DIGITALIZATION PLATFORM AND SUPERVISORY CONTROL OF A CONTINUOUS INTEGRATED BIOPROCESS BASED ON RAMAN SPECTROSCOPY

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In the last years, the implementation of Raman spectroscopy, multivariate data analysis (MVDA) and advanced control algorithms gained increasing interest in the biopharmaceutical industry through the PAT initiative. However, there is still a huge gap towards an efficient implementation of modern process analyzers, a centralized data mining combined with online use of MVDA and the integration of process knowledge into a supervisory control frame.

To bridge this gap, a digitalization platform for a fully continuous integrated manufacturing bioprocess was developed in collaboration with leading companies for process digitalization solutions, advanced monitoring sensors and cell cultures (Siemens, Kaiser Optical Systems and Merck). The potential of online Raman spectroscopy in upstream and downstream was tested to gain as much as possible process information. Different media, products and cell lines were monitored and diverse spiking strategies and advanced modeling algorithms were investigated to improve the robustness and predictive power of the models. Finally, dedicated runs were performed to develop and tune control algorithms.

The developed IT platform facilitates the efficient collection and centralized storing of all process data. In addition, it is able to interact with the control systems of each process unit and close the control loop. Advanced multivariate statistical and mechanistic models as well as process control and optimization tools, can be integrated. In particular, the possibility to decently predict the dynamic evolution of central process variables including glucose, viable cell density and product titer, all amino acids and even quality attributes (aggregates and glycosylation patterns), outlines the important role of online Raman spectroscopy in the supervisory control. The hierarchical control system enables the handling of process perturbations and optimization of diverse objectives such as productivity, efficiency and product quality. The efficient implementation of Raman spectroscopy, facilitated by the IT platform, and the innovative control system provides a very important basis to intensify the main advantages of continuous integrated manufacturing and fully follows the trend of industry 4.0.
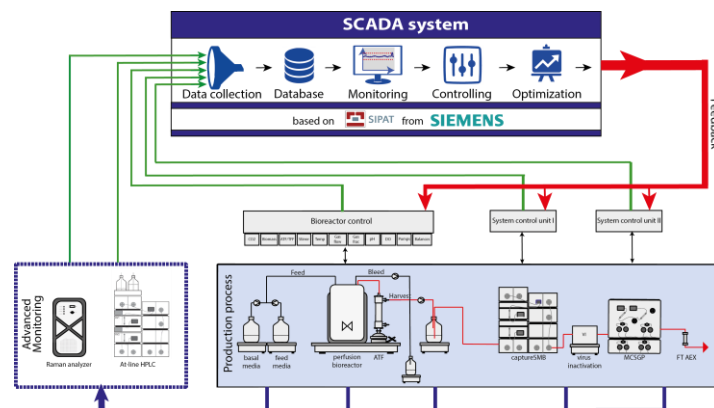

Figure 1 - Supervisory and data acquisition system of the process