Biomedical production of implants by additive electro-chemical and physical processes

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ABSTRACT

Biomanufacturing integrates life science and engineering fundamentals to produce biocompatible products enhancing the quality of life. The state-of-the-art of this rapidly evolving manufacturing sector is presented and discussed, in particular the additive electrical, chemical and physical processes currently being applied to produce synthetic and biological parts. This fabrication strategy is strongly material-dependent, so the main classes of biomaterials are detailed. It is explained the potential to process composite materials combining synthetic and biological materials, such as cells, proteins and growth factors, as well the interdependencies between materials and processes. The techniques commonly used to increase the bioactivity of clinical implants and improve the interface characteristics between biological tissues and implants are also presented.

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1. Introduction

The ageing population, high expectations for a better quality of life and the changing lifestyle of modern society require improved, more efficient and affordable healthcare care. This poses new challenging problems regarding the increasing number of implants required, new diseases to be treated (e.g., Parkinson's and Alzheimer's) and organ shortage problems. On the other hand, some medical devices ideally should survive without experiencing any failures for the patient's lifetime.

The loss or failure of an organ or tissue is a frequent and costly problem in health care. Today, treatments include either transplanting organs from one individual to another or performing surgical reconstructions by transferring tissue from one location in the patient's body into the diseased site. The disparity between the need and availability of donor tissues has motivated the development of tissue engineering approaches aimed at creating cell-based substitutes of native tissues [16, 17, 151].

To address some of these demanding issues, a new scientific domain called biomanufacturing emerged in 2005, during the Biomanufacturing Workshop hosted by Tsinghua University in China and defined as the use of additive technologies, biodegradable and biocompatible materials, cells and growth factors to produce biological structures for tissue engineering applications [22]. More recently, in a meeting sponsored by the American National Science Foundation in the spring of 2008, biomanufacturing was defined as the design, fabrication, assembly and measurement of bio-elements into structures, devices, and systems, and their interfacing and integration into/with larger scale structures in vivo or in vitro environment such that heterogeneity, scalability and sustainability are possible. In 2009, during the 59th CIRP General Assembly, a Collaborative Working Group (CWG) on biomanufacturing was established based on three main pillars: Biofabrication, Biomechatronics and Biodesign, and Assembly. The goal of this CWG is to contribute to a coherent strategy for the development, dissemination and exploitation of biomanufacturing. To pursue this goal, the CWG aims to optimise current technologies and develop new ones in the areas of computer-integrated surgical systems, tissue engineering, bio-informatics and nano-diagnosis/medicine, based on the theories and the technologies established in each CIRP Scientific Technical Committee (STC).

This review follows the establishment of the CIRP CWG's focus on current healing and repairing strategies. Despite the complexity associated with the design, fabrication and implantation of appropriate medical implants, this paper addresses only three critical topics: biomaterials, manufacturing processes and surface treatments for the fabrication of clinical implants, the only biomedical implants considered here (Fig. 1). Biomanufacturing
is a strongly material- and process-dependent fabrication procedure in which materials not commonly used in conventional production engineering are considered. The main characteristics of those materials strongly determine the electro-chemical and physical additive manufacturing processes to be used, as well as the application range of these production technologies. The application context of this work is detailed in Section 2, where the main characteristics of the considered clinical implants (permanent and temporary) are described. Section 3 is fully dedicated to the four main classes of biomaterials (metals, polymers, ceramics and composites) used to produce the considered implants. Understanding of the main properties of these biomaterials and the interdependences between materials and biological tissues is fundamental not only for selecting the right material for a specific application but also for selecting the appropriate manufacturing process. Materials such as hydrogel and biomaterials/cells composites are also introduced due to their relevance. Section 4 introduces the most relevant electro-chemical and physical additive processes used for the production of clinical implants. The main characteristics, applications and materials used by each of these technologies are explained. The integration between materials (Section 3), processes (Section 4) and applications (Section 2) are summarised at the end of Section 4 (Table 7). Finally, in Section 5, some techniques are introduced to enhance the bioactivity and the establishment of strong connections between biological tissues and implants.

2. Medical implants

Medical implants are devices placed either inside or on the surface of the body to accomplish some particular function, such as to replace, assist or enhance the functionality of some biological structure(s). Many implants are prosthetics, intended to replace missing body parts, while other implants deliver medication, monitor body functions, or provide support to organs and tissues. Implants are classified as permanent or temporary. According to the United States Food and Drug Administration (FDA), a “permanently implantable device is a device that is intended to be placed into a surgically or naturally formed cavity of the human body for more than one year to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device.” Examples of permanent implants include stents and hip implants. Temporary implants are commonly used in sports and medical surgeries, especially in shoulder and knee ligamentous reconstruction and spinal reconstructive surgery [203]. They are usually made of biodegradable polymers like screws, suture threads and plates. Scaffolds are permanent or temporary porous structures implanted to favour tissue or bone regeneration.

2.1. Biodegradable implants

Degradable implants or scaffolds serves as temporary skeletons to accommodate stimuli to new tissue growth (Fig. 2). They play a major role in tissue engineering representing the initial biomechanical support for cell attachment, differentiation and proliferation [16,17,142,148].

An ideal scaffold must satisfy the following requirements [16,17,92,142,144,182]:

- Biocompatibility. Both raw and processed materials should interact positively with the host environment without eliciting adverse host tissue responses.
- Biodegradability. Scaffolds must degrade into non-toxic products with a controlled degradation rate that matches the regeneration rate of the native tissue. The in vivo degradation process of polymeric scaffolds is influenced by different and often conflicting variables, such as those related to the material’s structure (i.e., chemical composition, molecular weight and molecular weight distribution, crystallinity, morphology, etc.), its macroscopic features (i.e., implant shape or size, porous shape, size and interconnectivity, etc.) and environmental conditions (i.e., temperature, pH of the medium, presence of enzymes or cells and tissues).

The chemical degradation of polymers may principally proceed via either degradation by biological agents (enzymes), hydrolytic degradation (hydrolysis), which is mediated by water, or a combination of both coming into contact with living tissue. Several authors have investigated the degradation process of a wide range of biomaterials [55,68,80,197], Lee et al. [129], Sung et al. [197], Agrawal et al. [23] and Lu et al. [146] studied the degradation of poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) and found that the degradation rate depends on the molecular weight and hydrophobicity. Lam et al. [124] showed that the hydrolytic degradation of PCL scaffolds is governed by their high molecular weights, crystallinity, hydrophobicity, surface-to-volume and porosity. On the other hand, incorporating certain other materials, such as calcium phosphate, significantly increases the degradation rate [124]. Domingos et al. [55,56] observed the in vitro degradation of PCL scaffolds in simulated body fluid (SBF) and the phosphate buffer solution (PBS) for 6 months. Results show a more significant degradation process of the
scaffolds in SBF than in PBS, due to the formation of calcium phosphate deposits on PCL scaffolds, which decreases the degradation kinetics.

Many environmental factors are involved in the gradual degradation of calcium phosphate ceramic after implantation, including physiochemical processes (dissolution-precipitation) and the effects of various cell types [83,135,213]. Cells such as fibroblasts and osteoblasts degrade ceramics by either phagocytic mechanisms or an acidic mechanism with a proton pump to reduce the pH of the microenvironment, resorbing these synthetic substrates [83,141]. The cellular mechanisms of calcium phosphate degradation are modulated by several parameters, such as the properties of the ceramic itself, the implantation sites and the presence of various proteins (cytokines, hormones, vitamins, ions, etc.) [83,141].

- **Appropriate porosity, pore size and pore shape.** Generally, a high level of porosity is required (>90%) because it increases the surface area, enabling high cell seeding density and proliferation, as well as neovascularisation [121]. Pore size plays an important role in terms of cell adhesion/migration, vascularisation and new tissue ingrowth [17,85,99,128,136,164,180]. Macro-pores (i.e. >50 μm) are of an appropriate scale to influence tissue function, while micro-pores (i.e. <50 μm) influence cell function (e.g. cell attachment), given that mammalian cells typically are 10–20 μm in size and nano-porosity refers to pore architectures or surface textures at the nano-scale level (i.e. 1–1000 nm) [93]. Optimum macro-pore sizes of 20 μm have been reported for fibroblast ingrowth, 20–125 μm for hepatocytes and 100–250 μm for the regeneration of bone. If the macro-pores are too large or too small, cells will fail to ingrow and form networks through the scaffold. Smaller pores enhance cell adhesion and differentiation in vitro, while bigger pores promote higher cell adhesion and viability in vivo. It is important to define an optimal macro-pore size range for supporting cell and tissue ingrowth. These limits vary greatly depending upon cell type and the culture conditions, but in general they fall in the range of 100–500 μm. Pore interconnectivity (100% interconnected network of internal channels are required) is also a critical parameter in terms of cell viability and tissue regeneration, maximising the diffusion and exchange of nutrients and the eliminations of waste. Pore interconnectivity can be measured by either determining the flow rate of fluid flowing through the scaffold or using techniques, such as mercury intrusion porosimetry, micro-computed tomography (μCT) or image analysis [103,204].

- **Bioactive.** Scaffolds should be bioactive, promoting and guiding cell proliferation, differentiation and tissue growth. This can be achieved by adding growth factors and functionalizing the scaffold with proteins or adhesion-specific peptide sequences, which often resemble the extracellular matrix providing appropriate signals to cells.

