Large Scale process optimization using Bayesian modelling with Reduced Scale process priors

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'Well, Miss Jones, it seems our scale up procedure worked. Question now, is, do we blister pack or bottle?

BAYES 2018

Context of the study

- Objective: Determination of a design space in the context of vaccine manufacture
  - Impact of medium characteristics on a particular stage of the manufacture of the drug substance

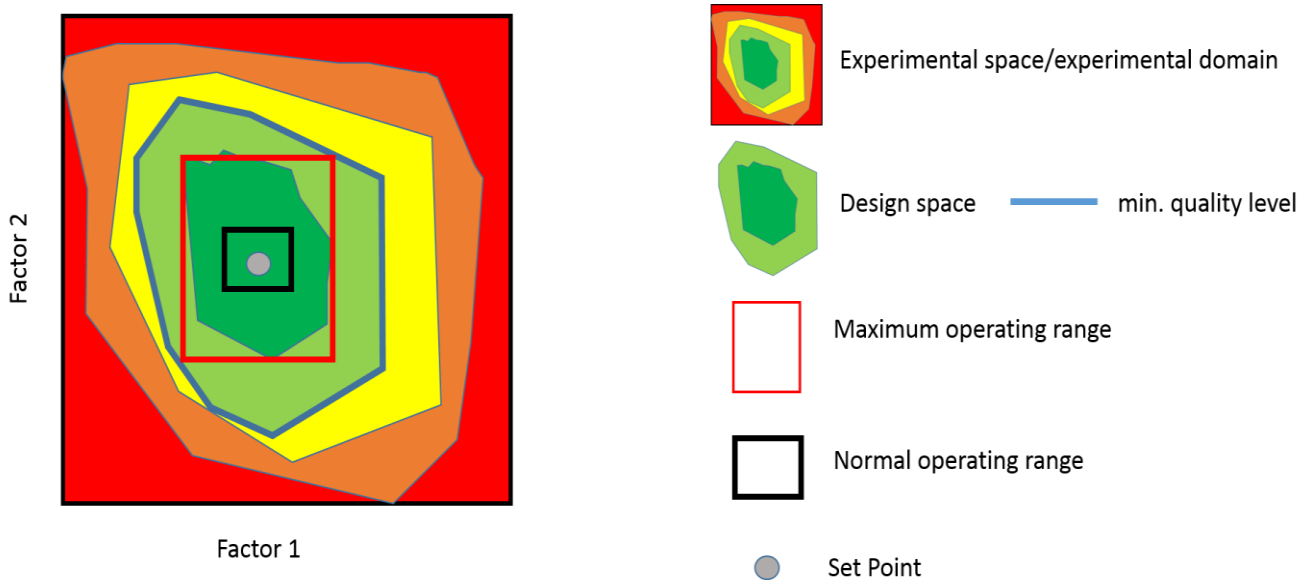
- What are the Critical Process Parameters (CPPs) impacting 5 selected Critical Quality Attributes (CQAs)?

- Scientists are primary interested in results obtained at Large Scale (LS)
  - However, experiments can be costly and many CPPs need to be assessed

    → Evaluate effects of CPPs in a Reduced Scale (RS) model to limit the number of experiences to be performed at LS

- In practice:
  - 10 CPPs to be investigated (pH, medium storage characteristics,…)
  - 5 CQAs of interest (virus particles, and infectivity titers, impurities)

