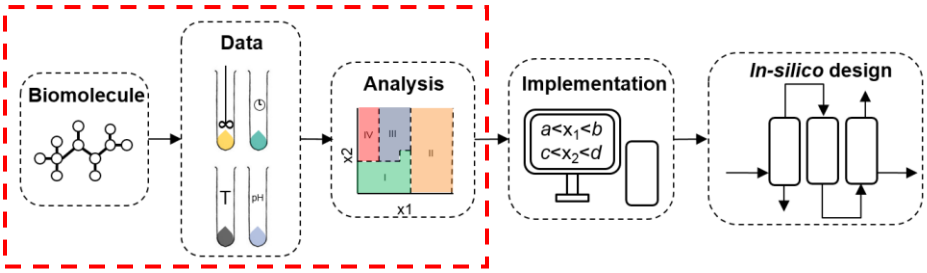
MSc. Thesis Proposal
Start: Fall/Winter 2016

Institute of Engineering in Life Sciences
Section IV: Biomolecular Separation Engineering
Building 40.12, Engler-Bunte-Ring 3

Karlsruhe Institute of Technology



Multidimensional experimental data for identification of the window of operation for model-based process design.

Problem description

Development of purification processes for biopharmaceuticals is hindered by the complexity of biomolecules and lack of knowledge of the influence of process parameters [1]. For time and cost efficient purification process design one of the approaches is to use robust mechanistic modelling, which will generate information on appropriate unit operations, their order and the required process conditions to fulfill the specific requirements of the end product [2]. Mathematical optimization algorithms do not contain knowledge of the product, therefore it is needed to retrieve experimental information on the behavior of the biomolecules under possible process conditions. Experimentally defined behavior of biomolecules can be used as restrictions in these algorithms and will result in a biologically relevant and product specific model-based process design. In order to retrieve this knowledge, the influence of a range of process conditions for key process parameters should be investigated. The interpretation of experimental data is not straightforward and it is required to perform multiple experiments to achieve understanding of the effect on protein behavior [3]. Multidimensional data analysis is therefore needed to identify regions that can be used as mathematical optimization restrictions.

Objectives & Assignment

The objective of this project is to obtain a window of operation of multiple process parameters and conditions (e.g. loading density, pH hold) that will serve as optimization restrictions in model-based process development algorithms. This is done by identifying processable protein states using empirical phase diagrams [4] constructed with multidimensional experimental data. To reach this objective the following tasks should be performed:

1. Literature study: protein stability experiments, data processing, biopharmaceutical process parameters, empirical phase diagrams;
2. Design of experimental setup and data generation for samples from industry;
3. Processing of experimental output signals;
4. Multidimensional data visualization and interpretation using empirical phase diagrams;
5. Identification of process restrictions of the tested experimental search space.

Challenges & Qualifications

Experimental methods to investigate the influence of process parameters and conditions on the biomolecule need to be chosen. Secondly, the biologically relevant range of conditions should be investigated. The processing of data output needs to be optimized, as the multidimensional data analysis is a general method that can be applied to multiple problems.

The thesis will be carried out within an international collaboration between industry and academia, therefore it will be necessary to deliver the thesis and final presentation in English. The level of your scientific English will not affect your grade. It would be beneficial, but not required, to have programming skills as processing of experimental data will be done in MATLAB and/or R. Lab experience is a prerequisite as part of the project will be experimental work.

Research group & Information

Daily supervisor	Marieke Klijn MSc., PhD-student at KIT in the group of prof. dr. Hubbuch
Co-supervisor	Silvia Pirrung MSc., PhD-student at Technical University of Delft in the group of dr. Ottens
Industry partners	DSM, Synthon
University partners	Technical University of Delft, University of Twente
BE-Basic project information	High throughput biopharmaceutical process development, F2.003
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Literature

1. Nfor B.K., Ahamed T., van Dedem G.W.K., van der Wielen L.A.M., van de Sandt E.J.A.X., Eppink M.H.M., Ottens M., 2008, *Design strategies for integrated protein purification processes: Challenges, progress and outlook*, Journal of Chemical Technology and Biotechnology, 83(2):124-132
2. Hanke A.T., Ottens, M., 2014, *Purifying biopharmaceuticals: Knowledge-based chromatographic process development*, Trends in Biotechnology, 32(4):210-20
3. Alsenaidy, M.A., 2014, *Protein comparability assessments and potential application of high throughput biophysical methods and data visualization tools to compare physical stability profiles*, Frontiers in Pharmacology, 5(39):1-19
4. Maddux, N.R., 2011, *Multidimensional methods for the formulation of biopharmaceuticals and vaccines*, Journal of Pharmaceutical Scienes, 100(10):4171-4197