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A Debottlenecking Study of an Industrial Pharmaceutical Batch Plant

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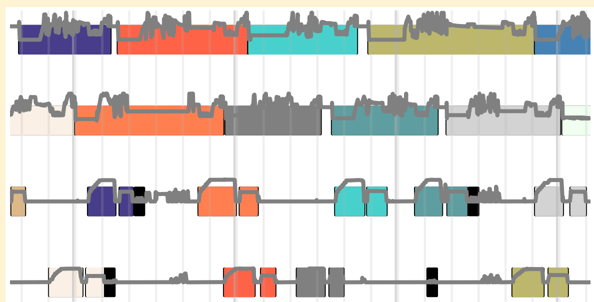
ABSTRACT: Operational complexity in batch-operated plants is large, and companies struggle to produce at high equipment utilization. Owing to high fixed costs, capacity utilization is an important operational directive. Many current plants are not in a state that allows the application of rigorous process systems engineering tools due to modeling challenges. This work proposes identifying the right engineering projects based on statistical evidence. In the case of incomplete process monitoring strategies in semiautomated facilities, these analyses are specifically challenging. The power of modern data processing tools in this context is shown as a case study in an industrial pharmaceutical production. This includes the development of a recursive monitoring algorithm as well as plant performance evaluation based on established heuristics.



1. INTRODUCTION

The operational paradigm of batch process plants producing high-value products at comparably low volumes differs from that of bulk chemical processes. Such batch plants are frequently encountered in specialty chemical-, pharmaceutical-, and biobased industries. Due to operational complexity especially in multiproduct scenarios, it is difficult to operate these plants at maximum throughput. Therefore, incremental debottlenecking is generally among the primary production objectives. If high fixed costs arise from quality control and quality assurance in the context of good manufacturing practice (GMP) compliance,[1,2] the importance of high capacity utilization is increased even more. Furthermore, reductions in public healthcare spending by means of price caps or endorsed production of generic (nonbranded) drugs is expected.[3] This forces pharmaceutical enterprises to streamline existing production facilities and supply chains.[4] The situation is complicated further for research-driven pharmaceutical enterprises due to the complex interrelations between capacity planning, risk management (i.e., from failed new drug development processes), and operational issues.[5]

Incremental debottlenecking of continuous plants by installing additional recycles or by other means of deflecting workload from the bottleneck to less pressed units is generally possible.[6] Yet, flexibility in such plants is limited compared to designs with parallelized, intensified units[7] (scale-out vs scale-up). Accordingly, systems of parallel standard units facilitate organic growth, enabling plants to track markets more flexibly. This requires continual (expensive) engineering expertise and therefore effective project execution. Not least, parallel standard units facilitate performance monitoring and predictive maintenance as trends from equipment wear and tear are more easily distinguishable from trends induced by fluid properties.

Several frameworks exist for retrofit debottlenecking of batch process systems, the most recent by Amaran et al.,[9] and a large base of works has been presented by and around Petrides et al.[10] All of these frameworks advocate the use of computational tools, which fits well the desire to more consciously apply process systems engineering methods in the biobased and pharmaceutical industries.[10] In an industrial context it is however not so that model-based work is apt for all projects. Particular challenges arise in biobased production, and model-building as well as verification are likely to be expensive or even impossible due to unmeasured, uncertain, and unknown variables. This can stem from the complexity of solid−liquid suspension properties,[11] a large natural process variability,[12] but can also be due to nondeterministic manual control and incomplete process monitoring systems. This work discusses these and other challenges, and proposes a solution approach. To this end, first the general notion of batch processing, economical considerations, and arising operational challenges are introduced in section 2. Regard is paid to the special case of biobased processes. Identification and handling of bottlenecks are discussed in section 3. Important heuristics are extracted from batch process plant debottlenecking frameworks. An algorithm for the reconstruction of machine states based on time-series values of commonly measured variables is introduced in section 4. This is necessary to identify scheduling bottlenecks in process plants without conclusive monitoring schemes, as is also the case in the regarded production plant. This industrial case study is described in section 5,

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functionality of the algorithm shown, and debottlenecking candidate projects derived accordingly. Operational challenges and generalizations are discussed in section 6, hereafter the work is concluded.

2. BACKGROUND

This section discusses batch processes at a high level of abstraction as well as disadvantages and challenges immanent in them. This is embedded in the context of biobased processes before introducing retrofit process redesigns aimed at debottlenecking.

2.1. Economics of Batch Process Plants. In a single-product scenario, continuous plants outperform batch processes. An estimate for possible savings is given for instance by Calabrese and Pissavini.[13] Bauer and Craig[14] state that there are less batch processes than continuous in the chemical, petrochemical, and refining industries. This prevalence of continuous processes over batch production in large sectors of the chemical industry is a good indicator for their economic superiority, as batch operation constituted the first paradigm.[15] One explanation for this lies in lower equipment efficiencies,[16] which may be as low as 30% in pharmaceutical plants.[17]

Furthermore, reductions in equipment scale and consequently also temperature/concentration gradients due to better heat and mass transfer are expected for continuous reactors.[18] Costandy et al.[19] offer an optimization-based framework for the comparison of batch- and continuous reactors based on first-principles. A more practical approach to evaluating the benefits of continuous processing including downstream lines is presented by Teoh et al.[20], Continuous processes can also be preferable for safety reasons due to reductions of hazardous material hold-ups,[21] and have been classified as more easily automatable.[19] Finally, a batch schedule impedes process integration as the points in time of heating and cooling may change relative to one-another.[22] This requires either advanced scheduling, which is expectedly connected with some cost, or extra equipment in the form of an intermediate thermal storage to decouple the integration events in time.

2.1.1. Batch Production of Specialty Chemicals. To reap the benefits of economies of scale, suppliers of volume-limited markets need to operate flexible multipurpose plants.[23] Because of changeover and shut-down as well as start-up costs, continuous multipurpose plants can be unattractive. Furthermore, batch duration as an extra degree-of-freedom renders systems highly flexible. Fifteen years ago, Edgar claimed that, in total, there were more batch operated plants than continuous plants in the United States.[24] More recently, Kano and Ogawa[25] or Amaran et al.[8] mention the growing importance of specialized products and consequently batch processes. An alternative lies in the development of flexible multipurpose continuous plants, which is however connected with substantial technological challenges.[26]

2.1.2. Biobased and Pharmaceutical Batch Production. In biobased production, but especially in the case of pharmaceuticals, the plantwide production regime is traditionally batch, likely for three reasons:

- Fermentation was initially a batch process (and frequently still is); this operational regime is propagated through the downstream line.
- Recurrent cleaning and sterilization of units is necessary to prevent cross-contamination between batches and accumulation of biological cell matter in general.
- Limited batch durations reduce the risk of mutation in the deployed organisms.

