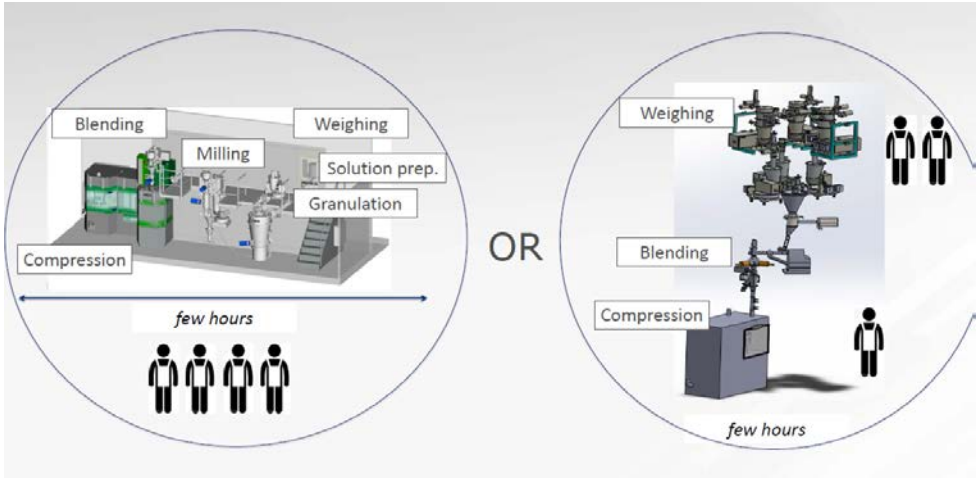
Context

PAT and Continuous manufacturing

Batch vs Continuous manufacturing





Potential benefits

- Reduced footprint: smaller facilities
- Easy scale-up from development to commercial production
- Faster reaction to market: flexible output of commercial line based on market demand
- Improved product quality: better quality control over the product given continuous monitoring of the critical quality attributes

Sampling options

- Batch process: off-line and at-line
- Traditional analytical methods “in lab”

- Continuous process: on-line and in-line monitoring needed
- Understanding of process, quality by design, feedback loops, real time release

- Process analytical technology: various types of sensors that allow continuous evaluation of material in the line
- Spectroscopy very commonly used (NIR)
- Broader use: some PAT leveraged in batch process as well

NIR for content uniformity

- Near-infrared signal send through the tablet
- Part is absorbed in the tablet and remaining signal is captured
- Output: of spectroscopy nature, wavelengths of the absorbed signal
- Model transform this signal into the amount of API in the observed material => content uniformity measurement after weight adjustment

- Gold standard method: High-performance liquid chromatography (HPLC)
- Wet chemistry approach
- Destructive method
- Measures API in whole tablet at once

- NIR looks only at one part of the tablet => is there risk of heterogeneity?

Design

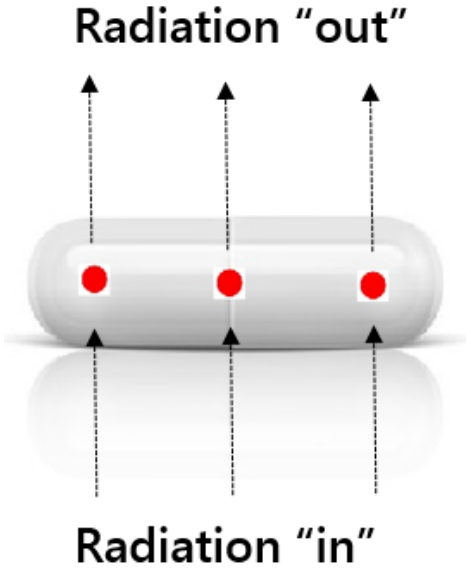
Objective

Investigate potency homogeneity within tablet & compare NIR with HPLC

- NIR locations: Left, Center, Right
- HPLC runs: two analytical runs

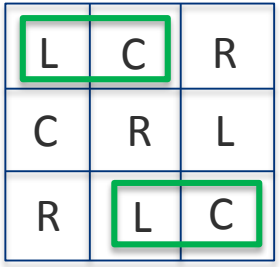
- Systematic measurement ordering=> possible carryover (residual) effects

- Solution: use an augmented residual effects design (Williams)



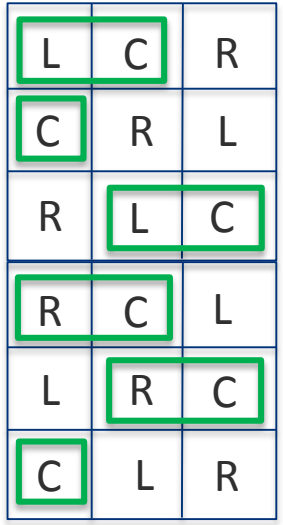
Latin square

- NIR per tablet: three locations
- A Latin Square of order 3: each symbol appears once in each row and column
- Problem: unbalanced for pairs (LC twice vs. no LR)
- Location effects C is confounded with carryover effect coming from L
- If carryover => biased location effects



