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On-line monitoring of downstream bioprocesses

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Downstream bioprocessing can benefit significantly from using on-line monitoring methods for surveillance, control and optimisation. Timely information on critical operational and product quality parameters provided by on-line monitoring may contribute to high product quality, more efficient process operation and better production economy. Here, recent advances in analytical techniques and tools are critically reviewed and assessed based on their capability to meet typical needs and requirements in the biotechnology industry. Soft sensors, which merge the signals generated from on-line monitoring devices into mathematical models, are highlighted for accessing critical information in downstream processing.

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Introduction

In industrial bio-production, process performance depends on parameters that are directly or indirectly related to the production organism, the product and the technical design and operation of the process. Parameters typically controlled in upstream processing are temperature, pressure, pH or dissolved oxygen. In downstream processing (DSP), however, additional parameters related to each downstream step are critical for achieving high quality and yields. This can be enhanced by incorporating on-line monitoring for acquiring critical information on process parameters and attributes [1,2].

So far, on-line or at-line monitoring opportunities are sparsely discussed in downstream processing, while monitoring and control of upstream processes have attracted considerable attention [3,4••,5•]. However, monitoring and controlling single or sequential downstream processing steps could have very significant impact already in the process development phase [6] and may extensively improve the total process yield, product quality and enhance the economy of the whole process [7,8••].

The typical downstream process in the biotechnology industry consists of several steps aiming to remove adverse product variants, and other impurities such as DNA and host cell proteins (HCPs) [9]. The final product has to be of high purity in order to meet set quality specifications and should achieve a high yield to be economically feasible. A generalised outline of a typical downstream bioprocess is shown in Figure 1. Commonly monitored and controlled process parameters (shown in white boxes) in the downstream operations seldom allow more than rough estimations of the process performance. Very rarely the concentration or composition of the target protein is measured. By introducing on-line monitoring along the downstream process, such critical information (light blue) can be accessed directly. This information might then serve as signals in feedback control loops for fine-tuning the operation of a process unit, for example, by facilitating fraction pooling decisions in a chromatographic step or tuning the speed of a centrifuge. Although each DSP step encounters different critical conditions, on-line or at-line monitoring may contribute to reveal information on those critical conditions directly, in a timely manner, and allowing appropriate corrective actions [1,10,11].

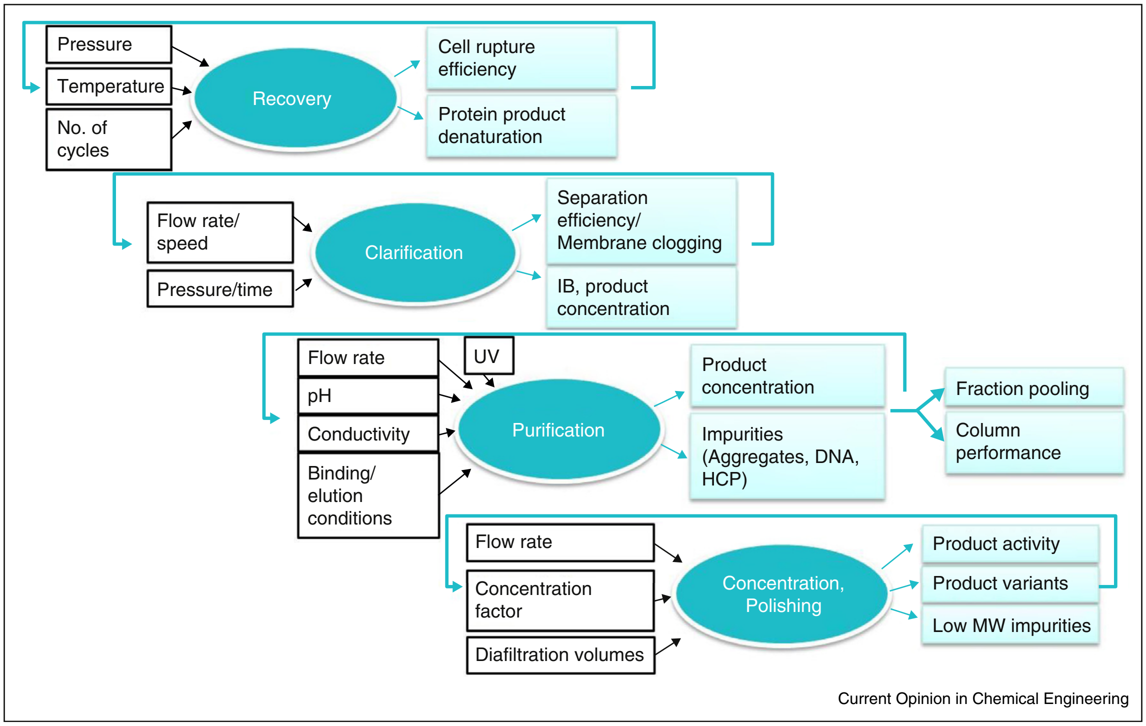
Here, we review the potential of existing analytical techniques as on-line monitoring tools in downstream bioprocessing. The impact of on-line monitoring on product quality and production economy is elucidated as well as the ability of the on-line monitoring tools to meet regulatory demands. Recent analytical advances and new tools for monitoring in downstream processing are discussed and the prospects of soft sensors are highlighted.

