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Master of Science HES-SO in Life Sciences

Integration of experimental observations over multiple scales for chromatography development

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DESCRIPTION

Pharmaceutical companies strive for faster and more efficient process development, reducing time-to-market. Automated high-throughput liquid handling systems (LHS) allow parallelization and miniaturization, facilitating rapid exploration of a wide operating space. However, miniaturization can lead to scale effects that must be addressed in process development.

In this thesis, differences between high-throughput liquid handling systems (LHS) and lab-scale were assessed, focusing on a cation exchange resin (POROS™ XS), and using experimental and mechanistic modeling approaches.

OBJECTIVES

1. Transfer the standard development approach for a cation exchange chromatography step (for Poros™ XS) to the LHS.

2. Evaluate differences between LHS and lab-scale using a monoclonal antibody.
   → Run lab experiments (gradient and step elution runs) for comparison.
   → Use mechanistic modeling in the open-source software CADET-Process to expose differences.

RESULTS

First, gradient and step elution runs with a monoclonal antibody on the LHS and lab scale were performed to compare the two scales. The experiments were very comparable demonstrating satisfactory overlay (**Figure 1**).

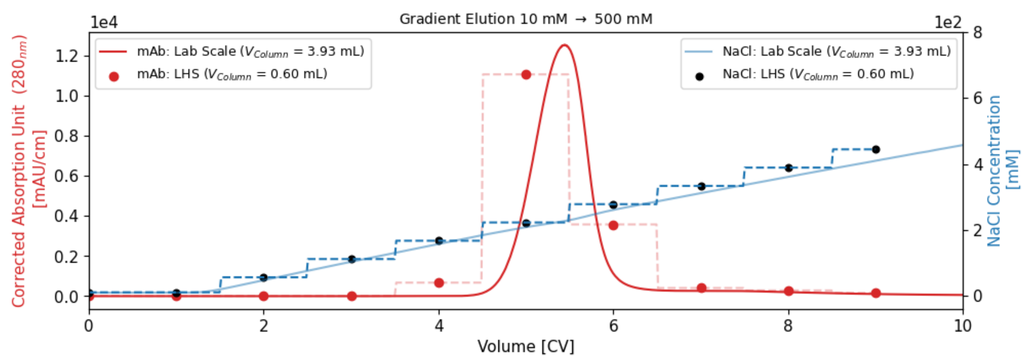

Figure 1: Overlay of gradient elution runs at different scales (LHS and lab scale).

Further differences were exposed using mechanistic modeling. A system of partial differential equations describing mass transfer (lumped transport-dispersive model) and binding (steric mass action isotherm) was calibrated at lab-scale (**Figure 2**) and at LHS-scale (**Figure 3**) at low loading densities of 2 g/L and 10 g/L resin.

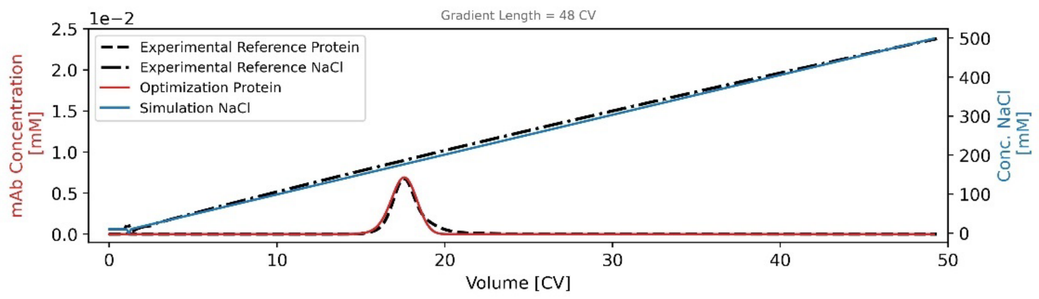

Figure 2: Part of model calibration process at lab-scale, comparing simulation (red & blue) with experimental reference data (black).

