A model based approach to an adaptive design space in chromatography

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Problem definition

We considered an industrial hydrophobic interaction chromatography step, used in the purification of a commercial therapeutic protein. The step had a complex mixture of impurities in the feed stream and a multi component product (Figure 1). The step must deliver a specific distribution of six product forms in the elution peak whilst maintaining product recovery and impurity removal.

The chromatography is particularly challenging because the resin has been found to exhibit lot to-lot-variability which significantly limits the achievable design space.

In this work, we use a mechanistic model to generate probabilistic design spaces for the two most extreme resin lots, a high binding resin and a low binding resin. We then use the probabilistic design spaces to explore the possibility of *adapting* the chromatography design space based on the resin lot in use, rather than fixing the design space for all resin lots.

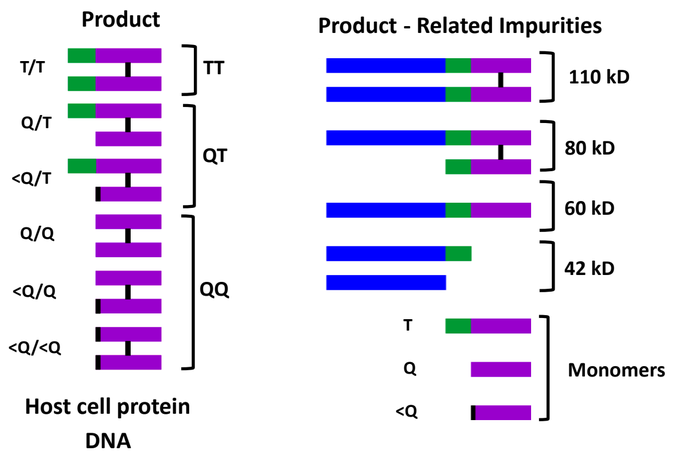
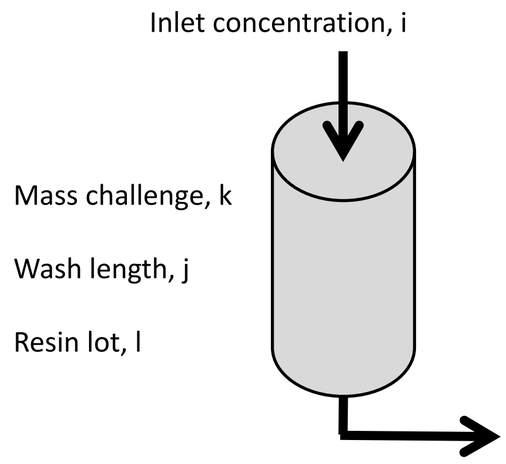


Figure 1. Illustrating the six forms of the multi-component product, the lumping of the 6 forms into three components (TT, QT and QQ), and impurities present in chromatography feed material



~~**Impurity removal** -~~ **not considered**

Percentage T in elution peak, p

Product recovery, r

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

Figure 2. Modelling objectives

Model development

In this work, we developed an equilibrium dispersive model coupled with a competitive Langmuir isotherm (Guiochon et al., 1994), coded within gPROMS, an equation based modelling and optimization software package (Process Systems Enterprise, 2012). The model equations are illustrated in Figure 3.

We utilize a stepwise approach to determine key model parameter values (Figure 4), using targeted scale down experimental studies to quickly generate data for estimation of model parameters, before employing an iterative procedure where laboratory scale column runs of the industrial process are used to refine parameters in a sequential manner until model predictions exhibit satisfactory agreement with experimental data.

Parameter estimation conducted within gPROMS was used to estimate the competitive Langmuir isotherm adsorption parameters using data from experimental micro well plate competitive batch adsorption studies., and the apparent axial dispersion coefficient from scale down column studies.

The total column porosity were calculated using the retention time of an unretained small molecule during pulse injection experiments.

