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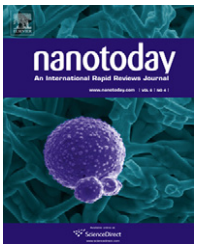

NEWS AND OPINIONS

Shaky foundations of hierarchical biological materials

Steven W. Cranford[a,b], Markus J. Buehler[a,b,*]

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

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Summary It is popular stance that successful growth — be it structural, economic or biological — requires a stable foundation. The hierarchical structure of native biological materials and tissues introduces variations in form and function across a multitude of scales. Yet, many synthetic scaffolds and substrates in which such materials are assembled, the foundation, are designed at a single scale. The result is an uncertain or shaky foundation for material assembly and tissue growth, where changes in the scaffold properties and architecture result in unpredictable behaviors in tissue development, and proven, reliable scaffolds for one tissue type may be completely unsuitable for another. This is in contrast to the behavior of foundations for civil engineering structures, which provide a decoupling of the foundation from the building design since different foundations can support equivalent functional structures. Current advancements in the design of biologically active foundations shed light on proven scaffolds and substrates, but cannot be used to design and predict success from the bottom-up. This is because while the phenomenological coupling between materials and substrates has been well investigated and has yielded methodologies for biomaterial synthesis, the underlying mechanisms of self-assembly and growth are not fully understood. A potential solution lies in the utilization of hierarchical material foundations, with molecular, fibrillar and other interactions designed across all length- and time-scales with engineered, predictive, and repeatable outcomes. The potential to realize such hierarchical multiscale scaffolds can be found in the exploitation of responsive, or mutable, polymer systems that exhibit precise control and variegated chemical functionalities for applications in diverse areas such as regenerative medicine, cancer treatment or drug delivery.

Introduction

The design and assembly of any safe structure requires a thorough knowledge of the foundation. No structural engineer would approve the construction of a skyscraper without a complete geotechnical report, where the stability of the foundation below supports the building above. Yet,

* Corresponding author at: Laboratory for Atomistic and Molecular Mechanics, Department of Civil and Environmental Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave. Room 1-235A&B, Cambridge, MA, USA.
E-mail address: mbuehler@MIT.EDU (M.J. Buehler).

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at the macroscale, the groundwork and the structure are sufficiently decoupled. As long as the foundation satisfies minimum requirements, there is no adverse effect on the overlying structure. What the building ''sees'' is limited to a single scale and characterized by the design parameters of the foundation, including settlement restrictions and bearing capacity and such phenomena are at the same scale as the structural system. Assuming that the critical parameters are met, more detailed and smaller scale properties (such as material type or microstructure) have no external affect on the borne structure, and different engineered foundations can support equivalent functional structures. One can design and construct a building independent of the structural foundation, as long as it is assumed *a priori* that the foundation has satisfied the required design parameters such as maximum settlement and bearing capacity. On a more complex level, one may also consider seismic and slope stability, pore water pressure variation, and other parameters. The point being is that the foundation is designed independently of the structure — one need not know the details of either for a successful design, only the design requirements (Fig. 1a). In the development of biological tissues, however, this fundamental relationship changes. 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. Consider this: when you walk into a building, be it a residential complex or a shopping mall, can you tell what type of foundation it is built on? The answer, without any other cues, is clearly no. For biological tissues, however, cellular processes recognize the foundation properties at multiple levels, and they are inextricably linked as the details of the foundation define what tissue grows.

Indeed, different substrates induce different affects, are not transferable, and are more complex. The complexity (and hence challenge) arises from the multiscale and hierarchical nature of this relation. Changes can easily be made for system-level properties (such as stiffness, porosity, etc.), but the changes have effects that subsequently cascade downward from the system-level to the fundamental molecular interactions at the nanoscale (Fig. 1b). From a cursory perspective, they are uncertain — or shaky — foundations for assembly. This shaky attribute is a result of a single-scale perspective in the current design paradigm and one that can potentially be remedied if we had the fundamental knowledge to exploit them (both in theory and in practice). Currently, there is no single set of ''design parameters'' that will satisfy more than the most rudimentary system. Interactions between the functional system and material substrates or scaffolds are inevitably complicated by the multiscale processes that are involved. Tissues and biological materials are commonly hierarchical as there is underlying structure and function at a multitude of diverse scales [1—3]. As a result, slight variations at a lower scale, such as scaffold topology or material choice, can propagate and express at larger scales, typically to the detriment of the growth or assembly of the system. This is in contrast to macroscale engineered systems, in which structural details, such as spacing of piers for example, do not affect the above structure (assuming alternate designs have equivalent mechanical performance). Likewise, material details, such as the choice of reinforced concrete or structural steel components, do not affect the borne structure. The overlaying structure does not ''care'' what supports it — it will function the same. Thus, a fundamental challenge of tissue engineering and biological material synthesis lies within the understanding of material—substrate interactions across all scales, from individual atoms, to molecules, to subsequent tissues and entire organisms. Continuing the analogy with foundation engineering, not only do you have to analyze properties of the soil, in the case of biological tissues you have to know the behavior of each individual rock, mineral, and grain.

