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Functionally graded materials for orthopedic applications – An update on design and manufacturing

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ABSTRACT: Functionally Graded Materials (FGMs) are innovative materials whose composition and/or microstructure gradually vary in space according to a designed law. As a result, also the properties gradually vary in space, so as to meet specific non-homogeneous service requirements without any abrupt interface at the macroscale. FGMs are emerging materials for orthopedic prostheses, since the functional gradient can be adapted to reproduce the local properties of the original bone, which helps to minimize the stress shielding effect and, at the same time, to reduce the shear stress between the implant and the surrounding bone tissue, two critical prerequisites for a longer lifespan of the graft. After a brief introduction to the origin of the FGM concept, the review surveys some representative examples of graded systems which are present in nature and, in particular, in the human body, with a focus on bone tissue. Then the rationale for using FGMs in orthopedic devices is discussed more in detail, taking into account both biological and biomechanical requirements. The core of the paper is dedicated to two fundamental topics, which are essential to benefit from the use of FGMs for orthopedic applications, namely (1) the computational tools for materials design and geometry optimization, and (2) the manufacturing techniques currently available to produce FGM-based grafts. This second part, in its turn, is structured to consider the production of functionally graded coatings (FGCs), of functionally graded 3D parts, and of special devices with a gradient in porosity (functionally graded scaffolds). The inspection of the literature on the argument clearly shows that the integration of design and manufacturing remains a critical step to overpass in order to achieve effective FGM-based implants.

1. Introduction: a brief history of functionally graded materials

A Functionally Graded Material (FGM) is a special material, usually a composite, whose composition and/or microstructure vary smoothly in space according to a designed law. Due to the gradual change in composition, also the FGM properties (physical, mechanical, biochemical, etc.) vary in space to meet the specific requirements for a given application (Birman and Byrd, 2007; Kawasaki and Watanabe, 1997). For example, it is possible to couple a strong material, such as alumina, on one side of a device and a bioactive material, such as bioglass, on the other side, as exemplified in Figure 1. However, the absence of any abrupt interface greatly contributes to the system's reliability.

The constituent phases of an FGM are usually defined as "elements" or preferably as "material ingredients" (Miyamoto et al., 1999). In the simplest case, two material ingredients change from one to the other along one spatial direction, as already seen in Figure 1; nevertheless, some applications may also require a functional gradient along two or even three different directions (Jackson et al., 1999).

Even if the most common idea of FGM implies that two different constituent phases change gradually from one to the other (for example, from ceramic to metal), FGMs include all those functional materials whose properties change locally according to a specific design, arbitrarily introduced to fit an intended application or to enhance a wide variety of properties, especially the mechanical ones (Miyamoto et al., 1999; Rabin and Shiota, 1995). As a matter of fact, if appropriately designed, the presence of a functional gradient at the microscale may result in improved properties at the macroscale (Wu et al., 2014). For instance, as proved by Suresh and co-workers in various contributions, the damage and failure resistance to normal and sliding contact or to impact can be changed substantially by means of a controlled gradient in elastic properties at the contact surface (Jitcharoen et al., 1998; Suresh, 2001; Suresh et al., 1999).

Some pioneering contributions revealed the potentialities of graded materials already in 1972, when Bever and Duwez (1972) considered various composites with graded compositions, and Shen and Bever (1972) analyzed graded polymers. However, the first explicit formulation of the FGM concept dates back to the end of the '80s, when it was introduced in Japan to describe new thermal barrier coatings, thanks to the research project "Fundamental Studies on the Relaxation of Thermal Stress by Tailoring Graded Structures" (Koizumi and Niino, 1995). That was the first systematic description of FGMs as special materials with a compositional and functional gradient arbitrarily designed to meet non-homogeneous service requirements.

2. Graded materials in nature and the human body

Apart from the technological definition, it is interesting to note that graded materials are quite common in nature (a futuristic – as well as artistic – reading of natural multifunctional composites is provided by the new material method advocated by Neri Oxman at M.I.T., Boston (MA) (Oxman, 2010; Oxman, website: http://materialecology.com/)). Some examples of natural graded systems are bamboo structures (Amada, 1995; Low and Che, 2006; Nogata and Takahashi, 1995; Silva et al., 2006), mollusk shells, with their hierarchical architecture and related graded ligaments (Chateigner et al., 2000; Kaplan, 1998; Moshe-Drezner et al., 2010; Ritchie, 2014; Ono, 1995), the exoskeleton of arthropods, that is a mineralized fibrous chitin-based nanocomposite with a strictly hierarchical organization (Raabe et al., 2005), the spider fang, which is something like a natural injection needle (Bar-On et al., 2014), the narwhal tooth, with its graded cementum-dentin junction (Grandfield et al., 2014) and mussel byssus threads (Claussen et al., 2012).

Multi-layered and graded materials play a substantial role in the human body, too. For instance, human skin is a complex multi-layered system, consisting of the epidermis, dermis and underlying hypodermis, each layer having a specific and age-related mechanical behavior (Flynn and McCormack, 2009; Jor et al., 2013).

Striking examples of "natural" graded systems in the human body are also offered by the so-called "interface tissues", which are specialized zones at the interface between different tissue types, such as tendon-to-bone and cartilage-to-bone (Seidi et al., 2011). The tendon-to-bone insertion, for instance, is a ligament that connects two extremely different tissues across a millimeter-wide region: on one side, the tendon, which is a "soft tissue" (inherently compliant), and on the other side, the bone, which is a "hard tissue" (inherently stiff). Genin et al. observed that the tendon-to-bone insertion is able to withstand such a difference in mechanical behavior thanks to the concomitant action of a compositional gradient and a structural one (Genin et al., 2009). According to recent experimental outcomes, the configuration of the insertion site would be even more complicated, due to the presence of non-linear functional gradients (Liu et al. 2012).

The human intervertebral disc is another sophisticated example of graded system in the human body. Three regions can be defined within the disc, namely the annulus fibrosus, the nucleus pulposus, and the cartilage endplates. The annulus fibrosus surrounds the nucleus pulposus, with a very gradual transition from the former to the latter, whereas the cartilage

endplates are responsible for the connection of the intervertebral disc to the vertebral bodies above and below it. In more detail, the annulus fibrosus, in its turn, includes two concentric structures: the external annulus, which is a fibrous structure mainly composed of type I collagen fibers that bundle to form long parallel concentric lamellae (from 20 to 62), whose thickness gradually varies both circumferentially and radially; and the inner annulus, which is something like a "transitional region". If the cartilage endplates are considered, they provide an interface between the soft nucleus and the hard bone of the vertebrae. Moreover, they act as a biomechanical barrier that avoids a direct pressure to the bone. Again, the endplate tissue, which is structurally similar to articular cartilage, gradually transitions into bone through a region of calcified cartilage, which eliminates any abrupt interface (Cassidy et al., 1989; Humzah and Soames, 1988; Pezowicz et al., 2006; Shapiro and Risbud, 2014; Silva-Correia et al., 2013).

The bone tissue itself can be regarded as a functionally graded system (Haïat et al., 2009). In fact, in the human body, bones can be classified in various groups, but all of them present complicated graded structures. A typical example is given by long bones, which are characterized by a long shaft with a compact (cortical) bone layer that encases a central cavity containing cancellous (spongy or trabecular) bone, marrow and fat. If the cross section of a long bone is considered, there is no obvious interruption or abrupt interface between the external cortical bone and the internal cancellous bone. Moreover, the cortical bone is thicker in the mid-part of the shaft, whereas the cancellous bone is denser towards the epiphyses (Baron, 2012; Nather et al., 2005). Again, the structural change from cortical bone to cancellous bone is gradual and the smooth change in pore distribution determines a gradual change in mechanical properties, such as tensile strength and elasticity. The data available in the literature are disparate, especially for cancellous bone, whose characteristics are strongly site-specific and susceptible of re-alignment processes. However a gradual decrease in mechanical properties can be observed moving from cortical bone to cancellous bone, as reported in Table 1 (Beaupied et al., 2007; Nouri et al., 2010; Rho et al., 1998).

Also teeth are functionally graded structures. In fact, the surface of teeth is composed of hard enamel with prismatic hydroxyapatite (HA) crystallites, whereas the internal core is composed of dentine, a composite system with collagen fibrils and HA. As a result, the surface of teeth is hard, brittle and extremely wear resistant, whereas the internal part is relatively soft and flexible. The transition from enamel to dentine is provided by an intermediate layer, where the composition gradually transitions from one material to the

other (Chen and Fok, 2014; Cui and Sun, 2014; Du et al., 2013; Giannakopoulos et al., 2009; Ho et al., 2004; Huang et al., 2007; McKittrick et al., 2010; Niu et al., 2009).

The pervasive presence of graded structures within the human body is witnessed even at the molecular level. For example, native extracellular matrix displays a gradient of fibrous proteins and polysaccharides that are nanoscale structures (Seidi et al., 2013).

Since the best grafts are often those which resemble the natural tissue as much as possible (Nather et al., 2005), it is not surprising that FGMs have been used so far for a variety of biomedical applications (Pompe et al., 2003; Tomsia et al., 2005), including (just to give some examples) mitral valves (Rausch et al., 2012) and medical guide wires (Sutou et al., 2004). Nonetheless, the most common destinations fall into two main groups: dental restorations and orthopedic devices. Comprehensive review articles have been published recently on FGMs for dental implants (Mehrali et al., 2013); that's the reason why the present contribution is dedicated to FGMs for bone repair solely.

In detail, after a discussion of the motivation for grading the properties of materials in orthopedic implants, the following sections encompass two fundamental topics related to the use of FGMs for orthopedic applications, namely (1) the materials design and geometry optimization by means of computational simulations, and (2) the manufacturing techniques currently available to produce FGM-based grafts. This second part, in its turn, is structured in order to account for the production of functionally graded coatings (FGCs), of functionally graded parts with a three-dimensional geometry (i.e. FGMs which do not insist on a substrate, which is typical of FGCs), and of special devices with a gradient in porosity (functionally graded scaffolds). Great emphasis has been made on the necessity of integrating design and manufacturing to take full advantage of the benefits of FGMs.

3. Bone remodeling and the need for FGMs

Between 1990 and 2002, the revision burden for total hip arthroplasty in the U.S.A. ranged between 15.2% and 20.5% (average, 17.5%); for total knee arthroplasty, it varied between 7.3% and 9.7% (average, 8.2%) (Kurtz et al., 2005). Unfortunately, in spite of ongoing technological and surgical advances, the incidence of revision surgery is expected to increase steadily over the next years (Kurtz et al., 2007). Apart from obvious social and economic considerations, revision procedures are problematic, since they represent a further physical strain for the patient. Moreover the insertion of the new graft is usually very challenging due to the inevitable degradation of the peri-implant bone. So it is essential to reduce as much as possible the incidence of aseptic loosening. Of course

patient-related factors, such as poor bone quality and high body mass index, play a key role; nevertheless, mechanical factors, including wear phenomena e stiffness incompatibility, are reputed to be the main cause for implant failure (Kowalczyk, 2001). Foreign-body reaction against wear particles of various biomaterials is thought to be a relevant reason for aseptic loosing; as a consequence, an accurate material selection becomes a key issue to control wear phenomena (Langton et al., 2010; Thamaraiselvi and Rajeswari, 2004). Several solutions have been proposed in the literature to limit the risk of debris-induced aseptic loosing and indeed new materials, such as wear-resistant ceramics (for example, zirconia-toughened alumina, ZTA (Kurtz et al., 2014)) and wear-resistant metals (for example, special Co–Cr–Mo alloys (Goldsmith et al., 2000)), are under investigation; moreover, specific coatings (for example, TiN, DLC, etc. (Ching et al., 2014)) can be applied or surface treatments can be performed on bulk metal devices. Also cushion bearings (hydrogels; PU) have been introduced in multi-layered joint components to limit the release of debris (Sonntag et al., 2012). However revision surgeries are most often engendered by a deficiency in structural compatibility between the implant and the original bone (Khanoki and Pasini, 2012). Two concomitant factors must be considered:

- Many materials used for orthopedic implants (including titanium and titanium alloys, stainless steel, alumina, zirconia, and even calcium phosphates) are generally stiffer than natural bone tissue (scaffolds are an exception, but at present they are usually addressed to support bone healing and not to stand for load-bearing applications); this alters the stress distribution with respect to the "normal" physiological condition (Staiger et al., 2006).
- Unlike artificial grafts, natural bone is dynamic, since it is able to adapt to changes in mechanical stimulation and it is even capable of self-repair: in other words, it is a living material (Taylor, 2006). In fact, as proposed by the mechanostat theory and its derivatives (Frost 1996; Jee, 2000; Liebschner and Wettergreen, 2003; Sugiyama et al., 2012), mechanical factors govern the biologic mechanisms that control changes in postnatal bone and bone tissue is sensitive and responsive to its mechanical usage over time (Liebschner et al., 2005).

Since the stress and strain distributions within a bone are governed both by the external applied load and by the shape and properties of the bone itself, if a portion of bone is substituted by an implant with different mechanical properties, the original stress and strain configurations are inevitably altered, even if the external load is nominally the same. In fact, the natural load transfer along the bone's trabecular structure and the cortex is

deviated to the bone-implant interface. Moreover, the load is now shared with the stiffer biomaterial. In accordance with the Wolff's law, the modified stimulation within the bone will activate a process of strain-adaptive remodeling. In particular, as the biomedical device is stiffer than the original bone, the stress level will become lower than it should be and the bone will resorb, a process known as "stress shielding" (Huiskes, 1993) (a circumstantiated discussion on the validity of the Wolff's law has been provided by Pearson and Lieberman (2004)). Unfortunately the bone resorption around the graft undermines the implant support, and this leads to bone fracture and implant loosening. Many alternative implant designs have been proposed to work out the problem. For example, in order to reduce the difference in stiffness that is the origin of the stress shielding effect, composite and isoelastic stems have been introduced. Nevertheless, the reduced stiffness of the implant increases the shear stress between the implant and the surrounding bone, an outcome that sensibly raises the risk of interface motion (Trebse et al., 2005). A very delicate compromise is hence required, since excessive stiffness of the implant promotes bone resorption, whereas excessive flexibility of the stem jeopardizes interface stability (Harvey et al., 1999). Already at the end of the '90s, Kuiper and Huiskes (1997) clearly outlined the opposing terms of the problem and suggested to resort to innovative non-homogeneous materials, such as FGMs. As already mentioned, FMGs are indeed more than two-phase materials with a smooth change in composition: they are functional materials whose properties can be tailored to face specific service requirements, especially if a complex stress state is involved (Jitcharoen et al., 1998; Miyamoto et al., 1999; Rabin and Shiota, 1995). Kuiper and Huiskes (1997) even advanced a numerical optimization method to define the optimal stiffness distribution to balance the contrasting stress needs, and this paved the way for the progressive development of FGMs (and FGCs) for orthopedic applications (Kuiper and Huiskes, 1997; Khanoki and Pasini, 2012).

4. Optimization studies and computational simulations

This section encompasses the available literature on the design of FGMs for orthopedic devices. Such topic is considered first because computational simulations are essential to understand the relationship existing between compositional gradient and performance of FGMs. Even more, mathematical modeling and design are critical to select both the ingredient materials and the distribution profiles which best satisfy the assigned service demands (Hirano and Wakashima, 1995; Miyamoto et al., 1999). As a matter of fact, if FGMs are involved, it is not possible to define the "best profile" *tout court*; on the contrary,

the gradient in materials' composition and related properties must be always adjusted to the specific geometry and to the given application (Markworth et al., 1995). So, optimization studies are the starting point to create functionally graded devices, and this holds for biomedical prostheses, too.

As previously mentioned, the design of FGMS is inherently application-oriented. For this reason, the articles reviewed in this section are grouped according the FGM end-usage, such as knee prostheses, hip and femur implants, and so on. The concluding paragraph is dedicated to the analysis of porous graded materials, which deserve a separate description because the presence of (a gradient in) porosity requires specific multi-scale modeling methods. Moreover, Table 2 offers an easy-to-read snapshot of the literature.

4.1. Knee

Bahraminasab et al. (2012, 2013a, 2013b, 2014a, 2014b) have addressed an extensive computational research activity to the combined optimization of geometry and compositional gradient in Total Knee Replacement (TKR) implants. For example, if the pegs of the femoral component are considered, the sophisticated computations performed by Bahraminasab et al. (2014b), which are based on the finite element (FE) method combined with a design of experiment procedure, suggest that conical pegs made with 60% porous titanium are the best solution if they are combined with a porous metal-ceramic FGM femoral component; however, this conical geometry wouldn't be the optimal choice for conventional (not graded) Co–Cr femoral components, where cylindrical pegs would be preferable. So, the results proposed by Bahraminasab et al. clearly reveal that the design of the component's geometry cannot disregard the component's material composition, and vice versa (Bahraminasab et al., 2014b).

Hedia and Fouda (2013) focused their attention on the tibial component of TKR implants. They implemented a two-dimensional axisymmetric FE model including both the surviving tibia and the tibial prosthesis to define the best FGM components and the best direction of the gradient profile in order to control the stress distribution. In spite of the simplified geometry (in two dimensions) of the model, it was possible to observe that the optimal design required to grade the composition vertically, from HA at the end of the tibial stem to collagen at the upper layers of the tibia plate. This induced a sensible reduction of the stress shielding effect.

Similar results were obtained by Enab and co-workers, in a multi-step research activity dedicated to tibia tray components. At first, Enab (2012) used a two-dimensional FE model

to predict the biomechanical behavior of knee implants under various loading conditions and to evaluate the effect of vertical and horizontal gradations of the elastic modulus. Then Enab and Bondok (2013) proposed two-dimensional FE method-based models to simulate the bone and interface stresses for six different tibial prostheses, graded and not-graded. The best results were achieved by the FGM with a gradual change in elastic modulus along the vertical direction downwardly, which sensibly reduced the stress shielding effect in the surrounding tissue. Additional studies on tibial prostheses for TKR proved that increased advantages might be obtained using bi-directional FGMs instead of uni-directional ones (Enab, 2014).

4.2. Femur and hip prostheses

Hedia and co-workers devoted great attention both to the design of graded surface coatings and to the development of "bulk" graded systems for cementless hip prostheses. For example, if graded coatings are considered, Hedia and Fouda (2014) changed the Young's modulus of the coating along the vertical direction using the rule of mixtures for FGMs and, with FEM simulations, they found that the optimal design of the coating consisted of HA at the upper layer of the coating graded to collagen at the lower layer. According to the FE models, this graded design increased the maximum von Mises stress in the surrounding bone at the medial proximal region of the femur by 65% and 19% compared to homogeneous titanium stems and to titanium stems coated with conventional (not graded) HA, respectively. Moreover, the maximum lateral shear stress was reduced by 23% and 12%, respectively. As an alternative design, Fouda (2014) suggested to grade the materials' properties along the horizontal direction instead of the vertical one.

As previously mentioned, besides graded coatings, Hedia and co-workers also considered functionally graded "bulk" devices, where the compositional gradient was not limited to an external layer but spanned all over the component itself. At first, Hedia et al. (2004) used the FE method combined with an optimization technique to compare two different designs of the stem, namely as one-dimensional FGM (1D-FGM) and as two-dimensional FGM (2D-FGM). According to the definition introduced by Nemet-Alla (2003), 1D-FGMs include two ingredient materials, which create a mono-dimensional gradient, whereas 2D-FGMs include three ingredient materials, which create a two-dimensional profile. So, in the analysis by Hedia et al. (2004), in the case of the stem designed as 1D-FGM, the gradation of the elastic modulus was alternatively changed along the vertical direction or along the horizontal direction, in order to define the optimal gradation direction. It was found that

the best solution was to change the elastic modulus along the vertical direction from 110 GPa (which the Authors associated to HA) at the top of the stem to 1 GPa (collagen) at the bottom. Even better results were achieved when a third material ingredient was added, thus creating a 2D-FGM. In fact, if HA, Bioglass, and collagen were used, the graded stem induced the same stress shielding reduction as in the case of the vertical 1D-FGM, but the maximum interface shear stress was reduced further (Hedia et al., 2004). In a subsequent contribution, specifically addressed to the comparative analysis of various 2D-FGMs for cementless hip stems, Hedia et al. (2006) compared different patterns and they confirmed that the best configuration had two elastic moduli (HA and collagen) gradually changing along the upper stem surface, and the third elastic modulus (Bioglass) constant along all the lower surface of the stem. According to the FE simulations, this FGM design was expected to reduce the stress shielding at the proximal medial part of the femur by about 91% with respect to conventional titanium stems. In addition, the maximum interface shear stress was reduced by about 50% for both the medial and lateral sides.

More recently, Hedia et al. (2014) extended their research to cemented stems. They obtained the most promising results with a profile from titanium at the upper stem layer to collagen at the lower stem layer. In this way, the stress shielding effect at the proximal-medial femoral region was reduced by 98% with respect to a conventional titanium stem. Similar conclusions were achieved by Al-Jassir et al. (2013), who compared various materials, graded and not-graded, to reduce the stress shielding effect. However, it is worth noting that, beside the compositional gradient, Al-Jassir et al. (2013) considered an additional factor, namely the stem length. From the 3D FE simulations, it emerged that, for all the implant materials (graded and not-graded), the Von Mises stresses at the bone cement increased significantly with the stem length, whereas the shear stress decreased.

Oshkour et al. (2013a; 2013b; 2014a; 2015) used full three-dimensional FE models to analyze different geometrical configurations (cross section and profile) of FGM femoral prostheses; they also took into account various working conditions, such as with/without cement and before/after bone ingrowth (the latter defined as nonbonded/bonded configurations, respectively). Independently of the single profiles optimized in each contribution, the simulations proved that the stress distribution and variation could be adjusted by means of a combined design of gradient index and implant geometry, a result which is expected to prolong the duration of hip replacements.

Moreover, it is worth noting that Oshkour et al. (2014b) adapted their models to account for the different anchoring solutions to the spongy bone as well as for different loading

conditions induced by everyday life activities, such as walking and stair climbing. The models are interesting because they help to understand from a biomechanical point of view how and why stair climbing induces more dangerous effects to femur prostheses compared to normal walking, by causing more stress, with a different distribution.

As a step forward, Gong et al. (2012, 2103) implemented the bone functional adaptation theory into their FE models in order to account for the long-term response of femoral implants. In fact, after a preliminary contribution based on very simplified geometries (Gong et al. 2012), Gong et al. (2013) integrated the quantitative bone functional adaptation theory with accurate FE models to reproduce the remodeling phenomena occurring in proximal femur after implantation. According to the simulations, FGM implants caused less bone loss than conventional titanium alloy stems, with optimal results for the titanium/HA/collagen graded device which was able to relieve the stress shielding effect most efficiently.

To conclude, Hedia (2005) applied the same computational approach described above, based on the comparative study of 1D- and 2D-FGMs, to the specific optimization of the backing shell of the acetabulum in a cemented hip implant. Even if the reduction in the stress shielding factor was greater with 2D-FGMs than with 1D-FGMs, Hedia (2005) recommended to fabricate the shell with a 1D-FGM and not with a 2D-one, because the manufacturing cost for the former would be lower and the performance would be about the same, especially if the effect on the stress distribution in the overall shell-cement-bone system is concerned. Similar results were predicted also for graded cementless metal-backed acetabular cup prostheses (Hedia et al., 2005).

4.3. Intervertebral discs

Migacz et al. (2014) applied a combined experimental-computational approach to investigate the mechanical properties of various FGMs based on carbon fiber/polysulfone composites, and to compare them to the properties of a natural intervertebral disc. In particular, the computational simulations, based on a simplified FE model of the C6-C7 level segment, aimed to verify if a proper elastic gradient could meet the biomimetic criteria of mechanical behavior.

From an experimental point of view, the elastic modulus of all the graded materials was in good agreement with the property range of the spongy bone, the vertebral arch, the annulus fibrosus of the intervertebral disc and the endplate. Moreover all the graded materials displayed a good durability under long-term static load during *in vitro* tests. Also

the fatigue tests on selected materials gave positive results. However, the computational activity suggested that the materials with a gradient based on a change in the fibers' volume could be more advantageous than the ones based on a change in the fibers' orientation, because the elastic profile associated with the volume change induced a proper stress distribution at the implant-bone interface, similar to the natural stress pattern for intervertebral discs. Apart from the definition of a promising FGM for artificial intervertebral discs, this contribution is interesting because it demonstrates the usefulness of numerical models to simulate the behavior of potential biomedical devices without testing them directly in the human body. Moreover, this is one of the very few contributions which combine experimental activity with computational simulations and which take into account (from an experimental perspective) other properties, such as strength, beside the elastic modulus.

4.4. Orbits

Within a wide research activity dedicated to implants to repair orbital blow-out fracture, Al-Sukhun et al. (2012) also considered stiffness-graded devices. Quite interestingly, the FE model was generated directly on computed tomography scan images of a patient who suffered an orbital blow-out fracture, preliminary treated with (not-graded) biodegradable poly-L/DL-lactide. Then the model was modified to account for a gradient in elasticity. According to the models, the use of a graded implant instead of a conventional one reduced the stress shielding effect and induced higher compressive stresses at the fractured surface, thus promoting bone healing.

4.5. Bone plates

Fouad (2010, 2011) concentrated on the simulation of functionally graded bone-plates to support the healing process of fractured long bones, such as the human tibia. In fact, for relatively simple fractures, the state-of-the-art approach is based on the insertion of an internal fixation device, such as a bone-plate, which is fixed to the bone over the fracture site by means of metal screws. The bone-plate holds the bone fragments in position, avoids tensile stresses at the fracture site and even induces a critical amount of compressive stress at the fracture interface to accelerate bone healing. Unfortunately, current bone-plates are made of high-stiffness metals, such as titanium and its alloys or stainless steel, which are a main cause for the stress shielding effect. After the seminal works by Ramakrishna et al. (2004, 2005) and Ganesh et al. (2005), who proposed to use contacted

functionally graded bone-plates instead of conventional ones, Fouad (2010, 2011) suggested to combine the idea of a stiffness-graded material with a new implant design, characterized by the presence of a gap between the bone-plate and the fractured bone. The results of the simulations proved that the stress level on the fractured long bone, especially at the fracture site, increases significantly when the torsional load is considered in addition to the compressive load. So, a realistic simulation of internal fixation devices should take into consideration such combined loading condition. However, according to the simulations, the stress shielding effect can be reduced using functionally graded plates instead of conventional ones, and a further benefit derives from the non-contacted geometry.

4.6. Porous graded devices

Several contributions investigate the effect of porosity on the mechanical behavior of bone tissue and potential artificial substitutes (Wang et al., 2008). The simulation activity in the field is extremely difficult, because multiscale approaches are required to account for the complex architecture of graded porous materials (Tang et al., 2011).

