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Improved control strategies for the environment within cell culture bioreactors

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ABSTRACT

This paper describes the development of improved control strategies for the standard environmental conditions in a fed-batch bioreactor used for monoclonal antibody cell culture. The consequences of relying on fixed parameter PID based controllers are considered and poor performance is demonstrated as a consequence of non-linearity and loop interactions. The benefits from adopting a more sophisticated control strategy are considered. Model Predictive Control (MPC) relies on a process model that can be identified from small system perturbations. It considers the predicted longer-term response and consequently can deliver improved control and satisfy user defined constraints. Results from experimental trials demonstrate the capability of MPC and the merits are discussed with regards to industrial application.

1. Introduction

Mammalian cell cultures now account for over 50% of the biotherapeutics market and with a large pipeline of products this is set to increase (Al-Majmaie et al. 2021). The global market for mAbs was valued at USD 122 billion in 2019 and is estimated to surpass USD 200 billion in 2024 at a CAGR of 6.9% (Hong et al. (2018)). Consistent active pharmaceutical production is a major concern to the biopharmaceutical industry, which requires precise control of all manufacturing process aspects. Factors influencing the quality of CHO based therapeutic proteins are discussed by Ha et al. (2021). They categorise the factors into three groupings (culture environment, chemical additives and host cell proteins) and review the literature relating to each. They note the diversity of products and changes in sensitivity to variations that result. This makes generic statements on degree of impact problematic. However, they raise an important operating principle in that while the extent of impact may differ, minimising variation of critical quality attributes, with due consideration to critical process parameters is key. In this, they stress the need for tight environmental control.

It would be reasonable to assume that for those involved in biomanufacturing, the effective, tight control and optimisation of the bioreactor would be a prime focus of attention to maximise yield and achieve product quality aligned to patient need. However, from an operational sense, the reality is that control philosophies have changed little over the last few decades. Standard environmental measurements (e.g. pH, temperature, dissolved oxygen) are controlled using fixed PID controllers and operator in the loop offline sampling based control is deployed to regulate other crucial

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parameters. Infrequent offline sampling, system nonlinearities experienced in batch operation and natural biological variability combine to lead to poor control performance. Evolving biopharma-based therapies are characterised by the high cost of media and batch to batch variation through biological variability and yield losses through poor control amounting to considerable losses. For example, Van Beylen et al. (2020) described the impacts of variability on viability, causing around 8% out of specification product for a Novartis cell culture product. More generally, estimates of between 10%– 20% losses for some products have been reported (Hippach et al., 2018).

Existing data gathered during operation and data available from online process analytical sensors could be used to fundamentally upgrade the control systems to address loss of yield and reduced quality issues. In addition to the requirement for accurate and responsive online measurement of environmental parameters, tight environmental control brings with it the need for responsive control systems with control strategies suited to the task. However, bioprocessing is a complex operation and the conventional control systems are not always effective. The pH and dissolved oxygen (DO) control loops can interact and nonlinear behaviour is observed as batch characteristics change with culture age, making behaviour under conventional PID based control either sluggish or oscillatory and frequently impacting on-product yield. The predominant industry attitude is to accept the status quo and adopt PID control systems that are at best a compromise across the nonlinear behaviour or worse, more poorly tuned so performance is degraded.

Focusing specifically on the impact of culture environment variations, Hippach et al. (2018) considered cultures exposed to significant high frequency variations in DO concentration due to ineffective control. They classified cultures into those where significant oscillations were present and those where control was effective. It should be noted that for those cultures where there was oscillation, the DO levels did not fall below acceptable levels for the culture. For those experiencing ineffective and oscillatory control, lactate was found to accumulate in the latter half of the culture and the viable cell density was statistically significantly lower than those where control was good. Regarding titre, an average 24% loss in specific productivity was observed. Although only eight batches were considered, the results of their study indicate the potential for a significant loss of productivity from ineffective control of DO.

The implications of such yield loss and the motivation to act on it can be considered by assessing the financial implications. Using information provided by Xu et al. (2017), if a production vessel of 2000 litres is considered as being the largest single use reactor, a 20% yield loss would correspond in terms of feed costs of value $20 K-$30 K/batch for a typical culture. A thorough financial assessment of the financial implications of reduced yield is more complex than this but this 'ball-park' consideration indicates that improving the quality of control is a worthy undertaking.

The challenge faced in controlling cell culture environment throughout the batch is discussed by Simutis and Lübbert (2015). They describe how fermenter manufacturers deliver systems with single-input single-output PID controllers and that the fixed parameter nature of these controllers results in degradation in performance that is either characterised by oscillations or is sluggish. The issue is not one of tuning, although clearly poor tuning impacts on performance, but of nonlinear system behaviour meaning that to be effective the settings of a controller need to change during a batch. They point to the solution being controller gain scheduling where predefined gains are specified or models of the system used to determine gain changes. The recognition of the need to modify controller setup to accommodate batch dynamic changes was reinforced in the work of Aehle et al. (2011). They demonstrated that with appropriate gain changes, tight control of a CHO culture could be achieved using conventional control of oxygen uptake rate. While this is feasible for a fixed process, when several processes are going through development, establishing such a gain schedule is difficult. They also raise the use of model predictive control as an alternative but question the financial return from a more sophisticated and costly control approach.

This paper directly addresses this issue and assesses the potential of MPC. The paper considers the pilot scale experimental system and experimental protocols adopted. MPC concepts are then briefly described before discussing the performance observed in their implementation in pilot scale trials. Finally, the practicalities of the MPC approach are discussed with consideration of implementation within a regulated manufacturing environment.

2. Model based predictive control

A review of the application of control strategies in bioprocessing and future technology prospects was presented by Rathore et al. (2021). While they describe a broad range of control approaches (from linear through to nonlinear data-based model or mechanistic model), of those considered, MPC is by far the most common in industrial application. Importantly, they stress the need to achieve 'high levels of precision, accuracy and robustness'. Simutis and Lübbert (2015) describe how MPC can deliver against such operational requirements but questioned the financial benefits given the implementation cost. However, based on the arguments of Xu et al. (2017) payback has the potential to be rapid for mAb implementation. Thus, MPC is a potential financially viable route to improved mAb process control. This observation is supported by the arguments of Sommeregger et al. (2017) who argue for the potential of MPC in mAb manufacturing but their contribution describes the potential without evidencing capability.

Performance benefits are not the sole criterion of consideration as the implementation of control systems in a validated environment must be considered. For example, there is a need to incorporate automation at the earliest stages of process development if it is to form the basis of manufacturing scale control. The concern with the use of MPC expressed by Rathore et al. (2021) was the availability of robust models required in biotech sector applications. This has negative implications for MPC resulting from the paucity of model information that could be available at this stage and raises the need for automated and robust model development. Jelsch et al. (2021) took the opposite view in reviewing the opportunities for MPC in biomanufacturing operations. They considered the ability of MPC to identify a model of complex process as a distinct advantage and stated 'MPC seems to be a promising control strategy for the manufacture of pharmaceutical products'. This view was reinforced by Luo et al. (2021) who stress the potential but also observe that

applications are limited due to a limited number of case studies proving the worth.

