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Intelligent, model-based control towards the intensification of downstream processes

Maria M. Papathanasiou[a,c], Fabian Steinebach[b], Massimo Morbidelli[b], Athanasios Mantalaris[a], Professor Efstratios N. Pistikopoulos[c,*]

[a] Dept. of Chemical Engineering, Centre for Process Systems Engineering (CPSE), Imperial College London, SW7 2AZ London, UK
[b] Institute for Chemical and Bioengineering, ETH Zurich, Wolfgang-Pauli-Str. 10/HCI F 129, CH-8093 Zurich, Switzerland
[c] Artie McFerrin Department of Chemical Engineering, Texas A&M University, College Station, TX 77843-3372, United States

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ABSTRACT

Process Intensification (PI) has been gaining increasing interest as industrial trends urge a shift towards more eco-efficient processes of significantly decreased operation and capital costs. In this direction we focus on the development of advanced control strategies of the Multicolumn Countercurrent Solvent Gradient Purification Process (MCSGP), an industrial, semi-continuous, chromatographic process, used for the purification of several biomolecules. We present a novel control approach that manages to drive the process towards continuous, sustainable operation. The presented controllers are designed within the PARametric Optimization and Control (PAROC) framework/software platform that enables the development of intelligent, model-based controllers through a step-by-step approach. The controllers are successfully tested against various disturbance profiles and they manage to track the predefined setpoints without significant offset.

1. Introduction

Current industrial trends indicate a shift towards eco-efficient processes of reduced environmental footprint. In monoclonal antibody (mAb) production this is coupled with the rise of novel products (such as biosimilars) of reduced production costs that stress the necessity of re-evaluation of standard practice (Xenopoulos, 2015; Klutz et al., 2016). Recently there has been increasing interest in the investigation of the needs as well as the improvement possibilities of the processes that are used currently in the production of mAbs (Walther et al., 2015; Girard et al., 2015; Klutz et al., 2016), while most of the related studies suggest the transition from batch to continuous operation. The latter would provide a steady-state operation, where product purity would remain constant throughout the process (Zydney, 2016; Steinebach et al., 2016). In addition, a shift to continuous operation will significantly decrease the capital equipment cost, while it will yield operations of higher productivity and improved product quality as the equipment will be in continuous use, running with greater uniformity.

The production of mAbs considers two main processing steps: (a) the upstream that corresponds to the culturing of the cells and the production of the antibody and (b) the downstream that is responsible for the separation of the impure mixture that comes from the upstream and the purification of the targeted product. In particular, advances in continuous cell culture systems are being reported for a long period of time (Arathoon and Birch, 1986), however downstream processing is still facing significant challenges. Recent studies, identify the latter as the limiting factor towards the development of fully continuous bioprocesses, as currently handling limited amount of load, thus preventing the upstream from further improvements and bounding the productivity of the bioprocess (Gronemeyer et al., 2014; Strube et al., 2012; Kelley, 2009; Chon and Zarbis-Papastoitsis, 2011; Dünnebier et al., 2001). As reported, up to 80% of the manufacturing costs in bioprocessing arise from the purification steps (Hunt et al., 2001; Girard et al., 2015). Moreover, long downstream processing times can impact negatively the product quality (Gillespie et al., 2012; Gospodarek et al., 2014). Therefore the need to decrease production costs, while maintaining high product purity and achieving increased productivity gave rise to novel semi-continuous separation configurations,

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* Corresponding author at: Artie McFerrin Department of Chemical Engineering, Texas A&M University, College Station, TX 77843-3372, United States.
E-mail address: stratos@tamu.edu (E.N. Pistikopoulos).

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such as the Periodic Counter-Current Chromatography (PCC), the Multicolumn Countercurrent Solvent Gradient Purification Process (MCSGP) and the Continuous Countercurrent Tangential Chromatography (CTC) (Zydney, 2016).

In this work we focus on the twin-column MCSGP (Aumann and Morbidelli, 2007; Krättli et al., 2013b) for the development of advanced control strategies that will ensure optimal, continuous operation. MCSGP is a semi-continuous process, described by a highly complex, nonlinear Partial Differential and Algebraic Equation (PDAE) model and periodic operation profile. The latter corresponds to input/output profiles being repeated over the cycles and can be encountered in various other systems such as Simulating Moving Bed (SMB) and Pressure Swing Adsorption Systems (PSA). The control of MCSGP has been previously studied following a 'cycle-to-cycle', Model Predictive Control (MPC) approach (Grossmann et al., 2010), as well as through classical PID (Krättli et al., 2011) aiming to maximize the recovery yield, while achieving high product purity. MCSGP falls in the challenging class of periodic systems that steady operation and the achievement of cyclic steady state (CSS) still remain open challenges (Nilchan and Pantelides, 1998; Degerman et al., 2006; Kawajiri and Biegler, 2006).

