Modelling an industrial bioseparation in the face of process variability

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Centre for Process Systems Engineering

Pfizer

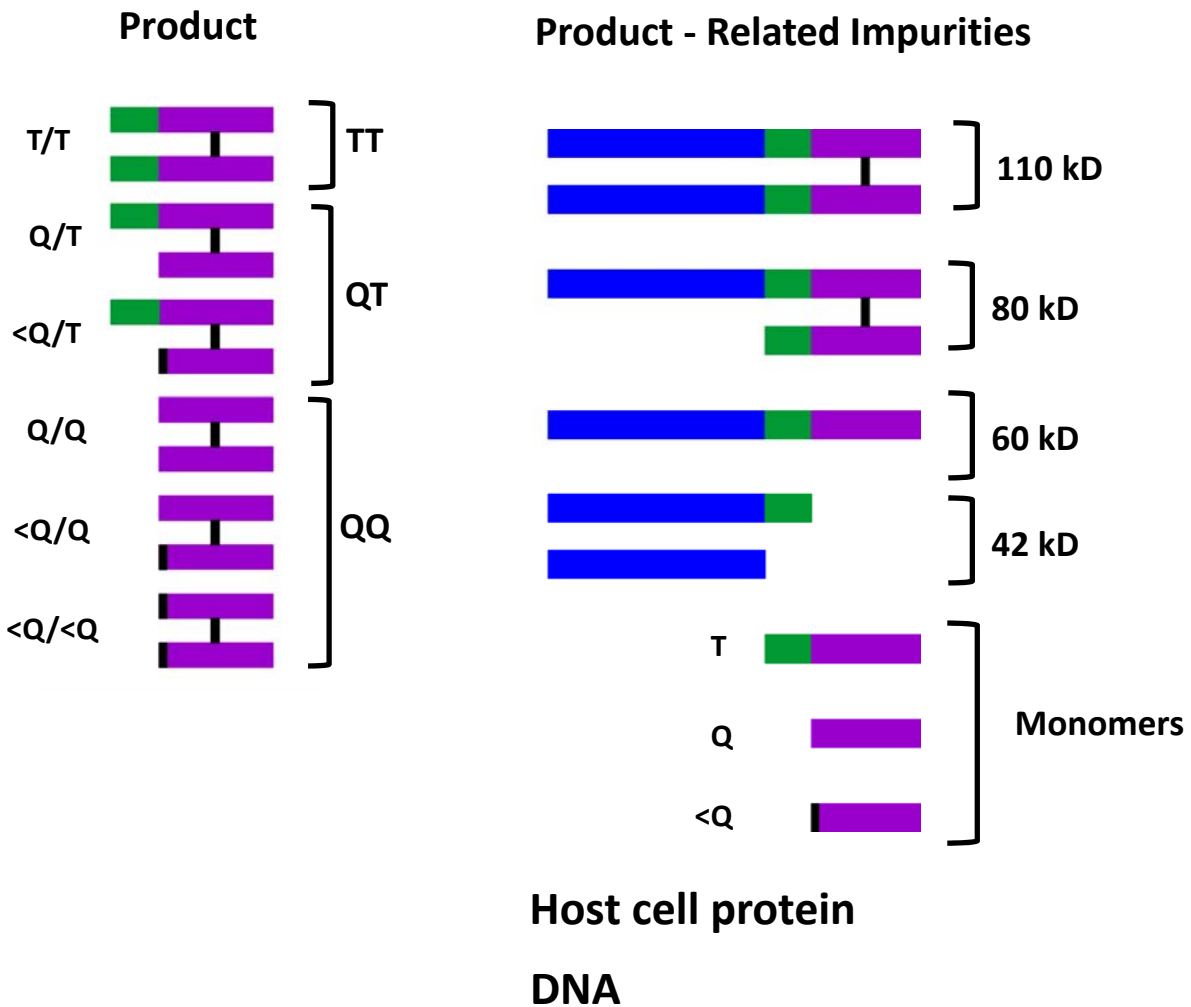
EPSRC Life Sciences IMRC Bioprocessing

Overview

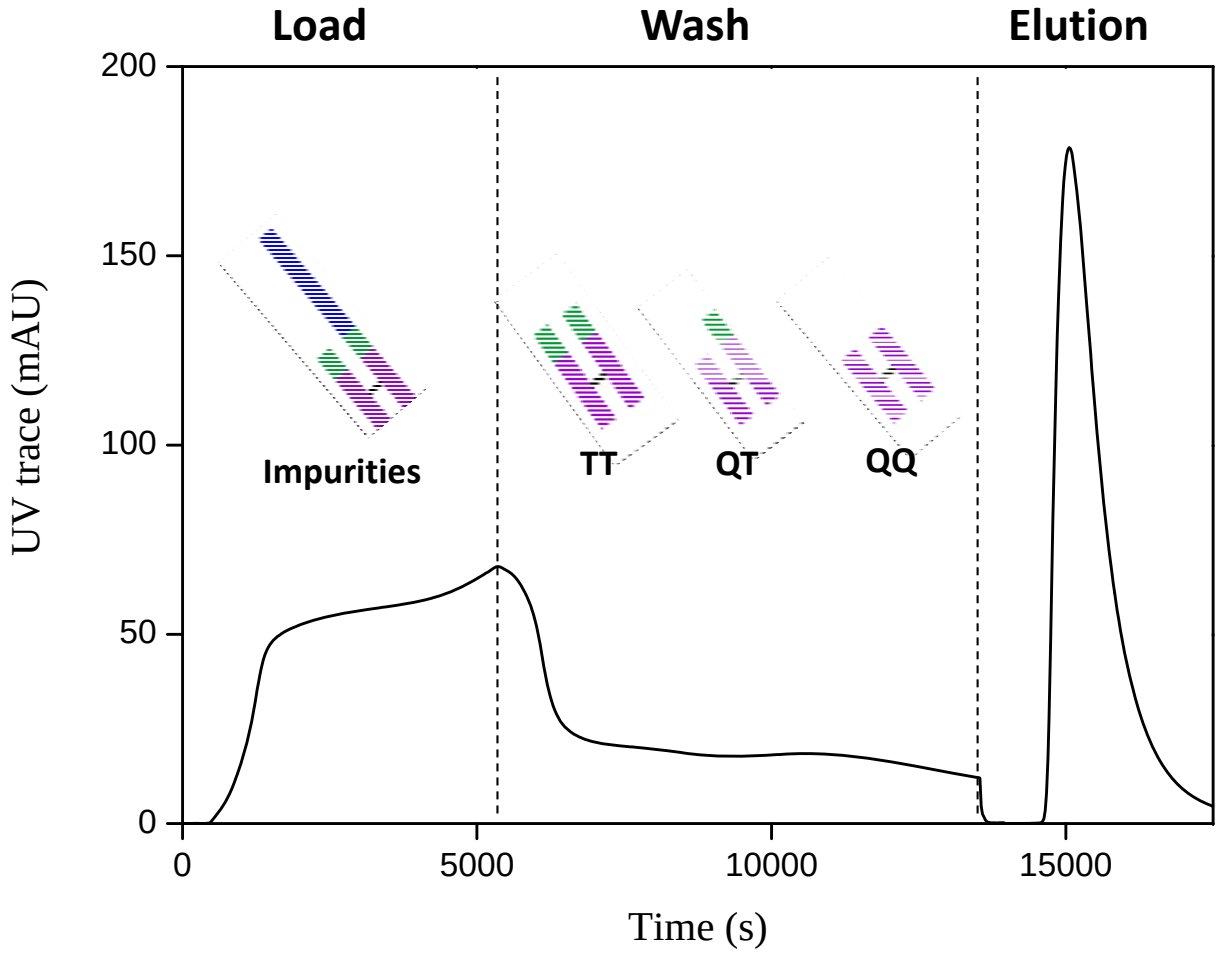
- Problem definition
- Proposed solution
- Model development
- Results
- Concluding remarks

