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Computational and Theoretical Materiomics: Properties of Biological and *de novo* Bioinspired Materials

Markus J. Buehler

Laboratory for Atomistic and Molecular Mechanics, Department of Civil and Environmental Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave. Room 1-235A&B, Cambridge, MA, USA; Center for Computational Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA, USA; Center for Materials Science and Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA, USA

Computational and theoretical efforts towards a quantitative understanding of biological as well as synthetic bioinspired and biomimetic materials (e.g., DNA, proteins, mineralized structures as well as soft tissues), their assembly, properties, and interaction with their environment has evolved into an active area of research at the interface of physical sciences and biology. The use of theoretical and computational multi-scale approaches enables critical progress in linking the chemical or molecular, and mesoscopic structures of these materials to macroscopic properties, across disparate scales, an effort defined as computational materiomics. Such studies are crucial in understanding the impact of genetic mutations, structural flaws and defects, hierarchical structures, solvent or pH changes, and other chemical stimuli on the properties of materials. In the study of these materials, the integrated use of a suite of computational and theoretical approaches is vital to cover all relevant material properties and scales, and includes first principles calculations, atomistic and molecular modeling, "coarse-grained" multi-scale approaches as well as continuum theory based methods. The objective of this review article is to summarize recent progress made in this field of research and to highlight opportunities of computational and theoretical efforts to contribute to nanomedicine, nanoscience and nanotechnology. Properties of interest broadly include mechanical, biological/bioactive, optical, thermal, as well as electronic properties. To illustrate applications of materiomics, we highlight a case study of material performance of alpha-helical protein filaments, and discuss opportunities associated with combining disparate material properties in *de novo* bioinspired nanomaterials.

Keywords: Hierarchical Materials, Nanoscience, Nanotechnology, Nanomechanics, Materiomics, Biological Protein Materials, Experiment, Simulation, Bottom-Up.

CONTENTS

1. INTRODUCTION

The properties of materials are of fundamental importance to biological tissues, organs, organisms and species, and are crucial to providing functional properties to all living systems. Example properties that are crucial in biology include the strength toughness of bone,[1–4] the elasticity of spider silk,[5–7] or the stretchiness of the skin and other soft tissues.[8–14] Most fibers, tissues, organs and organisms found in nature show a highly hierarchical and organized structure, where features are found at all scales, ranging from protein molecules (≈50 Å), protein assemblies (≈1 to 10 nm), fibrils and fibers (≈10 to 100 μm), to cells (≈50 μm), and to tissues and organs (≈1000 s and more μm).[15–23] Figure 1 shows a summary of the structural makeup of two example protein materials, intermediate filaments and amyloids, revealing their hierarchical structures that range from nano to macro. The fact that virtually all biological structures feature nanostructural elements at the most fundamental level suggests that new insight into nanoscience and nanotechnology can be derived from the study of these materials, in particular given that biological materials feature an intriguing set of properties as listed in Table I.[24]

Recent research has revealed that this hierarchical makeup of biological materials is elementary to their ability to provide specific biological functions. However, at this point it remains poorly understood what the role of these distinct hierarchical structures are, how they regulate the growth and function of biological systems, and what the driving forces are for their formation. A materials science

approach is a powerful strategy to investigate synthetic and biological systems from this perspective, a field of study referred to as materiomics,[25,26] where Table II includes a definition of relevant terms. Figure 2(A) shows the conventional materials science triangle that links structure, process and property. Figure 2(B) displays the materials science paradigm applied to the hierarchical structure of protein materials. Thereby *Hi* refers to hierarchy levels $i = 0 \ldots N$, and *Ri* refers to material property requirements at hierarchy levels $i = 0 \ldots N$. The expanded triangle shown in Figure 2(B) specifically includes the link of material properties and genetic processes (s.a. gene activation), which play a key role in understanding adaptability of biological materials. Thereby, biochemical processes facilitated by sensing of the environment of cells (for example in angiogenesis[27]) may change gene expression or activation, which results in inducing a change in cell behavior.

