Jessica Riley, *Shells*
Artwork from Reflections Art in Health

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janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Outline

- Part 1 Weibull Model (restricted to IR formulations)
  - Advantages/Disadvantages of profile modeling
  - Proposed paradigm for establishing criteria during product development
  - Case study
- Part 2 Application of Statistical Designs to dissolution experiments
  - Latin square design
  - Incomplete Block Design
- Summary
- References

Part 1 Pros/Cons of Profile modeling

Advantages

- Flexible hierarchical model to represent known sources of variability
  - Batch, Tablet, Analytical
- Allows estimation of non-observed time points
  - Permits assessment of time change or criterion, Q, for USP/NF dissolution testing
- Parameters related to rate and extent of dissolution in a first order process
- Permits a concise comparison in relation to parameters of the model which have a natural interpretation

Disadvantages

- Some complexity, modeling may require special statistical tools for predictive calculations
- Practicality of 3 parameters, when is a 4^{th} necessary
- No optimal design considerations carried out in practice
- Early part of the time dependent profile frequently not well characterized

Weibull Model

- $\left(Y_{tj}|t,\theta_1,\theta_2,\theta_3\right)=\theta_1*\left[1-e^{-\left(\frac{t}{\theta_2}\right)^{\theta_3}}\right]+\varepsilon_{tj}$ i,j indexes tablet and time
  - θ_1 - dissolution extent parameter
  - θ_2 - time to achieve 62.5%, a rate parameter
  - θ_3 - shape parameter
- Can rewrite to shift the rate parameter to a desired γ*100%
  - let $\tau=ln\left(\frac{1}{1-\gamma}\right)$, $0<\gamma<1$, then $\left(Y_{tj}|t,\theta_1,\theta_2,\theta_3,\tau\right)=\theta_1*\left[1-e^{-\tau\left(\frac{t}{\theta_2}\right)^{\theta_3}}\right]+\varepsilon_{tj}$

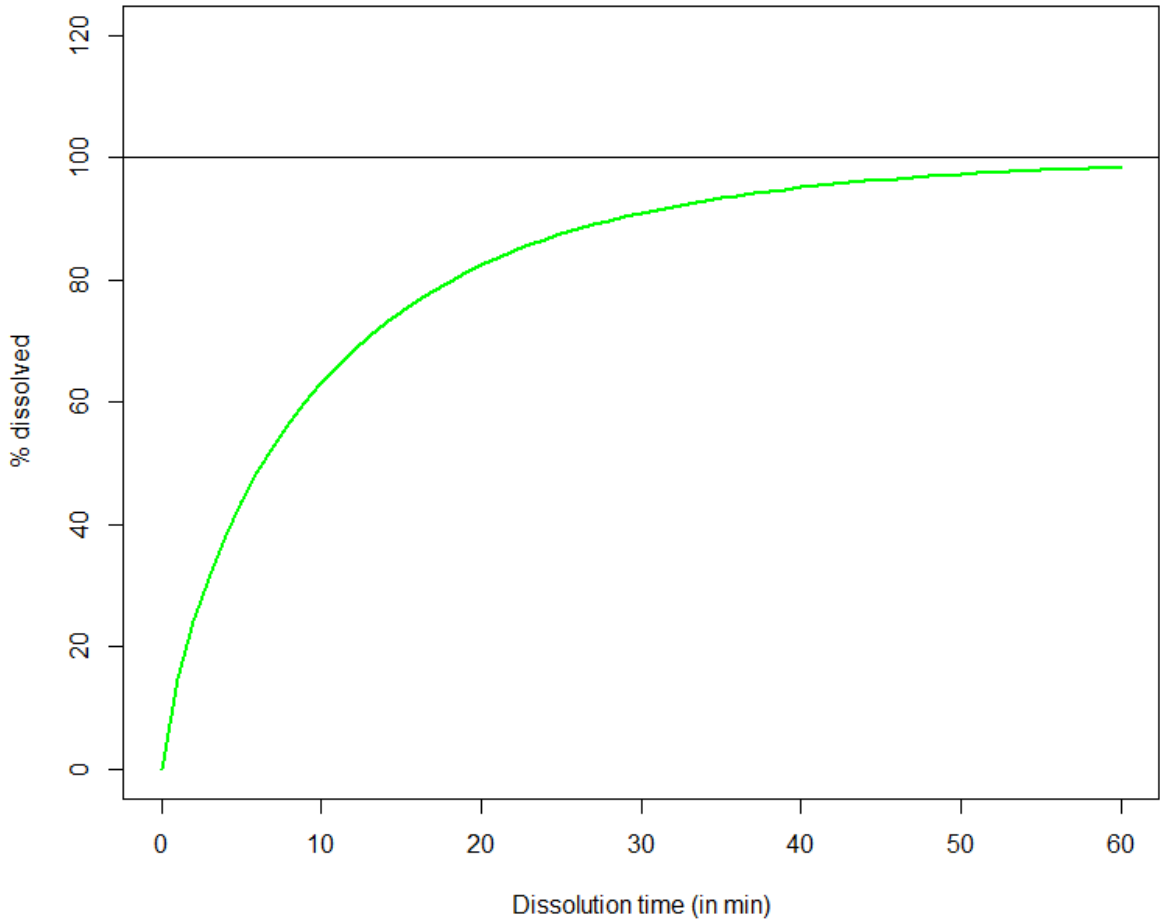
- For computational purposes, it is sometimes easier to fit the following reparameterized form:

  $\left(Y_{tj}|t,\theta_1,\theta_2^*,\theta_3^*\right)=\theta_1*\left[1-e^{-e^{\theta_3^*(logt-\theta_2^*)}}\right]+\varepsilon_{tj}$

  and if we include the τ parameter, this can be rewritten as

  $\left(Y_{tj}|t,\theta_1,\theta_2^*,\theta_3^*,\tau\right)=\theta_1*\left[1-e^{-e^{\log\tau+\theta_3^*(logt-\theta_2^*)}}\right]+\varepsilon_{tj}$

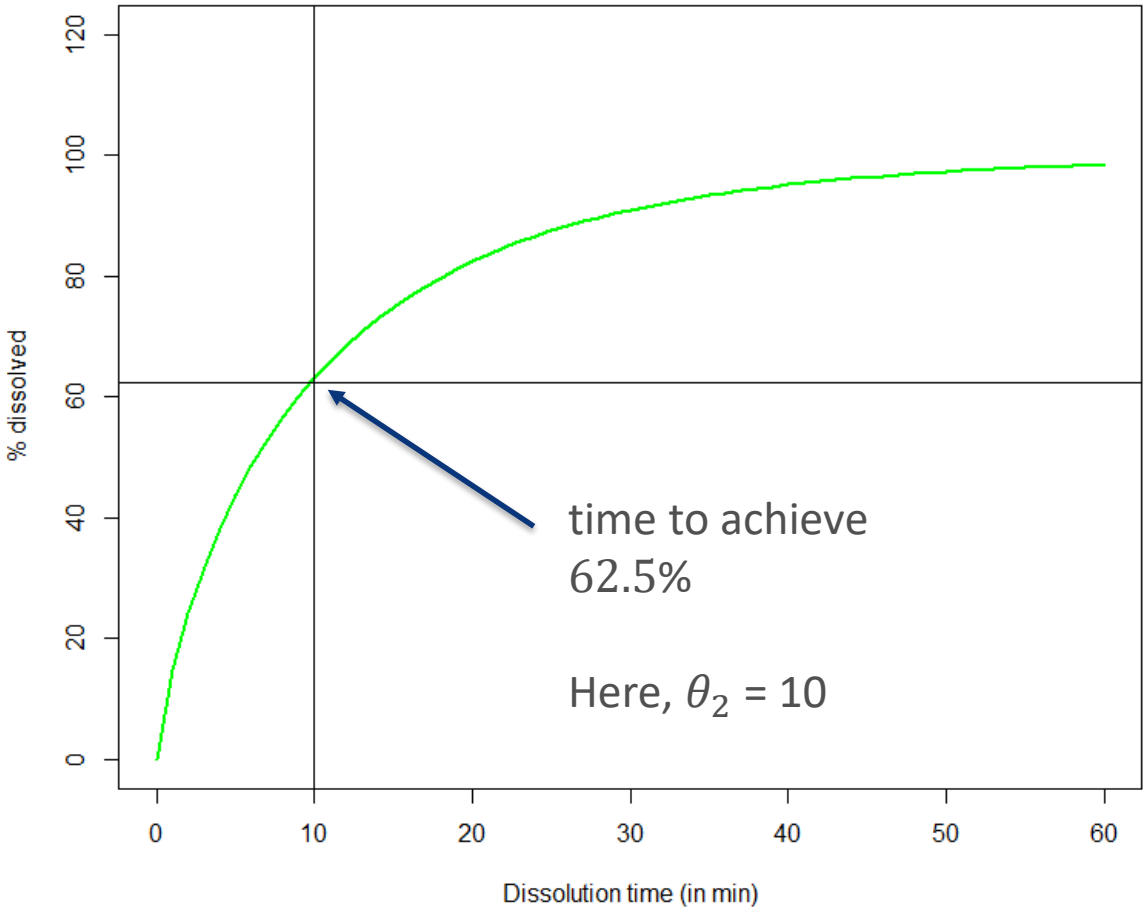
Weibull Model, interpretation of parameters:



