Systems & Control Transactions

Research Article
Foundations of Computer Aided Process Design (FOCAPD 2024)
Breckenridge, Colorado, USA. July 14-18, 2024
Peer Reviewed Conference Proceeding

PSE PRESS

Towards 3-fold sustainability in biopharmaceutical process development and product distribution

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ABSTRACT

The (bio-)pharmaceutical industry is facing crossroads in an effort to ramp up its global capacity, while working to meet net-zero targets and to ensure continuous drug supply. Beyond geopolitical challenges faced worldwide, (bio-)pharmaceutical processes have been historically very complex to design, optimise and integrate in a global distribution network that is resilient and adaptable to changes. In this paper we offer a perspective of how Process Systems Engineering (PSE) tools can support and advance (bio-)pharma practices with an outlook towards 3-fold sustainability. The latter is considering three main pillars, namely social (drug supply), economical and environmental sustainability. We discuss PSE contributions that have revolutionised process design in this space, as well as the optimisation of distributions networks in pharmaceuticals. We do this by means of example cases: one on model-based unit operation design and a second one on sustainable supply chain networks in the space of advanced therapeutics. As such, this contribution offers a perspective on how PSE methodologies can offer a systematic way to integrate social, environmental, and economical sustainability throughout process design and product distribution.

Keywords: Process Design, Biosystems, Supply Chain, Machine Learning, Dynamic Modelling, Industry 4.0, Sustainability

INTRODUCTION

As the world moves towards truly sustainable development, the process industries are re-evaluating their operations and consider the wider environmental impacts of their products. While the biopharmaceutical and life sciences sector is at the forefront of the economy (UK turnover of £81B and USA turnover of US$285B) [1], its growth is linked to an increase in biohazardous waste, including disposable plasticware, media waste, and high volumes of purification buffers and resins. To establish profitable and resilient operations, (bio-) pharmaceutical manufacturers will need to revolutionise the current state-of-the-art. Radical changes are necessary to tackle challenges related to material-intensive research and development (R&D) and wasteful manufacturing operations. This goal has been embraced by (bio-) pharmaceutical companies, many of which have committed to ambitious net-zero targets that require a step-change to their current modus operandi [2–6].

(bio-) pharmaceutical challenges and future directions

Achieving resource-efficient R&D and manufacturing requires in-depth understanding of this industry that is governed by stringent regulatory constraints. Product quality and production rate are typically conflicting Key Performance Indicators (KPIs) with the former prioritized over the latter. The current, often purely experimental, approach to the identification of suitable operating conditions that satisfy quality KPIs is resource- and time-intensive and typically leads to suboptimal, inflexible processes. Within the biopharmaceutical sector, the adoption of platform processes means that upstream process operation follows fixed protocols that often overestimate nutrient requirements. The lack of end-to-end process design further exacerbates the above challenges. As the industry tends to work in silos, upstream and downstream

operations for the same manufacturing process are developed by different teams. Successes in increasing upstream product titres achieved over the past 3 decades have generally shifted the majority of operating costs downstream [7, 8]. Despite the Quality by Design initiative, development of quantitative process understanding often relies on statistical approaches, which are not generalizable and transferable across production processes. At the same time, the sparsity of available datasets or even unavailability of measurements, particularly in the case of cell-based biopharmaceuticals production, points to the need for mechanistic mathematical representations or hybrid approaches.

Against this background, the (bio-)pharmaceutical industry is currently transitioning to personalised therapeutics, which are manufactured for individuals or small cohorts of patients. An example of these are viral vectors for gene therapies [9]. Personalised therapeutics pose new challenges because they require on-demand manufacture and delivery to the clinic within constrained timeframes [10–12]. To meet patient needs, the industry needs to now consider drug product delivery to the patient within its operations envelope. In other words, manufacturing and supply chain design must be considered in tandem, with both economic and, primarily, patient-centric KPIs in mind.

The concept of 3-fold sustainability in (bio-) pharma and the role of Process Systems Engineering (PSE)

The positive health impact of Life Sciences on the society has been, so far, outweighing the environmental footprint of the sector. This has been leading decisions around process and product development, ensuring that therapeutics meet the purity constraints and manufacturers demonstrate control over their process operation. Nonetheless, and despite scientific advances in this space, regulators report drug shortages due to batch failures as one of the most pressing challenges. At the same time, COVID-19 demonstrated that the resilience of the global (bio-)pharma network is susceptible to unforeseen events, raw material shortages, as well as rapid increase in the demand for advanced therapeutics. This is now jeopardising the overarching goal of the industry to always meet drug demand.

