

In-Silico Process Development Success Stories

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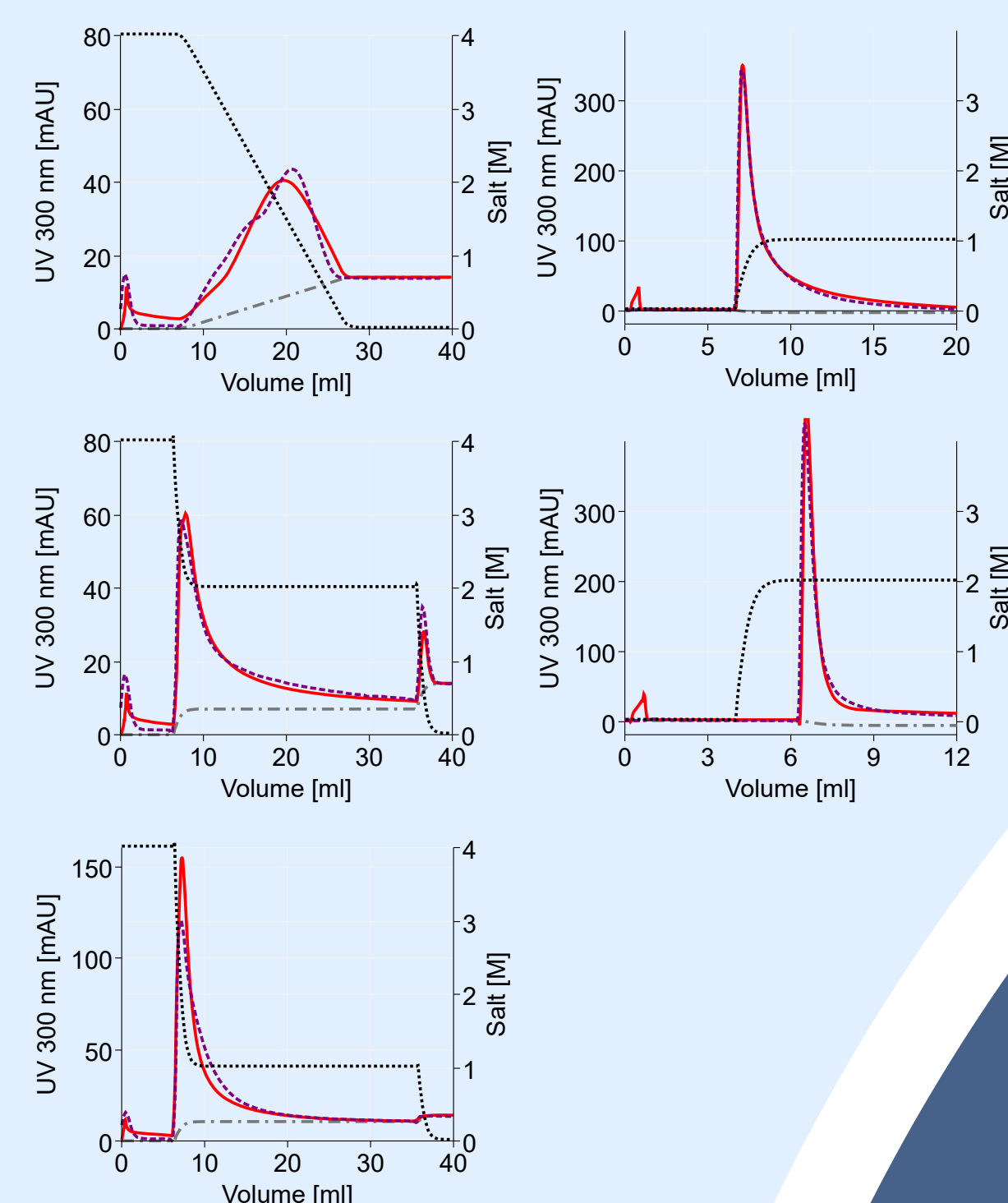
Optimal Experimental Design for Efficient Model Calibration

<http://dx.doi.org/10.5445/IR/1000051444> (Chapter 5)

The ChromX task O.E.Design optimizes the experimental settings, such that the estimation of unknown model parameters is facilitated. The objective is defined by the sensitivities of the selected model

parameters. Technically, O.E.Design alternates between estimating the quality of the unknown parameters and optimizing the experimental parameters. To allow for an estimation, measurement data must be available for the current experimental setup. Here, we used Glucose Oxidase on Capto adhere with an extended General Rate Model:

$$D_p(c_{salt}) = \frac{D'_{p0}}{1 + D_{p1} \cdot \exp(D_{p2} \cdot c_{salt})}$$



While the visual inspection of the model fits are certainly very good, only the calculated 95% confidence intervals for ks and the charge are acceptable. This finding highlights the necessity of a sound scientific basis for the selection of experiments for model calibration.

