A Paradigm for the Integration of Biology in Materials Science and Engineering

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The integration of biology in materials science and engineering can be complicated by the lack of a common framework and common language between otherwise disparate disciplines. History may offer a valuable lesson as modern materials science and engineering itself resulted from the integration of traditionally disparate disciplines that were delineated by classes of materials. The integration of metallurgy, ceramics, and polymers into materials science and engineering was facilitated, in large part, by a unifying paradigm based upon processing-structure-property relationships that is now well-accepted. Therefore, a common paradigm might also help unify the vast array of perspectives and challenges present in the interdisciplinary study of biomaterials, biological materials, and biomimetic materials. The traditional materials science and engineering paradigm was modified to account for the adaptive and hierarchical nature of biological materials. Various examples of application to research and education are considered.

INTRODUCTION

Most materials scientists and engineers recognize the tremendous opportunities available at this time in history for advances in biotechnology or biomedicine and, closer to home, the intersection of materials and biology. Materials science and engineering is expected to play a highly significant role in the foreseeable future of biomedicine.[1,2] Conversely, noting that materials science finds its roots in solid state physics and chemistry, biology is logically the next great frontier for materials science and engineering.[2–4] However, researchers and educators working to integrate biology or biomedicine into materials science and engineering, and vice versa, have invariably encountered several challenges. These challenges may be grouped into two aspects of "biocomplexity."

How would you…

…describe the overall significance of this paper?

The materials science and engineering paradigm was modified to account for the adaptive and hierarchical nature of biological materials. The modified paradigm may be useful for the integration of biology and biomedicine in materials research and education, as well as in advocating the application of materials science and engineering principles in biomedical research and education.

…describe this work to a materials science and engineering professional with no experience in your technical specialty?

Materials science and engineering is expected to play a highly significant role in the foreseeable future of biomedicine. Conversely, noting that materials science finds its roots in solid state physics and chemistry, biology is logically the next great frontier for materials science and engineering. Therefore, materials scientists and engineers who wish to make an impact at the intersection of materials and biology must become increasingly knowledgeable, or at least conversant, in biology and biomedicine.

…describe this work to a layperson?

The integration of traditionally disparate disciplines of study can be complicated by the lack of a common framework for critical thinking and common language for communication. The integration of metallurgy, ceramics, and polymers into modern materials science and engineering was facilitated, in large part, by a unifying paradigm based upon processing-structure-property relationships that is now well-accepted. Therefore, a common paradigm might also help unify the vast array of perspectives and challenges present in the interdisciplinary study of biomaterials, biological materials, and biomimetic materials.

First, biomaterials replace or interface with biological substances, especially tissues and cells. Biological tissues, or biological materials, are living, adapt to chemical and physical stimuli, perform multiple functions, and exhibit hierarchical structure with precise organization over multiple length scales.[5] Therefore, biological materials exhibit complex processing-structure-property relationships, unmatched in engineering materials, which are only beginning to be established.

In contrast, the vast majority of biomaterials used in biomedical devices have historically included common engineering materials (e.g., stainless steel, titanium, alumina, porcelain, polyethylene, polymethylmethacrylate, etc.) that exhibited desirable properties that were borrowed for biomedical applications.[1,6] These biomaterials enhanced the quality of life for countless individuals through passive interaction with biological systems (bioinert). In other words, "do no harm."[7] Thus, metallurgical or materials engineers were well-positioned to contribute to the design and manufacturing of a conventional stainless steel implant, for example, through traditional education in physical metallurgy or materials structure-property relationships, with little consideration of biology.