- **Mechanical strength.** Scaffolds are required to withstand both in vitro manipulation and stresses in the host tissue environment. In vitro, engineered tissue constructs should maintain their mechanical properties to preserve the required space for cell growth and matrix formation. For in vivo applications, it is important that scaffolds mimic as closely as possible the mechanical properties of the native tissue in order to provide a temporary mechanical support for tissue regeneration. Initially, the scaffold must withstand all stresses and loads in the host tissue environment before gradually transferring them to the regenerated tissue (Fig. 3).

- **Adequate surface finish.** This guarantees a good biomechanical coupling between the scaffold and the tissue.

- **Easily manufactured and sterilised.** Implants should be rapidly produced with high accuracy and repeatability and easily sterilised by exposure to high temperatures, UV light, γ-radiation, plasma, ethylene oxide (ETO) gas, or by immersion in a sterilisation agent, remaining unaffected by either of these processes [4,64]. However, a few suitable techniques are available to sterilise biodegradable polyester scaffolds because they are susceptible to degradation and/or morphological degeneration under high temperatures and pressures. The effect of sterilisation on both surface topography and material properties should be considered. It was previously observed that ETO and, for example γ-radiation, induces degradation and shrinking of poly(α-hydroxysters) [27,86]. Cotnam et al. [44] observed that gamma irradiation significantly decreased the rate of degradation of PCL discs, although the rates depended on the initial mass of the polymer. Gamma irradiation also significantly increased the mechanical yield stress, but not the failure stress of PCL. Andrews et al. showed that sterilisation method modifies the topography of scaffolds (Fig. 4) [5].

![Mechanical Contribution of Scaffold](image-url)  
**Fig. 3.** Schematic representation of the mechanical contribution of a scaffold over time as it degrades, and the mechanical contribution of the new host tissue as it forms in the presence of appropriate mechanical loading [11].

![AFM images](image-url)  
**Fig. 4.** AFM images of electrostatically spun polyurethane scaffolds: (A) virgin; (B) UV-ozone sterilised; (C) ETO sterilised [5].
2.2. Permanent implants

The first evidence of head surgery dates back to 8000 BC. The practice of immobilising members began around 3000 BC, and the use of metal and other material implants, such as bone, for dental restoration and cranioplasty can be observed in archaeological museums all over the world.

According to the National Institutes of Health Consensus Development Conference, an implant is “a medical device made of one or more biomaterials intentionally placed within the body, either totally or partially buried beneath an epithelial surface” that can be in contact with tissue for a significant period of time [12]. The biocompatibility of implants is time dependent and application related: a material can be biocompatible for a short period of time but incapable of long-term contact with tissue. It can also be biocompatible for one application but not for another, depending on the surrounding tissue.

Medical implants have been used for about 50 years; today, a high percentage of people have such a device, especially in developed countries where access to health care is affordable and research/technology more developed. However, all implants are subject to failure, and long-term data concerning their performance and host response are vital for improvements.

Implants can be functional or cosmetic. A broad variety of applications exist for functional implants, which are intended to accomplish the organ’s function. Examples include hip and other joint implants, vascular prostheses, artificial ligaments, heart valves, cages, spinal fusion and spacer devices, some cochlear implants, artificial hearts and dental implants [10,33,112,206]. Cosmetic implants can be used to provide shape or improve aesthetic functions for breast, nose, ear, hand, and foot prostheses, among many others. Fig. 5 shows a cosmetic, or bucomaxillofacial prosthesei, developed by the Renato Archer Information Technology Center (CTI, Brazil) using the concept of BioCAD [102]. Beyond aesthetic purposes, this prosthesis showed functional results, improving patient speech and feeding.

Fig. 6 shows the sequence used for producing of a cranial hollow prosthetics made of polyethylene-hexamethylene-carbonate-PHMC. The design of the prosthetic was designed using a Magnetic Resonance segmented model of the lesion area (duramater membrane), and its function was to keep intracranial pressure stable, giving shape to the external area.

Implants can be mechanically fixed with screws, pins, wires, mechanical interference, glue or cement. Biological fixation is also possible with surface treatments and improvements with biomaterials and chemical modifications. Augmenting of surface roughness and area with microspheres, meshes, and filaments is also of great importance when biological attachment through tissue ingrowing is expected.

Implants are expected to be durable and stable with an excellent interface when in contact with tissue. For example, a biomaterial in contact with blood, as in stents and heart valves, cannot permit any blood disorder, such as attachment or coagulum formation. On the other hand, metal stems for hip implants with biological attachment are expected to have a better tissue growing response to promote fixation. Implants must be designed to be as least invasive as possible during installation and maintenance.

Some problems related to implant failure, such as loosening, breaking and migration, are usually caused by the wrong design (not designed for a specific patient), material selection, application, manipulation, installation and misuse. Some of the causes are biologically related, such as infection and excessive tissue responses, while others are mechanically-related, such as stress concentration, micro-displacements, surface scratches affecting the passivation layer (surface film created to reduce chemical reactivity), and wear generating particles or debris. Fatigue and corrosion are very common in metal implants, and wear is frequent in polymeric parts of implants; therefore, to successfully accomplish its task, an implant has to be designed considering several criteria, such as physicochemical properties, strength, fatigue endurance, wear resistance and material dimensional stability, always taking into account the application and surrounding tissue.

3. Materials

Biomaterials are materials that interface with biological entities [29,174,202,214]. The National Institutes of Health Consensus Development Conference defined a biomaterial as “any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body” [214]. A distinctive difference between a biomaterial over other materials is its benign coexistence with a biological system with which it interfaces [81]. The use of bioinert, bioactive materials (first generation of biomaterials) is an important response to the growing medical needs of a rapidly ageing population. Subsequently, the biomaterials field began to shift from bioinert materials to bioactive materials, which can elicit controlled actions and reactions within the body. Currently, four classes of biomaterials are used:

- Acellular tissue matrices (biological scaffolds);
- Metallic materials;
- Ceramic materials;
- Polymers (naturally derived and synthetic polymers);

Biological scaffold materials, composed of an extracellular matrix (ECM), are not considered in this paper, as they are not processed through the manufacturing processes considered here. The preparation of these biological matrices commonly involves a combination of physical (freezing, direct pressure, sonication and agitation), chemical and enzymatic methods to remove cell bodies from the remaining extra-cellular matrix [45,67].

3.1. Metals

Metals and their alloys, due to their mechanical reliability, strength, stiffness, toughness and impact resistance, were used for load-bearing implants, such as hip and knee prostheses and fracture fixation wires, pins, screws, and plates (Fig. 7). Metals have...
also been used as parts of artificial heart valves, vascular stents, and pacemaker leads [112].

Important characteristics to be considered for medical applications are biocompatibility, appropriate mechanical properties, corrosion resistance and structural integrity [175]. Metallic biomaterials are classified as inert materials because they elicit minimal tissue response. In physiological environments, metals can suffer from corrosion, thus releasing ions, which may reduce biocompatibility and put at risk the use of implants.

Major metals used in medical applications include commercially pure titanium and its alloys (α + β alloys, Ti–6Al–4V, Ti–Al–Nb and β–Ti alloys), co-balt-based alloys (Co–Cr–Mo, Co–Ni–Cr–Mo, Co–Cr–W–Ni), stainless steel (primarily type 316L), Ni–Ti alloys, Au-based materials, and Ag–Sn alloys [31,41,150].

Titanium has one of the highest strength-to-weight ratios and corrosion resistance of metals [86]. It has excellent biocompatibility due to its non-corrosive properties, low ion-formation tendency in aqueous environments and a dielectric constant comparable to that of water [31,62]. The material passivates itself in vivo by forming an adhesive oxide layer [31,62]. It also displays the unique property of osseointegration, by which it connects both structurally and functionally with the underlying bone [62,75]. Controlled formation of TiO2 and Ti3Si on the surfaces of a number of Ti-alloys can induce apatite formation when these surfaces are immersed in a simulated physiological media of the appropriate ionic concentration, enhancing early binding of Ti-alloys to bone [109]. Similarly, treating Ti-alloys with an aqueous solution of NaOH, followed by heat treatment at 500–800°C, results in a thin titaneate layer, which can then form a dense, bone-like apatite layer when placed in physiological media, thus enhancing the strength of the bone/implant interface [75,106]. For permanent implants, Ti–6Al–4V has a possible ‘toxic’ effect resulting from released vanadium and aluminium, so this alloy is being replaced by vanadium- and aluminium-free alloys (Ti–13Nb–13Zr and Ti–12Mo–6Zr) [62].

Table 1 presents some mechanical properties of several metallic biomaterials. In general, these materials have high tensile and fatigue strength compared with ceramic and polymers. However, the elastic moduli are much higher than that of natural bone, which can cause “stress shielding,” a phenomenon characterised by bone resorption in the vicinity of implants.

3.1.1. Shape memory alloys

Shape memory alloys (SMA) are materials that retain their original shape after severe deformations when subjected to heat above their transformation temperature [24,123,159]. Shape memory alloys have two distinct crystallographic phases, namely, austenite and martensite. The martensitic phase is a low-temperature, stable phase with the absence of stress. The austenite phase is stable at a high temperature and displays a stronger body-centre cubic structure [147]. SMAs are capable of large amounts of bending and torsional deformation and high strain rates (6–8%) in the martensitic phase [194]. Another unique property of SMAs is pseudo-elasticity, wherein the two-phase transformation occurs at a constant temperature.

