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Current Opinion in Biotechnology

Review

Window of sustainable bioprocess operation: towards merging environmental sustainability assessment and process operation at early-stage bioprocess development

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Developing and optimizing sustainable bioprocesses require integrating technical feasibility and environmental sustainability assessment at an early stage of process development. Therefore, environmental impact estimations need to be performed alongside the development of novel bioprocesses, and 'feasibility' windows need to be defined, in which a bioprocess can be operated robustly and economically while being as environmentally friendly as possible. In this opinion, we summarize the progress made in the field of environmental sustainability assessment and its integration into bioprocesses at an early stage. We propose the 'window of sustainable bioprocess operation' (SBO window) as a concept to find operating conditions that match economic and environmental constraints. The insights obtained by the SBO window enable the back-translation of environmental constraints into bioprocess design optimizations and thus lay the foundation for a successful implementation of sustainable bioprocesses in the future.

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Current Opinion in Biotechnology 2025, **93**:103292

This review comes from a themed issue on **Energy Biotechnology**

Edited by **Gregg Beckham** and **Alissa Bleem**

Available online xxxx

https://doi.org/10.1016/j.copbio.2025.103292

Introduction

Enhancing environmental sustainability is the primary incentive for transforming the current fossil-based economy into a bioeconomy based on renewable resources. To achieve a biologization of the industry, the successful translation of bioprocesses from the laboratory to the industrial scale plays a key role [1]. Current bioprocess development focuses mainly on technical feasibility, especially in the early stages of development, aiming at economic competitiveness compared to established processes [2]. Because of the complex and multivariate nature of bioprocess development, optimal operation conditions bordered by design constraints for both process conditions and cells are defined. Renownedly, these are visualized in a 'window of operation' [3], which classically focuses on constraints in agitation and aeration in a stirred-tank reactor or variants of it applying different process parameters [4]. While defining these technical constraints provides the basis for ensuring the technical feasibility of the envisioned process, an assessment of environmental sustainability at early-stage bioprocess development is often missing, contradicting the initial incentive of the bioeconomy. Reasons might be that bioprocesses are often regarded as green or sustainable *per se* [5], which is demonstrably incorrect [6], or missing awareness and expertise to evaluate sustainability. Instead of integrating environmental sustainability in the bioprocess development pipeline at early stages, it is often assessed only at full-scale operation when data are easily accessible [7,8]. This could eventually prove to be economically detrimental as cost-intensive retrofitting or a redesign of the entire process chain might be required, especially regarding changing regulatory limits or charges for emissions. An assessment of the environmental sustainability of a bioprocess at an early stage is, therefore, of utmost importance [9] and needs to be incorporated into the bioprocess development pipeline. Therefore, before spending vast amounts of resources on developing suboptimal processes, decisions improving environmental sustainability can be made early on in bioprocess development. However, available tools are either inadequate for early estimations, missing, or not consequently applied for sustainability-driven bioprocess development.

Prerequisites for environmental sustainability assessment and existing tools

Tools with different complexities and accuracies are available for assessing environmental sustainability. These encompass rather simple metrics, such as the Process Mass Intensity, the $E^{(+)}$-Factor, or the Product CO_2 Footprint, each indicating the ratio of resources used or waste generated per product obtained (Table 1). Further, semiquantitative metrics (e.g. EcoScale [10]) or rather qualitative estimations based on the 12 Principles of Green Chemistry [11] can be applied. While these metrics can help give a rough estimate, a full Life Cycle Assessment (LCA) can provide a more comprehensive picture of the environmental sustainability of a process. However, because of its complexity and partial retrospective nature, large amounts of data are required, often not available at early-stage process development [12]. For compensation, a substantial number of assumptions have to be made, which reduce accuracy. As critically reviewed by Talwar & Holden, many bioeconomy LCA studies fall short due to inaccuracy or incompleteness, for example, due to narrow system boundaries or unavailability of data [13]. Therefore, a full LCA at the early stages of bioprocess development might not be suitable. Here, a focused approach on categories important for the specific (biochemical) reaction or process should be considered. Water usage and energy consumption could be classic impact categories, certainly applicable for a wide range of bioprocesses, as particularly fermentations and downstream process unit operations are often water- and energy-intensive [14]. Further, greenhouse gas emissions can be quantified to compare the bioprocess to a chemical pendant. However, the impact categories need to be chosen and compiled specifically for the process or unit operation considered.

