

Calibrating dissolution surrogate model via conditioning for real time release testing of drug product

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Discovery and Manufacturing Statistics
23/09/2026
NCS2026, Padova

Dissolution

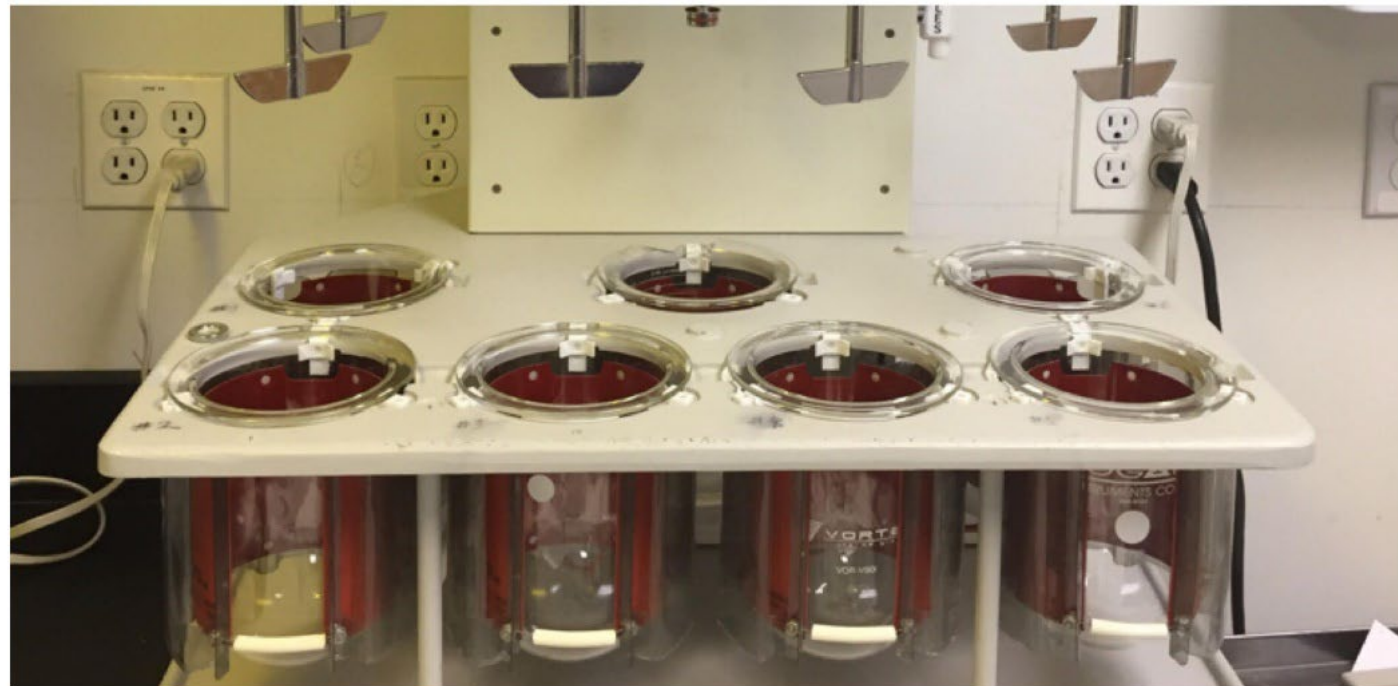
Dissolution in laboratory

Gold standard with “challenges”

