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# Classification of biomaterial functionality

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## Abstract

The rapid evolution in biomaterial performance over the last decade calls for an ever-increasing need in the classification of their functionalities. In many cases, emerging biomaterials are expected to be multifunctional, customisable, and biologically active. It is also likely that the future of biomaterials will assume even greater roles in terms of their bioactive capabilities making it all the more difficult to be regulated. As such a functional classification of biomaterials allows to consider both the safety, performance, and application while facilitating the selection of the best candidate material. Although every biomaterial undergoes rigorous experimental evaluation, they are often classified similarly to conventional materials based on their composition. This contributes to the challenges in biomaterials selection, evaluation, and use, which can subsequently lead to convoluted regulations, and inherent biases. The paper, therefore, provides a general introduction into the classification of biomaterials based on their functionalities. In this regard, the biomaterial qualifiers are introduced and summarised into an overall framework in a way that allows for meaningful classification. Furthermore, the framework that is presented can accommodate both traditional and emerging biomaterials based on their existing biomechanical performance and evolving functionalities.

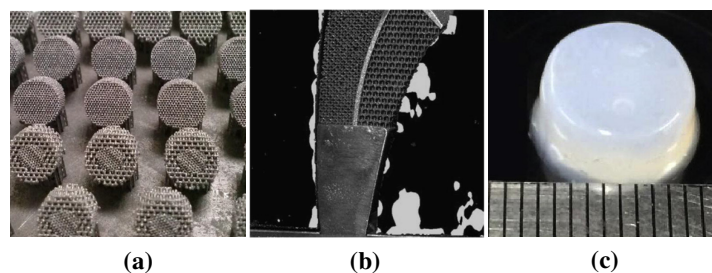
**Keywords:** Biomaterial functionalities; qualifiers; biocompatibility, mechanical performance; porosity; tissue attachment.

## 1. Introduction

Over the years, the term ‘biomaterial’ has been interpreted in many ways based on the context in which they are clinically applied [1–4]. Traditionally biomaterials were distinguished as a base-material other than drugs used to treat, augment, replace or support organs, tissues, or bodily functions [5,6]. However, the newer definition of biomaterials calls for the requirement to have ‘adequate functionality’ for a material to be qualified as a biomaterial [7]. In generic terms, any material that augments or supports living tissues while performing a certain function can be classified as a biomaterial. These biomaterial functionalities may include:

- i.* Partial substitution or full replacement of tissues and organs.
- ii.* Enhancement of tissue functions, aesthetics, or biomechanics.
- iii.* Facilitate tissue integration, provide infection resistance, accelerate healing or diagnosis of tissue damage or disease.

In this regard, biomaterials are a category of biocompatible materials that meets a certain functional characteristic that is appropriate for the nature of the application. Traditionally, biomaterials were classified similar to normal materials according to their chemical composition such as metals, ceramics, polymers, etc.; while simplistic, this classification neither aids in determining the role of biomaterial or facilitates material selection based on their functionality [8–10]. A composition-based classification also limits the scope and leads to the misrepresentation of functional characteristics of these diverse and growing ranges of biomaterials [11,12]. For example, the new class of porous-biomaterials [13,14] and meta-biomaterials [15] where performances are driven by structures cannot fit into this classification. Since the biomaterials are in continuous contact with living tissues, a functional characterisation irrespective of their chemical makeup such as metallic, ceramic, polymeric, or composite is also required.



**Fig. 1.** Examples of emerging biomaterials showing (a) additively manufactured microporous titanium tissue engineering scaffolds [16], (b) hybrid meta-biomaterial for functional hip implants [15] and (c) cylindrical-shaped meniscus-derived injectable hydrogel [17].

Classification of biomaterial functionality is also important considering the latest advances in fabrication such as additive manufacturing, material characterisation, and tissue engineering. In this emerging role, biomaterials are expected to act as substrates for host tissue integration rather than standalone devices [18,19]. These roles of biomaterial are not only important to

facilitate the host tissue functions but also to repair them predetermined interactions. Biomaterial scaffolds for tissue engineering (Fig. 1a), hybrid meta-biomaterials (Fig. 1b), and injectable hydrogels (Fig. 1c) are all examples of new biomaterials that challenges the boundaries of the traditional biomaterials requiring functional classification.

Evaluating biomaterials by their functionalities also allows providing profound insights about the interactions of biomaterials with surrounding tissues. Most important of all, the classification of biomaterial functionality is critical to establish efficient regulations required for the evaluation of emerging biomaterials. Accordingly, the subsequent sections of this paper briefly introduce the elements that are required for the classification of biomaterial functionalities followed by the summary of the framework that can accommodate both traditional and emerging biomaterials. This will allow choosing the most appropriate candidate material for the biomedical application to facilitate the required functional requirement. For example, a well engineering biomaterial for bone has to have a suitable structural performance for load-bearing while featuring an open-pore architecture [20], bifunctionality [21], and permeability [22,23] while being biocompatible. The biomaterial should also promote distinctive interaction with the surrounding tissue for osseointegration [24] while reducing stress-shielding [25] and maladapted stress concentration [26].

## 2. Established biomaterial types and application

The traditional classification of biomaterials allows for four primary types: (*i*) metallic, (*ii*) ceramic (*iii*) polymeric, and (*iv*) composites as summarised in Table 1 [27]. Amongst these, metallic biomaterials are mostly consulted for load-bearing applications. This includes most hard-tissue internal fixation devices such as orthopaedic wires, screws, plates, scaffolds, total joint replacements such as knees and hips [28–31]. Biomaterials based on metallic materials are often the candidates for maxillofacial [32], cardiovascular [33], and dental restorations [34]. The most common metallic biomaterials in this regard are based on titanium (Ti), cobalt-chromium (Co-Cr), and stainless steel [35–37]. Co-Cr alloys, in particular, have been the most used biomaterial to manufacture the femoral component for total joint replacements such as knee hip [38,39]. Consequently, the surface hardness and wear performance of Co-Cr alloys are of significant interest for further development [40].

