Methodology for fast development of digital solutions in integrated continuous downstream processing

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Abstract

The methodology for production of biologics is going through a paradigm shift from batch-wise operation to continuous production. Lot of efforts are focused on integration, intensification and continuous operation for decreased foot-print, material, equipment and increased productivity and product quality. These integrated continuous processes with on-line analytics becomes complex processes, which requires automation, monitoring and control of the operation, even unmanned or remote, which means bioprocesses with high level of automation or even autonomous capabilities. The development of these digital solutions becomes an important part of the process development and needs to be assessed early in the development chain. This work discusses a platform that allow fast development, advanced studies and validation of digital solutions for integrated continuous downstream processes. It uses an open, flexible and extendable real-time supervisory controller, called Orbit, developed in Python. Orbit makes it possible to communicate with a set of different physical setups and on the same time perform real-time execution. Integrated continuous processing often imply parallel operation of several setups and network of Orbit controllers makes it possible to synchronize complex process system. Data handling, storage and analysis are important properties for handling heterogeneous and asynchronous data generated in complex downstream systems. Digital twin applications, such as advanced model-based and plant-wide monitoring and control, are exemplified using computational extensions in Orbit, exploiting data and models. Examples of novel digital solutions in integrated downstream processes are automatic operation parameter optimization, Kalman filter monitoring and model-based batch-to-batch control.

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Introduction

The methodology for production of biologics is going through a paradigm shift from batch-wise operation to continuous production. A lot of efforts are focused on integration, intensification and continuous operation for decreased foot-print, material, equipment and increased productivity and product quality (Ng et al 2012, Godawat et al 2012, Baur et al 2016a, 2016b, 2018, Sellberg et al 2017, Gomis-Fons et al 2020B and 2021, Moreno-González et al 2021). On-line analytics are needed in these continuous processes to reach their potentials with the final goal of real-time release testing, RTRT (Farid 2007, Shukla and Thömmes 2010, Godawat et al 2015, Walthers et al 2015, Konstantinov and Cooney 2015, Zydney 2015, Shukla et al 2017, Kesik-Brodacka 2018, Vogg et al 2018). These integrated continuous processes with on-line analytics become complex processes, which requires automation, monitoring and control of the operation, even unmanned or remote, which means bioprocesses with high level of automation or even autonomous capabilities. The development of these digital solutions becomes an important part of the process development and needs to be accounted for early in the development chain. Lab-scale automated continuous bioprocesses have been reported (Steinebach et al 2017, Feidl et al 2020, Gomis-Fons et al 2020B, Rathore et al 2021, Schwartz et al 2022, Tiwari et al 2022). The software used in these experimental platforms were very different from locally developed PLC to commercial process automation SCADA systems. This work discusses a platform that allows development, advanced studies and validation of digital solutions for integrated continuous downstream processes. It uses an open flexible and extendable real-time supervisory controller developed in Python. Python is a well-known programming language with a large user community that supports the language with a large set of external packages for different kind of applications, for instance in data handling, machine learning, simulation and optimization.

The paper presents the properties of the supervisory controller, called Orbit, and networks of controllers implemented in Python, and how it impacts the development of downstream processes (Andersson et al 2017, 2022). Orbit makes it possible to communicate with a set of different physical setups and on the same time perform real-time execution. Integrated continuous processing often imply parallel operation of several setups and network of Orbit controllers makes it possible to synchronize complex process system. Data handling and data analysis is an important property for handling heterogeneous and asynchronous data generated in complex downstream systems. Advanced model-based and plant-wide monitoring and control are used as examples of novel digital solutions in integrated downstream processes.

Materials and methods

Integrated continuous downstream system

A process for continuous production of an antibody was developed and studied in lab-scale, Scheffel et al 2022, and scaled-up and operated in pilot-scale, Schwartz et al 2022. The upstream process consisted of a high cell-density perfusion bioreactor with a membrane system for production of clear cell-free supernatant. Between the upstream process and the downstream process there was a harvest tank making it possible to disconnect the downstream process for up to 20 hours. Under normal conditions, the feed flow rate to the downstream process was set for the control of the liquid amount in the harvest tank, meaning that the production rate in the complete process was controlled by the perfusion rate selected in the upstream process.

The downstream process consisted by four units; continuous periodic counter-current chromatography system (PCC) for antibody capture, viral inactivation unit (VI) based on two parallel batch reactors, one cation exchange chromatography step (CEX) in bind-and-elute mode mainly for aggregate removal and finally one anion-exchange chromatography step (AEX) in flow-through mode for final polishing. The PCC and the loading of VI was configured on one ÄKTA setup and the VI control together with the IEX polishing train on a second ÄKTA setup. Each setup was controlled by an installation of the research software Orbit, through the Unicorn control system for the ÄKTA system. The lab-scale process was operated continuously for 9 days and the pilot-scale process for 19 days, for details see Scheffel et al 2022 and Schwartz et al 2022.