Very slow method

Solvents required

Large run-to-run variability



Dissolution profile

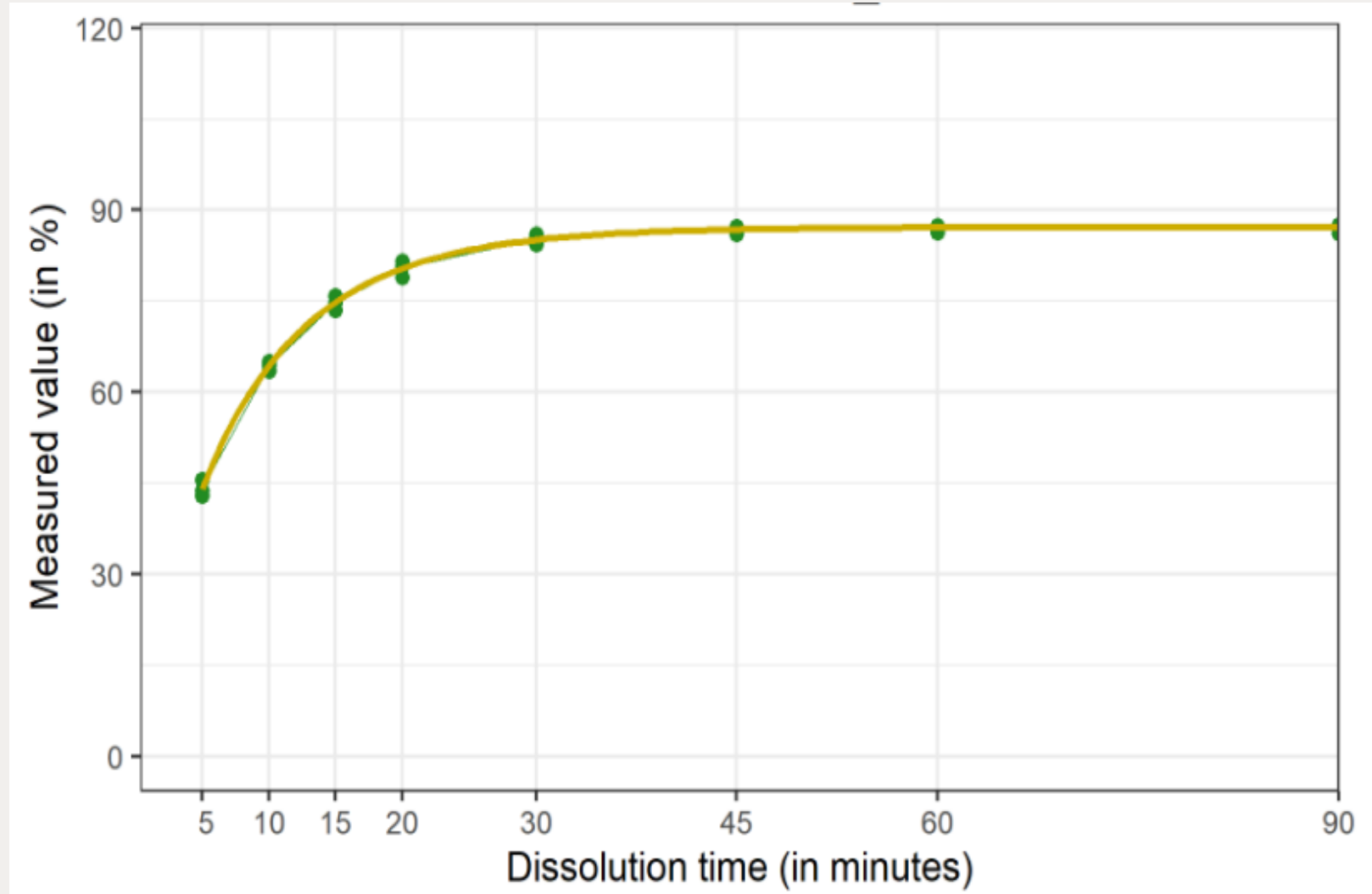
Collected data

Properties

Infinite dissolution

Dissolution shape

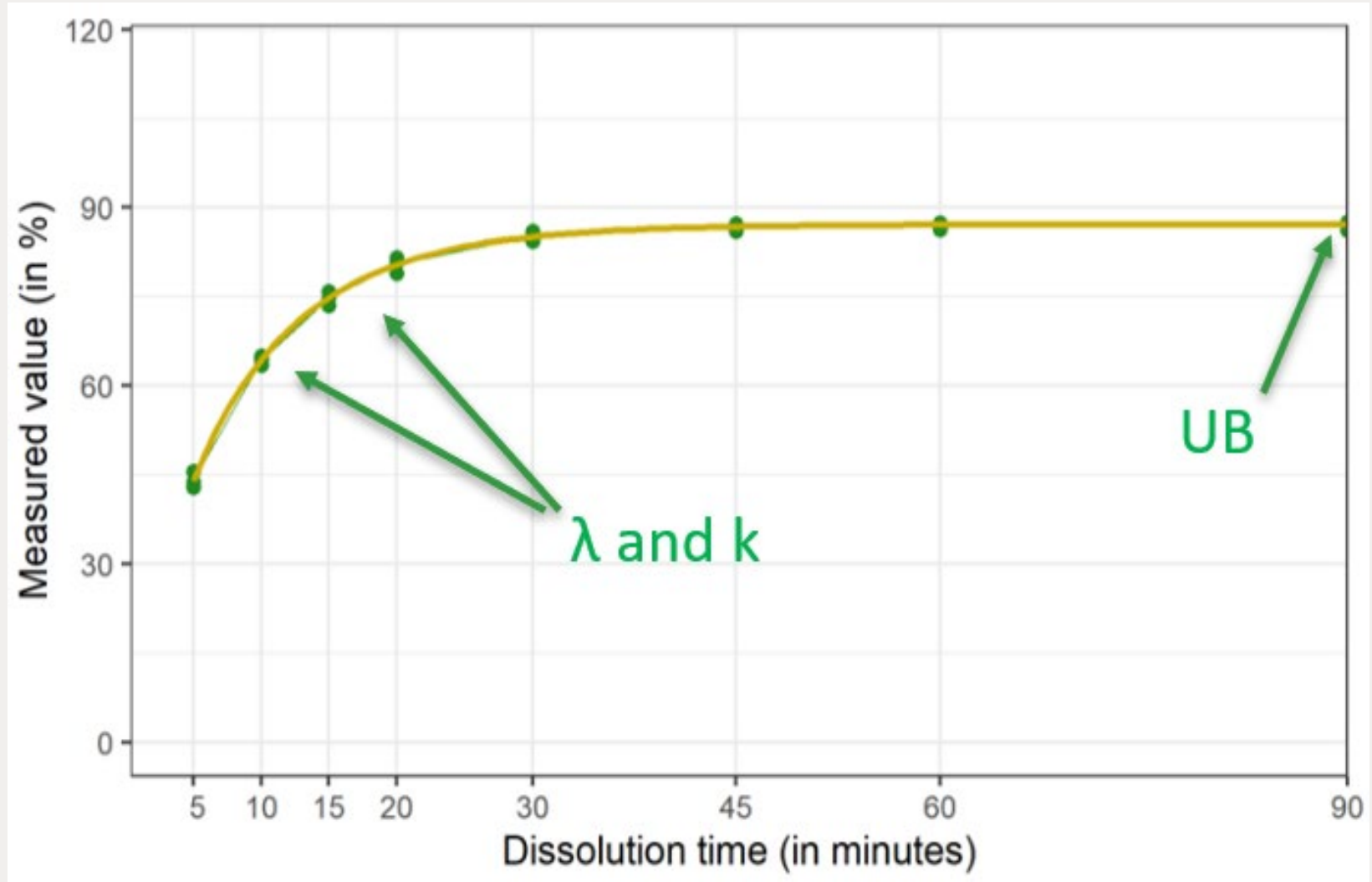
Relevant timepoints



Weibull model

Model

$$\begin{aligned} \text{Disso} = & \\ & UB - UB * e^{-\left(\frac{\text{dissoTime}}{\lambda}\right)^k} + \\ & \text{error} \end{aligned}$$



What influences dissolution?