Low adverse tissue reaction, high hardness, and compressive strength were the primary interest in ceramics as a biomaterial. As listed in Table 1, some carbons are also used as implants for applications such as heart valves that are blood interfacing. Ceramics are also favoured as reinforcing phases as a result of their unique mechanical behaviour in the development of composite biomaterials [41]. Looking at the mechanical properties, the nature of the bonding in ceramics means that they are difficult to shear plastically unlike metals and polymers [42]. However, the brittle nature of ceramics means that they are susceptible to microcracks and are prone to catastrophic failure post-yield [43]. Ceramics also tend to have comparatively low tensile

performance in comparison to compressive. Nevertheless, the hardness and bio-inertness of ceramic make them a highly suitable biomaterial for surface coatings [44,45].

**Table 1.** Traditional classification and application of biomaterials [46].

<b>Classification</b>	<b>Application</b>
<b>Metals and alloys</b>	
Stainless steel, silver, gold, titanium (and its alloys such as Ti-Al-V, Ti-Al-Nb, Ti-Mo-Zr-Fe), cobalt-chromium (and its alloys Co-Cr-Mo, Cr-Ni-Cr-Mo) and nickel-titanium.	Fracture fixation devices, wires, scaffolds, stents, plates, surgical instruments, components for total joint replacements, implants for dental application, pacemaker encapsulation, heart valves, antibacterial devices.
<b>Ceramics</b>	
Calcium phosphates, bioactive glasses, Alumina, porcelain, zirconia, and carbons	Implant components for total joint arthroplasty devices, dental application, orthopaedic implants, surface coatings to increase hardness and reduce wear, heart valves.
<b>Polymers</b>	
Poly -ethylene, -propylene, -ester, -urethanes, PET, polyamides, PTFE, silicones, hydrogels	Total hip and knee arthroplasty, suture devices, prosthesis to support vasculature, devices that facilitate soft-tissue replacement, components for drug-delivery systems, blood interfacing devices, dental restorations, lenses, ophthalmologic devices.
<b>Composites</b>	
bisphenol A-glycidyl-quartz/silica filler, polyvinyl chloride-glass fillers	Dental restoration and cements.

While metallic materials are preferred for load-bearing applications, polymers form the most widely used category of synthetic biomaterials to date [47]. This is primarily because of the compatibility that polymers offer in comparison to tissues, proteins, and polysaccharides. It is widely considered that polymers with their long-chain architecture allow for a better integration when it comes to tissue response [48]. Furthermore, injectable polymers that are developed through the synthesis and polymerisation of monomers can exhibit biodegradable performance while facilitating permanent installation [49]. Innovation in polymeric chemistry also facilitated the development of functional films for the dental industry in addition to bespoke dental sealants, drug carriers, and biodegradable scaffolds [48,50].

Composite materials are a mixture of multiple materials where each act to compliment the performance of the other. Each of these material components can take various forms such as particles, fibres, etc. that are surrounded by the other material which can be referred to as the matrix material [51]. Composite biomaterials are these of mixture materials that show the required biocompatibility for various biomedical applications. Composite biomaterials allow combining the benefits of materials from different classes, i.e. advantages of both the embedded (reinforced) and the surrounding material (matrix) from any class such as metal, ceramic, or polymer. Although exceptions apply, the materials that are embedded in the matrix are generally

strong with low densities surrounded by the matrix which can be ductile or tough. However, for composites, the multiple materials work together in a complimentary fashion to accommodate load transfer in the most efficient manner [51–53].

When it comes to the mechanical performance of hard tissues such as bone, they feature a wide range of properties, which are often hard to meet with monolithic biomaterials [54,55]. In this regard, composite biomaterials allow achieving targeted properties to that of biological hard tissues through the combination of compatible materials while each offers unique advantages. Furthermore, biomechanical and tissue attachment properties of composite biomaterials such as hydroxyapatite-collagen [56] are far superior to the performance of their constituents [57]. Therefore, composite biomaterials are a suitable choice for several biomedical applications including coatings that allows achieving tailored properties with increased functionalities [58–60].

### 3. Functional qualifiers of a biomaterial

#### 3.1. Biocompatibility

When a material possesses acceptable biocompatibility to meet the requirement of a biomedical application, it can be defined as a biomaterial [61]. Therefore, the qualification of a material as a ‘biomaterial’ depends on it meeting the biological and chemical comparability requires for the targeted application. However, the question then arises; “How can one quantify the biocompatibility of biomaterials for designing medical devices?”. In its simplest form, a biomaterial must satisfy biocompatibility, which may be interpreted as an acceptable material functionality without any unwarranted reaction at the tissue level or to the immune systems. If a material satisfies all these requirements, then it can be classified biocompatible [62–64].

**Table 2.** The categorisation of biomaterials for biocompatibility assessment.

<b>Biomaterial category</b>	<b>Device classification</b>	<b>Definition</b>	<b>Biocompatibility requirement</b>
Class I	Surface devices	These are materials that are in surface contact with the tissue. Examples include bandages, burn dressing, catheter, etc.	Low
Class II	Externally communicating devices	These are materials that are occasionally in direct contact with the tissue such as dialysis units, ventilators, etc. (most of the medical devices that are not implanted falls under this category)	Medium
Class III	Implanted devices	These are materials that are in permanent contact with tissue such as bone scaffolds and hip implants.	High

It is important to note that the biocompatibility requirement of biomaterials differs from one material to another, depending on their types and uses [65]. In general, the properties of metal

or ceramic-based biomaterials differ from polymers and composites. Overall the required biocompatibility of a biomaterial is dictated by its clinical use [66]. Therefore, the biocompatibility of biomaterials is generally characterised based on their associated classes as listed in Table 2.

