Biological and Bioinspired Composites with Spatially Tunable Heterogeneous Architectures

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The design and fabrication of synthetic structural components often result in homogeneous materials with uniform microstructures and properties. In contrast, nature has evolved structural composites exhibiting rich heterogeneous architectures and tunable site-specific properties. Creating synthetic systems with the heterogeneous nature of biological materials should enable the fabrication of composites with extended durability under severe mechanical demands or with adequate properties using, for example, a more restricted selection of bioresorbable or environmental-friendly basic building blocks. Here, the heterogeneous structures of the tooth and of the tendon-bone interface are revisited to identify design strategies that have been naturally selected to best respond to the non-uniform stresses distributions typically found in such load-bearing structures. Recent attempts to replicate some of these strategies in man-made materials are also shown to illustrate the variety of unusual properties that can be achieved through the proposed bioinspired approach. Finally, the creation of heterogeneous architectures with local microstructure and properties deliberately tuned to match non-uniform loading conditions is suggested as a new pathway towards the development of "material systems" with unprecedented functionalities and durability in mechanically challenging applications.

1. Introduction

The selection of materials for load-bearing structural purposes is markedly different in nature and engineering. In engineering, the stresses and strains involved in a particular application are first estimated by simulating the actual loading conditions on a hypothetical material exhibiting uniform mechanical properties. Materials with mechanical properties that surpass the maximum simulated stresses and strains are then selected with the help of charts displaying the properties of a wide range of available materials, known as Ashby diagrams.[1,2]

An artificial hip joint is shown in **Figure 1** as an example of such engineering approach for materials selection. After defining an appropriate shape for the implant based on the required end function (Figure 1a,b), bulk homogeneous materials with well-defined mechanical properties are selected and assembled together into a final synthetic multicomponent structure (Figure 1c). To compensate for the flaw intolerance of brittle inorganic materials and thus ensure extended lifetime, safety factors are often used in the structural design and materials much stronger and stiffer than required are typically employed. As a result, high mismatches in elastic moduli occur at the interface between the synthetic materials and the bone host tissue (Figure 1d), and eventually between the homogeneous materials of the prosthesis itself. Such mismatches may significantly limit the long-term functional response and durability of the prosthesis. Due to its much higher stiffness, the stem takes most of the stresses originally applied to the host tissue, leading to bone loss around the implant (Figure 1e).[3] Bone loss also results from inflammatory reactions to debris particles generated by the excessive wear of the polymeric lining of the cup in contact with the hard metallic ball. These mechanisms ultimately loosen the implant, which is the most common reason for a revision surgery.[4] Despite major research and development efforts to circumvent such issues through improvements in the design and fixation of the multicomponent structure shown in Figure 1c, newer approaches lead to equal or even worse clinical performance compared to older, established hip joint replacement solutions.[5] This clearly indicates that current technology has approached its limits and that a paradigm shift in the way such prostheses are designed and manufactured is required to further extend the long-term performance of such synthetic implants or to generate sufficiently tough temporary restorative materials that can be later eventually resorbed and replaced by natural bone.[6]

In contrast to the engineering approach, load-bearing structures in nature result from a long "trial-and-error" process likely driven by evolutionary selective pressures.[7] In this case, materials are locally reinforced only in those parts that experience the highest stress levels during use. Following on the example shown in Figure 1, this explains the unique architecture of bone, which consists of a softer and lighter porous architecture in its interior (trabecular bone) and a stiffer and tougher dense structure in its load-bearing contours (cortical bone). As a result, the elastic modulus of bone can vary over a wide range of values depending on the location within the material (see large red circles in Figure 1d). In the context of

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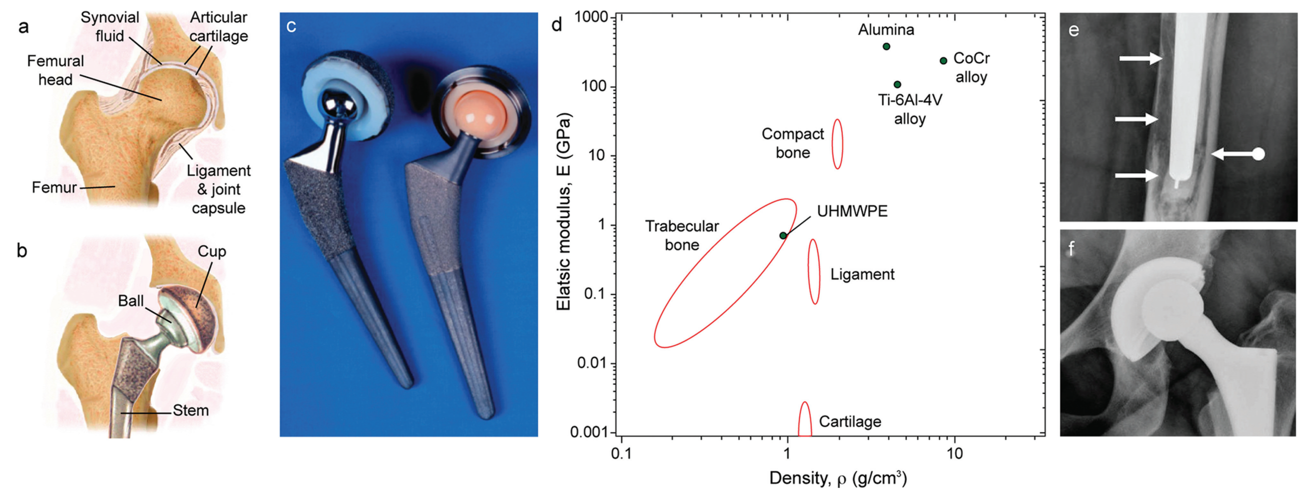

Figure 1. Artificial biomedical implant currently used for hip joint replacement. a) Anatomical drawing of a human hip joint. b) Drawing illustrating the three individual components of the artificial implant (stem, ball and cup) and how the artificial implant is positioned to replace the natural joint. c) Combinations of bulk homogeneous materials currently used as individual components of the implant. Left: CoCr metallic ball on ultra-high molecular weight polyethylene (UHMWPE) polymeric cup. Right: Al_2O_3 ceramic ball on Al_2O_3 cup. A titanium alloy with the composition Ti-6Al-4V is typically used for the stems. Panels (a-c) were adapted with permission.[36] Copyright 2007, American Ceramic Society. d) Ashby diagram indicating the wide range of elastic moduli and densities of the heterogeneous composites that constitute the natural hip joint (compact and trabecular bone, ligament and cartilage), as opposed to the homogeneous bulk materials with very sharp and distinct mechanical properties that are used in prosthetic hips (Alumina, CoCr alloy, Ti-6Al-4V alloy and UHMWPE). Data obtained from Wegst and Ashby.[2] e,f) Typical issues arising from the very distinct mechanical properties of the homogeneous materials used in synthetic implants and the resulting interfacial mismatch: e) loosening of the femoral stem due to osteolysis and f) off-centering of the ball caused by extensive wear of the polymeric cup. Panels (e,f) were reproduced with permission.[4] Copyright 2012, Elsevier.

natural selection processes, this general strategy of spatially controlled reinforcement leads to a clear competitive advantage with regards to feeding, body support and defense against predators, since it enables the combination of unusual properties like stiffness, toughness and light-weight within the same material. Since the reinforcement is spatially defined, this fundamentally distinct selection process has led to structural materials in biology that are far more heterogeneous in comparison to their engineering counterparts.

While the homogeneous nature of synthetic materials greatly simplify the simulation, selection and fabrication processes in engineering applications, the more complex heterogeneous architecture of biological materials enables tuning of the local elastic modulus, strength and toughness of the material to match the non-uniform mechanical loads and the uneven local deformations around stress concentrators encountered in most structural applications (e.g., holes, defects, convex surfaces). Locations of the material, which would otherwise experience large deformations, can be locally stiffened in a heterogeneous composite to minimize strain gradients and stress concentrations throughout the structural component. In the particular example of the artificial hip joint shown in Figure 1, a heterogeneously reinforced composite could be devised to better match the mechanical properties of the host tissue and thus extend the lifetime of the prosthesis under the severe mechanical loads encountered in such application. Mimicking in synthetic systems the concept of spatial tuning of mechanical properties found in nature should increase the durability of structural materials in existing applications and also allow for the fabrication of unusual composite structures and geometries whose lifetime has been so far limited by excessive stress concentrations.

