Online appendices for

Integrating upstream and downstream planning to increase biomanufacturing profitability

Appendix A: Model formulation for the separate optimization approach

We present a separate optimization approach consisting of an upstream (USP) and a downstream (DSP) MDP model as outlined in Section 3.2. Both models make condition-based decisions for their respective stage maximizing profitability.

Decision epochs: $t \in \{0, \tau, 2\tau, 3\tau, \dots\}$ for $\tau > 0$.

State spaces:

$$\text{For USP: } s_t^{USP} \in \{x_t\}, \text{with } x_t \in \{\mathbb{R} | 0 \le x_t \le \overline{X}\} \tag{18}$$

$$\text{For DSP: } s_t^{DSP} \in \{z_{t-1}\} \text{ with } z_{t-1} \in \{\mathbb{R} | 0 \le z_{t-1} \le 1\} \tag{19}$$

Action spaces:

$$\text{For USP: } a_t^{USP} \in \begin{cases} Ferment\,(F), \\ Harvest\,\&\,purify\,(H). \end{cases} \tag{20}$$

$$\text{For DSP: } a_t^{DSP} \in \begin{cases} Harvest\,\&\,purify\,(H), \\ Harvest, purify\,\&\,exchange\,resin\,(E), \end{cases} \tag{21}$$

as well as the number of purification cycles c_t to purify the harvested batch in case of action *Harvest* and *Exchange*. For c_t, the same rules apply as described for the integrated model in Section 3.1.

Cost and rewards: Fermentation cost ν, batch harvest and setup cost ζ, cost per purification cycle η, night shift fix cost η_n, and resin exchange cost ξ are the same as for the integrated model in Section 3.1. Note that the USP model assumes full purification capacity when calculating the expected product quantity in Equation (23).

$$\text{For USP: } \mathbb{E}(\mathcal{R}^{USP}(s_t)) = \pi \cdot \mathbb{E}(\mathcal{P}^{USP}(s_t)), \text{ where} \tag{22}$$

$$\mathbb{E}(\mathcal{P}^{USP}(s_t)) = min \begin{cases} x_t \cdot \chi, \\ c_t \cdot \theta \cdot \psi \end{cases} \tag{23}$$

$$\text{For DSP: } \mathbb{E}(\mathcal{R}^{DSP}(s_t)) = \pi \cdot \mathbb{E}(\mathcal{P}^{DSP}(s_t)), \text{ where} \tag{24}$$

$$\mathbb{E}(\mathcal{P}^{DSP}(s_t)) = min \begin{cases} \mathbb{E}(x_t(\widetilde{x}_{Sep})) \cdot \chi, \\ c_t \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi \end{cases} \tag{25}$$

Transition functions: The evolution of the product concentration in the USP problem and the decay of the purification capacity in the DSP problem follow the same structure described for the integrated model in Section 3.1.

Value functions:

$$\text{For USP: } \mathcal{V}^{USP}(s_t) = max \begin{cases} -\nu + \mathcal{C}^F(s_t) & if\ a_t = F, \\ \mathbb{E}(\mathcal{R}^{USP}(s_t)) - \zeta - \eta \cdot c_t + \mathcal{C}^H(s_t) & if\ a_t = H, \text{ with} \end{cases} \tag{26}$$

$$\mathcal{C}^F(s_t) = \delta \cdot \int_{-\infty}^{\infty} f(\alpha | x_t) \cdot \mathcal{V}(x_t + \alpha)\ d\alpha \tag{27}$$

$$\mathcal{C}^H(s_t) = \delta \cdot \mathcal{V}(0). \tag{28}$$

$$\text{For DSP: } \mathcal{V}^{DSP}(s_t) = max \begin{cases} \mathbb{E}(\mathcal{R}^{DSP}(s_t)) - \zeta - \eta \cdot c_t + \mathcal{C}^H(s_t) & if\ a_t = H, \\ \mathbb{E}(\mathcal{R}^{DSP}(s_t)) - \zeta - \eta \cdot c_t - \xi + \mathcal{C}^E(s_t) & if\ a_t = E, \text{ with} \end{cases} \tag{29}$$

$$\mathcal{C}^H(s_t) = \delta \cdot \int_{-\infty}^{\infty} g(\gamma | z_{t-1}) \cdot \mathcal{V}(z_{t-1} - \gamma)\ d\gamma \tag{30}$$

$$\mathcal{C}^E(s_t) = \delta \cdot \mathcal{V}(1) \tag{31}$$

Appendix B: Proofs

Proof of Theorem 1. We neglect the time indices in x_t and z_{t-1} for a compact formulation of the following proof. Assume two values for x so that $x^+ \geq x^-$ and any z. A control-limit structure policy would imply the following optimal actions $\mathbb{P}^*(a|x^-,z) = F$ and $\mathbb{P}^*(a|x^+,z) = H$. Assume by contradiction that $\mathbb{P}^*(a|x^-,z) = H$ and $\mathbb{P}^*(a|x^+,z) = F$.

$$\mathbb{E}(\mathcal{R}(x^-,z)) - \zeta - \eta \cdot c(x^-,z) + \mathcal{C}^H(x^-,z) \geq -\nu + \mathcal{C}^F(x^-,z) \tag{32}$$

$$\mathbb{E}(\mathcal{R}(x^-,z)) - \eta \cdot c(x^-,z) - \mathcal{C}^F(x^-,z) \geq \zeta - \nu - \mathcal{C}^H(x^-,z) \tag{33}$$

$$\mathbb{E}(\mathcal{R}(x^+,z)) - \zeta - \eta \cdot c(x^+,z) + \mathcal{C}^H(x^+,z) \leq -\nu + \mathcal{C}^F(x^+,z) \tag{34}$$

$$\mathbb{E}(\mathcal{R}(x^+,z)) - \eta \cdot c(x^+,z) - \mathcal{C}^F(x^+,z) \leq \zeta - \nu - \mathcal{C}^H(x^+,z) \tag{35}$$

$$\mathbb{E}(\mathcal{R}(x^-,z)) - \eta \cdot c(x^-,z) - \mathcal{C}^F(x^-,z) \geq \mathbb{E}(\mathcal{R}(x^+,z)) - \eta \cdot c(x^+,z) - \mathcal{C}^F(x^+,z) \tag{36}$$

$$\mathbb{E}(\mathcal{R}(x^+,z)) - \mathbb{E}(\mathcal{R}(x^-,z)) - \eta \cdot \left[c(x^+,z) - c(x^-,z)\right] \leq \mathcal{C}^F(x^+,z) - \mathcal{C}^F(x^-,z) \tag{37}$$

In the contradiction hypothesis, $\mathbb{P}^*(a|x^-,z) = H$ implies the condition in Equation (32) and $\mathbb{P}^*(a|x^+,z) = F$ the condition in Equation (34). Note that $c(x,z)$ represents the number of purification cycles chosen if the batch is harvested in state (x,z). The batch setup cost ζ, and fermentation cost ν are independent of x. Also, based on Equation (7), $\mathcal{C}^H(x,z)$ is independent of the product concentration x_t, because the product concentration is zero after the harvest. Hence, the right hand sides of Equation (33) and (35) are equal, leading to Equation (36). Rearranging leads to Equation (37) with the left hand side being the immediate, incremental revenue difference of x^+ and x^-, reduced by the purification cost difference in case that more purification cycles are chosen for x^+ than for x^-. The right hand side quantifies the incremental benefit of having a higher product concentration in the batch in the current period and continuing to ferment. We use Equation (6) to further analyze this term, leading to Equation (38).

$$\begin{aligned}
\mathcal{C}^F(x^+,z) - &\mathcal{C}^F(x^-,z) \\
&= \delta \cdot \int_{-\infty}^{\infty} f(\alpha|x^+) \cdot \mathcal{V}(x^+ + \alpha(x^+), z)\; d\alpha \\
&\quad - \delta \cdot \int_{-\infty}^{\infty} f(\alpha|x^-) \cdot \mathcal{V}(x^- + \alpha(x^-), z)\; d\alpha \qquad (38)\\
&\overset{\substack{A.3\ \& \\ x^- \geq \hat{x}}}{\leq} \delta \cdot \int_{-\infty}^{\infty} f(\alpha|x^+) \cdot \mathcal{V}(x^+ + \alpha(x^+), z|P(a) = H)\; d\alpha \\
&\quad - \delta \cdot \int_{-\infty}^{\infty} f(\alpha|x^-) \cdot \mathcal{V}(x^- + \alpha(x^-), z|P(a) = H)\; d\alpha \qquad (39)\\
&= \delta \cdot \Big[\mathbb{E}(\mathcal{R}(x^+ + \alpha(x^+), z)) - \zeta - \eta \cdot c(x^+ + \alpha(x^+), z) + \mathcal{C}^H(x^+ + \alpha(x^+), z)\Big] \\
&\quad - \delta \cdot \Big[\mathbb{E}(\mathcal{R}(x^- + \alpha(x^-), z)) - \zeta - \eta \cdot c(x^- + \alpha(x^-), z) + \mathcal{C}^H(x^- + \alpha(x^-), z)\Big] \qquad (40)
\end{aligned}$$

Assumption 3 leads to $\alpha(x^-) \geq \alpha(x^+)$ if we are beyond the inflection point $\hat{x}$ of the product formation curve, hence $x^- \geq \hat{x}$. This means, the expected potential gain of action F, in a state with x^- is larger than for a state with x^+. Correspondingly, the potential value loss when choosing action H over an alleged optimal action F is larger for x^-. This is formalized in Equation (41) and leads to Equation (39).

$$\mathcal{V}(x^+, z|P^*) - \mathcal{V}(x^+, z|P(a) = H) \leq \mathcal{V}(x^-, z|P^*) - \mathcal{V}(x^-, z|P(a) = H) \tag{41}$$

With Equation (7) we get Equation (40). The batch setup cost ζ and the expected future contribution of the harvest action $\mathcal{C}^H(x,z)$ are independent of x. Inserting Equation (40) into the right hand side of Equation (37), we get the condition in Equation (42), which contradicts Equation (12).

$$\begin{aligned}
&\mathbb{E}(\mathcal{R}(x^+,z)) - \mathbb{E}(\mathcal{R}(x^-,z)) - \eta \cdot \left[c(x^+,z) - c(x^-,z)\right] \leq \\
&\qquad \delta \cdot \left[\mathbb{E}(\mathcal{R}(x^+ + \alpha(x^+), z)) - \eta \cdot c(x^+ + \alpha(x^+), z)\right] - \\
&\qquad\qquad \delta \cdot \left[\mathbb{E}(\mathcal{R}(x^- + \alpha(x^-), z)) - \eta \cdot c(x^- + \alpha(x^-), z)\right] \quad \square
\end{aligned} \tag{42}$$

LEMMA 7. *Every USP batch is eventually harvested.*

Lemma 7 shows that there is a finite upper bound on the length of each batch fermentation and that each sequence of $Ferment$ actions eventually ends with a $Harvest$ or $Harvest\,\&\,exchange$ action.