A second generation of biomaterials began to introduce materials that are favorably reactive to biology, including bioactive ceramics and glasses (e.g., hydroxyapatite and bioglass, respectively) and biodegradable polymers (e.g., polylactide and polyglycolide).[6,7] In the present age, so-called third generation biomaterials are intended for proactive interaction with biology.[6,7] Examples include: tissue engineering scaffolds able to guide cell differentiation and tissue growth via signal transduction;[7–9] vehicles for controlled and/or targeted delivery of pharmaceuticals, proteins, and nucleic acids;[10,11] and multifunctional diagnostics and sensors;[11–13] among others. Materials scientists and engineers who wish to contribute to these and other exciting applications of biomaterials must become increasingly knowledgeable, or at least conversant, in biology and biomedicine.[2,3]

Second, biomaterials research and development requires diversity among contributors and collaborators. For reasons discussed above, no single individual or discipline of study can be expected to possess sufficient depth in the full breadth of knowledge required for most biomaterials applications. Thus, product development teams in industry and (increasingly) collaborators in use-inspired basic research in academia may include individuals educated in engineering (chemical, materials, mechanical, etc.), science (cell biology, biochemisty, etc.), basic medical sciences (anatomy, pathology, pharmacology, etc.), and clinical medicine (cardiology, orthopedics, radiology, etc.). The diversity of thought contributed by each field of expertise is recognized as a great benefit in interdisciplinary work. However, a significant challenge facing bioengineering as a discipline, as well as the integration of biology in traditional disciplines, including materials science and engineering, is the lack of a common framework and common language for synthesizing the diversity of thought and expertise.[3]

See the sidebar for a glossary of biological materials terminology.

LESSONS FROM OUR PAST

The history of materials science and engineering provides valuable lessons that can be applied to the present challenge of integrating biology in materials science and engineering. Modern materials science and engineering resulted from the integration of traditionally disparate disciplines that were delineated by classes of materials, *viz.*, metals, ceramics, and polymers. As early as the 1950s materials education was nascent, but critics suggested that the breadth of a materials curriculum without traditional demarcations between material classes would compromise depth of study.[18] Proponents of materials-generic education, such as Gerald L. Liedl, recognized the opportunities and challenges:

> "The diversity in the field is, on one hand, a major asset in addressing problems, but on the other hand, a major obstacle in unifying an educational approach. This problem is not new since we have faced it over time as information and knowledge expands."[19]

Despite the pre-existing traditions and human nature to resist change, materials science and engineering has evolved over the last fifty years into a unified discipline of study with an identifiable, common core curriculum.[20–23] The integration of metallurgy, ceramics, and polymers into materials science and engineering was facilitated in large part by a unifying paradigm based upon the underlying principles of processing, structure, properties, and performance, and their interrelationships, that is now well-accepted (Figure 1).

Interestingly, the reservations once raised against materials education have been similarly raised against bioengineering education, as well as the integration of biology in traditional disciplines, including materials science and engineering. Considering the history of materials science and engineering, a common paradigm might also help to unify the differing backgrounds, perspectives, and terminology of those who find themselves at the intersection of materials and biology. The objective of this paper is to introduce possible modifications of the materials science and engineering paradigm for the integration of biology. Conversely, the modified paradigm may also be used for the application of materials science and engineering principles to the study of biomaterials, biological materials, and biomimetic materials.

GLOSSARIES

Intersection of Materials and Biology

Adapted from various sources.[14–16]

Biological Material: A natural material produced by a biological organism. Examples include bone, skin, seashells, wood, silk, etc.

Biological Materials Science: The application of materials science and engineering principles to the study of biological materials, including the design, synthesis, and fabrication of biomaterials and biomimetic materials from biological lessons.

Biomaterial (or *Biomedical Material*): A synthetic material or processed biological material engineered to evaluate, treat, augment, or replace any component or function of a biological organism, while in continuous or intermittent contact with biological substances.

Biomimetic Material (or *Bioinspired Material*): A material engineered to be physically, chemically, or functionally similar to a biological material.

Biological Properties of Materials

Adapted from various sources.[7,14,17]

Bioactivity: The ability of a biomaterial to elicit or modulate a favorable response ("activity") from any part of a biological organism.

