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BACKPASS IN BIOMANUFACTURING: EFFECTIVE STRATEGIES FOR SHARING BIOREACTORS

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ABSTRACT

Biopharmaceutical drugs have transformed modern medicine, yet their manufacturing processes remain challenged by yield variability and rising production costs. This paper explores a promising application in a new domain to improve biomanufacturing efficiency through the *backpass* production method. Our production setting consists of two bioreactors: a dedicated bioreactor for production of a high-value product A, and a shared bioreactor for product A and a lower-value product B. The backpass method allows biomass to be transferred from the dedicated to the shared bioreactor, enabling additional production of product A while bypassing extensive upstream processing steps. We examine the performance of three backpass strategies, defined based on feedback from our industry partner, and use discrete event simulation to answer industry-specific questions related to the system's performance regarding throughput and profitability. This analysis provides practitioners with a decision-support framework for capital investments and operational planning.

1 INTRODUCTION

Biopharmaceutical drugs have transformed modern medicine and improved the health and well-being of both humans and animals. The use of living organisms in biopharmaceutical manufacturing introduces unique challenges, including uncertainty and variability in yield, lead times, and costs. As market demand and competition rise, the industry shifts to optimizing operations by improving throughput and resource allocation, ultimately reducing the costs of these life-saving biopharmaceuticals. A typical biomanufacturing process consists of two main steps: upstream processing (USP) and downstream processing (DSP). The USP involves growing bacterial cultures through a series of fermentation processes progressing from laboratory-scale setups to large bioreactors, all aimed at producing biomass under carefully controlled conditions. A bioreactor is a controlled environment, typically a stainless steel vessel, where microorganisms, cells, or enzymes are cultivated to carry out fermentation. Fermentation is a biochemical process that converts substrates (such as sugars) into products (such as biomass) through metabolic activity. DSP then purifies the biomass using centrifugation, filtration, and other steps (Martagan et al. 2024).

One approach to addressing the challenges in biomanufacturing is to increase bioreactor profitability and optimize resource allocation by implementing the emerging backpass production strategy. The backpass principle is applicable for a biomanufacturing system consisting of two bioreactors operating in parallel. The first bioreactor is dedicated to producing a high-value product in a batch-wise campaign. Throughout this paper, we refer to the high-value product as *product A* and the corresponding bioreactor as the *dedicated bioreactor*. The second bioreactor serves as a shared resource between the two production lines within the biomanufacturing facility. By default, it produce batches of *product B*, which has a lower value compared to product A, but it can also be used to produce an additional batch of product A through a backpass action.

We will refer to this flexible bioreactor as the *shared bioreactor*. During a backpass action, a predetermined fraction of the biomass from the dedicated bioreactor is transferred to the shared bioreactor, after which the biomass accumulation continues in both bioreactors until the growth stops and the biomass is harvested. By performing a backpass action, an additional batch of product A is produced in the shared bioreactor without requiring the time consuming scale-up steps prior to the main fermentation in the shared bioreactor. However, the backpass action carries inherent risk, as there is a chance of failure that could result in the loss of the transferred biomass. Therefore, the success of the backpass depends on carefully balancing the potential gain in high-value product against the risk of losing it.

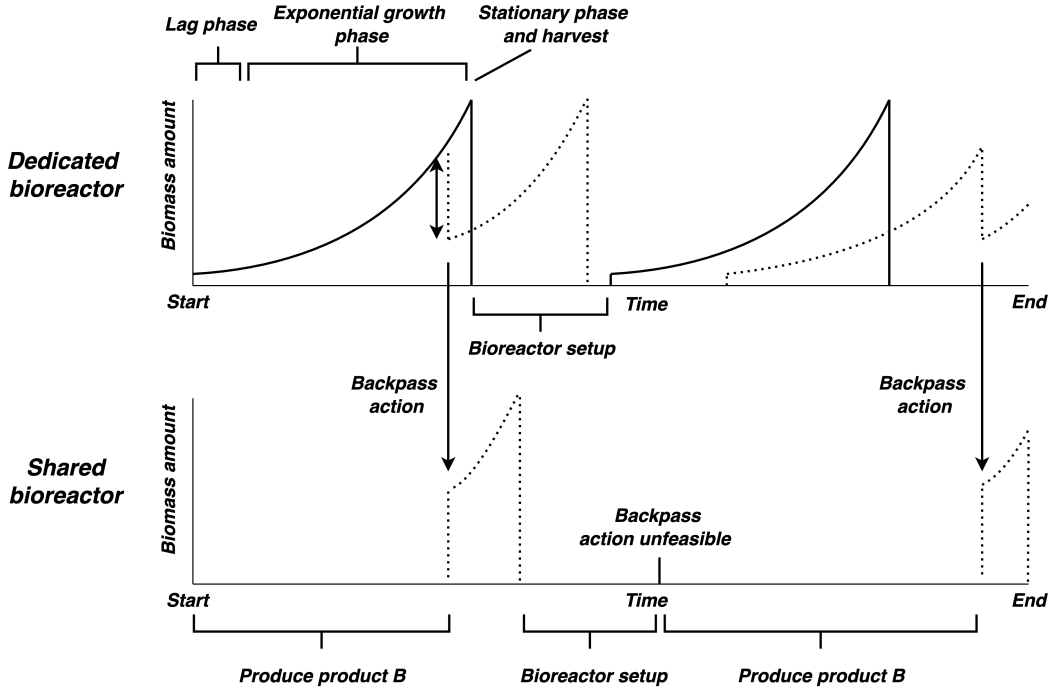

Figure 1: Illustrative example of the backpass production strategy.