**Table 3.** Categories for biocompatibility assessment.

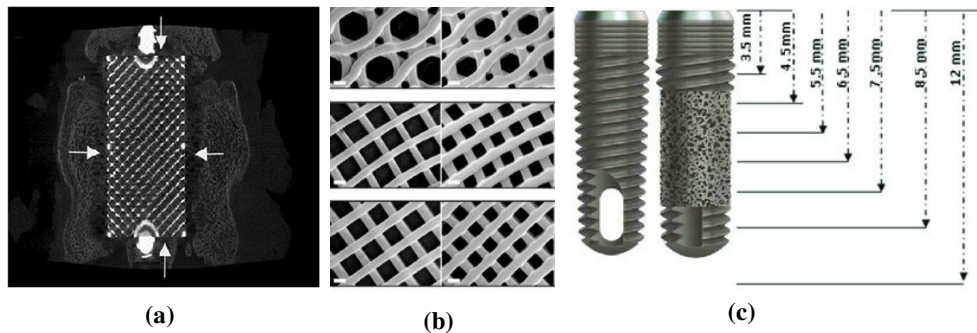
Biocompatibility assessments	Short definition
Cytotoxicity	Capacity to induce cell or tissue death
Carcinogenicity	Capacity to induce cancer formation
Mutagenicity	Capacity to damage genes
Pyrogenicity	Capacity to induce adverse immune response such as fever
Allergenicity	Capacity to cause sensitisation and allergic reactions
Thrombogenicity	Capacity to induce blood clotting

According to Ramakrishna *et al.* [66], class III biomaterials requires the highest biocompatibility as they are in direct contact with biological tissues and are and expected to initiate biointegration processes. Nevertheless, for any material to be deemed biocompatible, they should satisfy the acceptable performance requirements under all categories as shown in Table 3. Based on these assessments, acceptable biocompatibility can be defined as the effect to which the biomaterial does not induce any measurable harm. Put simply, no harm to the host body as a result of the biomaterial defines biocompatibility [5,67].

### 3.2. Porosity and pore architecture

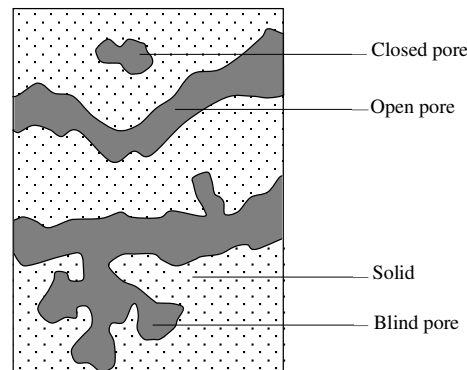
#### 3.2.1. Characteristics of porous biomaterials

Up until recently, biomaterials featuring a targeted structural behaviour required material manipulation at the chemistry level to create new alloys, ceramics, or polymers. However, advances in fabrication techniques such as additive manufacturing (3D printing) are enabling the development of new biomaterials where the properties are not dictated by material chemistry instead through structural mechanics [68,69]. In this approach, the micro-mechanics of carefully conceived pore architecture is used to design biomaterials with novel properties [70,71].



**Fig. 2.** Examples of porous biomaterials showing (a) titanium spinal implants in sheep [72,73], (b) porous architecture of a polymer biomaterial [74] and (c) solid vs. porous dental implant [75].

While there is no doubt that this approach requires micro- and nano-scale interconnected pores; the method allows the behaviour of the material to be tuned [76] in a way that is favourable for tissue engineering as shown in Fig. 2a-c. The targeted functionality of the material could be the stiffness, strength, permeability (Fig. 2b), or cell attachment (Fig. 2c). Zadpoor [77] suggests that porous biomaterials can be approached almost like composites where the carefully conceived pore architecture becomes the second material phase that affects the overall performance of the material. The most important feature of porous biomaterials is, therefore, their advantage in offering a way to realise multiple biomechanical properties that are hard to meet through solid materials. This makes pore architecture to be an important aspect to be considered for functional characterisation. For classification purposes, porosity can be classified as the percentage of void in a material that affects its overall performance at the macro scale [78]. In this regard, the vacancy facilitated in a porous material can be sub-classified into three types: closed, open, and blind pores as shown in Fig. 3 [24,79].



**Fig. 3.** Pore structure evaluation in biomaterials.

Generally, closed pores are inaccessible to fluids which makes them unfavourable when it comes to the biomaterial property called ‘permeability’. The blind pores terminate inside the material allowing for fluid build-up raising the chances of infection in certain cases [26]. Accordingly, the open pores are the most favourable as they facilitate the complete passageway of fluids. A porous biomaterial often refers to a class where the porosity is largely constituted because of open and blind pores.

Porous materials that facilitate closed pores have a significant influence on the overall material behaviour; while open pores alone are favourable for both permeability and cell migration when exposed to compatible tissues. As a result, porous metals with interconnected porosity is of interest from an orthopaedic implant point of view due to their high potential in facilitating tissue ingrowth [28,80–82]. Furthermore, a surface that features porous architecture can be favourable for tissue-biomaterial interlocking resulting in higher interface stability, better vasculature, and load transfer.

Underlying structures at the tissue level are often hierarchical, porous approach in biomaterial design enables the recreation of these architectures to facilitate targeted functionalities such as strength, stiffness permeability, and diffusion properties [83,84]. These structures are highly complex three dimensional (3D) anatomical shapes, which are also hard to emulate through material chemistry. Aspects such as permeability, diffusion, and vasculature are critical to supply cells with nutrition and prevent fluid build-up. Furthermore, there is evidence to show that pore architecture better supports migration and attachment of cells required for tissue reintegration in comparison to dense biomaterials. Table 4 summarises some of the common porous biomaterials, their manufacturing process, and associated pore characteristics.

**Table 4.** Pore size ( $\varphi$ ), porosity ( $\phi$ ), manufacturing (Manuf.) and application of some emerging biomaterials.

