Auxetic Metamaterials for Bone-Implanted Medical Devices: Recent Advances and New Perspectives

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Abstract

Auxetic metamaterials and structures are characterized by their negative Poisson's ratio meaning that they exhibit lateral expansion under tensile axial loads and densification under compressive loads. The unique properties of the auxetic metamaterials have been generated by designing the micro- and macro-structures with various materials/designs. These types of structures are attracting interest for different reasons such as high energy absorption and improvement in mechanical and biological properties of medical devices. However, some of their interesting characteristics have not been widely explored yet in the field of biomedical engineering. This review aims at highlighting the applications of the auxetic structures in various bone medical devices. Additionally, it investigates different unit cells that were introduced as auxetic designs. The potential of using the auxetic structures in bone tissue engineering is discussed as well.

Keywords: Auxetics; Negative Poisson's ratio; Bones; Implants; Medical devices.

1. Introduction

Various materials and structures have been used in biomedical engineering for different purposes (Askari et al., 2021; Cheikho et al., 2022). One of the most important characteristics of these materials is the mechanical properties and deformation behavior. A metamaterial is a class of materials designed to have properties that are not naturally available in nature. These properties can be distinct mechanical properties under different loading scenarios (Al Rifaie et al., 2022; Wallbanks et al., 2021; Zhang et al., 2022b). Therefore, researchers have tried to use different strategies like analytical methods to calculate mechanical properties of the metamaterials (Lahbazi et al., 2022). Moreover, designing the internal structure is one of the strategies to program the essential mechanical properties of metamaterials such as negative Poisson's ratio (NPR) (Chen et al., 2020; Soman et al., 2012b). For instance, auxetic materials exhibit NPR behavior laterally expanding under the tension loads and contracting under compression loads (Lvov et al., 2022). Some tissues in the human body including tendons, skin, annulus fibrosus disks, arteries, and cancellous bone show auxetic behavior under tension loads (Derrouiche et al., 2019; Gatt et al., 2015; Lee et al., 2016; Williams and Lewis, 1982).

There are many applications for auxetic materials mentioned by research studies, such as bone implants, running shoes, and shape memory foams, aerospace engineering, because of their high energy absorption, variable permeability, and fracture toughness (Han et al., 2022; Kolken and Zadpoor, 2017; Namvar et al., 2022). Auxetic structures show high anisotropy, and it has an impact on mechanical properties. These structures can elevate energy absorption by 1.6 times more than conventional structures like honeycomb (Wang et al., 2020b; Zhang et al., 2020a). Furthermore, auxetic materials can be used as tissue engineering scaffolds. They can not only illustrate unusual mechanical properties but also improve cell proliferation under external loads (Choi et al., 2016; Kim et al., 2017; Park and Kim, 2013). As has been mentioned previously, cancellous bone shows auxetic behaviors; therefore, the auxetic structure of the tissue-engineered scaffolds can follow the mechanical behavior of the host tissue to accelerate bone tissue formation (Kim et al., 2017). However, auxetic structures and their superior biological properties have not been extensively investigated by previous studies, and the present review aims to demonstrate the potential and applications of the auxetic structures as bone scaffolds and bone implants.

A large number of bone implants are fabricated with materials such as titanium alloy and stainless steel because of their high strength and biocompatibility. However, the problem is their high mechanical strength which can lead to a mismatch between the host tissues and bone implants, which leads to stress shielding meaning that a considerable amount of the load is not transmitted to the surrounding bone tissue and is tolerated by the bone implants (Al-Tamimi et al., 2017; Sumner, 2015). The stress shielding can induce a reduction in bone resorption, aseptic loosening of the implants, and chronic pain in patients (Garner et al., 2022; Zhang et al., 2020b). Over time, numerous studies have tried to reduce stress shielding in bone implants. One of the main approaches is the fabrication of porous materials rather than bulk ones, but the problem is that increasing the porosity can elevate the risk of fracture in the implant. Therefore, designing the internal architecture can play a crucial role in reducing stress and increasing the longevity of the implant (Wang et al., 2016; Yu et al., 2020a). Because auxetic architectures have high fracture toughness and high energy absorption, they can be an excellent choice for bone implants.

However, such complicated architectures require precise fabrication techniques (Abdelaal and Darwish, 2012). Fortunately, by emerging and developing additive manufacturing (AM), the fabrication of complicated structures has been facilitated (Contessi Negrini et al., 2022; Noroozi et al., 2022a; Noroozi et al., 2022b; Shirzad et al., 2021). Hence, numerous researchers have combined AM techniques with biomedical engineering to fabricate auxetic bone implants such as femoral bone implants and bone screws. It should be mentioned that porous lattice implants are designed to match the stiffness of the implants with the bone, and they should be appropriately programmed to prevent stress shielding (Jafari Chashmi et al., 2020; Kolken et al., 2018; Liverani et al., 2021).

Because of the importance of the topic, several researchers have tried to review the application of metamaterials and auxetic structures for various goals. (Surjadi et al., 2019) studied the mechanical metamaterials and indicated the superior mechanical performance of metamaterials. They also investigated applications of mechanical metamaterials in biomedical, thermal management, photonics, and acoustics. (Wang et al., 2022) reviewed different architectures of metamaterials and their advantages for biomedical applications. The mentioned study investigated various cellular geometries such as auxetic, non-auxetic, triply periodic minimal surfaces (TPMS), and other useful structures for biomedical applications. One of the most comprehensive studies of auxetic metamaterials was conducted by (Wallbanks et al., 2021). They evaluated different types of auxetic unit-cells and their specific applications and discussed manufacturing techniques and testing methods to fabricate and analyze auxetic structures. (Mardling et al., 2020) reviewed applications of auxetic materials in tissue engineering. First, the study introduced human tissues with auxetic behavior and reviewed the effects of auxetic structures on the biological behavior of the scaffolds. Furthermore, they precisely investigated papers that used auxetic materials for neural differentiation, vascular differentiation, and applications of auxetic structures to bone and cartilage tissues.

However, to the best of the author's knowledge, there is no literature to review the applications of auxetic structures in bone medical devices. In this review, for the first time, different auxetic structures such as re-entrant (Choudhry et al., 2022), chiral (Gao et al., 2021a), and rotating rigid structures (Gao et al., 2021b) will be explained and their advantages and weaknesses will be discussed. Also, the applications of the auxetic structures in various engineering topics including bone medical devices will be introduced. Afterward, the potential of using the auxetic structures in bone tissue engineering will be discussed as well. Finally, ideas for future works to utilize auxetics in bone tissue engineering and bone implants are suggested.

2. Types and characteristics of auxetic structures

2.1. Re-entrant structure

The re-entrant structure is the most typical auxetic structure that can be fabricated by the periodic connection of two units with negative angles. Figure 1 shows the common unit cells of the re-entrant structures. As it was mentioned above, the auxetic concept can be described as materials or structures that expand in the transversal direction under a uniaxial tensile load. Similarly, the edges of re-entrant structures undergo bending and pulling and show expansion under tensile loads (Shen et al., 2021b; Wang et al., 2018). Changing the angles and edges in the re-entrant structures can lead to several re-entrant architectures with different properties (Figure 1). However, the re-entrant structures are not limited to the shapes mentioned in Figure 1. Figure 1 shows the most common re-entrant structures that were used by researchers. Their auxetic behavior results from the opening of the polygon, which stretches under tensile loads (Koutsianitis et al., 2019; Logakannan et al., 2022; Shokri Rad et al., 2015).