Dumarey, M., Carducci, T.M., Walworth, M.J. *et al.* **Dissolution of Oral Solid Dosage Formulations: Surrogate Models and Real-time Release.** *AAPS J* **27**, 115 (2025).
<https://doi.org/10.1208/s12248-025-01102-0>

Batch level properties

Drug substance parameters (e.g. Granule Particle size distribution)

Process parameters (CQAs, CPPs setpoints or average measurements)

Tablet level properties

DS Content via PAT

Some IPCs (tablet weight, hardness, thickness)

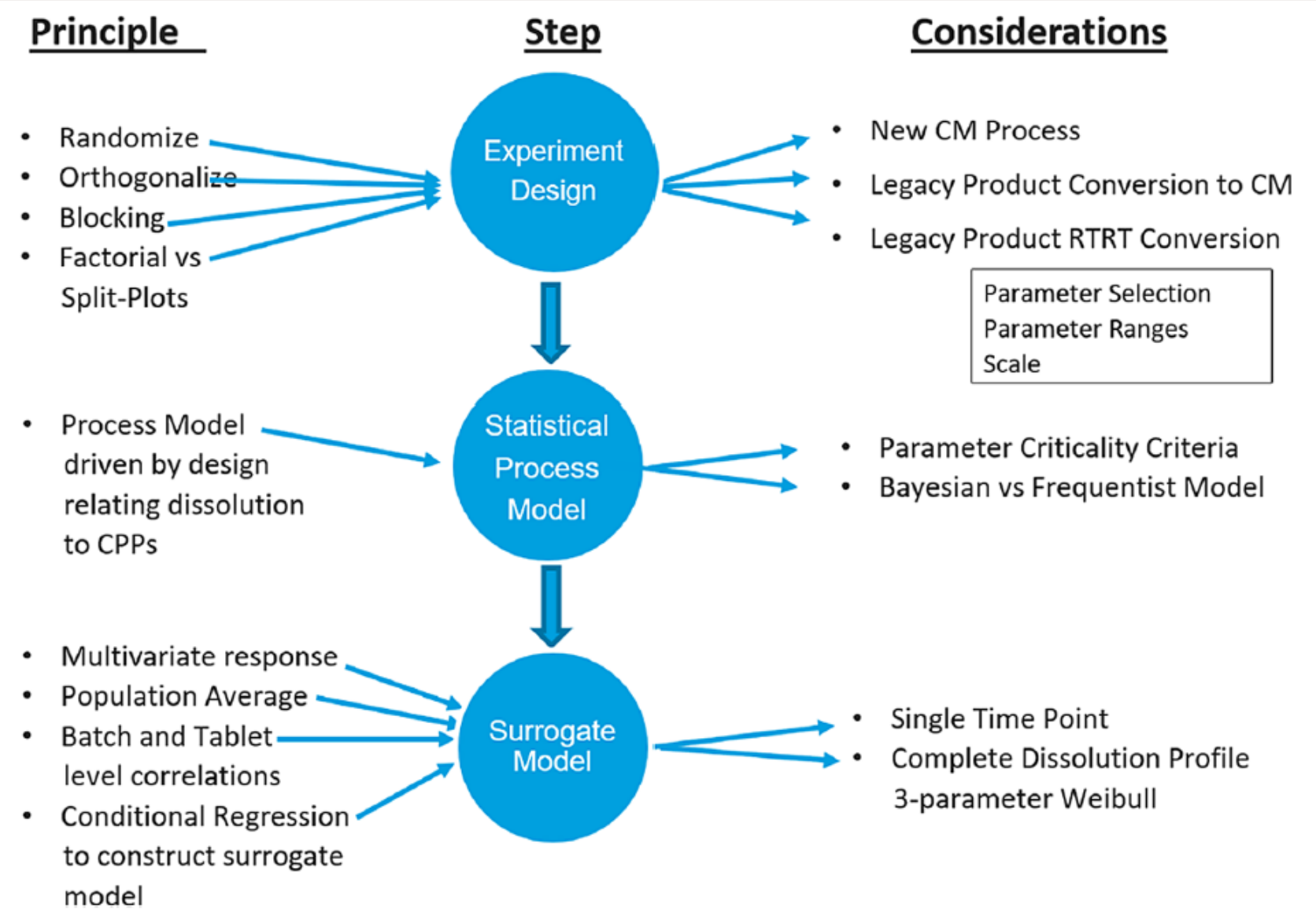
Dissolution as response

Local level properties

IPCs (tablet weight, hardness, thickness)

