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Review

# Advanced Manufacturing of Biomedical Scaffolds: Modeling Simulation and Process Optimization Approaches

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## ABSTRACT

**Background:** It can be vital in the process of tissue engineering and regenerative medicine since biomedical scaffolds offer the structural support that allows the process to enable cell attachment, cell proliferation, transporting nutrients, and metabolic waste. The traditional scaffold fabrication techniques like the solvent casting and freeze-drying are usually less able to provide a control over the scaffold architecture and mechanical characteristics. The current developments in additive manufacturing (AM) and computational modeling have provided a new opportunity in generating highly regulated and functional scaffolds in bone and orthopedic tissue engineering. **Objective:** The proposed review will address the latest works in the high-level production of biomedical scaffolds with the combination of additive manufacturing methods with computational modeling and data-driven optimization strategies to improve the design and functioning of scaffolds. **Materials and Methods:** Different additive manufacturing methods, such as stereolithography, selective laser sintering/selective laser melting, fused deposition modeling, electron beam melting, laser-engineered net shaping, two-photon polymerization, and laser-based bioprinting among others are discussed. Such manufacturing methods are complemented by computational algorithms like finite element modeling (FEM), computational fluid dynamics (CFD), and machine learning (ML) to control the geometry of scaffolds, mechanical behavior, and mass transport. Biodegradable polymers, collagen, and ceramic-based composites as scaffold materials are also tested on the basis of mechanical strength, bioactivity, and the degrading nature. **Results:** Additive manufacturing can provide control of pore architecture, pore size, and interconnectivity, both in control with customized scaffolds made with increased biological functionality. Computational modeling like the FEM and CFD can be used to predict the mechanical rigidity, stress distribution, and fluid transport in scaffolds. The best scaffold performance can be noticed by ensuring that the values of the elastic modulus remain between 0.1–10 Gpa, pore interconnectivity is more than 90 percent, and shear stress degree lies between 0.1–1.0 Pascals to support cell growth and transport of nutrients. The machine learning methods also speed up the design of the scaffolds by minimizing the number of experiments and also predicting how to optimize scaffolding designs. **Conclusion:** The combination of additive manufacturing and FEM, CFD, and machine learning will be a potent platform to develop the next generation biomedical scaffolds with enhanced mechanical stability and biological performance. Such computationally controlled production methods allow the accurate stress distribution, permeability and nutrient transport to be predicted resulting in a more efficient

development of scaffolds. Although there are still some barriers surrounding manufacturing variability, in vivo validation and regulatory issues, these methods promise a great deal in terms of creating personalized regenerative medicine and orthopedic tissue engineering.

**Keywords**—*Biomedical scaffolds, Tissue engineering, Computational modeling, Finite element modeling (FEM), Computational fluid dynamics (CFD), Additive manufacturing, Regenerative medicine, Bone tissue engineering (BTE), 3D polymeric scaffolds.*



## INTRODUCTION

Biomedical scaffolds are used in tissue engineering, thus playing an important role in tissue regeneration because they provide the cells with an environment for growth, differentiation, and tissue formation. These scaffolds simulate the extracellular matrix (ECM) of tissues and present an ideal environment in which the tissue healing and regeneration activities of cells occur. Scaffolds are essential in tissue engineering because they serve as temporary structures that support other tissues and enhance tissue regeneration as well as transit of nutrients and wastes.[1]

Figure 1 illustrates the evolution from traditional to additive manufacturing (AM) approaches for orthopedic scaffold production. Traditional methods, which are represented on the left-hand side, are severely limited. Such issues are failure to regulate pore morphology, lack of connection between pores, and lack of a variety of ways to produce scaffolds.[2,3]

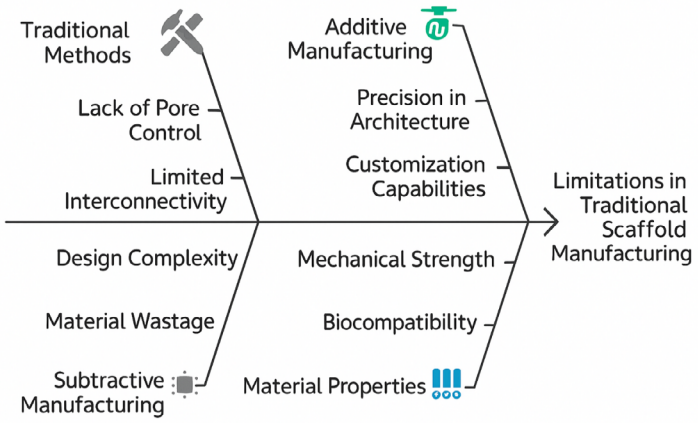


**FIGURE 1.** Evolution of scaffold manufacturing in orthopedics.[2,3]

Three-dimensional (3D) polymeric scaffolds are a key element in bone tissue engineering (BTE) and represent an alternative tool for common bone grafts. The health of these scaffolds offers a supportive environment for cell attachment, proliferation, differentiation, and regeneration of bone tissues. Synthetic and natural polymers are versatile, meaning that scaffold properties can be modified to fulfill particular biological and mechanical needs.[4]

Figure 2 shows an in-depth schematic representation of bone tissues. The bone structure in section (A) is partitioned by hierarchy, including the macro structure of the whole bone, micro-structure, such as osteons, and then further minimized into sub-microstructures, such as collagen fibre, the nanostructure of collagen fibril, collagen molecule, and the sub-nanostructure of hydroxyapatite (HA) crystal. Section (B) describes the anatomical aspects of bone, including that the functional unit is osteon and also includes the aspects of concentric lamellae, spongy and compact bone, periosteum, osteocytes in lacuno-canalicular structure and canaliculi, nerve supply, and blood supply, all of which contribute to the strength and functional aspects of the bone. Section (C) depicts bone composition: the matrix forms 98%, with 95% HA and the remainder as collagen and proteins, while bone cells make up 2%, including osteoblasts, osteoclasts, osteocytes, and lining cells. Essential elements, such as sodium, magnesium, zinc, and calcium, are also represented along with water content.[5]

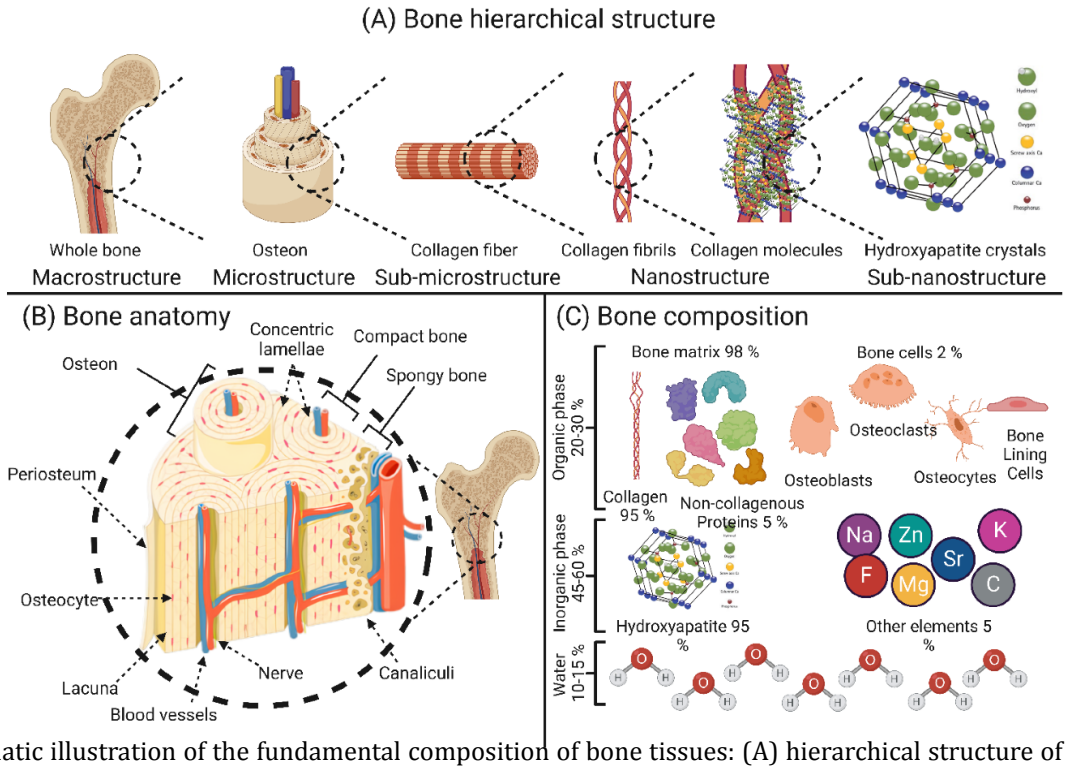


**FIGURE 2.** Schematic illustration of the fundamental composition of bone tissues: (A) hierarchical structure of a bone, (B) anatomical characteristics of a bone, and (C) elemental composition of a bone.[5] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