Drawing all objectives into the picture, one could summarise those as: (a) meeting the demand (social objective), (b) being economically efficient (economic objective) and (c) reducing the environmental footprint (environmental objective). The identification of the sweet spot that meets these three objectives requires holistic approaches that orchestrate R&D, manufacturing, and distribution decisions. In this new context, knowledge-transfer and wet-lab experimentation are no longer sufficient to advance the sector alone. The systematic use of computational approaches to guide R&D and end-to-end process design all the way to the clinic has the potential to yield a step increase in efficiency addressing both economic and environmental sustainability targets. Specifically, the use of generalizable, first-principles mathematical models of cell metabolism [13], cell culture operation [14] and chromatographic separation [15] can complement experimental investigations to accelerate process development for the purpose of flexibility analysis, and [16] process optimisation [17]. Similarly, model-based tools that can integrate manufacturing uncertainties in the supply chain network can revolutionise the decision-making process when it comes to investment and capacity planning across the product lifecycle.

PSE in (bio-)pharmaceutical process design and product distribution

The PSE community has a long-standing track record in developing cutting-edge methods and tools that can advance the way process and distribution networks are designed, optimised and operated. Specifically, in (bio-)pharmaceuticals, there have been contributions that investigate and propose methodologies for unit operation design, as well as end-to-end process flowsheet and optimisation, the fundamentals for many of which lie in seminal contributions in PSE [18, 19]. Indicatively, groups have proposed surrogate modelling [20–24], (adaptive) sampling [16, 22, 25, 26] and probabilistic approaches [27, 28] to map and identify a process design space. Other approaches consider variance-based methodologies to investigate the impact of design variables on the process performance and thereafter constrain the feasible space [29–31].

Similarly in operations, computer-aided tools can help assess trade-offs between KPIs during scale-up and supply chain development. Capacity planning under clinical trial and demand uncertainty pressures decision-makers to quantify cost benefits of early-stage scale up approaches, which are tied to higher initial capital investments and risk. In this space, stochastic programming and rolling horizon approaches are well-established tools in investment optimisation under uncertainty [32–35]. Network optimisation with respect to cost and environmental metrics has been explored by several contributions focusing of process industries and the pharmaceutical sectors [36–38]. These works integrate life cycle assessment (LCA) in the optimisation problem formulation, thereby quantifying environmental impacts of candidate solutions and constructing Pareto frontiers to explore cost-environmental trade-offs. In the specific context of biopharmaceuticals, pioneering work has studied the impact of single-use equipment in manufacturing of mAbs via LCA [39, 40]. There remain open questions regarding the identification of main sources of impact for emerging biopharmaceuticals and manufacturing platforms.

Optimisation-based PSE tools have an inherent potential to help assess trade-offs between cost and footprints and ensure therapy availability.

EXAMPLE CASES

Case study 1: Computer-aided design of chromatography

The system

Monoclonal antibodies have been the major growth driving force of the biopharmaceutical industry [41]. Their purification relies on a series of chromatographic separation steps and results in large requirements for buffers and chromatographic resins. When developing the downstream process for a new product, several commercially available resins are usually screened experimentally. Here, we demonstrate how computer-aided design space analysis can support resource-efficient resin screening as well as identifying suitable operating conditions that meet productivity and quality KPIs. Specifically, we consider the protein A affinity chromatography step (Fig. 1). The feed contains the product (mAb), as well as impurities that result from the upstream bioreactor that act as disturbances. The model describing this system is a Partial Differential and Algebraic Equation (PDAE) model and uses a general rate mass balance to describe the mass transport across the column length and radial axes [42]. The experimental validation of the model has been carried out for five different commercially available resins.

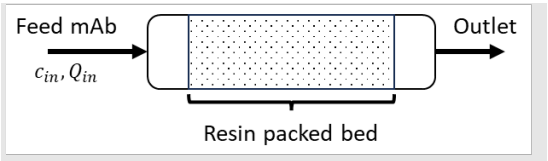

Figure 1. Illustrative schematic of the protein A column.