Support system automation

An ÄKTA explorer 100 was modified into a buffer preparation unit, BPU, by introducing additional valves and adapting the standard flow path. Two pumps were needed to perform the buffer preparation and delivery. The configuration enabled connection of 9 different stock solutions. In addition, 14 buffer mixing flasks were installed using the column valves, the outlet valve and the sample valve. In each of the buffer mixing flasks, a specific buffer could be prepared. Since the same buffer was prepared in the same mixing flask the whole time, no cleaning of the flasks was needed. At each of the client systems, the tube from the BPU was connected to a client inlet valve, which was used to distribute the buffers to the corresponding buffer flasks in the client. This setup allowed for the BPU to deliver buffer directly to the right buffer flask in the client system. The client inlet valve worked independently of the other tasks that the client system performed, meaning that the downstream process did not need to stop every time a buffer in the client was re-filled. For more detail see Isaksson et al 2023.

Quality analysis systems consists of a sample preparation system, a modified ÄKTA explorer 100, and a HPLC analysis system, Agilent 1260. The prep and analysis systems were connected via a tube between the prep system's outlet valve and the analysis system's injection valve. The client systems were connected to the prep system at several points allowing for sampling the flow path of for sampling a container with a pool, before further processing. The retrieved sample is prepared for analysis, which can mean dilution, buffer exchange, chemical modification etc., before sending to analysis. The analysis system consisted of an injection valve with an injection loop, a column valve with several analysis columns, a diode array detector and a refractive index detector. When the prep system was sending a sample for analysis, the flow path on the analysis system went through the injection loop and directly to waste. Based the kind of sample loaded the corresponding analysis protocol were performed. For more detail see Tallvod et al 2023.

Automation and operation of continuous downstream system

Orbit was originally created in 2015 and the current version is 3. Orbit was created to make complex, custom control of processes and to integrate several instruments together. The fundamental part of the orbit design is the orbit kernel that consist of one part where the system configuration and communication is defined and a second part where the real-time control is defined. A configuration of a system is designed with unit objects which contains methods to control the object. There are unit libraries where units for different type of system is defined. Every unit that communicates with an instrument has a defined protocol for the available methods. Tubes can also be defined to keep track of flow paths, dead volumes. The real-time kernel handles the time, current phases, sampling and communication to the instrument and between Orbit controllers. The user writes a script to define the phases of the process that could be run sequential or in parallel. The phases are defined by the methods in a method library to control the process. The methods can be commands executed at defined times or more complex event-based tasks like control. There is an existing library from different application, such as sequential polishing steps, PCC, MCSGP, conditioning, etc. A new phase starts when all the instructions in the previous phase are executed. For automation of integrated continuous downstream process discussed above two setups were automated using two Orbit supervisory controllers; one for the PCC operation on an ÄKTA pure and one for the sequential control of the polishing ion exchange train also on an ÄKTA pure.

Functionality of the orbit kernel can easily be extended. There are built-in extensions like monitoring, simulation and plotting and a user can easily create their own extensions to add for example control, optimization or predictions based on Kalman filters, see below.

In a process with several orbits there need to be communication between Orbit controllers. Every Orbit instance has a server enabled where it can be connected to by other orbit instances or for manual control. For larger processes this creates a network of Orbit controllers. The protocol for the communication is to send dictionaries with specified tasks and arguments to complete the task. One type of Orbit instances is called orbitX, where a service is offered for other Orbit controllers that can connect as clients. Examples of this is the quality analysis system and buffer management system discussed above. When for example ordering a buffer a task is sent with information about the recipe and the volume of the ordered buffer. In orbitX instances that handles requests from several clients there need to be a queue controller defined. The simplest version of a queue is to have the first-in-first-out principle. This can also be extended with a priority. For time critical requests where a buffer or analysis needs to be performed within a deadline, this can also be added and considered that the priority is high enough it is allowed to jump the queue.

When working with real-time processes a lot of data is created. A database has been implemented to handles Orbit data. The data to be stored is both the system configuration, but also run logs, signal information and data. This is automatically uploaded directly to the database during a run. In a process there typically exist sampling points from where a sample is taken for further analysis. In our QAS system this analysis is ordered and information about where the sample is taken is stored together with the result of the analysis.

Modelling and model-based monitoring and control

The Orbit supervisory controller requires a digital representation of the physical setup, with it is communicating. The representation is composed of a list of objects and a list of tubing, connecting the object ports. All objects and tubing have a mathematical representation in Orbit, allowing a simulation extension to perform a simulation of the complete setup models, i.e. automatic generation of a digital twin of the chromatographic system. A set of experiment can be executed to generate data for parameter estimation and model calibration, see Tallvod et al 2022A, based on methodologies presented in Borg et al 2014 and Saleh et al 2020. One example of real-time usage of a model is in on-line monitoring. A dynamic extended Kalman filter is implemented as a computational extension in Orbit for monitoring of the composition inside the column. A size exclusion application for the separation of two components with large size difference is presented for illustration. Both components can be measured using UV. A sample is introduced at 70s and passes through the column after 300s, with peak max at about 140s and 210s. The size exclusion model is calibrated using residence time experiments and the model were discretized using 55 mesh points. This means that the Kalman filter estimates 110 states, inside the column.

