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Pre-structuring Product Development Challenges in the Context of Advanced Biomanufacturing

Manuel Sonnenberg[a,b]*, Robert Miehe[b,c], Steffen Kiemel[b], Thomas Bauernhansl[b,c]

[a]Graduate School of Excellence advanced Manufacturing Engineering (GSaME), Universität Stuttgart, Nobelst. 12, 70569 Stuttgart, Germany
[b]Fraunhofer Institute for Manufacturing Engineering and Automation IPA, Nobelst. 12, 70569 Stuttgart, Germany
[c]Institute of Industrial Manufacturing and Management (IFF), University of Stuttgart, Allmandring 35, 70569 Stuttgart, Germany

* Corresponding author. Tel.: +49 711 970-1687. E-mail address: manuel.sonnenberg@gsame.uni-stuttgart.de

Abstract

With an increasing emphasis on research and design at the intersection of biological and cyber-physical systems, collaboration among disciplines is intensifying. Yet, there remains a lack of the integrated use of knowledge, methods, and approaches. This preliminary study examines challenges in product development within advanced biomanufacturing. The study addresses epistemological and methodological differences between sub-fields by compiling the literature's paradigms, obstacles, and design method requirements. The result is a pre-structure of design challenges, providing a basis for developing modular method fragments in the future.

Keywords: advanced biomanufacturing; product development; challenges

1. Introduction

Advanced biomanufacturing offers new prospects for innovation yet leads to a highly complex design task as the sub-disciplines' underlying mechanisms and design approaches diverge significantly. In traditional and more predictable manufacturing, process models such as the V-model for mechatronic systems [1–3] follow a straightforward verification and validation of predefined requirements. In contrast, more dynamic developments, such as software projects, predominantly use agile frameworks [4]. Due to the lack of rational design principles and the high complexity, working with living systems often requires an even more elaborate trial-and-error process, such as the Design-Build-Test-Learn (DBTL) cycle [5]. In addition to the challenge of harmonizing development processes for advanced biomanufacturing, it is difficult to transfer new findings and technologies into application [6] and reduce dependency on human skills and efforts [6]. Another challenge arises from the novelty of the designed systems and products, which require new marketing channels [7] and regulatory compliance [8]. Furthermore, using living cells is associated with more sophisticated process control and risks of fluctuating quality and yields [9], which requires a suitable bioreactor infrastructure and makes scaling complex [8, 10].

This paper pre-structures challenges in advanced biomanufacturing as preliminary work for designing a product and production development approach that suits the interface of living, technical, and digital components.

2. Data selection and analysis

Collecting and organizing challenges in developing advanced biomanufacturing applications serves to pre-structure them.

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Although we do not aim to present all obstacles in advanced biomanufacturing, we intend to present a relevant and representative selection.

The starting point for the structured literature search is the search string in Table 1, which was defined using a preliminary search on advanced biomanufacturing. The search string was used in the Scopus database in September 2024.

Table 1. Search string (date of access in Scopus data bank: 6th Sept. 2024)

Search string	Hits	Reviewed	Relevant
(advance* AND biomanufacturing) OR "biomanufacturing 4.0" OR "bioprocessing 4.0" OR (digital AND biomanufacturing) OR (smart AND biomanufacturing) OR (automation AND biomanufacturing) OR ("artificial intelligence" AND biomanufacturing) OR (AI AND biomanufacturing)	759	172	103

Based on the title and abstract, a relevance check is carried out for the hits using AS Review. This tool supports the search by attempting to pre-sort the literature based on past relevance decisions. A prerequisite for the relevance of an article, and thus the first inclusion criterion, is that the abstract must contain content related to living biological elements, advanced technologies in the digital, technical, or biological field, and aspects of manufacturing, i.e., product and production.

