# Implementing Quality by Design in biomanufacturing with the QUBICON® software

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## Software Functionality Overview

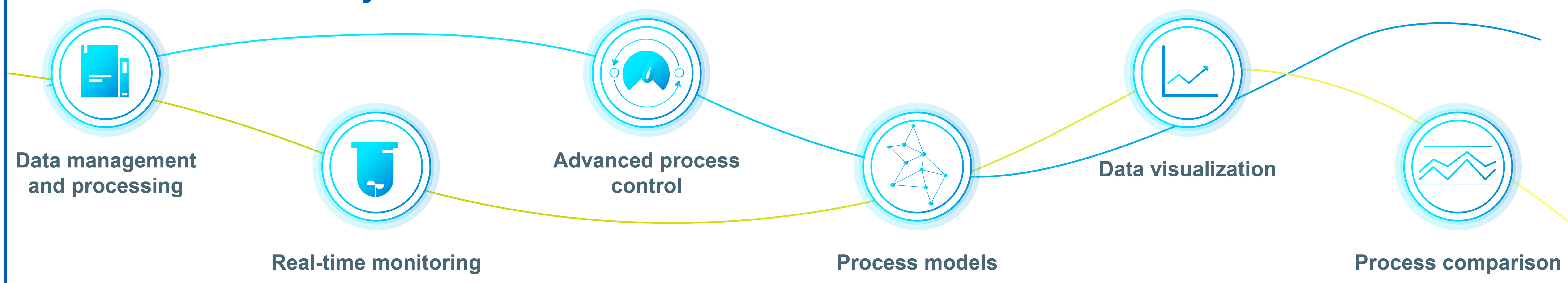


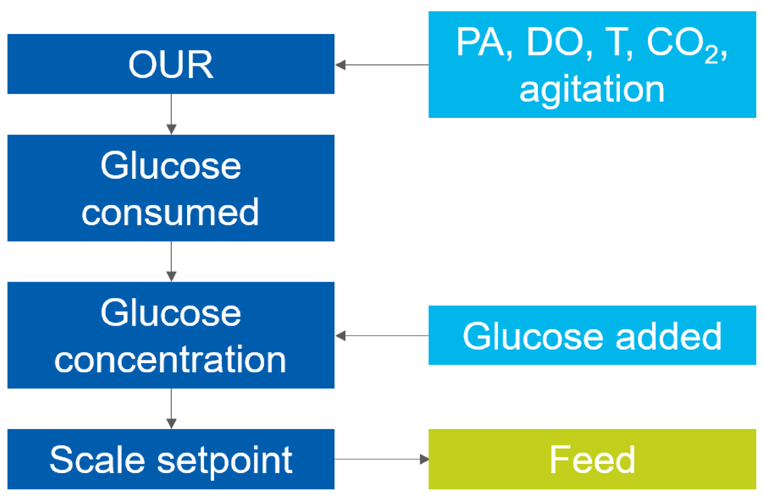

**Figure 1.** Qubicon® – the all-in-one software solution – stands for better product quality in biomanufacturing. Its key functionalities such as real-time monitoring and user-defined, in-process (model-based) control adjustments to performance deviations contribute to the reduction of product quality non-conformities. The versatile applicability of the software for better performing and cost-optimized processes is proven by diverse examples in the field of biomanufacturing – both in the area of Upstream Processing (USP) as well as in Downstream Processing (DSP).

## Adaptive Feed Control

Common feeding practices in the industry to keep the nutrient levels constant during a cultivation can have major weaknesses. However, Qubicon® offers a solution by realizing adaptive feed control.


**Figure 2.** A recombinant anti-hTNF-α IgG1 producing CHO-K1 cell line was cultivated in fed-batch mode with a glucose setpoint of 4.5 g/L. Glucose concentration was controlled via glucose uptake estimation based on the oxygen uptake rate (OUR). The bioreactor, the feed scale and pump were connected to Qubicon®.

**Figure 3:** Feedback control of the glucose concentration was based on the OUR calculation via a dynamic $k_La$ model[1]. Input variables are shown in light-blue, whereas the soft-sensor calculations are presented in dark blue. As output variable the necessary amount of feed was calculated and sent as a setpoint to the respective pump.



