1 Introducing materiomics

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1.1 Introduction to materiomics

The ability to regenerate and repair tissues and organs – using science and engineering to supplement biology – continuously intrigues and inspires those hoping that the frailty of our bodies can be ultimately avoided. From ancient times, a surprising range of unnatural materials have been used to (partially) substitute human tissues for medicinal purposes. For example, in the era of the Incas (*c*. 1500), moulded materials such as gold and silver were used for the 'surgical' repair of cranial defects. In addition, archaeological findings reveal a wide range of materials, such as bronze, wood and leather, being used to replace and repair parts of the human body. Continuous refinement led to the first evidence of materials successfully implanted *inside* the body, reportedly used to repair a bone defect in the seventeenth century (see Further Reading).

Even earlier than this, the relationships between anatomy (i.e. structure) and function of living systems had been explored by Leonardo da Vinci and Galileo Galilei, who were among the first few to apply fundamental science to biological systems. In the current age of technology, new materials for biomedical and clinical application have undergone a modern Renaissance, resulting in a surge in design and successful application (1–5). The concepts of tissue repair and substitution are constantly improving and becoming more accessible, as proven for example by the widespread occurrence (and popular approval) of total hip and knee replacements. But rather than replacement with synthetic analogues, can biological tissue(s) be directly engineered?

The first biomaterials arose to solve specific clinical problems, and it was only later that this became a field of research in itself. Polymers and ceramics (and other effective biomaterials) were not developed for implants *per se*, but rather were used because of their availability and proven (known) material properties. This need not be the case. The field of biomaterials has witnessed exciting and accelerating progression, partly owing to the emergence of physical-science-based approaches in the biological sciences. Consequently, developments have led to a number of blockbuster materials which currently play a substantial part in modern healthcare, with various clinical applications ranging from degradable intraocular lenses and sutures to coronary stents, heart valves and orthopaedic implants. But ultimately, where does this field lead?

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1.2 The challenge of 'living' materials science

Hitherto, the field of biomaterials has largely been characterized by trial-and-error experimentation, practical intuition and low-throughput research (6). As a result, identification and development of successful biomaterial candidates has frequently been iterative, employing *ad hoc*, piece-wise or one-off approaches to design and characterize materials for a specific application (7). Currently lacking is a single set of 'design parameters' that can satisfy more than the most rudimentary system – there is neither a standard 'code' for biological systems nor a standard 'toolset' for analysis.

Despite continuous advances both in the understanding of the natural function of biological materials and systems and in the synthesis and regeneration of certain tissues (such as bone), a cohesive and systematic approach is still wanting. What is the primary impediment? Biological tissues, organs and materials exploit multiple structures and functions across scales – they are universally hierarchical (8, 9). Such multiscale *hierarchies* consequently make any single-scale analysis and prediction a hypothesis at best. While studies have successfully characterized components at specific scales (e.g. the molecular structure of DNA or the sequence of a multitude of proteins), superposition of the structure or the functional properties of individual components (defined differently according to scale) is insufficient to understand the complete system (10). In simpler terms, '$1 + 1 \neq 2$'. We utterly fail in the 'design' and 'construction' of such material systems – we cannot accurately or reliably predict behaviour of the final product. Indeed, whether through a lack of critical system variables or understanding of system response, we are unable to model larger (living) multiprotein systems and networks, let alone the structural role that such materials play in a cellular tissue. This is the exact opposite of the definition of engineering, where it is necessary to prescribe the performance of system components with reliable and repeatable accuracy.

Conversely, understanding the interaction of materials with biological ('living') tissues across all scales – from atoms and molecules to tissues and eventually at the organism level – remains a crucial hurdle in tissue engineering and biomaterial development. The challenge is intrinsically double-sided, yet highly intertwined. The scientific complexity at both sides of the interface – the material on the one hand and the organism on the other – needs to be considered (Figure 1.1). The fundamental problem of combining living (biological) and non-living (synthetic) components can be encapsulated by the popular adage, 'The whole is greater than the sum of its parts' (commonly attributed to Aristotle, who probably was not referring to the interface of biology and materials). The complex interactions between materials and biological systems require a certain flair to analyse deterministic (or predictive) behaviours and material properties. Nature, through meticulous trial and error over centuries of optimization and refinement, has intricately combined material structure, properties and functionality (9). 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?