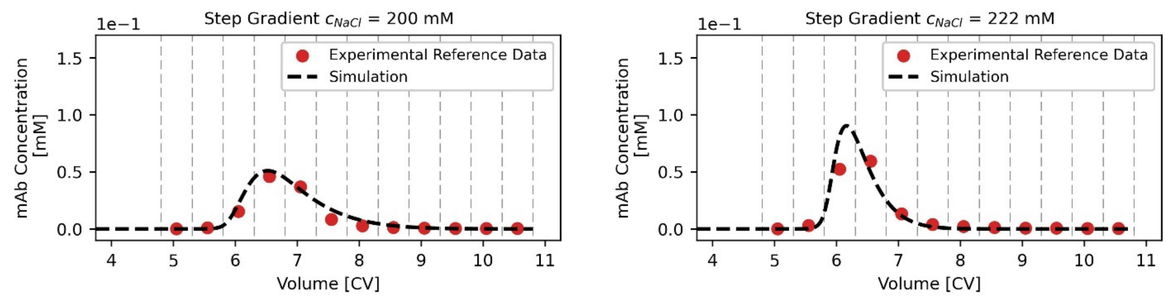

Figure 3: Part of model calibration process at LHS-scale, comparing simulation (black) with experimental reference data (red).

The previously described models were compared by simulations at lab scale with parameters either estimated from the LHS or from lab scale, revealing small differences in peak location and broadening (**Figure 4**).

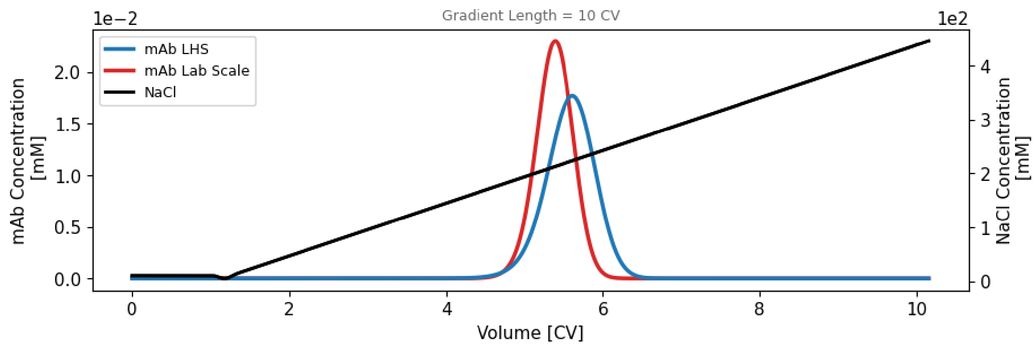

Figure 4: Comparison simulations at lab-scale and LHS-scale.

Lab-scale: k_{eff} = 4.04e-06 m/s
LHS: k_{eff} = 2.41e-06 m/s

The calibrated models showed more peak broadening at LHS scale with an estimated two-fold slower mass transfer. This difference in mass transfer was a compensation by the model, as mass transfer instead of axial dispersion was scaled with velocity. Literature suggested that increased relative axial dispersion may be a more accurate explanation of peak broadening at LHS (Benner et al. 2019).

CONCLUSION

Gradient and step elution runs at both scales turned out to be very comparable. Regarding mechanistic modeling, the calibrated models showed more peak broadening at LHS scale. The model failed to properly predict chromatography profile at higher loading densities, which should be assessed in future experiments.

In summary, it was shown that mechanistic modelling is a powerful tool to model, understand and predict chromatographic separations.

Possible future applications of mechanistic modeling include the prediction of chromatography at different scales. Further, mechanistic modelling could not only be used to find the optimal conditions for a single chromatography step, but potentially a global optimum over multiple chromatography steps.

[1] Benner et al., 2019. “Prediction of Lab and Manufacturing Scale Chromatography Performance Using Mini-Columns and Mechanistic Modeling.” Journal of Chromatography A 1593 (May): 54–62. https://doi.org/10.1016/j.chroma.2019.01.063.

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