Graphical Abstract

Computational modeling and optimization of biofabrication in Tissue Engineering and Regenerative Medicine - a literature review

R Bardini,S Di Carlo

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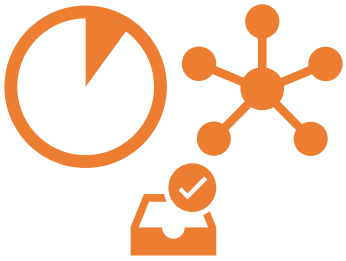
Scope

In silico approaches to biofabrication for Tissue Engineering and Regenerative Medicine.

Methodology



Bibliometric analysis, science mapping and literature review with a focus on modeling and optimization.

Results

Analysis of publications organized by process phase, with a focus on their integration of biological complexity.

Highlights

Computational modeling and optimization of biofabrication in Tissue Engineering and Regenerative Medicine - a literature review

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- A bibliometric analysis shows that the scientific interest for biofabrication of Tissue Engineering and Regenerative Medicine products is rising
- Science mapping and review of the literature shows that computational approaches support innovation and quality of biofabrication processes and products
- While most the analysed solutions focus on the non-living components in biofabrication, they will need to comprise biological complexity as well in order to truly impact the biofabrication of Tissue Engineering and Regenerative Medicine products

Computational modeling and optimization of biofabrication in Tissue Engineering and Regenerative Medicine - a literature review

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ABSTRACT

Biofabrication is the generation of biologically functional products from living cells and biomaterials through bioprinting and subsequent maturation processes. Technological and scientific domains are underlying biofabrication ranging from biology to automated manufacturing and culture systems. Among its application domains, Tissue Engineering and Regenerative Medicine poses strict quality requirements for biofabrication, requiring fast and disruptive innovation for processes and products to comply. Innovation in biofabrication is slow and incremental, relying on R&D processes that are inefficient (slow, risky, and costly), ineffective (products have sub-optimal quality), and challenging to replicate. While automation and digitalization support process execution, design, and innovation, they often work as tools for empirical, problem-specific, and operator-dependent approaches. On the other hand, computational approaches support biofabrication process modeling, design, and optimization of experimental activity to improve the quality of processes and products. To express their full potential, computational methods must factor in the biological complexity underlying biofabrication. This review analyzes computational approaches to biofabrication process modeling, design, and optimization with a focus on solutions explicitly accounting for biological complexity.

1. Introduction

Biofabrication is *"the automated generation of biologically functional products with the structural organization from living cells, bioactive molecules, biomaterials, cell aggregates such as micro-tissues, or hybrid cell-material constructs, through Bioprinting or Bioassembly and subsequent tissue maturation processes"* [1]. TERM is a challenging biofabrication application field bringing the promise to revolutionize the biomedical sector [2]. TERM applications require biofabrication products to be biomimetic, that is, to recapitulate the structural and functional features of their *in vivo* counterparts [3]. The degree of biomimesis in a product, based on the similarity of structural and functional features to physiological counterparts, determines its quality and clinical relevance. In biofabrication *"the process is the product"*, i.e., biofabrication processes and the resulting products are strictly intertwined, so it is their quality. Thus, ensuring product quality implies controlling process quality [4].

Quality control in TERM biofabrication requires analyzing the complex features determining the product quality, considering them as a function of defined critical process parameters [5]. To tackle this challenge, multi-technology biofabrication processes combine existing technologies to consider the product's relevant scales and aspects. Automation and digitalization optimize the execution of existing biofabrication processes or parts. Finally, the search for improved or new process schemes is moving from inefficient trial-and-error paradigms to intelligent design.

Computational approaches play a role in each of these tasks. They work to harmonize multi-technology schemes with automation, optimizing existing processes and supporting rational research design. This helps better organize the experimental activity to make process improvement more efficient. Besides enabling existing technologies and experimental designs to work together, computational approaches have untapped potential to innovate biofabrication process designs. While computational models often target the non-organic components of biofabrication, to truly impact biomimetic quality, intelligent design approaches must address the biological complexity underlying biofabrication. The following paragraphs briefly introduce the current role of computational approaches in multi-technology biofabrication (subsection 1.1), process optimization (subsection 1.2) and experimental design (subsection 1.3), highlighting how models of biological complexity can support intelligent process design (subsection 1.4) and

[*] **Abbreviations:** three-dimensional (3D), Three Dimensional Convolutional Neural Network (3D-CNN), Artificial Intelligence (AI), Artificial Neural Networks (ANN), Bidirectional Evolutionary Structural Optimization (BESO), Bioprosthetic heart valve (BHV), Computer-Aided Design (CAD), Computer-Aided Engineering (CAE), Computer-Aided Manufacturing (CAM), Convolutional Neural Network (CNN), Failure Modes and Effects Analysis (DFMEA), Digital Imaging and Communications in Medicine (DICOM), Deep learning (DL), Design-of-Experiments (DoE), Design Space Exploration (DSE), Digital Twins (DTs), Finite Elements (FE), Finite Elements Methods (FEM), Fluid-Structure Interaction (FSI), Intelligent Digital Twin (IDT), induced Pluripotent Stem Cells (iPSC), Multi-attribute Decision Making (MADM), Multi-Criteria Decision Making (MCDM), Metropolis Monte Carlo (MMC), Multi-objective Decision Making (MODM), Machine Learning (ML), Magnetic Resonance Imaging (MRI), One Factor at A Time (OFAT), Rapid Prototyping (RP), Robotic Process Automation (RPA), Solid Isotropic Material with Penalization (SIMP), Standard Tassellation Language (STL), Topology Optimization (TO), Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS), Triply periodic minimal surfaces (TPMS), Quality by Design (QbD), SIMulation using Metropolis Monte Carlo method (SIMMMC), Tissue Engineering and Regenerative Medicine (TERM), Total Publications (TP)

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framing the scope of this review in the presented context (subsection 1.5).

Statement of significance

Issue Innovative computational approaches to multi-technology TERM biofabrication have untapped potential to innovate process designs. While computational models often target the non-organic components of biofabrication, to truly impact biomimetic quality, intelligent design approaches must address the biological complexity underlying biofabrication.

What is Already Known Several computational approaches exist for different phases of the biofabrication process, and existing maps and reviews analyze them thoroughly. However, the scientific domain of innovative computational approaches to TERM biofabrication lack focus on the integration of biological complexity in analyzed solutions.

What this Paper Adds This work provides a bibliometric analysis and science mapping of the computational approaches to TERM biofabrication scientific domain, followed by an analytical comparison of optimization and simulation solutions organized by process phase, with a focus on their integration of biological complexity.

1.1. Harmonizing combined capabilities: multi-technology biofabrication

Biomimetic TERM products must replicate the complex and hierarchical structure of their *in vivo* counterparts. However, individual biofabrication technologies are designed to control particular aspects of the final product. Even considering a single class of technologies, such limitation appears. Biomimetic scaffolds, for instance, must have a hierarchical architecture, including application-specific surface properties. However, each fabrication approach usually targets a specific resolution range, which poses limitations to the fabrication of hierarchical structures [2]. To overcome this limitation, hybrid biofabrication process schemes combine different fabrication approaches to expand the dimensional range covered and thus achieve biomimetic architectures [6].

Extending this reasoning to different classes of technologies, one can say that biofabrication approaches are today designed to control partial aspects of the final product. For example, bioprinting approaches control spatial organization. Automated culture systems control functional maturation. Directed differentiation of cells governs the functional specialization of the biological building blocks for biofabrication.

Therefore, to control product quality, biofabrication processes can combine different technologies. Generalizing this, Castilho et al. introduce the concept of multi-technology biofabrication, the combination of heterogeneous technological approaches, ranging from additive manufacturing to automation and computational process design, working together towards fully biomimetic TERM products [7]. Multi-technology biofabrication goes beyond combining different techniques, focusing more on their synergistic integration. Computational methods are crucial in enabling integration and rational harmonization in multi-technology procedures.

1.2. Optimizing existing processes: automated and digitalized biofabrication

Biomanufacturing is moving towards fully integrating the Industry 4.0 principles in designing, executing, and optimizing manufacturing processes. Indeed, research automation and digitalization are spreading in the life sciences domain. For instance, fast biofoundries in synthetic biology are *"specialized laboratories that combine software-based design and automated or semi-automated pipelines to build and test genetic devices"* [8].

Several biomanufacturing applications rely on RPA, i.e., the use of a *"pre-configured software instance that uses business rules and predefined activity choreography to complete the autonomous execution of a combination of processes, activities, transactions, and tasks [...]"* [9, 10]. Digitalization is a fundamental part of process automation, and it includes two main aspects: the *digitization* of existing operations and the creation of *digital twins* of existing processes. The *digitization* of existing laboratory processes is the transformation of analogical and manual operations into digital and semi-automated processes, i.e., the compilation of a laboratory diary or the acquisition and storage of newly collected data. Digitization and automation can work together to increase biofabrication process traceability, control, and quality [11].