In order to bypass the limitations of conventional metal-based femoral stems, such as the stress shielding effect and the potential release of debris from tapered junctions, Hazlehurst et al. (2013a, 2013b, 2014) proposed to produce Co–Cr–Mo monoblock stems with a controlled gradient in porosity in order to modulate the local stiffness. At first, Hazlehurst and co-workers concentrated on the feasibility by selective laser melting (SLM) of square-pore Co–Cr–Mo cellular structures with and without a gradient in porosity (Hazlehurst et al. 2013a and 2013b, respectively). Subsequently, Hazlehurst et al. (2014) combined experimental results and computational simulations to evaluate the performance of various SLM graded porous Co–Cr–Mo stems. All the graded designs included a fully-dense Co–Cr–Mo outer skin (1 mm thick) and a porous core with a square pore cellular structure. The Authors could demonstrate that graded porous stems were lighter and less stiff than conventional fully dense prostheses, with relevant advantages in terms of stress distribution. From a technological point of view, it is worth noting that SLM porous graded stems can be used for either cemented or cementless prostheses, since the outer metal skin can be polished for cemented fixation, whereas the surface can be processed to obtain a porous beaded topography for cementless fixation. Nevertheless, as stressed by Hazlehurst et al. (2014), some concern remains about the repeatability of cellular structures with a strut size lower than 0.5 mm.

In a first contribution, Khanoki and Pasini (2012) investigated the potentiality of functionally graded cellular materials to produce hip implants for total hip arthroplasty. More in detail, the new implants were characterized by a lattice microstructure with non-homogeneous distribution of material properties. The Authors used the homogenization method to define the implant's mechanics at the micro- and macro-scale. Then they utilized a multi-objective optimization approach to determine optimum gradients of material distribution in order to minimize both bone resorption and bone-implant interface shear stresses. The procedure, which was based on a two-dimensional model, was applied to the design of a left implanted femur; moreover, to define the loading conditions, the simulation was limited to the stance phase of walking (static load). In spite of these simplifications, the results were interesting, since the optimized cellular implant induced a reduction of 76% of bone resorption and 50% of interface stresses, with respect to a conventional fully dense titanium implant. In addition, the Authors manufactured a proof-of-concept of the optimized graded cellular implant by rapid prototyping. Even if the template was fabricated in polypropylene and it was simplified from a geometric point of view, it was nonetheless an important evidence of the feasibility of implants with an optimized gradient in relative density.

As previously mentioned, this first contribution (Khanoki and Pasini, 2012) was limited to simulate the stance phase of walking, which implies a static loading condition, whilst a hip prosthesis is expected to face cyclic dynamic forces generated by everyday life activities, like walking (Khanoki and Pasini, 2013a). Consequently, in a recent contribution, Khanoki and Pasini (2013b) widened their models to account also for fatigue phenomena under high cycle regime. The two-dimensional simulations included a Ti–6Al–4V implant with a graded porosity and both square and Kagome lattices were considered. According to the simulations, the amount of bone loss for the square and Kagome lattice implants was respectively 54% and 58% lower than that for a fully dense titanium graft. The maximum shear interface failure at the distal end of the implant decreased as well, with a reduction of about 79%. To conclude, a set of 2D proof-of-concepts was produced via electron beam melting (EBM) to prove the manufacturability of the new implants.

Wang et al. (2006) worked on graded cellular structures and proposed them to enhance the stability of implant-bone interfaces in cementless grafts. In particular, the Authors designed a new acetabular cup based on a cellular structure with a gradient in porosity for hip replacement. By means of an analytical approach, the cellular structure was adaptively distributed from high porosity at the bone-implant interface to solid metal at the joint's

articulating surface. Then, a CAD model was created to compare the new cellular design with existing products. Appropriate manufacturing techniques, based on additive manufacturing via three-dimensional printing, are now under investigation to produce such graded cellular structures (Williams et al., 2011).

Gabbrielli et al. (2008), instead, proposed a microstructural shape design approach based on spatial periodicity to outline open porous materials for (generic) bone substitution and they assessed the feasibility of such porous structures by rapid prototyping.

5. Manufacturing techniques

As previously outlined, several optimization studies are available in the literature, but most of them are merely theoretical, since they only propose the best material or the best material-geometry combination for a given application as determined by means of computational simulations and numerical approaches. Unfortunately, this is not enough, because appropriate technologies are required to turn the hypothetical design into a real device (Miyamoto et al., 1999). The research is intensive in the field, and indeed new deposition processes are emerging to create graded coatings and also new technologies are disclosing the possibility to produce functionally graded three-dimensional (3D) parts (Jamaludin et al., 2013; Kieback et al., 2003; Mahamood et al., 2012; Sobczak and Drenchev, 2013). For the sake of clarity, it should be underlined that, in the present contribution, "3D FGMs" should be intended as "self-standing FGM bodies". In such terms, the definition is somewhat generic, because it includes a variety of geometries, from simple cylinders to complex femur prostheses. However, all of them share a common feature, i.e. the absence of a substrate.

The following paragraphs will be dedicated to a brief description of the principal techniques proposed in the literature to produce graded coatings and 3D FGMs for orthopedic applications. However it is worth noting that some techniques, such as electrophoretic deposition, are suitable to produce both graded coatings and 3D graded parts, so the distinction is simply indicative. To conclude, a final section is dedicated to FGMs with a gradient in porosity ("graded scaffolds"), which need attention since they are an emerging class of materials to support bone healing processes (Pompe et al., 2003).

5.1. Functionally graded coatings

The introduction of biologic coatings may be extremely advantageous to promote the clinical outcome of orthopedic patients, since, according to their composition and

properties, such coatings can improve osteointegration, limit the foreign body reaction and reduce the risk of infection (Bosco et al., 2012; Goodman et al., 2013; Odekerken et al., 2013; Surmenev et al., 2014). Nowadays, last-generation coatings are emerging, which include functionally graded structures and/or hybrid organic-inorganic composites (Sun et al., 2012).

Multi-layered and continuously graded coatings may be regarded as a development of conventional bi-layered coatings, which simply comprise a bond coat and a functionalizing topcoat. The bond coat primarily serves to improve the topcoat's adhesion and stability. However, the benefits deriving from the presence of a bond coat are manifold, especially in biological applications, because the bond coat is expected to increase the coating durability, to hinder the release of metal ions from the metal substrate and to reduce the fatigue phenomena caused by the cyclic loading-unloading of the implant in service conditions (Goller, 2004; Heimann, 1999, 2006; Kurzweg et al., 1998; Oktar et al., 2006).

However, with respect to conventional bi-layered coatings, multi-layered and functionally graded structures are more favorable, since they integrate different materials without inducing severe internal stresses and, at the same time, they combine different properties in one material system. Unfortunately, against such benefits, multi-layered and continuously graded coatings are more complicated to produce.

Even if the state-of-the-art is deposition by thermal spraying, and especially atmospheric plasma spraying (Heimann, 2006), several techniques are now available to manufacture coatings for biomedical applications and many of them have already been applied successfully to obtain compositionally graded systems (Bellucci et al., 2011; Surmenev et al. 2014). In the following sections, some of the most relevant deposition techniques for FGCs in orthopedic implants will be analyzed and discussed. Table 3 provides a synthetic overview, which guides the reader to locate "at a glance" the various approaches available in the literature to deposit FGCs.

5.1.1. Conventional thermal spraying (on dry powders)

As already said, thermal spraying techniques, particularly plasma spraying ones, are widely diffused, due to their high productivity and excellent flexibility. Moreover they have the ability to keep the substrate at relatively low temperature, which is helpful to avoid microstructural alterations and thermal distortions.

In conventional thermal spraying techniques, a flux of dry powder is injected in a hot gas jet, the jet melts the particles and accelerate them towards the substrate. Then, the molten

(or semi-molten) particles impact onto the substrate, flatten and solidify, thus assuming the typical lamellar morphology ("splats"). The coating therefore results from the progressive overlap of many layers of splats, which adhere to one another (Fauchais, 2004; Herman et al., 2000; Tucker, 2013).

The use of thermal spraying to fabricate FGCs for orthopedic applications was precocious and early attempts date back to the '90s (Kyeck and Remer, 1999). Not surprisingly, almost all of the available literature is dedicated to the production of HA-based coatings, in the attempt of working out the numerous drawbacks of conventional HA coatings, such as poor adhesion and thermal degradation during deposition (Cheang and Khor, 1996). With this aim, different approaches have been attempted, which implies the introduction of a structural gradient, as a result of the deposition of HA powders with different size ranges, or the development of compositional gradients, as a result of the combined processing of HA powders with other phases, such as α-tricalcium phosphate (α-TCP), Ti-6Al-4V, titanium, titania, zirconia. In Figure 2, a simplified sketch summarizes the different approaches applied to produce HA-based FGCs by conventional plasma spraying.

For example, the former strategy, based on a *structural gradient*, was proposed by Khor et al. (1998), who processed HA powders with different size ranges and hence with different thermal responses to the plasma flame. As a term of comparison, they also considered a compositional gradient obtained by mixing HA and α-TCP in various proportions (see also Wang et al., 1998). To investigate the influence of the feedstock powders further, Wang et al. (1999) analyzed again various coatings produced from different flame spheroidized HA powders. They compared the resulting HA structurally-graded coatings with FGCs sprayed using mixtures of flame spheroidized HA powders and spherical α-TCP powders, and using mixtures of flame spheroidized HA powders and titania powders. Coherently with the results of the studies by Kweh et al. (2000), which were focused on single phase not-graded HA coatings, Wang et al. (1999) concluded that the mechanical reliability of the FGCs was adversely affected by the particle size distribution of the flame spheroidized HA powders, since the fracture toughness of the coatings decreased as the feedstock particle size increased. However, it is worth noting that in the composite graded coatings proposed by Wang et al. (1999), the presence of a tougher ceramic phase, either α-TCP or titania, was useful to improve the fracture toughness with respect to pure HA coatings, which confirms the advantages of *compositional gradients*.

The toughening effect of titania was also exploited by Lu et al. (2004), who plasma-sprayed a two-layered coating, consisting of a composite titania/HA bond coat and of a HA topcoat,

on titanium substrates. The composite bond coat was helpful to reduce the thermodilatometric mismatch between the HA topcoat and the metal substrate. Moreover the presence of titania hindered the crack propagation and reduced the near-tip stresses resulting from stress-induced microcracking.

More articulated but still very controlled titania/HA FGCs were built up by conventional air plasma spraying by Cannillo et al. (2008a, 2008b, 2009a, 2009b). In order to obtain the compositional gradient, titania and HA powders were sprayed together in appropriate proportions by means of parallel feeding systems. However, the co-deposition implied an accurate pre-optimization of the spraying parameters, since pure titania is thermally stable and requires "hot" deposition conditions, whereas HA is susceptible to thermal decomposition (Cannillo et al., 2008b, 2009b). The Authors paid great attention to eventual post-deposition treatments to control the degree of crystallinity of HA on the working surface, which played a controversial role. In fact, increasing the degree of crystallinity improved the mechanical behavior, but it also increased the chemical resistance, thus reducing the reaction kinetics in SBF (Cannillo et al., 2008a, 2009a). An example of the as-sprayed titania/HA graded coatings (polished cross section) is reported in Figure 3.

In order to improve the affinity to the titanium alloy substrate, Khor et al. (2003) combined HA with Ti-6Al-4V to create the compositional profile. The contribution by Khor et al. (2003) is particularly interesting on account of the approach applied to create the FGC. As a matter of fact, the thermally sprayed FGCs described in the literature are often obtained starting from single-phase powders. In that case, the single powders are either pre-mixed before spraying (and the gradient is built up by the progressive deposition of various powder mixtures) or separately injected through different feeding lines. Khor et al. (2003) proposed instead an alternative route, based on the deposition of *ad hoc* composite powders. In fact, they prepared two composite powders with different compositions (50 wt.% HA/50 wt.% Ti–6Al–4V and 80 wt.% HA/20 wt.% Ti–6Al–4V) by means of a ceramic slurry mixing technique and they used Polyvinyl alcohol (PVA) to glue the HA particles (smaller than 20 μm) onto the Ti–6Al–4V particles (between 50 and 105 μm). The powders were treated and stabilized prior to deposition. The final FGC comprised three layers, the first one (in contact with the metal substrate) composed of the 50 wt.% HA/50 wt.% Ti–6Al–4V composite powder, the second one composed of the 80 wt.% HA/20 wt.% Ti–6Al–4V composite powder, and the third one (topcoat) composed of pure HA.

Chen et al. (2006) used titanium as second phase. In particular, the compositional gradient, from pure titanium at the interface with the substrate to pure HA on the surface, was

created by changing gradually the feeding rate and the input power for the two seprate powders. The surface chemistry and morphology of the FGCs were comparable to those of conventional HA plasma sprayed coatings, however the bond strength values of the as-sprayed FGCs were superior. Beside the structural advantages, the compositional gradient exerted a beneficial effect on the fatigue resistance of the coatings, both as-sprayed and soaked in Hank's balanced salt solution (HBSS).

Thick titanium/HA FGCs were produced by Inagaki et al. (2001) using a radio-frequency (RF) plasma spraying process. First, pure titanium powder was applied to the substrate (either commercial titanium plates or commercial titanium alloy plates, type SP700) in order to create a rough surface. Then a graded titanium/HA coating was created by means of a differentiated feeding ratio of the feedstock powders, with the coating's composition becoming richer in HA toward the outer surface. The X-ray diffraction (XRD) patterns clearly showed that the HA-rich layer on the surface had an apatite structure with a preferred (0 0 1) crystallographic orientation (i.e. in the c-axis). However, the degree of preferred orientation was lower for the graded coatings applied on the introductory titanium interlayer than for pure HA coatings deposited on bare metal substrates, which indicates that the surface roughness and composition affect the degree of preferred orientation on the HA surface.

A more complicated compositional profile was proposed by Ning et al. (2005), who produced titanium/zirconia/HA FGCs on Ti–6Al–4V substrates by means of a net-energy controlled plasma spraying process. In particular, three independent microfeeders were used for the feedstock powders and the starting compositions were adjusted to change gradually from titanium-rich deposition at the bottom layer (in close contact with the titanium alloy substrate), to zirconia-rich deposition at the middle layer, and to HA-rich deposition at the top layer. The resulting gradient in composition induced a smooth change in hardness and elastic modulus from the substrate to the HA topcoat. The bonding strength of the FGC was much higher than that of a reference HA single coating having the same thickness (both coatings thermally treated at 750 °C for 2 hours in atmosphere).

To conclude, it is interesting to note that thermal spraying techniques can be adapted to create also porous graded coatings (Zhang et al., 2007) (for a wider presentation of porosity graded materials, see section 5.3). Yang et al. (2000), for example, obtained graded porous titanium coatings on titanium substrates by plasma spraying in an argon atmosphere. The gradient in porosity was controlled through an accurate regulation of the feeding powder and the spraying power. As a result, the coating included three layers: the

external one was rich of macropores (diameters up to 150 μm), the intermediate one displayed both macro- and micro-pores, and the internal one was very dense and perfectly bonded to the substrate. Even if such graded porous coating was originally proposed for dental implants, the rich porosity of the external layer could be optimal for bone tissue ingrowth and, at the same time, the dense internal layer could assure long-term stability. Therefore, the graded porous coating could be suitable not only for dental application, but also for orthopedic usage.

5.1.2. Innovative thermal spraying (on suspensions)

With respect to conventional thermal spraying methods, which operate on "dry" powders, the new suspension spraying techniques, both Suspension Plasma Spraying (SPS) and High-Velocity Suspension Flame Spraying (HVSFS), make it possible to process suspensions of very fine particles, in the sub-micrometer or even in the nanometer range. The fine and compact microstructures provided by suspension spraying techniques usually result in thin (few tens of microns) and extremely dense layers, in which all the peculiar features of thermal sprayed coatings are refined. Additionally, very thin layers are less sensitive to residual stresses (Gadow et al., 2008; Pawlowski, 2009).

Suspension methods have been proposed for both HA-based and bioactive glass-based FGCs. For example, Tomaszek et al. (2007) produced titania/HA multi-layered coatings using the SPS technique. It is worth noting that the use of such deposition method is expected to affect the titania polymorphism. In fact, as suggested by the available literature on the argument (Tomaszek et al., 2006), the presence of rutile is expected if large particles are processed with conventional spraying techniques; to the contrary, since the cooling rate is modified for small particles with respect to large ones, the formation of anatase, which is the metastable phase of titania, is expected while spraying very fine powders with the SPS technique. As proved by Tomaszek et al. (2007), the titania/HA multi-layered coatings obtained by SPS presented a good interface with the titanium substrate. As a general trend, if the electric power input to the torch increased, the cohesion and compactness of the coatings got better, but the structural integrity of HA got lost due to thermal decomposition. So the Authors could define an optimum value of the electric power input (40 kW) to compromise between such opposite trends. According to the accurate investigations on the argument carried out by Jaworski et al. (2010), the use of an internal continuous stream injector fed by a pneumatic suspension feeder seems to be the way to limit the porosity of titania/HA suspension sprayed coatings.

Cattini et al. (2103, 2014a, 2014b) concentrated their attention on advanced HA/bioactive glass coatings deposited on 316L stainless steel by means of the SPS technique. The basic idea was to combine the high bone-bonding ability of bioactive glasses with the long-term stability of (highly crystalline) HA. In an introductory contribution, Cattini et al. (2104a) could ascertain the effectiveness of a thin bioactive glass topcoat applied on an air-plasma-sprayed HA layer to fasten the reactivity in a Simulated Body Fluid (SBF). Then, in a second paper, Cattini et al. (2104b) produced various types of HA/bioactive glass biphasic coatings in order to emphasize the effect of the constituents' distribution. The Authors compared three different systems, i.e. (1) a conventional 50-50 HA/bioactive glass composite coating, (2) a 50-50 bi-layered coating consisting of a pure bioactive glass topcoat on a pure HA intermediate layer, and (3) a preliminary 50-50 multi-layered HA/bioactive glass graded coating. The results confirmed that the presence of a bioactive glass layer on the working surface was effective to promote the bone-bonding ability of the coating, since the reactivity in SBF of both the bi-layered coating and the initial FGC was definitely higher than that of the composite coating. On the other hand, the sharp interface between the glass topcoat and the HA intermediate layer was detrimental to the scratch resistance of the conventional bi-layered coating and hence the FGC, with its gradual change in composition, emerged as the optimal choice. In a third and concluding article specifically devoted to bioactive glass/HA FGCs, Cattini et al. (2103) improved the SPS method by tuning the suspension feeding rates in order to account for the different deposition efficiency of bioactive glass and HA powders. Moreover the spraying parameters were optimized in view of an industrial application of the coatings. The obtained FGCs had a strong reactivity in SBF and preserved a high scratch resistance even after soaking, thus confirming their potentiality for biomedical applications.

5.1.3. Glass-based functionally graded coatings by firing/enameling

Apart for thermal spraying techniques, which are relatively complicated and expensive, alternative methods exist to produce glass-based graded coatings for biomedical applications. A very common approach is given by the "enameling technique", which implies to create a graded coating by firing and melting a glass-based surface deposit. The literature on the subject is rich, however some basic trends can be outlined, as represented in Figure 4. A basic distinction can be made according to the substrate, which can be a ceramic body (Figure 4a-d) or a metal body (Figure 4e-g). The enameling technique is indeed relatively simple if it is applied to a ceramic substrate such as alumina, which

benefits from its excellent thermal stability. Moreover, it is known from the literature that the glass, in the molten state, is able to penetrate through the grain boundaries of the ceramic (polycrystalline) substrate, thus creating a graded zone (Cannillo et al., 2006b; Kuromitsu et al., 1997). An example of bioactive glass coating enameled on alumina is presented in Figure 5. Instead, if metal substrates are involved, an accurate assessment of the firing conditions (time, temperature and, if required, working atmosphere) is mandatory to avoid the thermal degradation of the substrate (for example, the α → β transformation is situated between 885 °C and 950 °C for unalloyed titanium and between 955 °C and 1010 °C for Ti–6Al–4V, with slight differences which depend on the presence of impurities (Lopez-Esteban et al., 2003)) and to limit as much as possible any adverse reaction between glass and metal (Gomez-Vega et al., 1999; Sola et al. 2014). In order to create a compositional gradient, a single glass is enough if the substrate is a ceramic body, due to the aforementioned percolation process (Figure 4a, Figure 5). Of course, more complicated profiles can be achieved if two (or more) glasses are applied in sequence (Figure 4b). Instead, if the substrate is a metal body, one glass is not enough to create a FGC, since the percolation process is not active. So, in order to create a glassy FGC on a metal substrate, at least two glasses are required (Figure 4e). For both types of substrate, ceramic and metal, the enameling technique can be adapted to produce "composite" FGCs, which should be intended as glass-based FGCs where the glass works as a matrix for a second (non glassy) phase, such as HA, used to modulate the bioactivity, or zirconia, used to improve the mechanical resistance (Figure 4c and Figure 4f). To conclude, as a borderline case of "composite" FGCs, the glass can be also thought simply as a glue to "fix" a surface layer for other particles (e.g. HA) to the substrate (Figure 4d and Figure 4g).

Ceramic substrates: An example of FGC based on the percolation of only one glass into a ceramic substrate is described by Kim et al. (2010). In fact, the Authors exploited the percolation process to apply a silicate-based glassy FGC to both sides of a zirconia plate. As proved by frictional sliding tests, the engineered gradient in elastic modulus at the ceramic surface resulted in a significant increase in the fracture load, by over a factor of 3, with respect to the original pure zirconia substrates (Kim et al., 2010).

Verné et al. (2000) and Vitale-Brovarone et al. (2001, 2012) conducted an extensive research activity on bioactive glass-based FGCs on alumina substrates. At first, Verné et al. (2000) and Vitale-Brovarone et al. (2001) built up the graded deposits by combining different glasses, used alone or eventually reinforced with zirconia particles, in order to smooth the thermodilatometric change, which is reportedly one of the main causes for

interface failure. Vitale-Brovarone et al. (2012) developed such approach further to create bioactive glass-derived trabecular coatings. In fact, they joined a glass-ceramic scaffold to an alumina substrate by means of a dense glass interlayer.

In order to obtain glass-based "composite" FGCs, Kim and Jee (2003) focused their attention on the controlled and selective crystallization of the glass. The Authors suspended a first glass powder in an acetone solution and spray-coated it directly on the alumina substrates; such glass layer was intended to act as a bond coat. The second glass layer on top was fired either at 1100 °C, to induce the prevalent crystallization of β-wollastonite, or at 1200 °C, to favor the development of α-wollastonite. When the samples reacted in SBF, the leaching rate of α-wollastonite was faster than that of β-wollastonite and hence the HA-forming rate in SBF was faster for the sample fired at 1200 °C. For both systems, the Authors could not detect any silica-rich layer underneath the HA layer precipitated in SBF.

Besides the contribution by Vitale-Brovarone et al. (2012) mentioned above, the idea of using the glass like a glue was not completely new, since it had already been proposed in the past (Evans et al., 1994). For example, Yamashita et al. (2008) prepared various glass-HA mixtures with increasing amounts of HA and then they painted the mixtures on zirconia substrates; to conclude, they added a pure HA topcoat. The samples were fired at 900 °C to melt the glass, which cemented the HA particles. However, it is worth noting that, unlike Vitale-Brovarone et al. (2012), Yamashita et al. (2008) considered the glass mainly to fix the HA particles, and not to impart specific functionalities.

Metal substrates: An interesting paper by Foppiano et al. (2006) is focused on the reproducibility of the enameling technique with metal substrates and on the stability of the corresponding glassy FGCs under cell culture conditions. The coatings were fabricated on Ti–6Al–4V plates using a glass containing 61 wt.% silica in contact with the substrate and a bioactive glass containing 55 wt.% silica on the external surface. After drying in air at 80 °C for 48 h, the green coatings were fired in air in a dental furnace. With respect to the original glass used on the surface, which remained amorphous after thermal treatment, the firing process induced a partial crystallization in the FGCs. However, it is worth noting that the degree of crystallization was similar for various batches of FGCs (about 5.9 vol.%). Moreover, also the average thickness of the FGCs was the same for various batches, which proved the repeatability of the enameling process. In spite of the partial devitrification, the bioactivity in SBF was the same for the FGCs and for the original glass. Nevertheless, the sub-surface glass silica network in the FGCs was compromised by cell culture conditions

and therefore an SBF-pre-conditioning was useful to stabilize the coatings. A subsequent investigation of cytocompatibility and effectiveness on gene expression (Foppiano et al., 2007) proved that the pre-conditioned FGCs are cytocompatible and that appropriate compositional adjustments are expected to induce preferred gene expression.

If glass-based "composite" FGCs are considered, Du et al. (2006) mixed various composite powders with different bioactive glass-to-nanohydroxyapatite ratios and used them to overlay titanium substrates with several layers to create the compositional profile. A thermal treatment was performed at 800 °C to consolidate the FGC. In a subsequent paper, Xie et al. (2010) reported the results of histologic and histomorphometric studies performed on such bioactive glass/nanohydroxyapatite FGC. The Authors found that the bone-implant contact and the new bone volume were much greater for the grafts with the FGC than for those with a bare surface or with a conventional HA coating.

Yamada et al. (2001) proposed the "Cullet" protocol to obtain bioactive glass/HA "composite" FGCs on titanium (or titanium alloy) substrates. This is a peculiar method, because the various bioactive glass-HA powder mixtures are preliminary sintered at 900-1000 °C for 5-10 minutes and then pulverized and sieved. In this way, very well homogenized bioactive glass-HA composite powders can be obtained ("Cullet powders"). The Cullet powders with various glass-to-HA ratios are then used for coating and firing repeatedly. After the last firing step, the specimen is etched in a mixed acid solution of 3% HF and 5% HNO_3 to remove the superficial glass in excess and expose the HA particles. *In vivo* tests proved that the implants bonded to bone directly and that bone was able to grow into the FGCs. Moreover, pull-out experiments confirmed the reliability of the coatings and the strong bond to bone tissue.

Kasuga et al. (2003) induced a controlled devitrification to create the compositional profile. The Authors considered a calcium-phosphate invert glass with the composition: 60 CaO-30 P_2O_5-7 Na_2O-3 TiO_2 in mol%. They produced the glass by a conventional melting technique and used the milled glass to dip-coat pure titanium, Ti–6Al–4V alloy and β-type Ti–29Nb–13Ta–4.6Zr (TNTZ) alloy substrates. The green coatings were fired in air at 800 °C for increasing times, up to 12 h. According to the Authors' findings, the glass devitrified and the crystals precipitated from the glass partially melted during the thermal treatment; this activated a viscous flow process. At the same time, the metal substrate experienced an oxidation process. The Authors reasoned that the concomitant occurrence of these phenomena (namely controlled crystallization, viscous flow of the melt and build-up of an oxide surface layer) was responsible for the attachment of the coating to the substrate and

for the automatic development of a compositionally graded profile. Nevertheless it is worth noting that the adhesion strength was deeply affected by the substrate's nature, which governed the thickness of the oxidized layer. In fact, thick oxidized layers, which were typical of pure titanium and Ti–6Al–4V alloy, were associated with large tensile stresses, which undermined the coating's stability. In contrast, the oxidized layer grown on the TNTZ alloy substrate was very thin and therefore it did not generate large residual stress. As a consequence, it was effective to promote the coating's adhesion. The work by Kasuga et al. (2003) deserves a special mention, since this is one of the very few contributions in the literature dedicated to FGCs based on invert glasses, instead of silicate ones that are definitely prevailing due to the established role of Bioglass® 45S5 (composition in wt%: 24.5% Na_2O, 24.5% CaO, 6% P_2O_5, 45% SiO_2) in orthopedic devices (Hench, 2006).