Design Space

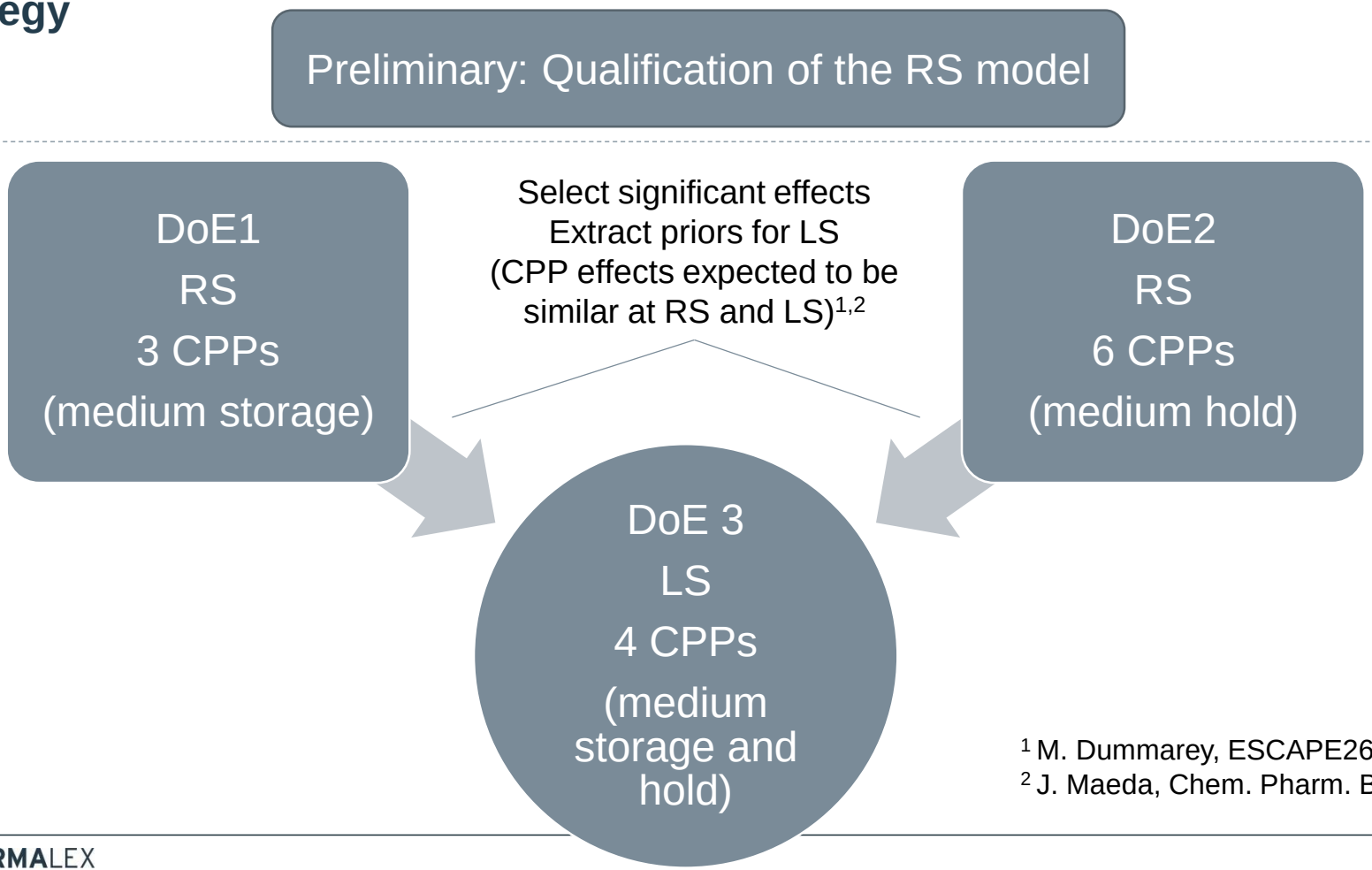


Design Space: range of values of CPPs providing assurance of quality

ICH Q11 development and manufacture of drug substances

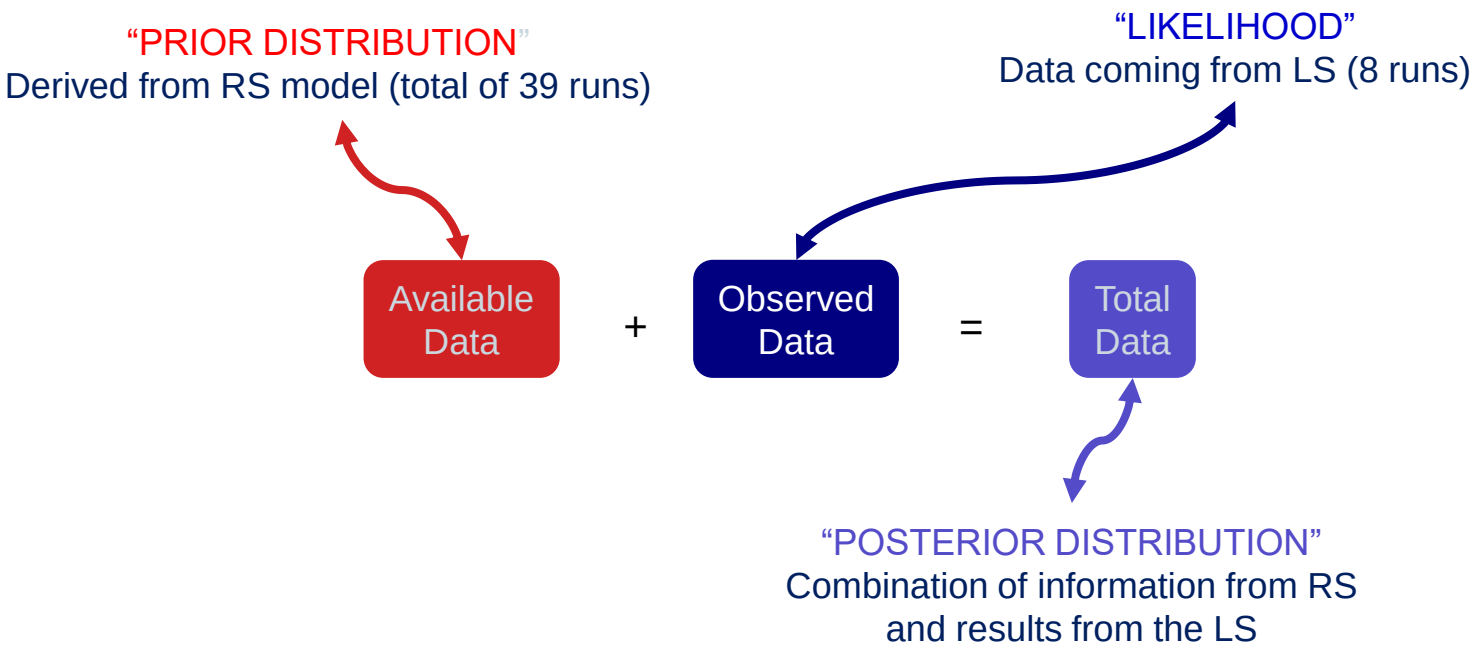
- Small-scale models can be developed and used to support process development studies. The development of a model should account for scale