Proof of Lemma 7. This proof considers a single upstream batch in state $s_t = (x_t, z_{t-1})$. The value function $\mathcal{V}(s_t|\mathbb{P})$ is the expected value of being in state s_t and following policy $\mathbb{P}$. Policy $\mathbb{P}^F$ in Equation (43) represents an infinite sequence of *Ferment* actions starting in state s_t, and the policy $\mathbb{P}^E$ in Equation (48) represents a *Harvest, purify & exchange (E)* action. As we consider a single batch, policy $\mathbb{P}^E$ only contains one action as this implies the end of the batch. Note that it is sufficient to compare these two cases as either the harvest action H or the exchange action E need to have a higher value than the ferment action F for the hypothesis to be true.

$$For\ \mathbb{P}^F(a|s) := F\ for\ all\ s \in \mathbf{S}: \tag{43}$$

$$\mathcal{V}(x_t, z_{t-1}|\mathbb{P}^F) = -\nu + \mathcal{C}^F(x_t, z_{t-1}) \tag{44}$$

$$= -\nu + \delta \cdot \int_{-\infty}^{\infty} f(\alpha|x_t) \cdot \mathcal{V}(x_t + \alpha, z_{t-1})\ d\alpha \tag{45}$$

$$= -\nu + \delta \cdot \mathcal{V}(x_{t+1}, z_{t-1}|\mathbb{P}^F) \tag{46}$$

$$\overset{A.3}{=} -\infty \tag{47}$$

$$For\ \mathbb{P}^E(a|s) := E\ for\ s = s_t: \tag{48}$$

$$\mathcal{V}(x_t, z_{t-1}|\mathbb{P}^E) = \mathbb{E}(\mathcal{R}(x_t, z_{t-1})) - \zeta - \eta \cdot c(x_t, z_{t-1}) - \xi + \mathcal{C}^E(x_t, z_{t-1}) \tag{49}$$

$$= \mathbb{E}(\mathcal{R}(x_t, z_{t-1})) - \zeta - \eta \cdot c(x_t, z_{t-1}) - \xi + \delta \cdot \mathcal{V}(0, 1) \tag{50}$$

$$\overset{A.1\&A.2}{\geq} -\zeta - \eta \cdot \omega - \xi \tag{51}$$

The expected revenue $\mathbb{E}(\mathcal{R}(x_t, z_{t-1}))$ is by Assumption 1 non-decreasing in $x_t \in \mathbf{X}$ and it is the only positive reward in the value function (Equation (5)). Hence for the value function holds, $V(x^+, z) \geq V(x^-, z)$ for $x^+ \geq x^-$ and for all $z_{t-1} \in \mathbf{Z}$. Following policy $\mathbb{P}^F$ with its repeated *Ferment* actions the product formation rate will eventually decrease with $\alpha(x_t) \to 0$ for $x_t \to \infty$, based on Assumption 3. This leads to Equation (47), with the product concentration staying constant from t to $t+1$, but the state value $\mathcal{V}(x_t, z_{t-1}|\mathbb{P}^F)$ reduces by the fixed fermentation cost ν and the discount factor δ. Following policy $\mathbb{P}^E$, the expected future contribution when selecting the action *Harvest, purify & exchange* $\mathcal{C}^E(x_t, z_{t-1})$ imply the state transition to a new batch with $x_{t+1} = 0$ and $z_t = 1$ (Equations (49) to (50)). In Equation (50), $\mathbb{E}(\mathcal{R}(x, z)) \geq 0$ by Assumption 1 and $\mathcal{V}_{t+1}(0, 1) \geq 0$ by Assumption 2. The remaining cost terms are constant, or have an upper bound ω in case of the decision on the number of purification cycles c. This leads to a finite lower bound for the state value $\mathcal{V}(x_t, z_{t-1}|\mathbb{P}^E)$ (Equation (51)). From this, the result follows that $\mathcal{V}(x_t, z_{t-1}|\mathbb{P}^E) \geq \mathcal{V}(x_t, z_{t-1}|\mathbb{P}^F)$. □

Proof of Lemma 1. We use the Bellman optimality equation to analyze the productivity and profitability over the duration of a single batch fermentation. Consider the value function for a state $s_t = (x_t = 0, z_{t-1})$ with a new batch that contains no product yet and any last known purification capacity. From Lemma 7 we know that every batch is eventually harvested. If a policy $\mathbb{P}$ is implemented that ferments the batch for $n-1$ periods and harvests after n periods (Equation (52)), $\mathcal{V}(s_t|\mathbb{P})$ is the expected value of being in state s_t and following this policy $\mathbb{P}$ (Equation (53)). Note that $c(x_t, z_{t-1})$ represents the number of purification cycles chosen if the batch is harvested in state (x_t, z_{t-1}). $\mathcal{C}^H(x_{t+n}, z_{t-1})$ is the expected future contribution when selecting the action *Harvest* in the given state.

$$For\ \mathbb{P}(a_{t'}|s_t) := \begin{cases} F & \text{for } t' = t, ..., t+n-1, \\ H & \text{for } t' = t+n \end{cases} \tag{52}$$

$$\begin{aligned}\mathcal{V}(x_t = 0, z_{t-1}|\mathbb{P}) = &\sum_{i=0}^{n-1} \delta^i \cdot (-\nu) + \delta^n \cdot \mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right) \\ &- \delta^n \cdot \left(\zeta + \eta \cdot c\left(x_{t+n}, z_{t-1}\right)\right) + \delta^n \cdot \mathcal{C}^H(x_{t+n}, z_{t-1})\end{aligned} \tag{53}$$

The profitability for an individual batch P^B can be calculated by dividing the cost and revenue terms in Equation (53) with n leading to Equation (54). The productivity of the system can be calculated by dividing the product formation over n fermentation periods and divide by n, neglecting the fermentation cost and harvesting cost. The productivity and profitability are not defined for $n=0$, hence, if the batch is not fermented for at least one period.

$$P^B = -\frac{\sum_{i=0}^{n-1}\delta^i\cdot\nu}{n} + \frac{\delta^n\cdot\mathbb{E}\left(\mathcal{R}(x_{t+n},z_{t-1})\right)}{n} - \frac{\delta^n\cdot(\zeta+\eta\cdot c(x_{t+n},z_{t-1}))}{n} + \frac{\delta^n\cdot\mathcal{C}^H(x_{t+n},z_{t-1})}{n} \tag{54}$$

We determine the structure of the profitability by analyzing the cost and revenue terms in Equation (54) for the batch fermentation lengths n and $n+1$. For the following derivations we will assume a discount factor of $\delta=1$, which is reasonable because we deal with the short horizon of a single batch. From Equation (55) and (56) we observe that the fermentation cost is a constant term in the profitability.

$$-\frac{\sum_{i=0}^{n-1}\delta^i\cdot\nu}{n} \overset{\delta=1}{=} -\frac{n\cdot\nu}{n} = -\nu \tag{55}$$

$$-\frac{\sum_{i=0}^{n}\delta^i\cdot\nu}{n+1} \overset{\delta=1}{=} -\frac{(n+1)\cdot\nu}{n+1} = -\nu \tag{56}$$

The expected revenue and product quantity for batches fermented for n and $n+1$ periods are shown in Equation (57) and (58), respectively.

$$\frac{\delta^n\cdot\mathbb{E}\left(\mathcal{R}(x_{t+n},z_{t-1})\right)}{n} \overset{\delta=1}{=} \frac{\pi\cdot\mathbb{E}\left(\mathcal{P}(x_{t+n},z_{t-1})\right)}{n} \tag{57}$$

$$\frac{\delta^{n+1}\cdot\mathbb{E}\left(\mathcal{R}(x_{t+n+1},z_{t-1})\right)}{n+1} \overset{\delta=1}{=} \frac{\pi\cdot\mathbb{E}\left(\mathcal{P}(x_{t+n+1},z_{t-1})\right)}{n+1} \tag{58}$$

To analyze the structure of the expected revenue term we need to differentiate whether the expected product quantity $\mathbb{E}(\mathcal{P}(x_t,z_{t-1}))$ is determined by the product concentration in the USP batch or the remaining purification capacity in the DSP (cf. Equation (2)). In Case A, the product concentration in the USP batch determines the harvested product quantity, hence $x_t\cdot\chi \le c(x_t,z_{t-1})\cdot\theta\cdot\mathbb{E}(z_t)\cdot\psi$, the following holds:

$$\frac{\mathbb{E}\left(\mathcal{P}(x_{t+n},z_{t-1})\right)}{n} \overset{Case\ A}{=} \frac{x_{t+n}\cdot\chi}{n} \tag{59}$$

$$\frac{\mathbb{E}\left(\mathcal{P}(x_{t+n+1},z_{t-1})\right)}{n+1} \overset{Case\ A}{=} \frac{x_{t+n+1}\cdot\chi}{n+1} \tag{60}$$

$$\frac{x_{t+n}}{n} < \frac{x_{t+n+1}}{n+1},\ for\, n\, for\, which\ \frac{x_{t+n}}{n} = \frac{\sum_{i=0}^{n-1}\alpha(x_{t+i})}{n} < \alpha(x_{t+n}) \overset{\text{A.3}}{\le} \frac{\dot{x}_{t+n}(z_{t-1})}{n} \tag{61}$$

$$\frac{x_{t+n}}{n} > \frac{x_{t+n+1}}{n+1},\ for\, n\, for\, which\ \frac{x_{t+n}}{n} = \frac{\sum_{i=0}^{n-1}\alpha(x_{t+i})}{n} > \alpha(x_{t+n}) \overset{\text{A.3}}{\ge} \frac{\dot{x}_{t+n}(z_{t-1})}{n} \tag{62}$$

Equation (59) and (60) represent the productivity for batches fermented for n and $n+1$ periods, respectively. The productivity is strictly increasing (decreasing) in n when it is smaller (larger) than the expected product formation rate of period n (Equation (61) and Equation (62)). As the productivity only depends on the product formation rate, Assumption 3 leads to the productivity to have a global maximum at $\dot{x}_t(z_{t-1})$, be strictly increasing for $x_t < \dot{x}_t(z_{t-1})$ and strictly decreasing for $x_t > \dot{x}_t(z_{t-1})$. This also results in the product concentration at the global maximum of the productivity to be larger or equal than the product concentration at the inflection point of the product formation curve, hence $\dot{x}_t(z_{t-1}) \ge \hat{x}_t$. Note that the maximum depends on z_{t-1} due to Equation (2).