The latter also implies that, aside from the complications in heat-integrating processes, material recycles may be entirely forbidden due to cross-contamination risk policies calling for rigorous cleaning-in-place (CIP) or sterilization-in-place (SIP) barriers.

Because of the historical prevalence of batch processes, regulatory entities (U.S. Food and Drug Administration, European Medicines Agency, etc.) as well as industrial stakeholders have accumulated a lot of experience from frequent qualification of these processes. This is also mentioned by Wu et al., who acknowledge that batch processes are likely to have lower efficiencies, but bear the convenience of the "three-batch process validation approach". This adds a lot of inertia in a transition to continuous process regimes, as especially in first-to-market scenarios commissioning delays are likely to outweigh suboptimally high operational costs—even if they persist for numerous years.[27] Nevertheless, there is a push for the pharmaceutical industry to rely more on continuous and semicontinuous processing technology.[28−30] This is enabled by the fact that product batches which undergo final testing and are ultimately sold need not strictly stand in relation to a single upstream batch.[31,32]

Beyond the process-oriented economic arguments, there are upstream processes that favor a continuous production regime due to biological properties.[33] Schaber et al. compared costs for continuous and batch processing for a large-scale pharmaceutical production and conclude significant cost savings in the case of continuous processing technology.[34] While most big players in pharmaceutical production engage in related research projects, the industry perspective is not without restraint, especially concerning the replacement of an existing (batch) infrastructure.[35] Croughan et al. point out that production scales of pharmaceuticals are in general not comparable to bulk chemical- and petrochemical industries. Therefore, they conclude "[⋯] should we close existing batch operations? The answer, at least for now is no, but the factory of the future embodied in new facility design is likely to evolve around integrated continuous bioprocessing".[36] All in all, there is strong evidence that batch plants in today's chemical and especially biochemical industries are of economic relevance.

2.2. Operational Objectives in High-Value Biobased Production. In the above it has been mentioned that biobased plants tend to operate in batch regimes. In these plants, operational complexity is substantial due to the additional scheduling tasks on the unit operation layer. Low- and high-level automation is complicated by the absence of reliable property models, the presence of uncertainties and delays, and not last, entirely unmeasurable states.[37] Furthermore, the comparably small scale of the facilities and the indicated disproportion between cost of utilities and fixed costs (i.e., quality control) may complicate the business cases for automation projects. Finally, due to fault-tolerant processes and equipment breakdowns, flexible control systems are needed. This flexibility is added in most easily by including educated operators into the control structure, which implies operating mistakes due to human error.[38] All of the above may lead to suboptimal operation conditions including suboptimal capacity utilization, which can easily go unnoticed in a complex environment. Therefore, if fixed costs (for quality control, quality assurance, GMP facility depreciation, and labor)

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outweigh the cost of utilities, full capacity utilization of installed equipment is likely to be the primary operational objective as long as the market is not saturated.

2.2.1. Retrofit Process Design. Most enterprises have to react to market evolution in a recurrent manner. This may be due to changes in demand, product line-up, raw material supply, energy prices, and emerging or disappearing competitors. In the operated plants this implies an ongoing sequence of engineering projects, which aligns well with the also iterative plantwide control task.[39] Reoptimizations are especially important in newly built plants after experience has been gathered, or after significant process or market changes. In these projects, economic plant performance should be evaluated based on accumulated sales, process, and product data, but also extraordinary sampling campaigns may be sensible. This usually requires manual processing as, unlike in the case of control system performance monitoring,[40] data sets are relatively heterogeneous and unstructured, and on top of that case-specific, making it difficult to apply a set of standard tools. It is important for an enterprise to enable efficient and robust execution of these projects; similarly process designs that allow incremental capacity increases may be a conscious choice.

3. DEBOTTLENECKING METHODOLOGY

Several frameworks and articles incorporating best practices specifically for or including debottlenecking of batch process plants have been presented.[8,9,23,41−44] Many of these include application examples, and further cases have been studied.[45−50] Most of these frameworks advocate the use of models to augment decision-making. Undoubtedly, the dynamic behavior of complex batch process systems is hard to conceptualize for the human mind, calling for computational support. However, not every production facility or enterprise is apt for model-based optimization. This is discussed for instance by Guimarães et al. for the case of discrete-event models.[51] Here, with reference to ref 52, a basis for a maturity measure for an organization's aptitude for process modeling is introduced. The latter depends both on the production process itself, which has to be structured and operate in stable routines, furthermore automatic data collection needs to be in place. Finally, the right skill-set needs to be available within the enterprise. These measures are subject to some ambiguity, not last stemming from a lack of documented industrial cases.

3.1. Identification of Bottlenecks. Any unit not capable of handling a throughput increase is per definition a bottleneck.[53] In stable, continuous processes, personnel are usually able to pinpoint this unit or these units with high precision. This information can also be concluded from statistical analysis of process data.[54] Alternatively, the plant can be tried in a maximum throughput trial. However, the shortness of a trial bears the risk of missing effects that would become relevant in the long term. Second, it usually happens that operators are more attentive during out-of-the-ordinary temporary scenarios. Capacity estimates can also be based on for instance model-based extrapolation of the current state. This may be necessary if capacity is elevated past several bottlenecking stages at once. However, if fluid properties change frequently and transient periods make up a substantial part of uptime, the task takes on a more complicated character. Here, a more advanced analysis including statistical elements is required.

3.1.1. Identification of Bottlenecks in Batch Plants. In a batch plant all of these complications can arise in the same way. Recalling section 2.1.2, complex scenarios are actually more probable, as batch plants are more likely to produce multiple products. Furthermore, operation may be less regular due to operators being actively in-the-loop. Also, one needs to refine the definition of a bottleneck in a batch processing context. According to Koulouris et al.,[41] bottlenecks can be either *size* or *time* inflicted.

The size bottleneck limits the amount of coherent material ("a batch") passing through the system. It is evidently so that the size bottleneck's volume should be utilized to the maximum in each batch. Note that there can be multiple size bottlenecks in processes where the product changes streams (for example elution processes) or processes with purge streams.

Time bottlenecks are those with the largest *stage cycle time*, or those where it takes longest to process a batch until starting the next. Ideally, time bottlenecks operate at 100% equipment uptime; it is then also trivial to understand that throughput on these units cannot be increased further. However, due to operational complexity, it may not be possible to challenge a plant in a maximum throughput scenario, thus some form of extrapolation from a nominal production rate may be of need.

