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Biomateriomics

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Biomateriomics

With 159 Figures

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For Deborah, LOML—S.W.C.

To my family—M.J.B.

Preface

The holistic study of biological material systems has emerged as an exciting area of research. While such systems are commonly complex, we frequently encounter similar components—universal building blocks and hierarchical structural motifs—which result in a diverse set of functionalities. Similar to the way music or language arises from a limited set of musical notes and words, the relationships between form and function can be exploited in a meaningful way by recognizing the similarities between Beethoven and bone, or Shakespeare and silk. Through the investigation of material properties, examining fundamental links between processes, structures, and properties at multiple scales and their interactions, materiomics explains system functionality from the level of building blocks. *Bio*materiomics specifically focuses the analysis of the role of materials in the context of biological processes, the transfer of biological material principles towards biomimetic and bioinspired applications, and the study of interfaces between living and non-living systems. Inevitably, materiomics also holds great promise for nanoscience and nanotechnology, where material concepts from biology might enable the bottom-up development of new structures and materials or devices.

The challenges of biological materials are vast, but the convergence of biology, mathematics and engineering as well as computational and experimental techniques have resulted in the toolset necessary to describe complex material systems, from nano to macro. Applying biomateriomics can unlock Nature's secret to high performance materials such as spider silk, bone, or nacre, and elucidate the progression and diagnosis or the treatment of diseases. Similarly, it contributes to develop a *de novo* understanding of biological material processes and to the potential of exploiting novel concepts in innovation, material synthesis and design. With this impetus, the field of biomateriomics attempts to reconcile all aspects of a biological material system—from universal motifs of nano-scale building blocks to macro-scale functional properties—with a focus on studying the mechanisms of deformation and failure by utilizing a multi-scale materials science approach.

This book encompasses the current work reflective of many review articles and journal papers under a common banner, and makes this exciting field of research accessible to the broader engineering and science community. It should provide a valuable reference for engineers, materials scientists, and researchers in both academia and industry and will hopefully ignite extended discourse and inquiry. Indeed, many technical details are omitted *in lieu* of presenting key concepts and simple ideas. Many of the examples are adapted from studies carried out by the authors of this book, and some of the discussion should therefore not be considered as a comprehensive review with respect to the wider range of available results. Rather, they represent a set of specific illustrative examples of materiomics, including theoretical aspects, associated principles, and applications. The primary text provides an overview of the field of materiomics, including earlier work and future opportunities and intellectual challenges for research, and is organized into three main parts:

Part I: A Materiomics Perspective provides an introduction to biomateriomics. This is especially important given that the entire field is being developed and potential applications explored. The outside resources and investigations we henceforth refer were never intended to encompass materiomics *per se*—but yet contribute to its foundation and future progress. Admittedly, we are standing on the shoulders of others and declaring their work to be in a newfangled (and as yet unproven) field. Therein lays the stimulus for such a paradigm: only by the convergence of disparate fields can materiomics find its worth—from the astute combination of advancements in chemistry, biology, physics, materials science and engineering (further discussed in Chap. 1: Introduction). Such a combination is clearly beyond the capabilities of any individual (including these humble authors) but clearly achievable by the scientific community. The chapters constituting Part I present our interpretation of a *materiomic perspective*. The fundamental goals need only to be defined—our intent is to shed light on those goals.

For these reasons, we base this book's content around our own experience—specifically, the mechanical characterization of biological materials founded at the molecular level. We shall see that this is just one aspect of a complex *materiome*, and far from a complete picture desired (and implied) by the "omics" suffix (there is a more detailed discussion of this in subsequent chapters). Nevertheless, a focus on atomistic and molecular mechanics has various advantages:

1. It is based on fundamental principles of physics and chemistry, which are ultimately defined by quantum mechanics, providing a common starting point regardless of the specific material system(s) considered.
2. It is representative of some of the most relevant and critical topics and, most importantly, challenges in the field of biomaterials.
3. It allows us to present some case studies, which, although based on a particular scale, can easily be used as frameworks for other problems.
4. It enables other researchers to contribute to the field of materiomics, in addition to the molecular perspective emphasized here.

If our objective was to encompass all disciplines, bridge all fields, and tie together all scales of biological materials from the atomistic sequence of amino acids to a functional biological tissue or organ—we would never come to completion. Instead, we hope that through a focus on simple examples, the potential of a more holistic perspective of biological materials—discovering the relations between structure and function across multiple scales—will be apparent. As such, Part I presents the emerging field with the associated scope, thematic paradigms, and an outline of essential concepts (Chap. 2: The Materiome), as well as an in depth discussion of biological materials as the motivation for the development of a materiomics framework (Chap. 3: The Challenges of Biological Materials), and the unifying categorization and abstraction necessary for modeling and understanding such complex materiomic systems (Chap. 4: Universality-Diversity Paradigm: Music, Materiomics, and Category Theory).

Part II: Methods and Tools discusses the ever-expanding toolset required for materiomic investigations. A selection of the most promising strategies to investigate materiomics and analyze the properties and behavior of complex materials are reviewed, with examples, case studies, and theoretical background when appropriate.

In order to realize the promising opportunities that arise from an improved understanding of complex biological materials several critical challenges must be overcome. Up until now, theories fully describing hierarchical biological materials are still lacking. Only recently has the understanding about how specific features at distinct scales interact, and for example, participate in mechanical deformation, begun to emerge for complex biological systems. In recent years, the development of new quantitative experimental, analytical, and computational methods have lead to advances in understanding of some details of complex biological and synthetic systems. Theoretical, numerical, and experimental methods now enable the investigation of nanoscale mechanics of materials using quantitative analysis techniques—an area referred to as "nanomechanics". For example, development and application of nanoindentation, atomic force microscopy, and other tools enables scientist to probe the origins of mechanical properties, with forces in the range of piconewtons, and at scales approaching that of individual atoms (Ångstroms) and molecules (nanometers). At the same time, computational methods, computational power, and theoretical approaches have led to significant advances in addressing nanomechanics from a first principles perspective. This combination of experiment, theory, and computation has proven to be very fruitful, and could lead to major advances in materials theories and engineering.

