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Integrating process and demand uncertainty in capacity planning for next-generation pharmaceutical supply chains

Miriam Sarkis[a,b], Nilay Shah[a,b], and Maria M. Papathanasiou[a,b*]

[a] The Sargent Centre for Process Systems Engineering, Imperial College London, London, United Kingdom
[b] Department of Chemical Engineering, Imperial College London, London, United Kingdom
* Corresponding Author: maria.papathanasiou11@imperial.ac.uk

ABSTRACT

Emerging sectors within the biopharmaceutical industry are undergoing rapid scale-up due to the market boom of gene therapies and vaccine platform technologies. Manufacturers are pressured to orchestrate resources and plan investments under future demand uncertainty and, critically, an early-stage process uncertainty for platforms still under development. In this work, a multi-product multi-stage stochastic optimization problem integrating demand uncertainty is presented and augmented with a worst-case optimization approach with respect to process uncertainty. Results focus on a comparison between fixed equipment facilities and modular technologies, highlighting an inherent flexibility of the latter option due to shorter recourse actions for capacity scale-out. The impact of process uncertainty integration is quantified. With more conservative decisions taken in first-stages of the time horizon, expected costs result lower for modular single-use equipment. This suggests that capacity adjustments also help adapt to varying process performance and reduce the propagation conservative design decisions.

Keywords: Supply Chain, Planning & Scheduling, Stochastic Optimization, Technoeconomic Analysis, Advanced Pharmaceutical Manufacturing

INTRODUCTION

Pharmaceutical capacity planning is crucial to meet product demands from clinical to commercial stages. In recent years, the market boom of gene therapies and demand for vaccines in pandemic contexts has highlighted a need to improve responsiveness of supply chains to demand fluctuations and unforeseen events. To this end, the industry has seen an uptake of single-use equipment (SU) to substitute more inflexible stainless-steel multi-use (MU) facilities, allowing for rapid scale-up and scale-out of manufacturing capacity. In this space, investment planning is challenged by a need to make scale-up decisions before processes are fully intensified and process capabilities known for certain[1]. Furthermore, process uncertainty in early stages of planning is combined with an uncertainty in future demands. In this context, an over-estimation of attainable production targets and sub-optimal demand forecasting can result in shortages and exacerbate costs[2].

The complexity of investment planning problem under demand uncertainty can be represented as a stochastic optimization embedding a multi-stage scenario tree for demand outcomes. The PSE literature presents a number of decision support tools based on stochastic programming finding a direct application in capacity planning in pharmaceutical contexts. First stage variables include initial capacity investments, product selection and initial allocation of manufacturing resources to products. Second stage recourse decisions consist in additional capacity investment or sale of capacity, re-allocation of products to resources. Extensive research in PSE has focused problems of capacity planning using stochastic programming[3,4]. Alternatively, simulation-based approaches[5,6] and rolling horizon strategies[7,8] have been proposed to decision-making based on simulated demand outcomes.

This work focuses on investigating whether early-stage process uncertainty which characterizes advanced biopharmaceutical products undergoing rapid scale up is worth integrating in capacity planning optimization problems. The proposed approach accounts for the different time scales of uncertainty and differentiates the flexibility of MU-based and SU-based equipment, which thus far has not been considered explicitly in the context of biopharmaceutical planning under uncertainty. The presented planning tool integrates process uncertainty using a worst-case approach, using previously quantified process uncertainty[9] and cost-related inputs obtained via techno-economic models, and demand uncertainty using stochastic programming and uses. Comparative analyses for SU and MU cases discuss the impact of process uncertainty integration compared to a deterministic-process counterpart and focus on network responsiveness to demand uncertainty.

METHODOLOGY

Problem statement

The capacity planning problem considered in this study is aimed at minimizing total supply chain capital and operating cost and determine a set of demand scenario independent design decisions and scenario-dependent decisions. These differ based on whether equipment is multi-use (MU) or single-use (SU).

The optimization considers:

- A set T of time periods t;
- A set I of products i;
- A set N of nodes n;
- A set T of time periods t;
- A set A of process scales a;
- A set S of process section s;
- A set L of process lines l;
- A set DS of demand scenarios y;

In the MU case, the partition of first-stage and second-stage scenario-dependent decisions results as follows:

1. Network structure and links between nodes;
2. Investment in manufacturing facilities;
3. Scales of manufacturing and number or parallel lines;
4. *Scenario-dependent* manufacturing levels,
5. *Scenario-dependent* transportation flows;
6. *Scenario-dependent* supply flows at each demand node.

In the SU case, the optimization considers the selection of scales and parallel lines as *scenario-dependent*, hence treating it as a recourse action or second-stage decision.