Biocompatibility: Generally refers to the response of a biological organism to the presence of a material, not vice versa, with varied meaning. (1) The ability of a biomaterial to perform its desired function with an appropriate host response in a specific application.[14] (2) The ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy.[7]

Biodegradability: The ability of a material to be broken down or decomposed by a biological organism.

Bioinert: The ability of a biomaterial to remain unchanged by a biological organism and to not elicit biological activity.

Bioresorbability: The ability of a material to be gradually resorbed or dissolved by cellular and/or metabolic processes. *Bioabsorbability* may be used to specify metabolism of the material, and *bioerodibility* may be used to specify surface erosion.

Toxicity: The degree to which a material may permanently destroy or impair any part of a biological organism.

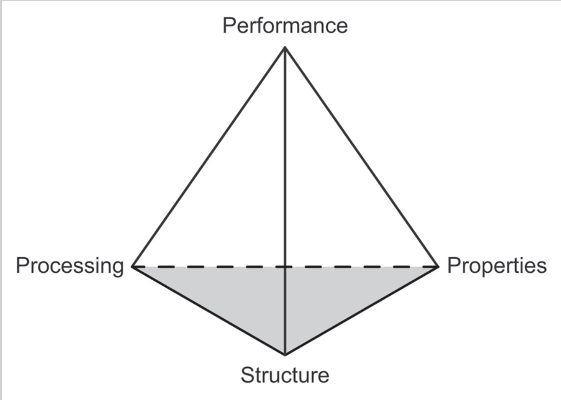

Figure 1. The materials science and engineering paradigm showing the underlying principles at vertices and their interrelationships along edges of a tetrahedron. The base is shaded to highlight that processing-structure-property relationships have historically received greater attention by materials scientists and engineers than considerations of performance.

DEVELOPMENT OF THE MATERIALS SCIENCE AND ENGINEERING PARADIGM

The materials science and engineering paradigm has itself evolved from a triangle to the tetrahedron shown in Figure 1.[15] Aspects of the processing-structure-property vertices have been detailed in various formats similar to that shown in Figure 2. Material properties can be further identified in categories based on the application. For example, properties of interest for cements used in bone fracture or implant fixation include mechanical properties (e.g., elastic modulus, ultimate strength, fracture toughness, fatigue life, and precured viscosity), chemical properties (e.g., setting time and reaction yield), thermal properties (e.g., exothermic temperature), and biological properties (e.g., biocompatibility, bioactivity, and bioresorbability), irrespective of the material of choice (e.g., acrylic or calcium phosphate cements). Material structure can be subdivided by aspects unique to non-crystalline versus crystalline materials contained within the microstructure (Figure 2).

Materials processing lagged behind structure-property relationships in the adoption of materials-generic concepts and curricula, which were proposed by Merton C. Flemings and colleagues[18] and implemented by Kevin P. Trumble and colleagues.[24] Chemical processing, or primary production, involves the conversion of raw materials into engineering materials. Structural processing, or shape forming, involves the conversion of engineering materials into objects or components, which may be subsequently assembled into a system. Shape forming processes can be grouped by common underlying mechanisms for achieving a change in shape rather than by classes of materials.[18,24] Deformation processes involve the application of force to achieve a shape change via crystal plasticity or viscous flow. Deposition processes involve a gas or liquid to solid state change upon surfaces, such as evaporation and condensation. Powder processes involve the consolidation and densification of powders. Solidification processes involve a liquid to solid state change via crystallization or glass transition.

MODIFICATIONS FOR THE INTEGRATION OF BIOLOGY

A pentahedron was originally proposed by Eduard Arzt[25] and modified by Marc A. Meyers to incorporate unique aspects of biological materials, where the five vertices corresponded to aqueous synthesis under near-ambient conditions, self-assembly, multifunctionality, hierarchical structure, and evolution/environment effects.[5,15] The first three aspects are all readily captured within the processing-structure-property scheme in Figure 2 by adding biological processes. The latter two aspects will be incorporated below in proposed modifications of the materials science and engineering paradigm for the integration of biology.

