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Research Article

Bioreactors in Medical and Biotechnological Processes: A Scientometric Review

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ABSTRACT

Automated cell-culture bioreactors-systems integrating monitoring and control to cultivate mammalian or microbial cells-are increasingly central to bioprocess engineering, particularly for biomanufacturing and advanced therapies. Despite rapid growth, research on automated bioreactors for cell culture remains fragmented across disciplines, and a consolidated scientometric understanding of its intellectual structure and emerging research fronts is still limited. This study maps the field using records retrieved from the Web of Science Core Collection and Scopus (2003-June 9, 2024). After cross-database harmonization and deduplication, the final dataset comprised 525 unique publications. We analyzed publication and citation trends, country/journal/author contributions, and collaboration and citation networks; the intellectual structure was synthesized through the Tree of Science (ToS) framework using the SAP algorithm. The ToS synthesis identifies three dominant research fronts: (i) automation-enabled microbial bioprocessing and adaptive laboratory evolution (ALE), (ii) automated cell-culture bioreactors for therapeutic manufacturing-particularly mesenchymal stromal cells (MSCs) and chimeric antigen receptor T (CAR-T) workflows-and (iii) high-throughput and intensified biomanufacturing platforms (e.g., micro/mini-bioreactors, sensor integration, perfusion/continuous concepts, and modular automation). The USA leads production (155 articles; 4862 citations; 82 in Q1), followed by Germany (96 articles; 2706 citations; 52 in Q1). At the source level, Biotechnology and Bioengineering is the most prolific journal (50 papers; Q2; H-index 213), while author-level results highlight recurrent contributions from leading researchers (e.g., Friedrich Srienc: 10 papers; H-index 10). Overall, this mapping provides a data-driven baseline to support strategic decisions in automated cell-culture bioreactor research, highlighting priorities for AI-enabled control, scalable closed systems, and sustainability-oriented bioprocess design.

Keywords: Automated Systems, Bioprocess Engineering, Bioreactor, Cells, Biotechnology, Culture, Scientometrics, Monitoring, Optimization, Research Trends, Tree of Science.

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INTRODUCTION

In the expansive domain of bioprocess engineering, the bioreactor stands as a pivotal component, meticulously engineered to optimize and sustain diverse biological reactions and enhance microorganism or cell populations. Bioprocess engineering combines industrial microbiology, biochemical engineering, and process chemistry to convert biological reactions into scalable and reproducible production processes. In this context, bioreactors provide the controlled environment-mixing, aeration, pH, temperature, and feeding-required to translate laboratory cultivation into reliable biomanufacturing and biomedical applications. These systems are crucial for key industries such as pharmaceuticals, food production, and agriculture (Wu *et al*., 2025). Over the past few decades, bioreactor technology has undergone significant advancements. In the late 1990s and early 2000s, bioreactor work in industrial bioprocessing and cell/microbial cultivation was predominantly performed in bench-to pilot-scale systems, which typically required substantial utilities (e.g., mixing, aeration, temperature control) and were comparatively resource-intensive. In the early-mid 2010s, a notable shift occurred toward miniaturized and microbioreactor platforms (milliliter-scale systems) to support faster experimentation, improved parallelization, and more efficient scale-down/scale-up learning. These innovations not only reduce resource consumption but also serve as a robust foundation for understanding and scaling up processes for large-scale industrial production (Bareither *et al*., 2013; Krupczak *et al*., 2024; Meinert *et al*., 2017).

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Despite these significant advancements, a comprehensive review that traces the chronological evolution and intellectual structure of bioreactor research through scientometric methods remains largely absent. While existing literature-mostly accessible via electronic databases-offers insights into various bioreactor types, methodologies, and applications, it often lacks an integrated perspective on the field's overall development, key turning points, and emerging trends. Importantly, the rapid expansion of automated bioreactor research has also increased fragmentation across disciplines (bioprocess engineering, automation and control, microscale systems, and cell-based manufacturing), with heterogeneous terminology and platform designs that make the field difficult to synthesize and compare. At the same time, several practical bottlenecks continue to limit translation from laboratory studies to robust biomanufacturing-particularly reproducibility across scales, closed and automated operation for contamination control, real-time monitoring and control for consistent product quality, and cost-effective scalability (especially for cell therapy workflows). In this context, a scientometric review is not merely descriptive; it provides an evidence-based way to identify the dominant and emerging trajectories, locate intellectual milestones, and highlight underexplored areas where methodological and technological breakthroughs are still needed.

This article addresses that gap by consolidating diverse perspectives and methodologies to present a detailed, data-driven account of the progressive evolution of bioreactor technologies. Specifically, it employs scientometric techniques, including the Tree of Science (ToS) framework, to map the historical trajectories and intellectual landscape of the field (Robledo *et al*., 2024). The analysis is informed by systematic searches in the Web of Science (WoS) and Scopus databases, covering an extensive timeframe to capture the historical development and recent trends. We curated a harmonized dataset and applied ToS/SAP to identify foundational works, core developments, and emerging fronts, providing a benchmark for research prioritization and technology roadmapping. In this review, the term bioreactor refers specifically to automated bioreactor systems used for cell culture (i.e., platforms integrating monitoring and control for cultivating mammalian or microbial cells), rather than all bioreactor types used across biotechnology.

To clarify the contribution of this study, our review goes beyond prior narrative or general scientometric overviews by focusing specifically on automated bioreactor systems for cell culture and by integrating a dual-database strategy (WoS and Scopus) with a harmonization and deduplication workflow that enables consistent downstream network analyses. Building on this curated dataset, we apply the ToS approach (via the SAP algorithm) to reconstruct the field's intellectual structure and to classify influential works into roots, trunk, and branches, thereby linking historical foundations to current research fronts. This combination provides a transparent, data-driven benchmark of the field's evolution-covering production and citation dynamics, geographic and collaboration patterns, and the most influential journals and authors-while also identifying the dominant emerging trajectories (branches) in automated bioreactors relevant to medical and biotechnological applications.

The central objectives of this study are to:

- **(a)** Identify and analyze temporal trends in publications and citations related to bioreactor technologies.
- **(b)** Map the key research areas, influential countries, institutions, journals, and authors contributing to the field.
- **(c)** Elucidate the intellectual structure of bioreactor research by identifying foundational work, major developments, and emerging research fronts using the ToS methodology.
- **(d)** Discuss the implications of these findings for the future research, development, and application of bioreactor technologies, particularly in medicine and biotechnology.

This review concludes with an in-depth discussion on the contemporary relevance of bioreactors, highlighting their expanding role in critical areas such as drug manufacturing, personalized therapies, and other cutting-edge biotechnological applications. Our analysis reveals that advances in bioreactor technologies have played a crucial role in driving microbial evolution by enhancing growth efficiency, facilitating the use of alternative substrates, and improving resilience under adverse environmental conditions (Bertaux *et al*., 2022). By presenting a comprehensive scientometric overview, this work offers strategic insights for researchers, engineers, and policymakers. It summarizes past milestones, outlines the current research landscape, and identifies future opportunities for innovation in the field of bioreactor technology.