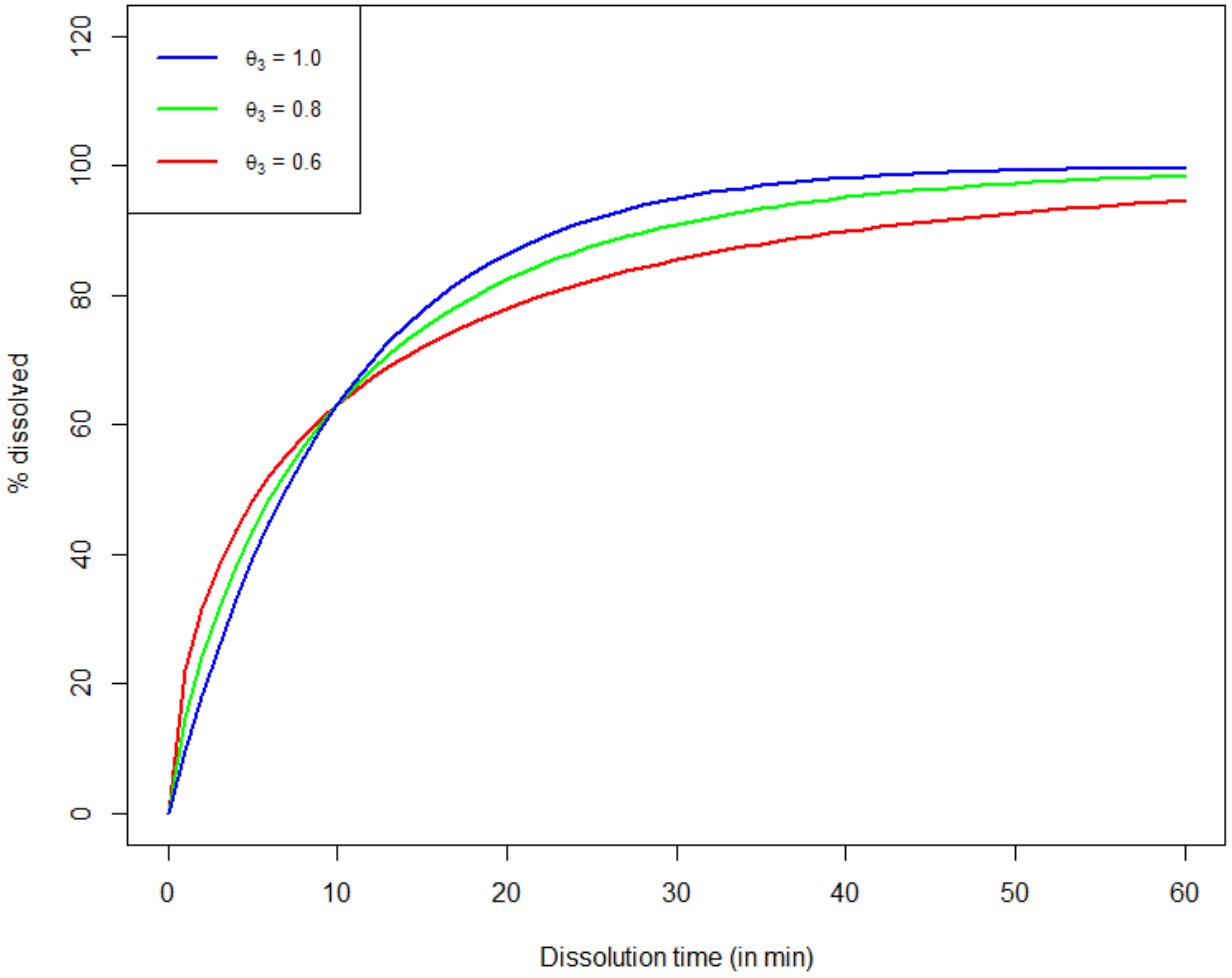
Dissolution extent parameter

Here, θ_1 = 100

Weibull Model, interpretation of parameters:



Weibull Model, interpretation of parameters:



Impact of different shape parameters

Here, θ_3 = {0.6, 0.8, 1.0}

A few normative requirements from 3 authors

- Tsong et al (1996) - A well-defined similarity limit of the pre change product is established before comparing the dissolution data of the test and reference batches. The similarity limit is set either by the knowledge of the characteristics of the product or by the empirical experience on the batch-to-batch and the within-batch difference of the existing reference product.
    - Global similarity
    - Local similarity
- Eaton et al. (2003) - A specified function of population parameters (not involving data or experimental design) should be used to define dissolution profile similarity.
- Leblond et al (2016) - The test for similarity should make clear the inference space for the conclusion. For instance, does the conclusion apply to the populations of test and reference batches or only to those batches providing data for the comparison.

Tsong et al (1997) Multipoint Dissolution Specification and acceptance sampling based on profile modeling

- Proposed a release testing strategy based on a nonlinear modeling approach
  - Example using the Weibull model
  - Multivariate confidence region on location and shape parameters
- Compares individual tablet Weibull fit parameter estimates with the multivariate confidence region for decision rule

Shen et al (2011) A Bayesian Approach to Equivalence Testing

- Proposed a Bayesian aproach to equivalence testing of dissolution profiles through a Nonlinear mixed effects model (3-parameter Weibull) with respect to a similarity factor g_2.
  - random batch component associated with the Upper Bound parameter
  - Similarity factor $g_2 = \frac{1}{p}\sum_{i=1}^{p}|d_i|, p = 4$.
  - Equivalence claimed between 2 processes if

$$\Pr(g_2 \leq \delta) \geq 0.95$$

  i.e. the equivalence criterion exceeds a predefined limit with a prespecified probability.
- Offers a statistically appropriate alternative to the f2 approach.