The performance of chromatographic units in bioprocessing is typically assessed via two KPIs; namely yield (K_{YD} in %) (Eq.1) and productivity (K_{PD} in mg/ml/min) (Eq.2). Although the yield is constrained, productivity is usually monitored and aimed to be maximised. In this example, we introduce resin utilisation (K_{RU} in %) (Eq.3) as a third KPI. This is in an effort to design innovative separation processes that not only meet the product specifications, but also make better use of the materials towards more sustainable operation.

$$K_{YD} = 100\frac{m_{fed}-m_{lost}}{m_{fed}} \quad (1)$$

$$K_{PD} = \frac{m_{fed}-m_{lost}}{60V(1-\varepsilon_c)t} \quad (2)$$

$$K_{RU} = 100\frac{m_{fed}-m_{lost}}{1000q_{max}V(1-\varepsilon_c)(1-\varepsilon_p)M} \quad (3)$$

where m_{fed} is the amount of mAb fed into the column, m_{lost} is the amount of mAb that leaves in the breakthrough, V volume of the column, ε_c and ε_b porosity of the column and the bed, respectively, t time, q_{max} maximum binding capacity, and M molar mass of the mAb. The productivity calculated is per volume of resin packed inside of the column, which enables comparison among the resins. For the purposes of this paper, the methodology and results are presented and discussed on the industrially relevant resin, MabSelect SuRe™.

Design Space Identification

To identify a feasible design space for this operation, we follow the framework in Fig. 2 presented by Sachio et al. [16].

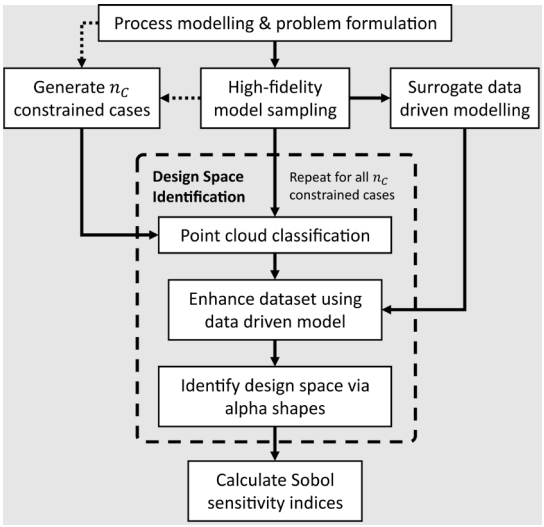

Figure 2. Framework for model-based design space identification via machine learning.

Problem formulation

For any given process, the design space is identified as a set of points that satisfy user-defined constraints of the KPIs. For this, first, a design problem is formulated (Eq.4-6).

$$y = f(\theta) \quad (4)$$

$$\theta_L \leq \theta \leq \theta_U \quad (5)$$

$$g(y) \leq 0 \quad (6)$$

where $\boldsymbol{y}$ is the vector of monitored KPIs, f is the process model, $\boldsymbol{\theta}$ vector of the design decisions, $\boldsymbol{\theta}_L$ and $\boldsymbol{\theta}_U$ are the vector of lower and upper bound of the design decisions, respectively. While $\boldsymbol{g}$ represents the target KPI constraints that need to be satisfied. These can be upper and/or lower bound constraints on the monitored KPIs.

Data generation

Next, the design decisions are identified, and the high-fidelity model is sampled for the generation of a

point cloud that captures the process performance. Varying the design decisions within the bounds in Table 1, 4096 computational experiments are generated via Sobol sampling. Each combination of those decisions results into a different set of the process KPIs. Real-world processes are often highly nonlinear, therefore challenging computationally quasi-random sampling methods. For this, we integrate in the workflow, the development of an Artificial Neural Network (ANN) surrogate to be used as data interpolator. The objective of this is to increase the resolution of the search space, bypassing the computational complexity of sampling the high-fidelity model. This facilitates the identification of smooth boundaries and decreases the risk of void areas to be included in the design space.

Table 1: Design decisions considered and their respective bounds.