The remainder of the paper is organized as follows: Section 2 describes data collection, harmonization, and the scientometric/ToS procedures; Section 3 reports trends and network results at the country, journal, and author levels; Section 4 synthesizes the ToS roots-trunk-branches structure and discusses implications and research gaps

METHODOLOGY

This study employs a scientometric approach to analyze the evolution and impact of bioreactor research within the biotechnology and medical industries. The methodology encompasses several stages: data collection, preprocessing, scientometric analysis, and the application of the ToS framework.

Data collection

Systematic searches were conducted in two major multidisciplinary citation databases (WoS Core Collection and Scopus) to maximize coverage and minimize database-specific bias in the retrieval of automated bioreactor research. Comparative evidence shows that WoS is more selective, whereas Scopus indexes a substantially larger set of source titles; importantly, nearly all journals covered by WoS are also indexed in Scopus, but each database still contains unique sources. Using both databases therefore improves retrieval completeness and reduces distortions associated with relying on a single index (e.g., disciplinary and language-related coverage differences) (Gavel and Eyelid, 2008; Singh *et al.*, 2021). The search strategy targeted literature published between 2003 and June 9, 2024. Search strings were applied using each database's field tags and syntax, and records were exported with full bibliographic metadata (and reference lists when available) for downstream harmonization and analysis. Table 1 reports the complete search queries and filters used in WoS and Scopus.

Data Preprocessing and Screening

The data collection and screening process followed a structured four-stage methodology, as illustrated in Figure 1 (Duque and Tabares, 2024; Grisales *et al.*, 2023; Guerrero-Sierra *et al.*, 2024; Vargas-Hernández *et al.*, 2024). Merging datasets from Scopus and WoS presents a significant challenge due to their inherently different reference formats (Robledo *et al.*, 2024). Records retrieved from WoS and Scopus were harmonized and deduplicated prior to analysis. Cross-database merging is nontrivial because WoS exports commonly include DOIs but provide limited reference metadata, whereas Scopus provides richer reference strings (e.g., author list, title, source, year) but may omit DOIs. To ensure comparability, we standardized all records into a unified schema (DOI, normalized title, normalized authors, year, and source). Metadata gaps were addressed through DOI-based enrichment using Crossref for WoS records, while Scopus reference strings were parsed to extract the corresponding bibliographic fields. Duplicate detection was then performed using DOI matches where available and normalized metadata matching otherwise. After harmonization and deduplication, the resulting dataset was used as the basis for all subsequent analyses.

The harmonized dataset was further enriched to support trend and source analyses by computing annual publication and citation counts and assigning journal quality indicators (SJR quartiles) using year-sensitive matching. The same standardized structure enabled the construction of analysis-ready networks, including co-authorship, journal citation, and document citation networks (Hurtado-Marín *et al.*, 2021). Finally, the document citation network was used as input to the SAP algorithm to generate the Tree of Science outputs (roots, trunk, branches) (Valencia-Hernandez *et al.*, 2020). To keep the main text concise while improving reproducibility, a worked harmonization example and the standardized output schema are provided in the Supplementary Material (Table S1).

Scientometric Analysis

The scientometric analysis was structured around key dimensions to comprehensively assess the development and impact of bioreactor research. First, publication trends were examined by analyzing annual scientific output and total citations, offering insights into the growth trajectory and scholarly influence of the field. A country-level analysis evaluated the academic contributions of different nations, considering the number of publications, total citations, and journal quality based on Scimago quartiles. International collaboration networks were also visualized to illustrate cross-border research dynamics. In parallel, journal analysis identified the most productive and influential journals in the field by assessing impact factors, H-indexes, and quartile rankings, while also mapping citation relationships between journals. Author-level metrics were analyzed to rank leading researchers by publication count and H-index, alongside a visualization of their collaboration networks. Standard scientometric indicators were calculated, and network visualizations were generated using Gephi (Bastian *et al.*, 2009).

ToS Framework

To map the intellectual structure and evolution of bioreactor research, the ToS framework was applied (Valencia-Hernandez *et al.*, 2020; Zuluaga *et al.*, 2022). This methodology organizes scientific literature into three main components: roots, representing foundational studies that provide the theoretical basis of the field, typically older and highly cited papers. Trunk, comprising key works that consolidate and structure the core knowledge of bioreactor technology, bridging foundational literature with contemporary research. Branches represent current research fronts, often characterized by recent, high-impact publications that explore emerging and specialized areas. The classification of articles into these categories was guided by citation analysis, including local and global citation scores, and validated through expert review.

RESULTS

Scientometric Analysis

Scientific Production and Citation Trends

Figure 2 summarizes annual scientific production and citation dynamics in automated cell-culture bioreactor research from 2003 to 2024. The bars show the number of publications indexed in Scopus and Web of Science (WoS) each year, while the red line represents the annual output of the merged, deduplicated dataset

Table 1: Search parameters used in both databases.

Parameter	WoS	Scopus
Range	2003-2024	
Date	June 9, 2024	
Document Type	Paper	
Words	Title-abs-key (automated AND cell AND bioreactor)	
Results	305	453
Total (Wos+Scopus)	525	

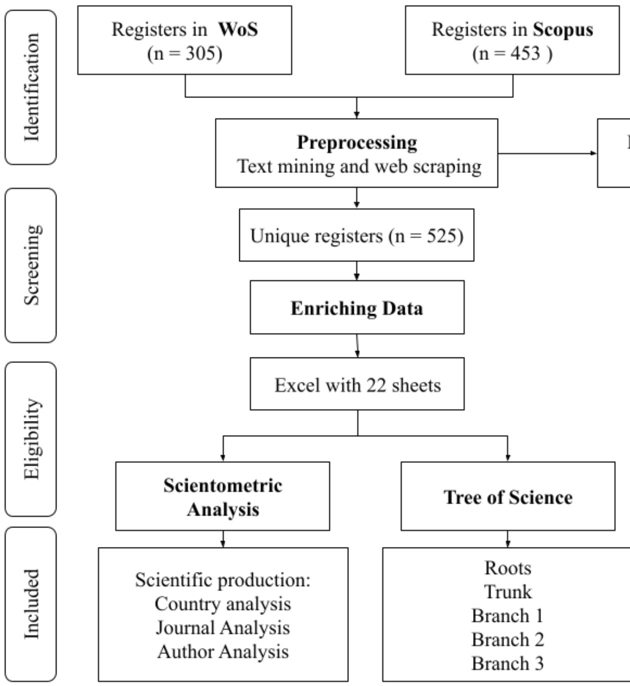

Figure 1: Illustration of the four-stage data collection and preprocessing pipeline.

(unique publications). The purple line shows the total citations accumulated by the publications (both databases combined). To facilitate interpretation, the timeline is divided into three periods-Period 1 (2003-2009), Period 2 (2010-2017), and Period 3 (2018-2024)-reflecting changes in publication volume and citation patterns.

A key point for interpreting citation-based indicators is citation lag: recent publications have had less time to accumulate citations. Therefore, citation growth rates are interpreted primarily as within-dataset benchmarks across periods, rather than as absolute indicators of impact.

