Biomaterials: Properties, variation and evolution

Mason N. Dean,[1],[*] Brook O. Swanson[†] and Adam P. Summers[*],[‡]

[*]Ecology and Evolutionary Biology, University of California, 321 Steinhaus Hall, Irvine, CA 92697–2525, USA; [†]Biology Department, Gonzaga University, Spokane, WA 99258, USA; [‡]Friday Harbor Labs, University of Washington, Friday Harbor, WA 98250, USA

This is an energizing time to be a biomaterials scientist and an appropriate moment to examine the state-of-the-art, current trends and future directions in biomaterials research. In nearly every area of mathematics, physics, and engineering, there is a movement toward using biology as a source of interesting questions. In addition, the tools available for materials research have progressed to where they can be usefully applied to the complex problems at the heart of biological systems. It is clear from our symposium not only that biology is reaping the benefits of this collaboration, but that there is reciprocal illumination when biology provides new systems, directions, and techniques that drive related fields forward. In this short introduction to the symposium, we will highlight some of the trends that are emerging and point out some of the larger lessons that can be drawn from the examples that were presented.

To adapt Otto Schmitt's opinion of biophysics, a symposium on biomaterials is less a focus on a single discipline than a celebration of a point of view (Harkness 2002). The studies here are odd bedfellows: they share little in terms of individual technique, focal taxon, or ecofunctional niche. However, they all take advantage of the synergy at the interface between the materials sciences and biology. Fields as disparate as surface chemistry, biology, and materials science converge in their interest in biomaterials; unfortunately, researchers in one discipline are often not aware of, or informed about, the techniques and perspectives of another. We feel this has largely been a problem of insufficient contact between different disciplines and also the (necessarily) restrictive scopes of most research programs. Investigations have focused on either proximate (e.g., nanostructural and microstructural relationships with material properties) or ultimate questions (e.g., ecological and evolutionary impacts of material variation), with the connecting flows of information inadequate to unify the levels into a broader examination of performance.

We are excited to present this symposium at a time when disciplinary divisions are blurring and biomaterials researchers of strikingly different backgrounds are working toward common ends and languages. The volume of biomaterial data is reaching new critical masses, for instance, allowing us to compare material stiffnesses across tissues, from nacre to bone to cartilage, and physical science tools (such as testing techniques for nanomaterials and Finite Element Analysis) are increasingly accessible to comparative biologists. Evolutionary biologists and physiologists are collaborating with engineers and computer scientists to study skeletal stresses in biting and running, deformations in wings and fins, and gripping in toes and tails. The scales of investigation spanned by these collaborations and the ever-increasing resolution of testing and imaging techniques stretch the scope of possible questions from genetics and protein interactions up through material and organismal performance and evolution.

Modern biomaterials science, then, is a flavor of systems biology—a holistic approach to examining the functions and interactions of natural materials at multiple scales and from the perspectives of multiple disciplines. It is our hope that the assemblage of topics, presented in the contexts of organismal biology and evolution, will help to broaden the often mechanistic viewpoint of materials science and promote physical science approaches to biology.

Extreme performance

We see the recent upswing in biomaterials research as shaped by two things: quantification of the properties of high-performance biological materials and

structures, and the manufacture of high-profile man-made analogs. Of course, humans have exploited the performance benefits of natural materials for centuries, using plant and animal tissues and products in their native or near-native forms for shelter, weapons, tools, and clothing. Our successful harnessing of biological materials arose from a largely qualitative understanding of functional niches: hard tissues support compressive loads, fibrous tissues are good for pulling, and waxes are waterproof. These intuitions surely grew in part from the observations of early anatomists and naturalists, who had astute eyes for intriguing behaviors and morphological novelties (e.g., Thompson 1917). Until relatively recently, the engineers who might have described the mechanical properties of biomaterials were busy investigating problems of material support from another perspective by asking "How do we build stiff or strong or resilient synthetics?" rather than searching for existing examples of materials with particular properties.