As far as the "glue approach" is concerned, Gomez-Vega et al. (2000) used silicate-based glasses with a coefficient of thermal expansion similar to that of Ti–6Al–4V to create an "adhesive" layer and to embed Bioglass® or HA particles on the surface, in order to enhance the bioactivity. The HA particles were immersed partially during firing and hence they remained firmly glued after cooling. No reaction occurred between HA particles and surrounding glass matrix. Instead the Bioglass® particles softened and some infiltration into the surrounding glass took place during firing. In order to stabilize the Bioglass® powder, relatively large particles (over 45 μm) were required. It is interesting to note that, independently of the nature of the added particles, either HA or Bioglass®, the concentration of the particles was limited to 20% of the available surface, since concentrations above this threshold value resulted in excessive stresses and cracks.

To conclude, García et al. (2006) modified the standard enameling procedure to deposit sol-gel derived coatings on Ti–6Al–4V substrates. In fact, the Authors used the sol-gel method to process glass-based double-layered coatings, where the top layer contained bioactive glass, glass-ceramic or HA particles. The presence of the coating greatly improved the corrosion resistance in SBF with respect to bare Ti–6Al–4V substrates. This improvement was likely caused by the reaction of the embedded particles with the physiological medium (i.e. SBF), which induced the formation of calcium phosphate crystals that blocked the porosity of the coating.

As a general consideration, which remains valid beyond the biomedical field, it is clear from the literature that both thermal spraying and firing are suitable methods to produce glass-based FGCs. Nevertheless, each of them has its pros and cons. According to the definition proposed by Mortensen and Suresh (1995, 1997), thermal spraying techniques

are "constructive processes" to fabricate FGMs, since the gradient is built up layer by layer; on the contrary, enameling is an example of "transport-based processes", since it exploits natural transport phenomena resulting in a smooth spatial change of composition and/or microstructure. In constructive processes, the procedure can be computer-controlled and automated, which ensures high reproducibility and easy industrial scale up; nevertheless the equipment required (for example, a plasma spraying plant) is usually extremely expensive and complicated to manage. Transport-based methods are less reliable, since the control on the final gradient is less strict; however, they are relatively simple and they often require a very basic apparatus (for example, a laboratory kiln) (Cannillo and Sola, 2010).

5.1.4. Electrophoretic deposition

Generally speaking, in the electrophoretic deposition (EPD) process, charged powder particles, which are dispersed or suspended in a liquid medium, are attracted and deposited onto a conductive substrate of opposite charge due to the application of a DC electric field. The technique is interesting, on account of its cost-effectiveness and its versatility with different materials (which can be processed alone or in combination) (Besra and Liu, 2007; Boccaccini et al. 2010).

The EPD has proved to be a very flexible method to produce also multi-layered and graded coatings. In principle, the basic idea to obtain multi-layered coatings is relatively simple, since the deposition electrode is moved to a second suspension for the deposition of a second layer of different composition after that the desired thickness for the first layer has been reached. By moving back and forth, a layered material can be built up. Analogously, FGMs can be produced by gradually changing the composition of the suspension from which EPD is carried out (Boccaccini et al. 2010; van der Biest and Vandeperre 1999). A great advantage of EPD with respect to the other techniques reviewed so far is that not only inorganic, but also organic phases can be processed.

For example, if merely *inorganic coatings* are considered, Balamurugan et al. (2009) built up bioglass/apatite FGCs on Ti–6Al–4V substrates using the EPD technique. The coatings, investigated for their structural, electrochemical and mechanical properties, proved to increase the chemical stability and corrosion resistance in SBF with respect to uncoated Ti–6Al–4V.

Again, working with the EPD method, Stojanovic et al. (2007) synthesized bioactive glass/apatite FGCs on Ti–6Al–4V substrates. They added nanostructured HA particles in

the glass topcoat, in order to enhance its bioactivity. The EPD resulted to be a reliable technique, since the deposition weight and coating thickness could be controlled strictly by tuning the deposition voltage and time.

Araghi and Hadianfard (in press) focused on the integrity of titania/HA FGCs on Ti–6Al–4V substrates and calibrated the concentration of iodine and polyethylenimine (PEI) additives in the EPD suspensions to obtain crack-free deposits. With respect to HA single layer coatings, the FGCs were more prone to decompose during sintering, but they achieved superior adhesion strength.

As previously mentioned, the EPD is suitable to deposit also *organic phases*, which may contribute to mimic the natural structure of bone tissue. For this reason, Grandfield and Zhitomirsky (2008) used the EPD to manufacture HA/silica/chitosan coatings of graded composition and various laminates. Pang et al. (2009) developed such approach further to obtain HA/$CaSiO_3$/chitosan composite coatings for biomedical applications. The presence of chitosan in the final coatings was intended to reproduce the bone tissue architecture; however, the use of chitosan solutions was useful from a technological point of view, too, because the inorganic particles were dispersed in the chitosan solution directly. In a contribution by Sun et al. (2009), not only HA/chitosan multi-layered systems and FGMs were produced, but also chitosan and heparin were co-deposited by EPD. Such chitosan/heparin composite coatings were used to modify the surface of HA/chitosan systems, because they were intended to improve the blood compatibility.

It is worth noting that, besides graded and non-graded coatings, recent contributions have demonstrated the feasibility of 3D objects by EPD, such as femoral ball-heads. In fact, the EPD has been successfully used as a near-net-shaping technique to obtain functionally graded femoral ball-heads composed of alumina (external part) and zirconia (core), thus proving the effectiveness of such method to deal with complex geometries (Anné et al., 2006).

It is clear from the literature that the EPD technique can be extended to the deposition of a variety of organic-inorganic composite coatings and even bodies of complicated shape. The research in the field is now focused on the possibility of providing the implant material with the hierarchical organization of structural features that is typical of bone (Zhitomirsky, 2011).

5.1.5. Laser Engineered Net Shaping (LENS) technique

The Laser Engineered Net Shaping (LENS) is an emerging technique, useful both to deposit (graded) coatings and to create self-standing 3D parts (an overview of the potentialities of the LENS technique to produce biomedical devices is provided by Das et al. (2013)).
One of the most interesting applications of the LENS is the production of reliable Co–Cr–Mo-based coatings on titanium and its alloys. In fact, the hardness and good wear resistance of Co–Cr–Mo are expected to counterbalance the relatively poor wear behavior of titanium alloys; at the same time, Co–Cr–Mo possesses an exceptional biocompatibility and a self-healing attitude that makes it a stable and long-lasting *in vivo* option (Walker and Erkman, 1972). Unfortunately the large mismatch in thermal expansion of titanium alloys and Co–Cr–Mo usually results in cracking and delamination of the coating. The problem may be worsened by the development of brittle intermetallic phases. Wilson et al. (2013) proposed to work out such hurdles by creating a multi-layered FGC by laser direct deposition. In particular, Wilson et al. (2013) fashioned the compositional gradient by mixing Co–Cr–Mo and Ti–6Al–4V up to 50% Co–Cr–Mo over four layers, followed by a pure Co–Cr–Mo topcoat. The experiment was successful, because the bond strength of the graded coating met the ASTM standard requirements. However Wilson et al. (2013) acknowledged the importance of performing additional tests, especially to determine the overall corrosion resistance, which may be affected by the eventual development of multiple phases within each layer, and the fatigue performance.
Also Krishna et al. (2008) applied a Co–Cr–Mo-based FGC on Ti–6Al–4V substrates with a metallurgically sound interface using the LENS technique. Unfortunately, a complete transition from Ti–6Al–4V to 100% Co–Cr–Mo was difficult to produce due to cracking. Nevertheless, using optimized LENS processing parameters, crack-free coatings containing up to 86% Co–Cr–Mo were achieved. The presence of Co–Cr–Mo, without any intermetallic phase in the transition region, significantly increased the surface hardness with respect to Ti–6Al–4V. In spite of the mechanical benefits, the high content of Co–Cr–Mo alloy raised some concerns about potential allergic reactions. For this reason, human osteoblast cells were cultured to test *in vitro* the FGC biocompatibility. As a general trend, increasing the Co–Cr–Mo concentration reduced the live cell numbers after 14 days of culture on the coating compared with base Ti–6Al–4V alloy. However, all the FGCs always showed better bone cell proliferation than pure Co–Cr–Mo.
Krishna et al. (2009) applied the LENS to deposit titanium/titania FGCs on titanium substrates. Quite interestingly, the laser parameters were set to create about 30% of porosity at selected sites, which was intended to favor the bone ingrowth after

implantation. The comparative characterization of various compositional profiles, with different titania contents in the surface layer, revealed that the higher wettability imparted to the surface by the presence of titania could promote the ability to form chemisorbed lubricating films, which can potentially lower the friction coefficient against ultrahigh molecular weight polyethylene liner (the typical component for hip joint counterpart), thus reducing its wear rate (Krishna et al., 2009).

As already discussed for the EPD, also the LENS method can be used to process both FGCs and 3D graded parts. For example, the LENS has been used to fabricate complex-shaped titanium implants with a three-dimensional functionally graded porosity, which is useful to reduce the effective stiffness for load-bearing implants to values similar to those of human cortical bone (Bandyopadhyay et al., 2009; Krishna et al., 2007) (for a detailed description of the techniques to produce graded porous materials, see Section 5.3).

5.1.6. Magnetron sputtering and related techniques

Considerable efforts have been devoted to the assessment of magnetron sputtering and related techniques to process FGCs for biomedical devices.

For example, porous tantalum devices (Levine et al., 2006) as well as tantalum and tantalum oxide films (Leng et al., 2006), have been increasingly investigated for their good biocompatibility and osteoconductivity. However, appropriate treatments are required in order for the surface to support cell growth. Singh et al. (2014) proposed to apply a magnetron-sputter inert-gas aggregation system to build up porous films with a graded oxidation profile perpendicular to the substrate starting from size-selected tantalum nanoparticles. The microstructural properties described by Singh et al. (2014) are promising; unfortunately, no cell growth tests are proposed in the paper.

Ding et al. (2014a) deposited titanium/TiB_2 multi-layered graded coatings on Ti–6Al–4V substrates by magnetron sputtering. The polycrystalline structure of the TiB_2 topcoat was improved by the presence of the titanium interlayer, which resulted in a very smooth surface. Moreover the layered coating achieved a higher corrosion resistance with respect to single TiB_2 coatings.

Brizuela et al. (2002) produced titanium alloyed diamond-like carbon (DLC) FGCs by means of a PVD-magnetron sputtering technique. During the mechanical tests, the graded coatings reached a higher elastic recovery and a superior tribo-performance with respect to conventional uncoated Ti–6Al–4V and Co–Cr–Mo alloys. The graded coatings also passed

the biocompatibility tests prescribed by international standards for orthopedic implant materials.

Again, DLC, which combines high corrosion resistance and biocompatibility, may be used as protective coating for Nitinol (Ni–Ti) substrates, provided that a good adhesion is achieved. To this aim, Liu et al. (2006), working by hybrid magnetron sputtering and plasma enhanced chemical vapor deposition, introduced a Si/SiC graded interlayer and they analyzed the effect of the interlayer's thickness on the adhesion and chemical resistance. The best results were achieved by the system with a 150 nm thick interlayer, since further increasing the interlayer's thickness induced negative effects on the coating's adhesion and, consequently, on its corrosion resistance.

ZrCN single layer and Zr/ZrCN multilayered hard coatings were processed by (reactive) magnetron sputtering; in particular, Balaceanu et al. (2010) experimentally proved that the presence of the zirconium interlayer was helpful to the biological behavior of the coatings. Besides ZrCN, also zirconium nitride (ZrN) has attracted great attention due to its mechanical properties, its corrosion resistance and its good biocompatibility. Joseph et al. (2012) produced both ZrN/HA nanocomposite coatings and FGCs on titanium substrates by radio frequency (RF) magnetron sputtering. The characterization proved that the crystallite size was smaller for FGCs than for "conventional" (i.e. not-graded) nanocomposite ones. This induced a denser grain arrangement in the graded coatings, which therefore exhibited higher values of hardness and modulus. Both graded coatings and nanocomposite ones were able to induce bio-mineralization.

In order to obtain a functionally graded titanium/HA film on a titanium substrate, Ozeki et al. (2002) also operated with the RF magnetron sputtering technique. The film was composed of five layers, with a total thickness of 1 μm. The titanium-to-HA ratio was governed by moving the target shutter; in this way, the titanium concentration was increased in proximity to the substrate, whereas the HA concentration was increased in proximity to the outer surface. Both the bond strength (pull-out test) and the critical load (scratch test) were much higher for the FGC than for a pure HA sputtered film and the graded film preserved its adhesion strength even after implantation *in vivo*.

5.1.7. Other techniques

Several alternative techniques are described in the literature to manufacture FGCs for biomedical applications. The greatest part of them applies to inorganic systems only, but

some contributions also propose specific methods to work with organic phases and even drugs.

If *inorganic systems* are considered, Narayanan and Seshandri (2007) combined titania and HA in various coatings on Ti–6Al–4V substrates, in order to profit from the corrosion resistance of the former and from the good biocompatibility of the latter. The best compromise between chemical stability in SBF and potential bioactivity was achieved by applying a 50-50 titania/HA top layer on a pure TiO_2 thermally-grown intermediate layer. Roop Kumar and Wang (2002) also considered titania/HA FGCs. They coated Ti–6Al–4V substrates with a first layer of titania powders, which was sintered at 900 °C for a few minutes. Then they applied a sequence of composite layers, with different titania-to-HA weight ratios. These layers were sintered again at 900 °C for a few minutes in order to ensure a good adhesion.

He et al. (2014) applied a three-layered graded coating on titanium substrates by a multi-step sol-gel method. The coating was composed of a porous HA layer on the surface, of a fluoro-HA intermediate layer and of a titanium oxide (TiO_2) internal layer. The scratch tests confirmed a good adhesion of the FGC to the substrate and osteoblasts cultured on the coating exhibited higher cell proliferation and ALP activity with respect to pure titanium and conventional HA coatings.

Bai et al. (2009) produced calcium phosphate coatings on titanium substrates using the ion beam assisted deposition (IBAD) technique and they induced a crystalline gradient in the coatings by manipulating the substrate temperature during deposition. The highly amorphous top layer was expected to boost the osteointegration in early stages after implantation, while the crystalline bottom layer provided the coating with long-term stability. The ion beam's action intermixed the coating and substrate atoms, thus creating a very strong adhesion, superior to that commonly observed for plasma sprayed deposits. Moreover, the coating's stability and mechanical resistance were improved by the very reduced thickness, much lower than 1 μm. The manufacturing process proposed by Bai et al. (2009) was also interesting because it didn't imply any post-deposition annealing, since the thermal treatment was performed in-situ, during the deposition itself.

Shanaghi et al. (2013) improved the properties of nanostructured TiC coatings deposited on Ni–Ti substrates via plasma immersion ion implantation by adding a thin titanium interlayer, acting as a bond coat.

Another example of titanium/HA graded coating on titanium alloy was proposed by Chen and Jia (2010). The Authors applied various composite layers with different compositions

by means of the laser cladding method. Even if the original HA decomposed into calcium phosphate during the fabrication process, a preliminary osteoblast adherence test showed that the coatings had promising biological effects.

Zheng et al. (2008) properly adjusted the composition of the precursor powders to obtain a HA-based FGC by laser cladding. In fact, keeping in mind that the stoichiometric Ca/P ratio in HA is 1.67, Zheng et al. (2008) prepared a mixture of 81.1 wt% $CaHPO_4 \cdot 2H_2O$ and 18.9 wt% $CaCO_3$, which corresponds to a Ca/P ratio of 1.4, to account for the burning-induced loss of phosphorus during laser irradiation. A little ceria was added because rare earth oxides are expected to favor the formation of bioactive phases. Then, to decrease the thermal stresses between the coating and the Ti–6Al–4V substrate during laser cladding, the Authors designed a three-layered coating, with a first stratum with 80% titanium, a second stratum with 40% titanium and a third stratum with pure calcium phosphate precursors on top. The final coating resulted metallurgically bonded to the titanium alloy substrate. At the same time, the special composition of the precursor powders promoted the development of HA and β-tricalcium phosphate. The compositional gradient implied a functional gradient, since the microhardness gradually decreased from the coating to the substrate, which could help stress relaxation. To conclude, the laser-cladded FGC induced more favorable osteoblast response with respect to the surface of untreated Ti–6Al–4V.

Tanaskovic et al. (2007) obtained multi-layered glass/apatite FGCs on titanium substrates by laser pulsed deposition (LPD). In order to limit the thermodilatometric mismatch, the Authors applied a first thin layer of a special glass (6P61) on the metal substrate. The coefficient of thermal expansion of this glass is indeed quite similar to that of pure titanium. However this glass is not bioactive and therefore the Authors added one or more layers composed of HA and/or another bioactive glass. The FTIR characterization proved that the deposition process had not caused appreciable changes in the activity of the functional groups of the HA topcoat.

Kongsuwan et al. (in press) processed a bioactive glass coating by continuous-wave (CW) laser irradiation and adjusted the processing parameters to induce a controlled gradient in morphology. The final glass coating presented a very porous top coat, with a low degree of crystallization, and a dense bond coat, with a ten microns wide mixed interfacial layer, which ensured a strong attachment to the titanium substrate.

As previously mentioned, some contributions propose to combine inorganic and *organic phases*, instead of merely inorganic phases. The organic phase may be a polymer, with specific mechanical requirements. For example, in a recent contribution by Huang et al.

(2014), a 50-50 nano-hydroxyapatite/polyamide (nHA/PA) composite was coated on injection-molded PA by means of a chemical corrosion and phase-inversion technique. In fact, the PA specimens were immersed in ethanol-based nHA/PA slurry, removed and left to dry at 60 °C for 1 day in air. During the last step, the phase change of ethanol from liquid to gas corroded the original PA surface and caused the development of an interconnected porous coating. The composite coating presented both a structural gradient and a compositional one, since the pore size as well as the Ca/P content increased from the substrate to the surface. The graded composite coatings tested *in vitro* had better cytocompatibility than pure PA and also *in vivo* they achieved superior biocompatibility and bond strength to bone.

Otherwise, the organic phase may be a naturally-inspired material, such as collagen. The combination of collagen and HA is indeed very interesting, since collagen accounts for 20-30% of the body proteins and HA is by far the main mineral component of bone tissue. If they are combined, they are reported to enhance the osteoblast differentiation and to accelerate the osteogenesis. Moreover, their mechanical properties are complementary, since collagen limits the brittle behavior of HA, whilst HA provides higher stability to collagen. The Drop-on-Demand microdispensing technique can be used to deposit both organic-inorganic composite coatings and FGCs in a single process and it is therefore ideal to obtain collagen-functionalized FGCs (Sun et al., 2012).

An original interpretation of the FGM concept is offered by the biodegradable coatings developed by Argarate et al. (2014), who used the dip coating technique to coat poly(d,l-lactide-co-lactide) (PLDL) substrates with poly(l-lactic acid) (PLLA). With sequential dipping steps, the Authors applied a bi-layered PLLA coating and they incorporated different drugs (eugenol and dexamethasone) in each layer, so as to induce a sequential drug release.

Sorensen et al. (2014) introduced a new strategy, based on co-precipitation of tobramycin with bio-mimetic HA formation, to obtain composite coatings for local drug delivery. The Authors added a submicron-thin HA interlayer that increased the adhesion and served as seed layer for the co-precipitation process.

Even if, strictly speaking, layer-by-layer coatings are multi-layered coatings but not FGCs, since they do not include a real functional gradient, they are worth mentioning, since they are increasingly common to induce and control a staged release of drugs and therapeutics or to promote a multi-step action. After the review by Tang et al. (2006), several examples can be found in the literature, for instance: Barbosa et al., 2009; Chiono et al., 2012; Choi et

al., 2012; Costa et al., 2011; Fejerskov et al. 2014; Kazemzadeh-Narbat et al., 2013; Keeney et al., 2013; Min et al., 2014; Shah et al., 2012; Sun et al., 2010; Zhao et al., 2009.

5.2. 3D graded parts

The present section overviews some of the available techniques to produce three-dimensional FGMs, i.e. graded systems which don't insist on a substrate. It is worth noting that the proposed geometries are usually limited to simple cylinders or parallelepipeds, whereas really few contributions propose more complicated (and realistic) shapes, such as ball heads, and this represents a great limit in the development of graded orthopedic devices. On the other hand, from a technological point of view, the achievement of an arbitrarily designed functional gradient is a challenging task, but it is even more challenging when biomedical implants are considered, since the ideal prosthesis should be patient-specific.

New digital tools are emerging to support the customized design and fabrication of functionally graded implants. For example, the multi-material virtual prototyping (MMVP) system can support the modeling step, process planning, and subsequent digital fabrication of discrete multi-material objects and FGMs. Its usage is expected therefore to open new opportunities for the fabrication of tailored biomedical objects (Choi and Cheung, 2011). In principle, also the development of appropriate additive manufacturing (AM) techniques could offer a potential solution to achieve tailored devices (Murr et al., 2010). In fact, AM can be applied to produce customized parts directly from digital data (Muller et al., 2013) and adaptive rapid prototyping/manufacturing (RP/M) algorithms are now available for FGMs, also for biomedical applications (Jin and Li, 2013). As a further advantage, AM is convenient from an economical point of view, since it implies substantial material saving with respect to conventional subtractive technologies (Nag and Banerjee, 2012).

At present, a variety of processing techniques are described in the literature to integrate specific material ingredients in new FGMs. Even if several approaches are dedicated to inorganic systems, some attempts have been made to include also organic ingredient materials, thus mimicking the natural composition of bone tissue. A brief guide is provided in Table 4.

As far as *inorganic FGMs* are involved, after the seminal work by Bishop et al. (1993) who processed titanium/HA FGMs by means of hot pressing starting from pre-treated samples, Watari et al. (2004) fabricated titanium/HA and other FGMs by means of various powder metallurgy (P/M) methods. The compositional gradient was induced either by

sedimentation in solvent liquid or by packing dry powders into a mould, followed by compressing and sintering. Various methods were applied to sinter the graded materials, including electric furnace heating, high frequency induction heating and spark plasma sintering.

Titanium/HA graded samples were produced via the P/M route also by Batin et al. (2011), who compared bi- and three-layered structures, all of them sintered in vacuum (0.01 Pa) at 1160 °C for 2 hours. The samples were sintered successfully, but they retained an interconnected porosity with small and large (up to 100 μm) pores. As a consequence, both the elastic modulus and the compressive strength of the FGMs were still higher than those of natural bone, but lower than those of the bulk (fully dense) materials with the same composition. Moreover it was possible to tune the mechanical properties through the FGM composition: the higher the HA content, the lower the mechanical properties.

After a seminal work on stainless steel/HA FGMs produced by pressureless sintering (Akmal et al., *in press*), Hussain et al. (2014) proposed the further addition of carbon nanotubes (CNTs), whose beneficial effect on the mechanical properties and bioactivity of HA are known in the literature (Balani et al., 2007; Xu et al., 2009). In more detail, Hussain et al. (2014) produced hybrid FGMs of CNT-reinforced HA (CNT constant amount: 0.5% in mass) with the addition of stainless steel, whose concentration was varied from 0% to 40% (in mass) with a progressive increment of 10% in each layer of a five-layered structure. The green samples were subjected to uniaxial compaction and then sintered by means of a pressureless sintering technique. The microstructural and mechanical characterization proved that the introduction of just 0.5% CNTs was enough to improve the densification and, hence, the local mechanical properties of the stainless steel/HA multi-layered materials; a further amelioration was observed when nano-sized HA powders were used. A companion contribution was addressed to the elimination of the cracks generated in FGMs as a consequence of thermodilatometric mismatch, a result which was obtained by controlling process parameters (temperature and time) and binder concentration (Hussain et al., 2015).

Yttria-stabilized zirconia (YSZ) can be also applied to reinforce HA (Matsuno et al., 1998), since it is bionert and, at the same time, it benefits from its high fracture toughness (about 10 MPa $m^{1/2}$ (Ariharan et al., 2012), whereas the toughness of HA is indicatively one order of magnitude lower, about 1 MPa $m^{1/2}$ (Suchanek and Yoshimura, 1998)). Spark plasma sintering has proved to be a promising route to produce YSZ/HA laminated and functionally graded composites. In fact, Guo et al. (2003) reported that zirconia/HA

laminates and FGMs could be densified at 1200 °C within 5 minutes with the spark plasma sintering process. In spite of the high-temperature treatment, the HA phase remained stable and the zirconia phase preserved the tetragonal polymorph; moreover the HA grain size was reduced by half due to the well-dispersed zirconia grains. As a result, the zirconia/HA laminated and functionally graded materials achieved superior mechanical properties with respect to pure HA samples.

Unfortunately, coupling HA and YSZ directly can be disadvantageous, since the strong difference in fracture toughness is expected to favor the crack propagation at the interface. For this reason, Afzal et al. (2012) incorporated alumina as a third phase to achieve a gradual transition in fracture toughness. More in detail, Afzal et al. (2012) considered a three-layered graded material, in which an alumina-20 wt% YSZ composite interlayer was inserted between a pure YSZ layer (to provide mechanical stability) and a HA-20 wt% alumina layer (to provide bioactivity). The graded material was successfully manufactured via spark plasma sintering, since it was possible to control the compositional gradient with care. The mechanical characterization confirmed a step-wise change in hardness and toughness along the cross section, whilst the HA-rich surface preserved its attitude to support cell adhesion and proliferation. Quite interestingly, the cell adhesion and proliferation also changed along the cross section as a result of the compositional gradient, which provides an opportunity to engineer the bioactivity of the FGM by tuning the respective amounts of the constituent phases. So, even if some concerns arise about the manufacturability of complicated geometries, the spark plasma sintering results to be a promising technique to produce graded materials with controlled bioactivity.

The effectiveness of the spark plasma sintering technique was also confirmed by the contribution by Kondo et al. (2004), who manufactured titanium nitride (TiN)/HA FGMs. The samples, whose composition varied from pure TiN at one side to pure HA to the other, were prepared by sintering at high temperature (900 °C to 1400 °C) under the pressure of 150 MPa. At 900 °C and 1000 °C, the TiN-rich volumes were not sintered completely; at 1300 °C and 1400 °C, the HA decomposed. So, the best samples were produced for intermediate temperatures (1100 °C and 1200 °C), with increasing mechanical properties (flexural strength and compression strength) for increasing temperatures. It is interesting to note that, in spite of the high processing temperature, the decomposition of HA was suppressed, probably due to the use of TiN instead of titanium. *In vivo* tests, performed on Wister strain rats, proved that no inflammation occurred throughout the implantation

period of 2-8 weeks. The new bone grew directly on the implants, but the maturation of new bone was reasonably more advanced on the HA-rich regions.

