

Materiomics: An -omics Approach to Biomaterials Research

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The past fifty years have seen a surge in the use of materials for clinical application, but in order to understand and exploit their full potential, the scientific complexity at both sides of the interface—the material on the one hand and the living organism on the other hand—needs to be considered. Technologies such as combinatorial chemistry, recombinant DNA as well as computational multi-scale methods can generate libraries with a very large number of material properties whereas on the other side, the body will respond to them depending on the biological context. Typically, biological systems are investigated using both holistic and reductionist approaches such as whole genome expression profiling, systems biology and high throughput genetic or compound screening, as already seen, for example, in pharmacology and genetics. The field of biomaterials research is only beginning to develop and adopt these approaches, an effort which we refer to as “materiomics”. In this review, we describe the current status of the field, and its past and future impact on the biomedical sciences. We outline how materiomics sets the stage for a transformative change in the approach to biomaterials research to enable the design of tailored and functional materials for a variety of properties in fields as diverse as tissue engineering, disease diagnosis and de novo materials design, by combining powerful computational modelling and screening with advanced experimental techniques.

universally hierarchical - there is underlying structure and function at a multitude of diverse scales.^[3,4] This introduces a level of system *complexity*, where piecewise understanding of individual parts (by scale or by function) cannot simply be superimposed and assembled.^[5]

In biology, if we consider a single scale, one phase, with perfect knowledge of composition and sequence, in controlled conditions, we can make predictions, e.g., with knowledge of constitutive amino acids (i.e., sequence), we may predict an α -helical structure for a short polypeptide,^[6] and its corresponding properties (such as strength^[7]). In turn, synthetic efforts such as “click” chemistry^[8,9] and recombinant DNA approaches^[10,11] can produce materials with desired (and engineered) properties and behaviors at a single scale, or assembled into simple hierarchies (e.g., fibers^[12–14] or films^[15–17]). We cannot, however, accurately predict the behavior of larger (living) multi-protein assemblies and networks, let alone the structural role such materials play in a cellular structure (e.g., the nuclear

envelope). We utterly fail in real-world applications – the exact opposite of the goals of engineering! For engineering, we can design the components of a system or structure with reliable and repeatable accuracy. The performance of a fabricated steel member can be utilized in the design of a truss, for example, which is subsequently implemented in a bridge design. A fundamental challenge of tissue engineering and biological material synthesis lies within the understanding of material interactions across all scales, from individual atoms, to molecules, to subsequent tissues and entire organisms, and how they interact with the nonliving, materials environment, and how that may be altered due to the actions (and reactions) of the living part.

We note that the scope of biological and materials systems in general cannot be succinctly encompassed by a single review article, and thus the following discussion can only highlight a small portion of the research at the interface of biological tissues and material functionality. As an unavoidable drawback, we limit discourse to a few well-known biological materials as case studies, such as the aforementioned silk and bone. Moreover, it is difficult to describe the complete library of synthetic materials beyond a few representative examples (a combinatorial issue to be further addressed). Without hesitation, interested readers are directed to the citations herein. Additionally,

1. Introduction

The past fifty years have seen a surge in the design and use of new materials for biomedical and clinical application.^[1,2] Advancements have been made in both the understanding of the natural function of biological materials and systems (such as spider silk), as well as synthesis and regeneration of certain tissues (such as bone), however, a cohesive and systematic approach (a general “design protocol”) is still lacking. The critical roadblock is that biological tissues, organs, and materials are

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we deliberately restrict focus to physical characteristics and mechanistic properties. Beyond particular systems, from a clinical perspective, such functionalities may be secondary to the physiochemical and biological role of materials, including performance in vivo, material induced signal transduction, coupled effect(s) of growth factors, etc. Our intent is to provide general and familiar metrics across fields, exposing potential symbiosis and cooperativity. Indeed, when we discuss material “function” and “interaction”, we imply the terms in the broadest possible sense, and stress all definitions are necessary to the field of materiomics (as implied by the *-omic* suffix). That is the unequivocal and primary motivation—a unification of currently disparate expertise.

1.1. The Challenge of Engineering “Living” Materials

In order to understand and exploit their full potential, the scientific complexity at both sides of the interface – the material on the one hand and the organism on the other hand – needs to be considered (see **Figure 1**). The combination of living and non-living components, namely biological and synthetic materials, presents a complex challenge that is rooted in the *emergent* behaviour,^[18] when a collection of components are incommensurable (i.e. one cannot deduce resultant behavior from a set of reduced factors). This phenomena can be summarized by the popular adage “*the whole is greater than the sum of its parts*”. Emergent properties are frequently considered irreducible across scales^[19] – a troubling perspective in that we wish to engineer such systems piece by piece, as emergent properties

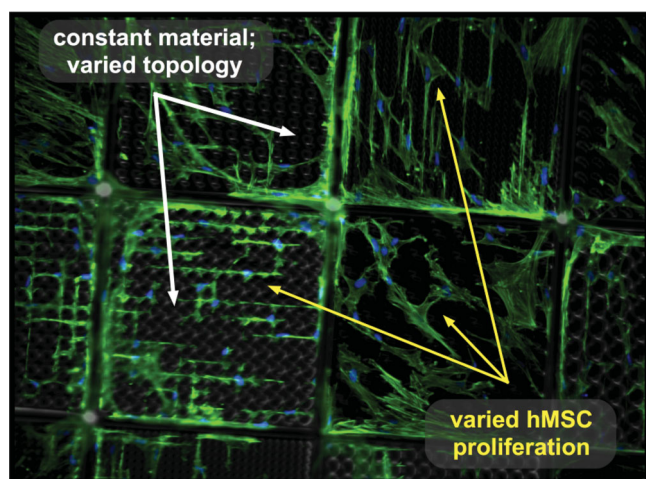


Figure 1. At the interface of material(s) and biology. In order to understand and exploit the full potential of complex biological materials, both sides of the interface needs to be considered simultaneously. The combination of living and non-living components - namely biological and synthetic materials - presents a complex challenge that can be summarized by the popular adage “*the whole is greater than the sum of its parts*”. Here, we see human mesenchymal stem cells (hMSCs) on a TopoChip.^[68] While the material substrate is constant, the geometry changes, and the living cells respond in different ways. Combined system behaviour cannot be predicted (or designed) by knowledge of each individual component in isolation—there is a coupled and reciprocal relationship between materials and Nature. TopoChip image courtesy of Frits Hulshof.

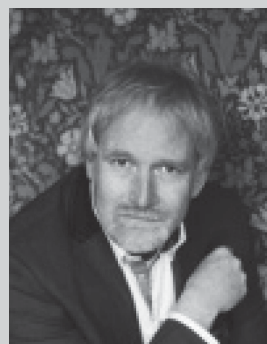


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His work has identified universal principles of structure-property relationships in hierarchically structured systems, including natural and synthetic materials, which has impacted the design of novel materials.

limit the deconstruction of complex systems and only arise via assembly.^[20] Yet, herein lies opportunity: emergent phenomena allow the capability of emulating large-scale behaviour without accounting for small-scale details. We simply need to determine the rules of interaction. If desired properties *emerge* from the interactions between constituent elements this means that components (e.g., material building blocks) can be simple as long as their interaction potential is rich.^[21]

Biological processes introduce complex living interactions to material systems, and thereby require certain tact to analyze mechanistic behavior and material properties. Nature, through meticulous trial-and-error and centuries of optimization, has intricately combined material structure, properties and functionality to the point in which they are indistinguishable.^[4] Structure and function are so intimately linked that one-to-one substitution of other potential materials is currently not possible—but need this be the case?

A key challenge is to extend physiochemical metrics, utilizing insight based on the material properties and mechanical function in a biological context, across the molecular, cellular, and tissue scales. Such analysis requires the integration of advanced experimental (atomic force microscopy,^[22,23] nuclear magnetic resonance (NMR) spectroscopy,^[24] small-angle scattering (SAS),^[25,26] time-of-flight secondary ion mass spectrometry (ToF-SIMS), X-ray photoelectron spectroscopy (XPS), water contact angle (WCA) measurements,^[27] etc.), computational (quantum mechanics and molecular dynamics (MD),^[28] image processing,^[29,30] data mining and bioinformatics,^[31] etc.) and theoretical methods, utilized to assess, monitor and predict mechanisms associated with protein materials and structures composed of them. The natural evolution of structure in biological systems is guided by the interactions between materials and environment. As a result, materials in biology (specifically those made of proteins) realize a diversity of functional properties such as catalysis, signal transmission, material transport, gene regulation and protein formation, structural support, and movement generation - many of them simultaneously - resulting in multifunctional materials. Significant evidence has recently emerged that proteins are organized in evolving functional networks,^[32] resulting in multi-functional structures that span many hierarchical scales.^[3,33] Before we can unlock Nature's secrets for our own gain (e.g., regenerative medicine and/or tissue engineering) we must fully understand the entire functionality of a given system, interaction with other materials (living or otherwise), and the intricate structure-function relationships, across all scales.

Nevertheless, while a complete understanding of a material system (biological or otherwise) is theoretically desired, advancements and immediate applications can be developed in a continuously refined and self-regulating cycle. To illustrate, we use bone/collagen as a specific example, with two specific research motivations: (1) complete understanding the material system ("discovering" Nature) and (2) exploiting what we learned for technological ends (engineering, or "unlocking" Nature), as depicted in **Figure 2**.

Understanding bone: Bone is often stereotyped as simply a protective and supportive framework for the body; though it does perform this function, it is actually a very dynamic organ that is constantly remodeling and changing shape to adapt to

the daily forces placed upon it. Like all natural materials, its mechanical properties are determined by its structure,^[3,34,35] which in turn is motivated by its (mechanical) function. Bone can be considered a biocomposite - a soft protein material phase (i.e., tropocollagen) combined with a hard mineral phase (i.e., hydroxyapatite) in a hierarchical structure, of which the specific composition and structure has been shown to vary with factors such as skeletal site^[23,36] and age,^[37] among other factors, making bone a very heterogeneous structure.^[38]

Even so, while a diversity of structural motifs exist between bone tissues at different microstructural length-scales^[39] the most common in bone is a lamellar unit of staggered mineralized collagen fibrils encapsulating hydroxyapatite crystals.^[35] These mineral crystals are relatively small (a characteristic thickness on the order of a few nanometers^[25,40]), with critical implications for its fracture behavior.^[41,42] The result is a composite material that can be thousands of times less susceptible to fracture than the pure mineral, and orders of magnitude stronger than pure protein.^[41] The combination of protein and mineral is more than an efficient use of building materials (in a kind of brick and mortar arrangement). Indeed, the combination of each phase is a kind of "material symbiosis" that should improve the performance of each component in a way that is currently unattainable by any engineered composite. The protein, the active biological component, benefits from the mineral by attaining strength and toughness otherwise unachievable. Moreover, the hierarchical structural arrangement introduces further enhancements to performance (such as toughness, self-healing, etc.), through a multitude of mechanisms (e.g., hidden length, microcracking, crack-bridging, etc.) only recently exposed and enumerated.^[36,38,43]

In spite of such mechanisms, even minute structural changes in the collagen molecule's architecture (such as point mutations) can have severe consequences for the macroscale tissue behavior, as is evident in genetic bone diseases such as *osteogenesis imperfecta*.^[44] leading to mechanically compromised tissues. While great strides are being made to understand such afflictions across scales,^[45] we cannot yet directly trace the root cause (e.g., specific amino acid mutation) to the system-level effect (e.g., compromised tissue function), beyond a few characteristic metrics. For example, we can rank specific point mutations in terms of disease severity (e.g., glycine substitute with alanine is more benign than valine), but we currently do not fully understand *why*. While the problem is complex, it is becoming more tractable, and does not prohibit the concurrent tutelage of what we already know (which is extensive) to more immediate and reciprocal gains.