Williams Crossover Design

- For even number, it is same as Latin square
- For odd number, two Latin squares need to be used to avoid problem of unbalance
- See that C follows twice L, twice R and twice is first location to measure



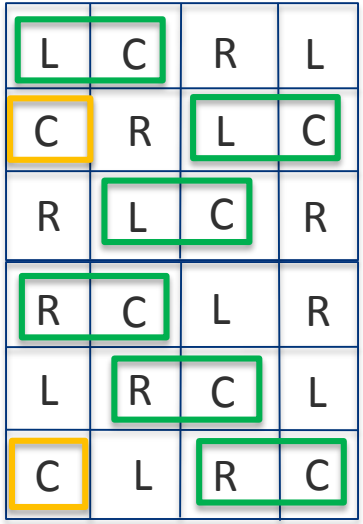
Williams Crossover Design Augmented

- Add one extra measurement for each tablet
- Same location as first location

- Allows to evaluate if there is any overall carryover effect from first to last measurement
- Interpretation: trend caused by NIR tool rather than location measured

- Multiple measurements of same tablet => unlike HPLC, we can separate tablet and analytical variability

- We keep balance of LC and RC pairs, but have one less measurement for C first

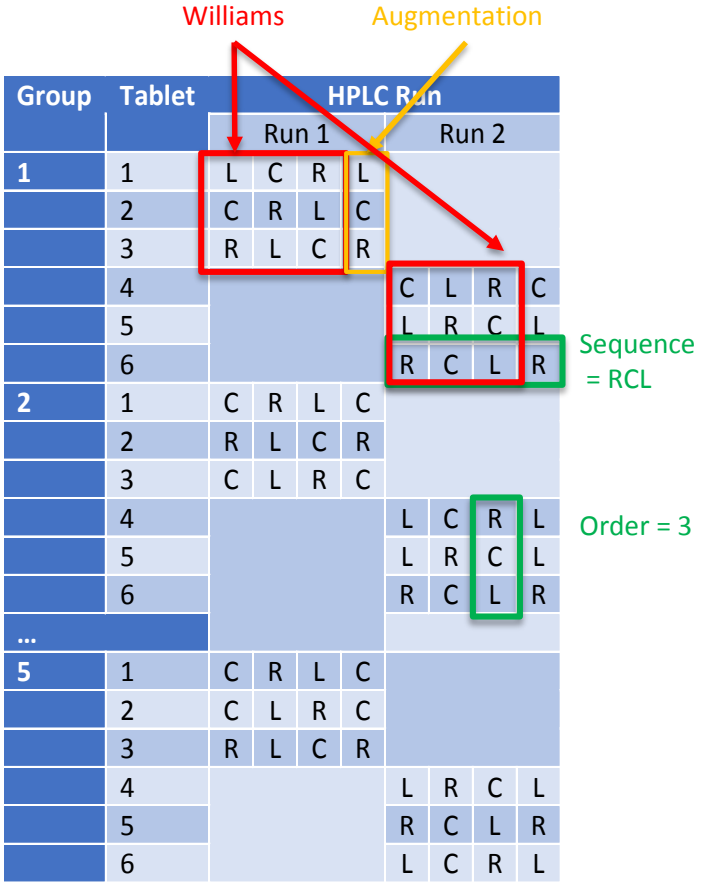


Extension of design

- Augmented Williams requires 6 tablets => no replicates
- Repeat whole design 5 times => 5 group => 30 tablets
- Permute the Latin squares

- Allows to evaluate effect of Sequence as such and effect of Order of measurement

- Each tablet measured with HPLC at the end => two HPLC runs (3 tablets in each run within each group)



Modelling considerations: Group

- Random effect vs fixed effects
- Degrees of freedom perspective: somehow borderline
- Design perspective: designed as if there is difference between groups to be estimated
- We use fixed effects for group