Figure 1 illustrates the backpass production method for our problem setting including the dedicated and shared bioreactor. The solid lines depict the current practice of batch fermentation within the dedicated bioreactor, characterized by a continuous cycle comprising a lag phase, an exponential growth phase, a stationary phase, and subsequent harvesting. This process is followed by a bioreactor setup before initiating the next batch of product A. Each time the shared bioreactor finishes producing a batch of product B and becomes available after a bioreactor setup, a decision must be made: either to perform a backpass action (i.e., transfer a predetermined fraction of product A from the dedicated bioreactor to the shared bioreactor) or to redirect the shared bioreactor to produce another batch of product B. In our problem setting, we assume only one backpass action per batch is allowed. If the decision is made to proceed with the backpass, there exists a risk of failing the backpass action, which would lead to a loss of the transferred biomass fraction. In addition, a failed backpass action inevitably results in a time consuming setup time in the shared bioreactor. If the transfer is successful, biomass for product A continues to grow in both bioreactors until the stationary phase is reached, after which the contents of the bioreactors are harvested. Note that the time until reaching the stationary phase after backpass is most likely not the same for both bioreactors, as it heavily depends on the starting biomass amount and inherent uncertainties. Subsequently, after being harvested and completing the required setup time, the dedicated bioreactor initiates a new batch of product A. After the setup time for the shared bioreactor, a decision must be made about whether to perform a backpass action. If a backpass is not feasible because the dedicated bioreactor is still in the

setup phase, the shared bioreactor will by default start the production of another batch of product B. A successful backpass action results in an additional batch of product A without requiring scale-up from seed to main fermentation. However, the timing of the backpass action is crucial as the risk of failure of the backpass increases with higher and lower amounts of biomass. If the backpass action is taken too early, the culture will still be in the slow-growing lag phase, resulting in insufficient biomass for effective growth. Conversely, if the action is taken near the end of the exponential growth phase, there is a risk that the culture is already transitioning to the stationary phase, where growth ceases. In both cases, the backpass is more likely to fail, potentially resulting in the loss of transferred biomass and requiring a setup time to clean and sterilize the shared bioreactor.

In practice, there is limited understanding on how to best use the shared bioreactor for backpass with the goal of increasing profitability while managing risk-reward trade-offs. Using Discrete Event Simulation (DES), we investigate the performance of different backpass strategies and their effect on profitability and throughput of product A and B respectively. Together with our industrial partner MSD, we determined three backpass strategies for performance evaluation: Naive Backpass (always perform the backpass regardless of risks), AB Backpass (a simple one-step look-ahead strategy based on expected profit), and Time Threshold Backpass (perform backpass during a prespecified time window). We will compare these strategies to the No Backpass benchmark policy, in which the dedicated and shared bioreactor exclusively produces product A and B, respectively.

The Naive and AB Backpass strategies focus solely on the fermentation environment and ignore USP and DSP planning constraints. However, the Time Threshold Backpass policy offers a more practical approach, as it does take planning constraints into account by limiting the backpass action to fixed time windows. Using a DES model, we will compare the performance of the Naive, AB, and Time Threshold Backpass strategies to obtain managerial insights on the performance effect of adhering to planning constraints. We will perform a sensitivity analysis for a wide range of practical settings to get a better understanding of the performance of different backpass policies. In addition, we will analyze the trade-off between increasing planning flexibility and the impact on profitability and throughput of product A and B respectively.

The remainder of this work is structured as follows. In Section 2, we review related literature from both a life sciences and operations research perspective. In Section 3, we outline our DES model, which is followed by our numerical experiments in Section 4. In Section 5, we provide concluding remarks and outline directions for future research.

2 RELATED WORK

From a (bio-)manufacturing perspective, backpass may seem similar but should not be confused with two-stage fermentation (also known as cascade fermentation), a common strategy in bioprocessing where fermentation occurs in two sequential bioreactors, each optimized for their own specific conditions. This approach enhances throughput and yield, exemplified by bioethanol production, where the first stage involves hydrolysis of biomass into fermentable sugars, followed by a second stage where yeast ferments these sugars into ethanol (Rastogi and Shrivastava 2017). The key difference between backpass and two-stage fermentation is that both bioreactors in two-stage fermentation serve a different purpose, whereas in backpass both bioreactors produce the same product. Backpass also shares similarities with bleed-feed, which is another biomanufacturing method in which a fraction of biomass is extracted from a bioreactor, allowing growth to continue while skipping a setup and hence enhancing overall biomass throughput. However, in backpass, the extracted biomass is transferred to a shared bioreactor for further fermentation, instead of being harvested and send to DSP (Koca et al. 2023).