The base of the tetrahedron in Figure 1 was shaded to highlight the observation that processing-structure-property relationships, as discussed above (Figure 2), have historically received greater attention by materials scientists and engineers than considerations of performance.[23] One can readily observe that materials performance is often more likely to be considered by engineers who are more concerned with an entire engineering system rather than the intricacies of the materials used. For example, a mechanical engineer may be concerned with how materials enable improved efficiency in an internal combustion engine; a chemical engineer may be concerned with how materials enable improved efficiency in catalysis; or an electrical engineer may be concerned with how materials can sustain Moore's Law for integrated circuits. Thus, the difference between material properties and performance may be simply a matter of perspective, or scale. The overarching concept is that of function, which is ironically the preferred term used in biology, and has been used in Michael F. Ashby's work on materials selection and design.[26]

Therefore, in order to account for

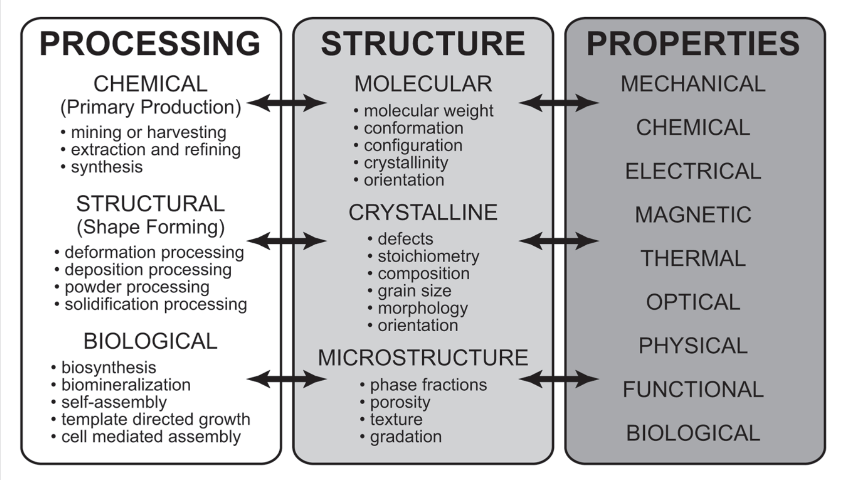

Figure 2. A more detailed description of the processing-structure-property vertices of the materials science and engineering paradigm in Figure 1, showing various categories and examples.

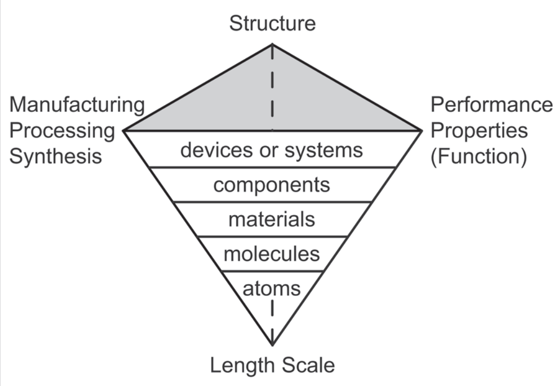

Figure 3. A modified materials science and engineering paradigm showing processing-structure-property relationships corresponding to triangles of increasing length scale from atoms to materials to engineering systems. Notice that terminology for synthesis, processing and manufacturing, or properties and performance may be envisioned to correspond to different length scales. "Function" is proposed to capture the essence of both properties and performance which were collapsed to the same vertex.

the hierarchical structure of biological materials, the properties and performance vertices in Figure 1 were collapsed together and the fourth vertex was changed to represent length scale. At the risk of sounding overly dramatic, the tetrahedron in Figure 1 was then turned upside-down, such that processing-structure-property relationships correspond to triangles of increasing length scale from atoms to materials to systems (Figure 3). Notice that terminology for synthesis, processing and manufacturing, or properties and performance are readily envisioned to correspond to different length scales. However, this modification of the materials science and engineering paradigm does not clearly account for adaption in biological materials and systems.