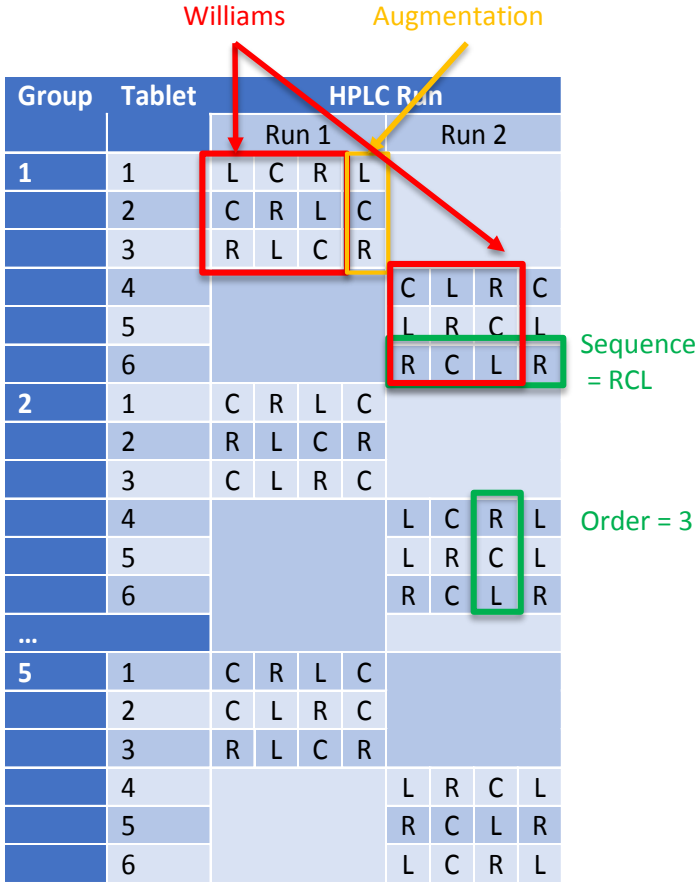
Modelling considerations: Sequence

- E.g. L-R-C-L vs R-C-L-R
- Two perspectives: nested within NIR or main effect for both NIR and HPLC
- Main effect: interpretation as sequence of NIR having impact on tablet itself => impact on HPLC as well
- Nested: interpretation as sequence having impact on NIR measurement due to process related to NIR tool

Final Design Layout

- Group (fixed or random)
- HPLC Run
- Tablets (random effect)
- Order (column effect)
- Sequence (row effect)
- Location
- Method

NIR / HPLC specific terms



Modelling goals

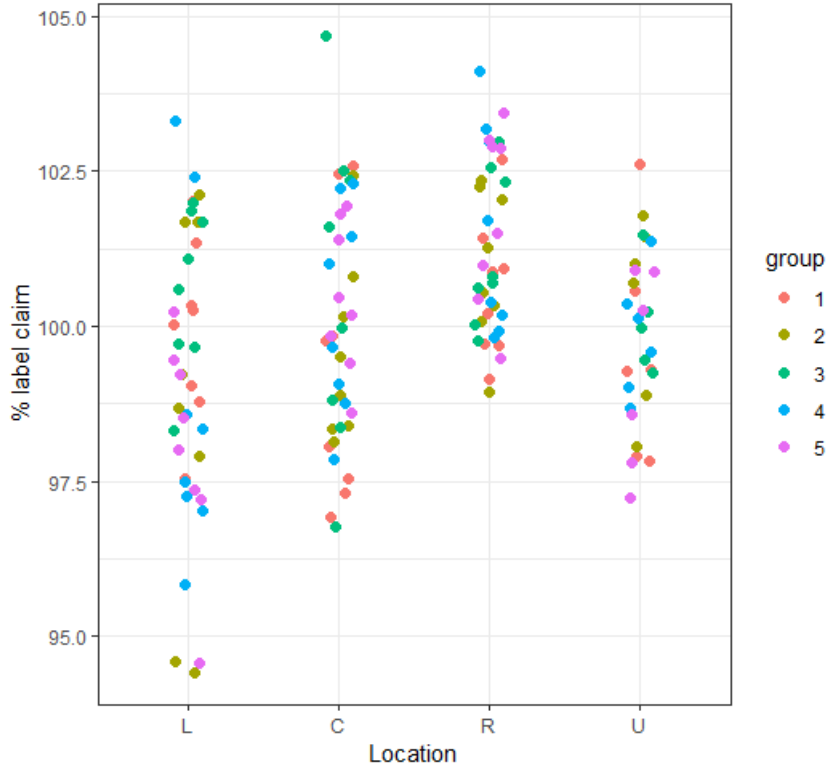
1. Direct effect of locations within tablet: within tablet homogeneity
2. Direct comparison of NIR method vs HPLC gold standard method
3. Tablet to tablet variability free of analytical uncertainty
4. Evaluation of possible carryover effects

- Unequal variance allowed (NIR vs HPLC)