Here, selected examples of heterogeneous biological materials are first revisited to illustrate some of the natural mechanisms used to spatially tune their mechanical properties in response to non-uniform deformations. The local concentration and orientation of reinforcing building blocks are shown to be major microstructural parameters utilized in nature to adjust the local properties of biological structures according to external mechanical demands. Processing routes that enable replication of such mechanisms in synthetic systems are then reviewed to highlight some of the enabling tools available for the creation of bioinspired materials with locally tunable microstructures and properties. The unusual combinations of mechanical properties that can be achieved in such bioinspired materials to address limitations in existing applications or challenges in emerging technologies are discussed. Finally, a bioinspired approach to potentially tackle the mechanical issues encountered in artificial hip joints is put forward and used again as an example to illustrate possible research directions towards the development of heterogeneous bioinspired materials with unprecedented lifetime and functionalities in mechanically demanding environments.

2. Heterogeneous Biological Composites

The unique structural design of biological composites at multiple length scales allows them to reach remarkable mechanical properties using weak basic constituents.[8,9] Structural features of natural materials that stand out in comparison to their synthetic counterparts include the optimized geometry of their building blocks, the thorough arrangement of such basic

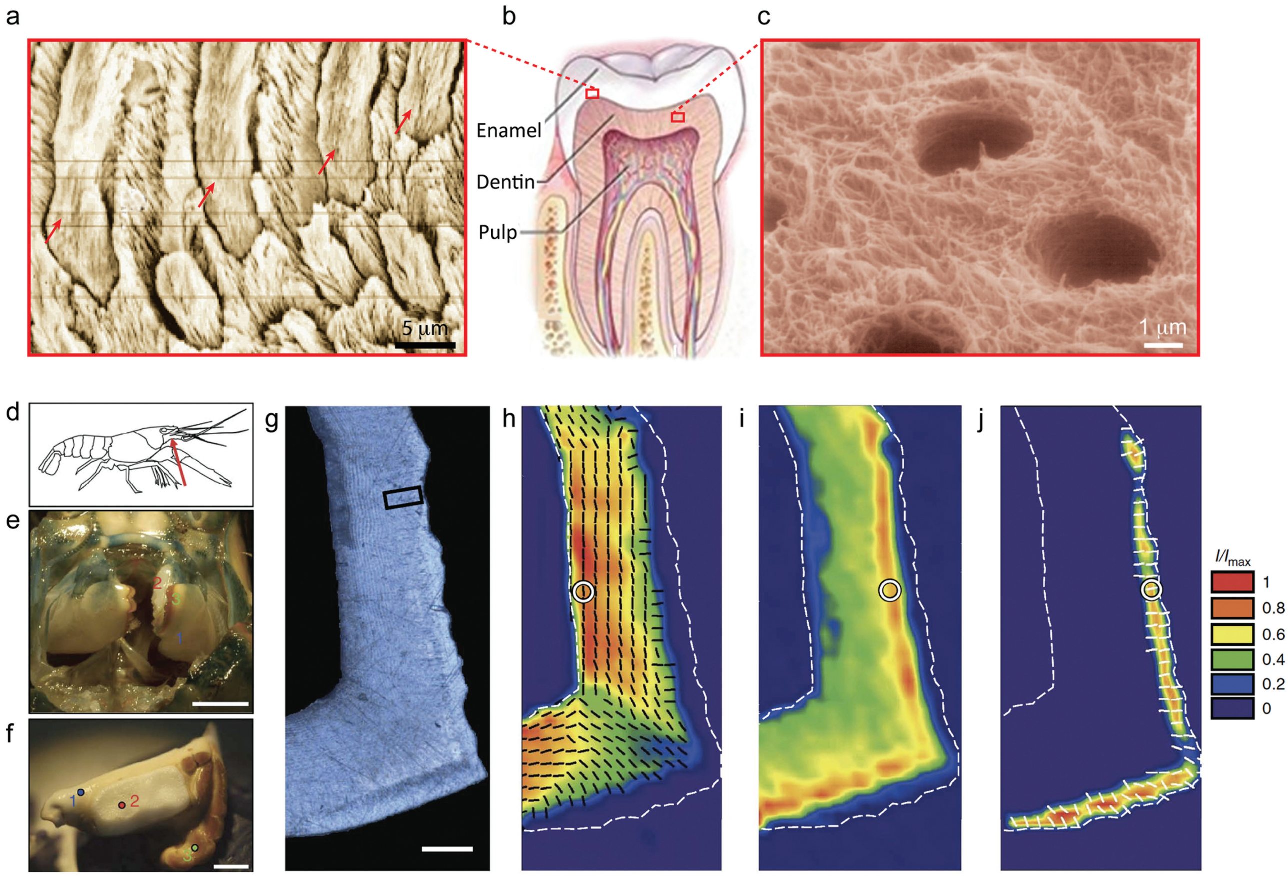

Figure 2. The structural design of selected natural teeth. a–c) Architecture of the tooth of humans and primates, highlighting the highly mineralized collagen fibers oriented perpendicular to the tooth surface within the prisms of the enamel layer (red arrows) and the 2D mesh of less mineralized collagen fibers aligned parallel to the surface in the inner dentin layer. Adapted with permission.[37,38] Copyright 1999, Wiley-Blackwell; Copyright 1997, Elsevier. d–j) Architecture of the tooth of a crayfish, a crustacean that is genetically very distant from vertebrates. d) Schematic drawing of the crayfish, indicating the location of the mandible (red arrow). e,f) Closer view of the mandible showing (1) the basal segment, (2) the anterior molar and (3) the outer incisor. Scale bar, 5 mm. g) Optical microscopy image of a cross-section of the anterior molar tooth of the crayfish. Scale bar, 200 µm. h–j) Structural analysis of the anterior molar by synchrotron scanning Wide angle X-ray scattering (WAXS), indicating h) the concentration (color coded) and the orientation of chitin fibers in the inner part of the tooth, i) the increasing concentration of amorphous carbonate and phosphate mineral phases towards the hard surface, and j) the concentration and orientation of fluorapatite crystals within the outer hard surface of the tooth. Panel (d–j) were reproduced with permission.[12] Copyright 2012, Nature Publishing Group.

elements in a hierarchical fashion, the subtle balance between weak and strong interactions among building blocks and the heterogeneous nature of their nano-/microstructure.[9–11]

Tuning the local orientation and concentration of reinforcing building blocks to form heterogeneous architectures has been shown to be a widespread strategy used in biological materials to best accommodate externally applied mechanical stresses or to generate unusual combinations of properties.[9,11–15] This design concept is discussed below taking the tooth and the tissue that connects tendon to bone as examples of biological composites displaying unique heterogeneous structures.

2.1. The Tooth

The tooth is a remarkably resilient bi-layered material that consists mostly of hierarchically organized collagen fibers, which are mineralized to different extents with hydroxyapatite anisotropic crystals.[16] To provide the outer layer with the high hardness required to withstand mastication forces in excess of 800 N[17] and the inner layer with the toughness needed to keep the material's integrity over time, the local concentration and orientation of such organic and inorganic building blocks are tightly controlled throughout the material. The outer enamel layer consists of prisms of highly mineralized collagen fibers (95% hydroxyapatite) oriented perpendicular to the tooth surface (**Figure 2**a,b). The inner dentin layer is comprised of a mesh of less mineralized collagen fibers (50% hydroxyapatite) oriented mostly parallel to the tooth surface (Figure 2b,c). The interface between the two layers, known as the dentin–enamel junction (DEJ), displays a gradual transition in the orientation and concentration of such building blocks. Remarkably, this overall architecture typical for teeth of vertebrates was recently found to also exist in the mineralized tooth of crayfish, a genetically very distant invertebrate (Figure 2d–f).[12] This suggests that the organization of organic and inorganic constituents in teeth might have indeed been driven by evolutionary selective pressures that ultimately led to similar, universal design principles. As in vertebrates, the teeth of crayfish exhibit a less mineralized inner layer containing organic fibers organized mostly parallel to the tooth surface (Figure 2g–i) and a highly mineralized outer layer with inorganic anisotropic particles oriented perpendicular to the outermost surface (Figure 2g,i,j). Such architecture prevails despite the different compositions of the organic and inorganic building blocks, which in the case of crayfish tooth consist of chitin and a mixture of carbonates and phosphates, respectively.