DTs [12, 13], are *"complete virtual descriptions"* of a physical process that are *"accurate to both micro and macro-level"* (adapted from [14]). DTs act as a digital counterpart of a physical process, dynamically modeling and analyzing it to actuate and modify the system in a risk-free environment, supporting new understanding and rational organizing of research activities. DTs can serve different scopes in biomanufacturing, from version control systems for synthetic biology [15], to bioprocess modeling [16] and optimization [17]. DTs and computational approaches will have an increasingly fundamental role in developing biomimetic TERM biofabrication products by supporting process execution optimization, and intelligent process design [18, 19].

1.3. Innovating existing processes: from empirical trials to intelligent design in biofabrication

Empirical approaches present fundamental limitations for exploring large and complex process design spaces due to the high resource costs and time associated with *in vitro* experiments. Automation and digitalization dramatically increase the yield of *in vitro* experimental campaigns, allowing a more significant number of experiments, thus a broader exploration of the design space.

However, even with automation and digitalization, sticking to a trial-and-error experimental paradigm only accelerates incremental innovation. This means improving existing process designs, which are often based on incomplete, unreliable, and non-reproducible literature knowledge [20], often selected after popularity more than performance [21].

Besides brute-force experimental strategies, trial-and-error approaches include OFAT campaigns that explore ranges of relevant system parameters one at a time. In contrast, the other parameters are held constant [22]. OFAT is expensive in terms of time and resources and overlooks inter-dependencies among system variables. This impedes drawing links between experimental results and realistic process designs. Real designs control multiple variables at a time. These limitations result in OFAT yielding sub-optimal processes and products [13].

The factorial experimental design supports multiple testing conditions and has been proven effective in investigating optimal conditions for stem cell differentiation [23]. DoE computational techniques [24, 13] support strategic and effective research design by enabling efficient, systematic exploration and exploitation of complex design spaces [22, 25]. DoE approaches [26] proved adequate to tackle multi-factorial problems in the optimization of directed cell differentiation [27, 28], and tissue engineering scaffolds [29].

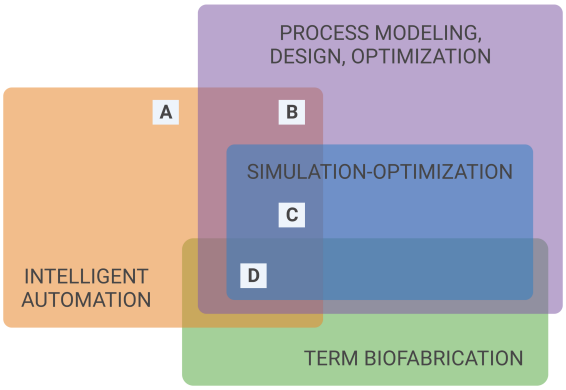

Figure 1: This work presents a review of the scientific literature on works that, following the principles of Intelligent Automation (A), leverage Process modeling, design and optimization (B), and in particular Simulation-optimization (C) techniques for TERM Biofabrication processes (D).

1.4. Comprising process complexity: model-based design in biofabrication

The application of computational tools and AI to process design and optimization of biomanufacturing processes allows moving beyond experimental trial-and-error approaches [30, 31]. Intelligent automation applies AI to automated and digitalized processes, supporting research design and analysis of results [30, 31]. AI technologies have the potential to automatically adapt experimental strategies as new data is being generated to maximize information extraction and process improvement efficiency [32]. An *IDT* is the Digital Twin of an intelligent automation process [33]. IDTs can combine computational models of biofabrication with optimization strategies to support process design: DoE, ML, and ANN can improve the accuracy of the bioprocess model [24]; *in silico* DSE approaches can support research design and optimization so to maximize information extraction, and process improvement efficiency [32, 33].

The design space of a biomanufacturing process is defined as a multidimensional region where input variables and process parameters determine the product quality [5]. In this perspective, modeling the high biological complexity underlying biofabrication processes poses several challenges to model-based DSE approaches.

A model that aims to express biological complexity must consider that physical parts used in biofabrication are multi-level systems, from the single bioprocess to the multicellular aggregate [34]. To capture their complexity, models must express multi-level and quantitative information, as well as the dynamic simulation of complex biological processes [35, 36]. Multi-level and hybrid modeling approaches consistently combine models based on different formalisms and centered over different system levels to comprise more of their hierarchical organization, and heterogeneity [37]. Such models of biological complexity have a high number of parameters, which often carry significant uncertainties [38]. Complex interactions between critical process parameters and model uncertainty generate a huge and probabilistic design space for biofabrication processes [39]. Exploration of such design space is prohibitive under an *in vitro* trial-and-error experimental paradigm [40].

Still, comprising biological complexity is critical for developing computational approaches for biofabrication in general [19], and for its process design in particular. To support informed decisions in process design, models of biofabrication must be accurate and predictive of output variables, interpretable and expressive of their structural and functional features, including process dynamics occurring between the conditions set up and the measurement of the output. While ML and ANN provide black-box models of the system, computer simulations offer white-box models of the process, capturing mechanistic relations, analyzing complex dynamics and their trajectories under different conditions [41].

1.5. Scope of this work

As thoroughly reviewed in [42], process design, modeling and optimization find a lot of applications to the different phases of TERM biofabrication.

As pictured in Figure 1, this review analyses the application of intelligent automation principles (Figure 1.A) in modeling, design and optimization (Figure 1.B), with a focus on Simulation-Optimization approaches (Figure 1.C) of TERM Biofabrication processes (Figure 1.D).

After a brief overview of the biofabrication process in section 2 and a bibliometric analysis in section 3, section 4 reviews and analyses the state-of-the-art approaches organizing them by process phase, and section 5 summarizes findings and open challenges in the field of computational design of TERM biofabrication processes.

2. The biofabrication process

Garcia et al. [43] highlight eight critical phases for biofabrication of TERM products: product modeling, raw

materials qualification (biomaterials and cells), cell culture (cell differentiation), product component fabrication (cell expansion and scaffold building), bulk fabrication (cell seeding or bioprinting of cell-embedded bio-inks), post-culture (tissue maturation), quality control and storage.

This review focuses on a subset of these phases:

- *Product modeling*. Product modeling (Figure 2.A) aims at defining the target product from expert knowledge or following a data-driven process using medical imaging to determine the desired features in the product.
- *Biomaterials qualification*. The product model definition guides the selection of biomaterials and cells to employ (Figure 2.B). The specific combinations of biomaterials must carefully adjust to the particular scopes and machinery available for biofabrication. For example, a bio-ink must be biocompatible with the cell type to be printed and printable using bioprinting technology. Cells for preparing cell-laden materials or seeded in cell-free scaffolds undergo selection or culture and differentiation before fabrication.
- *Fabrication*. Bioprinting and bioassembly organize the biomaterials and cells of choice in space to give an initial shape to the product (Figure 2.C).
- *Maturation*. Automated culture systems include different technologies ranging from microfluidic devices to bioreactors (Figure 2.D), which automatically administer signals to guide product maturation towards the desired structural and functional features.
- *Quality control*. Quality control assesses the presence of the desired functional and structural features defined in the product model (Figure 2.E), especially if biofabrication has a biomimetic purpose (Figure 2.A).

3. Bibliometric analysis

As illustrated in [44], several approaches exist to analyze a scientific landscape. This paper provides a literature review of simulation-optimization methods for biofabrication of TERM products (Figure 1). This section enriches the study with a brief bibliometric analysis of the relevant scientific landscape. The analysis relies on PubMed[1] queries that combine keywords related to Biofabrication, TERM, and computational approaches, plus synonyms and adjacent terms to search publications on the platform.

3.1. Quantitative analysis

To highlight the relevance of this work, this analysis starts with the claim that the scientific community's interest in biofabrication and TERM is rapidly growing. This claim can be supported by using `Query 1.1` to quantify the interest in Biofabrication and, more specifically, `Query 1.2` to focus on TERM Biofabrication. Results were analyzed considering the period between 2002 and 2021 and using the TP count as a performance metric [44].

Query 1.1 (Biofabrication): ("Biofabricat*" OR "Biomanufactur*" OR "Bioassembl*" OR "Bioprint*" OR "Biomaterial*")

Query 1.2 (TERM Biofabrication): ("Biofabricat*" OR "Biomanufactur*" OR "Bioassembl*" OR "Bioprint*" OR "Biomaterial*") AND ("Regenerative Medicine" OR "Tissue Engineering")

`Query 1.1` retrieved 108,008 TP while `Query 1.2` produced 28,549 TP, issued between 2002 and 2021. Figure 3 shows a steady increase in yearly TP during the last two decades, indicating a growing interest of the scientific community in the field. The term Biofabrication in general reported 1,221 TP in 2002, growing up to 12,921 TP in 2021 with a 958% increase. Of these publications, the portion on TERM Biofabrication grew from about 12% of the total (149 over 1,221 TP) in 2002 to about 27% in 2021 (3,516 over 12,921 TP).

Considering the 28,549 TP on TERM Biofabrication, the analysis considered publications on computational approaches to TERM Biofabrication (`Query 2.1`), and more specifically on computational approaches to TERM Biofabrication based on either modeling or optimization (`Query 2.2`), finally narrowing down the focus on computational methods to TERM Biofabrication based on combined modeling and optimization (`Query 2.3`).

