**Integration and Digitalization in the Manufacturing of Therapeutic Proteins**

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Increasing costs and time pressure, as well as diversifying pipelines asking for more flexible production concepts and better product safety and efficacy, are driving the biopharmaceutical industry towards continuous and integrated manufacturing. However, we are still far from an efficient implementation of such technologies. The full exploitation of their potential requires significant advances in process digitalization for online monitoring, control, optimization and maintenance.

In particular, we consider hybrid approaches, where statistical methods based on machine learning techniques are used online in combination with ad-hoc mechanistic models. As an experimental basis for discussion, we take an automated end-to-end integrated platform to produce a monovalent monoclonal antibody of industrial relevance. The process consists of a perfusion bioreactor, a continuous protein A capture step, followed by low-pH virus inactivation, and frontal and flow- through chromatographic steps for final polishing.

Applications include: development of soft sensors for up and down stream monitoring (Raman based), the hierarchical online process control and optimization of a capture twin columns unit and online maintenance (replacement of protein A based stationary phase in a monoclonal antibody capture process).

We discuss the need for an efficient centralized process data collection and hierarchical control system, firmly based on hybrid algorithms, to allow continuous integrated manufacturing of biopharmaceuticals to develop and grow in agreement with the trends of industry 4.0.