In general, batch plants ordinarily employ both "native" batch and semibatch units, but also semicontinuous units that only follow the batch regime of the incorporating plant. For a detailed overview of common nomenclature, the reader is referred to Barrera.[55]

3.1.2. Batch and Semibatch vs Semicontinuous Units. Batch processes are characterized by their size or volume, have specified filling, processing, draining steps, and no material may be added to or removed during the processing phase. In fermentations this requirement is usually relaxed as the addition of acids/bases for pH control purposes is allowed.[56] There is always at least one transient variable and a constraint value for it. This variable can be cycle time, in which case the transient is reduced to a timer. A batch process is depicted schematically in Figure 1 (left), where it can also be seen that

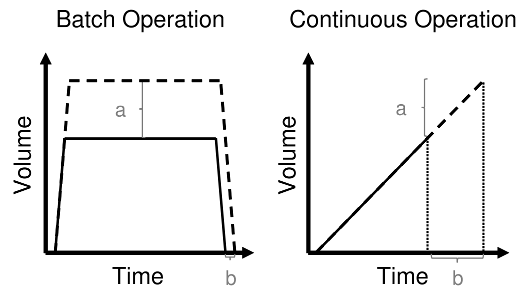

Figure 1. Native batch vs semicontinuous units and the effect of throughput increases "a" on cycle time "b".

for batch units with predominantly "holding" operations (size bottlenecks), debottlenecking by means of volume maximization is effective (for example fermentation).

Native batch units are contrasted with continuous units operated under a batch operating regime. A "semicontinuous" unit can be inactive due to planned downtime (as are all nonbottleneck units) or CIP/SIP/maintenance activities. However, start-up and shut-down procedures are generally negligible and the unit operates continuously during uptime. This is represented by Figure 1 (right), and it is also intuitive

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Table 1. Exemplary Machine States in Batch Operation Regime

type of unit	common machine states (aside from idle)						
batch reactor (fermentation)	fill	heat treatment	inoculate	ferment	stabilize (chemical, cooling)	drain	CIP
holding tank (storage)	fill (from)	wait for resource	drain (to)	CIP			
tank (flocculation, ...)	fill (from)	perform operation	wait for resource	drain (to)	CIP		
flow unit (centrifugation, filtration, ...)	active	reinitialise	CIP				

to understand that scheduling bottlenecks are more likely to arise upon batch-size increases on "flow" units (for example decantation).

The restriction of no addition or removal of material is removed in semibatch steps. A dead-end filtration process with uncertain cake properties is a semibatch process with, depending on the control strategy (flow rate or pressure controlled regime), an unknown duration or even unknown flow rate and duration.[57] These processes lie somewhat between batch and semicontinuous units in terms of how to identify and treat bottlenecks.

3.1.3. Engineering Projects. Implementation of debottlenecking strategies even in a continuous improvement cycle is usually project-based. Calandranis and Petrides list three primary debottlenecking strategies (increase number of cycles per batch for the limiting procedure, rearrange the equipment assignment, introduce new equipment). Amaran et al. suggest the following taxonomy of possible retrofit debottlenecking project turnouts which are applicable to a broader class of problems:

- "Type-1: operational improvements by removing slack and uncovering hidden capacity with current infrastructure".
- "Type-2: upgrades to current equipment, planning and scheduling improvements and improvements in operating discipline".
- "Type-3: fundamental improvements in operating policies".
- "Type-4: investment in new pieces of equipment/trains".

The framework by Amaran et al. takes a process systems engineering approach and these projects are turnouts of model-based simulation studies with an optimization substep. This allows balancing mathematical optimality and degree of subjectivity, and can therefore capitalize flexibly on skills and experience of the process optimization team. Amaran et al. propose to validate the discrete-event model by means of comparing simulated interbatch start times, overall production times, queue lengths, and individual processing and wait times to sets of historical data that are most descriptive of future operations. The cycle times of individual unit operation steps in turn are assumed to be captured by the process monitoring system. With a reference to the fact that validation can be a very time-consuming step, one could find that comparably little attention is paid to it. Further, Amaran et al. remark that especially implementation of Type-3 projects may be difficult as these also require *operational discipline*. The above classifications are adapted in the following, and projects will be defined in these terms.

4. MACHINE STATE RECONSTRUCTION ALGORITHM

The absence of control system state information due to manual operation makes it difficult to impossible to reliably identify scheduling bottlenecks, furthermore it is not possible to validate models merely by the collected time-series data. Sequential control systems are characterized by a set of discrete states S; examples are given in Table 1. These states define the control system outputs ω, and thereby finally the evolution of the set of continuous states X of the plant as a consequence of actuation. The continuous states furthermore experience significant process noise, for instance from slurry properties as a consequence of batch-to-batch variability in fermentations. The control system outputs in this sequential context are often binary or categorical (for instance open/closed valve position), but also continuous process data (flow, temperature, pH) are measured. Some of the continuous variables may be controlled, usually by means of proportional-integral control.

This knowledge needs to be harnessed into the state reconstruction algorithm. Further information available comes in the form of standard operating procedures, piping, and instrumentation diagrams, and not last, the experience of operators and engineers. A nondeterministic recurrent state machine RSM is chosen as a modeling basis:

$$\mathrm{RSM} = \langle M_1, \ldots, M_k \rangle \tag{1}$$

$$M_i = (S_i, s_{0_i}, \Sigma_{SFC_i}, \Sigma_{TS_i}, F_i) \tag{2}$$

For each component state machine M_i, S_i describes the set of discrete states and s_{0_i} the initial state (which for all machines is idle). The input alphabet Σ will be delineated in greater detail in the following. F_i denotes the set of final states for the component machines.

In the reconstruction algorithm, the outputs ω of the sequential batch control system become inputs to the state machine reconstruction algorithm:

$$\Sigma_{\mathrm{SFC}} = f(\omega, S) \tag{3}$$

This is intuitive, as every time a valve ($\in\omega$) opens or closes, or a flow magnitude changes persistently, this must have been dictated by a state transition in S. Note that in this, operators are control system elements and therefore introduce nondeterminism. They make mistakes and have delayed reactions. In general there may be some leeway in the operating procedures that are not strictly product-safety critical. Further, operators may have to react flexibly to changing fluid properties: sometimes a routine will have to be called multiple times instead of once until the desired effect is achieved. Finally, units malfunction, which also leads to extraordinary state sequences.

