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Review article

Fatigue behaviour of load-bearing polymeric bone scaffolds: A review

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ABSTRACT

Bone scaffolds play a crucial role in bone tissue engineering by providing mechanical support for the growth of new tissue while enduring static and fatigue loads. Although polymers possess favourable characteristics such as adjustable degradation rate, tissue-compatible stiffness, ease of fabrication, and low toxicity, their relatively low mechanical strength has limited their use in load-bearing applications. While numerous studies have focused on assessing the static strength of polymeric scaffolds, little research has been conducted on their fatigue properties. The current review presents a comprehensive study on the fatigue behaviour of polymeric bone scaffolds. The fatigue failure in polymeric scaffolds is discussed and the impact of material properties, topological features, loading conditions, and environmental factors are also examined. The present review also provides insight into the fatigue damage evolution within polymeric scaffolds, drawing comparisons to the behaviour observed in natural bone. Additionally, the effect of polymer microstructure, incorporating reinforcing materials, the introduction of topological features, and hydrodynamic/corrosive impact of body fluids in the fatigue life of scaffolds are discussed. Understanding these parameters is crucial for enhancing the fatigue resistance of polymeric scaffolds and holds promise for expanding their application in clinical settings as structural biomaterials.

Statement of Significance

Polymers have promising advantages for bone tissue engineering, including adjustable degradation rates, compatibility with native bone stiffness, ease of fabrication, and low toxicity. However, their limited mechanical strength has hindered their use in load-bearing scaffolds for clinical applications. While prior studies have addressed static behaviour of polymeric scaffolds, a comprehensive review of their fatigue performance is lacking. This review explores this gap, addressing fatigue characteristics, failure mechanisms, and the influence of parameters like material properties, topological features, loading conditions, and environmental factors. It also examines microstructure, reinforcement materials, pore architectures, body fluids, and tissue ingrowth effects on fatigue behaviour. A significant emphasis is placed on understanding fatigue damage progression in polymeric scaffolds, comparing it to natural bone behaviour.

1. Introduction

Bone fractures impose a significant cost on the healthcare system, particularly as the population continues to age, leading to workforce depletion and increased socioeconomic expenditures. In 2019, 178 million new bone fractures were reported globally, indicating a 33 % increase since 1990 [1]. Normally, bone can heal itself due to its self-healing capabilities. However, for large bone defects or situations in which the bone loses its self-healing functionality (such as infections or congenital abnormities), surgery is required. Routine surgical treatments include the replacement of the damaged bone with a healthy bone harvested from the host (autograft), the same species (allograft), or a different species (xenograft) [2]. Bone autograft has remained the gold standard and is still preferred to other techniques [3]. However, these approaches are associated with issues such as donor site morbidity, harvest tissue supply, immunogenic rejection, and the transmission of infections [4]. To address these limitations, tissue engineering was first in-

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Nomenclature

µCT	Micro computed tomography
µε	Microstrain
ABS	Acrylonitrile butadiene styrene
CaP	Calcium phosphate
DIW	Direct Ink Writing
DSC	Differential Scanning Calorimetry
DL-PLA	(D,L-polylactic acid)
ECM	Extra Cellular Matrix
FEM	Finite element method
FFF	Fused filament fabrication
GPC	Gel permeation chromatography
HA	Hydroxyapatite
HDPE	High-density polyethylene
L-PLA	L-polylactic acid
PA	Polyamide
PBS	Phosphate Buffered Saline
T_g	Glass Transition Temperature
PC	Polycarbonates
PCL	Polycaprolactone
PE	Polyethylene
LCF	Low cycle fatigue
HCF	High cycle fatigue
PDDLA	Poly(D,L-Lactic Acid)
PDO	Polydioxanone
PEG	Polyethylene glycol
PGA	Poly(glycolic acid)
PLA	Polylactic acid
PLCL	Poly(L-lactide-co-ε-caprolactone)
PLGA	Poly(lactic-co-glycolic acid)
PLLA	Poly(L-lactide)
PMMA	Poly(methyl methacrylate)
PPP	Poly(para-phenylene)
PVA	Poly(vinyl alcohol)
SBF	Simulated Body Fluid
SEM	Scanning Electron Microscopy
SLS	Selective Laser Sintering
TCP	Tricalcium phosphate
TGA	Thermogravimetric Analysis
TPMS	Triply periodic minimal surface
TPU	Thermoplastic polyurethane
UMA	Urethane methacrylate polymer
BTE	Bone Tissue Engineering
AM	Additive Manufacturing

troduced in 1933, when scientists found that the tumour cells of mice could be implanted via a biocompatible polymer membrane [5]. Tissue engineering aims to provide an engineering solution for reconstructing body tissues, including soft or hard tissues, via scaffolding or direct tissue fabrication. In the scaffolding approach, regenerating cells are seeded in an architecturally-designed porous biocompatible structure (scaffold) and are then implanted into the defect site of the body. Once implanted in the body, the cells are stimulated and natural tissue growth occurs through the pores of the scaffolds.

Fig. 1**(a)** illustrates the bone tissue engineering (BTE) using a bone scaffold. Bone scaffolds should exhibit physical characteristics that closely resemble those of the host tissue to provide adequate support during the healing process. Depending on the implant site, these properties may differ. The porosity of the cortical (or compact) bone which is the dense part of the bone, ranging from 5 to 10 % [6], while the trabecular (or cancellous/spongy) bone has a highly porous structure with porosities ranging from 60 to 85 % [6]. The mechanical strength of the cortical bone is usually higher than that of the trabecular bone.

Fig. 1(b) depicts the structure of femur bone as well as the mechanical properties of cortical and trabecular parts.

Bone scaffolds should mimic the architecture of the native bone and possess an acceptable level of bioactivity, biocompatibility, biodegradability, and structural integrity. Most importantly, scaffolds are expected to provide support for the development of new tissues while maintaining their integrity and interconnectivity during the healing process. Similar to native bone, bone scaffolds undergo different static and dynamic loads during their service life [11]. Static loads, such as body weight and momentum are applied to the skeletal system in standing mode, while cyclic loads are implemented during daily activities such as walking, running, climbing, cycling, jumping, and sports activities [12]. In this process, cyclic loads may cause scaffold collapse and enclosure of the interconnected passages under stresses much lower than the strength of the parent material, leading to malfunctioning in the vascularisation process and bone ingrowth. Conducted research shows that a hip joint experiences contact forces as high as 5.5 and 10 times of body weight during normal walking and running, respectively [13]. Thus, the fatigue behaviour of scaffolds affects their durability and resilience within the body. Although *in vivo* experiments in humans have shown that the fracture strength of the tibia bone is higher than induced strains during walking (−400 µε) and running (+850 µε), fatigue fractures may still occur in strains lower than these values [14].

In terms of mechanical strength, metals surpass polymers and ceramics. Ceramics are inherently brittle, while polymers have relatively poor mechanical properties and a low elastic modulus. Thus, it appears that using metal scaffolds made of titanium (Ti), magnesium (Mg), iron (Fe), or Co-Cr alloys as implants appears to be sufficiently durable. However, the application of metal bone scaffolds is associated with some major challenges, including high fabrication cost [15], lack of bioactivitiy [16], the release of metallic ions [17,18], stress shielding [19,20], and an improper biodegradation rate [21]. Since bone stiffness and healing rate notably vary with age [22], materials with adjustable stiffness and biodegradation rates are required for scaffolding. Polymers possess stiffness comparable to that of native bone, whereby they avoid the stress shielding in surrounding tissues. Unlike the relatively limited number of implant alloys, a wide range of natural and synthetic medical grade polymers with adjustable degradation rates are available [23]. Load-bearing tissues, such as human bone, exhibit viscoelastic behaviour when stretched or compressed [24], a characteristic that can be seen in polymers at body temperature (approximately 37 °C). Therefore, polymers are better suited for mimicking the behaviour of load-bearing tissues when subjected to various loads. Polymers such as PCL, PLA, and PVA avoid some issues associated with metallic scaffolds as they possess low material and production cost, higher flexibility, high degradation tuneability, favourable biocompatibility and low toxicity. However, their relatively low mechanical performance has hindered their application in load-bearing sites. In the last decade, the development of new fabrication techniques such as additive manufacturing (AM) and the potential application of high-strength polymers such as PEEK or polymer composites in tissue engineering, has resolved the weak point of polymers to some extent [25]. Nonetheless, a significant research gap exists in understanding the fatigue performance of these materials. While prior investigations have primarily focused on the durability of bone scaffolds under static loads, it is imperative to recognize the essential role of dynamic loads in the mechanical strength of bone implants. Despite considerable efforts directed at improving the static properties of these scaffolds through techniques such as strengthening with reinforcing materials, the existing literature has not sufficiently addressed the fatigue

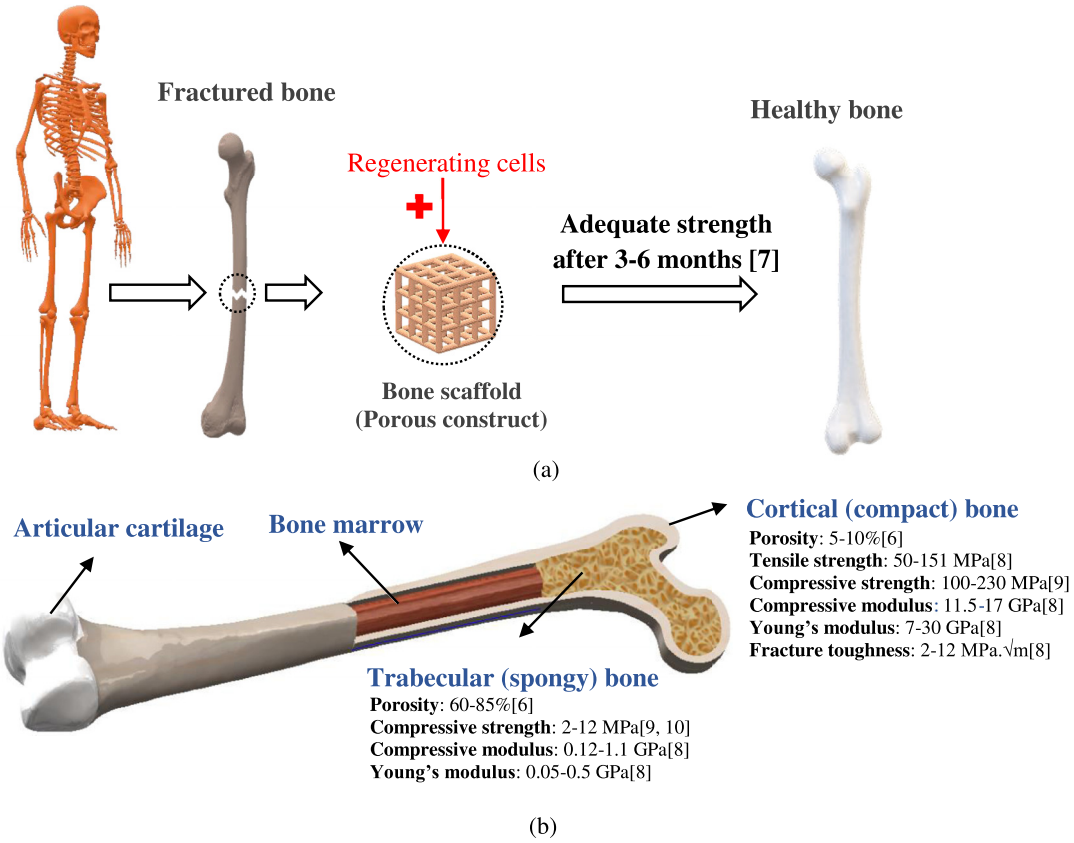


Fig. 1. (a) Bone tissue engineering (BTE), and (b) schematic representation of femur bone structure highlighting the distinct mechanical properties of cortical and trabecular bones [8].

performance of polymeric scaffolds [12,26,27]. The core of the current research lies in examining how polymeric bone scaffolds respond to fatigue loads and uncovering the factors that either enhance or degrade their fatigue performance. This study contributes to advancing the effective utilisation of polymeric scaffolds in load-bearing applications within the biomedical field.

The ability of polymeric scaffolds to withstand repeated stress over time, known as fatigue life, is affected by a variety of factors including material properties and composition, loading type and amplitude, topological features, and environmental factors such as temperature, moisture, and acidity [28–30]. In bone scaffolds, the environment is affected by *in vivo* conditions such as exposure to body fluids and tissue ingrowth. Fig. 2 depicts a diagram of the parameters that influence the fatigue performance of polymeric scaffolds. This review provides a closer account of every parameter and its effect, as reported in the literature to date.