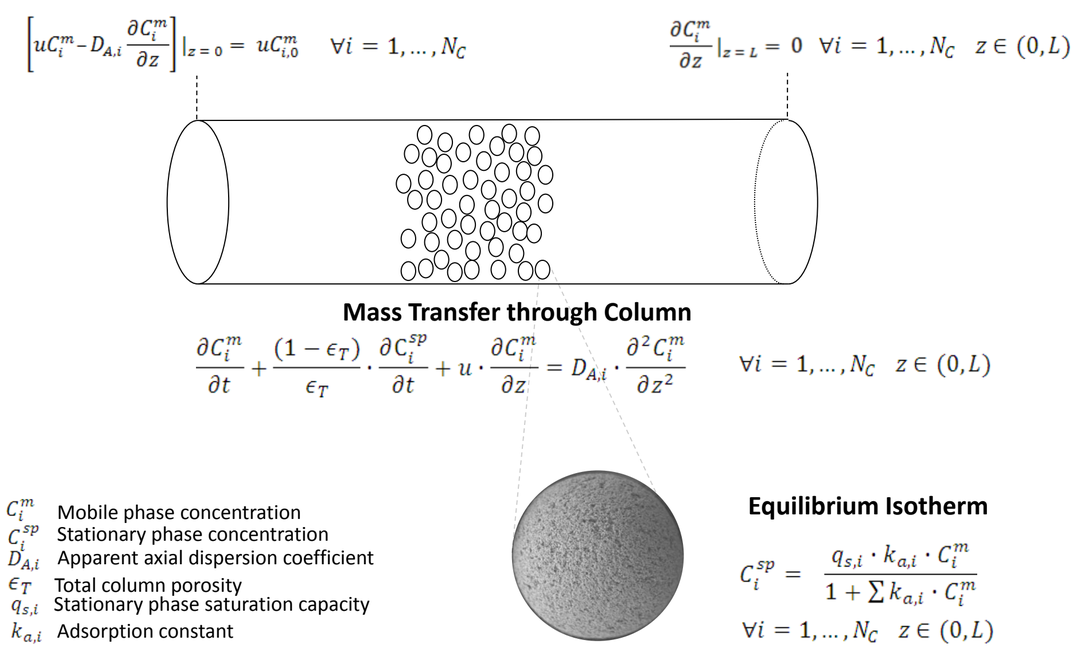


Figure 3. Model equations

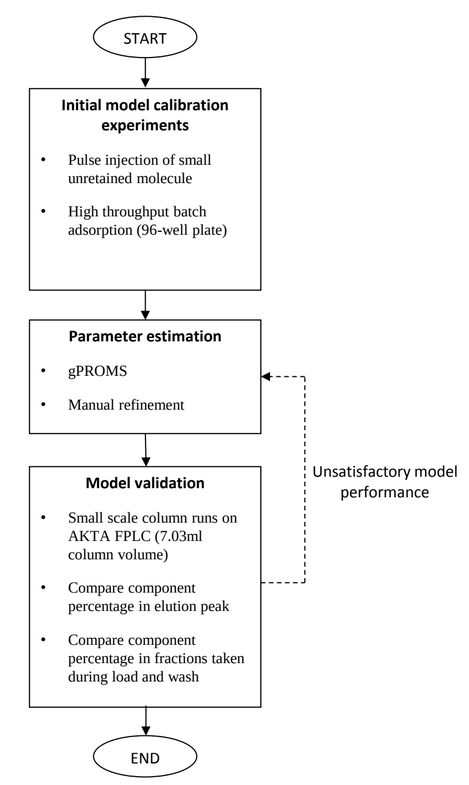


Figure 4. Model calibration procedure

Model validation

We validated the model performance by comparing model predictions with experimentally determined percentages of product forms in the elution peak, and in samples taken every column volume (CV) during five different runs of the industrial process. We found good agreement between model predictions and experimental results, an example is shown in Figure 5, 6, 7 and 8. In this example the predicted product form distribution in the elution peak was 93.2 % total Q and 6.8 total T, the experimentally measured values were 93.5 % total Q and 6.5 % total T.