Query 2.1 (Computational approaches to TERM Biofabrication): ("Biofabricat*" OR "Biomanufactur*" OR "Bioassembl*" OR "Bioprint*" OR "Biomaterial*") AND ("Regenerative Medicine" OR "Tissue Engineering") AND ("In silico" OR "In-silico" OR "Comput*");

Query 2.2 (Computational approaches to TERM Biofabrication based on either modeling or optimization): ("Biofabricat*" OR "Biomanufactur*" OR "Bioassembl*" OR "Bioprint*" OR "Biomaterial*") AND ("Regenerative Medicine" OR "Tissue Engineering") AND ("In silico" OR "In-silico" OR "Comput*") AND ("Optim*" OR "Simulat*" OR "Model*")

Query 2.3 (Computational approaches to TERM Biofabrication based on modeling and optimization combined): ("Biofabricat*" OR "Biomanufactur*" OR "Bioassembl*" OR "Bioprint*" OR "Biomaterial*") AND ("Regenerative Medicine" OR "Tissue Engineering") AND ("In silico" OR "In-silico" OR "Comput*") AND ("Optim*" AND "Simulat*" AND "Model*")

Starting from the result of `Query 1.2`, `Queries 2.1-2.2` retrieved 1,642 TP for computational approaches to TERM Biofabrication (about 6%). Among these, 966 TP discuss computational approaches to TERM Biofabrication based on either modeling or optimization (about the 60%). Figure 4 shows the TP per year for TERM Biofabrication, highlighting the presence of scientific activity on Computational approaches to TERM Biofabrication in time, which constitutes 5% (101 publications) of TP between 2002 and 2006, and 6% (785 publications) for the period between 2017 and 2021, as illustrated in Figure 5. Figure 6 shows that publications

[1] https://pubmed.ncbi.nlm.nih.gov/

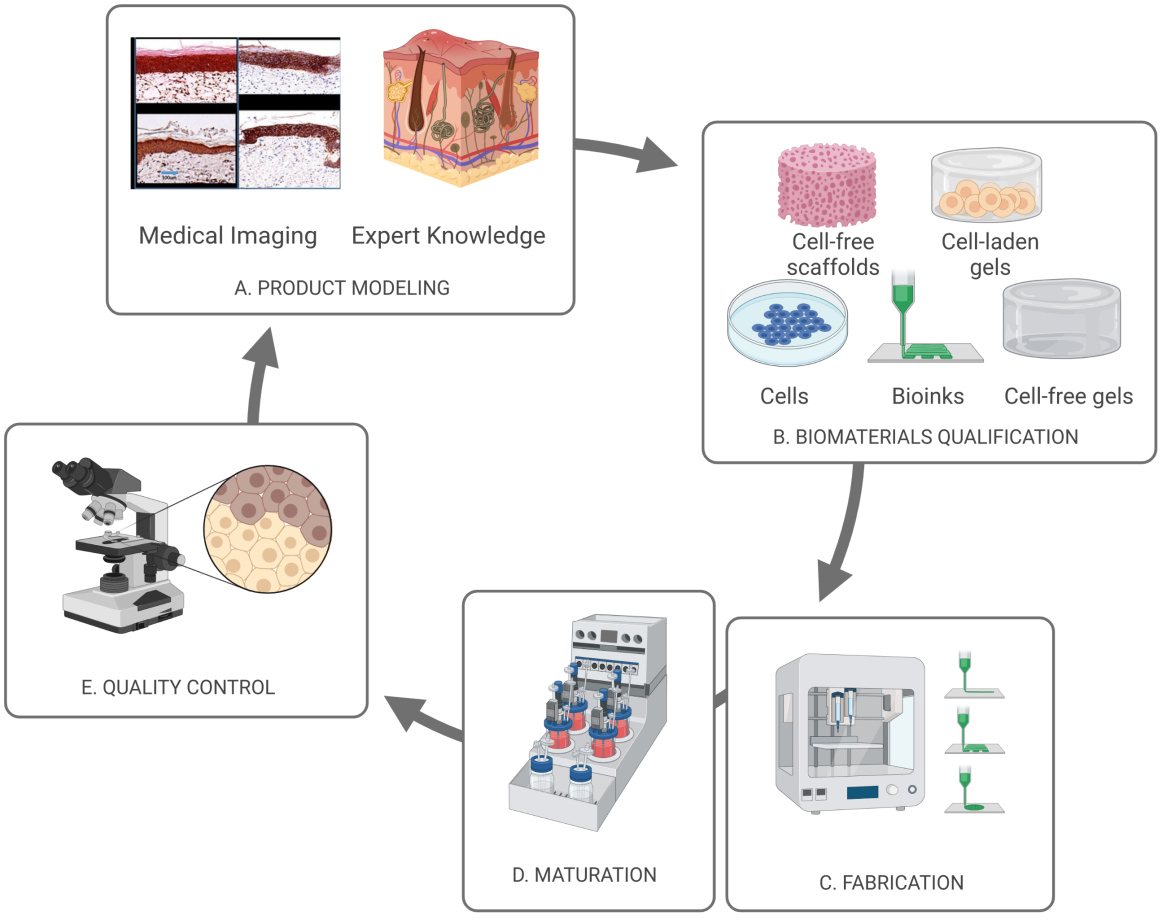

Figure 2: Overview of a biofabrication process: (A) medical images and expert knowledge define a model for the target product, which guides the (B) choice and combination of biomaterials and cells used for (C) fabrication, via bioprinting and bioassembly, followed by (C) construct maturation; (D) the quality of the mature product is evaluated measuring its closeness to the structural and functional features of the defined target.

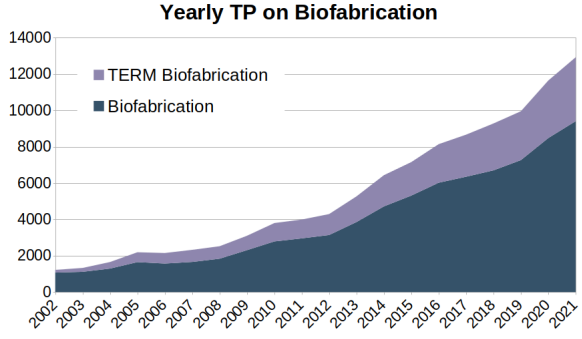

Figure 3: Total Publications per year on *Biofabrication*, with an highlight on the contributions on *TERM Biofabrication* (*Queries 1.1-1.2*).

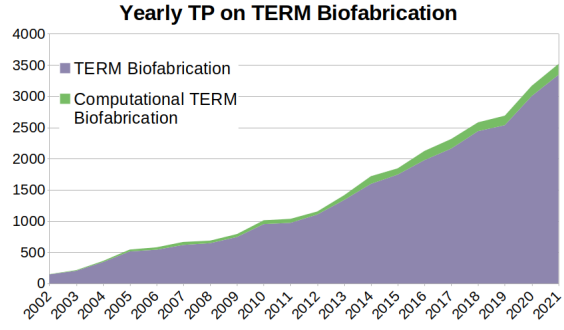

Figure 4: Total Publications per year on *TERM Biofabrication*, with an highlight on the contributions on *Computational approaches to TERM Biofabrication* (*Queries 1.2 and 2.1*).

on computational approaches to TERM Biofabrication based on either modeling or optimization constitute 50% (50 over 100 publications) of TP on computational methods to TERM Biofabrication between 2002 and 2006 and the 57% (785 publications) for the period between 2017 and 2021.

Finally, Figure 7 illustrates the TP between 2002 and 2021 on computational approaches to TERM Biofabrication based on either modeling or optimization (`Query 2.2`, 966

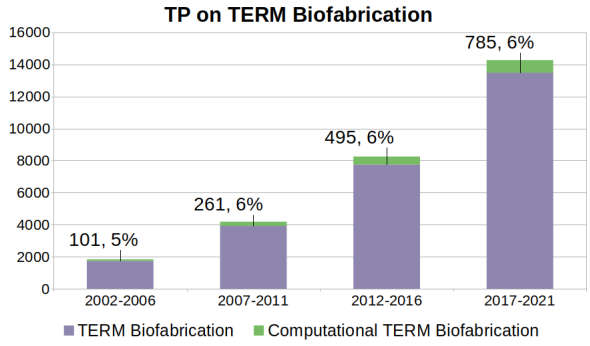

Figure 5: Total Publications on *TERM Biofabrication* aggregated over five-years periods, with an highlight on the contributions on *Computational approaches to TERM Biofabrication* (*Queries 1.2 and 2.1*), that constitute between 5-6% of TP across all time periods from 2002 to 2021.

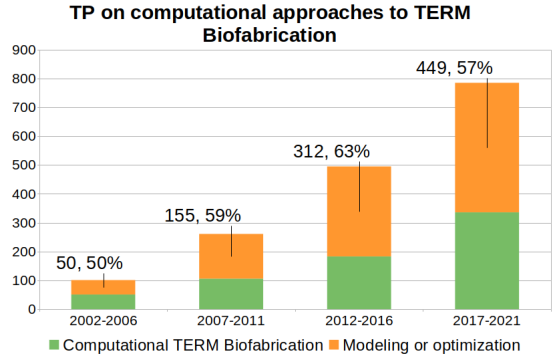

Figure 6: Total Publications on *Computational approaches to TERM Biofabrication* (*Query 2.1*) aggregated over five-years periods, with an highlight on the contributions on *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*), that constitute 50% of TP between 2002 and 2007 (50 publications), grow to 63% for the period between 2012 and 2016 (312 publications), and decrease to 57% for the period between 2017 and 2021 (449 publications).