Section 2 of the present review explores the fatigue failure mechanism in polymeric scaffolds. Sections 3 to 6 discuss and examine the impact of material type, scaffold topology, body fluids, and tissue ingrowth on the fatigue resistance of polymeric scaffolds. Lastly, a comprehensive summary of current achievements, identified research gaps, and recommendations for future investigations are provided. The current review is specifically focused on exploring the fatigue performance of polymeric bone scaffolds, which has received less attention than other aspects of bone scaffold requirements. To the best of our knowledge, no comprehensive review has ever been conducted on this topic. It is noteworthy that this review does not delve into the safety considerations associated with the immunological response to materials released from polymer degradation within the body, nor does it address the broader biological properties of these scaffolds.

2. Fatigue failure mechanisms

During daily activities such as walking and running, the bones experience cyclic loading and strain with each movement. Vigorous human activities can induce deformations lower than 2000 με (around 1100 με), with uphill and downhill zigzag running causing the most strains. Maximum strain rates have also been observed during sprinting and downhill running [31]. Since these actions are performed regularly at a certain pace, they impose cyclic or fatigue stresses on the skeletal systems, causing repeated deformation and relaxation with each cycle. Fatigue failure can occur at low cycles (low cycle fatigue; LCF) or high cycles (high cycle fatigue; HCF), depending on the applied stress or strain and the material's characteristics (Fig. 3). LCF involves only a limited number of cycles (less than 10^4–10^5 cycles) before failure, and may occur under relatively high stress conditions, which eventually leads to localized damage and failure of the part. LCF is characterised by repeated plastic deformation in each cycle. On the other hand, HCF occurs over an extensive number of loading cycles ($>10^5$ cycles) typically under lower stress levels and is characterised by elastic deformation. HCF could result from prolonged cyclic loading under conditions that may not lead to immediate failure on their own. Over time, repeated cyclic loading can cause gradual material degradation, weakening its structural integrity, and possibly leading to failure even under moderate stresses. The stress or strain where the material can endure unlimited number of fatigue cycles is termed the endurance limit.

In viscoelastic materials, fatigue failure can occur due to mechanical damage, thermal damage, or a combination of the two. Due to the viscoelastic nature of natural bone, it does not fully recover to its initial shape once the applied load is removed, result-

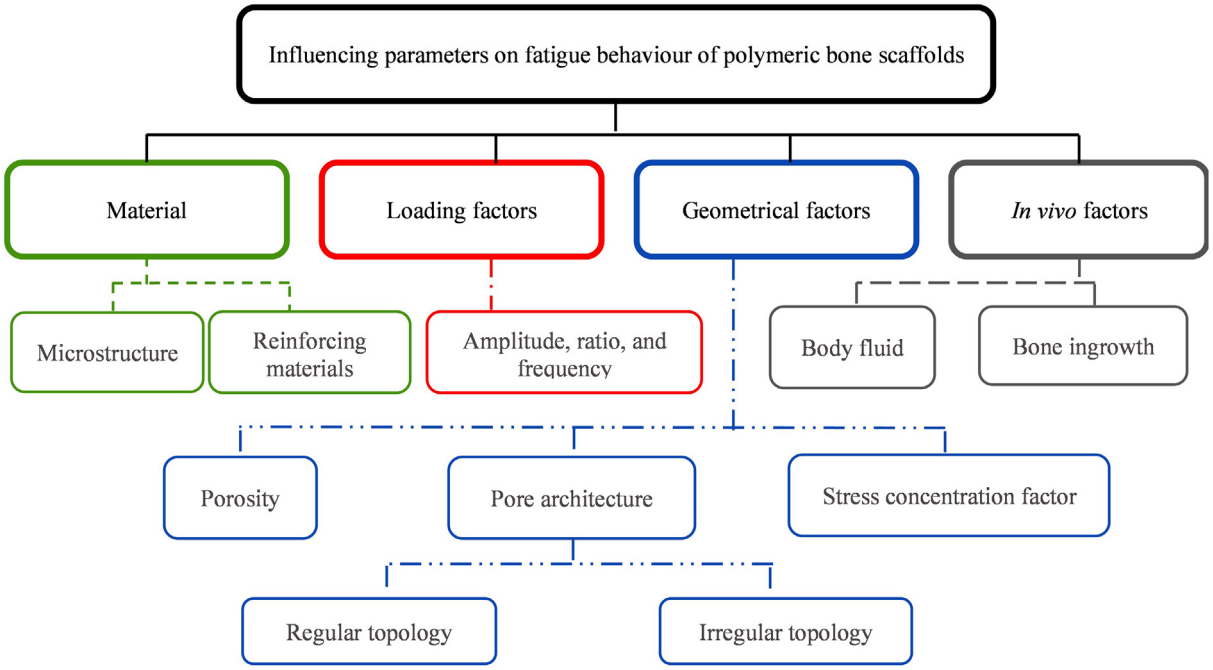


Fig. 2. Influencing parameters on the fatigue behaviour of polymeric bone scaffolds.

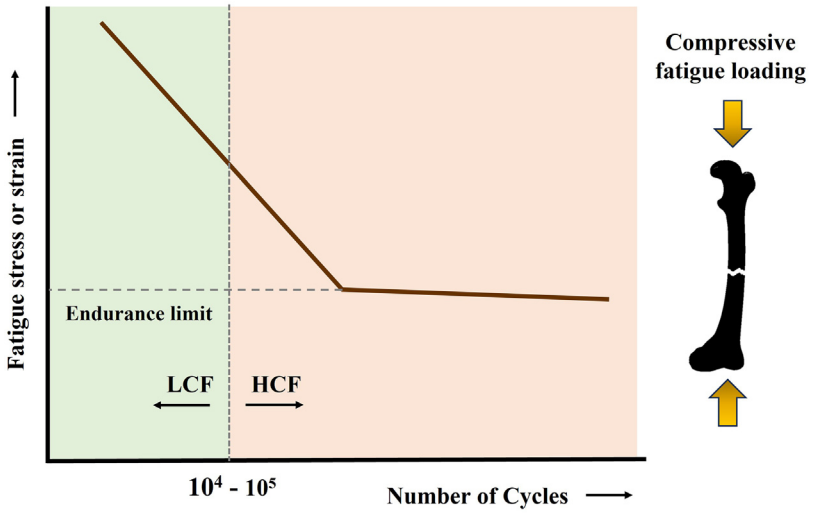


Fig. 3. Low cycle fatigue and high cycle fatigue domains.

ing in a certain amount of residual strain (or mechanical damage) persisting after each cycle. The accumulation of residual strains over fatigue cycles is associated with a decrease in stiffness and peak stress [32,33], as shown in Fig. 4.

Research has demonstrated that cyclic loading can also alter the microstructure and porosity of the bone matrix and affects its mechanical strength [34]. Once bone loses its initial stiffness by 50 to 90 % (depending on various criteria stated in literature [35–37]), mechanical fatigue failure occurs. The loss of stiffness in bone tissues during fatigue is highly correlated to the maximum applied strain [38].

Fatigue failure can also occur as a result of thermal damage caused by internal heating. Under cyclic loading, the strain induced in each cycle is transformed into heat. However, due to the low thermal conductivity, the generated heat remains trapped within the material, thereby leading to overheating and gradual degradation of polymeric chains. The dissipated energy is represented by the area enclosed in the hysteresis curve (known as the hysteretic area as shown in Fig. 4) and is converted to heat within the material, resulting in gradual thermal degradation of polymeric chains [39].

2.1. Mechanical fatigue

Ductile and amorphous polymers are extensively used in BTE [40]. Although polymeric scaffolds exhibit trends in the accumulation of residual strain and reduction of stiffness over fatigue cycles similar to those seen in natural bone, they exhibit different responses to cyclic loadings [41]. Ductile polymers possess inherent ability to undergo significant plastic deformation without fracturing [42]. This behaviour is particularly beneficial for load-bearing implant materials. On the other hand, amorphous polymers lack a well-defined crystalline structure, making them tuneable for BTE applications [43].

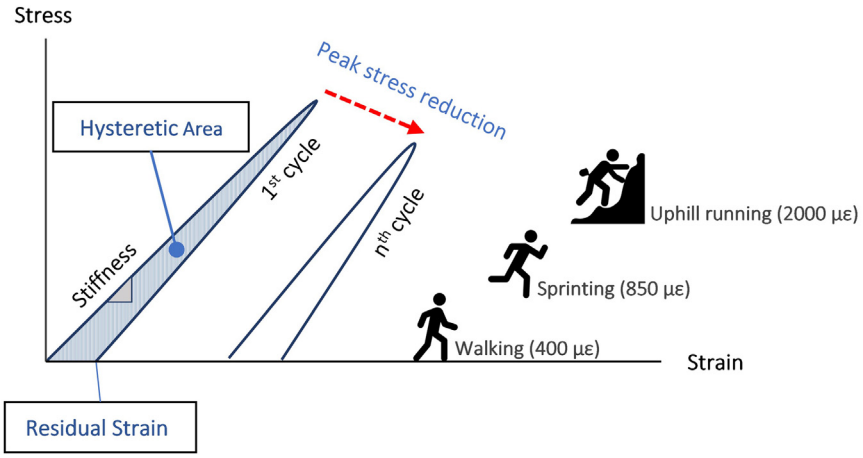


Fig. 4. Fatigue cycles in native bone: the evolution of damage is correlated with the applied strain and leads to reductions in stiffness, peak stress, and hysteretic area.

The dominant fatigue failure mechanism of ductile polymers is plastic deformation. During each cycling load, ductile polymers are subjected to alternating stresses that result in the accumulation of plastic strain [44]. This enables the material to undergo a large number of cycles before failure. This characteristic is beneficial for BTE applications where the implant is experiencing cyclic loading and deformation, as it aids the material to dissipate energy and resist failure. On the other hand, amorphous polymers show a combination of fatigue failure mechanisms [43]. One such mechanism is chain scission, where molecular chains break due to repeated stress cycles, leading to a weakening or deterioration of the overall strength of the polymer. Another mechanism is crazing which is distinguished by the formation of microvoids and fibrillar structures in confined areas caused by plastic deformation. The final fatigue failure mechanism of amorphous polymers is crack propagation. This mechanism involves the growth and extension of pre-existing cracks under cyclic loading which leads to material failure. However, these mechanisms in amorphous polymers vary based on the molecular structure of a given polymer, temperature, loading conditions, and environmental factors.

When a bone fracture occurs, bone scaffolds can be implanted into the fracture site to support the regeneration of new bone during the healing process. While complete bone healing may take several years, adequate strength emerges within three to six months after the bone fracture [7]. Thus, it is expected that bone scaffolds withstand the cyclic forces during this period. For instance, considering that an average patient takes roughly two million steps per year [45], each leg experiences approximately one million cycles during the 6-months healing period. In the literature, 1 Hz is considered the frequency of walking [46]. Therefore, the bone scaffold is subjected to around one million fatigue cycles at a loading frequency of 1 Hz which takes one million seconds in a laboratory environment. Since this process is time-consuming, costly, and damaging for fatigue testing apparatuses, some researchers have used accelerated fatigue tests. In these tests the duration is significantly reduced while the loading frequency is increased to up to 15 Hz [47,48]. However, this may not capture the real behaviour of polymeric scaffolds, as the mechanical response of polymers is highly sensitive to the loading rate.

In low cycle fatigue, which is the dominant mode of fatigue in load-bearing polymeric scaffolds, the damage (strain) produced in each cycle is accumulated over time and leads to the failure of the scaffold. Similar to native bone, damage evolution in polymeric scaffolds can be illustrated by stiffness reduction, peak stress reduction, and strain accumulation. Fig. 5 compares the stiffness reduction, peak stress reduction, and strain accumulation in real bones (dotted lines) and polymeric scaffolds. The normalized stiffness denotes the ratio of the measured stiffness at each cycle to the initial stiffness (at the first cycle). Similarly, normalized peak stress can be calculated by dividing the current stress by the initial stress. The normalized cycle is also calculated as the ratio of the current fatigue cycle to the maximum cycle (cycle before failure). Maximum cycles are provided on each figure's label. As illustrated in Fig. 5(a), the early stages of cyclic loading are associated with a temporary increase in stiffness (as shown by the green area), which then declines to lower levels. The stiffness increase in the early stages of fatigue is mainly attributed to the collapse of micropores and rigidity of the structure at initial cycles. The continuation of cyclic stresses leads to the accumulation of micro-damages or strain (Fig. 5(c)), prevailing the rigidity of the structure and lowering its resistance (Fig. 5(b)). However, depending on the applied strain, topological design of the scaffold, parent material and the running time, some scaffolds resist modulus reduction when exposed to cyclic loadings. For instance, Shimko et al. fabricated porous PMMA scaffolds using the salt leaching method and evaluated their behaviour over 80,000 compressive cycles at the strain rate of 0.5 % and 2 % strain in each cycle [49]. Despite losing around 65 % of their mechanical strength, scaffolds exhibited no modulus reduction. Similar results were obtained for PPP scaffolds, in which polymeric constructs retained their compressive modulus for most of their fatigue life [47]. PMMA and PPP are known as biocompatible polymers, exhibiting mechanical properties well-suited for load-bearing applications. Nevertheless, under high cyclic stress or strain (higher than the yield strength of a scaffold's constituting material), modulus reduction may begin in the early cycles. For instance, early modulus reduction has been observed for PLA scaffolds undergoing higher compressive cyclic stress (27 MPa) than yield strength (21 MPa) [50]. With the onset of pore collapse, the softening of construct occurs, resulting in compressive modulus reduction. Accordingly, peak compressive stress that represents mechanical strength of the scaffold declines (Fig. 5(b)).