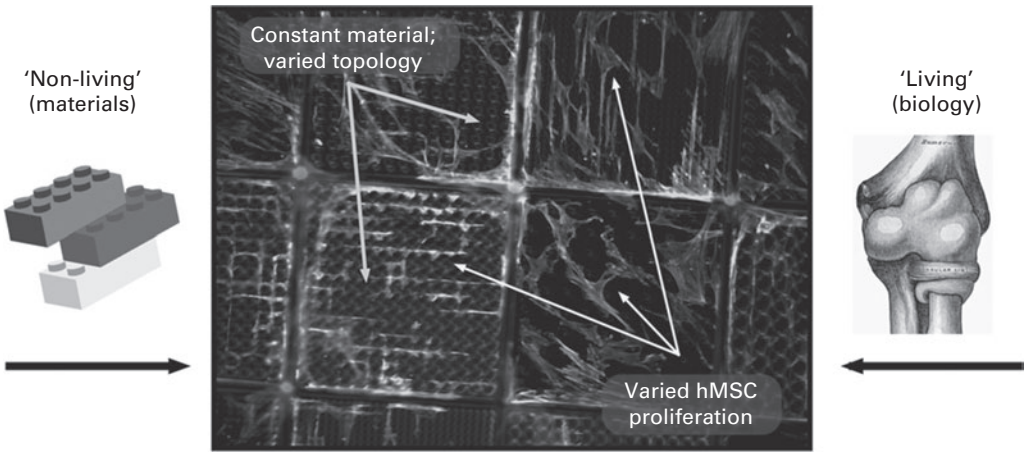

Figure 1.1 At the interface of materials and biology. The combination of living and non-living components – namely biological (represented by a human knee joint) and synthetic materials (represented by building blocks) – presents a complex challenge that can be summarized by the adage, 'The whole is greater than the sum of its parts'. Here, the image shows the differential response of human mesenchymal stem cells (hMSCs) to different underlying topographies on a so-called 'TopoChip' (11). Image courtesy of Frits Hulshof.

1.3 Dealing with complexity

Clearly, the concepts of Nature cannot be omitted from the equation when developing materials for biological applications. Evolutionary processes have resulted in intricate biological systems, with robust and adaptable redundancies, as well as multifunctional and multiscale components, which hamper compatible materials research – there are no material 'standards' that all of biology must follow. This intrinsic complexity impedes full understanding and limits developments in materials research for biological applications. Yet modern research has not sat idle, and has certainly led us to realize the *de facto* complexity associated with biological systems. From a broad perspective, the causes of this complexity can be grouped into common categories: multiscale; combinatorial and temporal (see Figure 1.2).

While the composition of biological materials is controlled by a relatively small set of elements (carbon, hydrogen, oxygen, nitrogen and a few metal ions), this restriction is not imposed on biomaterials research (yet the laws and principles of materials science and chemistry remain applicable, allowing exploration beyond the confines of Nature). Nature is highly successful in creating diversity from this limited set of 'building blocks' – as was indisputably demonstrated by the discovery of the structure of DNA by Watson and Crick in 1953, creating the illusion of a simple origin of life (relying on only four nucleotides). As a result, the idea of growing any desired tissue from its basic DNA code, along with emerging expertise in (biological) material processing, became viable. One could foresee growing any desired tissue from the necessary DNA (along with requisite raw materials), similar to the chemical vapour deposition of carbon