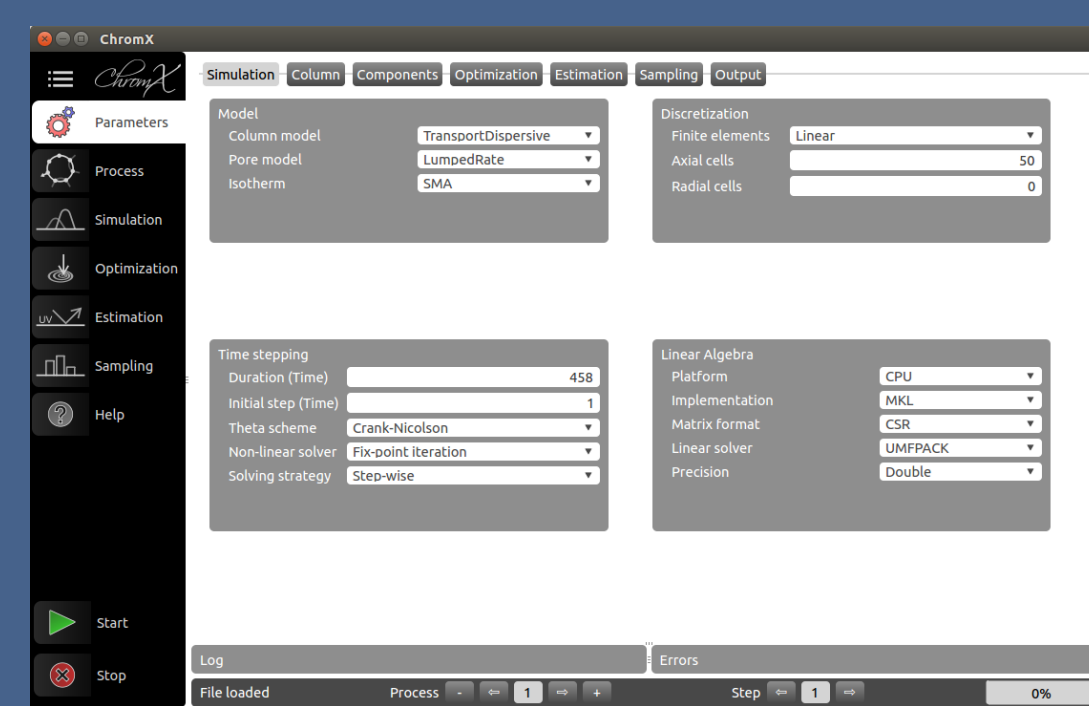
The highly efficient finite element solver is build on top of a flexible hardware-aware linear algebra layer for utilizing the computational power of multi- and many-core

Simulation

processors. The results of the simulations can be evaluated with interactive charts or exported as chromatograms or time-series of intra-column processes.

Models

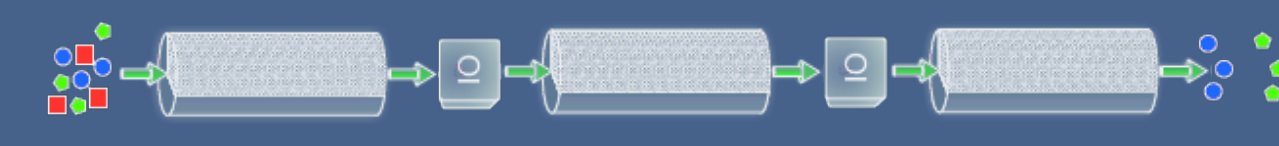
- Flow
 - Axial
 - Radial
- Diffusion Effects
 - Axial Dispersion
 - Film Diffusion
 - Pore Diffusion
- Adsorption
 - Langmuir
 - IEX (Brooks, Cramer)
 - HIC (Mollerup)
 - Mixed Mode (Ottens et al.)