Impact of on-line monitoring on product quality, economy and regulatory compliances at industrial scale

Before implementing on-line monitoring at industrial scale it is important to consider carefully the purposes and motives of the monitoring, what kind of benefits it should accomplish and what capacities the monitoring set-up must exhibit.

Table 1 highlights these considerations by providing an overview of a variety of critical properties, factors and conditions in DSP where on-line monitoring may have substantial impact. Three areas of impact are assessed: product quality, production economy and regulatory compliance. As elucidated, on-line monitoring of quality-related criteria, such as product activity and impurities,

Figure 1



On-line monitoring of DSP steps can facilitate process decisions. Commonly monitored and controlled process parameters (white boxes) of the DSP steps are highlighted as well as the critical information desired (grey boxes). By applying on-line monitoring techniques those information can be directly provided to adjust the control parameters and to optimise each DSP step. *Note*: In this example DSP homogenisation is chosen as recovery; filtration and centrifugation as clarification; chromatography as purification; ultrafiltration and size exclusion chromatography as concentration/polishing step.

Table 1

The potential impact of monitoring on critical properties, factors and conditions in downstream processing

Critical properties, factors and conditions	Purpose/ motivation	Product quality	Production economy	Regulatory compliance
Product related properties				
Product activity	Immediate information on of product activity during DSP	↗	↗	↗
Product variants	Evaluation and separation of different product variants	↗	↗	↗
Impurities	Assurance of sufficient removal of impurities (HCP, DNA)	↗	↗	↗
Contaminants	Detection of possible fungal, microbial, yeast bioburden	↗	↗	↗
USP media components & introduced chemicals, resin leakage	Assurance of sufficient removal of USP media components and introduced chemicals	↗	↗	↗
Economic factors				
Investment costs of instrumentation	-	–	↘	–
Operational and maintenance costs	-	–	↘	–
Training costs of personnel	-	–	↘	–
Productivity	Productivity improvement based on monitoring	–	↗	–
Direct batch release after formulation	Batch release after final DSP step, no storage	–	↗	↗
Process endpoint monitoring	Facilitation to determine endpoint of each DSP step	↗	↗	↗
Life time of instrument	Usage for a long period of time	–	↗	↗
Monitoring of batch to batch variations	Determination of batch variations and comparison to previous results (batch trajectory)	↗	↗	↗
Conditions by regulatory demands				
Online monitoring and process control	Possibility to fine-tune each DSP step in a timely manner and take corrective actions	↗	↗	↗
Robustness of monitoring system	Adoption to changing process environment	↗	↗	↗
Identification of critical quality attributes	Increase process understanding and impact of CQA in DSP steps	↗	↗	↗
Process automation	Improve process efficiency	–	↗	↗
Risk assessment	Evaluations of risks and risk-based product development	↗	↗	↗
Fulfilment of final product specifications	Ensuring quality criteria of each batch	↗	↗	↗

Note: ↗ indicates a positive impact, a negative impact is indicated by ↘ and – shows no influence.