Problem definition

Molecule


Product
T/T
TT
Q/T
QT
<Q/T
Q/Q
QQ
<Q/Q
<Q/<Q
Product - Related Impurities
110 kD
80 kD
60 kD
42 kD
T
Monomers
Q
<Q
Host cell protein
DNA

Process



Equil / Load / Wash – 1M NaCl, pH 7
Elution – 20% Propylene Glycol, pH 7
Regeneration – 0.1M Na Acetate pH 4

OBJECTIVES

- **Impurity removal (80kDa < 0.25%)**
- **Product recovery (> 52%)**
- **Percentage T in elution peak (25 < %T < 45)**

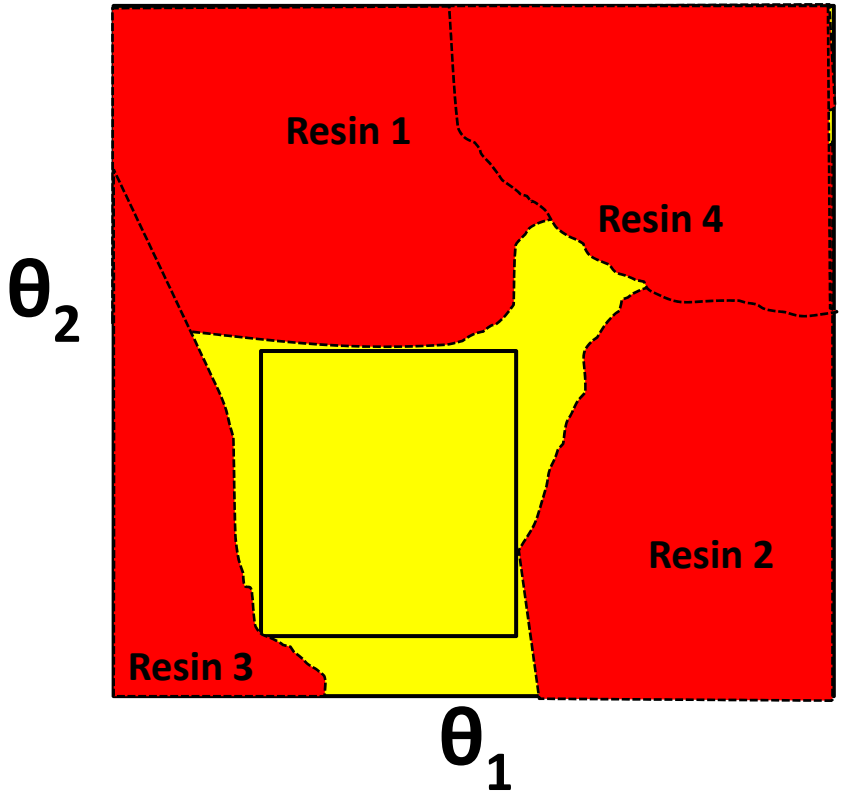
PROBLEM : RESIN LOT-TO-LOT VARIABILITY

Proposed solution

Objective 1: Identify fixed design space

Design Space

CQA failure



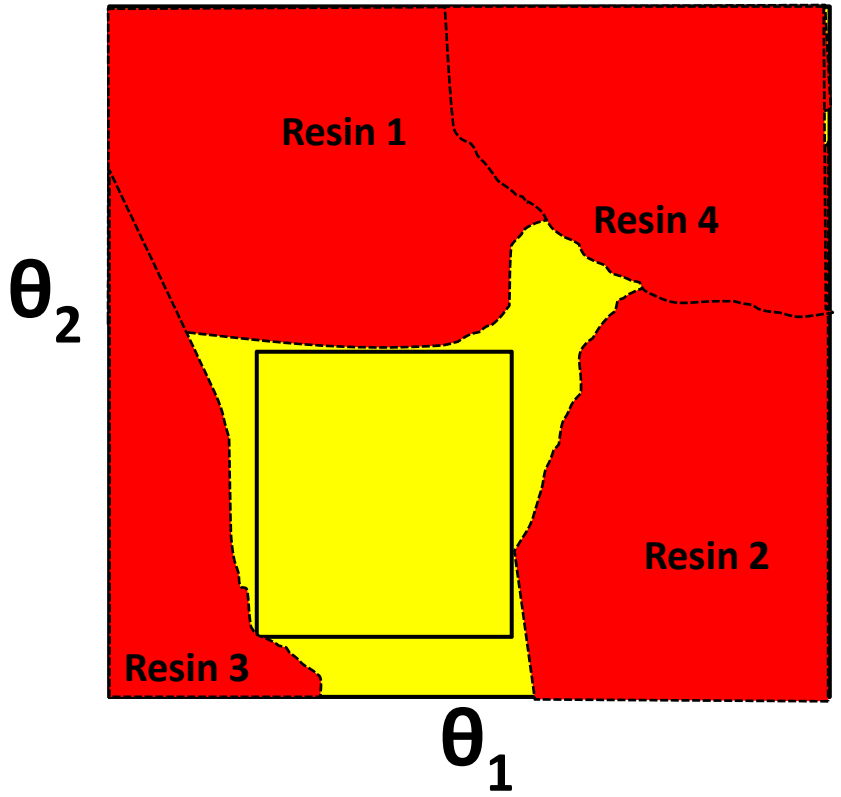
Resin Lot Variability – Identify design space