Predictive dissolution model

Workflow



Shi Z., Altan S. et al. (2023)
Predictive In-Vitro Dissolution for Real-Time Release Test (RTRT) for Continuous Manufacturing Process on Drug Product,
In "Continuous Pharmaceutical Processing and Process Analytical Technology",
Narang A. S., Dubey A. (Eds.), CRC Press

DoE

Experimental Design Layout

Exptal Run	Rep	Run Order	Factor 1	Factor 2	Factor 3	Factor 4		
						Low	Mid	Hi
Run01	1	9	-1	-1	-1	-1	0	1
Run02	2	12	-1	-1	-1	-1	0	1
Run03	1	8	-1	-1	1	-1	0	1
Run04	1	5	-1	1	-1	-1	0	1
Run05	1	10	-1	1	1	-1	0	1
Run06	1	6	0	0	0	-1	0	1
Run07	2	13	0	0	0	-1	0	1
Run08	1	1	1	-1	-1	-1	0	1
Run09	1	3	1	-1	1	-1	0	1
Run10	1	4	1	1	-1	-1	0	1
Run11	1	2	1	1	1	-1	0	1
Run12	2	7	1	1	1	-1	0	1
Run13	3	11	1	1	1	-1	0	1

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Multivariate process model

Full model

$$\left(\hat{\theta}, NIR\right)_{j(ik)} | X, B \sim \text{MVN}_4(\mathbf{x}_{i(jk)}^t B, \Sigma).$$

Altan S., Banton D., Coppenolle H., Kovarik M., Otava M., Schmid C. (2022) **A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing**, In "Case Studies in Bayesian Methods for Biopharmaceutical CMC", Faya P., Pourmohamad T. (Eds.), Chapman and Hall/CRC

Parameter Group	Parameter	Posterior Mean	SE	95% Credible Limits
Mean structure: θ_1 model	Intercept	98.8	0.2	(98.5, 99.1)
	Factor 1	9.9	0.2	(9.6, 10.2)
	Factor 2	2.5	0.2	(2.2, 2.8)
	Interaction F1×F2	0.1	0.2	(−0.2, 0.4)
Mean structure: θ_2 model	Intercept	7.8	0.1	(7.7, 7.9)
	Factor 1	0.4	0.1	(0.3, 0.5)
	Factor 2	0.4	0.1	(0.1, 0.3)
	Interaction F1×F2	0.03	0.1	(−0.1, 0.1)
Mean structure: θ_3 model	Intercept	0.8	0.0	(0.8, 0.8)
	Factor 1	0.0	0.0	(0.0, 0.0)
	Factor 2	0.0	0.0	(0.0, 0.0)
	Interaction F1×F2	0.0	0.0	(0.0, 0.0)
Mean structure: NIR model	Intercept	100.1	0.1	(99.8, 100.4)
	Factor 1	9.2	0.1	(8.9, 9.5)
	Factor 2	0.0	0.1	(−0.2, 0.3)
	Interaction F1*F2	−0.2	0.1	(−0.5, 0.1)
Variance components: Σ_λ	$ \sigma_{\lambda,\theta_1} $	0.6	0.2	(0.2, 1.0)
	$ \sigma_{\lambda,\theta_2} $	0.3	0.1	(0.2, 0.4)
	$ \sigma_{\lambda,\theta_3} $	0.0	0.0	(0.0, 0.0)
	$ \sigma_{\lambda,NIR} $	0.7	0.1	(0.6, 0.1)
	$\rho_{\lambda,\theta_1,NIR}$	0.0	0.3	(−0.5, 0.5)
	$\rho_{\lambda,\theta_2,NIR}$	−0.3	0.2	(−0.6, 0.1)
	$\rho_{\lambda,\theta_3,NIR}$	0.5	0.2	(0.1, 0.7)
Variance components: Σ_ε	$ \sigma_{\varepsilon,\theta_1} $	1.0	0.1	(0.9, 1.2)
	$ \sigma_{\varepsilon,\theta_2} $	0.2	0.0	(0.2, 0.3)
	$ \varepsilon, \sigma_{\theta_3} $	0.0	0.0	(0.0, 0.0)
	$ \sigma_{\varepsilon,NIR} $	0.4	0.0	(0.3, 0.4)
	$\rho_{\varepsilon,\theta_1,NIR}$	0.3	0.1	(0.0, 0.5)
	$\rho_{\varepsilon,\theta_2,NIR}$	−0.1	0.1	(−0.3, 0.2)
	$\rho_{\varepsilon,\theta_3,NIR}$	0.0	0.1	(−0.2, 0.3)