2.2. Energy dissipation

The primary cause of fatigue failure in polymers is attributed to hysteretic heating which leads to ductile fractures [57]. When the rate of heat generation exceeds the rate of heat dissipation, it often leads to thermal degradation and decrease in the strength of the polymer. As a result, the process of crack growth becomes more facilitated or accelerated [58]. Fig. 6 depicts the progress of mechanical hysteresis (known as ratcheting deformation) in some polymeric scaffolds, and natural bones under cyclic loading, as re-

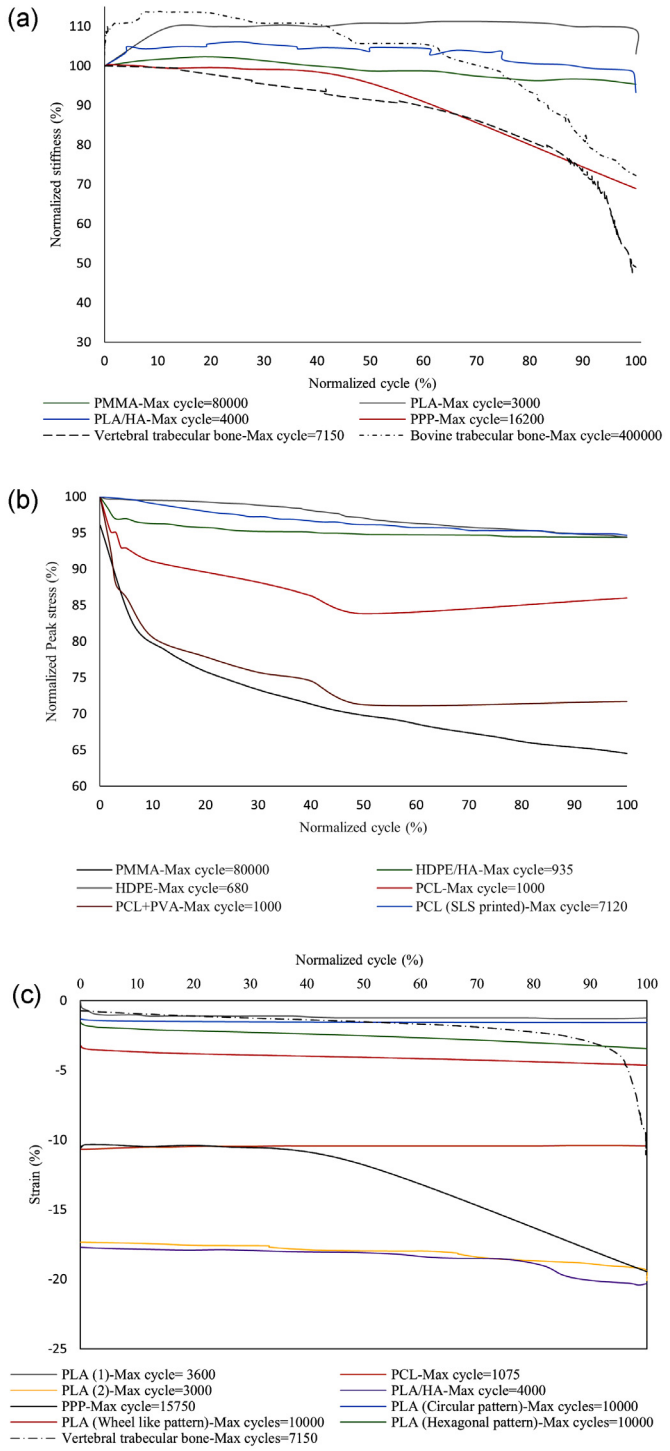


Fig. 5. Damage evolution in polymeric scaffolds and natural bones during compressive fatigue. (a) Normalized stiffness *vs* normalized cycles: PMMA [49], PLA and PLA/HA [50], PPP [47], Vertebral trabecular bone [32], Bovine trabecular bone [35] (b) Normalized peak stress *vs* normalized cycles: PMMA [49], HDPE/HA and HDPE [51], PCL and PCL+PVA [52], PCL (SLS printed) [53], (c) Strain accumulation in PLA (1) [54], PCL [55], PLA(2) and PLA/HA [50], PPP [47], PLA (circular pattern) [27], PLA (wheel like pattern) and PLA (hexagonal pattern) [56], and vertebral trabecular bone [32].

ported in the literature. As depicted in Fig. 6, the hysteretic area gradually increases at initial fatigue cycles and then contracts at later stages. In initial stages, pores and cavities increase the energy absorbing capability of constructs, but at later stages, this capability is reduced due to the collapse of internal structures. As opposed to metals, crack initiation accounts for at least 95 % of the fatigue life of polymers [59]. However, crack initiation and propagation occur much faster in tensile cycles in comparison to compression mode, leading to a shorter life. Since ligaments, tendons, bones and articulate cartilage experience different modes of fatigue loadings during their service life, this issue should be considered when designing load-bearing scaffolds. If the internal heat reaches the T_g of polymer, mechanical characteristics deteriorate rapidly. Hence, it is advantageous to use materials with higher glass transition temperatures such as poly(para-phenylene) [47], PTFE, and Polyurethane [60] in scaffolds. Studies have shown that materials with high T_g exhibit favourable fatigue behaviour [47].

3. Influencing factors on fatigue behaviour of polymeric scaffolds

As mentioned in Section 1, there are several parameters that can affect the fatigue behaviour of polymeric bone scaffolds, including material, topology, loading conditions, and environmental conditions. While these parameters influence the static behaviour of polymeric scaffolds, their effect and intensity can differ when the polymers are subjected to cyclic loading. This is because fatigue behaviour is a more complex phenomenon than quasi-static behaviour, as it involves the accumulation of damage over time and the interaction between mechanical and thermal effects [58]. Quasi-static loading typically involves only a few cycles or even a single loading event while fatigue loading involves a large number of loading cycles. In fatigue loading, mechanical failure usually occurs due to the accumulation of small cracks and defects over loading cycles, while in quasi-static loading, failure typically occurs due to the initiation and propagation of a single large crack or defect. Therefore, the impact of topology and stress concentration can be more pronounced when studying the fatigue behaviour of polymers. Besides, under fatigue loading, the temperature within the scaffold increases during fatigue cycles as a result of hysteretic heating, which leads to thermal failure. This is while the temperature rise during static loading is usually small and does not exceed a few degrees Celsius [63]. Although the static behaviour of polymeric scaffolds has been extensively studied in the literature [64,65], there is limited research on their fatigue behaviour. Table 1 provides a summary of previous works carried out on the influence of different parameters on the fatigue properties of polymeric scaffolds designed for load-bearing bones.

In the following sections, the influence of different parameters including material, topology, environmental and loading conditions on fatigue response of polymeric scaffolds is explored according to the existing literature.

4. Material and microstructural effects

Various natural and synthetic polymers can be employed for the construction of load-bearing scaffolds, with each possessing its own physical, chemical, and mechanical characteristics. Natural polymers such as collagen, chitosan, fibrin, gelatine, silk, alginate, cellulose, and starch have been frequently employed in BTE in the form of scaffolds, hydrogels, and spheres. Despite possessing the requisite biocompatibility for bodily environments, they are seldom used in their monolithic form for load-bearing applications due to their poor mechanical properties and uncontrollable degradation rate [68,69]. The compressive strength of trabecular bones ranges from 2 to 12 MPa, and that of cortical bones ranges from 100 to 230 MPa [9]. In comparison, chitosan-based scaffolds have a significantly lower compressive strength than that of natural bones, ranging from 0.0038 to 2.56 MPa [70]. Accordingly, alginate scaffolds with a compressive strength of about 3 MPa cannot also be employed in BTE [71,72]. Collagen scaffolds also lack a

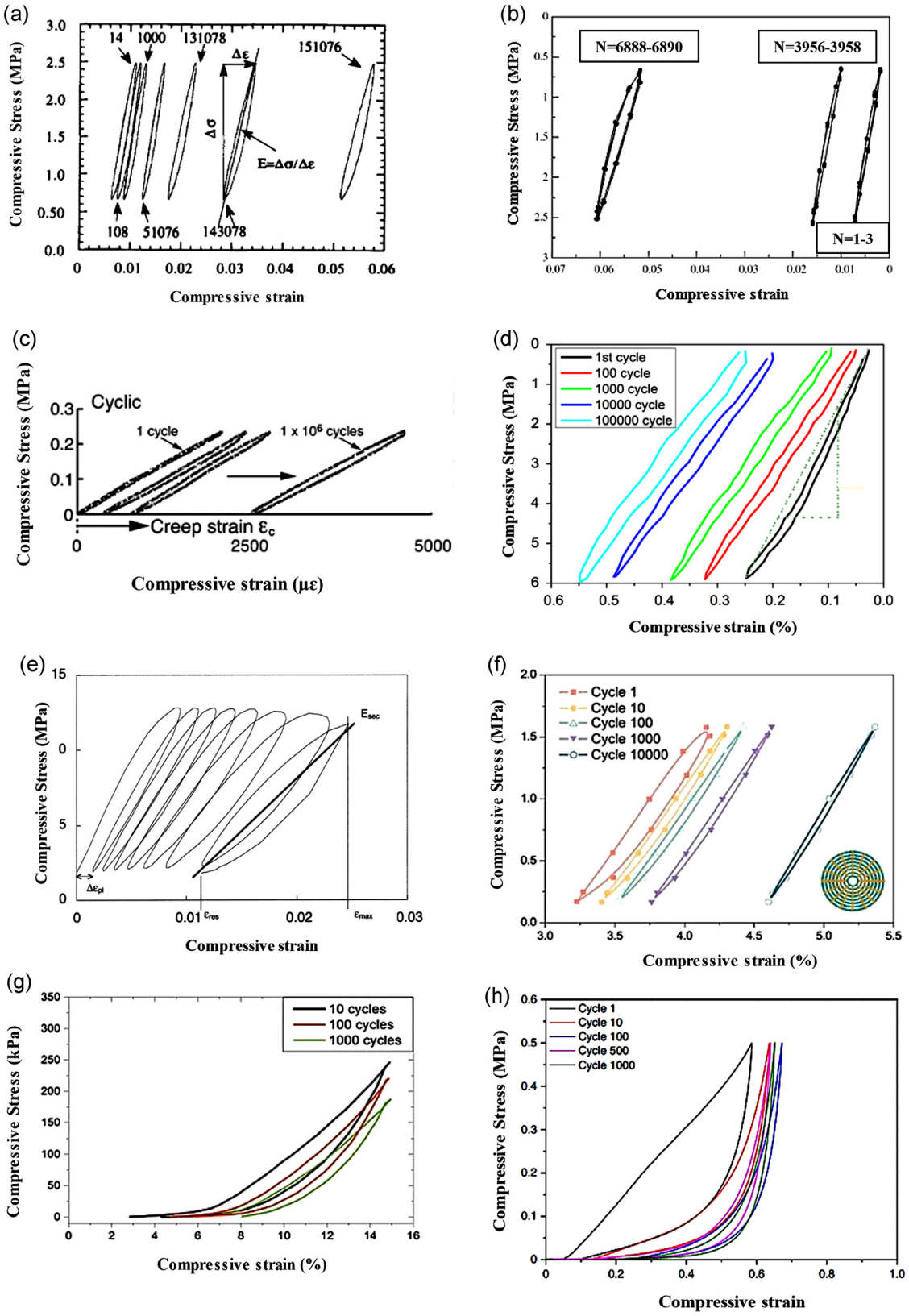


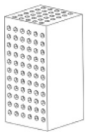
Fig. 6. Compressive fatigue hysteresis loops in trabecular bones (a-e), and polymeric scaffolds (f-h) (a [35], b [32], c [61], and d [33]: Adapted with permission from Elsevier, e [38]and f [56]: CC-BY-4.0, [52], and h [62]: (Adapted with permission from Wiley).