It is clear from the literature that, in the majority of cases, HA-based FGMs for orthopedic applications are intended to regulate the mechanical behavior of bone grafts. However, many other combinations of useful properties can be achieved using the FGM concept. For example, Kon et al. (1995) observed that the solubility of α-TCP is much higher than that of HA and they also remarked that α-TCP/HA mixtures bond with bone faster than HA alone. So HA/α-TCP FGMs are expected to elicit a controlled sequence of reactions after implantation: the α-TCP-rich surface will dissolve quickly to supply calcium and phosphate and, after the dissolution of α-TCP, fresh HA will be uncovered very close to the highly concentrated calcium phosphate solution, thus promoting the subsequent bone bonding. In order to produce such HA/α-TCP FGMs, Kon et al. (1995) spread the surface of HA "green bodies" (pressed but not sintered) with fine diamond powder and fired at 1280 °C under reduced pressure, followed by firing under atmospheric conditions. The spontaneous combustion of the diamond powder on the surface induced the decomposition of HA to α-TCP and therefore the content of α-TCP in the sintered bodies gradually decreased with increasing depth from the surface; vice versa, the content of HA increased with increasing depth. The graded α-TCP-to-HA ratio was governed by the firing time for each sintering step, i.e. under reduced pressure or under atmospheric pressure. A similar approach was followed by Manjubala et al. (2000), who exploited the partial conversion of coralline HA into TCP catalyzed by the thermal decomposition of silver oxide (Ag_2O) to obtain calcium phosphate graded materials. The same effect was observed in microwave-treated FGMs. In fact, Katakam et al. (2003) microwave-heated a multi-layered sample, obtained by stacking a layer of HA powder, a layer of anatase (TiO_2) powder (10 mol%) and a top layer of silver oxide powder (5 mol%). The final FGM contained metallic silver instead of silver oxide and rutile instead of anatase. Moreover, the development of calcium titanate ($CaTiO_3$) was detected. To conclude, as previously described, the presence of silver oxide catalyzed the decomposition of HA to β-TCP.

Beranič et al. (2005) and Novak et al. (2007) processed step-graded composite flat samples and ball heads composed of a zirconia-toughened alumina (ZTA) core and an alumina surface by the sequential slip-casting of aqueous suspensions. In a first contribution, dedicated to the optimization of the production method, Beranič et al. (2005) observed that large defects, such as big agglomerates, air bubbles and large circular pores at layer interfaces, which were induced by the processing conditions, deeply affected the

mechanical resistance of the multi-layered graded material. In a subsequent paper, Novak et al. (2007) demonstrated that ZTA/alumina FGMs with a controlled distribution of residual stresses achieved superior mechanical properties. In fact, the residual compressive stress at the alumina surface hindered the crack nucleation and propagation, with beneficial effects on the tribological behavior. In particular, both surface wear and friction decreased with an increase in the compressive-stress level. However, Novak et al. (2007) remarked the importance of reaching an optimal stress balance, since the residual tensile stress at the zirconia core might exceed the critical value for crack formation. According to tests performed by Novak et al. (2007), the zirconia content in the core should be lower than 22 vol.% to limit the residual stresses responsible for crack formation.

The sequential slip-casting procedure was also chosen by Morsi et al. (2004) to process graded alumina samples with a progressively decreasing grain size across the thickness. The basic goal was to limit the use of high-quality nano/ultrafine powders to the implant's surface only, where superior wear and mechanical properties are needed. After de-agglomerating the alumina powders, four green layers of decreasing particle sizes, from 250 nm to 50 nm, were deposited by means of the sequential slip-casting procedure. The green materials were dried and then treated via pressureless sintering or by hot pressing. Unlike pressureless sintering, which was ineffective to consolidate the samples, hot pressing achieved interesting results, since the obtained materials were nearly fully dense and the grain size gradually changed across the thickness.

To conclude, some contributions also cover FGMs with *organic ingredient materials*. For example, Nindhia et al. (2008) exploited the impressive properties of silk to improve the mechanical performance of HA. The samples, cylinders with a diameter of 15 mm and a target thickness of 1.6 mm, included 4 layers (each of them having the same thickness) whose composition varied from 100% silk fibroin to 70% silk fibroin + 30% HA. Pure silk film (100 μm thick) was applied as a bound between adjacent layers. The Authors used the pulse electric current sintering method to consolidate the samples. During 3-point bending tests, the silk film could arrest the crack propagation and, in this way, sudden fracture could be avoided.

Boss and Ganesh (2006) proposed to use graded composite rods with a longitudinal gradient in stiffness to limit the stress shielding effect after implantation. The rationale to reduce the tensile modulus from one end of the rod towards the other one was to provide a high stiffness at the region where the implant supports high mechanical loads and to provide a relative low stiffness, i.e. comparable to that of the natural tissue, at the other

termination of the implant, in close contact with the surrounding bone. With this aim, Boss and Ganesh (2006) developed hybrid rods, with a straight carbon fiber core sheathed with a braided Kevlar fiber preform. The braiding angle was changed gradually and, in this way, it was possible to vary the stiffness by 60% along the length of the rods.
As a further step, Watanabe et al. (2004) focused their attention on biodegradable organic implants for orthopedic applications. In particular, the Authors proposed to produce graded fillers for bone defects with resorbable polymers, such as poly (L-lactic acid) (PLLA), instead of metals and ceramics, as reviewed so far. The basic idea was that the degree of crystallinity and the degree of orientation of polymer chains control the mechanical properties. On the other hand, the degree of crystallinity depends on the thermal cycle and the degree of orientation depends on the shear deformation during processing. So, it is possible to govern the local mechanical properties through the fabrication conditions. In order to create a gradient in hardness, Watanabe et al. (2004) processed the PLLA at high temperature and attempted two types of extrusion, i.e. conventional direct extrusion and equal channel angular extrusion. The former provided the PLLA FGM with a symmetric hardness gradient along the diameter of the extruded rod, whereas the latter produced an asymmetric (skewed) hardness gradient. After incubation in a physiological saline solution, at first the mass of the PLLA graded samples increased, then it started to decrease about 2 weeks later and eventually reached about 80% mass loss at 7 weeks.

5.3. FGMs with a gradient in porosity

Generally speaking, special materials with a gradient in porosity have been developed for two basic applications, namely to face bone defects and to face osteochondral defects. The following paragraphs will summarize the state-of-the-art for both implementations.

5.3.1. FGMs with a gradient in porosity for bone defects

Highly porous implants may offer several advantages for orthopedic applications (Carletti et al., 2011; Chan and Leong, 2008; Karageorgiou and Kaplan, 2005; O'Brien, 2011; Yang et al., 2001). For example, for high-modulus materials, such as metals (titanium and alloys; steel) and ceramics (alumina; zirconia), the controlled presence of pores decreases the implant's stiffness, thus limiting the stress shielding effect. As a basic requirement, if pores are large enough (indicatively > 100 μm) and if porosity is interconnected, extensive fluid

flow and nutrient transport are possible. Moreover, the progressive bone ingrowth into the pores increases the implant-tissue fixation without using screws and bone cements.
On account of such beneficial effects, several techniques have been proposed to create highly porous materials starting from a wide range of single-component and (not-graded) composite materials (Boccaccini and Blaker, 2005; Chen et al., 2008, 2011; Cheung et al., 2007; Dhandayuthapani et al., 2011; Fu et al., 2011; Gao et al., 2014; Gerhardt and Boccaccini, 2010; Hutmacher 2000; Kim et al., 2012; Leong et al., 2003; Liebschner and Wettergreen, 2003; Liu and Ma, 2004; Nouri et al. 2010; Ryan et al., 2006; Sachlos and Czernuszka, 2003; Sopyan et al., 2007; Tsang and Bhatia, 2006; Yang et al., 2002).
After the groundbreaking research carried out by Hirshhorn and Reynolds (1969), who successfully produced graded porous femoral stems as early as 1968, a recent review draws attention on special porous materials for biomedical applications, namely those materials which present a gradient in porosity (Miao and Sun, 2010). Such materials are particularly interesting because they are suitable to mimic the bimodal porous structure of cortical and cancellous bone, which provide a site-specific optimized mechanical response (Leong et al., 2008; Low and Che, 2006; Lu et al., 2003; Wang et al., 2008).
Of course, bone scaffolds should be highly porous, but this is not enough: in fact, bone scaffolds should also posses a high degree of connectivity, which is essential for bone ingrowth, new vascularization and circulation of nutrients (Khan et al., 2008; Miao and Sun, 2010), as well as an appropriate internal architecture. As early as 2003, a proof-of-concept study demonstrated indeed that channel size, porosity content, and pore size of scaffolds can be used to influence new bone formation and calvarial defect healing. In more detail, the paper by Roy et al. (2003) analyzed degradable polymer-tricalcium phosphate scaffolds in rabbit models, and the results proved that scaffolds with engineered macroscopic channels and with porosity gradients had higher percentages of new bone area compared to scaffolds without engineered channels. The engineered scaffolds with porosity gradients also had higher percentages of new bone area compared to unfilled control defects, which suggested that appropriate combinations of scaffold material and architecture could be used to drive the repair of bone defects.
The greatest part of the contributions in the literature describes *graded porous samples with planar geometry*. They usually include a denser layer, to give mechanical resistance to the implant, and a more porous one, to support the bone healing process. The gradient from the denser layer to the more porous one can be either step-wise or continuous. To fabricate such flat graded porous structures, various techniques have been attempted, such

as multiple and differentiated impregnation of sponges and subsequent sintering in planar geometries (Tampieri et al., 2001); multiple tape casting (Pompe et al., 2003; Roncari et al., 2000; Werner et al., 2002); controlled reaction between dicalcium phosphate ($CaHPO_4$) and calcium carbonate ($CaCO_3$) (eventually calcined) powders (Arita et al. 1995); multiple slip-casting (Vaz et al., 1999); slip-casting with mixtures of conventional powders and void balls (Andertová et al., 2007); various adapted versions of salt-leaching, which implied the compaction and sintering of samples with several layers characterized by different salt-to-powder proportions (Torres et al., 2012, 2014a) or a sequential injection molding (Nishiyabu et al., 2005); and modified P/M techniques (P/M combined with a loose-sintering process (Torres et al., 2014b); P/M based on sintering, with and without pressure, of stacks of metal powders with different grain sizes (Oh et al., 2003); P/M combined with silicon-assisted liquid-phase sintering (Thieme et al., 2001); P/M based on cold compaction and sintering (Becker and Bolton, 1997)).

Planar geometries with more complicated porosity profiles have been achieved by means of camphene-based freeze-casting. For example, Hong et al. (2011) prepared an alumina-camphene-dispersant slurry and poured it into a silicone rubber die. Due to the special architecture of the mould, the top surface of the cast body was exposed to air, which induced the controlled evaporation of the molten camphene, and the bottom was cooled by ice-water and liquid nitrogen. In this way, the alumina samples were extremely porous, with a characteristic four-type porous structure, which comprised a surface dense layer, a transition layer affected by the dendritic morphology of camphene crystals, an aligned pore distribution region and an inner porous region. Jung et al. (2009) proved the effectiveness of the camphene-based freeze-casting process to fabricate titanium scaffolds with a controlled gradient in porosity and pore size. The Authors observed that, independently of the camphene content, the pore size could be increased by increasing the freezing time. The versatility of the camphene-based freeze-casting method was proved further by a contribution by Macchetta et al. (2009) dedicated to HA-TCP composite scaffolds with a graded porous structure. The Authors could produce a range of structures with different pore sizes by varying the solid loading of the mixture and the freezing temperature. In more detail, the freezing temperature governed the pore size distribution, whereas the initial solid loading determined the overall porosity content. Due to the use of camphene, no shrinkage was observed after sublimation of the samples prior to sintering, which is a great advantage with respect to classical water based-ceramic slips that experience shrinkage during drying, which may cause cracks and other defects even prior to sintering.

Kim et al. (2011) combined the sponge replica method with a subsequent dipping process to fabricate multi-layered multi-material scaffolds, consisting of zirconia and biphasic calcium phosphate (BCP), which is a mixture of HA and tricalcium phosphate. In fact, highly porous zirconia scaffolds were manufactured by means of the replica method. Then, such zirconia scaffolds, which served as a main frame, were dipped twice in a 50-50 zirconia-BCP slurry to create an intermediate layer and eventually dipped twice in a pure BCP slurry to create the highly bioactive outer layer. The graded scaffolds displayed highly interconnected pores and achieved good material properties, with a compressive strength of 7.2 MPa. From MTT assay and SEM observation of osteoblast-like MG-63 cells, the graded scaffolds showed good cell viability and fast proliferation behavior.

Sophisticated multi-layered scaffolds for tissue engineering could be also produced with the Multi-nozzle Deposition Manufacturing (MDM) technology. In fact, this digital forming technology, originally developed starting from the layer-by-layer manufacturing principle of solid freeform fabrication, proved to be effective to make customized graded scaffolds, with compositional and/or morphological gradients (Yan et al., 2003).

Even if planar systems are very common in the literature, some papers also deal with more complicated ones, including *concentric geometries*, with a radial gradient in properties. For example, radial graded scaffolds were fabricated by means of a spinning technique applied to a collagen-glycosaminoglycan suspension (centrifugation + freeze drying) (Harley et al., 2006); a similar technique was also applied to polycaprolactone fibrils (Oh et al., 2007). Liu et al. (2010) developed a new template-casting method, which could be successfully used to prepare biodegradable β-tricalcium phosphate scaffolds. Both the architecture and chemistry of the scaffolds could be controlled by means of an appropriate design of the templates and casting materials. As a result, various pore arrangements, including radial gradients, could be achieved (Liu et al., 2010; Yang et al., 2011).

In order to produce both multi-layered flat samples and multi-shelled cylindrical ones, Hsu et al. (2007) joined together various polymeric foams with different pore-per-inch densities by stitching and/or press fitting them; the polymeric foams were infused with HA-TCP slips by vacuum impregnation and then thermally treated. Wang et al. (2012) also obtained multi-layered flat samples and multi-shelled cylindrical ones by pressing (0.9 to 1.0 MPa) and sintering (800 °C for 3 hours) various mixtures of calcium poly-phosphate with stearic acid and paste. As an alternative method, various graded scaffolds, with different shapes and different porosity profiles, were produced by the foam replication

technique, simply pre-forming the polyurethane foams, which were used as sacrificial templates, in appropriate metallic moulds (Bretcanu et al., 2008).
Also Bellucci et al. (2010) produced highly porous glass-based sintered bodies, with a locally differentiated porosity comprising an extremely porous core and a strong surface all around the sample (the so-called "Shell"), by using a modified replica technique. In order to combine a macroporous internal core with a non-macroporous external layer, Lindner et al. (2014) synthesized instead β-TCP scaffolds using a lost wax casting technique, which resulted in a very controlled microstructure and good mechanical properties.
Muthutantri et al. (2008) could obtain porous structures with a radial gradient by means of electrohydrodynamic spraying of zirconia powders on polyurethane sponges and subsequent thermal treatment. The Authors could control the pore network by varying the process parameters, such as spraying time, sintering temperature and polymeric template. The approach is interesting, since the process can be extended to other ceramic powders and also to various geometries.
Titanium cylindrical structures, this time with a concentric architecture consisting of a solid core and a porous outer shell, were fabricated by means of a P/M approach by Wen et al. (2007). The porous external shell was addressed to favor the bone ingrowth in vivo.
All the contributions reviewed so far describe the production in the lab of porosity-graded materials for subsequent implantation. However, the research by Xu et al. (2007) demonstrated that relatively simple, bi-layered porous systems could be obtained directly in-situ (after implantation) using calcium phosphate cement (CPC), by combining a macroporous CPC layer with a strong CPC layer. The basic idea was that the macroporous layer could accept the tissue ingrowth, whereas the strong, fiber-reinforced layer could provide the required mechanical strength at early stages. A biopolymer chitosan was also incorporated to strengthen both layers.

5.3.2. FGMs with a gradient in porosity for ostechondral defects

Special scaffolds to face osteochondral disorders are now the focus of a fervent research activity. In fact, the osteochondral zone is particularly complicated, due to its strong functional gradient (and related architectural gradient) between bone and cartilage. Moreover cartilage deserves particular attention, since it suffers from a poor replicative capacity, which leads to the development of fibrocartilage, inherently inferior to cartilage from a functional point of view (Raghunath et al., 2007; Vinatier et al., 2009). Interfacial tissue engineering is now addressed to the development of artificial grafts that might

reproduce the natural sequence of interfacing tissue types (Castro et al., 2012; Dormer et al., 2010; Lopa and Madry, 2014). Both multi-layered and continuously graded scaffolds are described in the literature for interfacial tissue engineering applications, but the debate is still open on the ideal scaffold design (Liu et al., 2013). It is understandable that the contributions on the argument are more and more numerous and some recent reviews offer a wide panorama on the current trends and future developments of scaffolds for interfacial tissue engineering (Jeon et al., 2014; Nooeaid et al., 2012; Nukavarapu and Dorcemus, 2013; Seo et al., 2014). Just to give some examples, Laurenti et al. (2014) conceived a new graded biomaterial, which was composed of porous polyurethane and Bioglass® 45S5 microfiber. The graded material was designed to present an elastic-plastic tribological surface to the cartilage of the tibial plateau, and to progressively turn to an osteointegrable region for self-anchorage close to the subchondral bone. The polyurethane was indeed responsible for the elastic-plastic behavior, which produced a cushioning effect, whereas the bioglass microfiber conferred mechanical strength, stiffness, and adherence to bone. Additionally, the gradient from porous polyurethane to bioglass was mediated by a relatively porous interlayer, obtained by means of salt leaching. The graded samples, tested *in vitro*, caused neither direct nor indirect toxicity; to the contrary, they promoted cell growth and spreading. The samples were hence proved *in vivo*; as a result, they induced the development of a fibrocartilaginous tissue with highly vascularized chondrocytes at the polyurethane-rich side, and they supported bone formation and complete filling of pores at the glass-rich side.

Li et al. (2009) proposed to create special nanofiber-based scaffolds with a gradient in mineral content for repairing the tendon-to-bone insertion site via an "interface tissue engineering" approach. In fact, in order to create a continuously graded calcium phosphate coating on a non-woven mat of electrospun nanofibers, Li et al. (2009) immersed the electrospun membranes in a concentrated Simulated Body Fluid and they controlled progressively the amount of mineral (calcium phosphate) precipitated locally from the solution by adjusting the immersion time, the concentration and the feeding rate of the mineral solution, and the tilting angle of the membrane. The gradient in calcium phosphate content had functional consequences, since the Young's modulus along the scaffolds increased with increasing contents of mineral phase. Analogously, the MC3T3 cells seeded on the scaffolds preferentially adhered to and/or proliferated on regions with a higher content of calcium phosphate. Erisken et al. (2008) preferred instead a hybrid twin-screw extrusion/electrospinning process to fabricate polymer-based (polycaprolactone, PCL)

functionally graded non-woven meshes incorporated with TCP nanoparticles to mimic the bone-cartilage interface.

Levingstone et al. (2014) fabricated layered systems for osteochondral repair by means of an "iterative layering" freeze-drying method. The process was based on a repeated sequence of layer addition and freeze-drying, which offered an accurate control on the composition, porosity and properties of each layer. The final scaffolds mimicked the natural graded structure of osteochondral tissue, with a bone-like layer, composed of type I collagen and HA, an intermediate layer, composed of type I collagen, type II collagen and HA, and a cartilage-like layer, composed of type I collagen, type II collagen and hyaluronic acid. In this way, the scaffolds offered a perfectly integrated structure, but each layer had specific features to support the differentiated healing process of bone and cartilage.

In order to create a gradient in biological cues, besides HA, Zou et al. (2012) also introduced plasmid DNA in their electrospun graded scaffolds. In fact, the Authors produced gelatin grafts starting from electrospun fibers with a gradient in amino groups, then they created a gradient in HA content by means of a controlled mineralization in-situ and they added the DNA during the mineralization, in order to induce a graded distribution of DNA associated with HA.

Ding et al. (2014b) fabricated and tested a three-layered scaffold based on silk fibroin and HA. The scaffolds, produced by means of paraffin-sphere leaching combined with a modified thermal-induced phase separation (TIPS) technique, included a chondral layer, with a longitudinally oriented microtubular structure, a bone-like layer, with a 3D porous structure, and an intermediate layer, with a compact structure. The intermediate layer offered a connection between the external layers, but its compact structure also played an isolating role to prevent the chondral-related cells and the bone-related cells from mixing with each other.

Tampieri et al. (2008) reported the assessment of new graded scaffolds, which were intended to mimic the articular cartilage, on one side, and the subchondral bone, on the other, and to support the formation of such tissues differentially. With this aim, the Authors first applied a biologically inspired mineralization process to nucleate Mg-doped HA crystals on collagen fibers during their self-assembling. The new calcium phosphate phase was widely amorphous and non-stoichiometric, which is typical of new bone matrix. Then the Authors created a graded structure, combining a lower stratum of the bio-mineralized collagen, to simulate the subchondral bone, an upper stratum of collagen charged with hyaluronic acid, to simulate the cartilage, and an intermediate stratum with the bio-

mineralized collagen, but with a lower level of mineralization, to simulate the tidemark. The culture test and the in-vivo implantation confirmed the attitude of the graded scaffold to support the generation of cartilage and bone differentially.

As an alternative solution, Shi et al. (2013) described new gradient-regulated hydrogels. In fact, the Authors implemented a bio-microfluidic technique to create a graded hydrogel slab capable of driving a distinct differentiation of stem cells into chondrocytes and osteoblasts, due to its structure similar to the bone-to-cartilage graded interface.

Zhu et al. (2014) proposed collagen/chitosan-polycaprolactone (PCL) graded scaffolds to support cartilage repair processes. The Authors synthesized chitosan-PCL copolymers with various PCL percentages and blended them with type II collagen at prescribed proportions. Then the Authors used such blends to produce multi-layered graded scaffolds by means of a combinatorial processing technique, which included adjustable temperature gradients, collimated photothermal heating and freeze-drying. The scaffolds displayed a decreasing collagen content and an increasing chitosan content from the top layer to the bottom layer, with a structure similar to that of cartilage extracellular matrix.

6. Discussion

The structure of the present review substantially reflects the distribution of the available literature on FGMs for orthopedic grafts, in that the papers published on the argument can be roughly grouped into two main classes:

- Papers focused on the design of new FGMs for specific implants, and
- Papers focused on the current technologies to produce FGMs for bone prostheses.

The design of optimized gradients is described first, since theoretically it should guide the fabrication process, as proposed by the inverse design procedure (Hirano and Wakashima, 1995). However, as already stressed in the past by Mehrali et al. (2013), there is still a lack of integration between design of customized FGMs and subsequent fabrication. The papers that combine simulation and prototypal production are indeed very few. In a recent contribution dedicated to graded porous materials, Burblies and Busse (2008) remarked the importance of a close integration between design and manufacturing and, to solve the problem, they merged a new porosity design by multi-phase topology optimization with a feasibility study by 3D-printing and selective laser sintering processes. Even if the approach has a wide range of potential uses, which go beyond orthopedic surgery, Burblies and Busse (2008) proposed the area of medical implants as the primary future application. Generally speaking, the most promising solution seems to be offered by CAD/CAM-based

manufacturing and additive manufacturing techniques, which are suitable to produce also patient-specific graded and/or porous parts, even with complex shapes. From this point of view, interesting examples are provided by the review (and research article) by Parthasarathy et al. (2011), that describes the design of cellular mandible implants and hip prostheses and exemplifies the production of a patient-specific porous titanium cranioplasty plate by electron beam melting (EBM). As discussed in previous paragraphs (Section 4), some examples of design-production integration were proposed by Hazlehurst et al. (2013a, 2013b, 2014), who published an articulated research activity to model new Co–Cr–Mo cellular structures and to produce them by the selective laser melting (SLM) technique. Khanoki and Pasini (2012, 2013a, 2013b) proposed computational models to determine the potentiality of functionally graded cellular materials for hip implants and they also fabricated a proof-of-concept by rapid prototyping. The template was fabricated in polypropylene and it was two-dimensional, so it offered a very simplified representation of a hip prosthesis, but it was nonetheless an important evidence of the manufacturability of the designed materials. Wang et al. (2006) outlined a new acetabular cup with a gradient in porosity, whose actual production is now under evaluation (Williams et al. 2011). Gabbrielli et al. (2008) conceived graded porous structures and then produced them by rapid prototyping. Migacz et al. (2014) applied a combined experimental-computational approach to investigate the properties of FGMs based on carbon fiber/polysulfone composites for artificial intervertebral discs. Nevertheless these contributions represent just a small percentage of the available literature on the conceptual optimization of graded materials for bone grafts and they are mainly dedicated to porous implants, whereas the examples of not-porous graded devices are definitely infrequent. Moreover, none of such contributions go ahead with *in vivo* tests, which would be essential for biomedical uses.

It is defensible that, at present, no contributions in the literature bring together optimization design, manufacturing, preliminary microstructural, mechanical and biological characterization, and further *in vivo* evaluation, because this would imply a massive and multidisciplinary research activity, with long times of execution and numerous experts involved. Nevertheless, an effort should be done to achieve a comprehensive understanding of FGMs for orthopedic applications, including all their features, from modeling, to fabrication and to experimental validation.

Some specific concerns arise about the modeling activity, too. Basically, the simulations and analytical models proposed in the literature deal with two interconnected issues: they exploit the idea of “gradient” to create a smooth change between two dissimilar ingredient

materials, and/or they consider the appropriate material distribution to optimize the stress profile, which is necessary to reproduce the natural stress distribution, as previously described in Section 3. A smooth gradient in composition makes it possible to change from a material to a completely different one without the dangers associated to an abrupt interface, which would be responsible for anomalous stress concentrations (Miyamoto et al., 1999). Moreover, computational models, supported by experimental data, have proved that the reliability of graded structures may be improved by means of appropriate compositional profiles; for example, ceramic materials may be strengthened by creating a graded structure with an appropriate elastic gradient, which is responsible for a stress re-distribution (Zhang and Ma, 2009; Zhang et al. (2012)). However, notwithstanding the importance of FGMs as interface-free bi-material systems, the greatest part of the literature is focused on the control of stress distribution through the use of stiffness-graded implants. Actually, the adjustable stiffness of FGMs offers a valuable tool to decrease the bone shielding effect caused by orthopedic implants and to reduce the shear stresses at the same time, which is expected to result in a longer lifespan of the prosthesis. The relevance of stiffness-graded materials to control the stress distribution helps to realize why the greatest part of the literature on computational simulations deals only with the elastic property profile of FGMs, whereas other properties, such as strength, are often neglected. Though understandable, this is a limiting approach and further investigations would be required to reveal the impact of strength and other properties on the overall performance of FGMs.