In sync with the selection process, a qualitative content analysis, according to Mayring's approach, is conducted [11]. Like Chemaly's systems science methodology for mapping physical or abstract entities [12], newly coded and compiled challenges are grouped with similar, previously recognized ones to condense the findings during the selection process. This parallel approach makes it possible to apply the second inclusion criterion, according to which the text source under review must present a new aspect that has not yet been considered in the existing categories.

As a discontinuation criterion, ten consecutive suggested papers must not provide new aspects that cannot be assigned to the existing clusters. After reviewing 172 studies, this criterion was met. Based on the two inclusion criteria indicating relevance, 103 papers were selected. The inductive categorization during the relevance check is expanded based on all relevant papers.

3. Results

This section presents five areas that structure and summarize the challenges identified.

3.1. Understanding and automation

Better understanding the intricate relationship between product quality attributes and the process parameters and predicting performance by capturing complex relationships in high-dimensional data is challenging [13, 14]. For this reason, and due to the lack of real-time monitoring of critical process parameters, control measures are often manual tasks based on experience rather than data. [9] Here, the challenge is selecting "the best methods for a specific dataset to construct the most accurate and reliable model." [15] Digital twins are one approach to gain insights into each physical twin's present and future operational states [16] and to track the dynamic changes in cell composition [17]. However, they have not yet been fully implemented in biomanufacturing [18]. The reasons for the difficulty of monitoring include a lack of in-line sensors that provide continuous data [19] and "intrinsic physical limitation imposed by the cell wall/membrane" on intracellular monitoring [20]. With dramatic progress in automation and high-throughput experimentation, data collection and efficient storage are becoming the bottleneck [21], and software limitations have precluded more advanced maneuvers required to manipulate, maintain, and monitor hundreds of experiments in parallel. [22] With digitization, there is a growing concern about potential cyberattacks that can only be prevented if multiple stakeholders, including industry, governments, and healthcare providers, work together. [23]

Table 2. Challenge area 1: understanding and automation

Challenges	Segments	Examples
Monitoring and control	15	[9]
Modeling and simulation	8	[16, 18]
Data collection and analysis	8	[21, 24]
Sensor and software limitations	7	[22]
Data infrastructure and efficient storage	5	[21, 25]
Predictions and predictive control	4	[13]
Data and knowledge management	3	[14]
Cell composition and intracellular monitoring	3	[17]
Cybersecurity	3	[23]
Selection of best methods for dataset	2	[15]

3.2. Living systems, process quality, and consistency

Achieving the desired productivity and product quality consistently is an enormous challenge [26], as even minor deviations in process parameters, material constituents, and microenvironmental conditions significantly impact product quality attributes. [13, 27] Biological activities involving cell metabolism have trans-scale nonlinear properties in time and space. Failing to achieve dynamic global optimization and process management often leads to performance loss in titer, rate, yield, or combinations thereof. [28] Due to this complexity, biological processes such as fermentation require strict control of metabolites and nutrients to achieve optimal cell proliferation and viability and, thus, maximize product yield. [9, 29] High media consumption or low productivity is a common trade-off. [30] Further essential product parameters are quantity, purity and potency, bioburden, and adventitious agents. [31] Today's biomanufacturing processes are often still operated based on experience and thus can hardly cope with increasing bioprocess complexity. [32] One example of this complexity is the shift in metabolic activity in cell culture, which can lead to reduced quality characteristics. [33]

Moreover, there are still difficulties with the end-to-end process integration of upstream and downstream processes. [34] Efforts to intensify processes such as vaccine production are driven by the desire for cost control, process efficiency, and the desire to combat diseases. [35] Continuous processes are promising in this context but face new hurdles. [36] Inherent heterogeneities in cell populations and the methods used for cell extraction, culture, and processing lead to considerable variability and susceptibility to contamination in biological products with fragile macromolecular structures, complicating clinical implementation and therapies. [37, 38]