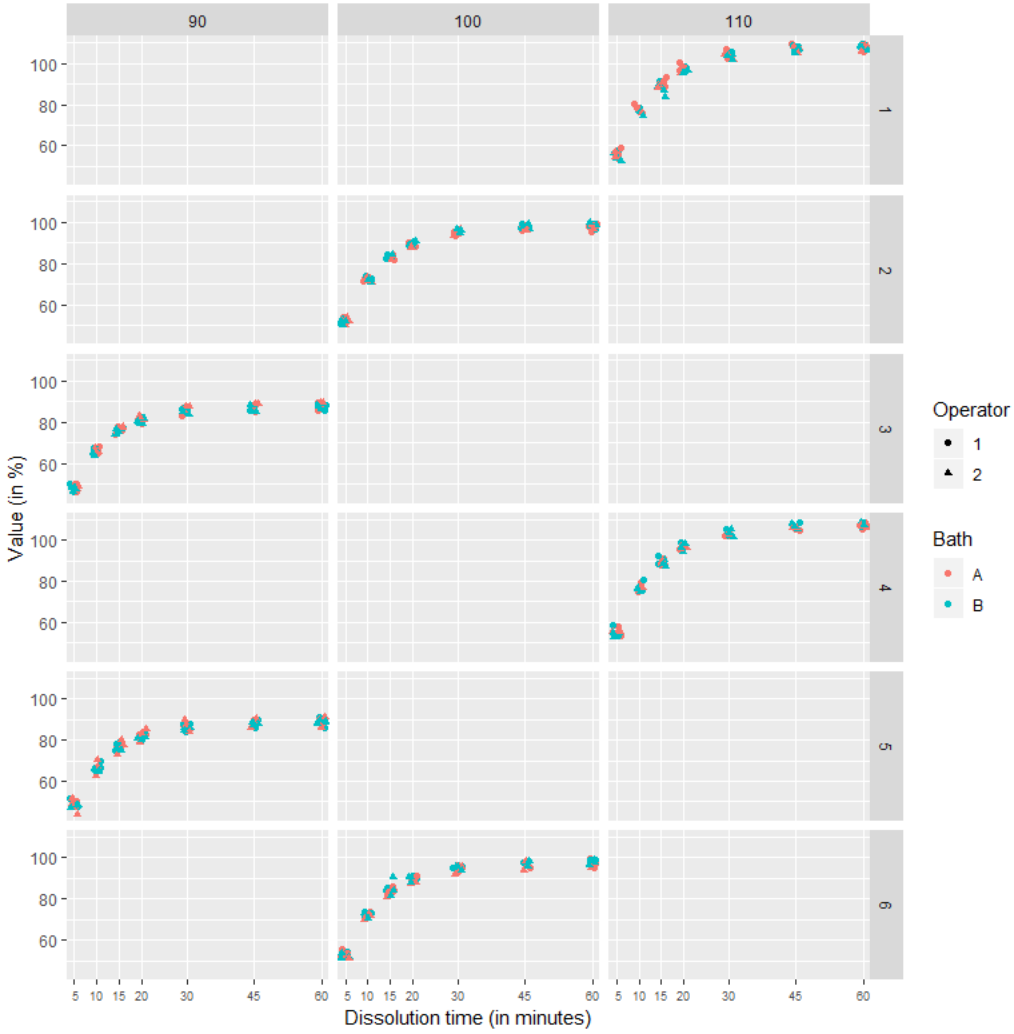
A paradigm for similarity testing

- Concept : Relate similarity criterion to a defined range of API concentrations (Goal posts)
  - Bioequivalence criterion is 80-125%
  - Content Uniformity internal limits is 90-110%
  - Therapeutic window
- Experimental Design recommendations
  - Manufacture batches at the goal posts and target
  - Include factors that impact dissolution, eg Particle Size, Compaction Force (dry blend process), Excipients
  - Use block designs to allocate batches to vessels to orthogonalize dissolution run, HPLC run and Batch effects
- Fit Weibull model to batch profiles, relate the parameters to regions representing similarity margins
- Future similarity tests whether at the process level or batch level must show a 90% CI fits within the limits

Case Study to illustrate the similarity testing paradigm

- Design
  - Concentrations 90, 100, 110% reflecting the range of allowable differences between batches
  - 2 batches at each concentration
  - Early experiments found MgStearate, Particle Size and other process parameters had negligible effect on dissolution

Study carried out - Plot of data



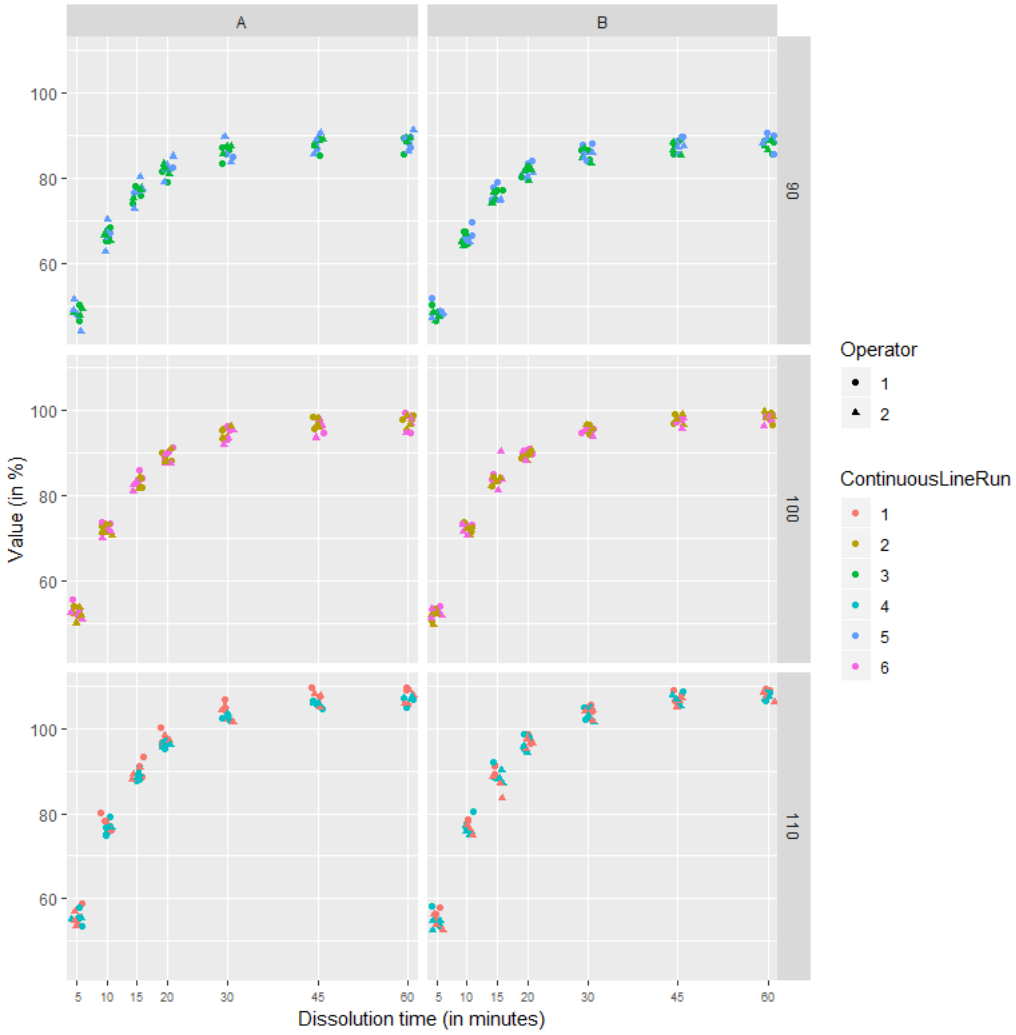
For each batch:

Bath	Operator	N
A	1	21
	2	21
B	1	21
	2	21

Total of 6 (vessels) * 7 (time points) = 42 vessels per run

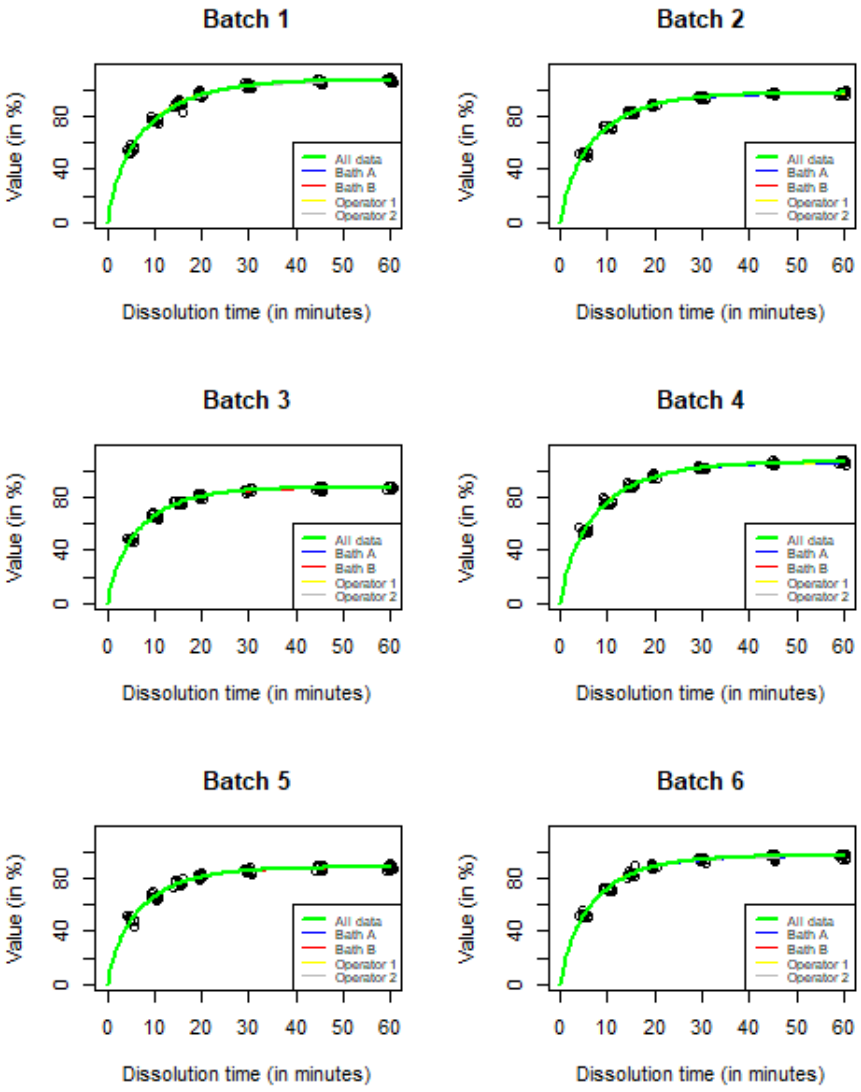
2 runs per batch, i.e., *N* = 84

Exploratory plot



- At 60 min, slightly below the nominal %API level
- B**ath and Operator** have little effect
- **Similar variability** for all dissolution time points across batches
- Some slightly deviating observations, but no ‘outliers’
- Fit Bayesian **fixed-effects three-parameter Weibull models** to the data of **each batch separately**:

Weibull fits for 6 batches



Batch-specific estimated Weibull parameters (fixed-effects models, means of posteriors):