Material	Manuf.	$\varphi$ ( $\mu\text{m}$ )	$\phi$ (%)	Application	Ref.
Hydroxyapatite	Sintering	90-350	38-80	Mandible defects, ectopic bone formation, bone marrow	[85–89]
Tricalcium phosphate	Salt leeching	0.2-8.7	31-62	Repair of bone defects	[90]
Bioglass	Foaming/sol-gel	100-200	5-40	Primary human osteoblast	[91,92]
Glass-ceramic	Sintering	100-200	40	Femoral defects in rabbits	[93]
Collagen	Freeze-drying	11-134	80-90	Tibia defects in rats	[94]
Silk fibroin	Salt-leaching	202	84-98	Bone marrow	[95,96]
Poly (lactide)	Salt-leaching	600	58-80	Dental implants	[97,98]
Polymeric foams	Emulsion polymerization	40-100	93-97	Rat osteoblast invitro	[99]
Hydroxyapatite-chitosan-gelatine	Freeze-drying	300-500	87	Tissue engineering	[100]
Titanium-boron	Self-propagating high-temperature synthesis	170	15-55	Bone	[101]
Titanium-calcium phosphate	Sintering	50-200	35	Tribological coating for tissue engineering	[102]
Silica-ceramic	Sintering	10-300	43-51	Femoral defects	[93]
Titanium alloy	Laser melting	200-300	68-91	Bone scaffold	[55,70, 103]

### 3.2.2. Evolution of porosity as a critical parameter

According to Netti [14], porous biomaterials are the only choice when it comes to applications that require vasculature, cell migration, and controlled regeneration. Applications of this include the development of biomedical devices in the following primary areas:

- i.* Prosthetic devices that feature a porous surface layer.
- ii.* Tissue-engineered scaffolds for regenerative medicine.

- iii.* Biomaterials for drug delivery sensing and diagnostic.
- iv.* Multi-dimensional cell culture systems for drug discovery and cell-based biosensors.

The field of application along with the characteristics of these biomaterials are based on the porous nature of the materials, which are often controlled through the selection of appropriate based materials and suitable manufacturing processes. For example, in designing porous scaffolds for tissue engineering, the pore architecture must be developed considering the surrounding tissue and their interconnection [104]. This is critical for controlling the cell behaviour guiding the development of new tissue. Numerous processing techniques (Table 4) have been developed, which are widely used for the fabricating porous biomaterials that allow for specific control over the pore morphology and the associated micro/nano features [105–107].

The rapid expansion of digital fabrication technologies [108–110] and microfluidic strategies [111–113] has made it possible to increase the resolution (lower pore size) of porous biomaterials achievable. This has facilitated the extension of biomaterial possibilities to allow for mechanisms underlying cell/material interaction which ultimately leads to the development of multifunctional micro-, -meso, macro-porous biomaterials and scaffolds with targeted functionalities [114]. This is currently an active research area where great efforts are being devoted to the design and fabrication of miniaturised biomaterial foams [115,116]. These foams have pore architecture at the nanometric scale that can combine technological potential with biochemical and biophysical clues. These multifunctional devices can serve different purposes, starting from being the building block for *in vitro* cell culture, tissue regeneration, biosensors, and actuators suitable for *in situ* clinical application.

### **3.3. Mechanical performance**

#### *3.3.1. Parameters of importance*

The opportunities that emerging biomaterials offer for structural optimisation asks the question: “what are the best mechanical properties that a biomaterial can offer? Generally, an ideal biomaterial mimics the mechanical behaviour of the biological tissue that is being replaced [117]. Researchers commonly use a wide variety of terms when it comes to describing the mechanical performance of tissues, biomolecules, and biomaterials. These terms fall within the domain of mechanics of materials and materials engineering in general [118]. However, the methodology cannot be broadly applied to select the biomaterial that offers the highest strength and biocompatibility. It is important to first determine the required parameters that constitute all the relevant parameters for each of the requirement, and how to control them. This is because what may seem like a suitable material under quasi-static loading may fail in other areas post-implantation. In this regard, it may turn out that for the loading scenario, a slightly weaker material with superior hardness may be the most suitable [119]. Since these terms may not be

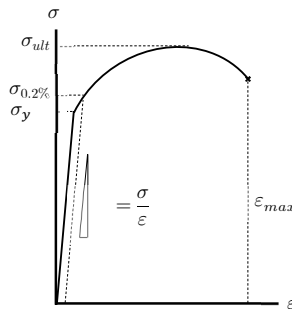
easily understood to researchers or practitioners in other fields, Table 5 summarises a simpler set of meanings for the mechanical parameters for importance.

**Table 5.** Parameters suitable to characterise the mechanical performance of a biomaterial.

Material properties	Equivalent meaning	Units
Young's modulus (E)	Stiffness Elastic modulus	$N/m^2$ o a
Yield strength ( $\sigma_y$ )	Elastic limit Strength	a
Ultimate strength ( $\sigma_{ult}$ )	Failure stress Stress at fracture	a
Strain at rupture ( $\varepsilon_{max}$ )	Extensibility Failure strain	-
Poisson's ratio ( $\nu$ )	The ratio of transverse contraction strain to longitudinal extension strain	-
Hardness	Resistance to wear	Rockwell hardness (HR)
		Brinell hardness (BR)
		Vickers hardness (HV)
		Knoop hardness (HK)
Toughness ( $U_T$ )	Energy to break per unit volume	$J/m^3$
	Energy to break per unit area	$J/m^2$
Modulus of resilience ( $U_r$ )	Energy to yield per unit volume	$J/m^3$
Fracture toughness ( $K_{IC}$ )	Capacity to resist crack growth	$a\sqrt{m}$
Fatigue life ( $N_f$ )	Durability	Number of cycles to failure

### 3.3.2. Quasi-static mechanical properties

The mechanical environment of a biomaterial is often complex where the static mechanical properties such as Young's modulus (E), yield stress ( $\sigma_y$ ) and ultimate strength ( $\sigma_{ult}$ ) are among the most important. When it comes to metallic biomaterials, the elastic performance often falls within 0.5% of strain under a quasit-static loading regime. Furthermore, the transition from elastic to plastic deformation is gradual for most metals making it difficult to determine the exact yield point. As a result, the yield stress is often determined using a 0.2% strain offset method as shown in Fig. 4.