The optimization requires information on costs of technologies at different manufacturing scales a, for different process sections s for the different products considered i and specific to MU-based equipment vs SU-based equipment. This is obtained via techno-economic modelling of the processes of interest. Furthermore, it requires input data with respect to storage and transport cost per unit (Sarkis et al.[10] – SI) and target demands for each product i, realizing over time and differing by scenario y.

Whilst demand realizes in stages, process uncertainty is mainly present in early stages of scale-up. Before process capabilities are known, decision-makers may consider adopting a *risk-averse* approach. Once process uncertainty realizes, true capabilities are known and optimization decisions can adapt accordingly. This concept is integrated through a two-stage worst-case optimization approach. Ultimately, by combining expected demand outcomes and this process uncertainty mitigation strategy, decision-makers can obtain *here-and-now* investment plans which minimize expected costs and mitigate early-stage shortage risks. Depending on underlying equipment-related recourse actions, the resulting planning solutions may differ.

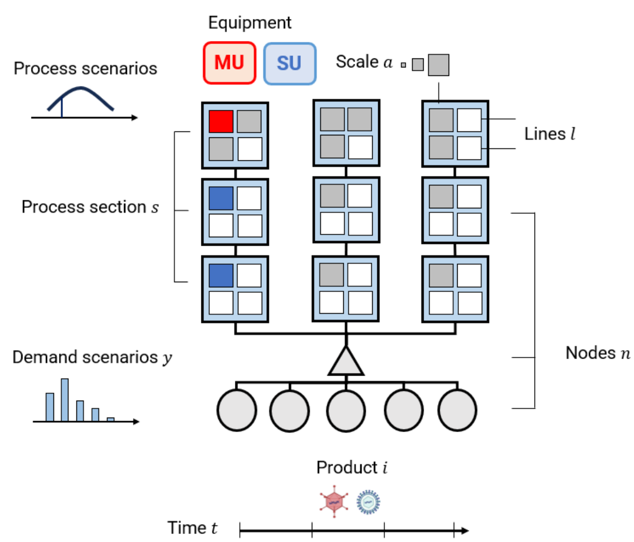

Figure 1. Optimization superstructure for multi-product supply chain case study.

Techno-economic performance quantification

Techno-economic models of the manufacturing technologies of interest are developed using SuperPro Designer (Intelligen). In this work, the focus is the quantification of techno-economic performance of MU-based and SU-based manufacturing at scale $a \in A = \{50,200,1000,2000\}$ and for products $i \in I = \{LV, AdV\}$.

Details regarding the development of underlying models is included in Sarkis et al.[9] (SI). Here, equipment has been modified to fully SU or MU accordingly. Techno-economic KPIs for each platform include batch size χ, cycle time τ, end-to-end process time α, and capital and operating costs c. Costs are assumed to be deterministic and dependent on equipment type, product i and scale a. Instead, throughput related uncertainty as quantified in Sarkis et al.[9] is considered, yielding ranges of performance for batch size $\chi \in [\chi^{min}, \chi^{max}]$, cycle time $\tau \in [\tau^{min}, \tau^{max}]$ and process time $\alpha \in [\alpha^{min}, \alpha^{max}]$ for each product- and scale-specific process.

Optimization formulation

The optimization considers a multi-period multi-product planning problem where $T = \{T_1, T_2, T_3, T_4\}$ and $I = \{LV, AdV\}$, where LV is a lentivirus-based product for gene therapy applications and AdV is an adenovirus-based product for vaccine applications. As mentioned, throughput related parameters are considered uncertain, whereas cost-related parameters are held at the deterministic value quantified via techno-economic modelling. On the demand side, a set of demand scenarios y is considered $DS = \{DS_1, DS_2 \ldots DS_N\}$, which result from combinations of individual product demands in a multi-stage stochastic scenario tree. The optimization formulation is summarized in Table 1.

As shown in Eq.1, the objective function z corresponds to the total expected supply chain cost, which a summation of capital and operating costs of manufacturing, storage costs and transport costs. These are scenario-dependent quantities and normalized by scenario probability Π_y. Manufacturing capital costs TC^{CAPj} embed equipment installation costs C^{EQj} for each node $n \in N^J$ and time t (Eq. 2.), which are a function of equipment installation cost coefficients c^{EQjl} and equipment installation binaries H, with respect to time t, node $n \in N^J$, scale a, line l, section s and scenario y (Eq. 3).

Manufacturing operating costs TC^{OPj} include labour related costs C^{LABj}, variable costs C^{VARj} and facility-dependent costs C^{FACj} (Eq. 4), which are respectively function of cost coefficients c^{LABj}, c^{VARj}, c^{FACj} for each scale a, section s and product i multiplied by either the number of batches B (Eq. 5-6), and product-specific equipment installation M (Eq. 7). Hence, the benefit of economies of scale on cost effectiveness is captured within the optimization, with a balance between costs that scale with production levels and fixed costs. Storage related costs TC^{OPk} are computed as multiplication of a handling coefficient c^{OPk}, which depends on scale a and product i and the sum of transport flows Q passing through all storage nodes at time t and in scenario y (Eq. 8). Transport costs TC^{T} consider a cost coefficient per km travelled and batch delivered c^{T} multiplied by distance ρ between nodes n and m and transport flows Q.