Table 1
Compressive fatigue properties of polymeric scaffolds designed for load-bearing bones.

	Manuf. method	Material	Application	Topology		Testing condition	Fatigue properties	Refs.
A	FFF	PLA	Trabecular bone	Orthogonal (0°/90°)		**Loading type:** Compressive stress **Stress level:** 9–14.5 MPa **stress ratio:** 0.1 **Loading frequency:** 0.25 Hz **Max cycles:** 3600 **Environment:** Dry **Tested samples:** 12.7 × 12.7 × 25.4 mm^3 with different porosities (30 %, 50 %, 70 %)	**Fatigue performance:** Orthogonal topology > Isometric topology **Effect of porosity:** Scaffolds with 50 % and 30 % porous scaffolds demonstrated proper fatigue durability even after 3600 cycles, whereas the scaffold with 70 % porosity experienced failure **Fatigue damage mechanism:** shear deformation	[11,54]
				Isometric (0°/60°/120°)				
B	FFF	PLA	Trabecular bone	Tetragonal (0°/90°)		**Loading type:** Compressive stress **Loading frequency:** 1 Hz **Stress level:** 18 to 180 N (sinusoidal) **Max cycles:** 10,000 **Environment:** Submerged in PBS **Tested samples:** Ø=12 mm, Height= 12 mm, Porosity of all samples is the same	**Fatigue life** tetragonal (4400 cycles) > hexagonal (3200 cycles) > wheel like (2500 cycles) **Hysteretic area (damping effect)** tetragonal > hexagonal > wheel	[56]
				Hexagonal (0°/60°/120°)				
				Wheel like				
C	FFF	PLA	Trabecular bone	Circular		**Loading type:** Compressive strain **Loading frequency:** 0.2 Hz **Strain level:** 0.7 %–3 % **Strain ratio:** 0.5 **Max cycles:** 10,000 **Environment:** Dry **Tested samples:** 33 × 33 × 33 mm^3, Porosity of all samples = 60 %	**Fatigue performance** Circular pore pattern exhibited higher fatigue performance than the triangular pattern **Fatigue damage mechanism** The scaffold experienced rapid strain accumulation during the initial 600 cycles, and then stabilized over the remaining cycles **Deformation mode** Buckling (for scaffolds with circular pores), Shear at 45° diagonal plane (for scaffolds with triangular pores)	[27]
				Triangular				
D	Salt leaching	PPP	Trabecular bone	Irregular (Foam-like)		**Loading type:** Compressive stress **Loading frequency:** 1–10 Hz **Max cycles:** Until failure **Environment:** Dry **Tested samples:** Ø=8 mm, Height= 15 mm Porosity = 75 %, Pore size: 420–500 µm	**Fatigue performance:** small modulus reduction until failure **Fatigue life:** 18,320 cycles **Fatigue limit:** 1.60 MPa **Deformation mode:** Shearing fracture	[47]
E	SLS	PCL	General	Irregular (Foam-like)		**Loading type:** Compressive strain **Loading frequency:** - **Strain level:** 5 % **Max cycles:** 7000 **Environment:** Dry **Tested samples:** 35 × 5 × 1.4 mm^3, scaffolds at three different porosities (by varying laser power and PCL particle size)	**Fatigue performance:** • Little variation in peak stress over fatigue life (= No significant plastic deformation) • Reducing the particle size and increasing the laser energy density (more pronounced influence) increased fatigue resistance	[53]

(*continued on next page*)

Table 1 (*continued*)

	Manuf. method	Material	Application	Topology		Testing condition	Fatigue properties	Refs.
F	Porogen leaching	PCL	Trabecular bone	Irregular (Foam-like)		**Loading type:** Compressive stress **Loading frequency:** 1 Hz **Stress level:** 5 to 50 N (sinusoidal) **Max cycles:** 1100 **Environment:** Immersed in PBS **Tested samples:** Ø=8 mm, Height= 5 mm, some scaffolds were seeded with human stem cells, Porosity: 74–80 %	**Fatigue performance** PCL+Tissue (after 14 days of cell culture) = Empty scaffold (due to short duration of cell culture - only 14 days- and lack of enough tissue) **Deflection during fatigue** PCL+Tissue (after 14 days of cell culture) < Empty scaffold	[55]
G	Porogen leaching	PMMA	bone	Irregular (Foam-like)		**Loading type:** Compressive strain **Loading frequency:** 0.5 % strain/sec **Strain level:** 2 % (saw-tooth profile), preloaded to 0.2 MPa **Max cycles:** 80,000 **Environment:** Immersed in PBS **Tested samples:** Ø=8 mm, Height= 12 mm, Porosity = 70 ± 3 %	**Peak stress** Rapid initial drop (10 % drop after 1000 cycles and 65+−3 % drop after the whole 80,000 cycles) **Compressive Modulus** No modulus reduction during fatigue (a small increase at initial stage followed by a drop to initial modulus and stabilizing at that level)	[49]
H	Porogen leaching	L-PLA DL-PLA PLGA	Bone	Irregular (Foam-like)	–	**Loading type:** Compressive strain (Four-point bending) **Loading frequency:** 2 Hz **Strain level:** 2500 με (60 Sinusoidal cycles every 4 h for 16 days) **Max cycles:** 5800 **Environment:** Immersed in PBS **Tested samples:** 26 × 5 × 2 mm^3, Pore size∼ 200 μm	**Fatigue Resistance** • DL-PLA > PLGA & L-PLA • PLGA scaffolds failed after only several hundred loading cycles, L-PLA scaffolds failed at low strains due to their brittle nature • DL-PLA scaffolds didn't exhibit notable macro or microscopic failure, creep or relaxation after 5800 cycles	[66]
I	FFF	PLA PLA/HA	Bone	Hexagonal		**Loading type:** Compressive stress **Stress level:** 18–33 MPa **stress ratio:** 0.1 **Loading frequency:** 0.2 Hz **Max cycles:** 3600 **Environment:** Dry **Tested samples:** 24 mm x12.5 mm, Porosity: 30 %, Pore size: 700 μm, PLA+15 wt. % HA	**Fatigue limit** PLA/HA scaffolds (21 MPa) > PLA scaffolds (18 MPa) **Damage accumulation rate** PLA/HA scaffolds < PLA scaffolds **Hysteretic area (damping effect)** PLA/HA scaffolds > PLA scaffolds **Compressive modulus** PLA/HA scaffolds > PLA scaffolds **Deformation mode** Bending of the printed layers	[50]
J	SLS	HDPE/HA	bone	Irregular (Foam-like)		**Loading type:** Compressive strain **Loading rate:** 1 Hz **Strain level:** 50 % **Max cycles:** 800 **Environment:** Dry **Tested samples:** 35 × 5 × 1.4 mm^3, Porosity: 45–48 %, Pore size: 30–180 μm, HDPE+10, 20 wt. % HA	**Fatigue performance** Fatigue strength of HDPE/HA > HDPE **Peak stress variation** HDPE/HA (∼No variation over 900 cycles) < HDPE (2.8 MPa for 760 cycles) Mechanical properties reduced by increasing the HA content (due to low chemical affinity between polymer and ceramic)	[51]

(*continued on next page*)

Table 1 (*continued*)

	Manuf. method	Material	Application	Topology		Testing condition	Fatigue properties	Refs.
K	SLA	UMA	Bone	Irregular (bone-like)		**Loading type:** Compressive strain **Loading rate:** 4 Hz **Strain levels:** 9500, 6500, and 4500 μe **Max cycles:** Until failure (4 % applied strain) **Environment:** Dry **Tested samples:** Ø=12 mm, Height= 30 mm, Porosity: 87–88 %	**Fatigue performance** • 20 µm increases in the thickness of rod-like struts (aligned transversely) = increase in fatigue life (at 9500 $\mu\varepsilon$ level) by ~900 % with small changes in density (4 %) and stiffness (20 %) • Thicker rod-like struts = less damage accumulation	[48]
L	FFF	PLA, PLA/316 L, PLA/Iron	Bone	Cubic		**Loading type:** Compressive stress **Stress level:** 0.9x, 0.8x, 0.7x, and 0.6 x compressive strength (sinusoidal loading) **stress ratio:** 0.1 **Loading frequency:** 1 Hz **Max cycles:** 12,000 **Environment:** Dry **Tested samples:** 12 mm x12 mm x12 mm, Porosity: 47 %, Pore size: 780–880 µm	**Fatigue life:** PLA-316 L > PLA/Iron > PLA	[67]

proper biodegradation rate and suffer from poor mechanical properties for load-bearing applications [68,73]. Furthermore, Gelatine has exhibited weak mechanical strength and a high biodegradation rate brought on by enzyme digestion [68]. It also lacks mechanical stability in *in vivo* conditions due to its high physiological solubility. Similarly, Starch was reported as a fragile material and sensitive to aqueous media, making it unsuitable for load-bearing sites such as bone tissues [74]. Silk fibroin scaffolds have shown promising properties owing to their proper mechanical strength and controllable degradation rate [75]. Silk fibroin has an elastic modulus of 10–15 GPa and a tensile strength ranging from 360 to 530 MPa [76], indicating proper mechanical properties under tension. However, their compressive strength is rather low, ranging between 0.005 MPa to 3 MPa [77,78]. Rodel et al. [77] investigated the mechanical and compressive fatigue properties of silk fibroin scaffolds. Hysteresis curves showed that 13 kPa of compressive force, induced 35 % strain in scaffolds, and the maximum force dropped rapidly after approximately 100 cycles.

Synthetic polymers, in contrast, provide higher mechanical properties and an adjustable degradation rate than natural polymers, making them suitable for BTE. Natural polymers, such as collagen or chitin, possess complex structures that have evolved for diverse biological functions [79,80]. While natural polymers offer advantages such as biocompatibility or biodegradability, their variability and heterogeneity may not always meet the mechanical requirements in certain applications [73]. Typically, they are tailored to specific environments, which might not match the mechanical needs of engineered applications in various settings. PCL, PLA, PLLA, PGA, PLGA, PVA, PC, TPU, PA, PEEK, PLCL, PDO, PMMA and HDPE are amongst the potential synthetic polymers that have been widely investigated for load-bearing applications. Poly(α–hydroxy esters) groups such as PLA, PGA and PLGA have received more attention in the biomedical field due to their adjustable properties, easy manufacturing, favourable biological properties and clinical approval from Food and Drug Administration (FDA) [81]. PLA and PEEK also possess physical and mechanical properties close to natural bone [82]. Despite having proper quasi static mechanical strength, polymers are highly susceptible to cracking when subjected to cyclic loadings. Shimko et al. fabricated bone scaffolds made of L-PLA, DL-PLA, and PLGA polymers using the porogen leaching technique, seeded rat bone marrow stromal cells into them and subjected them to four-point bending fatigue up to 5800 cycles (approximately 2500 με was applied in each cycle) [66]. Permanent deformation and failure were observed in PLGA scaffolds only after several hundred fatigue cycles. Despite having a higher yield strength than DL-PLA, PLGA was unable to withstand fatigue loading due to its high degradation rate in the testing medium (PBS). L-PLA scaffolds also failed at low strains because of their high brittleness. However, DL-PLA scaffolds resisted fatigue loads with no sign of cracks owing to possessing the fatigue resistance of L-PLA without its brittleness. Variation in the mechanical properties of different polymers is mainly attributed to their microstructural characteristics. Research has demonstrated a direct correlation between the molecular structure of the polymer and its fatigue resistance [29].