Thus, this input alphabet is not enough to reconstruct the machine states due to countless multiplicities: a valve opening/closing may result in different transitions depending on the current machine step—which may be unknown yet due to preceding multiplicities or irregular events. Therefore, characteristic points in the time-series data need to be translated into inputs

$$\Sigma_{\mathrm{TS}} = f(X, S) \tag{4}$$

which is described in more detail in section 4.2. Second, it may be necessary to call a subset of unique component state

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machines which will be supplied with the subsequent input sequence (both Σ_{SFC} and Σ_{TS}) to see which, if any, of the machines converges to a final state. Upon unequivocal convergence, the algorithm, recursive in its nature, will trigger a state transition at the point-in-time of initial execution of the subroutines. Otherwise it is concluded that an erroneous procedure must have occurred during processing of the active batch which is also logged.

4.1. Identification of Σ_{SFC}. As indicated, opening and closing of valves as well as switching motors on or off are trivial and usable indicators. However, in some cases and especially in the case of flow control, more scrutiny is needed. Changes in absolute values of rates (for example aeration) can allow pin-pointing specific steps. Second, in the case of strongly sequential operations (for example a sequence of 5-fold elution or washing steps), a component state machine is needed that keeps track of the sequence on the one hand, and potential duration of the steps on the other. These checks (range-, spread-, and timers) have proven to be powerful elements for sequential flowchart reconstruction.

4.2. Identification of Σ_{TS}. There are countless characteristic points in the time-series data, and it is neither realistic nor necessary to delineate each one of them as they are highly case-specific. The most trivial characteristic points are a flow stopping persistently on a "flow" unit, or a tank running dry for a "holding" unit. The respective unit then must be in *Idle/Empty*. Note that for holding units, *Empty* is an unambiguous state, whereas *Full* may be more difficult to pinpoint in the case of altering fill-levels. (Also for *Empty*, a tolerance may be of need due to sensor noise.) As the finalization of a draining procedure on one tank normally means that a fill procedure on another tank has been finished, this information is of 2-fold value.

Beyond these simple indicators, more advanced routines can easily be included into the algorithm. Moving-horizon linear fits, smoothers, maximum norms, or variance estimators can be used efficiently to detect and classify changes in uncertain environments. Averaged threshold values can usually be inferred from observations. These vector operations are however computationally expensive and should only be applied when scalar criteria fail. Finally, the duration of a procedure can be estimated early on and gives a good indication about its nature (standard operation, CIP routine, irregular event), enabling an a priori selection of component state machines that will be triggered subsequently. It should be noted that, at times, knowledge of future information may be needed in order to unambiguously classify an event. In these, the algorithm cannot be used for online monitoring purposes. However, the real-time requirements in production are rather soft as there is significant value in having knowledge about the past 12−24 h of production after a shift changeover even if there is some delay.

4.3. Superstructure, Equipment Assignments. Due to the predominantly forward-oriented flow of product in batch plants without recycle, a separation into subroutines is possible, which allows stepwise implementation and validation. Therefore, generally a link between unit state machines only has to be drawn when material is transferred, which may require identification of a resource (flow unit) in the case of parallel units, and identification of a target holding unit. By tracking material accumulation/depletion and by estimating the flow rates into and out of the respective tanks, this link can then be established with high certainty.

4.4. Illustrative Example. In a small excerpt of the case study plant (introduced in the next section), these principles will be demonstrated. The Gantt chart of the example plant in Figure 2 is limited to a single fermenter *FE*03, from where

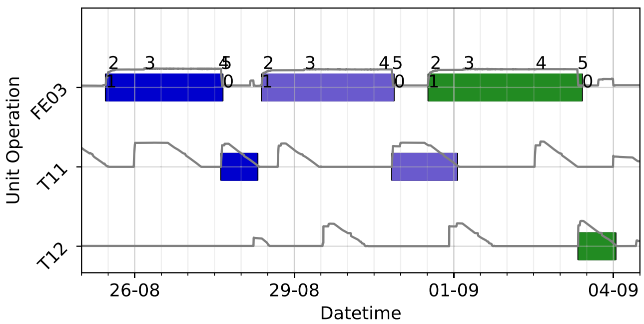

Figure 2. Gantt chart excerpt with propagation of the batch ID (color). Gray lines indicate level in the tanks. (Fermenter states: 0, idle; 1, filling substrate; 2, autoclaving and waiting for inoculation; 3, fermentation; 4, waiting for transfer; 5, emptying.)

material is transferred to holding tanks *T*11 and *T*12. In the pseudocode for algorithm 1 it is shown how machine states for

Algorithm 1 RSM Principle

```
T is vector of time-points
ω is matrix of inputs (valves initially closed), X is matrix of continuous states
S_FE03 is unknown fermenter machine state
procedure TRACKFERMSTATES(X, ω, T)
    S_FE03 = idle; t_k = T(1)
    while t_k < T(end) do
        if S_FE03 is idle then
            CheckTransitionsFromIdle(... X.FE03.Level, ω.FE03.ValveIn(t_k), T, t_k)
        else if S_FE03 is filling then
            CheckTransitionsFromFilling(...)
        else if S_FE03 is ... then
            Check transitions from...
        end if
        Increment t_k in T
    end while
end procedure
procedure CHECKTRANSITIONSFROMIDLE(Level, ValveIn, T, t_k)
    if ValveIn.opens then
        t_i = t_k;
        while Level(t_i) > 0 do
            Increment t_i in T(t_k : end)
        end while
        ΔT_Ferm and L_Ferm are thresholds
        Condition 1: t_i-t_k > ΔT_Ferm, Condition 2: avg(Level(t_k : t_i)) > L_Ferm
        if Condition 1 and Condition 2 then
            store(Ferm. nr. begins at t_k)
            store(Ferm. nr. ends at t_i)
            S_FE03 = filling                                    ▷ (Transition)
        else
            # Irregular event has occured
            Store time-points
            t_k = t_i                                           ▷ Jump period
        end if
    end if
end procedure
procedure CHECKTRANSITIONSFROMFILLING(ValveIn)
    if ValveIn.closes then                                      ▷ Simple Σ_SFC
        S_FE03 = waiting
    end if
end procedure
```

the fermenters are identified from Σ_{SFC} and Σ_{TS}. Second, the posterior propagation of batch numbers to the holding tanks is indicated algorithm 2. On plant scale this is necessary to create batch traceability, and for complex transitions. Furthermore, sometimes it is not possible to identify all necessary Σ_{TS} and Σ_{SFC} based on time-series values from one unit operation, and steps on preceding/succeeding units need to be included. In these cases, the batch ID needs to be propagated simultaneously with the RSM calculations. (For instance, this is different for the special case of the recycle section (tanks 31/

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Algorithm 2 Posterior Propagation of Batch ID

$T_{S,FE03}$ contains points in time of all fermenter state transitions from algorithm 1 as well as batch IDs
$T_{S,T11}$ and $T_{S,T12}$ contain holding tank state transitions
procedure PROPAGATEBATCHID($T_{S,FE03}$,$T_{S,T11}$,... $T_{S,T12}$)
  # Times of all tank filling events:
  $T_{Fill,T11} = T_{S,T11}.allBatches$.periodOf(filling)
  $T_{Fill,T12} = T_{S,T12}.allBatches$.periodOf(filling)
  for each $batchID$ in $T_{S,FE03}$ **do**
    $t_{drain} = batchID$.periodOf(draining)
    if $t_{drain} =$ any($T_{Fill,T11}$) **then**
      Propagate $batchID$ to batch in $T_{S,T11}$
    else if $t_{drain} =$ any($T_{Fill,T12}$) **then**
      Propagate $batchID$ to batch in $T_{S,T12}$
    else
      Throw Exception ▷ Indicates error in algorithm as each batch must be processed
    end if
  end for
end procedure

32, unit 3, tanks 41/42 in Figure 3) of the case study plant, which requires a more complex approach, namely one state machine model describing the simultaneous evolution on five units.)