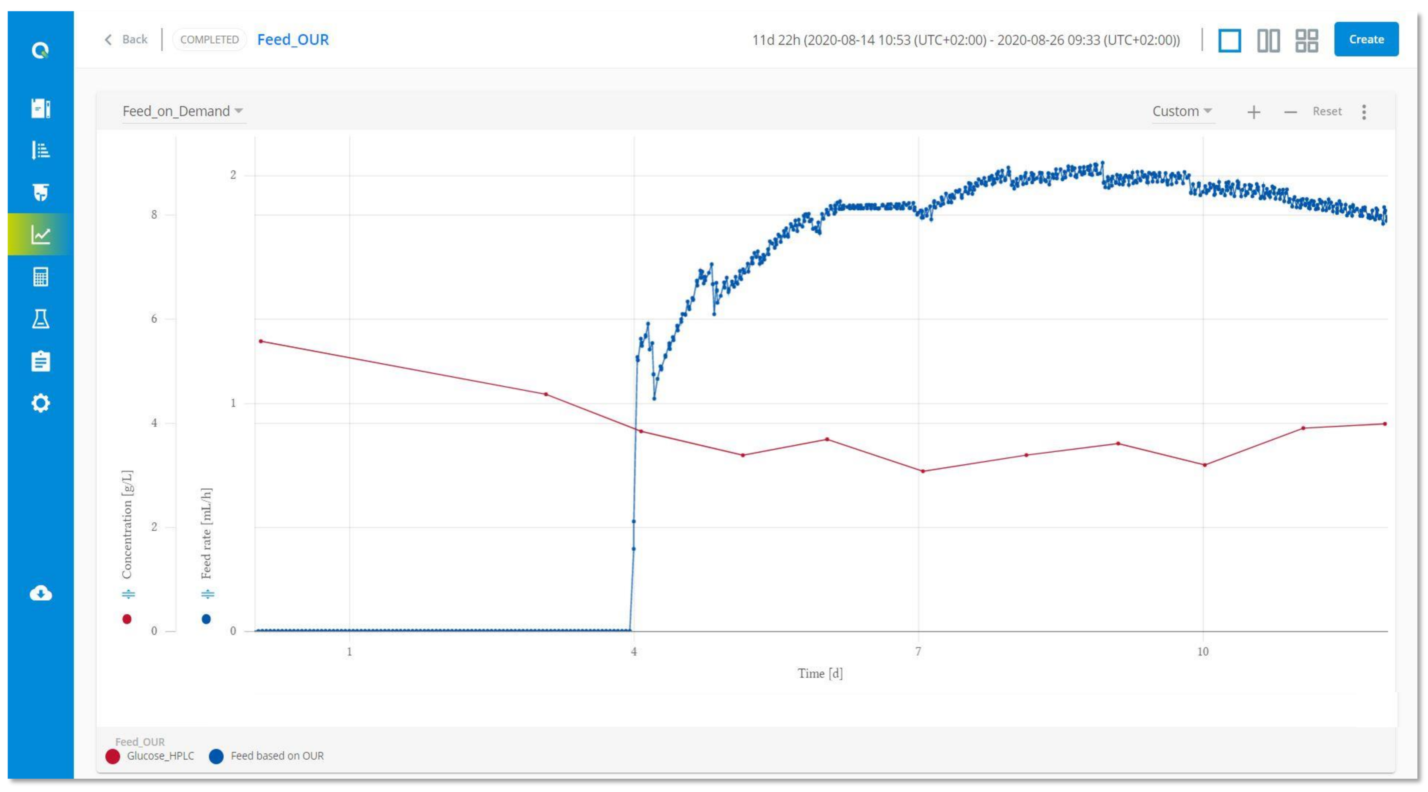



**Figure 4.** Graph presenting the feed rate (blue) and the offline measured glucose concentration (red). As a result of the adaptive feed control, the glucose level remained constant, in a tight range throughout fed-batch phase (after day 4).