Multi-Column Processes

Flexible inlet and outlet managers allow the construction of various multi-column processes.

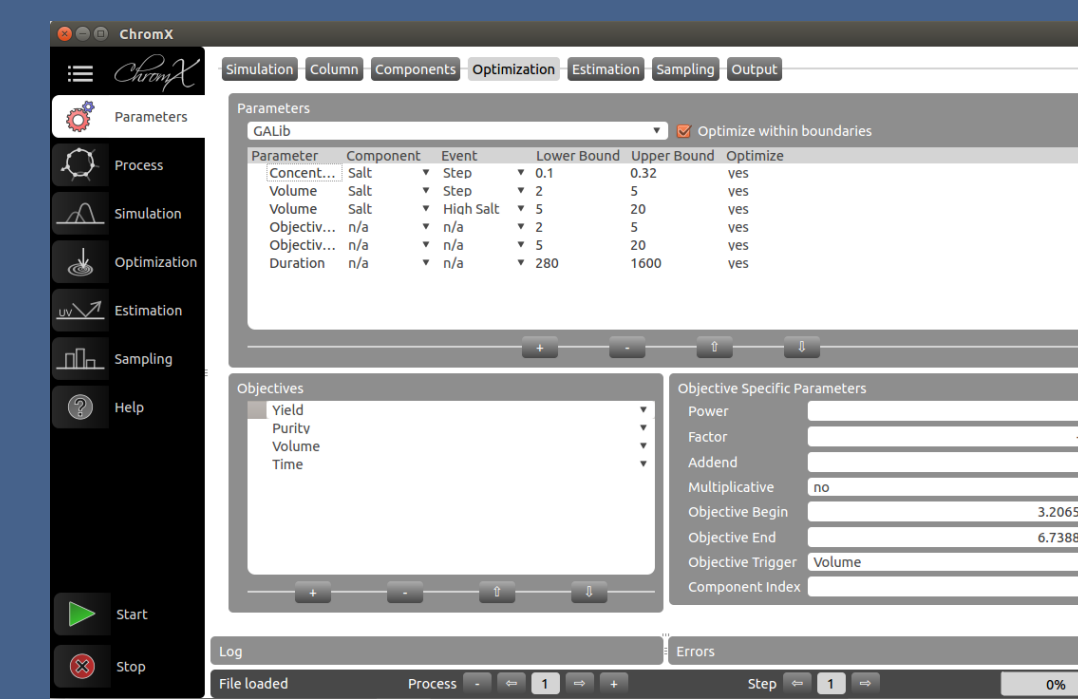
Intermediate operations, e.g. UF/DF can be included as response surface models.



Concerted optimization of multi-column processes finds the globally best set-up by avoiding over-optimization of single steps and unnecessary early product loss.

Optimization

Heuristic and deterministic algorithms are available for estimation, optimization and optimal control. Several built-in objectives can be weighted, added or multiplied, e.g. achieving minimal peak overlap by shaping the salt injection profile.



GO SILICO

GoSilico is a spin-off project of the KIT that develops software and methods for computer-aided – in silico – bio-process development.