Several methods, such as solvent casting, particle leaching, freeze-drying, and gas foaming, have been extensively used for preparing porous scaffolds. Such techniques are robust, yet not very precise for the shape control of a scaffold. 3D printing technologies, such as stereolithography (SLA)[6], selective laser melting (SLM)[7], fused deposition modeling (FDM)[8], and selective laser sintering (SLS)[9], enable the printing of scaffolds with complicated structures and controlled pores.[10]

Orthopedic porous scaffold design in AM: The designing of porous scaffolds used in orthopedics is an important research topic for designing structures with mechanical and biological behaviors similar to those of a natural bone. The SLM is mainly used to fabricate scaffolds to precisely control pore size, shape, and distribution. The aim is to maximize such characteristics to develop better osteointegration, mechanical strength, and biocompatibility for use in orthopedic applications.[11,12]

Figure 3 shows a comprehensive classification system for scaffold designing in applications of tissue engineering. Scaffold designing is classed into two major categories: whole design and unit cell design. The designing may be divided on three strategies. First, there are regular structures that have a regular pattern. Second, the scaffold has changing properties everywhere. Third, there is a math-based scaffold design which enhances performance. Unit cell design can be classified into two basic approaches: parametric and nonparametric approaches. Parametric designs are based on computed shapes, such as Voronoi patterns of uneven cells, and triply periodic minimal surface shapes. Mathematically, these may produce complicated interiors. Nonparametric designs are based on preset geometric forms, such as body-centered cubic and face-centered cubic crystal structures, and other polyhedral forms, such as dodecahedra and honeycomb patterns. This hierarchical architecture provides researchers and engineers with the ability to identify suitable scaffold architectures based on tissue engineering, mechanical strength, and biological functional demands.[13]

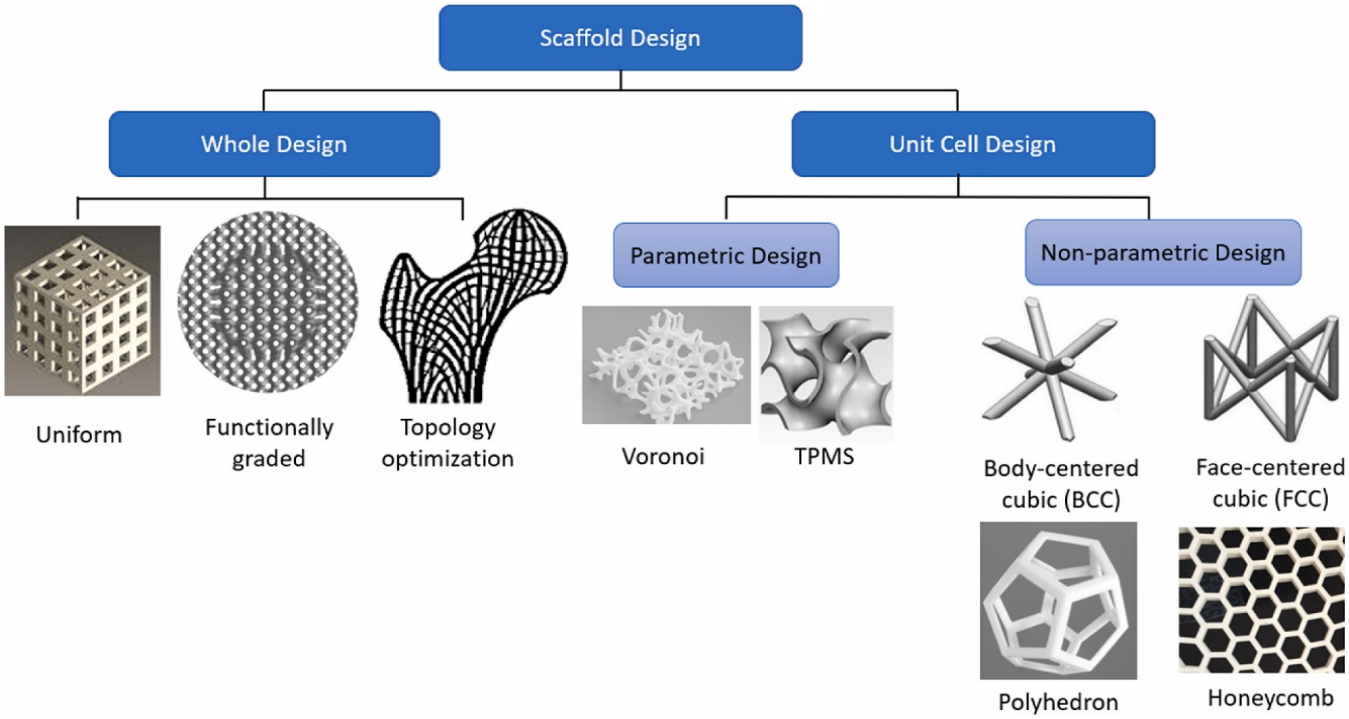


**FIGURE 3.** Flowchart of different scaffold design classifications according to the classification system provided in Chen et al.[13] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

Biomedical scaffolding manufacturing has progressed very rapidly because of the necessity of tissue engineering and regenerative medicine that require patient-specific functional and biocompatible implants. The development of advanced manufacturing techniques, such as AM, has enabled the fabrication of advanced designs of scaffolds with customized mechanical and biological functionality. Recent researches have discussed the use of computer models, simulations, and process improvements. Such studies tend to employ machine learning (ML) and multi-physics to provide structure design.[14]

The review provides a unique summary of the network of advancements in computational modeling frameworks, including finite element modeling (FEM) and computational fluid dynamics (CFD), as well as data-driven models, including ML, applied to create biomedical scaffolds, in particular. It provides an in-depth introduction to their joint application, outlines the main issues in their integration, and proposes new potential future research directions.

## LASER-BASED 3D PRINTING TECHNOLOGIES

The use of lasers in 3D printing technologies has achieved great success in orthopedic arena, where extremely complex patient-created message implants and surgical instruments are produced. Technologies such as the SLA system use lasers to crosslink photosensitive resins and build complex structures in layers. This enables them to attain the precision needed to produce orthopedic parts. 3D printing with medical imaging and computer-aided design (CAD) has been found as useful in orthopedic care. It assists in designing tailor-made solutions that suit a patient.[15]

The technique involves 3D printing of intricate implants with micro-holes with lasers. This assists implants to attach in a better way with the bone to become stable and durable. Laser-based 3D printing can create porous structures. These structures help the implant connect in a better manner with surrounding tissues because the bone can grow more easily. It is also through this technology that patient-specific implants can be made and fitted to the patient/anatomy to offer the best fitness and functionality. Moreover, implants manufactured through 3D printing can provide drug-eluting capability, which can further decrease the chances of infections and enhance the outcomes of any knee surgery. This is particularly useful in spine, foot, and ankle surgery.[16]

Three-dimensional printing provides an opportunity to create patient-specific surgical guides and instruments, enhancing the quality and accuracy of surgical interventions and shortening of working time. It supports surgeons to design individual fitting tools according to individual patient's anatomical shape, which increases the precision during surgery to include joint replacement and even tumor removal. The use of surgical guides printed in 3D can guarantee a decrease in the possibility of complications and adverse outcomes. The planning of surgery is achieved by using a 3D-printed model. This equips surgeons in a better way and, in a position, to take decisions. It is also cost- and time-saving in healthcare.[17]

This technology is used in regenerative medicine, where scaffold design can resemble the microenvironment of bone and cartilage and can be used to facilitate tissue engineering construction. Depending on needs of individual patients, these scaffolds can be altered to better suit their needs, thereby increasing the chances of successful tissue regeneration. By printing bioactive molecules or growth factors in structures, researchers can further enhance cell adhesion, proliferation, and differentiation. In addition, 3D bioprinting can be used to create multi-layered complex structures that closely match the complex structures of natural bone and cartilage tissues.[18]