Period 1 - Emergence and Initial Growth (2003-2009)

This phase shows early expansion, with an average annual citation growth of 8.89%, the highest among the three periods. The period culminated in a peak around 2007 (2,167 total citations). Among the highly cited works in this phase is Blommel and Fox (2007), which proposed an integrated strategy to improve large-scale production of Tobacco Etch Virus (TEV) protease-an enabling reagent in recombinant protein workflows where proteases are used to cleave fusion tags-illustrating early efforts toward more scalable and efficient bioprocess operations. Overall, Period 1 reflects foundational contributions that later research streams build upon.

Period 2 - Consolidation (2010-2017)

During this phase, the field maintained a steady pace of development, albeit with a slightly reduced average annual citation growth of 6.94%. Citation activity showed fluctuations, with peaks in 2012 and 2017, and dips in 2011 and 2014. These variations suggest a maturing field where foundational research began to branch into more specialized areas. While research output remained robust, its influence appeared distributed across emerging sub-themes within bioreactor studies.

Period 3 - Renewed Growth and Specialization (2018-2024)

The most recent period reflects renewed growth, with an average annual citation increase of 7.82%, slightly above Period 2. Publication volume rises sharply, reaching an all-time high in 2024 (Scopus: 44 papers). In contrast, citations for the most recent publications decline from 1,144 in 2020 to 49 in 2024, which is expected given citation lag. Taken together, Period 3 indicates an expanding research landscape with increasing output and evolving research fronts, while citation totals for the newest work remain temporally constrained.

Finally, Scopus reports more publications than WoS for the same query and time window (Scopus: n=453; WoS: n=305), which is consistent with Scopus' broader source coverage and WoS' more selective indexing. Nevertheless, both databases contribute unique records; therefore, merging WoS and Scopus increases retrieval completeness beyond either database alone. Across the full period, the overall citation trend indicates sustained accumulation of scholarly attention within this dataset (overall average citation growth: 7.85%).

Country Analysis

The academic production of countries reflects their strategic investment and research focus in the field of bioreactors. Table 2 displays three key variables for analyzing national academic output: total production (number of articles), citation impact (total citations received), and research quality (approximated by the distribution of articles in Scimago Journal Quartiles).

The USA leads in academic production with 155 articles (29.19% of the total) and the highest citation impact (4862 citations, 32.39% of total). A significant majority of its articles (82) are in Q1 journals. Germany follows as a key player, contributing 96 articles (18.08%) and garnering 2706 citations (18.03%), with 52 articles in Q1 journals. Other significant contributors include the United Kingdom, Switzerland, and Italy. China, while having a notable number of publications (15), shows a comparatively lower citation impact and a smaller proportion of articles in Q1 journals within this specific dataset, suggesting a different research focus or impact trajectory compared to Western nations in this particular search query.

Recent studies from leading countries highlight advanced applications. For instance, researchers in the USA have focused on optimizing high-performance Recombinant Adeno-Associated Viral (rAAV) vector production through multivariate bioprocess and transfection condition optimization, crucial for gene therapies (Coplan *et al.*, 2024). This exemplifies how precise adjustment of bioreactor parameters can transform therapeutic development.

Figure 3 presents the global network of collaboration among countries in bioreactor research. Three major communities are highlighted: the first led by the USA, Germany, and the UK; the second by Switzerland and Italy; and the third primarily by China. This visualization underscores the international nature of bioreactor research and identifies key collaborative hubs. For example, joint research between the USA and Germany has explored innovative Temporary Immersion Bioreactors (TIB) for micropropagation of commercially important tree species, demonstrating enhanced multiplication rates and highlighting TIB's potential for scalability and automation (Businge *et al.*, 2017). Swiss and Italian researchers have designed *in vitro* cardiovascular training programs using cyclic mechanical stimulation in bioreactors to develop functional cardiac tissue, advancing regenerative medicine (Massai *et al.*, 2020). More recently, researchers from China have utilized Raman spectroscopy with Design of Experiments (DoE) in bioreactors for real-time intracellular monitoring, significantly improving efficiency and precision in biopharmaceutical production (Dong *et al.*, 2024).

Journal Analysis

Table 3 presents the leading academic journals contributing to bioreactor research within the analyzed dataset. Most of these journals fall within the top two quartiles (Q1 and Q2) of the Scimago Journal Rank, indicating their strong influence and academic quality. Among them, Biotechnology and Bioengineering stand out as the most prolific, with a total of 50 publications across both WoS and Scopus. In contrast, Lab on a Chip holds the highest impact factor among the listed journals (1.246), reflecting its strong citation performance and relevance in high-impact biotechnological research.

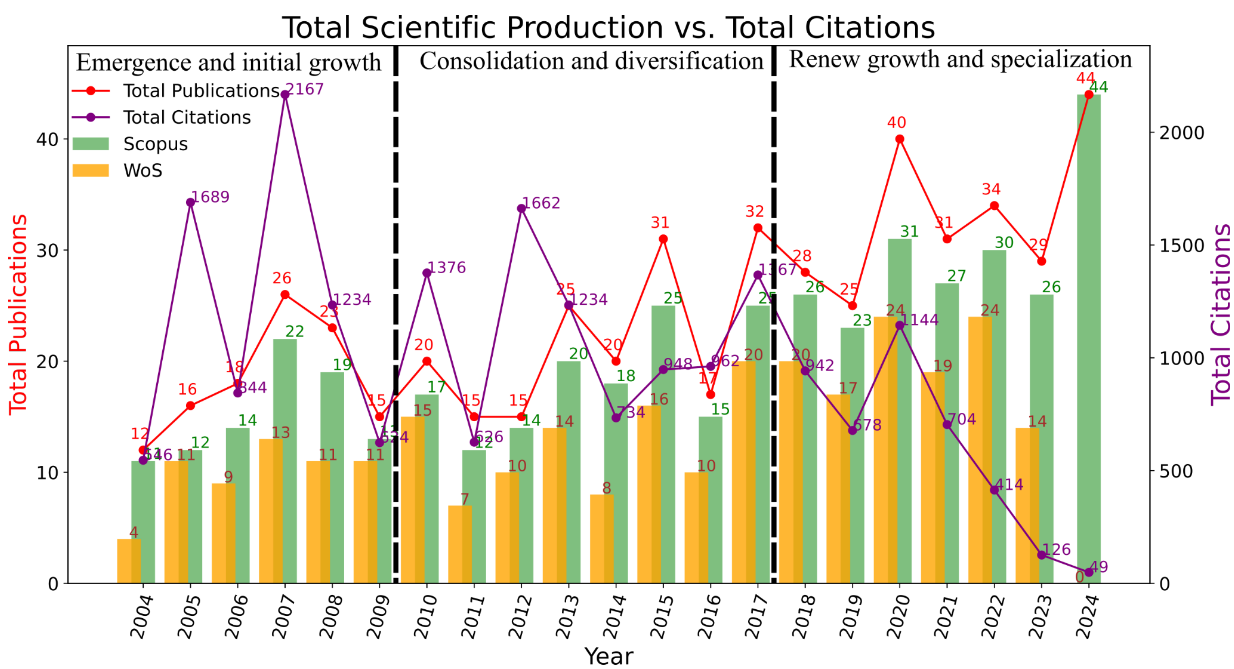

Figure 2: Scientific production and citation trends in bioreactor research (2003-2024).