The algorithms behind model based predictive control are well stated in the literature and comprehensively compared. An early review by García et al. (1989) provided a summary of MPC approaches and progression in the early stages of its development. Qin and Badgwell (2003) provide a highly cited comparison of the industrial model predictive control algorithms. They clearly describe the common underlying principles of the receding horizon algorithm and the objective function that the optimisers within the controller attempt to solve. Given the paper is nearly two decades old, the latter sections considering applications area breadth and next generation MPC are a little dated, nevertheless, as a review of the principles it stands the test of time. Lee (2011) provided a retrospective on MPC developments. In the last decade the applications of MPC have grown significantly in number and have broadened in scope. A recent review provided a summary of alternative algorithms and described challenges and opportunities in industrial application (Schwenzer et al. 2021). With the broad application of the algorithms, they notably describe how modelling and control skill set can be constraining in exploiting MPC, a view echoed by Forbes et al. (2015). More recently review papers have also focused on applications sector implementations. For example, Su, Ganesh et al. (2019) considered the implementation of MPC in pharmaceutical manufacturing to achieve Quality by Design (QbD) requirements by adopting a Quality by Control (QbC) philosophy. They described the whole process benefits before focusing on a case study implementation on a tablet press. Schwenzer et al. (2021) provided an up-to-date review of MPC technology applied in pharmaceutical manufacturing and again focused on the tablet press as a case study for QbC.

There are a limited number of applications of MPC to upstream mAb production that are experimental rather than simulation based. Van Beylen et al. (2020) built a model of a cell culture process using experimental data and demonstrated, using the model as a process simulation, that a single-input single-output (SISO) MPC was able to offer control benefits for the regulation of cell growth in the process. However, to be effective the MPC required the linear times series model to adapt to accommodate changing dynamics throughout the batch. Adopting a similar approach of building a mechanistic model and investigating MPC control improvement, Aehle et al. (2012) considered how oxygen consumption could be controlled to a profile to reduce batch to batch variability. They also needed to periodically update the controller model as dynamics changed throughout the batch. Although the operational challenges are somewhat different with a secondary metabolite microbial fermentation, they do possess several common control difficulties. Kager et al. (2020) compared the application of model predictive control and PID control to a penicillin production process. Although their results were predominantly from simulation, they did undertake limited laboratory trials and demonstrated the deleterious effect of batch dynamic change on control loop behaviour. The non-linearities necessitated control system re-tuning or gain scheduling. They also observed the improved control performance resulting in smoother response and an improved yield of 14% using MPC.

Considering the discussion above, there are potential opportunities to be gained from MPC and these need to be demonstrated on a laboratory-based system. Furthermore, evidence from PID implementation and MPC simulations indicates that the MPC implementation may require periodic model updating to accommodate through batch dynamic variations. To assess these assertions, a series of experimental trials were undertaken.

3. Materials and methods

3.1. *Details of cell culture system / bioreactor*

The stable CHO cells expressing the recombinant anti-Her2 IgG1 was used in this study and cultured in a chemically defined medium and feed. The base medium used throughout was CD FortiCHO (ThermoFisher Scientific). The inoculum trains started from vial thaws and were expanded in shake flasks with increasing volumes to generate sufficient cell number to inoculate the bioreactors. The shake flasks were maintained in 5% CO_2 shaking incubators at 37 °C, 85% humidity and 125 RPM. The bioreactor experiments were carried out in 10-L Biostat B-DCU bioreactor (Sartorius Stedim Biotech, Germany) with starting working volume of 7 L and was operated in fed-batch mode. The pH, DO, temperature and agitation were controlled at constant values of 7.00, 30% of air saturation, 36.5 C and 240 RPM, respectively. DO was controlled using nitrogen, air and oxygen supplied via a sparger. 1 M NaOH and CO_2 were used to control pH.

3.2. *MPC controller implementation*

Process models are employed at the heart of the MPC scheme to forecast behaviour and subsequently allow control moves to be determined. The controller models can be pre-built on process data, identified online from a series of identification sequences or prebuilt and updated as new information becomes available. In all instances, the purpose is to disturb the system, observe the response and fit an input / output relationship with an appropriately structured model. Pseudo random binary sequence (PRBS) testing is commonly adopted as it offers the ability to generate statistically rich data whilst producing on-specification product. In undertaking this task it is necessary to:

- Consider what variables need to be perturbed and by how much. In this instance as oxygen and air sparge are used for DO control and CO_2 sparge for pH control, impacts of their change need to be studied. Addressing size of change, it needs to be sufficient to distinguish process output variation from underlying noise but not too large as it could drive the process into non-standard areas of operation. A rule of thumb of 10/1 signal to noise is common.
- Specify how many changes are required. There needs to be sufficient change to assess impact per individual input as well as understand the impact of their change in a positive and negative direction. Around 5–10 steps of each input variable would be typical.
- Assess alternative model structures for representation capability. While there are numerous representation forms of linear models (time series, transfer functions, state space in continuous and discrete time), it is generally possible to transition from one to another. The prime challenge is selecting model order and here there is a balance between descriptive ability and over-fitting noisy data with high order models. Here metrics such as Akaikes

Information criteria (balancing error in fit against number of parameters) are useful (Ljung, 1999).

A general discussion of the practical aspects of system identification can be found in Tangirala (2015).

Step-test data from the Bioreactor was employed to identify a prediction model for MPC implementation. The linear time-series model used in this work is a special instance of the set of linear models:

$$\mathcal{M}\ (\theta)\text{: } y(t) = G(q;\theta)u(t) + H(q;\theta)\zeta\ (t)$$

$$(t) = \Lambda(\theta)\delta t,s$$

Where, (t) is a *ny*-dimensional output at time *t*, (t) is a *nu*-dimensional input and $\zeta(t)$ are sequences of independent and identically distributed (iid) random variables with zero mean. Further, $(q;\theta)$ is a function map of dimension $ny \times nu$, $(q;\theta)$ is a function map of dimension $ny \times ny$ and q^{-1} is the backward shift operator such that $q^{-}(t) = f(t-p)$. A recursive least squares (RLS) algorithm was used to identify an Output Error (OE) 2×2 multiple-input multiple-output prediction model for pH and DO, this model is a special instance of the set of models described above. Such MIMO OE model has the following structure:

$$y(t) = q^{-nk}\left[\frac{B_1 q^{-1} + B_2 q^{-2}}{I + F_1 q^{-1} + F_2 q^{-2}}\right]u(t) + \zeta(t)$$

Where y(t) is the vector of outputs or controlled variables (CVs) → pH and DO; u(t) is the vector of inputs or manipulated variables (MVs) → CO2 and O2 sparge, and *n* the input / output delay. Matrices B1, B2, F1, F2 and I are 2×2 matrices.

The MIMO OE model is embedded within an MPC architecture and used to compute output predictions and the difference between such predictions and their desired setpoints. In this work the MPC implementation consisted of a standard receding horizon approach, in which the following cost function was minimised over every iteration:

$$J = \sum_{i=0}^{N} [\boldsymbol{e}_{i+1}\boldsymbol{P}\boldsymbol{e}_{i+1}^{T} + \boldsymbol{\Delta u}_i \boldsymbol{Q}\boldsymbol{\Delta u}_i^{T} + \boldsymbol{f}_i \boldsymbol{R}\boldsymbol{f}_i^{T}]$$

Where:

e: set-point error
P: set-point weight (tuning parameter)
Δu: actuation incremental moves
Q: move weight (tuning parameter)
f: input variables' target
R: target weight (tuning parameter)

The MPC also considered the following constraints when minimising the cost function:

- Maximum incremental value of ***Δu*** allowed for each of the two MVs.
- Upper and lower limit values for the MVs.
- Upper and lower limit values allowed for the each of the CV setpoints.