In Case B, the expected purification capacity determines the expected product quantity that can be harvested, hence $x_t\cdot\chi \ge c(x_t,z_{t-1})\cdot\theta\cdot\mathbb{E}(z_t)\cdot\psi$ (cf. Equation (2)):

$$\frac{\pi\cdot\mathbb{E}\left(\mathcal{P}(x_{t+n},z_{t-1})\right)}{n} \overset{Case\ B}{=} \frac{\pi\cdot\omega\cdot\theta\cdot\mathbb{E}(z_t)\cdot\psi}{n} \tag{63}$$

$$\frac{\pi\cdot\mathbb{E}\left(\mathcal{P}(x_{t+n+1},z_{t-1})\right)}{n+1} \overset{Case\ B}{=} \frac{\pi\cdot\omega\cdot\theta\cdot\mathbb{E}(z_t)\cdot\psi}{n+1} \tag{64}$$

In Equation (63) and (64) ω, the maximum number of purification cycles, appear as the cost per cycle don't need to be considered when analyzing the productivity. This shows that the productivity is strictly decreasing in n once the expected purification capacity limits the expected product quantity that can be harvested. Note that this could also occur before the inflection point of the product formation curve in which case $\dot{x}_t(z_{t-1}) \leq \hat{x}_t$.

The harvesting cost per fermentation period for batches fermented for n and $n+1$ periods are shown in Equation (65) and Equation (66), respectively.

$$-\frac{\delta^n \cdot (\zeta + \eta \cdot c(x_{t+n}, z_{t-1}))}{n} \overset{\delta=1}{=} -\frac{\zeta + \eta \cdot c(x_{t+n}, z_{t-1})}{n} \tag{65}$$

$$-\frac{\delta^{n+1} \cdot (\zeta + \eta \cdot c(x_{t+n+1}, z_{t-1}))}{n} \overset{\delta=1}{=} -\frac{\zeta + \eta \cdot c(x_{t+n+1}, z_{t-1})}{n+1} \tag{66}$$

$$\frac{\zeta}{\eta} \geq \frac{\left(\frac{c(x_{t+n+1}, z_{t-1})}{n+1} - \frac{c(x_{t+n}, z_{t-1})}{n}\right)}{\left(\frac{1}{n} - \frac{1}{n+1}\right)} \tag{67}$$

In the right hand sides of Equation (65) and (66) we observe that the fixed batch harvest cost ζ per fermentation period is strictly decreasing in n. If we were also to consider a resin exchange after the batch harvest, we would have to include the resin exchange cost ξ here. Still, this would not change that the fixed cost at batch harvest are strictly decreasing in n. Equation (67) describes the condition for the total harvesting cost, including the variable purification cycle cost $\eta \cdot c(x_{t+n}, z_{t-1})$, to be non-increasing in n.

The fractional expected future contribution per fermentation period when selecting the action *Harvest* after n or $n+1$ fermentation periods are shown in Equation (68) and (69), respectively.

$$\frac{\delta^n \cdot \mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \overset{\delta=1}{=} \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \tag{68}$$

$$\frac{\delta^{n+1} \cdot \mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \overset{\delta=1}{=} \frac{\mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \tag{69}$$

Based on Equation (7), $\mathcal{C}^H(x_{t+n}, z_{t-1})$ is independent of the product concentration x_t, because the product concentration is zero after the harvest. Hence $\mathcal{C}^H(x_{t+n}, z_{t-1}) = \mathcal{C}^H(x_{t+n+1}, z_{t-1})$ resulting in $\mathcal{C}^H(x_t, z_{t-1})$ to be strictly decreasing in n.

From Equations (61) and (62) follows that the productivity has a global maximum at $\dot{x}_t(z_{t-1})$, is strictly increasing for $x_t < \dot{x}_t(z_{t-1})$ and strictly decreasing for $x_t > \dot{x}_t(z_{t-1})$. The fermentation cost per fermentation period are constant, the harvesting cost per fermentation period are non-increasing over the course of a batch fermentation if the condition in Equation (67) holds and the fractional expected future contribution of choosing action *Harvest* is strictly decreasing. Hence, the profitability also has a global maximum at $\ddot{x}_t(z_{t-1})$, is strictly increasing for $x_t < \ddot{x}_t(z_{t-1})$ and strictly decreasing $x_t > \ddot{x}_t(z_{t-1})$. $\square$

Proof of Theorem 2. Consider a state s_t with a new batch that contains no product yet, hence $x_t = 0$ and any last known purification capacity z_{t-1}. From Lemma 7 we know that every batch is eventually harvested. If a policy $\mathbb{P}^n$ is implemented that ferments the batch for $n-1$ periods and harvests after n periods (Equation (70)), $\mathcal{V}(s_t|\mathbb{P}^n)$ is the expected value of being in state s_t and following policy $\mathbb{P}^n$ (Equation (71)). Note that $c(x, z)$ represents the number of purification cycles chosen if the batch is harvested in state (x, z) and $\mathcal{C}^H(x, z)$ is the expected future contribution when selecting the action *Harvest* in this state.

$$For\, \mathbb{P}^n(a_{t'}|s_t') := \begin{cases} F & \text{for } t' = t, ..., t+n-1, \\ H & \text{for } t' = t+n \end{cases} \tag{70}$$

$$\begin{aligned} \mathcal{V}(x_t = 0, z_{t-1}|\mathbb{P}^n) = &\sum_{i=0}^{n-1} \delta^i \cdot (-\nu) + \delta^n \cdot \mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right) \\ &- \delta^n \cdot (\zeta + \eta \cdot c(x_{t+n}, z_{t-1})) + \delta^n \cdot \mathcal{C}^H(x_{t+n}, z_{t-1}) \end{aligned} \tag{71}$$

Equation (72) defines the policy if fermented for $k-1$ periods and harvested after k periods. In Equation (73), $\mathcal{V}(s_t|\mathbb{P}^k)$ is the expected value of being in state s_t, following policy $\mathbb{P}^k$ and neglecting fermentation and harvesting cost. This represents a value function calculating the productivity of the current upstream batch.

$$For\, \mathbb{P}^k(a_{t'}|s_t') := \begin{cases} F & \text{for } t' = t, ..., t+k-1, \\ H & \text{for } t' = t+k \end{cases} \tag{72}$$

$$\mathcal{V}(x_t = 0, z_{t-1}|\mathbb{P}^k) = \delta^k \cdot \mathbb{E}\left(\mathcal{R}(x_{t+k}, z_{t-1})\right) + \delta^k \cdot \mathcal{C}^H(x_{t+k}, z_{t-1}) \tag{73}$$

Equations (74) and (75) represent the profitability and the productivity, respectively. Note that this proof only holds for batches which have been fermented for at least one period. The conditions in Lemma 1, i.e. $\delta = 1$ and Equation (14), need to hold.

$$-\frac{\sum_{i=0}^{n-1} \nu}{n} + \frac{\mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right)}{n} - \frac{\zeta + \eta \cdot c(x_{t+n}, z_{t-1})}{n} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \tag{74}$$

$$\frac{\mathbb{E}\left(\mathcal{R}(x_{t+k}, z_{t-1})\right)}{k} + \frac{\mathcal{C}^H(x_{t+k}, z_{t-1})}{k} \tag{75}$$

Lemma 1 states that the productivity and profitability strictly increase before reaching a maximum at $\dot{x}_t$ and $\ddot{x}_t$, respectively, and strictly decrease thereafter. To proof Theorem 2, we need to show that the productivity reaches its maximum before the profitability, hence $\dot{x}_t \leq \ddot{x}_t$, or equivalently, that $k \leq n$ at the maxima. By contradiction, assume $k > n$ at the maxima. Without loss of generality, assume that the profitability has its maximum at n.

$$\begin{aligned} &-\frac{\sum_{i=0}^{n-1} \nu}{n} + \frac{\mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right)}{n} - \frac{\zeta + \eta \cdot c(x_{t+n}, z_{t-1})}{n} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \\ \geq &-\frac{\sum_{i=0}^{n} \nu}{n+1} + \frac{\mathbb{E}\left(\mathcal{R}(x_{t+n+1}, z_{t-1})\right)}{n+1} - \frac{\zeta + \eta \cdot c(x_{t+n+1}, z_{t-1})}{n+1} + \frac{\mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \end{aligned} \tag{76}$$

$$\frac{\mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right)}{n} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \leq \frac{\mathbb{E}\left(\mathcal{R}(x_{t+n+1}, z_{t-1})\right)}{n+1} + \frac{\mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \tag{77}$$

$$\begin{aligned} 0 \geq &\frac{\mathbb{E}\left(\mathcal{R}(x_{t+n}, z_{t-1})\right)}{n} - \frac{\mathbb{E}\left(\mathcal{R}(x_{t+n+1}, z_{t-1})\right)}{n+1} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} - \frac{\mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \\ \geq &\frac{\sum_{i=0}^{n-1} \nu}{n} - \frac{\sum_{i=0}^{n} \nu}{n+1} + \frac{\zeta + \eta \cdot c(x_{t+n}, z_{t-1})}{n} - \frac{\zeta + \eta \cdot c(x_{t+n+1}, z_{t-1})}{n+1} \end{aligned} \tag{78}$$

