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# Multiscale mechanics of biological and biologically inspired materials and structures

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**Abstract:** The world of natural materials and structures provides an abundance of applications in which mechanics is a critical issue for our understanding of functional material properties. In particular, the mechanical properties of biological materials and structures play an important role in virtually all physiological processes and at all scales, from the molecular and nanoscale to the macroscale, linking research fields as diverse as genetics to structural mechanics in an approach referred to as materiomics. Example cases that illustrate the importance of mechanics in biology include mechanical support provided by materials like bone, the facilitation of locomotion capabilities by muscle and tendon, or the protection against environmental impact by materials as the skin or armors. In this article we review recent progress and case studies, relevant for a variety of applications that range from medicine to civil engineering. We demonstrate the importance of fundamental mechanistic insight at multiple time- and length-scales to arrive at a systematic understanding of materials and structures in biology, in the context of both physiological and disease states and for the development of *de novo* biomaterials. Three particularly intriguing issues that will be discussed here include: First, the capacity of biological systems to turn weakness to strength through the utilization of multiple structural levels within the universality-diversity paradigm. Second, material breakdown in extreme and disease conditions. And third, we review an example where the hierarchical design paradigm found in natural protein materials has been applied in the development of a novel biomaterial based on amyloid protein.

**Keywords:** Biological materials, materiomics, mechanics, mechanical properties, mutability, tunability, deformation, failure

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## 1. Introduction

The generation of functional properties in materials in nature is astounding and plays a central role in realizing a diversity of functional properties such as gene regulation, catalysis, signal transmission, material transport, structural support or locomotion, many of them simultaneously, to yield multifunctional materials [1-5]. Many biological materials also provide access to disparate material properties such as extreme strength, toughness, extensibility combined with tunability and mutability, where functionality reaches a level not yet attained by most synthetic materials. Functionality is created often based on simple and abundant material constituents and with intricate feedback loops that facilitate the adaptation to changed environmental constraints (Figure 1).

The structural designs of biological materials have evolved under evolutionary pressures and are primarily governed by the desire to facilitate a species' survival, often in adverse environments where energy, material quality and quantity as well as time-scales available to produce materials are exceedingly scarce. These intrinsic limitations explain why many material constituents found in biology are functionally inferior material building blocks themselves that are exceptionally brittle (e.g. silica or other minerals) or extremely weak (e.g. H-bonding, Van der Waals forces or weak covalent interactions such as disulfide bonds). Notably, comparative studies of protein materials show that most biological materials are made up from only a few select universal elements such as  $\approx 20$  natural amino acids, despite their great functional diversity [6].

The question of how biology is capable of using such a limited number of elements to create highly diverse systems poses a fundamental question about the design of biological materials [7]. In particular, the mechanical properties of biological materials and structures play an important role in virtually all physiological properties at all scales (from the atomistic to the macroscale), which links research fields as diverse as genetics to structural mechanics and even architecture.

How can we develop a fundamental understanding of how mechanically functional materials are created in biology, and how they break down under extreme conditions such as disease, genetic mutations or injury? What kinds of tools provide the most powerful insights into underlying mechanisms? What will be the impact of this field for applications in materials design or medicine? Here we present a brief review of case studies and examples to demonstrate challenges and opportunities, specifically focused on the utilization of computational methods combined with experimental analyses, used to link the nano- to the macroscale. It is noted that the case studies presented here are largely focused on work reported by our group over the past years.

## **2. A materiomics approach**

A comprehensive understanding of protein materials requires an intimate connection of theoretical, computational and experimental efforts, applied at multiple scales, to provide a bottom-up description of this hierarchical material, and to understand how properties across the scales are linked, an effort defined as materiomics (Figure 1B and Figure 2) [8]. *In silico* models of biological materials have now developed into powerful tools to complement experimental methods, and can be applied to integrate vast ranges of both length- and time-scales, from nano to macro. Thereby, the process of validating computational models is essential and should be performed at all relevant scales as far as complementary experimental and theoretical approaches are available. The use of Atomic Force Microscopy (AFM), optical and magnetic tweezers and similar methods now provide access to the mechanics of single molecules and small fibers at length-scales of several nanometers. At larger scales, devices built based on MEMS and similar technologies enable us to test the mechanics of fibrils at scales of hundreds of nanometers to micrometers. Combined with powerful imaging techniques (x-ray, SEM, TEM, ssNMR, Rahman, etc.) these methods provide an exciting way to directly test the mechanics of complex materials at multiple scales.

Over the past decades, the use of a plethora of simulation tools to describe all relevant scales in a material has developed into a powerful approach, following the paradigm developed in pioneering works by Goddard and others since the 1980s. The basic idea in the development of such a multiscale approach is that several computational models are integrated and combined in the description of a material, where parameters are fed from most accurate methods (that typically operate at smallest scales) to less accurate methods (that typically operate at larger scales). Since the most fundamental computational methods are based solely on electrons, protons and neutrons (and thus provide a generic description of any chemical element and interactions between them), it was hypothesized that a first principles based (or *ab initio*) bottom-up description of materials could be achieved without relying in empirical parameters and eventually reach all the way to the macroscale. In recent years, this vision has been realized for an increasing number of materials, including biological ones.

How do multiscale methods work? At the most fundamental scale, multiscale models start with a description of the quantum mechanical interactions, which can be effectively described with methods such as Density Functional Theory (DFT). These models represent molecules based on the distribution of the core of atoms and electrons as well as their interactions in forming chemical bonds between atoms and molecules. DFT and related methods can be used to understand the nature of specific chemical bonds, such as H-bonds, or covalent bonds in the protein's backbone. DFT type models can treat at most thousands of atoms, and are thus typically confined to the nanoscale.

The quantitative insight derived from these types of calculations is used at the next level of modeling to develop models in which chemical bonds are represented as simple potentials—in which the effective behavior of a group of electrons is captured in springs or similar formulations (prominent models used are: Lennard Jones, Morse, Buckingham, etc. potentials). These models, implemented in so-called force fields such as CHARMM, DREIDING, or AMBER can be used describe up to millions of atoms on modern parallel supercomputers, and can thus be directly applied to derive insight into how molecules interact, mechanical properties of molecules and assemblies (fibrils). Yet, even though these simulation methods can reach scales of tens of nanometers they are far from describing micrometer scales that are of particular relevance for biology (due to the size of cells).

To reach even larger scales, the process of coarse-graining a finer system into a representation of groups of constituting elements is repeated, and here molecules are represented as groups of thousands of atoms that are combined into particles or beads. These so-called coarse-grained models are powerful techniques that can reach

scales of tens of micrometers. The inlay in [Figure 2](#) shows how such coarse-graining can be done for an amyloid fibril for the case of an amyloid plaque model [9], and illustrates how hundreds of atoms are grouped into particles. Since all parameters in this coarse-grained model can be determined based on full atomistic models there is no need to introduce empirical parameters. The process of coarse-graining can be repeated several times if needed to bridge through multiple length-scales. The use of coarse-grained models can be difficult in some cases, for example when the structure of the molecule does not easily suggest a particular coarse-graining approach (e.g. based on geometry). Other issues are the effect of solvent (which can be included by adding terms to simulate Brownian motion, or pressure), temperature, and fundamental structural changes of a molecule's geometry. It is noted that due to the grouping of atoms the usable time step in simulations can be increased and as such, a longer simulation span can be attained.

### **3. Case studies and applications**

#### ***Mechanics of structural materials in disease states***

Throughout the past centuries, the focus on understanding and treating diseases has derived primarily from a biochemical approach. However, advancements and increased understanding of quantitative measurements of materials phenomena at multiple scales has yielded an enhanced appreciation for the role of material mechanics of protein materials in various medical disorders. In this section, the role of biologically relevant material properties in the progression or activation of diseased states will be briefly discussed, reviewing a more extensive discussion presented in earlier articles [6, 10]. The effort of studying the role of materials in disease etiology and progression is also termed pathological materiomics.

For example, genetic disorders in collagenous tissues have been linked to the alteration of the material structure due to mutations in the genes that encode the tropocollagen molecule. *Osteogenesis imperfecta* is a genetic disease that enhances bone's susceptibility to catastrophic brittle fracture, a disease also referred to as "brittle bone disease" (see [Figure 1](#) where the impact of the disease on changing the strength and toughness of bone is schematically illustrated). The origin of this rare but severe disease resides in changes to the structure of tropocollagen molecules due to the substitution of a single glycine amino acid [11, 12]. Some collagen mutations prevent the formation of triple helical molecules (also termed "procollagen suicide"), while other mutations cause structural changes to tropocollagen molecules, leading to bending (e.g. due to kinks induced by amino acid substitutions), reduced mechanical stiffness (e.g. due to changes of the volume and hydrophobicity), or changes in the intermolecular adhesion (e.g. due to changes in surface charges) [11-14]. It was found that at mesoscopic scales where molecules interact with one another, these molecular-level changes lead to poor fibril packing [15, 16] and a decrease in cross-link density [16, 17]. Changes in the size and shape of mineral crystals in bone (e.g. less organized, more round-shaped crystals) have also been reported [18-20], which might be related to a change in the ability of tropocollagen to bind to the mineral phase of bone [21, 22]. At larger length-scales, the effects of *osteogenesis imperfecta* mutations lead to inferior mechanical properties of tendon and bone [23].

Taking a mechanics perspective has enables us to identify molecular-level insight into disease mechanisms ([Figure 3](#)). For example, the reason for the reduced strength of mutated collagen fibrils is that the presence of the mutation induces a change of the stress field within the fibril; causing a magnification of the stress at the points of mutations. This is because mutations severely reduce the intermolecular adhesion, thus creating small interfacial crack-like defects inside the tissue that lead to local stress concentrations. Interestingly, this relates directly to an earlier hypothesis that suggested that the universal length of collagen molecules of 200-400 nm is related to the condition of homogenous stress distribution within collagen fibrils (see [Figure 3B](#)) [24], providing optimal mechanical condition. However, the presence of mutations leads to a breakdown of this condition as local stress concentrations form in the material. Then, in spite of collagen molecules having the optimal length, the strength and toughness is compromised as failure occurs under initiation of local shear ([Figure 3C](#)). This consideration of the molecular deformation mechanism of collagen tissue under physiological and disease states provided important insight that complements medical research.

It is noted that the phenomenon of stress concentration formation is quite similar to the one known from cracks in solids, where local stress concentrations at defects can explain the sudden growth of cracks. Further research is needed to better understand these disease mechanisms and how they relate to materials failure phenomena under varying conditions. As explained in more detail elsewhere [6] a bottom-up simulation approach, used together with

simulation and theory, can be a powerful tool in investigating the initiation and progression of diseases such as brittle bone disease and related material mechanisms.

Indeed, the change of material properties and associated failure of a biological system can be a crucial element in many diseases. The translation of this knowledge would enable the detection of diseases by measuring material properties rather than by focusing on symptomatic biochemical readings alone. A close coupling of biochemical make-up, structural arrangement and mechanical properties at the nanoscale make molecular modeling tools and indispensable tool for a thorough understanding disease and failure. Altogether, understanding the role of different hierarchical levels of protein materials in diseases could potentially bring about a new paradigm of approaches to address medical disorders; however, further research is needed to elucidate the underlying multi-scale failure mechanisms. Following up on this point, it has been suggested that even though biochemical and image-based diagnostics will remain important, the integration of scales, as well as the mixing of physical, biological and chemical concepts into novel engineering designs could complement the current practice of disease diagnosis and treatment, as well as the design of new materials, and thereby unfold many opportunities for technological innovations.

### ***Tu(r)ning weakness to strength***

The discussion included here is based on a recent article in which biological mechanisms were summarized that enable these materials to turn weakness into strength [5]. Recent research suggests that the basis of understanding the remarkable properties of biological materials lies within the biological design paradigm where multifunctionality is created not through the use of high quality, or use of a large number of, distinct building blocks [5]. Rather, functionality is created by compiling simple and often inferior elements into structures where specific geometries are realized at multiple length-scales, resulting in hierarchical material architectures. In this hierarchical setup each level provides access to specific functional properties, which is achieved by defining a particular material structure at each hierarchical scale. This paradigm, the formation of distinct structures at multiple length scales, enables biological materials to overcome the intrinsic weaknesses of the building blocks, as shown schematically in [Figure 4 \(center\)](#).

The formation of such structures can be illustrated in the use of nanoconfinement that often results in enhanced strength and ductility despite the intrinsic brittleness of the same material in bulk form [25]. In an example relevant for sea creatures such as diatom algae [26], while silicon and silica is extremely brittle in bulk, the formation of nanostructures results in great ductility and extensibility, where the specific geometry used allows for a continuum of mechanical signatures [27, 28]. The realization of distinct structural designs provides a means to tune the material to achieve a great diversity of functional properties despite the use of the same building blocks. Moreover, if it is possible to alter the material's structure at specific hierarchy levels during use of a material, there exists the potential to achieve varied material properties depending on functional needs, resulting in mutable materials [29]. This is exemplified in sea urchins and other species that have the capacity to change their exoskeleton's modulus significantly through alterations of the cross-linking of underlying collagen molecules [30]. Mechanomutability also occurs in plants that track the direction of sunlight, through a mechanism that involves a change of the plant wall's stiffness exposed to light and resulting in bending towards the softer part and can also be utilized for the design of synthetic materials based on polymers [31, 32].

One of the most intriguing examples to demonstrate the biological material design paradigm is the case of spider silk, a remarkable material that must provide extreme levels of strength on the order of 1-2 GPa, toughness, and great deformability of around 50% tensile strain in order to fulfill its biological tasks (structural stability, prey procurement, etc.) [33]. Nevertheless, the structural basis of spider silk is extremely simple, and consists of only a few distinct few amino acids, arranged in long polypeptide chains and that interact only by weak interactions. Moreover, spiders must be able to produce silk at short time-scales and out of a limited stock of solvated protein [34]. The physiologic processing conditions in solvent, at room temperature, and at very short time-scales rules out enzymatic processes and suggests that self-assembly is the primary mechanism to form spider silk under these conditions. This necessitates the use of weak bonding in the fundamental interactions of the silk protein strands. Indeed, spider silk is known to be dominated by H-bonds, one of the weakest chemical bonds known, and also present in liquid water. But how is it possible to generate such a mechanically superior material out of clearly inferior constituents and constraints?



As described in a recent paper [5] the answer is that weak elements in the material, here H-bonds, are arranged geometrically in order to provide maximum strength and toughness. It has been found that the intrinsic weakness of H-bonds vanishes when grouped into clusters of  $\approx 4$  H-bonds, which allows them to work cooperatively—akin to a flock of birds—and thus reach maximum strength, as shown in [Figure 5](#) [35, 36]. The ability of H-bonds to work cooperatively is also critical to ensure enhanced robustness, where the loss of a single bond does not result in the breakdown of an entire system. Cooperativity is actually facilitated by the weakness of H-bonds, which implies a softness of bonding that endows them with the freedom (entropy) to explore a great variety of structural states such that they can most effectively resist deformation [36]. The assembly of H-bond clusters into geometrically confined beta-sheet nanocrystals, consisting of a pancake-like stack, results in the structural basis for effective cross-linking of multiple polypeptide chains in silk [37]. Because H-bonds can be reformed easily upon breaking, beta-sheet nanocrystals have another highly useful property, toughness, enabled by the ability of H-bonds to self-heal and thereby effectively preventing catastrophic brittle failure as often observed in materials with stronger bonding. Other considerations apply to beta-sheet silk crystals under shock loading, where it was found that they are highly dissipative mechanical elements when exposed to rapid mechanical loading [38].

Yet, due to the nature of the available building blocks (*i.e.*, their built-in limitations) it is not possible to achieve all desired properties at a single material scale. Thus, in order to achieve another functional property of silk, extensibility (in particular while maintaining the great strength facilitated by beta-sheet nanocrystals), the structural design is extended to higher structural scales, and specifically, at the next level through the formation of a nanocomposite achieved by using the same basic material building block (polypeptide) but arranged in a different geometry. Here strong and tough beta-sheet nanocrystals are combined with an additional protein secondary structure that consists predominantly of so-called  $3_1$ -helices that realize a more disordered phase. Through the provision of extreme amounts of hidden length, this protein constituent provides the capacity to generate large levels of deformability before the beta-sheet nanocrystal cross-links are deformed and eventually broken [39]. By tuning the relative ratio of the two phases in silk, or the geometric makeup of the beta-sheet nanocrystals, it is possible to achieve a diversity of mechanical signatures (e.g. stiff, soft, tough, elastic-plastic, extensible, etc.) without a need to define new constituents. This, in fact, is a mechanism spiders use to generate different types of silks to build complex architectures such as the cobweb.

These most salient design features of spider silk provide an insight into a much broader design paradigm in biology at the nanoscale, pertaining to biology's use of a universal 'cement', H-bonds, in the creation of mechanically stable materials. The formation of confined clusters of H-bonds is indeed observed widely in biology and not only in silk, pointing to a universal design paradigm that enables biological systems to overcome the intrinsic weakness of H-bonds and to form mechanically strong and tough materials. A comparison of the geometric size of H-bond clusters in a diversity of protein found in the Protein Data Bank confirms that H-bonds typically organize in clusters between 4-6 in beta-sheets and separated by disordered or differently structured elements, or in clusters of 3-4 in the turns of alpha-helices [36]. These H-bond clusters represent a geometric feature found across species and highly conserved in biology. It has been suggested that this is because this structure provides a simple, yet strikingly effective protocol to achieve mechanical strength out of weak chemical bonding that is thus widely implemented in biology.

There are recent reports in which the hierarchical design paradigm described here has been applied, for example in the development of a novel biomaterial based on amyloid protein. For example, a group around Knowles and Welland recently reported a novel approach [40] to making multifunctional hierarchical biomaterials by exploiting the self-assembling properties of amyloid fibrils, which are associated with severe neurodegenerative diseases such as Alzheimer's and Parkinson's [41], but are also found to be natural adhesives or bacterial coatings [42] (see [Figure 6](#)). The researchers used such amyloid proteins and developed a hierarchical material. The amyloid protein fibrils that were cast into thin films aligned and stacked in the plane of the film to form a strong material (with both nano- and micro-meter scale order) that could interact with visible light. [Figure 6](#) shows the basic concept behind their material development and also depicts images that demonstrate the functional properties of the material [40], and in particular the capacity to tune optical properties by changing the alignment of amyloid fibrils at the mesoscale.

For future research of particular future interest could be the implementation of the ability to switch the structure of the material at different levels of the hierarchy using external signals such as temperature, pH, magnetic or electric fields. Such mechanomutable materials may be used as small-scale valves (from the nanoscale upwards), sensors and actuators, or even as platforms for spatially and temporally controlling the growth of cells. Moreover, by

tuning the failure properties of a material, it may be possible to develop novel armor materials that can mitigate different types of impact loading.

### ***Failure mechanics of a hierarchical protein meshwork***

We now turn our attention to a study of failure properties of a protein material at the scale of micrometers. **Figure 7** shows the failure mechanism of a hierarchical filamentous protein material, here illustrated for intermediate filament meshworks (figure adapted from reference [10], where original data was reported in [43]). **Figure 7A** shows the seven levels of hierarchies are considered, from intrabackbone hydrogen bond (H0), alpha-helical turns (H1), filaments of alpha-helices (H2), to the representative unit cell (H3) of protein networks (H4) that form the cell nucleus (defects in the network highlighted) (H5) of eukaryotic cells (H6). The structure at each level is adapted to provide an optimal mechanical response and plays a key role in the overall mechanical behavior. Unfolding of alpha-helix turns (H1) proceeds via breaking of strong clusters of 3-4 H-bonds (H0).

The large deformation of alpha-helix filaments (with maximum strains of 100-200 %) (H2) is enabled by the serial arrangements of many alpha-helical turns (H1). The severe stiffening of the filaments is enabled by alpha-to-beta-sheet transitions and backbone stretching, followed by interprotein sliding at the filament level (H2), is a direct consequence of the structure of coiled alpha-helical proteins. The lattice structure (H3) is the key to facilitate large strain gradients in the protein network, enabling gigantic strain gradients at virtually no energetic cost at the network level (H4). This behavior is crucial for the flaw-tolerant behavior of the nuclear envelope level (H5), which is relevant to provide robust structural support to cells under large deformation (H6).

**Figure 7B** shows protein network deformation with marked strain gradient, illustrating the change of the crack orientation from a horizontal to a vertical one. **Figure 7C** depicts a schematic of crack geometry transition, plotting the crack corner stress concentration,  $\sigma_{tip}$ , and the applied stress far away from the crack,  $\sigma_0$ . The schematic shows that the initial horizontal crack orientation features a large stress concentration at the crack tip. In contrast, the transformed vertical crack orientation features only marginal stresses at its corners.

### ***Analogy between protein material mechanics and music***

As presented in a recent article [5] the biological paradigm of using multiple levels of structure to create diversity of function out of simple, universal elements can be explained by drawing an analogy to a different field, music [44]. Here we revisit the analysis reported in [5] and highlight the most important insights. In music, when one considers the synthesis of orchestral music based on universal wave forms, structures at multiple scales are similarly used to arrive at a functional system, which is the resultant assembly of multiple scales—for example in a symphony or other large orchestral pieces. The concept is schematically illustrated in **Figure 4 (right panel)**, where at a fundamental level, four basic oscillators (chosen here as a fundamental set of constituents) create sine, square, and other wave forms [45]. At the next level these basic oscillators are modulated using envelope generators that change the volume, pitch and duration of the waves over time, which shapes the sound of a particular instrument. An assembly of these modulated tones with different duration and pitch, or combinations of several of them into chords, creates melodies or riffs, where all pitches used come from a universal and limited set of harmonics, assembled into octaves. Through the combination of multiple instruments, each of which may play characteristic melodies, a complex orchestral sound is produced at the highest structural level, the ‘functional’ scale.

Mutability can be achieved by changing any of the levels—leading to variations in rhythm, tones, or melody, which in turn provide a different overall musical piece, or ‘function’. In jazz or rock jam sessions, music is continuously revised during performance in an adaptive feedback loop among the performers or between the performers and the audience. Similarly, the process of composing music can be regarded as an analogy to the evolutionary process. While the synthesis of complex sounds from the level of basic oscillators is now possible with modern synthesizers—resembling a bottom-up ‘nanoscale’ paradigm in creating music—composers in ancient days were limited by the availability of certain instruments, such as flutes or harps created from bone. Classical composers (for example: Bach, Mozart, Beethoven, and others) subsequently used more advanced instruments such as the violin or the piano, whose design was enabled by the materials and technology that became available at the time. Despite the limited set of available instruments (the basic building blocks), composers were able to create music that is considered some of most ingenious of all time.

It is important to note that subjective and cultural aspects may likely play a central role in the development and experience of music, an aspect that is evident from distinct types that emerged from different geographical regions and cultures. Nevertheless, the construction of music exemplifies how the interplay of diversity and universality

provides a powerful design paradigm, which relates directly to that found in biological materials and to what kinds of materials could potentially be designed based on synthetic approaches.

#### **4. Conclusion**

Here we described recent findings that provided insights into the important mechanical issues relevant to biological materials, focused on collagenous materials, silk and amyloid materials. A key lesson learned from studies of physiological material properties is that in order to create a diversity properties, it is not necessary to rely on strong or numerous building blocks. Rather, the design space can be expanded via the formation of hierarchical structures, realized in biology through the merger of the concepts of structure and material and in music through the creation of complex compositions inherent in symphonic pieces, as summarized in [Figure 4](#). This leads to highly functional material such as spider silk or intermediate filament meshworks, with intriguing damage tolerant material properties. On the other hand, in disease states where materials are under extreme conditions that include the presence of mutations, defects or large stresses, biological materials can break down, and cease to provide required functional properties.

By focusing on the between the scales, the application of mechanics to biological and biologically inspired materials and structures impacts the field in three major ways:

- Understanding, interpreting and predicting experimental phenomena,
- Demonstrating how disparate material scales can be integrated in order to form the next generation green, low-energy or bioinspired materials with novel properties (e.g. mutability), and
- Understanding the mechanisms of injury and disease by probing how structural changes (e.g. genetic mutations & other defects) alter material properties, by providing a materials science foundation to disease mechanisms (e.g. brittle bone disease).

It is apparent that many exciting research opportunities exist at the interface of mechanics and biology, and other fields such as materials science, physics, chemistry or medicine. The development of appropriate mechanics models that incorporate multiple length- and timescales, associated validation experiments and theories or simulations, and a set of tested approaches to probe multiscale mechanics will be a key challenge for the future.

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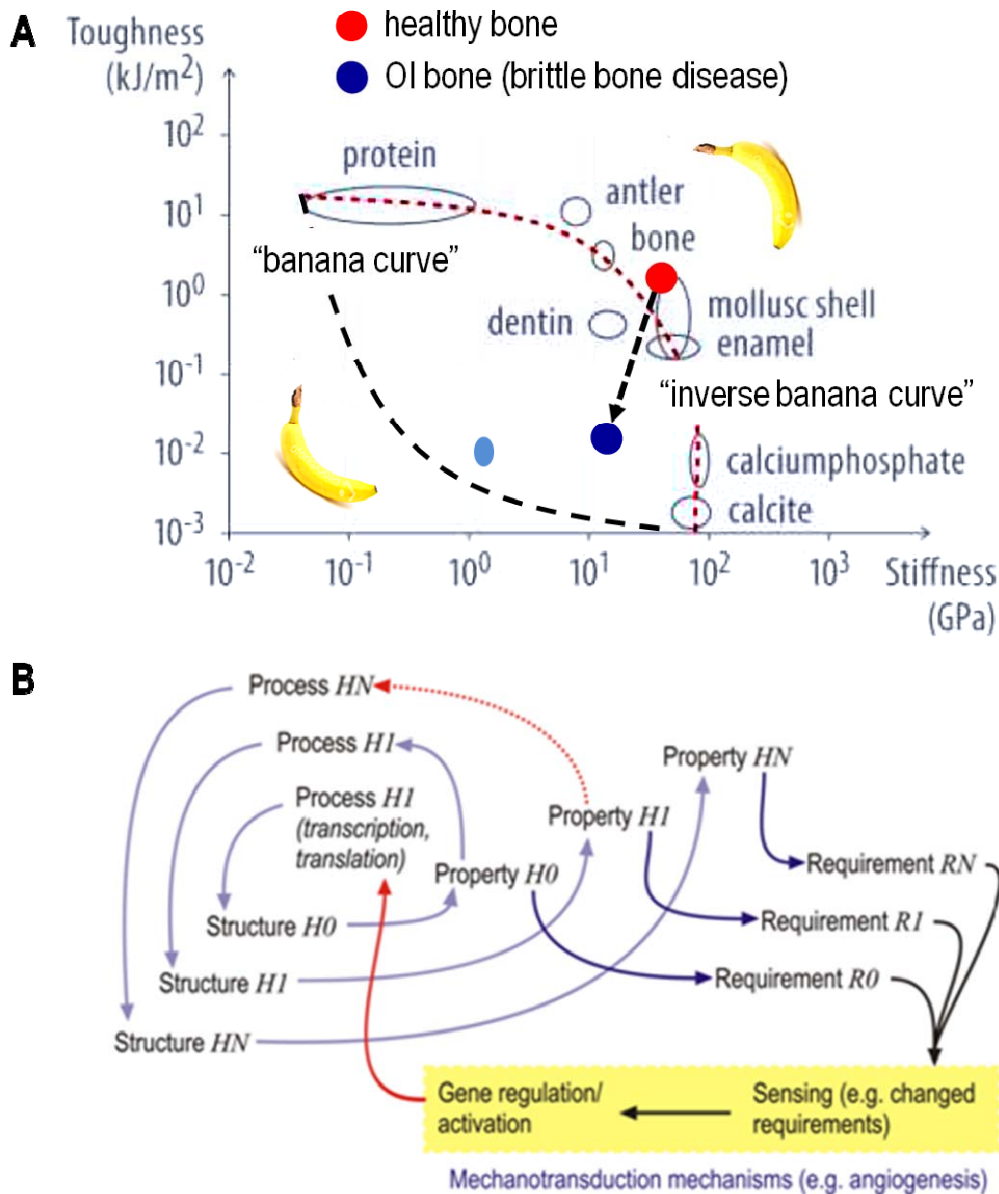
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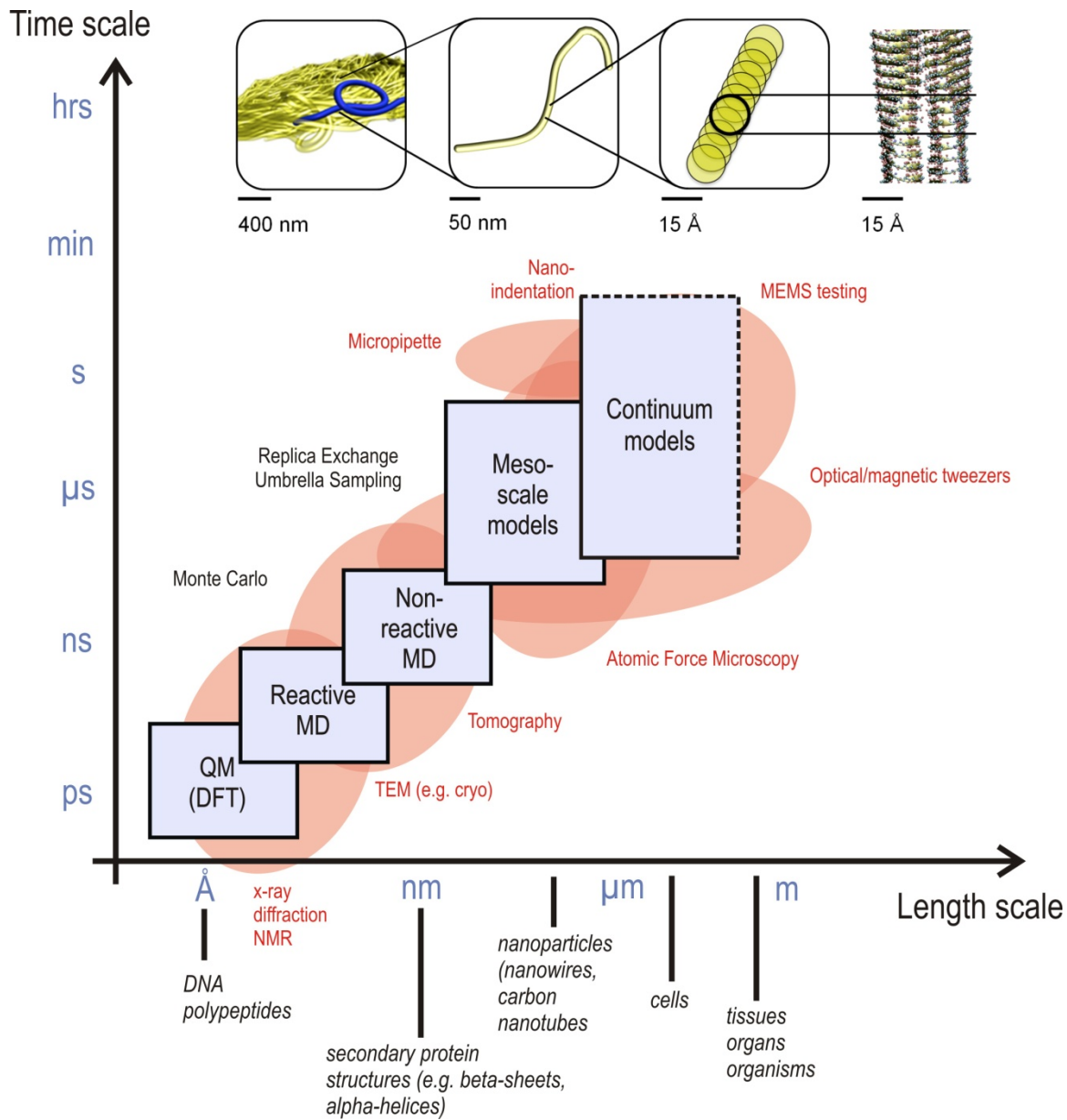
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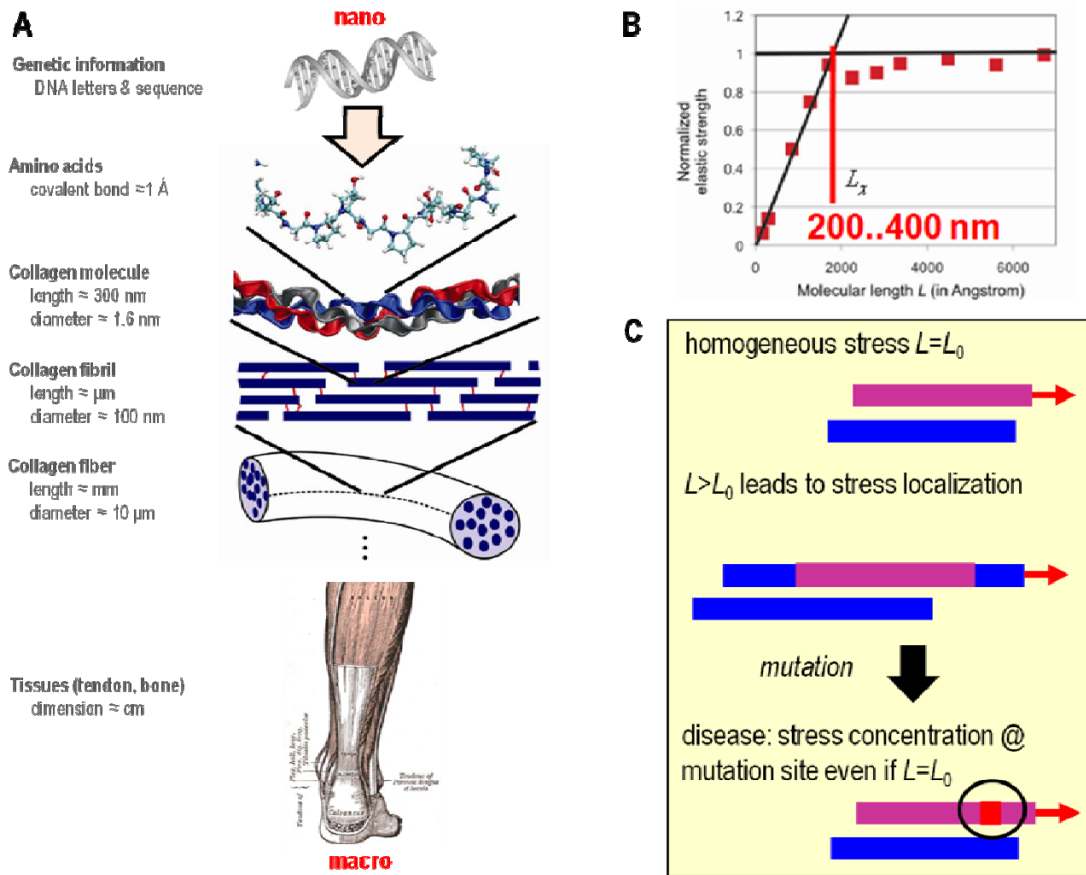
## Figures and captions



**Figure 1** | Combination of disparate material properties in biological materials (panel A) (adapted from [2]), and realization of adaptive material properties via the generation of feedback loops in hierarchical structures (panel B) [6, 46]. Panel A also visualizes schematically how high strength and toughness is lost in disease states such as brittle bone disease. The effort to understand how material properties across the scales are generated and linked, depicted schematically in panel B, is a field of research defined as materiomics [8].

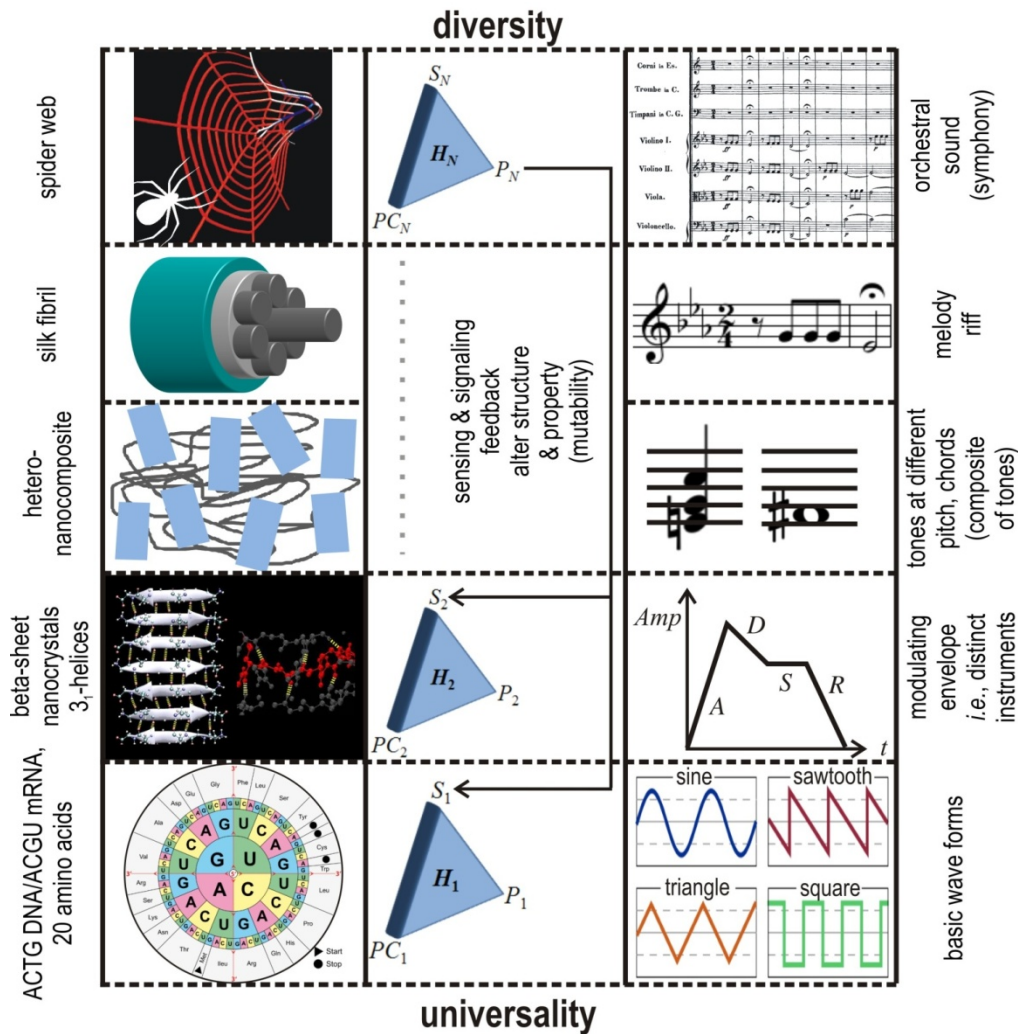


**Figure 2** | Hierarchical multiscale approach that combines experiment and simulation in the analysis of biological materials from the nano-to the macroscale [6]. The inset shows the multiscale approach as applied to a model of amyloid fibrils and plaques, where a systematic coarse-graining from atomistic-level fibrils, to a bead model, to a plaque model is used to bridge the scales from Angstrom to micrometers [9].

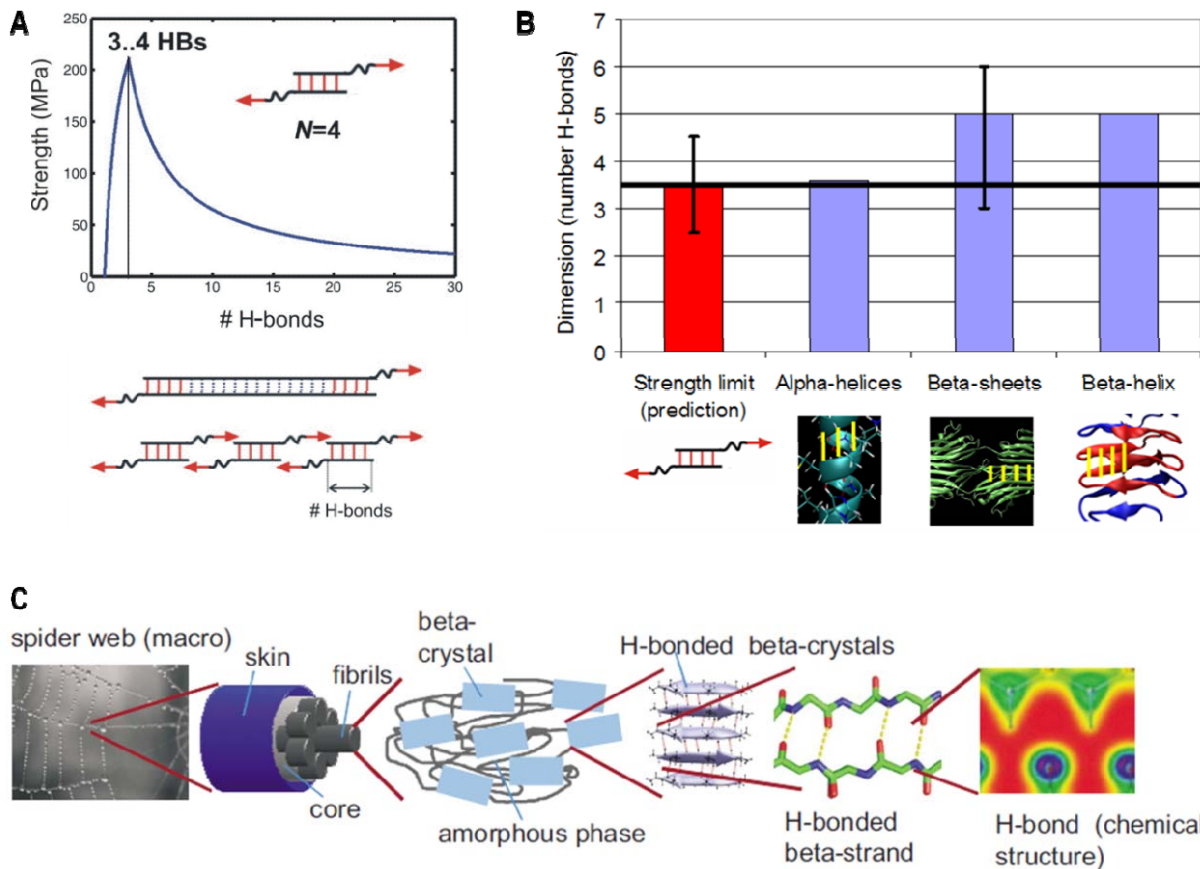


**Figure 3** | Hierarchical structure of bone (A) (from the level of genes to tissue), optimal length of collagen molecules for heightened strength and toughness as described in [24] (B), and breakdown of strength and toughness under existence of local mutations that lead to stress concentrations [13, 14] (C). Panel C illustrates schematically how two mechanisms control optimal mechanical strength of collagen fibrils; first, the length of the molecules and second, the existence of mutations (mutation site highlighted with circle). Strength and toughness reaches a maximum at a critical molecular length  $L_0$  where deformation is homogeneous along the molecule. The generation of stress concentration in disease states results in a weakening of the fibril.

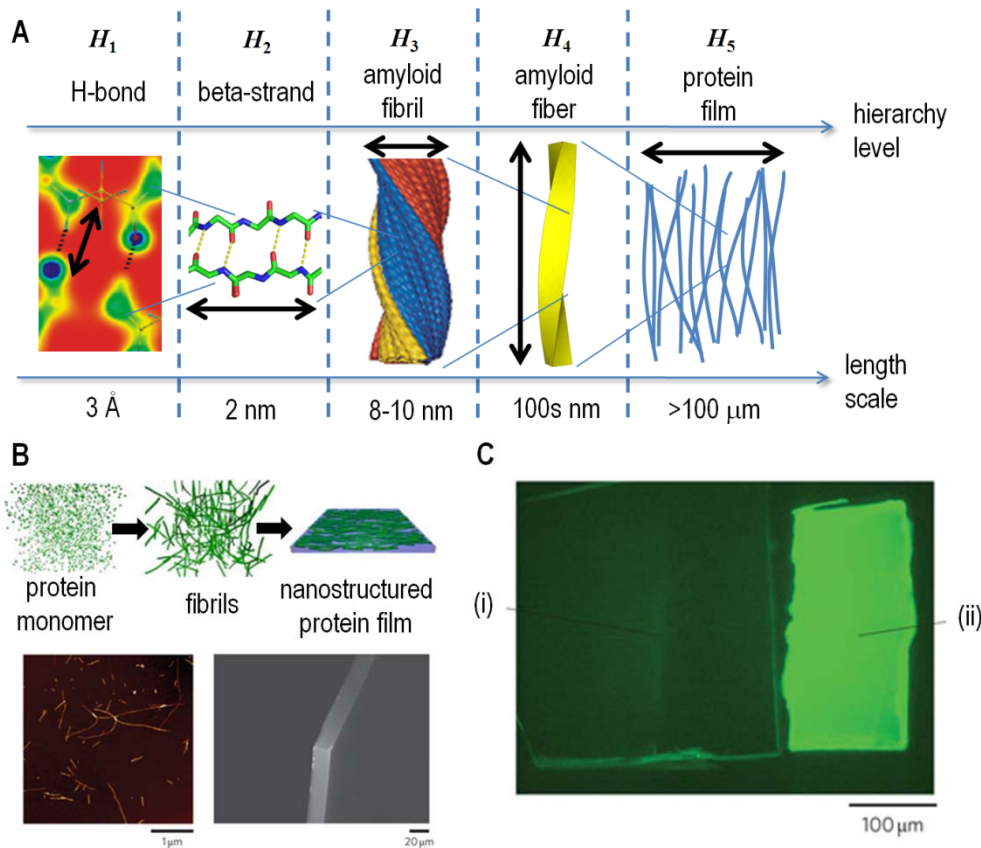




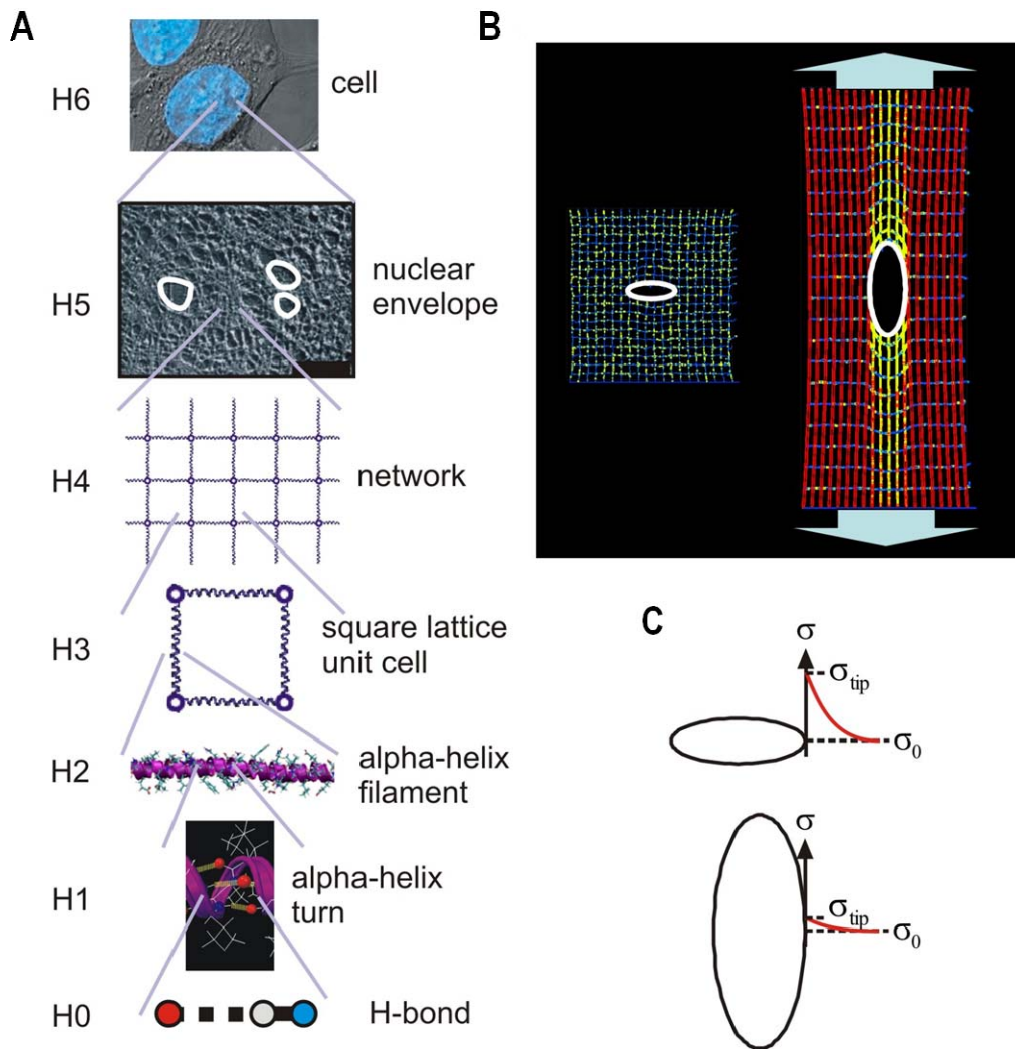
**Figure 4** | Illustration of multiscale hierarchical structure of protein materials, the interplay of universality and diversity, and an analogy to music (figure and text from reference [5]). In protein materials (left), multifunctional materials are created via the formation of hierarchical structures, where at each structural level  $H_i$  a structure ( $S_i$ )-process ( $PC_i$ )-property ( $P_i$ ) paradigm can be applied (center). The integrated view of properties at multiple scales provides the superior functionality of biological materials, despite the reliance on inferior or few distinct building blocks. The potential to sense new requirements, and translating them into alterations of structures at distinct scales, allows the realization of tunable, mutable and adaptable materials. Similar as in protein materials, in music (right), universal elements such as basic wave forms or a set of available instruments are used in hierarchical assemblies to provide macroscale functionality, and eventually a particular orchestral sound (e.g. a symphony). Universality tends to dominate at smaller levels, whereas diversity is found predominantly at larger, functional levels.



**Figure 5** | Turning weakness to strength via the formation of geometrically confined structures, here illustrated for the case of H-bond clusters in protein domains [5]. Panel A shows the strength of a beta-strand under shear loading, for varying number of H-bonds [35, 36]. Panel B shows a comparison of the size of H-bond clusters in various biological proteins [35, 36]. Panel C depicts the hierarchical structure of silk to explain the importance of H-bond clusters in the structural makeup of this material (figure adapted from [10, 35]). The beta-strand analyzed in panels A and B is visible at the second level from the right.



**Figure 6** | Hierarchical material self-assembled based on amyloid fibrils. Panel A shows the schematic makeup of the material following the discussion reported in [7]. Panel B shows the experimental procedure and both images of fibrils and the film. Panel C shows a fluorescence microscopy image of a non-functionalized (i) and functionalized (ii) fibril amyloid material, where the functionalization implemented at the scale of individual fibrils controls its mesoscopic organization (see level  $H_5$  shown in panel A). Panels B and C reprinted and adapted by permission from Macmillan Publishers Ltd: Nature Nanotechnology [40], copyright © 2010.



**Figure 7** | Hierarchical failure mechanism of a filamentous protein material, here illustrated for intermediate filament meshworks (figure and text adapted from reference [10], whereas the original data was reported in [43]). (A) Seven levels of hierarchies are considered, from intrabackbone hydrogen bond (H0), alpha-helical turns (H1), filaments of alpha-helices (H2), to the representative unit cell (H3) of protein networks (H4) that form the cell nucleus (defects in the network highlighted) (H5) of eukaryotic cells (H6). The structure at each level is adapted to provide an optimal mechanical response and plays a key role in the overall mechanical behavior. Unfolding of alpha-helix turns (H1) proceeds via breaking of strong clusters of 3-4 H-bonds (H0). The large deformation of alpha-helix filaments (with maximum strains of 100-200 %) (H2) is enabled by the serial arrangements of many alpha-helical turns (H1). The severe stiffening of the filaments is enabled by alpha-to-beta-sheet transitions and backbone stretching, followed by interprotein sliding at the filament level (H2), is a direct consequence of the structure of coiled alpha-helical proteins. The lattice structure (H3) is the key to facilitate large strain gradients in the protein network, enabling gigantic strain gradients at virtually no energetic cost at the network level (H4). This behavior is crucial for the flaw-tolerant behavior of the nuclear envelope level (H5), which is relevant to provide robust structural support to cells under large deformation (H6). (B) Protein network deformation with marked strain gradient, illustrating the change of the crack orientation from a horizontal to a vertical one. (C) Schematic of crack geometry transition, plotting the crack corner stress concentration,  $\sigma_{tip}$ , and the applied stress far away from the crack,  $\sigma_0$ . The schematic shows that the initial horizontal crack orientation features a large stress concentration at the crack tip. In contrast, the transformed vertical crack orientation features only marginal stresses at its corners.