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Review article

The role of stiffness-matching in avoiding stress shielding-induced bone loss and stress concentration-induced skeletal reconstruction device failure

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abstract

It is well documented that overly stiff skeletal replacement and fixation devices may fail and require revi- sion surgery. Recent attempts to better support healing and sustain healed bone have looked at stiffness- matching of these devices to the desired role of limiting the stress on fractured or engrafted bone to compressive loads and, after the reconstructed bone has healed, to ensure that reconstructive medical devices (implants) interrupt the normal loading pattern as little as possible. The mechanical performance of these devices can be optimized by adjusting their location, integration/fastening, material(s), geometry (external and internal), and surface properties. This review highlights recent research that focuses on the optimal design of skeletal reconstruction devices to perform during and after healing as the mechani- cal regime changes. Previous studies have considered auxetic materials, homogeneous or gradient (i.e., adaptive) porosity, surface modification to enhance device/bone integration, and choosing the device's at- tachment location to ensure good osseointegration and resilient load transduction. By combining some or all of these factors, device designers work hard to avoid problems brought about by unsustainable stress shielding or stress concentrations as a means of creating sustainable stress-strain relationships that best repair and sustain a surgically reconstructed skeletal site.

Statement of significance

Although standard-of-care skeletal reconstruction devices will usually allow normal healing and improved comfort for the patient during normal activities, there may be significant disadvantages during long-term use. Stress shielding and stress concentration are amongst the most common causes of failure of a metal- lic device. This review highlights recent developments in devices for skeletal reconstruction that match the stiffness, while not interrupting the normal loading pattern of a healthy bone, and help to combat stress shielding and stress concentration. This review summarises various approaches to achieve stiffness- matching: application of materials with modulus close to that of the bone; adaptation of geometry with pre-defined mechanical properties; and/or surface modification that ensures good integration and proper load transfer to the bone.

1. Introduction

Metallic skeletal hardware is used for primarily two types of skeletal reconstructive surgery applications, bone fixation or bone replacement. Orthopaedic and craniofacial skeletal fixation or re- placement surgeries are amongst the most frequently performed, and their rate of increase is amongst the highest of all surgical procedures. In 2017 approximately 22.3 million reconstructive or- thopaedic surgeries were performed worldwide [1]. The global or- thopaedic device market

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size was valued at USD $40.9 billion in 2021 and is expected to expand at a compound annual growth rate (CAGR) of 3.1 % from 2022 to 2030 [2]. Biometals are a cru- cial component in the development of medical implants and fixa- tion devices. As such, it is imperative that they are composed of elements that are both nontoxic and nonallergenic to the human body. In addition, biometals should possess high mechanical prop- erties, wear resistance, and resistance to corrosion in order to pre- vent the dissolution of metallic elements. Finally, biometals should

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have a low stiffness that is similar to that of bone. These require- ments ensure the safety and efficacy of biometals in the medical field [3 , 4]. The principal metallic biomaterials currently used in or- thopaedic and craniofacial fracture or osteotomy fixation or joint replacement devices consist of titanium alloys and, more rarely, stainless steel, nickel-titanium and cobalt alloys [5–8] . Also, or- thopaedic and craniofacial metallic devices play an important role in bone graft fixation for trauma, cancer, and arthritis reconstruc- tive surgery[3 , 9].

1.1. Background

While they have very different roles during the post-surgical healing period and the subsequent post-healing period, skeletal re- placement and skeletal fixation devices may disrupt the normal stress-strain trajectories that bring about healthy, sustainable re- modelling of cortical bone [10] . Although standard-of-care skele- tal devices ensure recovery in the majority of patients, the long- term prognosis for patients with significantly interrupted loading patterns includes a high risk of stress shielding-induced bone loss [11] , stress-concentration-induced device failure (e.g., screw loos- ening, plate exposure, and screw or plate fracture) [12] , or both. High stress concentration in the hardware causes accelerated strip- ping wear and fatigue, which might consequently result in its frac- ture or displacement [13 , 14]. Meanwhile, stress concentration in the surrounding bone results in bone resorption or insufficiency fractures [15] . Stress shielding is the reduction of bone density due to the redistribution of load that occurs when a skeletal de- vice takes over the load from the bones. According

to Wolff's law, healthy cortical bone maintains its shape and radiodensity due to a continuous remodelling process. Healthy remodelling is evidenced by the ratio of osteoclasts to osteoblasts. That ratio is a response to normal mechanical loading and the continuous presence of micro- fracturing and its repair (i.e., remodelling). The skeletal device, constructed of a material that is much stiffer than the surround- ing bone, supports the majority of a load and possibly the majority of the patient's weight, thereby demonstrating an unphysiological redistribution of force transmission and preventing the local bone from receiving sufficient mechanical stimulus during remodelling. As a result, the bone will tend to redistribute and resorb [16–19] . A decrease in bone mass and density may contribute to implant loosening and/or failure. The resorptive process generated by stress shielding has been reported as one of the main problems that lead to bone loss and revision surgery in craniofacial [20] , knee [21–23] , shoulder [24] , spine [25] , and hip [26] implants, and bone fixation plates [27–29] . Therefore, mechanical properties and geometry are critical factors that should be considered during skeletal device de- sign to address stress shielding and stress concentration.

The concept of medical device stiffness-matching is not well- established in the medical or device engineering communities. Conceptually, it is important for both communities to consider the performance of a skeletal device and the bone it is attached to as a construct which is used under physiological loading conditions. It is best not to conflate the stiffness of a particular medical de- vice or the reconstructed device and bone region with the Young's modulus of test coupons of the dense (i.e., non-porous) material used in a fixation or bone replacement device. When describing the properties of isolated metal components, it is most common to use Young's modulus. However, stiffness is a structural property, it is the resistance to elastic deformation, which is influenced by both the geometry of the device/bone region as well as the materials of which it is comprised. From this perspective, the reconstructed region could be considered as a multi-material device that is affected by the way the load is applied. Young's modulus (or elastic modulus) is a mechanical property that measures a fully dense material's ability to withstand changes in length when under lengthwise tension or compression. It is intrinsic to a particular mate- rial and is not influenced by the geometry of a medical device, a reconstructed region, or how the load is applied to both. How- ever, Young's modulus is, in essence, the stiffness of a device and is proportional to overall stiffness (i.e., the higher Young's modulus, the higher the device's stiffness). Bone has an anisotropic structure, which results in anisotropy, that is, mechanical properties depend on the direction in which they are measured. This can be explained using a relatively simple example of femoral cortical bone. The Young's modulus of femoral cortical bone measured along the lon- gitudinal direction is often approximately 18 GPa, while along the transverse direction, it varies between 5 and 10 GPa [30] . However, in the case of bone, Young's modulus is not as relevant as stiffness. Stiffness is a more representative factor that describes the mechan- ical properties of the bone since it incorporates the bone structure, geometry, and Young's modulus. Many factors influence bone stiff- ness, such as age, sex, state of health, the relative amount of cor- tical and trabecular bone, normal loading pattern, the amount and direction of load experienced during behaviour, and the anatom- ical site. The stiffness of different bones in the body varies from well below 3 GPa for some regions of trabecular bone, to often more than 20 GPa for the cortical region of large bones [30] . More- over, in the areas between hard and soft tissue— such as at the interface between cartilage, ligament, or tendon, and bone— the structure of adjacent soft tissue and bone can include a gradient of strength and elasticity [31] . The Young's modulus of the metals commonly used for skeletal repair or replacement devices, such as titanium alloys (e.g., Ti-6Al-4V), cobalt-chromium alloys, and stain- less steel are, approximately 116, 190, and 210 GPa, respectively, which makes them 4—10 times stiffer than the bone to which the device is attached [32] . Although highly stiff skeletal devices may provide strong immobilization immediately after reconstruc- tive surgery, their long-term use may redistribute the load needed to sustain the repaired bone once it has healed. This disruption in the bone's normal stress-strain trajectories can lead to one or more of three poor outcomes: (a) stress shielding and bone resorption, (b) stress concentration in the fixation device and device failure (e.g., plate or rod cracking or screw pull-out), and/or (c) failure to restore muscle power as the reconstructed bone heals. After the bone is healed and strength returns to the muscles that allow it to operate, the possibility of these three risk factors increases if remnant fixation hardware continues to redirect bone loading significantly or if bone replacement hardware fails to re-establish suf- ficient normal loading of the healed bone. When the bone and/or reconstructive hardware fails, reoperation itself may lead to further hazardous consequences (e.g., more bone loss and pain at graft donor sites, scar tissue and poor vascularity, additional and more difficult reoperation often due to the same phenomenon caused by stiffness mismatch). Therefore, reduction, if not elimination, of the need to reoperate is a primary objective of personalized (i.e., in shape, location, and material), stiffness-matched skeletal recon- struction (i.e., fixation or replacement) devices [33 , 34].