For the pH and DO MPC presented in this paper, the MIMO linear model identified for the MPC was employed in simulation to perform the initial tuning of the controller and determine the:

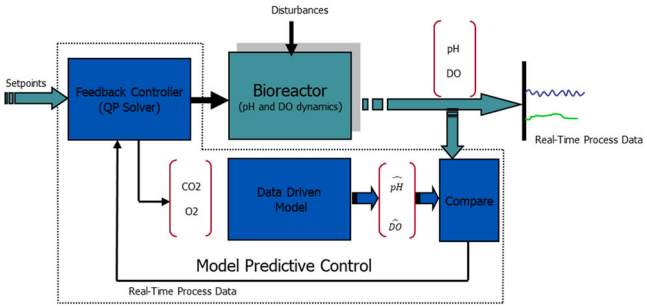

Fig. 1 – Block Diagram of the MPC controller implemented at the industrial partner, the Data driven model is a 2 × 2 MIMO OE model used to predict pH and DO in real-time, the difference between the prediction and the actual outputs are feedback into the control algorithm to compute the CO_2 and O_2 values that will drive pH and DO to the desired setpoints whilst keeping the system within constraints.

- Prediction horizon (set to be time to steady state for the slowest response from an input step change)
- Control horizon (set to match the prediction horizon to get smooth MV values)
- Move weights and move limits for the manipulated variables that reduced MV variability.
- Setpoints upper and lower limits, as well as MVs upper and lower limits, were set by the fermentation scientists. These limits are based on safe and acceptable operating conditions.

Also, white noise (with a 10/1 signal-to-noise ratio) was added to the simulation for tuning the MPC. After the MPC was tuned in simulation it was deployed in real-time to control the bioreactor. Small step changes where then applied to the pH and DO setpoints to fine-tune the controller's setpoint tracking. A block Diagram of the final controller is shown in the Figure below: Fig. 1.

4. Experimental Results

Fig. 2 shows the performance of the bioreactor control for an example run prior to the MPC studies. Variation of ± 2% dissolved oxygen and ± 0.01 pH are not excessive deviations from setpoint, but the control actions needed to achieve this are excessively severe, verging on on/off action, leading to the cycling of the output variables. The concern here is not the deviation from set point but the stress to the organism caused by severe control actions. A secondary concern is actuator wear and tear.

The potential for MPC to improve the control performance was considered and the first stage was to undertake a series of step tests on the bioreactor. Control performance has proven to be acceptable up to 100 h in the cell culture using PID control but when growth increases significantly beyond this control problems arise. Thus, the control studies focused on post 100 h performance. In this stage there are three potential control 'handles' for DO: stirrer speed, air flow sparge and oxygen sparge. Clearly the controller can only use one and thus a selection based on demand is used. Once stirrer speed hits maximum, air sparge is varied from its minimum to maximum flow for control. Once demand exceeds this, oxygen sparge is added to supplement the airflow for control. Hence, typically earlier in the batch there is no oxygen sparge

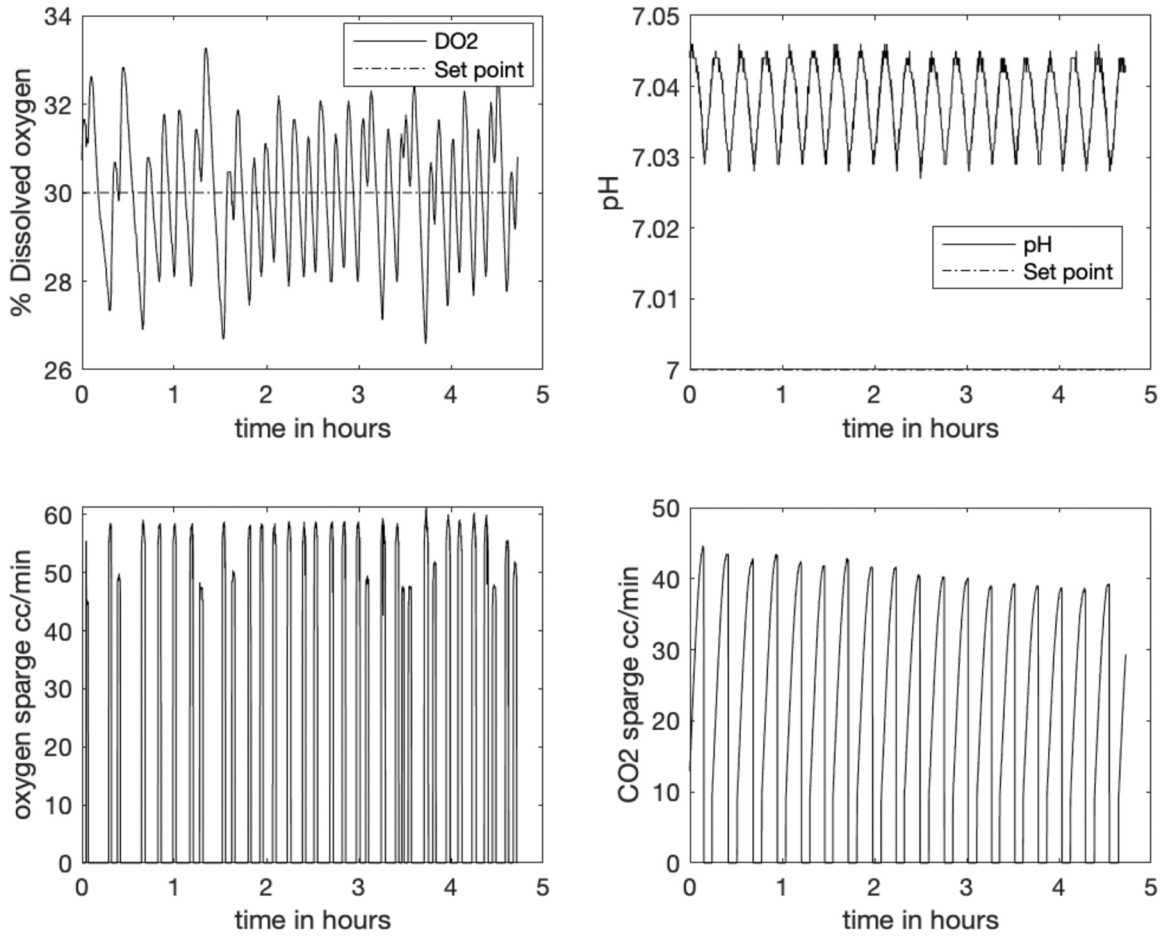

Fig. 2 – Example of controller response prior to the control studies in the mid stage of a mAb cell culture noting the significant and oscillatory nature of the manipulated variable changes. DO is controlled to a set point of 30% and pH to a set point of 7 with steady state offset.

but later control actions are through oxygen sparge, the region under consideration in this paper. Fig. 3 shows step tests when the stirrer is running at it maximum in air sparge and oxygen sparge, as well as carbon dioxide sparge at 240 h into the batch.