The contradiction hypothesis implies that the profitability decreases from n to $n+1$ (Equation (76)). The contradiction hypothesis also implies that the productivity increases from n to $n+1$ (Equation (77)). This leads to Equation (78) which contradicts Equations (55) and (56), and Equations (65)-(67) in the proof of Lemma 1. □

Proof of Theorem 3. Without loss of generality, consider a state s_t with a new batch that contains no product yet, hence $x_t = 0$ and any last known purification capacity z_{t-1}. Assume the product quantity in the bioreactor after n fermentation periods x_{t+n} is equal to the product quantity that can be purified with the maximum number of purification cycles ω, leading to Equation (79). Assumption 3 states that $\alpha(x_{t+n}) > 0$. This implies that the purification capacity still limits product output if the batch is fermented for one more period before harvesting (Equation (80)).

$$x_{t+n} \cdot \chi = \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi \tag{79}$$

$$x_{t+n+1} \cdot \chi \overset{A.3}{>} \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi \tag{80}$$

Lemma 1 shows that the profitability of a batch fermentation has a global maxima at $\ddot{x}_t(z_{t-1})$. To complete the proof it is sufficient to show that the profitability of the batch harvested after $n+1$ periods is lower than the profitability of the batch harvested after n periods. Assume by contradiction that the profitability increases from n to $n+1$ (Equation (81)). For the following derivations we will assume a discount factor of $\delta = 1$, which is reasonable because we deal with the short horizon of a single batch.

$$\begin{aligned} &-\frac{n \cdot \nu}{n} + \frac{\pi \cdot \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi}{n} - \frac{\zeta + \eta \cdot \omega}{n} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \\ \leq &-\frac{(n+1) \cdot \nu}{n+1} + \frac{\pi \cdot \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi}{n+1} - \frac{\zeta + \eta \cdot \omega}{n+1} + \frac{\mathcal{C}^H(x_{t+n+1}, z_{t-1})}{n+1} \end{aligned} \tag{81}$$

$$\frac{1}{n} \cdot \left[\pi \cdot \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi - \zeta - \eta \cdot \omega + \mathcal{C}^H(x_{t+n}, z_{t-1}) \right]$$
$$\leq \frac{1}{n+1} \cdot \left[\pi \cdot \omega \cdot \theta \cdot \mathbb{E}(z_t) \cdot \psi - \zeta - \eta \cdot \omega + \mathcal{C}^H(x_{t+n+1}, z_{t-1}) \right] \tag{82}$$

$$\frac{1}{n} \leq \frac{1}{n+1} \tag{83}$$

Simple reformulation leads to Equation (82). Based on Equation (7), $\mathcal{C}^H(x_t, z_{t-1})$ is independent of the product concentration x_t, because the product concentration is zero after the harvest. This leads to Equation (83) which is a false statement. □

Proof of Corollary 3 Corollary 3 follows directly from Lemma 1. Equation (54) defines the profitability of a batch as the expected revenue plus the contribution of future state values, reduced by the fermentation and harvesting cost, divided by the fermentation length. The fermentation cost are independent of z_{t-1}. The harvesting cost are independent of z_{t-1}, if the cycle cost η are neglected. For an individual batch, the purification capacity z_{t-1} is fixed. For all z_{t-1}, the harvest decision in state (x_t, z_{t-1}) has no impact on the future contribution, because after harvest the successor state is always $(0, z_{t-1} - \gamma(z_{t-1}))$. Equation (61) and (62) show that the expected revenue term is independent of z_{t-1} if Equation (13) holds. If Equation (13) does not hold, the expected revenue is proportional to z_{t-1} according to Equation (2). □

Proof of Lemma 2. The proof is done by induction on the value iteration algorithm. For all $x \in \mathbf{X}$, $z \in \mathbf{Z}$ and $t \in \mathbf{T}$, we define the initial state values $\mathcal{V}_i(x_t, z_{t-1})$ for iteration $i = 0$ without loss of generality as $\mathcal{V}_0(x_t, z_{t-1}) = 0$. Note that we neglect the time indices in x_t and z_{t-1} for a compact formulation of the following proof. In the value function (5), the fermentation cost ν, the expected future contribution when selecting the action *Ferment* $\mathcal{C}^F(x, z)$, the fixed harvesting cost ζ, and the resin exchange cost ξ are independent of z. To complete the proof, we show that $\mathbb{E}(\mathcal{R}(x, z)) - \eta \cdot c(x, z) + \mathcal{C}^H(x, z)$ is non-increasing with z decreasing for all $x \in \mathbf{X}$. Note that $c(x, z)$ represents the number of purification cycles chosen if the batch is harvested in state (x, z). Without loss of generality, we assume two values for the purification capacity so that $z^+ \geq z^-$ and z^- takes a value small enough to limit product output (cf. Equation (2)). Next, we proof the base case by determining the difference in the state value for z^+ and z^- for any $t \in \mathbf{T}$ and $x \in \mathbf{X}$ in the next iteration $i = 1$ of the value function algorithm:

$$\mathcal{V}_1(x, z^+) - \mathcal{V}_1(x, z^-) \tag{84}$$
$$= \mathbb{E}(\mathcal{R}(x, z^+)) - \eta \cdot c(x, z^+) + \mathcal{C}^H(x, z^+)$$
$$- \mathbb{E}(\mathcal{R}(x, z^-)) + \eta \cdot c(x, z^-) - \mathcal{C}^H(x, z^-) \tag{85}$$
$$= \mathbb{E}(\mathcal{R}(x, z^+)) - \eta \cdot c(x, z^+) + \delta \cdot \int_{-\infty}^{\infty} g(\gamma | z^+) \cdot \mathcal{V}_0(0, z^+ - \gamma) \; d\gamma$$
$$- \mathbb{E}(\mathcal{R}(x, z^-)) + \eta \cdot c(x, z^-) - \delta \cdot \int_{-\infty}^{\infty} g(\gamma | z^-) \cdot \mathcal{V}_0(0, z^- - \gamma) \; d\gamma \tag{86}$$
$$= \mathbb{E}(\mathcal{R}(x, z^+)) - \eta \cdot c(x, z^+) - \mathbb{E}(\mathcal{R}(x, z^-)) + \eta \cdot c(x, z^-) \tag{87}$$
$$= \mathbb{E}(\mathcal{R}(x, z^+)) - \mathbb{E}(\mathcal{R}(x, z^-)) - \eta \cdot (c(x, z^+) - c(x, z^-)) \tag{88}$$
$$> 0 \tag{89}$$

Equation (86) results from Equation (85) and (7). By definition, the values of the next states are $\mathcal{V}_0(0, z^+ - \gamma) = 0$ and $\mathcal{V}_0(0, z^- - \gamma) = 0$, resulting in Equation (87). The expected product function, defined in Equation (2), results in the expected revenue for z^+ to be larger than the revenue obtained with z^-. Albeit the number of purification cycles is a decision in the model, it can be expected that more cycles are chosen for lower remaining purification capacities, hence $c(x, z^+) \leq c(x, z^-)$. This leads to the inequality in Equation (89) proofing the statement for the first iteration $i=1$. Next, suppose the statement is true for iteration $i=k$ so that $\mathcal{V}_k(x,z^+)\geq\mathcal{V}_k(x,z^-)$. We now show the statement is true for iteration $i=k+1$:

$$\mathcal{V}_{k+1}(x,z^+)-\mathcal{V}_{k+1}(x,z^-) \tag{90}$$

$$=\mathbb{E}(\mathcal{R}(x,z^+))-\eta\cdot c(x,z^+)+\delta\cdot\int_{-\infty}^{\infty}g(\gamma|z^+)\cdot\mathcal{V}_k(0,z^+-\gamma)\ d\gamma$$
$$-\mathbb{E}(\mathcal{R}(x,z^-))+\eta\cdot c_(x,z^-)-\delta\cdot\int_{-\infty}^{\infty}g(\gamma|z^-)\cdot\mathcal{V}_k(0,z^--\gamma)\ d\gamma \tag{91}$$

$$=\mathbb{E}(\mathcal{R}(x,z^+))-\mathbb{E}(\mathcal{R}(x,z^-))-\eta\cdot(c(x,z^+)-c(x,z^-))$$
$$+\delta\left[\cdot\int_{-\infty}^{\infty}g(\gamma|z^+)\cdot\mathcal{V}_k(0,z^+-\gamma)\ d\gamma-\int_{-\infty}^{\infty}g(\gamma|z^-)\cdot\mathcal{V}_k(0,z^--\gamma)\ d\gamma\right] \tag{92}$$

$$\overset{A.5}{>}0 \tag{93}$$

As above, the expected revenue term and the purification cycle cost in Equation (92) are always positive. The remaining term is also positive by Assumption 5 and the induction hypothesis. This leads to the inequality in Equation (93) proving the inductive step. Next, we assume two values for the purification capacity again so that $z^+\geq z^-$ and this time, even for z^- the remaining purification capacity is not limiting the product output (cf. Equation (2)). In this case the expected revenue is the same for z^+ and z^-, but $\mathcal{V}(x,z^+)-\mathcal{V}(x,z^-)>0$ still holds based on the Bellman optimality equation. The value of $V(x,z^+)$ and $V(x,z^-)$ include the value of states with smaller remaining capacities, as assumed above. The result follows from the convergence of the value iteration algorithm. □

Proof of Theorem 4. We neglect the time indices in x_t and z_{t-1} for a compact formulation of the following proof. Assume two values for z so that $z^+\geq z^-$ and any x. A control-limit structure policy would imply the following optimal actions $\mathbb{P}(a|x,z^+)=H$ and $\mathbb{P}(a|x,z^-)=E$. Assume by contradiction that $\mathbb{P}(a|x,z^+)=E$ and $\mathbb{P}(a|x,z^-)=H$.