The most recent innovations have occurred in the field of nanotechnology and nanoscience, where cross-disciplinary interactions with the biological sciences present an enormous opportunity for innovative basic research and also technological advancement. Such advances could enable us to provide engineered materials and structures with properties that resemble those of biological systems, in particular the ability to self-assemble, to self-repair, to adapt and evolve, and to provide multiple functions that can be controlled through external cues. However, despite significant advancements in the study of biological materials in the past decade, the fundamental physics of many phenomena in biology continue to pose substantial challenges with respect to model building, experimental studies, and simulation. As materiomics is founded by a combination of multidisciplinary theories and multiscale techniques, approaches that integrate *experiment* and predictive *simulation* are essential to this new paradigm of materials research.

The behavior of biological materials, in particular their mechanical properties, are intimately linked to the atomic microstructure of the material. Different mechanisms operate at larger length scales, where the interaction of extracellular materials with cells and of cells with one another, different tissue types and the influence of tissue remodeling become more evident. The dominance of specific mechanisms is controlled by geometrical parameters, the chemical nature of the molecular interactions, as well as the structural arrangement of the protein elementary building blocks, across many hierarchical scales, from nano to macro. Thus, materiomic investigative approaches must also consider multi-scale schemes, both experimentally and computationally, to link hierarchical effects and mechanisms.

Much of the functionality that biological materials provide occurs through mechanical contact and behavior. Therefore, to completely understand the structure-property-functionality relationships of biological materials it is necessary to quantify the mechanical behavior and influences on biological and *de novo* materials. Thus, Part II includes the means of mechanical investigation, including experimental methods (Chap. 5: Experimental Approaches), computational methods (Chap. 6: Computational Approaches and Simulation), and the interpretation of results (Chap. 7: Mechanical Characterization in Molecular Simulation). Although descriptions of techniques are to be presented, with relevant case studies and applications, specific technical details (*i.e.*, application of molecular dynamics) are only outlined, with commentary of strengths and weaknesses of various approaches, and their applicability at different scales. When appropriate, suggestions will be made for more detailed texts and references in the field. In other words, the objective of the text is not to provide an in-depth handbook for analytical procedures, but rather to discuss the various means of biomateriomic investigation. As anticipated, biomateriomics requires an extensive "toolbox".

Part III: Applied Materiomics illustrates how we can immediately benefit from biomateriomic approaches. Application of materiomic principles and approaches has already been undertaken on a variety of biological systems throughout different fields of research. The combination of high-level structural control of matter as achieved in nanoscience and nanotechnology, multiscale analytical techniques, and integration of living and non-living components into systems and interfaces will lead to the development of new technologies that utilize the advantages of both micro and nanotechnology with the principles of biology. With an inevitable merger of material and structure, with increasing complexity, materials start to resemble dynamic systems or machines, so that the borderlines between conventional concepts such as "machine" and "material" also start to disappear. Such approaches have been used systematically by Nature for millions of years. However, their systematic exploitation for technological applications has so far been severely hindered due to lack of understanding of how to link the atomistic scale with material structure and device properties and function. Like all endeavors, we only get better with practice!

Part III discusses practical applications of materiomic techniques and approaches with three main focuses. Fundamentally, materiomics provides an integrated and holistic approach, advantageous in the investigation of complex biological material system phenomenon and system characterization (Chap. 8: Unlocking Nature: Case Studies). Moreover, materiomics can facilitate the development of novel diagnostic tools for disease and afflictions with mechanistic symptoms, predicting what components and functionalities "fail" under minute changes in material and structural conditions (Chap. 9: Pathological Materiomics). Finally, biomateriomics has a role in the design of *de novo* materials, or the synthesis and manipulation of biological materials, materiomic engineering, and nanomedical devices (Chap. 10: Synthesis and Design). Using natural processes as a guide, substantial advances have already been achieved at the interface of nanomaterials and biology.

Irrespective of the challenges still present in a thorough investigation and complete characterization of the materiome as discussed by prior chapters, current experimental and practical approaches exist that allow the immediate application of materiomics to real problems. This branch of materiomics, termed *applied materiomics*, is still in its infancy, yet has already demonstrated potential as a valuable basis for material design. A materiomic approach is likely to become an integral part of nanomaterials manufacture—where molecular assembly is control to attain macroscale behavior—requiring a deep understanding of individual molecular building blocks, their potential structures, assembly properties, dynamic behavior, and multiscale propagations. We hence focus discussion on broad areas of application that are becoming increasingly widespread (throughout different disciplines) and can be encompassed by the common field of applied materiomics. The applications, undoubtedly, are as variegated as Nature. The text is closed with an outlook to future opportunities in Chap. 11: The Future of Biomateriomics.

The discussions presented in this book are intended to be both a review of current materiomics research as well as a pedagogical discourse. While we embrace the term to encompass our own work, we believe the worth of materiomics will naturally emerge from the shared contributions of many scientists and research groups. It is not a term to lay claim, but a label to encompass a new perspective of chemistry, biology, and materials science. Indeed, any "closed-form" interpretation of materiomics will limit both the growth and potential of materiomics research. As biomateriomics is a relatively new field, it behooves us to include discussion to help define and explicate both the intent and scope with analogous examples, illustrating the integrative nature, universality, and benefits and impact of a materiomics approach. The perspectives and overviews presented throughout this book are intended to provide a broad overview. Further details can be found in the papers cited and recommended readings.

Most importantly, completing this book would not have been possible without the help and support of numerous people and institutions. The authors are indebted to all who have contributed to this book in some way. In particular, sincere gratitude goes to the many students and researchers who have collaborated with the authors within the Laboratory of Atomistic and Molecular Mechanics (LAMM) at MIT, whose enthusiasm and excitement regarding materiomics are unmatched. We are also thankful for many discussions with colleagues and friends that contributed to the development of this book. We gratefully acknowledge the support from the National Science Foundation, Army Research Office, Office for Naval Research, Defense Advanced Research Projects Agency (DARPA), Air Force Office for Scientific Research, and the Massachusetts Institute of Technology.

