Mechanistic chromatography modeling: Introduction to defining the project goal

A mechanistic chromatography modeling workflow typically includes the following steps: model selection, model calibration, and quality assessment (Fig 1). As an initial step, it is essential to define the project goal and the desired capabilities for modeling purposes. The future application of the model is relevant for the whole modeling process, from experimental planning to model calibration and quality assessment.

So, the first question that arises for you is "Why am I modeling this process?" as various models have different model capabilities that lead to changes in model complexity.

The model can be used along the entire development life cycle (Fig. 2). Typical applications of mechanistic chromatography models are:

- process development (optimization)
- process characterization
- scale-up
- risk assessment
- troubleshooting

The model needs to describe the process with more or less detail, depending on the desired application.

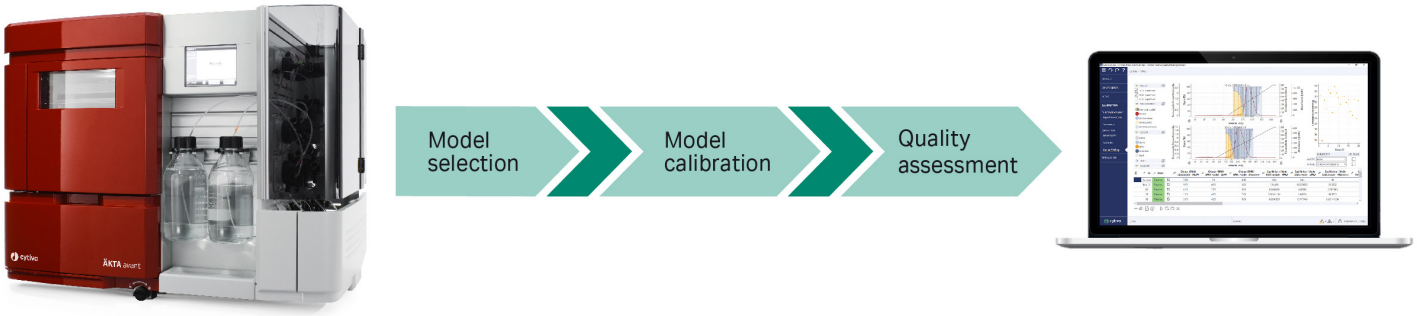

Fig 1. Outline of a mechanistic chromatography modeling workflow.

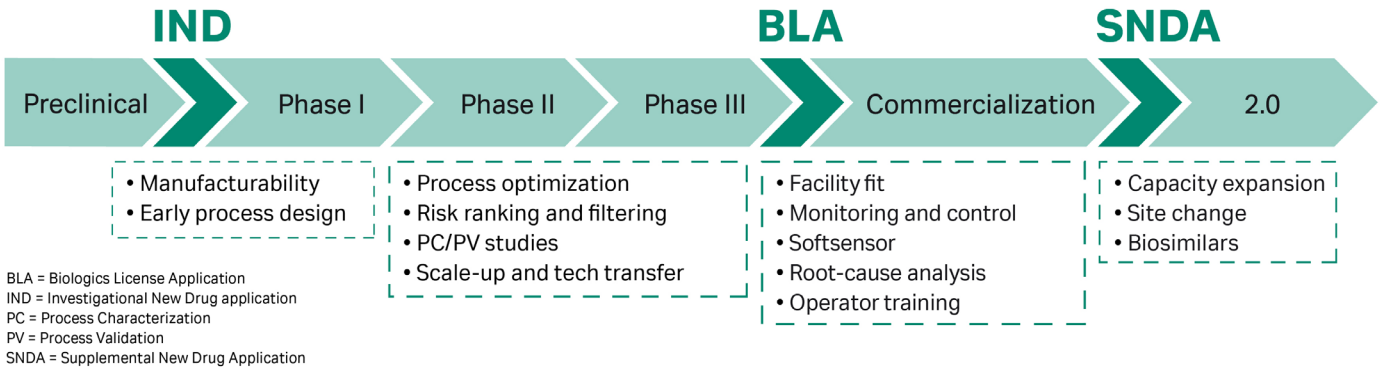

Fig 2. Areas of application for *in silico* downstream simulation throughout the bioprocessing life cycle.

As an example, a model that shall be used to determine first process conditions in early phase development requires less accuracy than a model that shall be applied for process characterization in later phase development. This results in differences in experimental planning, model selection and model calibration as the finished model should be able to fulfill its purpose without spending a lot of additional effort on implementing plenty of details that are not relevant for the individual project goal.

You should define the model clearly before planning the experiments. If the project goal is to obtain an optimized step elution, you should include at least one step elution in the calibration space. The information on the time-dependent protein parameters such as kinetic and mass transfer parameters will be insufficient and the model may be unable to meet its project goal. Also, if the flow rate is a potential optimization parameter, different flow rates could be included in the calibration experiments. This also applies to other process parameters such as large variations in the feed composition.

Furthermore, the selection of the mathematical models to describe the fluid-dynamic and thermodynamic effects of the system is dependent on the model purpose. There are different model equations with various complexity that are suitable for a broad range of applications.

These examples show the importance of defining the project goal initially.

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