TP), highlighting the contributions of computational methods to TERM Biofabrication based on combined modeling and optimization (`Query 2.3`).

3.2. Science Mapping

After quantitatively analyzing publications in the reference scientific domains, this section aims to analyze and visualize the structure of these domains by performing science mapping [45]. The analysis leveraged the VosViewer tool [46, 47] to search publications on the PubMed platform [48]. The analysis focused on results of `Queries 2.2-3` summarized Figure 6 and Figure 7.

The first step of the analysis was constructing a co-occurrence network from the PubMed file generated with `Query 2.2`. The co-occurrence network was created from text analysis of the *Title* and *Abstract* fields of each publication,

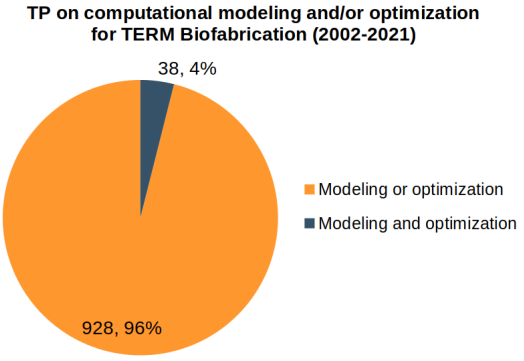

Figure 7: Total Publications between 2002 and 2021 on *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*, 966 TP), highlighting the 4% (38 TP) on *Computational approaches to TERM Biofabrication based on combined modeling and optimization* (*Query 2.3*).

then performing clustering analysis over the obtained network. Due to the high heterogeneity of terms in text data, this step employed a thesaurus file. Different versions of the same terms or concepts (plurals or singulars, synonyms, very close terms) were considered under the same umbrella term to facilitate network homogeneity and visualization.

Figure 8 shows the text-based co-occurrence map based on `Query 2.2`. Different colors indicate separate clusters within the network. While the green cluster at the top seems to include clinical and biological concepts, the blue cluster at the bottom centers on technological approaches and research organization. The smaller third cluster in orange contains terms related to biomaterials properties. Interestingly, terms about computational approaches exist in both the blue and orange clusters, with a predominance in the larger blue cluster. Figure 9 provides an enlarged view over the portion of the map where terms referring to computational approaches emerge.

A simplified text-based co-occurrence map on `Query 2.2` devising a different thesaurus file was also created to simplify situations in which different concepts of the same domain are grouped under the same umbrella terms. In particular, all terms related to modeling, simulation, and computational aids were combined under the term “computational approaches." “Regenerative medicine," “scaffolds," and “bioprinting" similarly grouped several synonyms and adjacent terms. This created nodes with higher total occurrences and aggregated co-occurrence links, creating a simpler network that was easier to visualize.

Figure 10 shows the resulting simplified co-occurrence map, which has two clusters. The green cluster on the bottom left centers over biological and clinical aspects. In contrast, the blue cluster on the top right centers on technology. Computational approaches belong to this cluster.

The second step of this analysis devised a second map from bibliographic data summarizing results of `Query 2.2`, in particular creating a co-occurrence network of MeSH

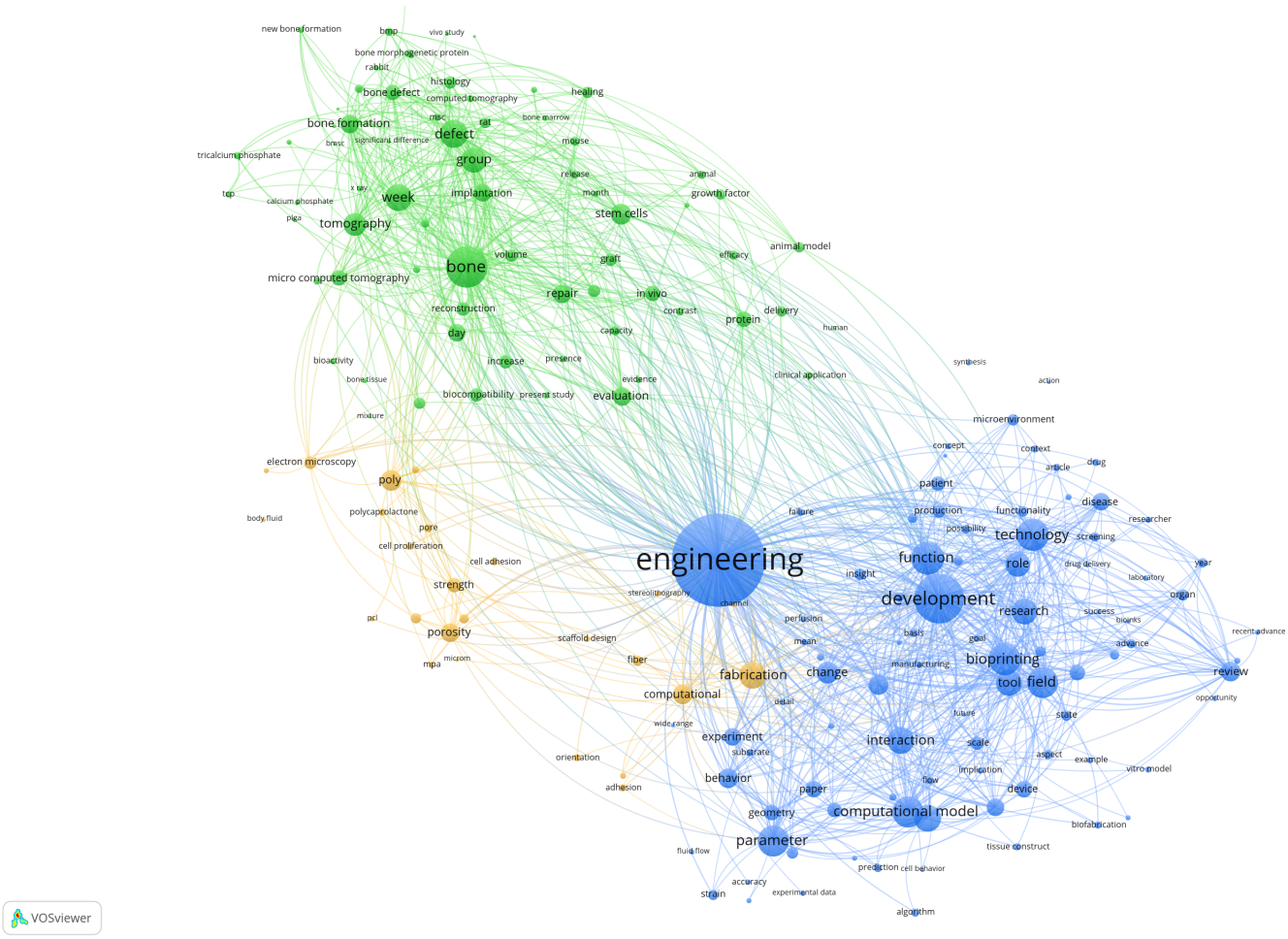

Figure 8: Text-based terms co-occurrence map of *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*). The map is based on text analysis over PubMed files and extracts co-occurrence information from the bibliographic database file obtained from the PubMed platform with *Query 2.2* performing binary counting of terms occurrences over the *Title* and *Abstract* fields, and considering the 60% most relevant terms among those occurring in at least ten documents (290 over 483). The relative size of term nodes indicates total occurrences, and link strength indicates co-occurrences. Colors indicate the three different clusters in the network. Clustering relied on Association Strength as a normalization method and a Resolution parameter value of 1.00.

keywords, employing the Fractional counting method, and considering only the 38 keywords occurring at least three times. Due to the high homogeneity of MeSH keywords in bibliometric data, this step did not employ a thesaurus file. Figure 11 illustrates the co-occurrence network of keywords obtained and the two clusters identified. The top blue cluster includes more details about the biological aspects of tissue engineering. The green cluster on the bottom contains more terms about computational modeling and analysis approaches.

To conclude, the analysis targeted the subset of 38 TP obtained with `Query 2.3`, and Figure 12 shows the text-based terms co-occurrence network with the related clusters.