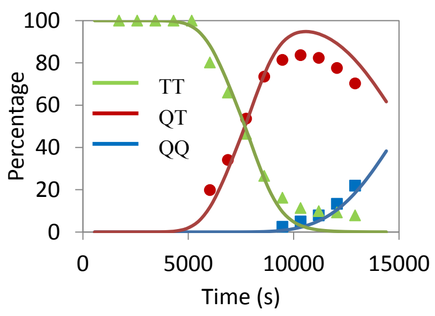


Figure 5. Comparison on model predictions and experimental product from distributions in samples taken during run of industrial process. Symbols: Experiment. Lines: Model predictions

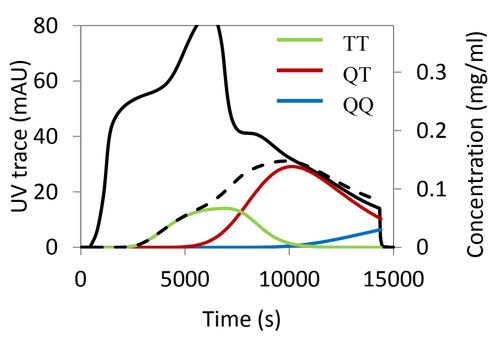


Figure 6. Overlay of predicted concentrations and experimental UV trace

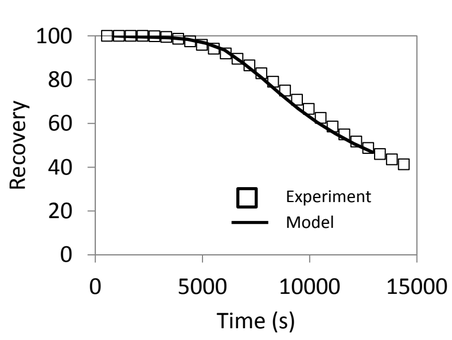


Figure 7. Comparison on model predictions and experimental recovery

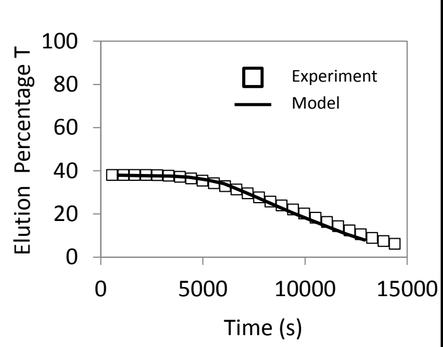


Figure 8. Comparison on model predictions and experimental percentage T in elution peak

Results and discussion

We used stochastic simulations to generate probabilistic design spaces for the high and low binding resins. The design spaces (Figures 9, 10 and 11) show the probability of meeting the chromatography objective (a specific distribution of product forms in the elution peak) as a function of manipulated variables (wash length and mass challenge) given the variability experienced during normal process operation in the inlet variables (inlet concentration of the multiple product forms).

The probabilistic design spaces generated in this work indicate that significant increases in process robustness can be made by adapting the design space based on the resin lot in use, rather than fixing the design space for all resin lots. An adaptive design space enables operation further away from high risk regions, increases the size of operating regions and improves flexibility to variations in process inputs.

The future, there are exciting possibilities to use the techniques developed in this work to develop deterministic design spaces, where using measured inlet variables we can quickly generate the available design space and quantify the risk associated with each unique operating point in that design space (Figure 12).