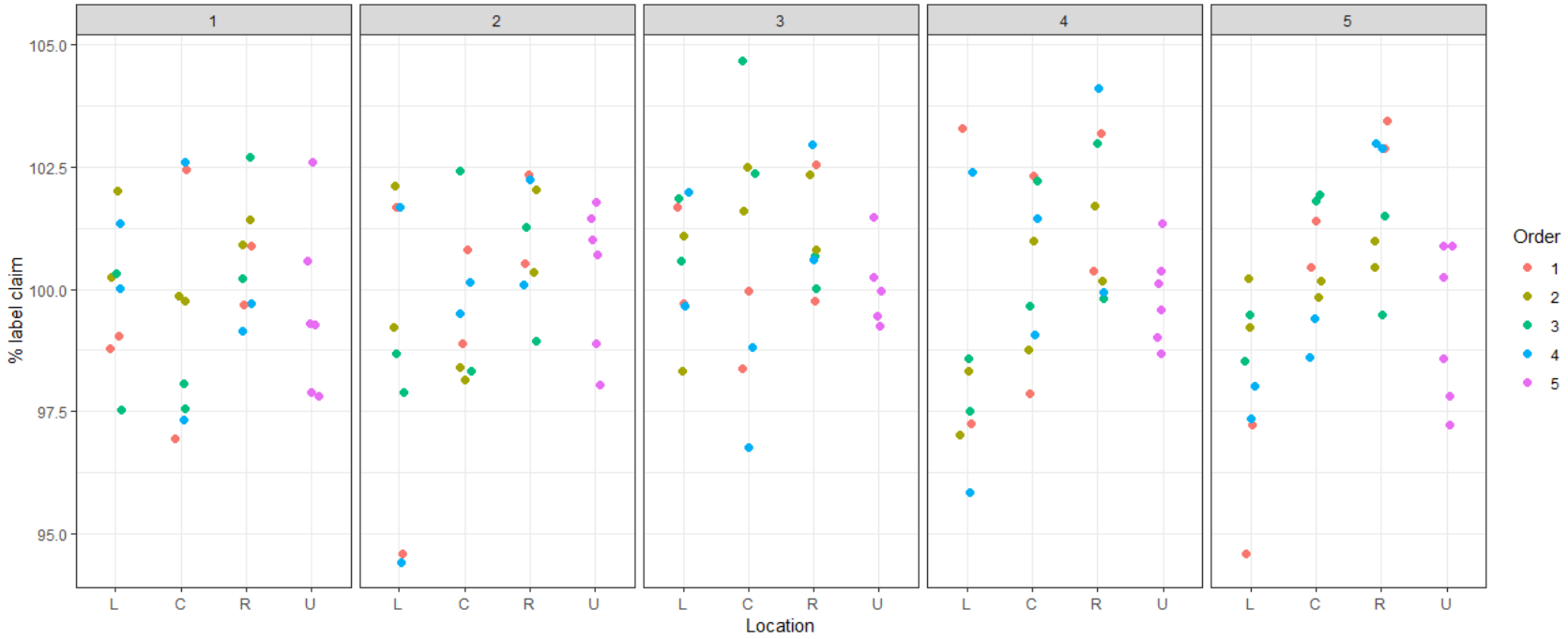
Exploratory analysis

Data plots: not real data, just computer generated simulation

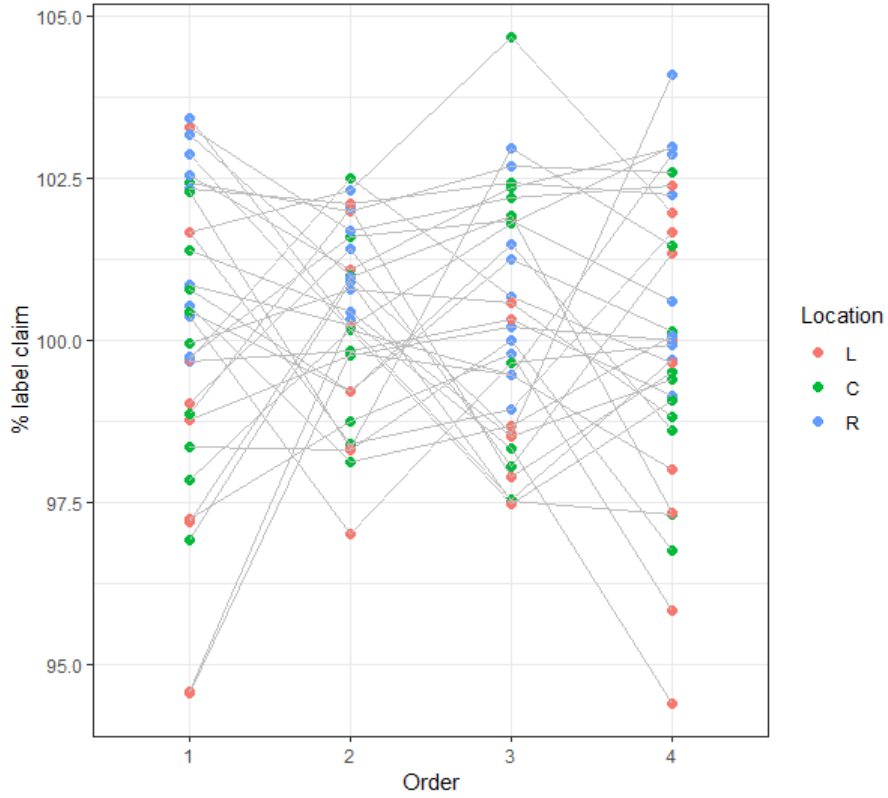
Data per location and group



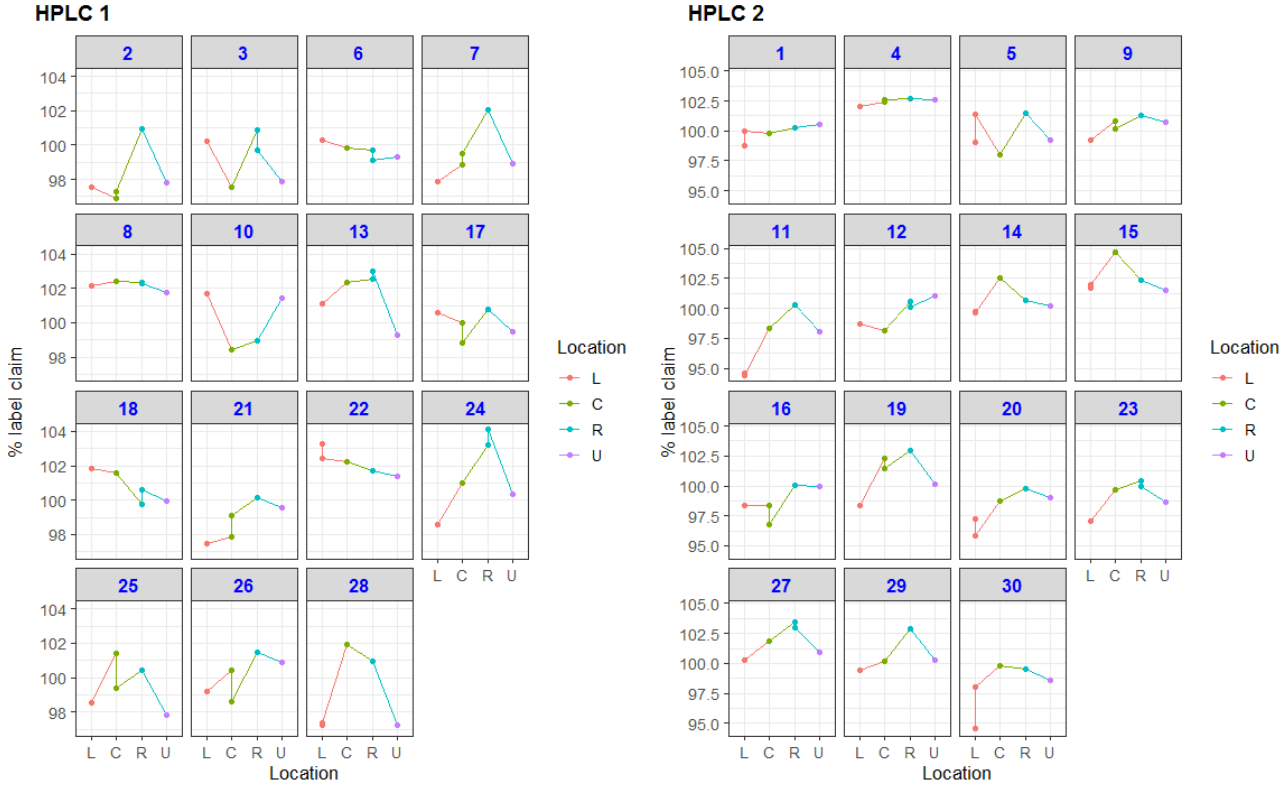
Data per location, group and order



NIR data only: tablet level



Tablet level data in detail



Modelling of effect of the location and method

Left-Centre-Right and HLPC-NIR

Modelling goals

1. Effect of locations
2. Comparison of NIR vs HPLC
3. Tablet to tablet variability

- Unequal variance per method (NIR vs HPLC)
- Fitted with SAS PROC MIXED

Mixed Effects Model

$$y_{k(i)jlmpr} = \mu + G_i + \tau_{k(i)} + M_j + L_{l(j)} + S_{m(j)} + O_{p(j)} + H_{r(j)} + \varepsilon_{k(i)jlmpr}$$

$y_{k(i),jlmpr}$ = response of the k^{th} tablet within the i^{th} group tested in r^{th} HPLC run with m^{th} sequence at l^{th} location as p^{th} measurement with j^{th} analytical method

G_i = i^{th} Group effect (1=1,2,…,5)

$H_{r(j)}$ = fixed effect of r^{th} HPLC run (r=1,2)

$\tau_{k(i)}$ = random effect of k^{th} tablet within i^{th} Group: N(0, σ_τ^2)

$S_{m(j)}$ = fixed effect of m^{th} Sequence (m=1,…,6)