Design Decision	Lower bound	Upper bound
c_{in} (mg/ml)	1.65	4.95
Q_{in} (ml/min)	0.50	2.50
T_{load} (min)	10	60

Condition screening against the KPI constraints and design space identification

In this step, the point cloud is screened via the application of constraint combinations of the KPIs. For this problem case, process yield is strictly constrained ($K_{YD} \geq 99\%$), while productivity and resin utilisation can vary between a lower and an upper bound ($0.3 \leq K_{PD} \leq 4.2, 3 \leq K_{RU} \leq 82$). We generate 1024 combinations of constraints which are used to classify the original 4096 points for their feasibility to meet the constraints. Based on the density of the cloud in each case, the ANN may need to be employed for the generation of additional points such that the design space boundaries can be smoothly identified. For the design spaces generated in this case, an ANN has been used in most of the cases, generating 1-927 additional points, based on the density of each given space. The boundaries of the design spaces are then defined using alpha shapes [16].

Resin performance and experimental validation

The 1024 identified design spaces are mapped against the two flexible constraints: productivity and resin utilisation (Fig. 3i). All the identified design spaces satisfy $K_{YD} \geq 99\%$ yield constraint. The presented approach further allows quantification of the generated design space, whereby $0\ mg$ is translated into absence of a feasible operating space under the given constraints. To display the density of each identified space, a colour-code is applied (Fig. 3i). On this occasion, black dots correspond to the absence of points that satisfy the given combination of constraints ($0\ mg$ space), while dark orange dots correspond to large design spaces ($> 160\ mg$). The size of the design space can be correlated to the operational flexibility of the process under the chosen constraints. The larger the design space (in mg), the greater the ability of the process to satisfy KPI constraints within the given bounds.

The presented approach enables manufacturers to gain insights on the process and material performance during the process development stages. For example, a trade-off between productivity and resin utilisation is observed (Fig. 3i), with the best achievable performance lying at $K_{PD} \approx 2.8 mg/ml min$ and $K_{RU} \approx 58\%$. It is observed that the flexibility of the unit operation is inversely correlated to both productivity and resin utilisation (Fig. 3ii and 3iii). Amongst the two constraints, productivity results the most stringent one for the size of the design space.

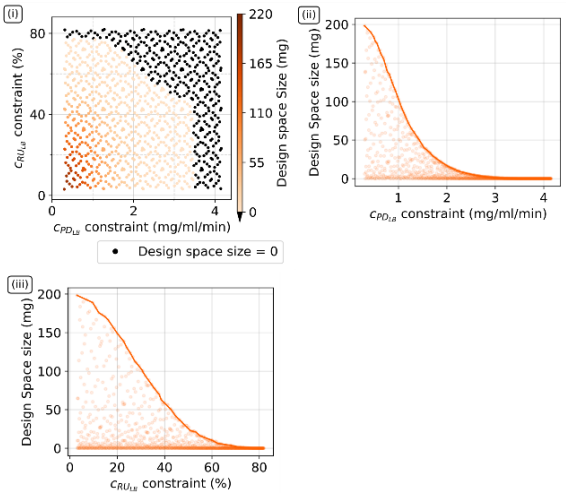

Figure 3. (i) 1024 design spaces generated as a function of the productivity and resin utilisation, (ii) design space-productivity constratint trade-off and (iii) design space-resin utilisation trade-off.

The generated design spaces have been validated using experimental data [42]. For the purposes of this paper, only the worst-performing scenario is displayed (Fig. 4). For this, the inlet product concentration (c_{in}) is fixed at $3.33\ mg/mL$ and the validation plot is presented in 2-D, where the design space is a function of the remaining two design decisions (Q_{in} and T_{load}). It is observed that the identified design space is in good agreement with the experimental runs. RT6 is of particular interest and criticality, as the high-fidelity model and all the model-based analysis thereafter were blind to this experiment. Even in this case, the identified design space captures accurately the process performance and does not include any false positive points. This is of high importance as any consideration of false positive points within the design space boundaries can jeopardise the process performance and therefore the product specifications.

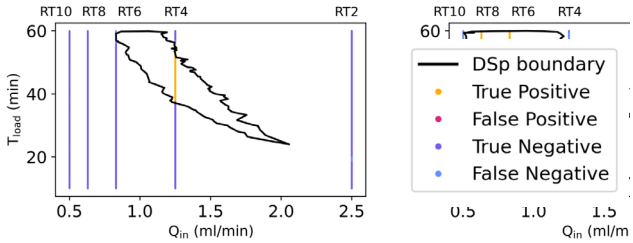

Figure 4. Experimental validation of the design space identified for the MabSelect SuRe™ resin.

