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Simplifying Progress

Multi-Column Chromatography Process Modelling for Process Performance Prediction

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Introduction

Multi-column capture chromatography methods performed on the BioSMB platform have the potential to unlock increases in process performance. However, experimental methods to determine optimal process conditions are time and resource intensive. Modelling strategies can help to reduce time and resources necessary to optimize the process. In this study we evaluate three modeling approaches, and the most accurate of the three was chosen to explore how the number of columns and the column configuration strategy can impact productivity and binding capacity.

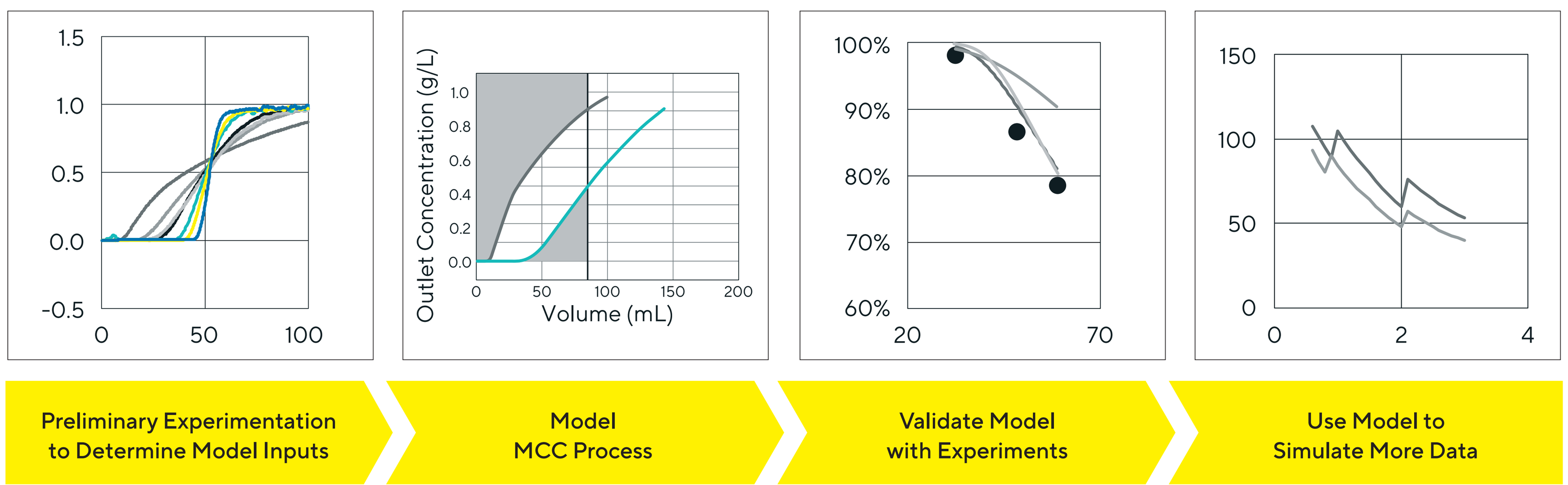
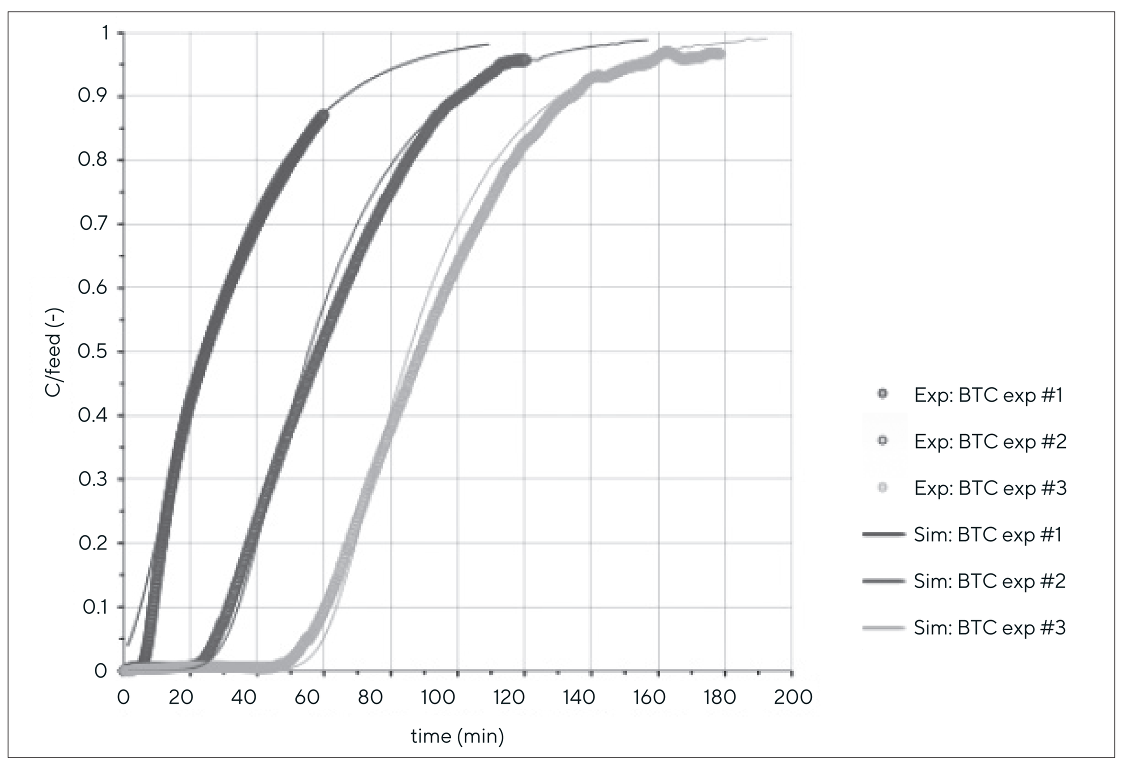