Table 1: Optimization formulation for multi-product, multi-stage, multi-period stochastic problem.

Objective function and cost components	
1	$\min z = \sum_{y \in DS} \Pi_y \left(TC_y^{CAPj} + TC_y^{OPj} + TC_y^{OPk} + TC_y^{T} \right)$
2	$TC_y^{CAPj} = \sum_{t \in T} \sum_{n \in N^J} C_{tny}^{EQj} \quad \forall y$
3	$C_{tny}^{EQj} = \sum_{a \in A} \sum_{s \in S} \sum_{l \in L} c_{as}^{EQjl} H_{tnalsy} \quad \forall t, n \in N^J, y$
4	$TC_y^{OPj} = \sum_{t \in T} \sum_{n \in N^J} C_{tny}^{LABj} + C_{tny}^{VARj} + C_{tny}^{FACj} \quad \forall y$
5	$C_{tny}^{LABj} = \sum_{a \in A} \sum_{s \in S} \sum_{l \in L} \sum_{i \in I} c_{asi}^{LABj} B_{tnalsiy} \; \forall t, n \in N^J, y$
6	$C_{tny}^{VARj} = \sum_{a \in A} \sum_{s \in S} \sum_{l \in L} \sum_{i \in I} c_{asi}^{VARj} B_{tnalsiy} \; \forall t, n \in N^J, y$
7	$C_{tny}^{FACj} = \sum_{a \in A} \sum_{s \in S} \sum_{l \in L} \sum_{i \in I} c_{asi}^{FACj} M_{tnalsiy} \; \forall t, n \in N^J, y$
8	$TC_y^{OPk} = \sum_{t \in T} \sum_{n \in N^K} \sum_{m \in N^J} \sum_{a \in A} \sum_{i \in I} c_{ai}^{OPk} Q_{tnmaiy} \quad \forall y$
9	$TC_y^{T} = c^{T} \sum_{t \in T} \sum_{n \in N^M} \sum_{m \in M^N} \sum_{a \in A} \sum_{i \in I} \rho_{nm} Q_{tnmaiy} \quad \forall y$
Sourcing constraints	
10	$X_{tnm} \le Y_{tn} \; \forall t, n \in N^J, m \in M^N$
11	$\sum_{n \in N^J} X_{tnm} \ge Y_{tm} \; \forall t, m \in N^K$
12	$\sum_{n \in K} X_{tnm} \ge Y_{tm} \; \forall t, m \in N^Z$
Equipment and product allocation constraints	
13	$\sum_{a \in A} V_{tnay} \le Y_{tn} \quad \forall t, y, n \in N^J$
14	$Z_{tnasly} \le V_{tnay} \quad \forall t, n \in N^J, a, s, l, y$
15	$M_{tnasliy} \le Z_{tnasly} \quad \forall t, n \in N^J, a, s, l, i, y$
16	$W_{tnasliy} \le M_{tnasliy} \quad \forall t, n \in N^J, a, s, l, i, y$
17	$N_{tnasly} = \sum_{i \in I} W_{tnasliy} - 1 \; \forall t, n \in N^J, a, s, l, y$
18	$C_{tnasliy \vert i=LV} = N_{tnasly} \; \forall t, n \in N^J, a, s, l, y$
19	$C_{tnasliy \vert i=AdV} = N_{tnasly} - 1 \; \forall t, n \in N^J, a, s, l, y$
20	$Z_{tnasly} \le Z_{t-1,nasly} + H_{tnalsy} \; \forall t, n \in N^J, a, s, l, y$
20’	$Z_{tnasly} = Z_{t-1,nasly} + H_{tnalsy} \; \forall t, n \in N^J, a, s, l, y$
Production constraints	
21	$T^{MIN} W_{tnasliy} \le T_{tnasliy} \le T^{MAX} W_{tnasliy} \; \forall t, n \in N^J, a, s, l, i, y$
22	$U_{tnasly} = \sum_{i \in I} T_{tnasliy} \; \forall t, n \in N^J, a, s, l, y$
23	$U_{tnasly} \le U^{MAX} \; \forall t, n \in N^J, a, s, l, y$
24	$B_{tnasliy} = W_{tnasliy} + \tau_{st} \left(T_{tnasliy} - \alpha_{st} W_{tnasliy} - \kappa C_{tnasliy} \right) \; \forall t, n \in N^J, a, s, l, i, y$
25	$\sum_{l \in L} B_{tnasliy} = \sum_{l \in L} B_{tna,s+1,liy} \; \forall t, n \in N^J, a, s, i, y$
Network balances	
26	$I_{tnaiy} = I_{t-1,naiy} + \sum_{l \in L} B_{tnasliy \vert s=F} + \sum_{m \in N^K} Q_{tnamiy} \quad \forall t, n \in N^J, a, i, y$
27	$\sum_{m \in N^J} Q_{tmnaiy} = \sum_{m \in N^Z} Q_{tnmaiy} \; \forall t, n \in N^K, a, i, y$
28	$\sum_{m \in K} Q_{tmnaiy} = S_{tnaiy} \; \forall t, n \in N^Z, a, i, y$
29	$\sum_{a \in A} S_{tnaiy} \chi_{ait} \ge D_{tniy} \; \forall t, n \in N^Z, i, y$
30	$D_{tniy} = \frac{D_{tiy}^{T}}{card(N^Z)} \quad \forall t, n \in N^Z, i, y$
31	$Q^{MIN} X_{tnm} \le \sum_{i \in I} Q_{tnmaiy} \le Q^{MAX} X_{tnm} \; \forall t, n \in N, m \in M, a, y$
Non-anticipativity constraints	
32	$x_{ty} = x'_{ty} \quad \forall y, y' \in \Delta^{t}$
MU case additional constraints	