The linear times series model fit to the data is also shown in Fig. 3. While a good fit is observed, it is important to assess the model characteristics and relate them to qualitative expectations from a process expert perspective. The most straightforward manner to do this is to consider the step response characteristics and whether the gains and the speeds of response are in line with expectations from experiential and scientific perspective. Table 1 shows the model parameters identified at two periods of batch operation. Note that the model fits included a time delay term but in all cases, this was insignificant compared to the time constant. Given the magnitude of CO_2 sparge change is of the order of 50 and O_2 sparge is of the order of 40, based on the models in Table 1 step changes in CO_2 are predicted to have a small impact on DO. For example, a model gain of 0.04 and steps of 50 in CO_2 sparge would result in a 2% change in DO. For O_2 sparge impact on pH, a change of 40 would result in a pH change of approximately 0.01. Thus, in terms of interactions between loops, the impacts are not significant but are observable given the probe resolution.

The issue of model variation during a batch also needs to be considered. In Table 1 the model fit comparison is between a model developed at 120 h in the control batch considered below and 240 h into a prior batch. Some degree of batch-to-batch variation will exist but historical results suggest this is small compared to the change in mid to end batch behaviour. While the fit for the model for 120 h is not shown, it is comparable to that at 240 h in Fig. 3. Air sparge has not been included in the table of comparison as it is set to its maximum value in the case of the model at 240 h. Significant changes in the process (and indicated by the model) suggest a fixed parameter controller potentially failing to provide consistently good performance. For the DO / O_2 sparge loop an increase in gain of 50% would be expected to reduce loop performance but the extent would depend on the tuning. However, a gain decrease of 200% for the pH control by CO_2 loop would likely lead to sluggish performance for a controller tuned to perform well earlier in the batch. This issue was of concern and the following simulation indicates that with appropriate tuning a balance between robustness and performance can be maintained across the batch.

Fig. 4b – MPC controller tuned for higher levels of robustness using 120 h model and reduced overshoot for 240 h model but sluggish performance at 120 h.

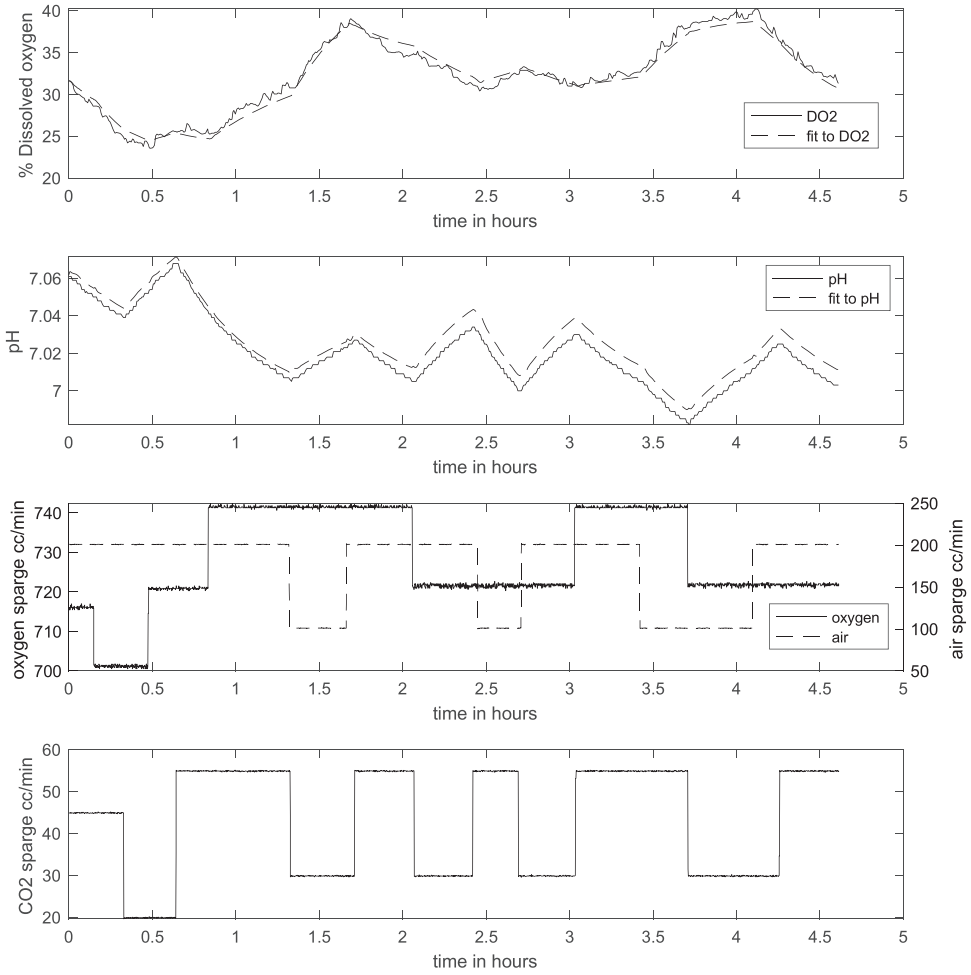

Fig. 3 – Disturbance sequence applied to manipulated variables and model fits to process data generated offline. A good quality of fit is observed for both pH and DO.

Table 1 – First order + transfer function model fits for step tests.

Transfer function	Model parameters at 120 h into batch	Model parameters at 240 h into batch
DO2 – O2		
Gain	0.21	0.329
Time constant (hours)	0.10	0.07
DO2 – CO2		
Gain	-0.04	-0.047
Time constant (hours)	0.22	0.025
pH – CO2		
Gain	-0.01	-0.005
Time constant (hours)	Approx. 0.01 (but note direction dependent)	0.000001
pH – O2		
Gain	0.0002	-0.00002
Time constant (hours)	0.657	0.906

In Fig. 4a perfect model is assumed for the MPC taking that at 120 h (Table 1) and a MPC setup to deliver a balanced level of robustness in Fig. 4a against a unity set point change at 1 h. The output horizon is set to cover a considerable portion of the settling time and the control action horizon set to one. Changes in controller increment weighting were used for fine tuning. It can be seen that for the plant-model mismatch that would arise at 240 h (Table 1) a significant overshoot results. If robustness is increased by more heavily penalising control moves (Fig. 4b) overshoot is reduced but the response at 120 h is more sluggish. This demonstrates that stability will be likely maintained for the DO loop providing a degree of confidence but the performance / robustness balance will likely need online tuning to provide desired behaviour across the batch.