Multivariate process model

After model reduction

$$UB = \mu_{UB} + \beta_{UB}F_1 + \varepsilon_{UB}$$

$$\lambda = \mu_{\lambda} + \beta_{\lambda 1}F_1 + \beta_{\lambda 2}F_2 + \varepsilon_{\lambda}$$

$$k = \mu_k + \beta_{k1}F_1 + \beta_{k2}F_2 + \beta_{k12}F_1F_2 + \varepsilon_k$$

$$NIR = \mu_N + \beta_N F_1 + \varepsilon_N$$

$$\Sigma = \begin{pmatrix} \sigma_{UB}^2 & \sigma_{UB,\lambda} & \sigma_{UB,k} & \sigma_{UB,N} \\ \cdot & \sigma_{\lambda}^2 & \sigma_{\lambda,k} & \sigma_{\lambda,N} \\ \cdot & \cdot & \sigma_k^2 & \sigma_{k,N} \\ \cdot & \cdot & \cdot & \sigma_N^2 \end{pmatrix}$$

Why is Content not a covariate

Like all the other input?

Unknown ahead

Content often measured with considerable error

Risk of poor model performance if not conditioned

Multivariate process model

After model reduction

$$UB = \mu_{UB} + \beta_{UB}F_1 + \varepsilon_{UB}$$

$$\lambda = \mu_{\lambda} + \beta_{\lambda 1}F_1 + \beta_{\lambda 2}F_2 + \varepsilon_{\lambda}$$

$$k = \mu_k + \beta_{k1}F_1 + \beta_{k2}F_2 + \beta_{k12}F_1F_2 + \varepsilon_k$$

$$NIR = \mu_N + \beta_N F_1 + \varepsilon_N$$

$$\Sigma = \begin{pmatrix} \sigma_{UB}^2 & \sigma_{UB,\lambda} & \sigma_{UB,k} & \sigma_{UB,N} \\ \cdot & \sigma_{\lambda}^2 & \sigma_{\lambda,k} & \sigma_{\lambda,N} \\ \cdot & \cdot & \sigma_k^2 & \sigma_{k,N} \\ \cdot & \cdot & \cdot & \sigma_N^2 \end{pmatrix}$$

Conditional model

Conditioning on observed NIR

$$\mathbb{E}[\theta | NIR = nir, \mathbf{x}_{\text{pred}}, B, \Sigma_{\lambda}] = (\mathbf{x}_{\text{pred}} \times B[:, 1 : 3])^t + \Sigma_{\lambda}[1 : 3, 4] \times \Sigma_{\lambda}^{-1}[4, 4] \times (nir - \mathbf{x}_{\text{pred}} \times B[:, 4]) = \theta^*$$

$$\begin{aligned}\theta_1^* &= 98.8 - 0.01(\bar{x}_{NIR} - 100.1) \\ \theta_2^* &= 7.8 - 0.01(\bar{x}_{NIR} - 100.1) \\ \theta_3^* &= 0.8 + 0.02(\bar{x}_{NIR} - 100.1)\end{aligned}$$

$$b1^* = 100.06 + 0.37^* (nir - 99.01),$$

$$b2^* = 8.05 + 0.14^* (nir - 99.01),$$

$$b3^* = 0.99 + 0.01^* (nir - 99.01).$$

Altan S., Banton D., Coppenolle H., Kovarik M., Otava M., Schmid C. (2022) **A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing**, In "Case Studies in Bayesian Methods for Biopharmaceutical CMC", Faya P., Pourmohamad T. (Eds.), Chapman and Hall/CRC