effects and be representative of the proposed commercial process. A scientifically justified model can enable a prediction of quality, and can be used to support the extrapolation of operating conditions across multiple scales and equipment.

Strategy



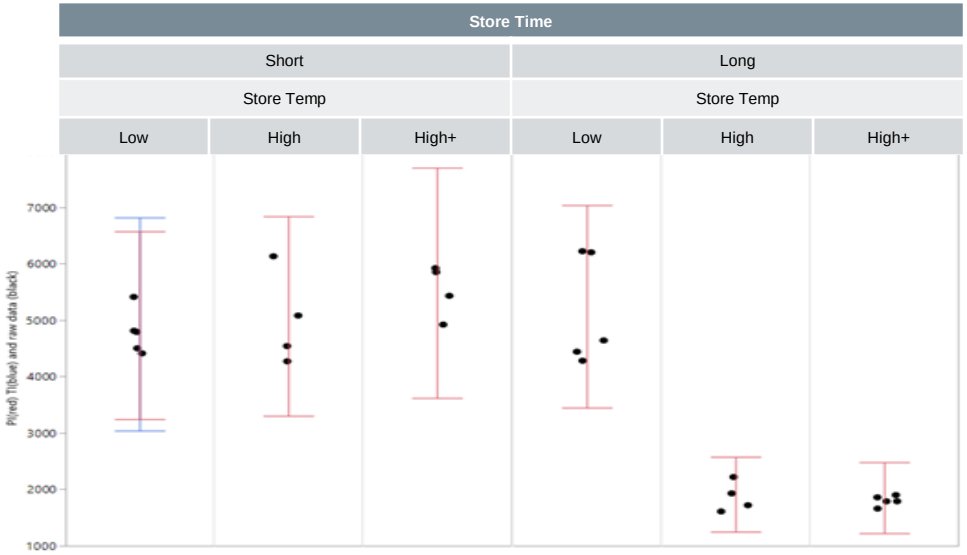
[1] M. Dummarey, ESCAPE26, 2016.
[2] J. Maeda, Chem. Pharm. Bull., 2012.