In this paper, we use simulation to analyze the performance of the backpass biomanufacturing environment. Recently, simulations such as digital twins have found their way into biomanufacturing with applications ranging from integration into bioreactor technology (Zobel-Roos et al. 2020) to advanced in-process control strategies for enhanced operational efficiency (Park et al. 2021), and real-time optimization (Udugama et al. 2021). A digital twin allows for the simulation of different scenarios and consequently

digital twins and simulation often appear together in the literature. For example, Van Den Houten et al. (2023) looked at a complex scheduling problem in multi-product biomanufacturing systems consisting of continuous and batch processes, focusing on optimizing production schedules for makespan and lateness. It compares the rolling-horizon approach to a global optimization strategy, showing that the rolling-horizon method outperforms the global strategy in both real and synthetic scenarios. Another simulation example within biomanufacturing is Morey et al. (2024), who used a hybrid approach to combine simulation and a queuing model for optimizing a biomanufacturing system that produces low-volume, high-variability, and individualized products in order to increase efficiency and support for bottleneck analysis in biomanufacturing design. A simulation methodology which is often used for modeling a manufacturing environment in order to identify bottlenecks, simulate resource allocation and complex system interactions as well as performing what-if scenario analyses is DES (Banks 2005). An example of a DES use case within biomanufacturing is Sachidananda et al. (2016), who present a DES model for a biopharmaceutical company to evaluate capital investments in manufacturing. It facilitates 'what-if' scenario planning and shows significant improvements over the current process, including reduced throughput time, better resource utilization, lower operating costs, and fewer bottlenecks. Also, Oyebolu et al. (2019) developed a DES for continuous bioprocesses within a scheduling context, exploring dynamic scheduling policies to improve operational decisions in multi-product facilities. Using shared resources is a frequently recurring theme in biomanufacturing since resources such as bioreactors are often shared for different products. Therefore, finding effective sharing strategies or coming up with a good schedule is of importance. Limon and Krishnamurthy (2020) studied biomanufacturing scheduling with "no-wait" constraints, using a mixed-integer linear programming model to minimize total tardiness and allow for schedule revisions. They proposed a dynamic scheduling approach and compared it to traditional methods, validated through collaboration with industry partners to create a practical scheduling tool.

Our work makes several contributions to the emerging field of simulation in biomanufacturing. To the best of our knowledge, this project is among the first to simulate the backpass concept and systematically analyze its trade-offs in terms of profitability and throughput. We evaluate the performance of three practical backpass strategies defined in collaboration with our industry partner. Using realistic industry data, our results provide actionable insights for practitioners and highlight the potential benefits of backpass technology in improving profitability and throughput.

3 SIMULATION MODEL

3.1 Performance Metrics

In this paper, we study the performance of a manufacturing system consisting of a dedicated and shared bioreactor operating in parallel. The dedicated bioreactor only produces consecutive batches of product A, which is our main product of interest. The shared bioreactor produces product B, but also has the ability to produce product A via a backpass action. The primary objective is to increase the overall profit generated by the facility through the production of batches A and B. The secondary objective is to obtain insights into how much product A and B can be produced under given backpass strategy. For any given backpass strategy and scenario evaluated in our simulation model, the production rate of product A and B produced is captured by Equation (1), which describes the biomass throughput TP_i for product $i \in \{A,B\}$. Here, x^i_{tot} is the total amount of biomass of product i produced during the simulation horizon T_{sim}. Given that the value of a unit of biomass for products A and B, represented by c_A and c_B, can vary in value, and considering that product A is deemed the more valuable product (i.e., $c_A > c_B$), we will express the overall profit Π of the system in terms of biomass units of product A using the throughput for both products and the (c_B/c_A) ratio, which is described in Equation (2). Therefore, our performance metrics will be throughput for product A and B and normalized profit per time respectively.

$$TP_i = \frac{x^i_{tot}}{T_{sim}}, \text{ for } i \in \{A,B\} \tag{1}$$

$$\Pi = TP_A + \left(\frac{c_B}{c_A}\right) TP_B \tag{2}$$

3.2 Biomass Growth and Risk Dynamics

We model biomass growth of product A using the Gompertz Equation (3), which is commonly used to describe the S-shaped growth curves of microbial fermentation processes (Wang and Guo 2024):

$$x(t) = c_1 e^{-c_2 e^{-c_3 t}}. \tag{3}$$

Here, x is the biomass in dimensionless units, t is the cultivation time in hours, and c_1, c_2 and c_3 are growth parameters. Figure 2 shows the biomass growth profiles and the corresponding Gompertz fit for 27 batches of product A coming from our industrial partner. The data has been anonymized such that biomass x ranges between 0 and $x_{max} = 20$. For product B, the production duration is randomly sampled from a normal distribution, where the mean (t^B_{avg}) and standard deviation (σ_B) are based on fermentation times coming from the Gompertz curves dataset as shown in Figure 2. Note that these distribution parameters are such that the probability of sampling a negative duration is negligible.

When performing a backpass action, in which a fraction b of the current biomass of product A $x^A_{current}$ is transferred from the dedicated to the shared bioreactor, there exists a probability that the action fails. Failure leads to the transferred cells (i.e., a biomass amount of $bx^A_{current}$) becoming non-viable for further growth in the shared bioreactor, thereby requiring disposal. The probability of a failed backpass action, denoted by $p(x)$, is dependent on the biomass amount x, where higher and lower biomass amounts correspond to increased probability of failure (i.e., $p(x)$ is convex in x). We model $p(x)$ as a modified, inverted Beta distribution represented by Equation (4) in which we first normalize biomass x via $\frac{x}{x_{max}}$, such that $\frac{x}{x_{max}} \in [0,1]$. Similarly, $u \in [0,1]$ is used to identify the maximum of the Beta probability density function, providing a normalization factor for consistent scaling. We additionally apply min and max operators to enforce the range $x \in [0,1]$. Note that similar to growth, the risk dynamics are a batch specific feature. Therefore, the risk profile $p(x)$ is scaled such that it ranges between 0 and the maximum biomass x_{max} for a given batch:

$$p(x) = \min\left(1,\ \max\left(0, 1 - \lambda \frac{\text{Beta}(\frac{x}{x_{max}}; \alpha, \beta)}{\max\limits_{u \in [0,1]} \text{Beta}(u; \alpha, \beta)}\right)\right). \tag{4}$$