Figure 4 shows the six laser-based 3D printing technologies. In SLA, an ultraviolet (UV) laser scans a liquid photopolymer in a resin tank to selectively cure the layers as the build platform decreases gradually. The SLS/SLM employs a roller to apply powders on the powdered material, which is subsequently fused by a laser on a powder delivery platform that moves downwards with every successive layer. The process of electron beam melting (EBM) is similar in that the metal powder is deposited and fused by an electron beam process in a vacuum that is replenished by a rake. Laser-engineered net shaping (LENS) uses a molten pool produced by a laser and shield gas on an X–Y table above a substrate, where the powder is injected coaxially. Two-photon polymerization (2PP) uses a laser of near-infrared (NIR) wavelength focused using a high-power objective to locally polymerize a photosensitive resin onto glass slides. Laser-based bioprinting involves focusing a laser source (NIR) on a thin film of gold, creating droplets of bio-ink that delivers live cells to a substrate.[19]

High-precision and possible customization of highly detailed implants and tools that fit the anatomic structure of a patient is of tremendous benefit, enhancing surgical outcome and client satisfaction. Such customized strategies enable surgeons to prescribe and make procedures more precisely. In addition, complex geometric and internal structures can be prepared through 3D printing, which may be difficult or even impossible to manufacture using conventional production technologies. Further developments can generate more novel orthopedics, such as bioprinting of tissues and organs that can be transplanted into the body as it develops.[20]

A diversity of materials is possible along with available metals, polymers, and ceramics, and it is possible to generate biocompatible and resorbable implants that closely match the properties of a natural bone. The versatility of materials allows adjustment of the properties of an implant, including strength, porosity, and degradation proportion, to the profile of a particular patient. Such a customized solution increases the process of implant anchoring in tissues, accelerates healing, and minimizes the likelihood of complications. Furthermore, the possibility of introducing bioactive compounds or growth factors into these materials creates a new facility for inducing bone regeneration and the overall enhancement of treatment success.[21]

Collagen, chitosan, and poly(lactic-co-glycolic acid) (PLGA) are among the most used materials because they are highly biocompatible and have mechanical characteristics. These polymers can be fine-tuned to mimic ECM, which is an appropriate environment for promoting cell growth and tissue regeneration. Natural polymers, such as collagen and chitosan, are highly biocompatible and can be degraded easily. Artificial polymers, such as PLGA, can be manipulated to be of varying strengths and dissolution proportion. Appropriate selection of a polymer is application-specific, and the tissue, scaffold characteristics, and timeline of degradation affect the choice.[22]

Scaffolds can be improved with the help of bioactive glass and Petri particles. They also render strength and stiffness to scaffolds to bear weight. Moreover, bioactive and ceramic nanoparticles can stimulate osteogenesis and angiogenesis to achieve improved bone regeneration and

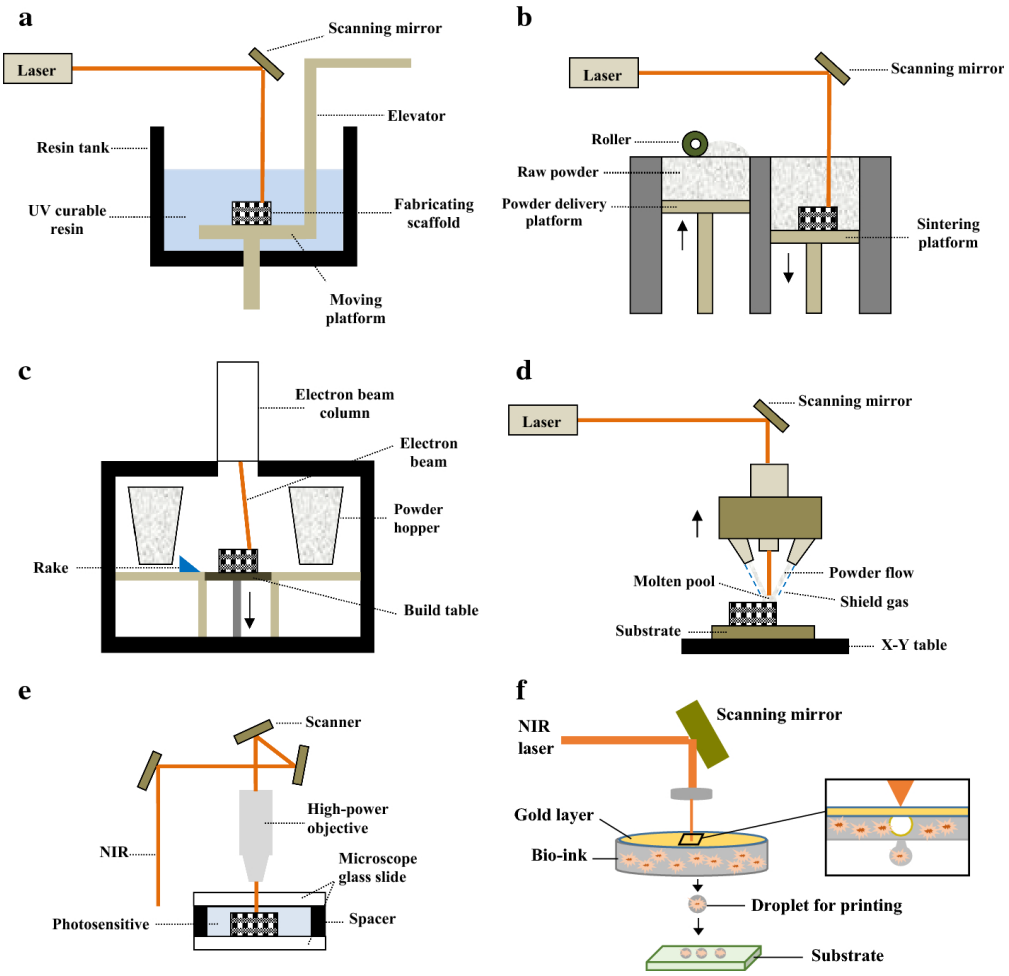


**FIGURE 4.** The overview schematic of laser-based 3D printing technologies: (a) SLA, (b) SLS/SLM, (c) EBM, (d) LENS, (e ) 2PP, and (f) laser-based bioprinting.[19] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

integration with adjacent tissues. These biocomposites are also biodegradable, with predictable degradation proportions that enable sufficient transfer of load onto newly formed tissues as scaffold degrades over time.[23]

Although laser-based 3D printing offers many advantages, several challenges remain, including the need to improve the biological functionality and biomimetic properties of bioprinted constructs. In addition, there should be specific concerns regarding market regulations for the safety of products, so that these technologies can be widely used for clinical purposes. Nonetheless, the possibilities of innovation and enhancement of orthopedic treatment using laser-based 3D printing are great.[24]

## MODELING AND SIMULATION APPROACHES

Computational modeling, namely FEM and CFD, is extensively applied for predicting and optimizing the mechanical and biological properties of scaffolds.[25]

To improve scaffold performance, we need to predict important factors, such as elastic modulus (0.1–10 GPa) for strength, pore interconnectivity (> 90%) for better nutrient flow, and shear stress limits (0.1–1.0 Pa) for cell growth. By using FEM–CFD simulations and ML, we can predict and adjust stress distribution, permeability, and nutrient transport. This helps to create scaffolds that better combine mechanical and biological functions.[25,26]

These factors have profound impact on simulation accuracy. Boundary conditions depict the interaction between the model and the environment in which it is located, and the mesh resolution defines the level of granularity of simulation. These two combinations ensure that the model reflects the physical system under study.[27]

FEM boundary conditions are significant in the realistic modeling of the mechanical interactions between implanted scaffolds, the surrounding bone and the adjacent soft tissues.The modeling of transfemoral amputees is highly sensitive to the choice of friction versus tied contact conditions, where the stress–strain behavior is found to be higher under friction contact conditions.[28] The approach to boundary condition simulation may vary; some methods only want to provide an accurate description of a part boundary by calculating stiffness matrices to accurately fulfil this purpose and save computation time.

