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Mathematical Modelling of Chromatography as a tool for process understanding and development acceleration

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To bring a new biopharmaceutical product to market is expensive and time-consuming. Traditional biopharmaceutical process development is based on experimental work by DoE, trying to explore all conditions in order to find an optimum and gaining a partial knowledge on the dynamics of the process. By traditional approach an optimal and economic process must be found exploring lot of parameters. In the downstream processing the most used purification process is chromatography. Integrating the standard procedure with a mechanistic model can increase our knowledge, speed up the process development and the scale up/down.

The aim of this study, carried out in the GSK Vaccines laboratories in Siena, is to identify the main principles guiding the chromatography behavior and describe them with a first-principle model. The starting case chosen for this study is the polishing step of a recombinant protein, that consists in a Hydrophobic Interaction Chromatography (HIC).

Since the hydrophobic adsorption behavior is still not very clear, a thermodynamic study is also ongoing using different commercial proteins with hydrophobic resins. Static methods (high-throughput experimentations) and dynamic methods (breakthrough curves) are used to obtain proteins' isotherms and the data obtained with the two methods are compared. The experimental data are fitted with different isotherm laws. At first, exponential Langmuir and power Langmuir laws are used to fit the experimental data. In order to validate these isotherm laws, some bind-elute experiments are performed with the same commercial proteins. The bind-elute tests are simulated with a code that can solve the system of Partial Differential Equations describing the component behavior in the column. Simulated and experimental tests are compared to confirm the model. Exponential Langmuir, a very simple way to describe the adsorption, turned out to be sufficiently accurate to describe the elution behavior of the proteins for both gradient and step elution. In the case of Lysozyme, even a linear isotherm law is a good assumption that really simplifies the model.

In order to investigate the impact of additional components on single-component adsorption behaviors, a high-throughput procedure was also applied to mixtures of commercial proteins. Binary, and then ternary, mixtures of commercial proteins are tested in different conditions to investigate their behaviors during hydrophobic interaction chromatography. Although not all combinations were tested, data obtained so far indicate that each protein maintains its single-component behavior, even in mixtures. The aim of this study is to mimic a typical industrial chromatographic step where a target protein has to be separated from mixtures of other proteins, thereby increasing the knowledge on this complex operation.

Furthermore, to define a suitable model for the industrial chromatographic step chosen, a commercial computational software is used (ChromX, now DSPX, from GoSilico). *In silico* simulation is supported by few experimental tests. DSPX is more accurate in describing the industrial process and requires less information and experimental work. The lesser need of experimental work to develop a model of an industrial process is crucial because it saves time and materials, that often are expensive and not available in large amount.

DSPX is also used to simulate the bind-elute tests of the commercial proteins to find parameters of different (and more complex) isotherms laws that are used by default from the software. This allows to compare different *in silico* methods to determine isotherms and mass transfer parameters upon some well-known biomolecules in terms of model complexity and information needed.

In silico models appear to be able to provide sufficiently accurate information about the process and can help the scale up/down and process development with a low workload.

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