Table 2: Evaluation of scientific production and citation impact by country, with quartile distribution (Q1-Q4 refer to Scimago Journal Quartiles based on the publishing journal).

Country	Production		Quality		Q1	Q2	Q3	Q4
	Count	%	Citations	%				
USA	155	29.19	4862	32.39	82	50	5	1
GERMANY	96	18.08	2706	18.03	52	33	3	0
UNITED KINGDOM	34	6.4	960	6.4	21	12	0	0
SWITZERLAND	30	5.65	955	6.36	14	9	2	0
ITALY	18	3.39	511	3.4	14	4	0	0
CANADA	17	3.2	417	2.78	13	1	1	0
CHINA	15	2.82	176	1.17	4	10	0	0
FRANCE	13	2.45	385	2.56	10	1	0	0
AUSTRIA	12	2.26	212	1.41	6	4	0	0
KOREA	12	2.26	250	1.67	6	4	1	0

Recent publications reflect a growing emphasis on integrating advanced analytics and automation in bioprocessing. For instance, a 2024 study by Sebastian *et al*., (2024) in Biotechnology and Bioengineering demonstrated the use of cell particle size data from automated cell counters to accurately predict monoclonal antibody harvest yields, streamlining process monitoring and control. This aligns with broader trends in bioreactor research toward intelligent, data-driven process optimization.

Figure 4 illustrates the citation network among key journals in the field, revealing three core thematic clusters (highlighted in purple, orange, and green), which are strongly associated with keywords such as and *Biomaterials*. These clusters underscore the multidisciplinary nature of bioreactor research. Notable studies from these journals include López *et al*., (2024) who explored large-scale Mesenchymal Stem Cell (MSC) production from Wharton's jelly, emphasizing the importance of initial cell adhesion to microcarriers and comparing serum-based versus serum-free media. Similarly, Goral *et al*., (2024) presented a novel Fixed-Bed Bioreactor (FBR) platform for adherent cell cultures, using computational modeling to optimize nutrient flow distribution, drawing analogies to architectural design principles for maximizing functional efficiency.

Author Collaboration Network

Table 4 highlights the leading researchers in bioreactor technology, ranked by their number of publications within the analyzed dataset and their H-index, Effective Size, Constraint, and Collaboration Diversity Index (CDI). Among the most prolific contributors are Friedrich Srienc and Wolfgang Wiechert, each with ten publications. These researchers have made significant contributions across a wide spectrum of bioreactor applications. For example, Sitton and Srienc explored the automation of cell culture monitoring using flow cytometry, enabling precise adjustments in fed-batch scheduling to improve consistency and efficiency (Sitton and Srienc, 2008). Similarly, Weichert, in collaboration with Hemmerich, investigated the optimization of culture media for industrial biotechnology by integrating laboratory automation and Microtiter Bioreactor (MBR) systems with Design of Experiments (DoE) methodologies (Hemmerich *et al*., 2018).

Table 4 presents also network metrics (Effective Size, Constraint, and CDI) which offer insights into their collaboration strategies. The Effective Size metric quantifies the number of non-redundant contacts in an author's collaboration network. A high effective size indicates that a researcher collaborates with individuals who are not connected to each other, fostering access to diverse knowledge and perspectives. In this regard, Researcher Peter Neubauer stands out with the highest effective size (180.05), suggesting that his collaborations span across loosely connected research communities, which may enhance the originality and interdisciplinary nature of his contributions.

The Constraint metric captures the extent to which an author's collaborations are confined within a tightly knit group. A higher constraint implies that a researcher invests their collaborative efforts within a cohesive team. For instance, Researcher Roberto C. Giordano exhibits a high constraint value (0.49), reflecting his close and recurrent collaboration with a specific group of co-authors-an observation also supported by the co-authorship network shown in Figure 5.

Lastly, the CDI indicates whether a researcher tends to explore new partnerships (low CDI) or consistently works with the same collaborators (high CDI) (E. Y. Li *et al*., 2013). Researcher Dirk Webster-Botz, with the highest CDI (0.20), appears to favor long-term collaboration with a stable set of co-authors. In contrast, Researcher Wolfgang Wiechert demonstrates the lowest CDI (0.08), highlighting his preference for engaging with a broader and more diverse set of collaborators, which can lead to the integration of novel ideas and methodologies into his work.

Figure 5 visualizes the collaboration network among these key authors, revealing intellectual and institutional linkages. One notable connection is between Neubauer and Wiechert, suggesting shared research initiatives. For instance, Neubauer contributed to the work by Kemmer (2023), which focused on the high-throughput expression of inclusion bodies in E. coli using automated mini-bioreactor platforms. This study exemplifies the growing shift toward automation in protein production. The use of mini-bioreactors enables real-time monitoring, rapid testing under different conditions, and accelerated optimization of both upstream and downstream processes. As a result, the overall workflow is streamlined, which improves efficiency, reduces costs, and enhances the quality and scalability of inclusion body production, while addressing the traditional challenges associated with time-intensive and complex protocols.

Mapping the Evolution of Bioreactor Technology

The ToS analysis offers a structured overview of the intellectual evolution of bioreactor technology by categorizing key literature into three levels: Roots (foundational works), Trunk (core developments), and Branches (emerging research fronts). Figure 6 visually illustrates the main areas of knowledge and their interconnections, as revealed through the ToS framework and keyword co-occurrence analysis. This visualization highlights how foundational research has shaped current advancements and how emerging trends are branching into new directions.

Root: Foundations in Automation and Controlled Cultivation

The foundational literature focuses on early innovations aimed at automating and controlling microbial and cell cultivation processes. Puskeiler *et al.*, (2005) marked a major milestone by developing seven bioreactors integrated with an automated system for fed-batch fermentation of Escherichia coli, significantly improving process efficiency and consistency. Around the same time, Dominici *et al.*, (2006) applied optimized automated bioreactors for MSC production, emphasizing the importance of controlled environments in enhancing therapeutic efficacy.

Further advancements were demonstrated by Hsu *et al.*, (2012) who evaluated Chinese Hamster Ovary (CHO) cell lines using integrated analyzers, and Moses *et al.*, (2012), who studied monoclonal antibody-producing cell lines in 3L bioreactors with similar analytical systems. Both studies confirmed that these integrated platforms could deliver results comparable to traditional bioreactors, reinforcing the promise of automation in bioprocessing.

Additionally, Martin *et al.*, (2004) explored the visionary concept of engineering living tissues and three-dimensional organs *in vitro*, highlighting both the transformative potential and the significant challenges, such as high costs and the complexity of developmental biology. Collectively, these pioneering works established automation, process control, and scalability as critical foundations in the evolution of bioreactor technology.