GoSilico is supported by

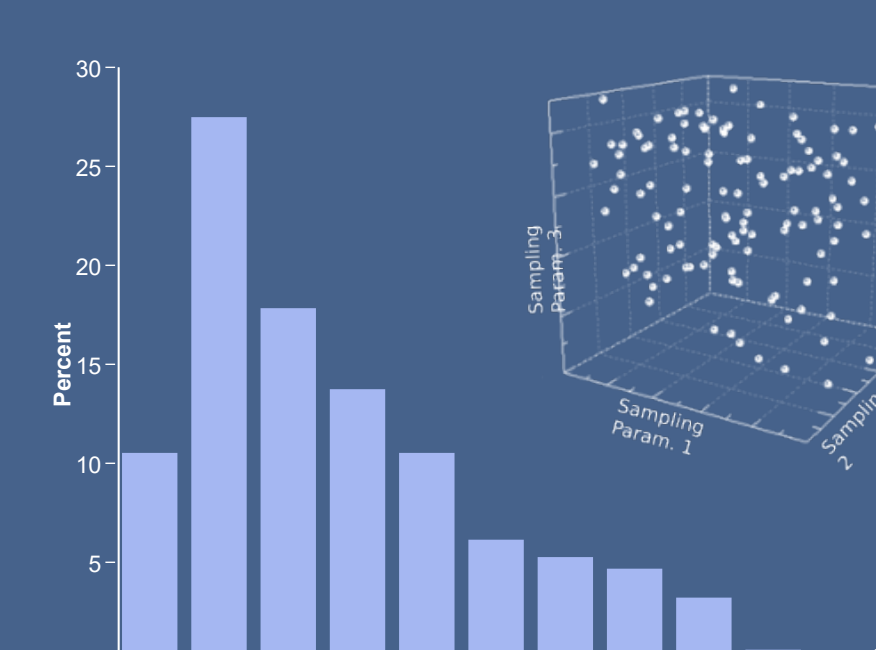


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Sampling

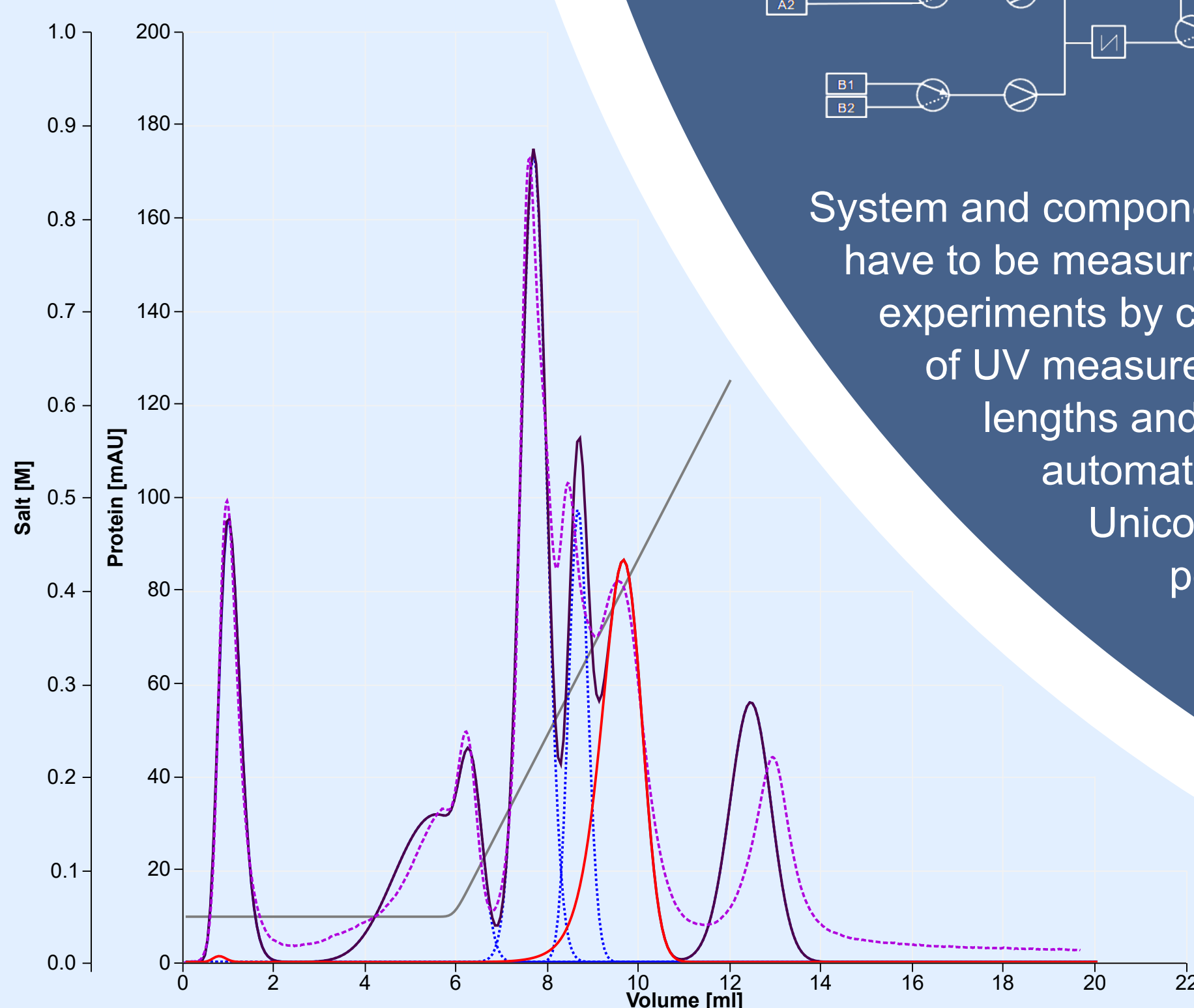
Monte Carlo or Latin Hypercube Sampling allow to study the probability distribution of an objective function with respect to uncertain input values.