Moreover, from a survey of the available literature, it is surprising to note that the greatest part of the modeling activity has been addressed to bones and joints in human legs. To the contrary, only few contributions are focused on intervertebral discs and orbits, whereas, to the Authors' best knowledge, no specific optimization study has been dedicated to other skeletal parts, such as, for example, shoulder or hand (an exception is the article by Parthasarathy et al. (2011) cited before, that also describes the design of cellular mandible implants). This is quite unexpected, if the social impact of disorders to skeletal parts other than legs is considered. For example, it has been reported that the incidence of fractures to the upper extremities is progressively increasing, implying more than 2 million emergency room (ER) visits in the United States per year (Taylor et al., 2009). A statistical evaluation extended to all British Columbia (Canada) in the interval from May 1, 1996, to April 20, 2001, documented more than 72,000 hand fractures (Feehan and Sheps, 2006). An up-to-date report released by the British Society for Surgery of the Hand registered more than

1.36 million ER visits for hand injuries in the United Kingdom per year, which corresponded to about 20% of the patients attending Accident and Emergency Departments. Of these injuries, more than 270,000 required specialist care, and more than 70,000 required surgery (Hand Surgery in the UK. Manpower, resources, standards and training. Report of a working party (2007)). In the light of the social and economic burden associated with these bone and joint disorders, specific contributions are certainly needed to develop new grafts. The problem is particularly relevant for FGM-based devices, since, as previously mentioned, the compositional and microstructural gradient must be optimized in function of the specific geometry and application (Markworth et al., 1995). So, it is not automatic that a gradient optimized for a hip prosthesis could work as well, for example, for a shoulder.

As far as the experimental assessment of graded materials is concerned, it should be mentioned that specific measurement techniques are often required to evaluate the properties of graded materials and coatings, because conventional approaches seldom apply to non-homogeneous materials (Fischer-Cripps, 2003). However, appropriate techniques have already been established to take into account the spatial change in properties which is the salient feature of FGMs and FGCs (Bertarelli et al., 2011; Cannillo et al., 2006a; Cannillo et al., 2007; Goossens et al., 2007; Gu et al., 2003; Jumel et al., 2003; Liu et al., 2001; Saharan et al., 2013). Moreover, it is interesting to note that, vice versa, the presence of a compositional gradient can be exploited for accelerated tests, as put forward by Bailey et al. (2013). In fact, the Authors prepared "hybrid" hydrogel scaffolds in the form of continuous gradients, so that each scaffold contained spatially varied properties, and then used the graded scaffolds to test simultaneously the cell response to different structures. In this way, the gradient could be used in a strategy for rapid screening of cell-scaffold interactions.

One more concern about the use of FGMs for orthopedic applications derives from economic considerations, since the production of graded materials (or graded coatings) surely implies additional costs with respect to conventional monoblocks. Nevertheless, many techniques, such as additive manufacturing by rapid prototyping and thermal spraying, are already suitable for an industrial scale up. Moreover, as previously mentioned, several fabrication methods proposed in the literature to manufacture graded materials are also appropriate for producing customized implants for individual patients, which could be extremely useful to improve the clinical results of new orthopedic implants. For example, tomographic images of the patient could be combined with CAD techniques to

provide *ad hominem* models, which could be processed by additive manufacturing (Parthasarathy et al., 2011). To conclude, it is worth noting that the additional costs potentially associated with graded implants would be largely compensated by the prolonged lifetime predicted for FGM-based grafts.

7. Conclusions

Functionally Graded Materials (FGMs) are special materials whose composition and/or microstructure and related properties vary in space according to an assigned law. Several examples of functionally graded systems can be detected in nature and even in the human body; in particular, human bone itself can be considered a graded material. Therefore it is understandable that FGMs could be ideal candidates for orthopedic grafts, since the functional gradient can be designed to mimic the properties of the original bone tissue, which is expected to reduce the so-called stress shielding effect and also to limit the harmful shear stresses at the bone-implant interface. The research in the field is intensive; however, the papers on the argument can be roughly divided into two groups, namely (1) papers focused on the design of new FGMs for specific implants, and (2) papers focused on current technologies to produce FGMs for bone prostheses. Now, a further step should be done in the effort of integrating simulation and production, as well as to validate the benefits deriving from the functional gradient.

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References

Afzal MAF, Kesarwani P, Reddy KM, Kalmodia S, Basu B, Balani K. Functionally graded hydroxyapatite-alumina-zirconia biocomposite: Synergy of toughness and biocompatibility. Mater Sci Eng C Mater Biol Appl 2012;32:1164–73.

Akmal M, Hussain M, Ikram, Sattar T, Jameel S, Kim JY, Khalid FA, Kim JW. In-vitro electrochemical and bioactivity evaluation of SS316L reinforced hydroxyapatite functionally graded materials fabricated for biomedical implants. Ceram Int, *in press*.

Al-Jassir FF, Fouad H, Alothman OY. In vitro assessment of Function Graded (FG) artificial Hip joint stem in terms of bone/cement stresses: 3D Finite Element (FE) study. Biomed Eng Online 2013;12:article 5 (17 pages).

Al-Sukhun J, Penttilä H, Ashammakhi N. Orbital stress analysis, Part IV: Use of a "stiffness-graded" biodegradable implants to repair orbital blow-out fracture. J Craniofac Surg 2012;23:126–30.

Amada S. Hierarchical functionally graded structures of bamboo, barley, and corn. MRS Bull 1995;1:35–6.

Andertová J, Tláskal R, Maryška M, Havrda J. Functional gradient alumina ceramic materials – Heat treatment of bodies prepared by slip casting method. J Eur Ceram Soc 2007;27:1325–31.

Anné G, Vanmeensel K, Vleugels J, Van Der Biest O. Electrophoretic deposition as a novel near net shaping technique for functionally graded biomaterials. Mater Sci Forum 2006;314:213–8.

Araghi A, Hadianfard MJ. Fabrication and characterization of functionally graded hydroxyapatite/TiO_2 multilayer coating on Ti-6Al-4V titanium alloy for biomedical applications. Ceram Int, *in press*.

Argarate N, Olalde B, Atorrasagasti G, Valero J, Cifuentes SC, Benavente R, et al. Biodegradable bi-layered coating on polymeric orthopaedic implants for controlled release of drugs. Mater Lett 2014;132:193–5.

Ariharan S, Gupta A, Keshri A, Agarwal A, Balani K. Size effect of yttria stabilized zirconia addition on fracture toughness and thermal conductivity of plasma sprayed aluminum oxide composite coatings. Nanosci Nanotechnol Lett 2012;4:323–32.

Arita IH, Castano VM, Wilkinson DS. Synthesis and processing of hydroxyapatite ceramic tapes with controlled porosity. J Mater Sci Mater Med 1995;6:19–23.

Bahraminasab M, Sahari BB, Edwards KL, Farahmand F, Arumugam M, Hong TS. Aseptic loosening of femoral components – A review of current and future trends in materials used, Mater Design 2012;42:459–70.

Bahraminasab M, Sahari BB, Edwards KL, Farahmand F, Arumugam M. Aseptic loosening of femoral components – Materials engineering and design considerations. Mater Design 2013a;44:155–63.

Bahraminasab M, Sahari BB, Edwards KL, Farahmand F, Hong TS, Naghibi H. Material tailoring of the femoral component in a total knee replacement to reduce the problem of aseptic loosening. Mater Design 2013b;52:441–51.

Bahraminasab M, Sahari BB, Edwards KL, Farahmand F, Hong TS, Arumugam M, et al. Multi-objective design optimization of functionally graded material for the femoral component of a total knee replacement. Mater Design 2014a;53:159–73.

Bahraminasab M, Sahari BB, Edwards KL, Farahmand F, Jahan A, Hong TS, et al. On the influence of shape and material used for the femoral component pegs in knee prostheses for reducing the problem of aseptic loosening. Mater Design 2014b;55:416–28.

Bai X, Sandukas S, Appleford MR, Ong JL, Rabiei A. Deposition and investigation of functionally graded calcium phosphate coatings on titanium. Acta Biomater 2009;5:3563–72.

Bailey BM, Nail LN, Grunlan MA. Continuous gradient scaffolds for rapid screening of cell-material interactions and interfacial tissue regeneration. Acta Biomater 2013;9:8254–61.

Balaceanu M, Petreus T, Braic V, Zoita CN, Vladescu A, Cotrutz CE, et al. Characterization of Zr-based hard coatings for medical implant applications. Surf Coat Technol 2010;204:2046–50.

Balamurugan A, Balossier G, Michel J, Ferreira JMF. Electrochemical and structural evaluation of functionally graded bioglass-apatite composites electrophoretically deposited onto Ti6Al4V alloy. Electrochim Acta 2009;54:1192–8.

Balani K, Anderson R, Laha T, Andara M, Tercero J, Crumpler E. Plasma-sprayed carbon nanotube reinforced hydroxyapatite coatings and their interaction with human osteoblasts in vitro. Biomaterials 2007;28:618–24.

Bandyopadhyay A, Krishna BV, Xue W, Bose S. Application of Laser Engineered Net Shaping (LENS) to manufacture porous and functionally graded structures for load bearing implants. J Mater Sci Mater Med 2009;20:29–34.

Bar-On B, Barth FG, Fratzl P, Politi Y. Multiscale structural gradients enhance the biomechanical functionality of the spider fang. Nat Commun 2014;5, 2014/05/27 online, article no. 3894, doi:10.1038/ncomms4894.

Barbosa JS, Costa RR, Testera AM, Alonso M, Rodríguez-Cabello JC, Mano JF. Multi-layered films containing a biomimetic stimuli-responsive recombinant protein. Nanoscale Res Lett 2009;4:1247–53.

Baron C. Using the gradient of human cortical bone properties to determine age-related bone changes via ultrasonic guided waves. Ultrasound Med Biol 2012;38:972–81.

Batin G, Popa C, Brândușan L, Vida-Simiti I. Mechanical properties of Ti/HA functionally graded materials for hard tissue replacement. Powder Metall Prog 2011;11:206–9.

Beaupied H, Lespessailles E, Benhamou C-L. Evaluation of macrostructural bone biomechanics. Joint Bone Spine 2007;74:233–9.

Becker BS, Bolton JD. Corrosion behaviour and mechanical properties of functionally gradient materials developed for possible hard-tissue applications. J Mater Sci Mater Med 1997;8:793–7.

Bellucci D, Cannillo V, Sola A. Shell Scaffolds: A new approach towards high strength bioceramic scaffolds for bone regeneration. Mater Lett 2010;64:203–6.

Bellucci D, Cannillo V, Cattini A, Sola A. Bioactive glass coatings: a review. Surf Eng 2011;27:560–72.

Beranič Klopčič S, Novak S, Kosmač T, Richter HG, Hecht-Mijic S. The preparation and properties of functionally graded alumina/zirconia- toughened alumina (ZTA) ceramics for biomedical applications. Key Eng Mat 2005;290:348–52.

Bertarelli E, Carnelli D, Gastaldi D, Tonini D, Di Fonzo F, Beghi M, et al. Nanomechanical testing of Alumina-Titanium functionally graded thin coatings for orthopaedic applications. Surf Coat Technol 2011;205:2838–45.

Besra L, Liu M. A review on fundamentals and applications of electrophoretic deposition (EPD). Prog Mater Sci 2007;52:1–61.

Bever MB, Duwez PE. Gradients in composite materials. Mater Sci Eng 1972;10:1–8.

Birman V, Byrd LW. Modeling and analysis of functionally graded materials and structures. Appl Mech Rev 2007;60:195–216.

Bishop A, Lin C-Y, Navaratnam M, Rawlings RD, McShane HB. A functionally gradient material produced by a powder metallurgical process. J Mater Sci Lett 1993;12:1516–8.

Boccaccini AR, Blaker JJ. Bioactive composite materials for tissue engineering scaffolds. Expert Rev Med Devices 2005;2:303–17.

Boccaccini AR, Keim S, Ma R, Li Y, Zhitomirsky I. Electrophoretic deposition of biomaterials. J R Soc Interface 2010;7:S581–S613.

Bosco R, Van Den Beucken J, Leeuwenburgh S, Jansen J. Surface engineering for bone implants: a trend from passive to active surfaces. Coatings 2012;2:95–119.

Boss JN, Ganesh VK. Fabrication and properties of graded composite rods for biomedical applications. Compos Struct 2006;74:289–93.

Bretcanu O, Samaille C, Boccaccini AR. Simple methods to fabricate Bioglass®-derived glass-ceramic scaffolds exhibiting porosity gradient. J Mater Sci 2008;43:4127–34.

Brizuela M, Garcia-Luis A, Viviente JL, Braceras I, Oñate JI. Tribological study of lubricious DLC biocompatible coatings. J Mater Sci Mater Med 2002;13:1129–33.

Burblies A, Busse M. Computer based porosity design by multi phase topology optimization. In: Paulino GH, Pindera M-J, Dodds jr RH, Rochinha FA, Dave EV, Chen L, editors. Multiscale and Functionally Graded Materials 2006 M&FGM 2006 (AIP Conference Proceedings / Materials Physics and Applications). Melville (NY): AIP Publishing (American Institute of Physics/Proceedings); 2008. p. 285–90.

Cannillo V, Manfredini T, Siligardi C, Sola A. Preparation and experimental characterization of glass–alumina functionally graded materials. J Eur Ceram Soc 2006a;26:993–1001.

Cannillo V, Manfredini T, Montorsi M, Siligardi C, Sola A. Glass-alumina functionally graded materials: their preparation and compositional profile evaluation. J Eur Ceram Soc 2006b;26:2685–93.

Cannillo V, Lusvarghi L, Siligardi C, Sola A. Characterization of glass-alumina functionally graded coatings obtained by plasma spraying. J Eur Ceram Soc 2007;27:1935–43.

Cannillo V, Lusvarghi L, Pierli F, Sola A. In-vitro behaviour of titania-hydroxyapatite functionally graded coatings. Adv Appl Ceram 2008a;107:259–67.

Cannillo V, Lusvarghi L, Sola A. Production and characterization of plasma sprayed TiO_2-hydroxyapatite functionally graded coatings. J Eur Ceram Soc 2008b;28:2161–9.

Cannillo V, Lusvarghi L, Sola A, Barletta M. Post-deposition laser treatment of plasma sprayed titania-hydroxyapatite functionally graded coatings. J Eur Ceram Soc 2009a;29:3147–58.

Cannillo V, Lusvarghi L, Sola A. Design of experiment (DOE) for the optimisation of titania-hydroxyapatite functionally graded coatings. Int J Appl Ceram Technol 2009b;6:537–50.

Cannillo V, Sola A. Different approaches to produce coatings with bioactive glasses: Enamelling vs plasma spraying. J Eur Ceram Soc 2010;30:2031–9.

Carletti E, Motta A, Migliaresi C. Scaffolds for tissue engineering and 3D cell culture. Methods Mol Biol 2011;695:17–39.

Cassidy JJ, Hiltner A, Baer E. Hierarchical architecture of the intevertebral disc. Connect Tissue Res 1989;23:75–88.

Castro NJ, Hacking SA, Zhang LG. Recent progress in interfacial tissue engineering approaches for osteochondral defects. Ann Biomed Eng 2012;40:1628–40.

Cattini A, Bellucci D, Sola A, Pawłowski L, Cannillo V. Suspension plasma spraying of optimised functionally graded coatings of bioactive glass/hydroxyapatite. Surf Coat Technol 2013;236:118–26.

Cattini A, Bellucci D, Sola A, Pawłowski L, Cannillo V. Functional bioactive glass topcoats on hydroxyapatite coatings: analysis of microstructure and in-vitro bioactivity. Surf Coat Technol 2014a;240:110–7.

Cattini A, Bellucci D, Sola A, Pawłowski L, Cannillo V. Microstructural design of functionally graded coatings composed of suspension plasma sprayed hydroxyapatite and bioactive glass. J Biomed Mater Res B Appl Biomater 2014b;102:551–60.

Chan BP, Leong KW. Scaffolding in tissue engineering: general approaches and tissue-specific considerations. Eur Spine J 2008;17:467–79.

Chateigner D, Hedegaard C, Wenk H-R. Mollusc shell microstructures and crystallographic textures. J Struct Geol 2000;22:1723–35.

Cheang P, Khor KA. Addressing processing problems associated with plasma spraying of hydroxyapatite coatings. Biomaterials 1996;17:537–44.

Chen C-C, Huang T-H, Kao C-T, Ding S-J. Characterization of functionally graded hydroxyapatite/titanium composite coatings plasma-sprayed on Ti alloys. J Biomed Mater Res B Appl Biomater 2006;78:146–52.

Chen K, Jia Y-E. Laser coating of multi layer hydroxyapatite on titanium alloy. In: Yu W, Zhang M, Wang L, Song Y, editors. Proceedings. 2010 3rd International Conference on Biomedical Engineering and Informatics – BMEI 2010 (Volume 4). Piscataway (NJ): the Institute of Electrical and Electronics Engineers (IEEE); 2010. p. 1704–6.

Chen Q, Roether JA, Boccaccini AR. Tissue engineering scaffolds from bioactive glass and composite materials (Ch. 6). In: Ashammakhi N, Reis R, Chiellini F, editors. Topics in Tissue Engineering, Vol. 4, 2008. Oulu, Finland: University of Oulu; 2008 (27 pages). Book available on-line at: http://www.oulu.fi/spareparts/ebook_topics_in_t_e_vol4/.

Chen Q, Mohn D, Stark WJ. Optimization of Bioglass® scaffold fabrication process. J Am Ceram Soc 2011;94:4184–90.

Chen Y, Fok A. Stress distributions in human teeth modeled with a natural graded material distribution. Dent Mater 2014;30:e337–48.

Cheung H-Y, Lau K-T, Lu T-P, Hui D. A critical review on polymer-based bio-engineered materials for scaffold development. Compos Part B-Eng 2007;38:291–300.

Ching HA, Choudhury D, Nine MJ, Abu Osman NA. Effects of surface coating on reducing friction and wear of orthopaedic implants. Sci Technol Adv Mat 2014;15:014402 (21 pages).

Chiono V, Carmagnola I, Gentile P, Boccafoschi F, Tonda-Turo C, Ballarini M, et al. Layer-by-layer coating of photoactive polymers for biomedical applications. Surf Coat Technol 2012;206:2446–53.

Choi J, Konno T, Takai M, Ishihara K. Regulation of cell proliferation by multi-layered phospholipid polymer hydrogel coatings through controlled release of paclitaxel. Biomaterials 2012;33:954–61.

Choi SH, Cheung HH. Digital fabrication of multi-material objects for biomedical applications (Ch. 3). In: Laskovski AN, editor. Biomedical Engineering, Trends in Materials Science. ISBN: 978-953-307-513-6, InTech; 2011. p. 65–86. Available from: http://www.intechopen.com/books/biomedical-engineering-trends-in-materials-science/digital-fabrication-of-multi-material-objects-for-biomedical-applications.

Claussen KU, Scheibel T, Schmidt H-W, Giesa R. Polymer gradient materials: can nature teach us new tricks? Macromol Mater Eng 2012;297:938–57.

Costa RR, Custõdio CA, Arias FJ, Rodríguez-Cabello JC, Mano JF. Layer-by-layer assembly of chitosan and recombinant biopolymers into biomimetic coatings with multiple stimuli-responsive properties. Small 2011;7:2640–9.

Cui C, Sun J. Optimizing the design of bio-inspired functionally graded material (FGM) layer in all-ceramic dental restorations. Dent Mater J 2014;33:173–8.

Das M, Balla VK, Kumar TSS, Manna I. Fabrication of Biomedical Implants using Laser Engineered Net Shaping (LENS™). Trans Indian Ceram Soc 2013;72:169–74.

Dhandayuthapani B, Yoshida Y, Maekawa T, Kumar DS. Polymeric scaffolds in tissue engineering application: a review. Int J Polym Sci 2011; vol. 2011: Article ID 290602 (19 pages).

Ding H, Zhou C, Zhang Y, Zhou G, Wang X, Yin F. Corrosion resistance of Ti/TiB2 multilayers in Hank's solution. Zhenkong Kexue yu Jishu Xuebao/Chinese Journal of Vacuum Science and Technology 2014a;34:611–5.

Ding X, Zhu M, Xu B, Zhang J, Zhao Y, Ji S, et al. Integrated trilayered silk fibroin scaffold for osteochondral differentiation of adipose-derived stem cells. ACS Appl Mater Interfaces 2014b;6:16696–705.

Dormer NH, Berkland CJ, Detamore MS. Emerging techniques in stratified designs and continuous gradients for tissue engineering of interfaces. Ann Biomed Eng 2010;38:2121–41.

Du J, Niu X, Rahbar N, Soboyejo W. Bio-inspired dental multilayers: effects of layer architecture on the contact-induced deformation. Acta Biomater 2013;9:5273–9.

Du RL, Zeng SX, Hu HY, Xie XH. Hydroxyapatite and bioactive glass composite coating on Ti-6Al-4V. Bioceramics 2006;19:589–92.

Enab TA, Bondok NE. Material selection in the design of the tibia tray component of cemented artificial knee using finite element method. Mater Design 2013;44:454–60.

Enab TA. A comparative study of the performance of metallic and FGM tibia tray components in total knee replacement joints. Comp Mater Sci 2012;53:94–100.

Enab TA. Performance improvement of total knee replacement joint through bidirectional functionally graded material. IJMME-IJENS 2014;14:104–13.

Erisken C, Kalyon DM, Wang H. Functionally graded electrospun polycaprolactone and beta-tricalcium phosphate nanocomposites for tissue engineering applications. Biomaterials 2008;29:4065–73.

Evans SL, Lawes KR, Gregson PJ. Layered, adhesively bonded hydroxyapatite coatings for orthopaedic implants. J Mater Sci Mater Med 1994;5:495–9.

Fauchais P. Understanding plasma spraying. J Phys D Appl Phys 2004;37:R86–R108.

Feehan LM, Sheps SB. Incidence and demographics of hand fractures in British Columbia, Canada: a population-based study. J Hand Surg Am 2006;31:1068–74.

Fejerskov B, Jensen NBS, Teo BM, Städler B, Zelikin AN. Biocatalytic polymer coatings: On-demand drug synthesis and localized therapeutic effect under dynamic cell culture conditions. Small 2014;10:1314–24.

Fischer-Cripps AC. Analysis of instrumented indentation test data for functionally graded materials. Surf Coat Technol 2003;168:136–41.

Flynn CO, McCormack BA. A three-layer model of skin and its application in simulating wrinkling. Comput Methods Biomech Biomed Engin 2009;12:125-34.

Foppiano S, Marshall SJ, Saiz E, Tomsia AP, Marshall GW. Functionally graded bioactive coatings: Reproducibility and stability of the coating under cell culture conditions. Acta Biomater 2006;2:133–42.

Foppiano S, Marshall SJ, Marshall GW, Saiz E, Tomsia AP. Bioactive glass coatings affect the behavior of osteoblast-like cells. Acta Biomater 2007;3:765–71.

Fouad H. Effects of the bone-plate material and the presence of a gap between the fractured bone and plate on the predicted stresses at the fractured bone. Med Eng Phys 2010;32:783–9.

Fouad H. Assessment of function-graded materials as fracture fixation bone-plates under combined loading conditions using finite element modelling. Med Eng Phys 2011;33:456–63.

Fouda N. Horizontal functionally graded material coating of cementless hip prosthesis. Trends Biomater Artif Organs 2014;28:58–64.

Frost HM. Perspectives: A proposed general model for the mechanostat (suggestions from a new skeletal- biologic paradigm). Anat Rec 1996;244:139–47.

Fu Q, Saiz E, Rahaman MN, Tomsia AP. Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives. Mater Sci Eng C Mater Biol Appl 2011;31:1245–56.

Gabbrielli R, Turner IG, Bowen CR. Development of modelling methods for materials to be used as bone substitutes. Key Eng Mat 2008;361–363:903–6.

Gadow R, Killinger A, Rauch J. Introduction to High-Velocity Suspension Flame Spraying (HVSFS). J Therm Spray Technol 2008;17:655–61.

Ganesh VK, Ramakrishna K, Ghista DN. Biomechanics of bone-fracture fixation by stiffness-graded plates in comparison with stainless steel plates. Biomed Eng Online 2005;4: art. 46 (15 pages).

Gao C, Deng Y, Feng P, Mao Z, Li P, Yang B, et al. Current progress in bioactive ceramic scaffolds for bone repair and regeneration. Int J Mol Sci 2014;15:4714–32.

García C, Ceré S, Durán A. Bioactive coatings deposited on titanium alloys. J Non-Cryst Solids 2006;352:3488–95.

Genin GM, Kent A, Birman V, Wopenka B, Pasteris JD, Marquez PJ, et al. Functional grading of mineral and collagen in the attachment of tendon to bone. Biophys J 2009;97:976–85.

Gerhardt L-C, Boccaccini AR. Bioactive glass and glass-ceramic scaffolds for bone tissue engineering. Materials 2010;3:3867–910.

Giannakopoulos AE, Kordolemis A, Zisis Th. Development of strong surfaces using functionally graded composites inspired by natural teeth – A theoretical approach. J Eng Mater-T ASME 2009;132:011009 (7 pages).

Goldsmith AAJ, Dowson D, Isaac GH, Lancaster JG. A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. Proc Inst Mech Eng H 2000;214:39–47.

Goller G. The effect of bond coat on mechanical properties of plasma sprayed bioglass-titanium coatings. Ceram Int 2004;30:351–5.

Gomez-Vega JM, Saiz E, Tomsia AP. Glass-based coatings for titanium implant alloys. J Biomed Mater Res 1999;46:549–59.

Gomez-Vega JM, Saiz E, Tomsia AP, Marshall GW, Marshall SJ. Bioactive glass coatings with hydroxyapatite and Bioglass® particles on Ti-based implants. 1. Processing. Biomaterials 2000;21:105–11.

Gong H, Wu W, Fang J, Dong X, Zhao MS, Guo TT. Effects of materials of cementless femoral stem on the functional adaptation of bone. J Bionic Eng 2012;9:66–74.

Gong H, Kong L, Zhang R, Fang J, Zhao M. A femur-implant model for the prediction of bone remodeling behavior induced by cementless stem. J Bionic Eng 2013;10:350–8.

Goodman SB, Yao Z, Keeney M, Yang F. The future of biologic coatings for orthopaedic implants. Biomaterials 2013;34:3174–83.

Goossens J, Leclaire P, Xu X, Glorieux Ch, Martinez L, Sola A, et al. Surface acoustic wave depth profiling of a functionally graded material. J Appl Phys 2007;102:053508 (8 pages).

Grandfield K, Zhitomirsky I. Electrophoretic deposition of composite hydroxyapatite–silica–chitosan coatings. Mater Charact 2008;59:61–7.

Grandfield K, Chattah NL, Djomehri S, Eidelmann N, Eichmiller FC, Webb S, et al. The narwhal (Monodon monoceros) cementum-dentin junction: a functionally graded biointerphase. *Proc Inst Mech Eng H* 2014;228:754–67.