Fig. 7 illustrates the schematic of three common molecular structures in polymers: amorphous, crystalline, and semi-crystalline. Increasing the crystallinity of polymers typically leads to higher fatigue resistance [83]. This is due to the ordered structure of the crystalline regions, which allows for stronger intermolecular bonds and greater resistance to deformation. Charentenay et al. found that increasing the crystallinity of PE by roughly 8 % led to a reduction in the rate of fatigue crack propagation [83]. Similarly, fatigue loading can increase the crystallinity of polymeric bone scaffolds, as demonstrated in the literature. Klouda et al. [84] observed that the crystallinity of PCL scaffolds increased from

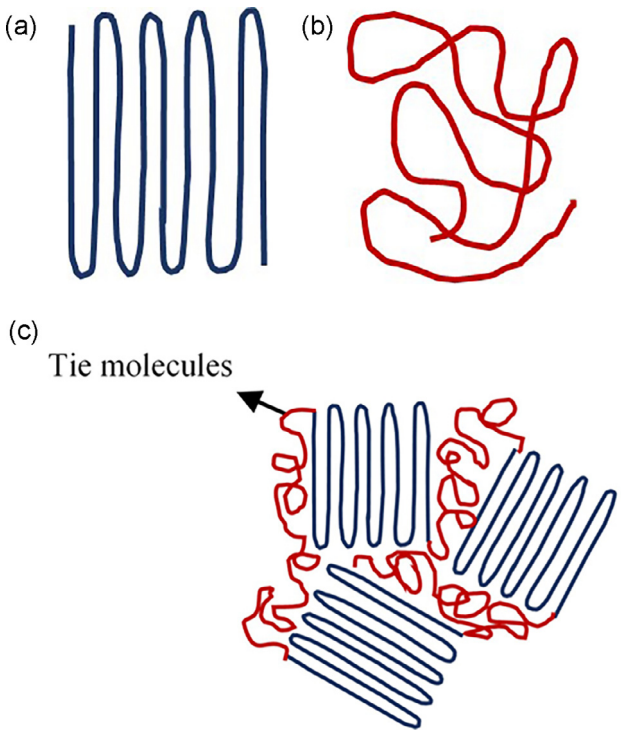


Fig. 7. Structural arrangements of the polymer molecules: (a) crystalline, (b) amorphous, and (c) semi-crystalline structures.

around 40 % to 50 % after being subjected to tensile fatigue loading in PBS for 15 days. Asghari *et al.* also reported that 2000 cycles of tensile stress at a rate of 300 mm/min significantly increased the crystallinity of polyamide 66 scaffolds, enhancing their yield strength and elastic modulus [85]. Tie molecules (curved strand in Fig. 7(c)) that connect the crystalline parts across the amorphous phase can also have a significant effect on fatigue resistance of polymers. A number of studies suggest that increasing the number of tie molecular chains results in higher fatigue strength [86,87].

Fatigue strength of polymers is also affected by the molecular weight. It has been shown that increasing the molecular weight enhances fatigue resistance in various polymers [28,88] including PE [89,90], polystyrene [91], PMMA [92], and nylon [93]. In fact, polymers with higher molecular weight possess longer chains, enabling them to exhibit enhanced resistance to fatigue stresses which is attributed to the development of a molecular entanglement network.

4.1. Reinforcing materials

Strengthening polymeric scaffolds by reinforcing materials is another way of improving their fatigue life. The improvement of mechanical properties in polymer-based composite scaffolds can be achieved through energy dissipation mechanism [94]. In accordance, a fraction of the applied force is absorbed by the reinforcing phase, leading to its deformation instead of generating heat within the polymeric matrix. Reinforcing materials can also adjust the degradation rate, biocompatibility, and osteogenesis of polymers [95,96]. In addition, composites better mimic the ECM of bone since natural bone is a polymer-ceramic composite tissue composed of collagen (natural polymer), ceramic minerals (HA, CaP), cells, and water [97]. Taking this into account, a wide range of biomaterials including polymers [98–100], ceramics [101], and metals [67,102] have been employed as reinforcing phase in polymers. Polymers are used as the reinforcement for enhanced bioactivity, biocompatibility and strength. Bioceramics and metals en-

hance bone scaffold functionality by improving biocompatibility for cell attachment and growth, promoting osteoconductivity for new bone deposition, stimulating osteoinductivity for cell differentiation, and optimising mechanical properties for physiological loads [103,104]. Polymers exhibit greater strength, bioactivity, cell adhesion, and hydrophobicity when blended with bioceramics such as HA and TCP (specific forms of CaP). Some biodegradable metals such as Mg can enhance mechanical strength and bioresorbability when added to polymers [105]. Although biological properties and quasi-static mechanical strength of polymer-based composite scaffolds have been widely discussed within the literature, there are limited accounts of their fatigue performance.

Senatov *et al*. fabricated PLA/HA composite scaffolds using an FFF printer and compared their fatigue properties to unreinforced PLA constructs [50]. They found that the addition of 15 wt. % hydroxyapatite, enhanced the fatigue limit of PLA scaffolds by 17 %. In addition, PLA/HA scaffolds appeared to have higher compressive moduli, larger crack resistance, and higher hysteresis energy compared to PLA scaffolds under similar conditions. In this study, both scaffolds exhibited compressive modulus reduction with fatigue time, but this rate was lower in PLA/HA scaffolds. In another work, HDPE/HA composite bone scaffolds with varying contents of HA (5, 10, and 20 %) were fabricated using SLS method and subjected to quasi-static test and compressive fatigue under strain controlled condition [51]. Interestingly, it was observed that the quasi-static strength of samples declined by increasing the content of HA particles, while their fatigue resistance increased. Lower flexural modulus, ultimate strength, and loss modulus of composite scaffolds compared to that of unreinforced samples were attributed to the low chemical affinity between polymeric and ceramic phases. However, the fatigue limit of samples increased with HA content, showing both higher resistance at the same cycle and less variation in peak stresses. The HDPE/HA scaffold containing 10 % HA showed almost no stress variation over the course of 900 cycles, while a 2.8 MPa change in peak stress was observed in 760 cycles for HDPE scaffolds [51]. Jiang et al. examined the contribution of 316 L stainless steel and Fe particles in improving the fatigue life of PLA scaffolds, concluding that reinforcing particles enhanced the fatigue life of PLA scaffolds considerably, with 316 L particles having a more pronounced effect [67]. This highlights the importance of understanding the fatigue failure mechanism in polymeric composites in designing tissue scaffolds.

The volume content and morphology of the reinforcing materials have a direct impact on the fatigue resistance of polymers. Kane *et al*. demonstrated that HA whiskers could enhance the fatigue life of HDPE four to five times more than those reinforced with HA particles [106]. However, it was also shown that increasing the volume content of HA from 20 to 40 % significantly decreased the fatigue life. Although this effect has been well studied for bulk constructs, no similar work has been conducted for porous polymeric scaffolds.

4.2. Effect of topology

When shaped into scaffold constructs, polymers exhibit different fatigue performance depending on their lattice topology and manufacturing technique/conditions [107]. The term “topology” in this review refers to the pore architecture, *i.e.*, shape, size, and distribution of pores, along the scaffold. Porosity refers to the ratio of pores to the entire volume of scaffold. Geometrical factors such as topology and stress concentration areas (*e.g.,* voids or defects) impact the fatigue performance of polymeric constructs by intensifying or alleviating the stress intensity and distribution within the scaffold’s structure [11,108].

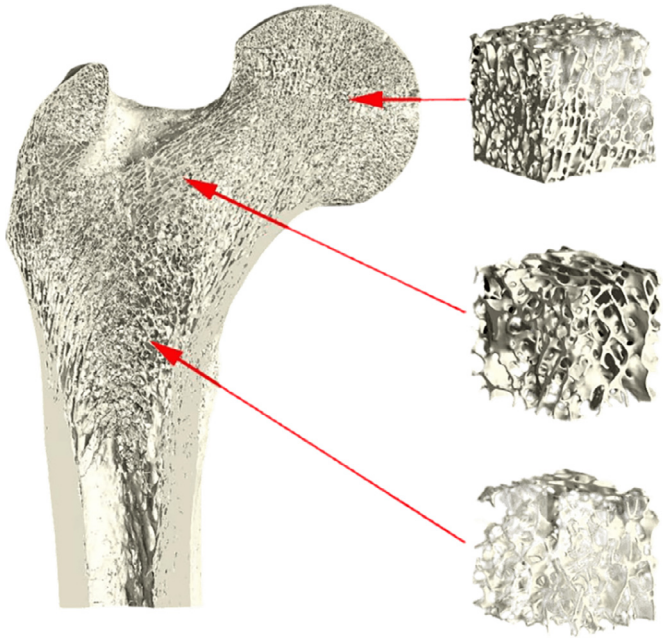


Fig. 8. Porosity-graded structure of a natural bone (Adapted with permission from Elsevier [110]).

4.3. Porosity and pore architecture

Human bone has a graded porous structure, characterised by a decrease in pore size from the trabecular (spongy) bone to the cortical (compact) bone [109]. The porosity of cortical and trabecular bones ranges between 5 and 10 % and 60–85 %, respectively [6]. Since polymeric materials are primarily used for trabecular bone scaffolds, scaffolds are usually designed with 60 % porosity [20]. Fig. 8 depicts the microstructural change in bone architecture of a 26-year-old male’s human femur.

Pore architecture not only affects mechanical strength, but also influences the biological properties of scaffolds by governing critical factors such as cell adhesion, proliferation, migration, and nutrient diffusion. An ideal bone scaffold should provide enough void space with interconnected pores for better permeability, vascularization and tissue formation [111]. It has been shown that higher porosity and bigger pore sizes enhance bone ingrowth and increase direct osteogenesis *in vivo* [112,113]. While polymers lack osteoinductivity by nature, if they are combined with osteoinductive biomaterials such as HA, the resulting polymeric scaffold can benefit from increased osteoinduction caused by higher porosities [114]. However, the positive influence of higher porosity on tissue formation comes at the price of lower stiffness and mechanical properties. Although synthetic polymers mimic the mechanical properties of trabecular bone, the distinct impact of scaffold porosity on their overall mechanical behaviour must be taken into account. Synthetic polymeric scaffolds, designed to mimic the porous structure of trabecular bone, often exhibit a significant decrease in mechanical properties compared to their solid bulk counterparts [115,116]. The introduction of porosity enhances biocompatibility and tissue ingrowth; however, it inherently leads to decreased stiffness, strength, and load-bearing capacity [117]. Therefore, there is a contradiction between porosity and fatigue strength of scaffolds [118]. The deteriorating impact of porosity on fatigue performance of polymeric scaffolds has been reported for PLA [11,54] and PCL [53] scaffolds. Balancing porosity-driven biological advantages with diminished mechanical performance is crucial in the designing synthetic polymeric scaffolds for BTE. Achieving successful clin-

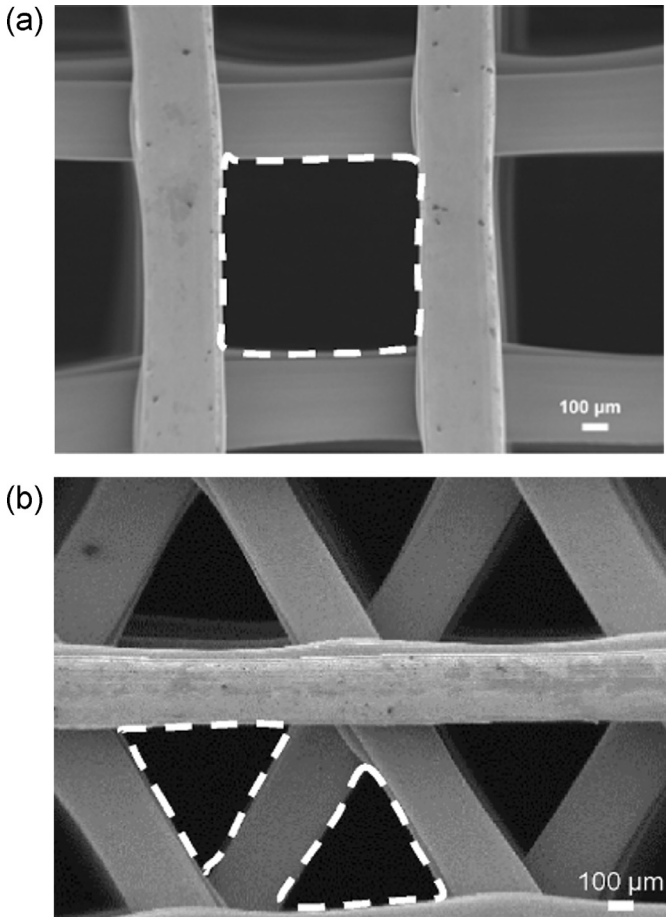


Fig. 9. PLA scaffolds with (a) orthogonal and (b) isometric pore structures (reprinted with permission from Elsevier [11]).

ical outcomes is dependent on striking a balance between porosity and mechanical integrity [119,120].

Porosity is not the sole factor that affects the biological and mechanical properties of a bone scaffold. Pore size and pore shape play a decisive role in growth of bone tissues [121,122]. Small pores allow for better cell adhesion, while large pores ensure ease of cell migration. Therefore, a hybrid design in which both macropores (100–300 μm) and micropores (10–60 μm) exist can satisfy biological requirements [123]. Moreover, research has suggested that the polymer scaffolds deteriorate more rapidly within the body's environment when larger pores are used, resulting in a shorter lifespan and lower mechanical strength [124]. Pore shapes can take on various geometries including regular (circle, triangle, cube, hexagon, tetragon, pentagon, etc.) and irregular shapes. Different pore shapes produce different stiffness in scaffolds. Baptista and Guedes fabricated bone scaffolds in two different configurations, *i.e.* orthogonal and isometric with different pore shapes and varying porosities ranging from 30 to 70 % [11,54]. They found that increasing the porosity lowered both compressive strength and energy absorption. Orthogonal pore shape structures [Fig. 9(a)] appeared to have a better mechanical performance than that of the isometric design [Fig. 9(b)] due to the higher slippage resistance between layers.