4.5. Logging Important Time-Series Values. While this information is not crucial for the identification and quantification of scheduling bottlenecks, values beyond points-in-time can be of relevance to the analyst. Volumes as indicators for size bottlenecks are of evident interest. Still, refined feature engineering is easy once the overall frame has been implemented, and tracking for instance a relative average pH change between two steps is trivial. On the other hand, once the time-steps for machine state changes have been identified, posthoc extraction of features is similarly easy and it is a matter of taste how to generate the specific data sets.

5. PHARMACEUTICAL PRODUCTION PLANT CASE STUDY

With the use of an industrial production of fermentation-derived antibiotic, the challenges mentioned above are delineated. Furthermore, it is shown that in the case of a strongly capacity-leveraged process, local improvements can be identified effectively using visual statistics and domain knowledge. The study is to be of descriptive value, outlining the challenges that are likely to exist in many semiautomatic production facilities currently in operation, while proposing some ways of how to handle them.

5.1. Process System Description. Figure 3 shows the process in terms of semicontinuous and batch units as well as those entailing strong elements of both. A more detailed description was not compliant with the intellectual property policy of the industrial partner, but this does not harm the analysis in the following. The CIP barrier running through a certain fraction of the downstream section is also indicated. In the regarded plant, the batch number is logged exclusively for fermentation units. For all other machines, only time-series data (i.e., flows, pressures, levels, pH) are available on the historian.

5.1.1. Application of State Reconstruction Algorithm. The proposed recursive state machine based algorithm is applied, which allows reconstruction of the machine states for an entire production campaign of almost 70 batches with high certainty. This enables taking advantage of the advanced plotting capabilities available in open-source software (here Python). Figure 4 shows a Gantt chart of the production campaign with the units from the process flowsheet (Figure 3) on the y-axis over date-time on the x-axis. The color code allows facile visual tracking of a batch through the system, furthermore the scaled time-series variable that best characterizes the respective process steps on the machines is displayed. The boxes on U1 have been omitted to show the discontinuous nature of this flow unit which may make reliable state identification difficult. As the information about unit-activity is implicitly defined both by the level evolution of upstream and downstream tanks, this induces no loss in informative value. Furthermore, a second indicator (the level in the wastewater treatment plant) has been added as a dotted line to units T21 and T22. High material inventory in the water treatment plant can delay a step transition on T21 and T22. However, as the water treatment plant as a resource is shared by several plants, there is substantial noise, and no unambiguous classification of delays was possible. Visual analysis of some operational patterns with engineers and operators was found to be insightful, but is not to be discussed in greater detail in this work.

5.2. Bottleneck Identification. By mere visual assessment of Figure 4, the density of the color-bars on units T21/T22 and U21/U22 indicates a bottleneck. Especially downstream of

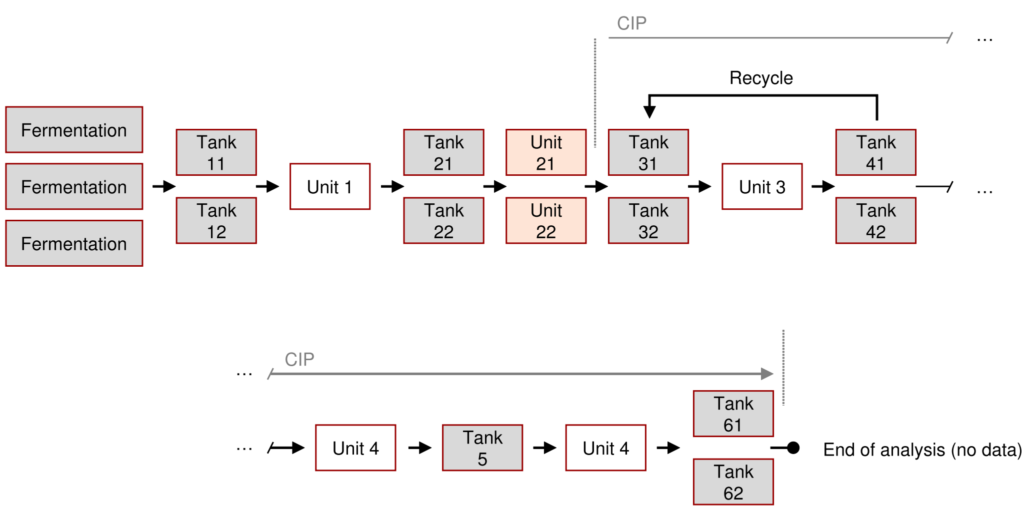

Figure 3. Indication of process flowsheet in terms of batch (predominantly holding: "tank") and flow "units". Units 21 and 22 (light orange underlay) with strong aspects of both. Note the structured CIP that passes through a certain fraction of the downstream line sequentially.