33 $V_{tnay} = V_{tnay'}$, $\forall t, n \in N^J, a, y$

34 $Z_{tnasly} = Z_{tnasly'}$, $\forall t, n \in N^J, a, s, l, y$

35 $M_{tnasliy} = M_{tnasliy'}$, $\forall t, n \in N^J, a, s, l, i, y$

Sourcing constraints impose that a link X at time t between nodes n and m is established only if the upstream node exists through the activation of binary Y (Eq. 10). Furthermore, all downstream nodes m must be sourced by at least one link with an upstream node n (Eq. 11-12). The equipment allocation constraint in Eq. 13 constrains the activation of scale a in node $n \in N^J$ at time t and scenario y to nodes which are active ($Y = 1$) and allows the selection of at most one scale at a time, as the sum on the L.H.S. cannot exceed 1. A line l of scale a within process section s can be installed through the $Z = 1$, if the respective scale is active within the node n, at time t and in scenario y (Eq. 14). Similarly, product-specific equipment installation through M is allowed if the respective line Z is active (Eq. 15). Product allocation occurs when $W = 1$, within manufacturing lines where equipment suitable for manufacturing of product i is installed (Eq. 16). A change-over occurs ($N = 1$) when both products i are manufactured within the same equipment, whereby the R.H.S. of Eq. 17 takes the value of 1. Product-specific change-over ($C = 1$) within the same time period t is counted only once with respect to the LV product switching to AdV (Eq. 18), whilst the AdV to LV switch is always 0 (Eq. 19). An equipment manufacturing line can exist ($Z = 1$) at time period t if investment has occurred through $H = 1$ or if it existed in the previous time period (Eq. 20). Noting the inequality sign which allows equipment to be deinstalled in the SU case, this becomes an equality constraint for the MU case (Eq. 20').

Production constraints in Eq. 21 bound the time allocated to manufacturing T of product i, as well as the total utilisation time U per year (Eq. 22-23). The number of batches B is a function of time allocated to production