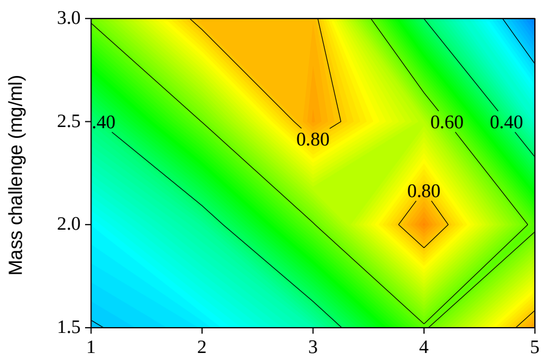


Figure 9. Fixed probabilistic design space (minimum probability of high and low binding resin). Graph shows probability contours

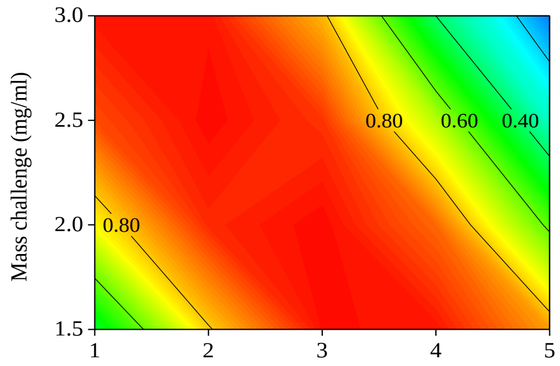


Figure 10. Probabilistic design space of low binding resin, used when using an adaptive design space. Graph shows probability contours

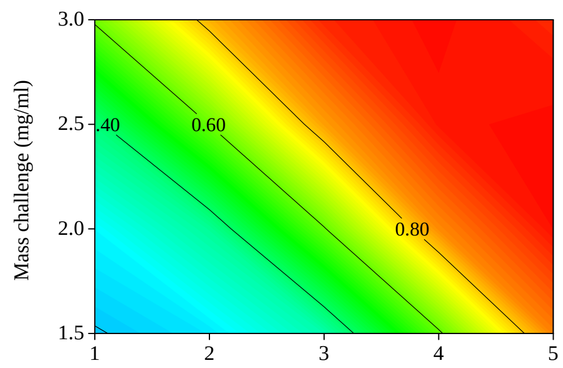


Figure 11. Probabilistic design space of high binding resin, used when using adaptive design spaces. Graph shows probability contours

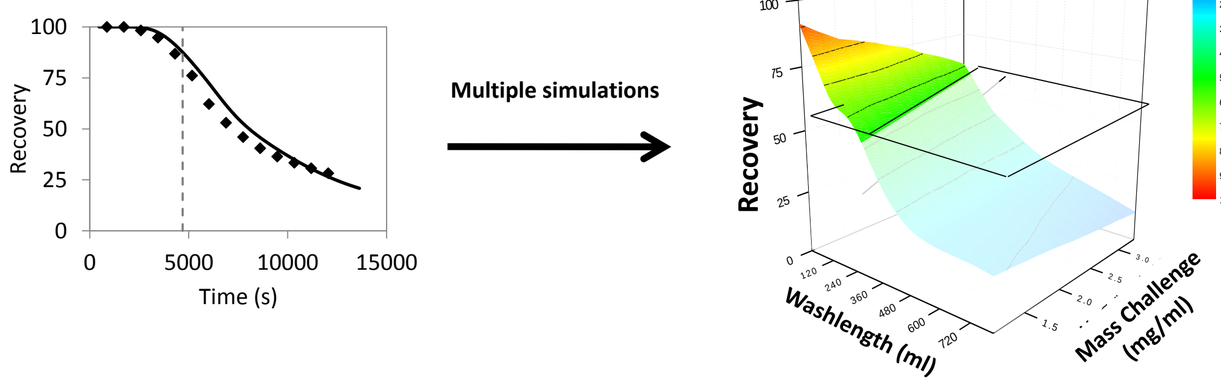


Figure 12. In the future, we will be able to use deterministic design spaces where given measured inlet variables, we can determine the available design space, and quantify the risk associated with operating in each unique region of that design space.

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