Bayesian principle



DoE 1: Medium storage characteristics (RS)

- D-Optimal design: 27 runs, 3 factors (one with three levels)
- Selection of effects → prediction intervals derived from Bayesian model
- Two CPPs and their interaction are selected
  - Medium storage time
  - A combined factor of storage temperature and light exposure



DoE 2: Medium hold (RS)

- Custom design: 12 runs, 6 factors

- Effects selection based on:
  - Parameters estimates for the different responses
  - **Scientific expertise**

- Two CPPs are selected:
  - Medium hold duration in the bioreactor
  - Medium hold pH

PROC OPTEX

- Search for optimal DoE (several criteria available), possibly **including priors**
- GENERATE statement to select the criteria to optimize the design
- In MODEL statement, use / PRIOR keyword
  - → Information matrix: X′X+P, with X the design matrix and P a diagonal matrix with prior weights
  - → `MODEL int b1 b2 / prior = 20/*int*/,0/*b1*/,5/*b2*/;`
  - → In our example (large values means stronger priors):

Term	Intercept	Block	StoreTemp (1)	StoreTemp (2)	StoreTime	Hold pH	HoldTime	StoreTemp* StoreTime (1)	StoreTemp* StoreTime (2)
Prior Information	20	0	5	5	3	5	5	5	5

DoE 3: LS

- D-optimal design generated with PROC OPTEX (prior information included in the DoE):
  - 8 runs
  - 4 factors (one categorical with 3 levels)
  - 1 interaction
  - 1 block

- Multivariate model:

$$Y_i = (VP_i, IU_i, CE_i, HCP_i, HCDNA_i)' \sim multiNormal\left(\left(\mu_i^{VP}, \mu_i^{IU}, \mu_i^{CE}, \mu_i^{HCP}, \mu_i^{HCDNA}\right)', \sum^2\right)$$

$$\mu_i^{VP} = \beta_{int}^{VP} + \beta_1^{VP} * x_i^{1a} + \beta_2^{VP} * x_i^{1b} + \beta_3^{VP} * x_i^2 + \beta_4^{VP} * x_i^3 + \beta_5^{VP} * x_i^4 + \beta_6^{VP} * x_i^{1a} * x_i^2 + \beta_7^{VP} * x_i^{1b} * x_i^2 + block_i^{VP}$$

$$block \sim \mathrm{N}(0, \sigma_{block}^2)$$

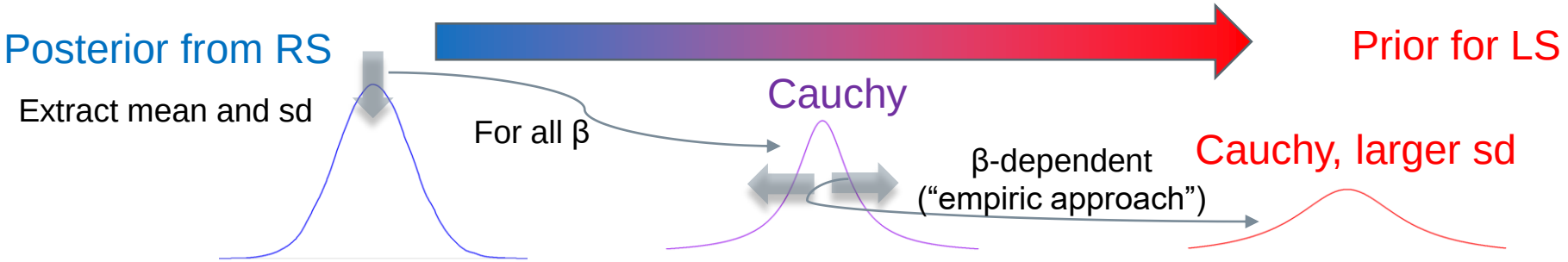
$\sum^2$ being the variance-covariance matrix including weak LKJ prior postulating a slight correlation between the responses

- Priors on $\beta_1 - \beta_7$ derived from Bayesian models fitted on data from DoE 1 and 2 (in Stan) and included as Cauchy distributions

DoE 3: LS … in practice!