3.3. Discussion

Taken together, performance analysis and science mapping provided in this section suggest that the scientific interest in TERM biofabrication is rapidly growing and that computational approaches have a great, probably underused potential in this field. Publications on computational approaches to TERM biofabrication constitute a small but constant portion of scientific production, and about half of them consistently center on modeling or optimizing biofabrication processes. Approaches combining simulation and optimization are a small subset of total publications on either simulation or optimization, indicating that current approaches tackle specific process phases, as the following sections illustrate, and specific computational problems separately. This highlights a great opportunity for holistic computational approaches to tackle different phases and issues in designing a biofabrication process. In the scientific landscapes under analysis, the position of computational approaches highlights their links to clinical and biological

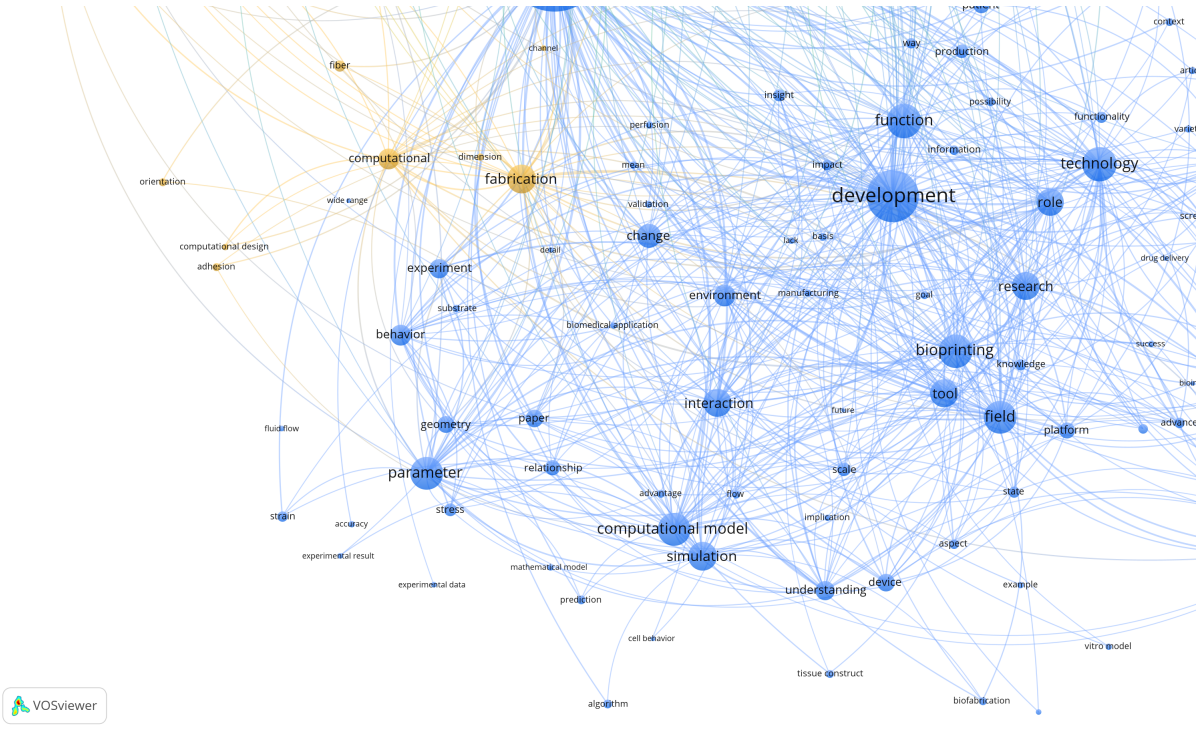

Figure 9: Enlarged portion of the text-based terms co-occurrence map of Total Publications between 2002 and 2021 on *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*). The map is based on text analysis over PubMed files and extracts co-occurrence information from the bibliographic database file obtained from the PubMed platform with *Query 2.2* performing binary counting of terms occurrences over the Title and Abstract fields and considering the 60% most relevant terms among those occurring in at least ten documents (290 over 483). The relative size of nodes indicates term occurrences, and link strength indicates co-occurrences. Colors indicate the three different clusters in the network. Clustering relied on Association Strength as a normalization method and a Resolution parameter value of 1.00.

aspects and technological methods to biofabrication, highlighting the flexibility of these approaches and their untapped potential to support biofabrication in different phases of the process.

The following sections provide a literature review of computational approaches to different biofabrication process phases, including and not limiting to the publications from `Query 2.3`, focusing on techniques combining modeling and optimization methods.

4. Computational methods for intelligent biofabrication

This section reviews the state-of-the-art computational methods applied to TERM biofabrication and organizes them around the process phases introduced in section 2.

4.1. Product modeling and design

Product modeling comprises the retrieval and usage of information on the product, its design, and the definition of the desired features. The ultimate goal of TERM biofabrication is fulfilling a patient's clinical need for regeneration. This usually implies a biofabricated product must be biomimetic; that is, it must faithfully recapitulate the biological structures to regenerate. This principle guides the product's design and modeling and defines quality metrics for obtained biofabrication products. The output of a biofabrication process is the product of fabrication and maturation, and its quality is assessed under the quality metrics defined during product modeling. This often means assuring that specific quantitative features are beyond a specified threshold. In particular, for TE and RM applications, product quality is often reflected in biomimetic fidelity to its *in vivo* counterpart since the ultimate goal is regeneration.

4.1.1. Information retrieval

Achieving biomimetic fidelity in a TERM biofabrication product depends on precisely defining the functional and structural features to replicate from physiology. Image-based biofabrication of patient-specific tissues for regenerative purposes builds CAD models of the product using processed images directly acquired from the patients. Most times, acquisitions allow building 3D reconstructions from MRI or Computed Tomography (CT) scans that are later converted to DICOM format [49] and then to STL files for printing [50]. This process finds application in orthodontic regeneration [51] and soft-tissue engineering [52]. A similar approach is foreseen in [53] for the generation of 3D heart valves. The process starts with 3D CAD model generation from slices of CT images and its 3D bioprinting using either

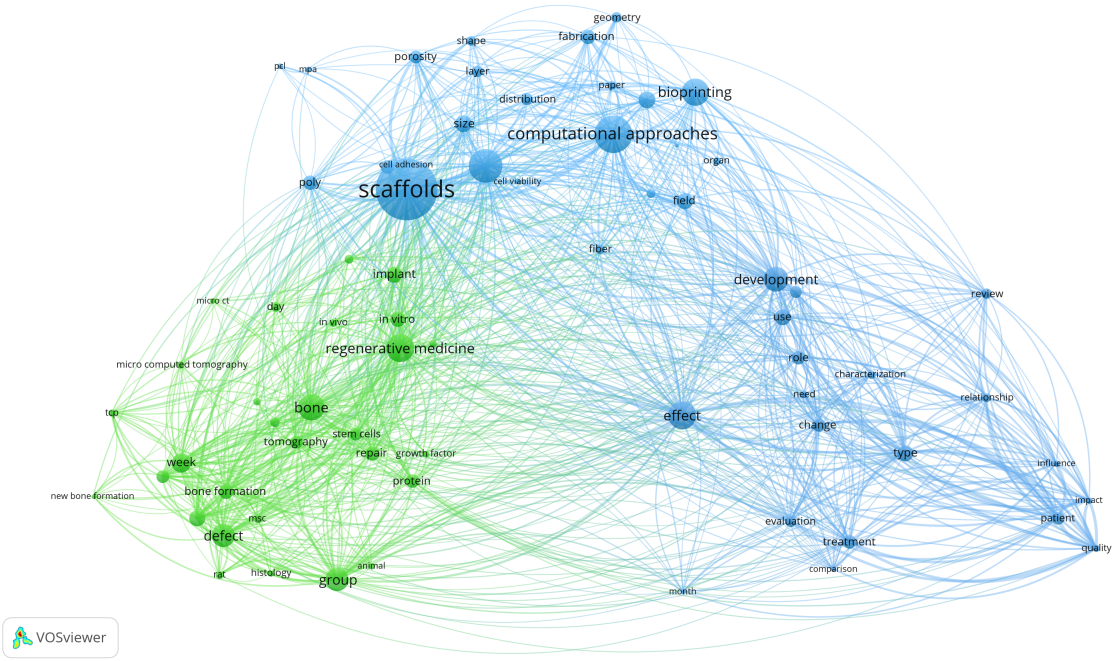

Figure 10: Simplified text-based terms co-occurrence map of *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*). The map is based on text analysis over PubMed files and extracts co-occurrence information from the bibliographic database file obtained from the PubMed platform with *Query 2.2* performing binary counting of terms occurrences over the *Title* and *Abstract* fields, and considering the 60% most relevant terms among those occurring in at least 30 documents (151 over 24820). The relative size of term nodes indicates total occurrences, and link strength indicates co-occurrences. Colors indicate the three different clusters in the network. Clustering relied on Association Strength as a normalization method and a Resolution parameter value of 1.00.

cell-free or cell-laden biomaterials, followed by development and initial tissue remodeling in perfusion bioreactor under dynamic pulsatile flow conditions.

As thoroughly reviewed in [54], machine intelligence supports developing TERM product models beyond image processing and translation to a product model. It allows the discovery of tissue architectures from imaging and spectral data, bridging the information from the *in vivo* tissue microenvironment to the construct properties at the scale that the bioprinting technology chosen can fabricate. DL super-resolution unsupervised approaches [55] can transform low-resolution images into higher-resolution versions, narrowing the gap between the average resolution of medical images on the millimeter scale and the resolution of bioprinting technologies, which lies on the micrometer scale [56]. Tissue images *per se* fail to provide information at the single-cell level. Thus, reconstructed 3D tissue models usually lack multi-scale cellular resolution and tissue- o organ-specific properties. Image processing based on ML proved helpful in extracting biological features at the cellular level in an unbiased and data-driven manner [56]. For example, authors in [57] leveraged a CNN to classify cells according to their cell cycle phase. These initiatives support the data-driven construction and enrichment of Intelligent Digital Twins comprising a multi-scale model of the target products' architectural and functional features, allowing for embedding biological complexity. One of the critical steps to enable computational approaches to facilitate biofabrication is to build and curate databases supporting IDT [58].