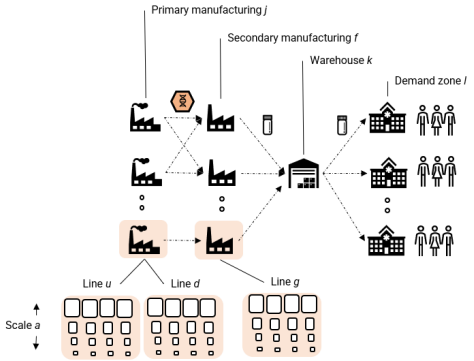

Figure 5. Superstructure of supply chain optimisation framework.

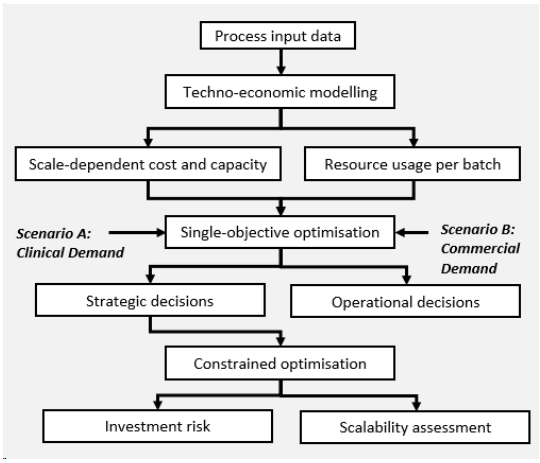

Figure 6. Techno-economic modelling and optimisation framework.

Remarks

The presented methodology harnesses the computational efficiency of model-based approaches to screen operating conditions and materials for their performance in an economically efficient manner. This also translates in overall better use of resources and more sustainable manufacturing platforms. The methodology can be used as an accompanying tool to accelerate process development in (bio-) pharmaceutical manufacturing and beyond. Importantly, the presented framework is adaptable and can be tailored to incorporate design decisions and KPIs of interest to the manufacturer. Critically, computational results of the example case compare favourably with wet-lab experimental data. This validation provides an additional level of certainty that the design spaces generated with this approach can be trusted and do not run the risk of false positive operating points to be included in the design. Case study 1 is a demonstration of a PSE tool for flexible process design. This effectively assists manufacturers in the development of continuous and robust manufacturing platforms operating in a more resource efficient fashion.

Case study 2: A sustainability assessment of advanced therapeutic supply chains

The system

The second case study focuses on the integration of sustainability considerations in biopharmaceutical supply chains. We consider a multi-site capacity and distribution optimisation for viral vector supply chains, where nodes include upstream (USP), downstream (DSP) and fill-and-finish (F&F) (Fig.5).

Data collection

The model [43] considers a generalized viral vector process that has been previously modeled in SuperPro Designer (Intelligen) for the calculation of batch sizes for each scale a, process times for USP, DSP, F&F, process bottleneck times and scale-dependent capital and operating costs. The techno-economic model also computes the resources (w) consumed and emissions per batch. In this case we focus on consumption of water and electricity and CO_2 emissions for each process section and scale a. The analysis is conducted on different scales of primary and secondary manufacturing (50, 200, 1,000L and 2,000L bioreactor working volumes). Storage costs, capacity and electricity usage for 2 fridge types was recorded, namely MATOS PLUS Cloud 300 UF (Cloud) and MATOS PLUS Eco 300 UF (Eco) freezers. Data on distances between supply chain nodes, logistics costs, and CO_2 emissions per km traveled was also collected.

The optimisation framework

The optimisation is formulated as a mixed-integer linear problem (MILP). Given the above set of scale-dependent manufacturing and logistics and a target demand, the optimisation determines network structures, selects manufacturing scale, production targets and computes associated costs and environmental footprint. The environmental footprint for each candidate design and scale assessed via the optimisation are calculated via formal LCA metrics, incorporating midpoint and endpoint categories. The environmental footprint is computed as the sum of the normalised mid-point impacts from water usage, energy usage and CO2 emissions, leveraging on the normalisation factors presented in the Environmental Footprint (EF) 3.0 framework [44] (Table 2).

The problem can be solved as a single-objective optimisation with respect to each of these indicators. In this

case, we illustrate an optimisation for cost minimisation and monitor environmental footprint and production targets as output variables of the supply chain model. We generate candidate supply chain structures by considering a set of scenarios. Specifically, we illustrate how *risk-averse* decision-making leads to an optimisation for a lower demand target (Scenario A), where *risk-taking* approaches consider a larger demand target (Scenario B). The former staged-approach minimises capital investment in early stages of development under clinical trials uncertainty, whereas the latter case represents an early-scale up strategy.