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Part I
A Materiomics Perspective

Chapter 1
Introduction

Abstract Biomateriomics refers to the holistic study of biological material systems. We can predict the performance of engineered materials in engineered systems, but there is an inherent disconnect when investigating Nature's materials, with little understanding of how functionality arises from both the material and complex structure with properties and interactions across scales. New developments enable a new perspective through the convergence of many scientific disciplines, and advancements in nanotechnology empower us to investigate material systems from the "bottom-up". If we hope to learn from Nature, we need a new holistic perspective: an "omic" approach. We begin with a definition and introduction of biomateriomics, presenting the emerging field with the associated scope, and thematic paradigms, to the tools required for investigations, to ongoing and future applications.

All sciences are connected; they lend each other material aid as parts of one great whole, each doing its own work, not for itself alone, but for the other parts; as the eye guides the body and the foot sustains it and leads it from place to place.

Roger Bacon, Opus Tertium (1266–1268)

1.1 Introduction

The introductory quotation from the thirteenth century is ideally suited for an introduction to *biomateriomics* for two reasons. Primarily, it encapsulates the intrinsic cooperativity of modern science. Previously disparate research fields now commonly borrow concepts, ideas and approaches from each other and collaborations are deemed essential for technological innovation and to tackle the greatest challenges. Biological systems, for example, are no longer limited to biologists and chemists—engineers design biomimetic devices, while materials scientists collaborate with medical researchers to develop bio-compatible implants. In the world of academia, interdisciplinary efforts are no longer a rarity, but are the current *status quo*.

Secondly, the words of Roger Bacon—whether referring to sciences in general or the human body—encompasses a popular idiom that most of us take for granted:

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the whole is greater than the sum of its parts. It is well agreed that we (as human beings) are more than just a combination of limbs, a cardiovascular system, and a functioning brain (among other things, of course). Even a cursory glance can deduce the difference between a dog and cat, which can be described by similar "components". Yet, such a high-level perspective is commonly lacking in more technical problems. While we can easily determine the "whole" for some systems, for others we are limited to a view of the "parts"—we are missing the proverbial *forest* to study the *trees*.[1] Such intellectual barriers are present in a wide variety of scientific challenges—the search for a grand unified theory in physics for example—in which each part of the problem is beyond the capabilities of a single researcher or field. The focus of this text is on yet another fundamental problem—the complexity of biological materials.

1.2 The Unpredictable Nature of Materials

Biological materials—neither steel nor concrete—are the most abundantly used materials on earth, yet we know (relatively) little about how they function. They are the main constituents in plant and animal bodies and have a diversity of functions. While biologists and materials scientists alike are impressed by the mechanical properties of silk [1–7] or the toughness of bone [8–11], there are difficulties in replicating the successes of Nature in a synthetic manner. While we can approximate such materials, they are often not as elegant as there natural counterparts. The key difference lies in the long-term "product development" stage of Nature. Whereas we attempt to design a material to suit a particular application (*i.e.*, choosing a material such as silicon to make computer chips due to its semiconducting properties, for example), Nature has implemented the simultaneous development of material and function (more commonly known as *evolution*). A complex biological material like bone was not "selected" to be a supporting structure for our bodies—it has specific material properties and characteristics to serve its own (intended and evolved) function. Unlike engineering materials, the distinction between material *properties* and material *function* is lost. The subtle difference between material function and application is further discussed in Chap. 2: The Materiome.

Another major difference between materials from Nature and engineering is in the way they are made. While an engineer selects a material to fabricate a part according to an exact design, Nature goes the opposite direction and grows both the material and the whole organism (a plant or an animal) using the principles of (biologically controlled) self-assembly—this is more commonly referred to as *growth*. Moreover, biological structures are even able to remodel and adapt to changing environmental conditions during their whole lifetime. This control over the structure

[1] We note that the reductionist approach of science (studying the *trees*) has continuing success in the explanation of fundamental phenomena in physics, chemistry, and biology, and the current discussion is not intended to be a criticism, but rather a complementary perspective.

at multiple scales is certainly the key to the successful use of (relatively) soft protein materials as robust structural components.

The consequence, of course, is that we must consider intended functionality in the investigation and design of biological systems and novel biomaterials. While easy to say, this task is complicated by the complex, hierarchical nature of such materials [12]. Functionality is ultimately rooted at the molecular scale [13, 14]. Through recent advancements in single-molecular assays, analytical chemistry, and computational approaches, we have made great strides in determining what a biological system is composed from the molecular level. Individual molecules and amino acids can be deduced *via* nuclear magnetic resonance (NMR) spectroscopy and segments of DNA and other protein structures can be sequenced. It is relatively easy to compile such information. We are collecting a vast amount of data on such materials—but how can we combine what we know (*i.e.*, what we measure) with what we think we know (*i.e.*, prediction of function)?

With all these advancements, we are unable to predict the behavior of a particular molecular sequence. As a result, we cannot engineer synthetic proteins designed for a specific function or application (such as attacking cancer cells or tissue regeneration). We have copious amounts data, but are unable (at this point) to use it. Unlike traditional structural engineering systems—we can predict the behavior of a building by the analysis of steel trusses, for example—there is an inherent disconnect in our ability to predict functional and mechanical behavior for biological systems (see Fig. 1.1). This has been exemplified by the difficulties in predicting structures from single protein folding—that is, the prediction of secondary, tertiary, and quaternary structure from a primary protein sequence (further discussed in Chap. 3: The Challenges of Biological Materials). Unlike in engineered structures, at the molecular level, the difference between material properties and structural function is not clear.

1.3 Differences Between Material and Structure

What is the fundamental difference between material and structure? This question can be alternatively posed, from a structural engineering perspective, *"What constitutes a structure?"* Popular answers will undoubtedly encompass bridges and buildings—the Golden Gate Bridge or the Empire State Building are undeniably structures in the traditional sense of the word. At such scales, it is also very easy to label what the "materials" are—a bridge may be build of concrete and steel, for example. Things get a little fuzzier as we reduce the size—where does the structure turn into the material? If we consider the glass sponge *Euplectella*, a deep-sea, sediment-dwelling sponge from the Western Pacific [15–17], we see a sophisticated hierarchial structure that performs a multitude of functions, yet is predominantly composed of the same constituent material—*silica*—which is intrinsically brittle. It has been shown that spicules in siliceous sponges exhibit exceptional flexibility and toughness compared with brittle synthetic glass rods of similar length scales [18, 19]—but why? Function is derived from the structure, but at what scale can we separate the material from the structure?