Figure 1
Flowchart of Total Modelling Process

Modelling Strategies

Three methods to model countercurrent multi-column protein A capture processes:

- An "empirical method" relying on contact time and integration of breakthrough curves
- A simplified computational model which assumes a linear isotherm
- ChromWorks, which assumes a linearly modified Langmuir isotherm and uses the linear driving force approximation with a mixing cells model



$$\bar{C}_j = \bar{\lambda}_j C_j + \frac{\bar{N}_j \tilde{K}_j C_j}{1 + \tilde{K}_j C_j}; \quad \bar{K}_j = \bar{\lambda}_j + \bar{N}_j \tilde{K}_j$$

$$\frac{d\bar{C}_j}{dt} = \frac{1}{t_j^i} [\bar{C}_j^* - \bar{C}_j]$$

LDF Mass Transfer Time

	Comp1
ti (s)	1338

Linearly Modified Langmuir Isotherm

	Comp1
$\bar{K}$	649.441
$\bar{\lambda}$	0.5
$\bar{N}$	101.93
$\tilde{K}$	6.3667

Figure 2
An Example of the ChromWorks Modelling Method with Equations for:
a.) The Linearly Modified Langmuir Isotherm and b.) The Linear Driving Force Equations

Experimentation-Model Generation

Product breakthrough curves were generated by loading a single Protein A column with 100 g mAb/L resin

- 21 breakthrough curves generated as input data for building each model
- Load concentrations at 1, 5, 8 g/L using pure mAb
- Load residence times ranging from 0.6 to 10.8 minutes