Many studies tried to optimize the mechanical and physical properties of re-entrant structures. (Li et al., 2018) presented two new re-entrant structures and added sinusoidal struts and extra vertical ribs to the classic re-entrant to improve the energy absorption of the re-entrant structure. The mechanical behavior of a novel re-entrant structure was investigated by (Shen et al., 2021a). They used AM techniques to fabricate re-entrant structures with titanium alloy. They also utilized the finite element method (FEM) to evaluate the compression behavior of that new structure. The results showed that compared to the classical re-entrant, their new design has better energy absorption and mechanical properties. Rather than experimental investigation and FEM, analytical methods can be employed to predict the mechanical properties of the re-entrant structure. (Li et al., 2017) proposed a new augmented re-entrant structure and deployed a classical beam theory to predict the mechanical properties of the augmented re-entrant structure. Furthermore, they compared the results of FEM and analytical methods and found that augmented structures can be more reliable than common three-dimensional (3D) re-entrant structures.

(Wang et al., 2017) established an analytical method for the investigation of the mechanical properties of a 3D re-entrant structure. However, their work was based on the energy method and considered more details that were neglected by others. In that study, an analytical method was employed to predict modulus and Poisson’s ratio, and their approach was validated by comparing their results with a numerical method. The results were also validated by the published experimental results. Another class of analytical study is related to the homogenization method to predict the mechanical properties of metamaterials (Reda et al., 2018). (Alavi et al., 2022) used the Timoshenko beam theory and continualization method to predict the mechanical properties of different Poisson’s ratio structures. They were successful in predicting the mechanical properties of those structures in comparison to the FEM results. The prediction of the effective elastic response of the auxetic structures under large strain was studied by (El Nady et al., 2017). They proposed a non-linear method to calculate the stress-strain relation in the repetitive auxetic structures.

Interestingly, their work is not limited to two-dimensional (2D) structures, that method can also be used in 3D architectures.

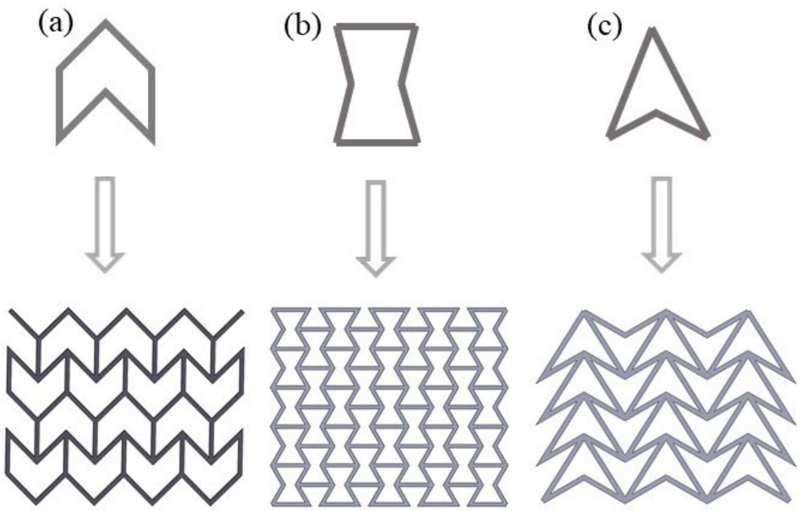


Figure 1. Different unit cells of the re-entrant structures (a) re-entrant zero, (b) re-entrant hexagonal honeycomb, and (c) re-entrant triangle.

2.2. Chiral structure

Another common structure with auxetic behavior is chiral structure. In this structure, a number of struts or ligaments are tangentially attached to a rigid ring, and this structure repeats in other directions. The NPR in this structure is the result of the rotation of the rigid rings. This rotation brings about the deformation and expansion of the attached ligaments. Figure 2 illustrates two unit cells of chiral structure (Mousanezhad et al., 2016; Saxena et al., 2016).

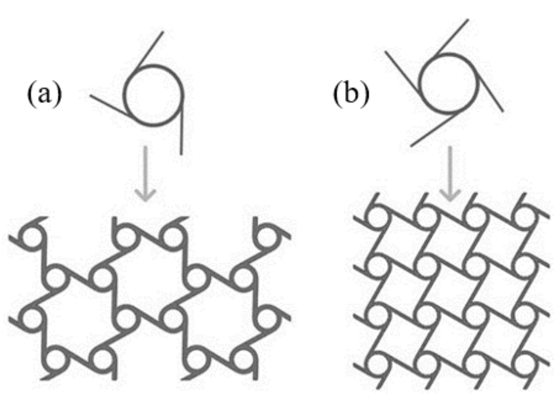


Figure 2. (a) Trichiral and (b) tetrachiral (Sangsefidi et al., 2021).

Chiral unit cells can be classified into three main sub-groups, which are called chiral, anti-chiral, and meta-chiral (Figure 3). It should be noted that, in the chiral architecture, rings are connected to the opposite sides of a ligament; however, in anti-chiral networks, rings are connected to the same side of a ligament (Tabacu et al., 2020). The meta-chiral structure is a combination of chiral and anti-chiral networks. Figure 3 appropriately illustrates the meta-chiral ligaments and rings (Kelkar et al., 2020). The idea of meta-chiral was introduced by (Grima et al., 2008b), and they used chiral and anti-chiral simultaneously.

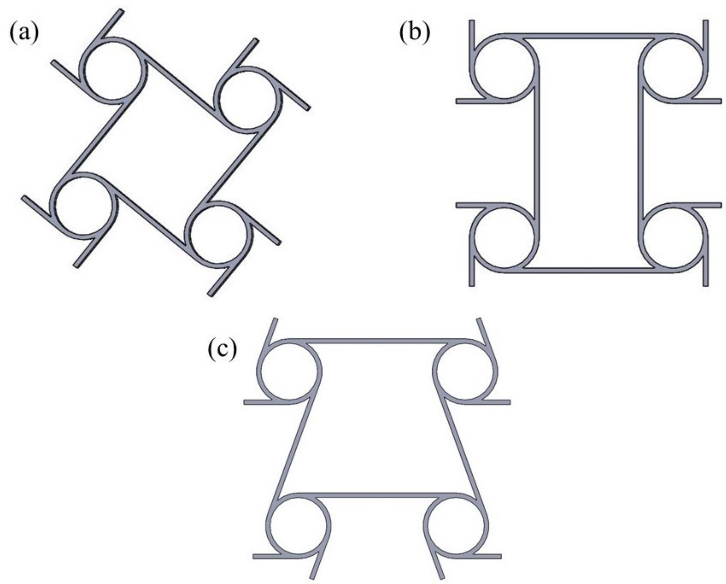


Figure 3. (a) Chiral, (b) anti-chiral, and (c) meta-chiral structures.

According to the different types of chiral structures, researchers have mentioned various applications for chiral networks and optimized their mechanical and physical properties. (Zhang et al., 2022a) proposed and studied a novel structure and investigated it experimentally and numerically. The main goal of that study was to improve the mechanical properties of the chiral structure. The results showed that adding circular holes could improve the energy absorption capacity and auxeticity of the chiral structure. One of the most important characteristics of auxetic structures is their compressive strength and their behavior under compressive loads. (Scarpa et al., 2007) investigated the elastic buckling pattern of a chiral structure under compressive load and utilized a combination of experimental, numerical, and analytical methods. Their suggested procedure can be an appropriate choice for the investigation of the buckling pattern of the chiral structures. According to the studies mentioned above, various auxetic structures require AM techniques to fabricate these structures, but the printing parameters can influence the mechanical properties of the auxetic architectures. The effects of printing parameters on the mechanical properties of an anti-chiral design were studied by (Teraiya et al., 2022). These printing parameters include printing speed, printing temperature, and layer height. They illustrated the fact that rather than designing auxetic structures, the fabrication parameters can change the mechanical properties.

2.3. Gradient and hybrid auxetic structures

A functionally graded structure changes the unit cell size, shape, or porosity over a prescribed volume. The gradient topology (Figure 4) can result in variation and distribution of different properties to elevate energy absorption and stiffness in auxetic structures or mimic an available structure in nature like a bone gradient pattern (Di Luca et al., 2015; Jelen et al., 2013). It should be considered that pore size can enhance or decrease cell numbers in scaffolds. Finding optimum size for each type of cell can be an intellectual strategy to improve cell adhesion and proliferation. For instance, suitable pore size for bone marrow mesenchymal stem cells is 200 µm, and this size is different for tendon cells (300 µm) (Han et al., 2021). Additionally, gradient pore sizes can provide a better environment for cells because of the easier transfer of oxygen and nutrients in lager pore size. However, larger pore sizes can increase the degradation of scaffolds; therefore, this negative effect can be supported by gradient architecture. Overall, layers with large pore sizes promote cell diffusion, whereas layers small pore sizes can provide appropriate mechanical properties (Abbasi et al., 2020). Sometimes these goals can be obtainable by combining auxetic design with some other unit cells including TPMS or honeycomb (Boldrin et al., 2016; Hou et al., 2013). All these studies tried to improve the efficiency of the auxetic pattern and make it suitable for their goals. A comparison between different auxetic structures is available in Table 1.

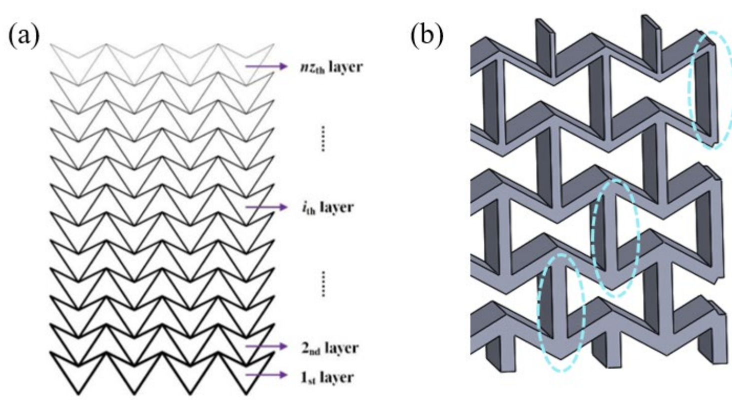


Figure 4. Gradient auxetic structures. (a) Re-entrant gradient triangle (Gao and Liao, 2021) and (b) re-entrant gradient hexagonal honeycomb structures.

(Hou et al., 2013) studied different gradient auxetic structures under flexural and bending loads and validated their experimental results with nonlinear finite element models. Furthermore, they mentioned that gradient patterns can improve the load-bearing behavior of the auxetic structure under bending load, and the damage morphology was investigated by imaging technique (Figure 5). Unit cells' parameters like length and angle can make gradient structures, but they will change the mechanical properties of auxetic materials. It should be noted that different materials do not show the same behavior, which means that results can be significantly different with the same condition in gradient auxetic structures fabricated by different materials. (Vyavahare et al., 2021) extensively studied this phenomenon in their experimental work. The reason behind this phenomenon is related to the distinct behavior of the inherent ductile and brittle nature of materials. Differences between gradient auxetic polylactic acid (PLA) and acrylonitrile butadiene styrene (ABS) were studied by (Vyavahare et al., 2021). ABS is more ductile than PLA, since, under the compression load, vertical struts of auxetic unit cells will buckle gradually (Figure 4 b). However, such buckling behavior is not observed in PLA. Therefore, a gradient structure with decreasing diameters of struts will intensify the effects of base material properties on the mechanical properties of the auxetic lattice structure.

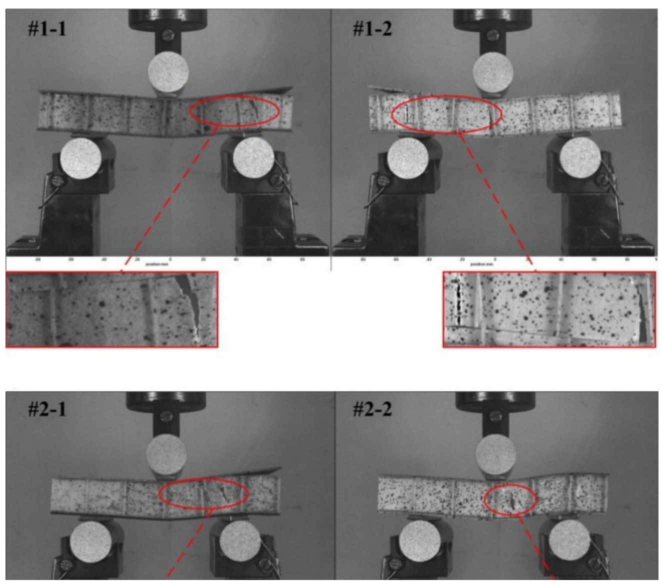


Figure 5. Using imaging techniques to detect damage morphology of gradient structure (Hou et al., 2013).

Improving mechanical properties and controlling auxeticity are the main goals of many studies on the auxetic material and structure topic. Hybrid materials and combining two or more structures can help researchers attain these goals. (Meena and Singamneni, 2021) combine different auxetic architectures to elevate the mechanical properties of auxetic structures and increase the auxeticity simultaneously. (Zhang et al., 2021) designed some innovative hybrid auxetic structures (Figure 6) and investigated their mechanical properties with different geometric parameters. Additionally, they fabricated these structures with cylindrical shapes and found the optimized internal architecture with FEM. Their cylindrical structures have the potential to be used in biomechanics, flexible electronics, and aerospace engineering.

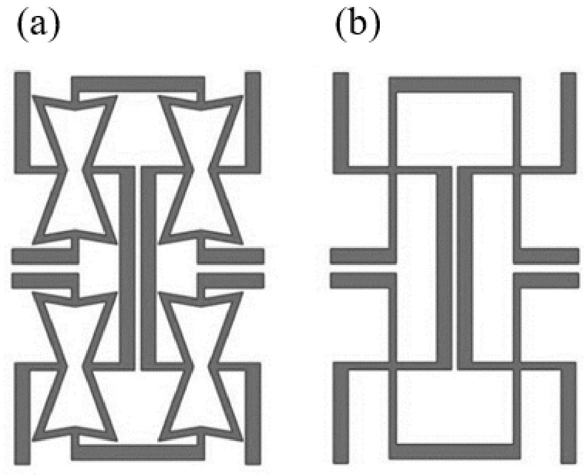


Figure 6. Innovative structures of hybrid auxetic design (a) star missing rib and (b) cross missing rib (Zhang et al., 2021).

2.4. Rotating rigid structures

Another group of auxetic shapes is rotating rigid, which is different from the previously mentioned groups. This is because a rigid rotating structure's auxetic behavior is the result of changing angles between rigid sections and their hinges. The rotation around the hinges generates expansion in axial and transversal directions to make an auxetic structure (Figure 7). The geometry of the rigid part makes a difference between the rotating rigid structures, but their deformation behavior can be altered by modification of the hinges (Dudek et al., 2017) (Figure 8).

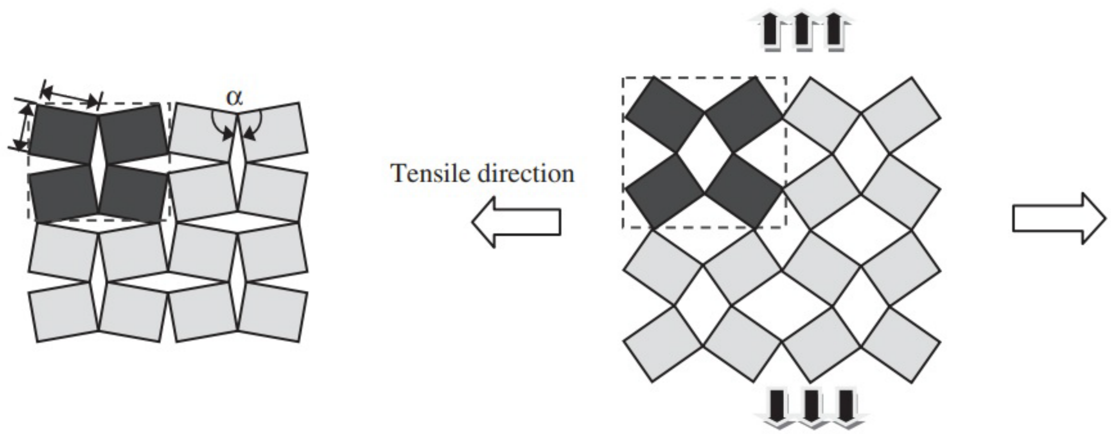


Figure 7. Auxetic behavior of rotating structure (Hu et al., 2011).

(Gao et al., 2021b) provided a strategy to design different 3D auxetic rotating structures, and they could design them with various mechanical and physical properties. Making small changes in the rigid part can affect the final results. In a study performed by (Sorrentino et al., 2021), they modified the rigid rotating structure by adding some arc fillets at the hinges and improving the global elastic strain in the rigid rotation pattern. (Dudek et al., 2017) investigated the deformation of hierarchical rotating rigid structures. Their results confirmed that hinges play a crucial role in the deformation behavior of the rotating patterns; therefore, to program this architecture, focusing on hinges is more important than the geometry of the solid area.

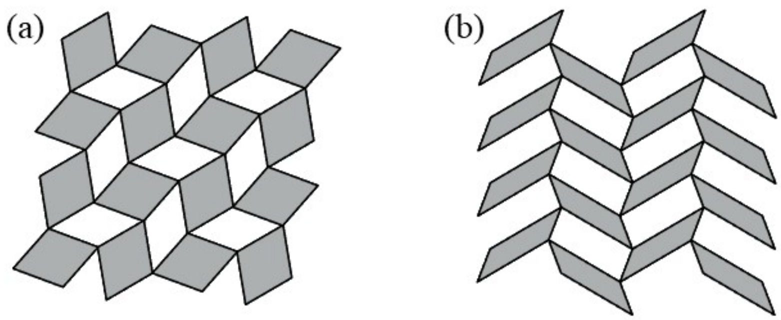
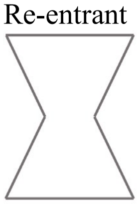
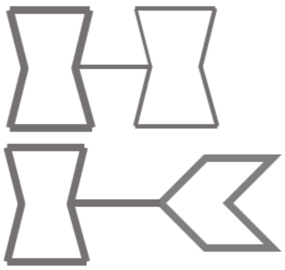
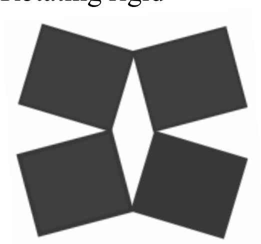


Figure 8. Different types of rotating rigid structures (a) rhombi, (b) parallelograms (Grima et al., 2008a).

Table 1. Different auxetic unit cells and their advantages and disadvantages.

Unit cell	Advantages	Disadvantages	References
Re-entrant 	Energy absorption. Fracture toughness. Variable permeability.	Contraction of cross-section under compression loads. Low rigidity	(Baran and Öztürk, 2020; Bodaghi et al., 2020; Rad et al., 2014; Winczewski and Rybicki, 2022; Yu et al., 2020b)
Chiral 	Vibration and sound attenuation. Energy absorption. Negative thermal expansion	Requiring advanced manufacturing techniques. Contraction under compression loads	(Baravelli and Ruzzene, 2013; Wei et al., 2018; Wu et al., 2019)
Gradient and hybrid auxetic	Mimic available structure. Improve the mechanical properties.	Difficulties in design and fabrication.	(Boldrin et al., 2016; Hedayati et

			al., 2018; Jiang and Li, 2018)
Rotating rigid 	Easy to tune mechanical properties. Showing auxetic behavior in various directions	Dependency of Poisson’s ratio on the hinges and rigidity of solid part. Anisotropic behavior	(Attard and Grima, 2012; Duncan et al., 2018; Grima et al., 2011)

3. Applications and potential of auxetic structures in bone tissue engineering

Tissue engineering (TE) is a multidisciplinary topic deploying the concepts of life sciences and engineering to restore damaged tissues. Among different tissues in the human body, bone has attracted the most attention because of its high potential for regeneration. Advances in bone tissue engineering have occurred by utilizing scaffolds. Bone scaffolds are porous media that are typically made of porous degradable materials like polymers (Bose et al., 2012; Pina et al., 2015; Shirzad et al., 2020b). However, an ideal bone scaffold should have some characteristics to work properly in the body. The most important characteristics of bone scaffolds include biocompatibility (Przekora, 2019), suitable mechanical properties (Shi et al., 2022), appropriate pore size and shape (Liang et al., 2022; Liu et al., 2021), bioactivity (Juan et al., 2021), and bioresorbability (Abdal-hay et al., 2020). Among these parameters, the shape of the unit cells can play a crucial role in bone tissue engineering because it can affect the mechanical, physical, and biological properties of the scaffolds (Deng et al., 2021; Montazerian et al., 2017; Torres-Sanchez et al., 2017). Auxetic structures and NPR materials with high energy absorption can be a good choice for bone tissue engineering due to the positive effect of NPR structures on cell proliferation. Specifically, it has been demonstrated that NPR structures can better work as the extracellular matrix (ECM) for cell proliferation and isotropically deliver the load to cells to stimulate cell proliferation (Tang et al., 2021). In the following sections, the application and potential of using these types of materials and structures in bone tissue engineering will be discussed.

3.1. Effects of auxetic materials and structures on bone cells proliferation and differentiation

Numerous researchers have investigated different variables that can affect the biological properties of scaffolds, and one of those characteristics is pore shape (Van Bael et al., 2012). Pore shape can also change mechanical properties such as Poisson's ratio. (Choi et al., 2016) fabricated auxetic scaffolds from poly (D, L-lactic-co-glycolic acid) (PLGA) to evaluate the cell proliferation behavior of auxetic scaffolds under mechanical stimulation. They also used PLGA to make conventional and auxetic scaffolds so they could compare how auxetic behavior affected the cell bone growth. The Poisson's ratio was decreased from 0.13 to -0.07, and MG-63 osteoblast-like cells were used for cell attachment and proliferation tests. It should be clarified that most auxetic structures can reach a Poisson's ratio of -1 or less, but in bone tissue engineering, the Poisson's ratio should be almost equal to -0.07 to mimic real bone structure (Saxena et al., 2016; Williams and Lewis, 1982). Their results showed that MG-63 osteoblast-like cells could be entirely attached after 24 h on the scaffolds. Additionally, from 24 to 72 h, negative Poisson's ratio could improve cell proliferation in the scaffolds, and they mentioned that mechanical stimulation for bone cell cultivation through auxetic scaffolds can be useful.

Cells interact with their surrounding structures and their interaction with other cells and exteracellular matrix (ECM) can affect cell adhesion and improve it (Özkale et al., 2021). Osteoblast-like cell behavior of the PLGA scaffolds under static and dynamic loads was investigated by (Kim et al., 2017). In their study, the auxeticity was measured by Poisson's ratio, and it was approximately -0.07. They divided their samples into three main groups: control, static stimulation, and dynamic compression. The cell proliferation in the second and third auxetic groups was 13.4% and 25.5% more than in the control group. They concluded that auxetic structures can isotropically deliver compressive loads to scaffolds and improve cell proliferation. Additionally, cycle time in dynamic compression affects cell proliferation. However, after five days of cultivation, effects of cyclic loads were decreased (Figure 9) because cell proliferation diminish the transference of the compressive loads. The potential for vascularization of auxetic structures was investigated by (Song et al., 2018). They seeded bone morphogenetic protein 4 on regular and auxetic scaffolds to evaluate vascular differentiation in both. It is worth mentioning that polyurethane foams were considered to fabricate auxetic scaffolds. Their results showed that more cytoplasmic retention is available in the auxetic scaffolds compared with regular scaffolds. Cytoplasm is a medium that can provide a medium for cell growth, expansion, and replication. Furthermore, MMP enzymes were observed in the auxetic scaffolds that are responsible for cells proliferation, migration and differentiation. Further research needs to be conducted to found the exact relation between auxeticity and cells response.

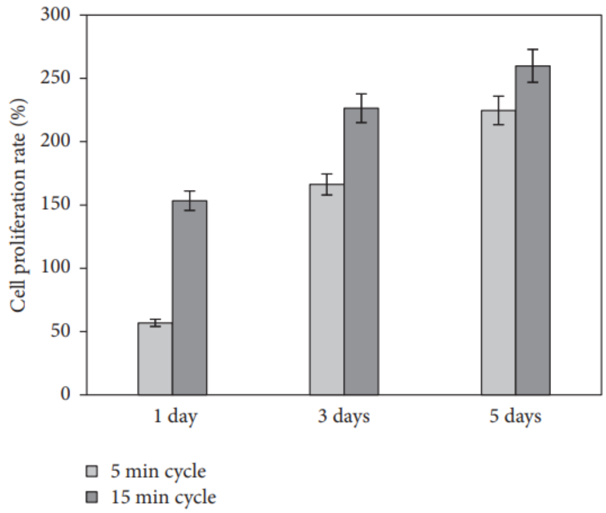


Figure 9. effects of cyclic loads in 1 day, 3day, and 5 days (Kim et al., 2017).

The human mesenchymal stem cell is an important source of regeneration, and it can differentiate into phenotypes like bone and cartilage. (Soman et al., 2012a) studied the polymeric material with zero Poisson's ratio (ZPR) as a scaffold and evaluated its biological properties. Their results showed that Poisson's ratio, specifically ZPR can be an appropriate choice for bone or cartilage tissue engineering; however, the difference between the ZPR and NPR materials was investigated in other studies. (Tang et al., 2021) used stereolithography to tune scaffolds' Poisson's ratio and simulate the mechanical behavior of natural tissue. Moreover, they used mouse bone marrow mesenchymal stem cells to study the biological behavior of the scaffolds. They fabricated positive Poisson's ratio (PPR), ZPR, and NPR scaffolds (Figure 10) and found that NPR scaffolds could provide a better growth environment compared to ZPR and PPR scaffolds with higher value of elastic modulus. Hence, stem cells could proliferate and differentiate more notably in NPR or auxetic scaffolds (Figure 10). Furthermore, (Lee Jr et al., 2022) developed an auxetic structure to find the effect of cyclic tensile force on bone regeneration of an auxetic scaffold. They utilized calcium silicate and gelatin methacrylate to fabricate scaffolds with the 3D printing method. They showed that auxetic scaffolds under cyclic tensile load could provoke bone regeneration. This section wants to show that the auxetic structure can be a good choice for bone cell proliferation and differentiation. However, using auxetic structure is not limited to improving the biological behavior of scaffolds or mimicking negative Poisson's ratio of the cancellous bone. The auxetic structures can enhance the mechanical properties of the scaffolds. The following section will discuss the superior load bearing behavior of the auxetic scaffolds. A summary of this section is provided in Table 2.

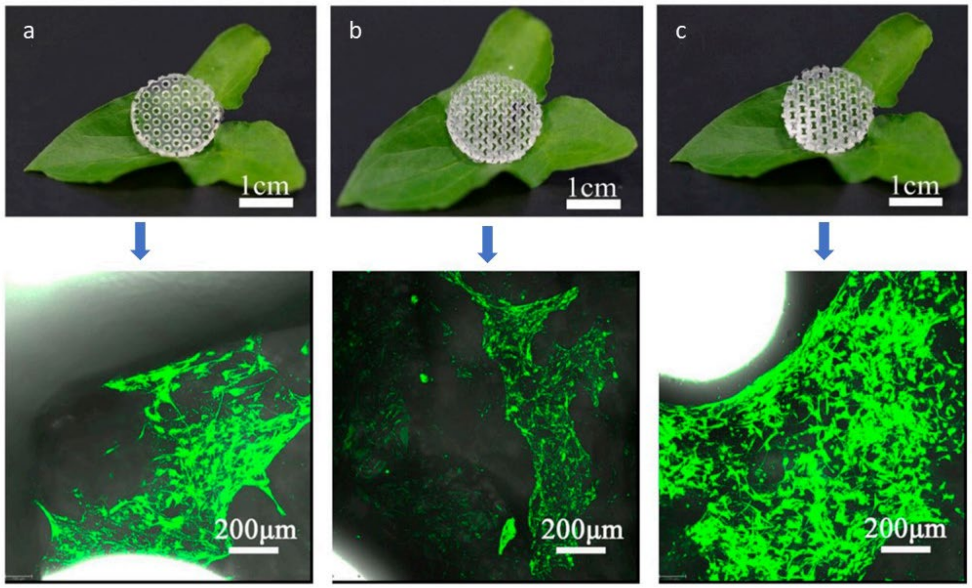


Figure 10. Different Poisson's ratio scaffolds and cell proliferation behavior: (a) PPR, (b) ZPR, and (C) NPR; fabricated scaffolds: (d) PPR, (e) ZPR, and (f) NPR (Tang et al., 2021).

Table 2. Summary of studies dealing with the effect of auxetic materials and structures on bone cell proliferation.

Study	Research objective	Research results
(Choi et al., 2016)	Effect of auxeticity on bone cells proliferation	Improving cells proliferation with auxetic structure
(Kim et al., 2017)	Effects of auxeticity on the osteoblast-like cells	Auxetic materials can isotropically deliver loads to the cells and improve proliferation
(Song et al., 2018)	Seeding bone morphogenetic protein on auxetic scaffolds	More cytoplasmic retention in auxetic scaffolds
(Soman et al., 2012a)	Study the biological properties of zero Poisson's ratio scaffolds	Zero Poisson's ratio structure is a good choice for bone and cartilage
(Tang et al., 2021)	Comparing biological properties of PPR, ZPR, and NPR scaffolds	NPR scaffolds are superior to ZPR and PPR
(Lee Jr et al., 2022)	Effect of cyclic tensile force on bone regeneration of auxetic scaffolds	Cyclic load can stimulate bone regeneration in auxetic scaffold

3.2. Effects of auxetic material and structure on the mechanical properties of the scaffolds

Applications of the auxetic scaffolds are not limited to the improvement of the biological behavior of the scaffolds. It can also affect the mechanical properties of the scaffolds and mimic the characteristics of the host tissue. (Ghazlan et al., 2020) were inspired by bone structure and combined auxetic and non-auxetic structures to fabricate a novel architectural scaffold (Figure 11). They mentioned that trabecular bone is a lightweight organ that possesses high energy absorption, therefore bone scaffolds should have similar properties. They introduced a hybrid re-entrant structure as a promising geometry for its high energy absorption. They also utilized the 3D printing technique and FEM to develop and investigate their novel architecture. Their results showed that using auxetic geometry can lead to superior energy absorption as a bone scaffold. However, in comparison to the normal re-entrant structure, the hybrid re-entrant structure has lower stiffness. It may be the result of PPR part in the scaffolds that can affect the whole structure.

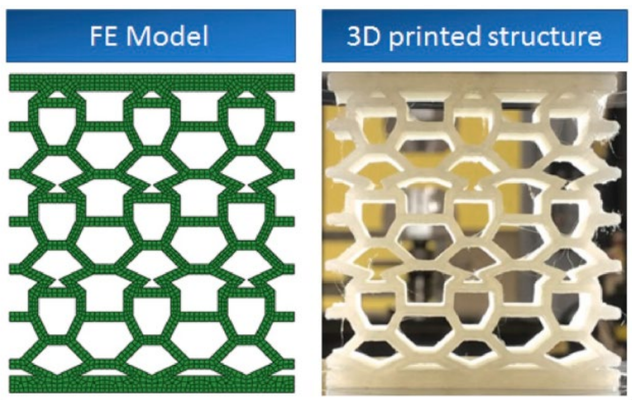


Figure 11. 3D printed and FE model of the combination of auxetic and non-auxetic structures (Ghazlan et al., 2020).

Unfortunately, the unique mechanical properties of auxetic structures have not extensively attracted attention in the field of biomedical engineering. The following part focuses on the potential of using auxetic structures as bone scaffolds. However, appropriate mechanical properties require suitable design and fabrication of scaffolds. (Jin et al., 2021) proposed a new method for the design and fabrication of auxetic scaffolds with tunable Poisson's ratio. They started by designing thick and thin fibers and used different patterns to tune the Poisson's ratio. It is worth mentioning that the Poisson's ratio was tuned by the intended deformation mechanism, and melt electro writing (MEW) was utilized to fabricate various geometries. The whole process was illustrated in Figure 12. The re-entrant angle was increased 10° rom 140° to 110° to find the optimum point for the mechanical properties of the scaffolds. The result showed that increasing re-entrant angle adversely influence the mechanical properties of the scaffolds.

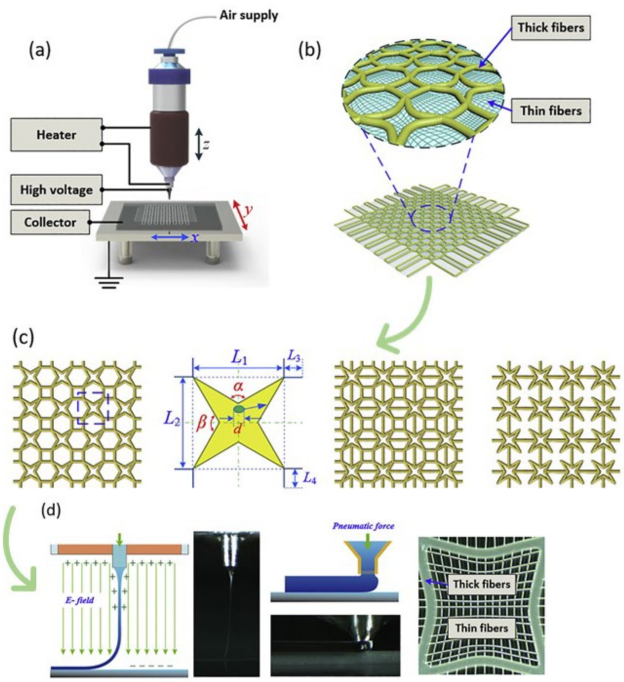


Figure 12. Design and fabrication of auxetic scaffold (a) MEW (b) incorporating thick and thin fibers (c) unit cells geometry (d) process of fabrication (Jin et al., 2021).

Numerous studies have tried to increase the porosity of the scaffolds and reach the porosity of a real bone. However, this improvement in the porosity can influence the mechanical properties of the scaffolds and reduce the fatigue strength (Baptista and Guedes, 2021; Kelly et al., 2019). Therefore, appropriate pore shape can play a crucial role to improve fatigue strength. Accordingly, (Kolken et al., 2022; Kolken et al., 2021) presented a 3D auxetic structure for bone implants and fabricated it with titanium and additive manufacturing. They investigated various relative densities, re-entrant angles, and ratio of re-entrant struts and found that auxetic structures were superior to non-auxetic 3D fabricated biomaterials. Furthermore, to design an appropriate auxetic metamaterials all of the mentioned variables should be considered. Therefore, implementing an auxetic structure with optimized values of relative densities, re-entrant angles, and ratio of re-entrant struts can be a good approach to elevate fatigue strength.

In the study performed by (Maciejewska and Jopek, 2020), the potential of using an auxetic structure was investigated to deploy as a skull implant. The auxetic structure could easily adjust to changes in the human body. Furthermore, it could transmit high values of stress and strain to the center of the implant and decrease the influence of local force on the implant. It is worth noting that bone has a hierarchical structure and the bone scaffold should be matched with this structure. Fabrication of hierarchical structure should positively affect mechanical properties and improve the load bearing behavior of scaffolds (Reznikov et al., 2014). (Zhan et al., 2022) proposed a 3D gradient re-entrant structure and fabricated it through the 3D bioprinting method. Their new architecture improved stiffness, initial-buckling strength, structural stability, and energy absorption. This finding and its hierarchical geometry can be used in bone tissue engineering to improve the mechanical properties and mimic host tissue.

Most of the structures that were used in this section have two dimensions (2D). However, 2D scaffolds cannot mimic the native ECM, and they should be fabricated in 3D architecture. 3D scaffolds can also better support cell proliferation. Therefore, using 3D auxetic structure should be implemented in future studies. Sections 3.1 and 3.2 illustrated that the biological and mechanical requirements of the scaffolds can be satisfied by the auxetic structures. Additionally, this structure has the potential to be more useful than conventional structure to mimic the internal structure of a real bone.

4. Applications of auxetic structures in bone implants

Nowadays, the development of bone implants plays a crucial role in people's lives because the need for implants has been increasingly accelerated in recent years (Ibrahim et al., 2017). This requirement leads to the fabrication of more durable implants and the optimization of their mechanical properties (Kelly et al., 2021; Pei et al., 2017). Auxetic metamaterials have inherent characteristics that can be an excellent choice for bone implants. They are not only appropriate for tolerating tensile loads (their NPR characteristic), but they also have the potential to show a high level of shear resistance, energy dissipation, and indentation resistance. Accordingly, in the following sections, the applications and benefits of auxetic structures in bone implants will be discussed (Hou et al., 2018; Kolken et al., 2022; Kolken and Zadpoor, 2017).

One of the most popular implants that are used in the human body is the hip implant. The prevention of failure of this implant has attracted the attention of many researchers. Designing unit cells is a prevailing strategy to improve the mechanical properties of bone implants (Buford and Goswami, 2004). (Kolken et al., 2018) designed different conventional and auxetic bone implants (Figure 13) as follows: three conventional, three auxetic, and six hybrid meta-biomaterial femur implants (combination of NPR and PPR unit cells). To study the performance of the implants, a test setup that could simulate implant-bone contact was designed. They tested all their samples under biomechanical loading and reported that hybrid implants can improve implant-bone contact and implant longevity. Additionally, various hybrid designs were used to find a good hybrid architecture.

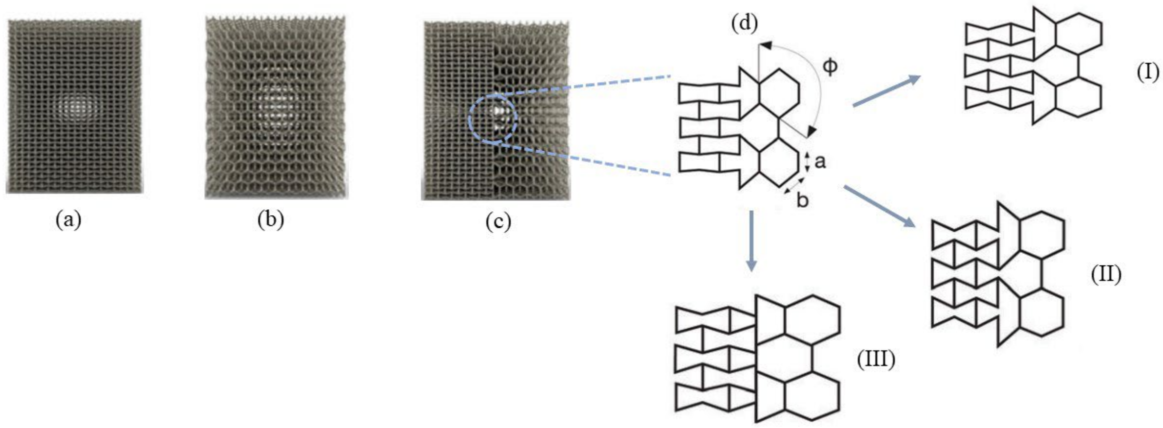


Figure 13. Different (a) conventional, (b) auxetic, and (c) hybrid femoral implants. (d), (d-I), (d-II), and (d-III) Different re-entrant angles and size of the struts (Kolken et al., 2018).

Micromotions and stress shielding are two of the most important problems in bone scaffolds, and tuning them can be challenging. (Ghavidelnia et al., 2020) tried to decrease the mismatch between the femoral hip implant and the surrounded bone by an analytical method. In their study, they considered elastic modulus and wide range of Poisson's ratio ($-2.414 \leq \upsilon \leq -0.8393$) as two important variables and indicated that using re-entrant structure could be a helpful strategy to solve stress shielding and micromotion. The mitigation of stress shielding of the auxetic structures is approved by another work carried out by (Vijayavenkataraman et al., 2020).

As was mentioned above, the internal structure can play a crucial role in the mechanical properties of implants. Auxetic structures, like conventional structures, can show a wide range of mechanical properties. The effects of different auxetic structures and relative density were studied in (Abdelaal and Darwish, 2012)'s research. They fabricated and evaluated different simple and gradient auxetic structures for biomedical applications. Additionally, they illustrated the fact that auxetic structures can be reliable for several biomedical applications such as bone implants. Improvement in the mechanical properties of auxetic structures was confirmed by other studies (Kolken et al., 2022; Sahariah et al., 2022). However, the application of auxetic structures is not limited to the improvement of the mechanical properties of bone implants (Namvar et al., 2022). A recently published paper by (Garner et al., 2022) showed that using the optimized version of hybrid auxetic femoral implants can simultaneously minimize the risk of fracture and improve bone remodeling. Figure 14 shows the hybrid design of this study.

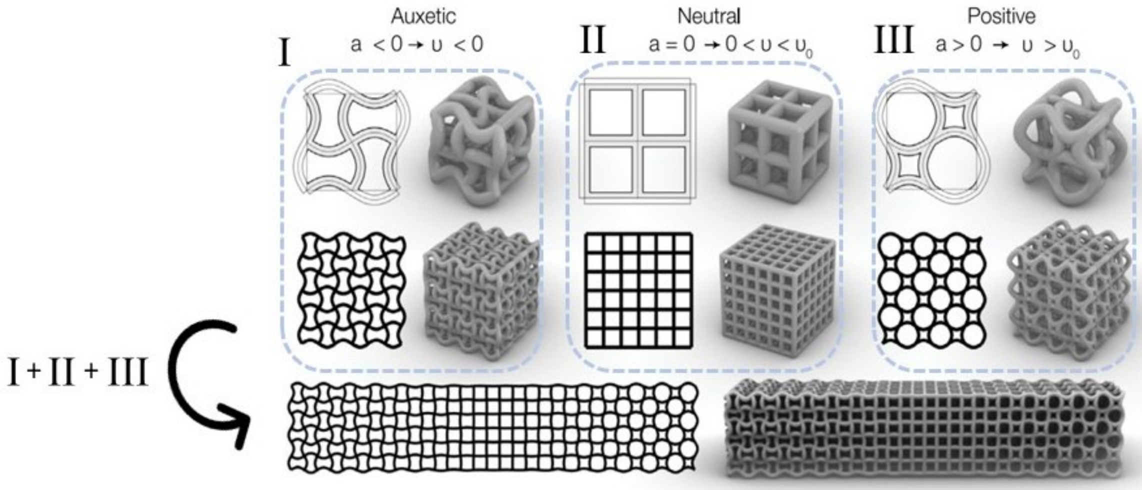


Figure 14. Hybrid design of bone scaffold (Garner et al., 2022).

The application of auxetic structures is not restricted to femoral implants and general bone implants. Auxetic structures have been utilized for different applications, such as bone screws and intervertebral disk implants. Bone screws, also known as pedicle screws, are widely used for providing stability to a spinal segment or fracture fixation. In this regard, designing an appropriate screw can play a crucial role in preventing the failure of these screws (Liu et al., 2019; Stahel et al., 2017). Screw loosening is a common mistake of the bone screws and finding a solution for this problem can be challenging. (Yao et al., 2021) introduced re-entrant auxetic structures for the bone screw and fabricated them with titanium (Figure 15). They also considered biomedical interactions between the bone and the screws and simulated the bone loosening with FEM. They demonstrated that an auxetic structure is a viable option for bone screw fabrication, and an optimal re-entrant angle can improve bone screw fixation because of the expansion under the tensile loads. Several auxetic structures were investigated in another work by (Yao et al., 2020). They studied re-entrant, chiral, and rotating structures as well as auxetic geometries and non-auxetic honeycomb structures (Figure 16). They proved different auxetic structures can help screw fixation, but the re-entrant and chiral structures had higher stiffness and strength.

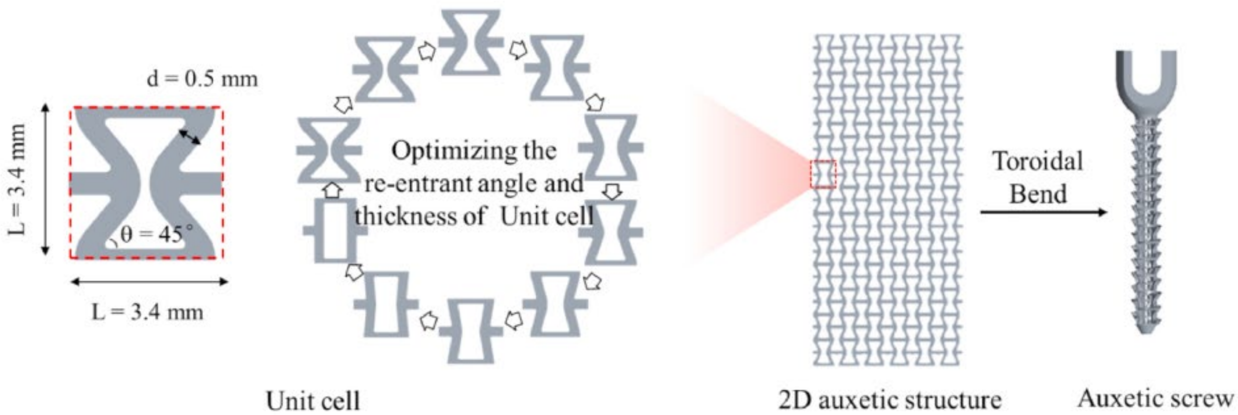


Figure 15. Re-entrant bone screw with different re-entrant angles (Yao et al., 2021).

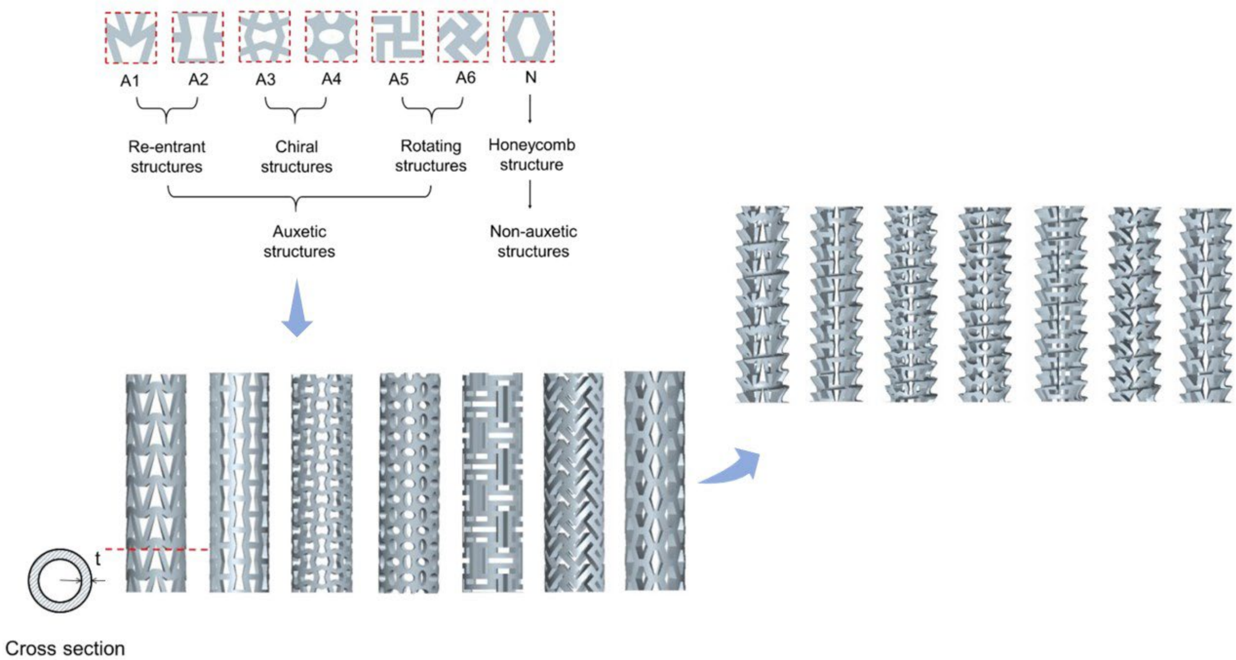


Figure 16. Process of designing unit cells to fabricate bone screws (Yao et al., 2020).

The energy harvesting, stability, and load distribution of auxetic metamaterials intervertebral disc implants were investigated by (Barri et al., 2022; Jiang et al., 2023) in separate studies. These new implants could better transfer the stress, and they had the potential to alleviate the symptoms of lumbar disc herniation. A summary of auxetic bone implant studies is summarized in Table 3.

Table 3. Summary of studies dealing with applications of auxetic structures in bone implants.

Study	Research objective	Research results
(Kolken et al., 2018)	Comparing conventional, auxetic, and hybrid bone implants	Using hybrid NPR and PPR bone implant improves implant-bone contact
(Ghavidelnia et al., 2020)	Decrease mismatch between the femoral hip implant and surrounded bone	Using re-entrant structure can solve stress shielding and micromotion problems
(Vijayavenkataraman et al., 2020)	Mitigating stress shielding with the auxetic structure of the bone implant	Auxetic structures can reduce stress shielding in bone implant
(Abdelaal and Darwish, 2012)	Evaluating mechanical properties of different bone implants	Approve the reliability of auxetic structures for different biomedical applications
(Garner et al., 2022)	Multi-objective designing of hybrid auxetic structures for bone implant	Simultaneously minimize the risk of fracture of implant and improve bone remodeling
(Yao et al., 2020; Yao et al., 2021)	Application of different auxetic structures for bone screw	Auxetic structures can improve bone screw fixation and show higher mechanical properties
(Barri et al., 2022; Jiang et al., 2023)	Using auxetic structure for intervertebral disk implant	Accurately transfers stress and possesses the potential to alleviate the symptoms of lumbar disk herniation

5. Future outlook for auxetics in bone tissue engineering and bone implants

The recent advancement and application of auxetic materials and structures in bone tissue engineering and bone implants are investigated in the present paper. However, more investigations and combinations of auxetics with other novel methods will improve the understanding of the effects of using auxetic microenvironments in the mentioned topics (Li et al., 2021; Mueller et al., 2022; Xin et al., 2020). Four-dimensional (4D) printing and the development of programmable materials have added one extra dimension to the 3D printed structures, which this dimension is time (Figure 17). 4D printed geometries, in response to environmental stimuli, can transform their morphologies or alter their functions during the time (Chen et al., 2022; Hamzehei et al.; Sahafnejad-Mohammadi et al., 2022; Zhao et al., 2019). One of the most important problems in bone tissue engineering and bone implants is the implantation of scaffolds in defects with an irregular shape. 4D printing is a suitable strategy to reshape the scaffolds and implants after implantation (Wang et al., 2020a). Furthermore, 4D printing of a scaffold with a shape memory polymer layer can promote bone cell formation (You et al., 2021). Additionally, the bone's hierarchical structure can be mimicked with 4D printing of scaffolds with actuators (Cao et al., 2022). However, increasing and decreasing the length of the scaffolds requires a structure to tolerate both tensile and compression loads. Auxetic structures with an NPR can be an appropriate choice for 4D printing because of their interesting mechanical properties under different types of loads.

As it was explained above, combining the concept of 4D printing and bone tissue engineering has been implemented by researchers. However, 4D printing of auxetic structures for bone implants and bone tissue engineering has not been touched yet. A combination of auxetic structures with 4D printing can result in self-fitting implants with appropriate mechanical and biological properties.

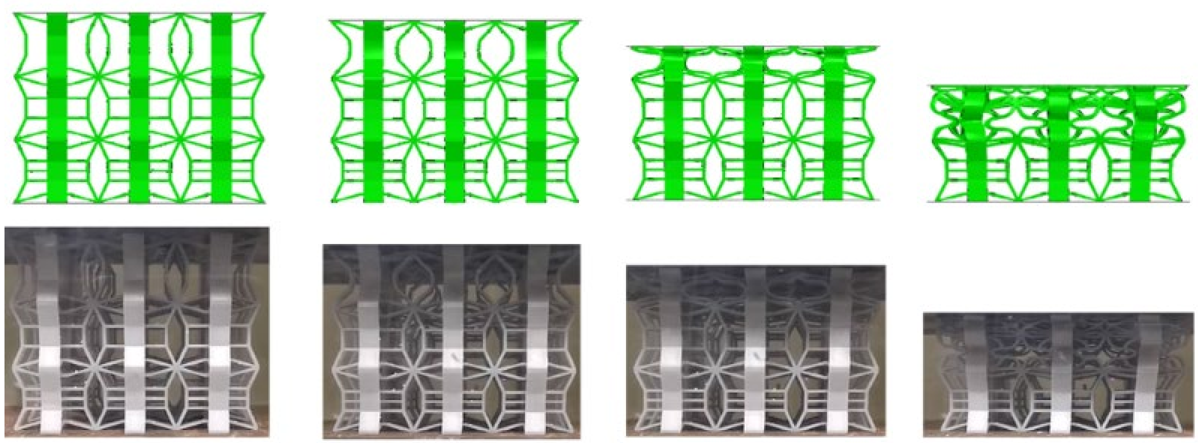


Figure 17. An auxetic 4D printed structure and its load bearing behavior (Hamzehei et al.).

To mimic the structure of the real human bone, gradient geometry is an option to fabricate scaffolds. Many researchers investigated different architectures with gradient geometry to make them suitable for use in bone tissue engineering (Bittner et al., 2019; Shirzad et al., 2020a). Both of biological and mechanical properties of the bone scaffolds can be affected by the gradient structure. Gradient architecture can enhance cell proliferation and migration (Abbasi et al., 2019). Furthermore, cancellous bone has an NPR behavior, and mimicking this characteristic requires an appropriate design (Williams and Lewis, 1982). Accordingly, a suitable bone scaffold or implant should satisfy both requirements of gradient and auxetic structures. Gradient auxetic or hybrid auxetic gradient structures can be an alternative to overcome limitations in bone tissue engineering. Some related topics were investigated by the present study, but it needs more research to mimic a natural bone architecture.

6. Conclusion

Auxetic structures display specific behavior under tensile and compression loads that have motivated researchers to use them for different topics. These fields of study can be medical, aerospace, or designing load-bearing structures. However, using auxetic geometries has yet to be thoroughly investigated in bone tissue engineering and bone implant fabrication. While auxetic structures have the inherent capacity to be an appropriate choice for biomedical engineering, they merely pay attention to these structures. In this review, various auxetic structures have been investigated, and their applications and potential in bone tissue engineering and bone implants have been discussed. It is found that auxetic structures can not only improve the biological behavior of bone scaffolds and bone implants but also enhance their mechanical properties. Furthermore, the present study suggested the potential of auxetic structures for future work to utilize them in 4D printing, bioprinting, and bone tissue engineering.

Acknowledgment

This work was supported by a Research Grant of Pukyong National University (2021)

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