1.2. Current status and challenges

Bone function may be restored by partial or full replacement of diaphyseal (shaft) or epiphyseal (joint, e.g., hip, knee, shoulder, hand, foot, or spine) skeletal segments, the latter clinically referred to as arthroplasty. The amount of motion that can be restored is a consideration. Science has allowed nearly full motion in hip, knee, and shoulder restoration, whereas intervertebral disc failure is usually treated by replacement (e.g., intervertebral fusion cage or scoliosis correction) with permanent skeletal immobilization instrumentation. Fracture and graft fixation can be problematic as surgeons are often unable to adequately anticipate or sufficiently personalize the device's mechanical properties and performance. While device personalization is commonly available, often at great cost, clinicians rarely have access to mechanical information on the patient's current or planned reconstructed skeletal anatomy or the loads it can be anticipated to encounter post-operatively. It would be useful for surgeons to have a way to anticipate the performance of a particular device irrespective of the level of personalization. Additionally, the performance must anticipate at least two mechanical goals for which the use of fixation hardware should not be in conflict as they occur at different points in the healing cycle. If planned well, skeletal fixation can promote the transition from the initial demands of fixation during healing to the subsequent mass-sustaining bone loads that can lead to the long-term stabil- ity of the newly healed, reconstructed bone. Virtual elimination of motion at the osteotomy site is the initial job of fixation hardware. In the best-case scenario, a fixation device will translate all load to the host and grafted bone as compression between these bone fragments. Minimization of torsion or tension at the osteotomy site will allow and stimulate bone to quickly bridge the osteotomy site with minimal formation of callus [35] . The completion of healing is also intended to restore the normal geometry and function of the newly healed bone both at the osteotomy site and through- out the affected anatomical segment(s). Maintaining compression at osteotomy or fracture sites will aid the healing of bone tissue and facilitate strengthening through remodelling. The planning and design of fixation must often account for healing and subsequently healed bone to be able to accept torsional or tensile load. There- fore, fixation

hardware should be designed to prevent torsion or tension (i.e., twisting or splaying) at the osteotomy site under all loading conditions, including perhaps, a patient's accidental fall. In designing fixation hardware and choosing its location, we would also look to allow the transfer of as much load encountered by the fixation plate, rod, or pin to its normal location in the bone once the bone has fully healed. It may be that the best design of a non- resorbable fixation device will be able to allow a sufficient load to pass normally, as if it were not there, through the healed bone for purposes of bone mass maintenance. Currently, physicians cannot attempt to design the location, shape, and material used in fixation devices to achieve the transfer of load following bone healing [36] . Thus, the restoration of the normal stress-strain trajectory, while simultaneously minimizing host-graft bone osteotomy site micro- motion at the early stages of bone healing, captures the overall challenge [37 , 38].

As noted, the choice of a fixation device's external shape (pat- tern, length, width, thickness) and internal shape (porosity and pore geometry), location, fit to the bone, and material properties (materials used) of a skeletal replacement or fixation device may allow healing to occur but thereafter can lead to the mechanical failure of the device. A broken skeletal fixation or replacement device requires surgical removal and replacement with sufficient bone and fixation hardware to support healing and sustainable bone remodelling thereafter. A non-personalized approach is usu- ally blind to stress concentration in the hardware and the poten- tial for thread-stripping wear between the screws and the fixation plate, screws pulling out of the bone [39] , or fixation plate fatigue failure [40] (i.e., cracking due to cyclic loading) which might conse- quently result in the device's fracture, displacement, and bone seg- ment dislocation. In addition to device failure, failing to consider the mechanical performance of the fixation plate can lead to stress shielding of the surrounding bone. By redirecting the normal bone loading pattern, the bone that previously received a sufficient load to sustain morphology-preserving remodelling may resorb and, potentially, incur insufficiency fracture.

Currently, physicians have limited control over the personalization of the external shape [41 , 42] of these devices and, thus, where they can be optimally located. Further, surgeons have virtually no input into the device's material properties, such as their constituent material, the amount of porosity [43 , 44] in that ma- terial, or the pore space's geometry [45–49] . If the device vendor chooses to construct the device from a biocompatible but highly stiff material, that device may serve the role of immobilization dur- ing healing, but during that time and after healing, it may redi- rect stress-strain trajectories in unphysiological directions that may give fixation hardware an unsustainable load and/or may prevent the healed and adjacent bone from receiving sufficient mechanical stimulus to bring about a healthy, sustainable remodelling process [50] . Interrupting the normal stress-strain trajectories may also lead areas of thick, load-bearing cortical bone to resorb through remodelling as the load they previously received is redistributed elsewhere. When bone receives an insufficient load, it is stress- shielded. Stress shielding can lead to bone loss. Because the de- vice cannot remodel (i.e., cannot repair itself), cyclic loading can lead to device fatigue failure or loosening of the device, which is associated with revision surgery for craniofacial [20] , knee [21– 23] , shoulder [24] , spine [25] , hip [26] implants, and bone fixation plates [27–29] . Therefore, mechanical properties, geometry, and the location of a bone replacement or bone fixation device can be used to avoid the negative outcomes associated with bone stress shield- ing and device stress concentration (Fig. 1). Current manufacturers of personalized joint replacement and fixation devices rarely pro- vide physicians with biomechanical data on these parameters for a device their patient will receive. Simulations of predicted device performance could provide physicians confidence in skeletal recon- struction device decision-making once information on outcome op- timization (i.e., anticipated performance) was available [45 , 51].

Surgeons are generally aware that overly stiff skeletal replace- ment or fixation devices carry a high risk of failure. However, they may not be aware that there is a remedy for this widespread tru- ism. There is often some confusion around concepts of stiffness- matching as it is often assumed that the best device, especially a fixation device, will have uniform strength and stiffness. For ex- ample, an oversimplified view would be to expect that the optimal condition always requires a device that has the same stiffness as the bone that the device is attached to [52] . However, with fix- ation hardware, this is not optimal as the device is not replac- ing the bone. Rather, it may be best if it were somewhat stronger and stiffer than the surrounding bone, sufficiently so to minimize micromotion at the fracture or osteotomy (healing) site. Thus, an optimal stiffness-matched fixation concept is likely to conceive of hardware that is matched to the need to immobilize healing bone segments during loading by bringing them into compression. Al- lowing tension at the osteotomy (healing) site would be detrimen- tal. Further, the optimal location for fixation is likely to accom- plish this goal without, or with only minimally, interrupting the normal, bone-preserving, stress-strain trajectories that are preva- lent after the bone has healed. Finally, it is expected that the op- timal stiffness would be the minimum needed to accomplish the goals of fixation so that as much as possible of the whole plate- fixation-bone complex could be engaged in compression during loading and therefore, prevent stress concentration in the device and drive remodelling through compression of the healing bone. An overly stiff fixation plate would be more likely to concentrate load around a screw or a relatively weak point in the plate or rod, thereby increasing the risk of failure due to stress concentra- tion and/or stress concentration plus cyclic loading (i.e., associated with fatigue failure). Material choice, careful screw planning (e.g., bicortical screws inserted at complementary, not uniform, angles) [53] , desirable surface modification, and strategic use of porosity can also help aid healing and prevent device failure.