Similar results were reported for PLA-PEG-CaP [125] and PEG-PCL-PLA [126] bone scaffolds in which orthogonal scaffolds (0/90 laydown pattern) exhibited higher compressive strength and modulus compared to other patterns. According to a review conducted by Bakhtiari et al. [108], the literature suggests that orthogonal patterns have demonstrated better compressive fatigue performance in 3D printed polymeric parts. In another study, low cycle fatigue analysis of 3D printed PLA scaffolds with hexagonal, tetragonal, and wheel like topologies with similar porosities was performed [56]. Results indicated that the tetragonal design had superior fatigue resistance (4400 cycles), compressive modulus (481.6 $\pm$ 10.2 MPa), and damping effect, with hexagonal and wheel like samples having fatigue life of 3200 and 2500 cycles, respectively. By analysing the stress relaxation of these three designs, the authors established that tetragonal topology had similar viscoelastic properties to articular cartilage. They also emphasised the importance of the number of junctions between filaments, concluding that more junctions led to better mechanical properties. Finite element analysis of the scaffolds mentioned above showed a homogenous stress distribution for all topology designs [56].

Scaffold topologies are not limited to regular pore shapes or patterns as discussed above. Fig. 10 depicts some of the most common topologies used in bone scaffolds. A detailed review of the topological designs for bone scaffolds can also be found in the literature [10,127,128].

Scaffolds with irregular pore shapes have shown high elastic recovery and fatigue performance. For instance, spring like structures appear to have higher damping capacity. Low cycle fatigue analysis of spiral (*S*-shaped) PLA lattice structures has demonstrated strong elastic resistance under compressive fatigue, recovering almost 96 % of the applied strain after 36 cycles [136]. Some irregular topological designs such as TPMS, Voronoi tessellation, functionally graded structures, and auxetic metamaterials in polymers have also been shown to possess promising load-bearing capacities [129,137–143]. However, their fatigue performance in polymers is not well understood. In particular, TPMS structures have shown potential in alleviating stress concentration because of their smooth surface transition at strut junctions [144]. Thus, TPMS seems to be an ideal design where high fatigue performance is required and can be the focus of future research studies.

In addition to mathematical topologies, some architectures draw inspiration from natural bone, commonly referred to as naturally occurring or bio-inspired architectures, as shown in Fig. 10. These designs benefit from their resemblance to the natural architecture of bone. Ashley *et al.* 3D printed a polymeric scaffold with bone topology, acquired by µCT imaging (as shown in Table 1, Row K), and conducted a detailed investigation on the contribution of structural elements of bone architecture to fatigue performance [48]. Consistent with *in vitro* experiments on real bone, they found that a small increase in the thickness of rod-like struts (structural elements aligned perpendicular to the applied load) can enhance the fatigue life of scaffold by 10 to 100 times while having a negligible effect on density and stiffness. Their FEM results revealed that transverse struts underwent tensile stress and acted as sacrificial elements during fatigue by accumulating damage, thereby protecting the structure in the longitudinal direction. Their findings highlight the significance of scaffold architecture and its determining effect on fatigue performance.

Considering all the geometrical factors and their contradictory effects, an optimum design that meets all the mechanical and biological requirements of bone scaffolds is only achievable through solving a multi-objective optimisation problem [145]. The size, shape, and distribution of pores, as well as material properties and real boundary conditions, should be optimised in light of the intended application of the scaffold. Some optimisation studies have been found in the literature for a limited number of design factors and materials (mostly metals) [146]. However, no study was found that accounts for the fatigue performance of scaffolds as an optimisation objective.

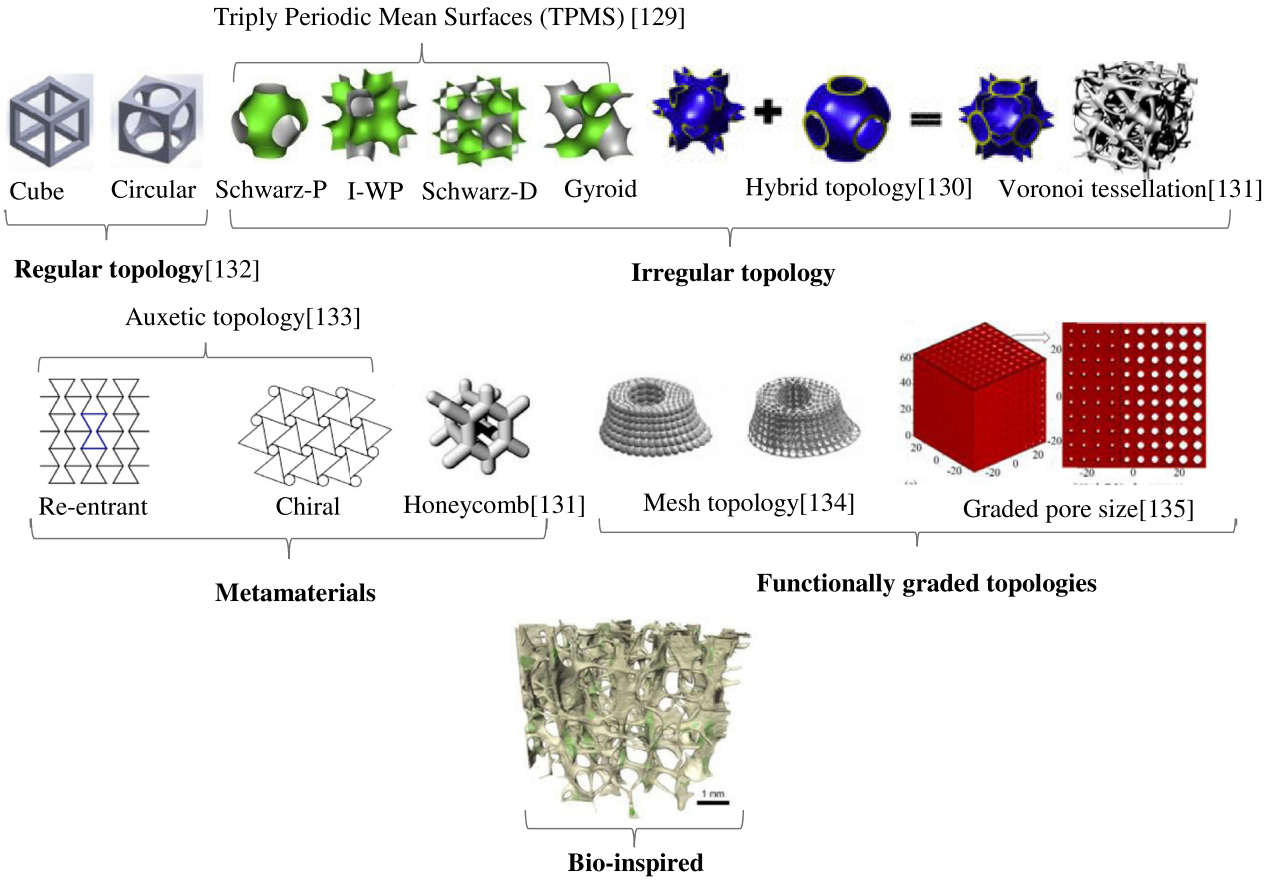


Fig. 10. Bone scaffold topologies [Copyright permission for: Regular topology, Voronoi tessellation and honeycomb (CC BY 4.0), Triply Periodic Mean Surfaces (reprinted with permission from Elsevier [129]), Hybrid topology (reprinted with permission from Elsevier [130–133]), Mesh topology (reprinted with permission from Springer Nature [134,135]), and bio-inspired design (reprinted with permission from [48])].

4.4. Stress concentration

Stress concentration is a determining factor in fatigue resistance of scaffolds. Stress concentrations usually occur at material or geometrical discontinuities, leading to the formation of highly stressed zones and early fracture. Pore shape has a direct impact on stress distribution along the scaffolds. It is believed that circular pores mitigate the structural collapse of a scaffold when subjected to cyclic loading due to more uniform stress distribution and less stress concentration [27]. However, cubic structures have indicated a superior strength under static compressive forces [147]. This difference originates from the different failure mechanisms under static and dynamic loads. Since fatigue failure is mostly influenced by stress concentrations, sharp corners may lead to early pore collapse under cyclic loadings, while porosity accounts for most failure under static loading [47]. Consistent with this, Haddock *et al.* evaluated the fatigue strength of vertebral and bovine tibial trabecular bones with different porosities and reported similar fatigue strength, despite having different monotonic yield strengths [37]. Similarly, fatigue experiments on poly(para-phenylene) scaffolds have revealed that scaffolds fail in different modes under cyclic (shearing fracture) and monotonic loading (buckling) [47]. Gong et al. conducted a study on stress distribution in 3D-printed PLA scaffolds with circular and triangular pore architectures [27]. While triangular topology exhibited higher compressive strength, the circular topology demonstrated improved dynamic stability due to a more homogeneous stress distribution. Moreover, scaffolds featuring triangular topology underwent shear fracture, whereas circular scaffolds failed through buckling mode. Likewise, in the work of Hoyt *et al.* the endurance limit of porous poly(para-phenylene) scaffolds with irregular (foam-like) pore architecture under compressive fatigue was reported to be 100 times lower compared to those of solid counterparts. This significant reduction was mainly attributed to the influence of stress concentration [47].

The way that a scaffold is produced affects its topology and mechanical performance. It has been demonstrated that the fatigue failure of additively manufactured porous structures are different compared to those manufactured by conventional techniques [148]. In FFF fabrication, polymeric filaments are deposited in a layered construct; hence, stress concentration may occur at layers interfaces followed by filaments debonding, layers debonding, and filament cracking [149]. In reality, deposited layer interfaces act as sliding planes, facilitating the slippage and delamination of filaments. Consistent with this, Baptista *et al.* observed microcracks within filaments as well as delamination between adjacent layers in PLA bone scaffolds [11]. In a research conducted by Hoque *et al.* PEG-PCL-PDLLA bone scaffolds were 3D printed in different laydown patterns using a robotic extrusion device [126]. In similar conditions, 0/90° pattern exhibited higher compressive modulus (0.192 MPa) and yield strength (0.357 MPa), compared to 0/60/120°, 0/45/90/135°, and 0/30/60/90/120/150° patterns. The authors stated that smaller laydown angles (*e.g.*, 30°, 45°, and 60°) resulted in wider fused zone at filament junctions, providing a larger sliding/shearing area for the structure. Senatov *et al.* conducted fractographical examinations on FFF-printed PLA scaffolds. The results indicated that fatigue failure was caused by defects and slippage at layer interfaces [50]. Stress inhomogeneities at filament junctions of adjacent layers in PLA bone scaffolds have also

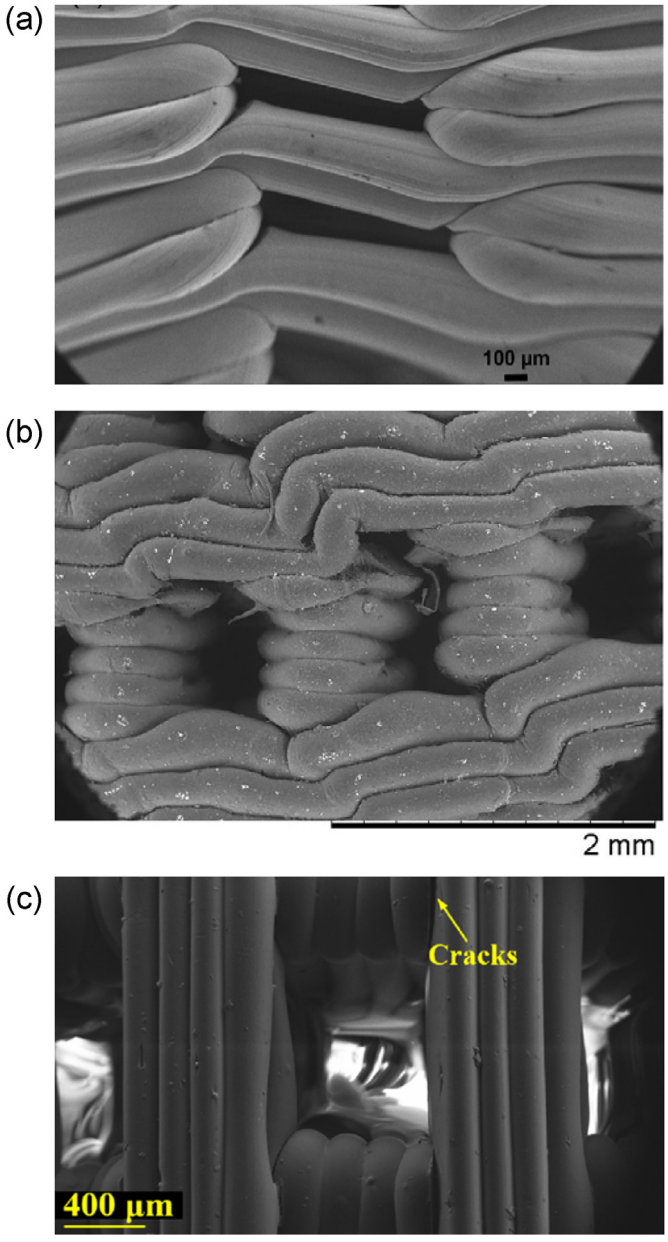


Fig. 11. Fatigue-induced delamination of layers in PLA scaffolds with various topologies: (a) orthogonal topology after 3600 cycles [11], (b) hexagonal topology after 4000 cycles [50], and (c) cubic topology after 10,000 cycles [67] (All figures were reprinted with permission from Elsevier).

been reported elsewhere [56,67]. In Fig. 11, filament shearing and layer debonding of some PLA scaffolds are shown when subjected to cyclic loading. Therefore, it is recommended that polymeric layers in scaffolds be printed perpendicular to the loading direction.

4.5. Manufacturing method

Both conventional (traditional) and advanced manufacturing methods have been employed for the fabrication of polymer scaffolds with each having its own advantages and limitations [150]. Amongst the commonly used conventional methods are salt leaching, solvent casting, phase separation, freeze-drying (also known as lyophilization), gas foaming, fibre bonding, and melt-moudling [151]. Advanced manufacturing techniques like AM (3D printing) have recently gained prominence, providing greater control over scaffold design, customization possibilities, and improved production efficiency [152]. Both conventional and advanced methods introduce microstructural and mechanical changes in the scaffold's characteristics. As a result, the manufacturing method employed can have a substantial effect on the fatigue performance of the produced scaffold. The key characteristics that are impacted by manufacturing methods concerning the fatigue life of a polymer scaffold are as follows:

(i) Pore structure and interconnectivity: Traditional methods have limited control over the pore structure and interconnectivity [153]. For example, in salt leaching, the use of salt particles as porogens can lead to irregular pore shapes and a nonuniform pore distribution, resulting in poor interconnectivity between pores. Similarly, in solvent casting and particulate leaching, the interconnectivity of pores is negatively affected due to inadequate control of pore size and distribution. The limited pore interconnectivity in traditional methods may not only impede nutrient transport, cell ingrowth, and load distribution throughout the scaffold, but also lead to localized stress concentrations and decreased fatigue life of the scaffold over time [154]. Advanced manufacturing methods such as AM, on the other hand, offer precise control over the pore shape and distribution, enabling the creation of well-defined interconnected pore networks [152]. Advanced techniques for controlling pore characteristics improve scaffold performance, making them better at withstanding repeated stresses and loads. However, due to the layer-by-layer configuration of 3D printed parts, they can exhibit lower fatigue performance than their conventional counterparts because of the stress concentration at the layers' interfaces. The literature reveals mixed results, with AM occasionally underperforming conventional methods but also surpassing them in terms of fatigue performance [108]. While several studies have compared the fatigue behaviour of 3D printed parts to their conventional counterparts, no similar investigation was found regarding the polymeric bone scaffolds which presents an opportunity for future studies.

(ii) Material anisotropy: Anisotropy is a cause of early fatigue failure in many parts, including human bone. A study revealed that off-axis loading substantially decreased the fatigue lifetime of trabecular bones [155], highlighting the significance of anisotropic features of bone scaffolds to be aligned with the applied load. Anisotropy of bone scaffolds can be rooted in its material's characteristics or geometrical features such as pore architecture. Both conventional and AM methods induce anisotropy within the scaffolds. This specially applies for AM techniques that produce layered constructs. Anisotropy of additively manufactured parts originates from two sources: a) geometrical imperfections and b) layering [156]. Geometrical imperfections may appear as cavities during the SLS process due to unmelted powders, or as wrapping and interlayer voids due to the incomplete bonding between layers during the FDM technique [157–161]. Layering is another cause of anisotropy, yielding its own disadvantages as it results in structural anisotropy which negatively affects the fatigue performance. In conventional methods, anisotropy may occur during multiple processing steps, that lead to uneven concentration of polymer molecules and additives.

(iii) Material and structural degradation: The manufacturing method affects the degradation of polymeric scaffolds in two ways, *i.e.*, material and structural degradation and thus affecting their mechanical and fatigue stability. The material degradation occurs when a thermal process is involved in the manufacturing of scaffold and the process causes changes in the molecular structure of parent material. Since low cycle fatigue is a thermomechanical process, thermal properties of polymers play an important role during cyclic loading [47,162]. Processing polymers at elevated temperatures leads to thermal degradation of molecular chains and consequently, reduced ductility, increased embrittlement and degraded mechanical properties. This should be accounted for when

choosing the method to fabricate a polymeric scaffold. For instance, when 3D printing is employed, low scanning speed (in SLS printing) or slow extrusion rate (in FFF printing) would expose polymers to excessive heat input and increases the possibility of thermal degradation [163]. TGA or GPC analyses could be used to examine the mass reduction or change in molecular weight of polymers as signs of thermal degradation. Further, the cooling process after 3D printing may change the crystallinity of polymers, altering their mechanical properties. Liang *et al.* measured molecular weight and thermal properties of PLA filaments before and after FFF printing using the GPC and DSC techniques, respectively [56]. No significant change in molecular weight or degree of crystallinity was detected for the printed scaffolds. Thus, a comparison of the molecular weight of the used polymer before and after printing can be accounted for.

Structural degradation of scaffolds refers to the effects of the scaffold's architecture on its degradation rate. It has been shown that the surface-to-volume ratio of scaffolds affects their degradation rate with higher ratios usually leading to faster destruction [164]. Conventional manufacturing methods can significantly affect the scaffold degradation pattern through affecting its architecture. Freeze-drying removes solvent from a frozen scaffold, forming a porous structure. While it can create interconnected pores, variations in pore sizes affect the degradation pattern. Gas foaming adds porosity by expanding gas bubbles in the polymer matrix. Variable pore size and distribution may result from gas diffusion and polymer viscosity during foaming. The uneven porous structure and interconnectivity affect the degradation rate of scaffolds [164] and consequently lead to uneven weakening of the scaffold and cause localized stress concentrations. Such inconsistencies can accelerate fatigue crack initiation and propagation, reducing the scaffold's fatigue life. The precise control over material deposition and pore structure via AM methods allows for more consistent pore sizes and interconnectivity, and thus, a more predictable and uniform degradation rate. Although materials with a slow degradation rate appear to have higher fatigue strength under the corrosive environment of body fluids [165], this is not favourable in bone scaffolds, which are expected to resorb at the pace of bone growth. Controlled degradation promotes uniform load distribution and mitigates the concentration of stress in specific areas. AM allows for aligning the degradation with tissue healing, maintaining the structural integrity during regeneration. This enhances the scaffold's ability to withstand cyclic loads and extends its fatigue life.

5. Effect of *in vivo* conditions

5.1. Exposure to body fluid

In vivo, scaffolds are exposed to body fluids, producing some mechanical and chemical interactions between the polymeric structure and the liquidous phase. These interactions and their impacts on fatigue behaviour of polymeric scaffolds have not been adequately studied in the literature. Such effects can be studied in two opposite perspectives: strengthening and deteriorating effects.

The strengthening effect of body liquids is due to their hydrodynamic nature. The hydrodynamic effect of stored water not only favours the load-bearing capacity of scaffolds but enhances the stress homogeneity within the scaffold struts. Since body liquids are incompressible fluids, they can uniformly distribute the applied loads and mitigate high stresses within scaffolds. Therefore, scaffolds are expected to exhibit higher mechanical strength in *in vivo* conditions. Panadero et al. demonstrated that fatigue life of PCL scaffolds increased from 100 cycles at dry conditions to 500 loading cycles when immersed in water [166]. In a similar study, Vikingsson *et al.* evaluated low cycle fatigue performance of PCL scaffolds in dry and wet conditions [167]. SEM images indicated that the dry scaffold collapsed entirely after 100,000 fatigue cycles while the wet scaffold (scaffold immersed in water during the cyclic loading) showed moderate deformation inside the scaffold's struts. Another possible effect of body fluids on enhancing the fatigue strength of polymeric scaffolds is due to their favourable thermal conductivity [168]. As mentioned in Section 2.2, internal friction and dissipated energy during fatigue cycles can cause hysteresis heating within polymers, resulting in temperature rise and thermal degradation of polymeric scaffolds. Body fluids can aid transmitting the generated heat from scaffold to the surrounding environment, thus favouring the cooling process and reducing the degradation effect [169]. Although there is no evidence in the literature showing that biological environments (*e.g.* body fluids) can aid reducing the thermal degradation of polymeric scaffolds, it is expected that polymeric scaffolds will resist more fatigue cycles when immersed in aqueous media. Nonetheless, the impact of this effect during cyclic loading is not well understood, and hence, further *in vitro* research is needed to clarify this phenomenon.

Conversely, the deteriorating impact of body fluids on polymeric scaffolds is attributed to two main factors: i) corrosive properties, and ii) plasticizing characteristics. Body fluid contains considerable corrosive elements, causing polymers to undergo chemical breakdown and degradation. Hydrolysis and oxidation are the main degradation mechanisms in polymers that cause the release of compounds such as aldehydes, ketones, and carboxylic acids into the surrounding environment. The release of such compounds leads to local pH changes that can accelerate the degradation of the implanted scaffold, thus lowering its mechanical and fatigue resistance [170,171]. Changes in the pH of body fluids result in the degradation of polymer molecular weight, subsequently leading to a decline in its mechanical strength [172]. It is believed that degradation of polymeric scaffolds at the exposure of body fluids would reduce their fatigue resistance through the hydrolytic decomposition [170]. However, the influence of biodegradation of polymeric scaffolds on fatigue strength has been investigated for a limited number of polymers. To simulate the corrosive environment of body fluids in laboratory, scaffolds can be immersed in a simulated body fluid (SBF) such as NaCl, Hank's balanced salt solution (HBSS), and phosphate buffered saline (PBS) [173]. However, PBS has been the most commonly used SBF in mechanical characterisation of polymeric scaffolds due to its similar ion concentration and pH to natural body fluids [174]. Klouda *et al.* investigated the decay of mechanical properties in PCL and coated PGA scaffolds when immersed in PBS for 15 days [84]. To provide the real physiological conditions, some wet scaffolds were subjected to tensile fatigue up to 10 % of strain and the loading frequency of 1 Hz, while other samples were kept unloaded in PBS. Results of uniaxial tensile tests confirmed the decrease of ultimate tensile strength and fracture strain in all wet scaffolds compared to dry scaffolds. Further, it was found that scaffolds which had been subjected to fatigue loading possessed lower mechanical strength compared to unloaded counterparts, implying that both degradation and fatigue loading contribute to the loss of mechanical strength in scaffolds. Given that PCL showed no degradation over the 15 days period, a decline in mechanical properties of PCL scaffolds was correlated to the plasticising effect of PBS. Like PCL, PMMA is a nondegradable polymer. Shimko and Nauman reported that exposing PMMA scaffolds to humidity decreased their elastic modulus from around 270 MPa, at no humidity condition, to 100 MPa, after seven days humidity exposure [49]. In the work of Liang *et al. in vitro* immersion fatigue performance for PLA scaffolds was studied [56]. 3D- printed PLA scaffolds with tetragonal, hexagonal, and wheel-like structures were immersed in a PBS solution (pH 7.2–7.4) and subjected to uniaxial compression test and low cycle fatigue experiments at 1 Hz. The authors concluded that the tetragonal scaf-

fold exhibited higher fatigue performance compared to the hexagonal and wheel-like scaffolds due to its higher number of junctions (connections) between the filaments. This high number of junctions contributes to the integration of the scaffold, facilitating the uniform distribution of applied loads and reducing stress concentrations.

It is important to note that PBS or other artificial SBFs can only replicate the body's environment to a certain extent, implying that the performance of scaffolds in an *in vivo* setting may vary in terms of bioactivity, corrosion, and stability [173]. An important consideration that is lacking in the literature is that the contradicting effects of body fluids on mechanical and fatigue properties of polymeric scaffolds should be seen at the same time, implying that *in vivo* experiments are still necessary for successful clinical application of any scaffold.

5.2. Tissue ingrowth

The mechanical response of tissue scaffolds *in vitro* is quite different compared to *in vivo*, thus cannot representing its real behaviour in physiological conditions. Once implanted into the body, tissue scaffolds are exposed to the constant flow of body fluids. At the same time, natural tissues such as bone and cartilage start to grow gradually inside the scaffold's pores. During the bone healing process, cartilage is initially formed at the fracture area, which is eventually transformed to bone through endochondral ossification [175]. Cyclic forces act as mechanical stimuli to cell activities, promoting tissue ingrowth and faster healing [176–178]. Tissue formation contributes to the fatigue resistance of scaffolds as they can retain a considerable amount of aqueous media. Water accounts for 15–25 % volume of bone [179] and around 75 % volume of articular cartilage. This matter has been investigated in a number of previous studies. The influence of cartilage formation on static and dynamic behaviour of PCL scaffolds has been studied by Panadero et al. [26]. PCL scaffolds were fabricated using porogen leaching method and filled with fibrin hydrogels. Chondroprogenitor precursor cells were then seeded in scaffolds and submitted to a bioreactor or a free swelling culture. Elastic modulus of scaffolds was found to be notably higher in cell- cultured scaffolds compared to PCL or PCL-fibrin scaffolds. Fatigue experiments also indicated that mechanical stability of scaffolds increased to 600 cycles after cell seeding, implying that the development of ECM inside the scaffolds positively affects the fatigue performance. However, the damping capacity (hysteretic area) of scaffolds declined as the fatigue cycles progressed. This is due to the thermomechanical degradation of polymeric structure caused by hysteretic heating and thermal softening as reported elsewhere [180]. Similar results were reported for collagen scaffolds seeded with mesenchymal stem cells [12]. Cylindrical collagen scaffolds in a woven pattern were soaked in PBS and kept hydrated during fatigue testing. After 28 days of cell culture, elastic modulus and compressive strength of scaffolds increased by 60 % and 31 %, respectively, compared to that of empty scaffolds. Low cycle fatigue performance of cell seeded scaffolds at 15 % strain amplitude showed enhanced mechanical stability. Scaffolds were able to preserve 92 % of their base load after 4500 cycles and when subjected to 40 % strain in uniaxial compression testing, they recovered 90 % of total strain [12].

Achieving enhanced mechanical properties *in vivo* is a step forward to the clinical use of polymeric scaffolds in load-bearing applications. Although assessing the mechanical response of scaffolds *in vivo* is crucial for understanding their performance and potential applications in physiological environments, providing *in vivo* conditions for tissue formation is a costly process. Some researchers have used bioreactors to simulate the ECM development and tissue formation inside scaffolds [181]. If only mechanical response of scaffolds is considered, a simpler methodology can be applied. It has been reported that liquid-filled porous media can properly mimic the behaviour of trabecular bone under compression [182,183]. To simulate the strengthening effect of tissue ingrowth inside PCL scaffolds, Panadero *et al.* investigated the fatigue endurance of scaffolds filled with PVA gels containing a high amount of water. They indicated that PVA hydrogels were able to properly simulate the strengthening effect of natural cartilage [52]. In addition, stiffness of PVA gel was tuned by altering the number of freezing/thawing stages to simulate the development of tissue ingrowth. Compared to unfilled PCL scaffolds, the fatigue life of PCL/PVA scaffolds increased [52], while their elastic modulus and compressive strength improved 3.28 and 2.75 fold, respectively [184]. In the work of Vikingsson *et al.* scaffolds filled with PVA gels showed no fatigue failure compared to complete failure of empty scaffolds, indicating the strengthening effect of tissue formation within the pores [167].

It is worth noting that bone tissues takes weeks to grow inside scaffolds. The bone healing process begins with an inflammatory phase (fracture haematoma formation) immediately after injury followed by repairing phase (2–3 weeks) and bone remodelling [185]. However, during the repair phase, cartilage and soft tissues are initially formed before being replaced by solid bone. Therefore, the strengthening effect of bone growth is expected to increase gradually over time rather than immediately. Some reports indicate that at least 4–8 weeks are required to identify the strengthening effect of bone growth in scaffolds [186]. Consistent with this, PCL scaffolds seeded with human fetal osteoblasts showed no significant enhancement in compressive strength and fatigue performance after 14 days of cell culture compared to unseeded counterparts [55]. Fig. 12 depicts the influence of *in vivo* conditions on fatigue properties of a typical bone scaffold during the healing process. Overall, the fatigue performance of bone scaffolds is influenced by both the strengthening and weakening effects of body fluids, occurring concurrently with bone growth. These effects should be considered in designing and materials selection of polymeric scaffolds.

5.3. Effect of loading parameters

Loading conditions, such as the amplitude, frequency, and type of loading, can have a significant effect on the fatigue behaviour of polymers [187]. It has been demonstrated that cyclic loading can alter the crystallinity and mechanical properties of polymers. Higher amplitude and loading ratios can cause a higher stress level in polymers and lead to a decrease in their fatigue life. The higher stress levels induce increased deformation and plasticity in polymers, resulting in the formation of additional defects and microcracks. Over time, these defects and microcracks have the potential to expand, eventually leading to failure. Jiang et al. demonstrated that the PLA-based bone scaffolds exhibited longer fatigue life at lower stress levels compared to higher stresses [67]. They applied low cycle fatigue stress on scaffolds made of PLA, PLA/Fe, and PLA/316 L. Compressive strength (σ) of each scaffold was first determined and each scaffold was subjected to four fatigue stress levels *i.e.*, 0.6, 0.7, 0.8, and 0.9 $\times$ σ. S-N curves indicated an abrupt decrease in fatigue strength at stress levels above 0.8 $\times$ σ, implying rapid fracture and crack propagation occurred at high stress conditions. Loading frequency can also affect the fatigue strength of polymer scaffolds and natural bones. The loading frequency, or the number of loading cycles per unit time, can also have a significant effect on the fatigue strength of polymeric scaffolds. In general, as the loading frequency increases, more heat is generated within the polymer which can lead to a decrease in fatigue life of the scaffold.

Loading rate sensitivity of polymers is contrary to the behaviour of natural bone. Generally, loading frequencies below 15 Hz have

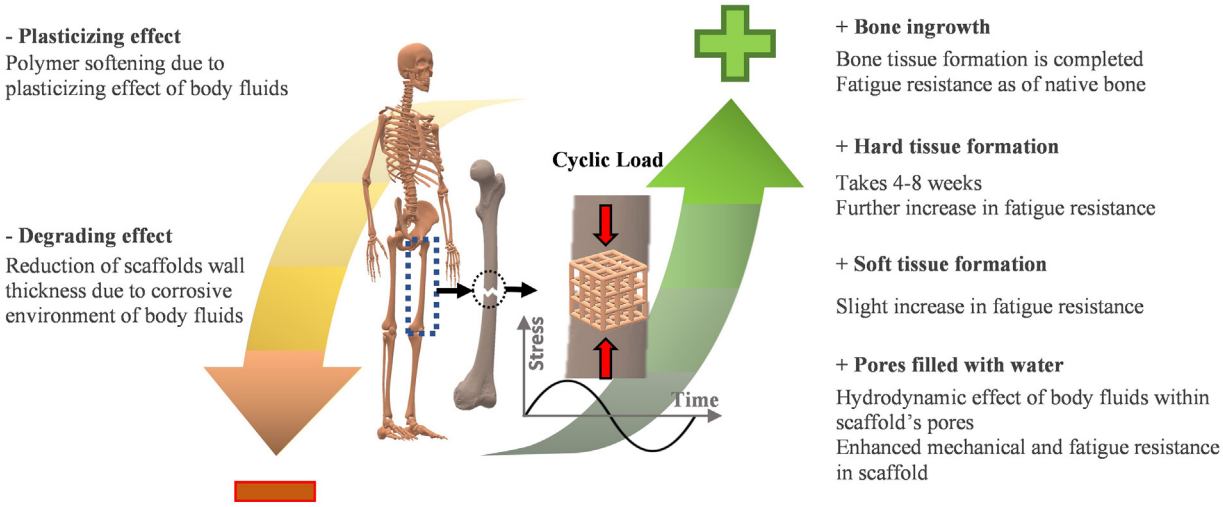


Fig. 12. Strengthening (+) and weakening (-) effects of *in vivo* conditions on fatigue performance of bone scaffolds.

negligible influence on the fatigue behaviour of cortical bone [188]. However, at higher frequencies, the likelihood of bone failure increases [189]. As mentioned in Section 2, steps are normally taken at a frequency of 1 Hz in daily walking activity [46], meaning one step in each second. Therefore, it is logical to perform fatigue experiments at this frequency for load-bearing scaffolds designed for human legs. Fracture is observed to occur shortly after loading at high stress levels and loading frequencies. This can be attributed to factors such as hysteresis heating or stress levels approaching the material's yield point. Conversely, at low stress and loading frequency, the mode of failure shifts to a quasi-brittle failure, which is characterised by the gradual nucleation and expansion of flaws over an extended period [190]. However, the effect of loading conditions on different polymers can be different [29]. Wang et al., concluded that the influence of loading frequency on fatigue life of ultra-high molecular weight polythene will be negligible since it has both strain rate hardening and hysteresis heating effects, which will neutralize each other [191]. Given the limited number of studies on the fatigue behaviour of polymeric bone scaffolds, it is imperative to conduct additional studies in this area to advance our understanding.

5.4. Future clinical perspectives

As the fatigue behaviour of load-bearing polymeric bone scaffolds is more understood, design, materials selection, and fabrication of bone scaffold can be optimised to suit the unique features of each patient. This concept is centred on fabricating implants that precisely match an individual's anatomical and biomechanical requirements. Careful attention to fatigue properties paves the way for custom-made implants that excel in both structural optimisation and fatigue resistance. This approach can significantly reduce implant failures, minimise complications, and improve patient comfort and quality of life. Furthermore, the integration of advanced manufacturing techniques, such as 3D printing, holds the promise in producing patient-specific scaffolds with precisely customised fatigue-resistant properties. This merging of technology and fatigue science allows for optimal performance and longevity for each patient's unique needs.

The study of fatigue behaviour in polymeric bone scaffolds also contributes to opening avenues for wider clinical use and regulatory approval. As we better understand scaffold fatigue resistance, we can create standardised testing protocols to ensure the safety and effectiveness of these materials in load-bearing applications. This speeds up regulatory approval, making innovative scaffold designs more accessible for mainstream clinical use. Furthermore, having detailed fatigue data can boost confidence amongst healthcare professionals and regulators, promoting wider acceptance of polymeric scaffolds as viable alternatives to traditional materials.

5.5. Concluding remarks

Polymers are widely used as tissue scaffolds for non-load-bearing and functional applications due to their promising biological and mechanical properties. However, their suitability for load-bearing applications such as bone has been under debate owing to their relatively low mechanical strength. In the present review, the fatigue performance of polymeric scaffolds has been investigated from different perspectives. The fatigue behaviour of polymeric scaffolds is influenced by a range of parameters, including material and microstructural characteristics, manufacturing methods, loading factors, topological design, body fluids, and surrounding tissues. On the other hand, due to the energy dissipation and heat generation that occurs within polymers during cyclic loading, thermal degradation of polymers is expected to occur after a certain number of cycles. Improving the fatigue properties of polymeric scaffolds can be achieved through the incorporation of ceramic and metal reinforcements, along with the optimisation of their topology. The manufacturing method also affects the fatigue performance of scaffolds due to its impact on pore structure, anisotropy, and degradation. Furthermore, the hydrodynamic effect of body fluids, coupled with the strengthening effect of tissue growth inside pores, also contribute to the fatigue resistance of polymeric scaffolds. However, a proper material with a suitable degradation rate should be chosen to minimise the degrading and plasticising effects of the body environment. Taking into account their myriad advantages and properties, polymers emerge as a compelling material for the development of load-bearing tissue scaffolds. The fatigue behaviour of polymer scaffolds has not been adequately examined under different cyclic loading types (tension-tension, tension-compression, flexural) or loading rates (based on daily activities). Further investigations are required to evaluate their fatigue performance under real working conditions. The literature currently lacks a comprehensive exploration of multiobjective optimisation related to the topology of polymeric scaffolds, which will play a key role in attaining optimal biological, mechanical, and fatigue performances. Understanding the fatigue behaviour of load-bearing polymeric bone scaffolds enables the development

of patient-specific implants with enhanced stability and facilitates regulatory approval for wider clinical use.

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