$$\mathbb{E}(\mathcal{R}(x,z^+))-\zeta-\eta\cdot c(x,z^+)-\xi+\mathcal{C}^E(x,z^+)\geq\mathbb{E}(\mathcal{R}(x,z^+))-\zeta-\eta\cdot c(x,z^+)+\mathcal{C}^H(x,z^+) \tag{94}$$

$$-\xi+\mathcal{C}^E(x,z^+)\geq\mathcal{C}^H(x,z^+) \tag{95}$$

$$\mathbb{E}(\mathcal{R}(x,z^-))-\zeta-\eta\cdot c(x,z^-)-\xi+\mathcal{C}^E(x,z^-)\leq\mathbb{E}(\mathcal{R}(x,z^-))-\zeta-\eta\cdot c(x,z^-)+\mathcal{C}^H(x,z^-) \tag{96}$$

$$-\xi+\mathcal{C}^E(x,z^-)\leq\mathcal{C}^H(x,z^-) \tag{97}$$

$$\mathcal{C}^H(x,z^-)\geq\mathcal{C}^H(x,z^+) \tag{98}$$

$$\delta\cdot\int_{-\infty}^{\infty}g(\gamma|z^-)\cdot\mathcal{V}(0,z^--\gamma)\ d\gamma\geq\delta\cdot\int_{-\infty}^{\infty}g(\gamma|z^+)\cdot\mathcal{V}(0,z^+-\gamma)\ d\gamma \tag{99}$$

In the contradiction hypothesis, $\mathbb{P}(a|x,z^+)=E$ implies the relation in the value functions represented in Equation (94) and $\mathbb{P}(a|x,z^-)=H$ the value function relation in Equation (96). Note that $c(x,z)$ represents the number of purification cycles chosen if the batch is harvested in state (x,z). The batch setup cost ζ, the expected revenue $\mathbb{E}(\mathcal{R}(x,z^+))$ or $\mathbb{E}(\mathcal{R}(x,z^-))$, and the purification cycle cost $\eta\cdot c(x,z^+)$ or $\eta\cdot c(x,z^-)$ are the same for action H or E, simplifying Equation (94) to Equation (95) and Equation (96) to Equation (97). The resin exchange cost ξ and the contribution of the exchange action $\mathcal{C}^E(x,z)$ are both independent of z. This leads to Equations (98) and (99). The proof of Lemma 2 and Assumption 5 contradict Equation (99). □

Proof of Lemma 3 We define the profitability of a single upstream batch fermented for n periods in Equation (100) for the integrated model as it was introduced in the proof of Lemma 1. Equation (102) represents the profitability function for the separate upstream problem. Equation (101) and Equation (103) represent the productivity over the duration of a single batch for the integrated and the separate system, respectively. Note that we assume a discount factor of $\delta=1$ for the following proof.

$$PF^B_{Int}(n)\quad=-\nu+\pi\cdot\frac{\mathbb{E}\left(\mathcal{P}(x_{t+n},z_{t-1})\right)}{n}-\frac{\zeta}{n}-\eta\cdot\frac{c(x_{t+n},z_{t-1})}{n}+\frac{\mathcal{C}^H(x_{t+n},z_{t-1})}{n} \tag{100}$$

$$PD^B_{Int}(n) = \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n}, z_{t-1})\right)}{n} + \frac{\mathcal{C}^H(x_{t+n}, z_{t-1})}{n} \tag{101}$$

$$PF^B_{USP}(n) = -\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n})\right)}{n} - \frac{\zeta}{n} - \eta \cdot \frac{c(x_{t+n})}{n} + \frac{\mathcal{C}^H(x_{t+n})}{n} \tag{102}$$

$$PD^B_{USP}(n) = \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n})\right)}{n} + \frac{\mathcal{C}^H(x_{t+n})}{n} \tag{103}$$

Comparing Equation (100) with Equation (101) and Equation (102) with Equation (103) we see that

$$PF^B_{Int}(n) \xrightarrow{\pi\to\infty} PD^B_{Int}(n)\ \forall\, n \in \mathbb{N}^0, \text{ and} \tag{104}$$

$$PF^B_{USP}(n) \xrightarrow{\pi\to\infty} PD^B_{USP}(n)\ \forall\, n \in \mathbb{N}^0. \tag{105}$$

The fermentation length n that maximizes productivity also maximizes profitability when $\pi \to \infty$. Hence, the harvest threshold $\widetilde{x}(z_{t-1})$ converges to the harvest threshold $\dot{x}(z_{t-1})$. Further, if Equation (13) holds, the expected product quantity at harvest only depends on x_{t+n}. This leads to $\mathbb{E}\left(\mathcal{P}(x_{t+n}, z_{t-1})\right) = \mathbb{E}\left(\mathcal{P}(x_{t+n})\right) = x_{t+n} \cdot \chi$. The productivity maximizing thresholds and hence the profitability maximizing thresholds of the integrated and the separate system converge to the same value. □

Proof of Lemma 4 We use the profitability functions as defined in the proof of Lemma 3. See Equation (100) for the integrated model and Equation (102) for the separate model. Consider we are in a state with full purification capacity $(x_{t+n}, z_{t-1} = 1)$ in the integrated model. When the resin exchange cost $\xi \to 0$ the state value of choosing action *Harvest* $\mathcal{V}(x_{t+n}, 1|H)$ is the same as choosing action *Exchange* $\mathcal{V}(x_{t+n}, 1|E)$. With this, the contribution of future state values $\mathcal{C}^H(x_{t+n}, z_{t-1})$ in Equation (100) can be replaced with $\mathcal{C}^E(x_{t+n}, 1) = \delta \cdot \mathcal{V}(0, 1)$ leading to Equations (106) and (107). This leads to the integrated model to always have full purification capacity $z_{t-1} = 1$. The separate USP model assumes full purification capacity and does not consider any decay. Without loss of generality, we can represent state (x_{t+n}) of the separate model with $(x_{t+n}, 1)$ in the integrated model leading to Equation (108). The future contribution of a *Harvest* in the separate model $\mathcal{C}^H(x_{t+n}, 1)$ leads to the same state value $\mathcal{V}(0, 1)$.

$$PF^B_{Int}(n) \overset{\xi\to 0}{=} -\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n}, 1)\right)}{n} - \frac{\zeta}{n} - \eta \cdot \frac{c(x_{t+n}, 1)}{n} + \frac{\mathcal{C}^E(x_{t+n}, 1)}{n} \tag{106}$$

$$= -\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n}, 1)\right)}{n} - \frac{\zeta}{n} - \eta \cdot \frac{c(x_{t+n}, 1)}{n} + \frac{\delta \cdot \mathcal{V}(0, 1)}{n} \tag{107}$$

$$PF^B_{USP}(n) = -\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n}, 1)\right)}{n} - \frac{\zeta}{n} - \eta \cdot \frac{c(x_{t+n}, 1)}{n} + \frac{\mathcal{C}^H(x_{t+n}, 1)}{n} \tag{108}$$

$$= -\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(x_{t+n}, 1)\right)}{n} - \frac{\zeta}{n} - \eta \cdot \frac{c(x_{t+n}, 1)}{n} + \frac{\delta \cdot \mathcal{V}(0, 1)}{n} \tag{109}$$

As Equations (107) and (109) are identical, the fermentation length n that maximizes profitability for both systems is also the same. Hence, the harvest threshold $\widetilde{x}_{Int}(z_{t-1})$ converges to the harvest threshold $\widetilde{x}_{Sep}$. □

Proof of Theorem 5 We use the profitability functions as defined in the proof of Lemma 3. See Equation (100) for the integrated model and Equation (102) for the separate model. Lemma 1 and Remark 1 show that the profitability of the integrated and the separate policies have global maxima. Without loss of generality, we assume that the integrated system reaches the profitability maximum after n fermentation periods ($\widetilde{x}_{Int} = \widetilde{x}_{t+n}$) and the separate system after k periods ($\widetilde{x}_{Sep} = \widetilde{x}_{t+k}$). To proof the assertion of the statement it suffices to show that $n \geq k$ at the respective maxima. Note that we assume a discount factor of $\delta = 1$ for the following proof.

We take the derivative of $PF^B_{Int}(n)$ with respect to n and $PF^B_{USP}(k)$ with respect to k and set both to zero. See Equation (110) for the integrated model and Equation (111) for the separate model.

$$\begin{aligned} 0 =& \pi \cdot \left[\frac{d\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+n}, z_{t-1})\right)}{n \cdot dn} - \frac{\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+n}, z_{t-1})\right)}{n^2}\right] \\ &+ \frac{\zeta}{n^2} - \eta \cdot \left[\frac{dc(\widetilde{x}_{t+n}, z_{t-1})}{n \cdot dn} - \frac{c(\widetilde{x}_{t+n}, z_{t-1})}{n^2}\right] - \frac{\int_{-\infty}^{\infty} g(\gamma|z_{t-1}) \cdot \mathcal{V}(0, z_{t-1} - \gamma)\ d\gamma}{n^2} \end{aligned} \tag{110}$$

$$
\begin{aligned}
0 =& \pi \cdot \left[\frac{d\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+k})\right)}{k \cdot dk} - \frac{\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+k})\right)}{k^2} \right] \\
&+ \frac{\zeta}{k^2} - \eta \cdot \left[\frac{dc(\widetilde{x}_{t+k})}{k \cdot dk} - \frac{c(\widetilde{x}_{t+k})}{k^2} \right] \qquad - \frac{V(0)}{k^2}
\end{aligned} \tag{111}
$$

Rearranging leads to Equation (112) for the integrated model and Equation (113) for the separate model.