Certainly, for the construction of a building, the foundation is of little importance to the overlying structure — a post-and-pier foundation on bedrock provides a similar platform to a slab-on-grade over clay, and a home built atop does not change functionality based on the foundation below. On the other hand, it is well known in tissue engineering that different substrates can result in different materials. One important difference is that the tissue grows itself whereas a building is ''grown'' by the external means (typically construction personnel). In the case of biological tissues the same cells can develop into different tissues depending on the substrate (foundation) they live. For construction, a structure can be designed independently from the foundation, whereas in biology, the foundation may dictate the structure! For example, 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 [4]. 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. Yet, the elasticity of the matrix can determine stem cell differentiation: soft matrices are neurogenic, stiffer matrices are myogenic, and rigid matrices are osteogenic [5,6]. This example focused on a simple and single parameter, stiffness, clearly shows that the properties of the foundation affect the resulting structure.

We must also account for the geometry of the foundation. At the microscale, for example, 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 [7,8]. 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 [7]. 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 [9—11]. 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. Be that as it may, such *ad hoc*

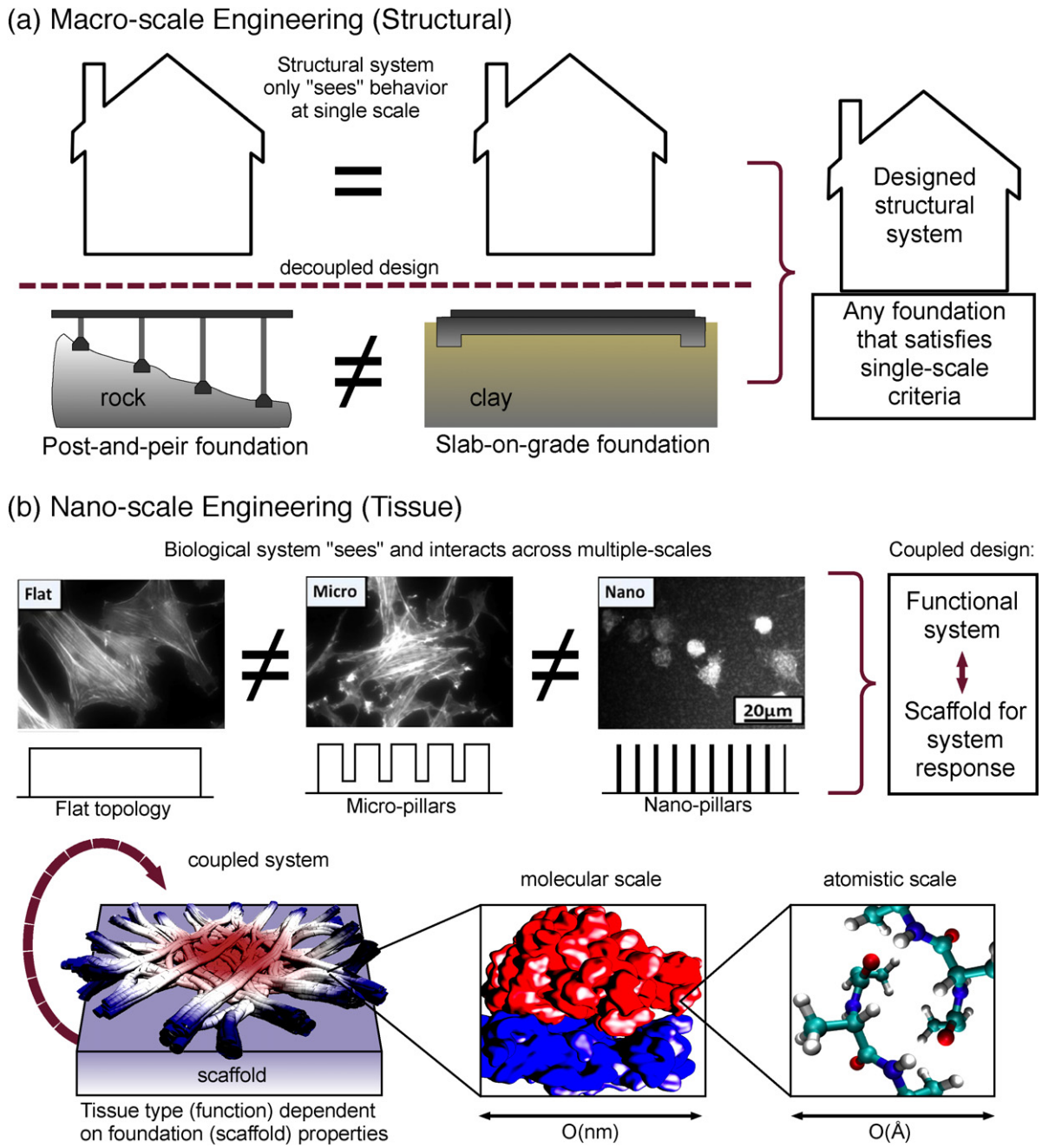

Figure 1 Illustrating the ''shaky'' foundations of biological materials. (a) Schematic of macroscale, structural engineering in which the designed structural system is decoupled from the foundation. The overlaying structure only ''sees'' foundation behavior at a single scale, encompassing critical properties such as settlement and bearing capacity, and any foundation that satisfies such properties (e.g. post-and-pier versus slab-on-grade) can support equivalent functional structures. More detailed ''small scale'' properties (such as material type or architecture) have no external affect on the borne structure. (b) In contrast, nanoscale foundations, such as biomaterial and tissue engineering scaffolds, have to consider interactions between the substrate and the desired system. There is a necessary coupling between the desired functional system (*i.e.* biological tissue) and the scaffold required for optimal response. The resulting material or tissue is a function of properties such as stiffness, porosity, interconnectivity, and other parameters. What the tissue ''sees'' spans several scales, across the hierarchies of the biological system, from nano (atomistic and molecular level interactions) to macro (tissue and larger levels). As an example, inset images depict variations in mesenchymal stem cell (MSC) differentiation with changes in the scaffold architecture, ranging from flat to pillars with micro- and nanoscale topography. From Jin and co-workers [42], reproduced with permission from *Acta Biomaterialia*, copyright ©2011, Elsevier Ltd.