One of the core aspects of the concept of stiffness-matched fixation devices is that they both facilitate the immobilization of reconstructed bone (e.g., skeletal fixation) and, following healing (i.e., fixated osteotomies heal), they facilitate the healed bone receiving a normal load (i.e., they do not re-direct that load, or only do so minimally). In the case of fixation, this means that the normal load is transferred to the repaired bone as it heals, often in association with the restoration of muscle power and mobility. Two principles are helpful here. First, it is recommended to start with devices no stiffer than they need to be to accomplish their function. In skele- tal fixation, that stiffness must be sufficient to redirect all loading to keep the healing osteotomy sites in compression, not tension. Second, the device should be flexible enough to engage the entire construct during loading, as local stress concentrations are more likely to lead to device failure. External surface and internal pore geometries can also be used to ensure restorative loading patterns that promote healthy bone loading and sustainable remodelling.

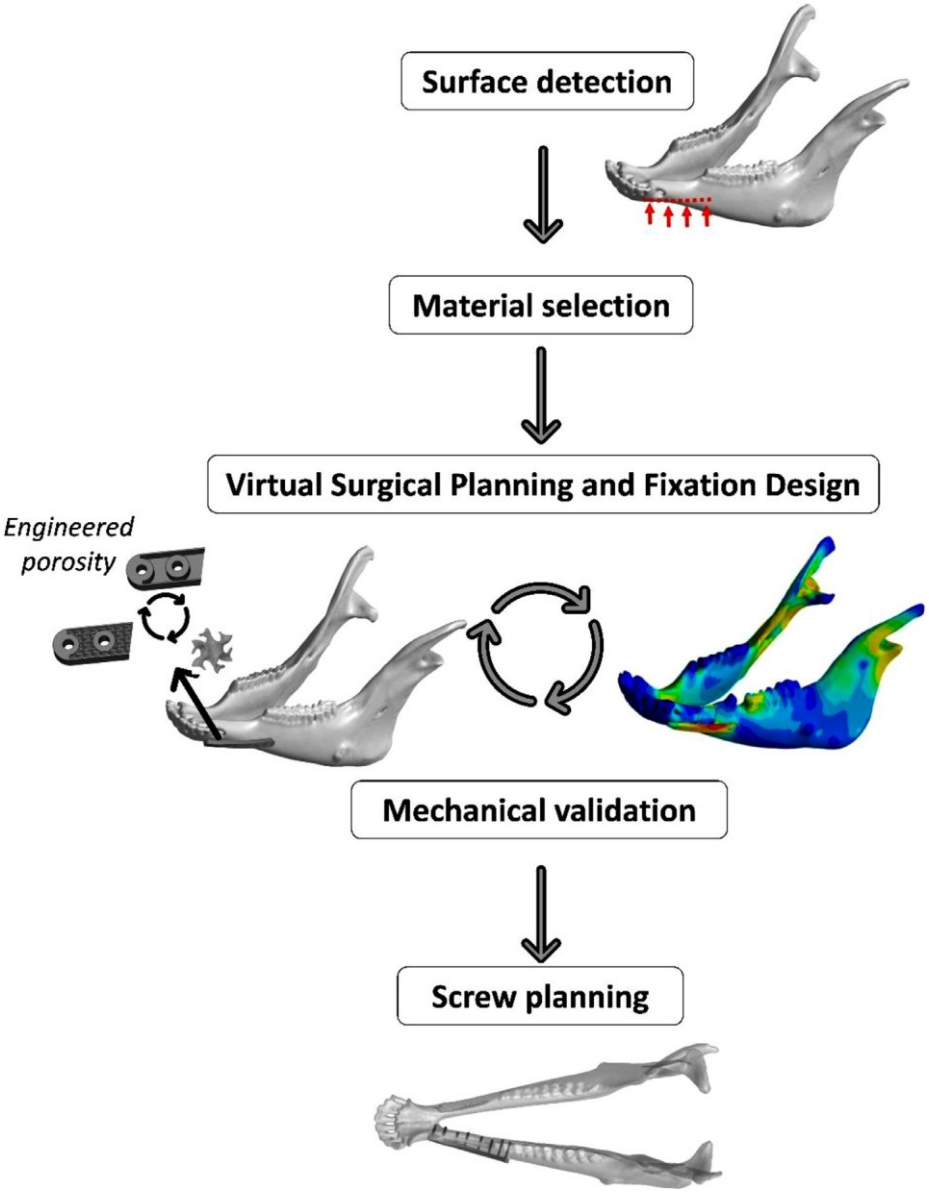

Fig. 1. Schematic illustration of optimization of a stiffness-matched mandibular graft fixation device in a Virtual Surgical Planning environment (sheep model).

Overall, one should envision stiffness-matched devices with personalized shapes and mechanical properties that restore the normal stress-strain trajectories of the repaired bone and match the stiffness to the work the device must perform in concert with the bone. Thus, the restorative device's properties are tailored, and personalized to work in concert with the host's anatomy and the long-term needs of the patient. Stiffness-matching can be achieved by different approaches: application of materials with modulus close to that of the bone,

adaptation of geometry with pre-defined mechanical properties, and/or surface modification that ensures good integration and proper load transfer to the bone (Fig. 2).

This review reports on recent research that focuses on the op- timal design of skeletal reconstruction devices to perform before, during, and after the change of mechanical regimes from healing reconstructed bone to healed bone. Moreover, this manuscript aims to provide a comprehensive summary of the most significant in- formation related to stiffness-matching that has been presented in various research papers and review articles.

2. Low-modulus materials

The initial approach to skeletal reconstruction devices was driven by a failsafe approach to mechanical properties and careful attention to biocompatibility together with high corrosion resistance [32 , 25 , 54–59]. Amongst metallic materials, titanium and its alloys have recently been considered the most suitable material for skeletal reconstruction devices, as they rapidly self-passivate and are less problematic than competing materials, such as stainless steel 316 L, Cr-Co alloys, and tantalum (Fig. 3) [60] . Table 1 pro- vides a comprehensive overview of the advantages, disadvantages, and challenges associated with the use of common biomaterials in orthopaedic implant applications. More recently, low-modulus titanium alloys, with various alloying elements, such as Nb, Mo, Zr, Ta, Mn, and Cr, have been found to improve mechanical per- formance. Low modulus alloys used for skeletal implants include, but are not limited to, Ti-13Nb-13Zr [61] , Ti-12Mo-6Zr-2Fe [61] , Ti-15Mo [62] alloys, Ti-45Nb [63 , 64] and Ti-35Nb-7Zr-5Ta [65 , 66]. Ex- tensive research has been performed on Gum Metal (TNTZ), which is a unique class of β-type titanium alloy. Initially, TNTZ was com- posed primarily of titanium, 23 % niobium, 0.7 % tantalum, 2 % zir- conium, and 1 % oxygen. It can exist over a range of compositions, including those with vanadium and hafnium contributions [67 , 68]. These alloys simultaneously offer high strength (> 1 GPa), a low Young's modulus (≈60 GPa), and good biocompatibility [69] . More- over, shape memory NiTi (*aka* Nitinol or nickel-titanium) alloys have found wide applications after initial problems with significant nickel ion release [70] . Nevertheless, the release of harmful allergenic and cytotoxic ions from titanium alloys, stainless steel, and Co-Cr alloys has been previously reported as well [71–73] . However, after improvements in alloying, NiTi has gained acceptance as a standard-of-care material for orthodontic arch wires, vascular stents, active catheters, trans-aortic valve replacement rings, and most recently, for skeletal applications such as spine-fracture staples, hallux restraint, and lumbar vertebral

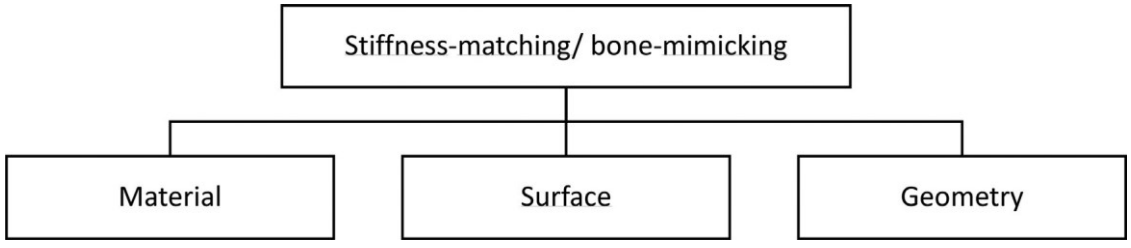

Fig. 2. Diagram of the basic approaches to a stiffness-matching objective.