The most commonly used SMA is nitiol, an alloy containing approximately 50% nickel and 50% titanium [89]. Titanium is non-toxic, while nickel is extremely toxic and carcinogenic. However, nitiol forms a passive titanium oxide layer that both acts as a physical barrier to nickel oxidation and protects the bulk material from corrosion [159]. As illustrated in Fig. 8, nitiol similar to bone and tendon, has high elasticity, low deformation forces and constant force over wide ranges of strain.

Cu-based SMAs, especially Cu–Al–Ni and Cu–Al–Mn, are also commercially available. They have a transformation temperature range (~200 to 200°C) similar to nitiol, but higher Young’s modulus, better machinability and better stability [89,184], though Cu-based alloys have toxic effects [198].

SMAs are used for hard tissue implants in orthopaedics and dentistry due to its porous structure, good mechanical properties, biocompatibility and shape memory effect [95,159,181].

3.2. Ceramics

Ceramics are inorganic materials with high compressive strength and biological inertness [59,134,211]. The most commonly used bio-ceramics are metallic oxides (e.g., Al2O3, MgO), calcium phosphate (e.g., hydroxyapatite (HA), tricalcium phosphate (TCP), and octocalcium phosphate (OCP)), and glass ceramics (e.g., Bioglass, Ceralital) [26,82]. Metallic oxides are considered to be nearly bioinert in biological environments, while calcium phosphate and glass ceramics can bond to bone when implanted. Bioceramics have been successfully used for hard tissue replacement due to their good biocompatibility and bioactivity. Their biocompatibility is a direct result of its chemical compositions, which contain ions commonly found in the physiological environment, such as Ca2+, K+, Mg2+, Na+ [211].

Bone tissue becomes integrated into the bioactive ceramics through the biomineralization of a thin layer of calcium phosphate at the interface between the ceramics and the host bony tissue [134]. The interstitial body fluid is the very first medium of a bioactive ceramic interface after being hosted in a bony defect. The structure of the ceramic changes for the biomineralization of calcium phosphate by the interaction with the body fluid, which contains various proteins that must be significantly involved with biomineralization [134,170]. This interfacial layer of calcium phosphate is almost independent of the ceramic type. Fig. 9

Table 1

<table>
<thead>
<tr>
<th>Relevant properties of metallic biomaterials [175].</th>
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<tbody>
<tr>
<td>E modulus [GPa]</td>
</tr>
<tr>
<td>Stainless steel</td>
</tr>
<tr>
<td>Co–Cr alloys</td>
</tr>
<tr>
<td>Titanium</td>
</tr>
<tr>
<td>Ti–6Al–4V</td>
</tr>
<tr>
<td>Cortical bone</td>
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</table>

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\[\text{Fig. 8. Stress vs. strain relationship for superelastic nitinol, stainless steel, bone, and tendon [159].}\]

\[\text{Fig. 9. In vitro mechanism of formation of calcium phosphate on the surface of Na2O–CaO–SiO2 glass in SBF [134].}\]
illustrates the in vitro mechanism of the formation of calcium phosphate on the surface of a Na\textsubscript{2}O–CaO–Si\textsubscript{2}O\textsubscript{3} glass in SBF.

The main calcium phosphate materials used for medical applications are indicated in Table 2. Synthetic hydroxyapatite (HA, Ca\textsubscript{10}(PO\textsubscript{4})\textsubscript{6}(OH)\textsubscript{2}) is a bioactive material, with chemical characteristics similar to hard tissues such as bone and teeth, that promotes hard tissue ingrowth and osseointegration when implanted into the human body [26,211]. The porous structure of this material can be tailored to suit the interfacial surfaces of the implant. As a bulk material, HA lacks sufficient tensile strength and is too brittle to be used in most load bearing applications [52]. In such cases, HA is coated onto a metal core or incorporated into polymers as composites [28]. HA is frequently used as a bioactive coating on hip prostheses [52]. The ceramic coating on the titanium implants improves the surface bioactivity but often fails as a result of poor ceramic/metal interface bonding [100]. An alternative is the production of composite materials containing titanium and bio ceramic as a reinforced phase [100]. Due to the low bioresorbability of HA much attention has been paid to TCP ceramics [28,101].

Several in vitro and in vivo works have shown that calcium phosphates support the adhesion, differentiation and proliferation of osteogenesis-related cells (e.g., osteoblasts, mesenchymal stem cells), besides inducing gene expression in bone cells [6,179,187,195,210].

Structural ceramics like alumina (high purity, polycrystalline, fine grained) and zirconia that is toughened and highly resistant to wear (TZP and Mg-PSZ) have been used for femoral heads of total hip prostheses due to their excellent tribological properties, improved fracture toughness and reliability [126]. Zirconia has high flexural strength and fracture toughness compared to other ceramics, which makes it more resistant to masticatory forces when used as crowns with exact precision of fit [104,228]. Zirconia implants also accumulate less bacteria in vivo [177] and undergo a lower rate of inflammation-associated processes than titanium [51]. Zirconia has also been used in shoulder reconstruction surgery and as a coating over titanium in dental implants [53].

Bioactive glasses, such as Bioglass, and A-W glass–ceramic have also been successfully used for tissue replacement [122,223]. Bioactive glasses stimulate the formation, precipitation and deposition of calcium phosphates from physiological solutions, enhancing the bone–matrix interface strength. Bioglass is bioactive with low fracture toughness [211,223], while the bioactive A-W glass–ceramic has excellent mechanical properties and high bioactivity (higher than HA), being clinically used for iliac and vertebral prostheses and intervertebral spacers [114]. It was observed that ionic dissolution products from Bioglass and other silicate-based glasses stimulate gene expression of osteoblasts [50]. Bioactive glasses also stimulate angiogenesis in vitro and in vivo, as well as antibacterial and inflammatory effects [4,72]. Table 3 presents some mechanical properties of several ceramic biomaterials.

### Table 2

<table>
<thead>
<tr>
<th>Ca/P molar ratio</th>
<th>Compound</th>
<th>Formula</th>
</tr>
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<tbody>
<tr>
<td>1.33</td>
<td>Oocalcium phosphate (OCP)</td>
<td>Ca\textsubscript{10}(PO\textsubscript{4})\textsubscript{6}(OH)\textsubscript{2}</td>
</tr>
<tr>
<td>1.5</td>
<td>α-Tricalcium phosphate (α-TCP)</td>
<td>Ca\textsubscript{5}(PO\textsubscript{4})\textsubscript{3}</td>
</tr>
<tr>
<td>1.5</td>
<td>β-Tricalcium phosphate (β-TCP)</td>
<td>Ca\textsubscript{5}(PO\textsubscript{4})\textsubscript{3}</td>
</tr>
<tr>
<td>1.67</td>
<td>Hydroxyapatite (HA)</td>
<td>Ca\textsubscript{10}(PO\textsubscript{4})\textsubscript{6}(OH)\textsubscript{2}</td>
</tr>
<tr>
<td>2.0</td>
<td>Tetracalcium phosphate</td>
<td>Ca\textsubscript{4}(PO\textsubscript{4})\textsubscript{2}</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Relevant properties of ceramic biomaterials.</th>
<th>Young’s modulus [GPa]</th>
<th>Compressive strength [MPa]</th>
<th>Tensile strength [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alumina</td>
<td>380</td>
<td>4500</td>
<td>350</td>
</tr>
<tr>
<td>Bioglass-ceramics</td>
<td>22</td>
<td>500</td>
<td>56–83</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>18–28</td>
<td>517</td>
<td>280–560</td>
</tr>
</tbody>
</table>

### 3.3. Polymers

Polymers for medical applications can be naturally derived or synthetic, the latter of which can be biodegradable or bioinert. Bioinert synthetic materials include polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP), poly(ethylene acrylic acid) (PEMA), polyethylene (PE), polytetrafluoroethylene (PTFE), polystyres, polamides (PA-nylon), polyurethanes (PUR), and polysilsioxanes (silicone) [26,96]. Biodegradable synthetic polymers include poly(glycolic acid), poly(lactic acid), their copolymers, and poly(p-dioxanone). Natural polymers include albumin, collagen, cellulose, hyaluronic acid, starch, chitosan, dextran, silk, heparin, and DNA [26,96].

Biodegradable synthetic polymers have been used in a number of clinical applications, such as resorbable sutures, drug delivery systems, orthopaedic fixation devices such as pins, rods and screws, and scaffolds for tissue engineering.

#### 3.3.1. Hydrogels

Hydrogels are cross-linked hydrophilic polymers that exhibit excellent biocompatibility, causing minimal inflammatory responses, thrombosis, and tissue damage. Hydrogels can also swell large quantities of water without the dissolution of the polymer due to their hydrophilic and cross-linked structure, which gives them physical characteristics similar to soft tissues [97,190,193]. They also present high permeability for oxygen, nutrients, and other water-soluble metabolites. Hydrogels are soft and elastic materials, generally used above their glass transition temperature ($T_g$).

Synthetic hydrogels can be formed from poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), propylene fumarate (PF), poly(butylene oxide) (PBO), polycaprolactone (PCL), poly(hydroxybutyrate) (PHB), polycycliclamide, poly(vinyl acetate) (PVAc), poly(vinyl acetate) (PVAc), polyacrylonitrile (PAN), poly(ethylene oxide) (PEO), poly(propylene oxide) (PPO), poly(hydroxypropyl methacrylamide) (PHPMA) and poly(2-hydroxyethyl methacrylate) (HEMA). Biological hydrogels can be formed from hyaluronic acid (HA), alginic acid, agarose, chitin, fibrin, collagen, dextran, agarose, gelatin, pullulan and carrageenan.