**Fig. 4.** Typical stress-strain curve of a metallic biomaterial under quasi-static loading.

In comparison to metallic materials, fracture in ceramic biomaterials often happens before any extensive plastic deformation at room temperature [120]. Some metallic biomaterials and many thermoplastics exhibit stress-strain curves with the so-called yield point phenomenon as well [121]. Plastic deformation is initiated at the yield limit, which is followed by a drop in stress. Elastomeric polymers, on the other hand, deform elastically to large strains, typically >100%, and rupture after limited plastic deformation occurs. The mechanical properties of some grade III biomaterials are summarised in Table 6.

**Table 6.** Mechanical properties associated with some common biomaterials [5,66,122].

<b>Biomaterial</b>	<b>E (GPa)</b>	<b><math>\sigma_y</math> (MPa)</b>	<b><math>\sigma_{ult}</math> (MPa)</b>	<b><math>K_{IC}</math> (MPa<math>\sqrt{m}</math>)</b>	<b><math>\epsilon_{max}</math> (%)</b>
Ti alloys	105-125	350-1050	600-1000	80	5-50
Co-Cr-Mo alloys	240	450-1500	600-1600	100	10-30
Steel (316L)	200	200-700	500-900	100	10-50
Al <sub>2</sub> O <sub>3</sub>	380-420	-	4000-4500	3-6	0.1-0.3
Hydroxyapatite (HA)	100	-	50-54	1	0.1-0.3
Polyethylene (PE)	0.8-1.6	20-30	40-50	90	350-550
Poly (methyl methacrylate) PMMA	3-3.5	60-64	35-80	1	2-55
Poly (lactic acid) PLA	3-15	30-60	30-80	3-5	2-60

When it comes to tissue engineering applications, the elastic modulus (E) of the biomaterial should be as close as possible to the biological tissue that it replaces. This is primarily because, mechanical stress is critical for tissue reintegration through remodelling; in this regard using a high stiffness biomaterial results in an unloading of the bone, which subsequently leads to poor load transfer at the tissue-bone interface. This increases the likelihood of bone resorption that adversely affects tissue regeneration leading to aseptic loosening, a well-documented phenomenon [123–126]. This effect is generally referred to as stress shielding [127–129] when it comes to hard tissue remodelling such as bone. However, there is no reason to assume that the same is true for strength ( $\sigma_y$ ) of the material. On the contrary for biomaterials, it is often beneficial to have a high  $\sigma_y$  while keeping the E as close to the surrounding tissue as possible. If such a biomaterial behaviour can be achieved, this will ensure the best balance between tissue compatibility and safety as the material can resist failure in the event of an increased biomechanical load [55,130].

From a bulk material property perspective, biomaterials often show a strong correlation between E and  $\sigma_y$ ; meaning the strength of a material is often assumed to be a measure of the elastic performance (E), furthermore accurate measurement of E in porous materials are challenging in comparison to  $\sigma_y$ . However, for certain classes of emerging biomaterials such as lattice-based microporous or meta-biomaterials the traditional correlations between E and  $\sigma_y$  or  $\sigma_{ult}$  can be different allowing the creation of functional biomaterials with targeted mechanical properties [131–133]. Accordingly to studies reported by Bobbert *et al.* [134], simply using  $\sigma_y$  or  $\sigma_{ult}$  as a

surrogate measure of E may therefore be unjustified as the mechanical properties of the biomaterial can often be altered by varying the micro-structural architecture.

### 3.3.3. Hardness

Hardness characterises the resistance of a material to a localised plastic indentation or abrasion and hence an important mechanical property when selecting the suitable biomaterial for clinical use [135–137]. A biomaterial that features high hardness exhibits less wear and can extend both the longevity and safety of the biomedical device. For load-bearing biomaterials, a low resistance to wear can result in aseptic loosening [138] in addition to the generation of loose particles commonly referred to as debris [139–141]. Although biomaterials offer a wide range of hardness, any two biomaterial surfaces that are engaged in load transfer will subsequently wear as a result of adhesive, abrasive, or fatigue mechanisms [138,142,143]. Sometimes, a combination of all of these three wear mechanisms acts simultaneously to drastically reduce the wear life of a biomaterial.

If wear itself is unavoidable, it is important to quantify the amount of acceptable wear for a biomaterial. Furthermore, if wear results in loose particles, then what are the associated characteristics that negatively impact a living tissue or its immune response. There is no doubt that the wear behaviour of a biomaterial is of significant concern and its detrimental effects depend largely on the characteristics of the debris, and the ability of the biological system to either isolate or tolerate them [144–146]. The result is often the adverse physiologic response to wear particles leading to unwanted effects such as osteolysis [147]. Therefore, the hardness of biomaterials is a critical area that needs to be functionally characterised and considered at the time of biomaterial selection depending upon the application.

**Table 7.** Knoop hardness of a range of biomaterials [148].

<b>Biomaterial</b>	<b>Density (g/cm<sup>3</sup>)</b>	<b>Knoop Hardness (HK)</b>
Tri-calcium phosphate	3.1	400-4500
Bioglass	2.9	4000-5000
Silica glass	2.2	7000-7500
Polyethylene	1.0	140-170
Titanium	4.52	1800-2600
Ti6Al4V	4.4	3200-3600

Nevertheless, it is important to note that hardness is not a well-defined material property [149]: meaning, it has been quantitatively measured using various techniques, with Rockwell and Britnell hardness tests being the two most common methods as summarised in Table 5. According to Callister and Rethwisch [150], when it comes to metallic biomaterials, strength, and hardness are indicators of its resistance to plastic deformation, where the hardness may be conceived as roughly proportional to its tensile strength. Hardness can also in certain cases become proportional to  $\sigma_y$  and E. In this regard, biomaterials that feature high stiffness generally

demonstrate good resistances to wear. Table 7 summarises the Knoop hardness values associated with some common biomaterials. Although there can be exceptions, in general ceramics are the hardest material, followed by metals and polymers. However, techniques such as ion implantation, nitriding, carburisation, and spray coatings can be used to significantly modifying the physical and chemical surface properties of a biomaterial for improved wear performance [151–154].