Trunk: Development of Scalable and Efficient Bioprocesses

The trunk of the ToS reflects the development and refinement of bioreactor systems towards greater efficiency, reduced costs, and enhanced control, particularly with the advent of smaller-scale and micro-bioreactors. Nienow *et al.*, (2013) highlighted remarkable advancements in bioprocesses over the preceding decade, with particular emphasis on small 15 mL bioreactors that proved as effective as 5L systems for initial studies,

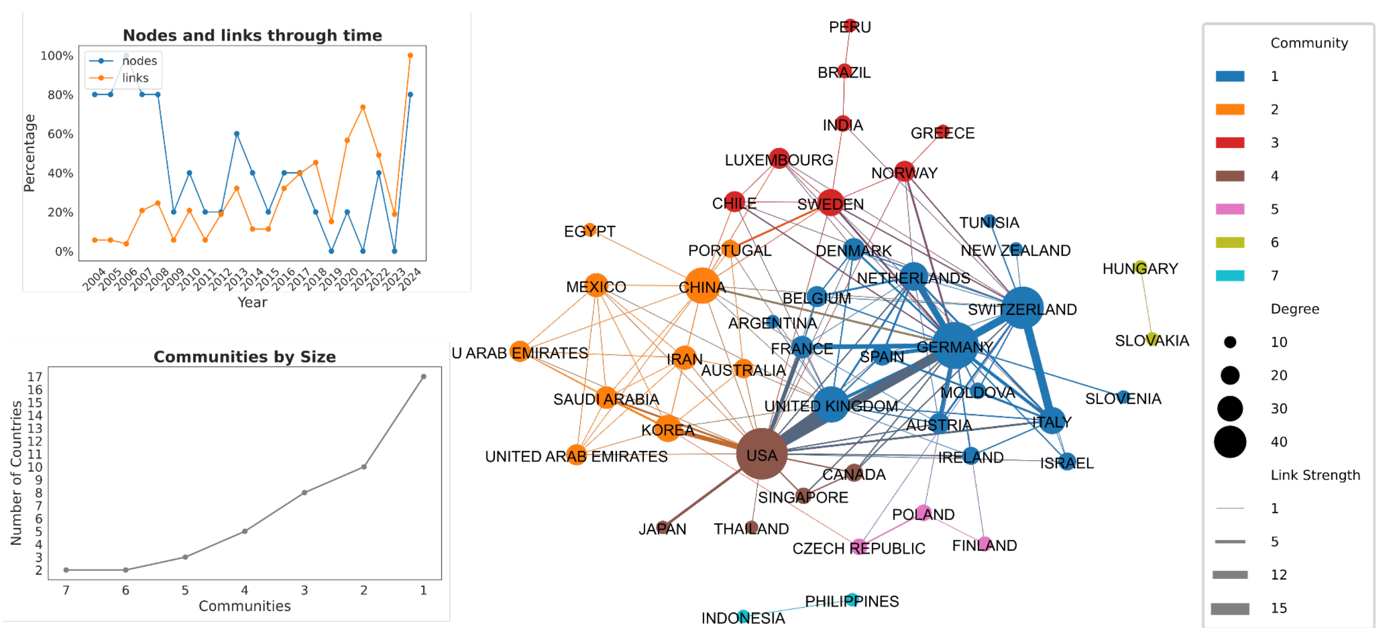

Figure 3: Global network of collaboration among countries in bioreactor scientific research, including community structure and temporal evolution of links and nodes.

facilitating easier scale-up. Bareither *et al*., (2013) conducted experiments with smaller-scale bioreactors (250 mL) for scaling studies, aiming to maximize yield through micro-analytical approaches. More recently, bioreactors as small as 10 mL have been developed, offering advantages like high efficiency, reduced costs, minimized variability, and enhanced automation (Meinert *et al*., 2017; Velugula-Yellela *et al*., 2018). The importance of fully automated systems for ensuring the safety and consistency of mesenchymal stem cell production was emphasized by Rojewski *et al*., (2013). Rameez *et al*., (2014) underlined the efficiency and high demand for bioreactors in cell culture for improving production and process safety. Hanley *et al*., (2014) noted that while MSCs represent a significant advancement for diabetes and cardiac issues, the high costs of traditional generation methods remain a barrier, suggesting that automated systems like the Quantum platform could provide a solution. Bareither and Pollard (2011) stressed the pharmaceutical industry's race for faster, cost-effective, high-quality processes and predictive models, envisioning "turbo mini-laboratory" bioreactors capable of running multiple reactions simultaneously. These works signify a concerted effort to make bioreactor technology more accessible, efficient, and suitable for diverse applications from research to industrial production.

In our dataset, the identified branches are interpreted as the dominant emerging trajectories because they concentrate a substantial share of the most recent publications while forming dense citation neighborhoods anchored in the trunk, indicating cumulative and ongoing research activity rather than isolated contributions. Conversely, topics that appear only sporadically in the citation network-represented by small, weakly connected clusters or single papers-are treated as marginal or underexplored within this query scope. These may reflect niche applications, early-stage approaches, or themes that fall partially outside our focus on automated cell-culture bioreactors and therefore warrant further investigation in future targeted searches.

Branches: Specialized Applications and Cutting-Edge Innovations

The branches of the ToS represent the cutting-edge frontiers of bioreactor research, highlighting advanced and specialized applications. These are grouped into three main thematic directions, each illustrated by representative studies.

Branch 1: Enhancing Microbial Processes and Adaptive Laboratory Evolution (ALE)

This area focuses on leveraging automation and control to evolve microbial strains and optimize microbial processes. Recent innovations have transitioned ALE from manual, labor-intensive protocols to more efficient automated platforms. For example, Halle *et al*., (2023) utilized a bioreactor system with microtiter plate recycling to improve microbial yield and longevity. Bromig and Weuster-Botz (2022) introduced a microtube bioreactor with gas-permeable Teflon for bubble-free oxygenation, enhancing microbial evolution efficiency. Li *et al*., (2023) proposed an automated liter-scale ALE platform using stirred-tank bioreactors for rapid serial passaging. Mechanistic models are crucial for understanding biological processes, but precise data for these models can be elusive. Complementing these, Anane *et al*., (2019) proposed a "toolbox" using advanced mathematics and simulations (Monte Carlo) to refine these models and improve reliability, while Haby *et al*., (2019) implemented a robotic setup with 48 mini-bioreactors for parallel cultivation and real-time process control. Together, these studies underscore a shift toward highly automated, precise, and scalable microbial bioprocessing systems.

Table 3: Top journals in bioreactor research by publication count, with Impact Factor (IF), h-index, and Quartile (Q) distribution from the analyzed dataset.

Nombre_Revista	SN	WOS	SCOPUS	Total	Impact factor	Quartile	h-index
Biotechnology And Bioengineering	00063592	25	46	50	0.811	Q2	213
Biotechnology Progress	87567938	21	30	35	0.527	Q2	143
Journal of Biotechnology	01681656	13	19	20	0.741	Q2	177
Biotechnology Journal	18606768	10	14	14	0.908	Q1	109
PLOS One	19326203	7	8	10	0.839	Q1	435
Journal Of Visualized Experiments	1940087x	0	9	9	0.449	Q2	131
Lab On a Chip	14730197	4	7	9	1.246	Q1	246
Bioprocess And Biosystems Engineering	16157591	4	6	8	0.64	Q2	83
Biotechnology Letters	01415492	4	6	8	0.519	Q2	127
Applied Microbiology and Biotechnology	01757598	3	6	7	0.957	Q1	267

Table 4: Top researchers in the field of bioreactors, by total articles, Google Scholar H-index, and affiliation.

