Chapter 2
The Materiome

Abstract The goal of materiomics is the complete understanding of the materiome—a holistic characterization of a complex material system. The balance of form and function throughout Nature is well recognized, but the materiome must enhance a basic characterization of complex biological phenomena, to enable the prediction and design of new technologies. Analogous to genomics and other "-omic" fields, there is an obvious difference in scope between a gene or genetic sequence, and the human genome. Here, we establish the scope of the materiome beyond the assembly of material components (*e.g.*, architecture or structure), the fundamental difference between application and function, the concept of material behavior scaling, as well as the challenges (and benefits) imposed by material hierarchies and complexity. Material and structure are no longer distinct, and the assembly of building blocks ranges across all scales from the nano to the macro level.

> *The structure of tissues and their functions are two aspects of the same thing. One cannot consider them separately. Each structural detail possesses its functional expression. It is through physiological aptitudes of their anatomical parts that the life of the higher animals is rendered possible… Tissues are endowed with potentialities far greater than those which are apparent.*
>
> *Alexis Carrel, Science, Vol. 73, No. 1890, pp. 297–303 (1931)*

2.1 Introduction

The above quote indicates a fundamental principal of materials science central to materiomics: the inherent (and reciprocal) relation between a material's *structure* and material's *function*. Superficially, in many applications—both engineering and biological—one can be directly inferred from the other. For example, a steel cable supporting a suspension bridge is constructed to withstand tension, while the bones in our bodies are relatively stiff to provide our limbs and muscles with structural support. The problem arises, of course, when one wishes to optimize and develop (in other words, *engineer*) both structure and function simultaneously. This, as indicated by Chap. 1: Introduction, is the approach Nature astutely implements through *growth*.

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Growth is a complex process that can be influenced by the external conditions including temperature, mechanical loading, and supply of light, water or nutrition. As such, biological materials are not produced in the same manner as engineering materials—the process is highly adaptive and responsive. Moreover, critical factors may differ not only in time, but in scale—what a material system "sees" at the nanoscale may be quite different than at the macroscale. Organisms must necessarily possess the ability of adaptation to external needs, while possible external influences on a technical system must be typically anticipated in its design. Multiscale response, temporal changes, and the need for robustness (applying "survival of the fittest" principle to materials science) are the primary culprits resulting in complex biological materials and systems. Even if you think you have a complete physiological and mechanistic understanding, the system can evolve. This usually means back to the metaphorical drawing board! Clearly, a biological material differs from common static and benign materials such as aluminum or glass (as everyday examples). For this reason, complex materials (in particular complex biological materials such as tissues and cells) need a more comprehensive and holistic framework to completely understand (and exploit) physical, chemical, biological and mechanical characteristics and properties. Such a holistic framework is known as the *materiome*.

Materiome: A holistic characterization of a material system, consisting of the material constituents (elemental building blocks and/or structural units), the cross-scale structure-property-process relations, and the resulting functionalities/requirements across *all* levels of hierarchy, from nano to macro.

An integrated and holistic perspective of biological materials is particularly fascinating for the materials scientist—and has likewise been approached in the past with various motivations. For example, the classical book by D.W. Thompson *On Growth and Form* relates the "form" (or shape) of biological objects to their physiological role [1]—an early insight into the integration of structure and function. Thompson quotes:

> An organism is so complex a thing, and growth so complex a phenomenon, that for growth to be so uniform and constant in all the parts as to keep the whole shape unchanged would indeed be an unlikely and an unusual circumstance. Rates vary, proportions change, and the whole configuration alters accordingly.

A recurrent theme of *On Growth and Form* is that contemporary biologists (circa 1919) overemphasized evolution as the fundamental determinant of the form and structure of living organisms, and underemphasized the roles of physical laws and mechanics. Thompson advocated *structuralism* as an alternative to survival of the fittest in governing the form of species. Yet a purely mechanistic approach is also limited in scope, failing to encompass adaptive physiological and environmental aspects of biological systems. From an integrated perspective, evolution and structuralism go hand-in-hand—they are aspects of the same "development" process, contributing to the materiome.

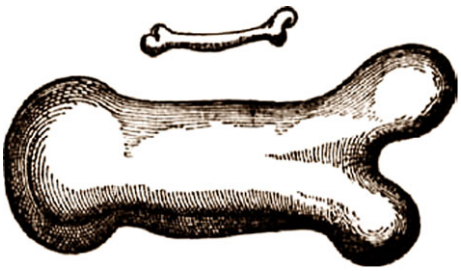

Fig. 2.1 Galileo's illustration of the same bone (femur) of a human (*top*) and a giant (*bottom*). Whereas the length of the bones differ by about three times, the width of the bones differ ninefold. Typically, "Galileo's bones" are used as an example of scaling of strength and weight (the so-called cube-square law). Here, the bones represent a variation in structure with function—the material (bone) is constant, but the *materiome* varies from human to giant. From *Discorsi e Dimonstrazioni Matematiche intorno a Due Nuove Scienze*, 1638

Even earlier, the relationships between anatomy (*i.e.*, structure) and function of living systems had been explored by Leonardo da Vinci and Galileo Galilei. One of the first to apply fundamental physics to biological systems, Galileo is often considered the father of biomechanics (albeit the modern approach to biomechanics is largely credited to the pioneering work of Y.C. Fung). Among his many other discoveries, Galileo recognized that the shape of an animal's bones are to some extent adapted to its weight. Long bones of larger animals typically have a smaller aspect ratio (see Fig. 2.1).

Galileo's explanation is the basis for the simple cube-square law: the weight of an animal scales with the cube of its linear dimension, while the structural strength of its bones scales with the square. Hence, the aspect ratio of long bones has to decrease with the body weight of the animal. Indeed, for this reason, large animals do not look like small animals: an elephant cannot be mistaken for a mouse scaled-up in size. The bones of an elephant are necessarily proportionately much larger than the bones of a mouse, because they must carry proportionately higher weight. Because of this, the giant animals seen in movies (*e.g.*, Godzilla or King Kong) are unrealistic, as their sheer size would break their bones! While the material properties of bone are similar from animal to animal (the composition of human bones is similar to mouse bones is similar to elephant bones, for example), the structure adapts to function. In other words, the *materiome* changes.

Beyond material properties (*e.g.*, strength or mass), early insights further linked biological processes—such as walking, running, and the flight of birds—using a mechanistic framework (see Fig. 2.2). It was a radical paradigm that all living systems, including the human body, could be described as simple machines ruled by the same mechanical laws. More recently, the works of Steven Vogel [2–6] has introduced the field of comparative biomechanics—application of biomechanics to non-human organisms and reducing the biomechanical universe to a set of simple tubes, surfaces, flows, beams, and levers, all amenable to simple calculation and estimation. In simplest terms, quantifying how living things stack up against non-biological physical reality. Biomechanics is closely related to engineering, because

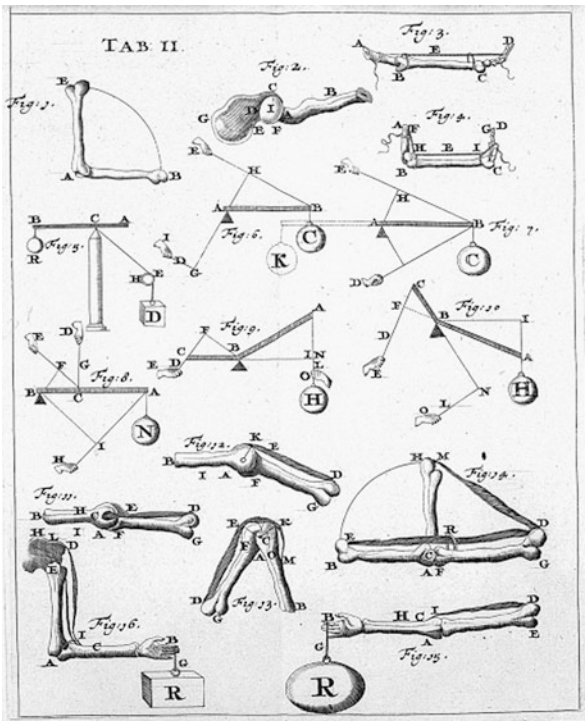

Fig. 2.2 Biology provides more than just materials, but functional mechanical systems. Illustration is a page of one of the first works of biomechanics, *De Motu Animalium* by Giovanni Alfonso Borelli (1608–1679). Borelli studied walking, running, jumping, the flight of birds, the swimming of fish, and even the piston action of the heart within a mechanical framework. Influenced by the work of Galileo, he had an intuitive understanding of static equilibrium in various joints of the human body well before Newton published the laws of motion

it often uses physical engineering sciences to analyze biological systems. Currently, the study of biomechanics ranges from the inner workings of a cell to the movement and development of limbs, to the mechanical properties of soft tissue, and bones, and the transport of fluids and nutrients *via* cellular mechanisms and large-scale vasculature.

In a similar manner, the challenges of understanding the relationship between material system, function, and adaptation are the focus of materiomics. The goal is not only to understanding such complex biological phenomena, but to enable the prediction and design of new technologies. Materiomics is a unifying field, attempting to merge the efforts of biologists, material scientists, and engineers alike. Indeed, many of the overarching themes and principles have been investigated under different motivations. In this chapter, we introduce and discuss the fundamental concepts of materiomics, such as the *materiome* (depicted schematically in Fig. 2.3), as well as guiding principles and nuances, such as the fundamental difference between function and application, structure-property-process relations, the prevalence of hierarchies and complexity, and the concept of material behavior scaling.