- For multiple resin lots, narrow individual variable ranges
  - SMALL available design space
- …and may EXCLUDE MANY FEASIBLE POINTS when design space is fixed

Objective 2: Identify adaptive design space

Design Space

CQA failure



Resin Lot Variability

Hypothesis: Advantageous to modify operating conditions based on RESIN LOT

- ADAPTIVE DESIGN SPACE

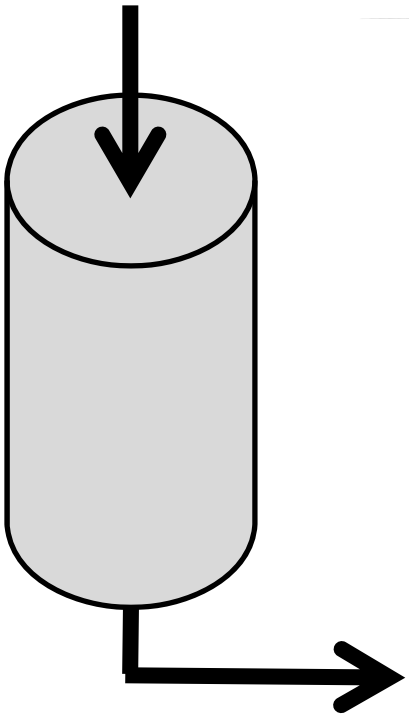
Summary

Inlet concentration, i

Mass challenge, k

Wash length, j

Resin lot, l



~~**Impurity removal**~~

Percentage T in elution peak, p

Product recovery, r

GIVEN: i, k, j, l **DETERMINE: p, r**

Model development

Approach

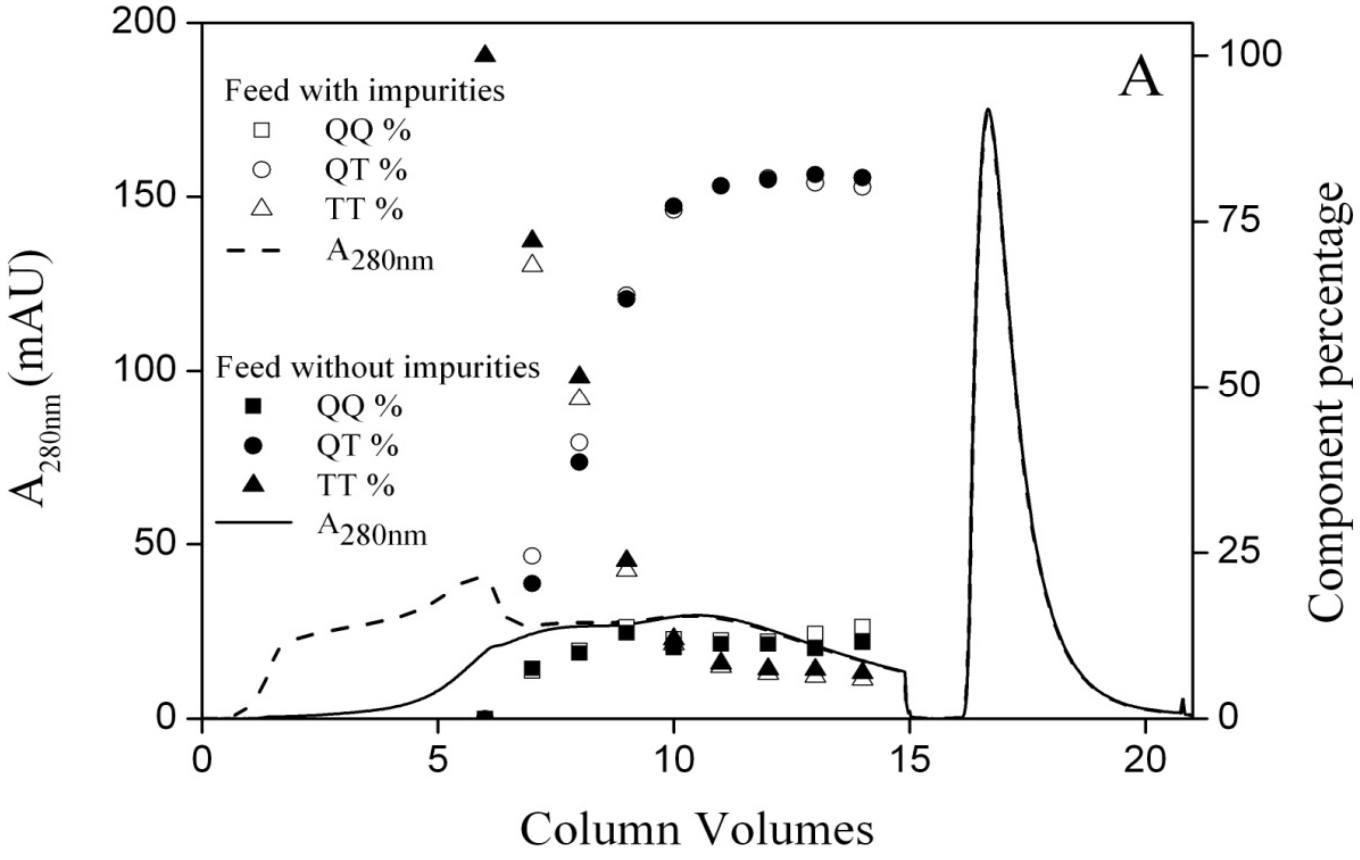
Goal : develop a model with ***sufficient accuracy*** for industry.