Theoretical and computational multi-scale approaches have emerged as a particularly promising strategy in pursuit of materiomics studies, through their ability to seamlessly link nano to macro. Figure 3 shows a schematic of a computational multi-scale approach, where the integration of computational methods from the atomistic, molecular, mesoscale, to the macroscale enables a seamless treatment of biological materials, tissues, and structures. The use of a broad variety of computational and theoretical techniques is required to cover all relevant material properties and scales. Relevant methods include first principles calculations, atomistic and molecular modeling, multi-scale approaches (e.g., coarse-graining), as well as continuum theory based methods. Both concurrent multi-scale methods (i.e., the use of methods of different accuracy in the same computational domain) and hierarchical multi-scale methods (i.e., the sequential, hierarchical use of methods through parameter passing) are applied. By providing a systematic analysis of material structures, properties and processes at distinct scales, the hierarchical materials science approach as shown in Figure 2(B) can be realized.

2. EXAMPLES

Biology utilizes hierarchical structures to create multifunctional materials. The requirement of natural systems to support multiple and diverse functions explains the formation of hierarchical structures with defined length-scales for key protein domains that are, as a consequence, found as universal features throughout biology. In fact, the formation of hierarchical structures facilitates the emergence of diverse properties created by universal building blocks, a concept referred to as the Universality-Diversity Paradigm (UDP).[17] Furthermore, a fundamental difference between engineered materials and naturally formed biological materials is that functionality in biology can be created by arranging universal building blocks in different patterns, rather than by inventing new types of building blocks, as typically done in many engineered materials.

Markus Buehler received his undergraduate education at the University of Stuttgart, Germany in Chemical and Process Engineering, and holds a M.S. degree in Engineering Mechanics from Michigan Technological University, USA. He worked at the Max Planck Institute for Metals Research in Stuttgart, Germany as a research assistant from where he also received his Ph.D. in Chemistry. Professor Buehler held an appointment as the Director of Multiscale Modeling and Software Integration at the Materials and Process Simulation Center at the California Institute of Technology before joining the Massachusetts Institute of Technology to assume a faculty appointment in the Department of Civil and Environmental Engineering. Professor Buehler's research focuses on bottom-up simulation of mechanical properties of biological, bioinspired and synthetic materials by utilizing a computational materials science approach. His recent work has focused on applying a computational materials science approach to study materials failure in biological systems, including the investigation of material breakdown in diseases. Professor Buehler has published more than 110 articles on computational modeling of materials using various types of simulation techniques. Among others, Professor Buehler has received the 2004 Materials Research Society First Prize Gold Graduate Student Award, the 2007 National Science Foundation CAREER award, the 2008 U.S. Air Force Young Investigator Award, the 2008 Navy Young Investigator Award, and the 2008 DARPA Young Faculty Award. In 2009, his work was recognized by the Presidential Early Career Award for Scientists and Engineers (PECASE). He was cited as one of the top engineers in the country between the ages of 30–45 through invitation to the 2007 National Academy of Engineering-Frontiers in Engineering symposium of the National Academy of Engineering. Professor Buehler serves as a member of the editorial board of several journals, including: PLoS ONE, International Journal of Applied Mechanics, Journal of Engineering Mechanics (ASCE), Mechanical Behavior of Biomedical Materials, Journal of Computational and Theoretical Nanoscience, and Acta Mechanica Sinica. He is a member of the U.S. National Committee of Biomechanics and the chair of the ASCE Biomechanics Committee. Professor Buehler currently holds the Esther and Harold E. Edgerton Career Development Professorship at MIT.

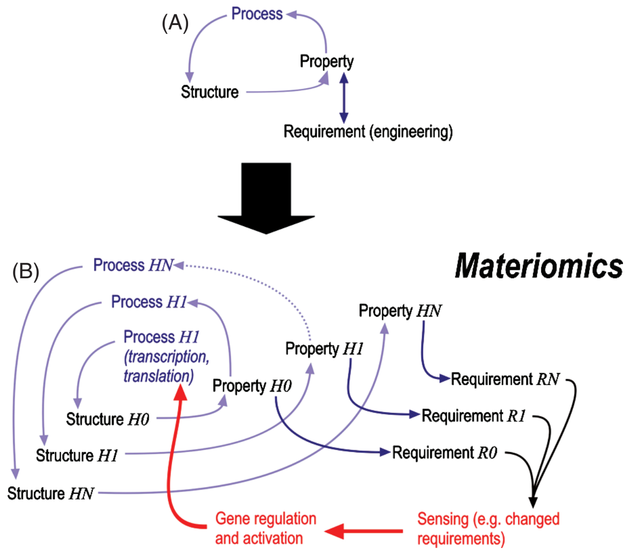

Fig. 1. Conventional materials science paradigm (panel A) and hierarchical materials science paradigm applied to biological systems, referred to as materiomics (panel B). The variables Hi refer to hierarchy levels $i = 0 \ldots N$, and Ri refer to material property requirements at hierarchy levels $i = 0 \ldots N$. Computational materiomics is defined as the use of computational methods to assess relations between processes, structures and properties at multiple material levels. Adapted with permission from [18], M. J. Buehler and Y. C. Yung *Nat. Mater.* 8, 175 (**2009**). © 2009, Nature Publishing Group.

The cause and effect of biological material mechanics is a complex process that is not restricted to a singular structure at a specific scale. Thus, the examination of how a range of material scales and hierarchies contribute to certain biological function and dysfunction is critical aspect in advancing our understanding of the role of materials in biology. Specifically, the origin of how naturally occurring biological protein materials are capable of unifying disparate mechanical properties such as strength, robustness and adaptability is of significant interest for both biological and engineering science.

Strength and robustness are properties of fundamental importance to biological materials and structures, and are crucial to providing functional properties to living systems. Strength is defined as the maximum force (or pressure) a material can withstand before breaking. Robustness is defined as the ability of a material to tolerate flaws and defects in its structural makeup while maintaining its ability to provide functionality. These properties are crucial for materials in biology (s.a. skin, bone, spider silk, or cells), which either must provide reliable structural support themselves (s.a. the skeleton formed by bone), or must reliably withstand mechanical deformation under normal physiologic conditions (s.a. cells and tissue associated with blood vessels that are exposed to the pressure of the blood).

We now proceed with the brief review of a case study of strength-robustness properties of filaments composed out of different hierarchical assemblies of alpha-helical protein domains.[28,29] The basic building block for all filaments considered in this case study is an alpha-helical protein domain as shown in Figure 4(A), stabilized by 3–4 H-bonds per turn (an alpha-helical turn has an average of 3.6 H-bonds[15]). The question examined here is to find out whether or not it is possible to build larger-scale protein material structures out of individual protein domains that maintain high levels of strength and robustness, a property that is crucial for physiological function (survival).

In this analysis, the concept of robustness is defined as the strength of an intact filament divided by the strength of a filament in which one element (here, one alpha-helix)

Table I. Definition of important properties of biological materials.

Term	Definition
Strength	The maximum applied force or stress (pressure) at which failure of a system occurs (e.g., through fracture, tissue break down, etc.).
Robustness	Measures the ability of a system to tolerate flaws and defects, that is, still being capable of providing the required function under the presence of flaws and defects. A definition of robustness related to strength properties is the ratio of strength of a flawed structure divided by the strength of a perfect structure.
Adaptability	Ability of system to respond to changes in the environment (s.a. formation of defects due to injuries, or changes in physiological requirements, or due to the formation of fractures, etc.).
Flaw (defect)	Deviation of the structure of a system from its perfect, ideal or reference configuration. Examples for defects include cracks, inclusions, protein misfolds, or mutations in the amino acid sequence.
Failure	Sudden, typically uncontrolled and irreversible loss of the functional properties of a system. An example is the breakdown of tissue due to injuries under very large applied forces.
Self-healing ability	Ability of a system to reform from a perturbed structure to its reference configuration (reassemble). May involve for example the curing of flaws and defects such as cracks or voids, or the replacement or the addition of tissue.
Changeability (mutability)	Formation of distinct (sometimes preprogrammed) structures with different properties, which can be controlled by external cues. Examples include the existence of multiple conformations of proteins based on pH, or applied forces.
Multifunctionality	Ability of a system to provide multiple properties to satisfy a set of target properties. An example is the combination of strength and robustness.
Evolvability	Ability of a system to evolve over generations of synthesis. In contrast to adaptability, evolvability reflects a change of structural makeup and/or properties over generations of synthesis.

Source. Adapted with permission from [17] and [24], T. Ackbarow and M. J. Buehler, *Theoretical and Computational Nanoscience* 5, 1193 (**2008**). © 2008; M. J. Buehler and Y. C. Yung, *HFSP Journal* 4, 26 (2010). © 2010, HFSP Publishing.

Table II. Definition of materiomics and related terms.

Term	Definition
Genetic code	Set of codes contained in DNA/RNA, translated into protein structures/sequences
Genomics	Study of an organism's entire genome (i.e., determine the entire genetic code of organisms, and associated mapping)
Proteomics	Study of the full set of proteins found in a type of tissue, or cell type (and effects of changes of the physiological environment)
Materiomics	Study of the properties, processes and structures of hierarchical materials, and the effect of different material levels on mesoscopic and macroscopic properties (Fig. 1(B))

is missing at the smallest level ("flawed"). The robustness R is then defined as (in the spirit of Kitano's definition[30, 31])

$$R(i) = \frac{F(\text{flawed})}{F(\text{intact})} \quad (1)$$

providing a measure for the sensitivity of the strength of the structure once a flaw is formed.

To explore the effect of structural variations on the performance in the strength-robustness domain, we first consider eight alpha-helices and arrange them in all possible geometries and measure their properties. To present the results, we use the following nomenclature $\{b_N, b_{N-1}, \ldots, b_2, b_1\}$ to uniquely describe the various hierarchical structures. The values of b_i in this expression thereby define the number of elements that are found in parallel with each other at a particular hierarchical level, from the largest to the smallest elements. A single alpha-helix is characterized by $\{1\}$, a bundle of two alpha-helices $\{2\}$ resembles a coiled-coil structure (CC2), and a bundle of four alpha-helices $\{4\}$ resembles a four-fold coiled coil structure (CC4) (see Fig. 4(B)).

Figure 5(A) depicts the geometries and results for eight alpha-helices (the definition of subelements and their arrangement are those shown in the inlay of the figure). The analysis shows that even though no additional material is used, the mechanical performance changes significantly as the hierarchical arrangement of the structure is varied. The $\{8\}$ structure represents a single bundle of eight alpha-helices in parallel; the $\{2, 4\}$ structure represents a fiber composed of two bundles of four alpha-helices; the $\{2, 2, 2\}$ structure represents a fiber composed of two bundles of two bundles of two alpha-helices each; the $\{4, 2\}$ structure represents a fiber composed of four bundles of two alpha-helices. It is found that the $\{8\}$ structure provide very high levels of robustness, albeit at low strength. In contrast, the $\{4, 2\}$ structure provide high strength, albeit at low robustness. However, there are some structures that provide an optimal combination of both properties, the $\{2, 2, 2\}$ and $\{2, 4\}$ structures. Among these, the $\{2, 4\}$ structure is the best performer as it provides the highest levels of strength and robustness. The $\{2, 4\}$ structure represents a fiber composed of two bundles of four-fold coiled coil alpha-helices (CC4).

We extend the analysis by considering a much larger number of filaments. As in the earlier study with only eight elements, the elements are assembled in all possible hierarchical structures and tested for their strength and robustness. Figure 5(B) depicts results for 16,384 alpha-helices, where an analysis of the distribution of structures and their performance shows that most structures (>98%)

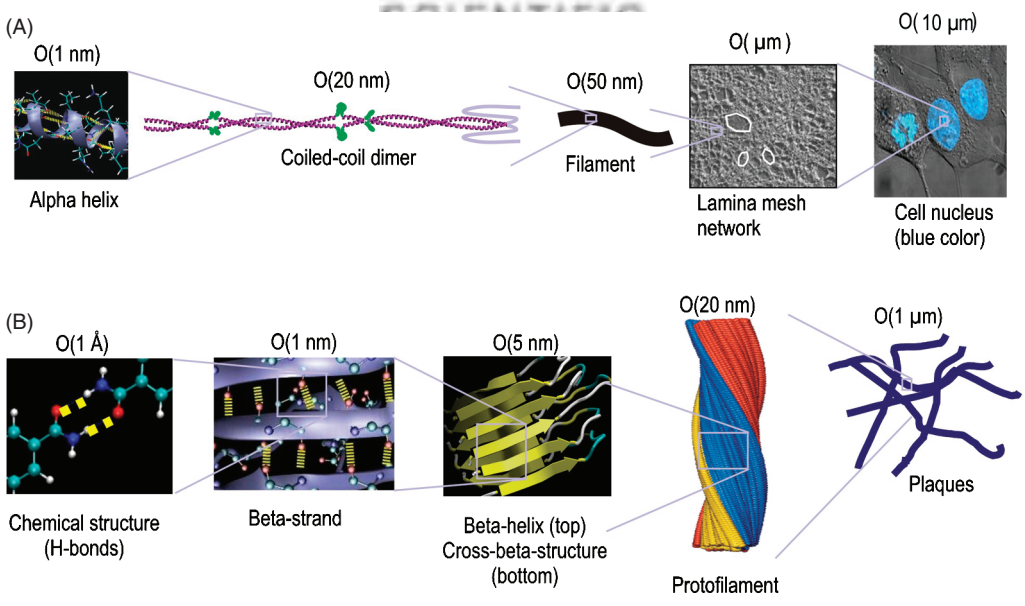

Fig. 2. Hierarchical structure of two example biological protein materials, intermediate filaments (panel A) and amyloids (panel B). Figure adapted with permission from [18], M. J. Buehler and Y. C. Yung, *Nat. Mater.* 8, 175 **(2009)**. © 2009, Nature Publishing Group.

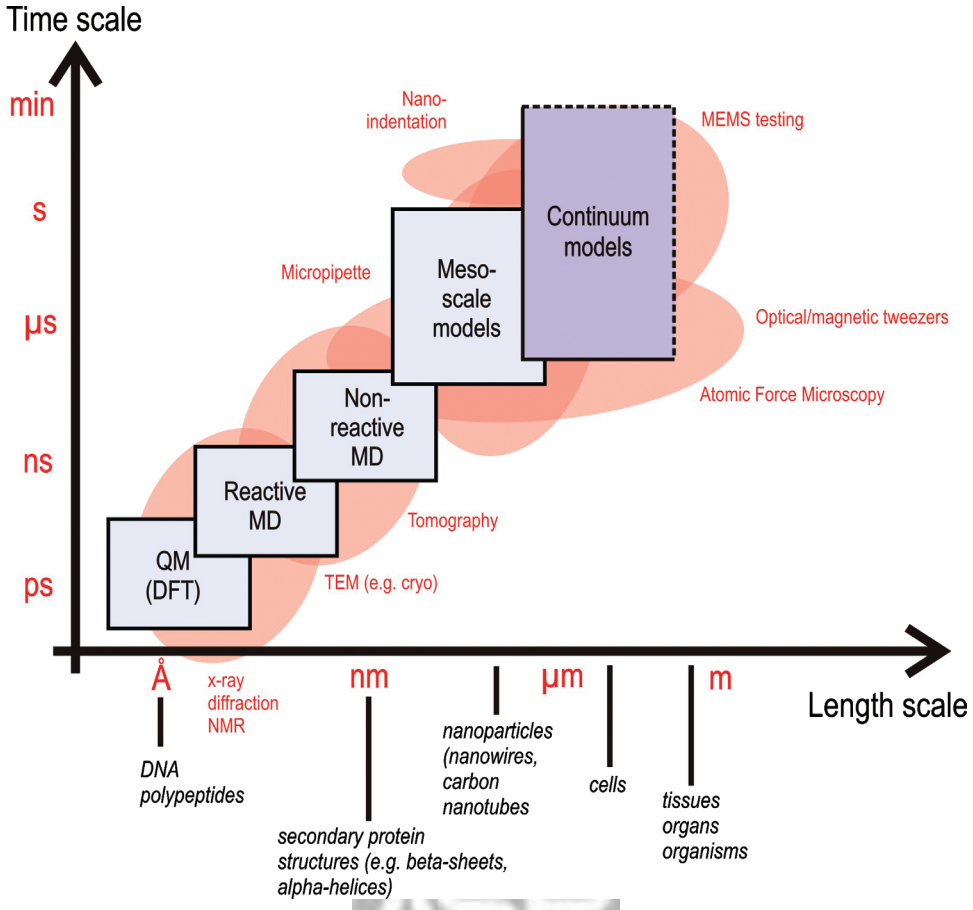

Fig. 3. Schematic of the computational multi-scale approach.[18] The integration of computational methods from the atomistic, molecular, mesoscale, to the macroscale enables a seamless treatment of biological materials, tissues, and structures from nano to macro levels. The lower part of the plot indicates example biological and synthetic structures at specific length scales.

in Figure 5(B) fall onto a curve referred to as the banana-curve, where strength and robustness are mutually exclusive properties. Only ≈2% of all structures lead to high strength and high robustness.

The analysis shows how high-performance materials can be made out of relatively weak (and structurally simple) constituents such as alpha-helices that are bonded by mechanically inferior H-bonds, by arranging them into specific hierarchical patterns. The resulting robustness-strength plots suggest a similar behavior as that found in many biological materials, as indicated in Figure 5(B), in that they combine disparate properties. The particular distribution of performance characteristics for a large number of elements may explain why most engineered materials (s.a. metals, ceramics, glass, etc.) show a poor performance of strength and robustness. This is because most randomly picked arrangements fall on the banana curve (>98%). Engineered materials often show this behaviour, where one possible reason behind this observation could be that hierarchical nanostructural geometries have not yet been utilized in engineering materials design. In contrast, biological materials may have achieved the particular high performance structures through evolutionary

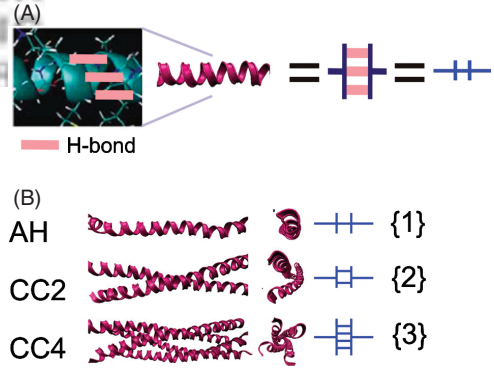

Fig. 4. Hierarchical assemblies of alpha-helices. Panel A shows the geometry of a single alpha-helix, composed of 3–4 H-bonds per turn.[28, 29, 34] To present the results, we use the following nomenclature $\{b_N, b_{N-1}, \ldots, b_2, b_1\}$ to uniquely describe the various hierarchical structures. The values of b_i in this expression thereby define the number of elements that are found in parallel with each other at a particular hierarchical level, from the largest to the smallest elements. Panel B: Illustration of sample structures and their representation. A single alpha-helix is characterized by {1}, a bundle of two alpha-helices {2} resembles a coiled-coil structure (CC2), and a bundle of four alpha-helices {4} resembles a four-fold coiled coil structure (CC4).