2.2 Motivation and Scope

Materiomics is defined as the systematic study of the complete material system and the effect on the macroscopic function and failure in their mechanical context,

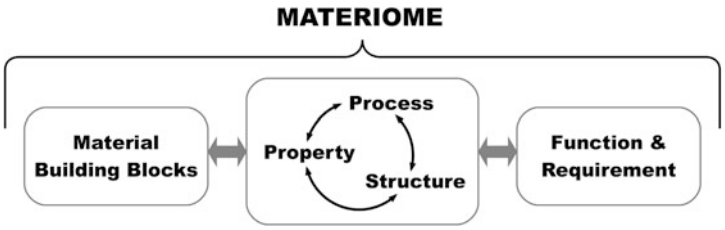

Fig. 2.3 Schematic representation of materiomic information, consisting of the material constituents (elemental building blocks and/or structural units), the cross-scale structure-property-process relations (structural geometry, stress and strain transfer, failure mechanisms), and the resulting functionalities/requirements (strength, robustness, toughness, and other mechanical properties)

linking processes, structure and properties at multiple scales, from nano to macro, through a materials science perspective, integrating experimental, theoretical, and computational methods. The term has been coined in analogy to genomics—the study of an organism's entire genome—where, indeed, the suffix "omics" refers to "all constituents considered collectively". The development of genomics is a direct result of the *Human Genome Project* [7, 8]—an ongoing international scientific research project with a primary goal of to identify and map approximately three billion base pairs that form the chemical rungs in DNA's signature double-helical shape, from both a physical and functional standpoint. It is a gross oversimplification to state that the aim of the project is to simply map the nucleotides contained in a human genome in a sort of extensive database. Rather, the ultimate goal is to understand the human genome—detailing a genetic instruction set, finding the genetic roots of disease, and providing a scaffold for future work. A common idiom states that the "whole is greater than the sum of its parts"(originating from Aristotle[1]), and the Human Genome Project is the attempt to discover the "whole" of our genetic make-up, assigning meaning to:

...ACCGTAAATGGGCTGATCATGCTTAAACCCTGTGCATCCTACTG...,

beyond a seemingly random sequences of nucleobases (where A refers to adenine, C to cytosine, G to guanine, and T to thymine, the four base pairs of DNA). Moreover, the effort to create a comprehensive map of the human genetic sequence was more than just a breakthrough for geneticists. Genomics marked the launch of a new era of "-omic"-based research [9, 10]. The focus was shifted from individual parts within a system, to the system itself (a holistic approach). In the field of systems theory, this integrative view is sometimes referred to as *emergence* [11]—the way complex systems and patterns arise out of a multiplicity of relatively simple interactions. Biological systems consist of a large number of mutually interacting and interwoven parts, but complex and adaptive systems are not limited to biology. Examples

[1] "...the totality is not, as it were, a mere heap, but the whole is something besides the parts.", *Aristotle, Metaphysics*, Book H, 1045a:8–10.

of non-biological systems in which emergence plays a role include social networks, ancient and modern cultures, languages and writing systems, and economies and ecosystems. Recently, the "omic" approach has found a particularly fitting niche within the field of integrative biology—the study and research of biological systems from a biological science, engineering and physical science perspective. Specific research may involve genetics or environmental studies, yet the goal is always to solve a larger, biological problem—from the smallest, molecular studies to broader studies of the biosphere [12, 13].

It is within this realm that materiomics can make a natural tangent—borrowing from the data collecting and consolidation of genomics and proteomics (among others; see Table 2.1), with the system-level perspective of integrative biology. Whereas genomics delineates genetic sequences, materiomics categorizes structural components; proteomics encompasses protein expression, materiomics can elucidate a material's behavior and function.

Although inspired by genomics, the forerunner of all contemporary "omics disciplines", the recent explosion and adoption of many omics by researchers (see Greenbaum *et al*. [14] for example) gives rise to clarification of the intention of defining materiomics. Traditionally, "omics" is a general term for a broad discipline of science and engineering for analyzing the interactions of biological systems in particular. Such fields are typically characterized by general systems (such as genomics for genes or proteomics for proteins) or processes (for example interactomics for cellular interactions or mechanomics for stress transfer). Indeed, even the term "Omics" (we use capitalization to denote the field rather the suffix) itself can refer the encompassment of all such bioinformatics research fields to understand all the biological information processing phenomena. Table 2.1 presents some common "omics" with their associated focus and scope. However, without prudence, the value of a new "omic" could be viewed as self-serving and counterproductive.

While the intent of omics in general is the collection of knowledge and information *via* holistic understanding and integration, the introduction of too many subfields and specialties can promote separation and reductionism of systems and processes under investigations. This is not to devalue the subfields of bioinformatics, where system complexity warrants specialization (*e.g*., characterizing DNA through genomics compared to RNA through ribonomics). Many such fields can be viewed as a hierarchical approach to genomic research (see Fig. 2.4 for an illustrative example of both genomic and materiomic "hierarchies"). To be meaningful beyond a label, new omics should be unifying rather than segregating. With this standpoint, materiomics is neither a subdiscipline of biomaterial engineering, materials science or mechanics, nor intended to be applied solely to biological systems. Unpresumptuously, materiomics is not *introducing* a new field of science, but rather *encapsulating* many fields under a common banner. Just as genomics has motivated research to elucidate biological processes ranging from molecular interactions to complete organisms, it is hoped that the field of materiomics will stimulate extensive research, establishing a hierarchical apex shared between many disciplines promoting integration and collaboration. The use of a materials science approach to studying biological materials may have broader impact beyond the areas of biological protein materials and biomimetic systems.

Table 2.1 Some common "-omics" with corresponding focus and scope; brief definitions meant to provide illustrative descriptions only

Omic	Focus	Scope
Omics	Analyzing the interactions of biological information in various "omes"	Applied research paradigm to produce knowledge *en masse* from networks of information *via* holistic principles and methods.
Genomics	An organisms' entire hereditary information; genome	Determination of entire DNA sequences of organisms, fine-scale genetic mapping including genes, regulatory and non-coding sequences.
Proteomics	Protein characterization; protein-coding regions of the genome; proteome	The entire complement of proteins produced by an organism or system, including protein structure, function, and expression.
Metabolomics	Metabolites and metabolic networks; metabolome	All the small molecules present in a cell in a specific physiological state; systematic study of the unique chemical fingerprints that specific cellular processes leave behind.
Transcriptomics	RNA transcripts produced by the genome at any one time; transcriptome	Examines the expression level of RNA in a given cell population, which vary with external environmental conditions, including mRNA, rRNA, tRNA, and non-coding RNA.
Interactomics	Interactions between all macromolecules in a cell; interactome	Analyses and characterization of gene-gene, protein-protein, or protein-ligand interactions; development of molecular interaction maps/networks.
Mechanomics	Mechanical systems and processes within an organism; mechanome	General role of force, stress transfer, mechanics, and molecular machinery in biology, encompassing biological motors, mechanical structures, and processes.
Materiomics	Material characterization through components, structure, and function; materiome	Analysis of material systems though constitutive components, hierarchical structure-property-process relations, cross-scale interactions, and effects on functionality.

Indeed, within the biological sciences, the field of genomics has advanced our knowledge base through the successful sequencing of entire genomes. In recent years however, extensive efforts have been initiated to move beyond genomics, where fields such as systems biology provide explanation to mechanisms of how genes affect phenotypes and biological function. Here, materiomics refers to the general study of a material system's *materiome*—the integrated view of materials cross-scale interactions that collectively define the material's properties, function, and purpose.

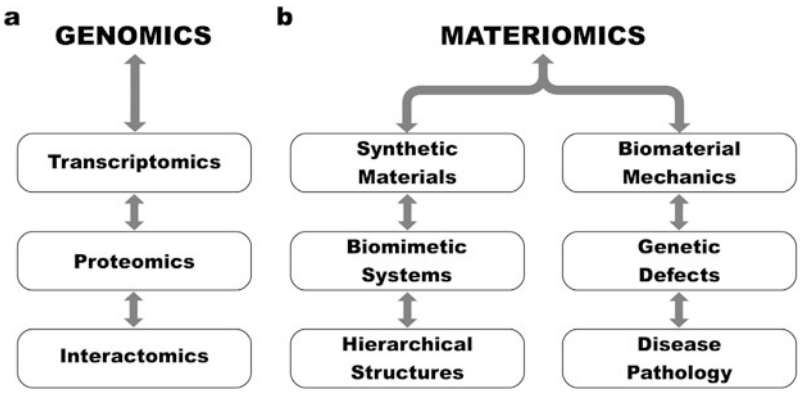

Fig. 2.4 Example flow of information under genomics and materiomics frameworks. (**a**) Genomics encompasses the entire genetic sequence, which includes specific DNA sequences transcribed to RNA molecules (*transcriptomics*), in turn, mRNA from a DNA templates carry the coding information required for protein synthesis and expression (proteomics), finally, the mapping of protein-protein interactions networks can be characterized by interactomics. It is noted that this is merely one possible flow of information under genomics, with many interactions possible between subdisciplines. (**b**) Two potential *paths* are given for materiomics. First, of all classes of synthetic materials being developed, a subset may find inspiration from biological materials. From these bio-inspired or biomimetic materials, the motivation may arise from multiscale hierarchical structures, such as those found in spider silk, wood, or bone. Materiomics provides a potential framework for the development of such *de novo* materials. Second, there is an advancing knowledge base on the mechanical behavior and properties of biomaterials, both at the molecular and system levels (*e.g.*, cellular mechanics or soft tissue behavior). At the molecular level, genetic point defects (*i.e.*, mutations) can lead to mechanical changes expressed at the macro-scale. Such pathology can be quantified and analyzed, leading to new diagnostic and treatment methods for certain diseases. The diverse aims of biomimetic material design and disease pathology can be unified under a materiomic paradigm through the understanding of material systems and functionalities

2.3 Material Versus Materiome

Materiomics, as currently presented, is the study of a system's materiome, or the "complete" material system—its constituents and structure, properties and processes, function, failure, and behavior—in its entirety. The goal is to link the disparate nature of the physical description of a material (*i.e.*, components and structure) with the related phenomenological functionalities (*i.e.*, strength and robustness). The approach is partially motivated by macro-scale engineering techniques such as structural analysis. For example, it is a rather trivial analysis procedure to determine the flexural behavior of a steel joist girder if the geometry and material properties of the truss members are known (see Fig. 2.5). The behavior of an individual joist, in turn, affects the behavior of the system in which it is contained (such as a simple roofing system). If we consider the truss arrangement as the first hierarchy, it is apparent that the mechanical properties of the material used to build the truss, as well as the structure of the truss itself, ultimately affect the mechanical properties and failure of the system. However, at the macro-scale, by convention, there is a distinct differentiation between the "material" and the "structural system".