Engineering bone: The basic approach to bone tissue engineering involves the development of porous 3D-scaffolds, having an interconnected pore network structure for cellular in-growth and signaling, and facilitating nutrient and waste exchange. Many synthetic polymers have been used in tissue engineering as 3D scaffolding materials for bone repair.^[46,47] Regeneration of tissues *in situ* can be achieved by providing the right cues to cells using functionalized instructive scaffolds—what cues can we extract from the knowledge of natural bone? For instance, by tailoring the microporosity and chemistry of porous calcium phosphate ceramic it has been possible to produce instructive materials. When these materials are implanted

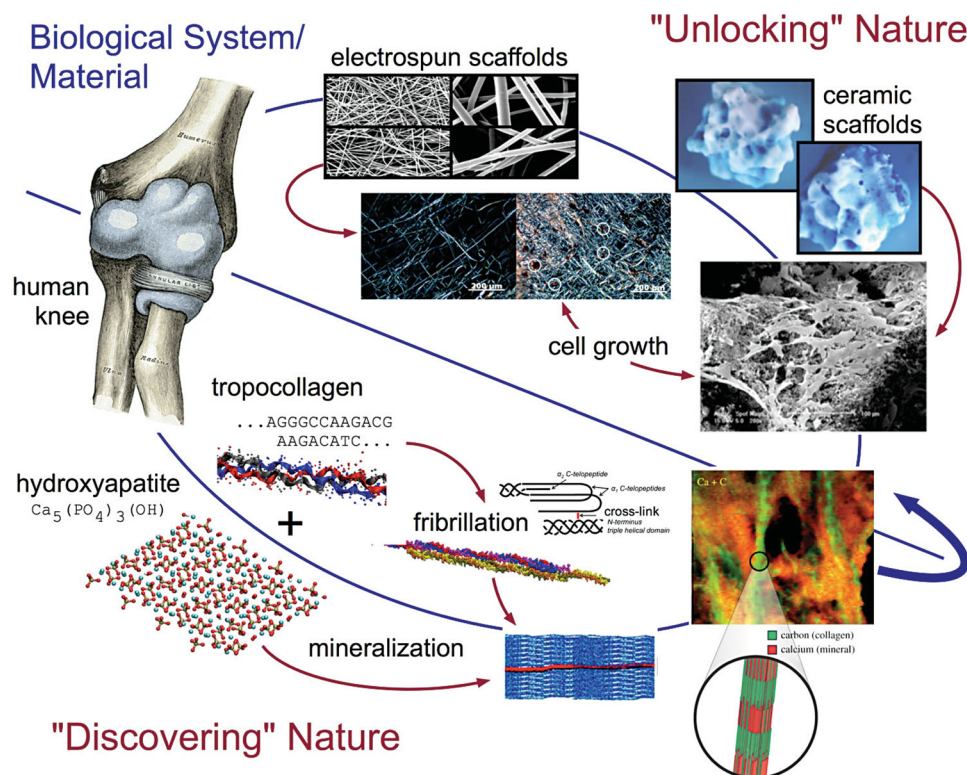


Figure 2. Advancement through concurrent “discovery” and “unlocking” of biological systems: bone as a case study. To successfully engineer biomaterials (and exploit their potential) we need to completely understand the materioime (consisting of all material properties, interactions, and functions) across scales. Here, bone is deconstructed into a composite of tropocollagen and hydroxyapatite, forming cross-linked mineralized fibrils/fibers, assembled into bone in a regularly repeating, staggered arrangement.^[3,35] An intimate knowledge of mechanisms across scales (such as the hydrogen bonding between polypeptide residues,^[240] effect of fibril cross-linking,^[241] or crystal orientation,^[242] etc.) is necessary to unlock Nature and fully engineer the synthetic assembly (e.g., growth) of regenerative tissue. Collagen fibril image and model reproduced with permission from Alexander et al.^[242] Copyright 2012, The Royal Society. Images of ceramic scaffolds reproduced with permission from Chatterjea et al.^[60] Copyright 2011, John Wiley & Sons, Inc. Images of electrospon scaffolds reproduced with permission from Nandakumar et al.^[50] Copyright 2010, John Wiley & Sons, Inc.

in muscle tissue, they induce new bone formation.^[48] A closer look at the molecular mechanism of this so-called osteo-inductive process shows that mesenchymal stromal cells will differentiate into osteoblast when exposed to high levels of calcium.^[49] The reciprocity between material sciences and bone biology is even more intimate when it was found that the osteo-inductive potential of ceramics is only seen in a certain strains of mice, not others, showing that genetic determinants control osteo-induction. However, as a first approximation for a *deterministic* approach, we can look to the fundamental building blocks of bone—namely, collagen and hydroxyapatite—a logical step toward creating scaffold for bone regeneration.^[50] Recent studies successfully demonstrated the combination of collagen and hydroxyapatite in synthetically assembled architectures.^[47,51] Indeed, some “lessons” learned from natural bone arose from such attempts: Thomas et al.,^[47] using nanocrystalline hydroxyapatite (particle size on the order of 100 to 150 nm), showed an increase in the Young’s modulus and hardness with increasing mineral content from 0 to 20 wt.% (which can be predicted by simple mechanical formulations^{[52])} whereas Song et al.^[51] demonstrated that higher weight percentages of mineral resulted in ineffective distribution of hydroxyapatite by the

collagen leading to precipitation of large clusters of mineral. Indeed, the principle of *nanoconfinement*, which arises in natural bone and increases the material toughness, is lost once the mineral phase aggregates, suggesting a refinement in scaffold preparation is prudent if increased mineral content is desired.

Beyond the simple combination of collagen and mineral phases, the mechanical properties of such scaffolds can be vastly improved either by cross-linking collagen or by combining them with an additional synthetic polymer—an option not readily available to Nature. Here we see the advantage of introducing synthetic materials as biological analogues. For example, researchers have combined commercially available polymers like Poly- ϵ -caprolactone (PCL), Poly-L-lactide (PLLA) and Poly([D,L-lactide)-co-glycolide] (PLGA) with either hydroxyapatite or a combination of hydroxyapatite and collagen.^[53] Additionally, PolyActive™ (PA) is a poly(ethylene oxide terephthalate)–poly(butylene terephthalate) (PEOT/PBT) block copolymer whose properties can be adjusted for various applications by changing the molecular weight and ratio of PEOT and PBT.^[50] This class of polymer has been used for bone^[54] and cartilage tissue engineering,^[55] among other applications.^[56] Such polymers have also been electrospun^[57,58] and

combined with 3D scaffolds for enhanced cartilage formation^[59] or biomimetically coated^[58] to enhance in vivo bone formation. Moreover, ceramics (such as calcium phosphate) have been successfully introduced as osteogenic grafts, serving as a substitute for the mineral phase of bone.^[60,61] Complicating matters, however, is that conditions that have been shown to promote cell differentiation in vitro does not necessarily translate to in vivo success,^[62] requiring further understanding of the cell-material interactions.

As proven by bone engineering, lacking a complete picture from genetic transcription to tissue function has not impeded successful advancements and utilization of the mechanisms and interactions we know (fairly) well. In a similar manner, there has been success in many biological systems, including the growth of engineered blood vessels^[63] and vascularized muscle tissue.^[64] It is well shown that the mechanical properties and cell behavior can be tailored depending on the type of material scaffolds used, and we can exploit past successes in a self-optimizing manner. More commonly, successful materials can be explored via high-throughput screening methodologies,^[65–68] optimizing potential scaffolds with increasing fidelity and efficiency, exploiting the ever-expanding library of materials (e.g., tailored polymer species and functional groups such as the aforementioned PolyActive or newly developed nanotechnology materials, such as carbon nanotubes^[69] or graphene^[70]). Engineering hubris and ingenuity, combined with clinical need, has laid the groundwork for future refinement, *but what could we achieve if we had the entire picture, a kind of multiscale material blueprint?*

Indeed, successful integration (and reliable design) of biomaterial systems require a means to define the structural components of biological and synthetic materials from a materials science perspective, and their role in mechanical phenomena, materials growth and failure, and in diseased or altered physiological conditions. Significant advances and convergence in experimental, theoretical and computational materials science have enabled a deeper understanding through the linking of material structure-process-property and functionality. The translation of such techniques to biological systems and tissues can provide critical insight to append the growing knowledge base of biological and biomedical sciences. The study of hierarchical material structures and their effect on molecular and microscopic properties, by utilizing structure-process-property relations in a biological context, provides a basis for understanding complex systems by translating material concepts from biology. But the inverse problem remains—that is, can we successfully introduce and exploit biological processes (such as healing or growth) seamlessly within a synthetic system, subtly eliminating the distinction of “material” and “tissue”?

1.2. Technological Advancement & Convergence

The systematic investigation of both biological and non-biological materials has advanced considerably in recent years, along with the advancement in the tools required for analysis. Indeed, there are constant updates and refinements of techniques providing new, more accurate means to measure, interpret, quantify, and model the relationships between chemistry, structures,

design and function. Progress in information technology, imaging, nanotechnology and related fields - coupled with developments in computing, modeling and simulation - have transformed investigative approaches of materials systems. The motivation has come from a vast assortment of disciplines: medicine (mechanical and physiological properties of soft and hard tissues, including skin, tendons, bone, etc., for prosthetic devices, replacement materials, and tissue engineering applications); biology (material aspects of adaptation, evolution, functionality, etc.); and materials science (thermal and electrical properties of novel hierarchical nanosystems, functionality performance of microscale devices, etc.) to name a few. The complexity of biological materials elicits contributions from a multitude of fields, and is an exciting field for biologists, chemists, and engineers alike. Further advancement is hindered, however, by such a “divide and conquer” approach, and dictates a convergence of scientific disciplines.

Traditionally, the science and engineering of synthetic material systems have been separated into classes of structures, length scales, and functionality that are used to differentiate disciplines. Nature, however, does not conform to disciplinary boundaries, and effortlessly balances chemistry, materials, structure, and function across a full range of length scales in order to react to a variety of environmental requirements and optimal functionality. Innovation and successful (predictive) biomaterial design involves a rigorous understanding of the properties and mechanisms of biological matter. While this is an easy statement, integration of multiple disciplines is difficult in practice. Due to the rich history and unique perspectives of diverse fields, questions of interest, approaches, tools and even vocabulary particular to each community (the “disciplinary lexicon”, so-to-speak) can impede communication and progress in this inherently interdisciplinary venture.

