Oct 23, 2025

# Bayesian Hierarchical Models for Enhanced Experimental Design

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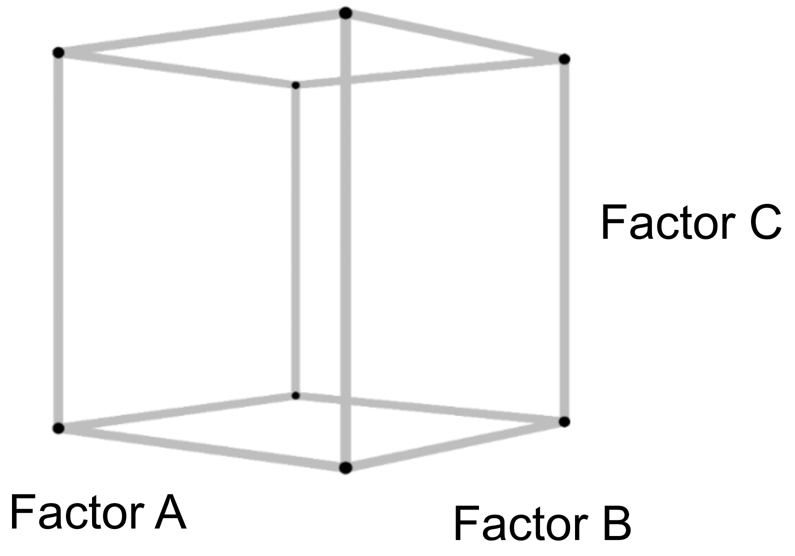
# Experimental Design in Development

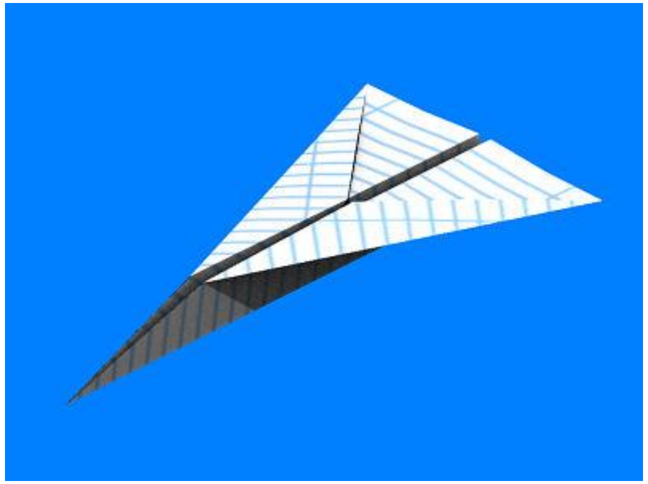
- Set of experimental conditions that help estimate multivariate relationships among factors for some set of responses

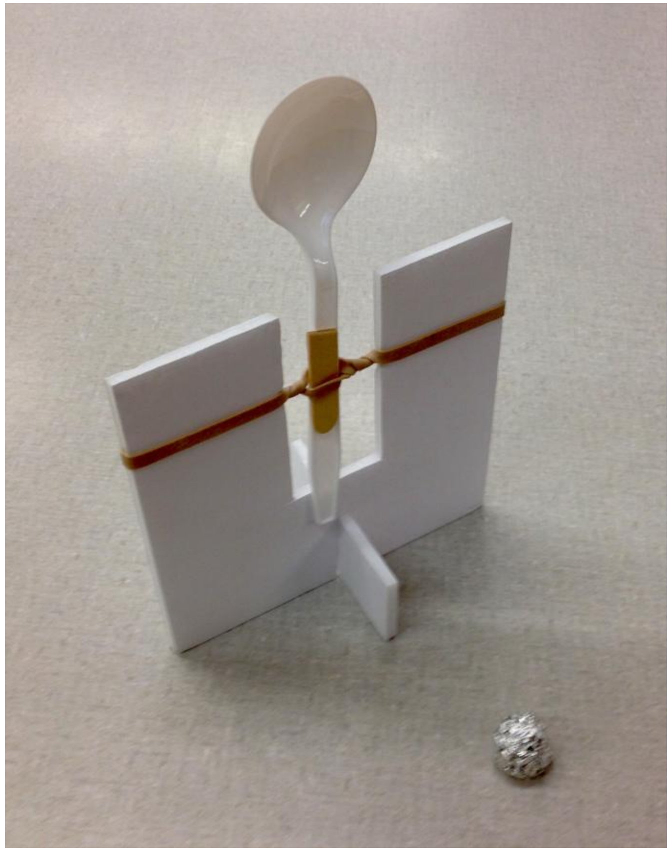
- Examples:
  - Drug substance unit operation characterization
  - Formulation robustness
  - Analytical method robustness



# Experimental design has not always been integrated…

- Years of education and promoting use of DOE
- Scientists developed appreciation, leading to embedded use of DOE