Hydrogels can be chemically tailored to respond to certain environmental stimuli, such as so-called temperature-responsive, potential-specific and pH-sensitive gels (Fig. 10) [190]. They are extensively used in medicine for applications such as contact...
3.3.2. Shape memory polymers

Shape memory polymers (SMPs) are degradable or non-degradable polymers that allow repeated shape changes and shape retention [153,192,216,221]. At temperatures above \( T_g \) the material enters a rubbery elastic state, so it can be easily deformed into any shape. When the material is cooled below its \( T_g \), the deformation is fixed and the shape remains stable. The original shape can be recovered by heating the material once again to a temperature higher than \( T_g \) [192,216]. SMP presents several advantages over SMA, such as the following [192]:

- Lightweight;
- The wide range of \( T_g \) (from –70 °C to 100 °C) allows a wide variety of potential applications in different thermal environments;
- High shape recovery (up to 400%);
- Large reversible changes of elastic modulus between the glassy and rubbery states;
- Excellent biocompatibility;
- Easy processing;
- Low cost (10% of the cost of existing SMAs).

SMPs are used for orthopaedic and dental applications, bandages and artificial skins, self-tightening suture materials, drug delivery systems, stents, intelligent electrodes and thrombectomy devices [192,216].

3.4. Composites

A wide range of polymer-based composite materials were developed and investigated for biomedical applications. These materials can be classified as shown in Fig. 11 [172]. A composite material made of an avital (non-living) matrix and reinforcement phases is called an “avital/avital” composite. Alternatively, a composite material comprising a vital (living) and avital (non-living) material is called a “vital/avital” composite [172].

4. Manufacturing processes

Additive electro-chemical and physical processes, through which physical objects are created from computer-generated models, emerged in the 1980s. The basic concept of additive fabrication is layer laminate manufacturing, in which 3D structures are formed by laminating thin layers according to 2D slice data obtained from a 3D model. The main advantages of additive electro-chemical and physical techniques are the capacity to rapidly produce very complex 3D models and the ability to use various raw materials. When combined with clinical imaging data, these fabrication techniques can be used to produce constructs customised to the shape of the defect or injury. Some processes operate at room temperature, thus allowing cell encapsulation and biomolecule incorporation without significantly affecting viability. This section describes the most relevant additive electro-chemical and physical processes either commercially available or under development.

4.1. Electrospinning

Electrospinning is the most relevant electro-chemical process to produce nano-scale meshes for tissue engineering [1,13,38,48,60,91,133,157,158,167,171,201]. It is a simple and versatile process by which nanofibers with diameters ranging from a few nanometers to several micrometres can be produced using an electrostatically driven jet of polymer solution (solution electrospinning) or polymer melt (melt electrospinning). The basic requirements of an electrospinning apparatus are shown in Fig. 12 including: (1) a capillary tube with a needle or pipette, (2) a high-power voltage supply, and (3) a collector or target. This collector can move in the vertical direction, enabling electrospinning as an additive technology. Electrical wires connect the high-power supply to both the capillary tube, which contains a polymeric solution, and the target. An example of a melt electrospinning apparatus is illustrated in Fig. 13. Fig. 14 shows two different heating configurations for melt electrospinning [48]. Melt electrospinning requires, the polymeric jet to be cooled, while solution electrospinning relies on the evaporation of the solvent to produce fibres.

Initially, as a result of surface tension, pendant droplets of the solution are held in place. A conical protrusion, known as a Taylor cone, is formed when a critical voltage is applied to the system. An approximately straight jet emerges from the cone but it cannot stand for long. The jet then emerges into a diaphanous and conical shape. The conically moving jet experiences bending instabilities and is directed towards the collector, which has the opposite electrical charge. The solvent evaporates, and dry polymer fibres are deposited until the jet reaches the collector. The parameters and processing variables affecting the electrospinning process are indicated in Table 4. Fig. 15 illustrates meshes produced with optimised and non-optimised parameters. Hollow nanofibers can be prepared by co-axial electrospinning (Fig. 16).

![Fig. 11. Classification of polymer-based composite biomaterials [172].](image1)

![Fig. 12. Electrospinning setup [201].](image2)

![Fig. 13. Melt electrospinning setup [1].](image3)
Materials commonly used in electrospinning include:

- **Solution electrospinning**: Polyethylene-co-vinyl acetate (PEVA/PLA), Polyactic acid (PLA), Polyvinyl alcohol (PVA), Polyacrylonitrile (PAN), PolyCarbonate (PC), Polybenzimidazole (PBI), Polyurethanes (PU), Nylon 6,6 (PA-6,6), Polyethylene oxide (PEO), Collagen/PEO. Polymethacrylate (PMMA)/tetrahydroperfluorooctylacrylate (TAN), Polyaniline (PANI)/Polyethylene (PS). Silk-like polymer with fibronectin functionality, Polyethylene Terephthalate (PET), Polyvinyl alcohol (PVA), Polyvinylchloride (PVC), Cellulose acetate (CA), PVA/Silica, Poly(2-hydroxyethyl methacrylate) (HEMA), Polycaprolactone (PCL), PAN/TiO2, PCL/metal (gold or ZnO), alginate and gelatine.

- **Melt electrospinning**: HDPE, Polypropylene (PP), Nylon 12 (PA-12), Polyethylene terephthalate (PET), Polyethylene naphthalate (PEN), PET/PEN.

### 4.2. Stereolithography

Stereolithographic processes produce three-dimensional solid objects in a multi-layer procedure through the selective photo-initiated cure reaction of a polymer [14,15,19–21]. These processes usually employ two distinct methods of irradiation. The first is the mask-based method, in which an image is transferred to a liquid polymer by irradiation through a patterned mask. The second uses a focused UV beam to selectively solidify the liquid resin. These two approaches can also be classified into two types, free-surface and constrained-surface (Fig. 17) [25,90].

Two-photon polymerisation represents a useful stereolithographic strategy to produce micro/nanoscale structures by focusing femtosecond laser pulses into the volume of a liquid photosensitive polymer or polymer mixture. In this case, the reactive molecules, which are present in the polymeric mixture, absorb two photons instead of one. The probability of electronic excitation of a molecule by the simultaneous absorption of two photons depends quadratically on the incident light intensity [219]. This allows a submicron 3D resolution, in addition to enabling 3D fabrication at a greater depth and an ultrafast fabrication. Lim [132,140] developed the so-called nano-stereolithography (NSL), based on the two-photon polymerisation process (Fig. 18). The system uses a mode-locked Ti:sapphire laser beam, with a wavelength of 780 nm, pulse repetition of 80 MHz and pulse width less than 100 fs. The beam is scanned across the focal plane using a set of galvano mirrors with a resolution of 2.5 nm. Microparts are fabricated using a voxel matrix scanning method or a contour offset method [132,140].

The main advantages of stereolithographic processes include the ability to cure quickly at physiological temperatures, enabling the production of scaffolds for tissue engineering applications. Stereolithographic processes have been used to produce hearing aids, micro needles for transdermal drug delivery and scaffolds for tissue engineering with or without encapsulated cells (Fig. 19) [25,165]. Stereolithography is also used to produce surgical guides for the placement of dental implants, temporary crowns and bridges and resin models for lost wax casting [163].

Levy et al. [137] used a direct irradiation stereolithographic process to produce hydroxyapatite (HA) ceramic scaffolds for orbital floor prostheses. A suspension of fine HA powder into a UV photo-curable resin was formulated and used as building material. The photo-cured resin acts as a binder to hold the HA particles together. The resin is then burnt out and the HA powder assembly sintered for consolidation. Similarly, Griffith and Halloran [73] produced ceramic scaffolds using suspensions of alumina, silicon nitride and silica particles with a photo-curable resin. The binder was removed by pyrolysis and the ceramic structures sintered. Briant and Anseth [32] used a photo-polymerisation process to encapsulate chondrocytes in poly(ethylene oxide) (PEO) hydrogels structures with thicknesses varying from 2 to 8 mm. The hydrogel structures were photo-cured at a low light intensity (~10 mW/cm²) for 10 minutes. The chondrocytes encapsulated in the hydrogel structures and cultured in vitro for 6 weeks remained viable and produced cartilaginous tissue. The results suggested...
and the acrylic mushroom cap were removed by pyrolysis and the HA green scaffold submitted to a sintering process. The finest channel size achieved was 366 μm with a range of implant porosity between 26% and 52%. Similarly, Kim et al. [107] used an indirect approach to produce HA scaffolds. Micro-stereolithography was used to produce a mould (4.2 mm × 4.2 mm) with an internal pore size of 250 μm and a line width of about 350 μm using a liquid polymer SL5180 resin (Huntsman) (Fig. 20a). Then the mould was filled with HA nanopowder with a particle size of 500 nm. The scaffold (Fig. 20b) was produced through a sintering process. Initially, the temperature was increased from room temperature to 1100 °C with a heating rate of 5 °C/min, held at this temperature for 2 h, and then decreased to room temperature with the same rate. An analogous strategy was used by Lee et al. [130].