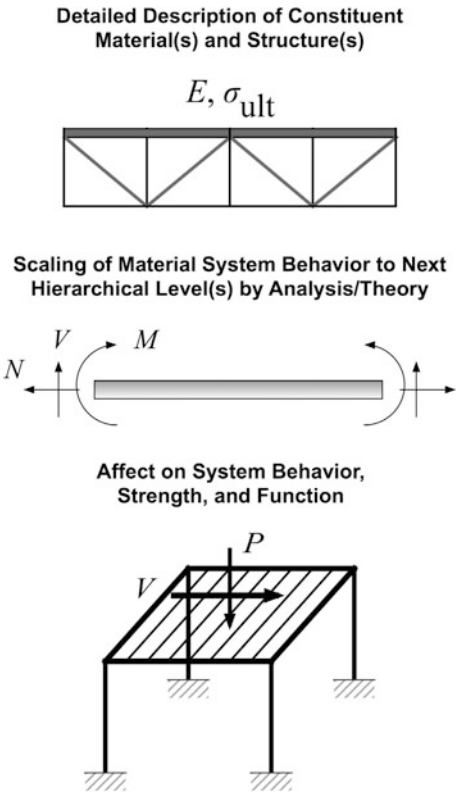

Fig. 2.5 Schematic of the material to system relationship in a typical engineered structure. The material building block is chosen (in this case, steel joist girder with known member properties such as ultimate stress, Young's modulus, etc., and geometry). The girder is fundamentally a flexural beam element with known behavior and load response from analysis of girder members. The behavior of this scale level (*i.e.*, hierarchy) is predictable and designed accordingly. Finally, these theoretical beam elements are used in analysis of structural frame. The material properties are directly expressed at the system-level behavior. Biological materials, however, neither have an analogue for "theoretical beam elements", nor have consistent properties from scale to scale

Typically, one would not associate conventional material properties such as Young's modulus and Poisson's ratio to a roofing frame. Moreover, the relation between the "material" and the "structure" is well-defined and predictable—a building made of steel is inherently stronger than a building made of wood (perhaps not by weight, but that is another issue). At the nanoscale, however, the "material/structure" distinction is not as clear, nor is the predictability of system-level properties from known building blocks. Knowledge of one does not infer the other.

Consider the hierarchical nature of bone or tendon as an example (depicted in Fig. 2.6), for which there has been ample research at multiple hierarchical levels [15, 17], including the triple-helical polypeptide structure, the subsequent formation of collagen fibrils, and the ultimate macro-scale system of bone/tendon through both

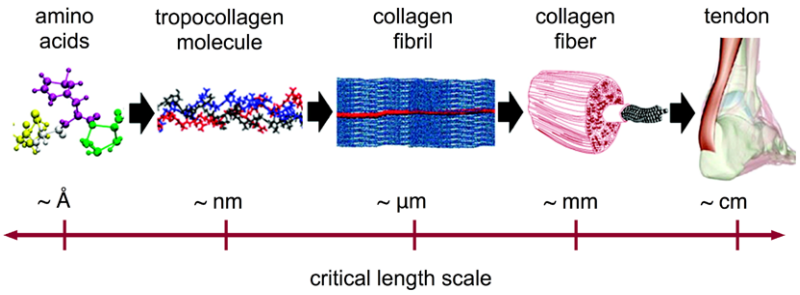

Fig. 2.6 Hierarchical structure of collagen protein materials [15]. Like all protein-based materials, the fundamental building block is a sequence of amino acids (on the order of *Ångstrom*). Each collagen molecule is made of three peptide chains that form the ∼300 nm long triple helical collagen molecule (*nanometer scale*). Collections of collagen molecules aggregate both in lateral and longitudinal directions to form fibrils (*micrometer scale*). Fibrils include tiny hydroxyapatite crystals in bone tissue, which provide stiffness and compressive load resistance. In tendons and ligaments, multiple fibrils make up collagen fiber (*millimeter scale*), formed with the aid of proteoglycans. Figure adapted from [16]

atomistic [16, 18], computational [19, 20] and experimental methods [21–23] (discussed further in Chap. 8: Unlocking Nature: Case Studies). Unlike a steel frame, however, the system-level (bone/tendon) properties are not reduced to the mechanical properties of the first hierarchical level (protein triple-helices). In fact, a literature review results in different Young's moduli defined for tropocollagen triple helices [16, 18], collagen fibrils [16, 24], and bone [25]. It is apparent that, as the scale of the material is decreased, the distinction between what exactly is labeled the "material" and the "structure" is simply a matter of perspective. Within the context of the materiome, the material and structural information is considered at *all* hierarchical levels. While a material description of bone can be defined by the macroscale properties such as Young's modulus or fracture strength, the complete materiome of bone necessarily includes the material information at all levels of hierarchy, the structure-property relations between hierarchies, and the associated functionalities of the system. In this context, Figure 2.3 only summarizes the information contained within *each* hierarchical level of the materiome—it is incomplete.

From a cursory perspective, the materiome may be considered merely a "multiscale snapshot" of a material system, that is, simply a catalogue of material properties and functions throughout different scales. What such a simple snapshot would lack, however, is the communication and cross-scale interactions that define the functionality of complex materiomic systems. In other words, the materiome provides not only the answer to what the material system is in terms of components, structure, and properties, but also to why the system is the way it is and how it is and/or can be manipulated. For example, knowledge of the spatial relationships and interactions of genes and regulatory elements in the cell nucleus are revealing an extensive network of communication within and between chromosomes [26]. Such interactions are, not surprisingly, inherently multiscale with nano-scale details exhibited throughout hierarchical levels [27]. A simple material description of the

chromosome nucleotides and structure is unable to construe such information, as the local environment and material requirement effect gene expression. Such gene adaptations continuously change the material but maintain a constant materiome, a clear differentiation of the two concepts. A crucial unresolved issue is the extent to which this organization affects gene function, rather than just reflecting it. By unlocking the complete materiomic information, efforts have been made to utilize gene regulation in the self-assembly and organization of structural DNA materials [28–30], discussed further in Chap. 10: Synthesis and Design. Such applications are only possible through the integration of multi-scale feedback, chemical interactions, and structural-property relations, which are central to the field of materiomics.

Inspired by biological materials hierarchical structures, decentralized processes, material properties and environmental requirements, materiomics amalgamates the combined effects to mutual completion. In contrast to the traditional paradigm in materials science, relations between "external" functions/requirements and "internal" properties exist on several scales resulting in multi-functionality. Though, as requirements are consistently changing (*e.g.*, changing loads, changing environment) on several time and length scales, in addition to multi-functionality, robust feedback loops are required and enable decentralized self-organization and self-optimization (see Fig. 2.7).

The consideration of the complete materiome of a material system allows a fundamental bottom-up design of purpose-specific materials from the atomistic to the continuum levels. Granted, the understanding of the materiome is still at its infancy, where the role of the relationship between processes, structures and properties of materials in biological organisms is thus far only partially explored and understood. Approaches in studying the materiome include multi-scale experiments (*e.g.*, AFM, optical tweezers, etc., discussed further in Chap. 5: Experimental Approaches), multi-scale simulation methods (*e.g.*, molecular dynamics, finite element analysis, see Chap. 6: Computational Approaches and Simulation), as well as high-throughput methods based on combination of these techniques. The objective is to ultimately bridge hierarchical levels and piece together not only material properties and structures at the nano- and micro-scales, but the ultimate effects on both the mechanical properties and function of the entire material system. A complete understanding of the materiome elucidates not only the cross-scale relations between hierarchies and mechanical properties, but also offers clues how to assemble new materials with disparate and mechanical properties from few constituent building blocks, and to identify novel approaches in designing materials that evolve autonomously to adapt to changes in environmental conditions.

2.4 Functionality Through Architecture

As will be discussed in subsequent chapters, biological materials have the capacity to integrate multiple, and at times, disparate properties, unaccounted for by a simple

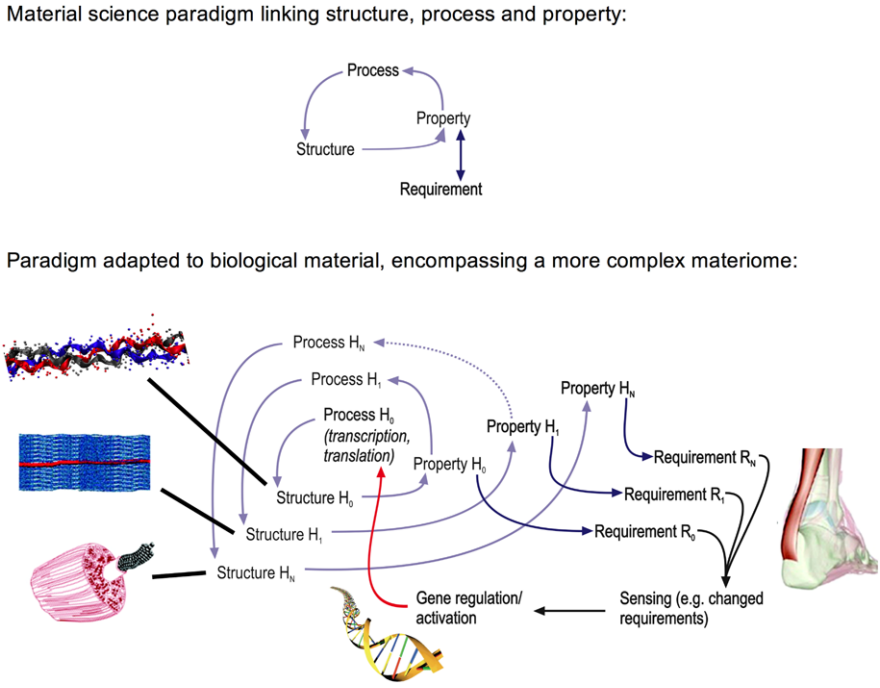

Fig. 2.7 Alternative schematic representation of materiomic information across scales, for a complex biological material such as tendon. Biological materials integrate hierarchical structures, decentralized processes, material properties and environmental requirements. A materials science paradigm applied to the hierarchical structure of protein materials is necessarily more complex (here, H_i refers to hierarchy levels $i = 0 \ldots N$, and R_i refers to material property requirements at hierarchy levels $i = 0 \ldots N$). The cycle initiates at H_0 (process H_0, the only level at which protein expression occurs) to form protein constituents (structure H_0). Their properties (property H_0) control the association at the next hierarchical level (process H_1 leading to structure H_1). This cycle continues through all hierarchical levels $i = 0 \ldots N$, where process and structure H_1 and beyond denote protein assembly stages. At each stage, the properties of the structure control the assembly at the next level. Overall, properties at different hierarchical levels (properties H_i) are regulated by corresponding physiologic demands (requirements R_i), which are sensed and transduced intracellularly to activate genetic regulation, resulting in changes to process H_0. Adapted from [31]

combination of material properties or "*rules of mixture*". The materiomic function is frequently a function of the system architecture and geometry (often across scales, or *hierarchical*). The addition of hierarchies is fruitless without consideration of hierarchical function—the structure at each hierarchical level is associated with a specific property and essentially compartmentalized at that scale. The goal is the definition and systematic characterization of structure-property-process (SPP) relation (*i.e.*, how the manipulation of one influences the other, and how to derive functionality intended combinations rather than *ad hoc* permutations). The ultimate functionality of the *materiome* is differentiated from that of the constituent *material* by the SPP relations.