In Equation (4), Beta is the Beta probability density function given by:

$$\text{Beta}(x; \alpha, \beta) = \frac{x^{\alpha-1}(1-x)^{\beta-1}}{B(\alpha, \beta)}, \tag{5}$$

in which $B(\alpha, \beta)$ is the Beta function with parameters α and β. In our simulation analysis, we consider three specific parameter sets for the distribution in Equation (4) to represent a broad range of realistic settings for the backpass failure probability. Figure 3 shows these three risk scenarios, representing no, medium and high risk. The distributions are modeled using Equation (4), where $\alpha = 1.5$ and $\beta = 1.5$ and where variations in the scale parameter λ influence the associated risk profiles. Specifically, $\lambda = 5$ corresponds to no risk, whereas $\lambda = 0.5$ corresponds to high risk.

3.3 Backpass Strategies

In our simulation, the benchmark policy is to not perform a backpass action, which we will refer to as the *No Backpass* (NB) policy. Under this policy, product A is continuously produced in subsequent batches in the dedicated bioreactor and the same holds for product B in the shared bioreactor. To evaluate the potential advantages of backpass under different scenarios, we examine the following three strategies and compare their performance metrics profitability and throughput to the benchmark policy:

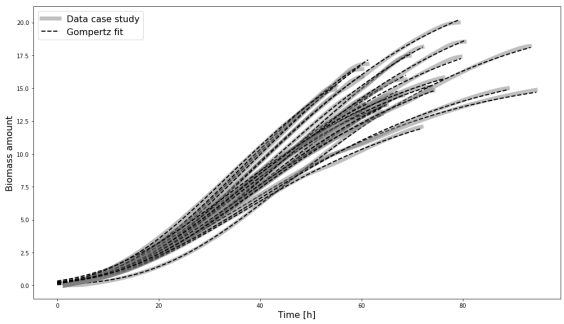

Figure 2: Biomass growth curves and Gompertz fit product A.

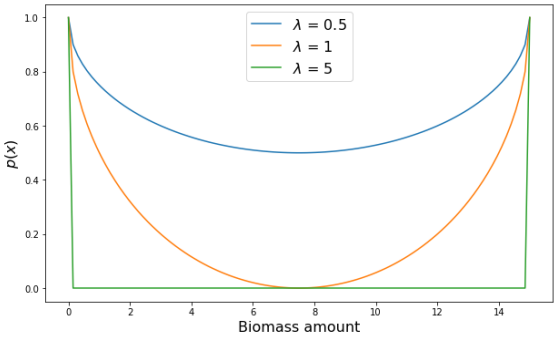

Figure 3: Risk scenarios inverse Beta distribution.

- *Naive Backpass* (NAB) always performs a backpass action if possible, which is when the dedicated bioreactor is growing product A and the shared bioreactor is empty and available after a setup time.
- *AB Backpass* (ABB) is a one-step look-ahead policy based on the expected profit. It compares the average expected profit for the next batch on both bioreactors when performing a backpass action to the expected throughput for the next batch on both bioreactors when no backpass is performed. It essentially assesses whether producing a batch of product A or product B in the shared bioreactor yields the highest short-term profit per time unit. If the condition in Equation (6) is met, i.e., if the one-step look-ahead expected profit under a potential backpass action exceeds the expected profit under no backpass action, a backpass action is performed. If the condition is not met, production continues under the no backpass scenario. In Equation (6), x^A_{avg} is the conditional empirical expected value of biomass product A given the current biomass has been reached without entering the stationary phase (i.e., the expected average biomass for $x^A_{max} > x^A_{current}$, where x^A_{max} represents the maximum biomass of the remaining Gompertz growth curves after $x^A_{current}$). More formally, $x^A_{avg} = \hat{\mathbb{E}}[x^A_{max} \mid x^A_{max} \geq x^A_{\text{current}}]$. The conditional empirical expected average fermentation time of a batch A, denoted as t^A_{avg}, is calculated in a manner analogous to that of x^A_{avg}. The terms t^* and t^{**} refer to the time for an average batch of A to reach biomass amount $x^A_{current}(1-b)$ and $x^A_{current}b$ respectively. The term $(1-p(x^A_{current}))$ represents the probability of a successful backpass action. For the NB situation, the expected profit for producing a batch of product B in the shared bioreactor is calculated using $x^B_{avg}(c_B/c_A)$ and t^B_{avg}, which is the average production time for a batch B.

$$\overbrace{\underbrace{\left(\frac{x^A_{avg}-x^A_{current}(1-b)}{t^A_{avg}-t^*}\right)}_{\text{Dedicated bioreactor}} + \underbrace{(1-p(x^A_{current}))\left(\frac{x^A_{avg}-x^A_{current}b}{t^A_{avg}-t^{**}}\right)}_{\text{Shared bioreactor}}}^{\text{Expected profit under backpass}} > \overbrace{\underbrace{\left(\frac{x^A_{avg}-x^A_{current}}{t^A_{avg}-t_{current}}\right)}_{\text{Dedicated bioreactor}} + \underbrace{\left(\frac{x^B_{avg}(c_B/c_A)}{t^B_{avg}}\right)}_{\text{Shared bioreactor}}}^{\text{Expected profit under no backpass}} \tag{6}$$

- *Time Threshold Backpass* (TTB) only performs a backpass if possible and if the time since the start of fermentation in the dedicated bioreactor falls within a prespecified time window $[T^*-\Delta, T^*+\Delta]$, which is coordinated with USP and DSP planning. Here T^* is the target time in hours with $T^* \in kT_w$, where T_w is the time window in hours, $k = 1,2,3,..$ and Δ represents the bandwidth in hours. The reason for a time-driven threshold is because some of the critical USP and DSP steps such as the media preparation work in fixed cycles. Using the TTB allows for the simulation of our most realistic backpass scenario, as it takes the coordination of a potential backpass action with USP and DSP planning into account.