Lee et al. [131] investigated the effect of 3D scaffolds with embedded growth factor-delivering microspheres for bone applications. BMP-2-loaded poly(ε-lactic-co-glycolic acid) (PLGA) microspheres were incorporated into a 3D scaffold produced through micro-stereolithography, with a suspension of microspheres and a poly(propylene fumarate) (PPF)-diethyl fumarate (DEF) photopolymer. By measuring released profiles in vitro, it was verified that the fabricated microsphere-containing 3D scaffold could gradually release the growth factor. The effect of BMP-2 was also assessed in vitro by observing cell differentiation using MC3T3-E1 pre-osteoblasts. It was also observed that these scaffolds have a superior bone-regeneration effect compared with scaffolds produced using a conventional method (Fig. 21).

Seck et al. [183] produced porous and non-porous biodegradable hydrogel structures using an aqueous photo-curable resin based on methacrylate-functionalised poly(ethylene glycol)/poly(ε-lactide) macromers and Lucirin TPO-L as a visible light cure sensitizer. This system was applied to produce porous hydrogel scaffolds, which were further used to produce scaffolds by micro-stereolithography. Fig. 19 is a SEM image of a mould produced using micro-stereolithography, showing the internal shape of the HA scaffold.

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photo-initiator (Fig. 22). After photo-polymerisation, the obtained structures were extracted with distilled water to remove soluble compounds, and dried at ambient conditions for 3 days. The structures showed good cell seeding characteristics, and human mesenchymal stem cells adhered and proliferated well on these structures.

Arcuate et al. [7–9] explored stereolithography for fabricating multi-material, spatially controlled bioactive scaffolds. To accomplish multi-material builds, a mini-vat setup was designed allowing for self-aligning X-Y registration during fabrication. The mini-vat setup allowed the part to be easily removed and rinsed and for different photocrosslinkable solutions to be easily removed and added to the vat. Multi-material scaffolds were fabricated by including controlled concentrations of fluorescently labelled dextran or fluorescently labelled bioactive PEG in different regions of the scaffold. Human dermal fibroblast cells were seeded on top of the fabricated scaffolds. Spatial control was successfully demonstrated in features as small as 500 μm.

To produce multimaterial functionally graded scaffolds, researchers from the Centre for Rapid and Sustainable Product Development of the Polytechnic Institute of Leiria (Portugal) are developing a new stereolithographic fabrication process called the stereo-thermal-lithographic process (STLG). This process uses ultraviolet radiation and thermal energy (produced by IR radiation) to initiate the polymerisation reaction in a medium containing both photo- and thermal-initiators (Fig. 23). The concentrations of both initiators are carefully selected, and the reaction begins only when there is a particular combination of UV radiation and thermal energy [21]. This way, the amount of each initiator must be low enough to inhibit the start of the polymerisation by only one of these two effects. However, at the point where the two effects intersect each other, sufficient amounts of radicals are generated to initiate the polymerisation process. Temperature is used to both produce radicals through the fragmentation of thermal-initiators and simultaneously increase the initiation and reaction rate of the photo-initiated curing reaction. As a result, the extent of cure is increased, and no post-cure will be needed. The main advantages of STLG over conventional stereolithography are as follows:

- Generation of radicals is more efficient;
- Small concentrations of the two types of initiators are used, enabling the radiation to penetrate deeper into the polymer;
- Combination of UV radiation and temperature increases the reaction rate and hence the fractional conversion values;
- Curing reaction is more localised, improving the accuracy of the produced models;
- The system has more tunability.

Four subsystems can be considered. Subsystem A uses ultraviolet radiation to solidify a liquid resin that contains a certain amount of photo-initiator. Subsystem B uses thermal energy produced by infrared radiation to solidify a liquid resin that contains a certain amount of thermal-initiator. Subsystem C uses heat produced using infrared radiation and ultraviolet radiation to solidify a liquid resin that contains a certain amount of photo-initiator. Subsystem D uses heat produced through infrared radiation and ultraviolet radiation to solidify a liquid resin containing a certain number of thermal-initiators and photo-initiators.

In addition to these key advantages, the system also contains a rotating multi-vat that enables the fabrication of multi-material structures (Fig. 24). STLG is being developed to produce multi-material microscopic engineering prototypes through nanostructures for exploitations in waveguiding and photonic crystals, multi-material functional graded scaffolds for tissue engineering, other biomedical components and micro-functional metallic or ceramic parts.

4.3. Laser sintering and melting processes

Selective laser sintering (SLS) and selective laser melting (SLM) are additive manufacturing processes that use high-energy light
sources to consolidate powder material [10, 47, 63, 71, 110, 120, 145, 225]. Contrary to SLS, SLM uses high-powered laser beams to directly create 3D metal parts by fusing very fine metallic powders. Table 5 summarises the major advantages and disadvantages of SLM to process metal powders.

SLM and SLS have been used to produce both permanent and temporary implants. Pattanyak et al. [116] explored the use of SLM to produce porous titanium constructs with complicated internal structures for bone ingrowth applications. The constructs were produced using Ti powder of less than 45 μm particle size. The compressive strength was in the range of 35–120 MPa when the porosity was in the range of 75–55%. Porous Ti constructs were subjected to NaOH, HCl, and heat treatment to provide bioactivity. Treated constructs formed bone-like apatite on their surfaces in a stimulated body fluid within 3 days. In vivo research also showed that new bone penetrated into the pores. Similar work was carried out by Imwinkelried [94] and Wang et al. [212].

Hollander et al. [84] used SLM to produce a wide range of Ti-6Al-4V medical implants, ranging from cylinders with regular porosity to a human vertebra model (Fig. 25). In vitro studies were performed with porous structures using human osteoblasts. Cell spreading and proliferation was observed. Similar studies were performed at the University of Leuven: some ten different scaffold geometries were produced and seeded with human periosteam-derived cells (Fig. 26). After 14 days of culture in a growth medium (GM based on DMEM and bovine serum) and osteogenic medium (OM + GM + dexamethasone + ascorbic acid), the cells were found to be viable and proliferating in all scaffolds. GM culture resulted in more cells and a greater extend of pore occlusion.

Partners in Belgium and the Netherlands (universities of Leuven and Hasselt, AM bureau LayerWise, etc.) cooperated to design and manufacture complex jaw implants (Fig. 27). The full lower implant shown in Fig. 27 was coated with bio ceramics and implanted in the chest of an 83-year-old lady. The cavities in the implant made it to weight only slightly more than a natural jaw bone and guaranteed good attachment of muscles and space for nerves.

Hao et al. [76] used SLM to directly process HA and 316L stainless steel (SS) powder mixture to develop load bearing and bioactive implants. The SS/HA composite implants fabricated using optimum parameters exhibited a tensile strength of 95 MPa, which is adequate for load-bearing applications.

| Material | No distinct binder and melt phases | Not suitable for well-controlled composite materials (e.g. WC-Co) |
| Cost and processing time | Elimination of time-consuming and costly furnace post-treatments for debinding, infiltration or post-sintering | High laser power and good beam quality (expensive lasers); smaller scanning velocities (longer build times) |
| Part quality | Suitable for producing fully dense parts in a direct way | Melt pool instabilities and higher residual stresses |

Table 5: Main advantages and disadvantages of SLM [120].

Kruith [119, 206, 207] explored SLM to produce implant-supported frameworks for dental prostheses using titanium and cobalt-chromium. Quality control has been performed on the produced frameworks to verify their mechanical, chemical, biocompatible and geometrical properties. The frameworks were clinically tested and are now commonly implanted in patients.

SLM and SLS combined with self-propagating high temperature synthesis (SHS) have also been used to produce Nitinol implants [61, 120]. The combined process resulted in implants with higher homogeneity in chemical composition, better biocompatibility and more porosity. The surface of porous Nitinol implants made by SHS/SLM had a significantly more favourable structure for mechanically interlocking with bone [185, 186]. Laser melting of Ti–Ni shape memory alloy was also investigated by Bourrell [123].

Rimell and Marquis [176] used SLS to produce linear continuous UHMWPE solid bodies for clinical applications without pre-heating.

Fig. 25. Examples of Ti-6Al-4V parts. (A) Cylinders with cubic pore pattern, (B) original (right) and analogue (left) human vertebra [84].

Fig. 26. Green fluorescence images revealing live cells (A) and SEM images revealing cell proliferation after 14 days.

Fig. 27. (A) Ti mandible plate and inner scaffold structure produced as one part by SLM and fitted into model of mandible produced by SLA (stereolithography); (B–D) full lower jaw in Ti.
Problems related to material shrinkage and material degradation were observed. Das et al. [49] used SLS to produce biomimetic Nylon-6 constructs of cylindrical and cubical periodic geometry with 800 μm channels and 1200 μm pillars. Results showed bone ingrowth into the pore channels after implantation into a Yucatan minipig mandible for 6 weeks. SLS of polyamide (PA12) is widely used for individual medical jig manufacturing, e.g., MyKnee® by Medacta Switzerland and SurgiGuide® by Materialise, Belgium. The MyKnee® cutting blocks are made to accurately match the surgeon’s preoperative planning and operation, based on an individual patient’s anatomy. The customised SurgiGuide® drilling jigs are delivered together with a LongStop Drill system of bushes and drills to precisely control the drilling depth as planned preoperatively by the SimPlant software.

The potential of SLS to produce PCL scaffolds for replacement of skeletal tissues was demonstrated by research teams of Das [215] and Kruth [205]. Das seeded the PCL scaffolds with bone morphogenetic protein-7 (BMP-7) transduced fibroblasts. In vivo results show that these scaffolds enhance tissue ingrowth, in addition to possessing mechanical properties within the lower range of trabecular bone. The compressive modulus (52–67 MPa) and yield strength (2.0–3.2 MPa) were in the lower range of properties reported for human trabecular bone.