Structure-Property-Process (SPP) Relations: The interplay and underlying correlation between a material system's *structure* (geometry and material components), resulting *properties* (stiffness, strength, stability, etc.), and mechanistic *processes* (including fabrication, synthesis, stress transfer, deformation, and eventual failure). The ultimate functionality of the *materiome* is differentiated from that of the constituent *material* by the SPP relations.

To exemplify, there has been much study on the structure-property relationships of numerous mollusk shell nacreous microstructures [32–34], in which it is generally concluded the amplification of mechanical properties (increase in strength and toughness) exhibited by biological composites compared to their individual constituent materials is beyond simple rule of mixture formulations.

The remarkable performance of biological materials is a consequence of their hierarchical structure, the specific design at each level of organization (such as the skeleton of a sea sponge, discussed in Chap. 1: Introduction). Another example is found in the cuticle of large crustaceans such as the lobster *Homarus americanus* [35], a chitin-based material containing proteins, mineral nanoparticles (mostly amorphous calcium carbonate with some crystalline calcite) and water. The hierarchical organization of the cuticle illustrates several generic design principles of crustacean exoskeletons (see Fig. 2.8). Synthetic structural materials that take advantage of the hierarchical structure-property relationships of such composite systems are increasingly being realized [36, 37].

Another recent study of a deep-sea hydrothermal vent gastropod [38] demonstrates the material properties of the multi-layered shell are dependent on the specific combination of different materials (building blocks), the microstructures, interfacial geometries, gradation and layering (structure-property-process), which are advantageous for penetration resistance, energy dissipation, mitigation of fracture and crack arrest, reduction of deflections, and resistance to bending and tensile loads (function and requirement). Such investigations help elucidate the gastropod shell materiome, integrating the effect of contrasting material components (compliant organic layers and stiff mineralized platelets) with the mechanical properties of the entire material system. Indeed, each layer of the shell is responsible for distinct and multifunctional roles in mechanical protection (see Fig. 2.9).

We can compare the "compartmentalized function" of a gastropod's shell with a more common macro-scale system, a reinforced concrete flexural member (depicted schematically in Fig. 2.10). Here, we consider the materiome of the composite concrete and steel system. We no longer consider the beam a heterogeneous material system composed of concrete and steel, but rather the beam holistically as a functional system. Indeed, as discussed in Chap. 1: Introduction, the concrete itself can be thought of as a complex hierarchical system, and micromechanical models of steel elucidate complex phenomena in steel such as dislocations and grain boundaries—yet typically both materials are treated with bulk macroscale properties. Through engineering of the cross-section, the structure and specific placement

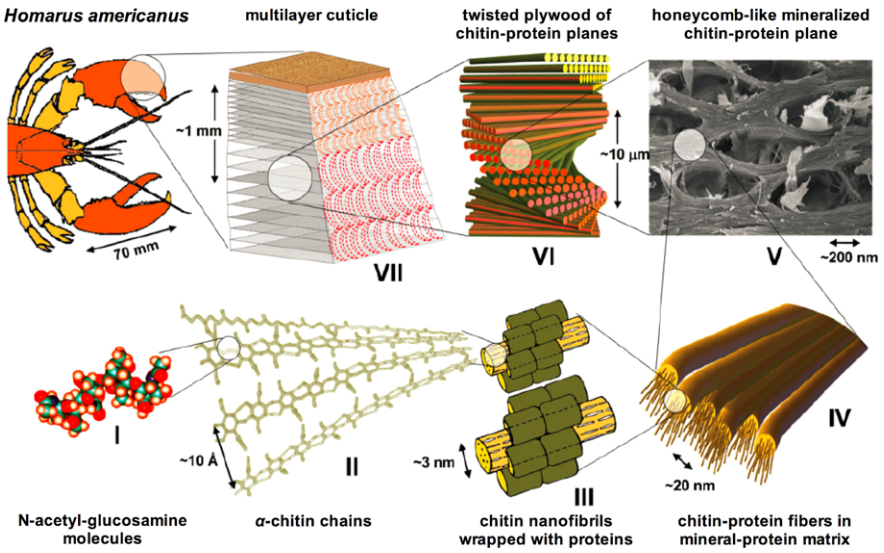

Fig. 2.8 Hierarchical structure of the lobster cuticle: **I**) N-acetyl-glucosamine molecules, **II**) antiparallel chains of α-chitin, **III**) chitin-protein nanofibrils, **IV**) chitin-protein fibers in a mineral-protein matrix accommodating and stiffening the chitin network (not shown), **V**) cuticle with pore canal system (the well-developed, honeycomb-like system of pore canals facilitates biomineralization by water-mediated transport of calcium and other ions across the cuticle), **VI**) chitin-protein fibers organized in a twisted plywood structure for reinforcement, and **VII**) three-layered cuticle at the macroscopic level. From Raabe *et al*. [35], used with permission, copyright © 2010 WILEY-VCH Verlag

of the material components serve a distinct mechanical role. The concrete serves as the primary load-bearing medium while protecting the steel elements from corrosion. The longitudinal steel reinforcement is designed to carry tensile stress, while the concrete carries compressive stress. Indeed, the amount of steel ultimately dictates the failure mechanism of the beam (brittle or ductile failure). Finally, the transverse steel stirrups increase the shear capacity of the member while limiting crack propagation. An integrated view of the flexural member's materiome provides complete view of the materials (concrete and steel), the structure-property-process relations (cross-sectional geometry, stress distributions, failure mechanisms), and the ultimate function (flexure). Of course, a concrete cross-section is a rather trivial example, not requiring a materiomics perspective. However, it illustrates the subtle interplay between structure-property-process relations and function. For example, based on the geometry of the cross-section alone (e.g., placement of the steel reinforcement), one could deduce the function of the member—as a beam subject to a positive bending moment. Alternate functions (such as a cantilever member, or as a column) would require variations in the structure, but could (potentially) implement the same material components. The structure—not the material—determines the function.

Functionally is ultimately obtained though material architecture. In the case of the concrete beam, an engineer, through analysis of structural requirements,

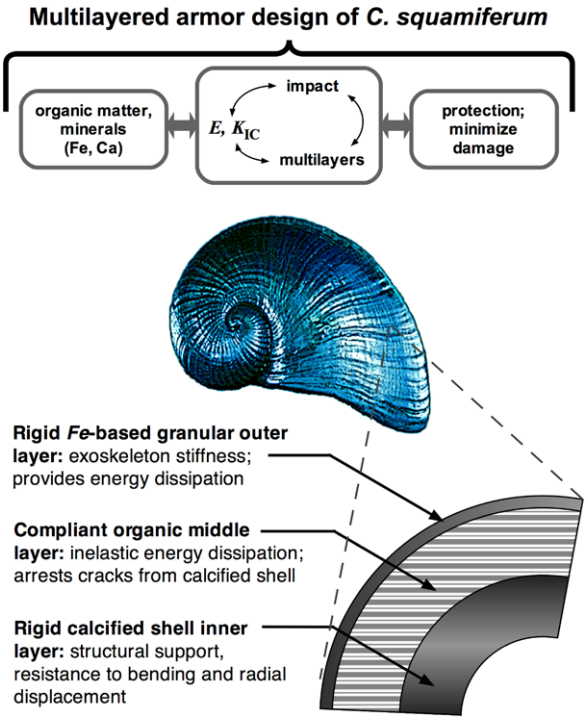

Fig. 2.9 Schematic representation of the materiome of a multilayered armor of *C. squamiferum*; adapted from Yao *et al*. [38]. Each material layer (structural component) serves distinct functional roles, contributing to the overall mechanical behavior of the shell. Variation of geometric parameters such as layer order of thickness would change the shell performance

determined macro-scale structure. However, the architecture of the gastropod shell, adequately summarized at the micro-scale as a composite of organic layers and mineralized platelets, explicates only the highest level of hierarchy. Hierarchical sublevels including the protein-based composure of the organic layer(s) [39, 40] and the properties of the organic-mineral interfaces [41] are still being investigated in nacreous materials, and are ultimately required for a complete description of the materiome and potential design of *de novo* synthetic materials [42].

2.5 Function Versus Application

It is apparent that the concept of materiomics is a subtle shift in the way we think about material systems. Materiomics attempts to ask more than simply what are the material components and properties of a system, but rather ask *why*. It shares a common goal with materials science in the fundamental understanding of materials, their structure and characterization, but extends breadth to multi-scale, multi-component attributes of the materiome. The overlap in concept between a material and materiome is discerning, and can easily muddle the distinction between the two. As such, a didactic example can be useful.

To facilitate the discussion, we consider the typical components of the materiome: (1) material components (building blocks); (2) structure-property-process

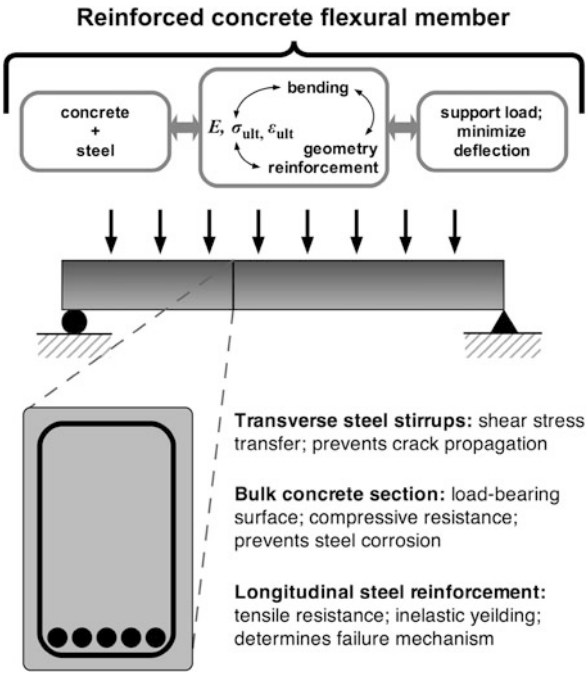

Fig. 2.10 Schematic representation of the materiome of a reinforced concrete flexural member as used in civil engineering. Each structural component is utilized for distinct purpose, the combination of which determines the properties and ultimate function of the flexural member. For example, relocation of the longitudinal steel reinforcement to the upper region of the cross-section is more suitable for cantilever beams—the same components can be assembled to serve difference functions

characteristics, and; (3) the function/requirement (depicted in general in Fig. 2.3; examples in Fig. 2.9 and 2.10). First we consider a typical material taught to many undergraduate students: copper. The critical question we ask is: *Do we need a materiomics approach to investigate bulk copper*?