approaches are quite advanced and ingenious, and have been successful in delineating appropriate substrates and scaffolds for particular tissues (such as collagen or bone [12]) and biological macromolecular structures (such as amyloid films [13]). However, the specific molecular mechanisms resulting in successful tissue generation remain largely unknown. Often, synthesis is achieved by experimental trials and screening, and the continuous refinement of previous insights. Such steps are necessary for the progression and immediate application to tissue engineering. At this time, a mechanistic framework from the molecules up is not yet practical, but can be attained in the near future.

Challenges and opportunities

The fundamental challenge lies in the complex hierarchical structure of the tissues and materials, where changes at the molecular level propagate and are expressed in unpredictable ways [14,15]. What a cell (with a diameter of 10–30 μm) in a collagen tissue ''sees'' can be very different in a natural system than in most currently used tissue-engineering scaffolding biomaterials. The structure and properties of the implemented scaffold are typically designed on the scale of tissue assembly, whereas the critical scales may be orders of magnitude smaller. What the cells see naturally is hierarchical and discrete, and it cannot be approximated by continuum or ''bulk'' properties and behaviors. Commonly used biomaterials are only developed for ''macroscale'' behavior such as stiffness, biochemical reactivity, drug release, and other properties [16]. How these materials function is quite different; there are molecules and specific proteins that bind to the cell and that pull at discrete points at the cell, and this insight has motivated the development of new candidate materials for tissue engineering applications [17]. 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 complex materials by the development of hierarchical foundations, where the form and function of the substrate are specifically designed at each scale (Fig. 2a). 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 extracellular matrix of bone is a hierarchical, heterogeneous material that has features with sizes that range from the nanoscale to the macroscale, subsequently given gives rise to a composite material with defined nano-, micro-, and macrophases. The multiscale complexity of bone necessitates hierarchical features of a scaffold/matrix such as commonly implemented electrospun porous nanofiber networks [12,18]. This presents a conundrum: we require thorough understanding and synthesis of complex hierarchical substrates to facilitate the synthesis and growth of complex hierarchical tissues. Moreover, *in lieu* of molecule-by-molecule constructions, self-assembly provides the only practical route to synthesize such hierarchical substrates. 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, but recent investigations of novel hierarchical substrate materials, e.g. as injectable cell carriers for *in vivo* tissue regeneration [11] are beginning to fill the necessary gaps.