A current dilemma is that at the early stages of bioprocess development, one must rely on straightforward metrics with less predictive accuracy because data are lacking for thorough environmental sustainability assessments. However, some previous studies in bioprocess design have attempted to tackle this conflict and serve as use cases.

State-of-the-art of early-stage sustainability assessments in bioprocess development

Most conducted studies considering an environmental sustainability assessment of a bioprocess focus on a specific product, ranging from bulk to fine chemicals. While many studies use relatively simple metrics for early-stage assessments, we focus here on LCAs. Regarding LCAs, there are often challenges in setting the system boundaries to be comparable, and differences in the selection of impact categories are common [25,26]. For example, in a study performing an early-stage LCA for citric acid production [27], the substrate and the operation modes of the fermenter are considered, thus focusing primarily on bioconversion. Other studies included process integration and intensification, considering reaction conditions, such as the selection of biocatalysts and feedstocks, and different routes for downstream processing (DSP), for example, for the production of aromatics [28], lactic acid [29], or monoterpenoid indole alkaloids [30]. Multiple studies investigating the fermentative production of different biosurfactants identified the fermentation, specific DSP unit operations, and proper scaling to have the highest impact on environmental sustainability and suggested optimizing the process accordingly [31–33]. Regarding biocatalyst selection, enzyme production was identified as potentially having a substantial effect on the environmental sustainability of the overall process [34]. Further, comparative LCAs have been conducted to assess if biocatalytic syntheses have an ecological advantage over chemical processes, for example, in the case of isopropyl palmitate [35], lactone [36], or cyclic dinucleotide production [37]. Additionally, specialized reactor and process setups were investigated regarding their environmental impact. Abel et al. analyzed electromicrobial production (EMP) systems with different substrate inputs (formate, H_2, acetate generated from electrolysis of CO_2 and H_2O using renewable energy) and three products (lactic acid, biomass, enzymes) compared with traditional bioprocesses [38]. EMP systems would be favorable if 90% renewable energy were used, and land use would be reduced by 95%. A subsequent techno-economical assessment modeling butanol production in an EMP revealed strong restrictions on prices for hydrogen, direct air capture, and renewable energy, as well as required process key performance indicators (KPIs) for the process to be economical [39]. While currently not economically viable, the targeted KPIs are not out of reach. Other bioeconomy LCAs or simpler methodologies focus on reactor design, for example, for photobioreactors [40], or aim to minimize the energy demand of stirred-tank reactors [41].

Although the application of LCAs and other metrics for environmental sustainability assessment at the early stages of bioprocess design is limited, further examples are present in the literature [42–47]. Wowra et al. [9] comprehensively reviewed the application of LCAs in (early-stage) bioprocess development and highlighted their importance for holistic assessments. However, LCAs heavily rely on data, which are missing at the early stages of process development. At the same time, the complexity of LCAs demands expert knowledge in modeling and validation to achieve a sound conclusion. Therefore, a trade-off needs to be made: While an LCA would be the ideal

Table 1

Overview and comparison of different metrics to evaluate the environmental sustainability of bioprocesses.