Author	Papers Total	Total Citations	H-Index	Effective Size	Constraint	CDI
Friedrich Sriench	10	382	10	34.68	0.07	0.3
Wolfgang Wiechert	10	469	7	90.08	0.04	0.08
Peter Neubauer	9	216	7	180.05	0.02	0.11
Dirk Webster-Botz	8	361	6	83.89	0.04	0.2
James Kacmar	7	306	7	5.6	0.35	0.19
Gary Lye	7	321	6	32.95	0.09	0.17
Qasim A. RAFIQ	7	123	5	7.0	0.25	0.11
Roberto C. Giordano	6	114	3	1.0	0.49	0.14
Jung-Kul Lee	6	75	4	110.58	0.03	0.12
Kee-Won Lee	6	46	4	114.06	0.03	0.17

Branch 2: Advancements in Cell Culture for Therapeutic Applications

This branch explores bioreactor applications in producing cells and cell-derived products for therapies. Recent developments focus on CAR-T cells and MSCs. Song *et al*., (2024) demonstrated that adjusting oxygen levels in bioreactors can fine-tune the CAR-T cell mix for specialized anti-cancer missions. Melocchi *et al*., (2024) developed a robotic system for automated, contamination-free cell cultivation in bioreactors. Larey *et al*., (2024) used bioreactors to scale up the production of extracellular vesicles from stimulated MSCs, crucial for intercellular communication. Duysens *et al*., (2024) perfected culturing equine muscle-derived MSCs in hollow-fiber bioreactors, achieving high cell numbers.

Innovative systems like those integrating mini-bioreactors with Liquid Handling Stations (LHS) and non-invasive sensors for real-time pH and dissolved oxygen measurement, coupled with mathematical modeling for control, are prominent (Markert and Joeris, 2017). Nickel *et al*., (2017) analyzed real-time bioprocess data from parallel fed-batch fermentations at the milliliter scale using a mini-bioreactor and LHS for offline measurements, reducing development time. These studies signify a move towards precision medicine and scalable cell therapies.

Branch 3: High-Throughput Systems and Next-Generation Biomanufacturing

This branch focuses on high efficiency tools and integrated systems for modern biomanufacturing. Gagliardi *et al*., (2019) developed high-throughput bioreactors like the ambr15 for simulating perfusion cell cultures at large scales, effective for mAb production in CHO cells. Velugula *et al*., (2018) used automated micro-bioreactors for co-culturing antibodies in CHO cells, allowing investigation of various culture conditions with minimal process variability. These systems often incorporate DOEs with multiple variables and integrated analyzers.

Russell *et al*., (2018) discussed automation for MSC expansion in regenerative medicine, balancing cost, time, and labor for clinical trials. Frank *et al*., (2019) highlighted the importance of coating agents in hollow-fiber bioreactors for large-scale, controlled MSC cultivation. Janzen *et al*., (2019) emphasized efficient, automated high-throughput cultivation platforms for early-stage microbial bioprocess development. The central theme, including studies by Rotondi *et al*., (2021) on improved ambr250 vessels and Cunningham *et al*., (2022) on hollow fiber perfusion for T-cell expansion is the drive for efficiency, automation, and practical applicability in biomanufacturing.

Further illustrating cell therapy advancements, Gabetti *et al*., (2022) introduced an intermittent agitation strategy in a cylindrical rotating bioreactor for CAR-T cell expansion. Carrabba *et al*., (2024) emphasized modular automation for T-cell production, reducing costs. Choi *et al*., (2022) studied low oxygen effects on T-cells, proposing *ex vivo* conditioning to enhance antitumor efficacy. Wang *et al*., (2019) compared automated and manual MSC manufacturing, finding both can yield high-quality cells, with the choice depending on scale and resources. Recent advancements also include automated, personalized scale-up systems for tissue-engineered product manufacturing, highlighting the move towards more adaptable and efficient production platforms (Melocchi *et al*., 2025). These innovations contribute to optimizing cell expansion for personalized therapies.

DISCUSSION

Scientific implications for automated bioreactors

The scientometric analysis and ToS framework depict automated cell-culture bioreactor research as a dynamic and rapidly evolving field. The sustained increase in publications and accumulated citations indicates continued scientific and technological relevance, driven by demand for more efficient, scalable, and tightly controlled biological production systems in medicine and biotechnology.

A dominant scientific trajectory is the shift from large-scale, resource-intensive bioreactors toward miniaturized, automated, and sensor-enabled platforms, including milli- and micro-bioreactors. Miniaturization, coupled with automation and advanced sensing, enables high-throughput experimentation, faster process optimization, and reduced material consumption (Bareither *et al.*, 2013; Markert and Joeris, 2017; Nienow *et al.*, 2013). This direction aligns with industrial initiatives such as Process Analytical Technology (PAT) and Quality by Design (QbD) in biopharmaceutical manufacturing, which emphasize in-process monitoring and control to ensure robust product quality (Rathore and Winkle, 2009).

The ToS narrative further clarifies how the field progressed from foundational automation principles (Roots) (Dominici *et al.*, 2006; Puskeiler *et al.*, 2005), through critical platform and scale-down developments (Trunk) (Bareither and Pollard, 2011; Nienow *et al.*, 2013), toward contemporary research fronts (Branches). These branches highlight three prominent scientific directions: advanced microbial engineering, including Adaptive Laboratory Evolution (ALE) in automated systems (Halle *et al.*, 2023; R. Li *et al.*, 2023); cell therapy manufacturing, including CAR-T and MSC production with strong emphasis on culture optimization, product quality, and safety (Melocchi *et al.*, 2024, 2025; Song *et al.*, 2024); and process intensification, including high-throughput and continuous/perfusion bioprocessing to enhance productivity (Gagliardi *et al.*, 2019; Rotondi *et al.*, 2021). Collectively, these trajectories suggest a future where automated bioreactors become increasingly central to personalized medicine, scalable biomanufacturing, and rapid response capabilities for emerging health needs.

Despite progress, several scientific gaps remain. First, there is a strong need for deeper integration of AI and machine learning for dynamic control, predictive modeling, and real-time optimization based on high-dimensional sensor data (Cheng *et al.*, 2023). Second, scaling patient-specific cell therapies continues to face practical bottlenecks, reinforcing the importance of closed, automated, and GMP-compliant systems that enable reliable scale-out strategies (Lipsitz *et al.*, 2016). Third, sustainability pressures increasingly motivate bioreactor and process designs that reduce waste, improve resource efficiency, and align with circular bioeconomy principles (Stegmann *et al.*, 2020). Finally, improved mechanistic and data-driven models remain necessary to better predict cell behavior-especially in complex settings such as co-cultures or tissue engineering applications (Anane *et al.*, 2019).

Methodological implications for scientometric research

From a scientometric perspective, this study illustrates how combining conventional bibliometric indicators with citation-network synthesis (ToS) can generate an interpretable map of a technological field's evolution. The ToS structure (roots-trunk-branches) complements descriptive performance indicators by linking influential historical contributions to current research fronts, helping translate network structure into a narrative representation of the domain.