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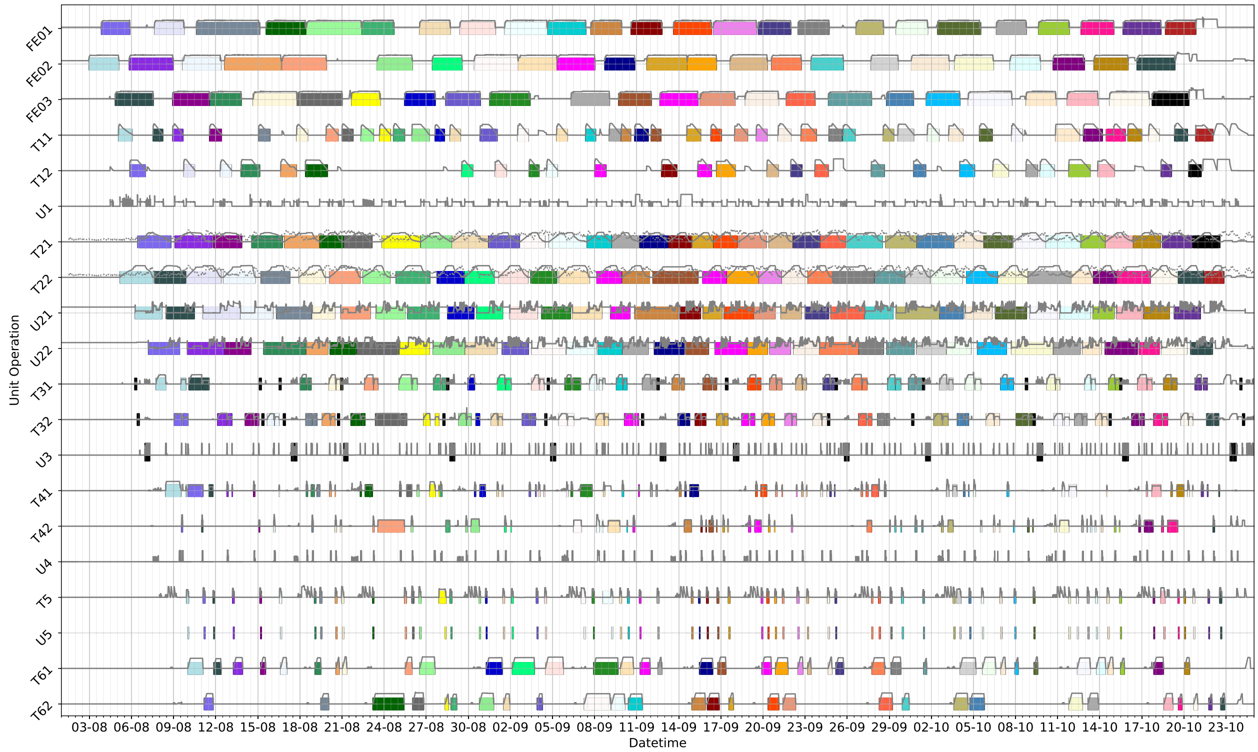

Figure 4. Reconstructed Gantt chart of an entire production campaign with unique color-code for batches and scaled time-series data (usually flows or volumes) as indicator of process step. Cleaning-in-Place with black underlay for units T31/T32/U3. Last batch of campaign has been excluded.

these units, long idle periods indicate free capacities. Upstream, the fermenters may exhibit long cycle times. However, this front-end process is easily plannable and long cycle times occur as material is prepared in advance to be ready for downstream processing. In the end this is possible due to overcapacity also on the fermenters.

5.2.1. Bottleneck Identification (Frequentist Statistics). There are multiple ways to assess capacity at current planning and operating skill. First, it is possible to draw an average over the entire campaign (76.5 days) in which 69 batches have passed through the largest part of the downstream line which gives a capacity of 0.9 batches per day.

Bar-plots showing the effective (normalized w.r.t. number of units) cycle times are a common visual tool for comparing equipment capacities. Figure 5 indicates a strongly leveraged process with a bottleneck around T21/T22 and U21/U22. Note that here waiting time between batches is not counted, and exclusively processing or waiting with material-in-the-loop is tracked. An equivalent visualization is shown in Figure 6, however expressed in batches per day which was preferred by the industry stakeholders due to its more expressive nature.

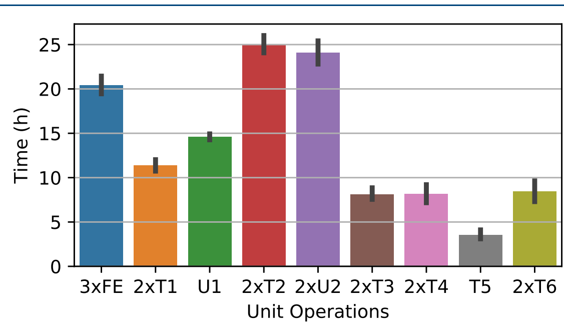

Figure 5. Effective cycle times (normalized by number of installed machines), excluding periods of waiting for material-transfer from upstream.

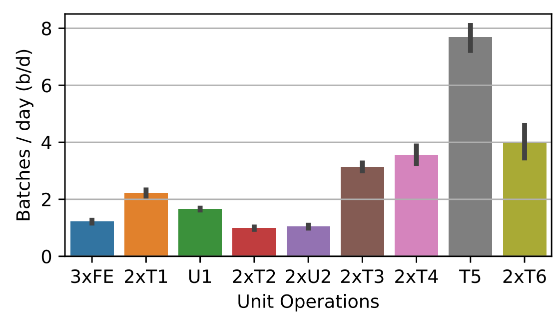

Figure 6. Effective capacity expressed in batches per day.

The average stage cycle time (including the time units wait for material from upstream) amounts to 53.3 h. Converting to the effective average stage cycle time, a capacity estimate based on the bottleneck can be made and adds up to

$$C = (24\ \mathrm{h/d})/(53.3\ \mathrm{h}/2\ \mathrm{b}) = 0.9\ \mathrm{b/d} \tag{5}$$

where b denotes batches. This is a good indication that the Frequentist analysis is meaningful.

A reduction of waiting for upstream material on the bottlenecking units would increase this to 1 batch per day. However, this requires substantial *operating discipline* and is thus both a difficult and risky project. Again, it is not possible to differentiate waiting periods further as there are many process steps with naturally varying durations due to changing slurry/fluid properties, and the reconstructed machine steps do not contain enough information to unambiguously characterize

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the waiting periods. It is known that CIP-procedures throw the downstream-line off of the planned fermentation schedule on a regular basis. Careful examination of the Gantt chart reveals that CIPs of units T31/T32 as well as U3 prohibit passing material on from U21/U22. This delays the already long processing step and furthermore propagates upstream to units T21/T22, which have previously also been identified to have naturally long cycle times. Figure 7 shows the results of an algorithm that classifies cycles on units U21/U22 into CIP-affected and non-CIP-affected (and post-CIP) populations. Despite large variability, CIP-affected cycles can be clearly distinguished and are substantially delayed, the cycle immediately after a CIP is already unaffected by this.

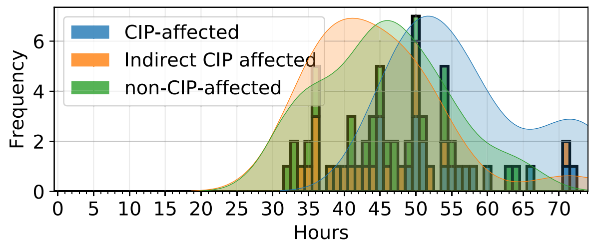

Figure 7. Effect of Cleaning-in-Place on cycle durations. Indirectly affected denotes the cycle after the CIP-affected cycle has been completed.