We can certainly define the material components simply as copper atoms. We can even expand this definition to include the electron density attributed to each atom (which is critical to the electrical properties of copper). The structure is known to be "face-centered-cubic", of "FCC" for short, thereby describing the repeating lattice structure. From this structure and properties of the constituent atoms, we can theoretically determine material properties such as Young's modulus and shear modulus. From this we know that copper is ductile and malleable, and can investigate the onset of yielding, plasticity, and dislocations and the ultimate effects on material behavior and properties. At this point, copper has a well-defined materiome, however, copper, in itself, has no function or requirement. Copper, albeit, has many applications, including copper wires, piping, circuits, etc. that take advantage of the properties of copper, but these applications are not beget by the material itself, but rather from the ingenuity and foresight of a material scientist or engineer—copper is *chosen* as a component because its material *characteristics match the needs* (schematic of bulk material to application for copper depicted in Fig. 2.11). It has neither evolved nor been grown for function in the natural environment. It seems that a materiomics

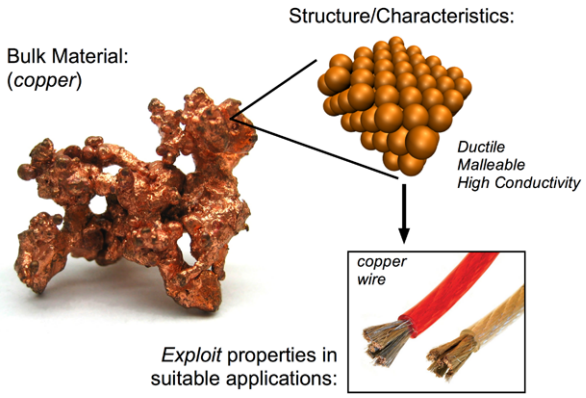

Fig. 2.11 Schematic of typical (non-materiomic) approach in determining material applications. A bulk material (in this case copper) is investigated to determine structural features, chemical make-up, and associated characteristics (mechanical and electrical properties, for example). From this checklist of features, suitable applications can be found that exploit the known properties—the malleability and high conductivity of copper, for instance, make it an ideal candidate for electrical wiring. The understanding we gain from copper allows us to look for other similar materials for similar applications (such as using gold, which has a similar crystalline structure), but copper—unlike biological materials—has no intrinsic *function* for which it has evolved or has been grown

approach—aside from offering a simple example—is superfluous in the description of copper.[2]

We can also consider a more "recent" material, such as carbon nanotubes [46]. Carbon nanotubes (CNTs) are among the most widely studied nanomaterials, with many potential applications that take advantage of their unique mechanical, electrical, thermal, and optical properties. There are many concurrent investigations involving carbon nanotubes, ranging from experimental synthesis to atomistic and continuum modeling with focus on a variety of properties, behaviors, and applications [47]. The superior mechanical properties of carbon nanotubes are appealing for their potential use in novel nanomaterials. For instance, the Young's modulus of a single-walled nanotube approaches a terapascal (10^{12} Pa) [48], with an ultimate stress approaching 60 GPa [49] implying that CNTs are one of the strongest known synthesized materials in terms of elastic stiffness and ultimate tensile strength [50]. Since their discovery over a decade ago [46], carbon nanotubes have been continuously studied, modeled, probed, and investigated for their potential applications in

[2]That is not to say, however, that we cannot improve on the properties of current widely used materials such as copper. Recent approaches have successfully enhanced the yield strength and ductility copper nanowires and films through a process of nanotwinning [43–45], exploiting the behavior of grain boundaries at the molecular scale. Improvements are possible, but such improvements can only enhance the intrinsic properties—new applications for copper may indeed emerge in electronics, biochips, NEMS, and many others, but if and only if the "new" enhanced properties satisfy the requirements of the chosen application.

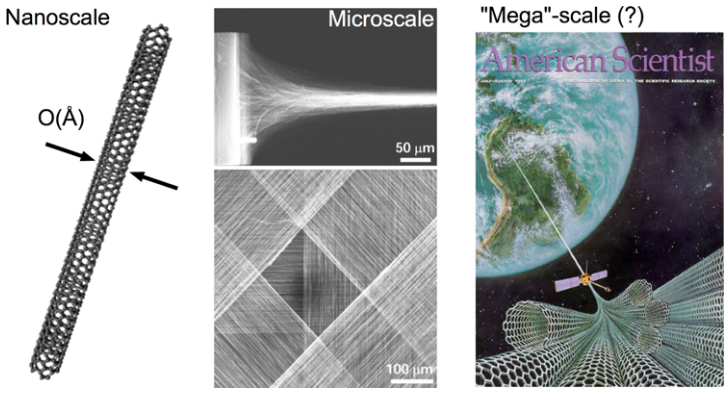

Fig. 2.12 Why can we not exploit the exemplary properties of carbon nanotubes for macroscale applications? At the nanoscale, carbon nanotubes are one of the strongest materials ever tested in terms of stiffness and ultimate tensile strength (*left*: molecular model of a (5, 5) single-walled carbon nanotube; length of 10 nm). Yet, when we combine multiple nanotubes together, either in sheets or in bundles, the intrinsic strength is lost (*center*: SEM micrographs showing the cooperative rotation of multi-walled nanotubes in a forest to form a sheet and a two-dimensionally reinforced structure fabricated by overlaying four nanotube sheets with shifts in orientation; printed with permission from American Association for the Advancement of Science, *Science*, [51] © 2005). Currently, the use of such high-strength carbon nanotube cables as a mega-scale "space elevator" from the Earth to a geostationary orbital tether is still the realm of science fiction (*right*: cover of American Scientists depicting an artistic interpretation of a carbon nanotube-based space elevator)

nanotechnological engineering. *Surely, the carbon nanotube is an ideal candidate for a materiomic description*?

Defining the material component is trivial: by definition, the building blocks carbon nanotubes are carbon atoms, specifically an allotrope of carbon consisting of covalent sp^2 bonds formed between the individual carbon atoms (similar to graphite). The structure is that of a cylinder, which can be defined by the length, diameter, number of nanotubes (*i.e.*, single-, double-, or multi-walled), and chirality (essentially the orientation of the rolled carbon structure). Further, there are also many known structure-property relations for carbon nanotubes, such as the buckling behavior of single- and multi-walled nanotubes [52, 53], the relation of chirality (*e.g.*, armchair or zigzag) to electrical conductivity [54, 55], or the effects of defects on thermal conductivity [56]. Indeed, one could easily claim that carbon nanotubes are perhaps the most thoroughly studied and investigated nanomaterial in recent years.

Amongst non-biological approaches, carbon structures such as carbon nanotubes offer exciting possibilities. Many potential applications have been proposed for carbon nanotubes, including conductive and high-strength composites; energy storage and energy conversion devices; sensors; field emission displays and radiation sources; hydrogen storage media; and nanometer-sized semiconductor devices, probes, and interconnects [47]. The pending question, or course, is what are benefits of a materiomics framework if it does not contribute to the understanding of a

material such as carbon nanotubes? Why should we bother with defining the materiome at all?

With all the interesting characteristics and extensive knowledge base developed for carbon nanotubes, they are not (currently) a prominent engineering material—a number of difficulties are associated with the large-scale implementation of such nanotubes. Indeed, with all the potential functions based on their unique properties, a practical *application* remains elusive (see Fig. 2.12). It seems carbon nanotubes, with all their potential, are still awaiting a purpose. Again, as with copper, the materiome is lacking intrinsic function.

While individual carbon nanotubes are like minute bits of string, and many trillions of these invisible strings must be assembled to make useful macroscopic articles. The question arises, to what extent are the extraordinary properties of CNTs scalable? One of the more exotic proposals for carbon nanotubes is the construction of a space elevator—a non-rocket spacelaunch structure which acts essentially as a tethered guideline from Earth to orbit. If the cable is long enough, centrifugal forces exceed gravitational forces and the cable will work under tension. The cable would represent the largest engineering structure, hierarchically designed from the nanoscale (single nanotube with length of the order of a hundred nanometers) to the megascale (space elevator cable with length of the order of a thousands of kilometers). A space elevator would revolutionize the methodology for carrying payloads into space at low cost, but its design is very challenging. The most critical component in the space elevator design is undoubtedly the cable [57], which requires a material with very high strength and low density—properties possessed by carbon nanotubes. While relegated to mere science fiction for over a hundred years, researchers are recently claiming that the feasibility of space elevator cable is now realistic, thanks to carbon nanotube technology, proposing its realization within a decade [58].

If we consider a space elevator cable with constant cross-section, the maximum stress reached at the geosynchronous orbit has been approximate to be on the order of is 60 to 70 GPa (if low carbon density is assumed for the cable). It is only recently, after the discovery of carbon nanotubes, that such large failure stresses have been measured experimentally, during tensile tests on ropes composed of single-walled [59] or multiwalled [60] carbon nanotubes, both of which were expected to have an ideal strength of >100 GPa, compared to steel and Kevlar at under ~ 5 GPa.

However, the current view of basing the design of the megacable on the theoretical strength of a single carbon nanotube has also been considered naïve [61, 62]. Indeed, the role of thermodynamically unavoidable atomistic defects (effecting fracture, fatigue and elasticity) is detrimental for scaling of nanotubes and nanotube bundles. In particular, the first *ab initio* statistical prediction for megacable strength suggest that a megacable of carbon nanotubes would have a strength lower than 45 GPa [62], and thus not strong enough for (current) designs of a space elevator. This result may not be surprising—inevitable defects in the nanotubes mean that nanoscale strength can never be realized. *Can we expect such scaling behavior in all materials*?