$L_{l(j)}$ = fixed effect of l^{th} location effect

M_j = fixed effect of j^{th} Method effect

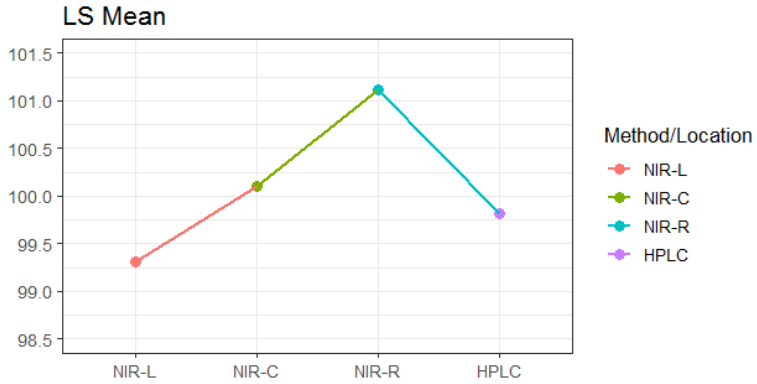
$\varepsilon_{k(i),jlmpr}$ = residual error: N(0, σ_{ej}^2)

Residual error refers to within tablet measurement variability

NIR / HPLC specific terms

Results

Method/Location	Point estimate	Standard Error	95% Confidence interval
HPLC	99.81	0.28	(99.26, 100.37)
NIR Left	99.31	0.36	(98.60, 100.02)
NIR Center	100.10	0.32	(99.47, 100.72)
NIR Right	101.11	0.27	(100.57, 101.64)



Results

Bias Estimates (NIR – HPLC)	Point estimate	Standard Error
NIR Left - HPLC	-0.50	0.32
NIR Center - HPLC	0.28	0.27
NIR Right - HPLC	1.29	0.22
NIR (average) - HPLC	0.36	0.20

Covariance Parameter	Median
Tablet effect SD	1.32
Residual SD NIR	1.35
Residual SD HPLC	0.71

Interpretation

1. Effect of locations: There seem to be upward shift from left to right NIR measurements

2. Comparison of NIR vs HPLC:
   - There seems to be an upwards bias in NIR
   - There seems to be unequal variance with respect to method
   - HPLC seems to be more precise than NIR

3. Tablet to tablet variability: Considerable random effect of tablet (in comparison to residual variability)

Modelling of carryover effects

Modelling goals

4. Carryover effects

- Extend the previous model to include the carryover (residual) effect of the locations towards next measurement (i.e. in data “what was previous location”)

- Unequal variance allowed (NIR vs HPLC)

Extended Mixed Effects Model

$$y_{k(i)jlmpqr} = \mu + G_i + \tau_{k(i)} + M_j + L_{l(j)} + S_{m(j)} + O_{p(j)} + H_{r(j)} + R_{q(j)} + \varepsilon_{k(i)jlmpr}$$

$y_{k(i),jlmpqr}$ = response of the k^{th} tablet within the i^{th} group tested in r^{th} HPLC run with m^{th} sequence at l^{th} location as p^{th} measurement with j^{th} analytical method having q^{th} previous location

G_i = i^{th} Group effect (1=1,2,…,5)

H_r = fixed effect of r^{th} HPLC run (r=1,2)

$\tau_{k(i)}$ = random effect of k^{th} tablet within i^{th} Group: N(0, σ_τ^2)

$S_{m(j)}$ = fixed effect of m^{th} Sequence (m=1,…,6)

$L_{l(j)}$ = fixed effect of l^{th} location effect

$R_{q(j)}$ = fixed effect of q^{th} carryover location effect (one previous location only)

M_j = fixed effect of j^{th} Method effect

$\varepsilon_{k(i),jlmpr}$ = residual error: N(0, σ_{ej}^2)

Re-parametrization needed to get appropriate fit. Bayesian framework was used: combination of R and JAGS.

Reparametrization

- Issues with SAS MIXED LS

- Re-parametrization and Bayesian framework utilized (JAGS) to clearly separate the various effects:
  - Explicit mean for HPLC and NIR
  - Other effects contrast that sums to zero
  - Effects specific to NIR only contributing to NIR (Sequence, Order, Location, Carryover), same for HPLC (Run)
  - Non-informative priors

- Example for HPLC part:

```
Y[i] <- meanHPLC*methodH[i] +
     betaG1*group1[i] + betaG2*group2[i] + betaG3*group3[i] +  betaG4*group4[i] -
     – (betaG1 + betaG2 + betaG3 + betaG4)*group5[i] +
     + betaR*run1[i] - betaR*run2[i] + ...
```

*run1[i] zero for all NIR observation

Results

Parameter	Mean	95% CI
Mean NIR	100.17	(99.60, 100.74)
Mean HPLC	99.81	(99.26, 100.37)
Mean NIR - HPLC	0.36	(0.01, 0.71)
Mean NIR Left	99.27	(98.57, 99.97)
Mean NIR Centre	100.10	(99.40, 100.80)
Mean NIR Right	101.14	(100.44, 101.84)
Carryover effect Left	0.00	(-0.47, 0.46)
Carryover effect Centre	-0.07	(-0.53, 0.39)
Carryover effect Right	0.07	(-0.39, 0.54)