In order to represent the adaptive or cyclical nature of biological materials and systems, the triangular slices of the tetrahedron in Figure 3 were changed to circles to form an inverted cone. In order to aid visualization, the inverted cone was then projected onto a two-dimensional surface shown in Figure 4. Processing-structure-function relationships are shown by three sectors and the circular representation reflects principles of biological adaption ("form follows function follows form"[27]). Hierarchical structure is shown by concentric circles of increasing length scale from atoms and molecules to materials to systems (Figure 4).

Key biological principles and terminology were readily mapped onto the modified materials science and engineering paradigm presented above (Figure 5). At each scale, parallels to biology are shown in parentheses, demonstrating the ability of the paradigm to describe the development (processing), anatomy or form (structure), function, and adaptation (in response to a stimulus) of biological systems. The stimulus might include mechanical loading, chemical gradients, electrical signals, and the like. The response of tissues to implanted biomaterials, and vice versa, can be readily considered hierarchically, ranging from altered tissue morphology to the release of cytokines and growth factors. Furthermore, a time scale could even be used to extend Figure 5 into a third-dimension.

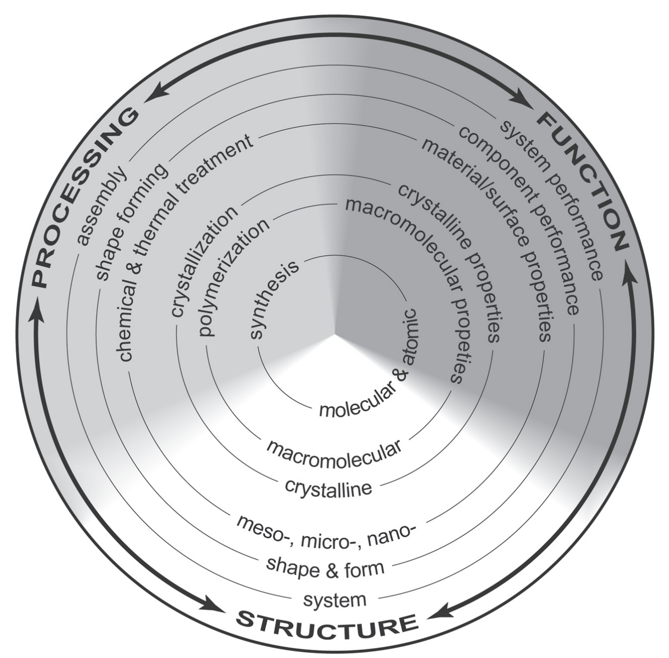

Figure 4. A modified materials science and engineering paradigm showing levels of scale corresponding to concentric circles of increasing size. Processing-structure-function relationships are shown as three sectors of a circle to reflect the dynamics of biological adaption. Interrelationships between sectors at each level of scale provide a framework to simultaneously consider complex multi-scale phenomena in interdisciplinary research, education, and design.

IMPLICATIONS FOR RESEARCH, DESIGN, AND EDUCATION

The modifications to the materials science and engineering paradigm (Figures 3–5) may be useful for the integration of biology and biomedicine in materials research and education, as well as in advocating the application of materials science and engineering principles in biomedical research and education, by providing a common framework for critical thinking and a common language for communication for those who find themselves at the intersection of materials and biology. Hierarchical processing-structure-function relationships provide a framework to consider complex, multi-scale problems involving biomaterials, biological materials, and biomimetic materials. Moreover, this framework may help one to better appreciate the full scope and potential ramifications of a seemingly simple engineering solution (e.g., systemic response to an implanted biomaterial).