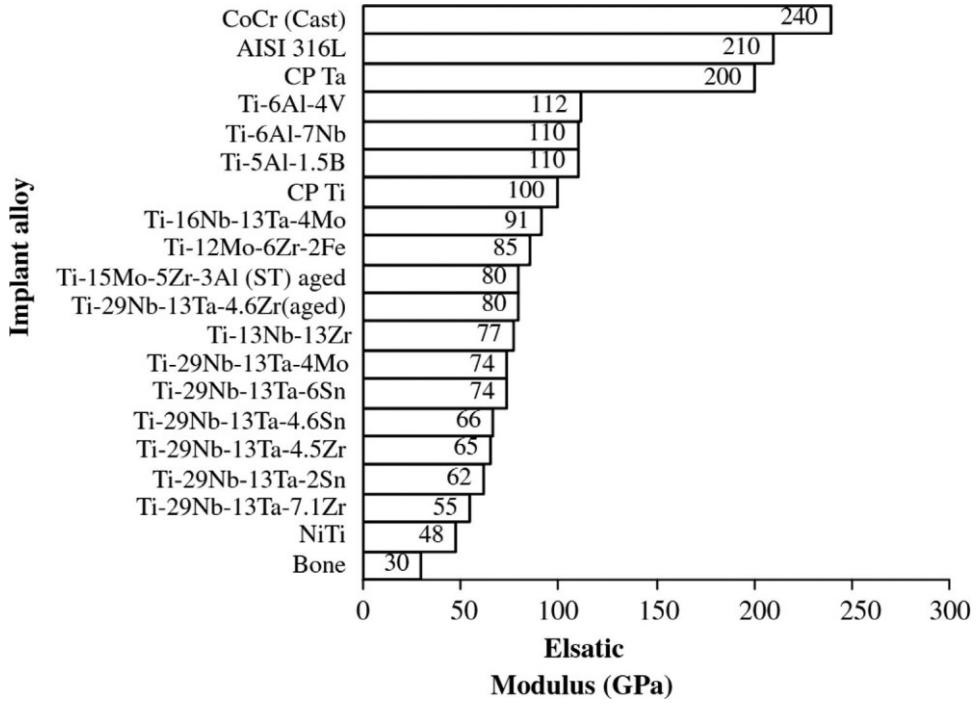

Fig. 3. Modulus of elasticity of biomedical alloys. Reproduced with permission from [89] .

fixation components [74–79] . Given the difficulty of forming NiTi, these devices have often been primarily formed via laser cutting or as drawn wire. However, more recently, the use of 3D-printed NiTi for bulk de- vices has been explored [47 , 80]. Biomedical interest in NiTi alloys, especially for bone restoration applications, derives from the low Young's modulus of these alloys (austenite: 70 GPa; martensite: 28–40 GPa) [81] and their biocompatibility when Ni ion release is minimized through careful alloying and surface treatments [70 , 82– 84]. Similarly, biomedically relevant magnesium alloys present a low modulus of elasticity (≈40 GPa), a value that is close to that of cortical bone (≈15–30 GPa). Moreover, in addition to biocompat- ibility and desirable mechanical properties, biomedically-relevant magnesium alloys have the added benefit of being resorbable. Re- cently, there has been extensive research into resorbable magne- sium alloys that will have sufficient strength for use in skeletal fixation hardware and will not degrade before the surgically re- constructed bone has healed [85–88] .

3. Surface conditions

The successful integration of medical devices into the human body heavily relies on the properties of their surfaces. In order to enhance biocompatibility, as well as mechanical, tribological, and antibacterial properties, a range of modifications can be applied to the surface. It is important to note that surface roughness at different scales, including macro, micro, and nanoscale, can has a significant impact on cell behaviour. Studies have shown that os- teoblasts tend to adhere and spread more effectively on surfaces that have micrometric roughness [100] . The enhancement of the implant surface has been shown to improve the initial process of osseointegration with the alveolar bone, resulting in a reduction in the duration of treatment [101] . Osseointegration is a critical pro- cess in which newly formed bone tissue adheres to the surface of a bone implant. The rate at which the initial process, as well as ongoing remodelling, occurs must be sufficient to ensure that the implant remains stable within the body. The level of remod- elling will likely depend on the load the attachment site receives over time. This phenomenon has been observed since the first use of bone implants in medical procedures and is of utmost impor- tance in orthopaedic applications. Furthermore, alterations to the surface of implants that result in an increase in surface area for attachment to bone have been found to enhance bone-to-implant contact (BIC). Techniques that can be employed to achieve this in- clude increasing surface roughness or surface porosity (i.e., tex- tured surface). Surface porosity can be generated utilizing meth- ods such as acid etching or anodizing. Electron Beam Powder Bed Fusion is also recognized as a means of creating a textured sur- face [102] . When surface porosity is established at the nanoscale and microscale level, it can significantly improve the absorption of biological fluids immediately following implantation. This, in turn, accelerates the growth of BIC dynamics, leading to quicker load- ing of the implant and an enhanced maximum value. Ultimately, this facilitates the implant's ability to bear larger loads once the osseointegration process is well udnerway [103] .

The stability of a replacement implant's integration or a fixa- tion device's attachment is a critical factor in determining its suc- cess. This stability is assessed at two stages: primary and sec- ondary. Primary stability is achieved right after surgery (i.e., prior to any healing, new bone formation, or bone strengthening) and relies on the quality of the bone at surgery and the interaction be- tween the bone and implant at the bone-implant interphase. On the other hand, secondary stability is attained during the healing period through the osseointegration process. This process involves the creation of new bone that tightly bonds with, if not infiltrates, the implant and matures over time. Hériveaux et al. [104] developed a 2-D finite element model for the bone-implant interphase to evaluate the impact of the bone Young's modulus, implant surface roughness, and the implant's material composition (Fig. 4). They indicate that lowering the BIC ratio leads to an in- crease in stress shielding, which can negatively impact the clinical outcomes of endosseous implants. Thus, it is imperative to model and then prioritize maximizing providing a sufficient BIC ratio to avoid stress shielding. Moreover, it was shown that matching the mechanical properties of bone tissue with implant material

Table 1
Most common biomaterials for orthopaedic implants. Reproduced with permission from [90] .