In addition, recent advances in science and technology have seen the creation of a multitude of biologically “themed” interdisciplinary research areas including bioinformatics, nanobiology, biomimetic materials, and systems biology. Such fields share a comparable, underlying research paradigm, recently defined as *convergence*. Through the merging of technologies, processes and devices into a unified whole, new pathways and opportunities for scientific and technological advancements are created inaccessible to any single discipline or knowledge base. The goal of convergence is not a particular scientific advance, but on a new integrated approach for achieving advances. The results are critical to biology-related fields, such as bioengineering, computational biology, synthetic biology, tissue engineering, and materiomics. Indeed, materiomics can be thought of as the inevitable convergence of materials science, biological science, and technological advancement (encompassing computational methods and experimental assays), as depicted in **Figure 3**. *But why is such a perspective necessary?*

1.3. A New Perspective: Materiomics

Traditional analytical methods encompassing fields such as engineering, materials science, and biochemistry lack a complete toolset required to describe the complexities introduced by multi-scale relations, discrete hierarchical materials,

Synthetic

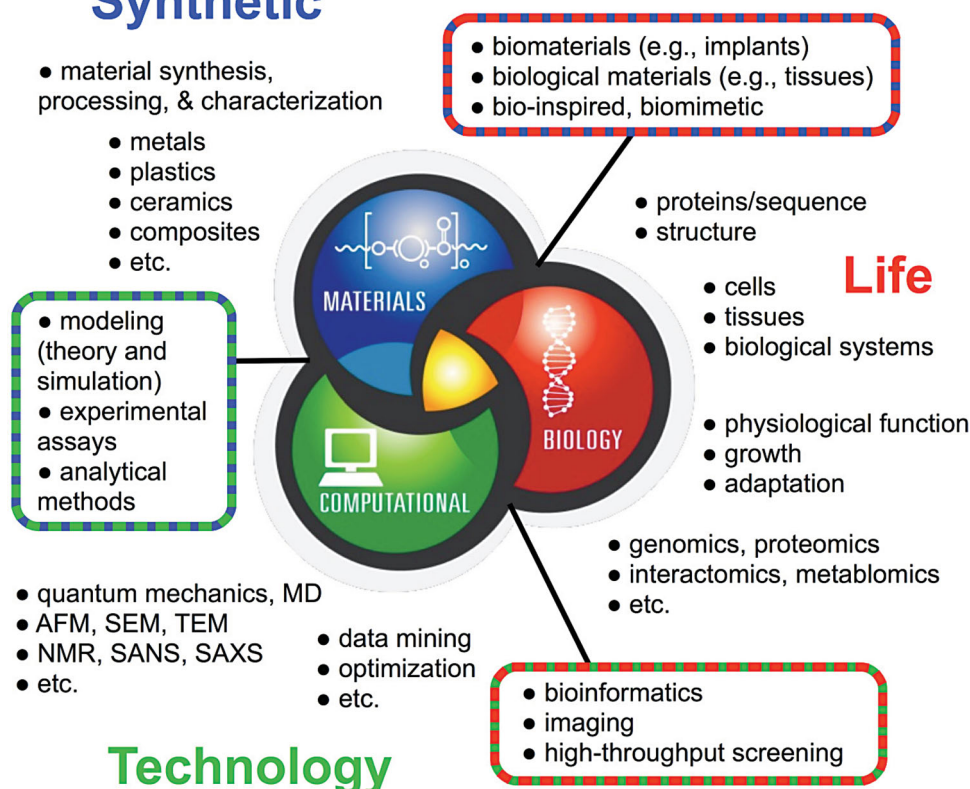


Figure 3. Materiomics – the convergence of disparate fields. The interface of materials science (“synthetic”) and biology (“life”) has been successful in the development of biomaterials, but recent technological advancements (computational capabilities, experimental methods such as AFM, imaging techniques such as NMR) allow for a truly integrated and holistic approach. While some biological materials have been investigated from a materials science approach, and some material developments have been inspired by Nature, complete understanding requires integrated and holistic approaches. One direction has been to uncover the functional relationships of biological materials (e.g., physiological function through proteomics attained via bioinformatics) while another direction systematically characterizes the material properties of tissues via modelling and experimental probes common to materials science (e.g., mechanistic interpretations of function derived from molecular simulation). Materiomics resides at the apex of these information streams, attempting to reconcile biological function with material interactions and properties.

cross-phase interactions, and structure-property dependencies across all scales, critical to all biological materials. Engineering notions of stress and strain, fracture and plasticity, toughness and robustness, are inherently linked to material behavior at the macro-scale, yet lack any metric to deal with “growth” or “life”. Similarly, chemical and biological techniques (including such fields as microbiology, proteomics, and condensed matter physics) shed vast insights on nanoscale phenomena, such as the chemical composition of materials or the interactions of residues, but lack an explicit association with predictive or mechanistic system functionality.

The study of material properties of biological protein materials has witnessed an exciting development over the past several years, partly due to the emergence of physical science based approaches in the biological sciences. The rapid expansion in the scope of materials science and engineering has led to incorporation of such fields as experimental and computational biology, biomedical engineering, and genetics, all in the context of natural and synthetic materials. In addition, there is accelerating interest in the discovery and understanding of Nature’s structural design rules,^[34,71] in particular for

nanoscopic hierarchical molecular structures and to make them available to engineers in order to invent and design tomorrow’s supermaterials (e.g., mutable or tunable materials, advanced composites, low-density low-energy structural materials, etc.), seamlessly blending synthetic materials with biological systems (e.g., tissue and biomedical engineering), and using basic biological systems as templates for design (e.g., biomimetic and bio-inspired materials).^[72,73] There is also a surprising relationship between these material design issues and the understanding (or rather lack thereof) of genetic diseases and disorders, where structural changes are due to mutations on the molecular level which lead to changed chemical and mechanical properties, which in turn lead to a malfunction of the protein network and/or cellular function.

The linking of mechanisms across multiple scales by using a materials science approach to provide structure-process-property links characterizes the emerging field of *materiomics*. Materiomics—a portmanteau of “material” with the suffix “omics”—can be simply defined as *the holistic study of material systems*. While typically applied to complex biological systems and biomaterials, materiomics is equally applicable to non-biological systems.

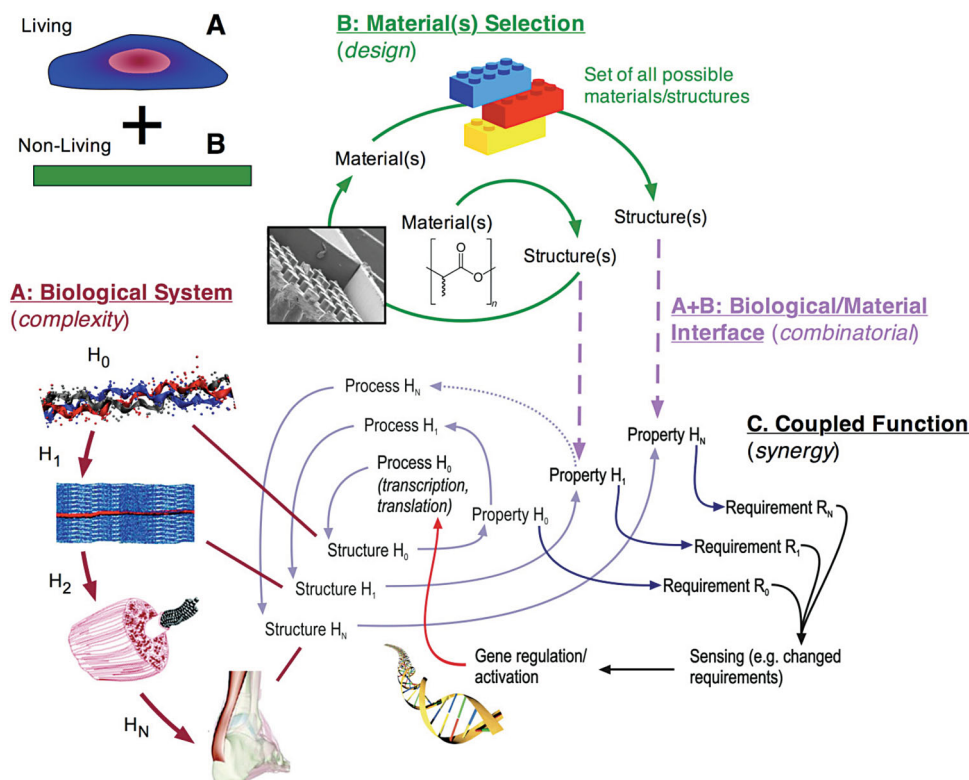


Figure 4. Defining the materiome - integrating “living” and “non-living” materials. The lower portion of the figure presents a schematic representation of materiomic information for a complex biological material system (A), such as tendon. Here, H_i refers to hierarchy levels (structure, process, and properties) and R_i refers to material property requirements at hierarchy levels $i = 0 \dots N$. The cycle initiates at process H_0 (protein expression) 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. Overall, properties at different hierarchical levels are regulated by corresponding physiologic demands (requirements R_i), which are sensed and transduced to activate genetic regulation. Adapted from reference.^[4] We wish to introduce a non-living component (B) to this complex, self-regulating system. As such, we need to design a suitable system across scales, combining complementary materials and structures. Since the choice of synthetic materials is vast, materials can be classified according to function (e.g., functional building blocks). At the interface (A+B), the designed multi-scale synthetic structure influences the behavior of the biological material, potentially altering the hierarchical properties and requirements. The goal is to attain knowledge of the entire system (e.g., the materiome) and all possible material interactions (e.g., a combinatorial problem), such that “A+B” results in coupled synergetic function (C), whereby the properties/requirements of the biological tissue can be anticipated and designed.

Complementary to the field of biomaterials, materiomics represents a necessary holistic approach to the investigation of biological material systems, through the integration of natural functions and processes (biological, or “living” interactions) with traditional materials science perspectives (physical properties, chemical components, hierarchical structures, mechanical behavior, etc.). The addition of -omics adds a subtle layer of complexity to the material systems we are interested in. The term *omics* generally refers to “all constituents considered collectively”. For instance, *genomics* and the study of the human genome refer to all of our genes, not just a single subset that determines if you have your mother’s hair or your father’s stubbornness. Similarly, materiomics encompasses much more than a piecewise cataloging of the properties and behavior of a material; it encompasses all possible functionalities and material interactions, from nano- to macroscale, in an abstract holistic sense. Knowledge of how bone tissue can be grown on a calcium phosphate scaffold under controlled conditions is a materials science and biological problem. Understanding how

bone tissue can be grown on any arbitrary material platform is a materiomics problem (see Figure 4).

The merger of such perspectives—e.g., materials science and biology - is mutually beneficial: materials scientists have extensive experience in treating structures, processes and properties of materials systematically and with rigorous mathematical methods, whereas biologists have gained a detailed understanding of biological systems and structures and related functions by utilizing both physiological models and powerful statistical correlations between, for example, genetics, physiology and pathology. At the juncture is the emergence of the *materiome*.

2. The Current State of Biomaterials

The field of biomaterials research has been very successful over the past fifty years by introducing a number of blockbuster devices that had relied on coordinated materials development,

such as heart valves, hip implants and contact lenses. More recently there have been advancements in recombinant DNA techniques, bringing together genetic material from multiple sources and creating sequences (and materials) that would not otherwise be found in biological organisms (manipulating sequence replication in *E. coli*, for example^[10]). The field has largely been characterized by trial and error experimentation and low throughput research.^[74] Most frequently, the identification and development of biomaterials was iterative - with materials being piece-wise designed and tested for their properties in combination with one specific application.^[75] Moreover, the initiative traditionally lay primarily with chemists with an interest in biomedical engineering. As a result, biomaterials were primarily investigated as a solution to a specific problem - not as a field of research and discovery unto itself. For example, first coronary stents were composed of stainless steel, most likely due to availability and known durability, as opposed to a custom designed and optimized "stent material". This need not be the case.

There is now an increasing interest in diverse range of applications (requiring materials that are green, self-assembled, low-cost, biodegradable, energy efficient, high performance, self-healing, etc.), such that "biomaterials research" encompasses all forms of biocompatible and biomedical materials, as well as biomimetic and bio-inspired systems.^[34,71] On the one hand, this has introduced a multitude of fresh perspectives and approaches, and on the other it has produced a seemingly insurmountable collection of data.