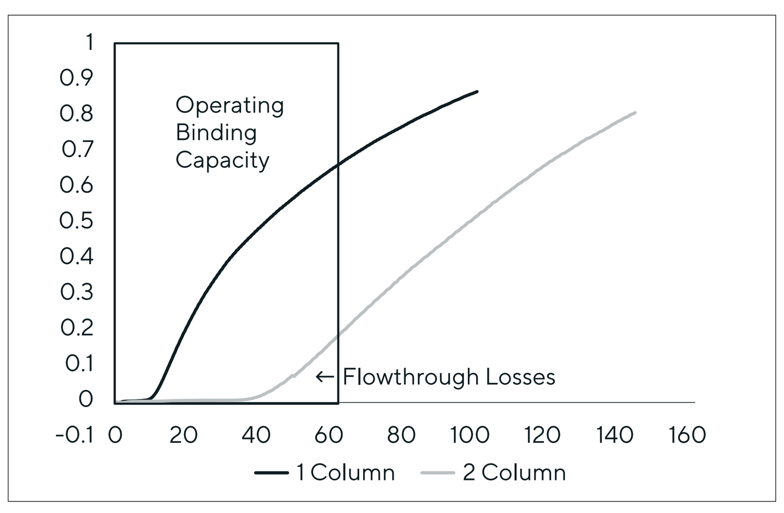


Figure 3
A Demonstration of the Empirical Modelling Approach

Experimentation-Model Validation

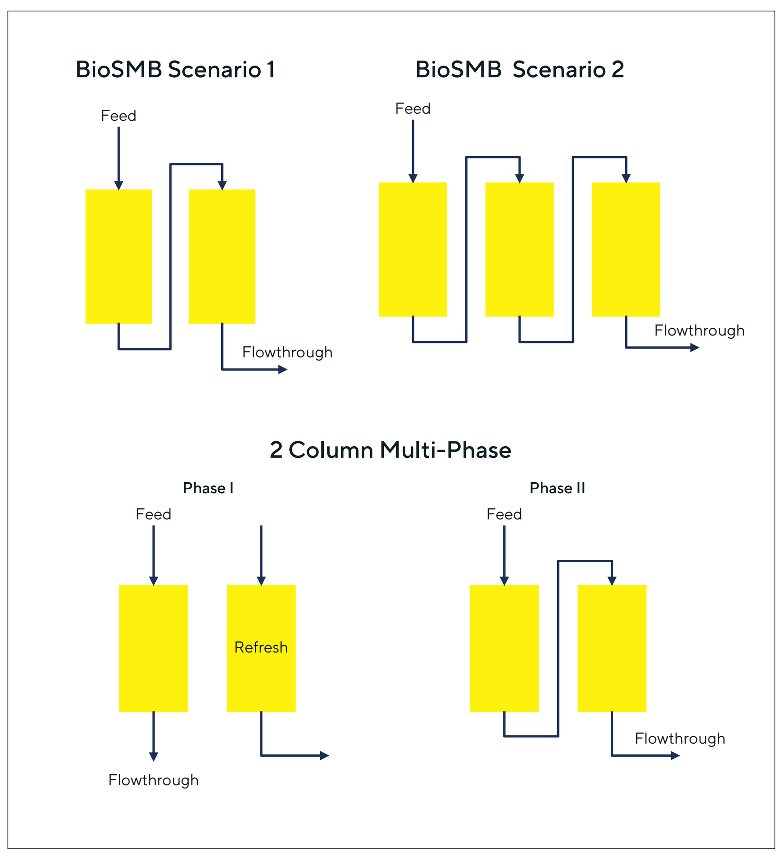


Figure 4
Flow Diagrams of the Three Load Scenarios Explored

Three different loading scenarios were examined

- BioSMB Scenario 1 with 2 columns in the load zone
- BioSMB Scenario 2 with 3 columns in the load zone
- 2 column multi-phase variable flow load

The design space for each loading scenario is bound by low and high feed concentrations at 0.6 min. load residence time. For each point, three MCC experiments were conducted to confirm the maximum capacity usage of the column. Capture efficiencies of 99,95 and 90 % were targeted.