Parameter	Median	95% CI
Tablet effect SD	1.35	(0.99, 1.91)
Residual SD NIR	1.41	(1.20, 1.67)
Residual SD HPLC	0.62	(0.08, 1.07)

- In line with previous output due to small carryover
- There seem to be only small (if any) carryover effect

Equivalence of NIR and HPLC

Bayesian probability calculation

Modelling goals

4. Comparison of HPLC and NIR method

- How to address it appropriately?
- Usual approach: focus on comparison of method mean
- Our proposal: move from mean evaluation towards individual tablet statement
- Probabilistic equivalence statement relative to closeness to true value (Manola et al)

Individual level equivalence

- Bayesian approach to the assessment of an individual analytical determination falling within a prespecified limit of the true value for comparing NIR vs HPLC

- Equivalence framework at individual level
- Clinical analogy:
  - Prescribability: can we replace A with B in population?
  - Switchability: can individual patient switch safely from A to B?

- Our case: can NIR replace HPLC for single tablet analysis

- Relative Performance Index

Relative performance index

- HPLC assumed as the gold standard method
- Probability of a single analytical determination *y* from HPLC (or NIR) falling within some interval Δ of the true value μ:

$$P_H = P(|y-\mu| \le \Delta | HPLC) = \phi\left(\frac{\Delta}{\sigma_{HPLC}}\right) - \phi\left(\frac{-\Delta}{\sigma_{HPLC}}\right)$$

$$P_N = P(|y-\mu| \le \Delta | NIR) = \phi\left(\frac{\Delta - \text{bias}}{\sigma_{NIR}}\right) - \phi\left(\frac{-\Delta - \text{bias}}{\sigma_{NIR}}\right)$$

- $\phi(.)$ = distribution function of standard normal distribution

- Relative Performance Index is defined as follows:

$$RPI = \frac{P_N}{P_H}$$

Interpretation

- RPI = 1 probability to be closer than Δ to true value is for comparable HPLC and NIR
- RPI < 1 probability to be closer than Δ to true value is higher for HPLC than NIR
- RPI > 1 probability to be closer than Δ to true value is lower for HPLC and NIR

Results: mean parameters

Parameter	Mean	95% CI
Mean NIR - HPLC	0.36	(0.00, 0.71)

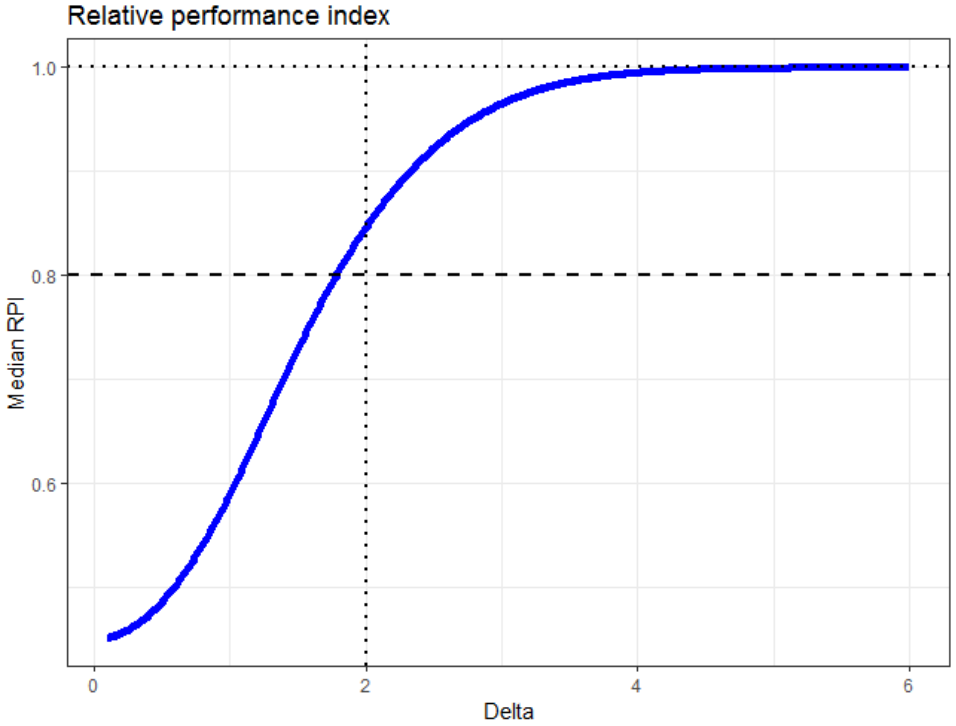
Parameter	Median	95% CI
Tablet effect SD	1.35	(0.98, 1.88)
Residual SD NIR	1.37	(1.18, 1.60)
Residual SD HPLC	0.65	(0.28, 1.11)