While it may be difficult to define biomaterials in a cohesive manner, what differentiates such systems from "traditional" materials such as metals (steel, copper, tungsten, etc.) and polymers (rubbers, plastics, etc.) is their inherent complexity. Complexity of molecular sequence, hierarchical structure, self-assembly (e.g., growth), and multi-functionality are common features of biomaterials.

2.1. Dealing with Complexity

The *de facto* hidden nature of complexity combined with a division of disciplinary expertise is a stringent barrier to the full understanding (and design) of biological materials and systems. Indeed, without such limitations, one could easily foresee growing any desired tissue from the necessary DNA (along with requisite raw materials), similar to the chemical vapor deposition (CVD) of carbon nanotubes or the polymerization and spinning of nylon. A key starting point in developing a conceptual and theoretical bridge to biology is robustness - e.g., the preservation of particular *functionality* despite uncertainty or minor variation in components and/or the environment.^[5] Such a paradigm is similar to the concept of systems biology with a focus on emergent rather than reductionist properties. However, critical behaviors/interactions/functions may emerge across multiple scales, with both bottom-up (e.g., molecular dependence) or top-down (e.g., environmental dependence) triggers, requiring a combination of both holistic and reductionist approaches, depending on scale. In effect, we must neglect the particulars of a system (such as peptide sequence), identify the fundamental building blocks (structure, key interacting

groups), and delineate the function of each (signaling, catalytic, mechanical, etc.).

Ultimately, the genome dictates the level of biological complexity, yet in biomaterial research, complexity depends on the number of variables produced by engineers. While biological materials are characteristically composed of a limited set of materials (carbon, oxygen, nitrogen, and a few metal ions), this need not be the case for engineered materials.^[76] Nevertheless all elements are governed by the same material/chemical laws. Observation and extraction of the general underlying principles (physical, chemical, optical, electronic, thermal, mechanical, etc.) of the structure-function relationship (using both experiments and theory) is required to make them available as a concept useful in materials science engineering beyond the biological occurrence,^[73] and open the doors to ever-expanding material libraries. But how can we (a) determine what function is required and (b) reduce the number of potential material candidates for our need? Complexity arises from three main factors, to be discussed in the following sections and summarized in Figure 5.

2.1.1. Searching for Universality Across Scales

Multi-scale hierarchies are a common feature of biological materials, making any single-scale analysis and prediction debatable (a hypothesis at best). One such approach to deal with multi-scale complexity is the so-called *universality-diversity paradigm*.^[77,78] The evolution of protein materials through genetic selection and structural alterations has resulted in a specific set of limited protein building blocks that define their structure (twenty amino acids), yet protein materials exist in an abundant variety. At higher scales, biological materials exploit a common set of structures (e.g., α -helices, β -sheets, random coils) during their formation and function, and the process or mechanism of use of this material (e.g., synthesis, breakdown, self-assembly) - the phenomenon of universality exists ubiquitously in biology. Similarly, cellulosic materials,^[79] such as wood, grasses, and other green plants, exhibit a wide array of macro-scale mechanical properties dependent on the fiber morphology and structure,^[80] yet are composed of similar molecular building blocks (various polysaccharides in both crystalline and amorphous phases^[81]). The *universality-diversity paradigm* (UDP) incorporates the recognition and analysis of biological materials based on the universality and diversity of its fundamental structural elements and functional mechanisms.^[77] It is apparent that using only a limited number of components, Nature has produced a broad range of materials with diverse properties and biological functions, and created multi-functionality (*diversity*) by changing structural arrangements of few (*universal*) constituents rather than inventing new building blocks. In protein materials, the coexistence of universality and diversity is enabled by utilizing hierarchies of structure, which serve as an expansion of the design space. Thus, from such an approach, the key lies in the structural organization of materials (e.g., complex hierarchies) rather than the material components themselves. Efforts must be directed to delineate the function of structure and material combined.

A similar concept is that of a universality class - a metric to define common properties of a large set of systems, independent of the lower-scale details of the system (i.e., desired quantitative

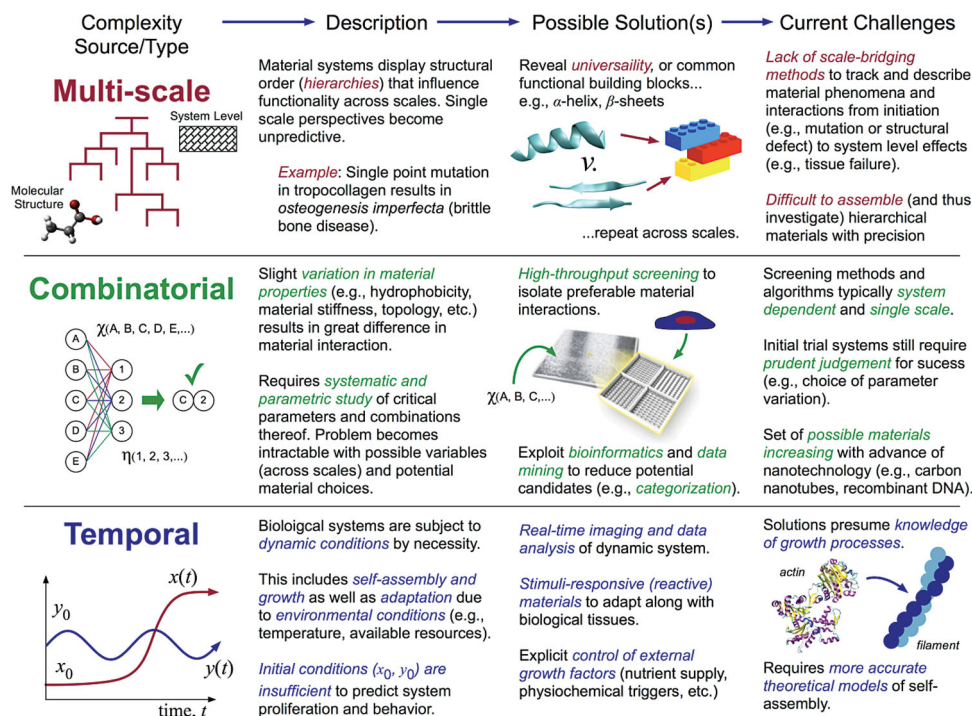


Figure 5. Sources of complexity in biological materials, with possible solutions via a materiomorphic approach.

features can be deduced from a few global parameters).^[82] Such systems typically display universality in an observed scaling limit, when a large number of interacting parts come together, and universality classes have been utilized in the description of polymers^[83] and folded proteins,^[84] as material examples. The concept can be extended to macroscale phenomena such as percolation of oil through porous media or traffic patterns through a city.^[85] The key insight is that universal mechanisms, interactions, or motifs can be applied *across* systems, even if the details significantly vary. Indeed, the concept of “flow” can be equally applied to both a fluid through pores or traffic on highways. Commonly, however, universality is not an obvious feature—rigorously linking the collapse of solids and the death of living organisms,^[86] or ferromagnetism and tumor growth,^[87] as examples, is non-intuitive at first glance.

Determination of such universal structures/functions or classes is similar to the field of proteomics and interactomics,^[88] but extended beyond the confines of a cell and tissue to interactions and properties of the material world. This becomes attractive, as if general material interactions can be defined in absence of biological conditions (or constraints), they should theoretically hold for similar synthetic material systems. Such efforts lie at the root of biomimetics,^[72,73] to exploit the principles of Nature for technological means beyond the evolved functionalities of a biological system. Indeed, spider silk is not a focus of intense research to allow us to swing from the skies like Spiderman, but rather the attraction of high performance, lightweight fibers. Required is the definition and categorization of key structures, relationships, and interactions between system components, beyond the current standard set of material properties. If such definitions are robust and theoretically

sound, it has been proposed one could draw insight from fields as diverse as art and music and apply general relationships to biology and material science.^[89] Such efforts, however, are in their infancy.

Diving down this rabbit hole, we find that the problem quickly becomes intractable - the sheer amount of possible material-material interactions is unbounded. By what means can we reduce the vast number of candidates? An increasingly successful approach in understanding and engineering of biological systems is the implementation of high throughput methods,^[65,66,90] which combine the best of holistic and reductionist approaches.

2.1.2. High Throughput Screening

High throughput combinatorial methods involve the synthesis, processing and screening of vast numbers of systems (e.g., molecular, material, cellular) in parallel.^[91] By definition, materiomimics involves the introduction of material sets into the screening process. To be practical, such methodologies require the advancement of complementary high throughput characterization approaches, to both define the chemical or material structure and “screen” the performance/success of the desired application^[92] (for extensive reviews, see Hook et al.,^[66] Simon and Lin-Gibson,^[65] Potyrailo et al.,^[90] and references therein).

In a holistic sense, no *a priori* assumptions are necessary regarding material performance or system behavior—any extensive set of material/system permutations can be generated and characterized. While known controls (such as growth factors) may be used for comparative purposes, it is intended that only results drive an iterative screening process (however, this does

not negate consideration of method of selection of training set compounds, training set size, applicability domain, variable selection, suitable parameters to indicate predictivity, etc.). Once a suitable candidate (or set of candidates) is found (e.g., reaching some performance metric), reductionist approaches may then be used to delineate the specific mechanisms or reaction pathways that instill success—and thus a foothold for refinement. For example, quantitative structure–activity relationship (QSARs) analysis combined with molecule mining may isolate a critical functional group through an automatic fragmentation scheme.^[93,94] Indeed, similar molecules with just a slight variation in their structures can exhibit a particular biological activity or quite different types of biological activities.^[94] Groups of “successful” molecules can then be scrutinized through full atomistic molecular dynamics or quantum mechanics, to isolate key or similar features (enhanced binding of fullerene derivatives to HIV-1 protease inhibitor,^[95] for example). Without high-throughput sampling of many candidates, characterizing the properties of a single “success” may prove inconsequential. Such analysis – uncovering the *universal* features of “success” – enables the elucidation of the relationship between surface chemistry and a biological phenomenon of interest, beyond any one-off system investigation.

Advantageously, high throughput methods can be highly successful when there is no theoretical basis for predicting performance (such as in complex biological systems). For example, a recent study by Hook et al.^[96] successfully screened hundreds of polymeric materials in a high-throughput microarray format^[66] to determine those resistant to bacterial attachment (bacteria and biofilm formation degrade the optimal performance of medical devices). A group of structurally related materials comprising aromatic and ester moieties was identified that substantially reduced the attachment of pathogenic bacteria – a class of materials that could not have been predicted to have this property from the current understanding of bacteria–surface interactions.^[96] Interestingly, this can be thought of as the inverse problem to determining material candidates for cell differentiation, where “success” implies growth.^[97,98] Extending such studies, holistic screening combined with reductionist analysis can be reciprocally beneficial, providing a self-optimizing protocol for delineating material system characteristics and performance, e.g., in the same study by Hook et al.,^[96] it is suggested that the ester moieties in close proximity to disparate chemical groups decrease bacteria attachment, similar to zwitterionic materials,^[99] warranting further investigation. While understanding the mechanism for performance is not required for a successful high throughput screening of a property, it can lead directly to a “hidden” or “surprise” structure–property relationships, such as ester and aromatic groups inhibiting bacteria growth,^[96] which can form the basis of the design of future materials.

Notable early examples of high throughput methods include the genetic screening of fruit flies (*Drosophila*),^[100] genomics,^[101] combinatorial chemistry for drug discovery,^[102] and systems biology.^[103] Most of these developments are driven by available engineering technology. For instance, our knowledge of the human genome and system biology is not possible without informatics and gene expression profiling as a resultant of DNA microarray technology. For materiomics, characteristics of

material systems can be analyzed and correlated to biological performance using high throughput surface analysis, including time-of-flight secondary ion mass spectrometry (ToF-SIMS), X-ray photoelectron spectroscopy (XPS) and water contact angle (WCA) measurements.^[27] Imaging, achieved via infrared and Raman microspectroscopy,^[104] or neutron scattering,^[105] can provide a means to measure the bulk chemistry of materials in a spatially resolved manner. It is of no surprise that few (if any) of these techniques were developed with a purpose of high throughput screening methods.