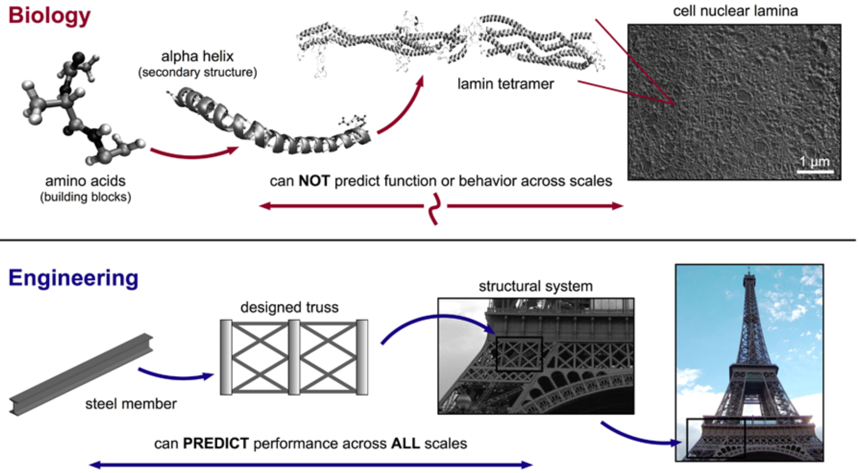

Fig. 1.1 Example of the inherent disconnect between biological systems and traditional structures. In biology, if we consider a single scale, one phase, with perfect knowledge of composition and sequence, in controlled conditions, we can make predictions. Here, with knowledge of the constitutive amino acids, we can predict an alpha-helical structure for short polypeptide sequences, and its corresponding properties (such as strength). We cannot (yet), however, accurately predict large scale behavior of larger protein assemblies, such as protein networks, let alone the structural role such materials play in a cellular structure (*e.g.*, the nuclear envelope) or in the context of other biological properties. We utterly fail in real-world applications—the exact opposite of the goals of engineering! For engineering, we can design the components of a structure with reliable and repeatable accuracy—the performance of a fabricated steel member can be utilized in the design of a truss, which is subsequently implemented in a structural system

The skeletal system of *Euplectella sp*. (as shown in Fig. 1.2) shows an intricate, cylindrical cage-like structure with lateral (so-called, oscular) openings. At the macroscale, the cylindrical structure is reinforced by external ridges that extend perpendicular to the surface of the cylinder and spiral the cage. The surface of the cylinder consists of a regular square lattice composed of a series of cemented vertical and horizontal struts, each consisting of bundled spicules aligned parallel to one another, with diagonal elements positioned in every second square cell. Cross-sectional analysis of these beams at the micrometer scale reveal that they are composed of collections of silica spicules embedded in a layered silica matrix. The constituent spicules have a concentric lamellar structure with the layer thickness decreasing from the center to the periphery. These layers are arranged in a cylindrical fashion around a central proteinaceous filament and are separated from one another by organic interlayers. At the nanoscale the fundamental construction unit consists of consolidated hydrated silica nanoparticles (50 to 200 nm in diameter). The assembly of a macroscopic, mechanically resistant cylindrical glass cage is possible in a modular, bottom-up fashion comprising at least *seven* hierarchical levels, all contributing to mechanical performance.

Clearly, we need to begin at some fundamental level. The question is at what scale? For the *Euplectella* sponge, we may want to focus on the constitutive ele-

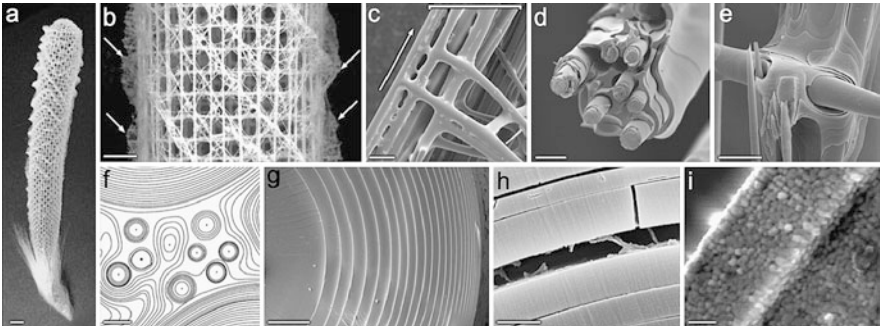

Fig. 1.2 Structural analysis of the mineralized skeletal system of *Euplectella*: (**a**) Scale: 1 cm; photograph of the entire skeleton, showing cylindrical glass cage; (**b**) Scale: 5 mm; fragment of the cage structure, showing the square grid lattice of vertical and horizontal struts with diagonal elements; (**c**) Scale: 100 µm; scanning electron micrograph (SEM) showing that each strut (enclosed by a *bracket*) is composed of bundled multiple spicules (the *arrow* indicates the long axis of the skeletal lattice); (**d**) Scale: 20 µm; SEM of a fractured single beam revealing its ceramic fiber-composite structure; (**e**) Scale: 25 µm; SEM of the junction area showing that the lattice is cemented with laminated silica layers; (**f**) Scale: 10 µm; contrast-enhanced SEM image of a cross-section through one of the spicular struts revealing that they are composed of a wide range of different-sized spicules surrounded by a laminated silica matrix; (**g**) Scale: 5 µm; SEM of a cross-section through a typical spicule in a strut showing its characteristic laminated architecture; (**h**) Scale: 1 µm; SEM of a fractured spicule, revealing an organic interlayer; (**i**) Scale: 500 nm; bleaching of biosilica surface reveals its consolidated nanoparticulate nature. Reprinted with permission from American Association for the Advancement of Science, *Science*, [15] © 2005

ments at the atomistic scale: silica (also known as chemical compound silicon dioxide, or SiO_2). One could subsequently ask, what makes silica a good choice for the sea sponge? Silica, or silicon dioxide, is a material that has been known since antiquity, most commonly found in Nature as *sand* or *quartz*—hardly robust structural materials. Additionally, silica is manufactured in several forms, used in the production of glass, and even optical fibers. We have exploited silica for many uses—but none have the hierarchical structure and intricacy of the skeletal system of a simple sea sponge. It would be trivial to state that the "fundamental" building block for the *Euplectella* sponge is SiO_2, yet, undoubtedly, it is the constituent material. If we simply begin at the component elements, we may overlook the necessary hierarchical structure necessary for the sponge to achieve such remarkable properties.