The exported data can be analysed with PCA or PLS methods to find correlations between parameters and Critical Quality Attributes.



CHROM X THE POWERFUL SOFTWARE TOOLBOX FOR LIQUID CHROMATOGRAPHY

— Salt
— Target
— Contaminants
— Sum Signal
— Measurement



With increasing miniaturization, characterizing crude mixtures from low sample volume is a challenging task. A typical setting is the screening of feed stocks from different clones and cultivation conditions for their suitability for platform downstream processing.

AEX Capture of Glutathione-S-Transferase from *E. coli*

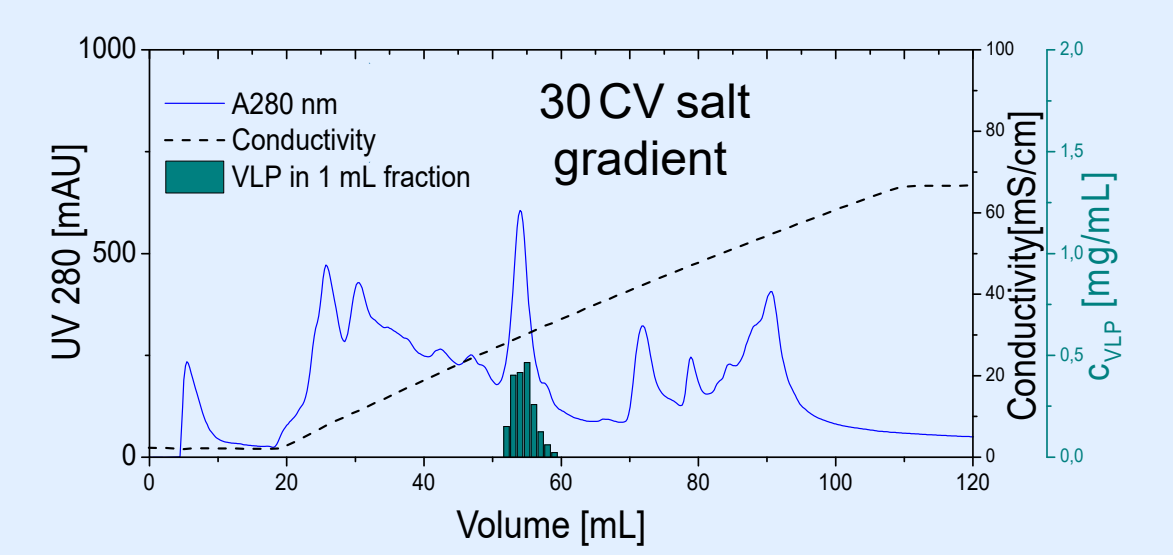
<http://dx.doi.org/10.1002/bit.25630>

This study succeeded without knowledge of feed composition in terms of molar or mass concentrations. The model equations were re-written to accept boundary conditions in UV absorption units.