In implementing a new control strategy, questions of robustness also arise in terms of safety and need to be fully addressed. In this instance this involved removing local feedback control through PID and implementing a MPC based on a local PC writing to the bioreactor control system. To gain confidence, the MPC control system was implemented in advisory mode and the suggested control actions implemented manually by the fermentation scientist, with the PID controllers in open-loop. Given this approach, the experiment is by necessity short. The results arising shown in Fig. 5, together with a thorough safety assessment were presented to and approved by the industrial partner safety committee. Note that the O_2 sparge outlier at 30 min was an entry error by the fermentation scientist. Of particular

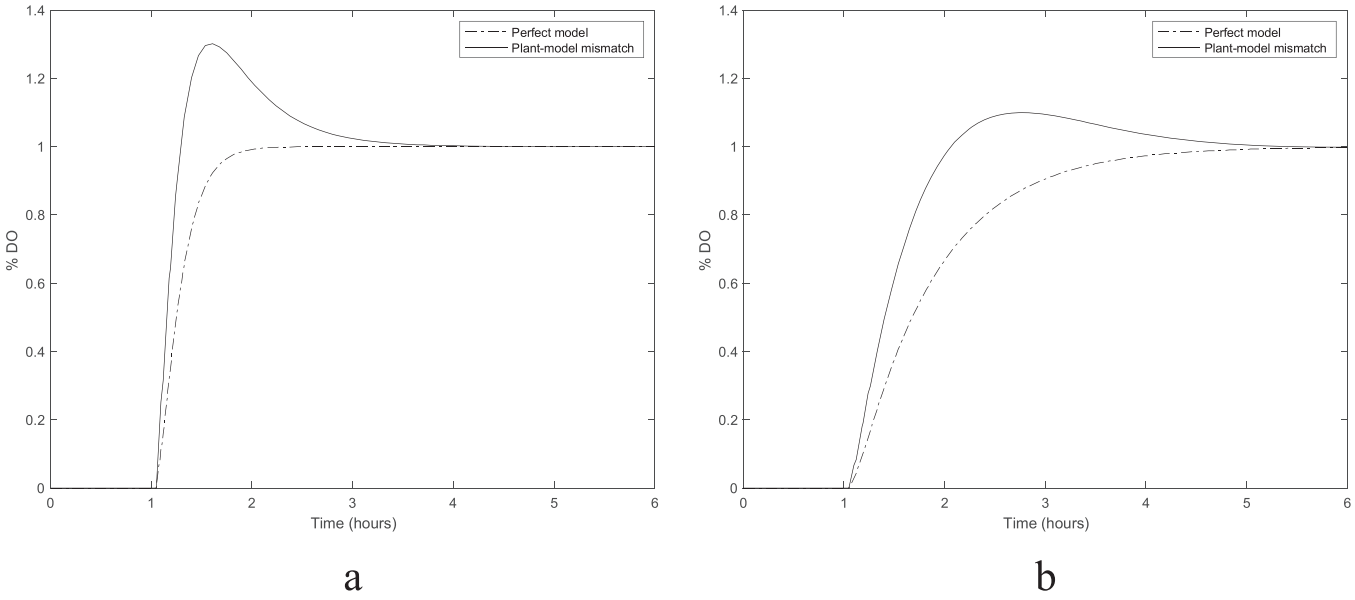

Fig. 4 – a MPC controller tuned for medium levels of robustness using 120 h model and overshoot for 240 h model.

importance to note is the smooth nature of the manipulated variable signals compared to that seen in Fig. 2.

With the confidence gained from initial trials, a closed loop implementation of MPC followed. A series of model identification steps were carried out at 120 h with the model summarised in Table 1. The real-time model adaption consisted of applying a series of automated step tests through adding non-invasive pseudorandom binary sequence (PRBS)

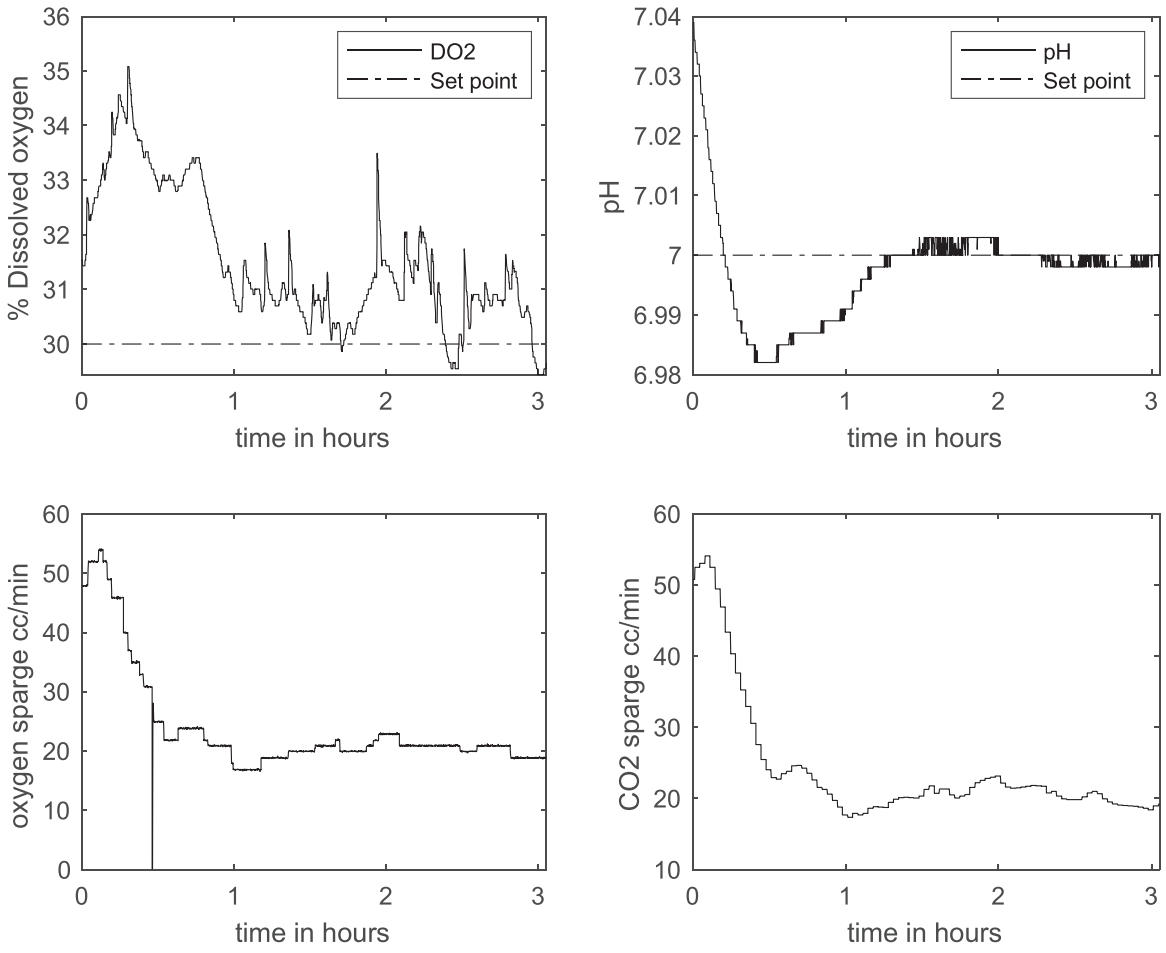

Fig. 5 – MPC running in advisory mode with the actions implemented by the fermentation scientist giving the initial confidence that MPC will provide effective control.