3.4 Simulation Flow

Figure 4 provides a high-level overview of the backpass DES flow. The simulation involves two bioreactors: (i) a dedicated bioreactor (D), which exclusively produces batches of product A; and (ii) a shared bioreactor (S), which can produce either a batch of product B or a batch of product A via a backpass action. At the simulation start ($t = 0$), one event is scheduled for each bioreactor. For D, this entails sampling a Gompertz growth trajectory from the empirical dataset shown in Figure 2. The resulting production event on D is assigned batch-specific properties: a start time t^D_{start}, an end time t^D_{end}, and a maximum biomass $x^A_{\max}$, which is reached at t^D_{end}.

For S, it is not initially known whether the event will be used for product B or for receiving a backpass of product A. It is assigned a start time t^S_{start}, indicating when the bioreactor becomes available. Both events are added to an event list, which is sorted chronologically by start time. At all times, the event list contains exactly two entries: one scheduled event for D and one for S. At each decision point, the simulation identifies the next event to execute, E_c, based on the earliest start time: $t = \min(t^D_{\text{start}}, t^S_{\text{start}})$.

If E_c is the event on S, this implies $t^S_{\text{start}} < t^D_{\text{start}}$, meaning D is unavailable (e.g., due to a setup time T_s). In that case, S is used to produce a batch of product B, yielding a reward of x^B_{avg}. A new production event on S is then scheduled by sampling a duration from $t^B \sim \mathcal{N}(t^B_{\text{avg}}, \sigma_B)$ and adding the setup time T_s, resulting in a new start time: $t^S_{\text{start}} = t + t^B + T_s$. If E_c is the event on D, a batch of product A is being produced in the dedicated bioreactor. A backpass is feasible if the shared bioreactor becomes available before D finishes: $t^S_{\text{start}} < t^D_{\text{end}}$. If backpass is infeasible (i.e., there is no overlap), the batch is harvested in D, yielding a reward of $x^A_{\max}$. A new event is then scheduled on D by sampling another Gompertz growth trajectory, with a start time of $t^D_{\text{end}} + T_s$. If backpass is feasible, whether it occurs depends on the policy being simulated. Under the NAB (naive always-backpass) policy, backpass always occurs. Under the ABB and TBB policies, the decision depends on expected profit or a predefined time window, respectively. If the policy conditions are not met, S is used to produce product B (as described above), and a new event is scheduled on S.

Meanwhile, production in D continues and may overlap with the newly scheduled S event. If the policy permits a backpass, the action is executed with a success probability of $1 - p(x^A_{\text{current}})$. If successful, a biomass amount of $b \cdot x^A_{\text{current}}$ is transferred to S, while $(1-b)x^A_{\text{current}}$ remains in D. Both t^D_{end} and t^S_{end} are updated based on the original Gompertz growth trajectory, which remains unchanged. Since the batch is split, each bioreactor contributes a reward of $x^A_{\max}$, resulting in a total reward of $2x^A_{\max}$. New events are then scheduled on both bioreactors. Importantly, each D event allows for at most one backpass. If the backpass fails (with probability $p(x^A_{\text{current}})$), the transferred biomass in S is lost and no reward is obtained. D continues its production to completion and yields $x^A_{\max}$ at harvest. New events are scheduled accordingly. This process repeats until the simulation reaches the time horizon T_{sim} at which point the performance metrics throughput and profit are calculated.

4 NUMERICAL EXPERIMENTS

We conduct an extensive set of numerical experiments based on representative industry data. In Section 4.1, we first present the experimental setup and the base case scenario parameters. In Section 4.2, we explore the trade-off between the expected profit and the throughput for products A and B. In these experiments, we range the value ratio $(c_B/c_A) \in (0,1]$, consider different backpass fractions $b \in (0,1)$ and capture the performance under several risk scenarios modeled through $\lambda \in \{0.5, 1, 5\}$. In Section 4.3, we investigate the effect of increased planning flexibility on our performance metrics. Specifically, the bandwidth parameter Δ of the TTB policy is analyzed by ranging $\Delta \in [1, 24]$.