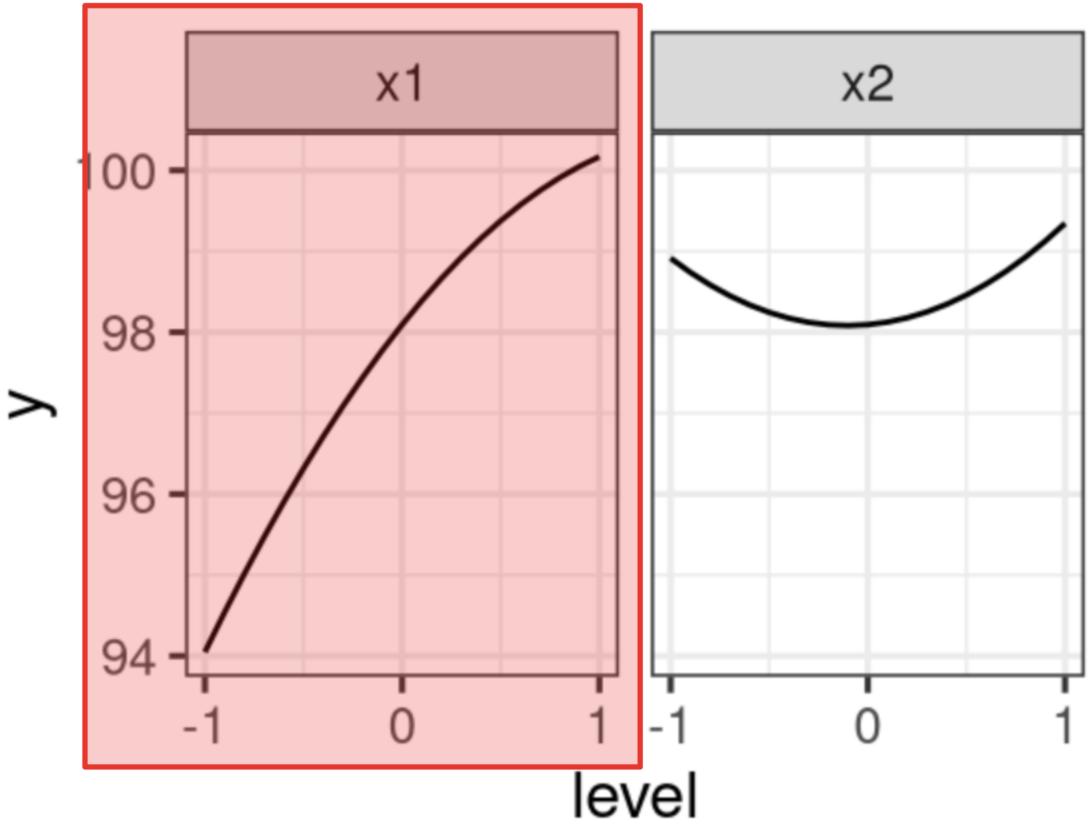


# Concerns

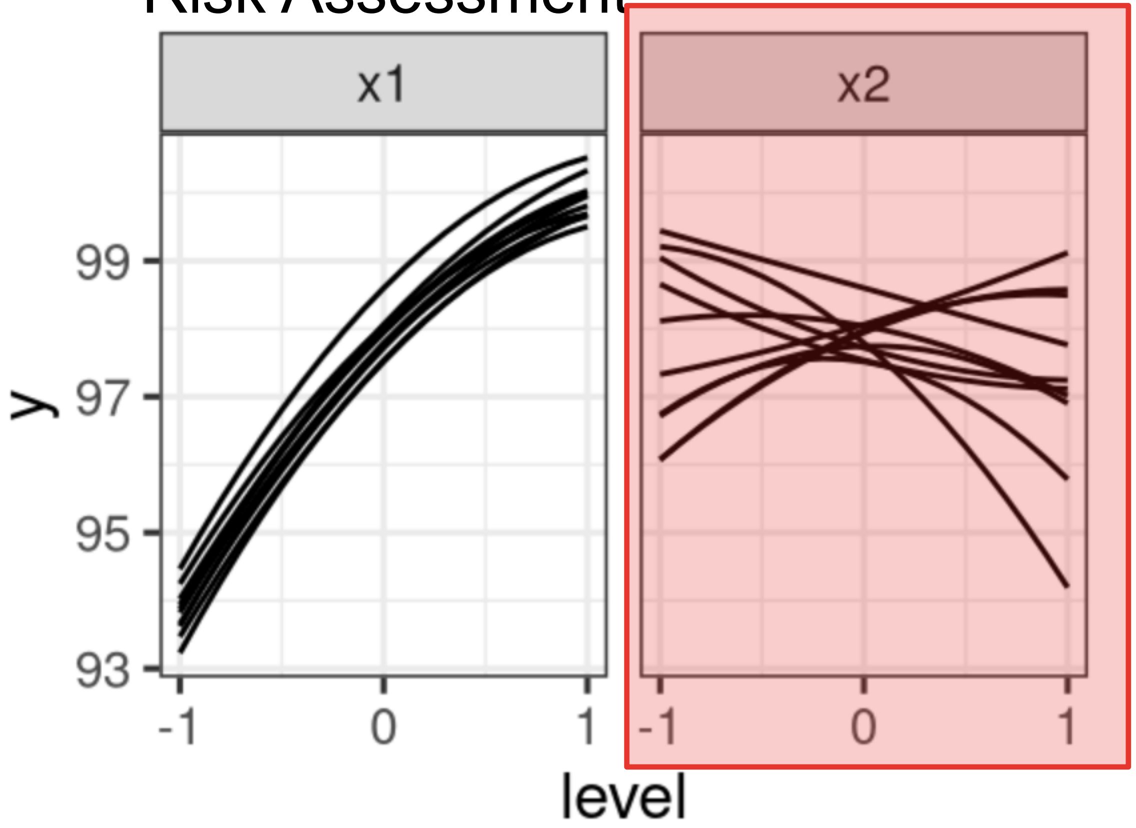
- Platform-based molecules may lead to similar conclusions
- Losing appreciation for DOE as a tool for better understanding
- Become check-the-box activities to satisfy BLA
- “Nothing is more tedious and draining than running studies where I don’t learn anything”
- For improved collaboration with scientists, designs and outcomes must provide meaningful insights

# DOE must adapt to platform knowledge

## Standard Risk Assessment




## Platform knowledge-based Risk Assessment



# Outline

- Overview of Bayesian hierarchical models
- Real example applied to Protein A purification characterization
- Hypothetical example using informative priors

# Single-study model

- For a single study, the relationship between the DOE factors and a given response can be described mathematically as…..

$$\boxed{y_i} \sim \boxed{\beta_0} + \boxed{\beta_1}\boxed{x_{i1}} + \cdots + \boxed{\beta_p}\boxed{x_{ip}} + \boxed{\varepsilon_i}$$

**Random Error**

**Observed Response** **~** **Magnitude Effect** **Known Experimental Conditions**

Each parameter is a single number

# Hierarchical models

- For multiple studies, the relationship between the DOE factors and a given response can be described mathematically as…..

$$\boxed{y_{i,k}} \sim \boxed{\beta_{0,k}} + \boxed{\beta_{1,k}}\boxed{x_{i1}} + \cdots + \boxed{\beta_{p,k}}\boxed{x_{ip}} + \boxed{\varepsilon_i}$$

**Random Error**

**Observed Response** ~ **Magnitude Effect for a given project** **Known Experimental Conditions**

**Each parameter fits to a distribution**

$$\boxed{\beta_{j,k} \sim N\left(\mu_{\beta_j}, \sigma_{\beta_j}\right)}$$

# Example: Protein A chromatography

- Experimental design quantifies impact to quality attributes within operating range
- Do prior experiments demonstrate sufficient platform knowledge to justify that the operating ranges provide adequate control without performing additional molecule-specific studies?

Journal of Chromatography A 1742 (2025) 465647

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

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## Leveraging prior knowledge for process parameter classification in mAb Protein A chromatography

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ARTICLE INFO

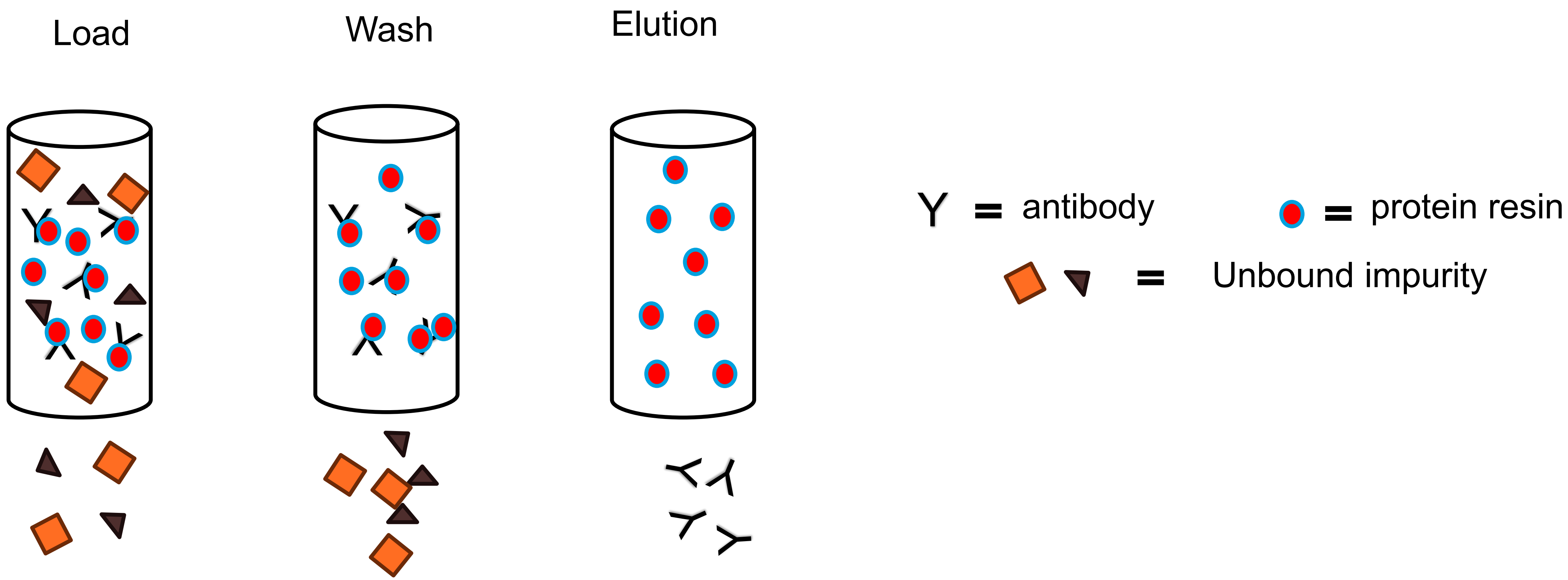
Keywords:
Protein A chromatography
Prior knowledge
Antibody
Process parameter characterization
Bayesian statistics

ABSTRACT

Protein A (ProA) affinity chromatography plays an essential role in purifying monoclonal antibodies (mAbs) and their analogues by reducing impurities like residual host cell proteins (HCPs), residual DNA, process additives, and potential viral contaminants. Decades of mAb process development and commercialization efforts have built extensive prior knowledge in the Protein A process. The prior knowledge facilities streamlined process development and minimized the need for extensive process characterization studies to inform manufacturing control strategies. This manuscript presents a comprehensive prior knowledge package, consolidating process parameter characterization data from ten molecules developed by Eli Lilly and Company using the Protein A chromatography process. Results from multiple Design of Experiment (DOE) studies on these molecules demonstrated that no process parameters significantly impacted critical quality attributes when operated within platform ranges. Additionally, a Bayesian hierarchical model was applied to analyze historical data and predict the effects of process parameters, further confirming that parameter effects were insignificant across the platform ranges for