Currently, screening is best achieved in a microarray format, which enables thousands of material–material, cell–material or tissue–material interactions to be monitored on a single chip. Polymeric materials are of particular interest for high throughput strategies, because of their high biocompatibility, relatively precise synthesis, and the large combinatorial space associated with the large number of functional monomers available and their possible combinations.^[106]

Beyond the constituent “material”, definition of the materiome must also incorporate the material “structure” in a rational manner. It is increasingly recognized that material surface topography is able to evoke specific cellular responses, endowing materials with instructive properties that were formerly reserved for growth factors. The same material constituents (e.g., building blocks) can be assembled in different topologies to direct the outcome of cellular differentiation. Currently, the interplay between surface topographies and cell behavior is complex and not completely understood. In terms of microarray screening, simple gradient investigations have been successfully employed, whereby the variation of the relative composition of two material properties results in a test surface that varies gradually (e.g., extremes in chemical composition or topography^[107,108]). Such investigations, however, typically employ simple topographical variation (e.g., smooth to rough,^[108] for example). Just like material combinations, however, near limitless permutations of topography of a system can be constructed at will in silico, with minimal effort (only a subset of possible permutations can be efficiently probed experimentally). The key obstacle, of course, is identifying the critical subsets.

To delineate the effect of *structure* from *material*, in a recent study, rather than the ad hoc choice of topography, mathematical algorithms were employed to design nonbiased, random surface features (using only three types of primitive shapes: triangles, circles, and rectangles) atop microarray chips, producing thousands of unique topologies per assay.^[68] Nature does not prescribe the optimal surface topography for a given biomedical application, and the number of possible surface patterns that can be created is virtually unlimited, considering that cells are in the order of tens of micrometers whereas patterns can be created at nanometer resolution. What a cell “sees” at various scales is unknown,^[109] and the underlying mechanisms defining the interplay of cells with substrates are only partially understood.^[110]

With the advent of new developments in micro- and nanotechnologies, it is possible to create surfaces with precisely designed feature sizes and shapes up to nanometer resolution, resulting in unprecedented control of material surface and the behavior of cells growing on them.^[111] Randomized libraries of surface topographies—implementing the same universal

building blocks - can be broadly applied to optimize the interplay between cells and surface, to find improved material surfaces, and yield novel design criteria. New materials may not be required—only general rules on how materials are assembled in higher order topologies (or hierarchies). This is at the very root of materiomics, to unlock the design space beyond traditional materials science metrics.

2.1.3. Growth and Temporal Complexity

Complicating matters further, *in vivo* the material system naturally changes with respect to time. For example, many protein materials obtain their specific functionality by post-translational modifications, which include hydroxylations (e.g., during formation of tropocollagen's hydroxyproline residues), phosphorylations, glycosylations (e.g., during formation of cartilage tissues), as well as enzymatic cross-linking. These modifications are particularly important for material properties of tissues, as they control the interaction between proteins and with other material components (e.g., inorganic materials, sugar-based components) as well as their bioactive properties. These modifications are particularly difficult to mimic *ex vivo* or through synthetic approaches, posing a major challenge in structure prediction (and design) and the development of biomimetic and biocompatible materials. Thus we encounter a new level of complexity unique to biological materials—temporal/dynamic variation due to growth and adaptation. Unlike engineering materials where change is often a result of degradation or failure (e.g., wear and tear), tissues may undergo complete physiological changes during multiple stages of growth.

From a molecular perspective, individual protein components self-assemble at different time-scales to form protein structures with hierarchical geometrical entities. Cell adhesion, cytokinesis and cell migration illustrate the power of the cytoskeleton to self-organize locally into complex structures. Assembly mechanisms have been investigated based on the combination of imaging tools with controlled assembly conditions (e.g., pH, temperature, solvent), typically focused on a single cellular component. For example, this approach has elucidated the mechanism of lamin assembly.^[112] In this process, lamin dimer association and axial growth is followed by radial growth to form larger fibrils, resulting in formation of a network (within the nuclear envelope). More recently, a similar “axial growth” model has been proposed for tropoelastin,^[26] driven by head-to-tail assembly of the protein structure. Understanding of such assembly mechanisms can be used to construct highly aligned elastin fiber networks,^[113] or exploit the head/tail proclivities (hydrophobicity, topography, etc.) of the protein to direct cellular adhesion.^[114] It is apparent that in order to be able to link material parameters to their higher order properties, predictive models are needed. Even beyond active networks (e.g., tissue growth), the process of *in vivo* assembly of many passive structural protein materials, such as spider silk,^[115,116] involves a dynamic change of physical and chemical conditions.

In addition, it is well known that biological materials have a propensity to self-assemble. The study of amyloidogenic plaque formation (a precursor to Alzheimer's disease^[117]) foreshadowed the development of synthetic amyloid films, for example.^[15,118] Amyloids and the associated plaques, however,

are a result of protein misfolds^[119] and are intrinsically stable (desired characteristics for potential biocompatible films). Can we hope to understand (and potentially exploit) the assembly mechanisms of a living tissue? As a primary step, we can simplify the problem.

A recent study focused on a minimal reconstituted system consisting of actin filaments, crosslinking molecules and molecular-motor filaments, which demonstrated a generic mechanism of structure formation.^[32] Again, insight was gained via the deconstruction to a few universal functional components, and variations thereof. It was shown that the local input of mechanical energy at the smallest scales by myosin filaments drives a constant reorganization of the actin network through forced unbinding and rebinding events, wherein a highly dynamic steady state of aggregated clusters emerges. The low force requirement and connectivity resulted in large structural responses for slight perturbations, enabling a rapid, local and highly robust mechano-sensing mechanism as observed in cytokinesis or on mechanical stimulation.^[120]

Systems of isolated actin filaments, however, are oversimplified. Many biological systems involve intimate interaction amongst multiple self-organizing and assembling components. Complicating matters, self-assembly mechanisms often operate on distinct spatiotemporal scales, resulting in instantaneous appearance of the aforementioned complex hierarchical architectures.^[3,4,28,109] Indeed, ever the efficient contractor, Nature can build the foundation, substructure, superstructure, and interior detailing simultaneously! For example, in cells, some dynamic components are self-organized while other structures self-assemble in precise locations and at particular times, indicating complex interplay between cellular components such as actin, microtubules, fibroblasts, ATP, GTP, etc.^[121,122]

Is it possible to understand and exploit such complex self-organization and self-assembly? For simple molecular systems, progress is continually being made. In macromolecular chemistry, for example, what a biologist considers “growth” is recognized as energy minimization processes and thermodynamic equilibrium.^[122]

2.2. Revolution in Microfabrication and Chemistry

While biological materials appear challenging and irreducibly complex, advancements in biomaterials synthesis and self-assembly are far from sitting idle. In addition to studies of naturally occurring biological protein materials, recent research led to the development of techniques that enables one to change their structural makeup, and to design and manufacture synthetic analogs through recombinant DNA techniques, RNAi knockdowns, or sequence insertions.^[123,124] Two primary routes of development pursued include *ex vivo* assembly (e.g., self-assembling peptide systems^[123]) and *in vivo* expression of protein materials (e.g., through bacterial hosts^[125]). The ability to control the DNA sequence information at a fundamental level provides us with the ability to engineer the structure of protein materials at the molecular (amino acid) scale. The knowledge about the details of the *in vitro* or *in vivo* processes enables one to mimic these processes *ex vivo*, as it has been demonstrated for spider silk fibers in microfluidic devices.^[116] Indeed,

we have become quite adept at producing arbitrary peptide sequences at will. The next step lies in the predictive assembly of such materials.

Additionally, in terms of synthetic polymer science and condensed matter physics, enormous libraries of materials can theoretically be produced (it is exactly these libraries of materials in which screening with biological tissues is required). A number of researchers have taken steps into materiomics by setting up the chemistry to produce libraries of materials^[126] such as libraries of block co-polymers^[127] or click chemistry,^[128] or by producing libraries of surface topologies,^[129] and the formal cataloging of biological materials in the protein databank (<http://www.rcsb.org/>). More immediate, in 2011 the government of the United States, through the White House, unveiled an ambitious *Materials Genome Initiative*,^[130] an effort to “double the speed with which we discover, develop, and manufacture new materials”, a direct nod to the *Human Genome Project*, which accelerated a range of biological sciences by identifying and deciphering the basic building blocks of the human genetic code. As such, there is a continuing drive for material development and characterization. A vast collection of material *data*, however, is not the same as material *knowledge*. While assembly of material libraries is important (and a necessary step), it is moot without associated understanding of material function - it is akin to collecting musical instruments without being able to play a single musical note. This is, of course, a gross oversimplification to stress that collections of materials are only the primary step to unlocking their potential.

Where to begin? Taking a page from the limited “set” of interactions utilized by Nature, the synthesis of increasingly intricate macromolecular structures generally benefits from exploitation of the simplest reactions available.^[9] This idea has led to the rapid adoption of “click chemistry” strategies in the field of macromolecular engineering.^[131] Like Nature, structure and function are intimately related in the field of polymer chemistry. Subtle manipulation of functional groups and chain architecture gives rise to new materials with dramatically different properties. A central theme of the “click” philosophy is the preferences of synthetic techniques are modular, reliable, and easy to implement—a goal shared by biological processes. Biology prefers rather simple and practicable means, i.e., developing enormous variability of proteins by combining only 20 simple building blocks (amino acids) in linear chains. Like biological processes, click reactions are highly efficient, robust, and capable of being conducted in a range of environments.^[131] Such reactions include strain-promoted azide-alkyne cycloadditions (SPAAC),^[132] Diels-Alder reactions,^[133] and thiol-ene reactions,^[134] as a small set of examples (for extensive reviews see Sumerlin and Vogt,^[131] or Lutz and Börner^[135] and references therein). The key insight from click chemistry is that single reactions can be exploited to assemble a variety of molecular systems—this resulted in the re-visiting of well-known and conventional reactions and extension of the “chemical toolbox”, so-to-speak, while similarly providing additional polymeric materials and macromolecular species.

Thus, independent of biomaterials research, click chemistry has been developing a universal categorization of reactions and functional groups for macromolecular synthesis. At our disposal is a wide range of molecules with different properties and

features—the missing link which would open a door to a multitude of potentialities is finding sufficient and general overlap with biological counterparts. Indeed, the discovered rules of click chemistry must follow the same physical laws and thus hold for polypeptides and proteins, and thus emerge as a powerful “clique” in itself. The implementation of biological platforms in click chemistry has been successful in the usage of DNA as a macromolecular scaffold,^[14,136] for example.

One approach is simple to modify known biological materials with more exotic engineered functional groups.^[137] For example, peptide-polymer conjugates have successfully expressed “unnatural” amino acids,^[138] including fluorescent, photoreactive and redox active amino acids, glycosylated amino acids, and amino acids with keto, azido, acetylenic and heavy-atom containing side chains.^[139] The goal is to direct self-assembly (e.g., peptide-peptide interactions) to known structures (e.g., beta-sheet^[140] or coiled-coil^[141] folding motifs) with exposed functional groups (e.g., metal nanocrystals^[142]) with designed intent (see Börner and Schlaad^[137] and citations therein).