### 3.3.4. Fatigue behaviour

Fatigue failure in biomaterials occurs as a result of crack generation and growth as a result of cyclic loading. In most cases, fatigue failures happen at stresses well below the quasi-static yield ( $\sigma_y$ ) of the material [155–157]. The reason for this is the cyclic nature of the load that initiates a microscopic crack that subsequently penetrates the material layers to form a macroscopic phenomenon (initiation phase). The crack can then continue to grow to a critical size that results in failure of the biomaterial component. Fatigue failure is a major concern associated with biomaterials as they lead to implant loosening, stress-shielding, and reduces implant life [158].

From the review carried out by Teoh [156] looking at the fatigue failure of biomedical devices, catastrophic fatigue failure is primarily of the brittle type where the observable plastic deformation is comparatively low. This shows the significance of fatigue failure where failure can be catastrophic with a little warning before rupture. This is critical as load-bearing biomaterials are expected to survive millions of cyclic loads over their lifetime making fatigue as the major cause of concern in the reduction of biomaterial life. For example, looking at various ISO tests (ISO7206-4 [159] and ISO7206-6 [160]), a sinusoidal load of 2300 N and 5340 N at  $10^6$  cycles are often applied. In a practical scenario, even  $10^7$  cycles can be expected. Fatigue of biomaterials is often evaluated using the most frequently acting loads, which can cumulatively cause failure over time. Metallic biomaterials are often capable of withstanding quasi-static stresses two to three times higher than the fatigue limits [161,162].

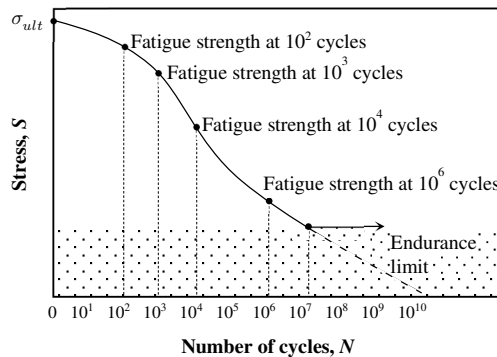


Fig. 5. A representative example of an S-N curve showing fatigue performance of a biomaterial.

Fatigue performance of a material is characterized using an S-N curve, also referred to as the Wöhler curve [163], which is a graph of cyclic stress (S) against the logarithmic number of cycles to failure (N). As shown in Fig. 5, the higher the external stress (S) so is the resulting dislocations leading to a lower number (N) of cyclic loads to reach failure. The fatigue limit or endurance limit refers to the highest cyclic stress (S) that can be applied to a biomaterial without causing fatigue failure, irrespective of the loading cycles [5]. Most nonferrous biomaterial alloys do not exhibit a clear fatigue limit, which means that the S-N curve continues its downward trend where fatigue will ultimately occur despite the stress magnitude [164]. For these materials, the number of  $+10^7$  cycles has been widely referred to as the fatigue strength or an infinitely large number of cycles. While experimental evaluation is required to accurately predict the fatigue strength of a biomaterial; there is often an approximate relationship that exists between the fatigue strength ( $\sigma_{fatigue}$ ) and ultimate tensile strength ( $\sigma_{ult}$ ) of materials as shown in Eqn. (1) which has to be used with extreme caution:

$$\sigma_{fatigue} \approx 0.5\sigma_{ult} \quad (1)$$

Despite the exceptions, Eqn. (1) is a useful guide in the selection of general-purpose materials for reasonable purposes where enough data is available. Therefore, in principle, traditional materials with high E,  $\sigma_y$  and  $\sigma_{ult}$  can be expected to have good fatigue performance. However, in the case of biomaterials, it is important to have an appreciation of the substructure of the surface and the surrounding physiological environment before the relationship can be deemed appropriate. The interaction of the material layers can be characterised as: (i) the molecular absorbed layer, (ii) the passive oxide film, and (iii) the deformed layer with the host tissue is of paramount importance to evaluate the long-term fatigue performance of a biomaterial [156,165,166]. Accordingly, the surface and subsurface failure modes that are exhibited during fatigue also need to be a consideration to select the most appropriate biomaterial.

For example, materials that are brittle that feature a high  $\sigma_y$  but low fracture toughness (bioceramics are an example of such material) can exhibit cone cracking phenomenon during fatigue significantly affecting the part performance [167,168]. This is because bioceramics featuring a fracture toughness less than  $1 \text{ MPa}\sqrt{m}$  are highly prone to brittle fracture requiring substantial quality control to avoid fatigue fracture. As a result, the direction of research point towards biocomposites that feature two or more different phases such as in interpenetrating network composites for superior fatigue performance [169,170]. The primary benefit of these composite biomaterials is their potential to facilitate chemicals that are suitable for controlled drug release [171], which subsequently results in superior host tissue interaction. In any case, developments of methods to accurately predict the surface performance during fatigue including *in vitro* characterisation and computational modelling is still largely unavailable for biomaterials [156].

### 3.4. Functional requirements for host tissue interaction

#### 3.4.1. Biomaterials and tissue attachment

Attachment of host tissue to a biomaterial is directly related to the functional interface that exists between the biomaterial and the tissue. In reality, no biomaterial can be considered completely inert when in contact with a biological tissue [52]. This means that irrespective of their classification, all biomaterials introduce a certain response from the host tissue in direct contact. Based on this principle, the types of biomaterial and tissue interaction can be classified into four types as listed in Table 8. In this regard, the response of a host-tissue to an unreactive biomaterial can be classified as the formation of a non-adherent fibrous capsule [172]. The thickness of this fibrous layer largely depends on the health of the host tissue, stability of the material-tissue interface, and the biomechanical load.