In the vast majority of silica-based materials, the silicon atoms are in a tetrahedral crystal configuration, with four oxygen (O) atoms surrounding a central silicon (Si) atom (the most common example is seen in the quartz crystalline form of silica). Thus, the first level of hierarchy can be said to be this crystalline structure (depicted in Fig. 1.3). Silica has a number of distinct crystalline forms in addition to amorphous forms, but, more importantly, any deviations from these common structures constitute structural differences in the resulting material. Crystalline minerals formed in the physiological environment often show exceptional physical properties (*e.g.*, strength, hardness, fracture toughness) and tend to form hierarchical structures that exhibit microstructural order over a range of scales. Such biominerals are crystallized from an environment that is undersaturated with respect to silicon, and under conditions of neutral pH and low temperature. Simply put, the sea sponge exploits hierarchical arrangements to overcome the brittleness of its constituent material, glass, and does so under accessible conditions that require very low energies. Can we employ the same principles for other materials?

Indeed, it is known that the first level is biologically produced glass composed of consolidated silica nanospheres formed around a protein filament. The resultant structure might be regarded as a textbook example in mechanical engineering, because the seven hierarchical levels in the sponge skeleton represent major fundamental construction strategies such as laminated structures, fiber-reinforced composites, bundled beams, and diagonally reinforced square-grid cells, to name a few. Apparently, the sea sponge is well versed in structural engineering practices and methods!

Again, if we consider the fundamental building blocks—consolidated hydrated silica nanoparticles—we see where “bioglass” fabricated by the sea sponge diverges from other silica-based materials: by implementing collections of nanoparticles rather than continuous crystals, for example, the intrinsically low strength of the glass is balanced at the next structural level. The structure is as important as the material. The structural complexity of the glass skeleton in the sponge *Euplectella sp*. is an example of Nature’s ability to improve inherently poor building materials. Moreover, such “bioglass” is not unique to sea sponges, and is also found in diatoms—unicellular algae—able to construct nanoporous silica with 3D precision of tens of nanometers, in a hierarchical manner, and with multifunctional properties [20]. Again, it has been shown that the mechanical properties of such materials can be changed my manipulating the nanostructure [21]. Synthetic mesoporous silica (depicted in Fig. 1.3) is currently being exploited for applications in medicine, biosensors, and imaging [22, 23].

Understanding what a material is composed of and how a material behaves has always been of great importance to enable and advance technologies [24, 25]. As such materials have played a major role in enabling civilization eras, from the stone age to the nano age, and are as such a cornerstone of all engineering disciplines. In the early days materials were obtained and tailored for our purposes from chopping up rocks or using natural resources such as rubber. For example, concrete is a compound material made from sand, gravel and cement. The cement is a mixture of various minerals which when mixed with water, hydrate and rapidly become hard binding the sand and gravel into a solid mass. The Romans found that by mixing a sand-like material (which they obtained from Pozzuoli) with their normal lime-based concretes they obtained a far stronger material. The pink sand turned out to be fine volcanic ash and they had inadvertently produced the first ‘*pozzolanic*’ cement. In the 2,000 or so years since they employed this naturally occurring form of cement to build a vast system of concrete aqueducts and other large edifices, concrete is presently the most widely used construction material in the world, found in large scale structures such as bridges and skyscrapers. Cement is so widely used as a building material that, even in the face of technological advances in materials, it will not be replaced anytime soon. Surely, the chemical details and material properties of such a widely utilized material is well-known from the molecules up?

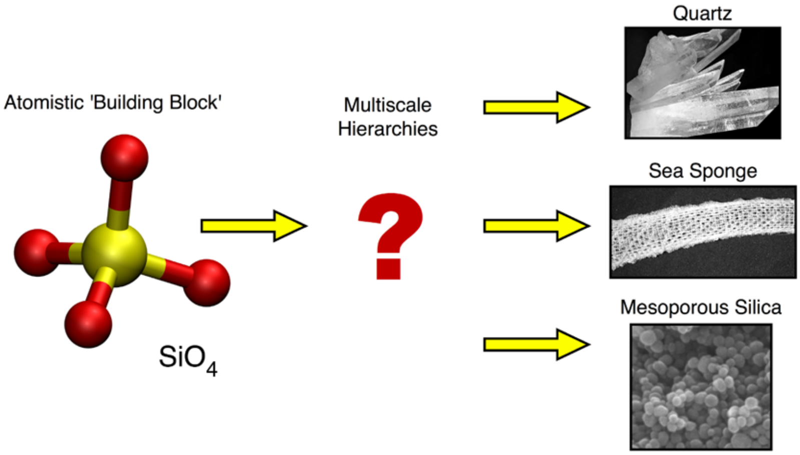

Fig. 1.3 What defines a material? If we consider the most fundamental atomistic building block—here tetrahedral silica (SiO_4)—we cannot predict the properties of the macrostructure. Depending on how silica is arranged in multiscale hierarchies, the resulting material at the macroscale shows extreme variation—from crystalline quartz, to the skeleton of a sea sponge, to synthetic microporous silica. While such structures can be analyzed to determine the structural hierarchies, the functionality of such hierarchies is difficult to predict and engineer. *Inset* SEM image of sea sponge printed with permission from The National Academy of Sciences [17] © 2004

Oddly enough, the three-dimensional crystalline structure of cement hydrate (*i.e.*, calcium silicate hydrate, or C–S–H)—the paste that forms and quickly hardens when cement powder is mixed with water—has eluded scientific attempts at decoding, despite the fact that concrete is the most prevalent man-made material on earth and the focus of a multibillion-dollar industry. The lack of a fundamental multiscale understanding does *not* preclude successful use of concrete as a building material—indeed, it is because of the improvements of concrete design, knowledge of its chemical reactivity, and keen development of additives that we have achieved high strength and corrosion resistant varieties of concrete, unmatched by anything the Romans may have stumbled upon. Such refinements, however, can only optimize a cement/aggregate/water system to a point. If we wish to develop new, stronger, and "greener" concretes, we must have complete knowledge across scales, from "nano" to "macro" (see Fig. 1.4).

