How can we solve the problem of bioprintability to overcome the bioprinting challenges?

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Background

Bioprinting for tissue engineering faces a significant challenge in achieving functional, organ-like printed tissues due to its complex interdisciplinary nature. According to the Global Observatory on Donation and Transplantation 2022 report, the number of patients on the waiting list is higher than the number of transplants.[1] For instance, from 2018 to 2022 in the United States only, an average of 20,000 patients per year did not receive a needed organ,[2] underlying the urgent need to overcome this challenge. The concept of "bioprintability" aims to address this complexity by establishing crucial links between various features. However, the definition of bioprintability remains ambiguous and evolves over time,[3] complicating research efforts. Moreover, the characterization of bioprintability is conducted through diverse protocols.[4] Standardized protocols would simplify data collection and sharing and improve field research. In its 2024 report, the World Health Organization (WHO) suggests that centralizing all results in a single database will promise the long-awaited breakthrough in bioprinting.[5] This article refers to basic concepts to comprehensively elucidate bioprintability and provide solid foundations for future research in bioprinting. We hope to bring the significant federation advances expected in this field.

Revealing the bioprintability problem: Clearing up confusion with performance indicators and cornerstones

Confusion is often made between printability and bioprintability. From a comprehensive standpoint, this confusion is the consequence of the interdisciplinary nature intrinsic to the bioprintability concept, considered the bioprintability problem. The term printability is mainly used in articles. Its definition has progressively converged toward a common one: "*the ability to print a 3D construct with both satisfactory shape fidelity and integrity*."[4] "Bioprintability" is less encountered in papers, but is defined and used similarly to "printability," creating confusion.[6,7] The specificity of the term bioprintability comes with the prefix bio- that includes the biological parts of the concept such as cell viability, proliferation, and differentiation. As achieving simultaneously material and cell functionalities is crucial in bioprinting,[6] it is an actively investigated challenge. Defining, and using bioprintability, linking both biological and nonbiological aspects along the complete bioprinting process, could help reach both functionalities.

The interdisciplinary nature of the bioprintability concept leads to too many bioprinting features measured and unorganized. In this article, we propose to organize and define these influences through two "performance indicators": Cell and Construct functionalities, characterizing the post-printing stage, and five "cornerstones": Material, Design, Printing Setup, Environment, and Cell, delineating the pre- and during-bioprinting stages (**Figure** 1a–b).

The performance indicator "cell functionality" covers the biological properties of the 3D construct, while "construct functionality" regroups its physical properties. In her study, Bercea[9] underlines the need to systematically investigate and correlate them to evaluate bioprintability.

Fu et al.[10] described features influencing the performance indicators and, therefore, the bioprintability. Herein, we propose to organize them in different cornerstones and complete the description already made in the literature. First, the cornerstone "material" regroups every material available for bioprinting and their respective properties. Hydrogel is commonly encountered, but polymer-ceramic composites are gaining popularity for bone tissue application.[11] Similarly, the cornerstone "design" covers the characteristics of the construct design. Indeed, filament orientation or spacing influence the

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shape fidelity.[4,10] Then, "printing setup" refers to the bioprinting features, such as nozzle geometry and extrusion pressure.[10] To complete what has been described in papers, we propose two more cornerstones. "Environment" regroups the characteristics of the bioprinting environment. For instance, bioprinting can be conducted in air or gel. Then, when bioprinting with cell-laden materials, the cornerstone "cell" is pertinent and covers the features linked to cells, such as cell types or density.

Nevertheless, when bioprinting features are organized in cornerstones and performance indicators, it is highlighted that bioprintability is partially described, as exampled in Figure 1c–d.

The standardization of the bioprintability definition is at reach. Despite the disparities around the concepts included in bioprintability, and the confusion around its use, there is a common goal when investigating it: uncover the features to characterize performance indicators and cornerstones. To overcome those remaining difficulties, the bioprinting community must agree upon a complete and standardized definition. Herein, we take the first step toward this standardization by suggesting a definition. "*Bioprintability: the capability to print a cellularized construct with satisfactory performance indicators (construct and cell functionalities), through the influence of five cornerstones (material, design, printing setup, environment, cell)*."

Solving the bioprintability problem: From ill- to well-posed problem with protocol standardization and data collection

All performance indicators and cornerstones are investigated through one or more features, and one feature can be evaluated through several methods in the literature. For instance, shape fidelity is investigated through filament spreading and collapse, and height maintenance.[3] If following a scientific approach, results should be compared between papers, but the lack of standardization does not allow for a comparison. Therefore, the conclusions reached can be questioned in terms of accuracy, robustness, and reproducibility. In recent years, many papers underlined the urge to standardize protocols[6] to share results and simplify measures.