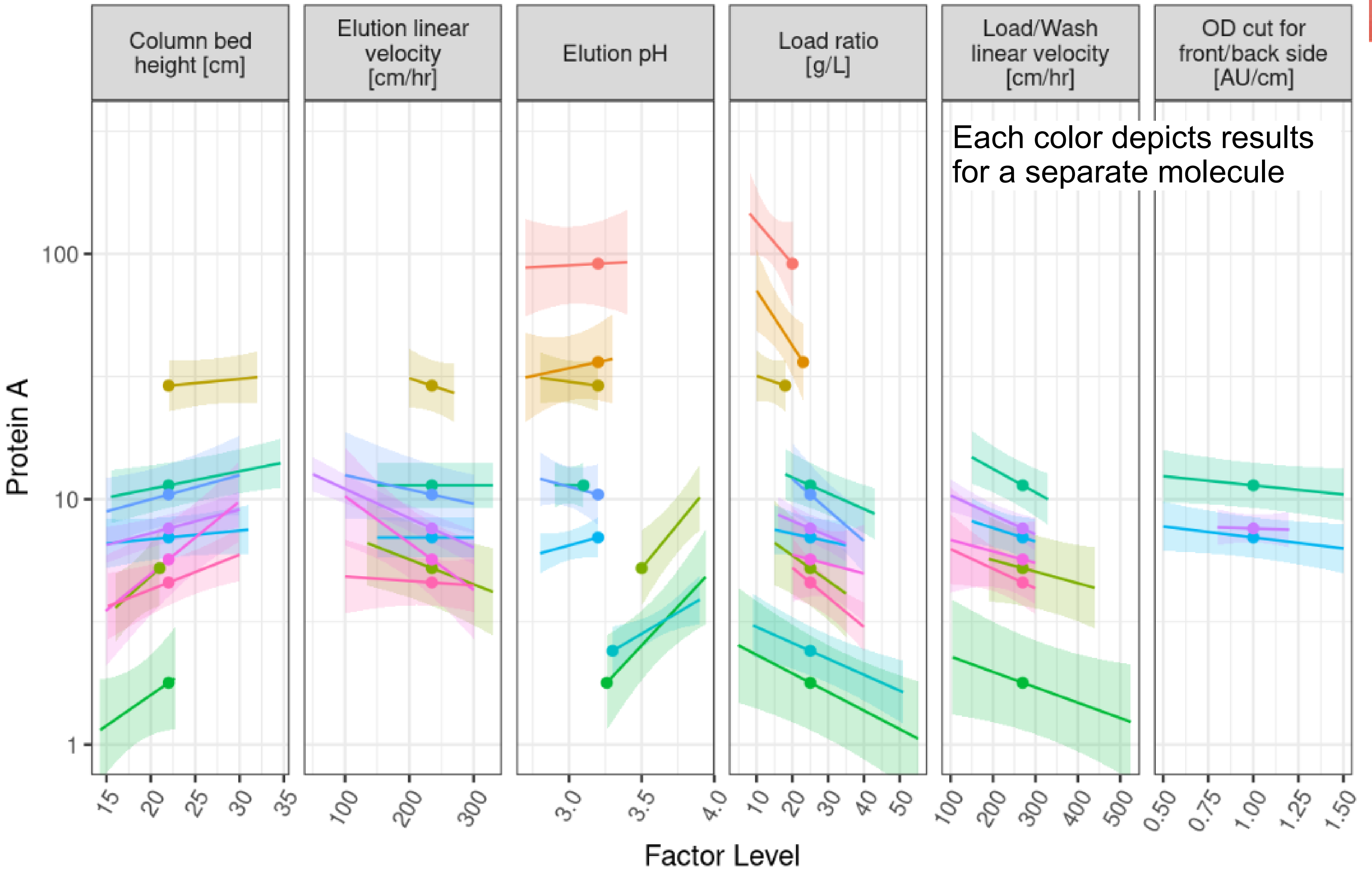
Tao, Yinying, Adam Rauk, Jinxin Gao, and Michael R. De Felippis. "Leveraging prior knowledge for process parameter classification in mAb Protein A chromatography." Journal of Chromatography A 1742 (2025): 465647.

# Scientific rationale supports that MAbs should perform similarly for this unit operation

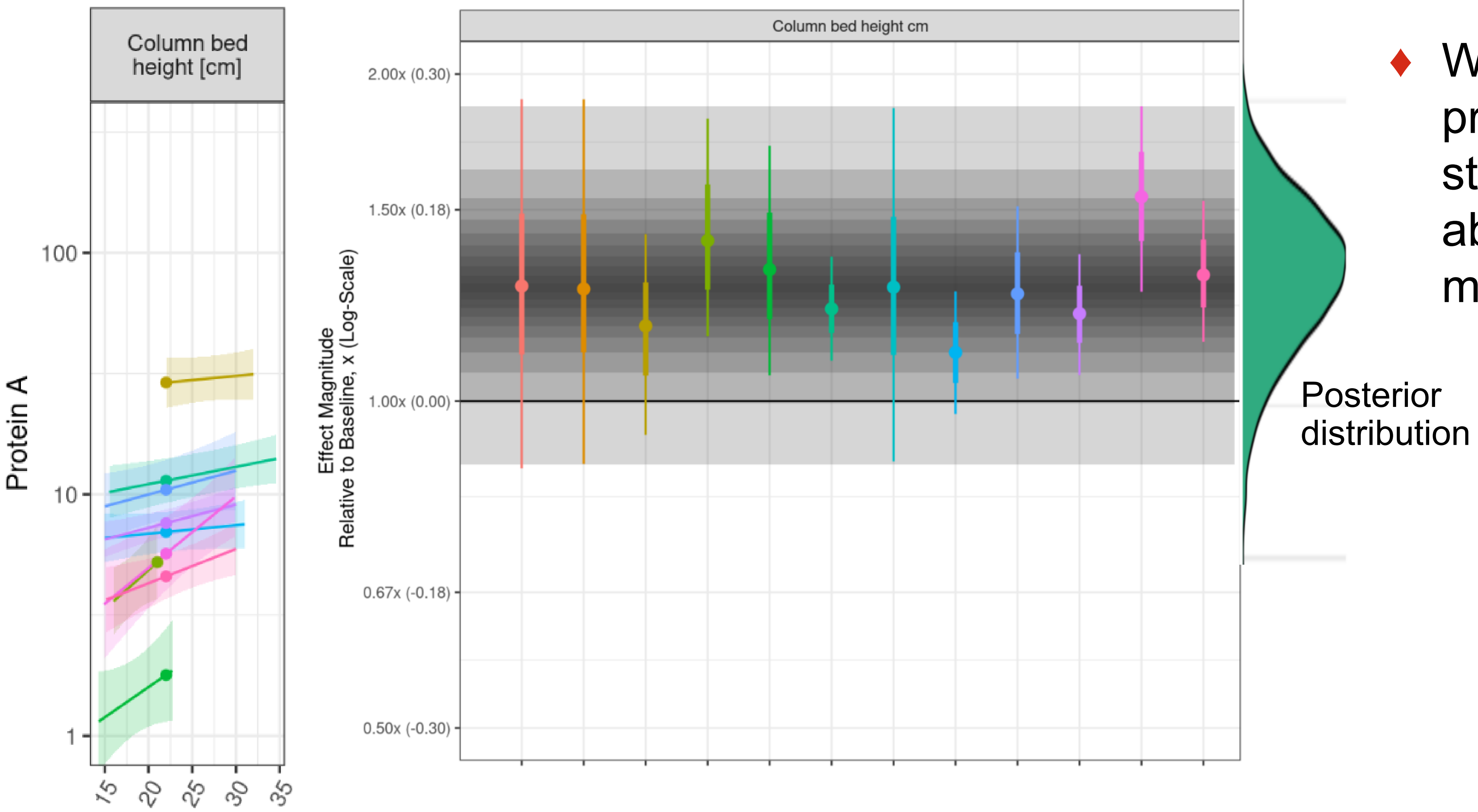


# Individual molecule overlay

- How do we quantify differences between molecules to draw a platform-wide conclusion?

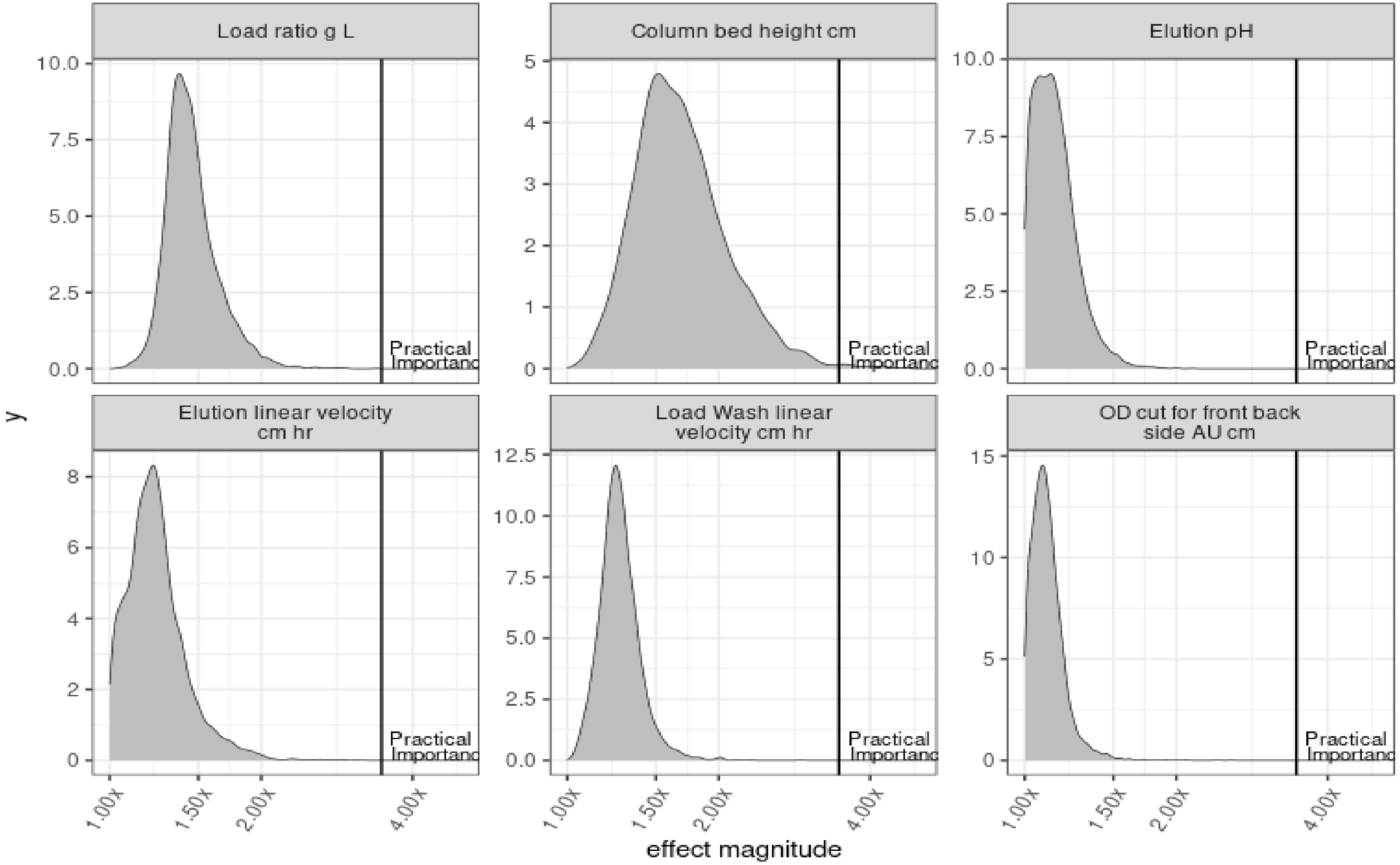


# Hierarchical model quantifies a distribution of likely parameter effects




- We can make probabilistic statements about the magnitude

# Posterior distributions show low CPP probability



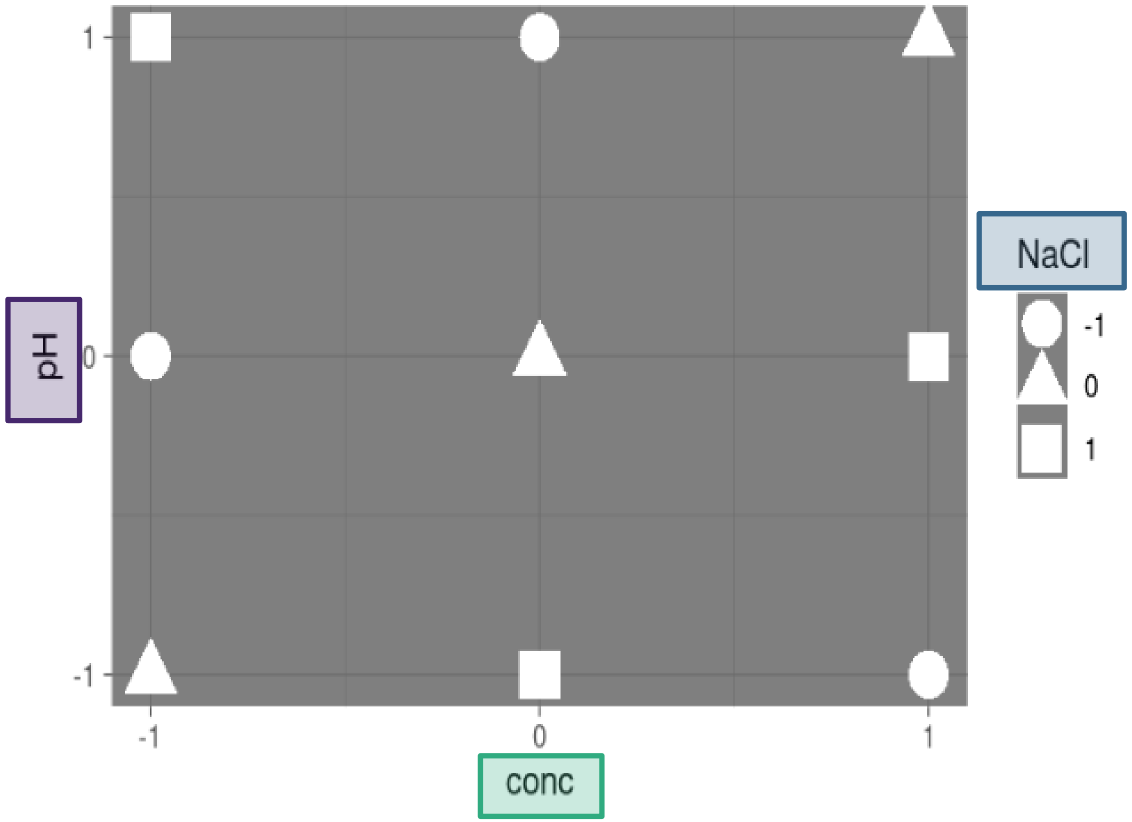

- Accounting for variation between molecules, there is low risk that any given parameter exceeds the CPP cutoff

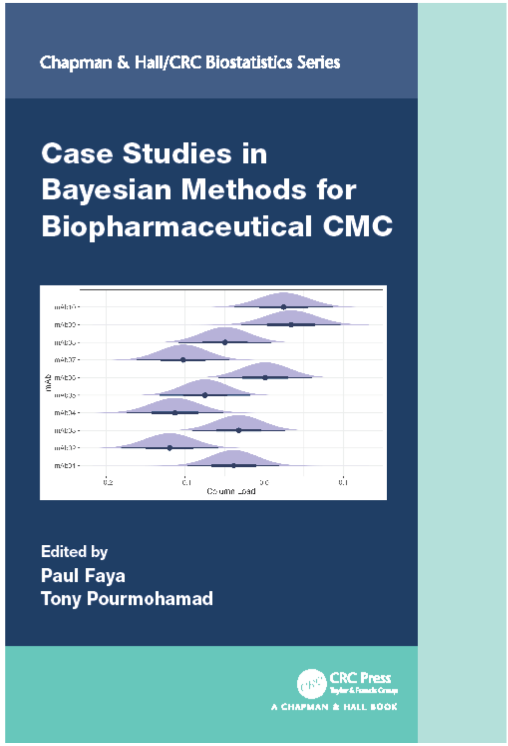
# Highlights

- Hierarchical model provided opportunity to collaborate with scientists that observed consistent conclusions from the protein A characterization study.
- Fit DOE result to a single model that quantifies differences.
- Able to support platform approach that demonstrates past variability poses low risk to future products.

# Example including informative priors

- Formulation robustness
- Definitive Screening Design
  - Concentration
  - pH
  - NaCl
- Same design was executed for 10 molecules