The microstructural design of the tooth has major implications on the stress/strain distribution and the resistance of the material to fracture when subjected to the mechanical loads applied during mastication. As opposed to the stress concentration observed under the mechanically loaded area of a tooth-shaped homogeneous material, the internal architecture of natural tooth is locally reinforced to withstand the highest stresses generated close to the contact load, minimizing strain gradients throughout the material (**Figure 3**a).[18] Local reinforcement close to the contact load is achieved by the high mineralization and the orientation of building blocks parallel to the loading direction (Figure 2). As a result, the outer layer of mammalian tooth is nearly 10-fold harder than the inner dentin layer (Figure 3b). However, the enamel layer exhibits relatively low resistance against crack propagation, with toughness values comparable to that of glass.[16] In fact, cracks that initiate within the enamel or at the DEJ are stopped within the dentin layer

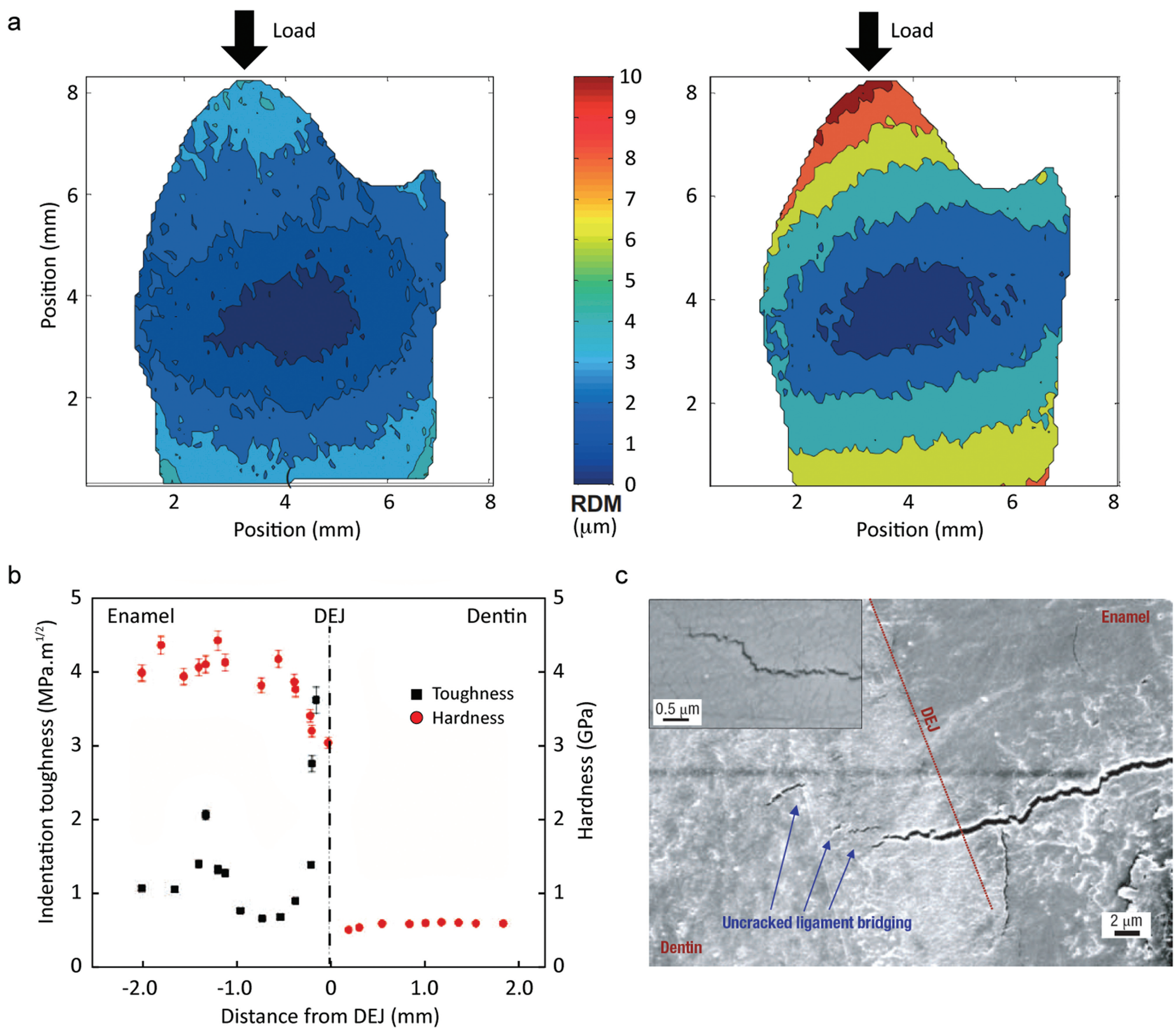

Figure 3. Local mechanical response and crack growth resistance of the human tooth. a) Strain distribution on the surface of a premolar tooth (left) and a homogeneous synthetic counterpart (right) when loaded at the cusp tip (RDM: relative displacement magnitudes). Adapted with permission.[18] Copyright 2006, Wiley-VCH. b) Local fracture toughness and hardness across the enamel and dentin layers of a human molar tooth.[14] c) Arresting of a crack at the dentin-enamel junction of the human tooth, highlighting the uncracked ligament bridging as a major toughening mechanism within the dentin layer. The inset shows the absence of bridging for cracks propagating within the enamel layer. Panels (b,c) were reproduced with permission.[14] Copyright 2005, Nature Publishing Group.

by the partially mineralized collagen fibers oriented parallel to the tooth surface. Such design leads to an abrupt increase in the fracture toughness of the material as a crack propagating from the surface reaches the DEJ. Uncracked ligament bridges formed by the oriented fibers are able to effectively arrest cracks within the dentin layer and prevent catastrophic failure of the tooth (Figure 3b,c).[14]

2.2. The Tendon-Bone Interface

Controlling the concentration and orientation of reinforcing building blocks is also a strategy found in the 100-μm-thick tissue that connects ligaments and tendons to bone in the musculoskeletal system of vertebrates, known as enthesis or the tendon-to-bone insertion site (**Figure 4**a).[19,20] Because the elastic moduli of bone and tendon differ by as much as two orders of magnitude, this tissue would be subjected to undesired stress concentrations if it were formed by an isotropic, homogeneous material. Instead, the tendon-to-bone insertion site is comprised of hierarchically structured collagen fibers and hydroxyapatite platelets with deliberately tuned orientations and concentrations to form a mechanically graded heterogeneous architecture of remarkable resilience. Recent studies suggest that a subtle balance between the reinforcing effects of these two fundamental building blocks controls the local mechanical properties of such biological material. On the one hand, collagen fibers are aligned parallel to the loading direction within the tendon, but slightly lose their orientation in the tendon-to-bone insertion site (Figure 4b). This effect alone is expected to decrease the elastic modulus of the insertion site as compared to that of the tendon. On the other hand,