Figure 5 presents the boundary conditions and mesh resolution of FEM for a cylindrical bone–implant assembly. U is a displacement (movement) of implant and y is the direction of implant along the Y-axis. The bottom surface is fixed vertically ($U_y = 0$) to ensure no vertical movement is allowed and the top surface is subjected to a distributed load of 1 kN, which varied by area ratio. This loading is done individually on an unmodified bone surface and at the region of implant. The X, Y, and Z positions are documented by providing axis coordinates. The density of the mesh is added around the implant, as shown in a high-magnification inset, to optimally capture stress gradients specifically within the heterogeneous band of the bone and implant contact surfaces. Far away from the implant, a rougher mesh is used to maximize computational efficiency. The graded meshing approach guarantees a satisfactory definition of local effects, such as stress concentration points at the boundary of a bone implant, without having excessive numbers of elements in less important areas.[29]

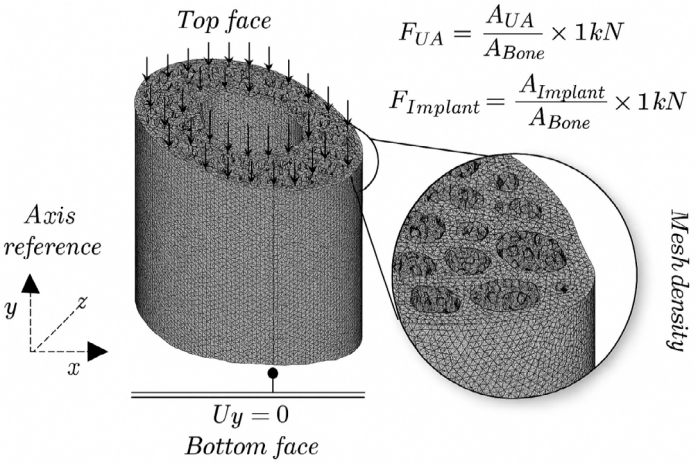


**FIGURE 5.** Boundary conditions and mesh resolution of finite element modeling (FEM).[29] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

Mesh resolution plays a significant role in determining the accuracy of FEM simulation. Generally, when a higher mesh is used, the results are more accurate. Performance and accuracy are achieved through various meshing strategies. An example is hierarchical multi-resolution models, in which it is possible to dynamically concentrate computational resources to be more efficient without missing details.[30] Adapted meshing also improves the enrichment of mesh in the regions of stress or deformation to increase accuracy in those critical zones. The type of element, as well as linear or quadratic elements, influences the precision and time consumed in simulation. Mesh resolution and computational resources (CPU time) optimization is significant in finite element analysis since too fine meshes may severely affect computation time without a marked benefit of solution accuracy.[31] Such a strategy provides greater precision, whereas a computation must be followed with a less uncalled-down-to-date supplement to the general computing intensity. Of great merit is the ability to substantially tailor mesh density and elements, consequently enforced to maximize patient-specific models that provide medically valuable output, and at a decent simulation duration.[32]

## FINITE ELEMENT METHOD (FEM) MODELING

The finite element method is one of the best promising computational strategies in tissue engineering. The method allows to construct and optimize complex 3D tissue

structures. FEM is a numerical approach where complex fields of biology are divided into smaller manageable components. This enables to examine the body in the way it reacts both mechanically and biologically under various circumstances. This has transformed the design process of medical related uses and is specifically used in the design of orthopedic devices and the dynamics of tissue growth.[33,34]

Finite element method helps to gain insight into the biomechanical characteristics of bioengineered tissue constructs that may prove useful in the interaction between cells and scaffolds surrounding them. It is also significant in the behavior forecast of cells, and their modification and formation in engineered tissues. This aids in the production and enhancement of scaffolds that closely resemble an actual tissue scenario. FEM is combined with CAD to reflect the geometry of scaffold and serve as an indicator of the designed structures to be both mechanically strong and biologically performing.[35]

This method offers high reproducibility and control of the deposition of material when used in combination with technologies of 3D printing and results in the creation of personalized, patient-specific scaffolds. The method of evaluating the scaffolds in terms of their applicability in tissue specific use is through the application of FEM which is employed to predict the mechanical performance of the scaffolds and also to assure that the mechanical properties of the scaffolds are suitable with the biological functions that they are to perform. Moreover, FEM-based predictive modeling speeds up the design-to-fabrication process by avoiding the use of large-scale experimental testing. This combined methodology makes it possible to develop regenerative medicine and 3D bioprinting technology by allowing the identification of the best scaffolding design in certain tissues and design and analysis approaches can be used for the optimum results.[36-38] Synergy is useful, especially in the management of multifaceted orthopedic problems, such as osteochondral injury and bone defects. It is possible to incorporate the use of FEM in the construction of high-fidelity biomodels that are sensitive to the mechanical properties of human tissues as well as their structures, for example, the knee, which consists of hard and soft tissues. Various applied conditions and distribution of stress are simulated by these biomodels, and they can act as an insightful reference for the biomechanics of joint and possible injury processes. Considerations, such as patient-specific data, are used to fit FEM to patient requirements, allowing personalized treatment planning and incremental optimization of implant design. Furthermore, FEM simulations can be applied to simulate the outcomes of various surgical interventions or rehabilitation strategies and allow clinicians to become more informed about their potential choices.[39]

Figure 6 presents a side-by-side comparison of a typical bioprinting process and FEM-assisted bioprinting for extrusion-based applications. The traditional workflow (top) is initiated by preparing the model, followed by the selection of cell and bioink, validating printability, parameter optimization, bioprinting of the construct, and mechanical and biological testing. If the printed construct fails to suit application standards, the procedures are retraced and corrected until a satisfactory result is attained. In contrast, the FEM-assisted method (bottom) integrates computational modeling before physical bioprinting, modeling physical and biological behavior of the construct during pre-printing, printing, and post-printing processes. FEM is used to virtually validate experimental data, inform design decisions, and predict non-measurable quantities, such as internal stress distribution. Such a predictive and iterative modeling streamlines the development of constructs and also enhances accuracy, providing an efficient and more informed way forward toward realization of functional bioprinted tissues or scaffolds to fit a particular application.[40]

Structural optimization of geometric variables applied in bioprinting spheres and orthopedics presupposes an in-depth examination of parameters to increase accuracy. In bioprinting, the concern is how the parameters are optimized to promote the accurate placement of bioinks, whereas in orthopedics, the concern is how structurally sound structures are created that fit the needs of a particular anatomical structure.[41]

The combination of natural hydrogels and synthetics, including polycaprolactone (PCL), is mandatory to achieve dimensional accuracy. The shape fidelity of these materials is also largely dependent on rheology.[42] The heating of nozzle could be ascribed to controlling substantial flow in the absence of degradation of hydrogels. There is also the

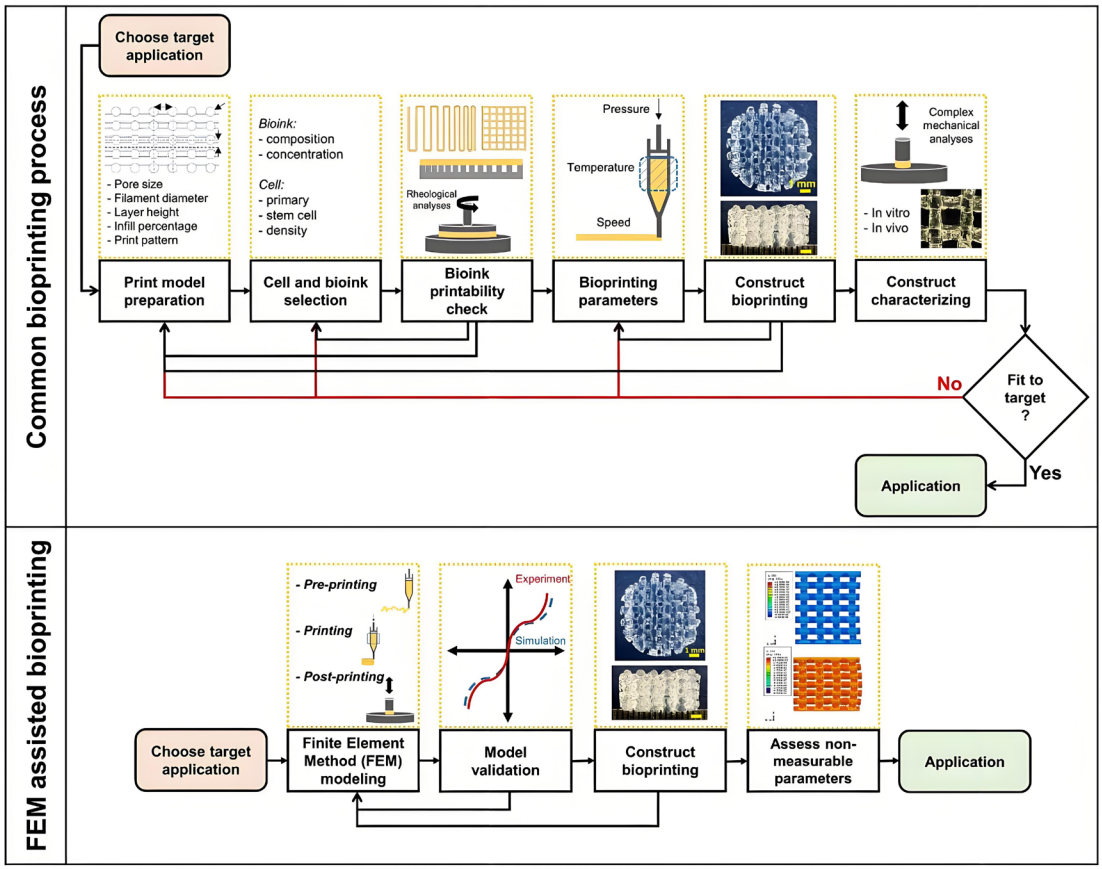


**FIGURE 6.** Schematic analysis of conventional bioprinting (top) and FEM-aided bioprinting (bottom).[40] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

attribute of speed of print, which influences the resolution and structural integrity of a printed construction; a slower speed tends to give a higher precision. The simultaneous adjustment of these parameters is important for attaining optimum print quality and meeting the desired mechanical properties of the final hydrogel structure.[43]