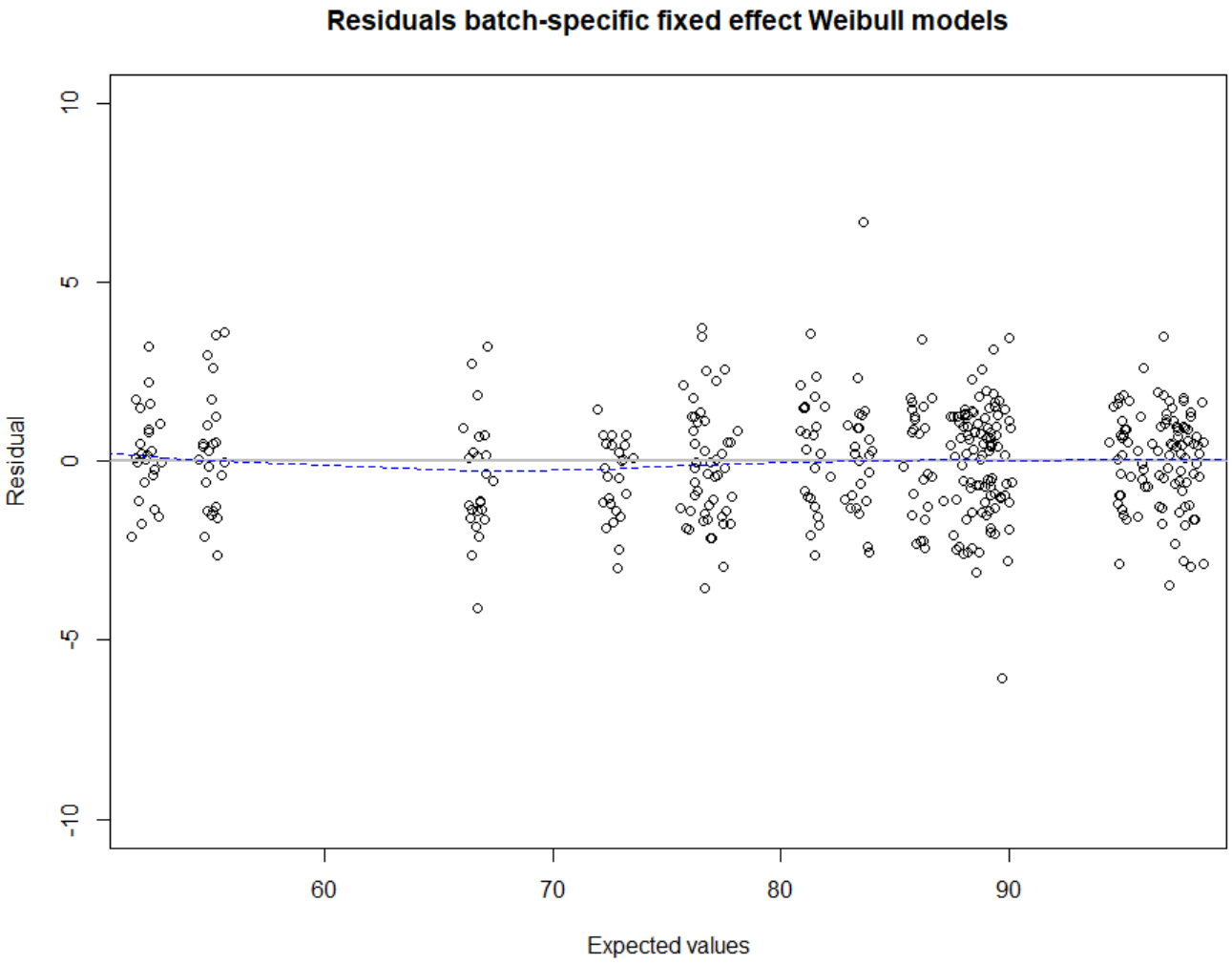
Batch	%API	UB	lambda	k
1	110	108.60	7.58	0.82
2	100	98.53	7.09	0.83
3	90	88.30	6.69	0.84
4	110	107.64	7.56	0.82
5	90	88.93	6.69	0.84
6	100	97.92	6.86	0.84

UB parameter differs substantially by %API. Also within a given %API, there is some batch-to-batch variability. Extent

lambda parameter differs quite substantially by %API. Within a given %API, there is very limited batch-to-batch variability. Rate

k parameter **very similar** for different %API

Plot of residuals all 6 batches combined:



Homoscedasticity assumption is **plausible**

Exploratory analysis main conclusions

1. **Dissolution profiles are well characterized by the** Weibull model - **fits are very close to the empirical data**
2. Model **parameters**
   1. UB parameter differs by %API. Batch-Batch variability apparent
   2. lambda parameter differs by %API, Batch-Batch variability small
   3. k parametery similar %API: common k-parameter
3. **Homoscedasticity** assumption reasonable

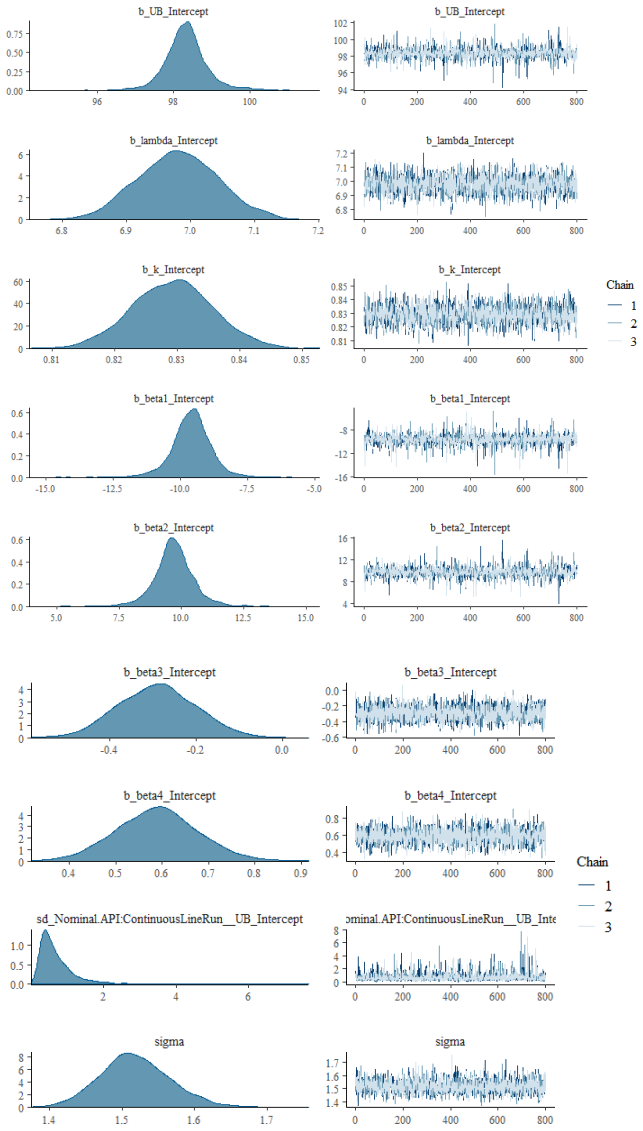
Modelling strategy

- fit **mixed-effects Weibull** with:
- **Fixed-effect** structure: %API-specific UB, %API-specific Lambda parameter, common k parameter
- **Random-effects** structure: random batch effect for UB nested within %API.
- **Residuals**: homoscedasticity assumed

Nonlinear mixed effects hierarchical three-parameter Weibull model: Prior distributions

- Weakly Informative Priors driven by exploratory fixed model
  - $UB_{\%API} \sim N(100, 5)$,
  - $\lambda \sim N(7, 5)$,
  - $\mathrm{k} \sim N(0.83, 5)$,
  - $\beta_1, \beta_2 \sim N(\pm 10, 5)$, β_3, $\beta_4 \sim N(0, 5)$
  - $\varepsilon_{ij}, \gamma_{i(d)} \sim half\ t(3, \mathrm{scale} = 15)$