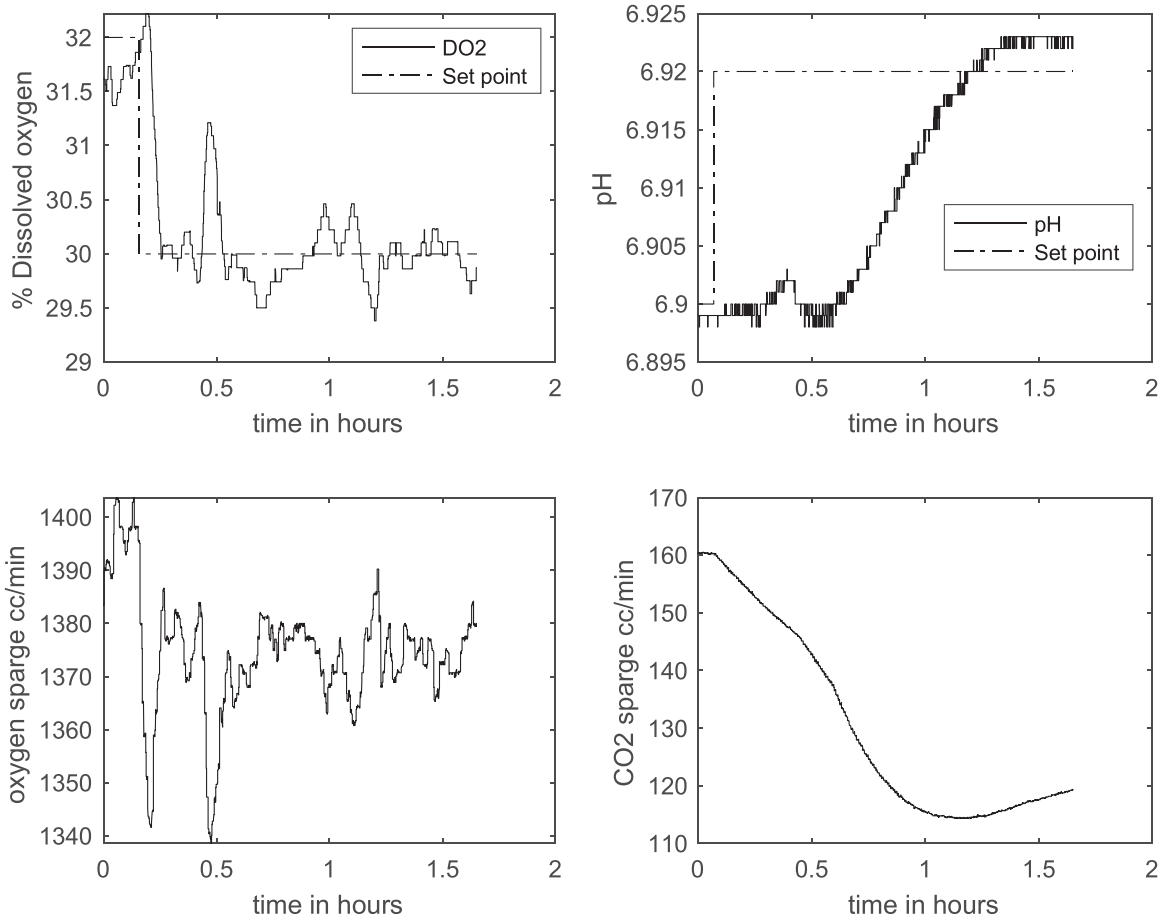

Fig. 6 – Response of multivariable MPC controller to set point changes at 215 h into a batch. Good set point control and disturbance rejection is demonstrated.

offsets around the control actions. This model was implemented within the MPC once generated and its performance monitored automatically throughout the batch to determine whether re-identification was necessary due to dynamic changes. The performance of the model embedded in the MPC was monitored during the entire duration of the cell culture. This allowed the detection of increased absolute prediction errors, at which point an automated model adaption could be triggered if necessary.

Figs. 6–8 show MPC results from the same batch run using the model from 120 h and demonstrate how the MPC was able to deliver better results when compared to the existing system PIDs, even with a sub-optimal model in the later batch stages, without the need for re-identification.

Step response and disturbance rejection capabilities are demonstrated in Fig. 6 at 215 h into the batch. Set point changes in DO early in the experiment are well controlled by the MPC controller. A disturbance due to a batch feed addition is apparent at 0.4 h into the experiment in the DO response and the MPC effectively removes this to return to set point. The general trend for reduction in CO_2 sparge to maintain a fixed pH is observable in the early part of the response in pH control. This is more clearly seen in Fig. 8 when pH setpoint is held constant. In Fig. 6, pH can be seen moving towards set point at around 0.25 h. The feed addition at 0.4 h acts as a disturbance and it is not until 0.5 h that effective pH is observed. Feedforward compensation of such disturbances is possible as their additions are known but was not implemented in this instance.

Fig. 7 shows results a day later for set point changes in pH and DO. Tight pH control is achieved with very little overshoot. The response for pH control demonstrates a direction dependency in the response with greater overshoot when stepping set point down (4.25 h) than up (1 h). This direction dependency is expected given the nature of the pH system characteristics and cell behaviour. It is important to compare the signals in Figs. 6–8 against the variation of manipulated variables seen with PID control in Fig. 2 and noting the change in graph scales. A much smoother manipulated variable response is likely more conducive to improving cell culture performance.

Towards the end of the batch, variation in the process would be expected to result in considerable plant-model mismatch (as suggested by Table 1). Nevertheless, the results from control to a fixed set point (Fig. 8) demonstrate that tight control of DO and pH is achieved, with the step like nature of the responses being the quantisation of the probe signal. The changes in demand of O_2 and CO_2 during the period being indicative of organism demand.

As the process evolved during the batch and the model mismatch increased, the MPC performance was consistent as seen in Figs. 5–8. This consistency was realised through the