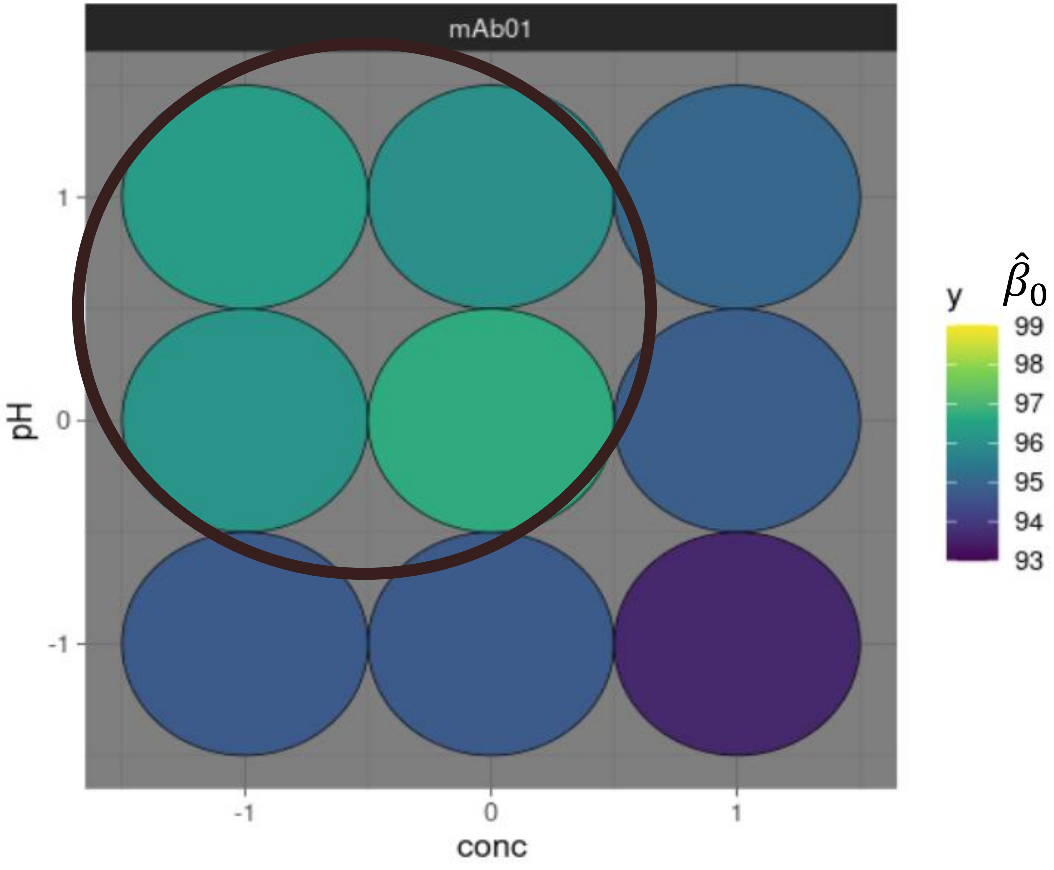


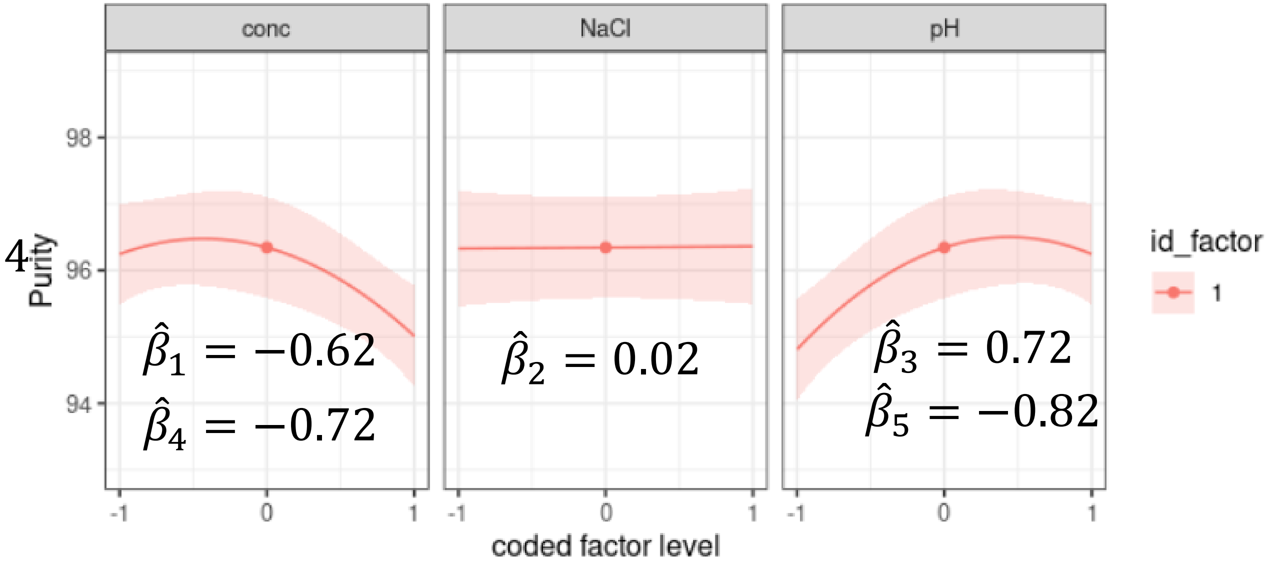

Rauk, Adam P., and Paul Faya. "Application of Bayesian Hierarchical Models to Experimental Design." *Case Studies in Bayesian Methods for Biopharmaceutical CMC*. Chapman and Hall/CRC, 2022. 119-134. https://github.com/BayesCMC/Book/tree/main/Chapter%20Code/Chapter%207

# DOE analysis for a single study

$$y_i \sim \beta_0 + \beta_1 x_{i,\text{conc}} + \beta_2 x_{i,\text{NaCl}} + \beta_3 x_{i,\text{pH}} + \beta_4 x_{i,\text{conc}^2} + \beta_5 x_{i,pH^2} + \varepsilon_i$$




$\hat{\beta}_0 = 96.34$




$\hat{\beta}_1 = -0.62$

$\hat{\beta}_4 = -0.72$

$\hat{\beta}_2 = 0.02$

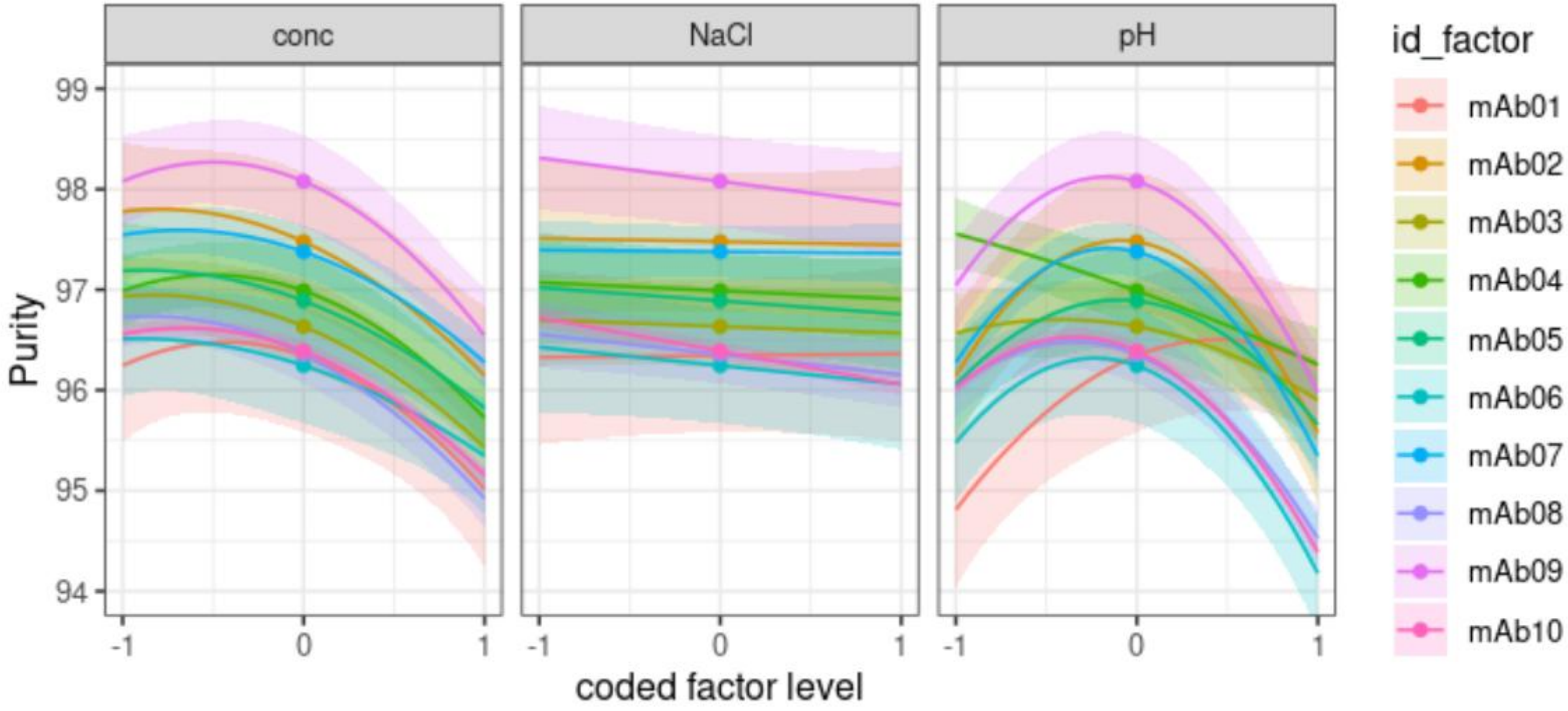
$\hat{\beta}_3 = 0.72$

$\hat{\beta}_5 = -0.82$

- Purity highest at:
  - Nominal-low concentration
  - Nominal-high pH

# Multiple least-squares model fits

$$y_i \sim \beta_0 + \beta_1 x_{i,\text{conc}} + \beta_2 x_{i,\text{NaCl}} + \beta_3 x_{i,\text{pH}} + \beta_4 x_{i,\text{conc}^2} + \beta_5 x_{i,pH^2} + \varepsilon_i$$