With this in mind:

- **Minimize use of purified material** - Model calibration techniques
- **Minimize experimental effort** – Make use of HTS expertise
- **Minimize computational effort** - Use simple as possible model

Assumptions

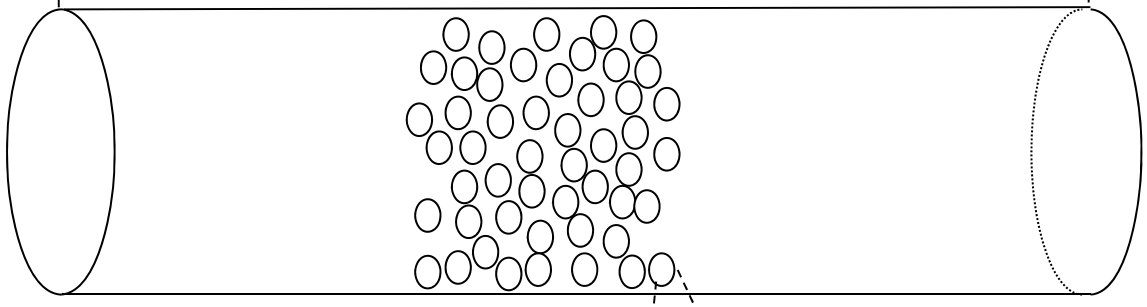
- **All product on column at end of wash is collected in the elution step**
- **Impurities in the feed stream had a negligible impact on the product separation**



Model

$$\left[uC_i^m - D_{A,i}\frac{\partial C_i^m}{\partial z}\right]|_{z=0} = uC_{i,0}^m \quad \forall i = 1,\dots,N_C$$

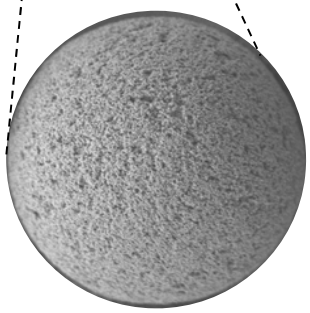
$$\frac{\partial C_i^m}{\partial z}|_{z=L} = 0 \quad \forall i = 1,\dots,N_C$$



Mass Transfer through Column

$$\frac{\partial C_i^m}{\partial t} + \frac{(1-\epsilon_T)}{\epsilon_T}\cdot\frac{\partial C_i^{sp}}{\partial t} + u\cdot\frac{\partial C_i^m}{\partial z} = D_{A,i}\cdot\frac{\partial^2 C_i^m}{\partial z^2} \qquad \forall i = 1,\dots,N_C \quad z\in(0,L)$$

C_i^m Mobile phase concentration
C_i^{sp} Stationary phase concentration
$D_{A,i}$ Apparent axial dispersion coefficient
ϵ_T Total column porosity
$q_{s,i}$ Stationary phase saturation capacity
$k_{a,i}$ Adsorption constant



Equilibrium Isotherm

$$C_i^{sp} = \frac{q_{s,i}\cdot k_{a,i}\cdot C_i^m}{1+\sum k_{a,i}\cdot C_i^m}$$

$$\forall i = 1,\dots,N_C \quad z\in(0,L)$$

Procedure for model calibration

START

Initial model calibration experiments

- High throughput batch adsorption
- Pulse injection of small unretained molecule

$$q_s \quad k_{a,i} \quad D_A \quad \epsilon_T$$

Parameter estimation

- gPROMS

Model validation

- Small scale column runs on AKTA FPLC
- Elution peak product distribution
- Fractions taken during load and wash product distribution