Biomaterials research and product development has a history full of unintended consequences, such as thrombosis, restenosis, osteolysis, allergic reactions, implant fracture, degradation, etc. Many were likely unavoidable due to the state of knowledge at the time. Nonetheless, a critical examination of history can reveal several potentially problematic paradigms that are described in Table I. Since everyone is at risk of being offended by the generalizations in Table I, note that each paradigm has unquestionably resulted in successful biomedical implants which have greatly improved human health. However, the shortcomings of each paradigm have also clearly resulted in clinical problems, such as those mentioned above, or a lack of clinical solutions to date. Research and design based upon hierarchical processing-structure-function relationships (Figures 3–5) could conceivably adopt the strengths and avoid the weaknesses of each potentially problematic paradigm.

When used in research and design teams, the modified paradigm may also enable improved understanding and appreciation between different individuals or disciplines that typically address problems from different perspectives originating at different levels of scale. For example, a chemist working on an aspect of a project at the molecular level may be able to better appreciate and integrate the work of a mechanical engineer at the systems level, and vice versa. In education, a "bottom-up" perspective on hierarchical structure may be most appropriate for materials scientists and chemists, but mechanical engineers, for example, may more readily assimilate content taught from a "top-down" approach.

Relative to other science and engineering disciplines, materials science and engineering finds itself located in the center of the length scale continuum (Figure 4). Perhaps this is why the materials science and engineering paradigm was so easily adapted to the breadth of biological systems (Figure 5). Thus, if materials science and engineering as a discipline embraces biology, the center can be a place of continued importance in enabling new systems-level biomedical technology in the same way the discipline has enabled new technology in the electronics, energy, and transportation industries. However, failure to embrace biology could result in being overlooked or marginalized as a discipline in the rapidly progressing technologies requiring proactive, third-generation biomaterials.

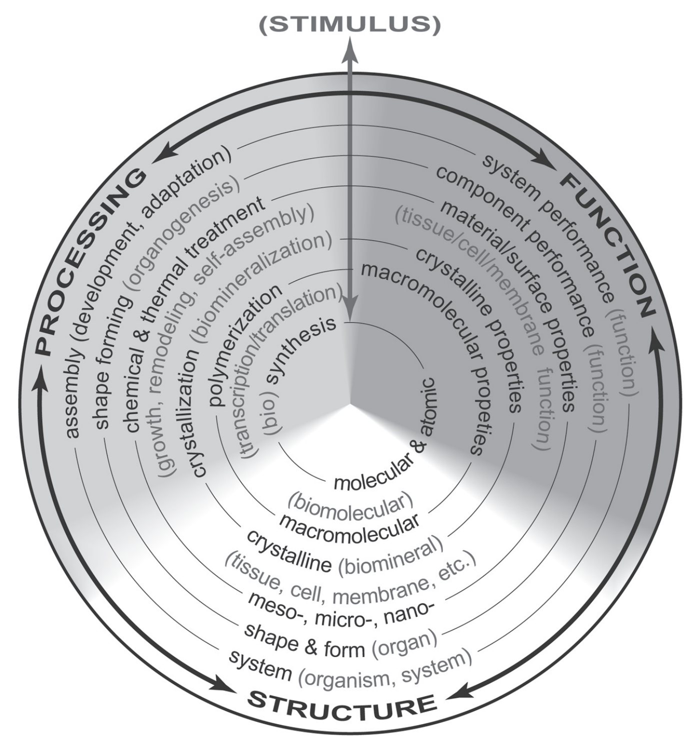

Figure 5. The modified materials science and engineering paradigm in Figure 4 showing direct parallels to biology in parentheses and demonstrating the ability of the paradigm to describe the development (processing), anatomy or form (structure), function, and adaptation (in response to a stimulus) of biological systems. The stimulus might include mechanical loading, chemical gradients, electrical signals, and the like.