4.1.2. Computer-assisted design

Bio-CAD, bio-CAM, and bio-CAE apply CAD, CAM, and CAD to biological processes and subprocesses. The bio-CAD process can be used to design tissue and organ blueprints, the bio-CAM method for manufacturing biological products, and the bio-CAE process to create complex architectures, validate and optimize biomanufacturing tools and bioproducts [59, 60]. CAD is the most widely employed method for designing scaffolds from scratch or using 3D scans of the target biofabrication product [61]. Computer-controlled RP can produce physiologically relevant structures of different dimensions [62, 63, 64].

Computer-aided design of TERM products must combine with computational modeling of tissue- and organ-level biological complexity to support complex functionality and clinical translation. As provided in recent reviews [65, 66], ML techniques support bioprinting in different ways. For example, they predict material properties related to various mixture compositions of the bio-inks and support scaffold designs by learning from an extensive database of materials

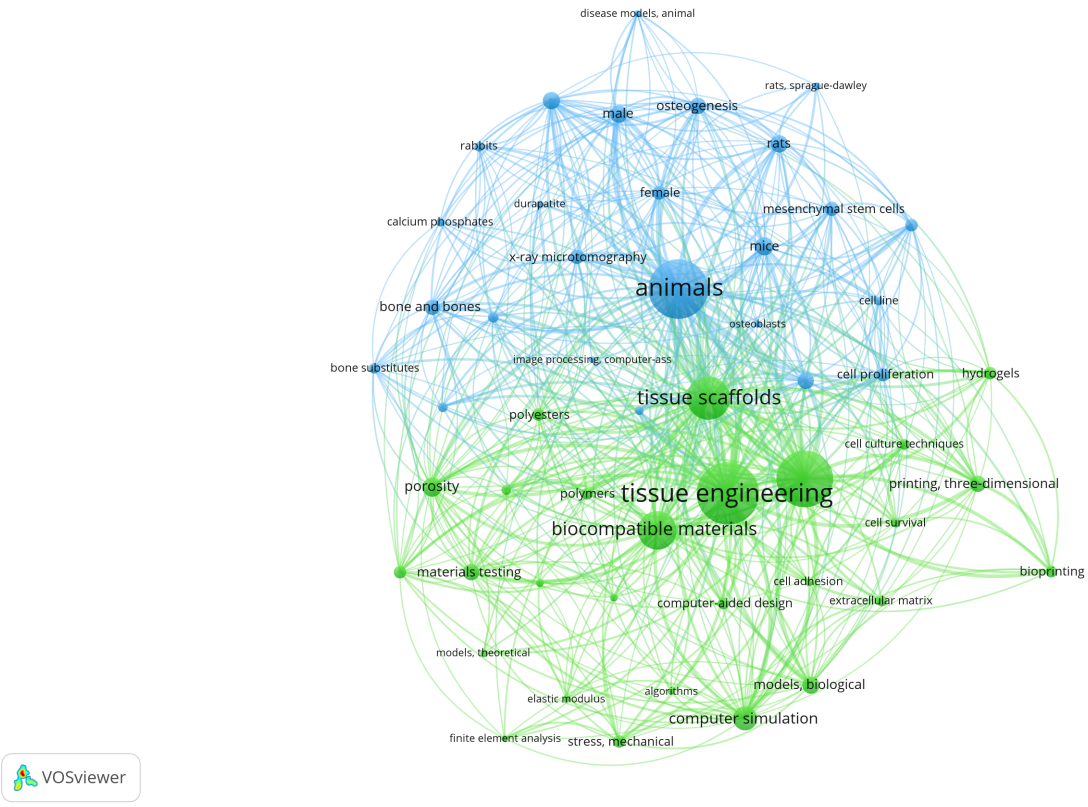

Figure 11: Bibliographic data-based co-occurrence map of *Computational approaches to TERM Biofabrication based on either modeling or optimization* (*Query 2.2*). The map is based on bibliographic analysis over PubMed files. It extracts MeSH keywords co-occurrence information from the bibliographic database file obtained from the PubMed platform with *Query 2.2*, performing Fractional counting of keywords occurrences and considering the ones occurring in at least 30 documents (52 over 1348). The relative size of nodes indicates keywords occurrences, and link strength indicates co-occurrences count. Colors indicate the two different clusters in the network. Clustering relied on Association Strength as a normalization method and a Resolution parameter value of 0.8.

and designs. ML algorithms can perform multi-objective optimization as well. In [67], hierarchical machine learning allows optimization of material process variables and formulate additive manufacturing of silicone elastomer through freeform reversible embedding.

Computational approaches often focus on the cell-free components of biofabricated constructs, falling short on the multi-scale complex biological aspects. An intelligent approach to bioprinting must consistently comprise biological complexity in modeling and optimizing the bioprinting process. Bioprinted and bioassembled cell-embedded products are poised for subsequent maturation, adapting to the stimuli received during maturation. This is usually referred to as four-dimensional (4D) printing. 4D printing produces dynamic structures whose functionality, shapes, and properties change based on the environmental inputs. Computational approaches can guide the deposition process not only for spatial features of the constructs but also to organize its potential functional responses to different stimuli [68]. In [58], leveraging biological data, a DT of the whole bioprinting process with the cellular resolution, is proposed as a strategy for a holistic and intelligent computational facilitation of biofabrication. To translate designs into tangible cell-laden constructs, computational tools for biofabrication must comprise multi-scale and high-resolution models of intracellular, cell-cell, and cell-biomaterials interactions during fabrication and subsequent maturation [69, 70, 71]. BHV computational modeling and design can not rely on simulation of continuum mechanics only. BHV presents unique challenges for computational analysis: the effect of hydrostatic forcing on a closed BHV may be simulated using standard FEM, but this approach fails to account for transient responses during valve opening or the so-called "water hammer effect" in valve closing, which contribute to long-term structural fatigue and thus to the risk of BHV transplant failure. BHV computational design must rely on models of the surrounding hemodynamics. In [72], authors propose a complete mechanical model of a BHV based on the immersogeometric FSI methodology. The integration of computational modeling in heart valve design proved

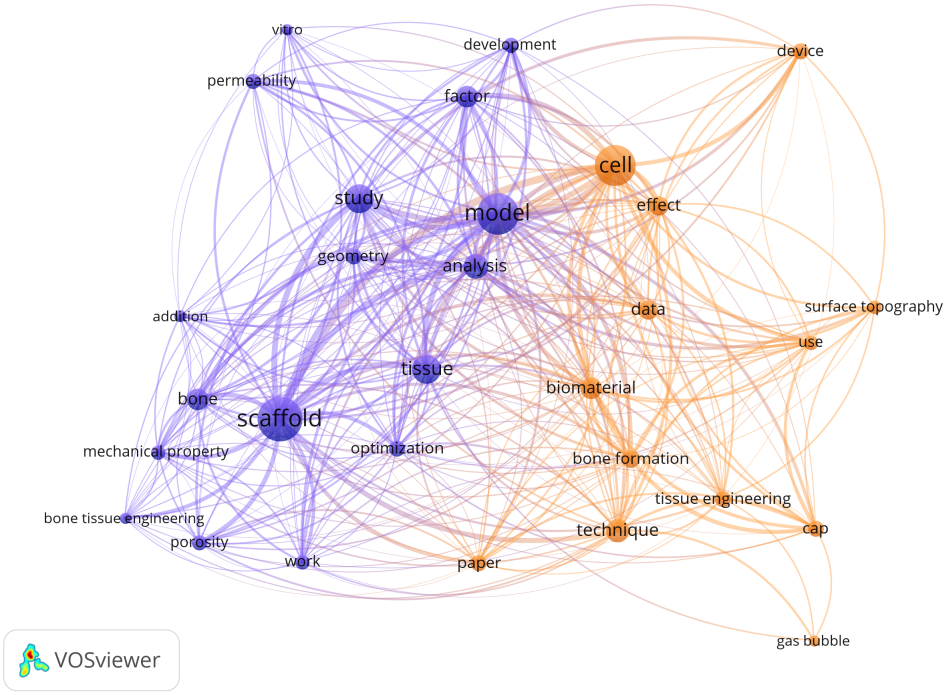

Figure 12: Text-based terms co-occurrence map of *Computational approaches to TERM Biofabrication based on modeling and optimization combined* (*Query 2.3*). The map is based on text analysis over PubMed files and extracts co-occurrence information from the bibliographic database file obtained from the PubMed platform with `Query 2.3` performing full counting of terms occurrences over the *Title* and *Abstract* fields, and considering the 30 terms occurring in at least six documents. The relative size of term nodes indicates total occurrences, and link strength indicates co-occurrences. Colors indicate the three different clusters in the network. Clustering relied on Association Strength as a normalization method and a Resolution parameter value of 0.70.

capable of predicting long-term in vivo performance, remodeling, and failure under non-physiological pressure loading in a translational sheep model [73].