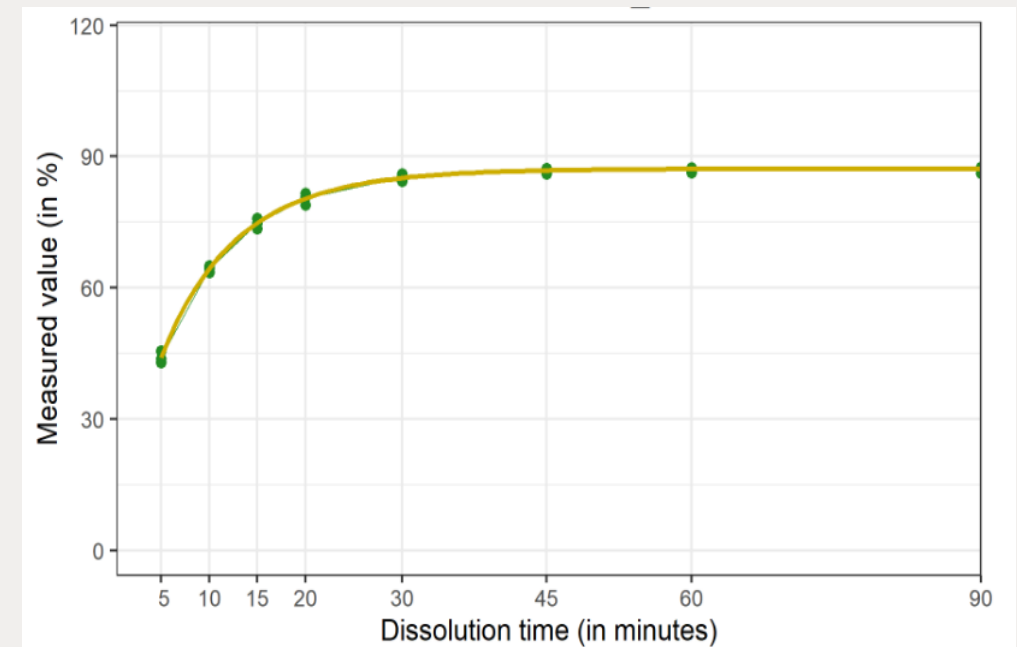
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Final prediction model