Figure 7 presents the evolution of key structural parameters as functions of two normalized geometric variables—strut spacing (s/D) and height (h/D)—for three unit cell diameters (264, 328, and 488 μm). Panel (a) shows that porosity decreases as struts widen (lower s/D) and height increases, with color-indicating values ranging from 10% to 65%. Specific surface area (SSA) in (b) remains relatively flat across the design space of about 4000–10,000 $m^{-1}$. The pore size (PS) in (c) spans 0–1000 μm, bounded by upper and lower limits that progressively eliminate infeasible designs (scaffolds on left: 150). Maximum mechanical performance ($MPSm_{ax}$) in (d) and average performance ($MPS_{av}g$) in (e) increase with lower porosity but narrow the viable region (61 and 16 scaffolds on left, respectively). Finally, (f) plots the normalized compromise index ($PS/PSm_{ax}$) against $SSA/SSAm_{ax}$ and porosity, highlighting trade-offs and identifying an optimal compromise solution balancing pore size, surface area, and mechanical strength.[44]

The method of computation aids in designing a scaffold. FEM is used to predict the behavior of scaffolds when subjected to various forces. They also forecast the behavior of scaffolds to fluid flow using CFD. This combination assists in comprehending the influence that the structure of scaffolds exerts on their strength and the flow of fluids through scaffolds. This has relevance in enhancing the design of scaffold in BTE. Researchers can enhance their capability to assist in the development of tissues by examining the behavior of scaffolds and the flow of fluids within scaffolds.[45]

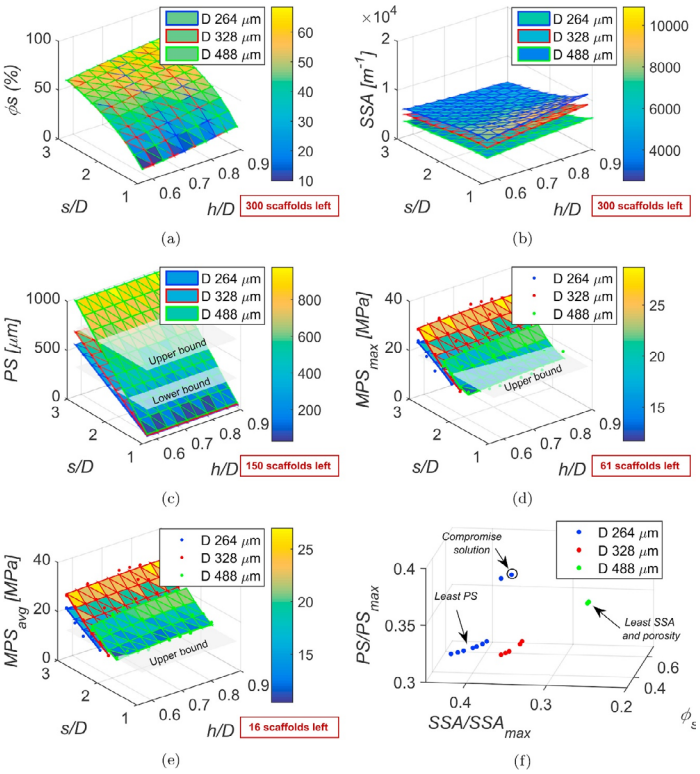


**FIGURE 7.** Surface development of parameters that are optimized in the structural optimization problem in terms of geometric variables.[44] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

It is necessary to verify that scaffolds have the capability of carrying physiological loads and must be able to sustain such loads without breaking due to structural failure. Such computational procedures enable scientists to optimize scaffold designs prior to physical construction, thus conserving time and resources. By modeling the conditions of all potential loading and various properties maintained by the material, engineers can optimize the architecture of scaffolds so that they best suit the mechanical characteristics of native tissue. CFD and FEM can also be used to detect possible weak areas or stress concentrations in scaffold design to perform repeated iterations and promote better performance and living limits.[46]

The mechanical and fluidic properties of scaffold are mutual. Permeability-enhancing designs have the potential to lower wall shear stress, which is important for cell growth and differentiation. On the other hand, the thickening of the walls that contributes to better mechanical strength may suffocate nutrients and waste disposal. The key to an optimal microenvironment that allows tissues to regenerate is to determine a right balance between these properties. The use of a gradient structure or multi-material composites can offer a viable future design solution to the conflicting mechanical and biological demands in scaffold design to allow both of these properties to be met.[47]

Computational fluid dynamics is important for the prediction and optimization of scaffolds and orthopedic biological and mechanical performance. CFD enables the simulation of liquid dynamics and mechanical load distribution, thus enabling knowledge of how a suitable scaffold architecture affects nutrient circulation, cell development, and mechanical integrity, all vital for the success of BTE. With the combination of CFD and scaffold design, it is possible to optimize pore size, shape, and distribution to optimize biological performance and mechanical properties.[48] This observation intends that tissue engineering scaffolds must be designed using biomimetic designs.[49]

The permeability of scaffolds can be optimized using CFD, and this is significant for the supply of nutrients and oxygen. The studies have revealed that the size of a pore is very important to determine permeability and large pores possess good flow characteristics.[50]

Figure 8 shows a CFD dynamics simulation of four scaffold structures, namely gyroid (G), primitive (P), I-WP (I), and triply periodic BI continuous cubic (TBC), of fluid flow properties. The pressure and velocity cloud charts of different scaffold structures are depicted (a). It is clear in these charts that pressure always decreases as it enters through scaffold structure to the exit and that fluid pressure is uniformly distributed to all four structures of a scaffold. Panel (b) quantifies the pressure drop (ΔP) across each scaffold, with the gyroid registering the highest ΔP (about 0.50 Pa) and the primitive registering the lowest (about 0.32 Pa). In panel (c), the calculated permeabilities follow an inverse trend: gyroid scaffolds have the lowest permeability (about $2 \times 10^{-9}$ $m^2$), whereas TBC achieved the highest permeability (about $4.6 \times 10^{-9}$ $m^2$).[51]

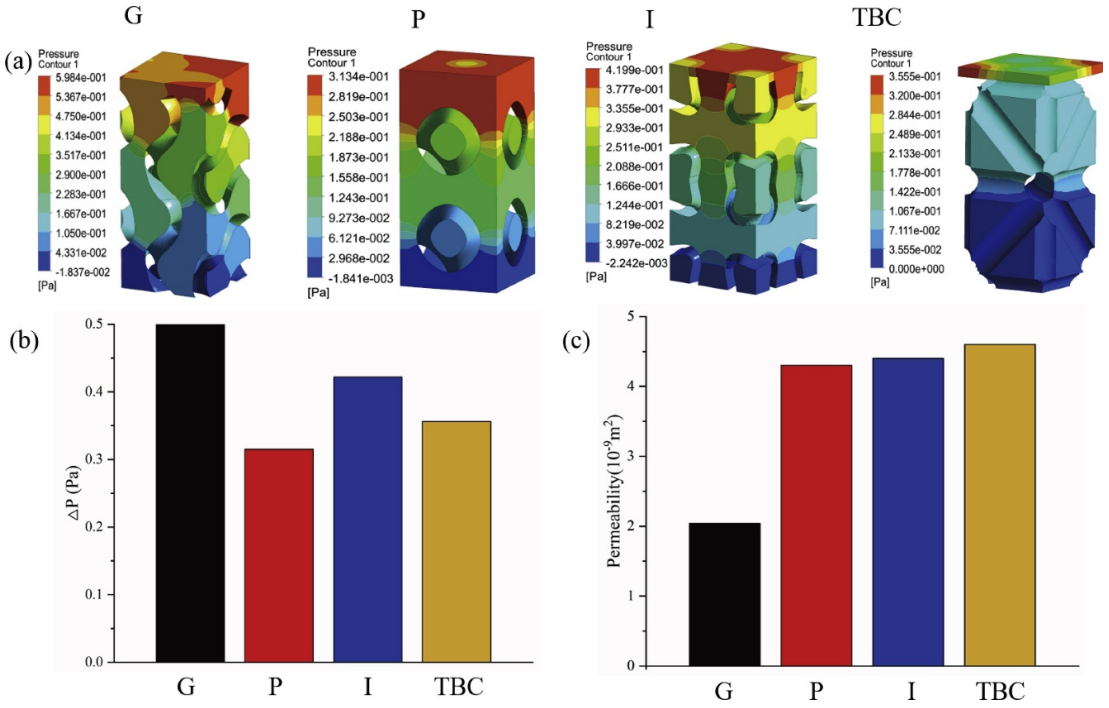


**FIGURE 8.** Computational fluid dynamics of four different scaffold frameworks: (a) pressure cloud chart, (b) pressure drop, and (c) permeability.[51] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