$$
\begin{aligned}
&\pi \cdot \left[\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+n}, z_{t-1})\right) - \frac{d\mathbb{E}\left(\mathcal{P}(x_{t+n}, z_{t-1})\right)}{dn} \cdot n \right] + \int_{-\infty}^{\infty} g(\gamma|z_{t-1}) \cdot \mathcal{V}(0, z_{t-1} - \gamma)\ d\gamma \\
&= \zeta - \eta \cdot \left[\frac{dc(\widetilde{x}_{t+n}, z_{t-1})}{dn} \cdot n - c(\widetilde{x}_{t+n}, z_{t-1}) \right]
\end{aligned} \tag{112}
$$

$$
\begin{aligned}
&\pi \cdot \left[\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+k})\right) - \frac{d\mathbb{E}\left(\mathcal{P}(\widetilde{x}_{t+k})\right)}{dk} \cdot k \right] \qquad + \mathcal{V}(0) \\
&= \zeta - \eta \cdot \left[\frac{dc(\widetilde{x}_{t+k})}{dk} \cdot k - c(\widetilde{x}_{t+k}) \right]
\end{aligned} \tag{113}
$$

Assume a purification capacity z_{t-1} so that Equation (13) holds and the expected product quantity at harvest is determined by $\widetilde{x}_{t+n}$ or $\widetilde{x}_{t+k}$ and the bioreactor volume χ. The second part of the revenue term represents the product formation in one period $\alpha(\widetilde{x}_{t+n})$ and $\alpha(\widetilde{x}_{t+k})$ as described in Equation (3). Further, we assume a maximum number of purification cycles ω. This results in Equation (114) and Equation (115). With the right hand side being equal we get Equation (116).

$$
\pi \cdot \chi \cdot \left[\widetilde{x}_{t+n} - \alpha(\widetilde{x}_{t+n}) \cdot n\right] + \int_{-\infty}^{\infty} g(\gamma|z_{t-1}) \cdot \mathcal{V}(0, z_{t-1} - \gamma)\ d\gamma \overset{c=\omega}{=} \zeta + \eta \cdot \omega \tag{114}
$$

$$
\pi \cdot \chi \cdot \left[\widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k\right] + \mathcal{V}(0) \overset{c=\omega}{=} \zeta + \eta \cdot \omega \tag{115}
$$

$$
\begin{aligned}
&\pi \cdot \chi \cdot \left[\widetilde{x}_{t+n} - \alpha(\widetilde{x}_{t+n}) \cdot n\right] + \int_{-\infty}^{\infty} g(\gamma|z_{t-1}) \cdot \mathcal{V}(0, z_{t-1} - \gamma)\ d\gamma = \\
&\pi \cdot \chi \cdot \left[\widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k\right] + \mathcal{V}(0)
\end{aligned} \tag{116}
$$

From Lemma 2 we know that the value function $\mathcal{V}(\widetilde{x}_t, z_{t-1})$ is increasing in z_{t-1} for all $x_t \in \mathbf{X}$. The separate USP model assumes full purification capacity and does not consider any decay. Without loss of generality, we can represent state (0) of the separate model with $(0,1)$ in the integrated model and get $\mathcal{V}(0) = \mathcal{V}(0,1) \geq \mathcal{V}(0, z_{t-1} - \gamma(z_{t-1}))$. Hence, for Equation (116) to hold the revenue term of the integrated model on the left-hand side of the equation needs to be larger than or equal to the term of the separate model on the right-hand side.

$$
\widetilde{x}_{t+n} - \alpha(\widetilde{x}_{t+n}) \cdot n \geq \widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k \tag{117}
$$

We define m as the difference in the fermentation length in the integrated and the separate system $n = k + m$. We use induction to show that Equation (117) holds for any $m \in \mathbb{N}^0$, which implies $\widetilde{x}_{Int} \geq \widetilde{x}_{Sep}$.

For the case of $m = 0$, Equation (117) leads to a true statement. Next, assume $m = 1$, which implies $\widetilde{x}_{t+n} = \widetilde{x}_{t+k+1} = \widetilde{x}_{t+k} + \alpha(\widetilde{x}_{t+k})$ leading to Equation (118).

$$
\widetilde{x}_{t+k} + \alpha(\widetilde{x}_{t+k}) - \alpha(\widetilde{x}_{t+n}) \cdot n \geq \widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k \tag{118}
$$

$$
\alpha(\widetilde{x}_{t+k}) \cdot (k+1) \geq \alpha(\widetilde{x}_{t+n}) \cdot n \tag{119}
$$

$$
\alpha(\widetilde{x}_{t+k}) \geq \alpha(\widetilde{x}_{t+k+1}) \tag{120}
$$

Equation (120) holds according to Assumption 3, proving the statement for $m = 1$.

Next, suppose Equation (117) is true for any m (Equation (121)). We now show that the statement is true for $m+1$, which implies $\widetilde{x}_{t+n} = \widetilde{x}_{t+k+m+1} = \widetilde{x}_{t+k+m} + \alpha(\widetilde{x}_{t+k+m})$ leading to Equation (122).

$$
\widetilde{x}_{t+k+m} - \alpha(\widetilde{x}_{t+k+m}) \cdot (k+m) \geq \widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k \tag{121}
$$

$$
\widetilde{x}_{t+k+m} + \alpha(\widetilde{x}_{t+k+m}) - \alpha(\widetilde{x}_{t+n}) \cdot n \geq \widetilde{x}_{t+k} - \alpha(\widetilde{x}_{t+k}) \cdot k \tag{122}
$$

$$
\alpha(\widetilde{x}_{t+k+m}) - \alpha(\widetilde{x}_{t+n}) \cdot n \geq -\alpha(\widetilde{x}_{t+k+m}) \cdot (k+m) \tag{123}
$$

$$
\alpha(\widetilde{x}_{t+k+m}) \cdot (k+m+1) \geq \alpha(\widetilde{x}_{t+n}) \cdot n \tag{124}
$$

$$
\alpha(\widetilde{x}_{t+k+m}) \geq \alpha(\widetilde{x}_{t+k+m+1}) \tag{125}
$$

Equation (121) and Equation (122) lead to Equation (123). As above, Equation (125) holds according to Assumption 3, proving the inductive step. □

Proof of Lemma 5 We use the Bellman optimality equation to analyze the profitability of the overall system over the lifetime of one resin batch. The state $s_t = (x_t = 0, z_{t-1} = 1)$ for any $t \in \mathbf{T}$ represents a fresh resin and a new upstream batch that contains no product. We define a policy $\mathbb{P}$ which harvests each batch $b \in \{1, 2, .., B-1\}$ following the optimal upstream policy after n_b periods and exchanges the resin after batch B was harvested (Equation (126)).

$$\mathbb{P}(a_{t'}|s_t) := \begin{cases} F & \text{for } t' \in \{t'' \in \mathbf{T} \text{ and } b \in \{1,2,...,B\} | t'' \neq t + \sum_{i=1}^{i=b} n_i \wedge t'' \geq t\} \\ H & \text{for } t' = t + \sum_{i=1}^{i=b} n_i \text{ and } b \in \{1,2,...,B-1\} \\ E & \text{for } t' = t + \sum_{i=1}^{i=B} n_i \end{cases} \tag{126}$$

$\mathcal{V}(s_t|\mathbb{P})$ is the expected value of being in state s_t and following policy $\mathbb{P}$ (Equation (127)). Since we assume to follow the optimal upstream policy we neglect the optimal harvest threshold $\widetilde{x}$ in the following for a compact formulation.

$$\mathcal{V}(s_t|\mathbb{P}) = \sum_{b=1}^{B} \left[\sum_{i=N_{b-1}+1}^{N_b} \left[\delta^i \cdot (-\nu)\right] + \delta^{N_b} \cdot \mathbb{E}\left(\mathcal{R}(z_{t-1+N_b})\right) - \delta^{N_b} \cdot \left(\zeta + \eta \cdot c\left(z_{t-1+N_b}\right)\right) \right] - \delta^{N_B} \cdot \xi \tag{127}$$

We get the profitability over the lifetime of a resin P^R by dividing $\mathcal{V}(s_t|\mathbb{P})$ with the accumulated batch fermentation times up to batch B, i.e., $N_B = \sum_{i=1}^{B} n_i$ (Equation (128)).

$$P^R = \frac{1}{N_B} \cdot \sum_{b=1}^{B} \left[\sum_{i=N_{b-1}+1}^{N_b} \left[\delta^i \cdot (-\nu)\right] + \delta^{N_b} \cdot \mathbb{E}\left(\mathcal{R}(z_{t-1+N_b})\right) - \delta^{N_b} \cdot \left(\zeta + \eta \cdot c\left(z_{t-1+N_b}\right)\right) \right] - \frac{\delta^{N_B} \cdot \xi}{N_B} \tag{128}$$

In line with Lemma 1, which describes the shape of the productivity and profitability for an individual upstream batch, we assume a discount factor of $\delta = 1$. With Equation (1) we get Equation (129).

$$P^R = \frac{1}{N_B} \cdot \sum_{b=1}^{B} n_b \cdot \left[-\nu + \pi \cdot \frac{\mathbb{E}\left(\mathcal{P}(z_{t-1+N_b})\right)}{n_b} - \frac{\zeta + \eta \cdot c(z_{t-1+N_b})}{n_b} \right] - \frac{\xi}{N_B} \tag{129}$$