Table 3. Challenge area 2: living systems, process quality and consistency

Challenges	Segments	Examples
Productivity	11	[28, 31]
Complexity and intricacy	9	[9]
Variability and reproducibility	8	[37]
Robustness and sensitivity to disturbance	7	[13, 27]
Intensified, continuous, and efficient processes	6	[35, 36]
Constant product quality	5	[26]
Contaminations	4	[31, 38]
Process integration	3	[34]
Cell viability and proliferation	3	[29]
Shifting metabolic activity	2	[33]
Media consumption and nutritional needs	2	[30]

3.3. Manufacturing and scalability

The existing manufacturing methods for cell therapies are still associated with several challenges related to costs, the origin of the immune cells, safety risks, and scalability. [39]

“Scale-up remains one of the most relevant topics in fermentation processes, as it is important to have reproducible critical quality attributes, such as titer and yield, on larger scales”. [40] The transition between scales changes the conditions. For example, the increase in bioreactor dimensions leads to less efficient mixing, and environmental gradients become more pronounced compared to more minor scales. These changes in the cultivation environment often strongly impact the cultivated organisms and, thus, the process performance. [41] A lack of standards and compatibility between different bioreactor infrastructures' various hardware and software components further complicates the scaling process. [10] To date, there is not yet a universal solution for overcoming the complex challenge of scalability and product development [42]

Besides scalability, there are also general manufacturing issues such as ensuring product quality, manufacturing robustness [14], reproducibility, cost-effectiveness [43], and production times. [44]

Producing high-quality biologics involves complex manufacturing processes, including cell culture, fermentation, purification, and formulation, which require specialized equipment and expertise [8]. Advanced biomanufacturing also places a wide variety of demands on the materials used. For example, existing biodegradable materials are unsuitable for application in microfluidic valves as they are generally too unstable. [45]

Table 4. Challenge area 3: manufacturing and scalability

Challenges	Segments	Examples
Scalability	16	[10, 39–42]
Cost	5	[39]
Quality and robustness	4	[14, 43]
Consistency and reproducibility	3	[43]
Production time	2	[44]
Materials	2	[45]
Need for facilities and expertise	2	[8]

3.4. Design and development

Time- and labor-intensive, iterative trial-and-error processes such as the Design-Build-Test-Learn (DBTL) cycle are necessary to manage the complexity of living systems, as there is a lack of rational design principles. [5] The manual acquisition, preparation, and analysis of samples during process and product development distracts from the actual development and leads to human error. [6] Current methods for producing cell therapeutics are costly, labor-intensive, and time-consuming, as they are based on a two-stage model from biologics development, in which stable cell lines are first established and then produced on a large scale in a bioreactor. The approach is, therefore, not suitable for patient- or donor-specific cell therapeutics. [46] The challenges mentioned in microbial sensor product development are accelerating development, improving performance, and overcoming limitations for use in the field [47].

The full potential of cell-based therapeutics can only be realized if new technologies enable the cost-efficient, consistent production of high-quality therapeutic cells on a large scale. [48] At the same time, it is a challenge for the industry to integrate technologies such as the Internet of Things into biomanufacturing processes, as its implementation requires a new mode of operation for the biopharmaceutical industry. [49] However, there are also simplifications through technology, such as using machine learning to accelerate the implementation of 'Quality by Design' in the biopharmaceutical industry. [13]

Bioreactors' design configuration and operation strongly impact the flow field around production cells, an essential factor in production performance. However, this aspect is currently insufficiently considered in reactor design. [50]

Table 5. Challenge area 4: design and development

Challenges	Segments	Examples
Inefficient product and process development	11	[5, 6, 46, 47]
Integration of technological advances	7	[48]
Mode of operation	4	[49]
Lack of design principles and techniques	2	[5]

'Quality by Design' implementation	2	[13]
Bioreactor design	2	[50]
Facilitate use in the field	1	[47]

3.5. Regulations, limitations and market adoption

This challenge area summarizes external requirements from stakeholder groups and entities such as the market, the environment, society and regulators.