More sophisticated CFD schemes, such as triply periodic minimal surfaces (TPMS), can analyze very complicated scaffold geometries. The models assist in finding the most effective design between the mechanical strength and fluid dynamics required to achieve effective bone reorganization. The TPMS-based scaffold is coupled with CFD modeling of nutrient movement and cell localization in porous structure, which is a useful knowledge in this regard.[52,53] Moreover, patient-specific data combined with AM and artificial intelligence (AI)-driven design optimization can potentially transform the area of BTE by providing the possibility to produce highly customized functional scaffolds with optimal designs that closely resemble natural bone structures.[54]

Although CFD can be used to gain meaningful information on the designing of scaffolds, the integration of CFD with optimization techniques to achieve better scaffold performance remains a challenge. Moreover, the mechanics and biology of scaffolds are not always separable, and a delicate balance should be established so that no property is sacrificed to maximize the other. The area of further research would be the creation of algorithms that would optimize multiple objectives (fluid dynamics, mechanical characteristics, and even biological performance).[55]

Microscaffolding of scaffolds also plays a major role in osteogenic capacity in bone tissue engineering (BTE). Micropores, which are generally between 1–10 μm, expand surface area, protein adsorption, and cell attachment, thus promoting the growth of bone cells and tissue regeneration.[56] Cell proliferation and differentiation through microporosity is also dependent upon cell adhesion and nutrient uptake. The biomimetic architecture is very similar to the natural ECM that provides scaffolds better biocompatibility and functionality.[57]

More protein adsorption sites, which are found in microporous scaffold, would help to enhance cell attachment and proliferation.[58]

The microporous structure also provides additional protein adsorption/surface area and cell adhesion which facilitate osteogenesis. Moreover, high-performance nutrient provision and waste evacuation are possible by mutually perforated microcurvatures that provide an ideal microclimate to bones.[59]

Scaffolds characterized by microporosity promote osteoblastic differentiation and increase alkaline phosphatase activity, which is a response marker during osteogenic differentiation in vitro. Introducing micropores in scaffold structures also favors the development of larger vascular networks, which are essential for the transport of nutrients and elimination of waste in newly regenerated bone tissues. In addition, microporous scaffolds promote the attachment and replication of osteoprogenitor cells, resulting in better bone regeneration. The results indicate that the optimization of microporosity in scaffolds may present an important campaign for achieving the overall effectiveness of applications of BTE methods.[60]

Figure 9 illustrates how evenly distributed microporosity within scaffold substrates enhances osteogenic cell behavior in vitro. At a microscopic level, the use of uniform pores (about 10 μm) allows body fluids to enter the pores, creating capillary forces that pull nutrients and signaling molecules into scaffold interior. Cells with osteogenic properties bind their receptors to pore walls through adsorbed proteins, and mechanotransduction pathways become activated with the landscape of interconnecting microarchitecture, inducing a curvature. The accelerated release of scaffold degradation products and calcium phosphate precipitates is promoted in micropores, resulting in a local microenvironment enriched in osteogenic and angiogenic cues. The signaling events between these chemicals and physical signals are synergistic, enhancing cell differentiation and extracellular bone mineralization. The microporous network also enhances protein adsorption and receptor binding by providing more available surface area, which can augment intracellular signaling and the presentation of growth factors at cell surface. Overall, the microporosity of a scaffold contributes to increasing nutrient delivery, mechanical stimulation, and delivery of bioactive ions, resulting in the stimulation of osteogenesis and vascularization of cultured osteogenic-related cells.[61]

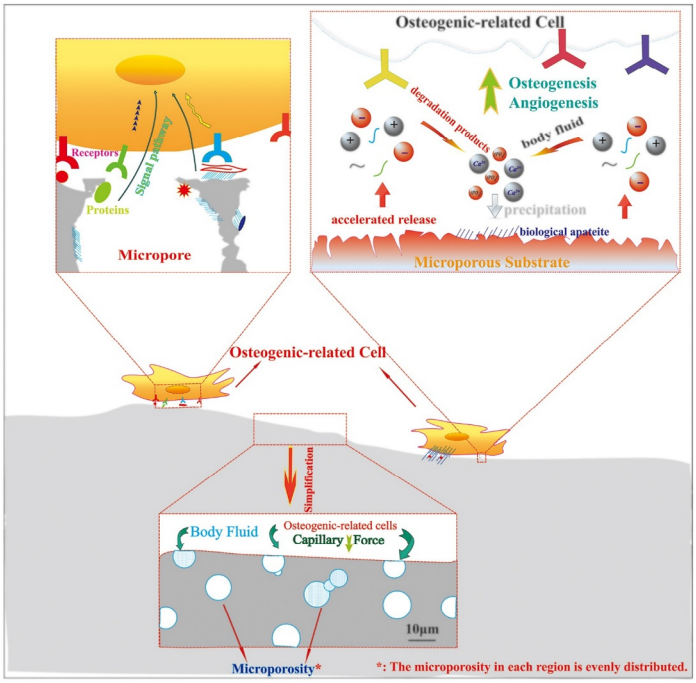


**FIGURE 9.** Scaffolds with microporosity mechanism diagram and its impact on osteogenic-related cells in vitro.[61] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

Microporosity may affect the mechanical properties of scaffolds. For example, scaffolds with enhanced microporosity exhibit superior bioactivity and accelerated bone growth in vivo. This improved performance is ascribed to the larger surface area supplied by micropores for improved cell adhesion and nutrient permeation. Moreover, the presence of micropores may modulate the scaffold degradation rate, enabling a more sustained release of bioactive agents. However, there is an optimal pore size wherein the highest pore size promotes appropriate cell interconnectivity and neovasculogenesis while maintaining structural integrity (which may decrease with increasing micro-porosity).[62]

Microporous scaffolds are found to improve the bioactivity of composites, such as Bioglass–PLGA, by supporting apatite deposition and protein adsorption. More interactions between scaffold and exterior biological environment are due to higher specific surface area of micropores. This increased interaction promotes cell attachment and growth, which in turn encourages tissue growth. Furthermore, the microporous structure may be beneficial for various mechanical properties of scaffolds,

which would better support the growth of organ tissues without compromising strength and flexibility.[63]

In vivo studies have also shown that microporous scaffolds allow for better bone growth and osseointegration. For instance, porous HA with higher microporosity had substantially higher bone growth and bone formation speed.[64]

Although microporosity has many advantages for osteogenic cell and BTE, the balance between porosity and mechanical strength must be maintained. From a biomechanical point of view, high microporosity has a potential risk for the mechanical stability of fabricated scaffolds for load-bearing applications. Thus, the optimization of microporosity is important for achieving a balance between biological activity and mechanical properties in scaffold design.[65]

## MACHINE LEARNING AND DATA-DRIVEN DESIGN

Machine learning is a branch of AI because computers learn to improve performance because of data of each problem, rather than being programmed. Such a strategy enables systems to automatically discover patterns, make decisions, and change according to new situations in order to respond to their experiences. ML algorithms can be implemented in numerous industries. ML technologies have increased, in turn, as the amount of big data and processing power has become increasingly abundant, thereby becoming increasingly sophisticated and capable of solving advanced real-life challenges.[66,67]

The orthopedic field is evolving due to innovations in its core technologies. Data-driven design and (ML) are transforming orthopedics, particularly in the development and optimization of tissue engineering scaffolds. Biologically inspired and complex structures can be designed more efficiently and produced using these technologies; therefore, they can be used to more effectively reproduce the mechanical functions of biological tissues and improve the efficacy of orthopedic and treatment implants. The application of ML to scaffold design and orthopedics is complex, entailing predictive modeling, improvements in property optimization, and the enhancement of diagnostic capacity.[68]

The mechanical properties of scaffolds are predicted using ML algorithms, including 3D convolutional neural networks (3D CNNs), which determine the mechanical properties of scaffolds based on CAD-derived digital tomographies. This method enables the designing of novel scaffolds with specific properties whose functionality might go beyond tissue engineering.[69] Scaffolds are also designed to suit the needs of individual patients with property variations of gradient mechanical to drug release. The combination of ML and 3D printing can reduce prototyping cycle and iteration time, thereby developing a new scaffold design much faster.[70]