Metric	Category	Calculation	Main advantage	Main disadvantage	Ref.
12 Principles of Green Chemistry	Application of the principles to favor environmentally friendly processes	–	Easily applicable	Subjective, no quantitative data	[11]
EcoScale	Usage of unfavorable unit operations causes penalties	$100 - \sum penalties$	Easily applicable	Subjective and inflexible	[10]
Process Mass Intensity	Material usage	$\frac{\sum m(materials)}{m(product)}$	Data is easily recorded	Completely mass-based, type and impact of hazards and toxicities neglected	[15]
E-Factor	Waste generation	$\frac{\sum m(waste)}{m(product)}$	Data is easily recorded	Completely mass-based, type and impact of hazards and toxicities neglected	[16]
E^+-Factor	Waste generation and energy consumption	$\frac{\sum m(waste) + W \cdot CI}{m(product)}$	Data is easily recorded	Mainly mass-based, type and impact of hazards and toxicities neglected	[17]
CO_2-Footprint	CO_2 generation	$\frac{m(CO_2)}{m(product)}$	Based on life cycle mindset	Data can be difficult to gather; dependent on system boundaries	[18,19]
Eutrophication	Generation of N- and P-equivalents	$\frac{m(N + P\ equivalents)}{m(product)}$	Based on life cycle mindset	Data can be difficult to gather; dependent on system boundaries	[20]
Global warming potential (GWP)	Greenhouse gas emissions originating from energy and resources consumed and disposed	GWP-estimate based on generalized equations whose composition depends on the catalyzed reactions*	Unified metric as CO_2 equivalents	So far limited to the developed and calculated examples; data for different unit operations is limited to date.	[21]
Water-related impact of energy	Energy requirement for the production of clean water used in the process	Various*	Comparability due to translation of the water requirement into CO_2 equivalents	Data can be difficult to gather; dependent on system boundaries and type of process	[22]
Life cycle assessment	Quantification of the environmental impact of a product during its life cycle	Complex models	Comprehensive; theoretically standardized	Difficult to calculate; data-intensive; multivariant and multiple impact categories make comparisons difficult	[23,24]

* Detailed calculations are listed in the reference.

method if sufficient data were available, the bioprocess engineer needs easily applicable tools to estimate environmental sustainability, enabling the adjustment and decision-making on process design considerations and parameters in the early stages of development. At the very least, data are gathered by these tools, preparing more sophisticated subsequent methods like LCAs.

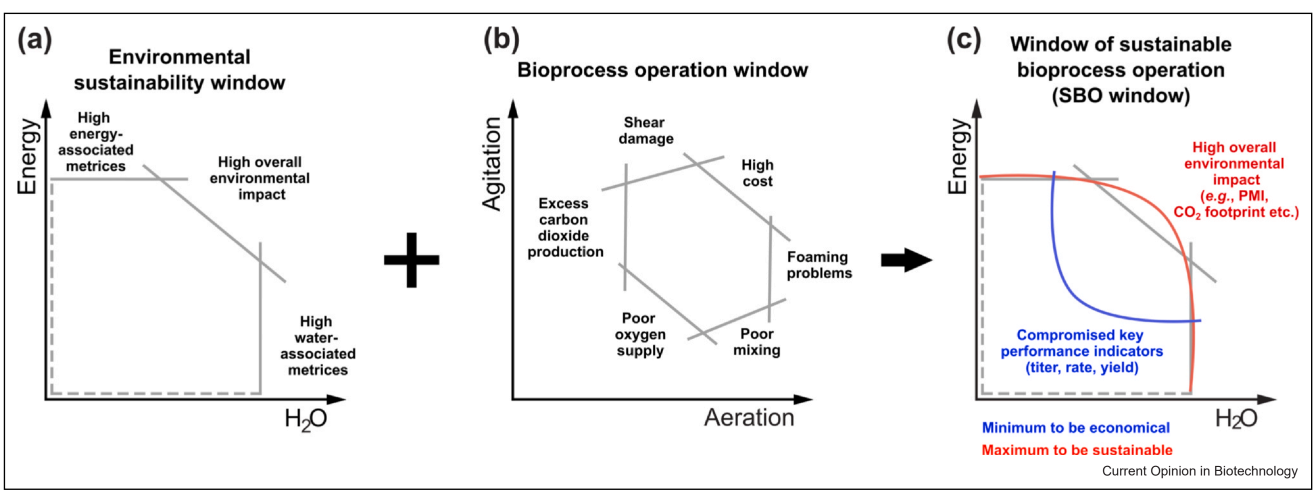
Integration of environmental sustainability assessment into bioprocess development