Material	Uses	Advantages	Disadvantages	Challenges
Titanium alloys [6 , 91]	Femoral hip stems Shoulder stems Fasteners, nails, rods, screws, wires Fracture fixation plates Pedicle screws and rods for spines	Lightweight Less biological response Biocompatible High corrosion resistance	Poor bending ductility Poor wear resistance Expensive High modulus	Biodegradable Biological inertness Antibacterial Stability in mechanical properties Wear reduction
Stainless steel alloys [92 , 93]	Plates, screws, pins, wires Sliding hip screws Flexible and intramedullary nails Cerclage cables	Widely available High ductility Accepted toughness Accepted biocompatibility	Very high modulus Allergic reactivity Stress shielding effect Poor wear resistance	Corrosion resistance Wear reduction Biological inertness
Cobalt-chrome Molybdenum [94]	Bearing surface in metal Plates and wires Shorter-term implants	Long term biocompatibility High corrosion resistance High wear resistance High impact durability	Stress shielding effect Poor machinability Biological toxicity due to release of Ni	Wear reduction Metallic fretting Biological inertness
Polyethylene /UHMWPE [95–97]	Bearing surfaces	Biocompatibility Wear resistance	Wear debris Lower mechanical properties Joint infections	Fatigue life
Alumina/ zirconia composites [98 , 99]	Bearing surfaces	High smoothness Biocompatibility	High fracture rate	Brittleness

prop- erties and morphology can result in a uniform shear stress field, which may aid in avoiding stress-shielding effects [104 , 105].

As already noted, in order to promote healing, both skeletal re- placement and skeletal fixation devices must become integrated, literally fastened, with the bone to restore normal stress-strain tra- jectories. Their integration will determine the reconstructed re- gion's ability to efficiently transduce load between surrounding muscles, ligaments, host bone, grafted bone (if any), screws, and a fixation device. There are many ways that "fastening" can be ac- complished. However, the most common way is the use of screws, a press-fit shape for a complex surface, bone "cement", and/or bone growth into the device. Indeed, more than one type of fas- tening process can be used at various locations of an implanted skeletal repair device. As noted, osseointegration of skeletal re- placement devices may benefit from surface texturing and/or coat- ings [106 , 107]. Surface modification may include but is not limited to coatings, layers, or surface texture (i.e., roughness). While rough surfaces may promote bone ingrowth (osteoconduction), they may also promote bone ingrowth into a porous region (i.e., osteoinduc- tion). Metallic skeletal device coating techniques include physical vapour deposition, chemical vapour deposition, electrochemical de- position, sol-gel coatings, plasma spraying, and micro-arc oxidation [108] . In addition to creating rough surfaces, ceramic or polymer coatings may contain bone or vascular growth factors, immune- modulating factors, or antibiotics. However, mechanical failure is to be avoided; in all cases, sufficient implant surface integration is necessary at locations where load transfer occurs [109] . High lev- els of micromotion should be prevented at both the bone-implant interface, screw/device interface, and at all osteotomy sites where the bone is expected to heal. Micromotion above 30 0–40 0 μm be- tween the device and adjacent host bone and especially at the healing site between two osteotomized bone fragments [37 , 110] may prevent bone bridging and healing its closure (i.e., non-union). Integration will improve load transduction between adjacent bone and the host. In doing so, it will reduce any callus that has formed. However, bone healing may have no effect on stress shielding- induced bone loss or stress concentration-induced device failure. Raffa et al. [111] showed the importance of maximizing bone- implant contact surface area, especially relative to areas where the load is transduced between the host bone and a skeletal fixation or replacement device. Careful attention to modelling and achiev- ing anticipated loads at this interface will facilitate the device/bone construct's integration and thus, its role in carrying a load in a skeletal replacement device or, in the case of a skeletal fixation device, maintaining osteotomy site compression and avoiding os- teotomy site motion that would prevent healing.

4. Geometry

Geometry pertains to the overall shape of the medical device, including its external and internal features. The design of a med- ical device is determined by a multitude of factors, including the space it must occupy (in the case of implants) or the surface it must be attached to (in the case of fixation devices). In the devel- opment of medical devices, achieving targeted stiffness levels ne- cessitates careful consideration of the device's shape and mechan- ical properties. Such requirements have a significant impact on the presence or absence of internal features, including truss structures and porosity, within the device's design.

4.1. Defined internal porous geometry and additive manufacturing

At best ordered, but usually random, porosity with varying permeability to bone or body fluids is the best outcome from the inclusion of porogens or other poorly controlled techniques for producing porous space (i.e., initially air and later, inside the body, fluid-filled space) in metallic medical implants. Somewhat ordered but still primarily random, pore geometries can be fabricated via conventional methods such as powder metallurgy, chemical or electrochemical deposition, vapour deposition, and liquidphase methods [20 , 112]. As a class, these regions are often referred to as foam structures. The inclusion of these pore spaces will reduce the stiffness of the device, but it is difficult to predict their final mechanical properties given the inhomogeneous and relatively unpredictable formation of porosity [113–117] . How- ever, the development of CAD/CAM

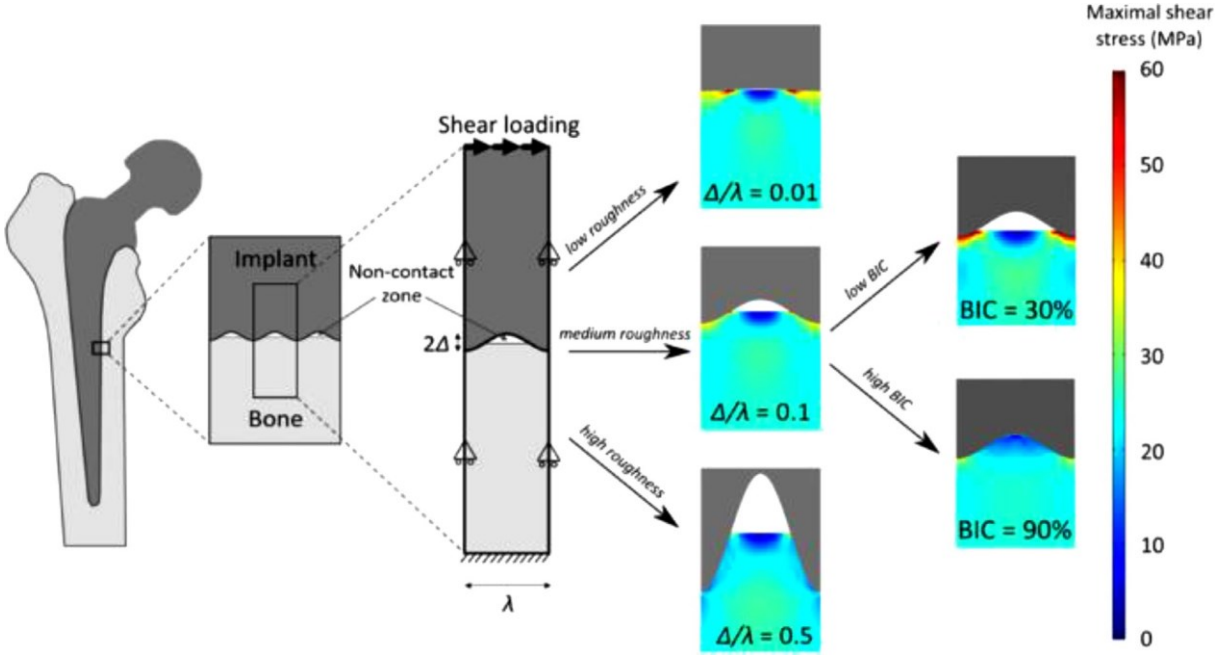

Fig. 4. Schematic illustrations of the 2-D finite element model used in the present study and spatial variation of the maximal shear stress in the periprosthetic bone tissue for different implant roughness and bone-implant contact ratios. Reproduced with permission from [104] .

