Development of a Generic Process Model for Dynamic Simulation of Protein Downstream Processes

C. Frerick, P. Kreis, A. Górak, University of Dortmund, Dortmund, Germany

Although frequently used in chemical industry detailed models for downstream processes have rarely been applied to the downstream processes of biological or pharmaceutical products. A typical downstream process for the purification of biological products comprises six general purification steps: cell removal, concentration, capture, purification, polishing and filling [Harrison 04]. Each purification step can consist of different unit operations like chromatography, filtration or membrane adsorbers. In order to increase the understanding of the complete downstream process detailed, dynamic models for different unit operations such as ultrafiltration, ion exchange chromatography, size exclusion chromatography and ion exchange membrane adsorbers have been implemented into the commercial simulation environment Aspen Custom Modeler™ (see fig. 2). For chromatography the implemented model complexity ranges from the nonlinear ideal stage model neglecting band broadening effects due to mass transport effects [Guichon 94] to a general rate model in which radial pore diffusion in the resin particles, film transfer and axial dispersion in the mobile phase are taken into account [Gu 90].

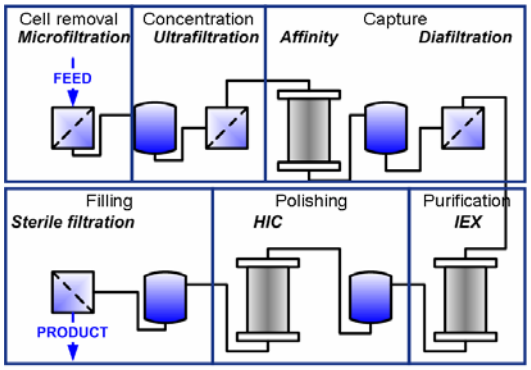

Fig.1: Typical downstream process for biological products

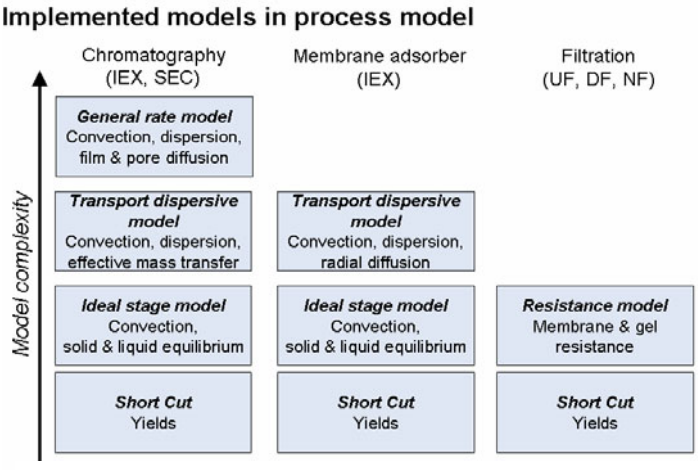

Fig. 2: Implemented models and their complexity

The transport dispersive model for the membrane adsorbers used in this study is

based on the model described by Suen and Etzel (1992). For ion exchange chromatography and membrane adsorbers the steric mass action model developed by Brooks and Cramer (1992) is used to model the competitive sorption of proteins onto the stationary phase.

Based on these models a complete, generic downstream process model has been developed in which each unit operation can be replaced easily by another one. Despite of model complexity the process model proves robust numerical convergence properties and offers valuable model flexibility.

This process model is used to compare and optimize different process setups of a chromatographic human serum albumin purification process which has been described by Curling 1980. The conventional chromatographic setup is compared with a setup incorporating ion exchange membrane adsorbers with respect to productivities and yields without the need of elaborate experiments.

References

[Brooks 1992] C.A. Brooks, S.M. Cramer, Steric Mass-Action Ion Exchange: Displacement profiles and induced salt gradients, AIChE Journal 39 (1992) 1969-1978.

[CUR1980] J.M. Curling, Albumin purification by ion exchange chromatography, in: J.M. Curling „Methods of plasma protein fractionation“, Academic press, London (1980) 77-90.

[Gu 90] T. Gu, G.-J. Tsai, G.T. Tsao, New Approach to a General Nonlinear Multicomponent Chromatography Model, AIChE J. (1990), 36, 5 784-788.

[Guichon 94] G. Guiochon, S. Golzan-Shirazi, L.R. Snyder Eds., Fundamentals of Preparative and Nonlinear Chromatography, Academic Press, Boston, MA, 1994.

[Harrison 04] R.G. Harrison, P. Todd, S.R. Rudge, D.P. Pertrides, Bioseparations science, Oxford, UK, Oxford University Press, 2003.

[Suen 1992] S.-Y. Suen, M. R. Etzel, A mathematical analysis of affinity membrane bioseparations, Chem. Eng. Science (1992), 47, 6, 1355-1364.