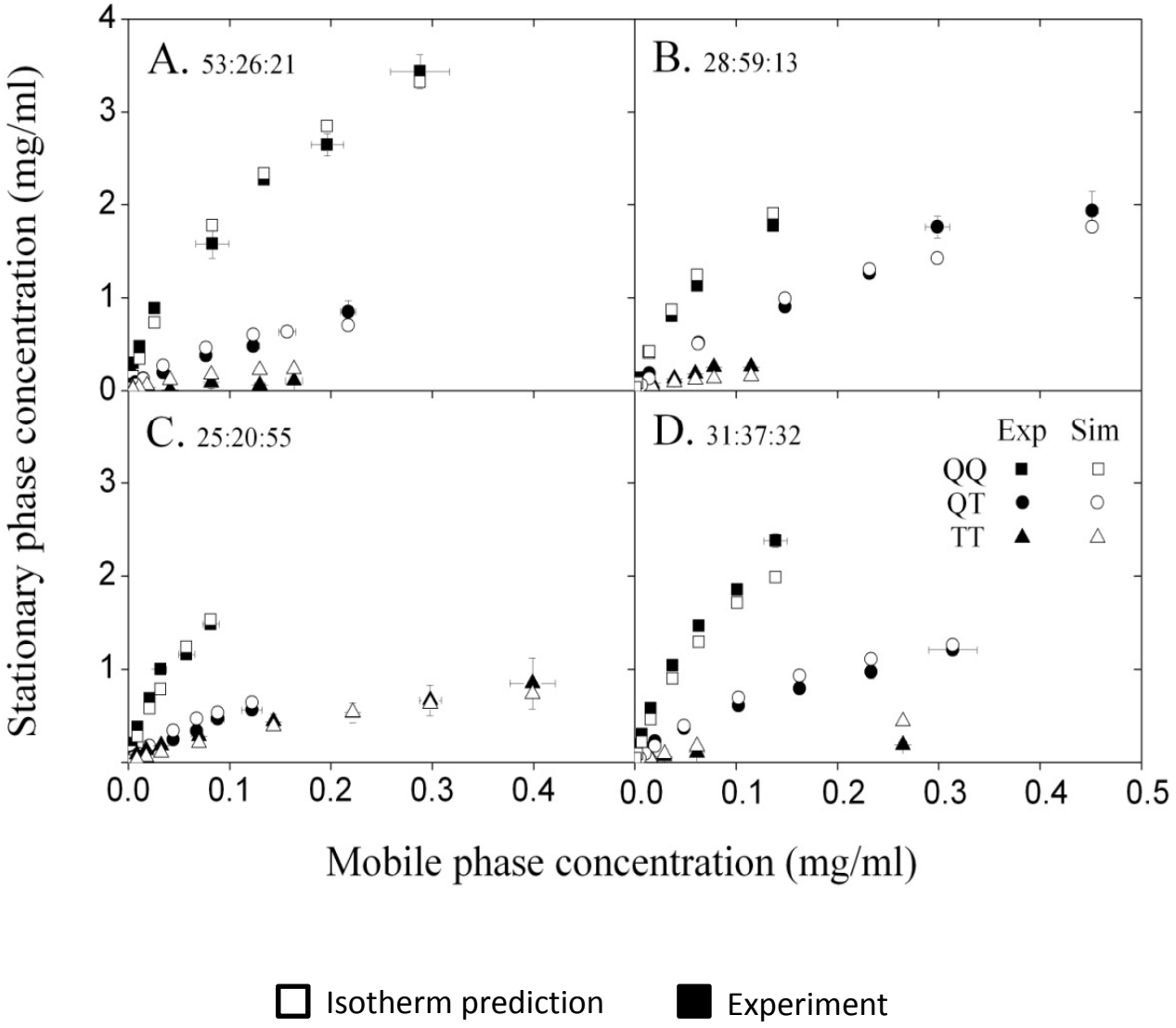
END

Unsatisfactory model performance

Isotherm

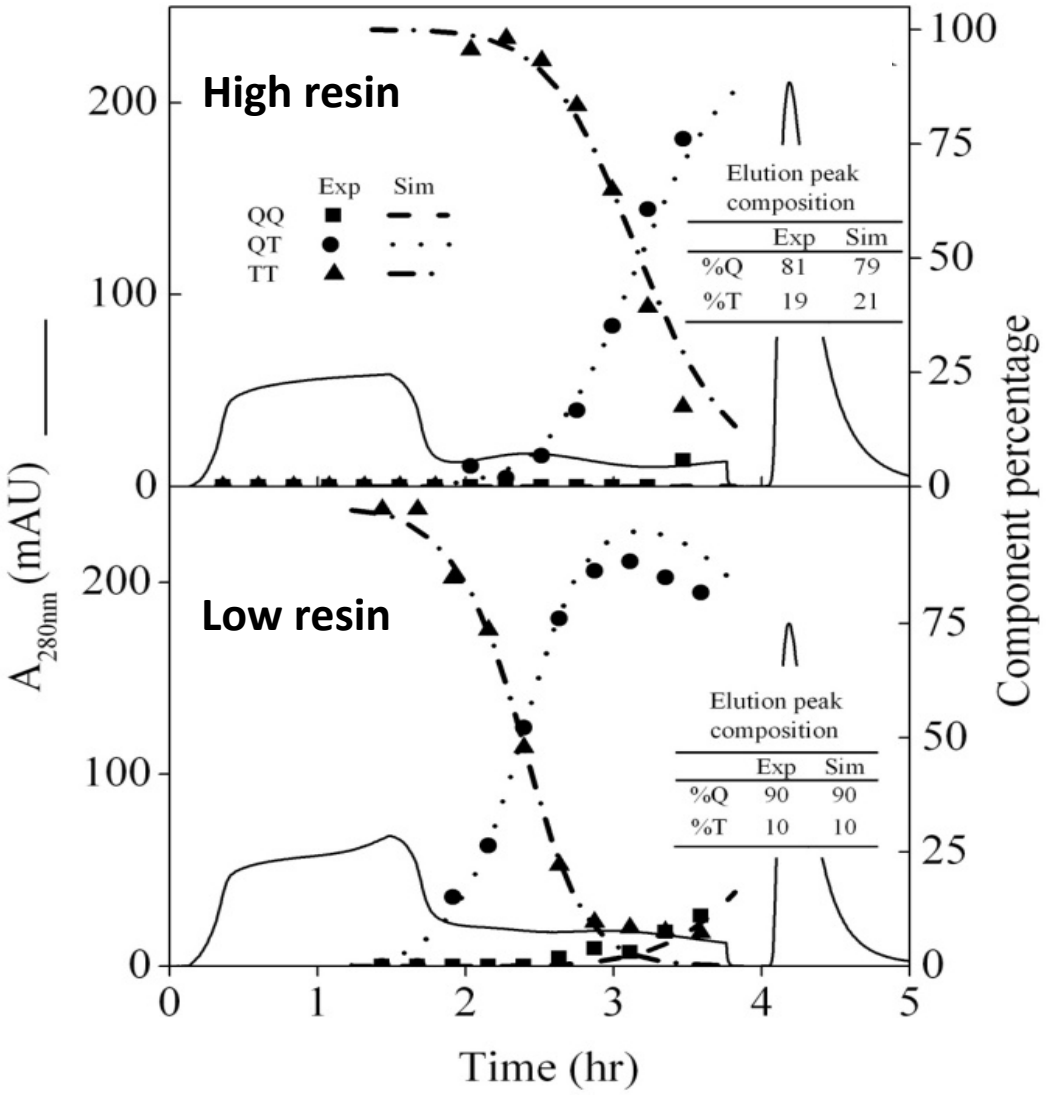
$$C_i^{sp} = \frac{q_{s,i} \cdot k_{a,i} \cdot C_i^m}{1 + \sum k_{a,i} \cdot C_i^m}$$

Parameter	High	Low
q_s	6.39	6.45
$k_{a,1}$	6.33	4.30
$k_{a,2}$	2.30	1.49
$k_{a,3}$	1.01	0.52