The modified paradigm may be useful for materials scientists and engineers seeking research funding from the clinically- and biologically-oriented National Institutes of Health (NIH). Materials science and engineering is well-accustomed as a discipline to use-inspired basic research rather than the historic dichotomy between basic and applied research in the United States.[28] However, materials scientists and engineers, like engineers from other "traditional" disciplines, may have difficulty understanding and expressing the clinical significance of their work. Thus, the modified paradigm may help the researcher to ask the right questions. "If you don't ask the right questions, you won't get the right answers."[29]

The modified paradigm may also be used as a conceptual framework for design, including concurrent engineering in product development and computational design of hierarchically structured materials. Concurrent engineering is a systematic approach for simultaneously, rather than sequentially, considering various aspects in product development spanning concept, design, materials selection, manufacturing, and service.[30–32] Materials science and engineering is also presently faced with new opportunities and challenges involving computational simulation for the "bottom-up" design[32] and "top-down" evaluation[33] of performance in hierarchically structured materials, and the integration of computational methods in curricula.[34]

The modified paradigm suggests that a significant number of biological concepts can be integrated into materials science and engineering curricula within existing common core courses. Moreover, biomaterials and biological materials can be used in these courses to stimulate interest in the underlying materials science. For example:

- The structure of important proteins like collagen can be introduced alongside synthetic macromolecules. In processing, the synthesis of proteins (polypeptides) from amino acids by transcription/translation and their self-assembly into extracellular matrix (e.g., collagen fibrils) can be compared and con-

Table I. Potentially Problematic Design Paradigms Showing Key Characteristics and Examples*

Design Paradigm	Emphasis on…	Potential problems may occur when…	Driven by…	Possible Clinical Examples
"Material-Mart"	Functionality	Materials are taken "off the shelf" with little initial regard for processing-structure-function relationships.	Physicians and FDA policies	Artificial heart, vascular grafts, breast implants, metallic orthopaedic implants, PMMA bone cement
"Make it and break it"	"New" materials and processing methods for an intended function	Design occurs by "trial and error" with little initial consideration of the effects of material structure.	Industry and systems level engineering	Dental/orthopedic composites, porous tantalum, bioresorbable polymers, nitinol stents
Biomimetics	Mimicking biology	One assumes a priori that the best way to achieve a desired outcome (function) is the way nature has done it.	Academics	Xenografts, synthetic bone graft substitutes, synthetic collagen

* Note that each paradigm has unquestionably resulted in successful implants which have greatly improved human health. However, the shortcomings of each paradigm have also resulted in clinical problems or a lack of clinical solutions. Research and design based upon hierarchical processing-structure-function relationships (Figures 3–5) could conceivably adopt the strengths and avoid the weaknesses of each potentially problematic paradigm.

trasted to the polymerization and molding of thermoplastic and thermosetting polymers.

- Wetting of solid surfaces by liquids is usually introduced early in undergraduate materials curricula and can be coupled with examples and particular concepts that are important in biological materials. See "Implications of Wettability in Biological Materials Science," by John A. Nychka and Molly M. Gentleman in this same issue of *JOM*.[35] Moreover, early introduction to the biological significance of surface energy can lay the groundwork for advanced electives on biocompatibility or tissue-biomaterial interactions.
- Composite biological materials like bone, dentin, and nacre provide wonderful examples for the discussion of hierarchical structure,[5] anisotropy,[36,37] micromechanical models,[37] toughening mechanisms,[38] and fatigue crack propagation[39] in texts and courses on the mechanical behavior and failure of materials. Furthermore, the adaptation and remodeling of biological materials in response to mechanical stimuli deserves consideration for introduction in related texts and courses, especially in light of recent interest in self-healing engineering materials.
- Surface plasmon resonance exhibited by metallic nanoparticles and surfaces has become important in biomedicine for tunable therapeutics, diagnostics, and sensors,[11,40] and could be included in courses covering electrical, optical and magnetic properties of materials or "functional" materials.