## Model-Based Protein Refolding

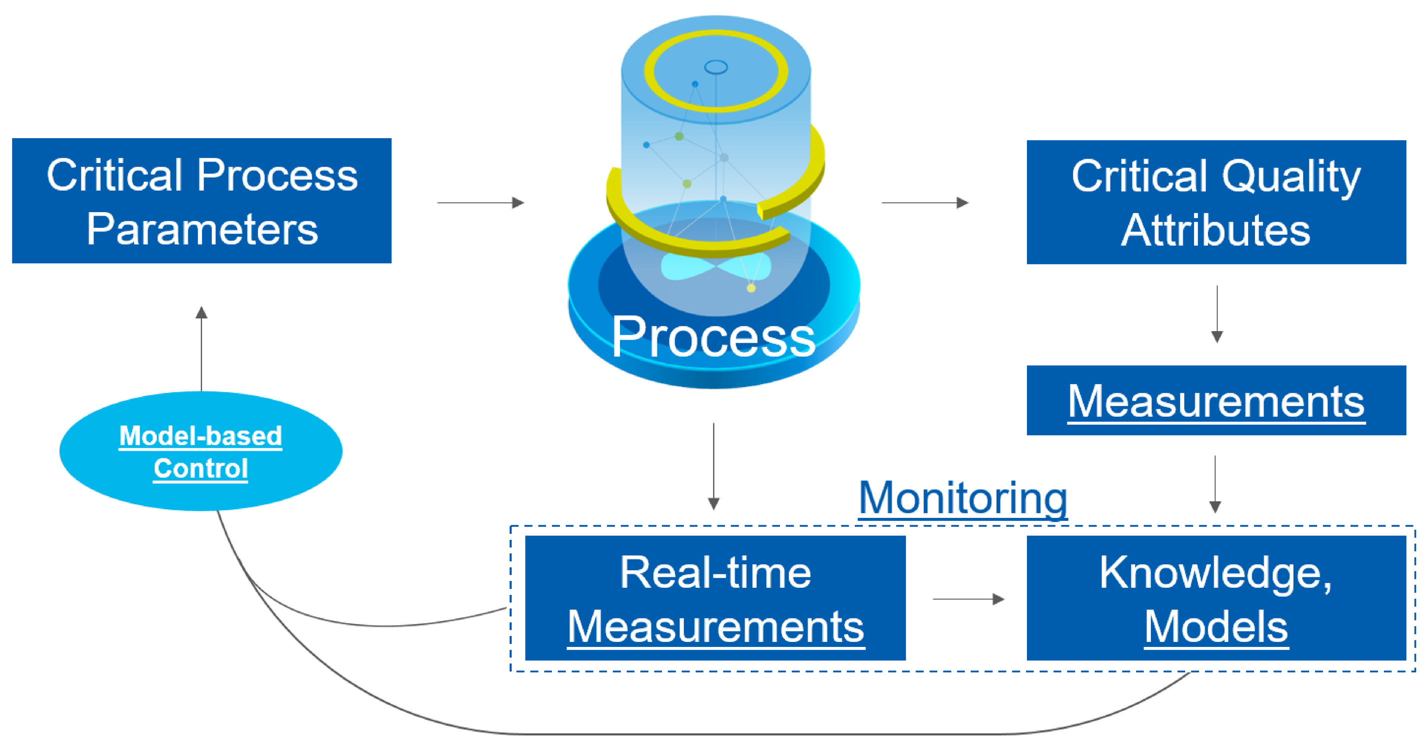



**Figure 5.** Towards enhanced monitoring and control of refolding processes.

### Implementing the M³C approach to refolding[2]

- Application of advanced process analytics
- Time-resolved analysis of refolding dynamics
- Model-based capture of process knowledge
- Deployment of predictive control strategies via Digital Twins
- Investigation of scalability and necessary model adaptations

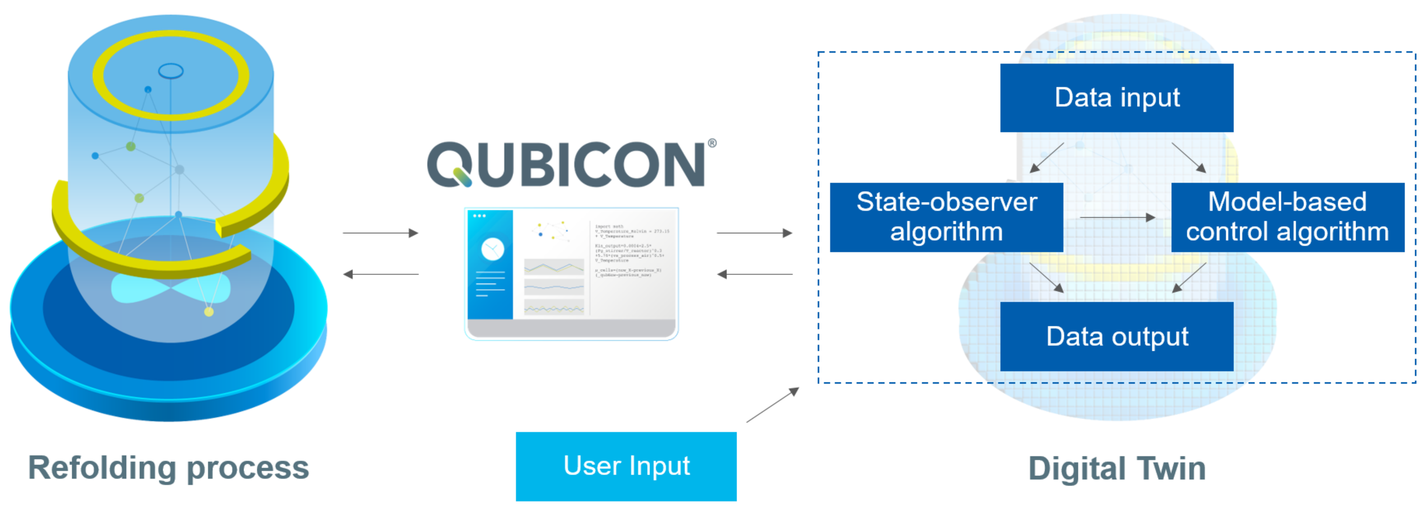



**Figure 6.** Schematic overview of the integrated platform approach for model-based monitoring and control of a protein refolding process with Qubicon®.

### Digital Twin

- Interaction of the process model with the refolding process
- Description and estimation of refolding kinetics
- Optimal control of refolding yield and space-time-yield by controlled addition of solubilized protein using model predictive control

[1] Pappenreiter et al., 2019. Oxygen Uptake Rate Soft-Sensing via Dynamic kLa Computation: Cell Volume and Metabolic Transition Prediction in Mammalian Bioprocesses. Front. Bioeng. Biotechnol. 2019; 7(195).
[2] Pauk et al., 2021. Advances in monitoring and control of refolding kinetics combining PAT and modeling. Appl. Microbiol. Biotechnol. 2021;105(6):2243-2260.

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