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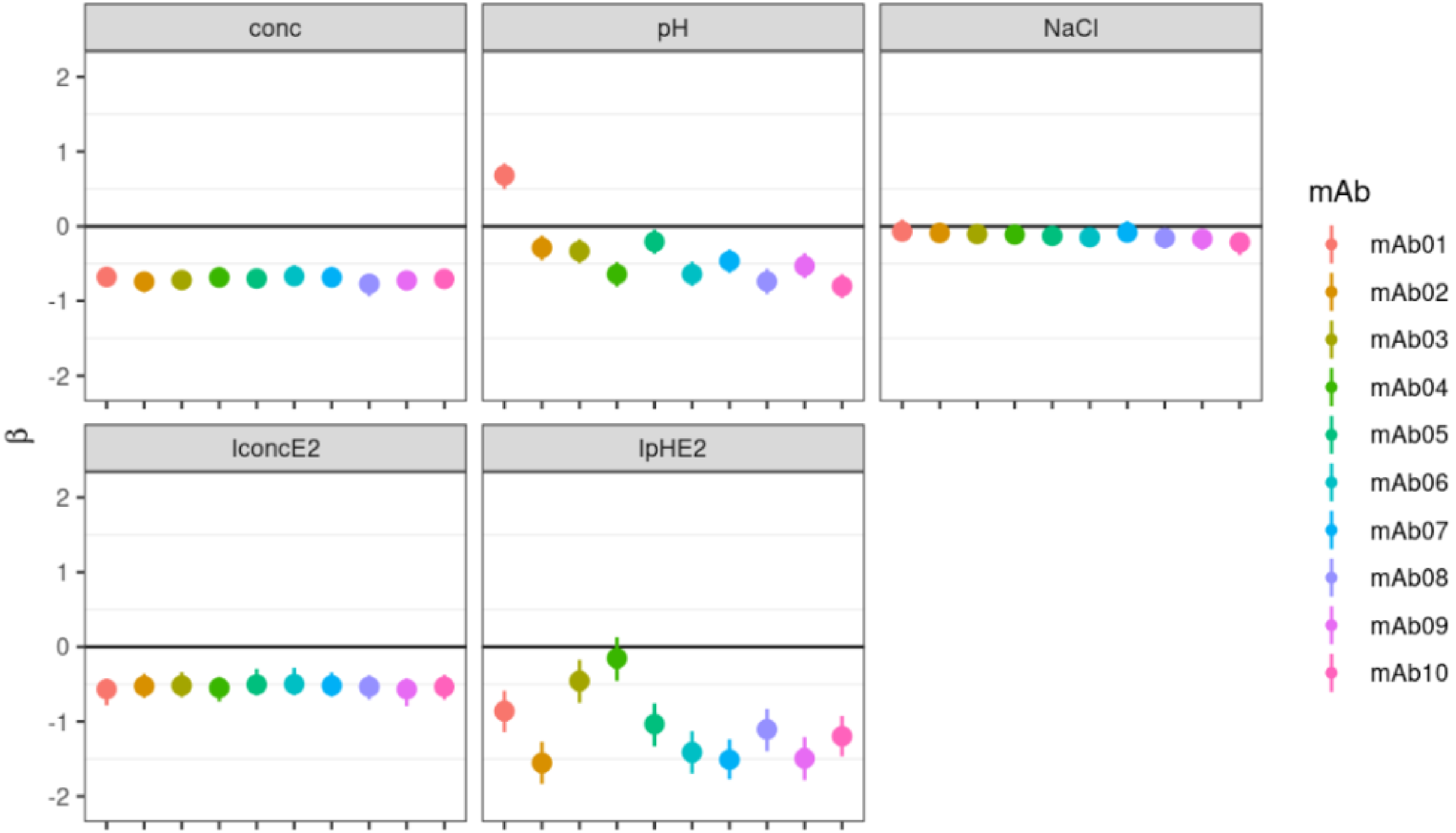
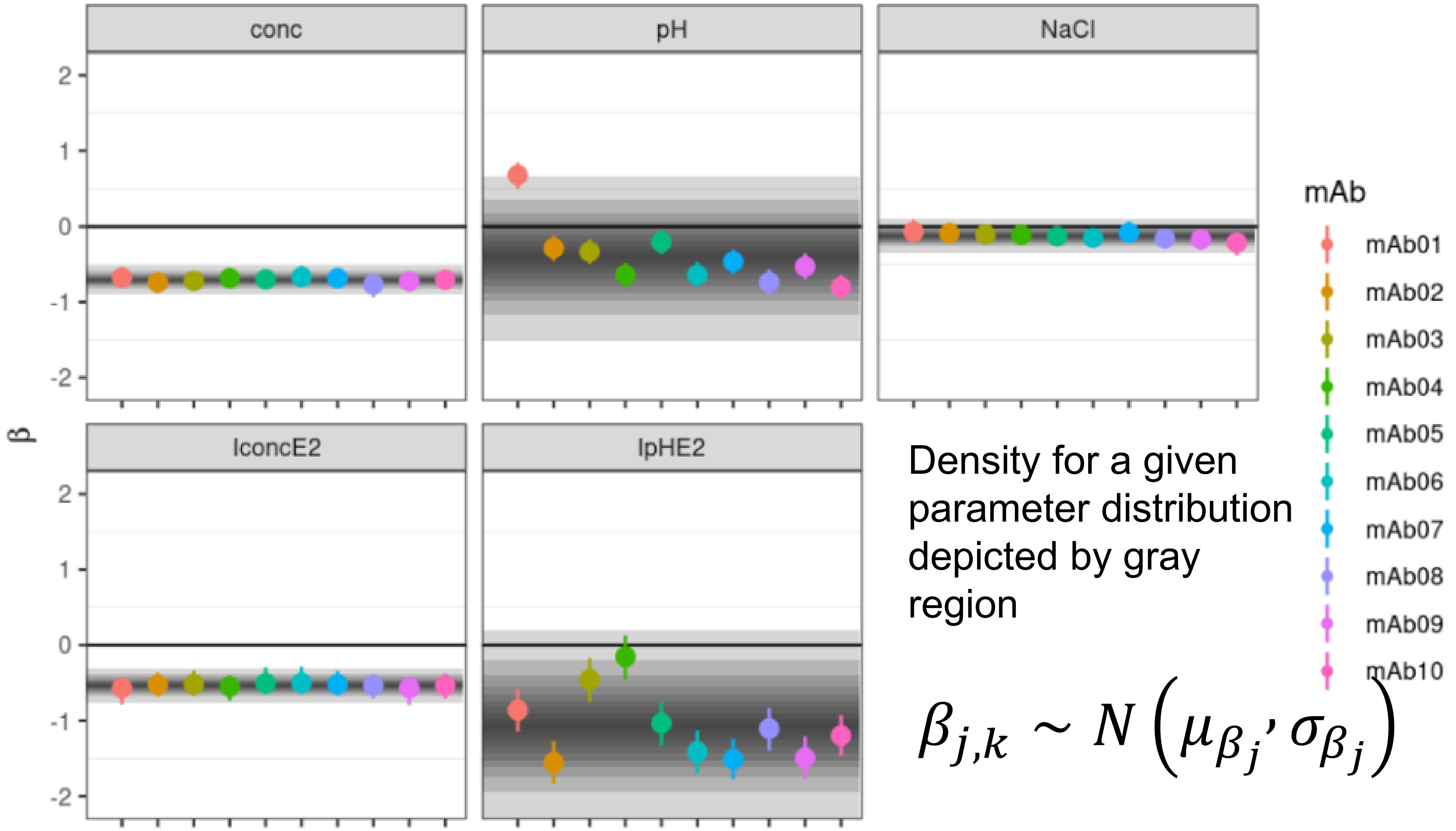
$$y_i \sim \beta_0 + \beta_1 x_{i,\mathrm{conc}} + \beta_2 x_{i,\mathrm{NaCl}} + \beta_3 x_{i,\mathrm{pH}} + \beta_4 x_{i,\mathrm{conc}^2} + \beta_5 x_{i,pH^2} + \varepsilon_i$$



# Hierarchical model

```
fit_brm2 <- brm(y~conc+pH+NaCl+I(conc^2)+I(pH^2)+(conc+pH+NaCl+I(conc^2)+I(pH^2)||mAb), data=sim2)
```