Methodologically, the work also reinforces the importance of cross-database strategies in domains where coverage varies across indexing services. Although WoS and Scopus provide broad access to peer-reviewed literature, they differ in indexing scope and exported metadata structures, particularly for cited references. This study therefore highlights the practical necessity of harmonization and deduplication using standardized fields (e.g., DOI, normalized title/authors, year, and source) to enable consistent downstream analyses such as co-authorship networks, journal citation networks, and document citation networks. More broadly, the approach provides a transparent workflow that can

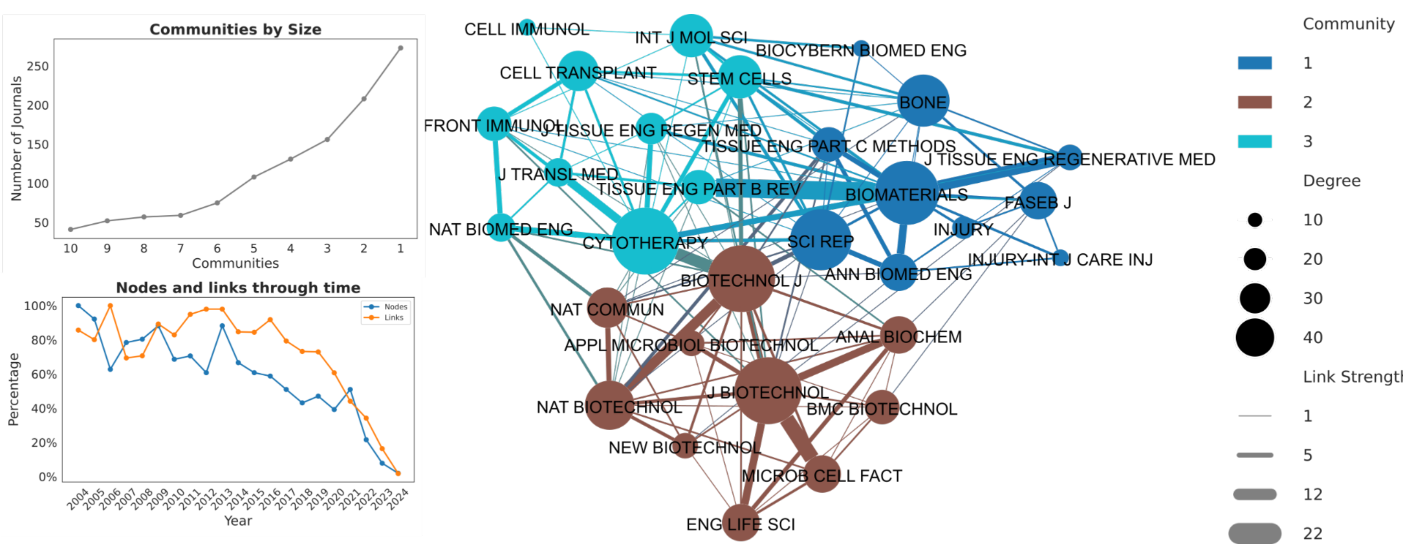

Figure 4: Citation network between journals highlighting collaboration communities in bioreactor research.

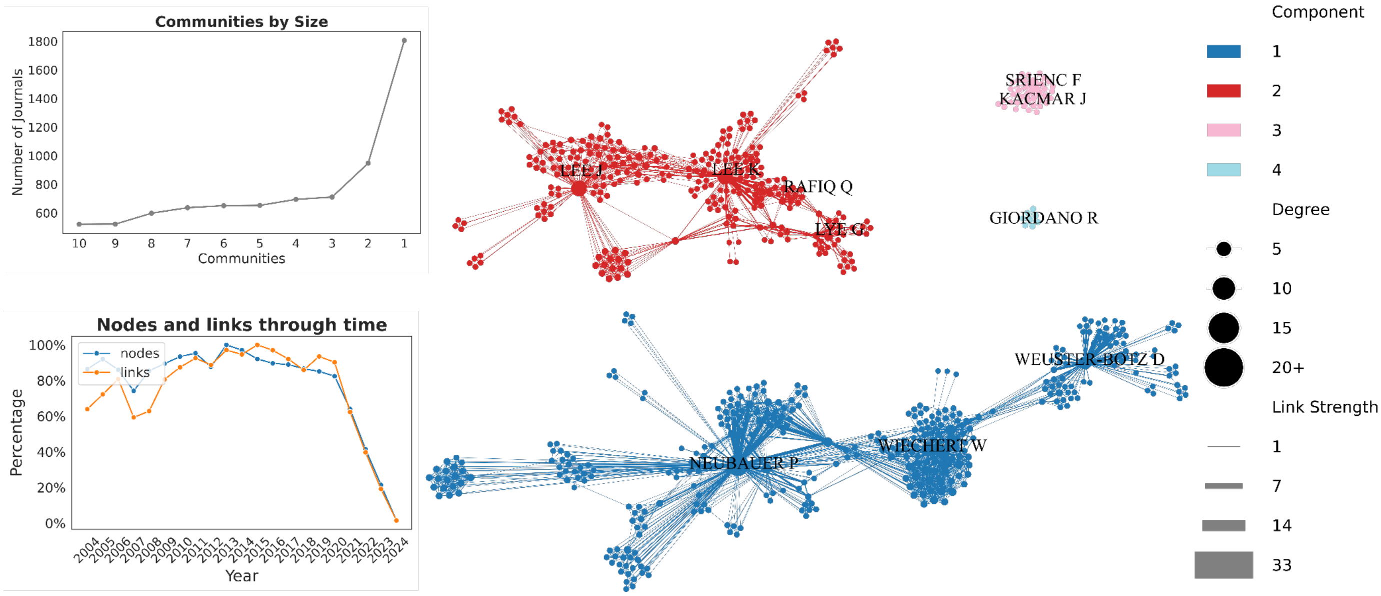

Figure 5: Collaboration network of prominent authors in bioreactor research, indicating links and community structures.