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 ''multiscale problem'', there is another challenge in the design of robust platforms, the temporal variations in system behavior and properties. Biological materials feature selectively tailored molecular assemblies and interfaces that elicit specific form and functionality, which can readily change and adapt to their environment. Natural systems often vary the stiffness, hierarchical structure, and other parameters over time to control how cells grow. 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 [19]. 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. Mutable materials are found widely in biology, characterized by a material's capacity to change its properties under external cues based on directed structural changes at specific material levels. Mutable materials are also inherently hierarchical, where property changes are often driving by interactions and processes at the molecular level. 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 (Fig. 2b).

Examples and applications

Potential candidates for such mutable materials are stimuli-responsive macromolecular nanostructures. 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. 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 [20]. The concept of mutability provides a paradigm shift and exciting opportunity in the area of cell growth — namely, dynamic control of

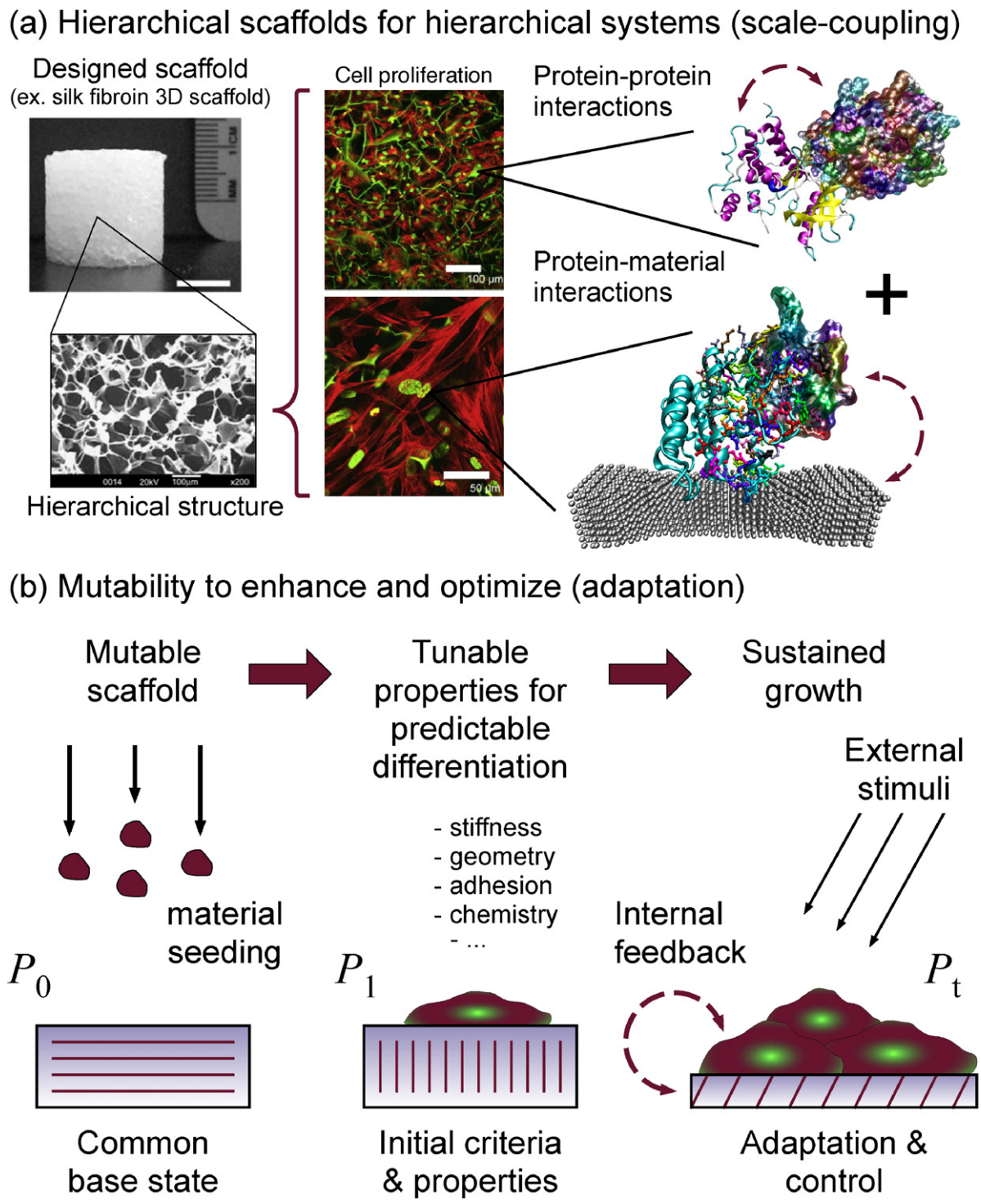

Figure 2 Potential foundation design through the use of hierarchical and mutable scaffolds. (a) Biological systems are intrinsically hierarchical, integrating cross-scale interactions from nano to macro. Successful (predictive) scaffold design requires a bottom-up, hierarchical perspective. Tissue growth is rooted in the discrete molecular-scale interactions (such as protein—protein and protein—material) that express themselves throughout a multitude of scales (photograph of silk fibroin scaffold from Kaplan and co-workers [43], reproduced with permission from *Bone*, copyright ©2008, Elsevier Ltd.; SEM images from [44], reproduced with permission from *Biomaterials*, copyright ©2009, Elsevier Ltd.). (c) The potential of implementing mutable/responsive materials within scaffolds. An initial property set (P_0; base state) could be varied depending on the desired tissue (neurogenic or osteogenic, for example), and desired stiffness, geometry and chemistry can be modified accordingly (P_1; initial criteria). Once differentiation is achieved, sustained growth can be enhanced by either internal feedback (mechanical or chemical cues) or by external stimuli (based on system monitoring) allowing dynamic adaptation properties (P_t) and precise control of tissue growth.

the self-assembly process. Like their biological analogues, a bottom-up approach is necessary to predict the structure and mutability of large-scale material properties from the nanoscale up. 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 [21], coatings that are capable of interacting with and responding to their environment [22,23], and composite materials that actuate and mimic the action of muscles [24]. Do such responsive polymer systems offer a suitable foundation for biological material assembly?

The effect of mechanical cues on the stimulation of cellular signal expression can exploit materials such as photo-crosslinking polymer composites [8,25] or pH-responsive systems [26,27]. 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 [28] and temporal variations [29] 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 [22,30], 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 [31—33], as well as exposing and masking potential biointerfaces and manipulation of cellular signals, protein interactions, and growth factors [34,35]. 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 [36—39].

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 hydrogen bonding [40] and chemical reactions [41]) 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.

Conclusion

A fundamental understanding of cross-scale interactions and mechanisms in self-assembly and tissue growth can be used 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 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 and top-down synthetic approaches, and ultimately, the stabilization of a shaky foundation. The implementation of system specific foundations can lend insight to the molecular foundations of disease and disease pathology rooted at the molecular scale (*i.e.* single amino acid mutations) — potentially tracking variations at the nanoscale and effects and expression at the tissue level. Ultimately, mechanistic understanding can complement robust screening methods to reverse engineer the complexity of biological materials and tissue growth. The combination of multiscale structural control and integration of living and non-living systems into technologies and interfaces may 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.

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Steven W. Cranford is a Ph.D. candidate in the Department of Civil and Environmental Engineering at the Massachusetts Institute of Technology and a member of the Laboratory for Atomistic and Molecular Mechanics. Cranford's research interests are advanced and novel structural materials at the continuum and atomistic scale, and the incorporation of biological design principles into engineering design at all scales. He holds a Bachelor of Engineering Degree from Memorial University in St. John's (Canada) and a Master of Science in Civil Engineering from Stanford University. He received several medals and awards, including a Schoettler Fellowship at MIT, the University Medal in Civil Engineering at Memorial University and the PEG-NL Award of Excellence at Memorial University.

Markus J. Buehler is an Associate Professor in the Department of Civil and Environmental Engineering at the Massachusetts Institute of Technology, where he directs the Laboratory for Atomistic and Molecular Mechanics (LAMM). Buehler's research focuses on bottom-up modeling and simulation of structural and mechanical properties of biological, bioinspired and synthetic materials across multiple scales, with a specific focus on materials failure from a nanoscale and molecular perspective. He serves as a member of the editorial board of several international journals and is the founding chair of the Biomechanics Committee at the Engineering Mechanics Institute of ASCE. His work has been recognized with several awards, including the Presidential Early Career Award for Scientists and Engineers (PECASE), the Harold E. Edgerton Faculty Achievement Award for exceptional distinction in teaching and research, and the Leonardo da Vinci Award.