4.1.3. Scaffolds

Porous scaffolds for TERM applications must present biological, biomechanical, and biomaterial functionality. This includes suitable pores size and geometry, allowing nutrients to diffuse uniformly and cells of the engineered tissue to invade the scaffold. Secondly, scaffold surfaces must have physical-chemical properties ensuring biocompatibility; that is, they must allow cells to adhere and develop the expected phenotypes. During fabrication, scaffold material must exhibit mechanical properties supporting the bearing of required loads during the regeneration process. Finally, scaffolds must be biodegradable or bioabsorbable once sufficient tissue has formed to guarantee mechanical support to the TERM product.

Computational modeling, optimization techniques, and experimental design methods effectively and reliably support the characterization, modeling, and design of complex and composite scaffolds for biofabrication [74], as reviewed in detail in [29]. Computational approaches support the controlled design of the scaffold microstructure and biomaterial properties to find optimal trade-offs among these complex requirements. As reviewed in [75], several computational approaches can be used to optimize mechanical and chemical properties of bone grafts scaffolds, such as porosity, micro-architecture, Young's modulus, and dissolution rate. Yet, careful consideration of biological complexity and cell-material interactions are crucial to the modeling and design of TERM bone grafts. Computational design must account for the influence of growth factors and other biochemical signals and the accurate simulation of dissolution processes, including the impact of the degradation products such as calcium ions and inorganic phosphate on bone formation processes.

FEM is a powerful modeling and optimization tool for biomechanical research [76, 77, 78, 79, 80]. FEM can also support the design and optimization of scaffolds for TERM, modeling not only biomechanical and geometrical aspects of the cell-free scaffold but dynamical features and the responses of specific cell types during later construct maturation [81]. In [82], the authors propose a model-driven computational framework for designing and optimizing a porous scaffold microstructure. This approach relies on the computational simulation of 3D bone tissue regeneration, including new bone formation and scaffold degradation. Simulation depends on the voxel finite element method. Authors in [83] present a computational design approach for

scaffolds with varying porosity. Authors in [84] combine experimental and computational modeling approaches, providing qualitative predictions of impaired bone formation after low cell seeding and scaffold decalcification, a strategy to ensure the correct bone formation process based on *in silico* results, and the design of optimal combinations of calcium-based biomaterials and cell culture conditions to maximize the quantity of formed bone. In [85], the authors propose a general design optimization scheme for 3D internal scaffold architecture to find a good trade-off between elastic properties and porosity. They introduce the homogenization-based topology optimization algorithm, demonstrating that the method can produce biomimetic structures mimicking anisotropic bone stiffness obtained with scaffolds of widely different porosity. Authors in [86] combine macro-scale mesenchymal condensation and biomechanical stimulation to fabricate a scaffold-free cartilage-like construct to study cartilage degradation in osteoarthritis, adapting an existing mathematical model to simulate matrix degradation. In [87], authors propose a 3D computational model based on Sussman–Bathe hyperelastic material behavior to study interpenetrated polymer networks (IPNs) for cartilage repairing, quantitatively simulating the distribution of fluid fluxes and nutrient supply within the different regions of a construct.

The geometric properties of scaffolds for tissue engineering directly affect cellular deposition. Using a computational model of osteoblasts behavior, the growth of bone matrix tissue in scaffolds with different pores geometry was predicted [88]. Authors in [89] optimize geometrical features of scaffolds, maximizing bone growth rate with an algorithm relying on parametric finite elements (FE) models of different scaffold shapes, computational models of the biomechanical behavior of cells, and optimization methods. A computational model of vascular adaptation and a formal optimization method support tissue-engineered vascular graft design in [90]. The comprehensive analytical and numerical modeling of the 3D and 4D additive manufacturing benefits biofabrication with understanding, predictive modeling, and optimization of the bioprinting process at different scales [91]. TO aims at optimizing bioprinted designs by organizing the placement of printing material in space. For instance, the need for sustaining increased mechanical stress in some parts of a construct more than in others can result in a porous structure with variable density. Among the most used TO approaches, SIMP [92], BESO [93], and level-set [94] can support the design of differentially dense and stiff structures. In [95] authors leverage TO on the performance of a chitosan hydrogel bioprinted soft actuator while maintaining the material's volume fraction. TPMS recently inspired the fabrication of biomimetic porous scaffolds since they support cell adhesion, migration, and proliferation. A versatile design method for TPMS sheet scaffolds, which can satisfy multiple requirements at once, was proposed in [96]. TO does not consider cell-related aspects in these applications: optimized parameters only involve a single scale and cell-free biomaterials. Yet, TO approaches are easily extended to cell-laden and multi-scale biomaterials. For instance, in [97], authors present a level-set-based topology optimization algorithm and a time-dependent shape derivative to optimize scaffold architecture for femur models, showing significant advantages in continuing bone growth compared to stiffness-based topology optimization, time-independent design, and typical scaffold constructs. The common usage of topology optimization and models of biological responses to different scaffold properties prove effective in supporting scaffold design [98]. In [99], authors leverage 3D-CNN surrogate models to perform multi-scale topology optimization on non-parametric micro-scale structures. Authors in [100] present different computational approaches, including surface hit detection and ordering and prediction of relevant surface properties and cell responses, aiming at optimizing surfaces to influence cell behavior. Vascularization of constructs is still a major limiting factor in the size and quality of TERM products. To achieve vascularized constructs, the computational design must comprise the multiple interdependent regulatory mechanisms in physiology. In [101], DoE optimization of the geometry and oxygen distribution within hydrogel constructs relied on computational simulations and microvascular network analysis. In bone tissue engineering, the passage from scaffold design to manufacturing requires compliance with the design control requirement that must be verified in a finished device. Authors in [102] propose a computational approach to investigate the accuracy of the final properties of polycaprolactone scaffolds fabricated by selective laser sintering [103]. Bone scaffold design relies on a multiscale TO model comprising geometrical and biological constraints.

4.2. Biomaterials qualification

TERM biofabrication consists either in the bioassembly of building blocks based on living cells, or in the bioprinting of biomaterials and cells. Some biofabrication processes rely on the combination of bioassembly and bioprinting techniques [104].

4.2.1. Inorganic biomaterials

The design and development of biomaterials for biofabrication must consider the non-trivial composition of multiple mechanical and biological properties, which often conflict with each other. Computational approaches support biomaterials characterization and explore optimal trade-offs between different desired features of biomaterials (e.g., biocompatibility with the cells employed versus printability for the bioprinting technology of choice). In [105] authors propose a non-integer order viscoelastic material model of soft biological tissues, demonstrating its capability to capture viscoelastic behavior observed experimentally. Following the flow presented in [106], the design of a new biomaterial starts with identifying functional requirements for a specific application. DFMEA and Quality Function Deployment (QFD) support this phase. Functional requirements dictate engineering and technical requirements, material properties, and performance metrics. MADM approaches support the selection process for the best constituent materials to employ. DFMEA can combine with DoE to search the design

space adequately, saving time and resources. Authors in [107] computationally optimize scaffold features with finite element modeling and test them with a DoE approach. Finally, MODM can be applied, which is necessary for the biomaterials design problem that seeks to satisfy multiple goals concurrently, e.g., adequate stiffness and degradation properties in bone scaffolds. Optimization provides more than one solution, tested by simulation and comparison with the benchmark biomaterials.

Cell-laden constructs require to comprise biological complexity into biomaterial design and optimization. Embedding multi-level models into rational algorithmic approaches for bottom-up design of biomaterials can minimize the experimental costs of iterative material synthesis and testing [29]. In this direction, computational approaches currently support the characterization and the choice of optimal biomaterials composition given a specific TERM application. In [108], authors use a coupled FE-optimization algorithm to characterize polyvinyl alcohol as a potential biomaterial for cartilage tissue engineering scaffolds. Biomaterials for tissue engineering must have a high degree of biological and mechanical functionality and be adaptable to specific patients' needs. In [109], authors present an *in silico* design library based on numerical modeling to predict composite biomaterials performance and support their design, applying it to articular cartilage engineering.

4.2.2. Organic biomaterials

Cells The selection of cell strains for biofabrication follows different objectives according to the specific application. In general, for TERM applications, cells often derive from the patient. The only choice is which cell types to employ or how to direct differentiative processes of iPSC for regenerative purposes. Computational tools can help the design of directed differentiation or transdifferentiation processes of cells. In [110], authors propose a computational framework that combines gene expression data with regulatory network information to predict the reprogramming factors necessary to induce cell transdifferentiation for TERM applications. In [111], authors present a computer-aided design tool relying on a computational framework for finding combinations of signals efficiently inducing cell conversions based on a stochastic gene regulatory network model embedding information on the transcriptional and epigenetic landscape of cells.