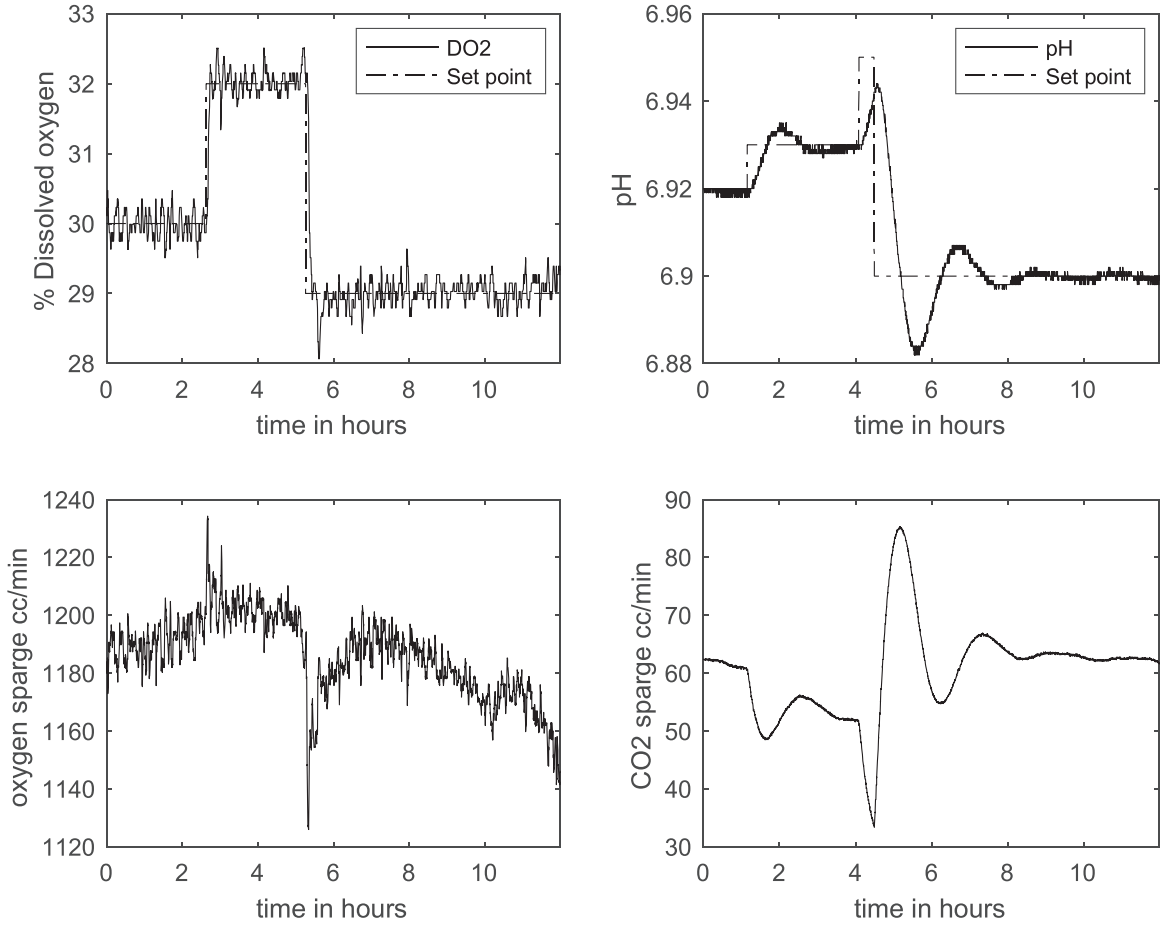

Fig. 7 – Response of multivariable MPC controller to set point changes at 240 h into a batch.

achievement of a suitable performance/robustness balance via tuning, the need for which was informed by experience from initial trials and demonstrated in Fig. 4. The controller tuning was finalised around 124 h into the batch and remained fixed throughout. Tuning parameters are as shown in Table 2.

The controller update interval was set to 15 s and the prediction horizon was 150 s (or 10 controller intervals). Note the large tuning weight for Air Sparge which was set at maximum throughout. The tuning was primarily via the move weights, with target and setpoint weights left at their default values. Thus, the improved performance over PID did not require significant additional complexity in controller tuning for this implementation.

Overall, the benefits over PID are smother manipulated variable actions (a 95% reduction of CO_2 sparge standard deviation (SD) and a 72% reduction of O_2 sparge SD). There is also a benefit in pH tracking with MPC offering an 80% reduction in pH SD when compared to the original PID control approach. This was mainly due to the implementation of a SISO PID that is not capable of taking into consideration the multivariate nature of the process in the control formulation. This is not an issue with MPC as it considers the multivariate interaction amongst all inputs and outputs when computing the control actions.

Note that model re-identification was not triggered in the batch and therefore Figs. 6–8 were achieved with the fixed model identified at 120 h. Fig. 4 considered in simulation the potential impact of plant-model mismatch. The results from the plant trials verified that model degradation did not of necessity trigger re-identification. With the initial model from 120 h, performance was maintained (i.e. accurate set-point tracking and smooth MV movements computed by the MPC) for the instant the MPC was switched to automatic at 120 h until harvest.

Fig. 9 shows a comparison of the steady state control performance of the PID controller (Fig. 2) with the MPC controller (Fig. 8) for a 'zoomed-in' section of the response. For dissolved oxygen control a standard deviation of 1.45% with PID was reduced to 0.16% with MPC. For pH control the standard deviation of 0.0052 was reduced to 0.0004 with MPC. Note that in the pH response graph, the MPC response sits on set point with variation so small that it is not observable. There is insignificant offset from set point for MPC but an offset of 0.04 for PID based control is observed.

5. Discussion and implications

This paper aimed to demonstrate that the MPC concept could give much improved environmental control in mAb cell culture. The intuitive nature of MPC tuning and the inherent means by which constraints and process interactions are addressed is appealing from an end-user perspective. The performance benefits demonstrated indicate that MPC is able to deliver a much smoother and well controlled response than conventional PID based controllers. However, while this study indicated potential, a number of practical considerations remain.

At the outset it was clear that significant dynamic change occurs during the batch. Online model identification has been demonstrated to effectively capture the current dynamic characteristics but online adaptation (particularly if

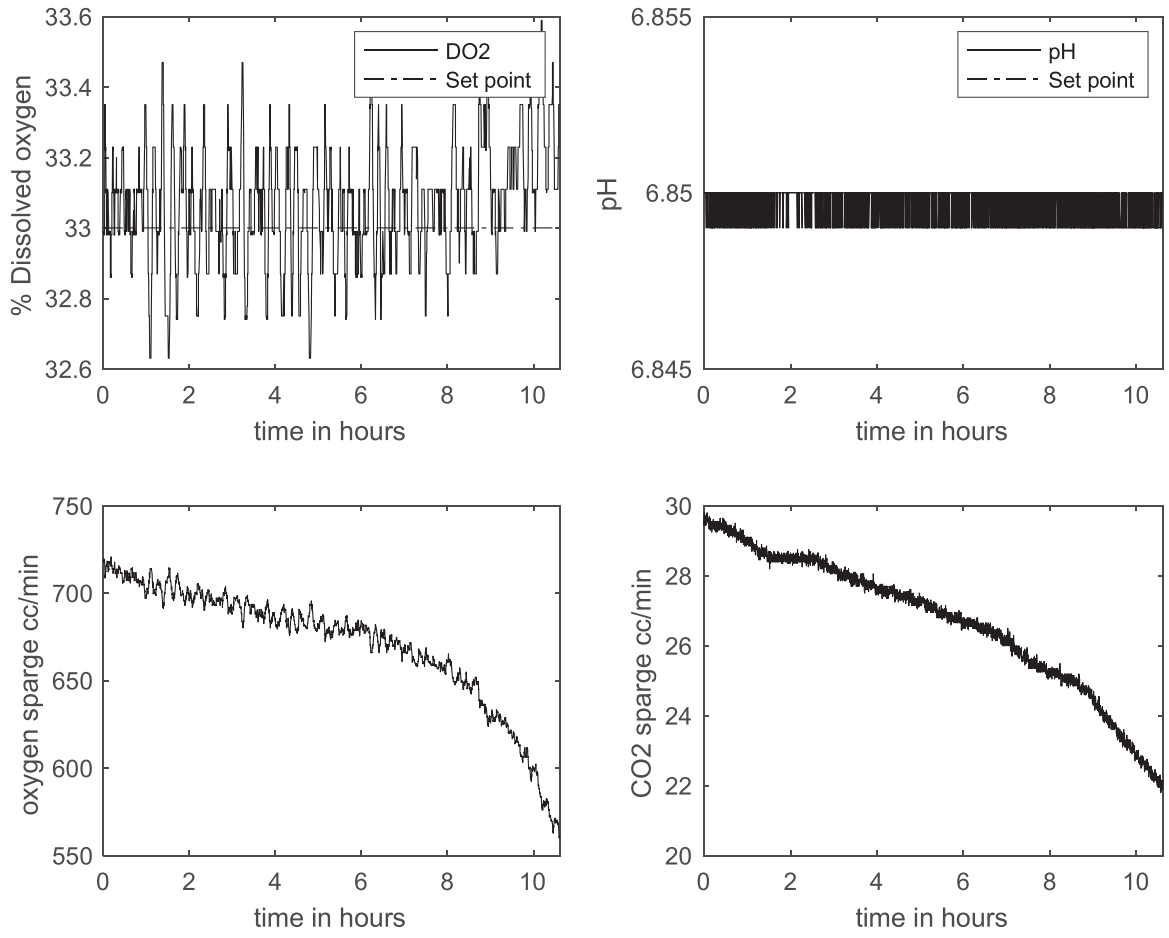

Fig. 8 – Control in the latter stages of a batch (321 h) showing that regulatory control is maintained effectively by the MPC. The falling values of manipulated variables are indicative of the behaviour towards the end of the batch.