In addition, cell–material interaction is significant in BTE. The prediction of scaffold properties allows researchers to optimize mechanical environment for the best growth and differentiation of cells. By altering the composition of materials, scientists can create scaffolds very similar to the natural bone ECM. This customized procedure not only increases cell adhesion and proliferation but also ensures the development of functional bone tissue, which in the long run can result in progressively positive bone regeneration.[71]

To design a back propagation neural network (BPNN), neural relationship must exist between structural parameters and mechanical properties. Then, an inverse search was implemented using a regenerative genetic algorithm (RGA) in ML to retrieve the required structure (Figure 10). Using forward prediction and evolutionary search, this unified framework accelerates the process of identifying microarchitecture that meets the desired performance characteristics and reduces the gap between performance demands and the designs constructed in a manufacturing facility.[72]

The use of CNNs includes the classification of various scaffold types, including airbrushed, electrospun, and steel wire scaffolds, using CNNs, for example, ScaffoldNet. This facilitates quick control and quality testing during the fabrication of scaffolds. ScaffoldNet can be used beyond classification to define an optimal set of scaffold design parameters suitable for a given tissue engineering application. Based on the structural characteristics defined by a network, scientists can optimize attributes such as porosity, direction of fibers, and topography of the surface to improve cell adhesion and cell proliferation. Not only

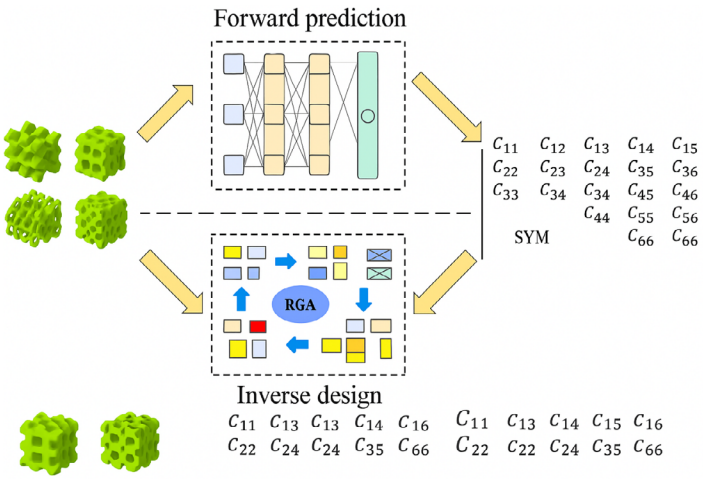


**FIGURE 10.** Flowchart of forward prediction and inverse design.[72] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

does this data-driven protocol speed up the creation of new scaffolds but it also generates useful information on the correlation between scaffold architecture and their biological performance.[73]

Machine learning algorithms find applications in the detection of fractures, diagnosis of bone tumors, and grading of osteoarthritis. Such programs enhance the accuracy of diagnosis and the speed of its completion and reduce human error. They have also contributed to the development of treatment planning and surgical guidance in orthopedic imaging studies. With the help of large sets of patient outcomes, ML models are able to predict the best treatment approaches to be used in specific cases. Besides its positive effects in enhancing patient outcomes, this personalized mechanism makes the best use of resources in healthcare facilities.[74]

Orthopedic implants fabricated using the ML-aided design of architectural materials are functional with optimized mechanical performance. Such designs have the potential to be superior in terms of loading capacity and biocompatibility, compared with the existing expert designs. With advanced production methods through ML and advanced manufacturing methods, such as 3D printing, high-efficiency versions of these implants are prototyped and optimized quickly. This interaction between AI and AM has the potential to speed up the process of development, as researchers test and optimize many material structures relatively quickly. Consequently, the patients could have more effective implants that are more personalized, better resemble the mechanical properties of the native bone, and have better surgical outcomes and shorter healing periods.[75]

Machine learning and AI are applied for clinical decision-making to increase the safety of patients and clinicians' reliability. These include the applications used in risk assessment, outcome assessment, and imaging. It has also been proven that such technologies can predict patient deterioration and possible adverse events that take place. AI and ML algorithms reveal minor patterns and anomalies that are overlooked by human clinicians through the analysis of larger amounts of patient data. Such an increased predictive ability enables more proactive and personal patient care, which possibly eliminates readmission and plays a positive role in the overall patient health.[76]

Although tremendous improvements have been made with ML in scaffold design and orthopedics, challenges still exist. The use of AI in clinical environments may have complexities that lead to impediments in the large-scale implementation of AI. Hence, additional studies are required to make ML models more accurate and effective in clinical settings.[77] Ethical considerations and data privacy issues of AI in the healthcare sector must be considered to ensure ethical use. Computer interfaces are designed such that they are user-friendly, and explainable AI models can be used by healthcare practitioners. AI scholars, clinicians, and bioengineers must work together to optimize and confirm ML algorithms in scaffold design and orthopedics.[78] Moreover, it is necessary to develop strong regulations and guidelines for medical technologies driven by AI to ensure the security and confidence of patients regarding novel methods.

## DISCUSSION

There is strong evidence to support the use of FEM, CFD, and ML to predict and enhance the performance of scaffolds.[79] Researchers have developed superior computer techniques. Such techniques assist them to modify the characteristics of scaffolds, such as porosity, rigidity, or disintegration speed. This further resembles the actual tissues of scaffolds. Computer modeling of the interactions between cells and scaffolds, as well as the dynamics of

nutrient diffusion, enables engineers to develop more biomimetic structures.[80]

A detailed plan involving FEM, CFD, and ML, commonly used in designing scaffolds, is shown in Figure 11. Their predictions are accurate depending on the adopted modeling strategies. More sophisticated methods in these directions are nonlinear material modeling, topology optimization, and multi-scale FEM or multi-physics FEM structural analysis. Biophysical and mass transport signals are simulated by patient-specific FEM and CFD. In computing, ML approaches, such as supervised learning models, deep learning, hybrid ML–FEM frameworks, and fuzzy inference systems, assist in streamlining information. They combine mechanical behavior, fluid dynamics, and intelligent optimization within one model and boost the forecasting of a scaffold behavior.[81–83]

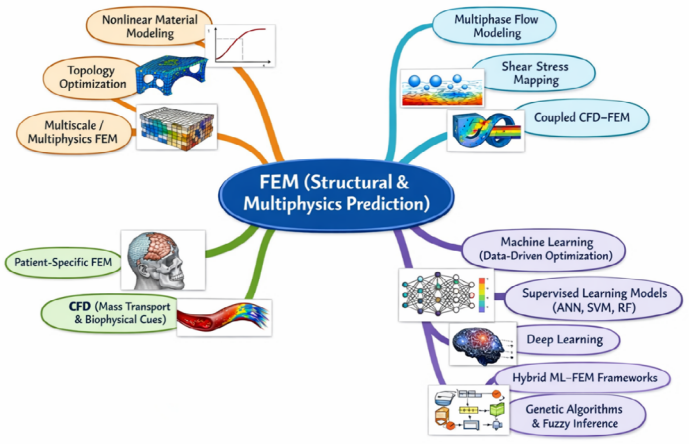


**FIGURE 11.** Finite element modeling approaches for scaffold prediction.[81–83] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

Transition to data-driven and AI-based strategies is decreasing the dependence on trial-and-error experimentation and propelling advances in patient-specific working scaffolds. This shift makes it possible to predict the material behavior in scaffolds more reliably and optimally before material fabrication. These data are used as a large-scale set of material properties, cell characteristics, and clinical outcomes to utilize ML algorithms to advise scaffold designing. Consequently, the discipline is becoming closer to fulfilling the promise of genuinely patient-specific tissue engineering-based solutions that accommodate the needs and anatomical disparities of individual patients.[84]

As shown in Table 1, advanced scaffold manufacturing employs 3D bioprinting, electrospinning, SLA, SLS, digital light processing (DLP), and FDM, along with computational optimization (FEA, CFD, multi-physics modeling, and fuzzy inference). Natural polymers (collagen, gelatin, and alginate), synthetics (PLA and PCL), and composites enable tunable mechanics and bioactivity. Hierarchical multi-scale designs control porosity and gradients to mimic tissues. Application-specific optimization enhances bone, cartilage, and vascular scaffold performance.