4.1 Experimental Setup and Base Case Scenario

Table 1 shows the base case scenario parameters which will be used as the default settings in our numerical experiments. The biomass growth dynamic values for $x^A_{avg}, x^B_{avg}, t^A_{avg}, t^B_{avg}$ and σ_B are based on the anonymized

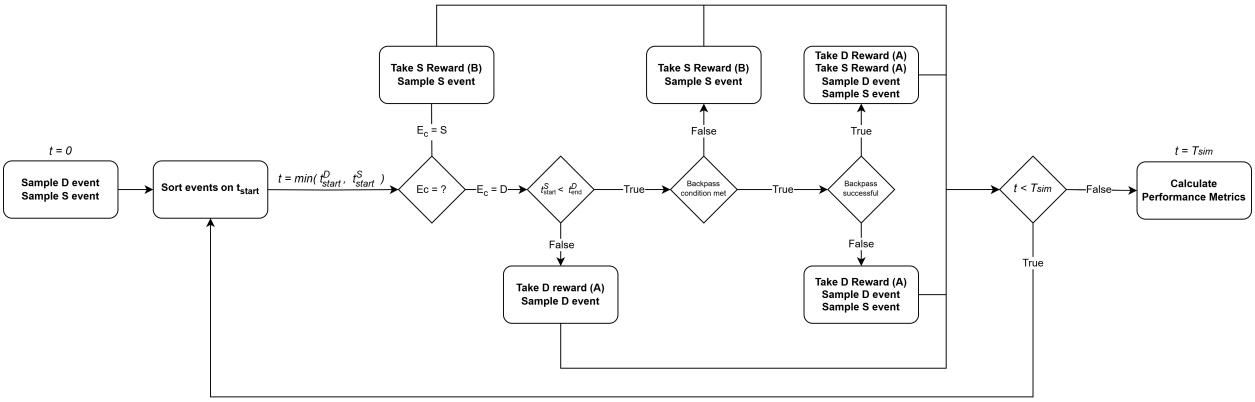

Figure 4: Flowchart backpass DES.

dataset from our industrial partner. As a default setting we consider the biomass value ratio (c_B/c_A) and the backpass fraction b to be 0.25 and 0.5 respectively. For the default risk scenario we take $\lambda = 1$ and keep α and β fixed at 1.5 as it represents the medium risk scenario. The bioreactor setup time T_s for both batch A and B is assumed to be 24 hours and after the warm-up period we will simulate for a year, which corresponds to 8736 hours. In accordance with our industrial partner, we will consider the TTB policy parameters T_w and Δ for the base case scenario to be 24 and 3 hours respectively.

Table 1: Parameters base case scenario.

Parameter	**Description**	**Value**	**Unit**
x^A_{avg}	Average biomass batch A	15.48	-
x^B_{avg}	Average biomass batch B	15.48	-
t^A_{avg}	Average fermentation time batch A	70.25	hours
t^B_{avg}	Average fermentation time batch B	70.25	hours
σ_B	Standard deviation fermentation time batch B	10.51	hours
(c_B/c_A)	Biomass unit value ratio	0.25	-
b	Backpass fraction	0.50	-
α	Risk scenario shape parameter	1.50	-
β	Risk scenario shape parameter	1.50	-
λ	Risk scenario scale parameter	1	-
T_s	Bioreactor setup time batch A and B	24	hours
T_{sim}	Simulation duration	8736	hours
T_w	Time window TTB policy	24	hours
Δ	Bandwidth TTB policy	3	hours

4.2 Analysis on Throughput and Profitability

We first consider the base case scenario and investigate the effect of changing the parameters (c_B/c_A) ratio, backpass fraction b and λ on the performance metrics profit and throughput.

Figure 5 illustrates the impact of varying the ratio of (c_B/c_A) on profit and throughput within the base case scenario. The analysis yields several managerial insights. First, beyond a certain threshold of the (c_B/c_A) ratio, it becomes from a financial perspective disadvantageous to engage in backpass actions, regardless of the backpass policy employed. Prior to reaching this critical juncture, the implementation of

backpass actions is most profitable, as both NAB and ABB policies exhibit alignment in their performance outcomes. Second, the ABB policy demonstrates a limited capacity to adjust to this turning point, as evidenced by the persistent profit gap when compared to the NB policy after the (c_B/c_A) threshold . This indicates that while the ABB policy attempts to adapt, it does not fully capture the risk-reward trade-off in this context. Third, the shift in this risk-reward trade-off, as indicated by the profit turning point, results in a decline in TP_A for the ABB policy whereas TP_B starts to increase. In contrast, the throughput metrics for the other policies remain relatively stable, as they lack the adaptability necessary to respond to fluctuations in expected profit.

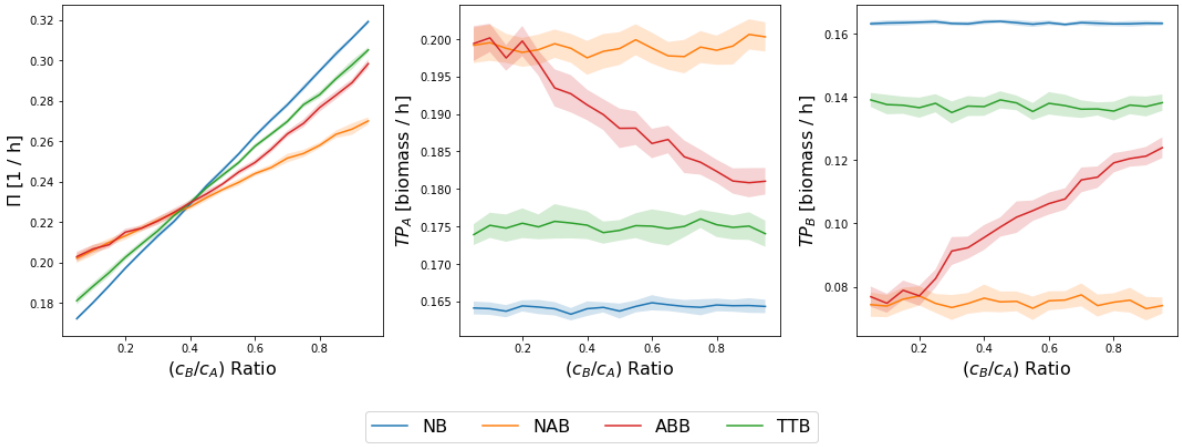

Figure 5: Effect of (c_B/c_A) ratio on profit and throughput for base case scenario parameters including 99% confidence intervals.