Lee and Barlow [127] coated calcium phosphate powder with polymer by spray drying a slurry of particulate and emulsion binder. The coated powder was then sintered to fabricate calcium phosphate bone implants. Afterwards, these structures were infiltrated with calcium phosphate solution or phosphoric acid-based inorganic cement.

Zhou et al. [230] studied the use of bio-nano-composite microspheres consisting of carbonated hydroxyapatite (CHAp) nanospheres within a PLLA matrix to produce scaffolds. PLLA microspheres and PLLA/CHAp nanocomposites were prepared by emulsion techniques. The resulting microspheres had a size of 5–30 μm, suitable for the SLS process. The use of PLLA/CHAp nanocomposite microspheres seems to offer a solution to the problem of removing the excess powder from the pores after fabrication.

Hao et al. [78] investigated the use of SLS to fabricate HA mixed high-density polyethylene (HDPE) scaffolds. Different scanning speeds and laser power values were considered. HA and HDPE powders with 40% HA by volume ratio were mixed using a high-speed blender. The results revealed that for low power or high scanning speeds, the layers were generally not sintered or very fragile. Powder blends of PEEK/HA have also been processed using SLS [199].

Although the SLS processes can build highly complex structures with internal architectures appropriate for bone tissue ingrowth and with the required external geometry, one of the critical drawbacks of the existing commercial SLS machines has been their inability to reach required part-bed temperatures during the direct processing of ceramics, which typically have higher glass-transition temperatures [144]. This leads to indirect selective laser sintering where the glass or ceramic particles are mixed with a polymeric binder and used as feedstock for the SLS machine to fabricate the green part. The fabricated green part is later heat treated to remove the binder and sinter the ceramic particles.

Leu’s research group at Missouri University of Science and Technology used a silicate based 13–93 bioactive glass with stearic acid as the binder to make scaffolds using indirect SLS [115–117,208]. The experimental results showed that the densification of the struts in the porous scaffold can be improved by controlling the SLS process parameters, particle size, binder content and post-processing schedule. Fig. 28 shows some of the parts made with 13–93 bioactive glass using SLS. The scaffolds have porosities of ~50% and highly interconnected pores in the range of ~300–800 μm. The compressive strengths varied from ~41 MPa for a scaffold that is ~50% porous to ~157 MPa for a fully dense part. The compressive strengths of the scaffolds are much higher than a trabecular bone but not comparable to a human cortical bone. By combining designs such as an inner porous and an outer solid shell, the mechanical strength of the scaffolds could be increased for human bone repair applications. Tests with simulated body fluid (SBF) showed a thick layer of HA formation on the surface of the scaffolds after 3 weeks. The in vitro results showed that SLS scaffolds offer a rough surface, which is favourable for MLO-A5 cells to attach, grow, and proliferate. The recent in vivo results showed complete bridging after 6 weeks in a rat segmental defect model, which was implanted with a 13–93 glass SLS scaffold with BMP-2 growth factor [207]. Partial bridging was observed in the control group that did not receive the BMP-2 growth factor. The results have demonstrated the potential of SLS in manufacturing scaffolds for low to medium load-bearing applications in human bone repair.

Dalgaro’s research group at Newcastle University used apatite based bioactive glass−ceramic systems to make scaffolds using indirect SLS [69,70,217,220]. The desired porosity was achieved after binder burnout and heat treatment. The scaffolds were later infiltrated with phosphate glass to improve their mechanical properties. Apatite–mullite scaffolds had flexural strengths of 16.2 MPa and those made with apatite−wollastonite had strengths ranging from 35 MPa for a porous part to 102 MPa for a fully infiltrated part. Although it was reported that no apatite layer formed when the scaffolds were immersed in SBF, new bone tissue growth was observed in the porous structure after 4 weeks of implantation in a rabbit tibia.

LENS (Laser Engineered Net Shaping), developed by Sandia National Laboratories, is an alternative process to SLM. This laser cladding based process uses a CAD-driven, high-power Nd:YAG laser (recent machines use fibre lasers) focused onto a metal substrate to create a molten pool (Fig. 29) [127,77,118]. Metal is then injected into the molten pool to increase the material volume. An inert gas is often used to shield the molten pool from atmospheric oxygen. Medical device materials commonly processed using LENS include titanium alloys, stainless steels, cobalt alloys, shape memory alloys and calcium phosphate bio-ceramics [124,37,117,118].

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4.4. Electron beam melting process

EBM (Electron Beam Melting) is an additive manufacturing process that uses an electron beam to scan a layer of metal powder on a substrate, forming a melt pool [77,113,149,163]. The system (Fig. 30) consists of the electron beam gun compartment and the specimen-fabrication compartment both kept in a high vacuum. Advantages of using EBM over SLM include very small spot sizes, very high beam-material coupling efficiency, high scanning speed and beam deflection without the use of moving mirrors [77]. The accuracy of EBM is in the range of 0.3–0.4 mm, and the surface finish tends to be rough, with an Ra value in the range of 25 μm [163]. Table 6 compares EBM and SLM.

EBM has been used to produce titanium root-form implants (Ti–6Al–4V ELI) [37], femur hip implants [79], dental implants [113] and knee replacement implants (Figs. 31 and 32) [162]. Kouja et al. [105] evaluated the in vivo performance of Ti–6Al–4V ELI dental implants fabricated via EBM and compared it to a commercially available porous-coated press-fit dental implant (Endopore, Innova Corp, Toronto, Canada). Cylindrical shaped implants 3 mm × 5 mm long were implanted in a rabbit tibia and retrieved after 6 weeks postoperatively. Histology results revealed osteointegration of surrounding bone with both implant types, suggesting that the implants produced by EBM perform equally well as commercial implants.

4.5. Extrusion-based processes

The extrusion-based technique, commercially known as Fused Deposition Modelling (FDM), was developed by Crump [46]. In this process, objects are formed by thin thermoplastic filaments, melted by heating and deposited by a NC controlled extrusion head. The material leaves the extruder in a liquid form and hardens immediately. The working platform is contained within an enclosed chamber that is held below the melting temperature of the thermoplastic material to aid in the bonding process [74].

The use of FDM to produce permanent implants has been limited to the fabrication of anatomic models that can serve as templates for the fabrication of custom implants. Gronet et al. [74] described the use of FDM to produce 3D models that serve as templates for the fabrication of custom acrylic implants for large defects with complex contours involving the anterior temporal region or defects where margins are inaccessible or difficult to detect by palpation (Fig. 33).

Extrusion-based processes are widely used to produce temporary implants (scaffolds) for tissue engineering in a wide range of medical applications.
of polymers and polymer/ceramic composites. Koh et al. [111] exploited the fact that when a warm PCL-HA/acetone solution is extruded into a reservoir containing ethanol, the extruded filament rapidly solidifies via solvent extraction, producing a continuous rigid filament to fabricate macro-channelled scaffolds. The diameter and morphology of the filament were controlled by adjusting the deposition speed and volume flow rate.

Tellis et al. [200] used micro CT to create biomimetic tissue engineering scaffolds. CAD models were exported to an FDM machine, producing polybutylene terephthalate (PBT) trabecular scaffolds. The scaffolds were compression tested at two different load rates (49 N/s and 294 N/s). Some scaffolds were soaked in a 25 °C saline solution for 7 days before compression. When compressed at 49 N/s, the dry trabecular scaffolds had a compressive stiffness ranging from 2.46 ± 0.55 MPa to 5.11 ± 1.89 MPa. At 294 N/s, the compressive stiffness values roughly doubled. It was also observed that soaking the scaffolds in saline solution had an insignificant effect on stiffness and that compressive stiffness decreased as pore size increased. Compressive trabecular scaffolds matched bone samples in porosity. However, physiologic connectivity density and trabecular separation requires optimisation of scaffold processing.

Ragaert et al. [169] used a Bioscaffold to extrude PCL, PCL-PEO, PCL-Collagen and PLA scaffolds mimicking heart valve leaflets and arteries, and compared their elastic and mechanical properties to those of natural tissues.

Wang et al. [209] used a process called Precision Extruding Deposition (PED) to directly fabricate PCL scaffolds with a controlled pore size of 250 μm and designed structural orientations (0°/90°, 0°/120° or combination of both patterns). In this process, material in pellet or granule form is fed into a chamber, where it is liquefied. Pressure from a rotating screw forces the material down a channel and out through a nozzle tip. Proliferation studies were performed using cardiomyoblasts, fibroblasts and smooth muscle cells. The surface hydrophilicity and total surface energy of PCL scaffolds was also increased with plasma treatment.

Woodfield et al. [218] used an FDM-like technique, called 3D Fibre Deposition, to produce poly(ethylene glycol)-terephthalate-poly(Butylene Terephthalate) (PEG/PBT) block co-polymer scaffolds with 100% interconnecting pore network for engineering articular cartilage (Fig. 34). By varying the co-polymer composition, porosity and pore geometry, scaffolds were produced with a range of mechanical properties closely resembling articular cartilage. The scaffolds seeded with bovine chondrocytes supported a homogeneous cell distribution and subsequent cartilage-like tissue formation.