If we shift our focus to Nature, we find a "natural" tension cables in the form of spider silk (specifically, the dragline silk implemented as structural components

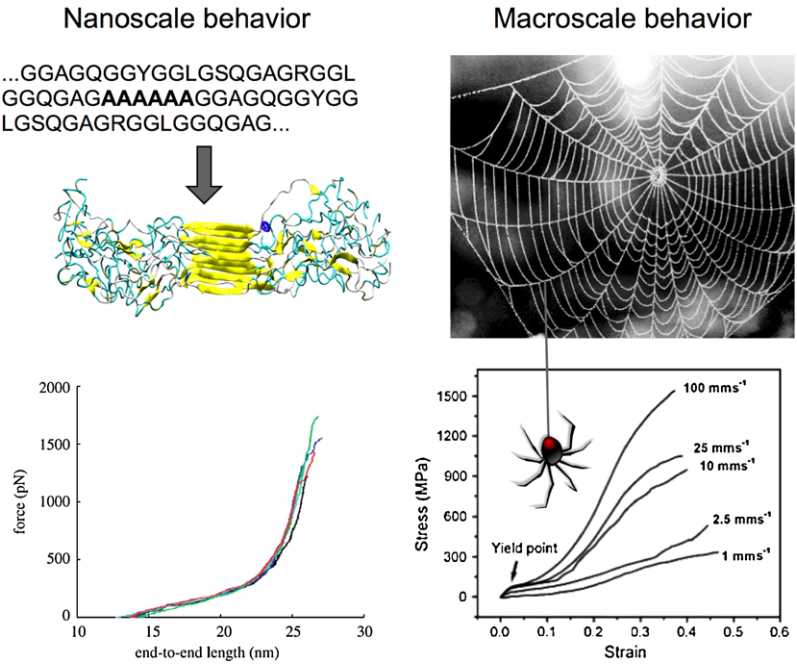

Fig. 2.13 Comparison of computational characterization of the molecular structure of dragline spider silk with experimental measurements of silk threads. Atomistic model constructed based on the known protein sequence, and the force-displacement behavior of the macromolecular structure can be investigated *via* simulation (plot from [64]). Converting the force-displacement behavior to stress and strain results in material behavior that closely resembles the results of macroscale experiments on silk threads, shown here for various spinning speed (plot from Du *et al*. [65], used with permission, Elsevier © 2006). Unlike ordered and synthetic nanotubes, the macroscale strength observed in silk threads is almost equivalent to the nanoscale strength observed in the protein structure (both on the order of ∼1 GPa) (see stress-strain graph in Fig. 8.8)!

in spider webs [63]). Spider silk will be discussed in more detail in Chap. 8: Unlocking Nature: Case Studies, but here we mention it for one remarkable fact: the macroscale strength observed in silk threads is almost equivalent to the nanoscale strength observed in the protein structure (both on the order of ∼1 GPa). Moreover, silk it is not even an ordered structure, like carbon nanotubes or crystalline metals, yet achieves strength by local, nanoscale crystalline regions of aligned β-strand protein segments (see Fig. 2.13).

While webs are obviously not on the scale of a space elevator, they are significantly large structures to the perspective of a spider, and yet the spider exploits the strength of silk at the molecular level in web construction. Is spider silk defect free? This is highly unlikely. Then how does Nature solve the scaling problem? Perhaps one key is the disorder of silk—it has been known for decades that crystalline materials are sensitive to defects, and that they show a clear drop in strength with increasing size. Crystalline structures typically lead to stress concentrations and brittle

fracture induced by the symmetric surfaces and slip planes, features avoided by more amorphous arrangements of materials, exemplified by silk.

While silk is characterized by the combination of disordered, semi-amorphous regions peppered with small sections of crystalline β-strands (similar to cross-linked polymers), silk is also composed of atomistic to macro-scale hierarchies, in a complex arrangement still being investigated. The hierarchies elicit flaw-tolerant behavior, inherently optimizing the performance of silk. The structure and robust properties of silk are attained by relatively few chemical constituents (amino acids), with interactions much weaker than those found in metals and nanotubes (*i.e.*, hydrogen bonding), yet silk accomplishes a feat we have yet to engineering—expressing nanoscale strength at macroscale functionality.

What can we learn from the complex materiome of silk? What are the underlying principles for flaw tolerance? Can we apply the understanding of silk to the use of carbon nanotubes in a space elevator? Perhaps the introduction of disorder, making the strength of individual nanotubes less crucial, and the introduction more hierarchies for a megacable? Quoting N. Pugno: "*... is the space elevator out of order*? *Our opinion is*: *at present, yes*; *but never say never*" [62]. Perhaps the key lies in Nature, and the understanding the materiome of silk, and what it may share with other material systems.

What kind of properties does materiomics discover? Unfortunately, the nomenclature and prospective metrics of materiomics are still being developed. Definitions and measures for material structure-property relations, hierarchical effects, links between functionality and requirement, and others, are crucial. Cooperativity, hierarchical degrees of freedom, multiscale interactions, flaw tolerance, and other concepts have qualitative meanings, but are more difficult to quantify and compare than traditional material properties such as mechanical stiffness of thermal conductance. Appropriate terminology for cross-scale relations such as scale separation, integration and interaction must be defined, encompassing all material components and effect on system properties and behavior. The field of materiomics will stimulate extensive research in these directions, beyond the investigation of one-off material applications, to the cohesive extension and design of materiomic function from nano to macro, and develop a distinct lexicon.

2.6 Material Behavior Scaling: Multiscale Perspectives

The previous section illustrated a critical problem in material selection: just because a material has exceptional properties at one scale (such as carbon nanotubes; Fig. 2.12), it does not mean we can exploit those properties at larger scales (yet accomplished by silk; Fig. 2.13). Perhaps we can use silk as a component of our space elevator? Even if we could train millions of spiders to spin our space elevator, there is another problem—silk, while extremely strong in terms of ultimate stress, is also extremely extensible (*i.e.*, stretchy). Steel, for example, has a yield strain of about 0.5 % whereas dragline silk can sustain strains of over 30 %. While the combination

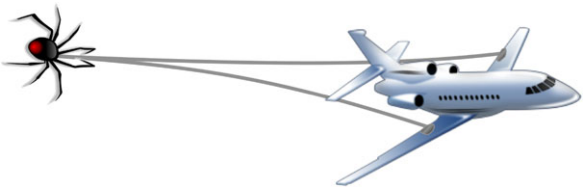

Fig. 2.14 Can we use spider silk to stop a plane in flight? Mechanically, the answer is yes. A one centimeter thick thread of silk can stop a plane traveling ~200 mph. Unfortunately, this is impractical for two reasons: (1) the thread would have to be over thirty kilometers long and (2) due to the extensibility of silk, the plane would need another nine kilometers to come to a complete stop. The full strength of silk is only realized at such high extension. It seems the properties of natural silk are not suitable for large scale applications. Can we improve over Nature's design?

of strength and extensibility enhances the toughness of silk (a good property if you want to catch flies in your web), practical problems arise if you try and envision macroscale structures made from silk. A popular statement about the strength of spider silk is:

> A pencil thick spider's silk thread is capable of stopping a Boeing-747 in full flight.

While mechanically true (Fig. 2.14), it would require a silk thread approximately thirty kilometers in length, which would stretch another nine kilometers before bring the plane traveling at approximately 200 mph to a stop [66]. The extensibility of silk is disadvantageous as the application gets larger—for example, a suspension bridge supported by silk would greatly sag in the center (where load is the greatest). If we assume Spiderman swings over Manhattan using natural silk, he would hit the streets more often due to the extreme stretchiness (of course, the radioactive spider that bit Peter Parker may spin silks with different properties).

A pertinent question immediately arises: How does the function of silk relate to its material properties? This question is currently being investigated by biologists and materials scientists alike to unlock the "blueprint" (or materiome) of silk across multiple scales. Perhaps in the future we *can* design bridges with silk-like cables or robust and tough silk-like textiles and armors. Can we likewise integrate carbon nanotubes in silk-like configurations? The key lies in the material scaling behavior of the constituent "building blocks", and how those blocks are assembled. This requires a multiscale perspective from the molecules up.

Even limited knowledge of the nanoscale structure combined with molecular (or atomistic) interactions or a material can potentially shed great insight into the mechanical properties and potential material applications (or functions) of a material. Again, we can examine a simple crystalline material (such as copper) as an illustrative example where this approach works extremely well. Due to the known homogeneous repeating crystalline structure, combined with a rudimentary (in terms of potential parameters) atomistic interactions, relatively accurate approximations of macroscale mechanical and bulk elastic properties can be deduced from a nanoscale perspective (see Fig. 2.15).

Such a "molecular mechanics" approach is encompassed by such techniques as the Cauchy-Born rule (in which atomistic potentials are equated with continuum

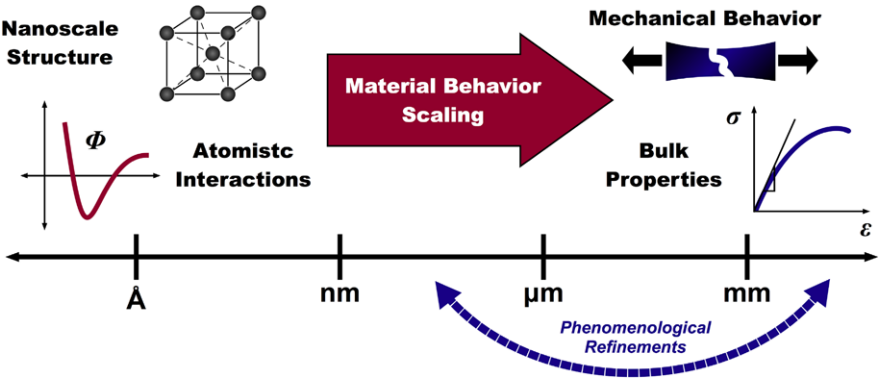

Fig. 2.15 Schematic of material behavior scaling, wherein known behavior at a fine-scale (such as atomistic) is adequate to describe large-scale behavior and properties. Here, we depict the scaling of a crystalline material (such as FCC based polycrystalline copper) wherein the atomistic interactions can be used to describe mechanical properties such as bulk modulus and fracture toughness through relatively simple approximations (*e.g.*, Cauchy-Born rule). Refinement is sometimes necessary to account for phenomenological effects, such as the presence of grain boundaries, inclusions or other defects

theories) as well as atomistic-scaled finite element formulations. In essence, it is assumed *a priori* that the behavior and properties between atoms can be easily (and suitably) extended to the micro- and macro-scales. The Cauchy-Born rule relates microscopic deformation fields with macroscopic stresses and strains [67, 68]. The central assumption of the Cauchy-Born rule is to express the energy of an atomic system as a function of an applied strain tensor, $\underline{\underline{\varepsilon}}$, and it is assumed such continuum fields can be mapped to the atomic scale (see Chap. 7: Mechanical Characterization in Molecular Simulation for further discussion). An atomic unit cell is selected as a representative volumetric element (RVE) to formulate the strain energy density, $\phi(\underline{\underline{\varepsilon}})$. In crystal lattices with pair-wise interactions, the strain energy density can be formulated as a some over all the bonds a unit cell, or:

$$\phi(\underline{\underline{\varepsilon}}) = \frac{1}{\Omega}\sum \phi_i(r_i) \tag{2.1}$$

The interatomic potential, $\phi_i(r_i)$ to represent crystalline metals, for example, can be the relatively simple Morse potential [69, 70], which is defined by three parameters, D, α, and r_0, or:

$$\phi(r) = D\left(1 - e^{-\alpha(r-r_0)}\right) \tag{2.2}$$

From the simple assumption of the Cauchy-Born rule, we invoke the atomic potential and structural information, and can directly derive material constants such as the bulk modulus, shear modulus, elastic modulus and Poisson ratio. For example, the bulk modulus can be determined as:

$$K = V_0 \frac{d^2\phi}{dV^2}\bigg|_{r=r_0} \tag{2.3}$$

With some further refinement, such scale-bridging extension has proven successful for many systems, especially crystalline and metallic systems with homogeneous repeating (*e.g.*, polycrystalline) structures (common materials subjected to micromechanical modeling; see Fig. 2.15). It would be trite to label such complex systems as "simple" and "completely described by the atomistic potentials" as there exists a multitude of complex phenomenon that require refinements and nontrivial model formulation for accurate predictions of such models including (but certainly not limited to) dislocations, grain boundary effects, defects and voids, composite material behavior, viscoelastic effects, or thermal transitions (*i.e.*, brittle to ductile behavior).