Gu Y, Nakamura T, Prchlik L, Sampath S, Wallace J. Micro-indentation and inverse analysis to characterize elastic/plastic graded materials. Mater Sci Eng A Struct Mater 2003;345:223–33.

Guo H, Khor KA, Boey YC, Miao X. Laminated and functionally graded hydroxyapatite/yttria stabilized tetragonal zirconia composites fabricated by spark plasma sintering. Biomaterials 2003;24:667–75.

Haïat G, Naili S, Grimal Q, Talmant M, Desceliers C, Soize C. Influence of a gradient of material properties on ultrasonic wave propagation in cortical bone: Application to axial transmission. J Acoust Soc Am 2009;125:4043–52.

Hand Surgery in the UK. Manpower, resources, standards and training. Report of a working party (2007). Released by the British Society for Surgery of the Hand. Available on-line at http://www.bssh.ac.uk/members/documents/ukhandsurgreport.pdf Accessed October 29, 2014.

Harley BA, Hastings AZ, Yannas IV, Sannino A. Fabricating tubular scaffolds with a radial pore size gradient by a spinning technique. Biomaterials 2006;27:866–74.

Harvey E, Bobyn J, Tanzer M, Stackpool G, Krygier J, Hacking S. Effect of flexibility of the femoral stem on bone-remodeling and fixation of the stem in a canine total hip arthroplasty model without cement. J Bone Joint Surg Am 1999;81:93–107.

Hazlehurst KB, Wang CJ, Stanford M. Evaluation of the stiffness characteristics of square pore CoCrMo cellular structures manufactured using laser melting technology for potential orthopaedic applications. Mater Design 2013a;51:949–55.

Hazlehurst KB, Wang CJ, Stanford M. The potential application of a Cobalt Chrome Molybdenum femoral stem with functionally graded orthotropic structures manufactured using Laser Melting technologies. Med Hypotheses 2013b;81:1096–9.

Hazlehurst KB, Wang CJ, Stanford M. An investigation into the flexural characteristics of functionally graded cobalt chrome femoral stems manufactured using selective laser melting. Mater Design 2014;60:177–83.

He G, Guo B, Wang H, Liang C, Ye L, Lin Y, et al. Surface characterization and osteoblast response to a functionally graded hydroxyapatite/fluoro-hydroxyapatite/titanium oxide coating on titanium surface by sol-gel method. Cell Proliferat 2014;47:258–66.

Hedia HS, Shabara MAN, El-Midany TT, Fouda N. A method of material optimization of cementless stem through functionally graded material. Int J Mech Mater Des 2004;1:329–46.

Hedia HS, El-Midany TT, Shabara MAN, Fouda N. Development of cementless metal-backed acetabular cup prosthesis using functionally graded material. Int J Mech Mater Des 2005;2:259–67.

Hedia HS, Shabara MAN, El-Midany TT, Fouda N. Improved design of cementless hip stems using two-dimensional functionally graded materials. J Biomed Mater Res B Appl Biomater 2006;79:42–9.

Hedia HS, Fouda N. Improved stress shielding on a cementless tibia tray using Functionally Graded Material. Materialprüfung/Materials Testing 2013;55:845–51.

Hedia HS, Aldousari SM, Abdellatif AK, Fouda N. A new design of cemented stem using functionally graded materials (FGM). Biomed Mater Eng 2014;24:1575–88.

Hedia HS, Fouda N. Design optimization of cementless hip prosthesis coating through functionally graded material. Comp Mater Sci 2014;87:83–7.

Hedia HS. Comparison of one-dimensional and two-dimensional functionally graded materials for the backing shell of the cemented acetabular cup. J Biomed Mater Res B Appl Biomater 2005;74:732–9.

Heimann RB. Design of novel plasma sprayed hydroxyapatite-bond coat bioceramic systems. J Therm Spray Technol 1999;8:597–603.

Heimann RB. Thermal spraying of biomaterials. Surf Coat Technol 2006;201:2012–9.

Hench LL. The story of Bioglass®. J Mater Sci Mater Med 2006;17:967–78.

Herman H, Sampath S, McCune R. Thermal spray: current status and future trends. MRS Bull 2000;25:17–25.

Hirano T, Wakashima K. Mathematical modeling and design. MRS Bull 1995;1:40–42.

Hirschhorn JS, Reynolds JT. Powder metallurgy fabrication of cobalt alloy surgical implant materials. In: Hirschhorn JS, Reynolds JT, Korstoff E, editors. Research in dental and medical materials. New York (NY): Plenum Press; 1969. p. 137–50.

Ho SP, Balooch M, Marshall SJ, Marshall GW. Local properties of a functionally graded interphase between cementum and dentin. J Biomed Mater Res A 2004;70:480–9.

Hong C, Du J, Liang J, Zhang X, Han J. Functionally graded porous ceramics with dense surface layer produced by freeze-casting. Ceram Int 2011;37:3717–22.

Hsu YH, Turner IG, Miles AW. Fabrication of porous bioceramics with porosity gradients similar to the bimodal structure of cortical and cancellous bone. J Mater Sci Mater Med 2007;18:2251–6.

Huang D, Niu L, Wei Y, Guo M, Zuo Y, Zou Q, et al. Interfacial and biological properties of the gradient coating on polyamide substrate for bone substitute. J R Soc Interface 2014;11:20140101 (10 pages).

Huang M, Wang R, Thompson V, Rekow D, Soboyejo WO. Bioinspired design of dental multilayers. J Mater Sci Mater Med 2007;18:57–64.

Huiskes R. Stress shielding and bone resorption in THA: clinical versus computer-simulation studies. Acta Orthop Belg 1993;59 Suppl. 1:118–29.

Humzah MD, Soames RW. Human intervertebral disc: structure and function. Anat Rec 1988;220:337–56.

Hussain MA, Maqbool A, Khalid FA, Bakhsh N, Hussain A, Rahman JU, et al. Mechanical properties of CNT reinforced hybrid functionally graded materials for bioimplants. T Nonferr Metal Soc 2014;24, Supplement 1:s90–8.

Hussain MA, Maqbool A, Khalid FA, Farooq MU, Abidi IH, Bakhsh N, Amin W, Kim JY. Improved sinterability of hydroxyapatite functionally graded materials strengthened with SS316L and CNTs fabricated by pressureless sintering. Ceram Int 2015;41:10125–10132.

Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. Biomaterials 2000;21:2529–43.

Inagaki M, Yokogawa Y, Kameyama T. Apatite/titanium composite coatings on titanium or titanium alloy by RF plasma-spraying process. Thin Solid Films 2001;386;222–6.

Jackson TR, Liu H, Patrikalakis NM, Sachs EM, Cima MJ. Modeling and designing functionally graded material components for fabrication with local composition control. Mater Design 1999;20:63–75.

Jamaludin SNS, Mustapha F, Nuruzzaman DM, Basri SN. A review on the fabrication techniques of functionally graded ceramic-metallic materials in advanced composites. Sci Res Essays 2013;8:828–40.

Jaworski R, Pawlowski L, Pierlot C, Roudet F, Kozerski S, Petit F. Recent developments in suspension plasma sprayed titanium oxide and hydroxyapatite coatings. J Therm Spray Technol 2010;19:240–7.

Jee WSS. Principles in bone physiology. J Musculoskelet Neuronal Interact 2000;1:11–3.

Jeon JE, Vaquette C, Klein TJ, Hutmacher DW. Perspectives in multiphasic osteochondral tissue engineering. Anat Rec 2014;297:26–35.

Jin GQ, Li WD. Adaptive rapid prototyping/manufacturing for functionally graded material-based biomedical models. Int J Adv Manuf Technol 2013;65:97–113.

Jitcharoen J, Padture NP, Giannakopoulos AE, Suresh S. Hertzian-crack suppression in ceramics with elastic-modulus-graded surfaces. J Am Ceram Soc 1998;81:2301–8.

Jor JWY, Parker MD, Taberner AJ, Nash MP, Nielsen PMF. Computational and experimental characterization of skin mechanics: identifying current challenges and future directions. Wiley Interdiscip Rev Syst Biol Med 2013;5:539–56.

Joseph AN, Lee JH, Hong SI. Nanocomposited and functionally graded ZrN/HA coatings on cp-Ti by RF magnetron sputtering. Appl Mech Mater 2012;248:37–42.

Jumel J, Lepoutre F, Terrien N, Arnould O, Roger J-P. Microscopic characterization of functionally graded materials. Rev Sci Instrum 2003;74:837–838.

Jung H-D, Yook S-W, Kim H-E, Koh Y-H. Fabrication of titanium scaffolds with porosity and pore size gradients by sequential freeze casting. Mater Lett 2009;63:1545–7.

Kaplan D. Mollusk shell structures: novel design strategies for synthetic materials. Curr Opin Solid State Mater Sci 1998;3:232–236.

Karageorgiou V, Kaplan D. Porosity of 3D biomaterial scaffolds and osteogenesis. Biomaterials 2005;26:5474–91.

Kasuga T, Nogami M, Niinomi M, Hattor T. Bioactive calcium phosphate invert glass-ceramic coating on β-type Ti–29Nb–13Ta–4.6Zr alloy. Biomaterials 2003;24:283–90.

Katakam S, Krishna DSR, Murugan R, Kumar TSS. Processing of calcium phosphate based functionally graded bioceramics using microwaves. Trends Biomater Artif Organs 2003;17:24–7.

Kawasaki A, Watanabe R. Concept and p/m fabrication of functionally graded materials. Ceram Int 1997;23:73–83.

Kazemzadeh-Narbat M, Lai BF, Ding C, Kizhakkedathu JN, Hancock RE, Wang R. Multilayered coating on titanium for controlled release of antimicrobial peptides for the prevention of implant-associated infections. Biomaterials 2013;34:5969–77.

Keeney M, Waters H, Barcay K, Jiang X, Yao Z, Pajarinen J, et al. Mutant MCP-1 protein delivery from layer-by-layer coatings on orthopedic implants to modulate inflammatory response. Biomaterials 2013;34:10287–95.

Khan Y, Yaszemski MJ, Mikos AG, Laurencin CT. Tissue engineering of bone: material and matrix considerations. J Bone Joint Surg Am 2008;90 Suppl. 1:36–42.

Khanoki SA, Pasini D. Multiscale design and multiobjective optimization of orthopedic hip implants with functionally graded cellular material. J Biomech Eng 2012;134:031004 (10 pages).

Khanoki SA, Pasini D. The fatigue design of a bone preserving hip implant with functionally graded cellular material. J Med Devices 2013a;7:020907 (2 pages).

Khanoki SA, Pasini D. Fatigue design of a mechanically biocompatible lattice for a proof-of-concept femoral stem. J Mech Behav Biomed Mater 2013b;22:65–83.

Khor KA, Wang Y, Cheang P. Thermal spraying of functionally graded coatings for biomedical applications. Surf Eng 1998;14:159–64.

Khor KA, Gu YW, Quek CH, Cheang P. Plasma spraying of functionally graded hydroxyapatite/Ti–6Al–4V coatings. Surf Coat Technol 2003;168:195–201.

Kieback B, Neubrand A, Riedel H. Processing techniques for functionally graded materials. Mater Sci Eng A Struct Mater 2003;362:81–106.

Kim CY, Jee SS. Hydroxyapatite formation on bioactive-glazed alumina. J Eur Ceram Soc 2003;23:1803–11.

Kim J-W, Liu L, Zhang Y. Improving the resistance to sliding contact damage of zirconia using elastic gradients. J Biomed Mater Res B Appl Biomater 2010;94:347–52.

Kim M, Franco RA, Lee B-T. Synthesis of functional gradient BCP/ZrO_2 bone substitutes using ZrO_2 and BCP nanopowders. J Eur Ceram Soc 2011;31:1541–8.

Kim TG, Shin H, Lim DW. Biomimetic scaffolds for tissue engineering. Adv Funct Mater 2012;22:2446–68.

Koizumi M, Niino M. Overview of FGM Research in Japan. MRS Bull 1995;1:19–21.

Kon M, Ishikawa K, Miyamoto Y, Asaoka K. Development of calcium phosphate based functional gradient bioceramics. Biomaterials 1995;16:709–14.

Kondo H, Yokoyama A, Omori M, Ohkubo A, Hirai T, Watari F, et al. Fabrication of titanium nitride/apatite functionally graded implants by spark plasma sintering. Mater Trans 2004;45:3156–62.

Kongsuwan P, Brandal GB, Yao YL. Laser induced porosity and crystallinity modification of a bioactive glass coating on titanium substrates. ASME 2015 International Manufacturing Science and Engineering Conference, MSEC 2015, *in press*.

Kowalczyk P. Design optimization of cementless femoral hip prostheses using finite element analysis. J Biomech Eng 2001;123:396–402.

Krishna BV, Bose S, Bandyopadhyay A. Low stiffness porous Ti structures for load-bearing implants. Acta Biomater 2007;3:997–1006.

Krishna BV, DeVasConCellos PD, Xue W, Bose S, Bandyopadhyay A. Fabrication of compositionally and structurally graded Ti–TiO_2 structures using laser engineered net shaping (LENS). Acta Biomater 2009;5:1831–7.

Krishna BV, Xue W, Bose S, Bandyopadhyay A. Functionally graded Co–Cr–Mo coating on Ti–6Al–4V alloy structures. Acta Biomater 2008;4:697–706.

Kuiper JH, Huiskes R. Mathematical optimization of elastic properties: application to cementless hip stem design. J Biomech Eng 1997;119:166–74.

Kuromitsu Y, Yoshida H, Takebe H, Morinaga K. Interaction between alumina and binary glasses. J Am Ceram Soc 1997;80:1583–7.

Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the united states from 1990 through 2002. J Bone Joint Surg Am 2005;87:1487–97.

Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780–5.

Kurtz SM, Kocagöz S, Arnholt C, Huet R, Ueno M, Walter WL. Advances in zirconia toughened alumina biomaterials for total joint replacement. J Mech Behav Biomed Mater 2014;31:107–16.

Kurzweg H, Heimann RB, Troczynski T, Wayman ML. Development of plasma-sprayed bioceramic coatings with bond coats based on titania and zirconia. Biomaterials 1998;19:1507–11.

Kweh SWK, Khor KA, Cheang P. Plasma-sprayed hydroxyapatite (HA) coatings with flame-spheroidized feedstock: microstructure and mechanical properties. Biomaterials 2000;21:1223–34.

Kyeck S, Remer P. Realisation of graded coatings for biomedical use. Mater Sci Forum 1999;308–311:368–73.

Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AVF. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement – A consequence of excess wear. J Bone Joint Surg Br 2010;92:38–46.

Laurenti KC, de Albuquerque Haach LC, dos Santos jr AR, de Almeida Rollo JMD, de Menezes Reiff RB, Minarelli Gaspar AM, et al. Cartilage reconstruction using self-anchoring implant with functional gradient. Mat Res (online) 2014; vol.17, n.3:638–49. Available from: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-14392014000300015&lng=en&nrm=iso>. Epub Mar 18, 2014. ISSN 1516-1439. http://dx.doi.org/10.1590/S1516-14392014005000030.

Leng YX, Chen JY, Yang P, Sun H, Wang J, Huang N. The biocompatibility of the tantalum and tantalum oxide films synthesized by pulse metal vacuum arc source deposition. Nucl Instrum Meth B 2006;242:30–2.

Leong KF, Cheah CM, Chua CK. Solid freeform fabrication of three-dimensional scaffolds for engineering replacement tissues and organs. Biomaterials 2003;24:2363–78.

Leong KF, Chua CK, Sudarmadji N, Yeong WY. Engineering functionally graded tissue engineering scaffolds. J Mech Behav Biomed Mater 2008;1:140–52.

Levine BR, Sporer S, Poggie RA, Della Valle CJ, Jacobs JJ. Experimental and clinical performance of porous tantalum in orthopedic surgery. Biomaterials 2006;27:4671–81.

Levingstone TJ, Matsiko A, Dickson GR, O'Brien FJ, Gleeson JP. A biomimetic multi-layered collagen-based scaffold for osteochondral repair. Acta Biomater 2014;10:1996–2004.

Li X, Xie J, Lipner J, Yuan X, Thomopoulos S, Xia Y. Nanofiber scaffolds with gradations in mineral content for mimicking the tendon-to-bone insertion site. Nano Lett 2009;9:2763–8.

Liebschner MAK, Wettergreen MA. Optimization of bone scaffold engineering for load bearing applications (Ch. 6). In: Ashammakhi N, Ferretti P, editors. Topics in Tissue Engineering, 2003. Oulu, Finland: University of Oulu; 2003. p. 1–39. Book available on-line at: http://www.oulu.fi/spareparts/ebook_topics_in_t_e/index.html.

Liebschner M, Bucklen B, Wettergreen M. Mechanical aspects of tissue engineering. Semin Plast Surg 2005;19:217–28.

Lindner M, Bergmann C, Telle R, Fischer H. Calcium phosphate scaffolds mimicking the gradient architecture of native long bones. J Biomed Mater Res A 2014;102:3677–84.

Liu C, Hu D, Xu J, Yang D, Qi M. In vitro electrochemical corrosion behavior of functionally graded diamond-like carbon coatings on biomedical Nitinol alloy. Thin Solid Films 2006;496:457–62.

Liu GR, Han X, Xu YG, Lam KY. Material characterization of functionally graded material by means of elastic waves and a progressive-learning neural network. Compos Sci Technol 2001;61:1401–11.

Liu M, Yu X, Huang F, Cen S, Zhong G, Xiang Z. Tissue engineering stratified scaffolds for articular cartilage and subchondral bone defects repair. Orthopedics 2013;36:868–73.

Liu X, Ma PX. Polymeric scaffolds for bone tissue engineering. Ann Biomed Eng 2004;32:477–86.

Liu Y, Kim J-H, Young D, Kim S, Nishimoto SK, Yang Y. Novel template-casting technique for fabricating β-tricalcium phosphate scaffolds with high interconnectivity and mechanical strength and in vitro cell responses. J Biomed Mater Res A 2010;92:997–1006.

Liu YX, Thomopoulos S, Birman V, Li J-S, Genin GM. Bi-material attachment through a compliant interfacial system at the tendon-to-bone insertion site. Mech Mater 2012;44:83–92.

Lopa S, Madry H. Bioinspired scaffolds for osteochondral regeneration. Tissue Eng Part A 2014;20:2052–76.

Lopez-Esteban S, Saiz E, Fujino S, Oku T, Suganuma K, Tomsia AP. Bioactive glass coatings for orthopedic metallic implants. J Eur Ceram Soc 2003;23:2921–30.

Low IM, Che ZY. Mapping the structure, composition and mechanical properties of bamboo. J Mater Res 2006;21:1969–76.

Lu WW, Zhao F, Luk KDK, Yin YJ, Cheung KMC, Cheng GX, et al. Controllable porosity hydroxyapatite ceramics as spine cage: fabrication and properties evaluation. J Mater Sci Mater Med 2003;14:1039–46.

Lu Y-P, Li M-S, Li S-T, Wang Z-G, Zhu R-F. Plasma-sprayed hydroxyapatite+titania composite bond coat for hydroxyapatite coating on titanium substrate. Biomaterials 2004;25:4393–403.

Macchetta A, Turner IG, Bowen CR. Fabrication of HA/TCP scaffolds with a graded and porous structure using a camphene-based freeze-casting method. Acta Biomater 2009;5:1319–27.

Mahamood RM, Akinlabi ET, Shukla M, Pityana S. Functionally graded materials: an overview. In: Ao SI, Gelman L, Hukins DWL, Hunter A, Korsunsky AM, editors. Proceedings of the World Congress on Engineering 2012 Vol III (WCE 2012, July 4-6, 2012, London, U.K.). Hong Kong: Newswood Limited; 2012. p. 1593–1597.

Manjubala I, Sivakumar M, Sampathkumar TS, Panduranga Rao K. Synthesis and characterization of functional gradient materials using Indian corals. J Mater Sci Mater Med 2000;11:705–9.

Markworth AJ, Ramesh KS, Parks Jr WP. Review. Modelling studies applied to functionally graded materials. J Mater Sci 1995;30:2183–93.

Matsuno T, Watanabe K, Ono K, Koishi M. Preparation of laminated hydroxyapatite/zirconia sintered composite with the gradient composition. J Mater Sci Lett 1998;17:1349–51.

McKittrick J, Chen PY, Tombolato L, Novitskaya EE, Trim MW, Hirata GA, et al. Energy absorbent natural materials and bioinspired design strategies: a review. Mater Sci Eng C Mater Biol Appl 2010;30:331–42.

Mehrali M, Shirazi FS, Mehrali M, Metselaar HSC, Kadri NAB, Abu Osman NA. Dental implants from functionally graded materials. J Biomed Mater Res A 2013;101:3046–57.

Miao X, Sun D. Graded/Gradient porous biomaterials. Materials 2010;3:26–47.

Migacz K, Chłopek J, Morawska-Chochół A, Ambroziak M. Gradient composite materials for artificial intervertebral discs. Acta Bioeng Biomech 2014;16:3–12.

Min J, Braatz RD, Hammond PT. Tunable staged release of therapeutics from layer-by-layer coatings with clay interlayer barrier. Biomaterials 2014;35:2507–17.

Miyamoto Y, Kaysser WA, Rabin BH, Kawasaki A, Ford RG. Functionally Graded Materials. Design, Processing and Applications. Dordrecht/London/Boston: Kluwer Academic Publishers; 1999.

Morsi K, Keshavan H, Bal S. Processing of grain-size functionally gradient bioceramics for implant applications. J Mater Sci Mater Med 2004;15:191–7.

Mortensen A, Suresh S. Functionally graded metals and metal-ceramic composites. I. Processing. Int Mater Rev 1995;40:239–65.

Mortensen A, Suresh S. Functionally graded metals and metal-ceramic composites. II. Thermomechanical behaviour. Int Mater Rev 1997;42:85–116.

Moshe-Drezner H, Shilo D, Dorogoy A, Zolotoyabko E. Nanometer-scale mapping of elastic modules in biogenic composites: The nacre of mollusk shells. Adv Funct Mater 2010;20:2723–8.

Muller P, Hascoet J-Y, Mognol P. A method for the manufacturing of functionally graded material parts. Adv Mater Res 2013;698:117–26.

Murr LE, Gaytan SM, Medina F, Lopez H, Martinez E, Machado BI, et al. Next-generation biomedical implants using additive manufacturing of complex, cellular and functional mesh arrays. Philos T R Soc A 2010;368:1999–2032.

Muthutantri A, Huang J, Edirisinghe M. Novel preparation of graded porous structures for medical engineering. J R Soc Interface 2008;5:1459–67.

Nag S, Banerjee R. Fundamentals of medical implant materials. In: Narayan R, editor. ASM Handbook, vol. 23, Materials for Medical Devices. Materials Park (OH): ASM International®; 2012. p. 6–17.

Narayanan R, Seshadri SK. Synthesis and corrosion of functionally gradient TiO_2 and hydroxyapatite coatings on Ti–6Al–4V. Mater Chem Phys 2007;106:406–11.

Nather A, Ong HJC, Aziz Z. Structure of bone (Ch. 1). In: Nather A, Editor. Bone grafts and bone substitutes - Basic Science and Clinical Applications. Singapore: World Scientific Publishing Co Pte Ltd; 2005. p. 3–17.

Nematt-Alla M. Reduction of thermal stresses by developing two-dimensional functionally graded materials. Int J Solids Struct 2003;40:7339–56.

Nindhia TGT, Koyoshi Y, Kaneko A, Sawada H, Ohta M, Hirai S, et al. Hydroxyapatite-silk functionally graded material by pulse electric current sintering. Trends Biomater Artif Organs 2008;22:28–33.

Ning CY, Wang YJ, Chen XF, Zhao NR, Ye JD, Wu G. Mechanical performances and microstructural characteristics of plasma-sprayed bio-functionally gradient HA-ZrO_2-Ti coatings. Surf Coat Technol 2005;200:2403–8.

Nishiyabu K, Matsuzaki S, Okubo K, Ishida M, Tanaka S. Porous graded materials by stacked metal powder hot-press moulding. Mater Sci Forum 2005;492–493:765–70.

Niu X, Rahbar N, Farias S, Soboyejo W. Bio-inspired design of dental multilayers: experiments and model. J Mech Behav Biomed Mater 2009;2:596–602.

Nogata F, Takahashi H. Intelligent functionally graded material: bamboo. Compos Eng 1995;5:743–51.

Nooeaid P, Salih V, Beier JP, Boccaccini AR. Osteochondral tissue engineering: scaffolds, stem cells and applications. J Cell Mol Med 2012;16:2247–70.

Nouri A, Hodgson PD, Wen C. Biomimetic porous titanium scaffolds for orthopedic and dental applications (Ch. 21). In: Amitava Mukherjee, editor. Biomimetics Learning from Nature. ISBN: 978-953-307-025-4, InTech; 2010. p. 415–50. Available from: http://www.intechopen.com/books/biomimetics-learning-from-nature/biomimetic-porous-titanium-scaffolds-for-orthopedic-and-dental-applications.

Novak S, Kalin M, Lukas P, Anne G, Vleugels J, Van Der Biest O. The effect of residual stresses in functionally graded alumina–ZTA composites on their wear and friction behaviour. J Eur Ceram Soc 2007;27:151–6.

Nukavarapu SP, Dorcemus DL. Osteochondral tissue engineering: current strategies and challenges. Biotechnol Adv 2013;31:706–21.

O'Brien FJ. Biomaterials & scaffolds for tissue engineering. Mater Today 2011;14:88–95.

Odekerken JCE, Welting TJM, Arts JJC, Walenkamp GHIM, Emans PJ. Modern Orthopaedic Implant Coatings — Their Pro's, Con's and Evaluation Methods (Ch. 3). In: Aliofkhazraei M, editor. Modern Surface Engineering Treatments. ISBN: 978-953-51-1149-8, InTech; 2013. p. 45–73. Available from: http://www.intechopen.com/books/modern-surface-engineering-treatments/modern-orthopaedic-implant-coatings-their-pro-s-con-s-and-evaluation-methods.

Oh I-H, Segawa H, Nomura N, Hanada S. Microstructures and mechanical properties of porosity-graded pure titanium compacts. Mater Trans 2003;44:657–60.

Oh SH, Park IK, Kim JM, Lee JH. In vitro and in vivo characteristics of PCL scaffolds with pore size gradient fabricated by a centrifugation method. Biomaterials 2007;28:1664–71.

Oktar FN, Yetmez M, Agathopoulos S, Lopez Goerne TM, Goller G, Ipeker I, et al. Bond-coating in plasma-sprayed calcium-phosphate coatings. J Mater Sci Mater Med 2006;17:1161–71.

Ono K, Functionally graded structure and properties of a bivalve hinge ligament. MRS Bull 1995;1:48–9.