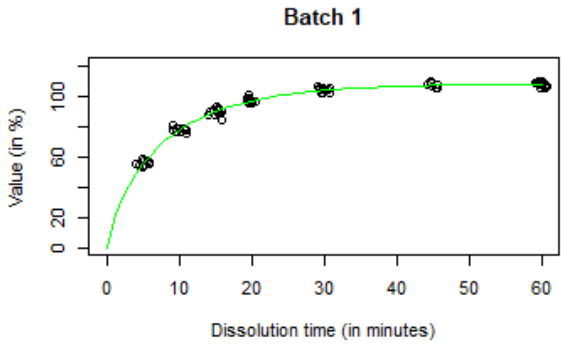
Fitted model Posterior Distributions

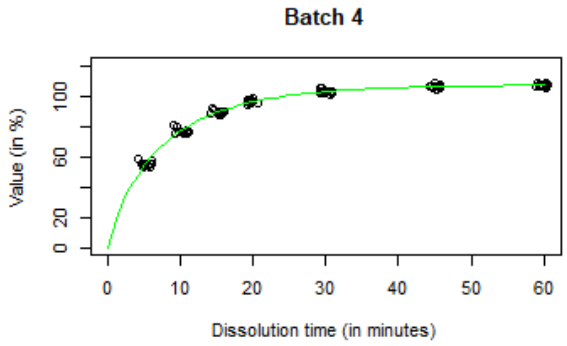


Parameter	Median	95% lower CI	95% upper CI
$UB_{\%API=100}$	98.327	97.150	99.746
Lambda (%API = 100)	6.980	6.861	7.105
K	0.829	0.816	0.842
β_1	-9.602	-11.374	-7.951
β_2	9.689	7.894	11.464
β_3	-0.289	-0.464	-0.111
β_4	0.590	0.419	0.767

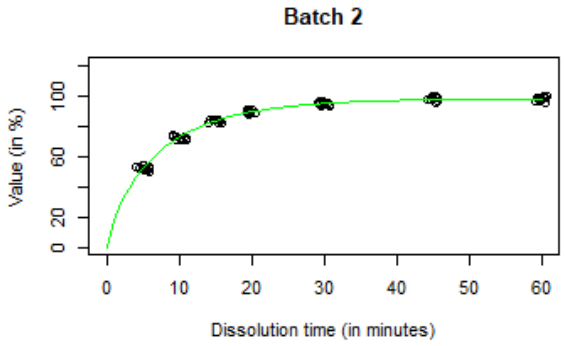
Parameter	5% PC	50% PC	95% PC
SD batch nested %API	0.227	0.578	1.809
SD residual	1.442	1.516	1.604

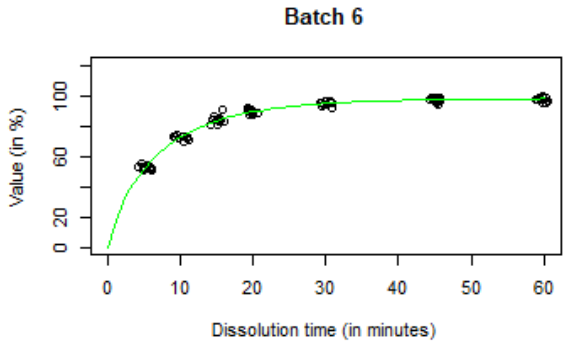
Fitted models, batch-specific predictions