technologies, especially addi- tive manufacturing, has allowed the fabrication of devices with pre-defined isotropic and anisotropic internal pore geometry and surface porosity (i.e., defined texture). This has created a revolu- tion in stiffness-matching (see Section 4.3) [102 , 118]. There are two commonly used approaches to designing porous structures. One involves direct (i.e., personalized) design through the use of pa- tient images, while the other involves indirect design through the use of parametric porous units. Defined internal porous geome- try incorporates precise specifications for pore morphology, such as strut shape and tortuosity, strut size (e.g., diameter) and dis- tribution pore shape and tortuosity, as well as pore size and pore size distribution. Moving from simple lattices where strut junctions are high angle stress concentrations [119 , 120] (e.g., orthogonal) to octahedral and Schwartz "D" (diamond) repeating units [46 , 121– 124 , 49 , 125 , 126], *aka* "pore cells" [40] , through a triply periodic minimal surface (TPMS) [127] geometries such as Schoen's gyroid [128] , Voronoi-Tessellation [128 , 129], and other auxetic structures [130 , 131]. Current research focuses on anisotropic pore geometries, which cannot only be used for stiffness-matching but also to direct the load [132] . Numerical analysis allows one to estimate mechan- ical performance in situ as part of a Virtual Surgical Plan (VSP) as well as the permeability of a device [133–137] . In situ mechani- cal properties of bone can be estimated from the geometry and inferred material constituents of musculoskeletal structures (i.e., bone, cartilage, muscle, tendon, and ligament) seen in 3D MRI, 3D ultrasound, or, more commonly, 3D CT images [138 , 139]. Moreover, recent studies have revealed that porous scaffolds with lower stiff- ness in comparison to the bone they are intended to replace typi- cally lead to a greater level of bone ingrowth (Fig. 5) [140 , 141 , 139].

Surprisingly, mechanical personalization is often touted. How- ever, physicians are rarely shown data on the anticipated mechanical performance of a device in their patient in an interactive VSP environment. Rather, consideration of a personalized device's mechanical performance in a particular patient is left to a confidential, company-specific, often trade secret and regulatory agencyapproved device design envelope that may not include any personalization but rather the anticipation that it will be sufficient for a wide range of mechanical conditions. Often, this certainty is gained, indeed claimed in an application for commercial clear- ance, from validation studies against known standards (e.g., ASTM F382, ISO 9585). Thus, the extent of the personalization and opti- mization of mechanical performance, if any, is not known outside the company. This is likely to change as physicians gain the abil- ity to model a fixation or replacement device's location, shape, and material properties and perhaps manufacture the modelled device, at the Point-of-Care. Point-of-Care Manufacturing (POCM) does oc- cur now at major medical centres (e.g., Walter Reed National Mil- itary Medical Hospital, MD, USA, and the Mayo Clinic, MN, USA, are amongst this select group). Once physician-informed design and POCM become widespread, the medical literature will begin to accumulate device-specific data and the evidence available to physicians on which to judge predicted, personalized, and opti- mized functional outcomes, they will then be able to advise their patients with a personally validated recommendation, versus an experience or literature-based evidence, for a personalized skele- tal reconstructive device design. As with the base metal's(s') mate- rial properties, pore and strut size and geometry (i.e., shape) can be adjusted to personalize a device's mechanical properties. Pore geometry need not be isotropic. It can be adaptive, for example, in order to keep healing bones in compression while subsequently transferring the load to the healed bone once the healing process is complete [142] . Perhaps most relevant are previous attempts to reduce device stiffness through the strategic use of porosity, such as Hazlehurst et al.'s [119] use of additively manufactured square pore structures in a CoCrMo device that achieved stiffness and strength characteristics similar to cortical and trabecular bone in the human femur or the incorporation of less stiff materials inside a metallic shell [143] . However, while theoretically, stiffness can be reduced by changing materials and/or geometry, it might be diffi- cult to avoid deleterious stress concentration with high-angle strut intersections or very thin struts that may fail due to fatigue in the future. This could occur due to cyclic loading if sufficient load is not transferred to newly healed bone [144] .

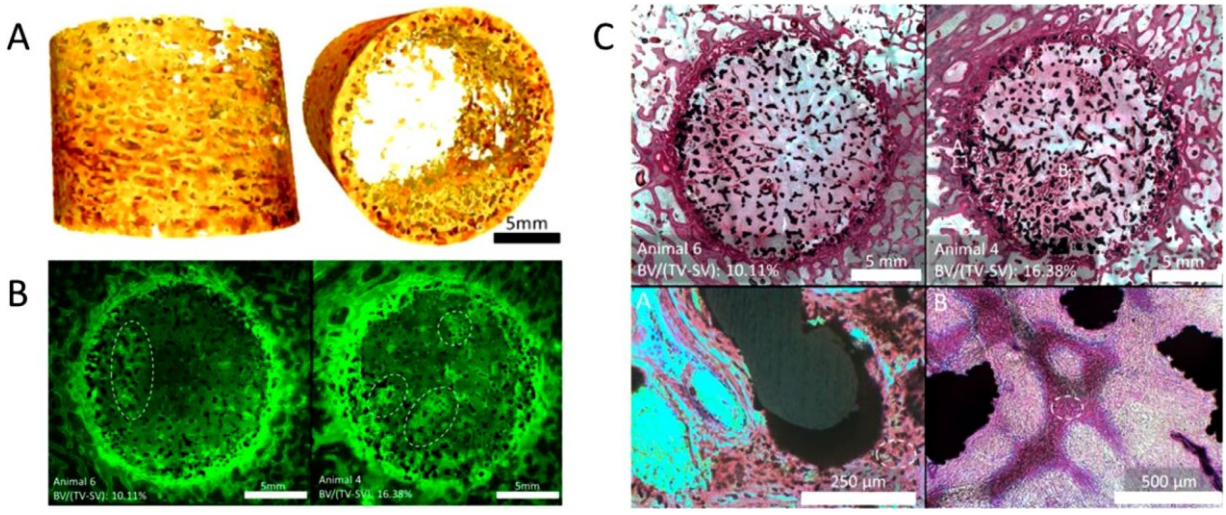

Fig. 5. A. CT-Renderings of bone ingrowth into a locally stiffness-matched porous scaffold (not shown) sheep model; B. Fluorescent Microscopy Images for animals 4 and 6. Islets of bone deep within the scaffold interior circled; C. Histology Images for animals 4 and 6. A and B are magnified sections of the scaffold periphery and interior respectively. Examples of osteocytes are circled. Reproduced with permission from [139] .

4.2. Meta-biomaterials

The term ‘meta-materials’ refers to engineered materials exhibiting novel properties not usually found in nature. Biocompatible meta-materials with novel properties such as negative compressibility, negative Poisson’s ratio, and negative elasticity offer new opportunities. Auxetic structures (*aka* NRP-Negative Poisson’s Ratio) are a specific class of meta-materials, that have a negative Poisson’s ratio thanks to their extraordinary ability to lat- erally expand in response to axial tension [145 , 146]. The medical variant of meta-materials is meta-biomaterials [147] . These ma- terials may have specialized applications in skeletal replacement devices if it is useful for the device to expand under pressure. Such expansion may allow the compression of adjacent bone by maintaining firm contact (Fig. 6). Kolken et al. [148–150] have made an extensive evaluation of auxetic meta-biomaterials for skeletal reconstruction. For example, it was found that rationally designed meta-biomaterials present an opportunity to produce a hip implant incorporating auxetic (negative Poisson’s ratio) and conventional (positive Poisson’s ratio) properties in order to maintain implant-bone contact and potentially reduce stress shielding-induced, so-called “aseptic” loosening [130] .