The term in square brackets in Equation (129) represents the profitability $P_b(z_{t-1+N_b})$ of upstream batch b. We see that the productivity term is constant in z_{t-1} if Equation (13) holds and strictly decreases otherwise. The harvesting cost term is constant in z_{t-1} if Equation (14) holds. Hence, the upstream batch profitability is constant in z_{t-1} if Equation (13) holds and strictly decreases otherwise. As z_{t-1} is non-increasing in b according to Assumption 4, the upstream batch profitability $P_b(z_{t-1+N_b})$ is also constant in b if Equation (13) holds and strictly decreases otherwise. From this, it follows that the weighted average over B upstream batch profitabilities (first term in Equation (129)) is constant as long as Equation (13) holds and strictly decreases otherwise. The resin exchange cost term is strictly decreasing in B, as $\frac{\xi}{N_B} > \frac{\xi}{N_{B+1}}$. Hence the system profitability over the lifetime of one resin P^R has a maximum at $\ddot{B}$, is strictly increasing in B for $B < \ddot{B}$, and strictly decreasing in B for $B > \ddot{B}$. The profitability maximum is given by the smallest $\ddot{B}$, for which holds:

$$\frac{\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b}{N_{\ddot{B}}} - \frac{\xi}{N_{\ddot{B}}} \geq \frac{\sum_{b=1}^{\ddot{B}+1} P_b(z_{t-1+N_b}) \cdot n_b}{N_{\ddot{B}+1}} - \frac{\xi}{N_{\ddot{B}+1}} \tag{130}$$

$$\frac{\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b}{N_{\ddot{B}}} - \frac{\sum_{b=1}^{\ddot{B}+1} P_b(z_{t-1+N_b}) \cdot n_b}{N_{\ddot{B}+1}} \geq \frac{\xi}{N_{\ddot{B}}} - \frac{\xi}{N_{\ddot{B}+1}} \tag{131}$$

$$\frac{\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b}{N_{\ddot{B}}} - \frac{\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b + P_{\ddot{B}+1}(z_{t-1+N_{\ddot{B}+1}}) \cdot n_{\ddot{B}+1}}{N_{\ddot{B}} + n_{\ddot{B}+1}} \geq \frac{\xi}{N_{\ddot{B}}} - \frac{\xi}{N_{\ddot{B}} + n_{\ddot{B}+1}} \tag{132}$$

$$\begin{aligned} &\left(N_{\ddot{B}} + n_{\ddot{B}+1}\right) \cdot \sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b - N_{\ddot{B}} \cdot \left(\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b + P_{\ddot{B}+1}(z_{t-1+N_{\ddot{B}+1}}) \cdot n_{\ddot{B}+1} \right) \\ &\qquad \geq \left(N_{\ddot{B}} + n_{\ddot{B}+1}\right) \cdot \xi - N_{\ddot{B}} \cdot \xi \end{aligned} \tag{133}$$

$$n_{\ddot{B}+1} \cdot \sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b - N_{\ddot{B}} \cdot P_{\ddot{B}+1}(z_{t-1+N_{\ddot{B}+1}}) \cdot n_{\ddot{B}+1} \geq n_{\ddot{B}+1} \cdot \xi \tag{134}$$

$$\sum_{b=1}^{\ddot{B}} P_b(z_{t-1+N_b}) \cdot n_b - P_{\ddot{B}+1}(z_{t-1+N_b}) \cdot N_{\ddot{B}} \geq \xi \quad \square \tag{135}$$

Proof of Lemma 6 We use the definition of the value function (Equation (5)) for this proof. Lemma 7 shows that each USP batch is eventually harvested. Hence, to prove the statement, it suffices to compare the *Harvest* and *Exchange* actions. When the action *Exchange* is optimal in state s_t, the following holds for the value function $\mathcal{V}(s_t)$:

$$\mathcal{V}(s_t, a_t = H) \leq \mathcal{V}(s_t, a_t = E) \tag{136}$$

$$\pi \cdot \mathbb{E}(\mathcal{P}(s_t)) - \zeta - \eta \cdot c_t + \mathcal{C}^H(s_t) \leq \pi \cdot \mathbb{E}(\mathcal{P}(s_t)) - \zeta - \eta \cdot c_t - \xi + \mathcal{C}^E(s_t) \tag{137}$$

The product price π, expected product quantity $\mathbb{E}(\mathcal{P}(s_t))$, batch setup and fixed harvesting cost ζ, and variable purification cost $\eta \cdot c_t$ are the same for the *Harvest* and *Exchange* actions leading to Equation (138). Substituting $\mathcal{C}^H(s_t)$ and $\mathcal{C}^E(s_t)$ from Equations (7) and (8), we get Equation (139).

$$\mathcal{C}^H(s_t) \leq -\xi + \mathcal{C}^E(s_t) \tag{138}$$

$$\delta \cdot \int_{-\infty}^{\infty} g(\gamma | z_{t-1}) \cdot \mathcal{V}(0, z_{t-1} - \gamma)\ d\gamma \leq -\xi + \delta \cdot \mathcal{V}(0,1) \tag{139}$$

As $\delta \cdot \mathcal{V}(0,1)$ is a fixed term, the right-hand side of Equation (139) decreases in the resin exchange cost ξ. With ξ increasing Equation (139) only holds for smaller z_{t-1} due to Lemma 2. Consequently, the threshold $\widetilde{z}_{Int}$ for choosing the *Exchange* action decreases as ξ increases. Using the same arguments, one can prove the monotonicity of the resin exchange threshold in the resin cost ξ for the separate model $\widetilde{z}_{Sep}$. □

Proof of Proposition 1 The separate model comprises two separate MDPs: One for the upstream stage (USP) and one for the downstream stage (DSP). The state space of the integrated model is $S_{Int}(x,z) = S^{USP}_{Sep}(x) \times S^{DSP}_{Sep}(z)$. For each $s_t = (x_t, z_{t-1})$, the optimal policy for the separate upstream model Π^*_{USP} selects one action $a_t(x_t)$ independently of the actual value of z_{t-1}. The optimal policy for the separate downstream model Π^*_{DSP} selects one action $a_t(z_{t-1})$ independently of the actual value of x_t. In contrast, the optimal policy for the integrated model Π^*_{Int} selects an action $a_t(x_t, z_{t-1})$ based on both state dimensions.

By definition, the value functions satisfy the Bellman optimality equations for their respective MDPs. The optimal value function in the integrated model is the maximum value under any policy:

$$V^*(x_t, z_{t-1}) = \max_{\Pi} V^{\Pi}(x_t, z_{t-1}) \tag{140}$$

The separate upstream MDP assumes a fixed value for z_{t-1}, which also exists in the integrated state space. Similarly, the separate downstream MDP assumes a fixed value for x_t, which also exists in the integrated state space. Therefore, the combined optimal policy for the separate model $\pi^*_{Sep} = (\Pi^*_{USP}, \Pi^*_{DSP})$ is a valid policy in the integrated model. With Equation (140) it follows that $V(x_t, z_{t-1} | \Pi^*_{Int}) \geq V(x_t, z_{t-1} | \Pi^*_{Sep})$. □

Proof of Theorem 6 Based on the compact form of Equation (129) in which we represent the upstream batch profitability for batch b with $P_b(z_{t-1+N_b})$ we define the difference in the expected profit generated with the integrated model compared to the separate model in Equation (141).

$$P^R_{Int} - P^R_{Sep} = \frac{\sum_{b=1}^{\ddot{B}^{Int}} P^{Int}_b(z_{t-1+N_b}) \cdot n^{Int}_b}{N_{\ddot{B}^{Int}}} - \frac{\xi}{N_{\ddot{B}^{Int}}} - \left(\frac{\sum_{b=1}^{\ddot{B}^{Sep}} P^{Sep}_b(z_{t-1+N_b}) \cdot n^{Sep}_b}{N_{\ddot{B}^{Sep}}} - \frac{\xi}{N_{\ddot{B}^{Sep}}} \right) \tag{141}$$

As $\pi \to \infty$, the upstream batch profitability, which depends on π, $P_b(z_{t-1+N_b}) \to \infty$. With Equation (141) follows $P^R_{Int} - P^R_{Sep} \overset{\pi \to \infty}{=} 0$. □

Appendix C: Parameters for numerical study

This appendix presents the parameters used for the *insulin* case presented in the paper and the *monoclonal antibody (mAb)* and *lysine* cases discussed in Appendix D. The parameters are based on Petrides et al. (2014), (Petrides et al. 1995), and (Carmichael and Petrides 2020), and summarized in Table 2.

We model the product formation rate $\alpha(x_t)$ as a continuous random variable following a bivariate normal probability distribution $\mathcal{N}_\alpha(\mu_\alpha, \sigma^2_\alpha | x_t)$. The mean μ_α and variance σ^2_α are defined in Equations (142)-(144) with the covariance

Table 2 Parameter definition for numerical study, based on Carmichael and Petrides (2020), Feidl et al. (2020), Goudar (2012), Petrides et al. (1995), and Petrides et al. (2014).

Parameter		Insulin	mAb	Lysine	Unit	Explanation
Modeling parameter	δ	0.999996	0.9999	0.999996		Discount factor
	τ	1	24	1	hour	Period length
	$\overline{X}$	8.0	2.5	100.0	$\frac{g}{L}$	Maximum product concentration
	Δx_t	40.0	10.0	400.0	$\frac{mg}{L}$	Product concentration discretization
	Δz_t	0.5	0.2	0.1	%-pts	Purification capacity discretization
USP bio-process parameter	b_1	6.60	2.15	80.0	$\frac{g}{L}$	Maximum product concentration
	b_2	95	185	90		Parameter in logistic product function
	b_3		0.6		$days^{-1}$	Rate constant for product formation
	b_3	0.40		0.17	$hour^{-1}$	Rate constant for product formation
	$c_v^{x_t}$	5.0	5.0	5.0	%	Product formation coefficient of variation
	ϕ	27	2	36	periods	Shelf life of harvested batch
	$\overline{\tau}_{USP}$	36	15	36	periods	Regulatory batch time limit
	χ	37.5	15	377	$L \cdot 10^3$	Bioreactor working volume
DSP bio-process parameter	o	4.5	0.17	12.0	periods	Purification cycle length
	$\overline{\tau}_{DSP}$	27.0	0.67	36.0	periods	Purification time window (day shifts)
	θ	40.0	27.5	110.0	$\frac{g}{L \cdot cycle}$	Maximum resin binding capacity
	$\overline{\gamma}$	1.5	2.0	0.2	%-pts	Mean decay per clean cycle
	κ	1.0	1.5	1.0		Weibull shape of mean decay rate
	λ	1.0	0.916	1.0		Weibull scale of mean decay rate
	c_v^{γ}	10.0	10.0	10.0	%	Decay rate coefficient of variation
	ψ	1.8	0.5	153.0	$L \cdot 10^3$	Purification working volume
Industry policy	$\widetilde{h}_{Ind}$	18	13	42	periods	Harvest threshold
	$\widetilde{e}_{Ind}$	30	25	100	batches	Resin exchange threshold
	ι	0.8	0.8	0.8		'Safety margin', or assumed fractional purification capacity
Cost parameter	ν	0.25	20	0.5	$\frac{\$ \cdot 10^3}{period}$	Fermentation cost
	ζ	350	340	75	$\frac{\$ \cdot 10^3}{batch}$	Batch harvesting & setup cost
	η	4.0	1.5	0.015	$\frac{\$ \cdot 10^3}{cycle}$	Purification cycle cost
	ξ	2.7	3.0	0.5	$\frac{\$ \cdot 10^6}{exchange}$	Resin exchange cost
	π	2.5	100	0.004	$\frac{\$}{g}$	Product sales price