In a study released in 2024, the WHO emphasizes the need for standardized protocols in bioprinting and suggests the creation of "*online platforms to share data on bioprinting and provide easy access to all stakeholders*."[5] Currently, there is an open-access database online that gathers the experimental features (bioprinting setups, biomaterial, and cells) described

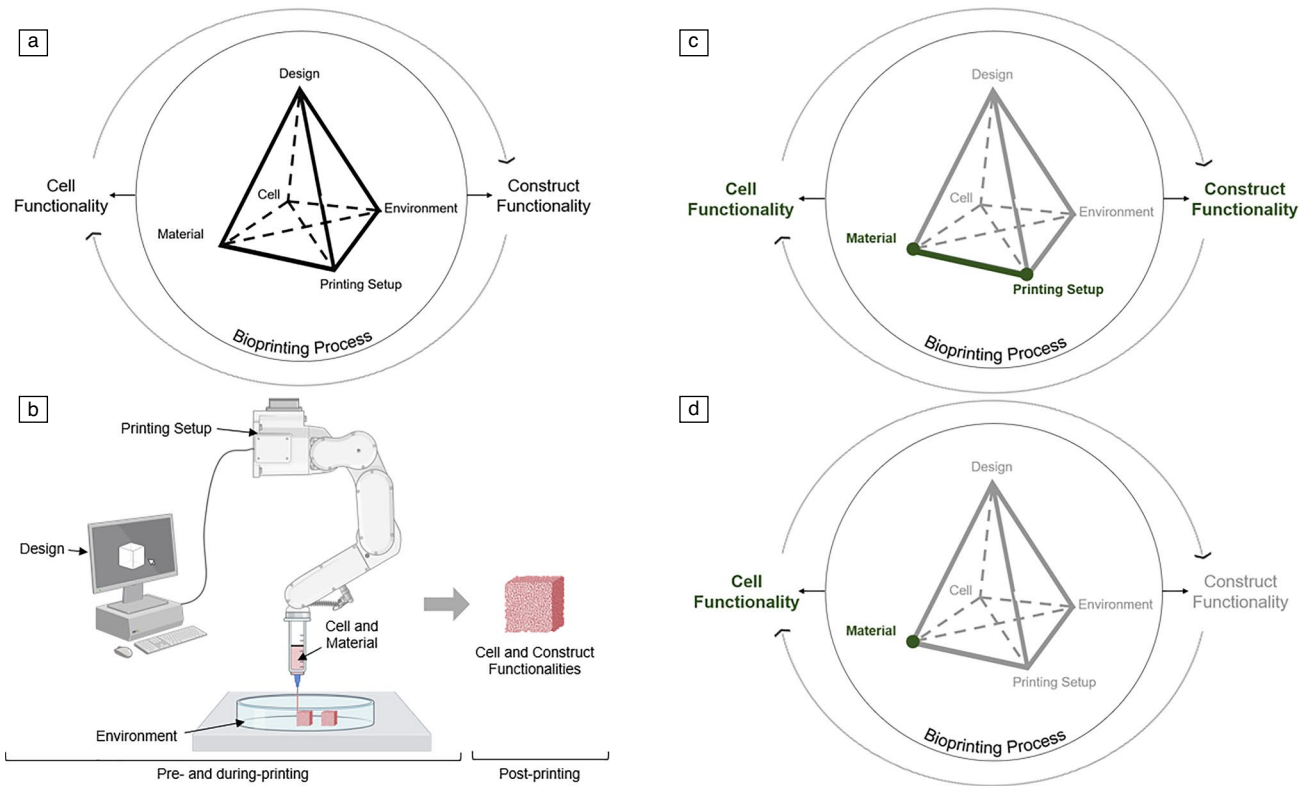

Figure 1. Bioprintability is defined through five cornerstones: cells, environment, material, printing setup, and design, governing two performance indicators: construct and cell functionalities. Our standardized bioprintability concept is presented in (a) while (b, created with Biorender) locates them within the bioprinting process (pre-, during-, and post-printing). The partial investigation of bioprintability in the literature is illustrated by two research articles: Theus et al.[6] (c) and Jinfen Chai et al.[8] (d) papers.

in bioprinting articles.[12] This database reflects the effort made by the bioprinting community to collect and share data. By rigorously defining standardized protocols and meticulously assessing the cornerstones and performance indicators delineated in this article, the database will be poised to catalyze advancements in the field of bioprinting research.

Conclusion

Bioprintability is a recent concept aiming to facilitate the bioprinting process linked to its interdisciplinarity. Thanks to the literature, the bioprinting community reached a common definition. Yet, because it does not cover the basis of the bioprintability concept, confusion remains between "printability" and "bioprintability." Printability should be used when acellularized biomaterials are printed, while bioprintability refers to cell-laden materials. Herein, we take the first step in standardizing the bioprintability definition by introducing five cornerstones (material, design, printing setup, environment, cell) and two performance indicators (cell and construct functionalities). Despite the great number of features investigated leading to multiple and nonstandardized protocols, there is a will within the bioprinting community to gather and share information through an open-access database. With standardization, the possibility would come to create a more complete and accurate database, as suggested by the WHO in 2024. As perspective, this standardized database will promise the use of frugal and powerful machine learning in the bioprinting field, facilitating the bioprintability prediction.

Author contributions

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Competing interests

Authors declare that they have no competing interests.

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