The interface between the implant and bone is more likely to fail under tension compared to compression, based on Hoffman’s failure criterion. Additionally, bone is more resistant to compres- sion than tension [151] . If the implant’s Poisson’s ratio remains constant, one side will retract from the bone while the other is compressed against it. Considering Hoffman’s criterion, the side that experiences tension (and therefore retracts from the bone) is more likely to experience interface failure due to the different mechanical strengths of bone in tension and compression. More- over, to prevent wear particles from entering the enclosed cavity, it’s crucial to ensure maximum contact between the implant and bone. Additionally, the fixation of the implant can be enhanced through osseointegration prompted by mechanical stimulation in accordance with Wolff’s law. Finally, Kolken et al. [130] concluded that all of these points emphasize the necessity of devising an implant that exerts compression on both sides of its neutral axis. Femoral implants with regions of negative, positive, and graded Poisson’s ratio unit cells were studied by Ghavidelnia et al. [152] . They concluded that they could use materials with negative and graded Poisson’s ratios to create a uniform distribution of micromotion at a bone-implant interface. Sorrentino and Castagnetti [153] designed and experimentally validated a titanium auxetic meta-biomaterial consisting of rotating cuboids connected by an optimized micro-structure, with bone-mimicking elastic modulus and low density for replacement of the region of trabecular bone in vertebral implants. Auxetic structures were also found to exhibit more effective stress transfer and attenuation under practical

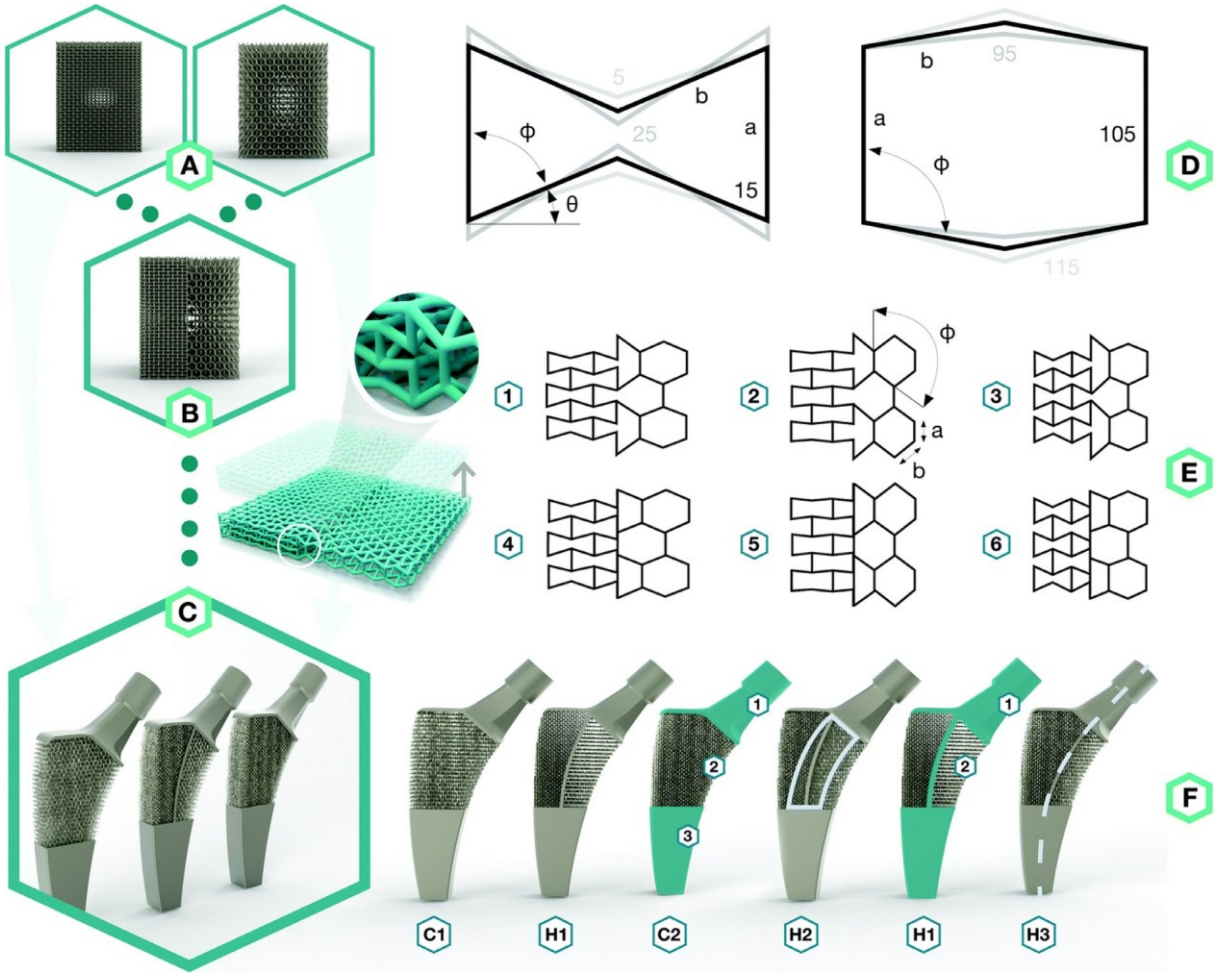

Fig. 6. Hybrid meta-biomaterials. (A) Test set-ups and image processing: (1) off-axis compression, (2) off-axis compression with an adherent layer used to improve visu- alization of strain distribution, (3) points plotted along the borders of a hybrid meta-biomaterial and the order in which they were numbered according to their position. (B) Horizontal strains in the tape surrounding hybrid meta-biomaterials types 1–6 at 2 mm displacement. (C) Mean maximum expansion during off-axis compression.
Reproduced with permission from [130] .

loading conditions compared with natural intervertebral discs and conventional 3D implants [154] . Given that meta-biomaterials are being considered primarily for permanent skeletal replacement, it will be important to confirm the number of cycles that these properties can be maintained without fatigue failure. Similarly, if they are to be used in fixation devices, it will be important to ensure that they allow sufficient load transfer to the newly healed bone to avoid stress shielding or the creation of unsustainable stress-strain trajectories (i.e., maladapted for the bone, especially its cortical component).

4.3. Tailored and functional gradient porosity – functionally graded materials

In most cases where 3D-printed pore geometries have been ex- plored, they have relied on uniform pore geometry (i.e., isotropic and uniform strut and pore diameters). Since most bones have pre- ferred loading patterns, these patterns are reinforced by irregu- lar and gradient distribution of cortical bone osteon structure. The number and density of such osteons will depend on local mechanical demands. Therefore, functionally graded pore geometry and/or materials may be able to mimic the hierarchical and gradient structure found in natural bone. This is particularly important for the long-term viability of skeletal replacement devices, where a model of the mechanical properties and predominant loading patterns of bone that is to be replaced by an implant could help one optimize the design of a skeletal replacement device. Moreover, graded structures could potentially improve osseointegration and wear resistance. Gradient structures can be obtained by a compo- sitional, microstructural, or geometric gradient from one surface of the material to the other, resulting in a material with continuously varying properties that could channel load in desired directions [31 , 155]. Indeed, the use of porosity to create functional gradients by changing the size of the pores, trabeculae, or both of these fea- tures by uniform and smooth gradients has been extensively ex- plored [156 , 157]. The tailoring of porosity gradients in porous hip stems has been shown to be effective in reducing Young's modu- lus and therefore, mitigating bone resorption

secondary to stress shielding (Fig. 7) [158–162] . Graded structures have also been im- plemented in dental implants to improve osseointegration [163–165] .

4.4. Design of stiffness-matched skeletal repair devices

Numerical analysis is the first step in determining the optimal location, shape (i.e., external surface and internal pore geometry, if any), and single or multi-material composition of a skeletal repair device. Choices in any of these parameters will interact [162 , 166 , 167 , 22 , 168 , 169]. Additionally, the reconstructed optimization of these parameters should be guided by the performance of the eventual part in situ. Loading patterns (direction, frequency, and magnitude of load) must be accu- rately and sufficiently predicted to determine the risk of stress shielding or stress concentration. Moreover, the device + bone construct may need to include muscles, tendons, ligaments, and screws.