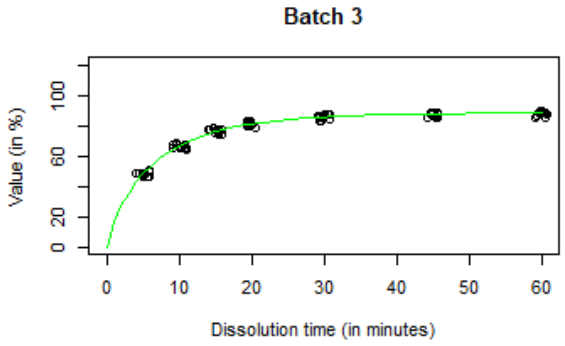


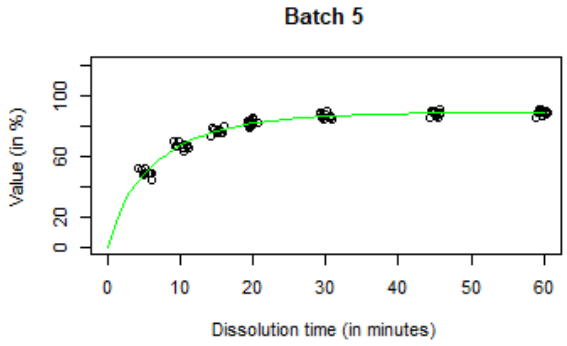
110% API





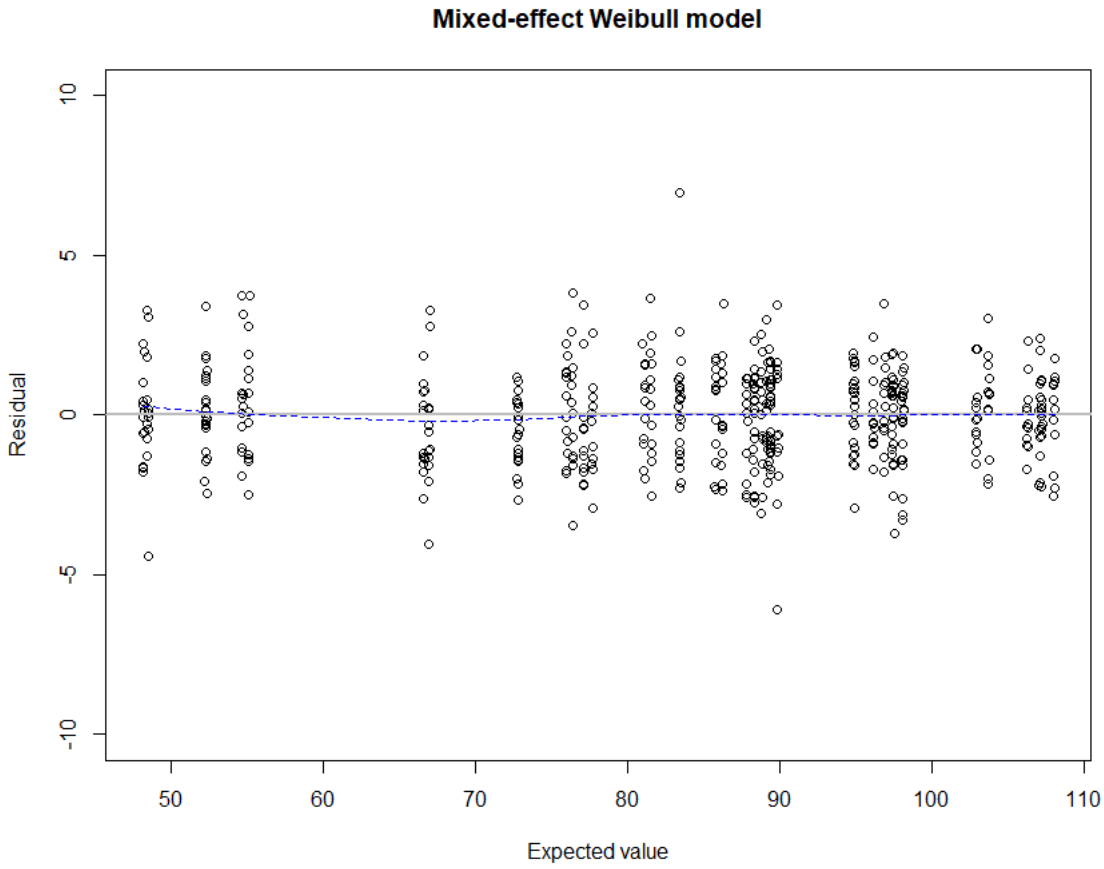
100% API





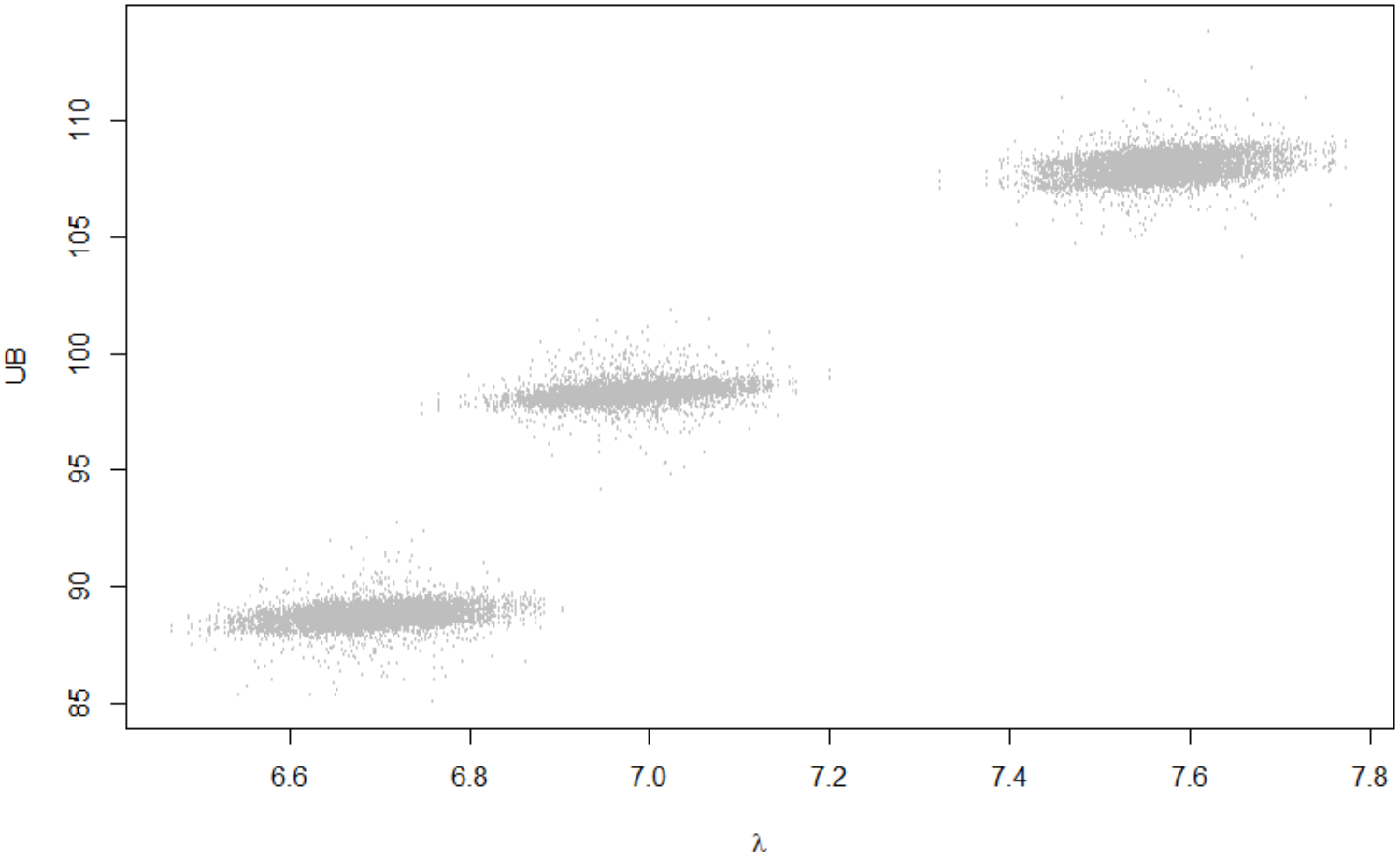
90% API

Residual plot



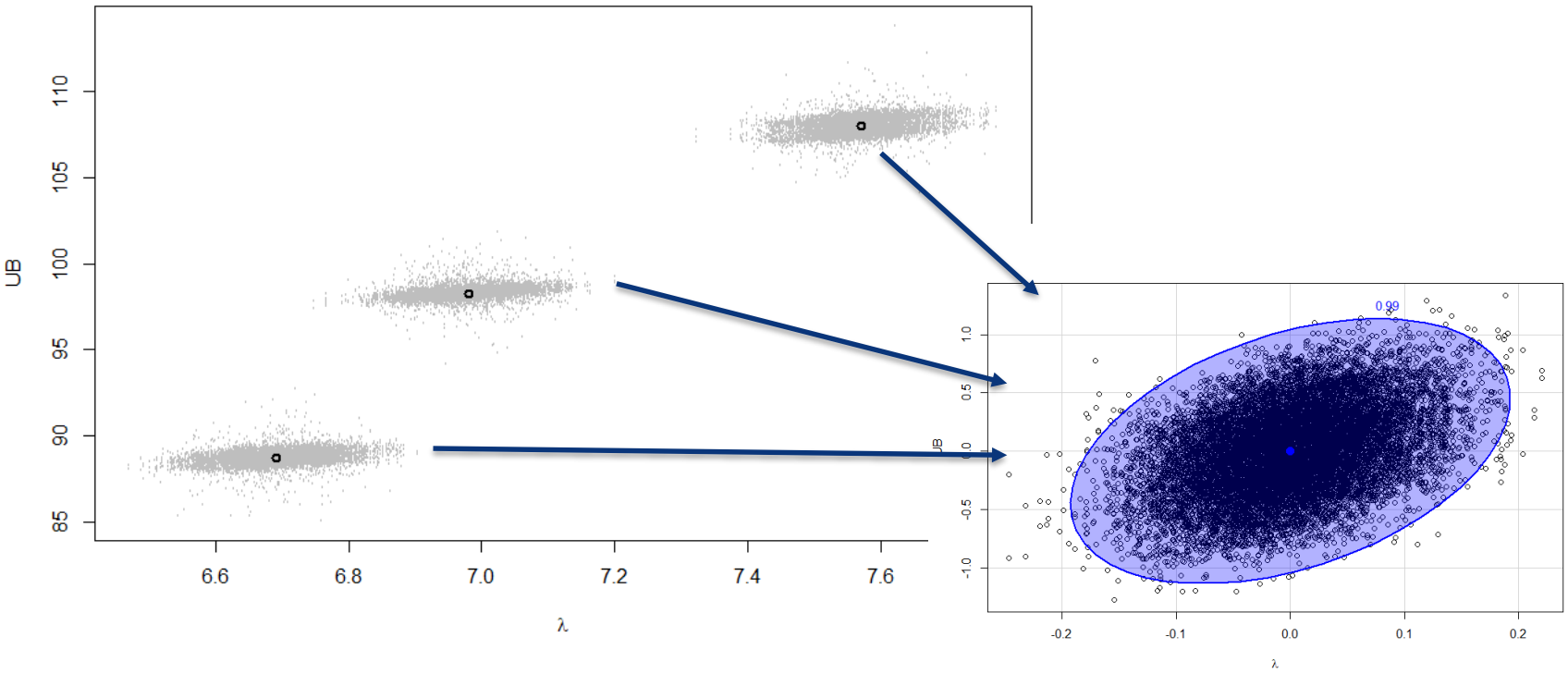
Homoscedasticity assumption is **plausible**

Scatterplot posterior samples



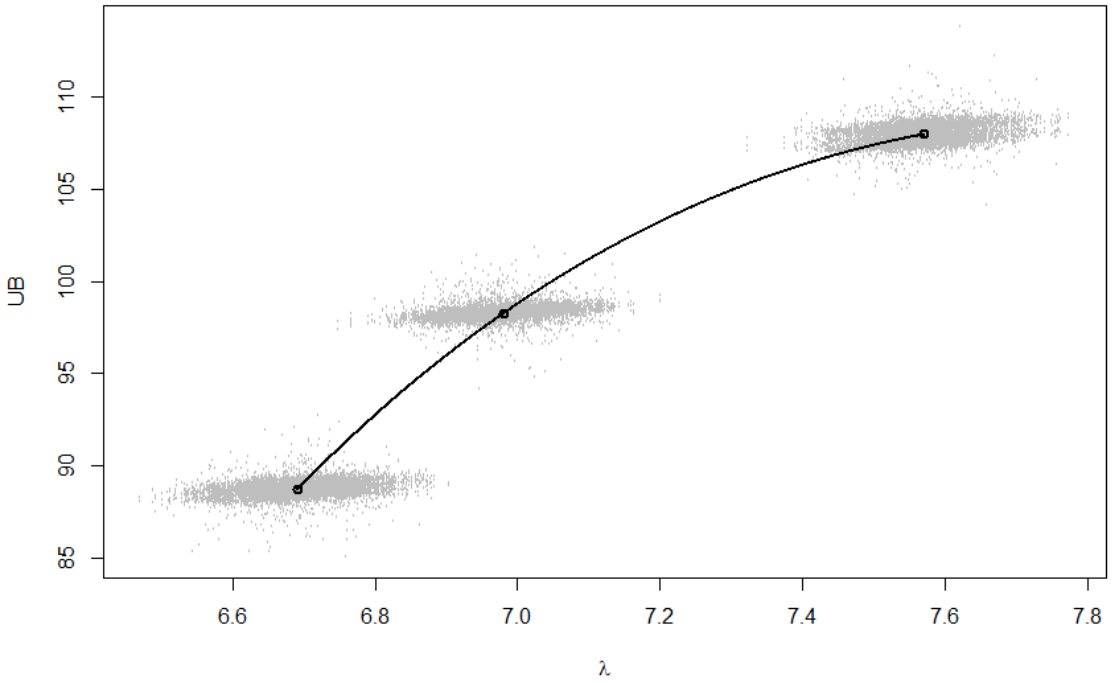
Defining the region of similarity

Center the posterior samples (around the %API-specific center points) and determine an **'overall' 99% prediction ellipse** (based on all 6 batches):