Only recently has the three-dimensional structure of the basic unit of cement hydrate been decoded, resulting in a first step toward a consistent model of the molecular structure of cement hydrate [26]. Scientists have long believed that at the atomic level, cement hydrate closely resembles the rare mineral tobermorite, which has an ordered geometry consisting of layers of infinitely long chains of silica tetrahedra interspersed with neat layers of calcium oxide. But it was determined the hydrates in cement aren't really crystalline. They are a hybrid that shares some characteristics with crystalline structures and some with the amorphous structure of frozen liquids, such as glass or ice. Concrete is more disordered and porous (like the silica skeleton of the sea sponge), than ordered and crystalline (like quartz).

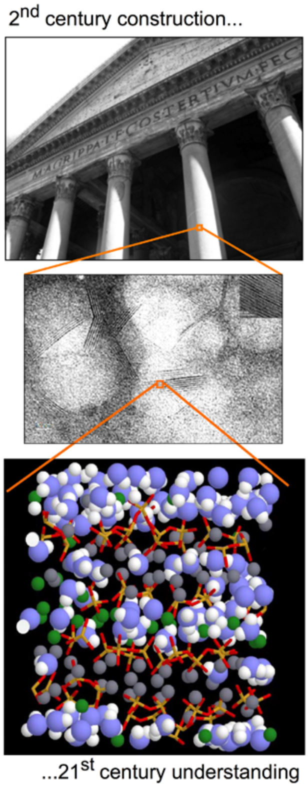

Fig. 1.4 Concrete, a construction material used for over 2,000 years, and yet only know being fully understood from the atomistic level. *Top*: Photograph of the Pantheon (Rome, Italy, 2008), constructed 126 A.D., an example of Roman concrete construction. *Centre*: TEM image of clusters of C–S–H (courtesy of A. Baronnet, CINaM, CNRS and Marseille Universite, France), the *inset* (*upper-right*) is a TEM image of tobermorite. *Bottom*: Atomistic representation of concrete: the molecular model of C–S–H. The gray and white molecules are oxygen and hydrogen atoms of water, respectively; the individual spheres are inter- and intra-layer calcium ions, respectively; connected sticks are silicon and oxygen atoms in silica tetrahedra. Figure adapted from [26]

This delicate balance between order and disorder within a structure is a concept that resembles many natural biological materials. But why is such disorder beneficial?

It is in this disorder—where breaks in the silica tetrahedra create small voids in the corresponding layers of calcium oxide—that water molecules attach, giving cement its robust quality. These material "flaws" in the otherwise regular geometric structure provide some give to the building material at the atomic scale that transfers up to the macro scale. When under stress, the cement hydrate has the flexibility to stretch or compress just a little, rather than snapping. Whereas water weakens a material like tobermorite, it strengthens the cement hydrate. The *disorder* or *complexity* of its chemistry creates a heterogenic, robust structure. The cement hydrates have a level of hierarchy that helps optimize water content and mechanical performance—analogous to Nature's hierarchical sea sponge. Serendipity was apparently on the Romans' side 2,000 years ago when concrete was discovered!

If we are only now beginning to understand the fundamental behavior and multiscale consequences of a material we have been using for thousands of years, how can we be expected to understand, design, or engineering complex biological materials? Materials that are not cast in place like concrete, but materials that grow and adapt to their environment? Clearly, a new approach is not only warranted, but

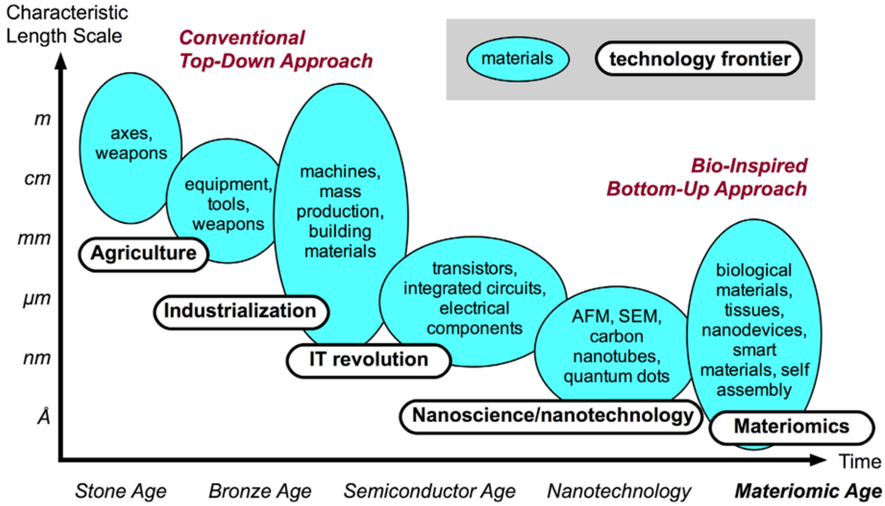

Fig. 1.5 Characteristic material scales from the Stone Age to nanotechnology and biotechnology. The plot illustrates the trend to create smaller dimensions of materials and structures as the technological frontier progresses. Currently we stand at a crossroads where nanotechnology and biology merge to provide a new bottom-up approach in the development of materials and technologies (Based on graph shown in [27])

necessary to address the challenges we face to support technological advancement and consequent economic growth.

1.4 Starting at the Bottom

The quantitative study of biological protein materials is a critical step towards the development of new technological frontiers through smarter use of (limited) resources. Aside from the Romans use of concrete, classes of materials have been used classify stages of civilizations, ranging from stone age more than 300,000 years ago, to the bronze age, and possibly the silicon age in the late twentieth and early twenty-first century. Figure 1.5 schematically displays the various stages of civilization together with an analysis of the characteristic material scales that were used in each period. The plot illustrates the trend to ever smaller material scales as humankind progressed through the ages, and the analysis may suggest that today we may stand at another cross-road in the advancement of technology. This next frontier involves the rigorous understanding of the properties (*e.g.*, mechanical, physical and chemical properties) and mechanisms (*e.g.*, chemomechanical conformation changes, enzymatic processes, mechanotransduction) of biological matter, which may enable us eventually to integrate concepts from living systems into materials and machine design, seamlessly. Solving these challenging problems may transcend the gap that currently exists between engineering and physical sciences and the life sciences.