Oshkour AA, Abu Osma NA, Yau YH, Tarlochan F, Abas WA. Design of new generation femoral prostheses using functionally graded materials: a finite element analysis. Proc Inst Mech Eng H 2013a;227:3–17.

Oshkour AA, Abu Osman NA, Davoodi MM, Yau YH, Tarlochan F, Wan Abas WAB, et al. Finite element analysis on longitudinal and radial functionally graded femoral prosthesis. Int J Numer Method Biomed Eng 2013b;29:1412–27.

Oshkour AA, Abu Osman NA, Bayat M, Afshar R, Berto F, Three-dimensional finite element analyses of functionally graded femoral prostheses with different geometrical configurations. Mater Design 2014a;56:998–1008.

Oshkour AA, Talebi H, Shirazi SFS, Bayat M, Yau YH, Tarlochan F, et al. Comparison of Various Functionally Graded Femoral Prostheses by Finite Element Analysis. ScientificWorldJournal 2014b;Volume 2014:Article ID 807621 (17 pages).

Oshkour AA, Talebi H, Shirazi SFS, Yau YH, Tarlochan F, Abu Osman NA. Effect of geometrical parameters on the performance of longitudinal functionally graded femoral prostheses. Artif Organs 2015; 39:156–64.

Oxman N. Structuring materiality: design fabrication of heterogeneous materials. Archit Design 2010;80:78–85.

Oxman N. website: http://materialecology.com/, accessed Nov. 24, 2014.

Ozeki K, Yuhta T, Fukui Y, Aoki H, Nishimura I. A functionally graded titanium/hydroxyapatite film obtained by sputtering. J Mater Sci Mater Med 2002;13:253–8.

Pang X, Casagrande T, Zhitomirsky I. Electrophoretic deposition of hydroxyapatite-$CaSiO_3$-chitosan composite coatings. J Colloid Interf Sci 2009;330:323–9.

Parthasarathy J, Starly B, Raman S. A design for the additive manufacture of functionally graded porous structures with tailored mechanical properties for biomedical applications. J Manuf Process 2011;13:160–70.

Pawlowski L. Suspension and solution thermal spray coatings. Surf Coat Technol 2009;203:2807–29.

Pearson OM, Lieberman DE. The aging of Wolff's "law": ontogeny and responses to mechanical loading in cortical bone. Yrbk Phys Anthropol 2004;47:63–99.

Pezowicz CA, Robertson PA, Broom ND. The structural basis of interlamellar cohesion in the intervertebral disc wall. J Anat 2006;208:317–30.

Pompe W, Worch H, Epple M, Friess W, Gelinsky M, Greil P, et al. Functionally graded materials for biomedical applications. Mater Sci Eng A Struct Mater 2003;362:40–60.

Raabe D, Sachs C, Romano P. The crustacean exoskeleton as an example of a structurally and mechanically graded biological nanocomposite material. Acta Mater 2005;53:4281–92.

Rabin BH, Shiota I. Functionally Gradient Materials. MRS Bull 1995;1:14–5.

Raghunath J, Rollo J, Sales KM, Butler PE, Seifalian AM. Biomaterials and scaffold design: key to tissue-engineering cartilage. Biotechnol Appl Biochem 2007;46:73–84.

Ramakrishna K, Sridhar I, Sivashanker S, Ganesh VK, Ghista DN. Analysis of an internal fixation of a long bone fracture. J Mech Med Biol 2005;5:89–103.

Ramakrishna K, Sridhar I, Sivashanker S, Khong KS, Ghista DN. Design of fracture fixation plate for necessary and sufficient bone stress shielding. JSME Int J C-Mech Sy 2004;47:1086–94.

Rausch MK, Bothe W, Kvitting JP, Swanson JC, Miller DC, Kuhl E. Mitral valve annuloplasty: A quantitative clinical and mechanical comparison of different annuloplasty devices. Ann Biomed Eng 2012;40:750–61.

Rho J-Y, Kuhn-Spearing L, Zioupos P. Mechanical properties and hierarchical structure of bone. Med Eng Phys 1998;20:92–102.

Ritchie RO. Armoured oyster shells. Nat Mater 2014;13:435–7.

Roncari E, Galassi C, Pinasco P. Tape casting of porous hydroxyapatite ceramics. J Mater Sci Lett 2000;19:33–5.

Roop Kumar R, Wang M. Functionally graded bioactive coatings of hydroxyapatite/titanium oxide composite system. Mater Lett 2002;55:133–7.

Roy TD, Simon JL, Ricci JL, Rekow ED, Thompson VP, Parsons JR. Performance of degradable composite bone repair products made via three-dimensional fabrication techniques. J Biomed Mater Res A 2003;66:283–91.

Ryan G, Pandit A, Apatsidis DP. Fabrication methods of porous metals for use in orthopaedic applications. Biomaterials 2006;27:2651–70.

Sachlos E, Czernuszka JT. Making tissue engineering scaffolds work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds. Eur Cell Mater 2003;5:29–39.

Saharan A, Ostoja-Starzewski M, Koric S. Fractal geometric characterization of functionally graded materials. J Nanomech Micromech 2013;3:04013001.

Seidi A, Ramalingam M, Elloumi-Hannachi I, Ostrovidov S, Khademhosseini A. Gradient biomaterials for soft-to-hard interface tissue engineering. Acta Biomater 2011;7:1441–51.

Seidi A, Sampathkumar K, Srivastava A, Ramakrishna S, Ramalingam M. Gradient nanofiber scaffolds for tissue engineering. J Nanosci Nanotechnol 2013;13:4647–55.

Seo SJ, Mahapatra C, Singh RK, Knowles JC, Kim HW. Strategies for osteochondral repair: Focus on scaffolds, J Tissue Eng 2014;5: 1–14 (article id: 2041731414541850, first published on July 23, 2014 doi:10.1177/2041731414541850).

Shah NJ, Hong J, Hyder MN, Hammond PT. Osteophilic multilayer coatings for accelerated bone tissue growth. Adv Mater 2012;24:1445–50.

Shanaghi A, Chu PK, Sabour Rouhaghdam AR, Xu R, Hu T. Structure and corrosion resistance of Ti/TiC coatings fabricated by plasma immersion ion implantation and deposition on nickel-titanium. Surf Coat Technol 2013;229:151–5.

Shapiro IM, Risbud MV. Introduction to the structure, function, and comparative anatomy of the vertebrae and the intervertebral disc (Ch. 1). In: Shapiro IM, Risbud MV, editors. The intervertebral disc. Molecular and structural studies of the disc in health and disease. Wien: Springer-Verlag; 2014. p. 3–16.

Shen M, Bever MB. Gradients in polymeric materials. J Mater Sci 1972;7:741–6.

Shi X, Zhou J, Zhao Y, Li L, Wu H. Gradient-regulated hydrogel for interface tissue engineering: steering simultaneous osteo/chondrogenesis of stem cells on a chip. Adv Healthc Mater 2013;2:846–53.

Silva ECN, Walters MC, Paulino GH. Modeling bamboo as a functionally graded material: lessons for the analysis of affordable materials. J Mater Sci 2006;41:6991–7004.

Silva-Correia J, Correia SI, Oliveira JM, Reis RL. Tissue engineering strategies applied in the regeneration of the human intervertebral disk. Biotechnol Adv 2013;31:1514–31.

Singh V, Grammatikopoulos P, Cassidy C, Benelmekki M, Bohra M, Hawash Z, et al. Assembly of tantalum porous films with graded oxidation profile from size-selected nanoparticles. J Nanopart Res 2014;16:2373 (10 pages).

Sobczak JJ, Drenchev L. Metallic functionally graded materials: a specific class of advanced composites. J Mater Sci Technol 2013;29:297–316.

Sola A, Bellucci D, Cannillo V. Enamelled coatings produced with low-alkaline bioactive glasses. Surf Coat Technol 2014;248:1–8.

Sonntag R, Reinders J, Kretzer JP. What's next? Alternative materials for articulation in total joint replacement. Acta Biomater 2012;8:2434–41.

Sopyan I, Mel M, Ramesh S, Khalid KA. Porous hydroxyapatite for artificial bone applications. Sci Technol Adv Mater 2007;8:116–23.

Sorensen JH, Lilja M, Åstrand M, Sorensen TC, Procter P, Stromme M, et al. Co-precipitation of tobramycin into biomimetically coated orthopedic fixation pins employing submicron-thin seed layers of hydroxyapatite. Curr Drug Deliv 2014;11:501–10.

Staiger MP, Pietak AM, Huadmai J, Dias G. Magnesium and its alloys as orthopedic biomaterials: A review. Biomaterials 2006;27:1728–34.

Stojanovic D, Jokic B, Veljovic Dj, Petrovic R, Uskokovic PS, Janackovic Dj. Bioactive glass-apatite composite coating for titanium implant synthesized by electrophoretic deposition. J Eur Ceram Soc 2007;27:1595–9.

Suchanek W, Yoshimura M. Processing and properties of hydroxyapatite-based biomaterials for use as hard tissue replacement implants. J Mater Res 1998;13:94–117.

Sugiyama T, Meakin LB, Browne WJ, Galea GL, Price JS, Lanyon LE. Bones' adaptive response to mechanical loading is essentially linear between the low strains associated with disuse and the high strains associated with the lamellar/woven bone transition. J Bone Miner Res 2012;27:1784–93.

Sun B, Lynn DM. Release of DNA from polyelectrolyte multilayers fabricated using 'charge-shifting' cationic polymers: Tunable temporal control and sequential, multi-agent release. J Control Release 2010;148:91–100.

Sun F, Pang X, Zhitomirsky I. Electrophoretic deposition of composite hydroxyapatite-chitosan-heparin coatings. J Mater Process Tech 2009;209:1597–606.

Sun J, Thian ES, Fuh JYH, Chang L, Hong GS, Wang W, et al. Fabrication of bio-inspired composite coatings for titanium implants using the micro-dispensing technique. Microsyst Technol 2012;18:2041–51.

Suresh S, Olsson M, Giannakopoulos AE, Padture NP, Jitcharoen J. Engineering the resistance to sliding-contact damage through controlled gradients in elastic properties at contact surfaces. Acta Mater 1999;47:3915–26.

Suresh S. Graded materials for resistance to contact deformation and damage. Science 2001;292:2447–51.

Surmenev RA, Surmeneva MA, Ivanova AA. Significance of calcium phosphate coatings for the enhancement of new bone osteogenesis – a review. Acta Biomater 2014;10:557–79.

Sutou Y, Omori T, Furukawa A, Takahashi Y, Kainuma R, Yamauchi K, et al. Development of medical guide wire of Cu-Al-Mn-base superelastic alloy with functionally graded characteristics. J Biomed Mater Res B Appl Biomater 2004;69:64–9.

Tampieri A, Celotti G, Sprio S, Delcogliano A, Franzese S. Porosity-graded hydroxyapatite ceramics to replace natural bone. Biomaterials 2001;22:1365–70.

Tampieri A, Sandri M, Landi E, Pressato D, Francioli S, Quarto R, et al. Design of graded biomimetic osteochondral composite scaffolds. Biomaterials 2008;29:3539–46.

Tanaskovic D, Jokic B, Socol G, Popescu A, Mihailescu IN, Petrovic R, et al. Synthesis of functionally graded bioactive glass-apatite multistructures on Ti substrates by pulsed laser deposition. Appl Surf Sci 2007;254:1279–82.

Tang CY, Tsui CP, Wei L, Wang ZW. Damage analysis on a graded porous biocomposite structure under flexural load using FEM. Strength Fract Complex 2011;7:241–52.

Tang Z, Wang Y, Podsiadlo P, Kotov NA. Biomedical applications of layer-by-layer assembly: From biomimetics to tissue engineering. Adv Mater 2006;18:3203–24.

Taylor D. The fracture mechanics of bone. An Mec Fract 2006;Vol. I:7–11.

Taylor ED, Khan Y, Laurencin CT. Tissue engineering of bone: a primer for the practicing hand surgeon. J Hand Surg Am 2009;34:164–6.

Thamaraiselvi TV, Rajeswari S. Biological evaluation of bioceramic materials - A Review. Trends Biomater Artif Organs 2004;18:9–17.

Thieme M, Wieters K-P, Bergner F, Scharnweber D, Worch H, Ndop J, et al. Titanium powder sintering for preparation of a porous functionally graded material destined for orthopaedic implants. J Mater Sci Mater Med 2001;12:225–31.

Tomaszek R, Pawlowski L, Gengembre L, Laureyns J, Znamirowski Z, Zdanowski J. Microstructural characterization of plasma sprayed TiO_2 functional coating with gradient of crystal grain size. Surf Coat Technol 2006;201:45–56.

Tomaszek R, Pawlowski L, Gengembre L, Laureyns J, Le Maguer A. Microstructure of suspension plasma sprayed multilayer coatings of hydroxyapatite and titanium oxide. Surf Coat Technol 2007;201:7432–40.

Tomsia AP, Saiz E, Song J, Bertozzi CR. Biomimetic bonelike composites and novel bioactive glass coatings. Adv Eng Mater 2005;7:999–1004.

Torres Y, Pavón JJ, Rodríguez JA. Processing and characterization of porous titanium for implants by using NaCl as space holder. J Mater Process Technol 2012;212:1061–9.

Torres Y, Pavón J, Trueba P, Cobos J, Rodríguez-Ortiz JA. Design, Fabrication and characterization of titanium with graded porosity by using space-holder technique. Procedia Mater Sci 2014a;4:110–4.

Torres Y, Trueba P, Pavón J, Montealegre I, Rodríguez-Ortiz JA. Designing, processing and characterisation of titanium cylinders with graded porosity: An alternative to stress-shielding solutions. Mater Design 2014b;63:316–24.

Trebse R, Milosev I, Kovac S, Mikek M, Pisot V. Poor results from the isoelastic total hip replacement. Acta Orthop 2005;76:169–76.

Tsang VL, Bhatia SN. Fabrication of three-dimensional tissues. Adv Biochem Eng Biotechnol 2006;103:189–205.

Tucker jr RC. Introduction to coating design and processing. In: Tucker jr RC, editor. ASM Handbook, Volume 5A: Thermal Spray Technology. Materials Park (OH): ASM International®; 2013. p. 76–88.

van der Biest OO, Vandeperre LJ, Electrophoretic deposition of materials. Annu Rev Mater Sci 1999;29:327–52.

Vaz L, Lopes AB, Almeida M. Porosity control of hydroxyapatite implants. J Mater Sci Mater Med 1999;10:239–42.

Verné E, Vitale Brovarone C, Moisescu C, Ghisolfi E, Marmo E. Coatings on Al_2O_3 by bioactive glass-ceramics. Acta Mater 2000;48:4667–71.

Vinatier C, Mrugala D, Jorgensen C, Guicheux J, Noël D. Cartilage engineering: a crucial combination of cells, biomaterials and biofactors. Trends Biotechnol 2009;27:307–14.

Vitale Brovarone C, Verné E, Krajewski A, Ravaglioli A. Graded coatings on ceramic substrates for biomedical applications. J Eur Ceram Soc 2001;21:2855–62.

Vitale-Brovarone C, Baino F, Tallia F, Gervasio C, Verné E. Bioactive glass-derived trabecular coating: a smart solution for enhancing osteointegration of prosthetic elements. J Mater Sci Mater Med 2012;23:2369–80.

Walker PS, Erkman MJ. Metal-on-metal lubrication in artificial human joints. Wear 1972;21:377–92.

Wang HV, Johnston SR, Rosen DW, Design of a graded cellular structure for an acetabular hip replacement component. In: Proceedings of The Seventeenth Solid Freeform Fabrication Symposium (August 14-16, 2006). Austin (TX): University of Austin; 2006. p. 111–23. Available on-

line at
http://utwired.engr.utexas.edu/lff/symposium/proceedingsarchive/pubs/Table%20of%20Contents/2006_TOC.cfm.

Wang M, Yang XY, Khor KA, Wang Y. Preparation and characterization of bioactive monolayer and functionally graded coatings. J Mater Sci Mater Med 1999;10:269–73.

Wang Q, Wang Q, Wan C. Preparation and evaluation of a biomimetic scaffold with porosity gradients in vitro. An Acad Bras Cienc 2012;84:9–16.

Wang Y, Khor KA, Cheang P. Thermal spraying of functionally graded calcium phosphate coatings for biomedical implants. J Therm Spray Technol 1998;7:50–7.

Wang ZW, Tang CY, Tsui CP, Gao B. Optimization design for graded porous tubular structures. J Serb Soc Comput Mech 2008;2:80–90.

Watanabe Y, Iwamoto T, Teramoto A, Abe K, Ohkoshi Y. Biodegradability of Poly (L-lactic Acid) functionally graded materials with hardness gradient. Mater Trans 2004;45:1005–9.

Watari F, Yokoyama A, Omori M, Hirai T, Kondo H, Uo M, et al. Biocompatibility of materials and development to functionally graded implant for bio-medical application. Compos Sci Technol 2004;64:893–908.

Wen CE, Tamada Y, Nouri A, Hodgson PD. Porous titanium with porosity gradients for biomedical applications. Mater Sci Forum 2007;539–543:720–5.

Werner J, Linner-Krčmar B, Friess W, Greil P. Mechanical properties and in vitro cell compatibility of hydroxyapatite ceramics with graded pore structure. Biomaterials 2002;23:4285–94.

Williams CB, Cochran JK, Rosen DW. Additive manufacturing of metallic cellular materials via three-dimensional printing. Int J Adv Manuf Tech 2011;53:231–9.

Wilson JM, Jones N, Jin L, Shin YC. Laser deposited coatings of Co–Cr–Mo onto Ti-6Al-4V and SS316L substrates for biomedical applications. J Biomed Mater Res B Appl Biomater 2013;101:1124–32.

Wu XL, Jiang P, Chen L, Zhang JF, Yuan FP, Zhu YT. Synergetic strengthening by gradient structure. Mater Res Lett 2014;2:185–91.

Xie X-H, Yu X-W, Zeng S-X, Du R-L, Hu Y-H, Yuan Z, et al. Enhanced osteointegration of orthopaedic implant gradient coating composed of bioactive glass and nanohydroxyapatite. J Mater Sci Mater Med 2010;21:2165–73.

Xu HHK, Burguera EF, Carey LE. Strong, macroporous, and in situ-setting calcium phosphate cement-layered structures. Biomaterials 2007;28:3786–96.

Xu J, Khor K, Sui J, Chen W. Preparation and characterization of a novel hydroxyapatite/carbon nanotubes composite and its interaction with osteoblast-like cells. Mater Sci Eng C Mater Biol Appl 2009;29:44–9.

Yamada K, Imamura K, Itoh H, Iwata H, Maruno S. Bone bonding behavior of the hydroxyapatite containing glass-titanium composite prepared by the Cullet method. Biomaterials 2001;22:2207–14.

Yamashita D, Sato H, Miyamoto M, Ban S. Hydroxyapatite coating on zirconia using glass coating technique. J Ceram Soc Jpn 2008;116:20–2.

Yan Y, Xiong Z, Hu Y, Wang S, Zhang R, Zhang C. Layered manufacturing of tissue engineering scaffolds via multi-nozzle deposition. Mater Lett 2003;57:2623–8.

Yang S, Leong K-F, Du Z, Chua C-K. The design of scaffolds for use in tissue engineering. Part I. Traditional factors. Tissue Eng 2001;7:679–89.

Yang S, Leong K-F, Du Z, Chua C-K. The design of scaffolds for use in tissue engineering. Part II. Rapid prototyping techniques. Tissue Eng 2002;8:1–11.

Yang Y, Kang Y, Sen M, Park S. Bioceramics in tissue engineering (Ch. 7). In: Burdick JA, Mauck RL, editors. Biomaterials for tissue engineering applications. Wien: Springer-Verlag; 2011. p. 179–207.

Yang YZ, Tian JM, Tian JT, Chen ZQ, Deng XJ, Zhang DH. Preparation of graded porous titanium coatings on titanium implant materials by plasma spraying. J Biomed Mater Res 2000;52:333–7.

Zhang HO, Hu BY, Wang GL. Simulation on controllable-porosity coating by plasma spray. In: Murple BR, Hyland MM, Lau Y-C, Li C-J, Lima RS, Montavon G, editors. Thermal Spray 2007: Global Coating Solutions – Proceedings of the 2007 International Thermal Spray Conference. Materials Park (OH): ASM International®; 2007. p. 254–9.

Zhang Y, Ma L. Optimization of ceramic strength using elastic gradients. Acta Mater 2009;57:2721–9.

Zhang Y, Sun M-J, Zhang D. Designing functionally graded materials with superior load-bearing properties. Acta Biomater 2012;8:1101–8.

Zhao J, Cai XM, Tang HQ, Liu T, Gu HQ, Cui RZ, Bactericidal and biocompatible properties of TiN/Ag multilayered films by ion beam assisted deposition. J Mater Sci Mater Med 2009;20 (Issue SUPPL. 1):S101–5.

Zheng M, Fan D, Li X-K, Li W-F, Liu Q-B, Zhang J-B. Microstructure and osteoblast response of gradient bioceramic coating on titanium alloy fabricated by laser cladding. Appl Surf Sci 2008;255:426–8.

Zhitomirsky I. Technology vision. Electrodeposition of ceramic materials and composites. Surf Eng 2011;27:403–6.

Zhu Y, Wan Y, Zhang J, Yin D, Cheng W. Manufacture of layered collagen/chitosan-polycaprolactone scaffolds with biomimetic microarchitecture. Colloids Surf B Biointerfaces 2014;113:352–60.

Zou B, Liu Y, Luo X, Chen F, Guo X, Li X. Electrospun fibrous scaffolds with continuous gradations in mineral contents and biological cues for manipulating cellular behaviors. Acta Biomater 2012;8:1576–85.

Figure captions

Figure 1 – Schematic representation of a FGM that combines a constituent phase "A" (for example, alumina, which provides mechanical strength) and a constituent phase "B" (for example, bioglass, which provides bioactivity) with a gradual change in composition and no abrupt interfaces.

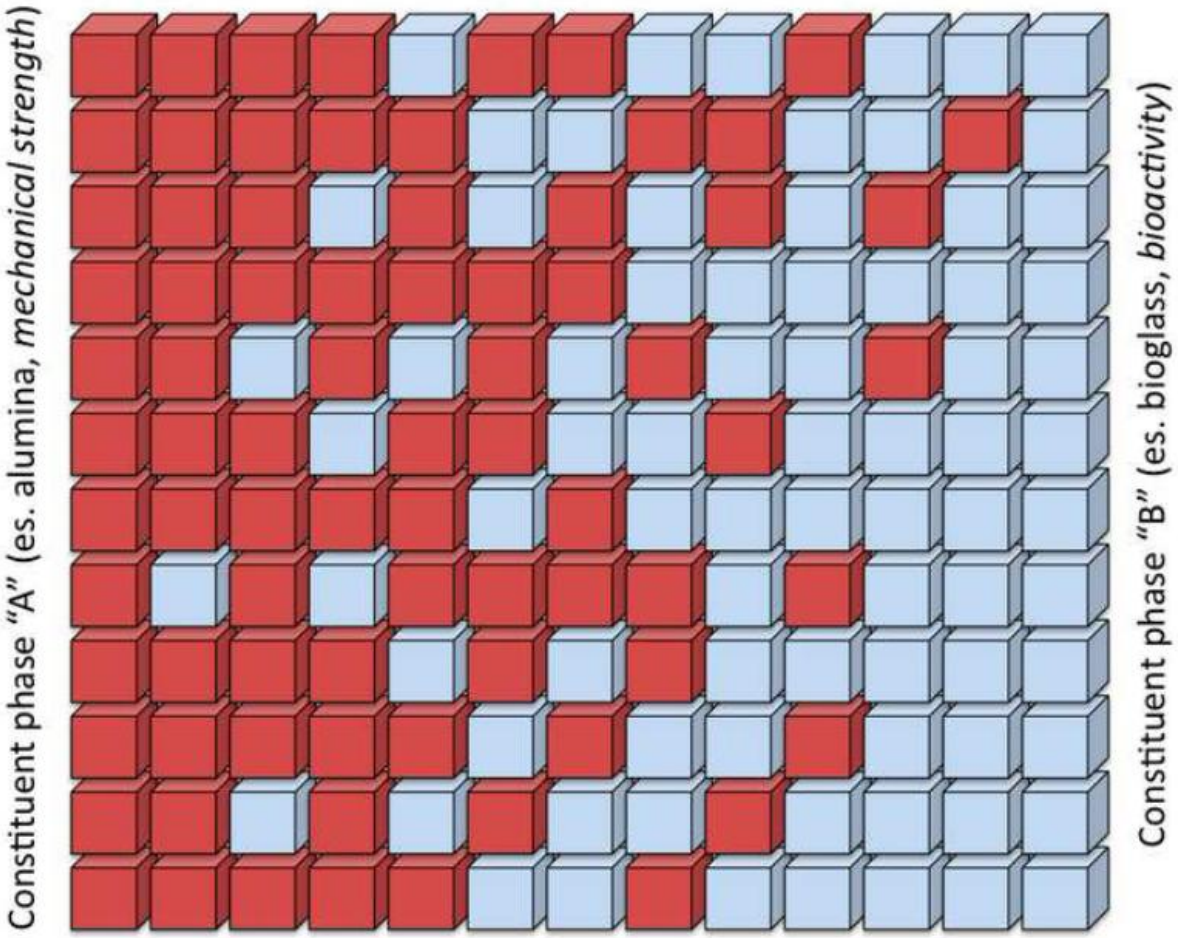

Figure 2 – Diagram of the basic approaches to HA-based FGCs produced by plasma spraying.

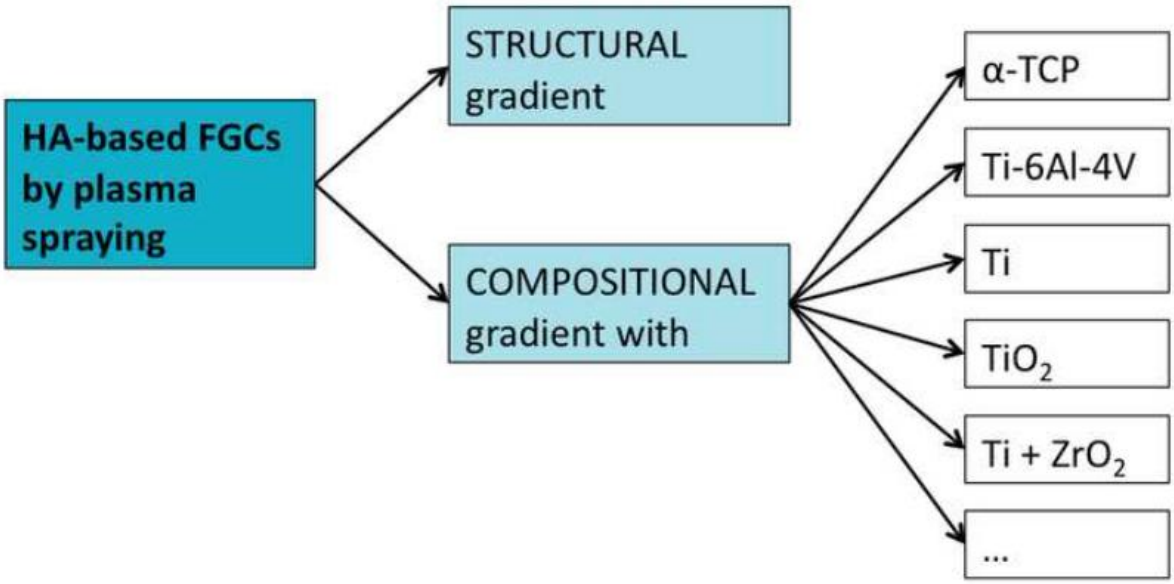

Figure 3 – Example of a titania-HA FGC applied on Ti–6Al–4V by means of air plasma spraying. Dark gray: HA; light gray: titania; white: Ti–6Al–4V substrate. The FGC presents the typical lamellar structure of plasma sprayed deposits. Scale bar: 50 μm.