The point, of course, is that knowledge of the nanoscale structure and interactions of copper atoms versus carbon atoms, for example, gives some indication (subject to refinement) of macroscale properties. One may infer, without any physical specimens to test, that carbon, with a more robust crystalline structure and stronger interatomic bonds, results in the stronger, stiffer material (*i.e.*, diamond) than bulk copper. As you may have guessed by now, such is not the case for biological protein materials. Hierarchical multiscale structures, seemingly disordered ordered arrangements (similar to polymer blends), complicated convoluted structures (*i.e.*, the quaternary structures of folded proteins), preferred interactions (such as protein "lock-and-key" mechanisms), and environmental influences (including solvent pH, temperature, etc.) make any kind of material property extrapolation from the nanoscale to the macroscale naive. On the one hand, just because we can investigate how actin[3] behaves at the molecular level [71, 72] does not mean we can deduce the behavior of the cytoskeleton [73] (see Fig. 2.16). Be that as it may, even limited understanding of keratin[4]—specifically the disulfide bond bridges at the molecular level—resulted in the popular "perm" hairstyle, which uses heat and chemicals to break the disulfide links in hair. It seems some molecular characteristics *are* expressed at the macroscale, for some protein-based materials. How do we know what we can predict and control at the macroscale?

Again, whereas there was an explicit dichotomy between materials with complex hierarchical structures (such as silk, collagen (bone or tendon), actin (cytoskeleton), keratin (hair), etc.) and homogeneous crystalline structures (such as copper or diamond) we also note a discrepancy in the scaling of the properties between material systems. To overcome this scaling issue, smaller increments of scaling must be introduced to bridge hierarchical levels. Thus, we introduce the concept of *material behavior scaling* (MBS) to our materiomics framework.

[3] Actin is a type of globular protein found in all eukaryotic cells in species as diverse as algae and humans, and is one of the three major components of the cytoskeleton. Actin participates in many important cellular processes including muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling, and the establishment and maintenance of cell junctions and cell shape.

[4] Keratin refers to a family of fibrous structural proteins, the key structural material making up the outer layer of human skin and the key structural component of hair and nails. It is part of the family of intermediate filament proteins.

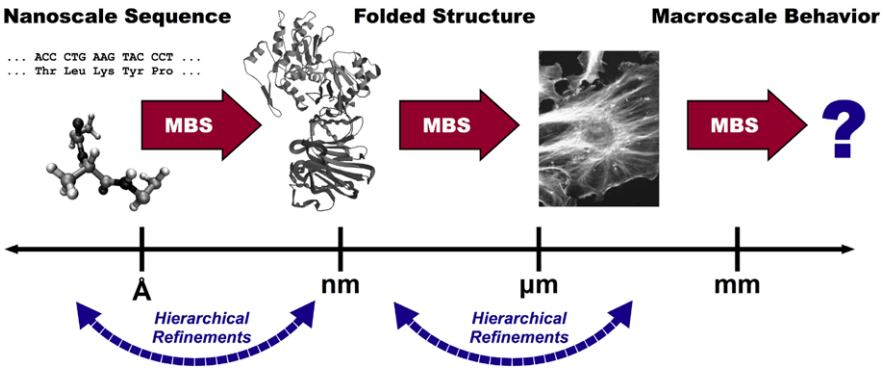

Fig. 2.16 Schematic of material behavior scaling for more complex material systems. Here, known behavior at a fine-scale (such as atomistic) is adequate to describe behavior and properties at the next subsequent scale only, where the ensuing structure is known. Thus, to predict ultimate macroscale behavior and properties, a hierarchical approach is required, wherein knowledge at each scale is combined in a materiomic framework. Here, we depict the scaling of actin, a protein material found in the cytoskeleton. Atomistic interactions can be used to approximate the folded structure, for example, but at this scale, interactions with other proteins (such as myosin) and the cellular environment must be taken into account to fully describe the cytoskeleton behavior affected by actin

Material Behavior Scaling: The extent in which a fine-scale description of the mechanical properties and behavior of a material adequately describes a larger scale. An *ideal scaling material* is one in which a small-scale description—considered here the *ab initio* material description—is sufficient to describe the material properties and behavior at *all* scale levels, transcending Ångstroms to meters. A *nonscaling material* exhibits disparate properties from one scale to another.

A complex materiome has, by definition, limited material behavior scaling—knowledge of the properties and behavior at any (arbitrary) scale gives little indication of properties at higher or lower scales. By extension, without consideration of the entire multi-scale system—bridging atomistic structure to intended functionality—analysis, investigation and understanding of a single (limited) scale is moot. This is not a new perspective attributed to materiomics. Indeed, it is a well known that modifications of ultra-small or nanoscale features in materials can lead to significant changes in the macroscopic behavior. Similar mechanisms have been known for a long time in the physics or mathematics communities, who have been studying the dynamical properties of nonlinear (or chaotic) systems. In fact, many optical or magnetic properties are based on such microscopic collective mechanisms, leading to dramatic changes at the macroscopic scale.

Basic concepts of mechanics of materials typically assert a “bulk” perspective to material systems. This is insufficient for complex materiomic systems in which

a multiscale perspective is necessary. Classical theories of the strength of solids, such as fracture mechanics or those based on the maximum stress, assume a continuum. Even if such a continuum hypothesis can be shown to work at the nanoscale for elastic calculations (such as in our example of copper), it has to be revised for computing the strength of nanostructures or nanostructured materials (such as carbon nanotubes). Biological materials, on the other hand, are particularly complex, which requires the analysis of mechanisms across multiple scales. For mechanics of materials, such concepts have thus far not systematically been exploited, and are often poorly understood. One reason is that in the past, structural changes at the nanoscale have not been possible, which made it difficult to confirm theoretical explanations and concepts that link nanoscale and macroscale quantitatively. However, such atomic-scale manipulations of matter is now reality.

For biological materials, and in particular those based on proteins, genetic engineering has become an important tool to address precisely these questions. These techniques enable scientists and engineers to change specific genes, leading to mutations in the sequence of proteins, at the scale of several Ångstrom. This has significant impact in understanding diseases, which often origin from such mutations. Concurrently, genetic manipulation also allows the creation of new materials. Nature can be exploited to produce new biological materials—known as biocomposites—derived from known structures modified to feature improved properties [74, 75]. Biocomposites are structural "green" materials made from renewable resources that biodegrade in an anaerobic environment after their useful service life to produce a fuel or feedstock to produce a biopolymer for a new generation of composites. Some of these, such as cellulose and starch are actively used in products today, while many others remain underutilized. Promising candidates for such biocomposites range from a diverse set of polysaccharides, proteins, lipids, polyphenols, and specialty polymers produced by bacteria, fungi, plants and animals [76]. Such materials are being researched and developed to replace less eco-friendly structural and non-structural materials used in the construction industry [77, 78]. The key for such material development and rapid advancement lies in the understanding of fundamental biosynthetic pathways and options to modulate or tailor these pathways through genetic manipulations—a process than necessitates a holistic bottom-up perspective. Such biologically produced systems are intriguing examples for a systematic microscopic changes in building block growth (resulting from, for example, genetically modified bacteria)—which can actually be performed, with extremely high accuracy—and whose affect on macroscale behavior can be measured. Complete understanding of interactions and growth factors across scales remains elusive. Yet, it is the key to decipher the origins of diseases, mechanisms of cellular and tissue processes, and the development of new biologically inspired materials.

2.7 Extending the Materiome: Hierarchies and Complexity

Clearly, from the discussions of bone and tendon (Fig. 2.6), lobster cuticles (Fig. 2.8), actin (Fig. 2.16), and spider silk (Fig. 2.13), as well as the deficiencies

of scaling carbon nanotubes (Fig. 2.12), and the simplicity of a material like copper (Fig. 2.11), a materiomic framework is most beneficial to describe complex, multiscale hierarchical materials—such materials common to biological systems and tissues. In this context, the term "hierarchical" is used loosely to indicate a material system with at least a single distinct differentiation between constituent material components and global system structure. Collagen fibrils found in tendon, for example, are composed of as tropocollagen molecules, while the tropocollagen fibrils are themselves composed of a hierarchical arrangement of polypeptide chains, which are also composed of constituent amino acids. Depending on the level of scrutiny, the defined "lowest level of hierarchy" need not be the fundamental building blocks of the system.

Hierarchical System: A system composed of stable, observable sub-elements that are unified by a super ordinate relation. Thereby, lower level details can affect higher levels and thus the overall system behavior. A common characteristic of biological materials.

The materiome must adequately encompass both the hierarchical structure and intrinsic complexity beyond a simple catalogue of scale-by-scale structures, properties and interactions. A holistic approach must integrate the information inherent to the materiome (consisting of the material constituents, the cross-scale SPP relations, and the resulting functionalities/requirements) across all-scales, as hinted by Fig. 2.7. Conceptually, this is depicted in Fig. 2.17. Note that each "hierarchy" and reduction in scale can represent multiple branches and material components that require investigation and characterization. For example, actin is only one of three primary components of the cytoskeleton, the other two being intermediate filaments and microtubules. Each structure can be characterized at the molecular scale, but the interactions must be collectively considered at the cytoskeleton scale and beyond.

The combinatorial nature of these building blocks results in the emergence of complexity within the materiome. Again, we see that "whole is greater than the sum of its parts". Even if we had a full molecular understanding of actin, intermediate filaments, and microtubules, we would not be able to predict the behavior of the cytoskeleton by simple additive (or similar) relations—the system is considered nonlinear. The system is more complex, with each protein material affecting the behavior and properties of the other in ways unpredictable from inspection of a single element. Note that this is different than the common structural engineering approach depicted in Fig. 2.5—we know how a steel truss will behave regardless if is in a system of other steel members, concrete walls, or wooden columns. Such inability to predict behavior limits potential scaling of such material components.