The 3D source data for this biomechanical scene may be used to suggest where both uniform and gradient porous structures may be used to direct sustainable loading patterns to promote healing and/or the integration of a skeletal replacement device such as to- tal joint replacements at the proximal femur or tibial plateau [170] . For example, porous hip femoral stems have been demonstrated effective in reducing bone resorption secondary to stress shielding [158–162 , 171 , 172]. Vance and Arjunan [132] modelled Ti-6Al- 4V segmental bone defect replacement implants and found that unsheathed cellular designs can release metal debris. They pro- pose an implant that combines an anatomically matched geometry and a stiffness-matching strategy that would

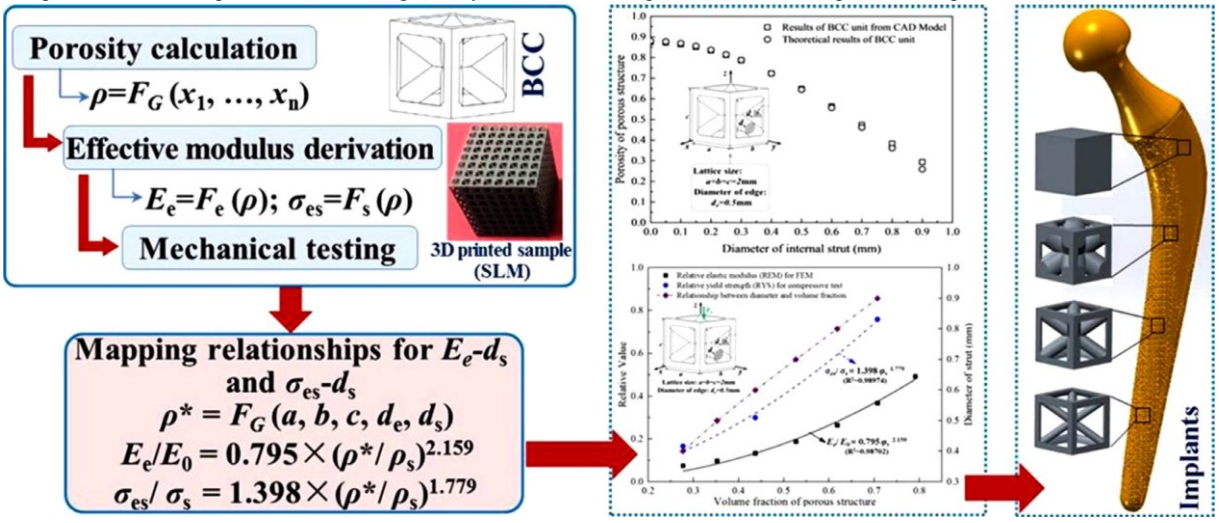

Fig. 7. Calculation and modelling of gradient porosity to yield desired mechanical properties for bone implants. Reproduced with permission from [160] .

Table 2
Overview of stiffness-matching skeletal repair devices.

Location/application	Porosity type	Porosity size	Vol.% of porosity	Manufacturing method	Mechanical properties	References
Tibia	Self-developed	723 μm	64.5	LPBF (DMLS)	E_{FEA} = 11.94 GPa	[132]
Hip femoral stem	Orthogonal struts- tailored and FGP Square pore-regular and FGM	60–700 ± 20 μm	23–70	DED (LENS)	$E_{experimental}$ = 14.58 GPa	[158]
Hip femoral stem		• 1.57 mm • 1.80 mm • 1.88 mm	< 50	LPBF (SLM)	E_{min} = 1.7 ± 2 GPa E_{max} = 27.8 ± 7 GPa • E = 4.79 GPa • E = 13.64 GPa • E = 17.98 GPa	[159]
Hip femoral stem	Diamond lattice structure-gradient	420–800 μm	40 45 50 55 60	–	• E = 18.12 GPa • E = 14.9 GPa • E = 12.02 GPa • E = 9.49 GPa • E = 7.28 GPa	[161]
Hip femoral stem	Tetrahedron-based topology	50–800 μm	> 50	LPBF (SLM)		[162]
Mandibular fixation plate	Orthogonal struts	1000 μm	45.7	LPBF (SLM)	E = 12 GPa	[47]
Mandibular fixation plate	Orthogonal struts	600 μm	46	LPBF (SLM)	E = 12 GPa	[137]

restore the original bone's stress-strain trajectories. Elahinia et al. have studied lowstiffness NiTi alloys with engineered porosity to optimize personalized fixation plates with stiffness-matched regions that are attached to the adjacent bone [46 , 47, 49 , 137]. Stiffness reduction can be achieved through the use of 3D Topological Optimization [173] . Rahimizadeh et al. [22] demonstrated a stemmed tibial compo- nent with a fully porous stem with a tuned tetrahedron lattice architecture. The porosity has been optimally tailored to mitigate postoperative bone resorption and end-of-stem pain while satisfy- ing the strength requirement necessary to sustain cyclic loading. The numerical results suggest that the overall amount of bone re- sorption around a graded porous tibial stem is 26 % lower than that around a conventional, commercially available, fully dense ti- tanium implant of identical shape and size. A similar result was found in a multimaterial (i.e., thin metal sleeve around the plastic core) total hip replacement device [143] . An interesting approach to restoring the normal loading of fixated bone following the heal- ing of bone segments is the bone bandaid concept presented by Moghaddam et al. [174] . Their releasable fixation mechanism effectively reduces the fixation device's stiffness, thereby preventing it from accepting a load after the bone is healed. The outcome here is similar to what would occur with a resorbable device. However, large, fully resorbable skeletal fixation devices must ensure that degrading fragments do not break free and lodge in adjacent tissues or joint cavities. The selected stiffness-matching skeletal repair devices are listed in Table 2.

5. Conclusions

As mentioned, the primary dichotomy between the perfor- mance of skeletal reconstruction devices is between skeletal fix- ation and skeletal replacement roles. While a device with a stiff- ness similar to that of adjacent bone will efficiently transduce load across the device-bone interface, this is not a sufficient design cri- terion to meet all of the demands of either type of skeletal repair device. As mentioned, skeletal fixation must be located where it can fix initially freely moving bone segments in compression under any load, especially the highest experienced load, throughout the healing period. Thereafter, the device must minimize, if not elim- inate, interference with the normal stress-strain trajectories that the bone's shape and mechanical properties, as well as the adja- cent muscles, are adapted to. Skeletal replacement devices must perform in this manner, i.e., to facilitate force transduction across the host bone-implant attachment site, as well as to ensure that the normal stress-strain trajectories of the remaining bone are not interrupted. Additionally, a skeletal replacement device must not undergo cyclic (fatigue) failure during its expected use life.

Recent research focuses both on the modelling of device location, shape, and materials and on finding new ways to man- ufacture devices that will bring about an optimal restoration of skeletal performance while reducing the risk of reoperation due to device and/or skeletal failure. In an effort to eliminate these problems, a holistic stiffness-matching approach to design and fabrication may be a promising option. As presented in this re- view, modification of the properties of the device can be achieved in several ways, such as modelling the mechanical performance of the relevant bone-device construct in a way that takes into account the forces it will undergo in the design of restorative devices, use of the materials with modulus close to that of bone, surface modification to enhance device/bone integration, auxetic materials to engender desired mechanical performance, homoge- neous or gradient (i.e., adaptive) porosity for the same purpose, and ultimately by combining all or some of these factors to avoid problems brought about by unsustainable stress shielding and/or stress concentrations. During healing, it is critical that skeletal fixation minimizes micromotion between healing bone segments. In the post-healing period following skeletal fixation, or on im- plantation of a skeletal replacement device, it is critical to restore, not interrupt, normal stress-strain trajectories. In addition to novel surgical planning software that includes device design based on performance modelling, further research on materials that can change their properties over time or can become mechanically irrelevant after the reconstructed bone has healed, including partially inert and partially resorbable multi-material devices (e.g. inert metal-resorbable metal, inert metal-resorbable polymer, inert metal-resorbable metal composite, etc.) is needed.

Data availability

This is a review paper. Thus, no new data have been presented. **Declaration**

of Competing Interest

David Dean holds founders' equity in RegenFix, LLC (Wilming- ton, DE). Agnieszka Chmielewska has no known competing finan- cial interests or personal relationships that could, or appear to, in- fluence the work reported in this paper.

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