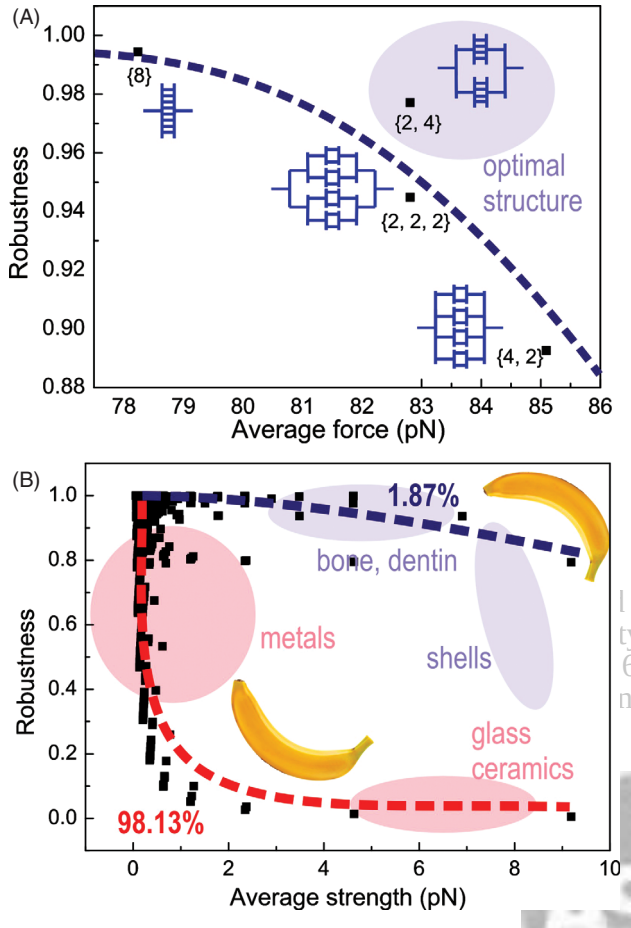

Fig. 5. Strength-robustness relation for alpha-helical protein filaments (results adapted from Refs. [28, 29, 34]). Panel A shows the results for eight subelements in the protein filament arranged in all possible hierarchical patterns. The definition of subelements and their arrangement are those shown in Figure 4. The {8} structure represents a single bundle of eight alpha-helices in parallel; the {2, 4} structure represents a fiber composed of two bundles of four alpha-helices; the {2, 2, 2} structure represents a fiber composed of two bundles of two bundles of two alpha-helices each; the {4, 2} structure represents a fiber composed of four bundles of two alpha-helices. Panel B shows results for 16,384 subelements in the protein filament. An analysis of the distribution of structures and their performance shows that most data points (>98%) in panel B fall onto the banana-curve. Only less than 2% of all structures lead to high strength and high robustness. This analysis shows how high-performance materials can be made out of relatively weak constituents such as alpha-helices that are bonded by mechanically inferior H-bonds.[28, 34] Plot adapted with permission from [24], M. J. Buehler and Y. C. Yung, *HFSP Journal* 4, 26 (2010). © 2010, HFSP Publishing.

adaptation of hierarchical structures. Thus the structure of biological materials may have developed under evolutionary pressure (critical for survival), in order to yield materials with multiple objectives, such as high strength and high robustness, a trait that can be achieved by utilization of hierarchical structures despite limitations of inferior or simple material building blocks.

The example discussed here illustrates the potential and opportunities associated with forming hierarchical materials, in which structures are designed from nano to macro.

3. CONCLUSION AND OUTLOOK

For a variety of applications, hierarchical multiscale effects will be critically important as we push the limits of what we can see, and how small and how effective we can design. For efficiency and conservation of (finite) resources, novel multi-scale modeling methods will be required that enable us to explore the full design space, from nano to macro. Thereby, the study of biological materials and structures could impact the advancement of nanotechnology. Material properties of nanomaterials are often found to be superior to conventional engineering materials (e.g., nanomaterials such as carbon nanotubes and graphene represent some of the strongest materials known to date). However, we are currently unable to fully exploit and translate these superior nanoscale properties to larger length-scales (micrometers and beyond), which is necessary for technological applications. For instance, carbon nanotubes are one of the strongest materials known, but have not been largely employed in structural materials due to our inability to utilize the properties of this material at larger length-scales. It is envisioned that understanding hierarchical biological materials will provide knowledge that can eventually be translated to connecting disparate material scales, from nano to macro. We may then be able to utilize these material concepts to impact the field by exploiting the full potential (higher strength, higher robustness, or properties such as adaptability or mutability) of multi-scale engineered materials. This could lead to the design of novel forms of construction materials (s.a. new generation cement and concrete[32]), adhesion systems or cables.

The advancement of nanoscience and nanotechnology associated with biological materials could also have significant impact in several areas of biomedical research. For example, atherosclerosis (hardening of blood vessels due to plaque formation), or blood clots in large vessels (e.g., carotid artery), and other blood vessel diseased states are related to a complex interplay of materials-cell interactions at multiple scales, including the nanoscale. Similar considerations hold for many other diseases, including: cancer, infectious diseases, genetic diseases, and injuries. For example, injuries and genetic diseases are often caused by structural changes in protein materials (defects), resulting in failure of the material's intended function. Materiomics approaches enable us for example to probe how mutations in structure alter the properties of protein materials. The long-term impact of materiomics could be used to predict diseases in the context of diagnostic tools by measuring material properties rather than focusing on symptomatic chemical readings alone, providing new strategies for treatment options. Indeed, nanomedicine is now emerging as a new field of study, in which the links between nanoscience and biomedical applications are investigated. Other applications in basic science could lead to breakthroughs in understanding evolutionary driving forces of protein structure formation, and perhaps one day enable

new paths forward to treating medical disorders associated with protein malfunctions by interfering at a fundamental, molecular or materials level.

The concept of designing materials with hierarchical structures, by deliberately determining a cascade of multi-scale mechanisms is a largely unexplored aspect in materials science that could lead to advances in *de novo* materials design. By utilizing self-assembly processes from nano to macro,[33] hierarchical structures may be the key that can enable us to take advantage of properties at all scales, and to exploit superior nanoscale properties at functional scales. This research has the potential to extend the current state of the art in nanotechnology and materials science towards developing a new generation of intelligent biomaterials that integrates structure and function, from the nano to macro scales through a merger of the concepts of structure and material.[18, 24, 35]

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