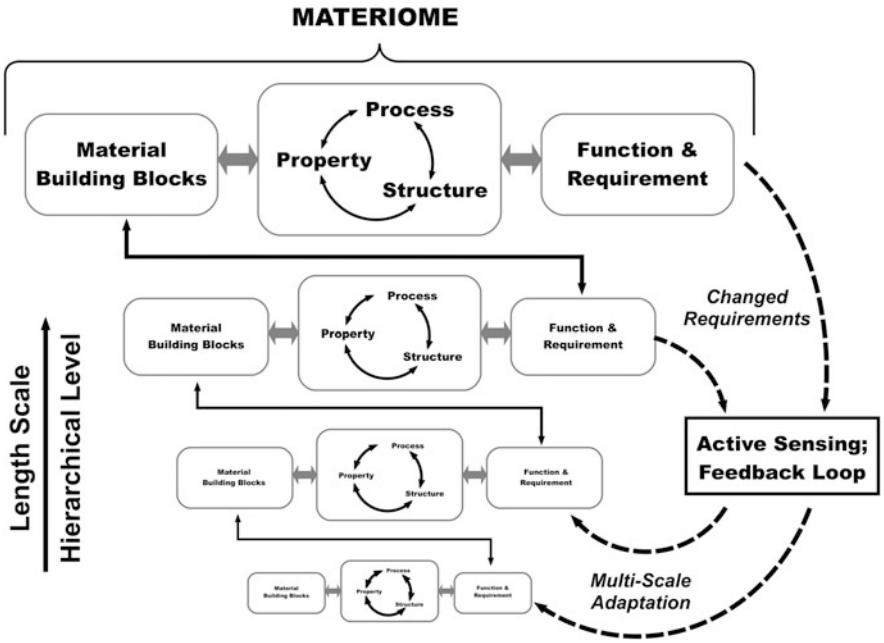

Fig. 2.17 Schematic of *extended* materiomic information, consisting of the material constituents, the cross-scale SPP relations, and the resulting functionalities/requirements across *all* levels of hierarchy. Commonly, biological materials exhibit hierarchical structures in which material properties and environmental requirements are brought together in mutual completion transcending multiple scales (*i.e.*, subtle changes at the molecular scale due to macroscale environmental influences). In contrast to a traditional materials science paradigm, relations between "external" functions/requirements and "internal" properties exist on several scales resulting in multifunctionality

Complexity: The existence of many interacting components and leads to emerging nonlinear behavior of a system. Complexity in a material system (*i.e.*, a complex *materiome*) necessitates the quantification of cross-scale interactions and mechanisms, which cannot be deduced from general scaling relations.

This complexity can be likened to the mathematical field of chaos. Chaos theory is a field of mathematics, with applications in several disciplines including physics, economics, biology, and philosophy. In simplest terms, chaos theory studies the behavior of dynamical systems that are highly sensitive to initial conditions—an effect which is popularly referred to as the butterfly effect.[5]

[5]The butterfly effect is the sensitive dependence on initial conditions where a small change at one point in a nonlinear system can result in large differences to a later state. The effect is coined after a thought experiment, where a butterfly flapping its wings in Japan can directly lead to creation of a hurricane in Florida.

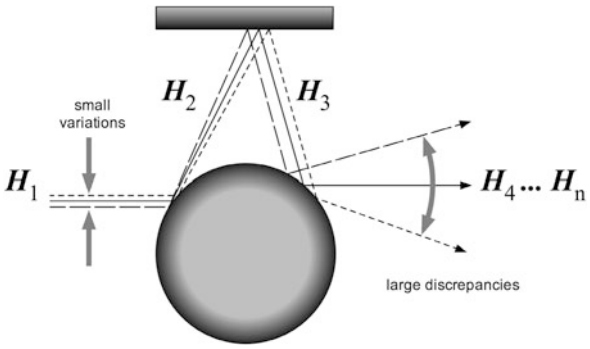

Fig. 2.18 Simple depiction of effect of variations in a complex hierarchical system (chaotic behavior). Slight perturbations in input (lowest level of hierarchy) propagate across all scales, resulting in large discrepancies in system-level (highest level of hierarchy) properties and behavior. Single-scale analysis and characterizations are rendered inadequate without consideration of system level effects

Chaotic behavior can be observed in many systems, such as the weather or financial markets. Small differences in initial conditions (such as those due to rounding errors in numerical computation) yield widely diverging outcomes for chaotic systems, rendering long-term prediction impossible in general. This happens even though these systems are deterministic, meaning that their future behavior is fully determined by their initial conditions, with no random elements involved. In other words, the deterministic nature of these systems does not make them predictable. This behavior is known as deterministic chaos, or simply chaos. From a materiomic perspective, small differences in initial conditions refers to a change in protein sequence, or a small geometrical re-arrangement in structure. Unlike the weather of financial markets, however, the chaos (or complexity) of a materiome arises due to multiscale interactions and bridging of hierarchies. Such chaotic behavior across hierarchies can be visualized by the path of a multiple reflected light beam (Fig. 2.18), where each reflection corresponds to a higher scale.

This may present a problem in the development and understanding of complex materiomic systems. If small perturbations result in divergent properties, any behavior or property observed in Nature, however, would be idiosyncratic to each individual system. Obviously, this is not the case. The self-assembly (or growth) of Nature's materials is not an ordered atom-by-atom (or even protein-by-protein) construction—it is a highly stochastic process driven by varying factors and environmental conditions which preclude systematic "quality controls". Yet the final systems are remarkable consistent in terms of behavior and functionality. If such systems are complex, chaotic, and unpredictable, *how does Nature achieve such dependable materials and systems*?

Nature, it seems, has developed multiple safeguards or buffers to ensure slight deviations in input do not result catastrophic changes in macroscale system behavior. They are robust by design, without resorting to the redundancies or backup systems typically introduced to engineered systems to prevent complete failure. This

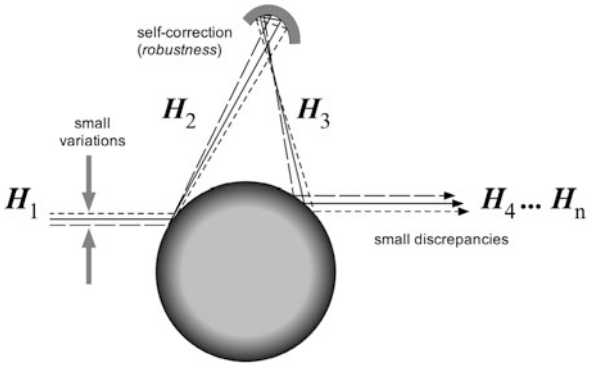

Fig. 2.19 Simple depiction of effect of variations in a complex hierarchical system with intrinsic robustness. Here, there is a natural "safeguard" mitigating divergent behavior from the first to second hierarchies (H_1 to H_2). Small variations at the lowest level have marginal effects at larger scales. Such safeguards can come in the form of geometrical arrangement, material combinations, etc., that reduce the chaotic behavior of biological materials and systems, without resorting to the redundancies or backup systems typically introduced to engineered systems

too can be represented by the reflecting light analogy—while deviations in input cause divergent behavior across hierarchies, natural safeguards at specific hierarchies reverse, reduce, or eliminate the divergent behavior. The result is such that the variations at lower scales have marginal effects at larger scales (see Fig. 2.19).

The means by which such safeguards are accomplished is highly dependent on system function and scale. For some systems, such as bone, elimination of divergent behavior can be seen in the geometric assembly, such as the characteristic length scale of collagen fibrils, which increases flaw tolerance, enhancing toughness. Unavoidable flaws such as voids or cracks in the mineralized hydroxyapatite, for example, do not propagate throughout they system and bone maintains its inherent strength (the toughening mechanisms in bone are discussed further in Chap. 8: Unlocking Nature: Case Studies). The same flaws would significantly decrease the strength of carbon nanotubes. At a larger scale, the composite shells of gastropods or lobster cuticles combine materials (soft protein-based materials with stiffer mineralized materials) that serve to arrest cracks and dissipate energy. Small structural defects are not detrimental to the system. Even the cytoskeleton—with a seemingly random arrangement of actin, intermediate filaments, and microtubules—exploits the mechanical properties of each in a synergistic manner (intermediate filaments provide tensional strength, while microtubles are compressive members, in a biological tensegrity structure, for example). The combined behavior within the cellular membrane is consistent, even if there are deviations amongst the structural members in spite of the seemingly random arrangement.

Nature effectively avoids the divergent aspects of chaotic systems, but does not eliminate the inherent complexity. Note, however, that Nature has not (and cannot) prevent the effect of all minute changes in initial (or molecular) conditions. For instance, single point mutations (a simple swapping of amino acids) within the

tropocollagen structure results in *osteogenesis imperfecta* (more commonly known as brittle bone disease), a disease discussed further in Chap. 9: Pathological Materiomics. Can such conditions be predicted? More importantly, can such conditions be avoided by understanding what kind of mutations propagate across the hierarchical scales? Which mutations are inherently "chaotic"? This are critical questions materiomics attempts to answer.

2.8 Summary

The preceding chapter has introduced a fundamental concept central to materiomics: the materiome. The materiome is a holistic perspective of a material system,—"the whole is greater than the sum of its parts"—that attempts to integrate properties, behaviors, and interactions beyond a simple scale-by-scale characterization. Like the genome, it will associate meaning with the constituent building blocks, and allow the decomposition of complex phenomena found in biological materials. Just as proteomics elucidates protein-protein interactions, materiomics can investigate the structure-property relationships of nutrient transport in tissue engineering, for example.

As discussed, a materiomic framework is necessary when the distinction between structure and material is difficult to define, and may change according to scale, and when functionality emerges from the materiome itself (not selected for an *ad hoc* application based on desired/required properties). Defining the materiome is not without challenges—characterized by multiscale hierarchies, complexity, and (sometimes) chaotic relationships inherent in biological materials. Such systems require new approaches to investigate, and warrant new metrics and heuristic techniques to characterize. Can abstract terms such as hierarchies and complexity be quantified? Can the system level effects of atomistic changes even be predictable? Are there universal motifs of structure and geometry within biological systems? What material combinations can possible enhance tissue growth? Can such design principles even be adapted to inorganic construction materials (such as carbon nanotubes)? Many of these questions are being investigated in one form or another, but are separated by disparate disciplines, motivations, and goals. They are all, however, defining the materiome. Therein lies the opportunity to exploit the designs of Nature.

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