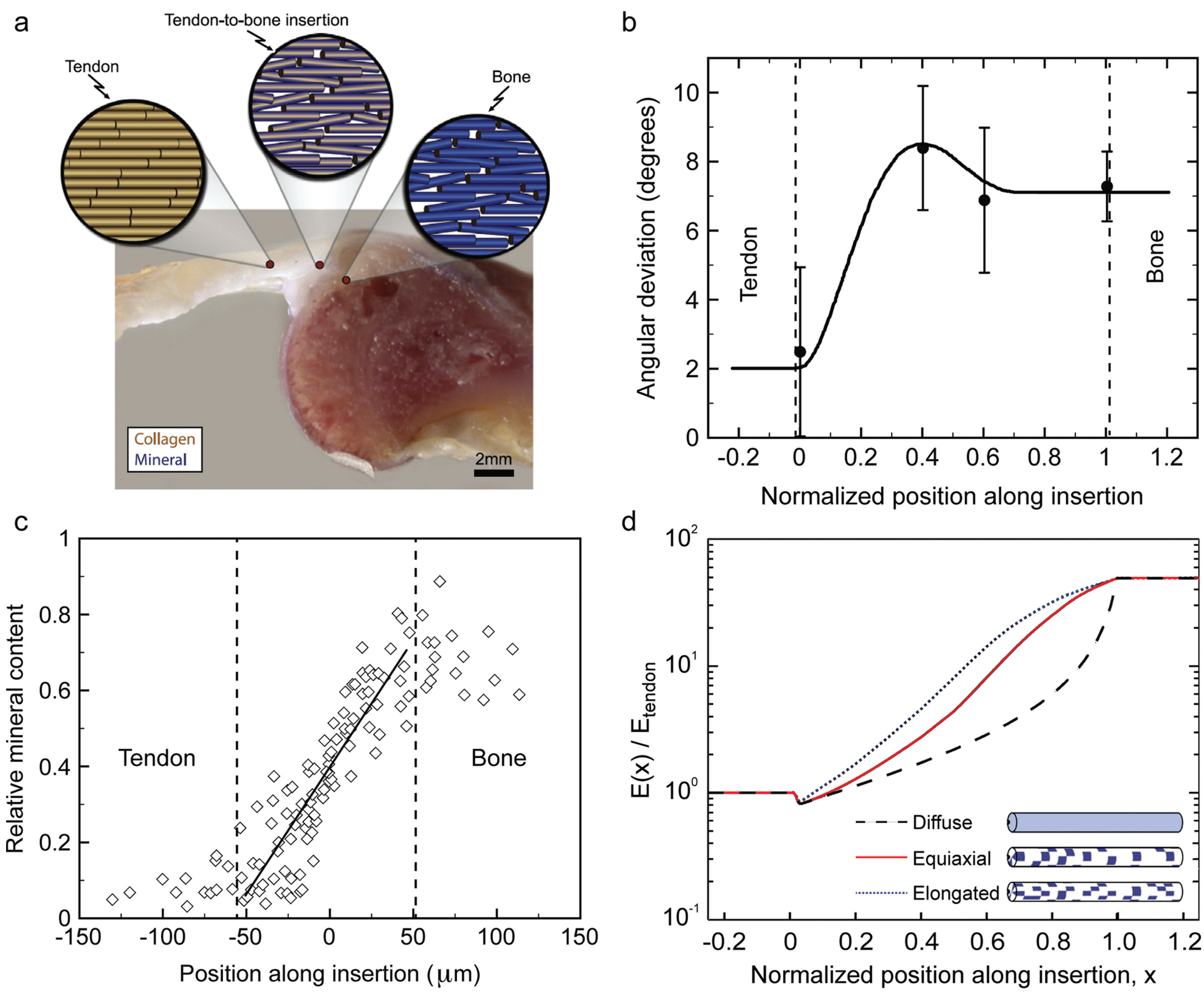

Figure 4. The microstructural design of the tendon-to-bone insertion site. a) Cross-sectional view of the insertion site, highlighting schematically the changes in the orientation of collagen fibers (in yellow) and in the degree of mineralization (in blue) between tendon and bone. b) Misorientation of collagen fibers and c) concentration of hydroxyapatite throughout the insertion site. d) Predictions for the combined effect of collagen fiber orientation and mineral content on the elastic modulus of the tendon-to-bone interface, assuming different arrangements of the mineral phase. All panels were reproduced with permission.[19] Copyright 2009, Biophysical Society.

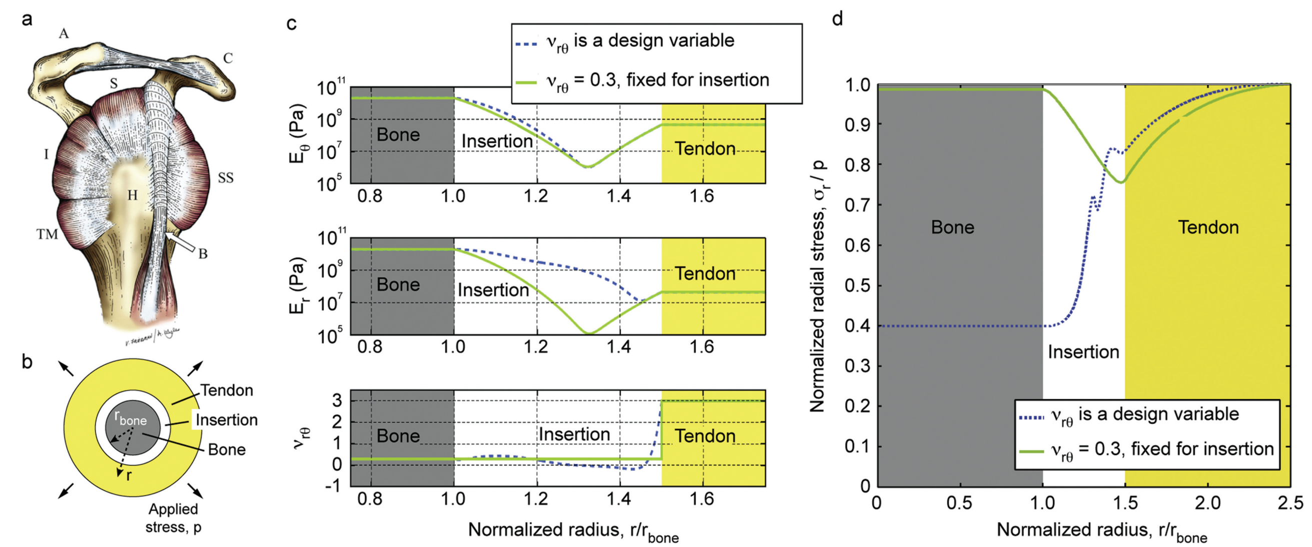

Figure 5. Simulated local mechanical properties and stress distribution along the tendon-bone interface of the rotator cuff.[21] a) Schematic side view of the rotator cuff, with tendons, muscles and bone indicated in white, red and tan, respectively. The four rotator cuff tendons (TM, I, S and SS) are shown to wrap around the femoral head (H) to effectively connect the muscles to the bone. b) Simplified model of a mechanically loaded tendon-to-bone insertion interface after removing the overlying structures A, B and C and unwrapping the four rotator cuff tendons. c) Local mechanical properties of the tendon-to-bone insertion that are predicted from numerical calculations to minimize the radial stresses throughout the idealized rotator cuff model shown in (b). E_r, E_θ and $\nu_{r\theta}$ are the radial elastic modulus, the tangential elastic modulus and the Poisson ratio of the insertion. d) Predicted radial stresses throughout the insertion site assuming the local mechanical properties shown in (c). All panels reproduced with permission.[21] Copyright 2012, Elsevier.

hydroxyapatite crystals mineralize within and between the collagen fibers, increasing linearly its concentration from the tendon to the bone surface (Figure 4c). Such a linear increase in mineralization level should increase the elastic modulus of the tissue, but only after a minimum percolation threshold is reached. Taking these opposing trends into account, the overall effect is that the elastic modulus of the tissue in the axial direction first decreases from the tendon towards the bone due to the misalignment of collagen fibers; this is then followed by a sharp increase in modulus as a result of the progressively higher mineralization level close to the bone site (Figure 4d).

To shed light on the possible reasons for the predicted decrease in elastic modulus within the insertion site to levels below that of tendon and bone (Figure 4d), numerical calculations were performed to estimate the stresses developed across model systems that capture the essential geometry and mechanical loading conditions at the tendon-to-bone interface of the shoulder's rotary cuff (**Figure 5**a).[21] Hypothetical materials, such as unmineralized (tendon-like), fully-mineralized (bone-like) or linearly graded insertion sites, were all found to increase the radial stresses throughout the material (σ_r) as compared to the external applied stress (p). In contrast, when the local mechanical properties are allowed to vary freely in the simulation, an elastic modulus distribution with a minimum value below that of tendon and bone was found to eliminate radial stress concentrations within the insertion site (Figure 5b–d). In this case, the radial stresses are reduced at the expense of tangential stresses, which were observed to increase beyond the externally applied stress. The radial strain and strain energy density were also found to increase for the optimized elastic modulus distribution, suggesting that the tissue architecture is designed to minimize radial stresses throughout the insertion site.

Interestingly, the two examples of heterogeneous biological materials in the human body discussed above well illustrate the ability of biological materials to address very different mechanical demands by simply controlling the spatial concentration and orientation of building blocks within the composite structure using the same basic constituents: collagen and hydroxyapatite.

3. Heterogeneous Bioinspired Composites

The rich hierarchical architectures of hard biological materials find no counterparts in synthetic composites. This has motivated extensive research in understanding the assembly mechanisms involved in the biomineralization processes used to construct such intricate natural composites. While significant progress has been made in elucidating crucial aspects of this natural process, continued major efforts are still needed to enable the widespread utilization of such complex cell-mediated route for the creation of load-bearing bulk structures. A promising alternative pathway towards the development of bioinspired composites consists in devising synthetic assembly approaches that could provide reliable processing platforms for replicating some of the key structural design principles of natural materials. The development of techniques that enable such level of control over the structure of materials at multiple length scales should not only result in new properties but also open the possibility to investigate thus far unexplored strategies and mechanisms to increase the durability of synthetic