Table 2: Impact categories and normalisation factors (NF).

Impact category	Units	NF
Climate change	$kgCO_2eq$	5.79×10^{13}
Water use	m3 water eq	7.91×10^{13}
Resource use, fossil-based	MJ	4.5×10^{14}

Scalability analysis & investment planning

The performance of candidate network structures for Scenario A and B respectively can be assessed by constrained optimisation. Specifically, the network configuration and scales obtained via the solution of the single-objective cost minimisation can be fixed and tested for a range of demand realisations. This approach enables the assessment of the worst-case cost and emissions in the case of a demand decrease (i.e. clinical trial fails.), as a first attempt to integrate environmental sustainability in the pharmaceutical workflow. This information can also be used to identify the scalability of the candidate investment plan. The total environmental footprint and mid-point impacts of the supply chain operations are recorded.

Cost-optimisation

The adoption of a risk-taking approach results in a centralised network consisting of 2 USP production lines, 1 DSP line and 1 F&F line. The scale selected is 2,000L, which is the largest available thereby maximising benefits from economies of scale given the target demand. At this cost-optimal point, total supply chain operating costs are computed as ~70M$/y, with variable costs of manufacturing (~30%) and equipment expenses (~60%) being the main contributors.

Notably, storage costs from installing cheaper storage (Cloud) are minimal. This is the case for the range of demand realisations (Fig. 7a, ii). The total environmental footprint is mainly due to CO_2 (58-66%) emissions and water utilised during manufacturing (41-33%), whereas electricity usage in manufacturing and storage is negligible (Fig. 7a, iii). A risk-averse approach results in a 200L scale being installed in USP, DSP and F&F, in a centralised manufacturing facility. The cost-optimisation results and scalability analysis highlight lower total costs and total footprint overall, with main cost drivers and environmental impacts remaining variable and facility-dependent expenses and water and CO_2 emissions for the range of demand realisations (Fig. 7b, iii).

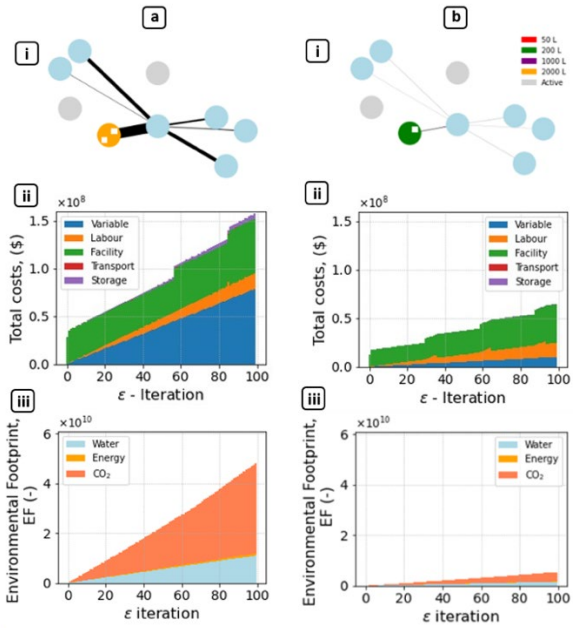

Figure 7. Performance of candidate networks. Risk-taking (a): (i) nominal network structure, (ii) total costs, (iii) total emissions computed through scalability analysis. Risk-averse (b): (i) nominal network structure, (ii) total costs, (iii) total emissions computed through scalability analysis. ε iterations correspond to the range of demand realisations from worst-case to best-case demand.

Trade-off analysis

The *social* sustainability of the biopharmaceutical supply chain can be understood as the amount of therapy delivered. Quantifying the supply chain performance under demand uncertainty helps quantify the scalability of each investment decision. In this fashion, candidate investments can be compared with respect to cost and emissions per dose delivered and their respective scalability. The risk-averse investment results in larger emissions per dose compared to the risk-taking investment. Resource used in manufacturing are better used at larger scales in a similar fashion to economies of scale. In addition, risk-taking strategies and investing in a larger scale allows covering for up to 60,000 doses (Fig. 8). This is 10-fold larger than the risk-averse case which uses 200L manufacturing platforms.