In the past several decades, the advent of more accessible testing techniques and unifying reference texts (e.g., Wainwright et al. 1976; Gordon 1978; Vincent 1990; Ashby et al. 1995; Gibson and Ashby 1999; Currey 2002; Fratzl and Weinkamer 2007; Chen et al. 2008; Meyers et al. 2008) has helped bridge the gap between biological and engineering/materials science techniques, establishing a range of shared tools and terminologies. For example, the availability of devices for testing nanoscale materials allowed an examination of a suite of material properties for dragline silk at an evolutionary scale (Swanson et al. 2009), correlation of radiodensity with stiffness in healing bone (Leong and Morgan 2009), and dynamic properties of individual chondrocytes (Ortiz 2009). Through this two-way disciplinary communication, the relevant materials tests can be contextualized correctly according to knowledge of organismal biology (e.g., typical loading conditions; Azizi et al. 2009) and then examined in the larger framework of natural and synthetic materials (e.g., How do the material properties of biological polymer composites compare to those of engineered ones?; Dudek et al. 2009; Ewoldt et al. 2009; Gorb 2009; Smith et al. 2009). In this broadest of comparisons, natural materials appear at first to be not particularly astounding: biological materials and composites are comprised of a comparatively limited array of materials, and their basic polymeric and mineral subunits are surprisingly weak (Mayer and Sarikaya 2002; Wegst and Ashby 2004; Chen et al. 2008; Meyers et al. 2008). Even natural composites do not attain the absolute performance

qualities of synthetic materials—no mollusk shell is as stiff as an engineered ceramic; no spider silk is as strong as a similar diameter of steel (Wegst and Ashby 2004; Meyers et al. 2008).

However, it is within the confines of these limitations that the material properties are impressive, and this is precisely what makes them interesting to engineers and biologists. Even though biomaterials are assembled from a restricted range of elemental building blocks, at physiological temperatures and in benign aqueous solutions, they straddle a staggering span—roughly five orders of magnitude—of stiffnesses and strengths. Although the properties of biomaterials fall within the range of those of synthetics, the latter are 30–300% denser than the densest biologicals (Wegst and Ashby 2004; Meyers et al. 2006, 2008). Biomaterials attain nearly the same performance as synthetics but at a minimum of weight, making them incredibly mechanically efficient; the tensile strength of spider silk is far greater than that of steel if the strands are of the same mass (Wegst and Ashby 2004). For all the high stiffness and toughness of biomaterials, we cannot forget that these materials are grown, that organisms must assemble them "on the fly" and from the limited set of biological constituents at hand.

Multipurpose

Man-made materials suggest a series of mechanical rules. Some properties are usually tightly correlated—stiffness with strength, toughness with deformability—whereas others are inversely related, such as damping with stiffness, and stiffness with ductility (Wainwright et al. 1976; Gordon 1978). Biomaterials break from these relationships by virtue of their composite nature; they are often less intriguing for a single extreme property than for their combinations of high-performance traits (Meyers et al. 2006). Many hard biological composites, such as nacre and bone, are both stiff and tough (Currey 1999; Mayer 2006; Walter et al. 2007; Chen et al. 2008), resilin is incredibly extensible and resilient (Dudek et al. 2009), and some spider silks can be both highly deformable and tough (Gosline et al. 1999; Swanson et al. 2009). That biomaterials typically have superior properties (e.g., toughness, stiffness) than their constituents is an indication of their structural and compositional complexity (Fratzl 2004; Mayer 2006; Munch et al. 2008). A block of bone is nearly as stiff as a monolithic block of hydroxyapatite, but it is 1000 times more difficult to generate a crack in bone (Wegst and Ashby 2004). In the nacre of mollusk shells, the layering of

aragonite plates with a small amount of organic material, like a thin layer of mortar in a brick wall, results in a material 3000–10,000 times tougher than the aragonite itself (Jackson et al. 1988; Kuhn-Spearing et al. 1996; Gries et al. 2008; Barthelat 2009).