**TABLE 1.** Critical trends in advanced biomedical scaffold manufacturing.

| Methodology | Scaffold Type/ Material | Mechanical Properties/Values of Porosity | Optimization/Modeling Approach |
|---|---|---|---|
| Multi-physics modeling with 3D bioprinting | Light-based 3D-printed biological scaffolds | Compressive modulus: 0.5–5 MPa; porosity: 60–80% | Multi-physics model integrating fluid dynamics, oxygen mass transfer, cell oxygen consumption, and cell growth processes.[85] |
| FEA with 3D printing | Bone scaffolds (HA nanoparticles functionally graded materials) | Compressive strength: 10–150 MPa; elastic modulus: 1–15 GPa; porosity: 40–70% | Parametric FEM considering pore shape, CAD modeling from medical images.[86] |
| CFD with bioprinting | Self-supporting perfusable tissue constructs (SSuPer) | Elastic modulus: 0.1–1 MPa; porosity: 75–90% | CFD modeling analyzing flow characteristics (net force, pressure distribution, shear stress, and oxygen distribution) through micro-channel patterns.[87] |
| Electrospinning | Nanofibrous scaffolds (poly(L-lactic acid [PLLA]), collagen, Nylon 6,6 | Tensile strength: 1–10 MPa; elastic modulus: 50–500 MPa; porosity: 70–90% | Dual extrusion electrospinning for geometric control, hierarchical structure design.[88] |
| FDM with FEA validation | Mandibular graft scaffolds (polylactic acid) | Compressive strength: 40–65 MPa; elastic modulus: 2–3 GPa; porosity: 55–70% | Topological optimization methods combined with FEM, CBCT image reconstruction.[89] |
| Extrusion-based 3D bioprinting with computational optimization | Gelatin-based bioink scaffolds | Compressive modulus: 10–100 kPa; porosity: 80–95% | Fuzzy inference system (FIS) with four inputs (concentration, flowrate, speed, and temperature) and precision/printability outputs.[90] |
| Stereolithography (SLA) | BTE scaffolds (photopolymer materials) | Elastic modulus: 100–500 MPa; compressive strength: 5–20 MPa; porosity: 50–75% | Controlled architecture fabrication with micrometer-level resolution, porosity, and pore size optimization.[91] |
| DLP with post-processing | Polyacrylamide-alginate hydrogel scaffolds | Compressive modulus: 20–200 kPa; porosity: 70–85% | Two-step process: DLP printing followed by Fe ion post-processing for secondary crosslinking.[92] |
| SLS | Multilayer osteochondral scaffolds (PCL and HA/PCL microspheres) | Compressive strength: 5–80 MPa; elastic modulus: 0.5–2 GPa; porosity: 40–60% | Bio-inspired multilayer design with gradient composition via SLS technique.[93] |
| CFD for bioprinting optimization | Shear-thinning biomaterials (alginate and gelatin) | Compressive modulus: 5–50 kPa; porosity: 85–95% | Numerical analysis of extrusion process in single-nozzle dispensing system with static mixer.[94] |

**Note:** CAD: computer-aided design; CFD: computational fluid dynamics; FDM: fused deposition modeling; DLP: digital light

processing; FEA: finite element analysis; SLS: selective laser sintering; HA: hydroxyapatite; PCL: polycaprolactone; BTE: bone tissue engineering.

Figure 12 outlines the integrated process of scaffold fabrication for bone regeneration applications. The workflow begins with the designing of a porous scaffold, followed by 3D printing to produce the desired geometry. After printing, scaffold freeze-drying was applied to coat it with a composite of alginate and HA to enhance bacterial activity and facilitate tissue attachment. In the bottom part, numerical simulations, that is, representative volume element (RVE) and FEM, are presented to evaluate the mechanical properties of scaffold with stress–strain relationships and elastic modulus. Microscopic studies of surface morphology and element distribution were performed using field-emission scanning electron microscopy with energy dispersive spectroscopy (FE-SEM-EDS), mineral phase detection using X-ray diffraction (XRD), and high cell compatibility of experiments with cell viability results. Finally, the right side depicts the clinical translation in which the optimized bioactive scaffold is introduced to a damaged bone fragment so that efficient tissue regeneration and functional recovery are achieved. This strategy shows synergy in the designing, simulation, and experimentation of advanced bone repair.[95]

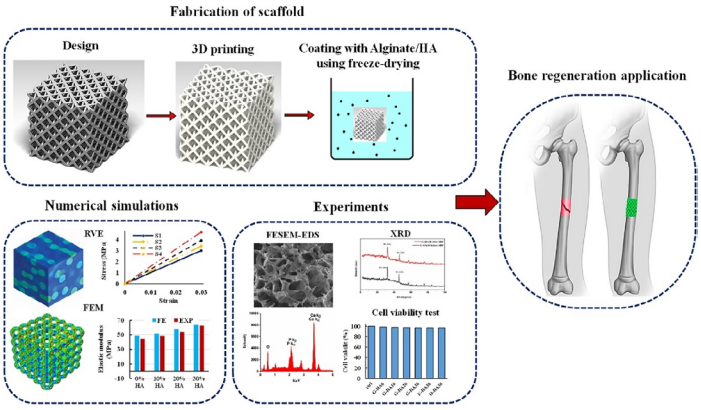


**FIGURE 12.** Fabrication of 3D-printed hydroxyapatite (HA) by freeze-drying.[95] (Used under a Creative Commons Attribution 4.0 International License [CC BY 4.0])

The issues in translating computational predictions to clinical practice remain, specifically in manufacturing variability, in vivo validation, and integration of degradation and tissue regeneration models. The literature highlights the necessity of multidisciplinary iterative workflows comprising a combination of computational tools.[96] Future studies should aim to create further refined computational models, considering manufacturing variability and in vivo conditions.

## CONCLUSIONS

Development of computational modeling, simulation, and optimization has brought immense contributions to the sophisticated production of biomedical scaffolds. Such innovations have allowed the architecture, porosity, and mechanical properties of scaffolds to be brought under more consistent control. Presently, scaffolds can be customized to the needs and types of tissues, and researchers can design scaffolds that they believe are more efficient in the repairing and regeneration process of tissues. The incorporation of smart materials and bioactive constituents into scaffolds has also provided new opportunities to make dynamic and responsive environments that even better mimic the behavior of natural tissues. CFD and mathematical process modeling, including FEM, are important in measuring the effectiveness of scaffolds. With sophisticated simulation methods, such as computer modeling of mechanics, fluid mechanics, and mass transport in scaffolds, the researchers are able to investigate the mechanics of scaffolds, fluid flow patterns, and mass transport. In scaffold prediction, nonlinear and multiscale FEM with topology optimization applied in mechanical analysis, CFD and FEM–CFD coupling applied in transport and mechanobiology, are the fields of interest. ML surrogate models and multiscale predictive frameworks can also be used to enable the efficient design and optimization of complex scaffold models. The behavior of scaffold in different conditions is studied by taking into account many factors, such as scaffold geometry, material properties, and the behavior of cells.

Moreover, such computational tools can be used to optimize the designing of scaffolds, minimize the time-consuming process of experimental validation, and reflect on formulating more successful tissue engineering applications. Such data-driven and ML design methods change scaffold design, predict properties, and optimize parameters. Advanced methods allow the exploration of very large design spaces within a short period of time, exposing new scaffold design architectures with superior performance properties. By using big data and

advanced algorithms, researchers are able to determine how combinations of material data (MD), geometries, and manufacturing processes are optimized to meet the needs of a particular tissue engineering application. In addition to the faster development of personalized scaffolds, the data-driven method also offers a higher probability of clinical success because it more closely resembles the sophisticated microenvironment of native tissues.

Computational techniques are combined to create biomimetic scaffold structures that support tissue regeneration and achieve better clinical outcomes. Such computational methods provide a high degree of control over scaffold architecture, porosity, and mechanical strength. By imitating elaborate hierarchical systems in natural tissues, biomimetic scaffolds have the potential to drive development, multiplication, and differentiation of cells. This can then be implemented using state-of-the-art structural design and manufacturing processes, including 3D printing, to create the best scaffold geometries with high fidelity. Bringing computational predictions into the clinic continues to be difficult, in part because of manufacturing variations, live animal testing, and model grounding.

More effective computer models should be discovered in future research and multidisciplinary workflows should be developed. To fill the gap between theoretical considerations and real-world practice of regenerative medicine, computational scientists, bioengineers, and clinicians are needed in this area of research.

## AUTHOR CONTRIBUTIONS

Writing–Original Draft Preparation, A.M.; Formal Analysis, A.M.; Writing–Review & Editing, H.V.; Data Curation, H.V.; Supervision, H.V.

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## DATA AVAILABILITY STATEMENT

Not applicable.

## CONFLICTS OF INTEREST

The authors declare they have no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## FURTHER DISCLOSURE

Not applicable.

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