The impact of varying the backpass fraction b on profit and throughput within the base case scenario is depicted in Figure 6. Overall, an increase in the backpass fraction is associated with a decline in profit. This phenomenon can be attributed to the fact that, in the event of a backpass action failure, a higher backpass fraction results in a greater loss of biomass. Consequently, it is advisable to maintain a lower backpass fraction to optimize profit.

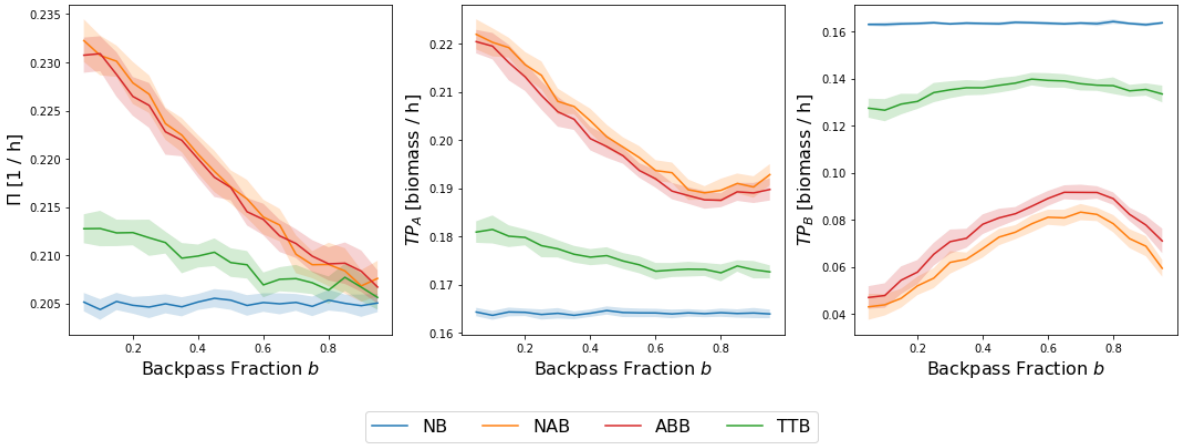

Figure 6: Effect of backpass fraction b on profit and throughput for base case scenario parameters including 99% confidence intervals.

Figure 7 illustrates the profit and throughput across various risk scenarios within the base case scenario. Consistent with our expectations, an increase in λ (indicating a lower risk of backpass failure) is associated with a more advantageous backpass environment. This favorable condition leads to an increase in profit, an increase in TP_A, and a corresponding decrease in TP_B.

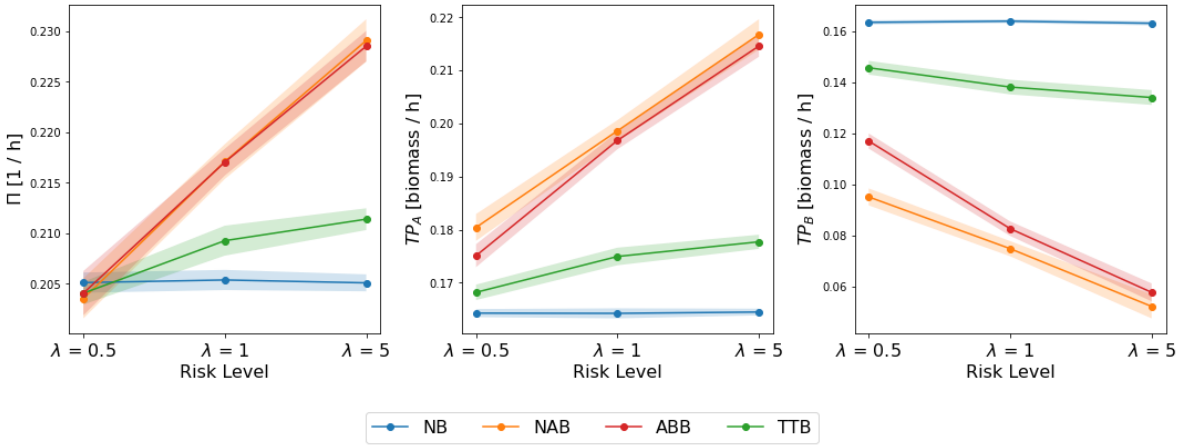

Figure 7: Effect of risk scenario parameter λ on profit and throughput for base case scenario parameters including 99% confidence intervals.

4.3 Analysis on Planning Flexibility

Upon examining the profit depicted in Figures 5, 6, and 7, it becomes evident that the optimal decision varies based on the specific scenario and parameters, with the choice being either to execute a backpass action or to forgo it entirely. In contrast, the performance of the TTB policy is positioned between these two extremes, as its effectiveness is constrained by adherence to the USP and DSP constraints. Consequently, either the NB policy or the NAB/ABB policy appears to yield the highest profit, contingent upon the simulation parameters, while the TTB policy remains intermediate in performance. This observation suggests the presence of a dual policy structure when the focus is solely on the fermentation environment, particularly in the absence of planning constraints. Figure 8 further substantiates the existence of such a dual policy framework, providing an overview of which action achieves the highest throughput for a given $\frac{c_B}{c_A}$ ratio and backpass fraction b.

When broadening the scope from the fermentation environment to encompass the entire production process (i.e., including USP and DSP), it becomes important to assess the performance loss attributable to adherence to planning constraints. Figure 9 illustrates the profit differential, accompanied by a 99% confidence interval, between the ABB policy, identified as the most profitable option alongside NAB in the base case scenario and the TTB policy, as the bandwidth Δ is varied for three simulated backpass fractions $b \in \{0.25, 0.50, 0.75\}$. From this figure, two key observations emerge. First, as Δ increases to 24 hours, the profit difference converges to zero, suggesting that the TTB policy increasingly aligns with the NB policy, which exhibits performance characteristics similar to those of the ABB policy in the base case scenario. Second, for lower bandwidth values of Δ, the profit difference relative to the best-performing policy is minimized at higher backpass fractions b. This phenomenon can be attributed to the advantageous nature of backpassing in the base case scenario. Whenever the opportunity arises, albeit infrequently with low Δ, it is beneficial to maximize backpassing efforts. In this context, the advantages gained from backpassing outweigh the risks associated with higher bleeding fractions, as demonstrated in the preceding subsection. Practitioners can utilize this information to make informed decisions regarding the allocation of investments in USP and DSP capacity, thereby facilitating an increase in Δ and enhancing overall profitability.

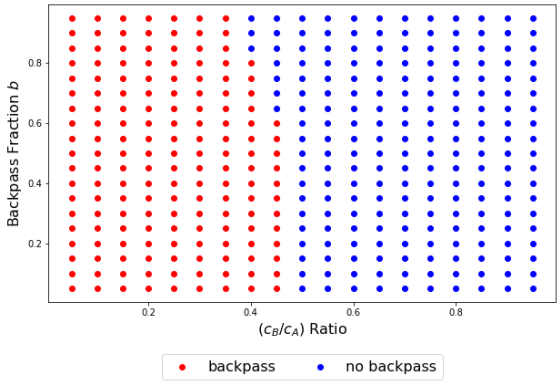

Figure 8: Dual policy structure for base case scenario.

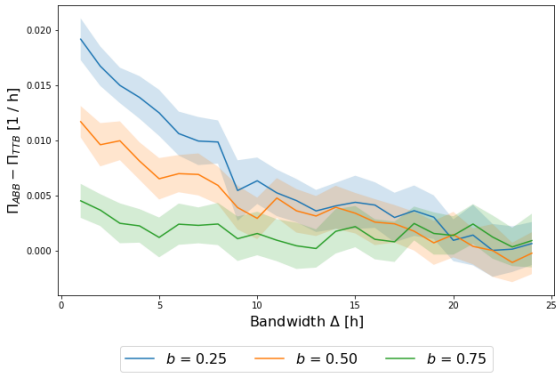

Figure 9: Profit gap between ABB and TTB policy as a function of Δ for base case scenario.

5 CONCLUDING REMARKS AND FUTURE RESEARCH

In this paper, we study the backpass production method, which is a relatively unexplored production setting consisting of two bioreactors operating in parallel. We simulate three distinct backpass policies that necessitate a trade-off between the production of a high-value product A and a lower-value product B. We study the performance of this system by evaluating the performance metrics profit and throughput for product A and B for a range of practical settings.

Overall, there exists a specific (c_B/c_A) ratio prior to which the risk-reward trade-off indicates that the implementation of backpass actions enhances profit relative to the NB benchmark policy. Furthermore, it is observed that higher backpass fractions and elevated risk scenarios are associated with reduced profitability. This decline in profit can be attributed to the increased biomass loss that occurs when a backpass action fails, particularly at higher backpass fractions. In the case of the TTB policy, which operates under the constraints of USP and DSP, a profit gap exists when compared to the more profitable NAB and ABB policies. As the bandwidth Δ increases, the profit differential diminishes, suggesting that the TTB policy increasingly aligns with the NAB policy, which exhibits performance characteristics similar to those of the ABB policy for the base case scenario. Additionally, at lower bandwidths, the profit difference is minimized at higher backpass fractions, indicating that the benefits of backpassing outweigh the risks associated with higher bleeding fractions. This insight provides valuable guidance for practitioners seeking to optimize investments in USP and DSP capacity to enhance overall profitability.

Future research could focus on several key areas. First, it is possible to assume a variable backpass fraction instead of a predetermined parameter. However, this approach may introduce complexities in simulations due to the large number of options this results in. Therefore, employing a Markov Decision Process (MDP) may be necessary to determine the optimal backpass fraction for any given state. Subsequently, the performance gap between the simulation results and the MDP outcomes can be assessed to gain insights into the effectiveness of the current simulation policies. Second, the simulation could be expanded to incorporate additional bioreactors, production lines, and coordination options. In addition, future research can analyze the utilization of bioreactors, seeking alternative strategies to maximize resource efficiency. Third, by integrating customer demand information for the various products into the model, we can provide managerial insights regarding market impact and identify the most effective approach for fulfilling contractual obligations based on throughput metrics. Finally, the simulation model developed in this study facilitates a comprehensive risk analysis that evaluates investments in USP and DSP process capacities against the potential increase in profit. By quantifying the additional profit gained from an expanded time window bandwidth Δ and offsetting this against the associated investments, practitioners are provided with a framework to generate strategic insights regarding the optimal balance between investments, profit and throughput.

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