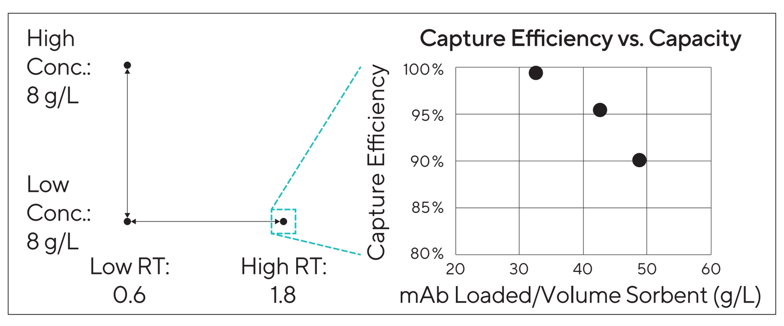


Figure 5
The Design Range Explored

Model Evaluation

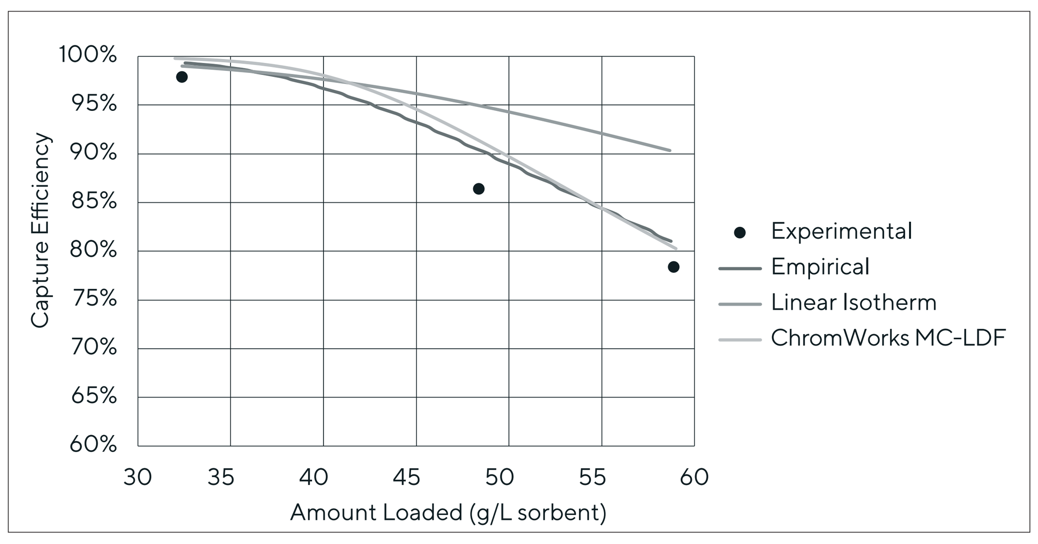


Figure 6
A Representative Comparison Containing Three Models and Three Points of Experimental Data: BioSMB Scenario 1, 1 g/L Feed Concentration, 0.6 Minute RT, Capture Efficiency vs. Capacity

Three experimental points were compared to the computational and empirical models. Residual sum of squares analysis was conducted on 12 experimental points per model to determine goodness of fit.

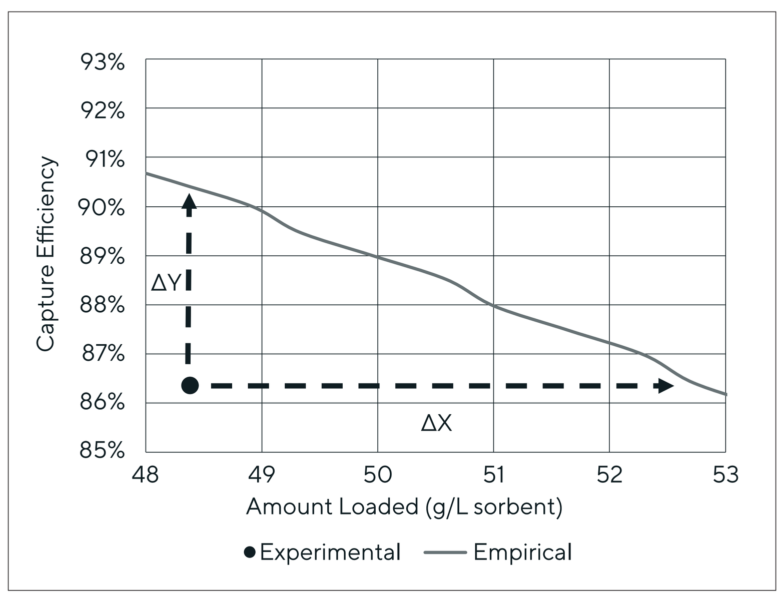


Figure 7
A Demonstration of the Residual Sum of Squares Calculation

	Empirical	Linear Isotherm	ChromWorks
99 % points	24	12	30
95 % points	197	278	148
90 % points	506	1205	277
Total SSRes	728	1494	506

Table 1
Residual Sum of Squares Values for Each Capture Efficiency Across All Loading Scenarios

From the BioSMB data, the ChromWorks computational model had the best fit.

Process Performance

For the BioSMB processes at each load residence time, varying load amounts were simulated in ChromWorks, and the amount that corresponded to 99% capture efficiency is reported as the operating binding capacity in figures 6 & 8.

The 2 column processes were simulated in ChromWorks to validate the absence of significant product loss.

A duration of 1500 seconds, corresponding to 25 total column volumes at a 1 minute residence time, was allocated in each cycle for wash, elution, and regeneration steps.

Residence times between 0.6 minutes and 3 minutes were simulated.

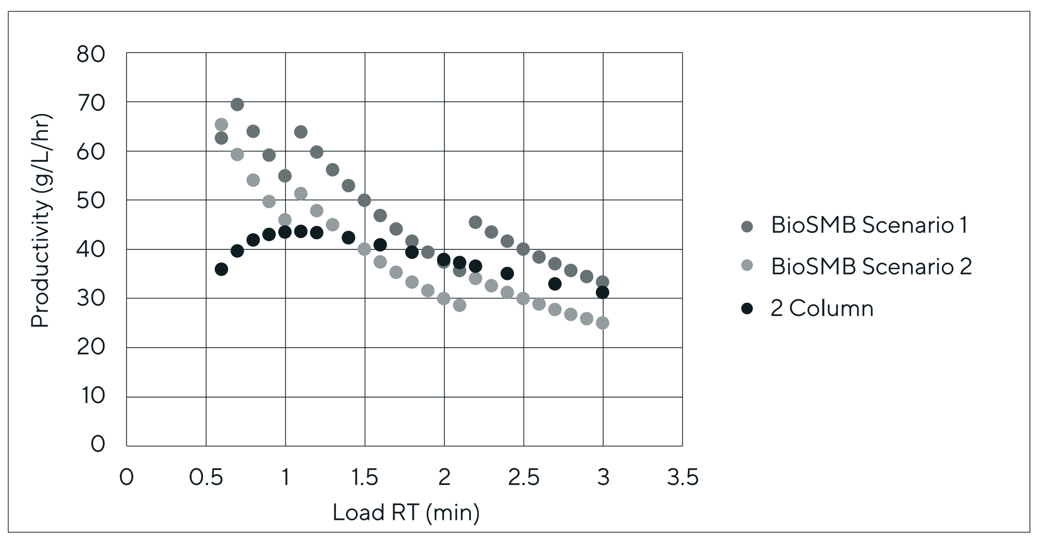


Figure 8
Specific Productivity vs. Primary Load Residence Time at 5 g/L Feed Concentration

Conclusions

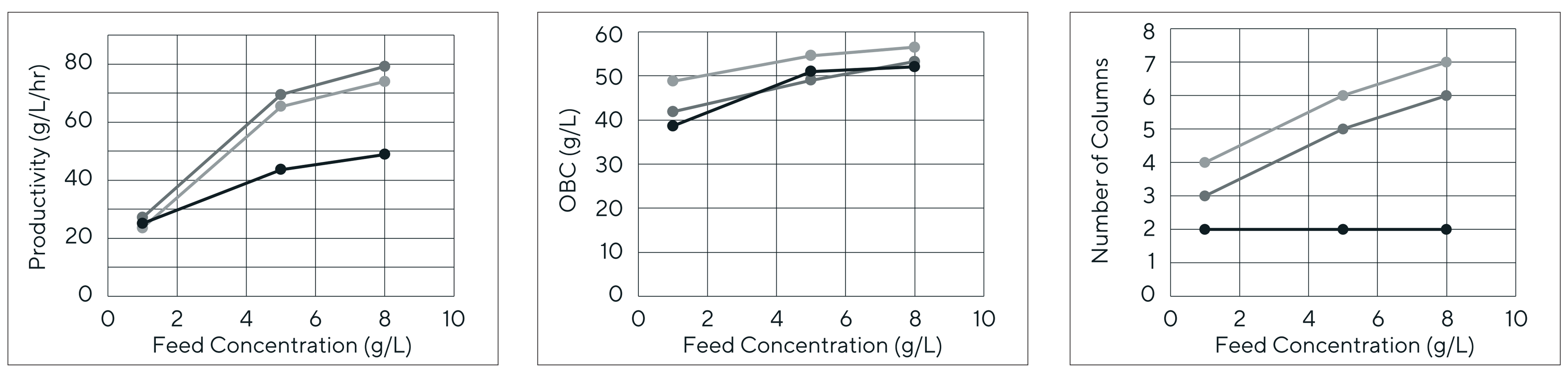


Figure 9
a) Points of Maximum Productivity for Each Loading Scenario at Each Feed Concentration
b) Operating Binding Capacities Corresponding to the Processes Reported in A
c) The Number of Columns Necessary to Run the Most Productive Scenario at a Feed Concentration

- A hybrid experimental and modelling approach for process prediction and optimization greatly reduces the amount of experimentation and time resources needed.
- At higher feed concentrations, BioSMB scenarios achieve large gains in productivity as opposed to 2 column processes, due to the ability to include more columns.
- In addition to the productivity advantages, BioSMB processes have the ability to load at a continuous, uninterrupted flowrate.

Note: The feedstock used in the experiments belong to Pall Life Sciences