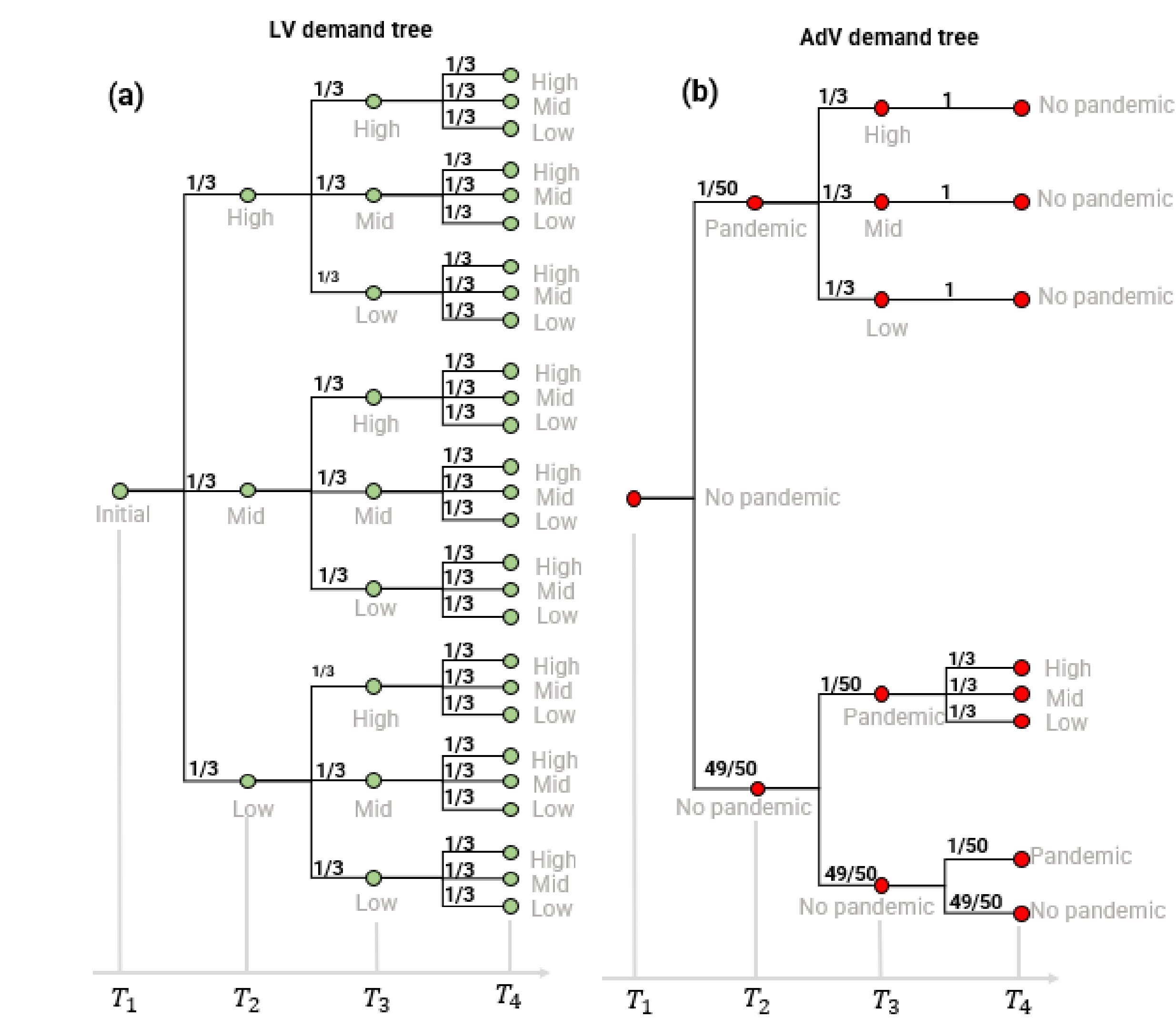

Figure 2: Demand scenarios for (a) LV and (b) AdV.

and process-specific throughput parameters, including the bottleneck time τ, the process time α and changeover time κ, accounting for the time required to process the first batch within the campaign and the subsequent ones in shorter intervals (Eq. 24). In Eq. 25 the number of batches processes within each section s is regulated by a material balance. Furthermore, network balances (Eq. 26-29) regulate the accumulation of inventory within the manufacturing nodes and the shipment of products so that the sales demand constraint is met (Eq. 29) for each product i, demand zone $n \in N^Z$ in each time period t and demand scenario y. The location-specific product demands D are a function of the total demand in each scenario D^T, which is an input within the optimization (Figure 2). Transport flows Q are also regulated by upper bounds and lower bounds (Eq. 31). Non-anticipativity constraints are included in the formulation to ensure that scenarios remain indistinguishable until realization (Eq. 32), enforcing that all scenario-dependent variables are equal across the set of indistinguishable scenario pairs Δ at each stage t .

Finally, the MU case requires additional constraints based on the assumption that the installation of additional capacity is not considered a recourse action, hence scenario-dependent. In Eq. 33-35, equipment installation binaries are forced to be equal across scenario and made *first-stage* decisions.

Demand scenarios

A total of 216 scenarios $y \in D^S$ each with a probability of Π_y is obtained by combining LV and AdV scenario trees. As can be seen in Figure 2a, LV scenarios consider that at a first stage demand corresponds to a nominal value (10,000 doses per year). As time progresses, demand may realize to be *high* (20,000 doses per year), *mid* (10,000 doses per year), *low* (5,000 doses per year), with equal probabilities 1/3 each year, capturing irregular demands for cancer therapies. Mariani et al.[11] estimate probability of a pandemic outbreak per year of 1/50, hence the AdV scenario tree (Figure 2b), captures *non-pandemic* and *pandemic* yearly outcomes. In the former case, the tree branches into pandemic/non-pandemic scenarios at T_2 . In the latter case, the demand for vaccines is *high* (400 million doses per year), *mid* (200 million doses per year), or *low* (100 million doses per year), due to market competition and/or issues with side-effects post commercialization. The pandemic is assumed to resolve within 2 years, hence demand is 0.

Process uncertainty integration

Early-stage process uncertainty is integrated within the problem via a two-stage worst-case optimization approach (WO). This is compared to a deterministic-process approach (DET), whereby process uncertainty is not integrated. In WO, risk-averse decision-making is assumed, in order to avoid early-stage shortages. Process uncertainty is present at $t \in T_1$, whilst a deterministic realization at a median value (Sarkis et al.[10]) is assumed in subsequent time period, as knowledge is acquired in later time periods. To this end, the throughput related uncertainty quantified in Sarkis et al. is assumed to be described by *box uncertainty* sets for each parameter. Therefore:

$$u = \begin{Bmatrix} \chi_{ait}^{MIN} \leq \chi_{ait} \leq \chi_{ait}^{MAX}, \forall a, i, t \in T_1 \\ \tau_{st}^{MIN} \leq \tau_{st} \leq \tau_{st}^{MAX}, \forall s, t \in T_1 \\ \alpha_{st}^{MIN} \leq \alpha_{st} \leq \alpha_{st}^{MAX}, \forall s, t \in T_1 \end{Bmatrix},$$

where χ^{MIN}, χ^{MAX} are bounds for process yield χ at scale a, for product i and the first time period, τ^{MIN}, τ^{MAX} are bounds for process time within section s, and $\alpha^{MIN}, \alpha^{MAX}$ are bounds for bottleneck time in section s. To formulate the worst-case deterministic optimization problem requires the following modifications for Eq. 24 and Eq. 29 within the first stage T_1, as follows:

Eq. 24': $B_{tnasliy} = W_{tnasliy} + \tau_{st}^{MAX}(T_{tnasliy} - \alpha_{st}^{MAX} W_{tnasliy} - \kappa C_{tnasiy}) \quad \forall t \in T_1, n \in N^J, a, s, l, i, y$

Eq. 29': $\sum_{a \in A} S_{tnaiy} \chi_{ait}^{MIN} \geq D_{tniy} \; \forall t \in T_1, n \in N^Z, i, y$

Computational statistics

The MU multi-stage formulation involves a smaller problem size compared to SU because it involves less scenario-dependent decisions (Table 2). The model is implemented in PYOMO, solved with GUROBI v11 via high-throughput computing (1 node, 48nCPUs, RAM:100GB). The optimality gap threshold is set to 10% to obtain a solution to compare within 48h. Strategies to address problem scalability are discussed as part of research outlook.

Table 2: Computational statistics of MU vs SU optimization: constraints, integer (binary) and continuous variables, optimality gap.

Case	CPU(s)	Cons.	Int. (Bin.)	Cont.	Gap(%)
MU	25,715	878,916	1,369,544 (1,120,280)	878,916	7.80
SU	36,513	2,258,780	1,379,864 (1,130,600)	878,916	4.19

RESULTS & DISCUSSION

Techno-economic analysis

Outputs of techno-economic analysis correspond to the optimization cost coefficients c, defined for each cost category *VAR*, *FAC* and *LAB*, process section s, scale a and product i. Figure 3 illustrates cost breakdowns for LV and AdV platforms implementing either SU or MU equipment, with a focus on the $a = 2000$.

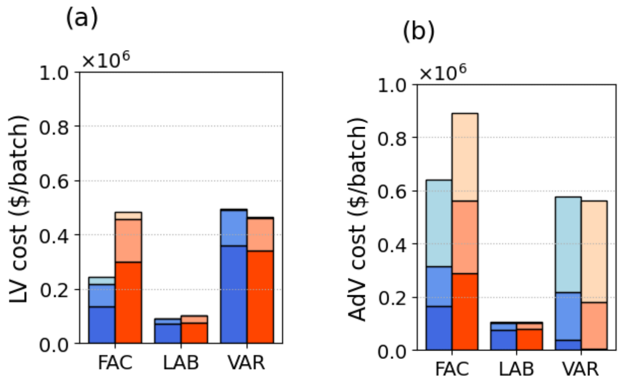

Figure 3: Cost breakdown for SU vs MU manufacturing platforms for LV manufacturing (a) and AdV manufacturing (b).

In Figure 3a, facility cost reductions up to 50% are achieved in the SU case for the production on LV in all parts of the process. This mostly holds for AdV too; however AdV facility costs of F&F are critical and are equivalent for both the MU and SU case, since only the formulation equipment is less costly through the use of disposable plastic bags alternatives (Figure 3b).

In comparison, labor-related costs are reduced by approximately 10% with respect to MU labor cost because of resulting shorter process times in the SU process. An underlying assumption of the techno-economic model is the linear relation between process times and total labor cost per batch which is obtained by multiplying process time by a predefined hourly rate. Due to shorter process times with removed steam-in-place/clean-in-place (SIP/CIP) steps, SU equipment results in lower labor costs per batch. Focusing on variable costs, the cost per batch in SU equipment is larger than the MU case (Figure 3a). This is due to a larger number of consumables being required in SU manufacturing compared to MU. This is also seen in AdV manufacturing (Figure 3b), where variable costs for USP, DSP and F&F result higher than the MU counterpart. Overall the percentage increase varies due to process differences, due to materials (LV) and process steps (AdV).