Defining the region of similarity

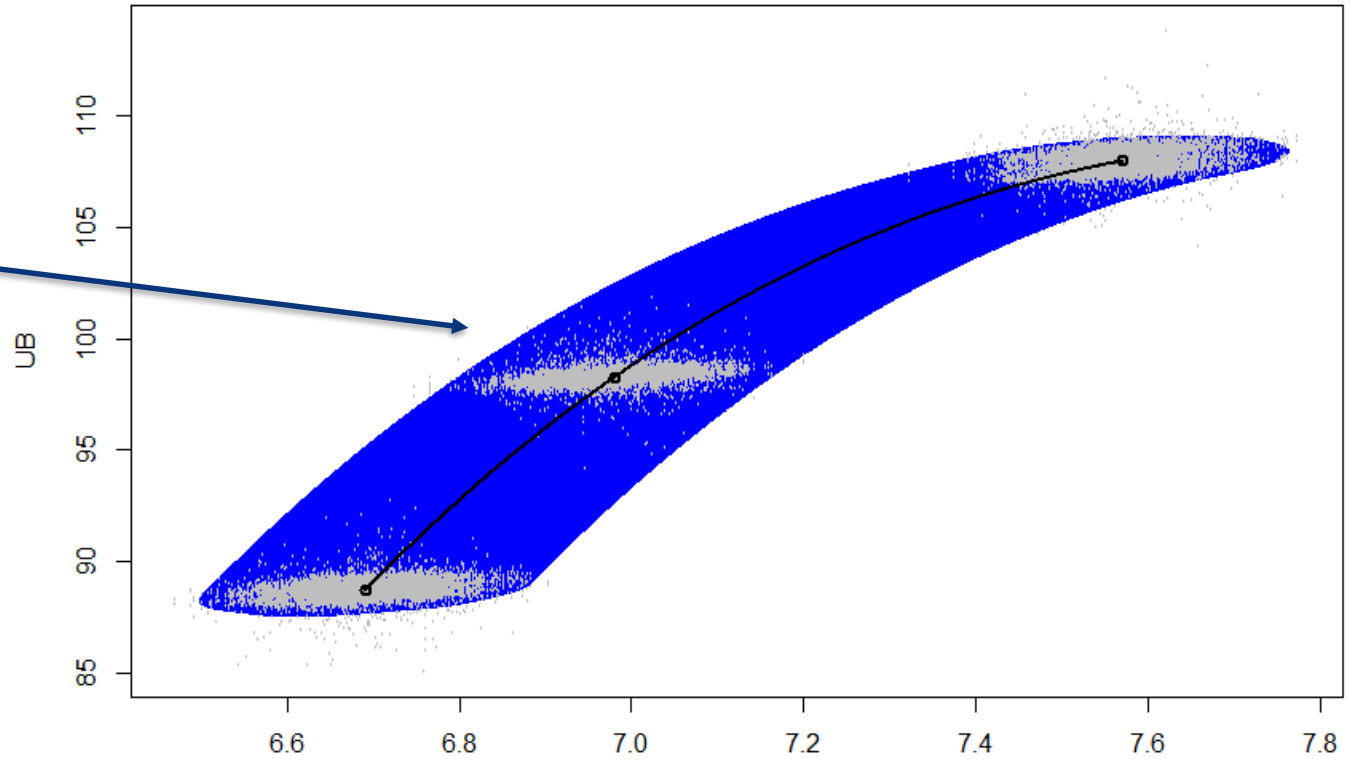
- Model the relation between the %API-specific center points (λ, UB) using a **fractional polynomial of order 2**



Defining the region of similarity

Assume the **same prediction ellipse** (that was determined earlier) across the entire prediction line.

Refer to this Simllarity Region as R_A



Future tests for Similarity

- Define the inference space – batch, process
- Design study
  - Number of batches
  - Number of tablets
  - Time points to be sampled
- Collect data following a clear dissolution experiment design
- Fit Weibull model
  - Fixed effects or mixed effects
  - Summarize joint means (UB, λ) by process or batch
  - Calculate a 90% coverage elliptical region, say R_t
- If R_t is contained within the similarity region R_A, then similarity can be defended.

Part 2 Application of block designs to dissolution experiments

- Design Principles
  - Orthogonality (Balance)
  - Randomization
  - Interpretable variance components (Dissolution run, HPLC run, Residual error)

Ordinary Dissolution Study Design for 6 Batches (12 tablets/batch)

- Each dissolution run is associated with a single batch
- Groups of dissolution runs are associated with a HPLC run
- Sources of biases
  - HPLC run
  - Dissolution run
  - Vessel
- ➔ Batch effects are confounded with HPLC and dissolution run effects

Typical Dissolution Study Design 6 Batches									
Bath	HPLC Run	Disso Run	Operator	zVessel					
				1	2	3	4	5	6
A	1	1	1	R1	R1	R1	R1	R1	R1
	1	2	1	R2	R2	R2	R2	R2	R2
	2	3	1	R3	R3	R3	R3	R3	R3
	2	4	1	R4	R4	R4	R4	R4	R4
	3	5	1	R5	R5	R5	R5	R5	R5
	3	6	1	R6	R6	R6	R6	R6	R6
B	4	7	2	R1	R1	R1	R1	R1	R1
	4	8	2	R2	R2	R2	R2	R2	R2
	5	9	2	R3	R3	R3	R3	R3	R3
	5	10	2	R4	R4	R4	R4	R4	R4
	6	11	2	R5	R5	R5	R5	R5	R5
	6	12	2	R6	R6	R6	R6	R6	R6

Latin Square Design

- A *Latin Square* of order v is a square array of dimension v, consisting of v symbols, such that each symbol appears once in each row and column.
    - Treatments are assigned at random within rows and columns, with each treatment once per row and once per column.
    - There are equal numbers of rows, columns, and treatments.
- Useful where the experimenter desires to control variation in two different directions

Examples

Order v=3

2	3	1
3	1	2
1	2	3

Order v=4

a	b	d	C
b	c	a	D
c	d	b	A
d	a	C	B

Allocating Batches to Vessels

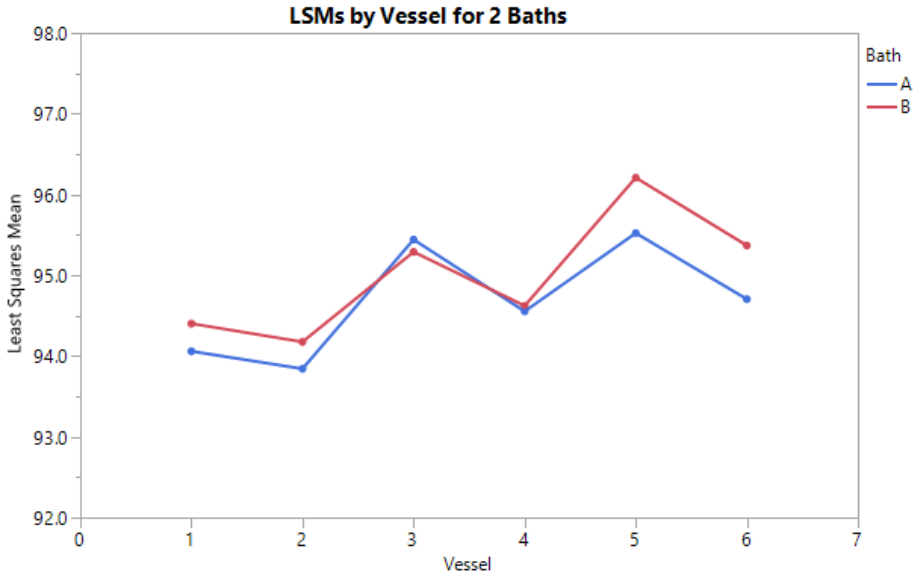
- Design objective
  - Orthogonalize vessel, dissolution run and HPLC run effects to provide an unambiguous estimate of Batch means
  - Bath and Operator can also be accommodated
- Limitation
  - Number of dissolution runs is restricted to 2xNumber of Batches assuming 12 vessels/batch
  - Consider number of baths, operators – some confounding is unavoidable, so interpret run effects accordingly

Latin Square Dissolution Design 6 batches

- Six batches manufactured
  - R1 – 110% of Target
  - R2 – 100%
  - R3 – 90%
  - R4 – 100%
  - R5 – 90%
  - R6 – 110%
- !2 tablets per batch sampled
- Balanced sequence of Batches to vessels for Baths A , B
- 12 dissolution runs with 6 HPLC runs
- Operator and HPLC run are confounded

Operator	Bath	Vessel						Apparatus	HPLC Run
		V1	V2	V3	V4	V5	V6		
1	A	R1	R2	R3	R4	R5	R6	A	1
	B	R2	R3	R4	R5	R6	R1	B	
	A	R3	R4	R5	R6	R1	R2	A	2
	B	R4	R5	R6	R1	R2	R3	B	
	A	R5	R6	R1	R2	R3	R4	A	3
	B	R6	R1	R2	R3	R4	R1	B	
2	B	R1	R2	R3	R4	R5	R6	B	4
	A	R2	R3	R4	R5	R6	R1	A	
	B	R3	R4	R5	R6	R1	R2	B	5
	A	R4	R5	R6	R1	R2	R3	A	
	B	R5	R6	R1	R2	R3	R4	B	6
	A	R6	R1	R2	R3	R4	R1	A	