Biological materials achieve their curious compound properties through inventive combinations and arrangements of component materials: the toughness of biological ceramics like bone, for example, is a function of the organic collagen framework that supports the inorganic mineral phase (Currey 2002; Fratzl et al. 2004). This explains why man-made mineralized materials are as stiff as bone, but lack bone's toughness and are brittle (Wegst and Ashby 2004; Munch et al. 2008). The cartilaginous skeleton of sharks and rays is a composite of uncalcified cartilage surmounted by calcified cartilage tiles; the layering of these tissues is mechanically synergistic, providing the skeleton a high level of damping and stiffness, a combination of properties unavailable to the individual phases of the tissue (Dean and Summers 2006; Dean et al. 2009).

Biomaterials can be powerful systems for investigating interesting and broad compound performance spaces. Engineers define classes of man-made materials by plotting one material property versus another, the resulting clusters demarcating ceramics, elastomers, and cellular solids (Ashby et al. 1995; Wegst and Ashby 2004). It is striking that the clouds for metals, bulk minerals, and ceramics are quite compact relative to the clouds for polymers, and were there sufficient data on biomaterials, we imagine the range of properties would dwarf them all (Ashby et al. 1995; Wegst and Ashby 2004). This is in part because biomaterials are composites of polymers and mineral salts, and also because there is an important fluid phase that extends the simple response to load into the time domain. In fact, in considering these fluid contributions, biomaterial scientists sometimes learn fundamental things about how to test materials (Ewoldt et al. 2009). A persuasive example of the broad span of properties encompassed by just a single biomaterial is that of alpha keratins (Meyers et al. 2008; Fudge et al. 2009). When in aqueous suspension as intermediate filaments the fibers are compliant, but in fingernails, hoofs, and horns, this same material is no longer water-soluble and is 11 orders of magnitude stiffer. Intermediate stiffness is seen in the partially dehydrated alpha keratins found in whale baleen (Fudge et al. 2009).

A complicating factor in performance tests of biomaterials is that the underlying material heterogeneity is almost always organized in some way that leads to anisotropic responses to loading (Wainwright et al. 1976; Currey et al. 1994; Rho et al. 1998; Fratzl 2004; Vincent and Wegst 2004). The orientation of trabeculae in spongy bone, helical protein structures in spider silk, and collagen fibers in skin and tendon, bias the response of the material to loads from particular directions. This almost always has biological relevance, as nicely demonstrated in Azizi et al.'s (2009) analysis of aponeuroses and the effect of biaxial loads on material strain. Plant tissue is also a composite of fibers in a polymer matrix. The orientation of these fibers has profound effects on the response of the tissue to load and is the morphological root of the tissue's "smart" anisotropy, enabling passive directional growth and movement (Burgert and Fratzl 2009).

Hierarchy

The complexity of biological materials is not just in their components and gross organization, but also in their fractal nature: at each size scale there are characteristic morphological patterns (Wainwright et al. 1976; Vincent 1990; Rho et al. 1998; Fratzl 2004; Fratzl and Weinkamer 2007). For example, at the nanoscale, the mammalian limb bone consists of collagen fibrils reinforced with mineralized plates but at the micrometer scale, the fibro-mineral material is organized into layers or concentric tubes with a system of communicating channels (Fratzl et al. 2004; Seto et al. 2008). These tissues are arranged at the millimeter scale into structures—a compact bony layer or struts distributed within a larger-scale cancellous network—and relegated to specific portions of the limb bone (Rho et al. 1998; Currey 2002). Finally, the skeletal element as a whole approximates a single, solid beam. These levels are not only morphologically distinct but also contribute to emergent material properties and performance in ways that are not possible to predict from knowledge of any one level (Rho et al. 1998; Fratzl 2004; Fratzl and Weinkamer 2007).