A batch-to-batch controller was implemented for the retention peak control of two components using the elution gradient, see for more details in Espinoza et al 2022B. Two proteins are separated with an ion-exchange chromatography column by a salt gradient, with a start value and an end value. These two values are the output from the controller. After the batch-wise separation, the retention time for the peak maximum is detected, which is the input to the controller. Based on the difference between the measured and desired retention time the controller computes the gradient profile. The controller parameters are found by using a process gain matrix, derived from the system model.

Results and discussion

Operation of integrated downstream processes

In a previous work a continuous antibody production process was operated continuously for 9 days in lab-scale and in pilot-scale for 19 days, for details see Scheffel et al 2022 and Schwartz et al 2022. The perfusion rate targeted 1.5 reactor volume per day which means that the upstream process together with the harvest tank had an approximated residence time of about 24 hours. The downstream process had a residence time of about 5 hours, with a column switching in the PCC every 40 min, a product pool passed the polishing ion exchanger train every second hours. The experimental data from the two different runs in lab-scale and pilot-scale, clearly indicated that the process dynamics in the process was slow, dominated by the time-scale in the upstream process. The time scale of changes in upstream outflow was about 24 hours. The downstream process consisting of four steps was configured on two ÄKTA setups for parallel operation of PCC, viral inactivation and polishing, see Figure 1.

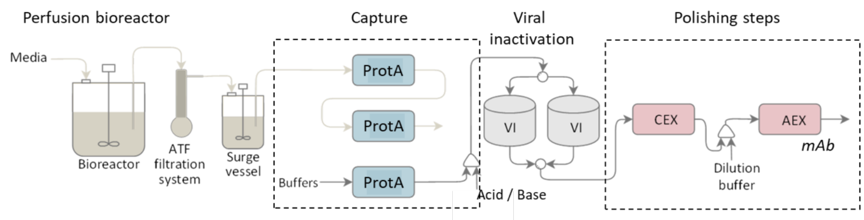

Figure 1: Process overview of an integrated continuous antibody production with perfusion bioreactor system, continuous capture system and a system for polishing, inspired by Schwartz et al 2022.

The integrated continuous process platform was well suited to be a testbed for studies of novel processing step, new analytical tools, data management, automation, real-time monitoring and control, and other digital solutions. Based on experiences a general platform, see Andersson et al 2022, for development studies and validation of digital solutions needs following features:

- Local supervisory controller for handling general setups with an open and flexible architecture for introduction of novel automation, feedback control and computational tools
- Network of supervisory controller with a general communication protocol for the configuration and operation of complex processing systems
- Automated support systems to run the continuous processing system almost autonomous, such as buffer management and quality analysis
- Common real-time database together with general tools for data handling and analysis that can handle heterogeneous, asynchronous and distributed data
- Embedded tools that can handle model based simulation, monitoring and control for digital twin applications

A lab-scale platform that contained all these features made it possible to implement and validate novel digital solutions with minimal resources. The lab-scale size reduced the amount of material needed to do long-time runs. Automation of the processing together with the support system means that operation can be unmanned or remote. The previous work was only manned during office hours, unmanned during nights and over weekends. This resulted in that efforts could be focused on implementing digital solutions at different levels of the complex system, some will be discussed below.

Local supervisory controller

The instruments are controlled with a local supervisory controller. An overview of the architecture can be seen in Figure 2, where it's divided into an orbit kernel, user code and application library. The user configures the system and designs a script defining the sequence of phases that should be executed, where each phase consists of the methods from the application library. The application library often shares many methods but is unique for every specific setup. For each local orbit a system configuration is defined and a method library for the current setup. The controller also handles tasks such as sampling, database communication and network communication with other orbits.

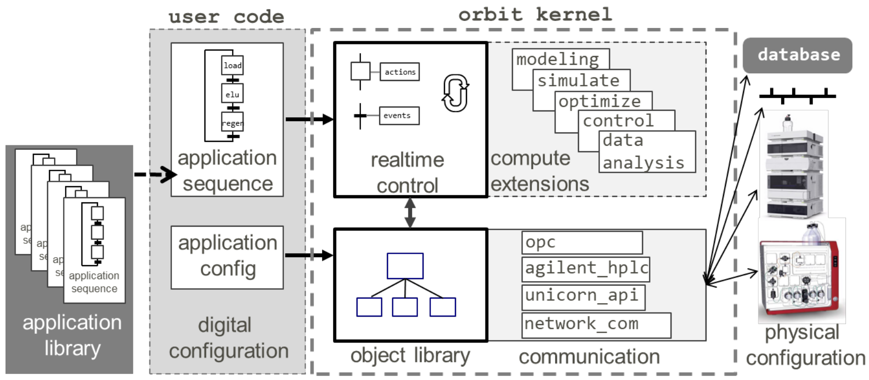

Figure 2: Orbit kernel architecture with the two layers; i) communication and ii) real-time execution, together with the application specification of its configuration and automation.