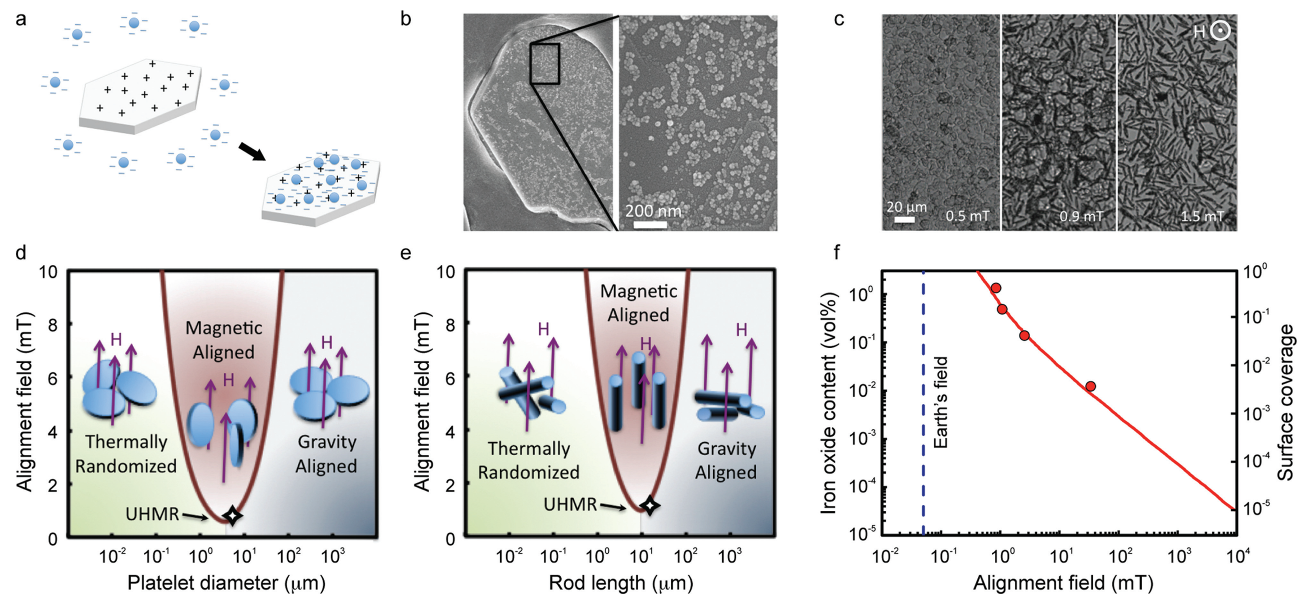

Figure 6. Control of the orientation of suspended reinforcing microparticles using low magnetic fields. a) Schematic drawing depicting the coating of non-magnetic reinforcing platelets with superparamagnetic nanoparticles through electrostatic adsorption in water. b) SEM image of a 7.5-µm-long alumina platelet coated with Fe_3O_4 nanoparticles. c) Response of Fe_3O_4-coated alumina platelets suspended in water when subjected to increasing magnetic fields in the direction normal to the sheet. Above a threshold magnetic field of 1 mT the horizontally oriented platelets (left) eventually align parallel to the direction of the field (middle and right). d,e) Theoretical predictions of the size dependences of the threshold magnetic field required for the alignment of platelets and rods, respectively. f) Relation between the magnetic fields required for platelet alignment and the amount of iron oxide nanoparticles used as magnetic surface coating. Symbols indicate experimental data, whereas the line shows theoretical predictions. Reproduced with permission.[26] Copyright 2012, AAAS.

materials. Some of the recent efforts towards this goal are described below.

3.1. Composites with Locally Tunable Reinforcement Orientation

Aligning anisotropic stiff elements in the direction of the applied load is the fundamental reinforcing concept used for many decades in the design of conventional fiber-reinforced and lamellar composites.[22,23] In composites reinforced with long continuous fibers, orientation is usually achieved using knitting, weaving, braiding and stitching techniques from the textile industry.[22,24] The macroscopic length of such fibers is key to enable alignment in deliberate directions in the plane and for the assembly of complex reinforcement arrays. In contrast, short discontinuous fibers cannot be manipulated with the same macroscopic tools, making their alignment far more difficult to achieve. Therefore, new approaches to control the orientation of reinforcing anisotropic particles have been devised in an attempt to replicate for example the unique brick-mortar architecture of the nacreous layer of seashells. This effort has led to the development of nacre-like lamellar composites with remarkable structures and mechanical properties.[25]

While replicating the structure of nacre has been well justified by the remarkable fracture toughness of its layered architecture, the examples of heterogeneous biological composites shown here reveal that the orientation of reinforcing elements is not always uniform as in nacre but can also vary spatially within the same material to give rise to unique site-specific mechanical response. To obtain composites with deliberate spatial control over the orientation of discontinuous reinforcing particles, a method was recently developed that enables the alignment of anisotropic reinforcing elements using low magnetic fields.[26] In this method, reinforcing microparticles are first made magnetically responsive by coating them with superparamagnetic Fe_3O_4 nanoparticles. The coating can be easily formed by dispersing the reinforcing particles and the magnetic nanoparticles in water under a pH at which the particle surfaces exhibit electrostatic charges of opposite sign (**Figure 6**a). Because of the mismatch in magnetic susceptibility between the coated particles and the surrounding fluid (Figure 6b), the modified reinforcing microplatelets can be easily manipulated in a fluid using magnetic fields as low as 1 mT (Figure 6c). This ultrahigh magnetic response results from the optimal size of the microplatelets, which are large enough to remain undisturbed by Brownian motion while sufficiently small to be unaffected by gravitational forces (Figure 6d). On the basis of a theoretical analysis of the gravitational, magnetic and thermal energies involved in the system, size ranges of 1–10 and 5–20 µm have been found to be optimum for the alignment of inorganic platelets and rods, respectively, using low magnetic fields (Figure 6d,e). Since the incorporation of significant amounts of magnetic material in the system might be undesirable in some applications, reinforcing particles within this optimum size range can also be coated with iron oxide concentrations as low as 0.01vol% while still remaining magnetically responsive when subjected to low fields of about 30 mT (Figure 6f).

The alignment of reinforcing particles in any deliberate orientation opens the possibility to produce unusual composite architectures if the initially fluid continuous phase is consolidated to fix the magnetically oriented structure. Consolidation can be accomplished by, for example, polymerizing an initially fluid monomer, removing the solvent of a polymer solution, gelling the fluid using external triggers or cooling down a polymer melt. These approaches have been exploited to fabricate composites with unusual architectures and properties, as illustrated by the selected examples shown in **Figure 7**. In the simplest configuration, alumina microplatelets can be oriented parallel to the loading direction to increase the elastic modulus and the yield strength of a polyurethane matrix by 150 and 60%, respectively (Figure 7a). The alignment of a small content of alumina microplatelets parallel to the loading direction was observed to increase by twofold the wear resistance of a filler-reinforced acrylate-based resin (Figure 7b). Magnetic fields have also been used to obtain deliberate reinforcement orientations in specific parts of monolithic composites. For instance, local reinforcement of a particular area of the composite surface can be achieved by concentrating the microplatelets using local gradients in magnetic field (Figure 7c). Alternatively, bilayer architectures can be constructed where the local reinforcement orientation is tuned to combine unusual properties, such as high surface hardness and high bending modulus, which cannot be obtained in monolithic composites reinforced in one single orientation (Figure 7d). High surface hardness is achieved by aligning the reinforcing particles vertically within the composite top layer, whereas high bending modulus is obtained by orienting the particles horizontally in the bottom layer. Such an optimum structure effectively captures the reinforcement architectures found in natural teeth (Figure 2) and in the mineralized shell of some mollusk species.

3.2. Composites with Locally Tunable Reinforcement Concentration

In addition to controlling the orientation of reinforcing particles, attempts have also been made to fabricate composites that replicate the unique graded architectures of biological materials. Although a variety of elegant functionally graded