Model-based Process Development for Virus-like Particles

<http://dx.doi.org/10.1016/j.chroma.2015.12.006>

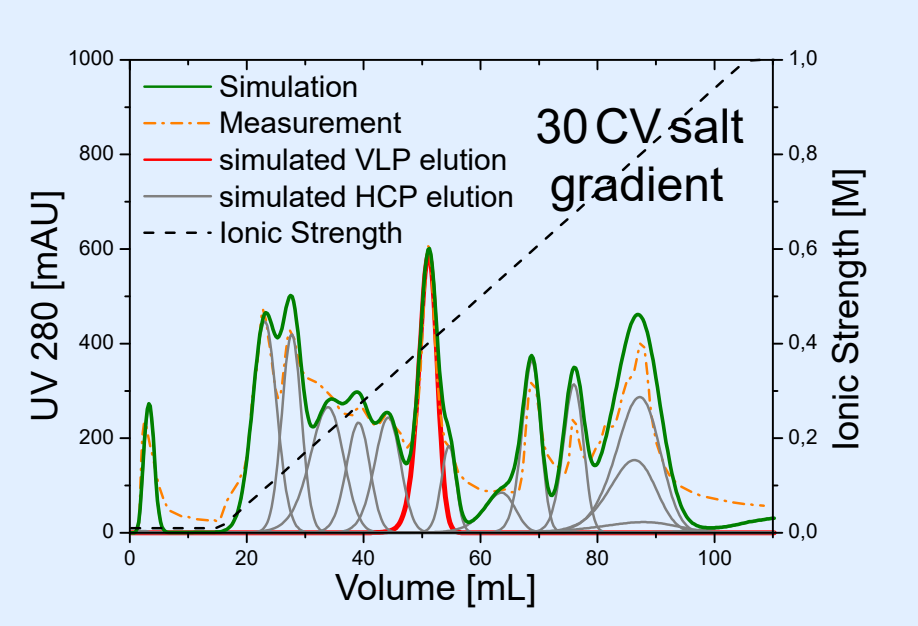
VLPs are composed of multiple copies of recombinantly produced viral structural proteins which assemble into empty particles. They can either mimic the structure of viruses or present epitopes of foreign pathogens or tumor cells on their surface. Apart from lab scale, time-consuming ultra centrifugation steps there is no platform form process available for purifying VLPs.



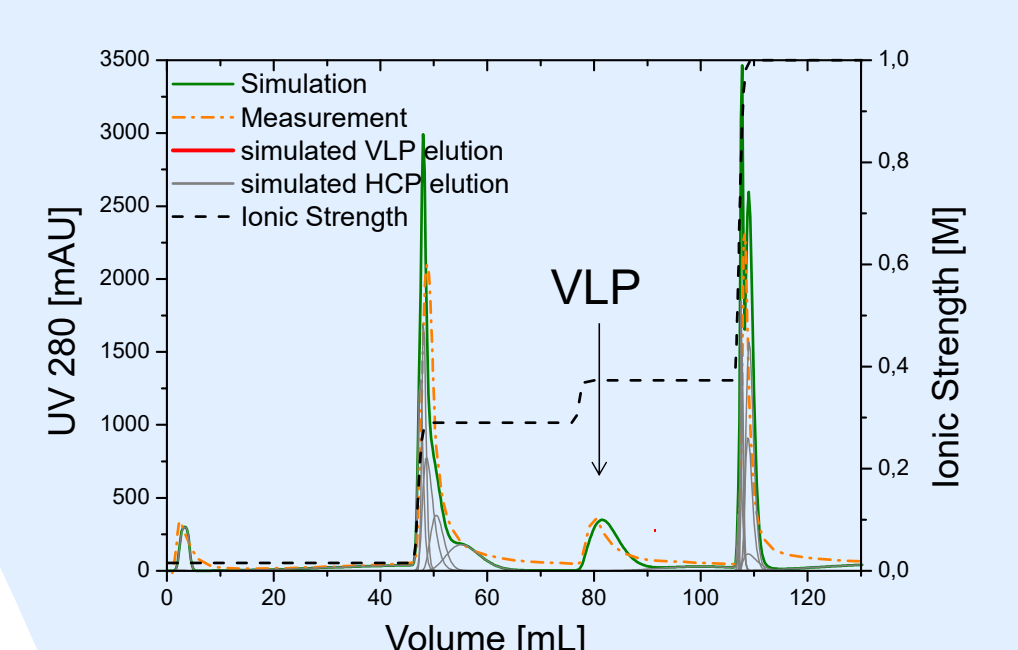
Case Study: Using AEX membrane capsules to purify Human B19 Parvo-virus-like particles (30nm) derived from insect cells.