Isotherm prediction Experiment

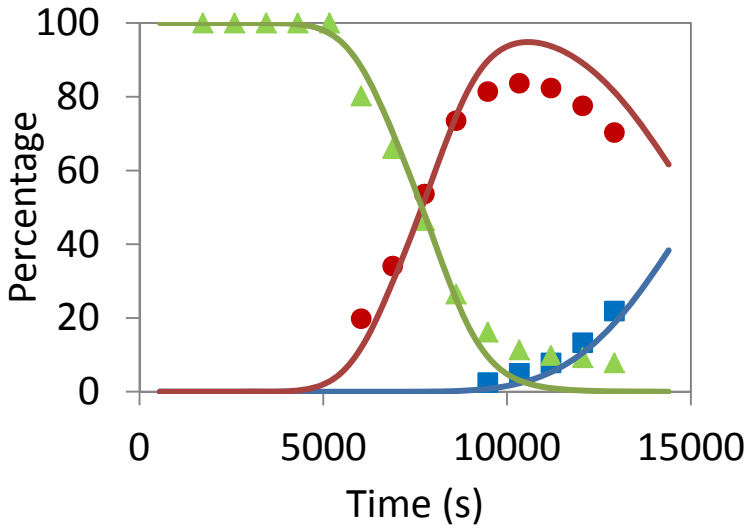
Model validation after refinement

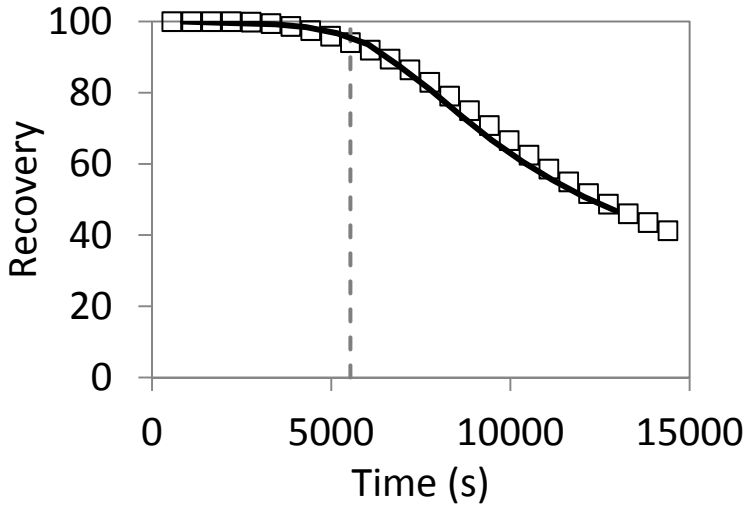


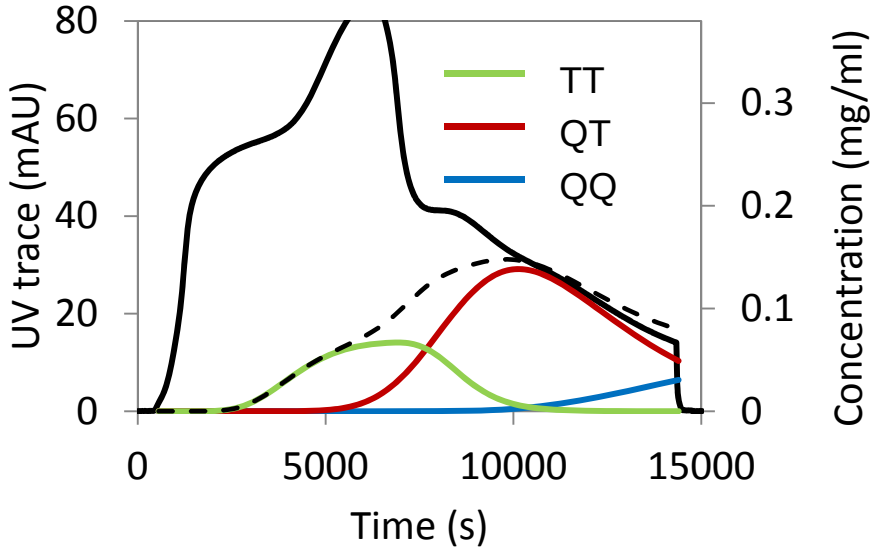
Load challenge (mg/ml)	1.5
Load concentration (mg/ml)	0.26
QQ load percentage	35
QT load percentage	35
TT load percentage	30

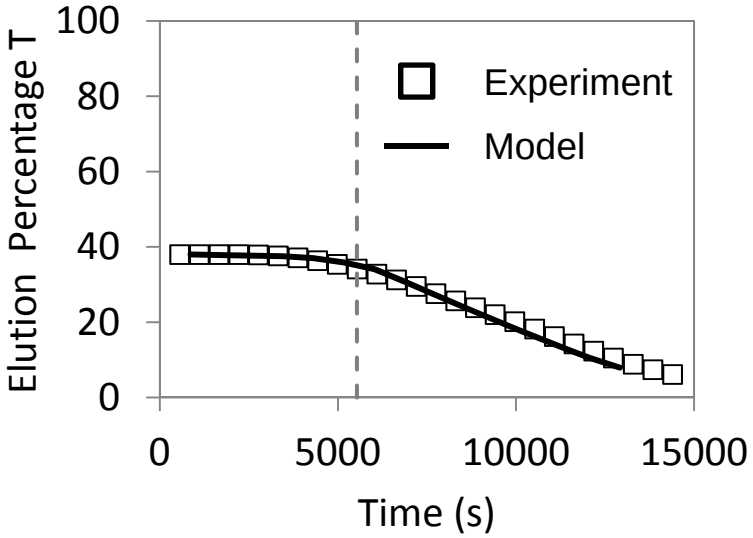
Parameter	Before	After
D_A	0.000229	0.003