Figure 3 displays costs normalized *per batch*, showing that SU results in lower costs per batch compared to MU. Reductions in facility-dependent cost outweigh the marginal larger variable costs and this already suggests the selection of SU equipment for all process sections, if a cost optimization is performed.

Optimization problem solution

In this work, early-stage throughput uncertainty is integrated in a multi-stage stochastic planning problem on the demand side, via a two-stage worst-case optimization approach on the process side, considering a time-dependent single uncertainty realization. The impact of this risk-averse approach to decision-making is mainly seen in first-stage decisions and initial investments. In Figure 4a, the MU case optimization (WO) installs a 4-times larger volumetric capacity compared to the deterministic-process (DET) stochastic solution. This is also seen in the cumulative volume trends in Figure 4a. In later

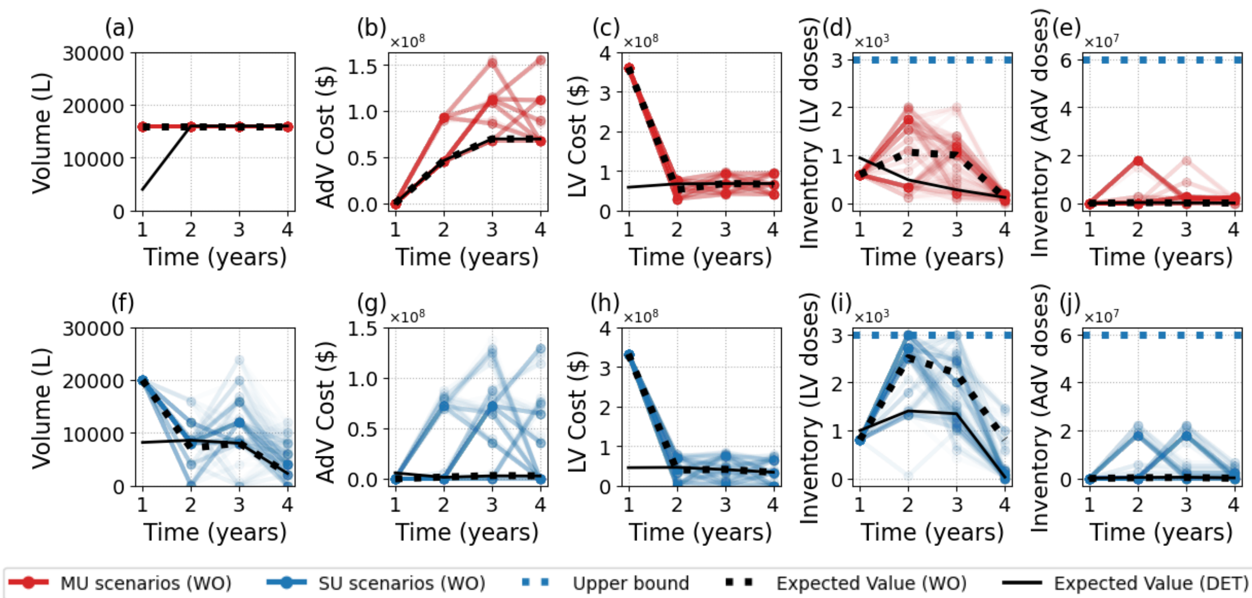

Figure 4: Stochastic optimization results for MU case (a-e) and SU case (f-j). Results integrating worst-case optimization w.r.t. to process uncertainty (WO) are displayed, alongside a deterministic (process side) benchmark (DET).

time periods, new investments are not required and capacity remains constant, fulfilling all demand scenarios and converging to the same investment plan proposed by the deterministic model. In the SU case, a significantly initial larger capacity is installed compared to the deterministic case (Figure 4e).

The initial overdesign of a WO approach propagates mainly to expected costs of LV productions, which result significantly higher initial costs compared to the DET stochastic solution (Figure 4c,h). Instead, AdV expected costs result similar in both the WO and DET approach (Figure 2b-g). In this case, risk-averse decision-making does not propagate to later stages of planning because of manufacturing of AdV starting only at $t > T_1$, whereby before $D_{AdV}^{T} = 0$ for all scenarios. Hence, process uncertainty impacts products manufactured within the time period of interest and its integration leads to 4-fold increases in cost for both MU and SU.