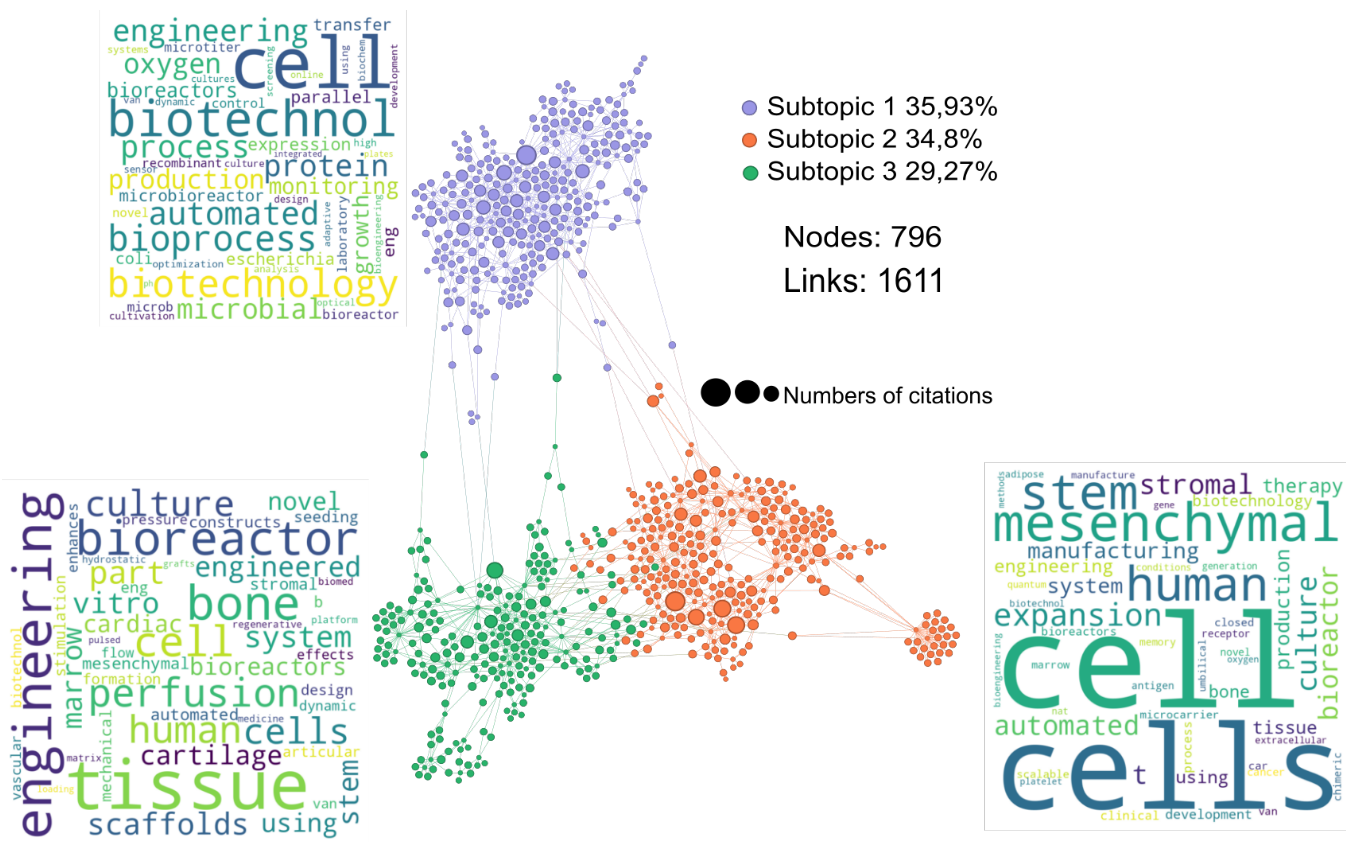

Figure 6: Main areas of knowledge in bioreactor research and their interconnections, as identified by scientometric analysis.

be adapted in future scientometric studies that rely on multiple databases and network-based synthesis methods.

LIMITATIONS

This review has several limitations. First, reliance on WoS and Scopus-while extensive-may exclude some regional journals and non-English publications. Second, the search query may omit relevant studies using alternative terminology. Third, recent publications naturally have fewer citations due to citation lag, which can affect perceived impact in citation-based indicators. Finally, while scientometrics offers a broad map of research structure and trends, detailed qualitative assessment of specific technological breakthroughs is beyond its scope; the ToS narrative partially mitigates this limitation by anchoring interpretation in highly influential and structurally central works.

CONCLUSION

This scientometric review, incorporating the ToS framework, has mapped the multifaceted evolution of bioreactor technology, highlighting its significant progress and diverse applications in the biotechnology and medical fields. The findings demonstrate a robust and growing research area, characterized by a clear progression from foundational automation principles to sophisticated, specialized systems.

The analysis of publication and citation trends, key contributors, and collaborative networks paints a picture of a dynamic global research ecosystem. The transition towards automated, miniaturized, and highly controlled bioreactor systems is evident, driving innovations in process optimization, efficiency, and the development of novel therapeutic modalities such as cell and gene therapies. The ToS analysis effectively structured the intellectual heritage of the field, from basic automation and cell culture control at its 'Root', through scalable and efficient bioprocess development in its 'Trunk', to current 'Branches' exploring adaptive laboratory evolution, advanced cell therapy manufacturing, and next-generation high-throughput biomanufacturing.

Several key takeaways emerge: bioreactor technology is a cornerstone of modern biotechnology, with increasing sophistication in automation, monitoring, and control; research is globally distributed but led by a few key countries, with international collaboration playing a vital role; and emerging frontiers are heavily focused on cell-based therapies, personalized medicine, and enhancing the efficiency and sustainability of bioproduction.

While significant advancements have been made, future research should continue to address challenges in AI integration, standardization for cell therapy manufacturing, sustainability, advanced *in situ* monitoring, and modeling of complex biological interactions within bioreactors. In conclusion, automated bioreactor systems continue to enhance efficiency in microorganism and cell production and improve safety and consistency in chemical and research applications. The collaborative efforts between industry and academia are crucial for translating innovative research into practical solutions that can address pressing societal needs in healthcare, sustainable production, and beyond. This review provides a comprehensive baseline and roadmap for stakeholders in the field, fostering a deeper understanding of its trajectory and future potential.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1: Worked example of cross-database reference harmonization (WoS vs Scopus).

Stage	WoS reference (as exported)	Scopus reference (as exported)	Harmonization method	Harmonized output (standardized reference fields)
Raw reference string	BIERNASKIE J, 2009, CELL STEM CELL, V5, P610, DOI 10.1016/J.STEM.2009.10.019	BIERNASKIE, J., PARIS, M., MOROZOVA, O., SKPS DERIVE FROM HAIR FOLLICLE PRECURSORS AND EXHIBIT PROPERTIES OF ADULT DERMAL STEM CELLS (2009) CELL STEM CELL, 5, PP. 610-623	-	-
Metadata available "out of the box"	First author; year; journal; volume; page; DOI present	Full author list; title; year; journal; volume; pages; DOI often missing	-	-
Enrichment / extraction step	Crossref API enrichment using DOI to retrieve structured metadata (full title, full author list, standardized journal name, etc.)	Text mining / parsing of the Scopus reference string to extract authors, title, journal, year (and other elements when present)	WoS: DOI → Crossref metadata; Scopus: regex/ string parsing + normalization rules	-
Standardization / normalization	Normalize author name format (e.g., "Last, F."), title case/spacing, journal naming, year format; remove punctuation inconsistencies	Same normalization rules applied to parsed fields; journal abbreviations/ variants harmonized	Unified formatting rules across both sources	-
Final harmonized record (used for matching/ dedup + citation network construction)	-	-	Merge fields into a single schema	DOI: 10.1016/J. STEM.2009.10.019 | Year: 2009 | Title: *SKPs derive from hair follicle precursors and exhibit properties of adult dermal stem cells* | Authors: Biernaskie, J.; Paris, M.; Morozova, O.; … | Journal: *Cell Stem Cell* | Volume: 5 | Pages: 610-623

Note: In cases where a DOI is not available (common in Scopus references), DOI recovery can be attempted via Crossref using a query based on title + year + journal and/or fuzzy title matching; otherwise, the reference is retained without DOI and matched using normalized bibliographic fields (title, year, source).