Researchers from Tsinghua University (China) developed a process called Low-Temperature Deposition Manufacturing (LDM) to produce scaffolds in low-temperature environments under 0 °C [222]. The LDM system comprises a multi-nozzle extrusion process and a thermally induced phase separation process. Scaffolds having a macroporous structure larger than 100 μm in diameter and a microporous structure smaller than 100 μm have been reported. The LDM process was used to produce poly(l-lactide) (PLLA) and TCP composite scaffolds with BMP growth factor. The scaffolds were implanted into rabbit radius and canine radius with large-segmental defects. After 12 weeks, it was possible to observe that the rabbit radius defect was successfully repaired, and the regenerated bone had properties similar to the healthy bone.

Moroni et al. [160] reported a strategy to create hollow fibres with controlled shell thicknesses and lumen diameters, organising them into 3D scaffolds. Hollow fibres (Fig. 35), were produced by extruding a blend of poly(butylmethacrylate-methylmethacrylate) (P(BMA/MM)) and poly(ethylene oxidedeterephthalate)-co-poly(butyleneterephthalate) (PEOT/PBT) using the Bioplotter system. While flowing through the nozzle of the extruder, due to viscosity differences, the polymer with lower viscosity tends to shift towards the walls. The consequent separation of the polymers produces a stratification effect. Hollow fibres are produced by removing the core polymer by selective dissolution. It was also observed that bovine primary articular chondrocytes grow and form ECM not only in the scaffold macro pores but also inside the hollow cavities. The use of these hollow matrices for selective drug release is being investigated.

The Centre for Rapid and Sustainable Product Development of the Polytechnic Institute of Leiria (Portugal) developed an extrusion-based system for scaffold fabrication called BioExtruder. This is a highly reproducible and low cost system enabling the controlled definition of pores into the scaffold to modulate mechanical strength and molecular diffusion, as well as the fabrication of multi-material scaffolds [58]. It comprises two different deposition systems: one a rotational system for multi-material deposition achieved using a pneumatic mechanism and the other for a single material deposition that uses a screw to facilitate the deposition process (Fig. 36). The rotational system has four reservoirs, two with temperature control and two without. A large number of nozzle diameters ranging from 0.1 to 1 mm can be used. PCL, PCL/HA, PCL/TCP, PCL/graphene and PCL/PLA were the

Fig. 34. (A) 3D Fibre Deposition system, (B) SEM sections of 3D deposited scaffolds with varying deposition geometries [218].

Fig. 35. SEM micrographs of a scaffold (A) before and (B) after leaching out the core material [160].
materials selected to produce porous scaffolds. Chemical, morphological, and in vitro biological evaluation performed on the polymeric constructs revealed the BioExtruder’s high potential for producing 3D scaffolds with regular and reproducible macropore architectures, without inducing relevant chemical and biocompatibility alterations of the material [38]. Several control parameters, such as temperature, screw rotation velocity, deposition velocity and slice thickness, as well as their direct influence on the morphological and mechanical properties of the extruded scaffolds, were studied [57]. Experimental results reveal that the deposition velocity and the screw rotation velocity have the highest influence in terms of the filament diameter and as a consequence on the porosity and mechanical behaviour of the structures [57].

Extrusion based processes have also been used to build scaffolds using ceramics and, more recently, bioactive glasses. Cesarano et al. [34,35] developed a process called Robocasting at Sandia National Laboratories (USA). In this process, the paste is extruded through an orifice while the table moves relative to the orifice. The process has been used to make scaffolds based on HA slurries [36]. The parts made were later heat treated to sinter the HA particles. The mechanical properties of the HA based scaffolds were comparable to human cortical bone with appropriate pore sizes and porosities. To overcome limitations in the process in order to build customised and anatomically shaped implants, an oversized scaffold was fabricated and later machined so as to fit in the mandible region of a 73-year old female patient as a proof of concept. The preparation of colloidal inks and the technique itself in preparing 3D periodic lattice structures were further researched by Lewis et al. [138,139,191]. Recently, this technique was used by Fu et al. [65] to make bioactive lattice structures for bone tissue engineering. In this process, a bioactive glass based ink is loaded in the syringe and the lattice is printed on an alumina substrate inside a non-wetting oil reservoir. Compressive strengths of ~136 MPa were reported for ~60% porous scaffolds.

Researchers at Missouri University of Science and Technology (USA) have developed a process of extruding and depositing aqueous based paste called Freeze-form Extrusion Fabrication (FEF) to produce lattice structures in a freezing environment [54]. The fabrication technique utilises a 3D gantry system. The paste extrusion nozzle movement is facilitated in X, Y and Z direction using orthogonal linear slides, which can cover a distance of 250 mm and is controlled by a programmable multi-axis controller. The extruder ram is connected to a syringe (paste container) for forced paste extrusion. The syringe is enclosed in a heating sleeve with a temperature controller to prevent the paste from freezing in the syringe as the entire setup is encased in a freezer box, where freezing temperatures down to ~30 °C can be achieved by means of ejecting liquid nitrogen. 13–93 bioactive glass powder, binder, surfactant and dispersant are mixed in different quantities with de-ionized water to form a semi-solid paste with a specific viscosity to achieve uniform extrusion through a nozzle. The signal generated from the load cell is used for feedback control to provide a constant ram force during the extrusion process. Fig. 37 shows the FEF operation from the CAD model to the final sintered part, as well as the microstructure of the sintered part.

The bioactive glass scaffolds made using the FEF process could achieve porosities in the range of ~50% and pore sizes in the range of ~500 μm. The mechanical properties of the scaffolds are comparable to that of a human cortical bone with compressive strengths measuring ~140 MPa with an elastic modulus of ~5.5 GPa. The scaffolds were incubated for 6 days after having been seeded with MLO-A5 cells [88]. The MT2 test results showed a good amount of proliferation of metabolically active cells on the scaffolds. These cells covered almost the entire surface and interior pores of the scaffold, demonstrating the strong potential of FEF in fabricating ceramic and glass based biomedical implants for load-bearing applications.

Biocell Printing is a multi-head extrusion-based system, in development at the Centre for Rapid and Sustainable Product Development of the Polytechnic Institute of Leiria (Portugal) that enables the integration and synchronisation of the different stages of production and culture of 3D matrices with reduced manual intervention [18]. Depending on the chosen strategies (acellular or cellular scaffolds), a precision robotic arm transfers the 3D scaffolds between the construction area (zone 1) to zone 2, where they are sterilised (Fig. 38). After sterilisation, scaffolds are homogeneously seeded with cells using a robotic dispenser (zone 3). Finally, 3D constructs with embedded or seeded cells are cultured in vitro under dynamic conditions in the bioreactor (zone 4). The integration of the different stages into a single device
significantly reduces the risk of contamination and increases productivity and the possibility of direct clinical application.

Mota et al. [161] developed dual-scale scaffolds consisting of three-dimensional constructs of aligned PCL microfilaments and electrospun PLGA fibres (Fig. 39). PCL constructs composed by layers of parallel microsized filaments (0°/90° lay-down pattern), with a diameter of 365 μm and interfilament distance of 191 μm, were produced using a melt extrusion-based additive manufacturing technique. PLGA electrospun fibres with a diameter of ~1 μm were collected on top of the PCL constructs with different thicknesses, showing a certain degree of alignment. Cell culture experiments employing the MC3T3 murine preosteoblast cell line showed good cell viability and adhesion on the dual-scale scaffolds. The influence of electrospun fibres on cell morphology and behaviour was evident, creating a structural bridging for cell colonisation.

4.6. Inkjet printing processes

Several additive manufacturing processes have taken advantage of ink-jet technology to build 3D parts. Inkjet printing technology can be summarised by two main configurations: a bonding method and a build-up method.

The bonding method was developed at MIT (USA) and is called three-dimensional printing (3D Printing). The process deposits a stream of microparticles of a binder material over the surface of a powder bed, joining particles together where the object is to be formed. A piston lowers the powder bed so that a new layer of powder can be spread over the surface of the previous layer and then selectively joined to it. After the building process, the unbounded powder is removed, and the porous model must be strengthened by a conventional pre-sintering process. The build-up method emits a stream of binder microparticles to an exact coordinate.

Kim et al. [108] employed 3DP with particulate leaching to create porous scaffolds, using poly(lactide-co-glycolide) (PLGA) powder mixed with salt particles and a suitable organic solvent. The salt particles were leached using distilled water. Cylindrical scaffolds measuring 8 mm (diameter) by 7 mm (height) with pore sizes of 45–150 μm and 60% porosity were fabricated. Hepatocytes were successfully attached to the scaffolds.

The influence of pore size and porosity on cell adhesion and proliferation were investigated by Zeltinger et al. [229]. Disc shaped poly(ε-lactide acid) (ε-PLA) scaffolds measuring 10 mm (diameter) by 2 mm (height) were produced through both 3DP and salt and leaching methods. The scaffolds were produced with two different porosities (75% and 90%) and four different pore size distributions (~38, 38–63, 63–106 and 106–150 μm), and tested with cell cultures using canine dermal fibroblasts, vascular smooth muscle cells and microvascular epithelial cells.