**Table 8.** Biomaterial classification based on the functional response from host tissue.

<b>Biomaterial classification</b>	<b>Tissue attachment type</b>	<b>Biomaterials used</b>
Nearly inert	Morphological attachment to host tissue (mechanical interlock)	Most biomaterials that are not biofunctionalised including Ti and Co-Cr in additions to materials such as Polyethylene, Zirconia, and Alumina.
Open-pore	Biological attachment to host tissue (tissue ingrowth into pores)	Porous implants, metallic implants coated with biofunctionalised hydroxyapatite.
Bioactive	Interfacial bonding with host tissue (bioactive fixation)	Hydroxyapatite, bioactive -ceramics and -glasses.
Resorbable	Biomaterial replaced by host tissue (resorbable interaction)	Dicalcium and tricalcium phosphate, hyaluronan, fibrin, collagen, chitosan, polylactic acid (PLA)

For a porous biomaterial, the bioactivity is through the ingrowth of tissue into the pores resulting in a biological fixation of the biomaterial. This fixation is superior to nearly inert biomaterials at the interface and it is capable of withstanding highly complex biomechanical stresses in comparison to dense and inert biomaterials. Nevertheless, for porous biomaterials to be effective, a pore size requirement within the range of 50-400  $\mu m$  is needed to allow for vascularisation.

#### 3.4.2. Bioactivity

Bioactive biomaterials can cause a certain predetermined tissue response that can result in improved integration between the biomaterial and the surrounding biological system. Bioactive materials can be primary characterised into two: (i) osteoconductive and (ii) osteopductive [172,173]. Biomaterials that show osteoconductive properties generally bond to hard tissues and facilitate tissue interaction along the surface of the bioactive biomaterial. Materials such as synthetic hydroxyapatite [104] and tri-calcium phosphate [93] ceramics are examples of these biomaterials as listed in Table 8. Osteopductive biomaterials, on the other hand, can stimulate

the growth of new tissue on the material away from the biomaterial interface. Bioactive glasses that bond to soft tissue such as cartilage is an example of osteopductive biomaterial. The mechanism of tissue bonding to bioactive biomaterials is primarily thought to be the result of hydroxyapatite generation on the biomaterial surface due to interaction with bodily fluids [174,175]. The hydroxyapatite layer formation happens the fastest on osteopductive materials in comparison to osteoconductive biomaterials.

#### *3.4.3. Bioresorbability*

Bioresorbable biomaterials can exhibit time-dependent controlled degradation and subsequently allow it to be replaced with host tissue [176,177]. However, in practice, due to the large quantity of the biomaterial expected to be handled by the tissues means that a resorbable biomaterial must be metabolically acceptable. Another requirement for a resorbable biomaterial is that the resorption rate must be matched to the repair rates of the biological tissue of the host. When using bioresorbable biomaterial in a clinical setting, it is important to consider that the mechanical properties of the biomaterial must allow for tissue repair. Overall, for an acceptable biodegradable biomaterial, the rate of degradation of the material must be controllable [172].

#### *3.4.4. Infection resistance*

Infection resistant biomaterials are one of the latest strategies that are being experimented to reduce microbial infections [178] following the focus over the last decades on antibiotic techniques, control of clinical sterility [179]. Despite the utmost care clinical hygiene procedures, infections associated with biomaterials and associated surgical procedures have been challenging to avoid entirely. Consequently, the strategy is to prevent infections by either inhibiting or terminating the unwanted microbes that come into contact with a biomaterial. To do this, the antimicrobial property should become an inherent property of the biomaterial or the device itself. One of the promising ways in this regard is to reduce biomaterial infections through the use of materials that can counteract microbial adhesion. As a result, the microbes cannot either attach to the biomaterial surfaces nor get killed in the process of doing so [180]. Research literature shows that experiments on infection resistant biomaterials are capable of:

- i.* Reduction of bacterial adhesion and protein adsorption [181].
- ii.* Reduction of the colonisation and assembly of bacteria and biofilms [182].
- iii.* Initiate antibacterial activity at the host tissue interface [183].
- iv.* Controlled release of active antimicrobial agents [184,185]
- v.* Interference and alternation of the pathogen physiology [186]
- vi.* Disruption of the cellular level structural integrity of microbes resulting in their termination [187].

In general, biomaterial surfaces that can prevent microbial adhesion are either classified antimicrobial or antifouling [180]. While the former (antimicrobial) can terminate microbes as

they interact or approach the biomaterial surface, the latter (antifouling) features the capacity for the prevention of microbial accumulation by interfering with the biofilm structure. Even though the development of infection-resistant biomaterials is an active area of research, some notable biomaterials that possess antimicrobial properties are listed in Table 9. One of the promising material in this regard is pure silver in as nanoparticles and coating surfaces [188].

**Table 9.** Example of antimicrobial biomaterials and their associated characteristics.

<b>Biomaterial</b>	<b>Characteristics</b>	<b>Ref.</b>
Ag/ Hydroxyapatite /Lignin	Antimicrobial performance against <i>S. aureus</i> , safe for healthy immunocompetent peripheral blood mononuclear cells (PBMC), and unsusceptible to corrosion.	[188–191]
Hydroxypropyl trimethyl ammonium Chloride chitosan	Antimicrobial performance against MRSA and safe for pre-osteoblasts.	[192,193]
Carboxymethyl cellulose (CMC)-based hydrogels with Ag nanoparticles	High antibacterial activity inhibiting <i>E. Coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , and <i>Bacillus subtilis</i> .	[194,195]
Quaternary ammonium poly(oxanorborneneimides) polymeric nanoparticles	Infection resistance to <i>P. aeruginosa</i> , <i>S. aureus</i> , and <i>En. Cloacae</i> complex biofilms and low cytotoxicity.	[196,197]
Cu releasing degradable phosphate glass fibres	Antibacterial activity showing inhibition <i>Staphylococcus epidermidis</i> .	[198]
Zn/Cu dicalcium silicate cement	Long-term antibacterial potential against <i>P. aeruginosa</i> , <i>E. faecalis</i> , <i>E. coli</i> and <i>S. aureus</i> .	[199]