5.2.2. Bottlenecks in a Transient Scenario. Because of the inability to differentiate interunit waiting and include this into the bar plot (Figures 5 and 6), the scenario needs to be assessed in the transient regime. The time-evolutions of the machine capacities are overlaid in Figure 8. (Here fermentation has been omitted as it is known that ample capacity is available.) Units T21/T22 and U21/U22 exhibit the lowest capacities over the entire campaign. It is known that they are strongly correlated, furthermore it appears that both can be rate-limiting at different times; therefore, in the following a selection of possible debottlenecking projects is identified from process knowledge substantiated with the statistical analysis.

5.3. Retrofit Engineering Projects. It is not a possibility to increase batch size further (avert "size bottlenecks"). Fermenter volume has been enhanced previously by increasing the height of the tanks, but another increase at this point is not realistic. However, a project aimed at substantially increasing the product concentration in the slurry by adjusting feed composition as well as feeding strategy is ongoing. This constitutes debottlenecking on the biochemical level, which suggests an extension of the classification size/scheduling bottleneck by a quality bottleneck, as it is not evident that all downstream unit operations can handle this increase (thinking for instance about resin capacity in chromatographic units[44]).

Having identified the scheduling bottleneck consisting of an interlinkage of units T21/T22 and U21/U22, it is time to capitalize on the process knowledge of the experienced engineers for the identification of possible engineering projects.

First, it is desirable to reduce the effect of downstream CIPs. These not only delay the bottleneck, but also induce substantial operational complexity due to the irregularity arising in the schedule. Currently, CIPs of U3 block both tanks T31/T32 (Figure 9) and therefore also the transmission of material from bottleneck U21/U22 for ca. 12 h. A reconfiguration of the CIP piping allows running a CIP on unit U3 with only one of the tanks (there will still be two shorter tank CIPs). This implies that the other tank is free to receive the upstream material-in-waiting, freeing up roughly 12 h of bottleneck operation once every 6−8 days as dictated by the CIP schedule. This is expected to yield a capacity increase of 0.5 batches per week for a comparably simple Type-2 project (3.1.3). Again, it must be pointed out that this reduction in delay is likely to reduce the propagation of delays into the upstream process, reducing operational complexity for

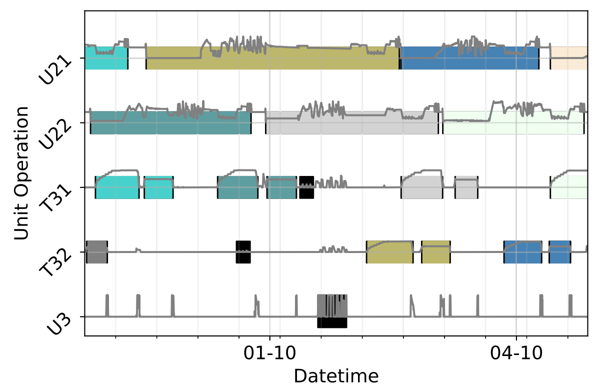

Figure 9. Strongly delayed material transfer from bottleneck (U21, olive-green batch) due to T31/T32 blockage by U3 CIP.

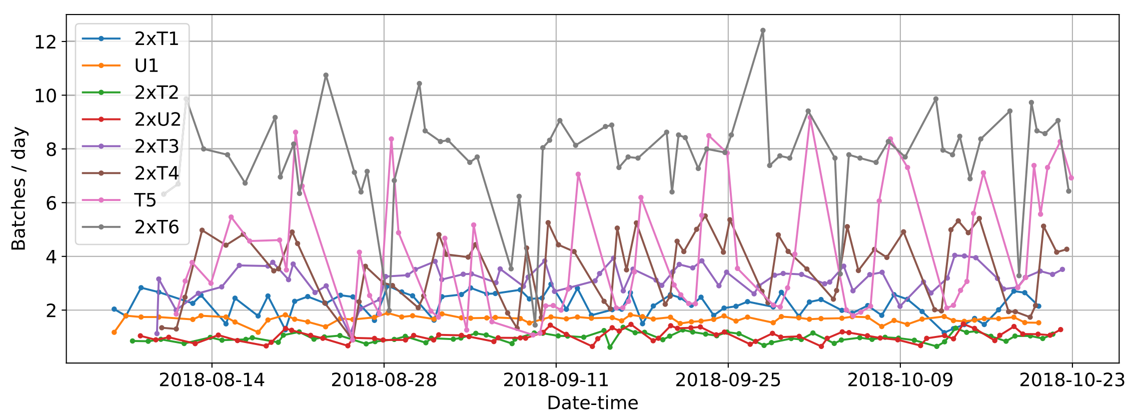

Figure 8. Effective capacities over time for all units but fermentation. Proximity in the process and similar capacities indicate a shared bottleneck on units T21/T22 and U21/U22; all other cycle times lie far below these two throughout the campaign.

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operators due to increased regularity, facilitating future optimization projects.

Second, aside from these irregular delays, it is desirable to elevate the baseline capacity on the bottlenecking units. Figure 10 shows some refined machine step statistics (anonymized).

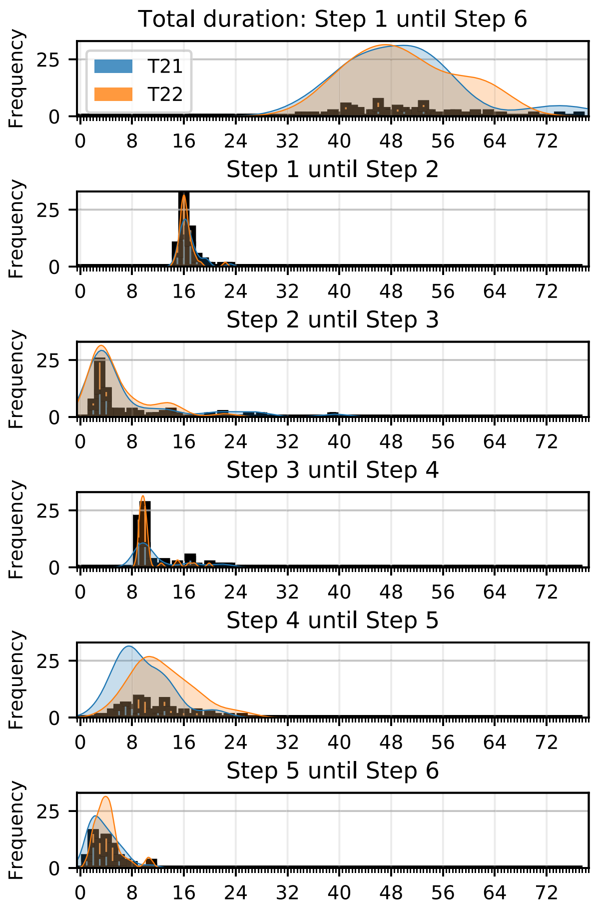

Figure 10. Granularity of the substeps with kernel-smoothed density estimates to facilitate comparisons between the two units.