Easily accessible tools are needed to better incorporate the importance of environmental sustainability and establish it as a decisive factor in process design. The necessity and relevance of integrating sustainability into early-stage process design have already been recognized in the chemical process engineering fields [48–50], leading to the concepts of 'industrial ecology' and 'design for environment' [51]. These concepts have not been discussed and transferred in the context of bioprocess development. We propose the 'window of sustainable bioprocess operation' (SBO window) as an emerging concept to integrate early-stage sustainability analysis into bioprocess development (Figure 1). Here, environmental sustainability windows (Figure 1a) are established, analogous to the renowned 'window of operation' [3] (Figure 1b) for technical bioprocess development. Specific impact categories, for example, water usage and energy consumption, span the parameter space, in which constraints for main contributors regarding environmental sustainability are set for a bioprocess (Figure 1a). These constraints define an optimal range within which the designed bioprocess must operate to be environmentally sustainable. In parallel, the classic 'window of operation' (Figure 1b) is applied to determine the process parameters under which the predefined constraints for the environmental impact categories are met. This ensures that the chosen operational parameters reflect technical feasibility and environmental sustainability. The combined application of both windows, defined as the SBO window (Figure 1c), illustrates the abstract, multidimensional parameter space of all selected environmental impact categories and their consequences, translated to process conditions.

Application of the SBO window in an exemplary case study

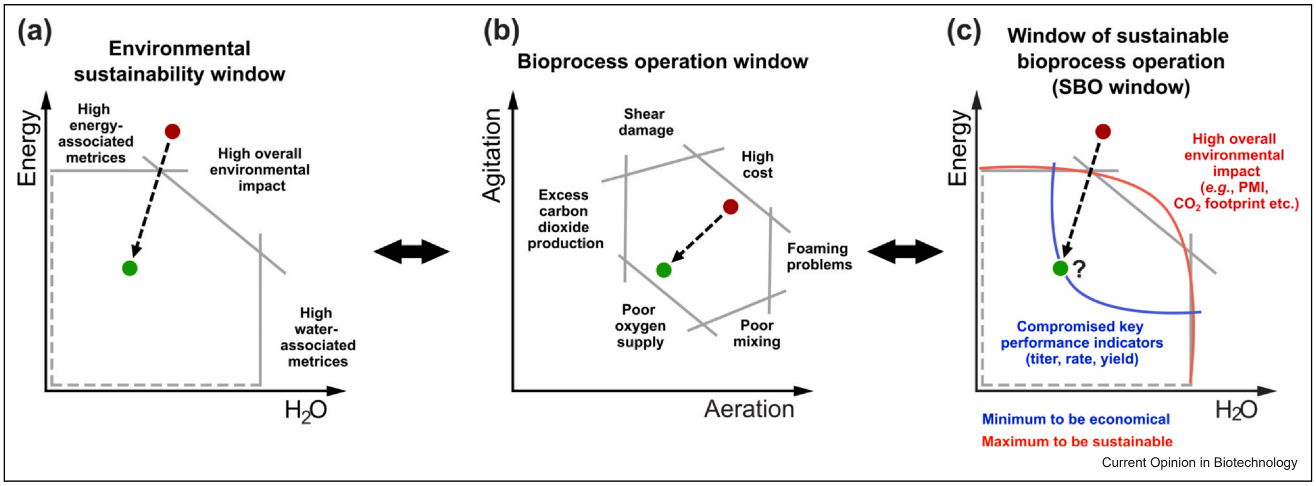
The SBO window has not yet been applied, but it can be transferred to various studies in the literature that aim to improve bioprocesses based on insights obtained by early-stage environmental sustainability assessments. Applied to biotechnological cellobiose lipid production, this exemplifies the SBO window's potential as a guiding tool for early estimations in developing an environmentally sustainable bioprocess [31]. In a cradle-to-gate LCA, Oraby et al. identified fermentation as a major contributor to all investigated impact categories (including abiotic depletion, eutrophication, and global warming potential), especially the energy required for agitation and aeration. Solutions suggested by the authors were to decrease fermentation time, which would require an increased space-time yield, and to be more energy-efficient by reducing aeration and sparging. However, economic viability must be met by reaching targeted KPIs, potentially contradicting suggested solutions favoring environmental sustainability. Here, the SBO window could support decision-making and finding a trade-off between maximum environmental sustainability and acceptable KPIs (Figure 2). In the case of cellobiose lipid production, decreasing energy consumption moves

Figure 1



Concept of the 'Window of sustainable bioprocess operation'. **(a)** Qualitative boundaries for selected impact categories (here energy and water) are visualized in the environmental sustainability window. **(b)** Qualitative operating boundaries for aerobic bacterial fermentation (based on Woodley [3]) are visualized in the bioprocess operation window. **(c)** Combining these windows allows for determining critical operation boundaries regarding technical, economic, and environmental sustainability aspects, visualized in the window of sustainable bioprocess operation (SBO window).