Other approaches attempt to exploit the self-assembly of known biological materials to form ordered structures in an efficient manner.^[143] These include the early success of self-assembled lipid tubules^[144] and surfactant-like peptides,^[145] to more recent construction of amyloid fibers and films^[15,118,146] and the invention of “DNA origami”.^[11] A step beyond pure biological components are self-assembled composite materials, including cellulose-based graphene nanocomposites that mimic natural nacre,^[147] amyloid/graphene composite films similar to the brick and mortar structure of natural bone,^[146] or small structured DNA linkers to assemble solution dispersed carbon nanotubes,^[148] among others. Here, the composites typically include one biological components (e.g., peptides, DNA) combined with a high performance synthetic material.

Finally, there are attempts to remove all natural components, and only use biology as a guide for structure, assembly, or function.^[149] In this realm—typically referred to as biomimetic materials—the end goal is to improve upon Nature’s design, substituting high-grade components for their natural analogues. Examples include dry adhesives inspired by the gecko’s foot,^[150] or superhydrophobic lotus-like materials.^[151] Comparing the diversity of structures and functions existing in biology with what is currently realized in synthetic materials science shows that the capabilities of chemists and materials scientists are still rather limited.

In attempts to compensate, computational modeling and informatics has been used to predict material properties and function across scales,^[28,42,152,153] as well as to mine data for cellular processes.^[30,154] One of the inherent challenges with high-throughput methods, for example, is the generation of copious amounts of data. Combined with new potentialities for material creation (whether biological, synthetic, or combinations thereof) such large data-sets require new approaches to facilitate characterization, categorization, and ultimately, design. Predictive techniques such as quantitative structure-property relationship (QSPR) and quantitative structure-activity relationships (QSAR) modeling have proven to be very successful in areas of molecular design, with the ability to sieve through a myriad of material candidates,^[155] including nanomaterials, catalysts, biomaterials, and polymers (see for example a review article

by Winkler et al.^[156]). Such holistic modeling methods may be the consequence of experimental findings, or likewise motivate new experimental initiatives, providing complementary data across scales (e.g., HTS to produce a data set of material candidates, QSAR to isolate common structural information of the successful candidates, high resolution MD simulations to quantify mechanisms). The dimensionality of materials property space is too large to be explored by even the most efficient high throughput methods, requiring complementary computational modeling and robust machine learning methods to leverage the data available.^[98] We have recognized, for example, that bone formation is a very complex physiological process (Figure 2), involving the participation of many different cell types and countless biochemical factors.^[157] To optimize scaffold selection, integrative mathematical modeling is necessarily combined with experimental data to qualitatively predict bone formation and design optimal combinations of governing factors (e.g., without requiring isolated one-to-one effects).^[158] Even beyond trial materials, such studies may even predict material candidates. For example, a study by Epa et al.^[98] exploited the physical HTS of stem cell hEB adhesion on polymeric surfaces to extract a theoretical set of material descriptors (via QSPR) of plausible polymer candidates. Indeed, the “ideal” polymer may not exist, but we know its properties. Using such toolsets, it is hoped we can exploit Nature’s complexity (in terms of producing functionality) and technological prosperity (in terms of available materials).

3. Under A Common Banner

The combination of experiment and computation in large-scale screening for systematic structure-property relations is an exciting field that has now reached a notable level of maturity.^[68,159] While motivations differ (bio-inspired materials, materials for tissue engineering, materials science approaches to disease, etc.), there are many researchers that can be said to be working in the field of materiomics, in hopes to fully understanding complex material systems. Here, we discuss further examples of merging “materials” with “biology”, from structure to function.

3.1. Exploiting Proven Materials

Successful use of “functional” materials requires cross-scale design and control and intimate knowledge of performance and behavior. Rather than start from “scratch” using synthetic materials (such as carbon nanotubes^[69,160] or synthetic hydrogels,^[161] as examples), we can exploit “proven” material systems, e.g., biological protein-based materials,^[4] including silks,^[162] collagen,^[163] elastin,^[164] fibrin,^[165] amyloidogenic materials,^[118] and others.^[2,166]

One of the attractive characteristics of biological systems is the ability of even the most intricate of its component molecular structures to self-assemble with precision and fidelity, wherein complex hierarchies arise naturally across scales, typically under limited external guides or controls. As such, biological materials, by their very essence, require a holistic view, i.e., complete

understanding of the materiome. One cannot hope to fully exploit function at a single scale without consideration of all other (possible) contributions. Such multi-scale analysis requires the integration of advanced experimental, computational and theoretical methods, utilized to assess, monitor and predict mechanisms associated with biological materials, from nano to macro. To illustrate the exploitation of such a material as well as gaps in current understanding, we turn to *elastin* as a case study.

Elastin is a critical biological material which imbues reversible deformation of elastic tissues such as the lungs, skin and vasculature that can withstand decades of repetitive force and extension cycles.^[167] Elastin is required to function in an environment of cellular contact^[63,167,168] without compromising elasticity, and as such suggests a promising candidate for robust cellular scaffolds.^[164,169–171] Indeed, similar to silk, the mechanical performance of elastin exceeds many synthetic elastomers.^[172] Yet, at the atomistic scale, very little is known about the structure, behavior, and hierarchical assembly of *tropoelastin*, a molecular precursor to elastin and the main elastic protein found in mammals. There is a dichotomy between our full understanding (or lack thereof) of the material from the molecules up and our successful implementation as a tissue scaffold or biomaterial.

Currently, the sequence of tropoelastin can be expressed and synthesized in vitro,^[173] but only recently has the macromolecular structure of full-length elastin been delineated using small angle X-ray (SAXS) and small angle neutron scattering (SANS).^[26] The study suggests a distinct ordered structure and self-assembly mechanism. The structural analysis revealed two dominant, functionally relevant parts of tropoelastin—a coil region which contributes to elasticity, and a foot region that facilitates cellular contact.^[26] That being said, there is still no information regarding the secondary structure distribution within the tropoelastin, nor complete sequence-structure correlation. Indeed, beyond predictions of domain locations and function (such as those involved in cross-linking^[174]), there is still knowledge gaps in the understanding of elastin from the sequence to tissue.

Other such protein materials, including collagen, silk, and others can be exploited for their known material properties, even when complete understanding of the material across scales is still wanting. For example, while the material-functional relationship is still being uncovered for spider silks (such as the relationship between the mechanical properties of dragline silks and the structural robustness of webs) we can exploit what we do know at the molecular level for our own needs. For example it is well known that silks are composted of beta-sheet structures due to the dominance of hydrophobic domains consisting of short side chain amino acids in the primary sequence. These large hydrophobic domains interspaced with smaller hydrophilic domains foster the assembly and imbue silk fibers with high strength and toughness.^[115] While the repeating beta-crystalline domains have a characteristic size in Nature, due to a constant number of alanyne repeats,^[152,175] recombinant silk sequences can be manipulated to either increase or decrease the level of crystallinity with predictable effects on mechanical properties.^[176,177] While such sequence variation seems obvious, the route to this insight was nontrivial. Indeed, the ability to “tune” silk properties is the result of a multitude

of techniques that have been employed in an attempt to gain insights into the structure and structure-function relationships of silk, including nuclear magnetic resonance,^[178,179] birefringence,^[180] X-ray scattering,^[13,181] infra-red spectroscopy,^[182] and a suite of mechanical tests, both experimental^[13,183,184] and computational,^[152,175,176,185,186] in order to identify constituents, extrusion conditions, and mechanical behavior. Even with such advancement in understanding, synthetic silks cannot yet achieve the performance of their biological counterparts.^[187]

Silks have been explored as potential biomaterials due to their outstanding mechanical properties such as high strength and toughness.^[188] As a result, silks are continuously being studied across scales,^[189] from protein sequence and structure,^[178,185,190] to threads and fibers,^[13,184,191] to silkworm cocoons^[192] and full spider webs,^[193] and show flexibility for a variety of bio-scaffolds, including sponges and films.^[162] Molecular engineering of silk sequences has been used to modify silks with specific features, such as cell recognition^[194] or mineralization.^[195] Several primary cells and cell lines have been successfully grown on different silk biomaterials to demonstrate a range of biological outcomes,^[162] and silk-based scaffolds have been successfully used in wound healing^[196] and in tissue engineering of bone, cartilage, tendon and ligament tissues.^[197]

The attractive strength and toughness of silk, however, is unlikely to be a governing constraint in biological applications. More limiting would be the relatively low yield strain,^[198,199] particularly for biomedical applications subject to cyclic loads (e.g., therapeutic replacement of collagen or elastin), because of the inability to mimic the complex ultrastructure of natural tissues. To counter this behavior, one approach lies in the modification of silk itself, through the exploitation of molecular building blocks that imbue mechanical properties,^[199] including engineered combinations of the ordered beta-crystalline regions and the disordered domains of the silk structure.^[200] Critical insight must be drawn from detailed studies at the molecular level to the final silk structure, linking mechanisms from sequence to tissue.

An alternative method would be the combination of two known materials: silk and elastin (see Figure 6). In a recent study, a structural protein blend system composed of silkworm silk fibroin and recombinant human tropoelastin was developed and tested.^[169,171] It was hypothesized that silk fibroin provides mechanical strength and controllable biodegradation (via controlled crystallinity), while tropoelastin provides elasticity and intrinsic biocompatibility. Upon successful synthesis, nanoin-