Network of supervisory controllers

When processes consist of several instruments communication of the instruments are vital. Orbit has support for communication between each other. An orbit can connect to another orbit as a client or act as a server to receive connections from other orbits. For a network of Orbit running instruments it's important to be able to communicate when a pool needs to be transferred. In that case there need to be a synchronization when both of the systems are ready. A system in a chain needs to synchronize with both the machine before and the machine after. The cycle of an instrument can therefore be generalized to be "ready to receive", "receiving", "processing", "ready to deliver" and "delivering". When an instrument is "ready to receive" and the previous machine is ready to deliver the delivering/receiving phase can start.

In the BMS and QAS OrbitX controllers, the OrbitX works as a service where other Orbits can connect and make an order. In that case the Orbit connects as a client and makes an order. A necessity is of course that there is a physical connection. Figure 3 illustrates the process where the integrated downstream process is communicating with each other. They are also connected to the support systems BMS and QAS for ordering of fresh buffer or analysis of the product. All communication happens in a local network. Each Orbit controller is it's own module and with this framework it's easy to extend the system with another process step or to add another service. All of the orbit instances are also connected to the database where all data are streamed to. The modularized approach creates a flexible, almost plug-and-play, architecture. Modules, a physical setup with a local Orbit supervisory controller, can be exchanged in the structure with minimal effort as long as the plant-wide synchronization protocol is kept constant.

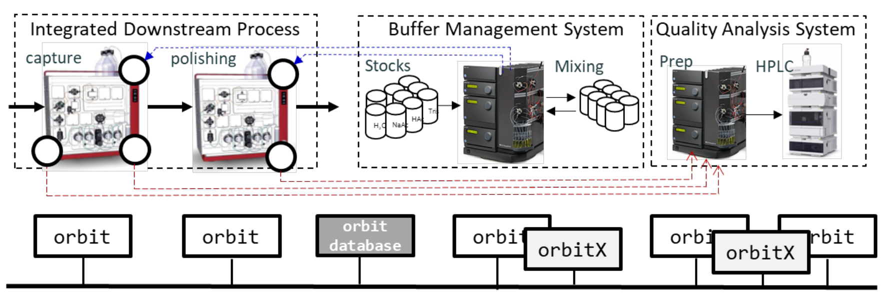

Figure 3: Decentralized control based on a network of Orbit controllers of an autonomous integrated downstream process with support systems.

Automated support systems

Automated operation of integrated continuous downstream process for a long time means a lot of support work, like preparing buffers and sample flow path for quality analysis and performing the actual analysis. This will actually generate more work than operate the processing system. For this reason, it is vital to automate these procedures in order to create a sustainable long-term lab-scale operation, which are needed for validation of digital solutions. Automated buffer management system and quality analysis system are briefly presented below.

Automated continuous downstream processes operate 24-hours, 7 days a week in a couple of months. During this time, it consumes a lot of different buffers even in lab-scale. After the automation of the actual processing line, it is important to automate the buffer preparation after demand of the process. One such system was implemented and studied in the lab-scale process and it is called buffer management system (BMS), see Isaksson et al 2023. The BMS is composed of four parts; i) monitoring of the buffer container levels at all clients to detect when they pass below an order level, ii) queue system for orders of needed buffers, iii) buffer preparation unit, BPU, and iv) delivery procedure from BPU to the ordering client.

Based on the digital application configuration of the physical system, Orbit keep track of the active flow path and therefore the size of the flow rate generated by the pumps. Orbit also automatically generate estimators of the levels of all containers in the flow path, like buffer flasks, waste containers and viral inactivation reactors. These estimators integrate the inflow and outflow in open loop. The level in the containers need to be updated based of measurements of the real container regularly, in order not to deviate too much. For the accuracy needed for predicting the buffer flask level this is not an important issue, but for more important processing units it can be. Associated to all container level estimators it is possible to add logic to generate events. One example is to trigger an order of more buffer when the estimated level passed below a given value.

The buffer order generated by the level estimator is sent to the buffer ordering queue system, an orbitX instance in Figure 3. The queue is a first-in-first-out (FIFO), but it is possible to rank the buffers in an importance order. The queue controller adds a new order into the queue and removes an order that is delivered. When the buffer preparation unit is ready it gets the first order in the queue from the queue controller. When the unit has delivered the buffer it communicates to the queue controller that the order has been performed, and the queue controller removes the order from the queue. An 11-days long operation of a lab-scale antibody platform is seen in Figure 4, where 55 order was handled by the buffer order queue controller.

BPU is an ordinary setup with a supervisory Orbit controller that on demand perform a procedure to prepare a specific buffer, following a predefined recipe, based on a set of stock solutions. The BPU used in this study can prepare up to 14 different buffers. The stock solutions are mixed in an intermediate buffer flask. The mixing can be operated in closed loop controlling pH and conductivity, but this feature had not been performed in this study. When the buffer is mixed, it is pumped to the client that ordered the buffer. The receiving client directs the buffer delivery valve to the right buffer flask. This required a communication between the buffer preparation unit and the ordering client over the network, see Figure 3. Each sample point in the downstream process has a collection loop on the preparation system.