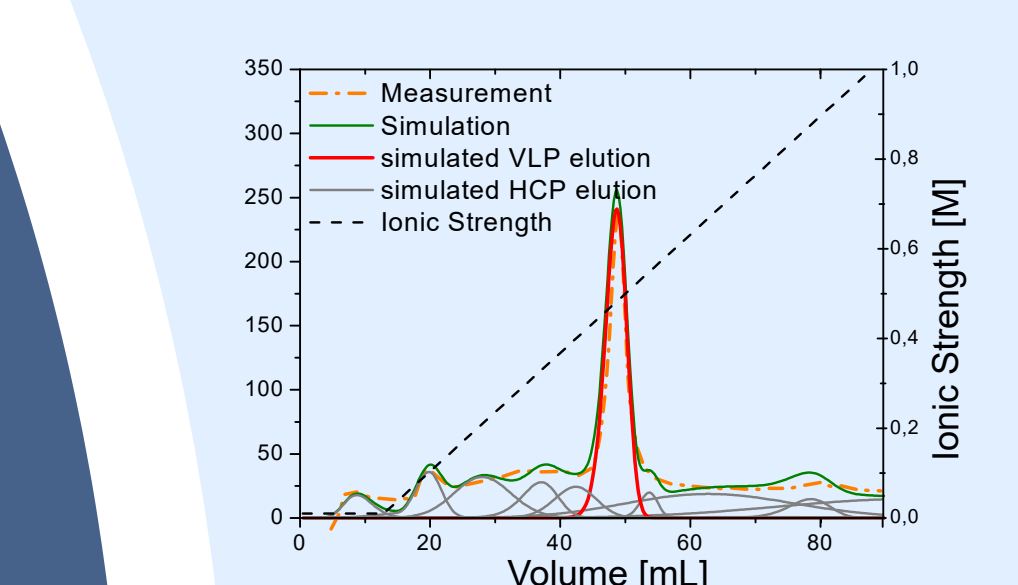
Product tracking during elution



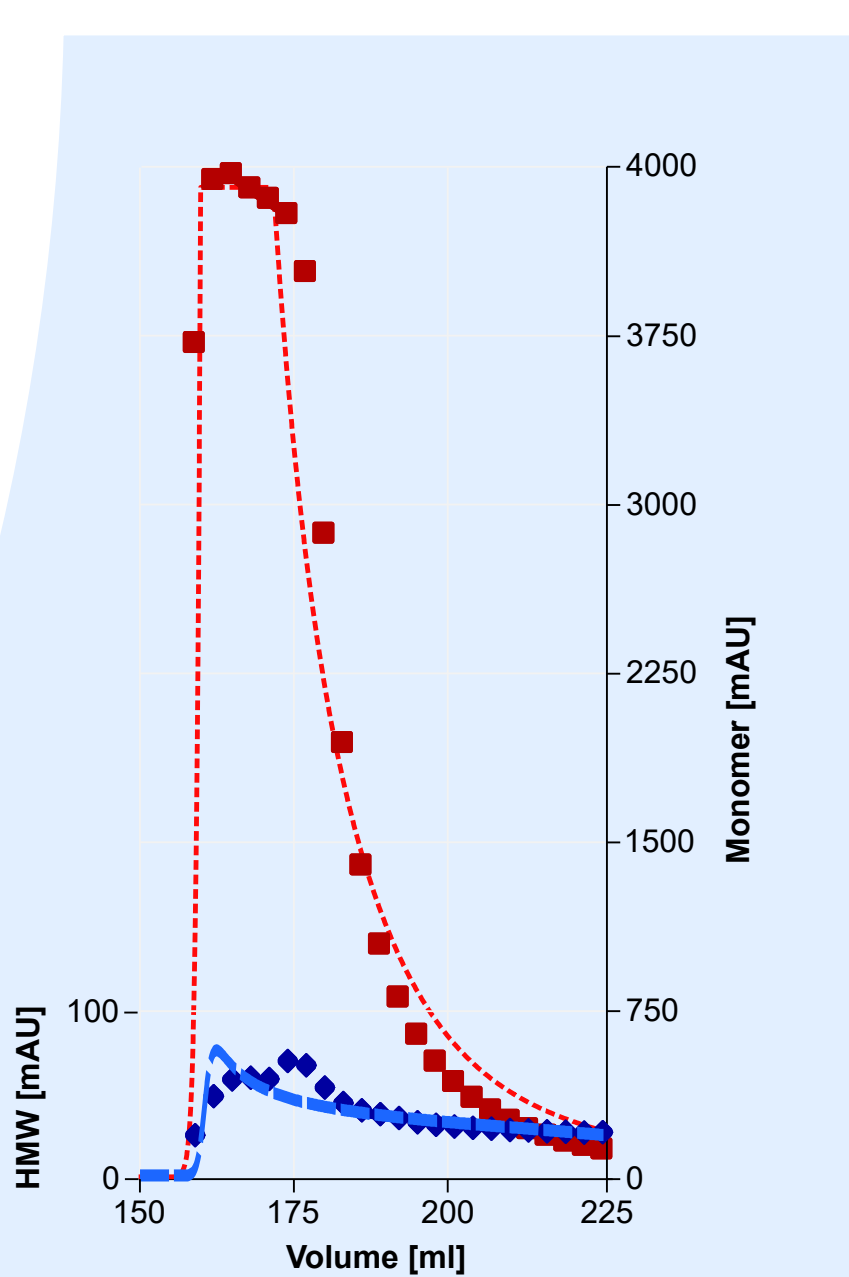
SMA parameter estimation



Validation & Optimization

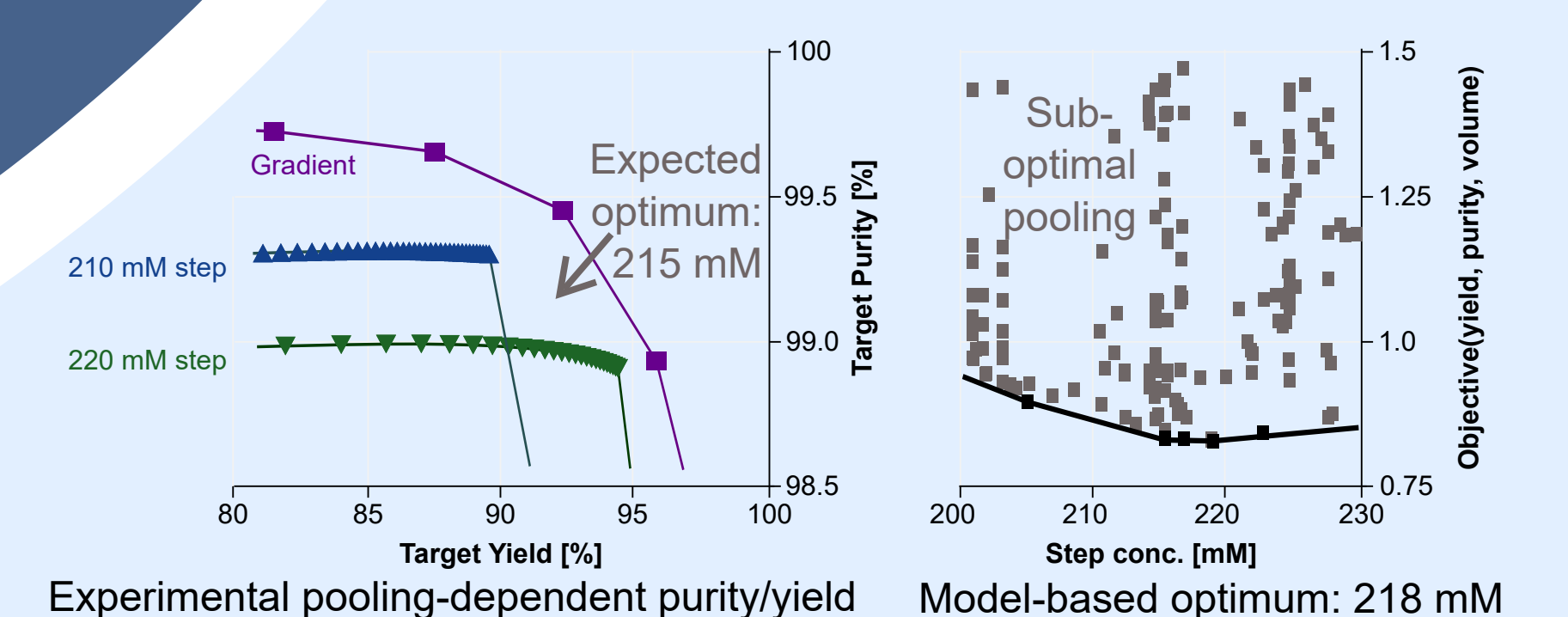


With ATPS & precipitation



Monomer
HMW

Calibration: 190 mM step



Experimental pooling-dependent purity/yield Model-based optimum: 218 mM

Model-based optimization determines optimal operating conditions, once the model has been calibrated to the specific process step. In this work, parameters for the Steric Mass Action model were estimated for the target protein and three contaminants of

an industrial cation-exchange step for mAb purification using only three chromatograms at different wavelengths and additional fraction analyses with size exclusion chromatography. The model-based optimization results agreed with conventional optimization.

CEX Optimization for mAb Purification after Protein A

<http://dx.doi.org/10.1002/elsc.201400248>