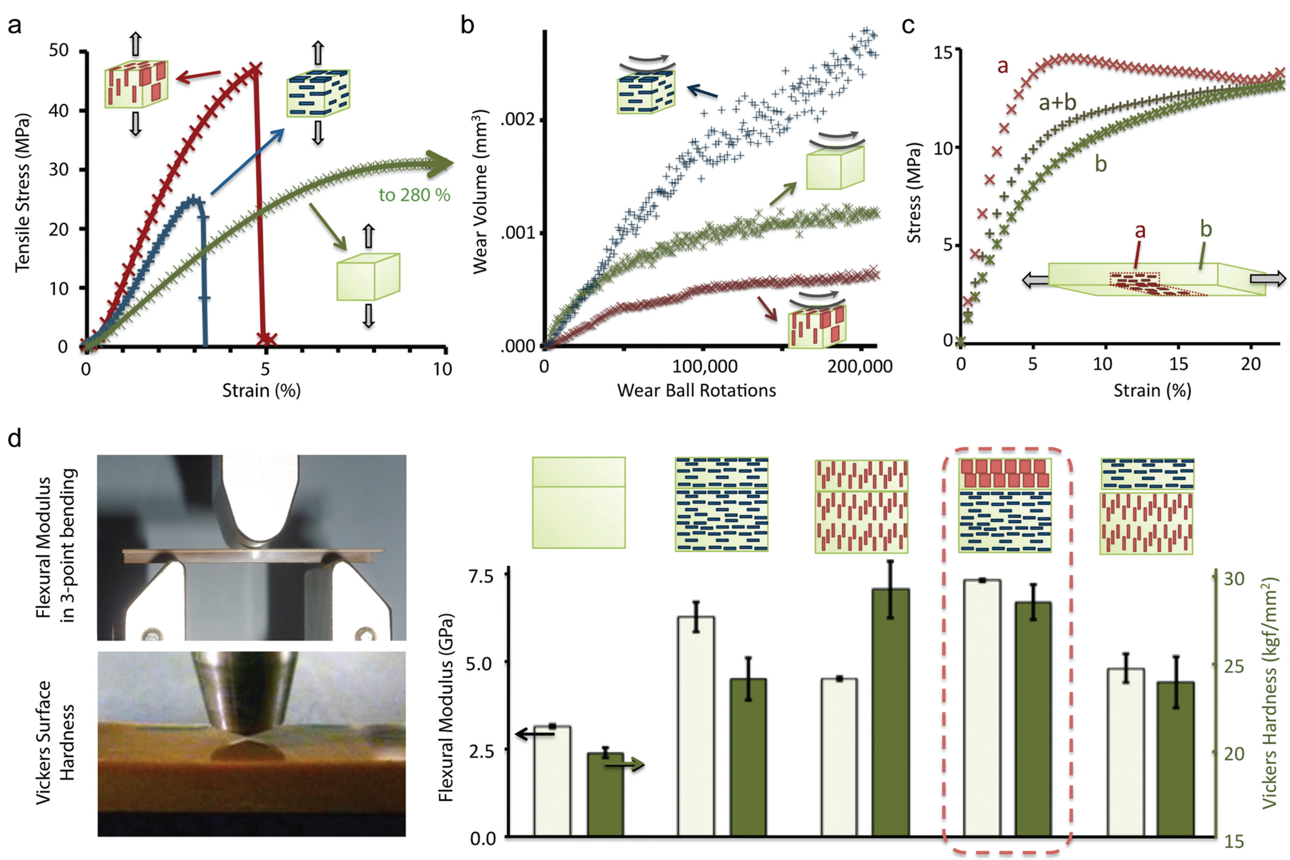

Figure 7. Mechanical response of synthetic composite architectures containing magnetically oriented alumina microplatelets as reinforcing elements.[26] a) Stress-strain curves showing the effect of alumina platelet orientation on the tensile properties of 20vol% reinforced polyurethane-based composites. b) Wear properties of an acrylate-based dental resin containing 85wt% inorganic fillers and further reinforced with 1vol% alumina microplatelets aligned in different orientations with respect to the loading direction. c) Stress-strain curves indicating the local reinforcement of a specific volume of a polyurethane film achieved by magnetically concentrating the alumina microplatelets using field gradients. d) Flexural modulus and surface hardness of heterogeneous epoxy-based bilayer composites exhibiting different reinforcement architectures. Both properties can be simultaneously enhanced if the local orientation of reinforcing particles within each layer is tuned to mimic the overall architecture found in the tooth and mollusk shell species (highlighted by red dashed line). Reproduced with permission.[26] Copyright 2012, AAAS.

materials have been designed and developed in the past decades,[27] efforts were mainly focused on the creation of metal/ceramic dense composites for thermal barrier applications.[28] Thus, mimicking the rich hierarchical architectures and remarkable span in mechanical properties of the polymer-matrix graded composites found in natural materials (Figure 1, Figure 4 and Figure 5) remains challenging and largely unexplored.

A key feature of graded composites in nature is the fact that their mechanical properties can vary locally by orders of magnitude while still keeping a highly compatible polymeric matrix as continuous phase (Figure 4 and Figure 5). The molecular entanglement expected within such polymeric phase is crucial to ensure efficient stress transfer between areas of different local mechanical properties throughout the graded composite. Replicating such concept in synthetic systems requires addressing the question as to which extent an initially soft but highly entangled polymeric matrix can be reinforced with stiff artificial building blocks. This question motivated the recent development of polyurethane-based composites that are hierarchically reinforced with hard polymeric crystalline domains, laponite nanoplatelets and alumina microplatelets at progressively larger length scales.[29,30] By controlling the concentration of such building blocks within the polymer matrix, it is possible to change the elastic modulus of polyurethane-based composites within a very broad range spanning over four orders of magnitude (**Figure 8**a). Because of the thermoplastic nature of the continuous polymer phase, individual layers with different reinforcement levels can be solvent welded together to form bulk composites with extreme gradients in elastic modulus (Figure 8b). In the example shown in Figure 8c, an additional 100 nm layer of Al_2O_3 was deposited on the stiff side of the bulk material to produce a polymer-based graded composite that is harder than bone on one surface while being softer than skin on the opposite surface. Such extreme gradient in mechanical properties within the same material approaches the range of elastic moduli found in highly graded natural composites like insect cuticles[31] and is far beyond the span of properties obtainable in metal/ceramic functionally graded materials.

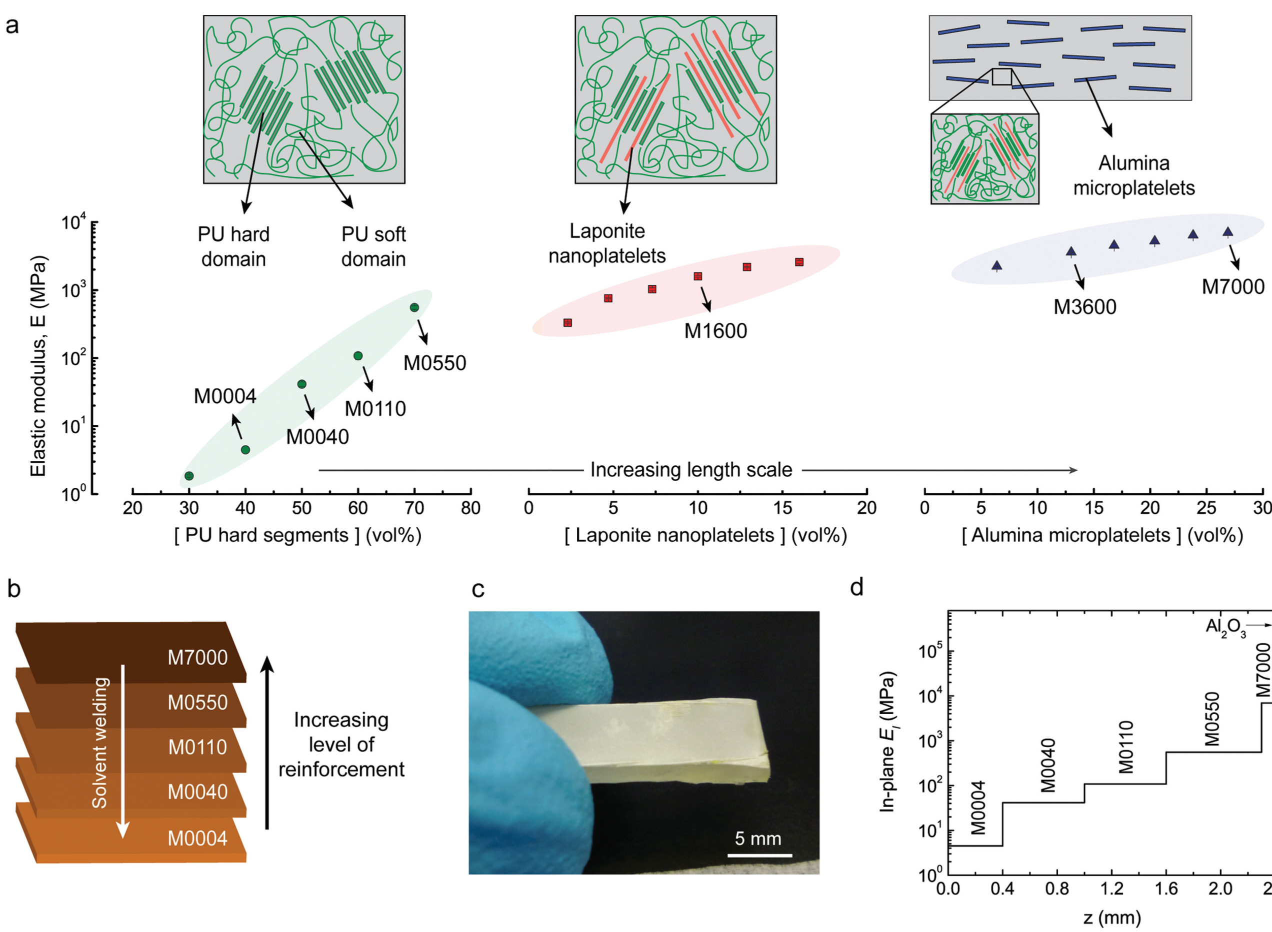

Figure 8. Control of the local concentration of reinforcing building blocks at multiple length scales to create hierarchically reinforced synthetic composites with extreme mechanical gradients. a) Elastic modulus of polyurethane-based materials with various concentrations of polyurethane (PU) crystalline hard domains, laponite nanoplatelets and alumina microplatelets used as reinforcing elements at increasing length scales. b–d) Example of synthetic composite exhibiting extreme through-thickness gradient in elastic modulus fabricated by solvent welding individual layers with different levels of reinforcement. Deposition of a 100-nm-thick Al_2O_3 layer on top of the stiffest layer (M7000) resulted in a bulk material with elastic modulus that varies locally by as much as five orders of magnitude in the absence of delamination-prone interfaces. Reproduced with permission.[30] Copyright 2012, Nature Publishing Group.