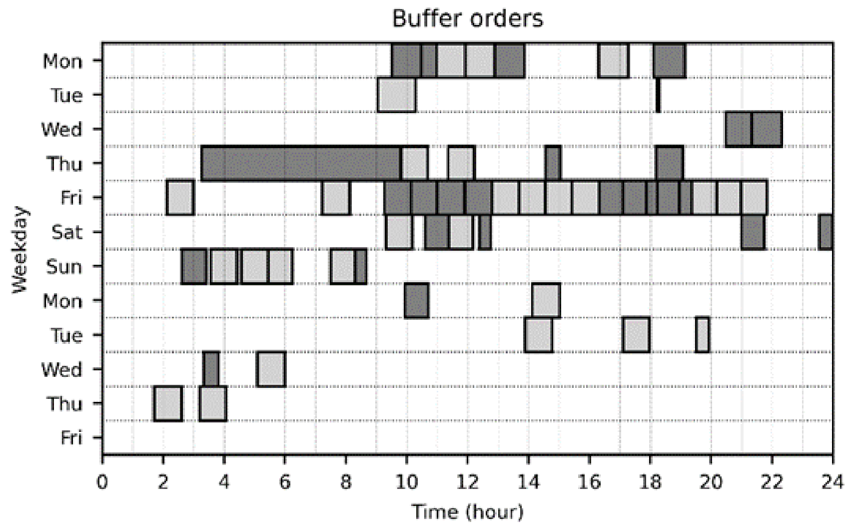

Figure 4: Performance of the buffer management system during 11 days of operation of a continuous antibody production.

The requirement on quality analysis can be handled almost in the same way as the buffer management system. As discussed above the continuous downstream process could assume the conditions in the harvest tank to be almost constant or changing very slowly. A set of performance and quality attributes were measured through chemical analysis of samples taken from different positions in the process flow path once a day. The sampling of the flow path were performed by the automation system but the chemical analyses were performed off-line and the actual attribute were calculated after the process were completed. The quality analyses were not used for monitoring of the operation, which would had been beneficial.

In lab-scale continuous downstream process there is no need to sample the flow path more often than a couple of times per day for any upstream based disturbance, based on the slow upstream dynamics compared to downstream. Assume that an HPLC analysis of a quality attribute takes 30 min and it is performed twice a day, then the HPLC is idle 23 hours every day. A general analysis system like HPLC can be configured to do a set of different analysis. If an analysis takes, in average, 30 min to perform it means that an on-line HPLC can handle almost 50 analysis per day. In lab-scale development resources are limited and an on-line HPLC needs to handle all on-line analysis in the processes. One such system was implemented and studied in Tallvod et al 2023 and 2022B. It is called quality analysis system, QAS. The physical configuration of the QAS was composed of two setups, one for sample handling and preparation, and a second dedicated analysis system, here a HPLC. The preparation setup handled the sample from the process and performed needed preparation, like dilution, conditioning buffer exchange and chemical modifications. The second setup, the HPLC, were configured to perform a set of different analysis. The automation part of the QAS is composed of three parts; i) sampling of the processing flow path, ii) queue system for orders of needed analyses iii) prepare the sample for analysis, and iv) preform the HPLC analysis and send data to database, see Figure 5.

The client application procedure does the necessary operations to do the actual sampling of the processing flow path. This sampling operation can be performed on demand based on an external order or by the client itself. The sampling can be a small amount directed to a sample loop or a complete pool shortly stored in a container, which is then pumped into a sample loop, before further processing in the process. The size of the sample depends on the analysis and the number of differ of analysis needed. Each sample point in the downstream process has a collection loop on the preparation system. When the sampling of the process flow path is completed, an order for analysis is sent to the QAS queue controller.

The queue in the queue controller, in an orbitX controller, is a first-in-first-out, but it is possible to rank the analysis in an importance order. Particularly if a time-critical-analysis is need for on-line control, which means that the analysis needs to be performed to generate a result in a given timeframe. The queue controller adds new orders into the queue and removes orders that are completed.

When the preparation/analysis unit is ready, it gets the first order in the queue from the controller. When the unit has performed the analysis it communicates that the analysis has been done and the queue controller removes the order from the queue. Note that the order can contain multiple analysis for different attributes. The generated data from preparation and analysis is sent to the Orbit database for further data processing. In some situations, it is convenient to do the data analysis locally, which is straightforward to do as a computation extension in the local Orbit controller.

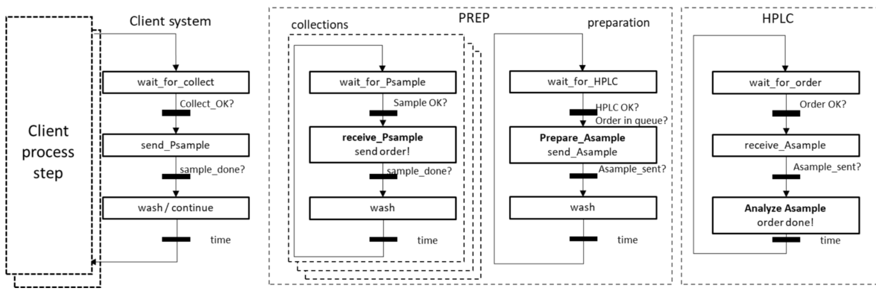

Figure 5: Queue based control of the quality analysis systems.