- 10 runs instead of 8
- … but 3 blocks (instead of 2) !
  - Blocks modeled as a fixed effects
- Levels tested for several factors do not match the DoE !
- Need to adapt the prior distributions
  - No prior → no convergence !
  - Inverse-Gamma on residual variance
  - Cauchy distribution on $\beta_1 - \beta_7$ (smaller sd when less data)
  - Use lighter priors (larger sd) when more points in the DoE
  - Adjust prior location postulating linear effects for levels not tested in RS

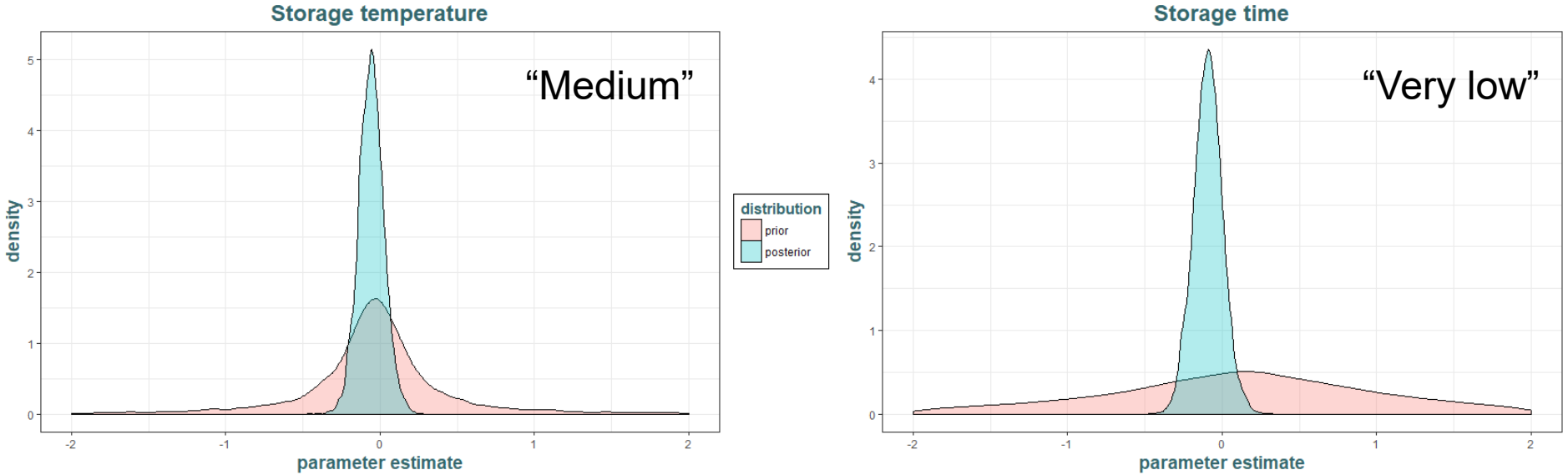
DoE 3: Prior definition



Term	Block	StoreTemp (Low)	StoreTemp (High+)	StoreTime	Hold pH	HoldTime	StoreTemp* StoreTime (Low)	StoreTemp* StoreTime (High+)
Level of information to build DoE	No	Medium	Medium	Low	Medium	Medium	Medium	Medium
Level of information to run model	No	Strong	Medium	Very Low	Medium	Low	Strong	Low
Broadening factor	/	1	2.5	10	2.5	5	1	5