Density for a given parameter distribution depicted by gray region

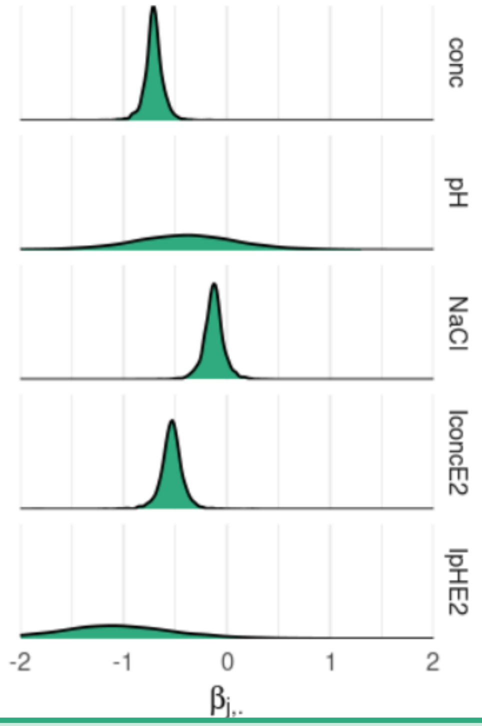
$$\beta_{j,k} \sim N\left(\mu_{\beta_j}, \sigma_{\beta_j}\right)$$

# Hierarchical Posteriors serve as priors

$$y_{i,k} \sim \beta_{0,k} + \beta_{1,k}x_{i1} + \cdots + \beta_{p,k}x_{ip} + \boxed{\varepsilon_i}$$

$$\boxed{\beta_{j,k}} \sim N\left(\boxed{\mu_{\beta_j}}, \boxed{\sigma_{\beta_j}}\right)$$

~

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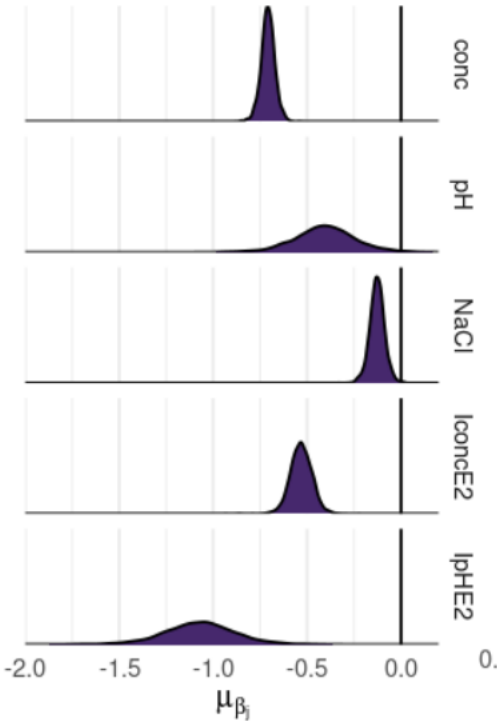
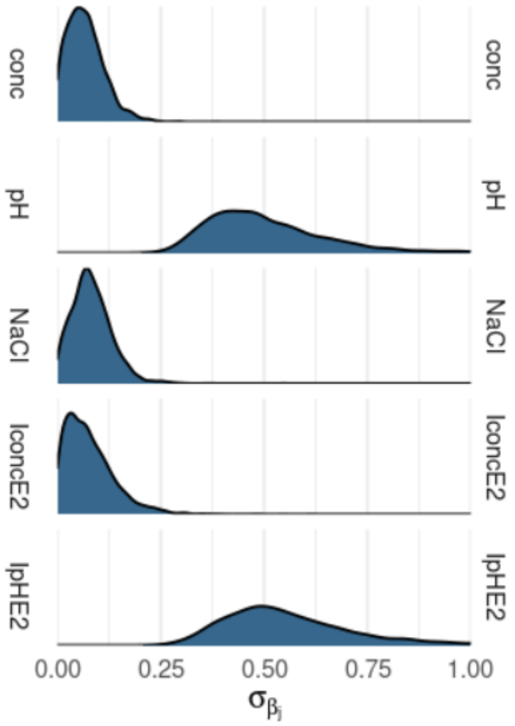


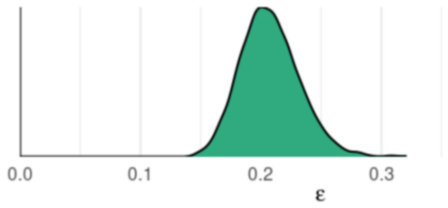

- Bayesian framework provides consistent transition from platform knowledge to molecule-specific outcomes

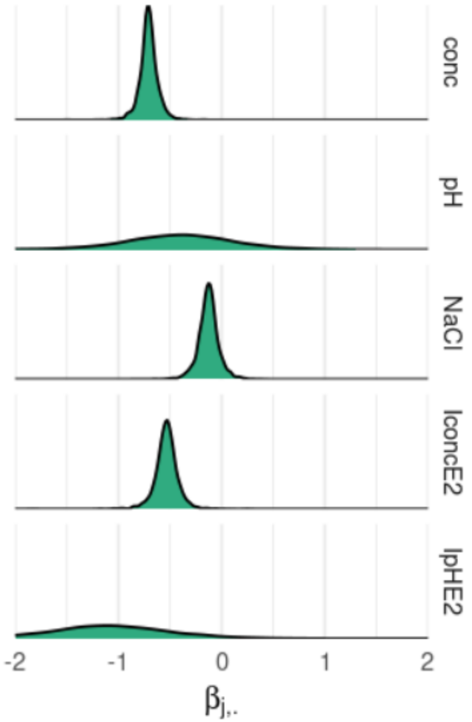
Reasonable prior distributions for future molecule

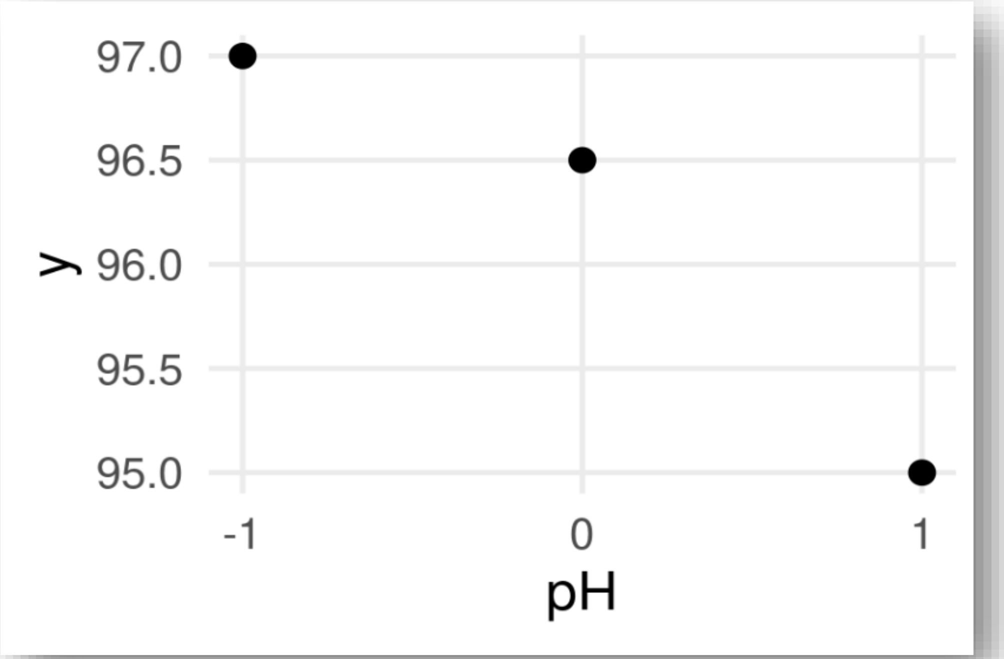
# New Study Data (with informative priors)

$$y_{i,k} \sim \beta_{0,k} + \beta_{1,k}x_{i1} + \cdots + \beta_{p,k}x_{ip} + \boxed{\varepsilon_i}$$