Figure 2



The concept of the 'Window of sustainable bioprocess operation' demonstrated in a case study of cellobiose lipids production. **(a)** The improvement of sustainability can be realized by shifting the point of operation (PoO) from high environmental impact into acceptable ranges (impact categories are energy and water in this case study). **(b)** Translation of the improved environmental sustainability results in a shifted PoO regarding process conditions (here reduced agitation and aeration). Iteratively, a PoO resulting in acceptable ranges for both environmental sustainability and process conditions is determined. **(c)** Optimally, operating conditions are found that reduce the environmental impact maximally (here energy and water below the red line) while enabling technical feasibility and economic feasibility (blue line).

the point of operation into the boundaries of the environmental sustainability window (Figure 2a). This requires decreasing agitation and aeration in the traditional 'window of operation,' moving the point of operation closer to the boundaries of 'poor oxygen supply' and 'poor mixing' (Figure 2b). The technical and environmental boundary conditions have to be merged as visualized in the SBO window (Figure 2c). If the point of operation lies outside of the boundaries, a redesign of the fermentation or the choice of a different (bio)chemical conversion route is required.

The boundaries of the sustainability window have to be defined individually for each process as they depend on different factors, for example, the type of product, the location of the production plant, access to substrates and renewable energy, the environmental sustainabilty of substrates, or (water) recycling strategies. The same applies to the axes, which should represent the impact categories that have the prospected highest influence on the environmental sustainability of the process. In the example described, minimal water consumption and energy usage would be ideal, but these are constrained by the minimum economic requirements for a viable process. The economic requirements can be represented by process metrics translated into KPIs. These KPIs include cost per kg of product, annual production, reaction yield, biocatalyst yield, product concentration, and space-time yield. Threshold assessment values have been defined based on the chemical industry market segment (pharmaceutical industry, fine chemical industry, and bulk industry) and enable cost and process optimization in the early development phase [2,52,53]. Similar thresholds have been established for waste generation [54]. However, additional thresholds for parameters assessing environmental sustainability, such as global warming potential or energy and water consumption of processes, are still missing.

We have demonstrated how establishing the SBO window can support environmental sustainability considerations early during bioprocess development, using the example of the existing study for cellobiose lipids production [31]. A translation and application to bioprocesses currently under development will further show its benefits. Here, fitting impact categories have to be chosen, and distinct thresholds and operating points for the respective windows have to be set, all iteratively revalued based on data acquired during process development. Furthermore, the concept needs to be transferred and applied in DSP to identify sustainable bioprocess operation parameters, covering all steps of bioprocess development, ranging from inoculation to product purification. Thereby, the concept of the SBO window will support the development of environmentally sustainable and, at the same time, technically feasible and economically viable bioprocesses.

Perspective

The application of environmental sustainability analysis at early-stage bioprocess development is an emerging field. Combined and merged with traditional bioprocess optimization tools, environmentally sustainable, robust, and economical bioprocesses can be developed. Much effort is invested into gathering data and performing complex sustainability calculations; however, the re-integration into bioprocess development is not systematically done. As bioprocess engineers, we need an easily applicable tool that can be integrated into the current bioprocess development pipeline for early-stage environmental sustainability assessments. This is where the proposed SBO window can contribute. While it is a rather qualitative concept at this stage, a more quantitative implementation must be pushed forward. We invite bioprocess engineers to integrate early-stage environmental sustainability assessments using and refining the concept of the SBO window. At the very least, it will raise awareness of the importance of early-stage environmental sustainability considerations during bioprocess development and gather data for subsequent complex methods like full LCAs.

CRediT authorship contribution statement

Philipp Demling: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Katrin Rosenthal:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Alexander Grünberger:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgements

We acknowledge Christin Koch, Judith Wegmann, Esther Hegel, and Karoline Wowra for their critical proofreading of this manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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- •• of outstanding interest

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