Orbit real-time database and data analysis

The processing platform with support systems discussed above generate a lot of data in form of structural information, input and control signals, detector signals, HPLC analysis, on-line software computations etc. The on-line generated data is heterogeneous, i.e. different types, asynchronous, i.e. in-line detectors vs advanced quality analysis, and distributed, i.e. generated on multiple physical detectors and different setups. A database was needed to handle real time process data and made it practical to handle for both local and plant-wide data analysis.

General tools for automatic data analysis of real-time data, on-demand at-line or off-line analysis, are important for process monitoring and process control. One example is the peak analysis of the PCC operation in the pilot-scale case study in Schwartz et al 2022. In Figure 6 the first two switches in the PCC are shown together with the automatic peak finder with associated peak measurement. The peak heights are plotted on right where peak B is the interesting product peak. As seen the three different PCC column do not behave exactly the same. They have slightly different peak heights, about 3% difference.

This kind of data analysis is based on the data stored in the database, which come from different sources in the process. In this case it was actually only from one detector on one setup, but in the general case it allows plant-wide data analysis using distributed data sources. Data analysis processing can be performed locally at the setup with the detector or at the setup needing the analysis results. An alternative suggested here is a plant-wide computational extension, in an orbitX controller, exploiting data in the database to perform more or less advanced data analysis for usage somewhere in the processing system or just for plant-wide monitoring. More advanced data analysis for data-driven modelling and machine learning are often performed off-line, but in some cases the results need to be validated in real-time. The architecture suggested here allow both off-line development and on-line validation.

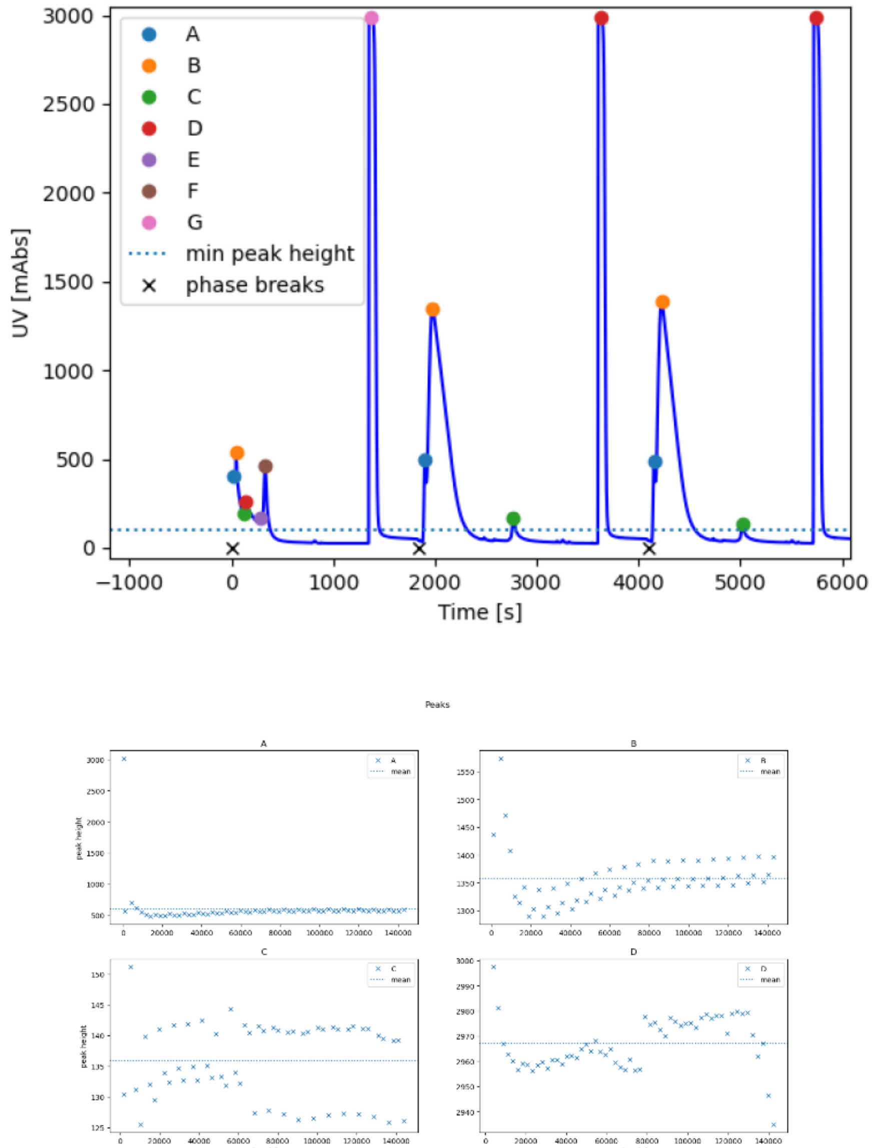

Figure 6: General peak data analysis used to monitor the PCC performance, left) the first two switches of the PCC together with automatic peak finding, right) PCC peak heights after about 40 hour operation.