It is not surprising then that the studies in this volume address very different levels of organization that characterize what the authors consider to be the "material" level of organization. Fudge et al. (2009) focus on the properties of intermediate filaments in hagfish slime at the expense of the mechanics of whole slime (Ewoldt et al. 2009; Smith et al. 2009), but Azizi et al. (2009) test structural-level effects of aponeurosis rather than the properties of their collagenous subunits. Whereas Leong and Morgan (2009) examine indentation moduli of the variety of skeletal tissues forming bone calluses, Ortiz

(2009) investigates the nanomechanics of the constituent cells of those tissues. What this suggests to us is that it is vital to understand the hierarchical nature of biomaterials and that we can usefully investigate them at a single size scale as long as we have a clear idea of the limitations that this view imposes.

At the heart of hierarchy is a jarring realization for biologists: the basis for the emergent properties, those that matter for whole animal performance, may be rooted in morphology at size scales that have typically been the province of the engineer (Gao et al. 2003). On the other hand, the engineer hoping to copy the emergent properties must realize that simple mimicry of any one size scale will not emulate the desired material or structural-level performance; it is only in the context of the larger size scales, integrating the mechanical effects of smaller structural levels, that the material shines (Wegst and Ashby 2004; Meyers et al. 2006). In our efforts to approximate the low density–high performance of biological tissues, there is a clear disconnect in our abilities to copy morphologies at small (material) and large (structural) size ranges (Wegst and Ashby 2004). This is reasonable: while we can construct a shape that affects the flow of fluids in the same way as a boxfish or seedpod, our technologies do not yet allow rendering of the smallest biological morphologies or the self-healing or growth response to load that characterize most biological materials, although "smart" engineered structures are likely a wave of the future (Mayer and Sarikaya 2002; Bar-Cohen 2006; Vincent et al. 2006; Meyers et al. 2008).

New directions

Our symposium also highlights some areas that are ripe for future investigation, both by virtue of new technologies and because we are gaining a clearer picture of the relative importance of factors that determine performance of biomaterials. We feel that in the near future some of the most profound advances in biomaterials research will address issues of "control" in tissues, either at more macroscopic and ultimate scales (e.g., management of complex loads, biomimicry of actuation mechanisms) or at the proximate, nanostructural level (e.g., the genetic roots of variation in materials).

Among the most important emerging areas is the recognition of the viscoelastic and/or poroelastic nature of virtually all biological materials (Wainwright et al. 1976; Weinbaum et al. 1994; Gibson and Ashby 1999; Ewoldt et al. 2009). The time-dependent and volume-dependent responses to load of these materials have not been well explored (with the exception of the orthopedic community's investigations of cartilage; e.g., Park et al. 2004) but are likely to be of great biological importance. We are also woefully ignorant of the magnitude and direction of biological loads, a situation that should be addressed as miniaturized sensors, and as telemetered collection of data become more widely available. Here we can learn from the biomedical community, which has pioneered devices for the measurement of microscale strain as well as implantable devices (e.g., Townsend et al. 1999; D'Lima et al. 2005). The complexity of biological loads, which often have three orthogonal components, is also an area that will be better understood, probably though the use of computer modeling (e.g., Finite Element Analysis, FEA; Ross et al. 2005; Grosse et al. 2007).

There is also great potential in a foundational property of biomaterials: growth. Because all biomaterials have an ontogenetic history, there is an opportunity to understand both hierarchical complexity and anisotropic nature by examining their genesis (e.g., Carter 1987; Cartwright and Checa 2007; Yao et al. 2008). In looking at growth series for biomaterials, we can begin to deduce rules by which new tissue is laid down and organized and old tissue is remodeled. In particular, this ontogeny is happening while the material is in use and so growth presents an opportunity for understanding how adaptable materials might be made. Beyond emulating a material's properties, we might begin to mimic its generation. This view of biomaterials could be built on a scaffold of DNA, exploiting a genetic understanding of the growth process and peptide-material levels of control to revolutionize the manufacture of biomimetic materials (Tamerler and Sarikaya 2007).

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Conflict of interest

None declared.

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