Model predictions in detail





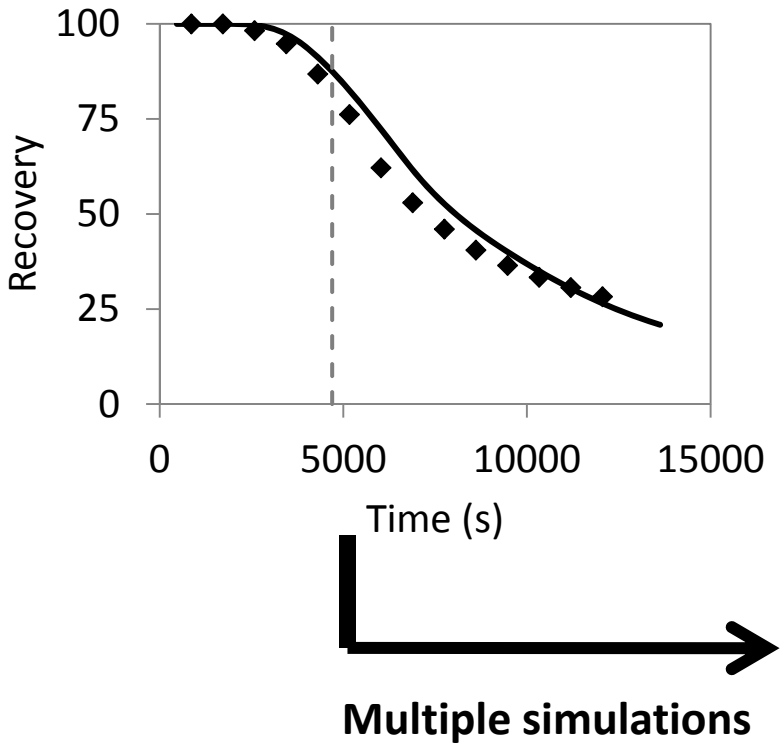


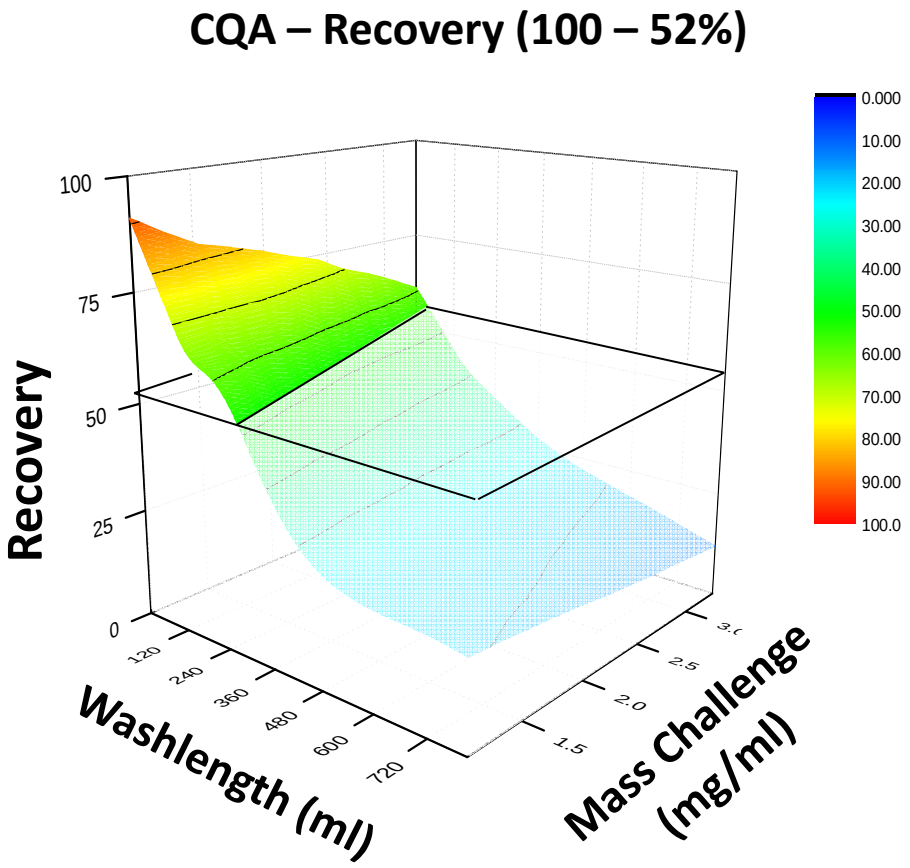


Results

Deterministic design space

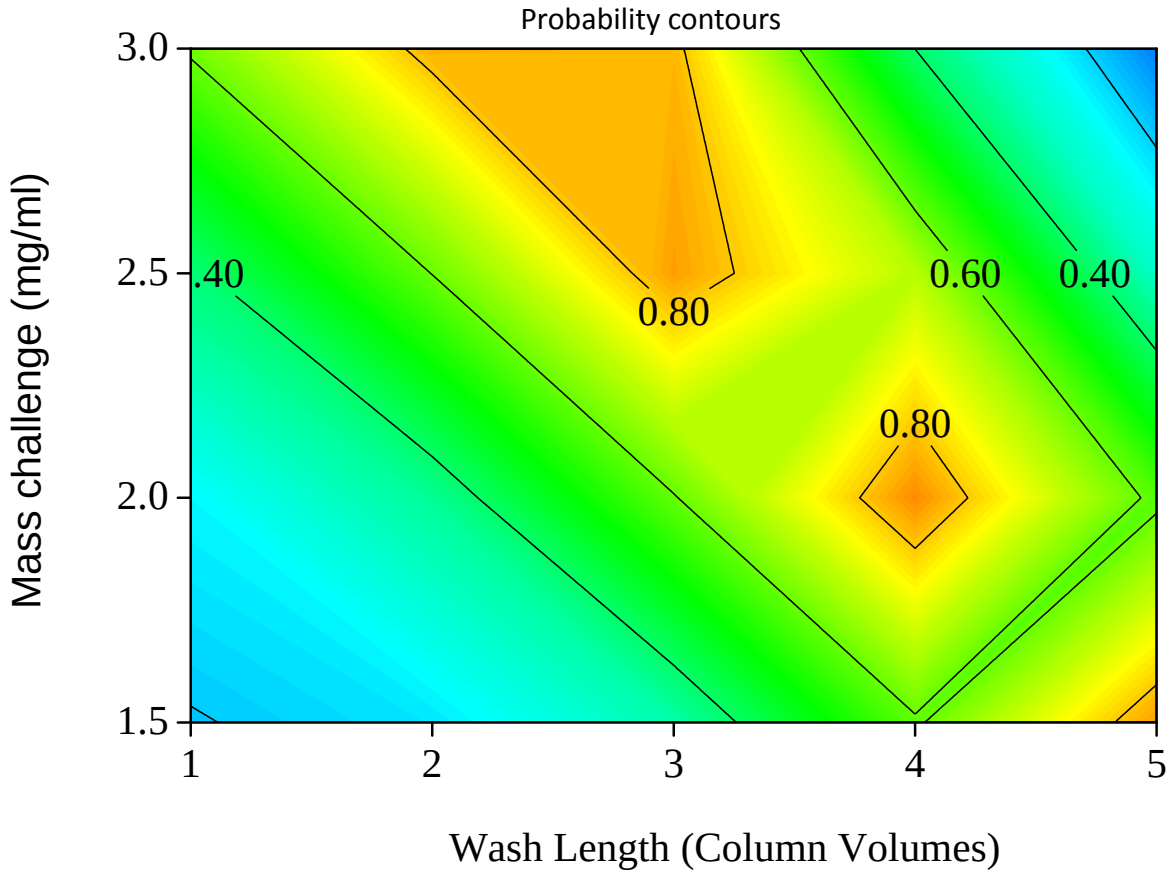
- For specific inlet concentrations, C_{IN} - determine region where CQA is met