- Based on model without carryover effects
- Bayesian model retained to calculate the probabilities

- NIR has bias -> but still can be “better” than HPLC (RPI > 1) if SD of NIR is lower
- Not our case => RPI < 1

RPI results

- If “close” is defined based on criterion Δ = 2%, RPI > 0.8
- The probability of NIR to be “close” to true value is 80% of the probability of HPLC to be “close”
- Is that sufficient for replacement of HPLC by NIR?
- Depends on context, product, generally on scientific evaluation



Conclusion

Summary

- Concise modelling framework to answer all our initial questions
- Enabled by complex design that allowed us to investigate various effects
- Enabled by flawless conduct of the design
- Bayesian approach utilized to obtain individual level probabilities

Key benefits:

- Clear comparison of method means
- Tablet to tablet variability free of analytical error
- Carryover effects investigated
- RPI allows to asses individual level equivalence of the methods

- Note on presented results: Not a real data, only simulation!

Follow-up questions beyond statistics

- No power calculations for this setting => exploratory to generate hypotheses

- The design has taken away lot of sources of possible location differences. Are there any other that we may have missed (e.g. equipment specific, sample handling, etc.)

- In general, if any difference between method is observed in NIR and HPLC (both in terms of bias and variability, what is generalizability of such finding?
- Do we expect the methods to perform differently based on particular equipment, product class (shape), product?
- Cross-industry discussion may be useful

References

- Manola, A. et al: A probability based equivalence test of NIR vs HPLC analytical methods in a Continuous Manufacturing process validation study (in print), in *Pharmaceutical Statistics: MBSW 39, Muncie, Indiana, USA, May 16-18, 2016*. Editors: Liu R. & Tsong Y. Springer Proceedings in Mathematics & Statistics. Springer

- Williams, E. J. (1949): *Experimental designs balanced for the estimation of residual effects of treatments*. Australian Journal of Scientific Research, Ser. A 2, 149-168.

Thank you

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04/10/2018

Appendix

Williams Crossover Design Construction

- Let v = 2m and consider the 0^{th} column of the Latin square as 0, 1, 2m–1, 2, 2m – 2, …, m-1, m+1, m. The i^{th} column is constructed by adding i to each new member of 0^{th} column in the modular algebra 2m for i=1, 2, …, 2m-1, to construct the latin square. For v = 6, this latin square is

0	0+1=1	0+2=2	0+3=3	0+4=4	0+5=5
1	1+1=2	1+2=3	1+3=4	1+4=5	1+5=0
5	5+1=0	5+2=1	5+3=2	5+4=3	5+5=4
2	2+1=3	2+2=4	2+3=5	2+4=0	2+5=1
4	4+1=5	4+2=0	4+3=1	4+4=2	4+5=3
3	3+1=4	3+2=5	3+3=0	3+7=1	3+5=2

- When v is odd, it's possible to construct a Williams design with 2 latin squares where every ordered pair occurs twice in consecutive rows.

Mixed Effects Model

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- $y_{k(i),jlmpr}$ = response of the k^{th} tablet within the i^{th} group tested in r^{th} HPLC run with m^{th} sequence at l^{th} location as p^{th} measurement with j^{th} analytical method
- G_i = i^{th} Group effect (1=1,2,…,5)
- H_r = fixed effect of r^{th} HPLC run (r=1,2)
- $\tau_{k(i)}$ = random effect of k^{th} tablet within i^{th} Group: N(0, σ_τ^2),
- $S_{m(j)}$ = fixed effect of m^{th} Sequence (m=1,…,6)
- $L_{l(j)}$ = fixed effect of l^{th} location effect,
- M_j = fixed effect of j^{th} Method effect,
- $\varepsilon_{k(i),jlmpr}$ = residual error: N(0, σ_{ej}^2).

Residual error refers to within tablet measurement variability

Source	df	Type III Expected MS
Group	4	$\sigma_\varepsilon^2 + \sigma_{Tablet}^2 + Q(group)$
Run	1	$\sigma_\varepsilon^2 + 2.4834\ \sigma_{Tablet}^2 + Q(Run)$
Tablet (Group*Run)	24	$\sigma_\varepsilon^2 + 4.1773\ \sigma_{Tablet}^2$
Ord(Method)	3	$\sigma_\varepsilon^2 + Q(Order(method))$
Sequence (Method)	5	$\sigma_\varepsilon^2 + Q(Sequence(method))$
Location (Method)	2	$\sigma_\varepsilon^2 + Q(location(methoth))$
Method	1	$\sigma_\varepsilon^2 + Q(Order,Sequence, location(meth),Meth)$
Residual	109	σ_ε^2


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