Table 2 – MPC Tuning parameters.

O2	
Move weight (**Q**)	2.1
Target weight (**R**)	0
CO2	
Move weight (**Q**)	4
Target weight (**R**)	0
Air	
Move weight (**Q**)	60
Target weight (**R**)	0
DO2	
Setpoint weight (**P**)	1
pH	
Setpoint weight (**P**)	1

automated) by its very nature reduces robustness and the risk of model corruption through outliers. A well designed 'jacket' to only respond to reliable measurements is feasible but adds to the configuration activity. A more robust strategy is to fix the process model. If the controller model is fixed, changes in dynamic characteristics through the batch give rise to the condition of 'plant-model mismatch'. In continuous process applications it can arise to a significant extent due to process change but in batch processes that progress through a trajectory and experience dynamic change as a consequence, process-model mismatch is an inherent characteristic. Methods for detecting significant levels of plant-model mismatch in MPC and reidentifying the model are broadly discussed and indeed were implemented in this application. While the literature is less comprehensive in coverage of performance degradation than MPC more widely, examples can be found such as Conner and Seborg (2005) and the work of the Shah group at the University of Alberta (Badwe et al., 2010, 2009). Reidentification was not however triggered in this application, with acceptable performance arising despite the plant-model mismatch. In our case, the objective of the controller model is not to provide absolute predictions but to be used as part of the MPC architecture to determine the impact of incremental changes that the inputs have on incremental changes of pH and DO, the impact of plant-model mismatch is reduced by the real-time feedback of the controlled variables. In other words, MPC receding horizon control, updated with new data at each sample interval, offers the potential for robustness against sub-optimal or a mismatched model that inherently occurs in batch operation.

More generally, process-model mismatch does not always warrant reidentification as considered by Badwe et al. (2010). Maintaining acceptable behaviour in the presence of process-model mismatch is complex as it depends on the direction of change and also on the manner in which the controller is tuned, with less aggressive action being more forgiving. Clearly severe circumstances such as gain sign change can be catastrophic but a batch process model applicable at a particular instance of a batch may be more appropriate than other instances. For example, models identified mid-batch could result in acceptable but not ideal behaviour in other periods or models at the end of batch could be more applicable – the strategy being dictated by the profile of gain

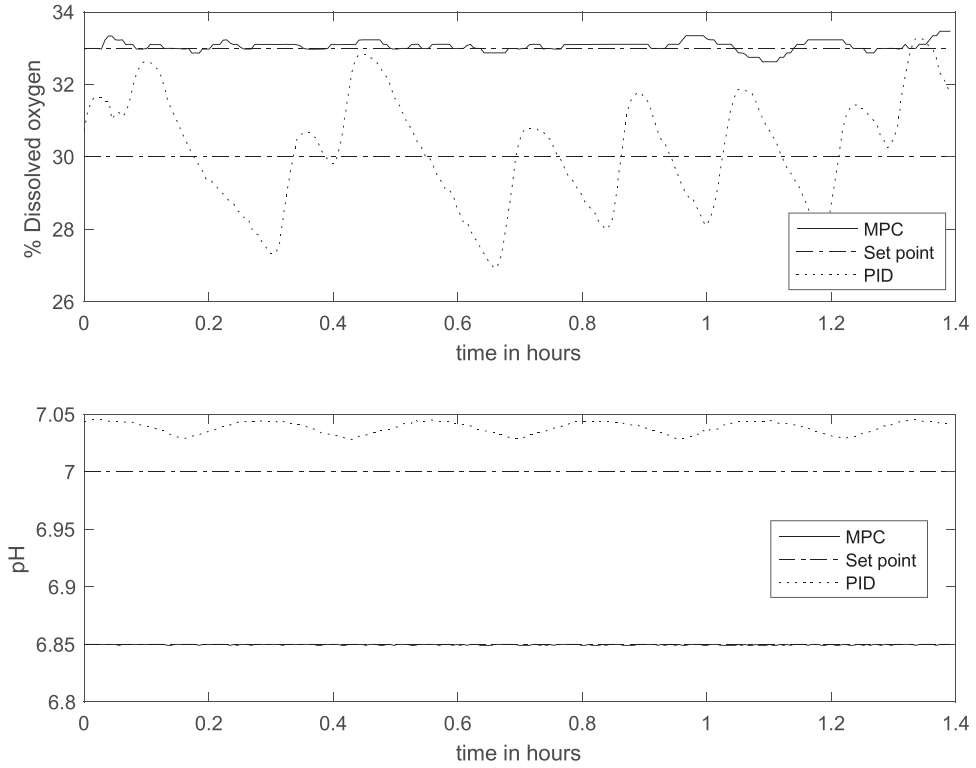

Fig. 9 – Comparison of PID performance from Fig. 2 and MPC performance from Fig. 8 demonstrating the reductions in standard deviation of the controlled variables.

change in particular. For such an approach to be effective, ideally model applicability across batches would be necessary. To extend this further, if historic information is representative, process model variation could be captured through understanding the linkage between model gain for instance and an indicator of current process condition. For example, it might be expected that an approximate linkage exists between model gain and cell number / batch age. Thus, a gain scheduling solution could be proposed avoiding model reidentification but allowing model change.

Clearly, practical solutions are available to the model building challenge but moves to more personalised treatments where batch numbers for a particular product could be very limited bring the challenge of data limitations to further compound the modelling problem. In this application, we have demonstrated the effectiveness of the MPC algorithm, the ability to identify models online and to use these models throughout a batch. Broader questions on model development and usage remain and will be important to address in the application to systems requiring validation.

Validation raises another issue, while the MPC approach is clearly effective from a performance perspective, the control strategy deviates from the accepted and common PID structure. In an industrial sector that is conservative with regard to new technology due to the pressures of validation, new technologies need to offer significant benefit over and above pure financial arguments, with risk being a prime consideration. If the model tracking aspects of MPC could be used to configure and accommodate through batch dynamic change, they could be used to update the parameters of a control system of PID structure with feedforward terms where appropriate. While it may not reach the performance of MPC, the benefits of control structure familiarity may outweigh the degradation in performance. In the longer term, as the benefits and robustness of MPC are recognised by the pharma sector, anxiety to adopt the MPC approach will dissipate, especially as performance improvements are recognised. From a robustness perspective, the long-term performance of the model could be included in an overall Continuous Process Verification (CPV) initiative, tracking process and controller performance over time. Additionally, MPC performance could be monitored using a complimentary PCA process condition monitor built around closed loop operation (AlGhazzawi and Lennox, 2009; Mercer et al. 2018).

Finally, based on scientific understanding, practical experience and limited literature-based evidence, it has been assumed that a well-controlled smooth process in terms of both critical environmental process parameters and the manipulated variables that influence them will lead to improved process behaviour from a yield perspective. A more comprehensive experimental study is required to verify this to be the case.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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