Fixed probabilistic design space

- **COMBINATION OF LOW AND HIGH - Minimum of p(low) and p(high)**

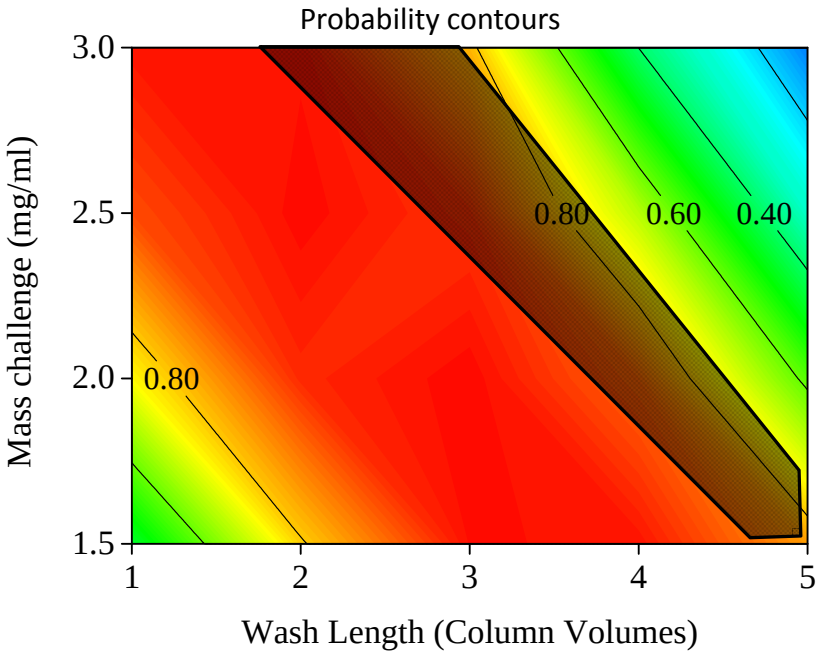


Small areas where P > 0.8

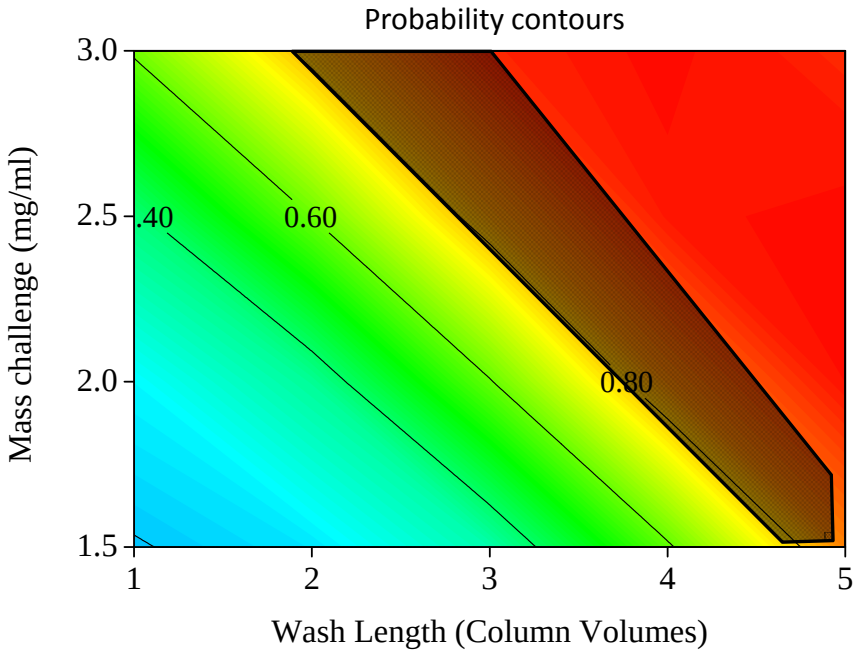
- **Conclusion: Fixing the design space is not an option**

Adaptive probabilistic design space

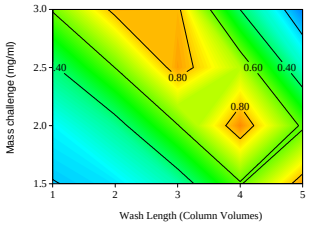
- **p(low) or p(high) depending on resin lot in use**



Low resin



High resin



- **Larger design space areas**
- **Enables operation in robust areas**

Concluding remarks

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- Better process understanding

- Optimum operation

- Quantify inherent risk due to uncertainty in
  i. Upstream (feed stream)
  ii. Controlled variables
  iii. Manipulated variables
  iv. Model parameters

- Identify where to prioritize R&D resources

Acknowledgements

- UCL Colleagues
- PPD Andover

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Thank you!

An adaptive design space in chromatography

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