We have now entered the era of nanoscience and nanotechnology where materials are made with atomistic precision—enabling advances in the design and synthesis of molecular building blocks that we can (theoretically) design and exploit. This bottom-up approach—designing a material/system through the behavior and combination of each constituent element and atom—was envisioned in the 1960's by Richard Feynman, the popular physicist and pioneer of nanotechnology. Feynman hypothesized the direct manipulation of individual atoms as the most powerful form of synthetic chemistry—unlocking the blueprints for atomistic construction. The challenge posed by Feynman is simple [28]: *What would happen if we could arrange the atoms one by one the way we want them*? From a biological perspective, this is exactly how natural materials are formed—the piece-wise combination of molecular building blocks.

"Feynman paradigm": Nanotechnological, bottom-up approach to material design, *via* the direct manipulation of individual atoms and molecules, and precise engineering of functional systems at the molecular scale. In its original sense, Feynman referred to the projected ability to construct items from the bottom-up, whereas the ultimate goal is to control macroscale structure and function from design at the atomistic scale.

The realization of the "Feynman paradigm" (see Fig. 1.6) has opened numerous new opportunities for research, products and development [29]. But its impact for real products and technologies hinges upon a major challenge, the linking of the scales, and to make nanoscale mechanisms visible at larger scales. Indeed, taking a closer look at the vastness of scales in our environment we realize that there are huge opportunities in designing structures and thus functions at multiple length-scales. Developed nanoscale components, once attained, must demonstrate the reproducibility needed to build functional materials and systems, and do so at a size and complexity difficult to achieve by traditional top-down approaches.

We recognize that the scales are separated, and that the scales can be connected by networks in the process of design. This design challenge has been solved by Nature and biology, where scale separation and connection are used effectively to create function from nano to macro through complex functional relations that link seemingly disparate concepts such as individual atoms or amino acids to strength to robustness. This is exemplified in the design of DNA, protein, tissue to organisms, and many others. This paradigm of using hierarchical structures can be used in engineering, to eventually eliminate the border between living and non-living systems. The applications are endless, and include self-healing cement, changeable airplane wings, and others.

But before the realization of what is possible, we first need a complete understanding of what is palpable. One possible approach to improve our understanding of what we can engineer is to turn towards Nature for inspiration. The development of new materials and the discovery of the complexity of existing materials are not

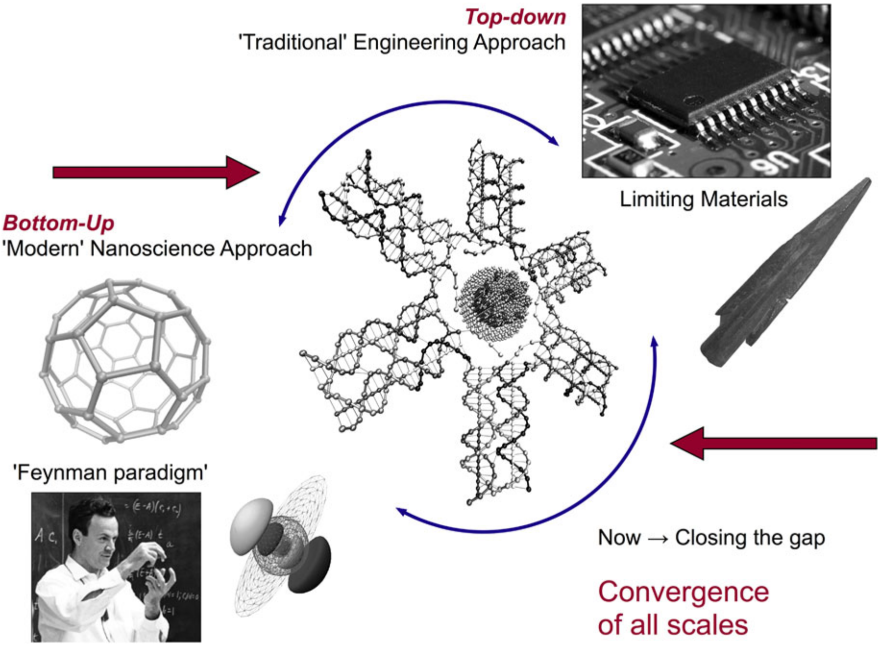

Fig. 1.6 Juxtaposition of the "Feynman paradigm" with "traditional" engineering approaches. Current top-down methodologies have advanced from simple manipulation of available materials (*e.g.*, crude stone age weaponry) to sophisticated exploitation of material properties (*e.g.*, semiconductors in integrated circuits). Nanotechnology has also developed the ability to investigate and manipulate materials on the atomistic and molecular scale from a bottom-up perspective. Currently, we are at the convergence of both bottom-up and top-down routes, closing the gap between material, structure, and function. As Feynman suggested, precise engineering and control at the nanoscale may dictate the future of material design, but we must also fully understand how nanoscale properties are expressed at the macroscale

mutually exclusive endeavors. Even if a complete and thorough understanding of complex phenomena is not attained, we can still learn lessons and insight from Nature providing guidance for new discoveries and distinct means by which heightened functionality is created in spite of limited resources.