There are seemingly endless possibilities besides those listed above. Thus, discretion on how much biology and biomedicine to integrate into core courses and curricula will ultimately fall upon instructors, curriculum committees, and perhaps, through the process of self-study and review, by the Accreditation Board for Engineering and Technology (ABET).

The ability to readily integrate biology into existing core courses and curricula does not diminish the need for complementary electives focused exclusively on concepts key to the interaction of materials and biology. The model of a single, catch-all course on "biomaterials" has run its course and should be seriously questioned due to the rapid growth of the field and the need for more serious engagement with biological concepts, as described above. Popular textbooks on the broad subject of biomaterials have been noted to be better-suited as reference books due to the need to introduce materials science (to biomedical engineers), biological materials, key concepts related to interaction of materials and biological systems, and biomedical applications.[41] However, the good news for materials science and engineering, compared to other disciplines, is that the integration of biology into lower-level courses, as suggested above, should enable advanced, elective courses to focus entirely on key overarching concepts. For example, an upper-level undergraduate and/or introductory graduate course on biocompatibility[7] or tissue-biomaterial interactions[17] could serve as the prerequisite for advanced electives of special interest such as tissue engineering scaffolds,[1,2,7–9] nanomedicine,[10–12] or a particular medical specialty (e.g., orthopedic biomaterials).

Materials science and engineering degree programs should not inhibit or discourage students interested in biomaterials from venturing out of department to take elective courses in cell biology, biochemistry, molecular biology, etc., in order to add further depth in biology than is possible even with the above recommendations. Moreover, efficiencies might be realized through partnership with bioengineering programs where both programs could utilize an introductory course to materials and a subsequent course focused on biocompatibility or tissue-biomaterial interactions, supported by the materials and bioengineering departments, respectively. Collaborative teaching could bring further benefits and should also be explored.

The modified paradigm (Figures 4, 5) has been implemented in an elective biomaterials course taught within the mechanical engineering department (with a graduate program and undergraduate minor in bioengineering) under my direction for the last four years with an average enrollment of 30 students/year. Students entering the course include seniors and first-year graduate students who have already taken an introduction to materials course. Therefore, the course emphasizes hierarchical structure-function relationships related to tissue-biomaterial interactions using published reports in the literature (including journal articles, Food and Drug

Administration pre-market approvals, patents, etc.) that are critically and independently evaluated by teams and individuals. Upon completing the course all students demonstrate the ability to identify and organize the key hierarchical structure-function relationships into a coherent framework for the biomaterials used in any biomedical application without prior knowledge of that application. In other words, students are able to see the entire scope of an open-ended biomedical problem and frame the role of materials within solution(s). Most students completing the course also demonstrate the ability to critically evaluate shortcomings in the state of knowledge, or application thereof, in light of their conceptual framework using the modified paradigm. Finally, some students demonstrate the ability to translate their critical thinking into proposed action.

The modified paradigm and the implications discussed above are certainly not perfect or complete. One drawback is that the modified paradigm presented in Figures 4 and 5 is admittedly quite busy. Nonetheless, the concepts and ideas presented in this article will hopefully stimulate further thought, ideas, and engagement for the integration of biology in materials science and engineering.

CONCLUSIONS

Materials scientists and engineers who wish to make an impact in research and technology at the intersection of materials and biology must become increasingly knowledgeable, or at least conversant, in biology and biomedicine. Therefore, the materials science and engineering paradigm was modified to account for the adaptive and hierarchical nature of biological materials. Hierarchical processing-structure-function relationships provide a framework for critical thinking involving complex, multi-scale problems involving biomaterials, biological materials, and biomimetic materials. The modified paradigm may be useful for the integration of biology and biomedicine in materials research and education, as well as in advocating the application of materials science and engineering principles in biomedical research and education.

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