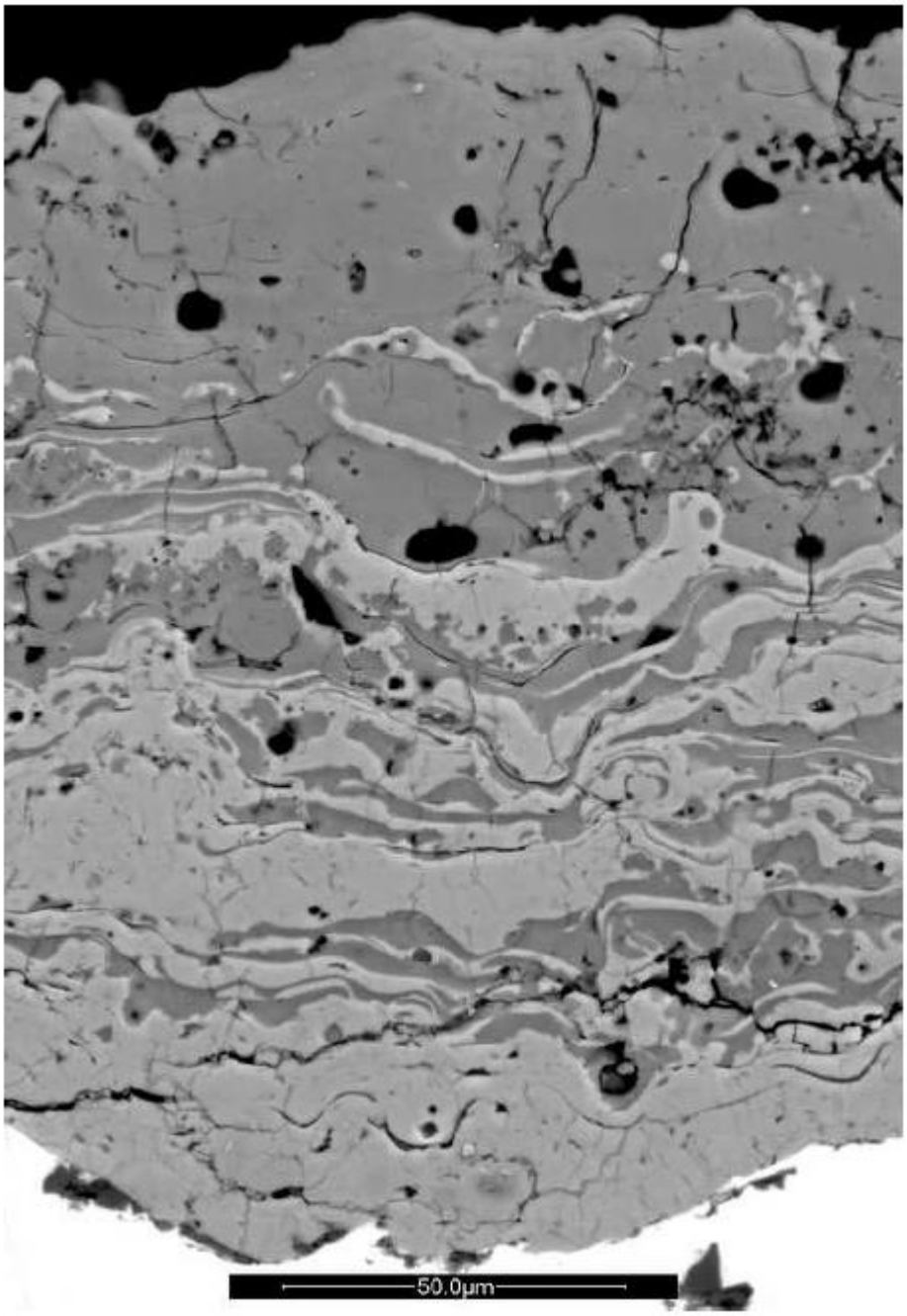

Figure 4 – Basic types of FGCs produced by firing/enameling on ceramic substrates (a-d) and on metal substrates (e-g). In order to obtain a glassy FGC, one glass is enough for ceramic substrates (a, b), whereas at least two glasses are required for metal substrates. As an alternative solution, a second (non glassy) phase can be introduced, thus creating a "composite" FGC (c, d, f, g).

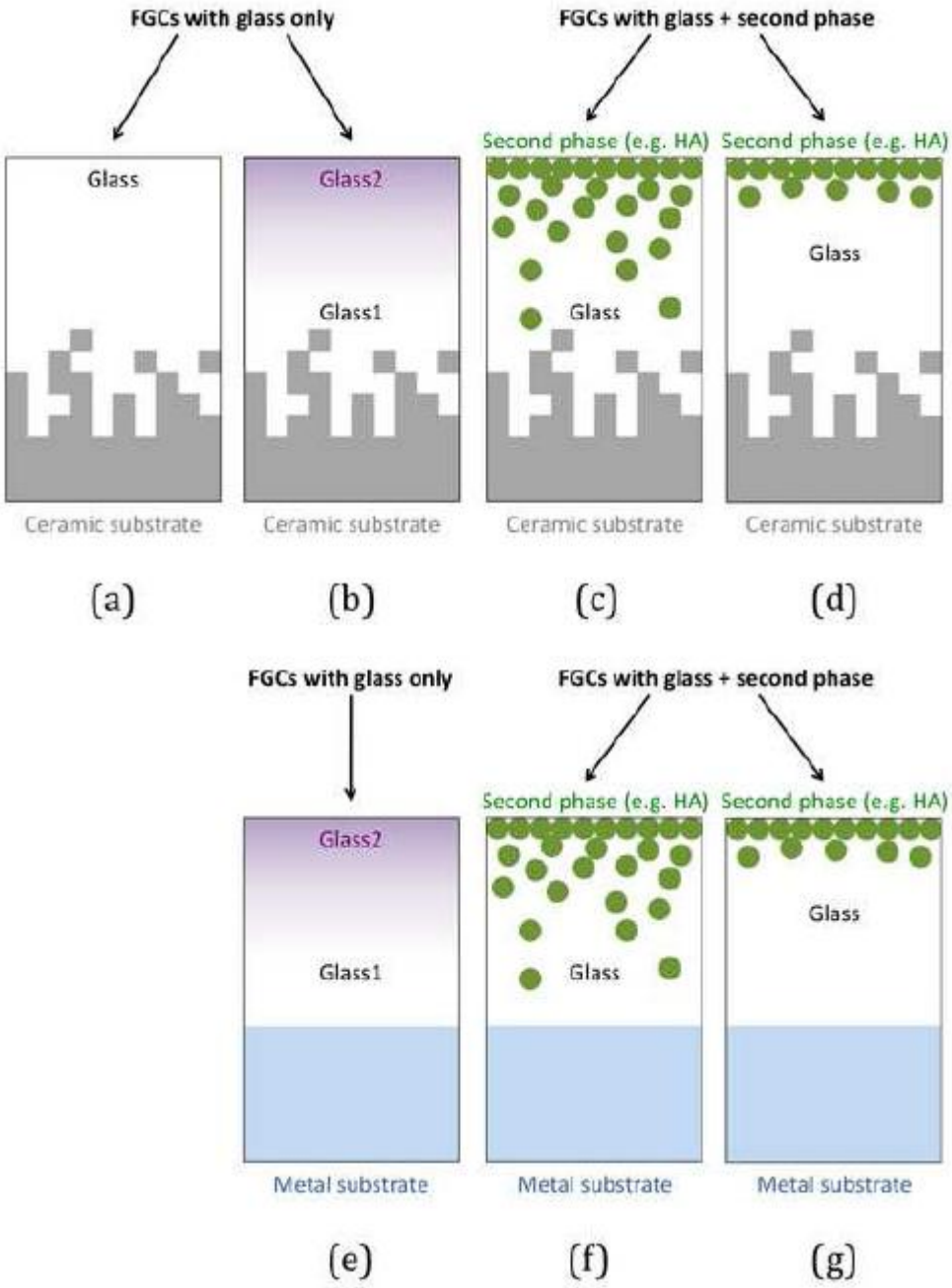

Figure 5 – Example of a bioactive glass-based FGC enameled on alumina. Light gray areas on top: glass; dark gray areas: alumina. Scale bar: 50 µm.

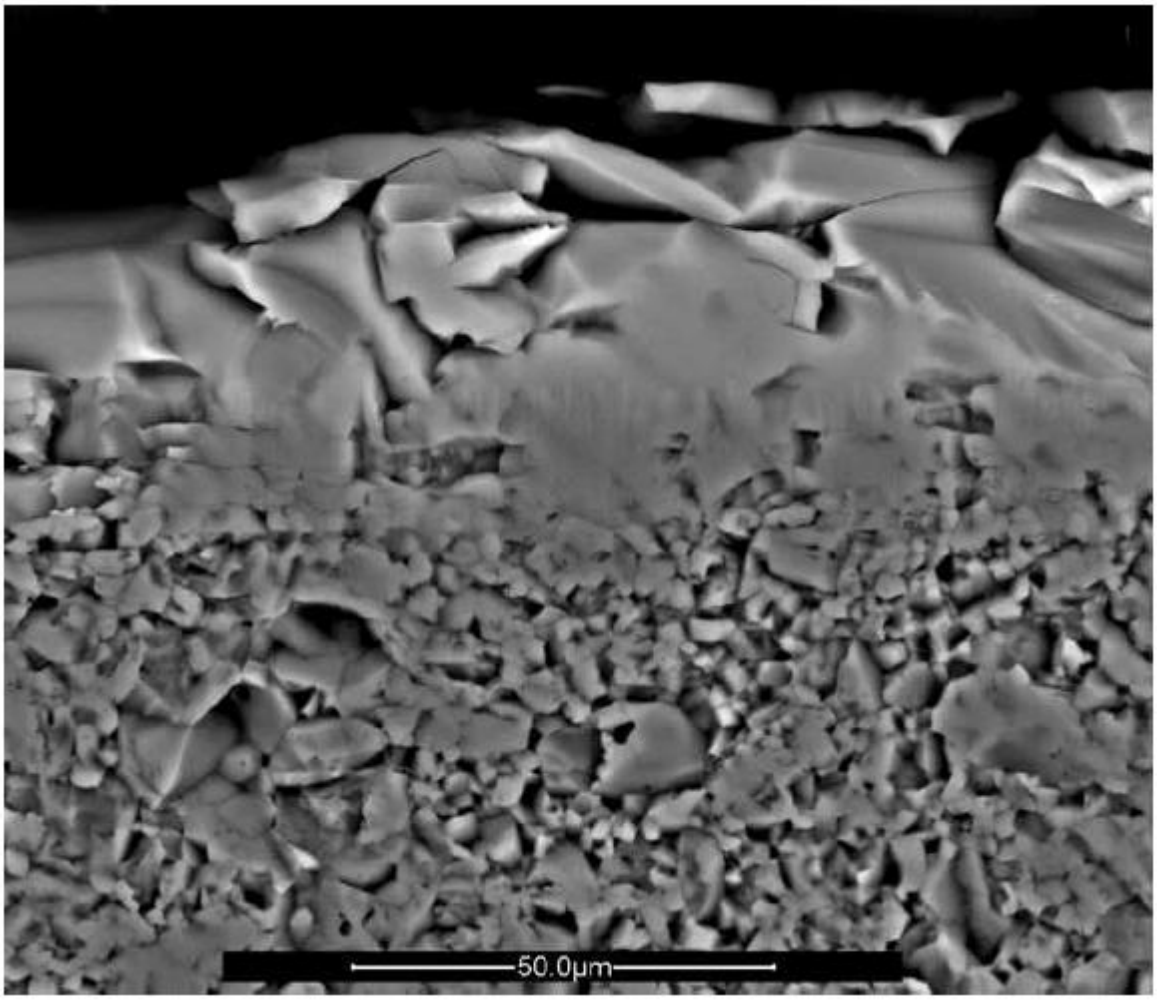

Table captions

Table 1 – Strength and elastic modulus of cortical bone (longitudinal and transverse directions) and of cancellous bone.

Table 2 – Overview of papers dedicated to the design of FGM-based orthopedic devices, grouped according to the end-usage.

Table 3 – Overview of papers dedicated to the production of FGCs for orthopedic devices, grouped according to the processing technique.

Table 4 – Overview of papers dedicated to the production of three-dimensional FGMs for orthopedic devices.

Table 1 – Strength and elastic modulus of cortical bone (longitudinal and transverse directions) and of cancellous bone.

Properties	**Cortical bone**		**Cancellous bone**
	Longitudinal	***Transverse***	
Strength, tension	79-151 MPa	51-56 MPa	2-5 MPa
Strength, compression	131-224 MPa	106-133 MPa	
Elastic modulus	17-20 GPa	6-13 GPa	0.76-4 GPa

Table 2 – Overview of papers dedicated to the design of FGM-based orthopedic devices, grouped according to the end-usage.

Application	Contribution(s)	FGM benefits	Approach	Comments
Knee				
Total knee replacement	Bahraminasab et al., 2012, 2013a, 2013b, 2014a, 2014b	Stress profile optimization (minimal stress shielding effect; maximum component resistance)	FE method and design of experiment	Combined design of geometry and FGM
Total knee replacement (tibia)	Hedia and Fouda, 2013	Stress profile optimization (minimal stress shielding effect)	2D axisymmetric FE model	
Total knee replacement (tibia)	Enab, 2012; Enab and Bondok, 2013; Enab, 2014	Stress profile optimization (minimal stress shielding effect)	2D FE model	
Femur and hip				
Hip prosthesis, cementless (coating)	Fouda, 2014; Hedia and Fouda, 2014	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	2D FE model and optimization technique	Systematic comparison of various 1D-FGMs and 2D-FGMs
Hip prosthesis, cementless/cemented (stem)	Hedia et al., 2004, 2006, 2014	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	2D FE model and optimization technique	
Hip prosthesis, cemented (stem)	Al-Jassir et al., 2013	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	3D FE model	Length of the stem considered as an additional parameter
Hip prosthesis, cementless/cemented, nonbonded/bonded (femur)	Oshkour et al., 2013a, 2013b, 2014a, 2015	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	3D FE model	Systematic comparison of various profiles and gradient indexes
Hip prosthesis, cemented (femur)	Oshkour et al., 2014b	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	3D FE model	Various anchoring solutions and various loading conditions (walking, stair climbing)
Hip prosthesis, cementless (stem, proximal femur)	Gong et al.,2012, 2013	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	2D FE model	Bone remodeling theory implemented into the simulation
Hip prosthesis, cemented (acetabulum)	Hedia, 2005; Hedia et al. (2005)	Stress profile optimization (minimal stress shielding effect; reduced shear stresses)	2D FE model and optimization technique	Costs/performance balance
Intervertebral disc				
Intervertebral disc (C6-C7 segment)	Migacz et al., 2014	Optimization of stress distribution at the implant-bone interface	3D FE model	Experimental-computational approach. Additional information on strength and resistance of materials.
Orbit				
Inferior orbital wall	Al-Sukhun et al., 2012	Stress profile optimization (minimal stress shielding effect; higher compressive stresses at the fracture surface)	3D FE model	FE model based on computed tomography scan images of a patient

Bone plates				
Bone-plates (contacted)	Ramakrishna et al., 2004, 2005; Ganesh et al., 2005	Stress profile optimization (minimal stress shielding effect)	Analytical equations; FE model	
Bone plates (non-contacted)	Fouad, 2010, 2011	Stress profile optimization (minimal stress shielding effect)	3D FE model	
Porous devices				
Hip prosthesis, cementless/cemented (stem)	Hazlehurst et al., 2013a, 2013b, 2014	Weigth reduction and flexibility increase	CAD-based FE models	Experimental-computational approach. Additional information on flexibility of materials.
Hip prosthesis, cementless (stem, proximal femur)	Khanoki and Pasini (2012)	Reduced bone resorption and reduced shear stresses under static load	2D FE model Multiscale homogeneization method (mechanics) Multi-objective optimization (porosity gradient)	Static load corresponding to stance phase of walking. AM prototype.
Hip prosthesis, cementless (stem, proximal femur)	Khanoki and Pasini, 2013a, 2013b	Reduced bone resorption, reduced interface failure and increased life expectancy under cyclic load	2D FE model Multiscale homogeneization method (mechanics) Soderberg fatigue criterion	Cyclic dynamic forces associated to walking. EBM prototype
Hip prosthesis, cementless (acetabulum)	Wang, 2006	Increased stability	Analytical equations; CAD model	On-going AM prototyping (Williams et al., 2011)
Graded porous structures for bone substitution	Gabbrielli, 2008	Increased strength	Microstructural shape design	Experimetal counterparts by rapid prototyping

Table 3 – Overview of papers dedicated to the production of FGCs for orthopedic devices, grouped according to the processing technique.

FGC composition	Substrate	Deposition technique	Contribution(s)	Comments
Conventional thermal spraying (on dry powders)				
HA powders with different size ranges HA/α-tricalcium phosphate	Ti–6Al–4V	Plasma spraying	Khor et al., 1998	
HA/α-tricalcium phosphate	Ti–6Al–4V	Plasma spraying	Wang et al., 1998	
Flame spheroidized HA powders with different particle size ranges Flame spheroidized HA powders/ α-tricalcium phosphate powders Flame spheroidized HA powders/ titania powders	Ti–6Al–4V	Plasma spraying	Wang et al., 1999	Analysis of the effect of particle size distribution
HA/titania	Titanium	Plasma spraying	Lu et al., 2004	
HA/titania	Ti–6Al–4V	Plasma spraying	Cannillo et al., 2008a, 2008b, 2009a, 2009b	Analysis of the effect of post-deposition thermal treatment
HA/Ti-6Al-4V	Ti–6Al–4V	Plasma spraying	Khor et al., 2003	Deposition from composite powders
HA/titanium	Ti–6Al–4V	Plasma spraying	Chen et al., 2006	
HA/titanium	Titanium; Titanium alloy	Radio-frequency plasma spraying	Inagaki et al., 2001	Analysis of the effect of substrate roughness on preferred orientation
HA/zirconia/titanium	Ti–6Al–4V	Net-energy plasma spraying	Ning et al., 2005	
Porous titanium	Titanium	Plasma spraying	Yang et al., 2000	Titanium-based FGCs with a gradient in porosity
Innovative thermal spraying (on suspensions)				
HA/titania	Titanium	SPS	Tomaszek et al., 2007	
HA/titania	Stainless steel, titanium, aluminum	SPS	Jaworski et al., 2010	
Bioactive glass/titania	Stainless steel	SPS	Cattini et al., 2103, 2014a, 2014b	Optimization study
Glass-based FGCs by firing/enameling				
Single glass	Zirconia	Enameling	Kim et al., 2010	Enameling on both sides of zirconia plates
Various glasses + zirconia	Alumina	Enameling	Verné et al., 2000; Vitale-Brovarone et al., 2001	
Various glasses + scaffold layer	Alumina	Enameling	Vitale-Brovarone et al., 2012	Addition of a ceramic scaffold on the working surface (like trabecular bone)
Various glasses + controlled crystallization	Alumina	Enameling	Kim and Jee, 2003	
Various glass-HA mixtures + HA particles on surface	Zirconia	Enameling	Yamashita et al., 2008	
Various glasses	Ti–6Al–4V	Enameling	Foppiano et al., 2006; Foppiano et al., 2007	
Various glass-nanoHA mixtures	Titanium	Enameling	Du et al., 2006; Xie et al., 2010	
Various glass-HA "Cullet" powders	Titanium; Titanium alloy	Enameling	Yamada et al., 2001	

Invert glass + controlled crystallization	Ti–6Al–4V; TNTZ	Enameling	Kasuga et al., 2003	Phosphate glass
Glass + HA or Glass particles on surface	Ti–6Al–4V	Enameling	Gomez-Vega et al., 2000	
Various glass-based mixtures	Ti–6Al–4V	Sol-gel enameling	García et al., 2006	
Electrophoretic deposition (EPD)*				
Bioglass/apatite	Ti–6Al–4V	Electrophoretic deposition	Balamurugan et al., 2009	
Bioglass/apatite	Ti–6Al–4V	Electrophoretic deposition	Stojanovic et al., 2007	
HA/titania	Ti–6Al–4V	Electrophoretic deposition	Araghi and Hadianfard, in press	
HA/silica/chitosan	Stainless steel, titanium, graphite	Electrophoretic deposition	Grandfield and Zhitomirsky, 2008	
HA/CaSiO3/chitosan	stainless steel, platinum, graphite	Electrophoretic deposition	Pang et al., 2009	
HA/chitosan/heparin	stainless steel, platinum, graphite	Electrophoretic deposition	Sun et al., 2009	
Laser Engineered Net Shaping (LENS)*				
Co–Cr–Mo/Ti–6Al–4V	Ti–6Al–4V; stainless steel	Laser Engineered Net Shaping	Wilson et al., 2013	
Co–Cr–Mo/Ti–6Al–4V/controlled porosity	Ti–6Al–4V	Laser Engineered Net Shaping	Krishna et al., 2008	
Titania/titanium	Titanium	Laser Engineered Net Shaping	Krishna et al., 2009	
Magnetron sputtering and related techniques				
Porous tantalum with graded oxidation	Silicon; Si_3N_4 (substrates for lab tests)	Magnetron-sputtering inert-gas aggregation	Singh et al., 2014	
Titanium/TiB_2	Ti–6Al–4V	Magnetron sputtering	Ding et al., 2014a	
Titanium-alloyed DLC	Co–Cr–Mo (substrates for lab tests)	PVD-magnetron sputtering	Brizuela et al., 2002	
Si/SiC graded interlayer + DLC	Ni–Ti	Plasma-enhanced CVD-hybrid magnetron sputtering	Liu et al., 2006	
Zr/ZrCN	Stainless steel	(Reactive) magnetron sputtering	Balaceanu et al., 2010	
HA/ZrN	Titanium	Radio frequency magnetron sputtering	Joseph et al., 2012	
HA/titanium	Titanium	Radio frequency magnetron sputtering	Ozeki et al., 2002	
Other techniques				
HA/titania	Ti–6Al–4V	Thermally grown TiO_2 layer + mixed techniques	Narayanan and Seshandri, 2007	
HA/titania	Ti–6Al–4V	Sequential sintering	Roop Kumar and Wang, 2002	
Porous HA/fluoro-HA/titania	Titanium	Sequential sol-gel	He et al., 2014	
Calcium phosphate with graded crystallinity	Titanium	Ion beam assisted deposition with thermal control	Bai et al., 2009	
TiC/Ti	Ni–Ti	Plasma immersion ion implantation	Shanaghi et al., 2013	
HA/titanium	Ti–6Al–4V	Laser cladding	Chen and Jia, 2010	HA decomposition to other calcium phosphates

Ceria-doped calcium phosphate precursors/titanium	Ti–6Al–4V	Laser cladding	Zheng et al., 2008	
Glass/apatite	Titanium	Laser pulsed deposition	Tanaskovic et al., 2007	
Bioglass with graded morphology	Titanium	Continuous-wave laser irradiation	Kongsuwan et al., in press	
HA/polyamide/pores with gradient in Ca/P ratio and pore size	Polyamide	Chemical corrosion and phase-inversion technique	Huang et al., 2014	
HA/titania/collagen	Titanium	Drop-on-Demand microdispensing	Sun et al., 2012	
Poly(l-lactic acid)/eugenol and dexamethasone	poly(d,l-lactide-co-lactide) (PLDL)	Sequential dipping	Argarate et al., 2014	Coatings for drug release
HA/tobramycin	Stainless steel	Co-precipitation	Sorensen et al., 2014	Coatings for drug release

* Suitable also for the production of 3D self-standing samples (an example in Anné et al., 2006)
** Suitable also for the production of 3D self-standing samples (an example in Bandyopadhyay et al., 2009; Krishna et al., 2007)

Table 4 – Overview of papers dedicated to the production of three-dimensional FGMs for orthopedic devices.

FGM composition	Manufacturing technique	Contribution(s)	Comments
HA/titanium	Hot pressing (Powder metallurgy)	Bishop et al., 1993	
HA/titanium	Electric furnace heating, high frequency induction heating, spark plasma sintering (Powder metallurgy)	Watari et al., 2004	
HA/titanium	Pressureless sintering (Powder metallurgy)	Batin et al., 2011	Residual interconnected porosity
HA/stainless steel, eventually reinforced with CNTs	Pressureless sintering (Powder metallurgy)	Akmal et al., in press Hussain et al., 2014 Hussain et al., 2015	
HA/zirconia	Hot pressing	Matsuno et al., 1998	
HA/zirconia	Spark plasma sintering	Guo et al., 2003	
HA/zirconia/alumina	Spark plasma sintering	Afzal et al., 2012	
HA/TiN	Spark plasma sintering	Kondo et al., 2004	
HA/α-tricalcium phosphate	In-situ HA decomposition induced by diamond firing	Kon et al., 1995	
HA/α-tricalcium phosphate	In-situ HA decomposition catalyzed by silver oxide	Manjubala et al., 2000	
HA/silver/titania	In-situ HA decomposition catalyzed by silver oxide	Katakam et al., 2003	
Alumina/zirconia	Slip casting + hot isostatic pressing	Beranič et al., 2005 Novak et al., 2007	Flat samples and ball heads
Alumina with graded grain size	Slip casting + pressureless sintering or hot pressing	Morsi et al., 2004	Pressureless sintering ineffective
HA/silk fibroin	Pulse electric current sintering	Nindhia et al., 2008	
Carbon fiber-Kevlar hybrid rods with graded braiding angle of kevlar sheath; exopy matrix	Textile preforming + pultrusion	Boss and Ganesh, 2006	
PLLA with graded degree of crystallinity and polymer chain orientation	Conventional direct extrusion or equal channel angular extrusion	Watanabe et al., 2004	Degradable implants

Highlights

- The composition of Functionally Graded Materials (FGMs) changes gradually in space
- The local properties of FGMs can be tailored to meet specific requirements
- Bone is an example of natural FGM
- FGMs are ideal materials for bone grafts
- Appropriate design and fabrication methods are required for FGMs for bone grafts