Entire dissolution profile

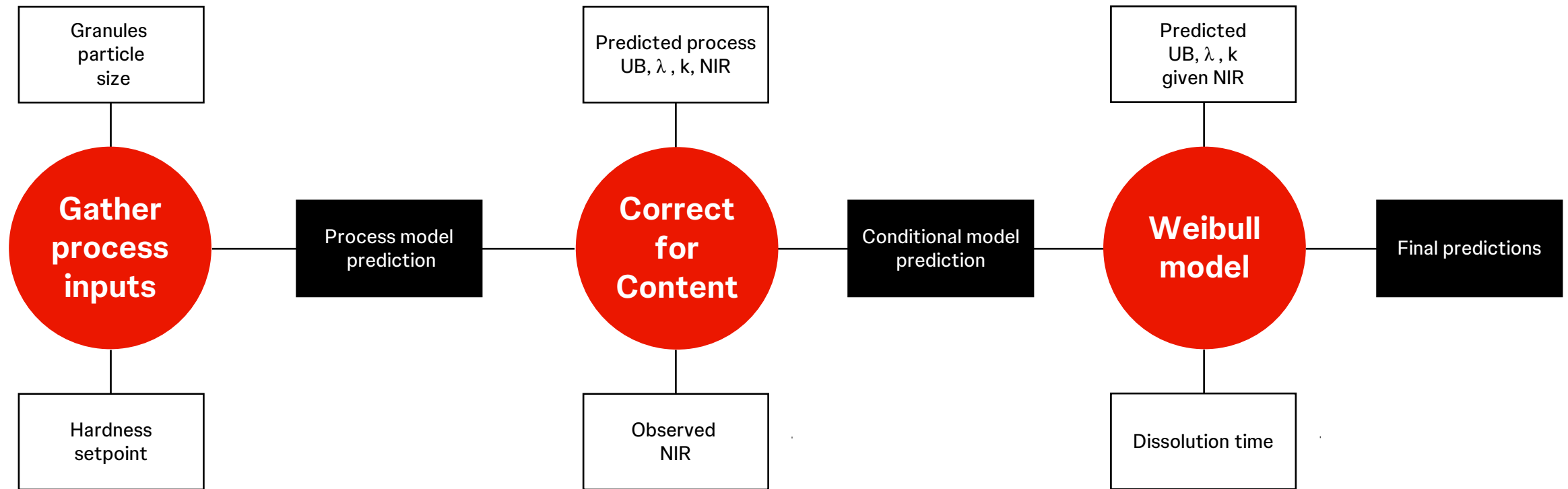
$$y_{\text{pred}}|t, \mathbf{x}_{\text{pred}}, \text{NIR} \sim N \left(\theta_1^* \left[1 - \exp \left\{ -\lambda \left(\frac{t}{\theta_2^*} \right)^{\theta_3^*} \right\} \right], \sigma_d \right)$$

Altan S., Banton D., Coppenolle H., Kovarik M., Otava M., Schmid C. (2022) **A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing**, In "Case Studies in Bayesian Methods for Biopharmaceutical CMC", Faya P., Pourmohamad T. (Eds.), Chapman and Hall/CRC

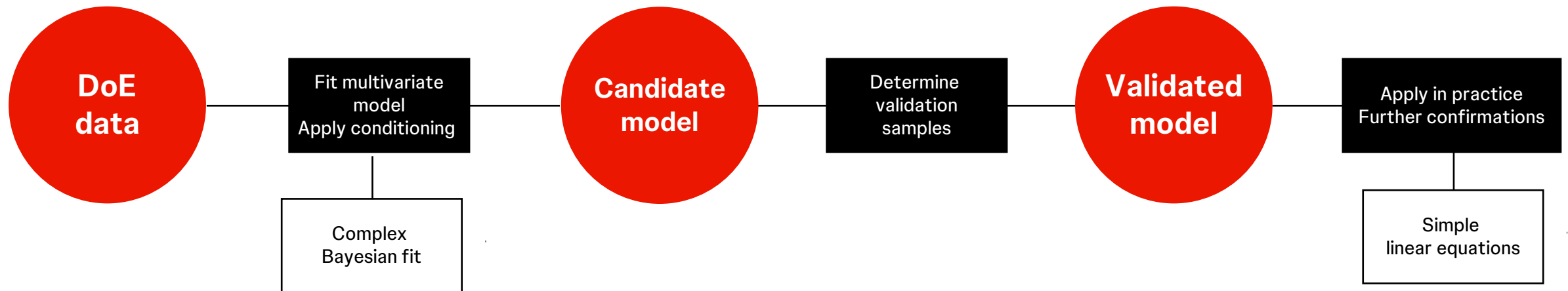


Summary

Model application



Prediction model framework



Conclusion

Why is the conditional model framework good idea

Comprehensive statistical framework correctly assessing error

Explicitly quantifies impact of each of the factors involved

Can handle various structures in the calibration data

Simple practical implementation

References

- Altan S, Banton D, Coppenolle H, Kovarik M, Otava M, Schmid C (2022) **A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing**, In "Case Studies in Bayesian Methods for Biopharmaceutical CMC", Faya P., Pourmohamad T. (Eds.), Chapman and Hall/CRC
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<https://doi.org/10.1016/j.xphs.2023.08.004>

Thank you

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Johnson&Johnson