To demonstrate the unusual functionalities that can be achieved using composites with extreme gradients in mechanical properties, the hierarchical reinforcement concept was combined with the solvent welding approach to develop highly stretchable substrates for flexible electronics.[30] This application requires substrate materials that are sufficiently soft and elastic to be easily stretchable and bendable, while still being hard enough to protect stiff electronic components from failure upon extensive mechanical deformation. This unusual combination of properties can be reconciled by depositing patchy stiff islands on an elastomeric substrate to mechanically shield brittle electronic materials.[30,32] Finite element simulations on a representative patch-substrate module suggest that patches with a graded architecture can reduce both the maximum strain developed at the patch surface as well as the stress peak at the patch-substrate interface (**Figure 9**a,b). Due to such lower interfacial stresses, experiments have shown that a substrate displaying a linearly graded patch can be stretched more than 300% without undergoing delamination (Figure 9c). In contrast, the high interfacial peak stress expected for substrates exhibiting a homogenously stiff patch leads to extensive delamination at tensile strains between 150 and 300%. Experiments were also conducted to confirm the very low strains developed on the surface of graded patches when the elastomeric substrate is subjected to increasing global strains (Figure 9d). This unique combination of high global stretchability and low local strain on the surface has enabled the fabrication of substrates that can effectively prevent failure of brittle LED devices even when reversibly stretched by as much as 150% strain (Figure 9e). This example illustrates the potential of synthetic composites with tunable mechanical properties in addressing technical issues that cannot be solved with currently available homogeneous materials.

4. Possible Future Directions

The unprecedented mechanical response that can potentially be achieved with bioinspired heterogeneous materials is expected to be a strong drive towards the investigation of new processing routes that enable deliberate tuning of the local composition, hierarchical architecture and mechanical properties of synthetic composites. In such a bioinspired approach, the local nano-/microstructure and mechanics of a given heterogeneous composite would be tailored to best respond to the local stress states within structural components subjected to non-uniform mechanical load. This strategy is illustrated in **Figure 10** taking as an example a synthetic material potentially suitable for hip joint replacement. The design and creation of the heterogeneous artificial material would first require the determination of an appropriate shape to fulfill the desired function, which in this particular example would be the shape of the bone to be replaced. This would be followed by an analysis of the distribution of stresses and strains throughout the structural component under externally imposed mechanical loading patterns. Specific design criteria would be used to "program" the composition, local architecture and mechanics of the heterogeneous material based on the stress analysis performed. One design criterion, for instance, could be to locally tune the elastic modulus of the composite to enable even re-distribution of the otherwise non-uniform stresses and strains throughout the structure, as observed in the natural tooth (Figure 3a). Alternatively, the local nano- and microstructure of the material could be tailored to render a graded profile in mechanical properties, which would optimize a specific target response. In joining technologies, for example, the elastic modulus pattern found throughout the tendon-to-bone-insertion (Figure 4 and Figure 5) could be used to minimize radial stresses in the graded interfaces joining dissimilar materials.

Implementing the programmed heterogeneous design obtained from the stress analysis into bulk composites will demand techniques that allow for 3D spatial control over the composition, concentration and orientation of selected building blocks. Possible processing tools that could offer such capabilities are solid freeform fabrication or rapid prototyping methods, including for example 3D printing, stereolithography and direct writing.[33,34] The use of 3D printing to create bulk materials with programmed heterogeneous architecture is schematically depicted in Figure 10c using the hip joint as a hypothetical example. Rapid prototyping has been widely used in many different fields and have led also to exciting developments and visions in the area of bioinspired materials.[35] However, the utilization of such additive manufacturing approaches to create graded composites with deliberately programmed heterogeneous architectures following the rationale shown in Figure 10 remains largely unexplored. The main challenges in this endeavor are to develop assembly routes that allow for multiscale control of the composite structure from nano- to macroscopic dimensions and to effectively use such tools to implement existing or novel nano-/microstructural design concepts that will optimize the functional response of the final heterogeneous material. Examples of nano- and microstructural design concepts that are known to provide toughening mechanisms at multiple length scales in bone are schematically shown in Figure 10d.[15] In view of the wide design space that has already been explored in biological materials through evolutionary selective processes, natural composites constitute a rich source of design strategies that are yet to be uncovered by investigating structure-property relations in natural composites and in their biomimetic counterparts. Understanding the interaction of propagating cracks with the elaborate nano-/microstructures to be developed through this approach should ultimately enable validation of the implemented design concepts and allow for further optimization of the assembly routes and the material's architecture in an iterative process. The types of building blocks that can be deposited using such additive manufacturing methods vary widely from polymers to powders to living cells. This flexibility can potentially be exploited to implement responsive building blocks into the structure, giving rising to a new generation of "materials systems" with exciting functionalities and dynamic adaptive properties. Given their disruptive nature in comparison to currently available static, homogeneous structural components, heterogeneous materials with such tailored architectures and adaptive response have the potential to revolutionize the way materials are utilized in numerous applications, including tissue regeneration, restorative dentistry and adaptive structures.