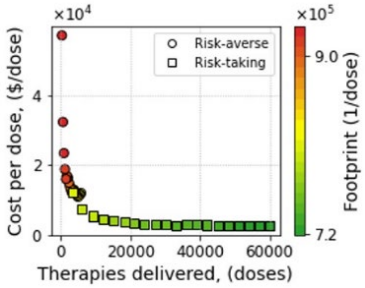

Figure 8. Trade-off between financial risk and 3-fold sustainability.

The presented *what-if* analysis offers a first insight into a key trade-off between financial risk of investment and the 3-fold sustainability of the supply chain. As the therapy availability is maximised, the cost and environmental sustainability of supply chain operations is improved. This is seen by comparing Scenario A to B which result in 2 different operating scales, as well as maximising throughput of the facility once the asset is fixed. These trends highlight that a risk-taking approach in early stages of scale up can minimise emissions throughout clinical trials, although entail larger initial capital investments and risk if the clinical trial fails.

Remarks

The proposed case study highlights that cost and environmental footprints for stainless steel facilities are not conflicting objectives. This may not be the case for other therapeutics and/or alternative equipment choices in manufacturing. We foresee more complex trade-offs by introducing in the framework the selection of equipment type for USP, DSP and F&F steps, comparing candidate manufacturing platforms relying on single-use and/or stainless-steel equipment. Each design decision would result in a range of environmental impacts from plastics disposal to water depletion and use of solvents for cleaning. In addition, the presented analysis focuses on 3 midpoint impacts within the LCA framework. The environmental footprint quantification can be augmented for a larger midpoint impact set as well as end-point aggregation. In this context, case study 2 illustrates a methodology to generate datasets for different candidate equipment technology and assess the sustainability of alternative manufacturing and network setups and its correlation to cost and service levels.

CONCLUSIONS

As the (bio)pharmaceutical industry commits to net-zero targets, ramping up the global capacity in an economically and environmentally sustainable fashion amid a background of regulatory concerns related to drug shortages will push manufacturers to take bold decisions on revolutionising their day-to-day operation. Adding the complex process dynamics of production systems results in a multifactorial, non-trivial problem that the sector is asked to solve in a timely manner.

In this setting, the legacy of the Process Systems Engineering (PSE) community in the development of cutting-edge methodologies, algorithms and tools becomes a vital enabler. PSE approaches are an excellent vehicle for the integration of social, economic, and environmental objectives when designing and optimising the next generation of (bio-) pharmaceutical processes and supply chains. Model-based approaches enable manufacturers to tackle challenges related to data unavailability, scale-up bottlenecks, raw material scarcity and uncertain demand profiles. Embedding such approaches in industrial workflows can shed light to novel process designs through better utilisation of the present assets or even by considering novel materials that offer improved performance. Another key advantage of PSE decision tools is the guidance towards better use of resources to reduce cost and impact per therapy/drug delivered.

To fully respond to today's needs, however, one needs to consider pathways whereby all available tools of the broad PSE portfolio are combined and used in a customised fashion. In that respect, high-fidelity process models remain a great resource that offers process insights and can help tackle challenges related to limited or complete lack of measurements. At the same time such models are highly transferrable across different products and modalities, following a suitable degree of re-parameterisation. On the other hand, Artificial Intelligence (AI) offers opportunities towards the reduction of the computational complexity of large-scale, nonlinear models, often encountered in this setting towards online deployment. Lastly, modelling manufacturing nodes dynamically and accounting for underlying uncertainties can enable the design of agile and responsive supply chain networks that meet regulatory, economic and patient related KPIs.

ACKNOWLEDGEMENTS

The authors would like to acknowledge funding from: the UK Engineering & Physical Sciences Research Council (EPSRC) for the i-PREDICT: Integrated adaPtive pRocEss DesIgn and ConTrol (Grant reference: EP/W035006/1) and the Future Targeted Healthcare Manufacturing Hub hosted at University College London with UK university partners Grant Reference: EP/P006485/1). The authors would like to thank Prof. Blaž Likozar and Dr. Martin Grom (Department of Catalysis and Chemical Reaction Engineering, National Institute of Chemistry, Ljubljana) for expert input and data used in the design space example case. Input from Mr Alasdair Fyfe in the supply chain example case is also gratefully acknowledged.

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