#### 4. Future perspective

The development of new biomaterials for decades has been focused on the synthesis and modification of material chemistry leading to biopolymers and metallic alloy with unique properties [200,201]. However, in recent years, an alternative pathway has been gaining momentum where development of new materials with desired mechanical, physical, and biological properties are through modulating the materials at the geometrical and molecular level [77]. This allows developing new materials with targeted properties giving rise to functional or designer biomaterials. A new generation of biomaterials is evolving in this regard driven by the need to achieve the required *in situ* qualifications for tissue regeneration and repair. There is also another category of biomaterials that are being developed to allow for tissue repair through minimally invasive surgery called deployable biomaterials. There are substantial benefits to each of these approaches; they drastically reduce patient recovery contributing to human capital and reducing the socioeconomic burden. It may be also feasible to develop a generation of gene-activating biomaterials tailored for specific patients and disease states. Generally, it is promising that significant developments are happening in the analytical and numerical methods to predict the performance of such innovative materials, which can also accelerate the development of highly innovative biomaterials with unique and targeted functionalities. It must be also

acknowledged that the rise in digital fabrication techniques such as additive manufacturing has enabled the exploitation of geometrically porous biomaterials which is one of the most promising classes of biomaterials. Though not immediate, what is more, interesting is the possibility of biomaterials that respond to bioactive stimuli that can be used to activate genes in a preventative treatment to maintain the health of tissues as people age. While some of these areas are in their infancy concerning the clinical realisation, it is important to remember that only a few years ago, these concepts would have seemed fiction. It is worth looking back that only 40 years ago the concept of a material that would not be rejected by living tissues seemed impossible. [202].

## 5. Conclusion

As discussed so far, the selection and development of a biomaterial depend on the specific medical application and the functional requirements of that application. This means that a biomaterial classification from the functional point of view is essential to not only capture the key features associated but also to provide an insight into the types of interactions it can facilitate with the surrounding tissues. It is also anticipated that a functional classification can also aid in the establishment of efficient regulations for both biomaterial selection and evaluation.

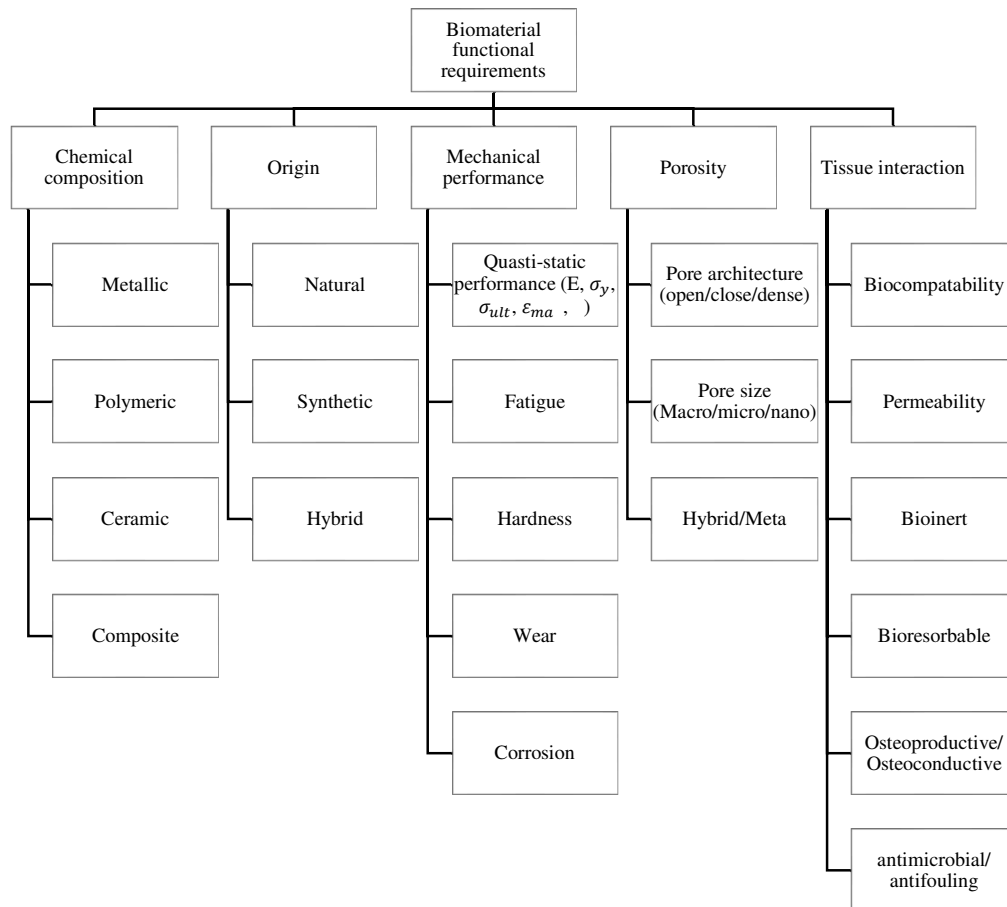


Fig. 6. A framework for the classification of biomaterial functionalities.

Based on qualifications presented in this paper, Fig. 6 summarises a framework that can be used for the classification of biomaterial functionalities that can accommodate both traditional and emerging biomaterial functionalities. This will allow the selection and development of a candidate biomaterial to be guided by their functional requirement. For example, a well engineering biomaterial for bone scaffolds must be biocompatible in addition to having suitable mechanical performance while featuring a compatible pore architecture that facilitates osteoproduction and permeability. The biomaterial should also accommodate distinctive interaction with the surrounding tissue for osseointegration while reducing stress-shielding and maladapted stress concentration. Despite the increase in the variety of biomaterials that are available, their clinical use has been limited. Improvements in this regard require conceptual classification refinements and practical reforms that are focused on biomaterial functionalities which this paper aims to contribute. Nevertheless, the implementation of such a functional framework for biomaterials requires collaborative effort between researchers, manufacturers, regulators clinicians and end-users.

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