Cui et al. [47] used a modified thermal inkjet printer and demonstrated the feasibility of printing microvacularure with human microvascular endothelial cell suspension in thrombin solutions onto fibrinogen solutions, which served as the substrate. The printed cells achieved the capacity to interact and proliferate within fibrin channels forming a tubular lining. An alternative process has been developed by Mironov et al. [154–156] and Yan et al. [226], who developed the concept of cell printing. This process prints gels, single cells and cell aggregates offering a possible solution for organ printing [151,154–156,224,226]. To be used for cell printing, the thermal or piezo-tip printheads and ink cartridges are modified to allow bioinks to be printed [95]. These bioinks usually consist of aqueous media, thermoreversible polymers, or polymer/hydrogel precursors combined with living cells [178]. Laser-assisted cell-printing techniques have also been developed [151,178]. These techniques comprise the so-called laser guidance direct write (LG DW), laser-induced forward transfer and modified laser-induced forward transfer processes (Fig. 40) [87,178]. The LG DW process was the first reported technique to print viable cells by forming patterns of embryonic-chick spinal-cord cells on a glass slide. Shortly after this, modified laser-induced forward transfer techniques (LIFT) and modified inkjet printers were also used to print viable cells and proteins, followed by the recently introduced electrohydrodynamic jetting (EHDJ) method [42,178].

4.7. Summary

Table 7 summarises the actual state of the art of biomaterial processing with appropriate electro-chemical and physical additive manufacturing for the fabrication of both temporary and permanent implants. However, this is an extensively researched area, and new options both in terms of materials and processes are continuously emerging.

5. Surface treatments and coating

An important requirement for the clinical success of implants is a strong and effective connection between the implant and the tissue [173]. Surface roughness has been suggested as one important factor for establishing clinically reliable bone attachments [30,152]. In the case of scaffolds, surface roughness plays an important role in adhesion, proliferation, differentiation and overall cell viability [39]. If the roughness level is too high, cells will not be able to establish
interconnections, which will dramatically compromise proliferation/migration. Experiments performed with compact carbon nanotubes revealed a higher number of osteoblasts adhering to the surface of the nano-tubes when compared with fibroblasts, chondrocytes and smooth muscle cells. Despite not yet being well understood, it is thought that nano-scale topology modulates the interfacial forces between the cells and the implants.

Polymer surface modification is a useful tool to improve the scaffold biofunctionality, creating or increasing specific binding sites where bioactive ligands may be immobilised to regulate specific cellular responses [125,168]. Plasma modification processes have been increasingly used to modify material surface properties due to their ability to tune, in a controlled way, the surface density of different functional groups without altering the implant’s mechanical properties [23,189]. Independently of the plasma process used (grafting with non-polymerizable gases such as O₂, N₂, NH₃, or polymerisation with organic monomers such as allyl amine, acrylamide, acrylic acid), scaffolds displaying surface polar groups (e.g., NH₂, COOH, OH, etc.) may alone increase the bioactivity of the substrate and improve cell adhesion and proliferation [189]. The plasma processes can also be quite helpful for the immobilisation and deposition of biomolecules such as enzymes, peptides, proteins, polysaccharides and others, onto plasma-modified substrates displaying properly selected binding functional groups [143,193].

Table 7
Actual state-of-the-art of biomaterials processing with appropriate electro-chemical and physical additive manufacturing for the fabrication of both temporary and permanent implants.

<table>
<thead>
<tr>
<th>Principle</th>
<th>Materials state</th>
<th>Material class</th>
<th>Application</th>
<th>Accuracy (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrospinning</td>
<td>Polymer melts or polymeric solutions</td>
<td>Naturally derived and synthetic polymers including SMPs</td>
<td>Temporary implants</td>
<td>0.1</td>
</tr>
<tr>
<td>Sterolithography</td>
<td>Photo-sensitive polymers</td>
<td>Naturally derived and synthetic polymers; polymeric systems highly reinforced with metallic and ceramic powders; hydrogels; SMPs, vital/avital composites</td>
<td>Temporary implants; drug delivery systems; functional graded scaffolds; scaffolds encapsulating cells; scaffolds containing growth-factors to be used as controlled-release systems</td>
<td>0.5–50</td>
</tr>
<tr>
<td>Laser sintering</td>
<td>Polymer, coated ceramic and metallic powders or ceramic/polymer and metal/polymer powders blends</td>
<td>Synthesized polymers, metals including SMAs, ceramics including bioglass</td>
<td>Permanent and temporary implants; scaffolds containing growth-factors to be used as controlled-release systems</td>
<td>50</td>
</tr>
<tr>
<td>Laser melting</td>
<td>Polymeric, metallic and ceramic powders</td>
<td>High melting point synthetic polymers, metals including SMA, ceramics</td>
<td>Permanent implants</td>
<td>20</td>
</tr>
<tr>
<td>Electron-beam melting Excretion-based</td>
<td>Metallic powder</td>
<td>Naturally derived polymers, synthetic polymers, hydrogels, polymer/ceramic composites</td>
<td>Extensively used to produce temporary implants</td>
<td>200–100</td>
</tr>
<tr>
<td>Inkjet printing Bonding method</td>
<td>Polymer, metal and ceramic powders</td>
<td>Naturally derived polymers, synthetic polymers, polymer/ceramic composites</td>
<td>Fabrication of temporary implants and fabrication of both permanent and temporary (ceramics) implants</td>
<td>50</td>
</tr>
<tr>
<td>Build up method</td>
<td>Liquid polymers</td>
<td>Hydrogels, vital/avital composites</td>
<td>Scaffolds incorporating cells, proteins and growth-factors</td>
<td>20–100</td>
</tr>
</tbody>
</table>

Table 8
Techniques to deposit biodegradable coatings of calcium orthophosphates on metal implants [196,227].

<table>
<thead>
<tr>
<th>Technique</th>
<th>Thickness</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal spraying</td>
<td>30–200 µm</td>
<td>High deposition rates; low cost</td>
<td>Line of sight technique; high temperatures induce decomposition; rapid cooling produces amorphous coatings</td>
</tr>
<tr>
<td>Sputter coating</td>
<td>0.5–3 µm</td>
<td>Uniform coating thickness on flat substrates; dense coating</td>
<td>Line of sight technique; expensive; time consuming; produces amorphous coatings</td>
</tr>
<tr>
<td>Pulsed laser deposition</td>
<td>0.05–5 µm</td>
<td>Coating by crystalline and amorphous phases; dense and porous coating</td>
<td>Line of sight technique</td>
</tr>
<tr>
<td>Dip coating</td>
<td>0.05–0.5 mm</td>
<td>Inexpensive; coatings applied quickly; can coat complex substrates</td>
<td>Requires high sintering temperatures; thermal expansion mismatch</td>
</tr>
<tr>
<td>Sol–gel technique</td>
<td>&lt;1 µm</td>
<td>Can coat complex shapes; low processing temperatures; relatively inexpensive as coatings are very thin</td>
<td>Some processes require controlled atmosphere processing; expensive raw materials</td>
</tr>
<tr>
<td>Electrophoretic deposition</td>
<td>0.1–2.0 mm</td>
<td>Uniform coating thickness; rapid deposition rates; can coat complex substrates</td>
<td>Difficult to produce crack-free coatings; requires high sintering temperatures</td>
</tr>
<tr>
<td>Hot isostatic pressing</td>
<td>0.2–2.0 µm</td>
<td>Produces dense coatings</td>
<td>Cannot coat complex substrates; high temperature required; thermal expansion mismatch; elastic property differences; expensive removal/interaction of encapsulation material</td>
</tr>
<tr>
<td>Electrochemical deposition</td>
<td>0.05–0.5 mm</td>
<td>Uniform coating thickness; rapid deposition rates; can coat complex substrates; moderate temperature, low cost</td>
<td>The coating/substrate bonding is not strong enough</td>
</tr>
</tbody>
</table>

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The surfaces of metallic implants can be modified by coatings, blasting with various substances, acid treatments, or a combination of such treatments [196,227]. Generally, chemical composition, charge, and tension of an implant surface are critical conditions for cell response. Acid etching will, in most cases, produce an increased thickness of the surface oxide layer and alter the physical and chemical properties. It has been suggested that the chemical properties of the oxide layer may benefit bone apposition, but its thickness and microstructure are of less importance. Table 8 presents relevant techniques to deposit bioreosorable coatings of calcium orthophosphates on metal implants.

6. Conclusions and future challenges

Recent investigations with additive electro-chemical and physical processes demonstrated the potential to fabricate customised permanent and temporary implants. A wide range of bio-compatible materials is available, ranging from metals and metallic alloys to ceramics and polymers, including hydrogels and SMPs. Several techniques also show potential for processing composite materials that combine synthetic materials and biological ones, such as cells, proteins and growth factors. However, the use of additive electro-chemical and physical processes in the medical field are still in its early stage. The rapidly growing field of biomaterials faces significant challenges and opportunities. Relevant challenges to be addressed in the future include:

- Establishing a directed materials and related processes and assembly technologies.
- Applying both nano and micro technologies for enhancing efficacy and precision.
- Standardising processes, design and metrology tools.
- Achieving a fundamental understanding of manufacturing processes and convergence of techniques for best and affordable health care.
- Development of in situ manufacturing strategies, such as in situ tissue engineering.
- Enhancing multidisciplinarity, linking clinicians and engineers to facilitate further developments and the clinical translation of the products/systems being investigated.
- Packaging, handling, transportation and accurate tracking, and deploying of biomaterialized parts and their building blocks.
- Scaling up additive electro-chemical and physical processes towards clinical application.

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References


Registration for 3D Experimental Local Strain Mapping on Porous Bone Tissue Engineering and Its Potential for Compression Fracture. European Conference for Non-Destructive Testing (ECNDT), Moscow, 7–11.


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