Spheroids Self-assembled 3D cell spheroids can replicate tissue functionality, working as in vitro models and building blocks for TERM products. In particular, they support in vitro tissue maturation before fabrication of macro-tissues by bioprinting or bioassembly. Robust and reproducible 3D cell spheroid fabrication and maturation can increase the efficiency of in vitro models and TERM products. Authors in [112] propose a combined experimental and computational approach for the modulation of non-geometrical parameters in 3D articular chondrocytes spheroid fabrication process design. In particular, the authors employed computational fluid dynamics to optimize the chip's geometrical features, then modulated cell concentration, flow rate, and seeding time to model cell trapping. The construction of larger tissues also relies on spheroid fusion, the aggregation of spheroids into larger constructs. With the increase in construct size, oxygen and metabolites are no longer uniformly accessible across the construct, hampering fabrication processes. Authors in [113] leverage a hybrid discrete-continuous heuristic model, combining a cellular Potts-type approach with field equations to describe metabolic effects over cells during spheroid-dependent fabrication. SIMMMC is a specialized application for predicting post-printing structure formation in bioprinted constructs, generating 3D models of various types of bioprinted constructs, and simulating their evolution [114]. SIMMMC supports the 3D modeling of specific biological systems, including living cells and biomaterials, and simulates construct evolutions in shape and function involving living cells, biomaterials, and cellular medium relying on the MMC algorithm.

4.3. Fabrication

Fabrication employs raw cells and biomaterials to build TERM constructs with a spatial organization. While this encompasses different techniques, this review focuses on bioprinting and bioassembly. Bioprinting is *"the use of computer-aided transfer processes for patterning and assembling living and non-living materials with a prescribed two- or three-dimensional (2D or 3D) organization to produce bioengineered structures serving in regenerative medicine, pharmacokinetic and basic cell biology studies"* (adapted from [115]). Bioassembly is *"the fabrication of hierarchical constructs with a prescribed 2D or 3D organization through the automated assembly of pre-formed cell-containing fabrication units generated via cell-driven self-organization or through the preparation of hybrid cell-material building blocks, typically by applying enabling technologies, including microfabricated molds or microfluidics"* [1]. Bioprinting can target both scaffolds for subsequent cell seeding and cell-embedded bioinks. Bioprinting of cell-free scaffolds is a form of additive manufacturing or, more colloquially, 3D printing technology. TO and spatial models support the shape design of scaffolds and cell-embedded constructs in bioprinting.

4.3.1. Printing process

As extensively reviewed in [54], optimizing bioprinting processes can have different objectives. Some approaches aim to optimize print fidelity; they search for combinations of printing parameters and set their values to enhance the similarity between product models and corresponding bioprinted objects. Other approaches aim at optimizing biomimetic fidelity; that is, they search for combinations of printing parameter values that enhance the construct's biological, mechanical, and rheological similarity to its *in vivo* counterpart. The current trend for bioprinting optimization points to the joint optimization of print fidelity and biomimicry. In [116], authors adopt a low-cost 3D

printer for precise cell placement and stem cell differentiation, providing also a computational approach to modeling fluid flows during extrusion as a function of microneedle geometry, using computational analysis to iteratively tune flow parameters until convergence to optimal needle geometry for the biofabrication of high resolution, fragile cell transfer of printed human iPSC. As reviewed in [117], process optimization can reflect the tuning of process parameter values. DL methods can optimize the bioprinting process by elucidating the complex relationships among the various printing parameters and predicting their optimal configurations for specific objectives [118, 119, 56]. For example, in [120] authors present a multi-objective optimization approach to improve printing accuracy and stability. In contrast, in [121] they propose a machine learning approach for effective and accurate drop-on-demand printing control. CNN support the data-driven detection of printing anomalies towards real-time process adjustment to ensure quality [122].

Process optimization, in other cases, implies the design or re-design of fabrication processes and systems. In [123], authors apply a fuzzy TOPSIS MCDM process for selecting the most suitable bioprinting process to optimize the biomechanical properties of the construct given the starting printing material. [124] reports using multi-physics computational models to design an extruder system tailored for biofabrication of vascular networks, maintaining cell viability during extrusion.

4.3.2. Cell seeding

Cell seeding in a biomaterial is a critical step in the biofabrication of TERM products. A large number of cells uniformly occupying the available space within scaffolds facilitates tissue culture functionality and reduces tissue maturation time. In [125], authors propose an effective cell seeding technique based on the combination of experimental and computational approaches. In particular, they target compression release-induced suction for cell seeding in scaffolds. They rely on a 2D FE model to predict that the permeability of the scaffold directly influenced cell seeding effectiveness *in vitro*, then use a fully factorial experimental design to assess the relative importance of permeability, thickness, and coating on cell seeding efficiency and uniformity on seeding effectiveness. In [126], by simulating the interactions between biomaterials, cells, and dynamic media in cell seeding under perfusion conditions, authors find an exponential relationship to optimize the seeding time and the number of cells seeded in the scaffold.

4.4. Maturation

As reviewed in [127], computational modeling supports the characterization and design of the construct maturation, predicting how the stimuli provided make the desired features emerge. Dynamical modulation of environmental cues affects product maturation and ultimately the emergence of the desired functional and structural features. DL approaches have the potential to predict functional activation from environmental stimuli of different kinds [56]. For instance, ANN can predict the induction of osteogenesis from biomechanical loading parameters [128]. Computational approaches support biofabrication process design by providing accurate predictions of process outcome and the respective product quality. They also must help meaningful, white-box representations explore the process through analysis and simulation. Authors in [129] performed a combined experimental and computational approach to link biological responses to mechanical stimulation to improve the understanding of the cause-effect relationship of mechanical loading. Modeling comprises the identity and quality of cues stimulating the system and their complex behavior in the physical environment of the maturation setup. CFD modeling can unravel the factors determining specific hydrodynamic patterns and study the influence of fluid dynamics on cell behavior during tissue maturation.

In [130], authors leverage CFD models to optimize the flow profile when designing the perfusion chamber of a perfusion bioreactor system to engineer human cartilage grafts.

In [131], computational models of the micro- and the macro-scale are combined with CFD simulation to represent cell colonization processes in a perfusion bioreactor and perform model-based optimization of the perfusion flow rate. In [132], the authors employ a model of tissue growth inside 3D scaffolds in a perfusion bioreactor and a multi-objective optimization strategy to find the most cost-effective medium refreshment strategy for maximizing tissue growth while minimizing experimental cost. Authors in [133] combine evolutionary computation and simulation of intra- and extracellular processes for efficient DSE of process designs for the biofabrication of human epithelial monolayers.

5. Open challenges and future trends

This review has the scope to present computational methods to model, design, and optimize TERM biofabrication processes, focusing on approaches comprising biological complexity. Most publications target TERM bone or cartilage engineering products among the reviewed applications. This is consistent with the science maps provided in Section 3, where the associated terms often recur. The biofabrication of more complex tissues or organs does not emerge as a frequent application domain, which is consistent with the notion presented in Section 1 that biofabrication processes and products are currently limited in the amount of biological complexity they can replicate in growing a biomimetic product. Towards the biofabrication of complex TERM products, computational tools can improve biofabrication processes. Most approaches perform substantial simplifications either on the modeling or the optimization sides. To truly leverage the potential of computational tools to support process innovation in biofabrication, the development of new approaches should consider the diversity of scientific and technological aspects in biofabrication and the underlying biological complexity, working towards holistic

solutions approaches to process modeling, design, and optimization.

In this direction, many open challenges exist, and they can group around the following main pillars.

Biological complexity: To support process characterization and design more meaningfully, system complexity must participate in processing modeling and optimization. In particular, computational methods must comprise multiscale architectures of fabricated constructs, multi-physics models of fabrication and maturation environments, and biological complexity of intracellular, intercellular, and cell-environment interactions in biofabricated tissues.

Holistic models: Existing approaches mainly target single phases of biofabrication. This makes the passage from one step to the next often manual, hindering the benefits of digitalization and automation. Computational approaches should comprise the whole process, drawing meaningful relations between process phases to support holistic modeling and optimization. In this perspective, new computational methods should either provide a structure for single-phase representations to convey in one or target individual phases with separate interoperable approaches.

Scalability: Modeling system complexity and holistically considering several process phases of biofabrication imply high computational complexity, an existing limitation of computational biology models in general. This requires the development of new strategies to increase the computational feasibility of newly developed approaches.

Flexibility: With the perspective of participating in developing clinically relevant products, computational methods for intelligent biofabrication will need to enforce QbD principles. TERM biofabrication must support product personalization to specific patients, besides adapting the process to clinical needs and regulatory requirements.

Interdisciplinary collaboration: a variety of scientific and technological domains flow into biofabrication. To foster interdisciplinary collaboration, computational tools must ensure usability and accessibility to stakeholders from this diverse user base.

By developing around these pillars, computational approaches can express their full potential in enacting QbD principles in TERM biofabrication, supporting the faster and cheaper development of more accessible, fully biomimetic products covering a more comprehensive range of personalized products and clinical applications, including more complex tissues. In the long term, computational approaches will be a critical factor in unlocking the potential of Regenerative Medicine to cure disease for a wider group of patients while fostering scientific discovery over the biological systems involved.

Competing interest statement The authors declare that they have no known competing interests that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

R Bardini: Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing - original draft; Writing - review and editing.. **S Di Carlo:** Conceptualization; Funding acquisition; Project administration; Supervision; Writing - review and editing..

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