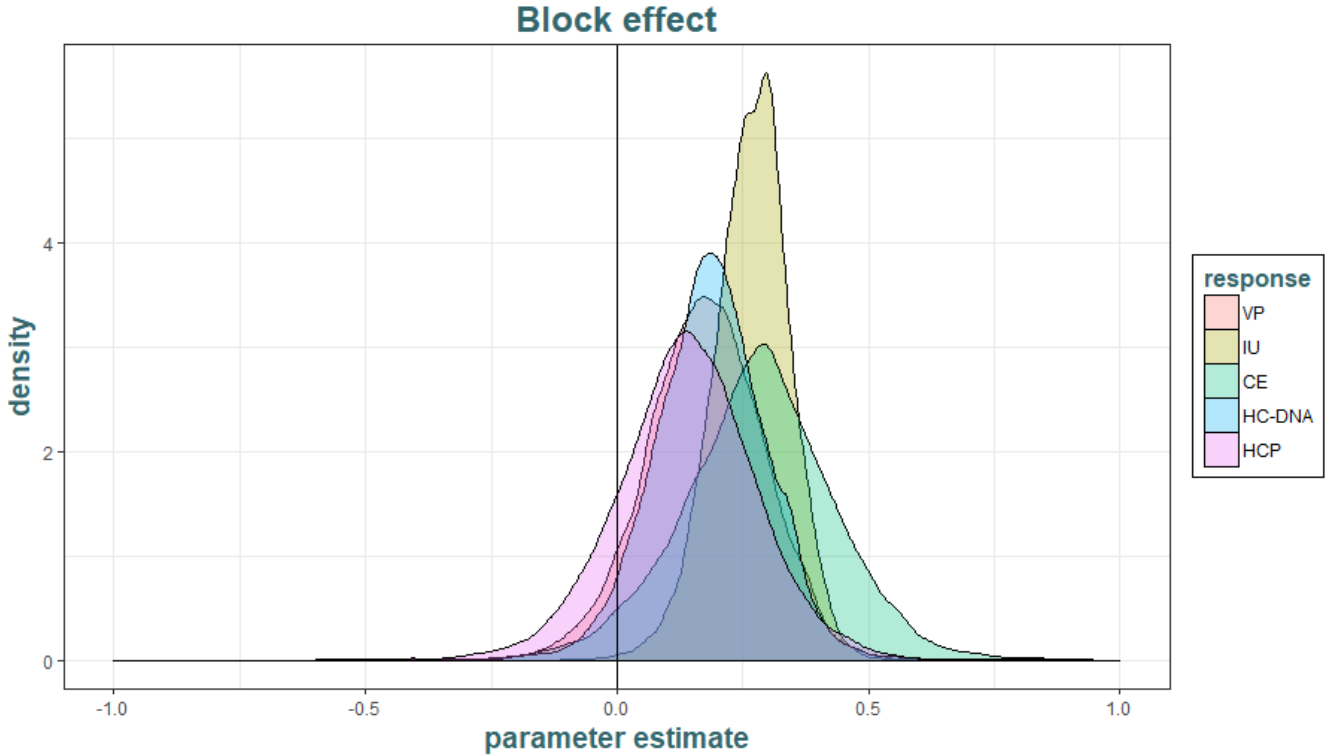
Results at LS

- Priors vs Posterior distributions of effects

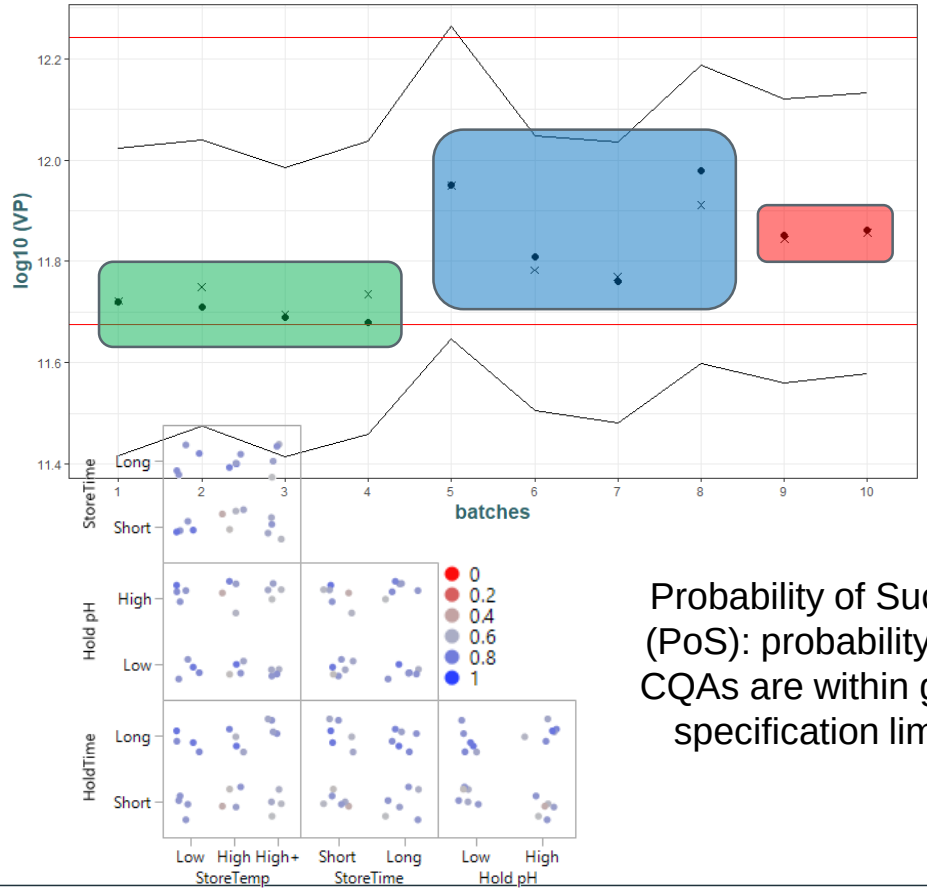


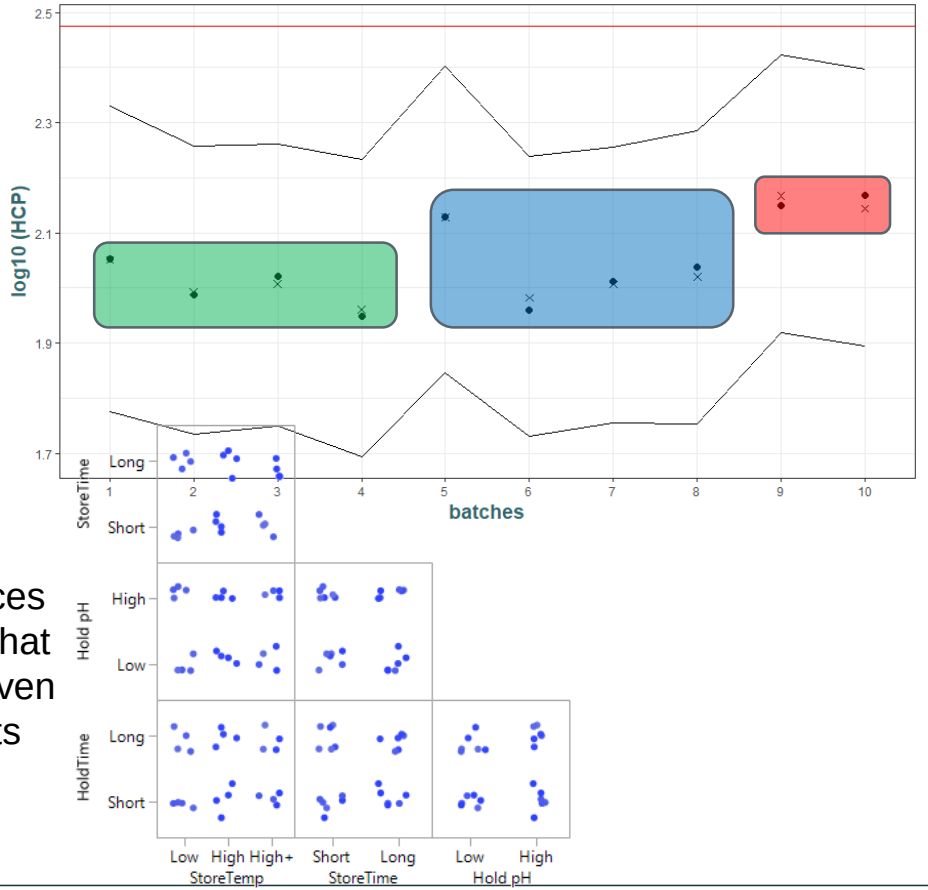
Results at LS

- The block has an impact for all responses (here block 3 *vs* block 1):



Exploiting results from DoE 3 at LS (1)





Probability of Succes (PoS): probability that CQAs are within given specification limits

Conclusions

- Collect data using a Reduced Scale Model

- Selection of effects
- Definition of priors

- Perform limited number of runs at Large Scale (LS)

Consider alternative approaches

- Estimation of Probability of Success (PoS) given current Specification Limits
- PoS are homogeneous in the range of experimental conditions tested at LS
- Underlying causes behind the Block effect

Due to starting materials (normalisation?)

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