$\sigma_{x_t x_{t+1}}$ or correlation coefficient $\rho_{x_t x_{t+1}}$ of the product concentration in period t and $t+1$. The variance $\sigma^2_{x_t}$ represents the measurement error when determining the product concentration, while $\sigma^2_{x_{t+1}}$ is the variance of the product concentration x_{t+1} observed in time period $t+1$.

$$\mu_\alpha = \mu_{x_{t+1}} - \mu_{x_t} \tag{142}$$

$$\sigma^2_\alpha = \sigma^2_{x_t} + \sigma^2_{x_{t+1}} - 2 \cdot \sigma_{x_t x_{t+1}} \tag{143}$$

$$\sigma^2_\alpha = \sigma^2_{x_t} + \sigma^2_{x_{t+1}} - 2 \cdot \rho_{x_t x_{t+1}} \cdot \sigma_{x_t} \cdot \sigma_{x_{t+1}} \tag{144}$$

Logistic functions have been used extensively to predict microbial and mammalian cell growth and product formation (Yatipanthalawa and Gras 2024). We use the following modified logistic function to predict product formation in cell cultures (Goudar 2012):

$$x_t = \frac{b_1}{1 + b_2 \cdot e^{-b_3 \cdot t}} \tag{145}$$

With Equations (142) and (145) we can calculate the mean value μ_α for the joint bivariate normal probability distribution describing the product formation rate $\mathcal{N}_\alpha\left(\mu_\alpha, \sigma^2_\alpha \middle| x_t\right)$. We assume that the product concentration x_t can be determined with a negligible measurement error, so that $\sigma^2_{x_t} = 0$. This assumption reduces the variance of the bivariate normal distribution to $\sigma^2_\alpha = \sigma^2_{x_{t+1}}$ (Equation (144)).

We model the decay of the purification resin per purified batch $\gamma(z_t)$ as a continuous random variable following a normal distribution is $\mathcal{N}_\gamma\left(\mu_\gamma, \sigma_\gamma^2 \middle| z_t\right)$. The mean μ_γ follows a 2-parameter Weibull failure rate function, with shape κ and scale λ (Equation (146)). $\overline{\gamma}$ represents the mean decay rate per cleaning cycle over the whole range of z_t.

$$\mu_\gamma(z_t) = \frac{\kappa}{\lambda} \cdot \left(\frac{1 - z_t}{\lambda}\right)^{\kappa - 1} \cdot \overline{\gamma} \tag{146}$$

The reason for choosing a Weibull distribution is its widespread use in reliability and lifetime engineering, as well as its flexibility in modeling a wide range of decay dynamics for different purification resins and cleaning procedures (Sun et al. 2024). Due to missing information on the decay dynamics of the resins used in the insulin and lysine cases, we model a linear decay with mean decay rates derived from Petrides et al. (1995), Petrides et al. (2014), and Carmichael and Petrides (2020). For the resin used to purify the mAb, the Weibull failure rate function parameters are fitted to the experimental data of the purification capacity decay published in Feidl et al. (2020).

Insulin is produced using a bacterial cell (*E. coli*) culture in fed-batch mode with a maximum expected product concentration $b_1 = 6.60\,\frac{g}{L}$ (Petrides et al. 1995, 2014). We choose a period length $\tau = 1\,hour$ for the bacterial cell culture. The discount factor $\delta = 0.999996$ results in an annual depreciation of 3.4%. The fermentation cost per period, ν, includes utilities (e.g., aeration, agitation, and temperature control), consumables such as culture media and feed streams, and variable operating labor associated with monitoring and running the fermentation process. Fixed batch harvesting and setup costs include cleaning and sterilization procedures, preparation of the initial culture media and inoculation materials, as well as other batch-level setup activities required prior to fermentation. In addition, these costs capture fixed downstream processing expenses that occur per batch but are not directly driven by resin usage, such as labor costs, preparatory and auxiliary purification steps. Variable purification cycle cost includes consumables (e.g., buffer solutions) and utilities. Because we are dealing with an operational problem setting, we treat equipment investment costs as sunk. Resin exchange cost is calculated by multiplying the resin cost in $\$/L$ with the size of the purification column. As an off-patent biopharmaceutical, insulin is subject to substantial price variation across markets, while actual transaction prices are often not publicly observable due to confidential rebates and contracting practices. To account for this lack of price transparency, we calibrate the base-case price using a target profit margin. Specifically, we solve the model for $\pi \in [2, 50]\,\frac{\$}{g}$ and select a base-case price of $2.5\,\$/g$ such that the stationary industry policy, derived from Petrides et al. (1995, 2014), yields an approx. 20%-profit margin.

The mAb is produced using mammalian cell culture in fed-batch mode with a maximum expected product concentration $b_1 = 2.15\,\frac{g}{L}$ (Petrides et al. 2014). The product is still patent-protected and sold at an average wholesale price of $1{,}000\,\frac{\$}{g}$. Assuming that the cost of goods (COG) accounts for 10% of revenue, this leads to an internal transfer price of $\pi = 100\,\frac{\$}{g}$ for the bulk product (Farid et al. 2020). A period length $\tau = 24\,hours$ is a common interval to determine the product concentration in mammalian cell cultures. The discount factor per period $\delta = 0.9999$ results in an annual depreciation of 3.6%. The parameters of the Weibull failure rate function, i.e., Weibull shape $\kappa = 1.5$, Weibull scale $\lambda = 0.916$, mean decay per cleaning cycle $\overline{\gamma} = 2.0\%$, and the coefficient of variation $c_v^\gamma = 10.0\%$ are derived from experimental data published in Feidl et al. (2020). Respecting the fermentation time window in the regulatory approval documents, we enforce an upper bound of 15 days for the batch fermentation time in the policy by capping the results of the MDP. The industry policy for the mAb is derived from Petrides et al. (2014): The batch is harvested after $\widetilde{h}_{Ind} = 13\,$days, which aligns with the cyclical operating procedure of setting up a new batch every two weeks. The purification resin is replaced after 60 purification cycles as described in Petrides et al. (2014). With four purification cycles per batch, this translates into $\widetilde{e}_{Ind} = 15$ cleaning cycles. The purification capacity of a new resin is $\theta = 27.5\,\frac{g}{L\cdot cycle}$. Assuming a safety margin $\iota = 80\%$, the capacity assumed by the industry policy is $22.0\,\frac{g}{L\cdot cycle}$ (Jagschies et al. 2018, Chapter 16).

Lysine is produced using a bacterial cell (*C. glutanicum*) culture in batch mode with a maximum expected product concentration $b_1 = 80.0\,\frac{g}{L}$ (Carmichael and Petrides 2020). Less severe cleaning procedures in animal feed manufacturing lead to longer resin lifetimes, explaining the low step decay. For the lysine cases, we are not comparing our modeling approach to an industry policy, but the same parameters could be derived from Carmichael and Petrides (2020).

Appendix D: Additional numerical results

D.1. Numerical results for the innovative drug (mAb) case

Results are summarized in Table 3. The separate and integrated policies achieve 3.98% and 3.90% higher profits than the industry policy, respectively. Both policies increase product output while reducing costs by significantly fewer resin exchanges. The industry policy exchanges the resin at a remaining purification capacity of 80.63%, while the integrated policy utilizes the resin until 53.30%. The integrated policy achieves a small but statistically significant increase in performance, with higher profits and lower costs than under the separate policy. The integrated policy maximizing profitability achieves 9.99% higher profits by setting up 18.46% more batches, with 9.83% higher productivity, than the batch-yield-maximizing policy. This quantifies the shortcomings of approaches that maximize the batch yield, neglecting the productivity contribution of the next batch set up after harvest.

Table 3 Results of the simulation, evaluating the integrated (1), separate (2), batch-yield maximizing (4), and industry policy (5) for the innovative drug (mAb) case.

Policy	Compared to (4) Industry			Resin ex-	Capacity at
	Profit [%]	Cost [%]	Product [%]	changes [$year^{-1}$]	exchange [%]
(1) Integrated	+3.98%	-3.36%	+2.22%	0.65 ± 0.0	53.30 ± 0.20
(2) Separate	+3.90%	-3.29%	+2.18%	0.65 ± 0.01	61.00 ± 0.17
(4) Batch-yield	-5.46%	-11.61%	-6.93%	0.60 ± 0.0	59.21 ± 0.23
(5) Industry				1.00 ± 0.00	80.63 ± 0.16

Note: Each number represents the average and standard deviation of 200 simulation replications with the same random seed for each policy. Profit and cost differences are statistically significant with $p \leq 0.001$.

D.2. Numerical results for the feed supplement (lysine) case

Results are summarized in Table 4. The separate and integrated policies achieve 83.4% and 81.9% higher profits than the industry policy, respectively. Both policies achieve slightly lower product output while reducing costs by significantly fewer resin exchanges. The industry policy exchanges the resin at a remaining purification capacity of 80.0%, while the integrated policy utilizes the resin until 59.1%. The integrated policy achieves a small but statistically significant increase of +0.83% in performance - a substantial improvement considering the low-profit margins in the animal feed sector of only a few percent.

Table 4 Results of the simulation, evaluating the integrated (1), separate (2), and industry policy (5) for the feed supplement (lysine) case.

Policy	Compared to (5) Industry			Resin ex-	Capacity at
	Profit [%]	Cost [%]	Product [%]	changes [$year^{-1}$]	exchange [%]
(1) Integrated	+83.4%	-11.9%	-3.1%	0.9	59.1
(2) Separate	+81.9%	-12.0%	-3.3%	0.9	60.0
(5) Industry				2.0	80.0

Note: Each number represents the average and standard deviation of 200 simulation replications with the same random seed for each policy. Profit and cost differences are statistically significant with $p \leq 0.001$.