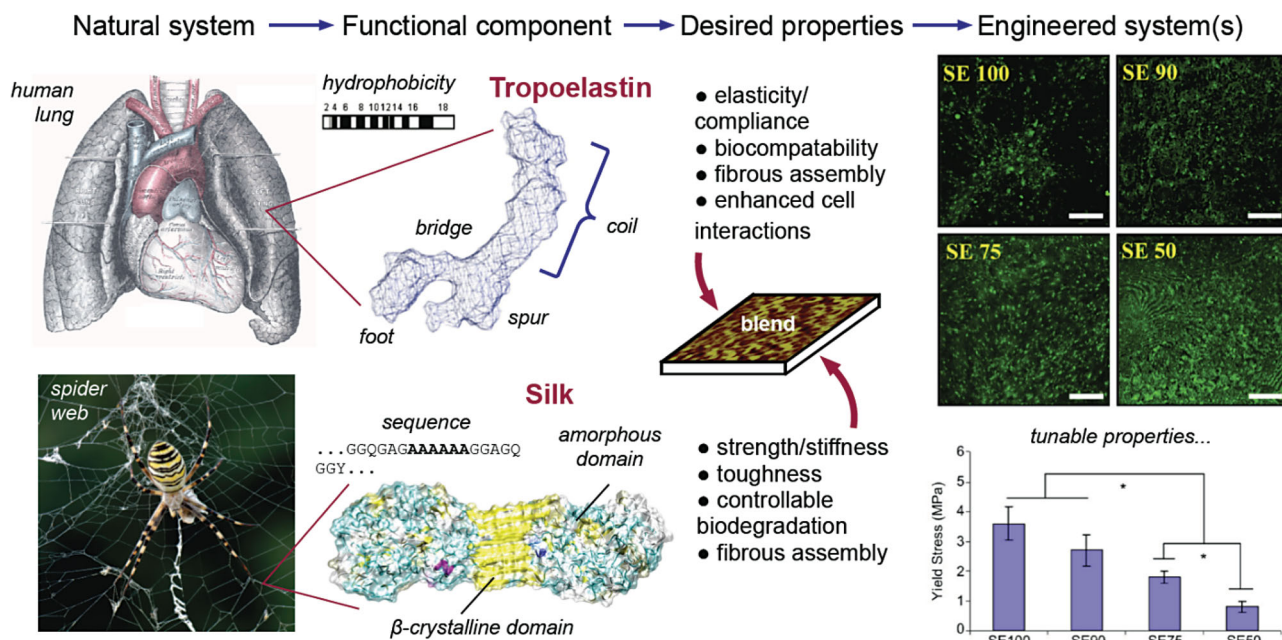


Figure 6. Combination of what you know: exploiting silk and elastin. While still not completely understood, recent molecular investigations of both dragline silk^[152,175,185] and tropoelastin^[26,174] have uncovered sufficient information to extract functionality for each material component. Dragline silk, for example, can be thought of as a composite material with relatively stiff crystalline domains, and relatively stretchy amorphous protein domains. The combination produces a strong and tough material (which is advantageous in the construction of spider webs^[193]). Less is known about the molecular structure of elastin, but at higher levels, the material results in enhanced elasticity and is intrinsically biocompatible. From a cursory perspective of the natural systems, there is nothing in common between elastic tissue (such as that found in a human lung) and a spider web. However, extractions of the fundamental “building blocks” suggest these materials are synergistically compatible. In a recent study, a structural protein blend system composed of silkworm silk fibroin and recombinant human tropoelastin was developed and tested^[169,171] - silk fibroin provided mechanical strength and controllable biodegradation (via controlled crystallinity), while tropoelastin provided elasticity and intrinsic biocompatibility (e.g., desired properties). This blended system was demonstrably tunable (e.g., engineered) by control of silk-to-elastin content, with resilience and elastic modulus on the order of that of elastin-like polypeptides,^[201] as well as development of micro- and nanoscale porous morphologies. Tropoelastin model from Mithieux et al.,^[243] used with permission, Copyright 2012, Elsevier Ltd. Experimental images and results reproduced with permission from Hu et al.,^[171] Copyright 2011, Elsevier Ltd.

mechanical characteristics, with resilience and elastic modulus on the order of that of native aortic elastin or elastin-like polypeptides.^[201] Significantly, during blending and drying silk-tropoelastin form micro- and nano-scale porous morphologies, promoting human mesenchymal stem cell attachment and proliferation beyond that of “pure” silk or “pure” elastin systems alone.

Such approaches are extending beyond combinations of biological materials, attempting to introduce synthetic (non-protein) components to novel material systems. Natural composite or hybrid materials are commonly formed through the concentration and subsequent nucleation of ions upon organic templates, such as calcium containing salts in bone, and iron oxide structures in magnetotactic bacteria. That being said, biological organisms are restricted to a limited set of (available) metal ions such as calcium and iron. In principle, we can exploit the assembly mechanism to utilize other ions to generate composites offers the possibility of new material properties, smartly designing a protein sequence with a propensity for ionization. One such example is to integrate chemical functionality of silver with silks, so-called *chimeric* silks.^[202] To attain such a composite, genetically engineered fusion proteins are created by the incorporation of nucleotides corresponding to short silver binding peptides identified by a combinatorial bio-screening process into the consensus sequence of silk from the spider, *Nephila clavipes* (not surprisingly, the same species studied extensively for dragline silk). The resulting chimeric silk–silver binding proteins provided a stable template material which could be processed into films, fibers, and three-dimensional scaffolds. Although the high stiffness resulting from these particular modifications may be detrimental for many biomedical applications, the study provides an interesting insight into the methods by which spider silk could be modified to become a more effective biomaterial. The opposite approach—the generation of “polymer-bioconjugates” or “macromolecular chimeras” via conjugation of synthetic polymers with biological segments—can be used to enhance the diversity and complexity of synthetic materials (such as the creation of functional hybrid block copolymers^[137]).

What else can we extract from silk? Knowledge of the cooperative functionality of hydrogen bonding in confined beta-sheet domains,^[203] such as those found in dragline spider silk^[152,175] or amyloids,^[118,204] for example, can be used as a guide for H-bond dominated synthetic systems ranging from self-assembling supramolecules,^[14,136,205] to stimuli-responsive polymer multilayers,^[17,206] to mechanically tunable graphene oxide composites/papers.^[207] Again, the impetus of studying spider silk is not a desire to spin super-silk and swing from skyscrapers like Spiderman – it is ultimately a desire to “learn from Nature”. The critical insight is not the physical material (e.g., protein or DNA sequence, or polymer species) but rather the functional behavior common to hydrogen bonds across systems—the abstract universal “building blocks”.

In a similar vein, the challenge in materiomics is to understand the underlying design principles and mechanisms that determine the optimized structural organization in biological material systems across scales, from molecule to organism, and the associated relationship to function.

3.2. Converging Technologies - Integration of Function Across Scales

Rather than solely providing platforms for biological tissue growth, knowledge of the complete *materiome* allows tailored functional materials to be integrated actively within a system, to substitute or complement biological factors.^[208] For example, a means to supply cells (e.g., directed material distribution) with intention to aid growth, observe or actively guide proliferation is undergoing continual advancements. Nanoparticles have been successfully used as intracellular sensors,^[209,210] contrast agents and vectors for drug delivery.^[211] Until now, the targeted introduction of such “carriers” has been limited - the delivery of nanoparticles to a particular location within the cell is inefficient because they are often either trapped inside tiny vesicles or form aggregates inside the cells.^[212] An ideal bioanalytical sensor should achieve real-time tracking of biological, chemical, and physical processes in live cells and in vivo.^[209] The use of nanowires^[213] and nanotubes^[214] to deliver nanoparticles into different compartments of the cell without affecting any cellular functions is attractive due to their uniform size, mechanical stability, and flexibility. Such methods benefit from the precision engineering of the nanocomponents - just as biological implants such as coronary stents^[215] benefit from predictable (and designed) mechanical and material behavior to function. As such, there is increased cross-over and synergy in the development and understanding of the performance of nanomaterials within biological systems,^[216] including the popular cases of carbon nanotubes and graphene.

More recently, techniques have been developed to probe the interior of a single cell through non-invasive approaches (e.g., without inducing significant cellular stress). A recent example, nanowire endoscopy can deliver payloads (e.g., drugs, genes or proteins) or light into specific cellular compartments in vivo, and also detect high resolution optical signals (potentially sensing chemical and physical properties and responses) from subcellular regions.^[217]

Such unprecedented abilities may advance to the point that temporal monitoring, and, more importantly, explicit nurturing and/or treatment (such as triggering subcellular reactions and provide necessary nutrients and materials). Such tools would necessarily be integrated into complex scaffolds, seamlessly combining active and passive material components. In the development of biological materials, systems, and tissues, however, this fundamental distinction between “material” and “biological tissue” is lost. The foundation for nano- and microscale assembly – the material substrate, scaffold, or matrix that will support cellular processes and mechanical requirements – is no longer disassociated from the assembled system; they interact intimately and are inextricably linked as the details of the foundation define what tissue grows. To illustrate, a promising candidate for a tissue engineering scaffold is the use of extracellular matrix (ECM), which is a key component in the natural regeneration and maintenance of tissues and organs.^[218] Methods of producing ECM-inspired tissue platforms have been successful in replicating the required physiochemical properties and structural features of their natural analogs, but, in most cases, do not match the mechanical properties of the tissue to be regenerated (nor are they required to). Yet, the elasticity of the matrix

can determine stem cell differentiation: soft matrices are neurogenic, stiffer matrices are myogenic, and rigid matrices are osteogenic;^[219] a simple and single parameter, stiffness, affects the resulting growth. The complexity (and hence challenge) arises from the multi-scale and hierarchical nature of this relation.

As we have seen, there must also be an explicit account for material geometry, topography, and/or architecture, which can no longer be considered subsidiary to the material “type”. At the microscale the advance of rapid prototyping techniques has significantly improved control over the pore network architecture (e.g., pore size, channel geometry) of tissue engineering scaffolds, which are known to influence the signal expression and subsequent differentiation of a transplanted cell population.^[220,221] Indeed, the interconnectivity of pores, permeability, confinement, and other geometric properties have been shown to affect the transport of oxygen and nutrients throughout tissue scaffolds.^[221] Yet, while we know variation in pore size elicits a response, there is no theoretical model to quantify and thus design a pore structure/network. There is a multitude of known design parameters considered important to achieve a successful synergy between material and substrate (cell and scaffold), including porosity, interconnectivity, surface properties, mechanical strength, the amounts and types of filler material, cell seeding density, and other exogenous growth factors.^[222,223] The common aspect of such design parameters is that they are typically considered at a *single scale*. While the results of such property variations are known, the underlying protein/substrate interactions are not fully understood, and finding the optimum material system is nontrivial. Be that as it may, single scale approaches are quite advanced and ingenious, and have been successful in delineating appropriate substrates and scaffolds for particular tissues (such as collagen or bone^[58]) and biological macromolecular structures (such as amyloid films^[15]). However, the specific molecular mechanisms resulting in successful tissue generation remain largely unknown. Successful synthesis is achieved by experimental trials and iterative high throughput screening, and the continuous refinement of previous insights. Such steps are necessary for the progression and immediate clinical application of tissue engineering.

A successful and predictive synthesis and assembly of biological tissues must incorporate these natural hierarchical structures when we design materials in which tissues are supposed to assemble or grow. One natural solution is to mimic the complexity of such materials by the development of hierarchical foundations, where the form and function of the substrate are specifically designed at each scale. The caveat, of course, is that this requires intimate knowledge of the specific molecular, protein, cellular, and tissue interactions across *all* scales. Hierarchical structures can be of great advantage for tissue engineering application as they provide a more natural environment for cells to grow and develop into tissues. For example, the multiscale complexity of bone necessitates hierarchical features of a scaffold/matrix such as commonly implemented electrospun porous nanofiber networks.^[50,58,224]

The complex hierarchical structure and interactions of biological materials presents fundamental challenges in the development and prediction of successful material foundations. However, even if we are able to solve this “multi-scale problem”, there is still a remaining challenge in the design of robust

platforms - the temporal complexity associated with growth. Biological materials feature selectively tailored molecular assemblies and interfaces that elicit specific form and functionality, which can readily change and adapt to their environment. A theoretically perfect scaffold for one stage of differentiation may be completely inadequate to *sustain* growth. Indeed, engineered tissues must not only grow to fill a defect and integrate with the host tissue, often they must also grow and thrive subject to the changing needs of a varying biological environment. Tissues capable of adapting with time could be engineered by supplying stimulus signals to cells from the biomaterial or scaffold used.^[225] Mimicking the target systems, a possible solution is to make the properties of the substrate dynamic and controllable via external stimuli or internal feedback, a concept known as *mutability*. Through monitoring of self-assembly and growth or by internal feedback (e.g., mechanical or geometric cues) mutable materials could potentially optimize according to the needs of the system.