1.5 Lessons from Nature: Biological Materials and Biomimetics

Nature exhibits the design guidelines for multi-scale adaption of structure and functionality. An organism evolves to survive because it uses the minimum amount of material to make its structures (be it internal to the organism, such as bone or tissue, or an external structure, such as a spider's web) and also because it can optimize its use of the available environmental sources. Nature thus provides an array of building materials and aptly chooses suitable means for a multitude of natural functions

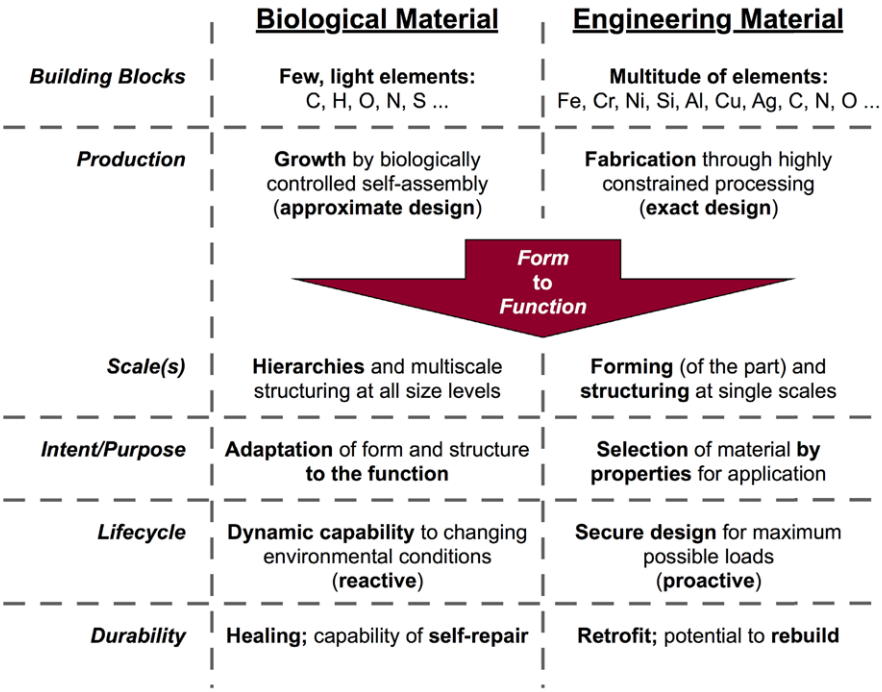

Fig. 1.7 Biological and engineering materials are governed by a very different choice of base elements (natural materials consist of relatively light elements few whereas engineering materials are characterized by many more elements) and by a different mode of material production (biological growth versus controlled fabrication). From these basic forms, there arise different strategies for materials choice and development (under the *arrow*) of function. Biological materials are inherently multiscale, whereas the performance of engineering materials are typically limited to a single scale. Biological materials have been adapted for a specific biological role/function, whereas an engineering material is typically selected based on desirable properties. Finally, biological materials are dynamic systems, capability of both self-adaptation and healing, whereas engineered systems are typically limited to the design specifications. Additional requirements and incurred damage necessitate reinforcement or retrofitting of a material or structural system. Extended and adapted from [25]

[15, 30–33]. The elasticity of blood vessels, the toughness of bone [8, 9] or the protection of nacre [11, 34–36] illustrate the *apropos* of Nature's material selection. Moreover, Nature has developed such materials with a comparatively poor set of base materials. Why can't we simply copy Nature's systems and substitute materials to maximize performance? If bone is made of proteins and minerals (*i.e.*, collagen and hydroxyapatite), can we simple replace with synthetic materials? Perhaps nylon (a robust synthetic polyamide) and titanium (a metal with high strength-to-weight ratio)? Unfortunately, we cannot. The design strategies of biological materials are neither immediately applicable to, nor compatible with the design of new engineering materials, since there are some remarkable differences between the strategies common in engineering and those used by Nature (see Fig. 1.7).

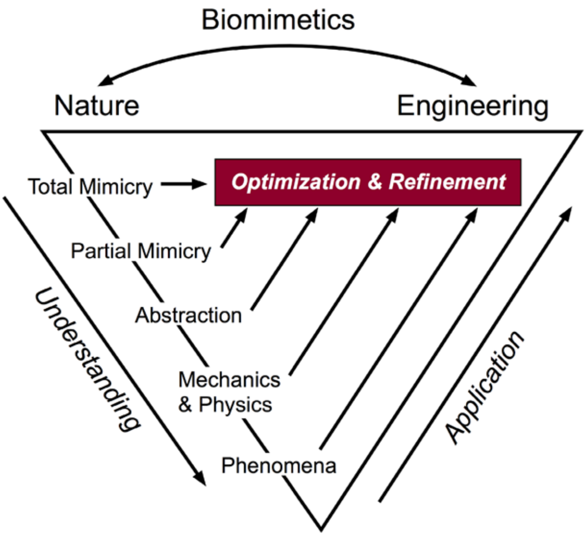

Fig. 1.8 A biomimetic "map" to illustrate the idea that the more abstract a concept is, the more adaptable it is within another discipline. Adapted from J.F.V. Vincent, "Stealing ideas from nature" in *Deployable Structures* [37]

A holistic knowledge of biological materials offers a unique opportunity to understand how complex materials science, engineering, and chemical principles arise routinely in Nature. Nature has been the motivation factor in a number of texts and studies, and, concurrently, provides the inspiration and stimulation to scientists and engineers for new material concepts, design strategies, and structural optimization. This field defines biomimetics—using ideas from nature to further technology—or, more colloquially, "*... the technological outcome of the act of borrowing or stealing ideas from Nature*" [37].

Biomimetics, however, is extending beyond the simple "stealing" of ideas, and evolving to a more didactic role—*i.e.* learning ideas from Nature. The difference lies not just in the abstraction of useful ideas (the invention of Velcro by the observation of sticking plant burrs is a popular example) but also in the detailed and mechanistic understanding of the processes involved. The transfer of ideas from biology is not limited to the ultimate form and function of a biological system—we are not interested in spider silk so we can swing from skyscrapers like Spiderman. Instead, we should look to Nature and biological systems (nay, models), to serve a technical application of practical purpose. The more this application deviates from the biological system, the more basic the analysis has to be in order to generate useful (practical) knowledge and understanding (see Fig. 1.8).

The general concept, as discussed by J.F.V. Vincent ("Stealing ideas from nature" in *Deployable Structures* [37]), is that the further down one can move from the natural origin, the more general and therefore more powerful the concept will be. The goal is the shift from total mimicry (stealing) to an understanding of the process at its basic level (abstraction), defining that process from an analytical perspective (mechanics and physics) and then exploiting the physical phenomena to our own ends. Throughout this text, investigations and studies discussed can be assigned to such categorizations, from the behavior of spider silk in Chap. 8: Unlocking Nature: