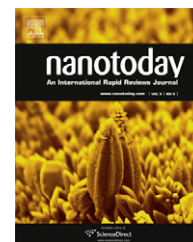


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NEWS AND OPINIONS

Tu(r)ning weakness to strength

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Abstract Biological systems contain highly functional and mutable materials ranging from inferior building blocks with weak chemical bonding (e.g. H-bonds in spider silk), to abundantly available materials (e.g. silica in some sea creatures), to structurally inferior materials (e.g. extremely brittle crystals in mineralized tissues like nacre or bone). Although wide and varying, biology commonly exhibits unlikely harmony within material structures and physiologic functionality. How can we exploit our knowledge of biological systems in designing synthetic materials, and can we extrapolate from this, a broad yet fundamental similarity between protein materials to a subject as classical and ancient as music?

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Proteins realize a broad 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 [1–4]. Another intriguing feature of many biological materials is mutability; the capacity of a material to selectively alter its properties, due to signals such as light, electric field, or pH changes. Within intricate feedback loops across all scales, these biological materials also demonstrate a stunning capacity to continuously adapt to altered environmental cues.

Despite this apparent complexity of functional properties, the structural designs of biological materials have

evolved under extreme evolutionary pressures to ensure a species' survival, often in adverse environments. As a result, these materials are created with low energy consumption, under simple processing conditions, and are exquisite as they often form from abundant material constituents. Notably, these abundant material constituents typically represent functionally inferior material building blocks that are exceptionally brittle, such as silica or other minerals, or extremely weak, such as H-bonding or Van der Waals forces. Moreover, comparative studies show that most biological materials are made up from only a few select universal elements, despite their functional diversity [5]. This is exemplified at different levels, such as in the occurrence of only 20 natural amino acids (which provides the basis for all known protein materials), and a few universal secondary structures such as alpha-helices, beta-sheets or random coils, or more fundamentally, the four DNA or mRNA nucleotides that are

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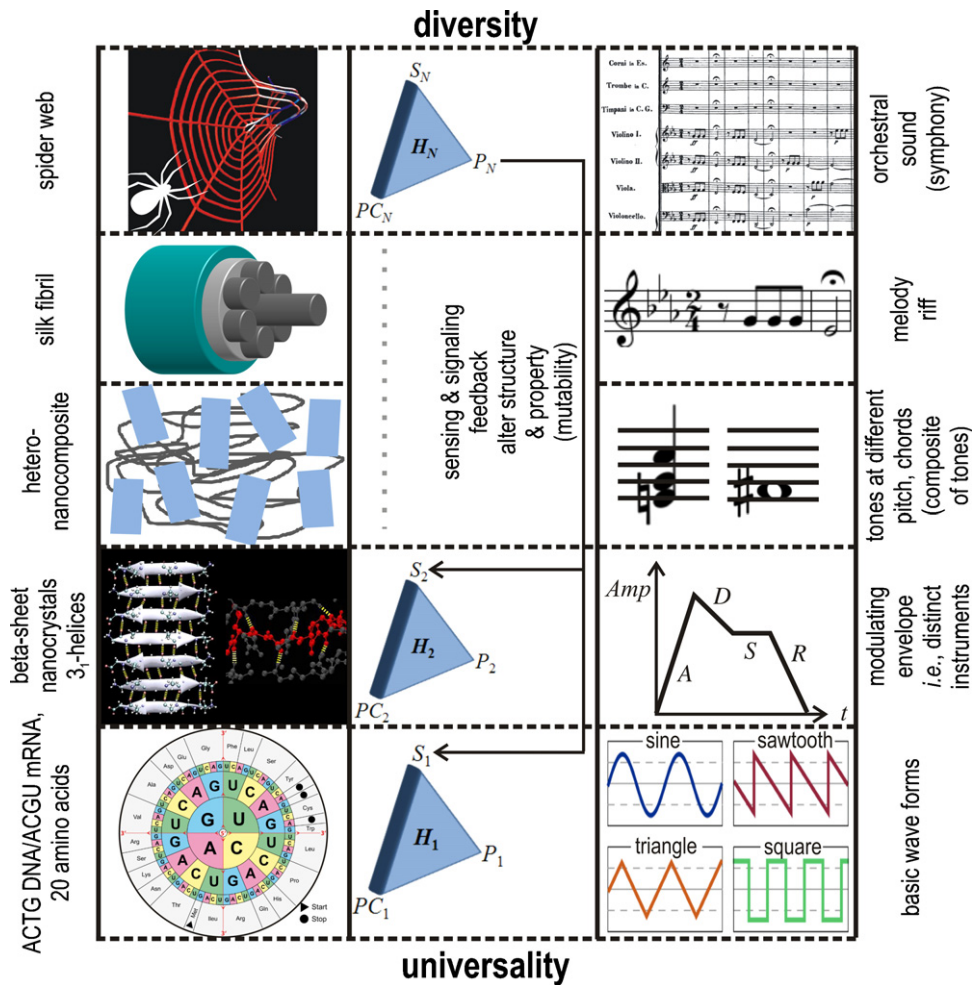


Figure 1 Illustration of multiscale hierarchical structure of protein materials, the interplay of universality and diversity, and an analogy to music. In protein materials (left), multifunctional materials are created via the formation of hierarchical structures, where at each structural level H_i a 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. Similarly 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.

universal to encode the structure of all protein materials at the genetic level.

The realization of how biology perpetually uses a limited number of elements to create highly diverse systems poses a fundamental question about the design of biological materials, and specifically, how such a great diversity of functional properties is achieved, despite the inferiority and universality of the building blocks [6]. Recent research suggests that the basis of understanding the remarkable properties of these 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. Rather, functionality is created by compiling simple and often inferior elements into assemblies where structures are created at multiple length scales, resulting in hierarchical material architectures. Thereby

each level provides access to specific functional properties, which is achieved by defining a particular material structure at each hierarchical scale (Figure 1, center). This paradigm, the formation of distinct structures at multiple length scales, also enables biological materials to overcome the intrinsic weaknesses of the building blocks. This 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 [7]. In an example relevant for sea creatures such as diatom algae, 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. Thus, the realization of distinct structural designs provides a means to tune the material to achieve a great diversity of functional prop-

erties despite the use of the same building blocks. More generally, if it is possible to alter the material's structure at specific hierarchy levels, independently and during use of a material, there exists the potential to realize varied material properties depending on functional needs, resulting in mutable materials [8]. This is exemplified in echinoderms (e.g. sea urchins) that can change their body's modulus manifold through alterations of the cross-linking of constituting collagen molecules. 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.

A powerful example to demonstrate the biological material design paradigm is the case of spider silk, a remarkable material that—in order to fulfill its biological tasks—must provide extreme levels of strength (1–2 GPa), toughness, and great deformability of up to 50% tensile strain (Figure 1, left panel) [9]. Yet, the structural basis of spider silk is extremely simple, and merely consists of 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 quickly, out of a limited stock of solvated protein [10]. 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?

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 ≈ 4 H-bonds, which allows them to work cooperatively—akin to a flock of birds—and thus reach heightened strength [11, 12]. Notably, 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. It is intriguing that 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, organized in small groups [12]. 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 [13]. 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. Yet, due to the nature of the available building blocks 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 (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. This is 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 constituent provides the capacity to generate large levels of deformability before the beta-sheet nanocrystal cross-links are deformed and eventually broken as they reach their strength limit [14]. By tuning the relative ratio of the two phases in silk, or the geometric makeup of the beta-sheet nanocrystals (e.g. their size), it is possible to achieve a diversity of mechanical signatures (e.g. stiff, soft, extensible, etc.) without a need to define new constituents, a mechanism spiders use to generate different types of silks.

The discussion of some of these most salient design features of spider silk strikingly provides 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 and 6 in beta-sheets and separated by disordered or differently structured elements, or in clusters of 3–4 in the turns of alpha-helices [12]. 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.

The biological paradigm of using multiple levels of structure to create diversity of function out of simple, universal element can be explained by drawing an analogy to a rather far and different field, music [15]. 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. The concept is schematically illustrated in Figure 1 (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 [16]. 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’. For example, in a jazz or rock jam session, music is continuously revised during performance in an adaptive feedback loop between the performers or with an 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 composers in ancient days were limited by the availability of certain instruments, such as flutes or harps created from bone. Classical composers (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 the most ingenious of all time—perhaps, because it required composers to utilize several levels of structure to achieve great functionality, which is apparently found appealing by the human brain. On the other hand, the impact of novel approaches to synthesize music from the bottom-up, with the use of arbitrarily complex sounds realized in *de novo* instruments (but few levels of hierarchical structures), remains unclear, and music with a distinct hierarchical structure remains preferred by many. Subjective and cultural aspects may likely play an important 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 can be designed based on synthetic approaches.

In summary, here we described important insights that provide an explanation for universally observed formation of geometrically confined hierarchical structures in protein materials [5]. The application of this concept can impact the technological use of abundant, however mechanically inferior (e.g. extremely brittle, or weak) materials such as H-bonded proteins or silica in the design of strong, tough and lightweight materials. Here the design of hierarchical structures could be the key to overcome their intrinsic weakness or brittleness, properties that currently prevent their widespread technological application. Broadly, this may result in the development of highly functional materials made of abundant, cheap and environmentally friendly constituents, and even materials that are currently considered waste. It suggests that there may exist an enormous technological opportunity that is based on the concept that functional material properties can be design based on almost arbitrary constituents, provided that multiple structural levels are created. An observation made based on the analysis of different materials suggests that universality tends to dominate at smaller scales (e.g. Angstrom and nanometer), whereas diversity is found predominantly at larger, functional scales.

The analogy between protein material design and music illustrates how biology is indeed a proficient composer, and that information can be derived to facilitate the develop-

ment of more sustainable materials that rely not merely on the strength of building blocks but rather, on the use of structures at multiple levels, to provide heightened functionality. The similarity between the design of music and that of materials in biology is intriguing and could merit further investigation, perhaps with the potential to unravel more general principles that govern mechanisms by which biological systems achieve functionality. Indeed, it was pointed out that functionality in certain animals (bees, ants, birds, etc.) does not rely on the strength of individual elements, but that functionality is achieved based on collective interactions of elements in clusters (via swarming, schooling, flocking, etc.) [17]. This concept is akin to the concept discussed here for the cooperative behaviour of H-bonds that turns their weakness into strength.

A key lesson learned is that in order to create a diversity properties, it is not necessary to rely on strong or numerous building blocks, but 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.

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