Model based simulation, monitoring and control

The concept of digital twins in real-time applications means to use digital representations and mathematical models for monitoring and control of the processing system. The architecture of the proposed system with Orbit supervisory controllers and network of Orbit controllers allows the user to implement, study, design and validate these real-time applications of digital solutions.

The generation and validation of mathematical models is as important as it is time consuming, requiring a lot of engineering resources, see Nilsson and Andersson 2017. An attractive idea is to automatically generate the process model and to have automatic methods to calibrate and validate the model to experimental data. One such idea was studied and presented in Tallvod et al (2022A). In Orbit, every object in the digital configuration of the physical system has a mathematical representation. It means that a complete model of the setup is automatically generated based on the described configuration. Many of the objects can be described quite well, because the behavior is dominated by measurable physical attributes, like volume, flow rate, concentrations etc. Other objects need to be calibrated to experimental data and therefore needs a design of experiments to generate high quality data for parameter estimation. Off-line experiment plans are straightforward to perform together with computational extensions for parameter estimations of different models, see Tallvod et al (2022A). During continuous operation it is much harder to do experiments for parameter estimations and model calibration, but limited disturbances are often allowed if the control system can handle the disturbances.

One example of real-time usage of a mathematical model is in Kalman filter based monitoring. Extended Kalman filter tools are implemented as computational extensions in Orbit, with the possibility to use the build in automatic model generation. A simplified example is illustrated in Figure 7, which is a size exclusion chromatographic separation of two components with vary large difference in size. This case is actually linear, which simplifies the Kalman filter design in the case, but it is still a dynamic filter with covariance update algorithm. In Figure 8, column concentration profiles are estimated using the Kalman filter at four different time instances. The Kalman filter predicts the profile based on the model and corrects their value using the measurement signal. The example illustrates the power of these kinds of real-time algorithms for soft sensing, parameter estimation and on-line prediction.

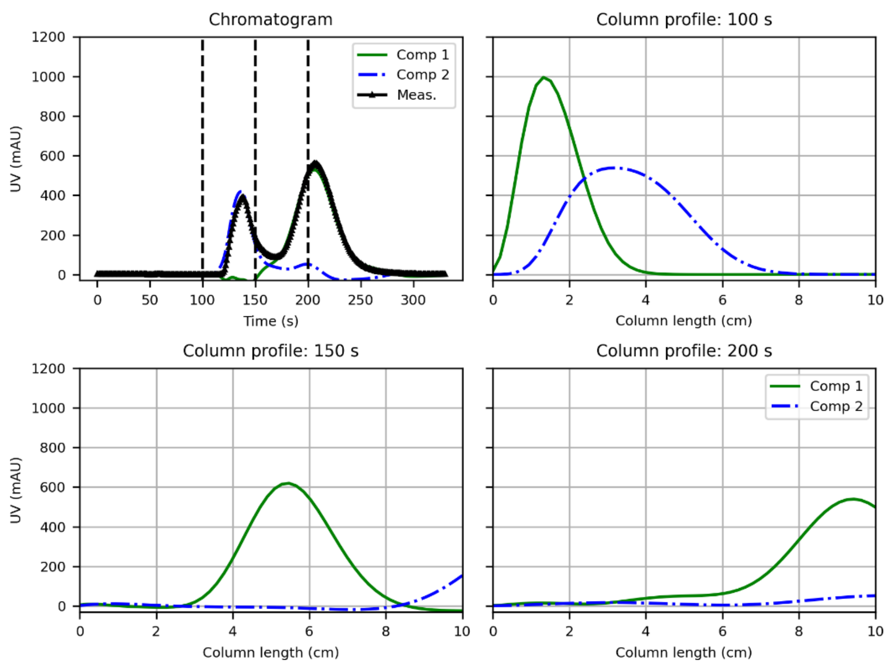

Figure 7: Size exclusion chromatography of two components with dynamic Kalman filter prediction of column profile using Orbit. Concentration profiles in the column together with outlet UV signal indicated at 100s, 140s, 170s and 210s.

As discussed above the integrated continuous downstream process can assume slow varying disturbances from the upstream process, like titer and other quality attributes. Other disturbances are buffer quality, which can change more drastically. For integrated downstream process with slow varying upstream disturbance it can be beneficial to control the separation using a batch-to-batch controller. The idea is to use previous batch behavior to compensate in the next batch. A batch-to-batch controller for retention time control using a salt gradient are presented in Espinoza et al (2022A) and (2022B), and an adaptive batch-to-batch controller for capture loading is presented in Löfgren et al (2021).