3.3. Opportunity for Responsive Materials

Potential candidates for such mutable materials are stimuli-responsive polymer nanostructures (which, in an abstract way, can also be a general description of biological materials). Scaffolds currently used in tissue engineering and cell therapy are mostly passive in that they deliver biological agents mainly through mechanisms involving molecular diffusion, material degradation, and cell migration, which do not allow for dynamic external regulations. Yet, in vivo, the structures of protein materials self-maintain or adapt via feedback loops by translating spontaneous demands in the microenvironment (via intracellular signaling) to regulate gene activation/deactivation to ultimately alter the material's structural makeup in order to better suit the local physiologic needs. Responsive polymer systems exhibit similar features as biological materials, and are capable of conformational and chemical changes on receiving an external signal. Such materials can adapt to surrounding environments, regulate transport of ions and molecules, change wettability and adhesion of different species on external stimuli, or convert chemical and biochemical signals into optical, electrical, thermal and mechanical signals, and *vice versa*.^[226] Synthetic polymer systems with desired characteristics are currently being developed for a multitude of biological applications, such as responsive biointerfaces that are functionally similar to natural surfaces,^[227] coatings that are capable of interacting with and responding to their environment,^[228] and composite materials that actuate and mimic the action of muscles.^[229]

The effect of mechanical cues on the stimulation of cellular signal expression can exploit materials such as photocrosslinking polymer composites^[220,230] or pH-responsive systems.^[231] Material properties (stiffness) and geometry (pore architecture and connectivity), can be tuned on a system-by-system basis to investigate the effect on cell growth. Other studies have been undertaken exploring potential spatial patterning^[232] and temporal variations^[233] in cross-linked polymer systems, resulting in the coupling between inherent responsive material properties and geometry. Such a material can offer

scaffolds with dynamic, tunable architectures and bulk properties, triggered at the molecular level. The responsive properties of reconstructable polymer systems are relevant to many biotechnological and biomedical applications^[228,234] because these materials can undergo dynamic changes in accord with changes in living systems. The possibility of tuning and switching adhesion between stimuli-responsive materials and proteins and cells has been explored for the control of cell and protein adhesion,^[235] as well as exposing and masking potential biointerfaces and manipulation of cellular signals, protein interactions, and growth factors.^[236] Moreover, precise control of the permeation of chemicals, nanoparticles, and ions through nanoporous membranes and 3D scaffolds offers a unique opportunity for control of assembly and growth process.^[237]

One important aspect of responsive material systems is the coupling that exists between the chemical and molecular scales. The challenge is to understand at each molecular species with as much atomistic and chemical detail as possible, leading to the rational design of mutable and hierarchical scaffolds. Prediction and understanding of thermodynamic, chemical, and structural properties is crucial, incorporating many of the different interactions (such as hydrogen bonding^[238] and chemical reactions^[239]) present in these systems. The resulting increased functionality of tissue-engineering materials may rival the complexity of the tissue itself. Responsive polymer systems can be used for a variety of applications, and biomaterials and tissue engineering is just an example of important areas that will benefit greatly from further development of tunable responsive materials. The critical feature, which could potentially be exploited for other material systems, lies in the mutability and dynamic control of properties and behavior. In fact, the challenge is to develop complex systems that are responsive to

biochemical signals during tissue growth (internal feedback) that mimics biological response. Such systems need a complex, hierarchical organization of the responsive chemical and molecular components to adapt to potential environmental factors and responses.

In the near future, exploiting materiomic information, one could hope to theoretically create an active three-dimensional scaffold akin to a normal tissue or organ—a kind of made-to-order tissue engineering approach (see Figure 7). Such a system might be made of synthetic polymers/materials/components/topographies that could be self-optimizing (and controllable) for specific applications. This hope, however, presents a conundrum: we require thorough understanding and synthesis of complex hierarchical substrates to facilitate the synthesis and growth of complex hierarchical tissues. Furthermore, in lieu of molecule-by-molecule constructions, self-assembly provides the only practical route to synthesize such complex hierarchical substrates, which - by default - approach the complexity of the target biological material. On what platform should such assembly occur? It seems we have arrived at a Catch-22! Currently, we do not have the technologies available to tailor-make a hierarchical substrate and rely on high throughput screening and discovery of universal protocols to attain efficient (but not optimized) materials. Recent investigations of novel hierarchical substrate materials, e.g., as injectable cell carriers for in vivo tissue regeneration^[222] are beginning to fill the necessary gaps.

A fundamental understanding of cross-scale interactions and mechanisms in self-assembly and tissue growth is necessary to exploit the process for both biological and synthetic materials. If assembly and growth is dictated by material/substrate interactions, an ability to dynamically tune substrate

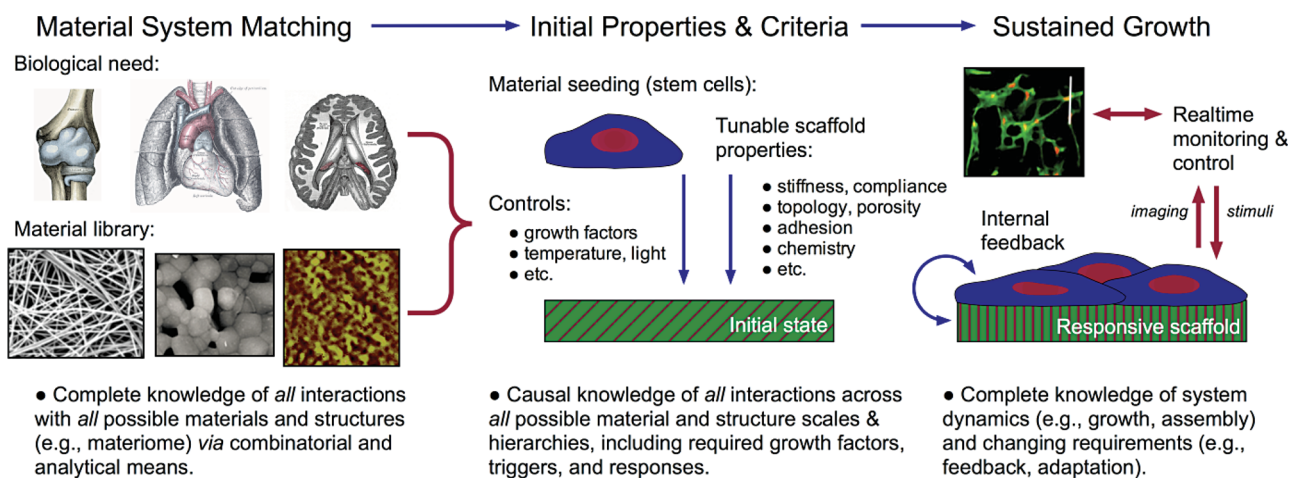


Figure 7. Made-to-order tissue engineering through materiomics. Complete knowledge of the materiome can be exploited (in theory) to produce any desired biological tissue. Once a biological need is identified (osteogenic, myogenic, neurogenic, etc.), a suitable and complementary materiomic system (e.g., material and structure) can be procured either from ready-made libraries, or attained via high-throughput combinatorial methods, based on knowledge of the target system (e.g., material system matching). Note that the material library is not simply a catalogue of material choices (e.g., PLA versus ceramics) but associates all possible interactions with all possible materials and variables. The system can then be refined for initial (tunable) scaffold properties (stiffness, geometry, etc.) and criteria (e.g., growth factors) across scales, ensuring desired interactions from nano to macro. Correct parameterization presumes intimate knowledge of cellular needs, structure, and assembly. Finally, reactive systems (such as stimuli responsive polymers) can be exploited to address the dynamic needs of sustained tissue growth. Changes in function and requirements are anticipated via internal feedback (e.g., material-tissue interactions, mechanical or chemical cues) as well as real-time monitoring of growth and control of external triggers, allowing dynamic adaptation.

properties provides vast potential for control across all scales. With increasing complexity, such systems start to resemble their biological counterparts (e.g., adaptation to their surrounding environment), mimicking the concepts natural systems have been relying on for millions of years. However, practical technological application has so far been severely hindered due to lack of understanding of how to link the atomistic scale with material structure and device properties and function. The exploitation of hierarchical interactions provides a novel paradigm to make progress in tissue engineering and unpredictability can be eliminated. Such an objective can be attained by the combination of bottom-up, multiscale investigations, top-down synthetic approaches, and high throughput screening to narrow the potential combinatorial space, e.g., materiomics.

4. Future Directions and Conclusion

In the past ten years, *-omics* technology has become available for every biologist due to the development of economical gene expression profiling techniques and user friendly software to mine the data. From a materials perspective, mechanistic understanding can complement robust screening methods to reverse engineer the complexity of biological materials and tissue growth. Pioneering researchers in the field have shown proof of principle for high throughput screening of biomaterials and a rapidly increasing number of investigations apply it. Further streamlining of the process from material banking to assay development, high content imaging and data mining will ascertain that the approach will become available for the biomaterial research community.

Is there a general approach to understanding the *materialome*? Unfortunately, it is neither an explicit sequence like the genome, nor a simple set of material properties. While we have listed various approaches in materials investigation, our intent here was to effectively review the challenges of materiomics—multi-scale, combinatorial, and temporal—succinctly summarized by Figure 5. Ultimately, for complex biological materials and their interactions with the physical environment, a holistic perspective is not just a sufficient, it is a necessary. Any investigative approach (theoretical, conceptual, computational, experimental) that contributes to this holistic perspective can be considered a *materiomic* approach. The key insight is not in the collection of data, but rather the combination of data, requiring the joint effort of material scientists, chemists, biologists, and engineers—collaborations that are exponentially increasing. Indeed, the authors of this review have distinctive approaches ranging from computational MD methods to HTS techniques. While material scales and analytical tools differ, we realize, in a holistic sense, we work on the same problem—attempting to identify how complex biological materials work, from nano to macro, molecule to tissue, with an ultimate aim of enabling the design of similar materials (for biomedical and other applications).

To fully explore the potential of materiomics, systematic development of general methodologies is needed that are applicable to a multitude of material systems, living and synthetic. This asks for development of new tools and insights in the

design of (evolutionary) search algorithms, performance metrics, and universal characteristics across systems. Enabled by the current state and convergence of technology and disciplinary fields, development of materiomics requires pushing the limits in imaging and nanoscale fabrication technologies, and most importantly, calls for a carefully designed hybrid of computational analysis and biological experiments. The combination of multi-scale structural control and integration of living and non-living systems into technologies and interfaces will lead to the development of new technologies that utilize the advantages of both micro and nanotechnology with the principles of biology and provide a new foundation for biological materials.

Materiomics, whether or not accepted as a field unto itself, is already a powerful driver in understanding and engineering new biomaterials. The convergence of methods from experiment to computational and across all scales presents a unique opportunity towards materials-by-design for biomedical applications, and more broadly, material design in general. Such materials with tailored properties will find immediate applications in a variety of fields:

- Nanomedicine (e.g., drug delivery via controlled release)
- Hierarchical composites (e.g., for tissue engineering, sutures, as well as the design and synthesis of armor materials)
- Self-healing biomaterials; mutable and tunable structures (e.g., multifunctional implants)
- Medical devices for diagnostics and treatment

Incorporation of iterative experimental and bioinformatics-based computational approaches for studying biomaterials will help us better understand cell–material, tissue–material, and material–material interactions in general. Simply put, if we can fully understand complex biological materials, more benign synthetic materials should be relatively simple.

The analysis of material properties at multiple scales is a crucial issue in understanding biological materials, as their structure changes with hierarchical level (and thus length-scale), and therefore most material properties are strongly dependent on the scale of observation. Multi-scale experimental and simulation analyses are the key to improve our systematic understanding of how structure and properties are linked. Typically this is achieved from a *bottom-up* approach, linking more sophisticated lower length-scale parameters, which form the building blocks of the system at that level, to coarser, larger length-scales. Purely “bottom-up” approaches, however, are incomplete if they lack the interpretation of large-scale behavior to small-scale phenomena, an iterative paradigm. Full stratification of different levels of hierarchy using such analysis develops a powerful feedback loop where the bottom-up modeling approach catalyzes the insights we gain at each layer of the material ladder, with the possibility of controlling properties at multiple scales simultaneously, and to examine their effect on system function. While a materials science approach can probe the physical and chemical components and structure of the system – a systematic “blueprint” – the whole is indeed greater than the sum of its parts. Such features (nay, challenges) necessitate a new, holistic and integrated perspective – an *omic* perspective, i.e., materiomics.

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