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Model Calibration and Optimization of a Protein Purification Process

In this thesis four different models were calibrated to describe the separation of a ternary protein mixture in an ion-exchange chromatography column. The thesis was concluded with an optimization of the separation process.

Chromatography is a separation technique that is widely used for both production and analytical purposes. In a chromatography process a mixture is introduced into a mobile phase. The mobile phase carries the mixture through a column that holds the stationary phase. Separation is achieved when the components in the mobile phase interact with the stationary phase. Components that adsorb strongly on the stationary phase will last longer in the column and will therefore be separated from the components that do not adsorb as strongly.

In the biopharmaceutical industry chromatography is a widely used technique. It provides high yield and productivity while maintaining an acceptable product purity. Since the chromatography process usually constitutes most of the manufacturing cost it is important to optimize the process. One way to facilitate the optimization process is to use a mathematical-model that describes the chromatography process. A well-defined mathematical-model, that is consistent with experimental result, can not only be used to optimize the chromatography process but can also reduce the amount of experimental work that is generally performed in the developing of the chromatography process and therefore reduce costs.

The models that were calibrated describe the interaction between the proteins and the stationary phase differently. Some models try to simplify the description of the interaction by for example assuming that proteins simply bind to one site on the stationary phase. Whereas other models try to give the description of the interaction a more physical meaning. These models consider the fact that proteins are large molecules with several charges on its surface and that they bind on several sites on the stationary phase.

To calibrate the models two kind of experiments were performed. Experiments at low protein concentrations and experiments at high protein concentrations. These were performed to capture the behavior of the proteins at different concentrations. The models fit the experiments very well at low protein concentrations, see figure 1. At high protein concentrations the models did not fit the experiments very well. It is difficult to say whether it was due to the models lacking or other phenomena.

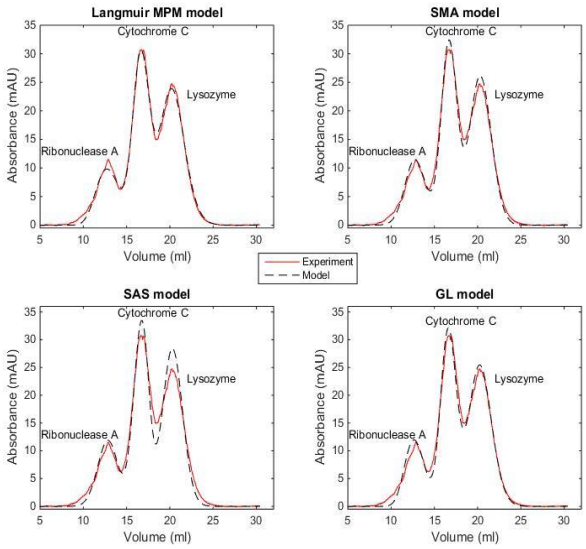

Figure 1 Simulated and experimental chromatograms of a calibration experiment.