Note that the controller needs good information about the real system and this information can be retrieved in two different ways. The first way is by an automatic modelling with calibration as discussed above to generate a simplified model for controller tuning. The other way, presented in Espinoza et al (2022B) is by performing a set of on-line experiments for on-line controller tuning.

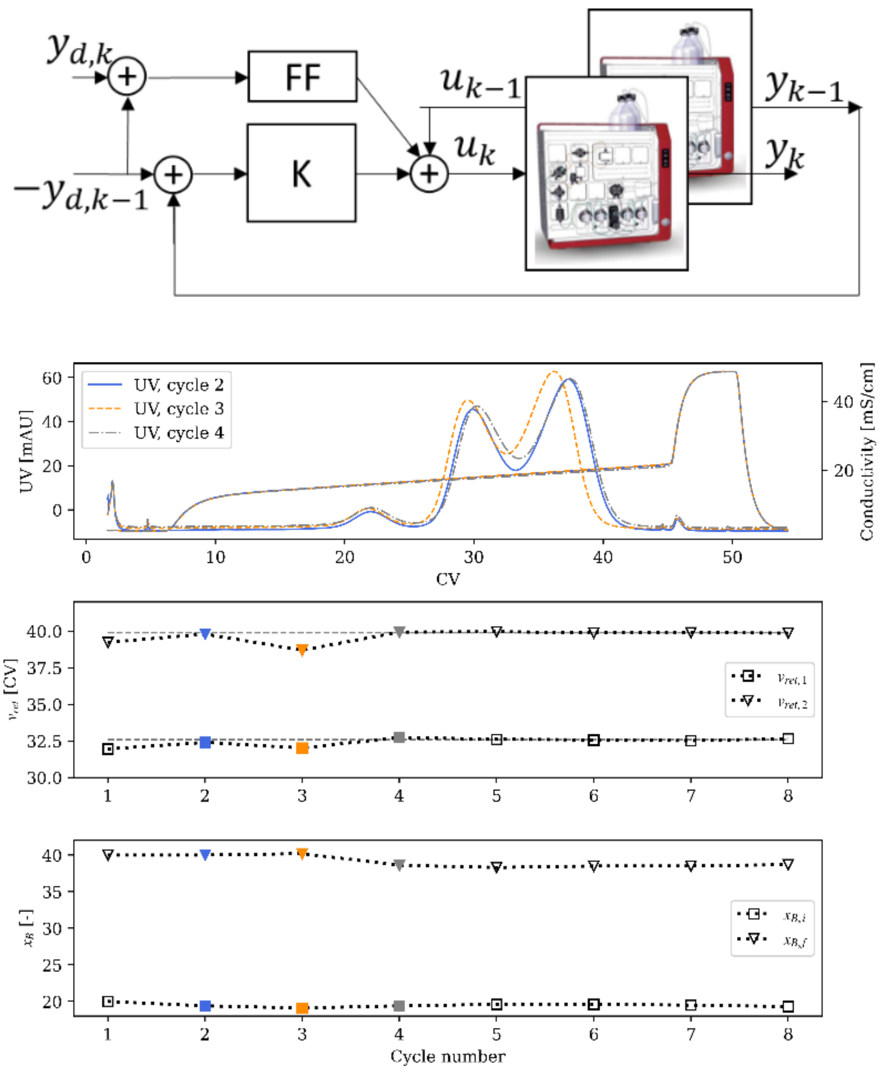

Figure 8: Batch-to-batch control of the peak retention time by the gradient elution of a two component separation by cation exchange chromatography, feed forward of desired set point, multivariable feedback controller with decoupling. A pH disturbance in the elution buffer is introduced in cycle 3, causing the controller to adjust the gradient to restore the retention times.

Conclusions

This paper presents a methodology, based on a lab-scale platform, for fast development of digital solutions in integrated continuous downstream processes. The fundamental building block is the Orbit supervisory controller that can control and communicate physical setups and their associated local control software. Orbit is an open, flexible and extendable software, which opens up the operation of the setup to any computational tool. Many different kind of processing steps and configurations has been implemented and operated using the methodology. These setups can be connected and configured into complex processing systems and a network of Orbit controllers makes it possible to operate almost autonomous. Both the configuration and automation of multiple processing steps and support systems are vital for sustainable and autonomous operation for long-term studies of digital solutions.

During processing of the integrated continuous downstream process platform data are streamed to the Orbit database. The on-line generated data is heterogeneous, asynchronous and distributed. The data are design and configuration information, real-time detector signals, asynchronous chemical analysis data, real-time data analysis information and on-line computational results. The Orbit software contains methods for automatic generation of mechanistic models and model calibration. This makes it possible to perform advanced data analysis, data-driven or mechanistic modelling, optimization and machine learning. The results can directly be implemented into the Orbit automation and control system for on-line processing. The conclusion is that the physical and digital platform are well suited for development, study and validation of real-time digital twin application in downstream processing.

CRediT authorship contribution statement

Niklas Andersson : Conceptualization, Methodology, Software, Writing (review & editing), Supervision, Visualization, Project administration.

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