Furthermore, an impact is seen in terms of operational decisions, specifically with respect to LV inventory planning. In Figure 4d, the WO approach leads to a stochastic plan with smaller expected inventories in early stages, as these are expected to be more costly to manufacture due to the worst-case performance assumed. To make up for lower initial inventories, LV inventories are accumulated in later time periods in both the MU case and SU case (Figure 4e,i). Specifically, in the SU case, given the expected lower costs, the optimization makes use of the assets available to accumulate inventories early on, allowing a shaper reduction in production levels at $t = T_3$ and $t = T_4$.

Finally, when comparing the expected costs and performance of SU-based equipment and the MU-based counterpart, the short recourse actions and adaptability of SU-based networks allows for a reduction in expected costs, especially for AdV manufacturing (Figure 4b). This mainly relates to scenario-independent equipment installation decisions, forcing designs to cater for pandemic scenarios irrespective of their probability of occurrence. This assumption can be modified to manufacturer-specific set-up timelines; however, options with better flexibility, allowing on-demand manufacturing, will be likely be tied with the most cost reductions during operation, which become more significant that those related solely to nominal techno-economic performance.

CONCLUSIONS & OUTLOOK

As the pharmaceutical industry requires the establishment of increasingly flexible and responsive manufacturing networks, the development of advanced planning tools that integrate various sources of quantifiable uncertainties becomes critical. In this work, stochastic optimization-based tools are developed to assess the flexibility of fixed multi-use manufacturing equipment compared to single-use manufacturing and quantify expected cost benefits. The problem also considers the integration of early-stage process uncertainty through deterministic approaches and allows the assessment of the impact of risk-averse decision-making versus disregarding this uncertainty. Overall, modular single-use equipment promises improvements in pandemic preparedness and reductions in expected costs, including cases whereby process uncertainty is considered. Effectively, this paves the way to resilient networks which can better withstand unforeseen events.

As further research, the integration of a product-dependent trajectory of the worst-case approach would allow process uncertainty to be considered at the first-stage with respect to the first realization of the corresponding demand. Additionally, investigating the integration of a formal two-stage robust optimization approach could reduce the conservativeness of worst-case solutions, as feasible solutions are sought and optimization is not performed considering the worst-case scenario exclusively, but rather the entirety of the uncertainty set. Finally, scalability issues could be addressed through shorter planning horizons, clustering scenario-outcomes or using decomposition-based approaches. In the former case, a rolling horizon approach would be suitable, thereby solving at each time step a reduced stochastic problem considering demand uncertainty and integrating process uncertainty once a demand for a new product is realized.

REFERENCES

1. Capra E, Gennari A, Loche A, Temps C. Viral-vector therapies at scale: today's challenges and future opportunities.
2. Lambrix E, Kent-Egan H. Viral vectors: shortages and innovation. Biotech Review of the Year.
3. Gatica G, Papageorgiou LG, Shah N. Capacity planning under uncertainty for the pharmaceutical industry. *Chemical Engineering Research and Design*. 2003;81(A):665-678. doi:10.1205/026387603322150516
4. Colvin M, Maravelias CT. A stochastic programming approach for clinical trial planning in new drug development. *Comput Chem Eng*. 2008;32(11):2626-2642. doi:10.1016/j.compchemeng.2007.11.010
5. Marques CM, Moniz S, de Sousa JP, Barbosa-Póvoa AP. A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties: A case from the chemical-pharmaceutical industry. *Comput Chem Eng*. 2017;106:796-813. doi:10.1016/j.compchemeng.2017.04.008
6. Gökalp E, Branke J. Pharmaceutical R & D pipeline

management under trial duration uncertainty. *Comput Chem Eng*. 2020;136. doi:10.1016/j.compchemeng.2020.106782
7. Siganporia CC, Ghosh S, Daszkowski T, Papageorgiou LG, Farid SS. Capacity planning for batch and perfusion bioprocesses across multiple biopharmaceutical facilities. *Biotechnol Prog*. 2014;30(3):594-606. doi:10.1002/btpr.1860
8. Badejo O, Ierapetritou M. Enhancing pharmaceutical supply chain resilience: A multi-objective study with disruption management. *Comput Chem Eng*. 2024;188. doi:10.1016/j.compchemeng.2024.108769
9. Sarkis M, Shah N, Papathanasiou MM. Characterization of key manufacturing uncertainties in next generation therapeutics and vaccines across scales. *J Adv Manuf Process*. Published online April 26, 2023. doi:10.1002/amp2.10158
10. Sarkis M, Shah N, Papathanasiou MM. Resilient pharmaceutical supply chains: assessment of stochastic optimization strategies in network design problems. *Comput Chem Eng*. Published online 2025.
11. Marani M, Katul GG, Pan WK, Parolari AJ. Intensity and frequency of extreme novel epidemics. *PNAS Environmental sciences Biological sciences*. 2021;118(35):1-4. doi:10.1073/pnas.2105482118/-/DCSupplemental