Steps 4–6 denote the transfer of material from T21/T22 to U21/U22 and therefore take up an equally long amount of processing time on both units. The distinction is drawn as step 4 is largely automatic, whereas step 5 requires substantial manual operation. Delays here arise especially due to challenging fluid properties as a result of variability in the fermentations. In the case of highly viscous slurries, the transfer of material requires a lot of manual retuning of set points. This can lead to delays if the operator is not disposable and can create problems in other parts of the process as the operator needs to keep an eye on the procedure. Installation of a new pumping system with a higher degree of automation as a Type-4 project is likely to shorten this step significantly. Furthermore, variability of the step duration will be reduced and the operator will be given more capacities to engage in other parts of the process. Roughly, each 5 h of shortening the procedure will increase capacity by 0.7 batches per week. It is not clear exactly how much time will be saved, but as indicated by Figure 11 there is high potential due to extreme delays. (The large tails in steps 2–4 in Figure 10 are, for instance, due to CIPs.)

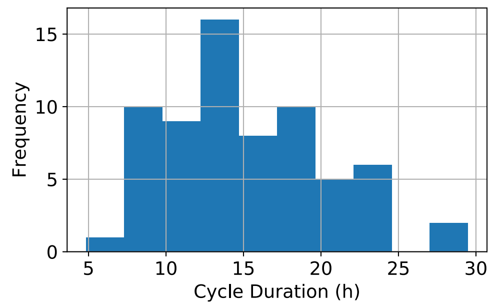

Figure 11. Distribution of cumulative transfer times (steps 4–6).

6. DISCUSSION

First, the case study has confirmed that it is not always possible or justifiable to apply a formal model-based systems engineering approach to optimization of industrial processes. Limitations in model-building and verification, as well as uncertainty regarding implementability especially of projects that require operational discipline are main inhibitors in this. On the other hand it is shown that modern data processing environments can be a viable tool in the incremental optimization of biobased processes, especially if the increments have only moderate impact on operations. Statistical means create a more explicit evidence-base than mental models. Furthermore, it has been shown that it is possible to reconstruct necessary cycle time information even in plants without a rigorous monitoring system, as is the case in many semiautomated facilities due to the difficulties that arise in monitoring manual process steps. The proposed algorithm is closely linked to process and plant structures, which render it intuitive and easy to maintain. Furthermore, it allows identifying batches that did not follow a standard pattern with high certainty.

In the regarded scenario, the recursive state machine functioned effectively despite of the uncertain process regime as many input sequences themselves were very reproducible (due to being automated or standardized operating procedures). Augmented by the time-series data from common sensors and domain knowledge, this enabled precise reconstruction of the schedule—it was however connected with a substantial programming effort. Accelerating this development process should greatly contribute to usability of the proposed methodology. The same applies to an extension of the method which better accommodates or even automatically handles irregular sequences or time-series profiles. Bayesian changepoint detection[58] seems to offer a theoretic foundation which can help with both ambitions. Here, thought should be given to balancing the programming effort with the workload which may arise in posterior validation of the algorithm, which expectedly grows with its flexibility/independence. Utilizing a flexible algorithm for detailed analyses within the superstates (which can be reliably generated by a robust embedding algorithm such as the one presented in this work) might constitute a good trade-off.

In terms of process optimization, Amaran et al.'s model-based approach is justified by setting an ambitious future production target. Because of the implied complexity, the debottlenecking of multiple stages at once calls for a notable level of formality. Still, small projects along the way must not be neglected, especially if they pave the way for these large projects by facilitating or enabling modeling, validation, and implementation.

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In these small projects, a model-based approach may not always be the correct choice. Again, besides unknowns on the physiochemical level, modeling may be difficult in the biobased industries because (i) machine steps are not tracked in semiautomated facilities (incomplete process monitoring); (ii) production processes are unsteady/irregular which makes validation of the models complicated and costly or even impossible; (iii) model-uncertainties and complex manual operations can create substantial uncertainty about the goodness of the results after implementation

On the other hand, the amount of products and number of parallel trains are usually quite manageable. It could be argued that Amaran et al. presuppose that this type of statistical analysis is a standard operation, but especially in smaller-scale and semiautomated facilities this is likely not so. Furthermore, in industry especially Type-1 and Type-2 problems will often not justify the dedicated development and validation of models, as it may be both too expensive and too time-consuming, calling for simpler approaches. The situation may be different if a digital twin of the plant is available and rigorously maintained. On the other hand, this is still an emerging technology and the economics behind it are in need of further illumination. In general, the value of creating a database as an enabler of rigorous process systems engineering should be acknowledge by industrial stakeholders. This calls for investments in new data acquisition and better data contextualization, but also in integrated manufacturing execution and control systems, which facilitate the often cumbersome data-collection process.[59]

In the above analysis, no performance indicators beyond current practices[8,23,41] are introduced. However, a statistical analysis should have its place in a framework directed at especially biobased batch plant debottlenecking. Modern data processing environments such as Python or R are attractive (cheap, fast, advanced, flexible) as they enable highly efficient analyses as well as visualizations. Thus, the case study should hopefully be of notable practical interest to industrial readers.

7. CONCLUSION

Batch processing is a relevant production paradigm especially in the biobased industries, and a number of generalizable operational challenges have been shown in an industrial case study. While several methodologies for debottlenecking of batch process plants exist in literature, it is likely that applicability in large parts of the biobased industries is limited. The reasons for that lie in the irregularities that arise as a cause of manual process control, but also from missing monitoring systems (both of biochemical properties as well as machine states). An algorithm has been introduced that is capable of reconstructing the machine states necessary to identify and avert scheduling bottlenecks. Based on visual statistics and heuristics, a powerful combination that maybe deserves a mention in a flexible framework, promising candidate debottlenecking projects have been identified in the case study plant. The chosen projects are robust and have a positive effect on reproducibility (process stability), and thus bring the plant closer to a state that allows rigorous model-based optimization. Transforming industrial process plants into predictable entities should be a general ambition both for academic and industrial stakeholders in order to reap the benefits of modern systems engineering tools. While it is a shared endeavor, it seems likely that the academy has to play an orchestrating role in this.

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Notes

The authors declare no competing financial interest.

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