Following our previous work (Papathanasiou et al., 2016) here we present a novel control approach where we design two control schemes: one for the batch and one for the continuous mode of the twin-column MCSGP setup. The controllers are designed following the PARametric Optimization and Control (PAROC) framework (Pistikopoulos et al., 2015), which comprises four major steps: (i) development of a detailed mathematical model, (ii) a model approximation step, (iii) the design of multi-parametric model predictive controller and (iv) a 'closed-loop', in silico system validation step.

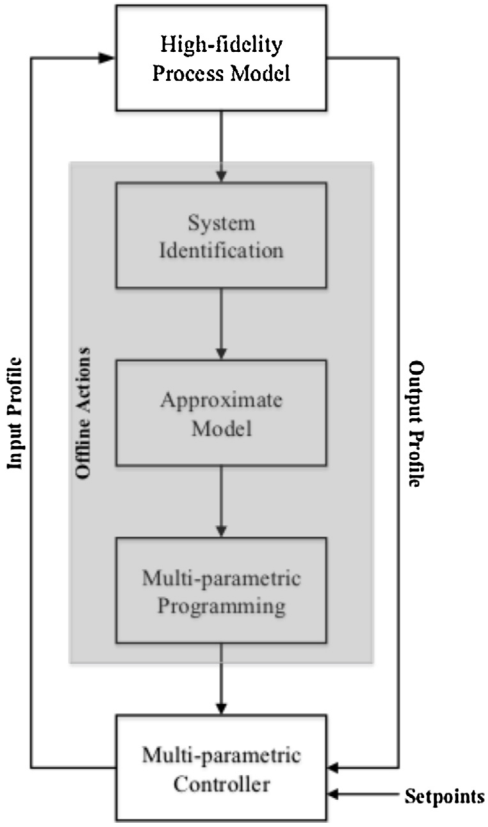

Fig. 1. The PAROC framework as used for this work.

2. Theoretical background

2.1. The PAROC framework and software platform

The feasibility and the performance of a process are directly correlated to its design as well as to the operational strategies applied. Therefore, in order to acquire the design, optimization and control approach that will lead to optimal and sustainable operation, we need to ensure that the process dynamics are fully understood and obeyed. In this direction, we have developed the generic framework, PAROC (Pistikopoulos et al., 2015) that suggests a detailed methodology for the in-silico design and testing of intelligent, model-based control systems. Here we demonstrate the PAROC framework (Fig. 1) as it has been tailored for this work. For an extended description of the framework/software platform and its applications the reader is referred to Pistikopoulos et al. (2015).

2.1.1. High-fidelity modeling and analysis

In this step a rigorous, dynamic model, based on first principles is formulated. The model is simulated using gPROMS® ModelBuilder (PSE, 1997–2016) that also serves the execution of optimization studies based on the developed model. The validity of the model developed in this step is of high importance as it is both the cornerstone of the entire development procedure as well as the testing platform for the multi-parametric controllers.

2.1.2. Model approximation

Usually, the models designed in the previous step contain large sets of Partial and/or Ordinary Differential and Algebraic Equations (PDAE and/or ODAE) that involve highly nonlinear terms, thus leading to computationally expensive simulations. Therefore, it is often necessary to simplify the model formulation and replace it with a linear system representation that will allow control studies to be successfully performed (Lambert et al., 2013; Rivotti et al., 2012). PAROC suggests the model approximation to be realized either via (i) system identification or (ii) model reduction techniques, based on the system requirements and/or characteristics. In this work, we perform the model approximation via system identification, using the System Identification Toolbox (*ident*) from MATLAB®. For the identification procedure we excite the high fidelity model under random input within the range of interest. More specifically, we vary both the input and the disturbances and we monitor the response of the tracked outputs. The nature of disturbances can be: (i) measured: corresponding to changes in the system inputs (e.g. composition of feed stream, sampling flow rate) that can be predicted and/or experimentally predefined or (ii) unmeasured: referring to disturbances that can unexpectedly occur during operation. The input/measured disturbance-output data set is used for the design of linear state space models.

2.1.3. Model-based control

The state space model designed in the previous step is used here for the formulation of the control problem, employing receding horizon policies. PAROC suggests the development of advanced controllers based on multi-parametric programming techniques. Multi-parametric Model Predictive Control (mp-MPC) techniques. Mp-MPC combines the advantages of classical MPC with the ability to solve the optimization problem offline, thus improving the controller performance during online operation (Bozinis et al., 2011). In comparison to other control strategies (such as PID control), mp-MPC is model-based and can therefore predict the system behavior in the future. In addition, the controller can account for disturbances that are crucial for the product quality in such systems. Moreover, the solutions can be stored in small devices ('MPC-on-a-chip') (Dua et al., 2008) that can be highly beneficial for

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