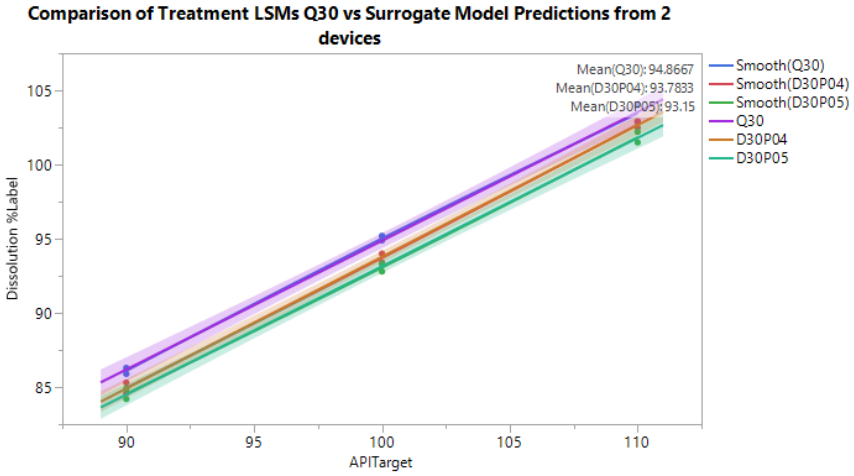
Vessel Least Squares Means



Least squares Means by Vessel (SE)		
	Bath	
Vessel	A	B
1	94.1 (0.6)	94.4 (0.6)
2	93.8 (0.6)	94.2 (0.6)
3	95.4 (0.6)	95.3 (0.6)
4	94.6 (0.6)	94.6 (0.6)
5	95.5 (0.6)	96.2 (0.6)
6	94.7 (0.6)	95.4 (0.6)

Batch Least Squares Means

Batch	API Target	Q30 LSM (SE)
R3	90	85.9 (0.3)
R5	90	86.3 (0.3)
R2	100	95.2 (0.3)
R6	100	94.9 (0.3)
R1	110	104.0 (0.3)
R4	110	102.9 (0.3)



Contrast	Q30 Estimate (SE)	P-value
Linear	8.71 (0.15)	<.001
Quadratic	-0.23 (0.26)	0.363

Variance Components		
Source	Estimate	% Total
HPLCRun	0.73	37%
Dissorun1(HPLCRun)	0	0
Batch(APITarget)	0.16	8%
Residual	1.10	55%

Incomplete Block Dissolution run Design for 8 and 12 batches

- Batch identifiers
  - R1, R2, …,RN (N=8, 12)
- 6 tablets per batch
- Balanced sequence of Batches to vessels
- HPLC runs must be chosen according to a group balance scheme
- Multiple Baths not considered but can be included

HPLC Run	Disso Run	V1	V2	V3	V4	V5	V6
1	**1**	R1	R3	R6	R8	R2	R5
	2	R4	R5	R2	R3	R1	R7
2	**3**	R5	R6	R3	R2	R4	R1
	4	R3	R7	R1	R6	R8	R4
3	**5**	R2	R1	R8	R7	R5	R6
	6	R7	R2	R5	R4	R3	R8
4	**7**	R6	R8	R4	R1	R7	R2
	8	R8	R4	R7	R5	R6	R3

HPLC Run	Disso Run	V1	V2	V3	V4	V5	V6
1	**1**	1	5	3	12	8	11
	2	12	4	10	9	11	7
2	**3**	4	10	9	3	1	5
	4	9	12	2	11	6	1
3	**5**	11	8	5	6	7	4
	6	10	3	8	7	12	2
4	**7**	2	1	7	4	5	12
	8	8	11	4	2	3	9
5	**9**	7	9	6	5	2	3
	10	6	2	1	8	4	10
6	**11**	5	6	12	10	9	8
	12	3	7	11	1	10	6

Latin Square Design Gage R&R Study

- Design Description
  - 4 Laboratories
  - 2 Analysts/Lab
  - 6 days/Analyst
  - Each analyst will carry out 1 dissolution run/day
  - Samples are assigned to 2 HPLC runs according to the design scheme
  - In total there will be 12 HPLC runs
- Permits unconfounded estimation of Repeatability and Intermediate Precision

Day	Diss Run	Oper	Bath	Vessel						HPLC Run
				1	2	3	4	5	6	
1	8	2	1	B	C	A	-	-	-	1
				-	-	-	B	A	C	2
	10	1	2	A	B	C	-	-	-	2
				-	-	-	A	C	B	1
2	1	1	2	A	B	C	-	-	-	4
				-	-	-	A	C	B	3
	9	2	1	C	A	B	-	-	-	3
				-	-	-	C	B	A	4
3	12	1	1	B	C	A	-	-	-	5
				-	-	-	B	A	C	6
	3	2	2	C	A	B	-	-	-	6
				-	-	-	C	B	A	5
4	6	2	2	B	C	A	-	-	-	8
				-	-	-	B	A	C	7
	4	1	1	A	B	C	-	-	-	7
				-	-	-	A	C	B	8
5	2	1	1	B	C	A	-	-	-	9
				-	-	-	B	A	C	10
	5	2	2	C	A	B	-	-	-	10
				-	-	-	C	B	A	9
6	7	2	1	A	B	C	-	-	-	12
				-	-	-	A	C	B	11
	11	1	2	C	A	B	-	-	-	11
				-	-	-	C	B	A	12

Summary

- Weibull modeling of dissolution profiles is a valuable tool.
- Profile comparisons using the Weibull model is a practical approach, and the proposed similarity test paradigm can be developed through considerations related to therapeutic window, product performance and bioequivalence rules as shown in the example case study.
  - Criterion can be proposed during product development, perhaps as a company developed voluntary standard
- Latin square and incomplete block designs permit elimination of variability in 2 directions , leading to estimates of relative contributions of dissolution run, HPLC run and Batch effects free of confounding.
  - Variance components analysis showed more than half of the total variability was attributable to residual error (mainly comprised of dosage unit variability and analytical uncertainty)

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Hierarchical model. %API-specific UB and lambda, random batch effect for UB

- **Nonlinear mixed effects** t**hree-parameter Weibull model**:

$$Y_{tji(d)} = (UB_{\%API} + \beta_1 D_1 + \beta_2 D_2 + \gamma_{i(d)}) - (UB_{\%API} + \beta_1 D_1 + \beta_2 D_2 + \gamma_{i(d)}) * e^{-\left(\frac{disso.time_t}{\lambda + \beta_3 D_1 + \beta_4 D_2}\right)^k} + \varepsilon_{tji(d)},$$

where

$Y_{tji(d)}$ = the observed IVR value for vessel *j* (= 1, 2, …, 6) at dissolution time point *t* (= 5 , 10, … , 60 min) for batch *i* (=1, 2) in %API *d (*=90, 100, 110*)*

$UB_{\%API}$ = the **upper bound** parameter for dose %API = 100%,

D_1, D_2 = **dummy variables for %API**, D_1 = 1 if %API = 90% and 0 otherwise, and D_2 = 1 if %API = 110% and 0 otherwise,

λ = the fixed **location** effect parameter,

$\gamma_{i(d)}$ = random effect for UB parameter, nested within %API,

k = fixed **shape** effect parameter,

$\varepsilon_{tji(d)}$ = the residual error for vessel *j* at dissolution time point *t* for batch *i* in %API dose d

Statistical Model for Gage R&R STudy

$$y_{ijklm} = \mu + B_i + V_{j(k)} + \alpha_l + \beta_{m(l)} + \gamma_{il} + \varepsilon_{ijklm}$$

y_{ijklm} = dissolution value measured from the *i-th* batch with *j-th* vessel in *k-th* lab for the *l-th* analyst at the *m-th* run,

μ = overall mean,

B_i = fixed effect due to *i-th* batch,

$V_{j(k)}$ = fixed effect due to *j-th* vessel in *k-th* lab,

α_l = random effect due to *l-th* analyst: $\alpha_l \sim N(0, \sigma_\alpha^2)$

$\beta_{m(l)}$ = random effect due to *m-th* run within *l-th* analyst: $\beta_{m(l)} \sim N(0, \sigma_\beta^2)$

γ_{il} = random effect due to the interaction of *i-th* batch and *l-th* analyst: $\gamma_{il} \sim N(0, \sigma_\gamma^2)$

ε_{ijklm} = residual errors: $\varepsilon_{ijklm} \sim N(0, \sigma_e^2)$

$$\textbf{\textit{Reproducibility}} = \sqrt{\sigma_\alpha^2 + \sigma_\beta^2 + \sigma_\gamma^2} \quad \text{and} \quad \textbf{\textit{Repeatability}} = \sqrt{\sigma_e^2}$$