$$\boxed{\beta_{j,k}} \sim N\left(\mu_{\beta_j}, \sigma_{\beta_j}\right)$$

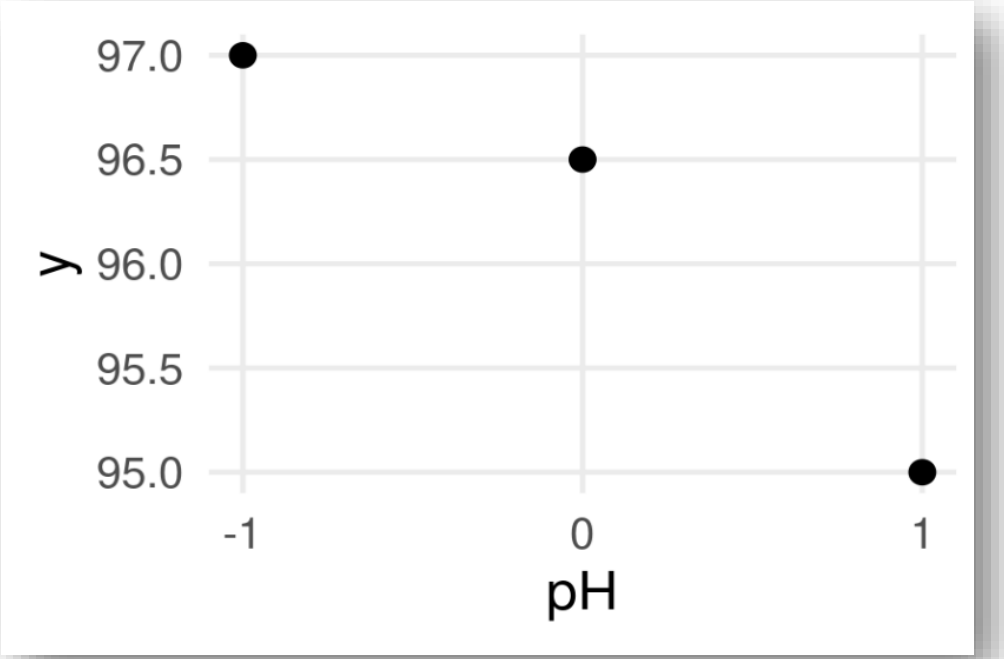


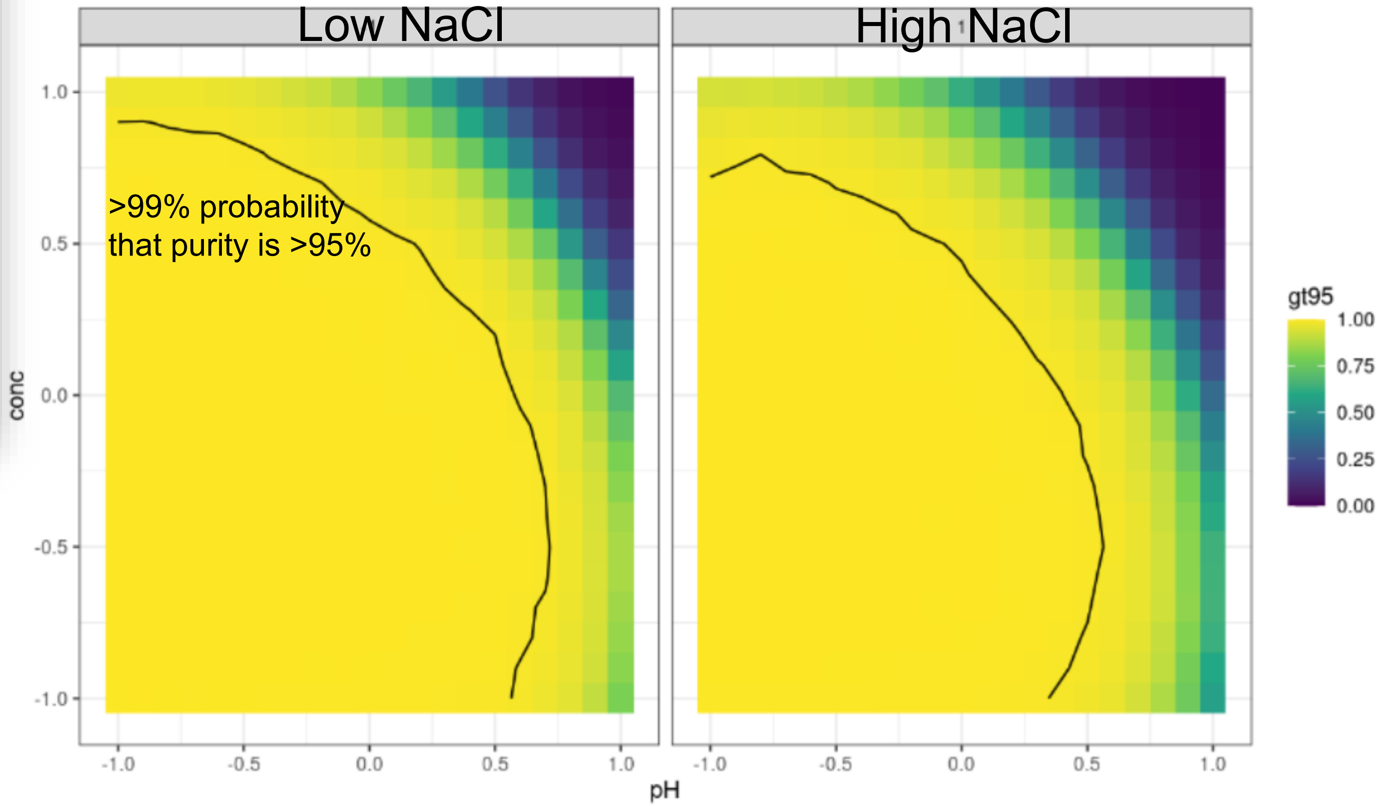




Reasonable prior distributions for future molecule

# New Study Data (with informative priors)




What is the probability that an observed purity is greater than 95%?




- Probabilistic inference
- Incorporates concentration and NaCl

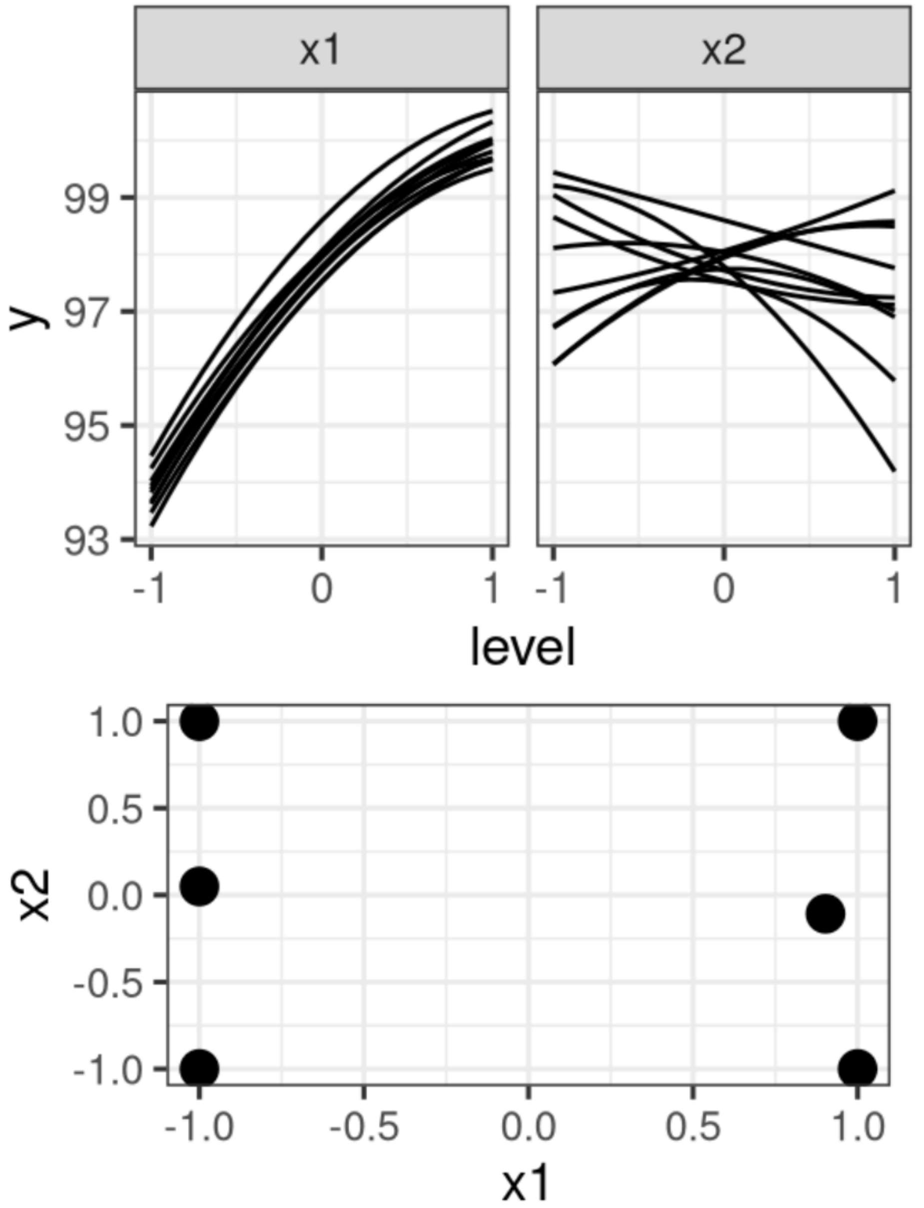
# Highlights

- Example demonstrates combination of platform knowledge and experiments focused on factor with molecule-specific behavior
- Provides mechanism to incorporate all prior study knowledge, with phase-appropriate weighting

# Study Design

Platform knowledge-based Risk Assessment

- ♦ Approximate coordinate exchange (ACE) from R package acebayes
- ♦ Minimize variability of model parameter posterior draws (sum of covariance matrix eigenvalues)



# Summary

- Statistical experimental design provides great value
- For improved collaboration, it must adapt to platform-based paradigms and include results from prior experiments