Despite their potential, methods, such as continuous bioprocesses and advanced therapies, are not yet established on the market due to unreliable, variable and cost-intensive production. [7, 34] Reaching the market successfully also requires reducing the footprint and might be restricted due to certain societal limitations. [47, 51] To assess biotherapeutics' safety, efficacy, and quality before clinical approval, complex biopharmaceutical processes are subject to stringent regulatory oversight and must comply with regulatory standards, such as good manufacturing practice. [8]

Table 6. Challenge area 5: regulations, limitations and market adoption

Challenges	Segments	Examples
Commercialization and market adoption	7	[7, 34]
Safety	4	[8]
Product quality and efficacy	3	[8]
Societal and environmental limitations	2	[47, 51]
Compliance with standards and regulations	3	[8]
Market demands	2	[51]

4. Discussion

The challenges identified in this study can be divided into five main categories: understanding and automation; living systems, process quality and consistency; manufacturing and scalability; design and development; and regulations, limitations and market adoption. The first three categories can be assigned to ‘advanced’, ‘bio’ and ‘manufacturing’. The remaining categories, design and development, as well as regulations, limitations and market adoptions, reflect additional aspects by which the system is designed and influenced or to which it is oriented. Several challenges span multiple areas, such as integrating digital and biological systems. However, the tabular categorization of the difficulties is one-dimensional and cannot depict cross-category interrelationships. For example, successfully implementing digital twins requires knowledge and skills about data and automation and the variability of biological systems. Similarly, scalability problems encompass technical, biological and regulatory influencing factors simultaneously. Surprisingly, there are hardly any reports on challenges related to artificial intelligence, although these are explicitly included in the search string.

A comparable study by Maechtlen et al. [52] with experts in biointelligent product development reveals similar challenges, such as the unique features of biological systems and the need for interdisciplinary project management. However, the study focuses more on compliance with standards and sustainability issues while neglecting technical problems.

The present study on challenges in product development in the context of advanced biomanufacturing is subject to limitations regarding the method and the underlying data, which will be discussed here. Assigning challenges and developing the category system is an iterative process subject to the authors' interpretation. Even if a comparison of word frequencies between the data set with 759 papers and the 103 papers selected as relevant indicates a high degree of representativeness, it remains unclear whether the selection process using AS Review could cover the entire data set with only 172 reviews. The discontinuation criterion was also somewhat undermined, as the initially inductively defined categories were summarized iteratively. A reference to all 103 literature sources considered relevant and used would have been in the interest of completeness but would have gone beyond the scope of this paper. Therefore, the segments and representative examples serve as less transparent and only partially meaningful substitutes, as multiple assignments were possible but not traceable for the reader.

The pre-structuring of challenges reveals significant multidisciplinary challenges and gaps in current product development methodologies.

5. Conclusion

At the interface of technical, living, and information technology components, diverse and interlinked challenges involve technological, methodological, and regulatory areas. The many connections between the categories paint a multi-layered picture of the challenges, which can only be presented to a limited extent in this paper. To realize the full potential of advanced biomanufacturing and successfully overcome the challenges described, close cooperation between research, industry and regulatory authorities is required in addition to modular and interdisciplinary design methods. The unique features and complexity resulting from biological and technical systems, technological advances, and the multidisciplinary nature of product development require interdisciplinary understanding and expertise from developers, or at least require interfaces and communication designed in such a way as to enable target-oriented collaboration.

An interview study with experts developing products and productions in advanced biomanufacturing and related areas will underpin and verify the pre-structuring of the challenges presented in this paper. This will reinforce a solid understanding of the challenges and shortcomings of existing approaches, serving as requirements for enhanced strategies. The process model with a methodological toolbox to be designed should enable an integrative alignment of the various disciplines involved by creating an all-encompassing model or a combined hybrid of existing approaches. The iterative improvement and validation of the process model will be carried out by re-consulting the experts and testing its suitability for practical case studies.

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