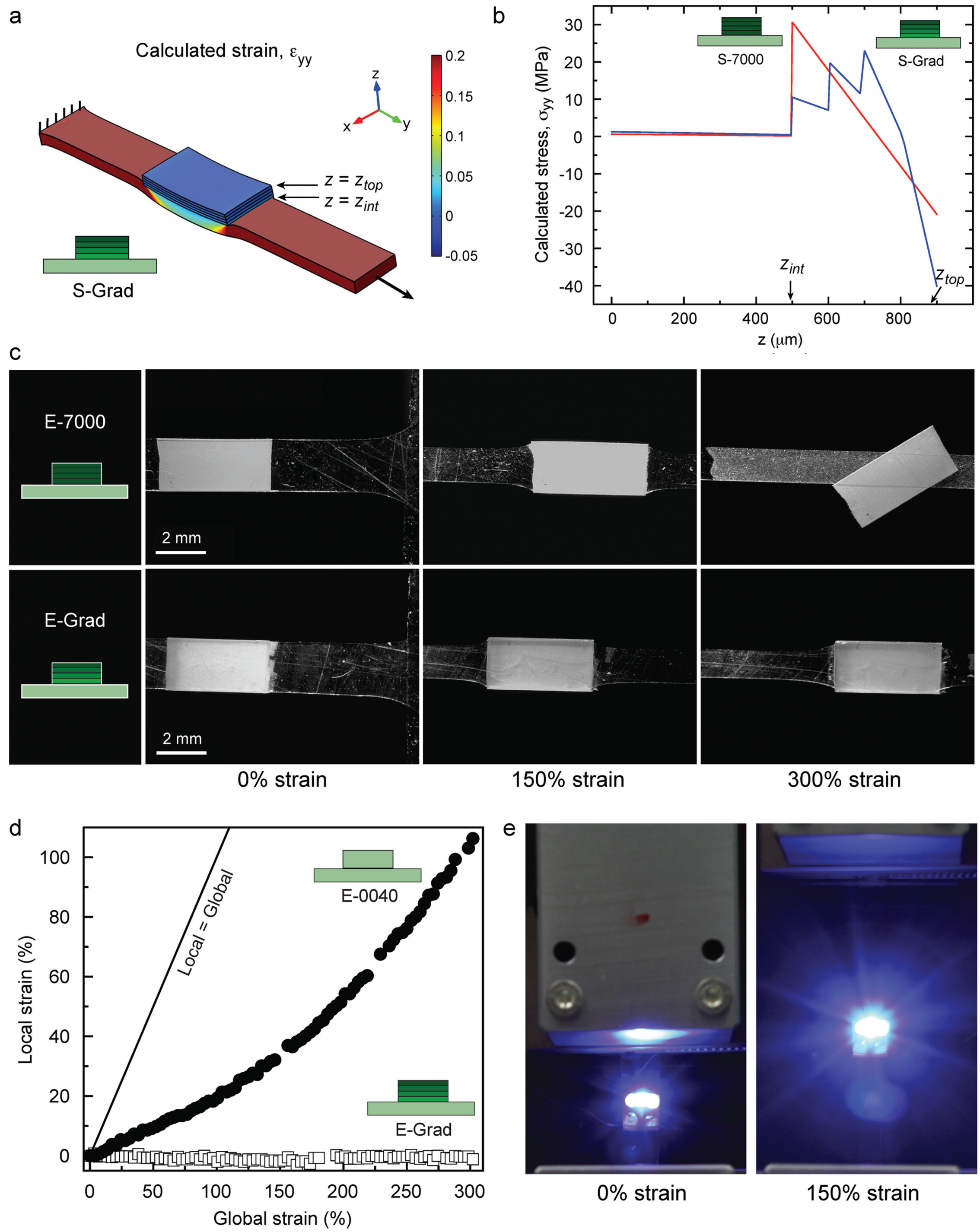

Figure 9. Design and mechanical response of a graded composite for stretchable electronics. a) Finite element analysis of a model composite comprising of a graded patch deposited on an elastomeric polyurethane substrate. The dark and light green colors in the cartoons represent locations of higher and lower elastic modulus, respectively, within the material. The mechanical analysis shows that the patch-substrate architecture leads to minimum strains on the top surface of the patch even upon large global deformations of the underlying substrate. b) Stress distribution through the thickness of the patch-substrate module, indicating that the graded architecture reduces peak stresses within the composite (S-Grad), as opposed to the high stress concentration observed for a homogeneously stiff patch (S-7000). c) Experimental validation of the high stretchability of the composite with graded patch, as opposed to the delamination observed for the reference material exhibiting high internal peak stress. d) Local strain on the top surface of the patch as a function of increasing global deformations of the underlying substrate, confirming the very low surface strains on the graded patch. e) Prototype of highly stretchable functional device consisting of a fragile light emitting diode (LED) deposited on the surface of the graded patch. The underlying substrate can be globally deformed more than 150% without failure of the electronic component. Reproduced with permission.[30] Copyright 2012, Nature Publishing Group.

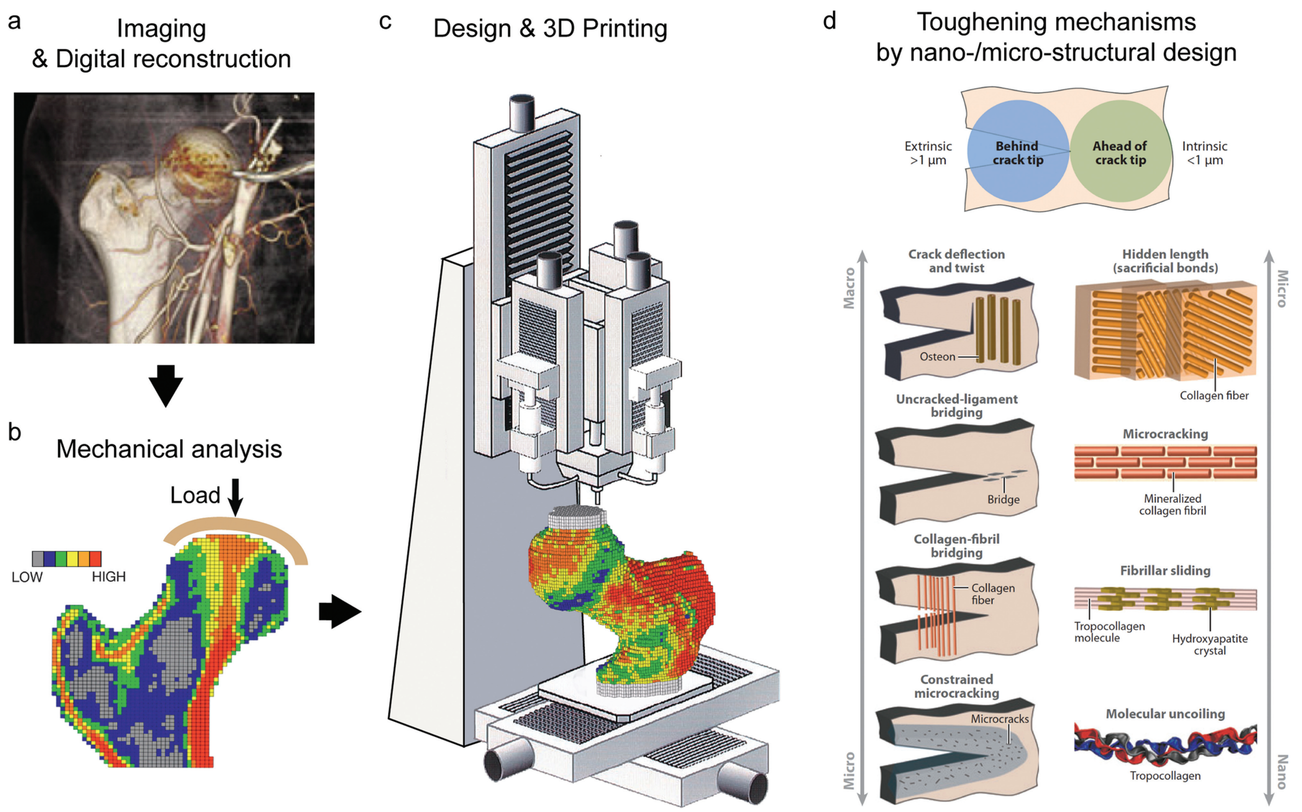

Figure 10. Envisioned processing route for the creation of bulk heterogeneous composites with locally tunable composition, structure and functional properties. The fabrication process is illustrated using a hip joint prosthesis as an example of a bulk structural component subjected to non-uniform mechanical loading. a) 3D imaging by micro-computed tomography and digital reconstruction of the structural component to be replaced with the graded composite. Adapted with permission.[39] Copyright 2013, Elsevier. b) Mechanical analysis using the finite element method to determine the distribution of stresses and strains throughout the component when subjected to typical loading conditions in use. Adapted with permission.[40] Copyright 2008, American Society for Bone and Mineral Research. c) 3D printing of bulk heterogeneous composite with local composition, structure and properties designed to provide optimum mechanical response to the non-uniform stress distributions predicted in the mechanical analysis. Adapted with permission.[33,40] Copyright 2008, American Society for Bone and Mineral Research; Copyright 2000, American Ceramic Society. d) Examples of nano-/microstructural designs that can potentially be employed at multiple length scales to increase the local toughness of the final heterogeneous composite. Adapted with permission.[15] Copyright 2010, Annual Reviews.

5. Conclusions and Outlook

Biological materials exhibit unique control over the local composition, concentration and orientation of building blocks at multiple length scales to best respond to the typically non-uniform mechanical load imposed by their natural environment. In the tooth, for example, anisotropic crystals are oriented in the direction of the mastication load and the concentration of inorganic reinforcement increases closer to the tooth's grinding surface. Similarly, the connection between soft tendon and hard bone in vertebrates is made strong and tough by tailoring the orientation of collagen fibers and the concentration of mineral phase throughout the material.

Recent developments in synthetic assembly processes have enabled the preparation of bioinspired synthetic materials with deliberately controlled concentration and orientation of reinforcing particles in a polymer matrix. While their architecture is far less elaborate than those of biological composites, artificial materials with unusual combinations of mechanical properties have been obtained by implementing in synthetic systems some of the design principles found in nature. For example, artificial composites combining high surface hardness and bending stiffness have been prepared following the architecture of mollusk shells and teeth. Likewise, reproducing synthetically the extreme gradients in elastic modulus found in the tendon-to-bone insertion site has enabled the fabrication of substrates for flexible electronics with unprecedented stretchability and delamination resistance. In contrast to the complex cell-mediated biomineralization processes used in nature, these purely synthetic approaches involve simpler, well-controlled steps and thus can potentially provide a scalable and reproducible platform for the development of composites with superior mechanical performance and functionalities.

Extending the biological concept of spatially tunable architectures to engineering and biomedical applications should lead to advanced graded composites with mechanical response tailored to optimize specific targeted functions. As opposed to the homogeneous and uniform nature of most existing structural materials, such bioinspired approach will lead to dynamic materials systems whose functional properties depend locally on the exact position within the 3D structure. In an Ashby diagram, the properties of a component would no longer be represented by a single point but by a cloud of points, each one of which representing the local property of a specific small volume (voxel) of the 3D structure. Achieving spatial control over the composition, microstructure and mechanical properties of such 3D structures should be possible by using well-established solid freeform fabrication technologies. The challenge consists in locally designing and assembling the composite architecture at multiple length scales to tune site-specific properties so as to optimize the global response of the graded material. The types of heterogeneous structures that can potentially be created will not only lead to more durable high-performance composites but will also open the possibility to produce materials with entirely new functionalities or with adequate functional properties under more stringent conditions. These may include new synthetic composites made with, for example, abundant or more environmental-friendly resources, light-weight constituents that minimize energy consumption, bioresorbable compositions that allow for full integration in the body or adaptive building blocks that enable tuning of the material's properties in response to variable external conditions. Such myriad of exciting possibilities will narrow the gap between synthetic and natural materials and eventually provide a new generation of synthetic "materials systems" with unprecedented properties and functions.

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