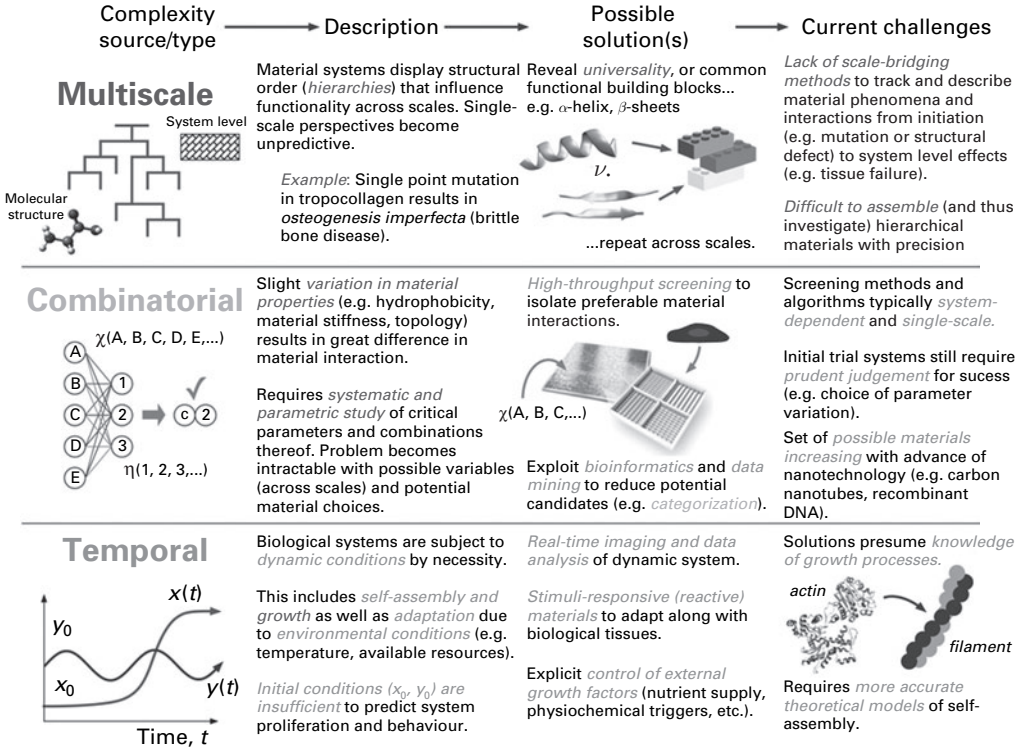

Figure 1.2 Sources of complexity in biological materials, with possible solutions *via* a materiomics approach.

nanotubes or the polymerization and spinning of nylon. It would merely be the assembly of the appropriate 'blocks', so to speak.

Yet Nature turned out to be more clever than that; evolution seamlessly intertwined structure and functionality. Despite protein materials being built, or 'transcribed', from a mere set of twenty amino acids, combinations of this limited set of building blocks produce a multitude of functionally distinct proteins (9). That being said, proteins acquire their functionality across multiple scales via a combination of peptide sequence and common structural motifs (such as α-helices and β-sheets) and a set of prevalent processes and mechanisms (e.g. synthesis, breakdown, self-assembly). The phenomenon of *universality* exists ubiquitously in biology. At higher scales, revealing the dimensions of biological complexity, proteins iteratively assemble into complexes: collagen fibrils, for example, which in turn form collagen fibres and eventually assemble together with additional inorganic materials, are the major constituents of bone tissue. The structural conformation of proteins might be highly conserved throughout different tissues, while concurrently (and contrastingly) being highly tissue-specific.

A key starting point in developing working models for such complex systems is the preservation of particular functionality despite uncertainty or minor variation in components and/or in the environment (10). We must neglect the physical idiosyncrasies of a system (such as specific peptide sequence), identify the fundamental building blocks

(e.g. structure, key interacting groups) and delineate the function of each (signalling, catalytic, mechanical, etc.). In essence, biological systems originate from their associated genomic sequence – a distinct sequence of simple base pairs. While true, such a description is as crude as describing Beethoven as a simple collection of notes or the works of Shakespeare as a linear sequence of letters (12–14). The structural hierarchy and associated functionalities across scales add extra layers of complexity.

Another level of complexity arises from dynamic changes in biological material systems over time, owing to growth or adaption, for instance. To illustrate, the functional properties of proteins are also highly influenced by post-translational modifications (e.g. hydroxylations, phosphorylations, glycosylations) or enzymatic cross-linking. These modifications are crucial for interaction with other proteins and material components, and so determine the properties of tissues. At larger scales, cell adhesion, cytokinesis and cell migration illustrate the power of the cytoskeleton to self-organize locally into complex structures. This complexity impedes understanding of biological processes, as they are difficult to mimic or predict *ex vivo* or through synthetic approaches, posing a major challenge in structure prediction (and design) and the development of biocompatible materials. Simply put, biological materials grow (and/or evolve), while synthetic materials do not (they are characterized by static/constant material properties). It is apparent that not only are predictive models of assembly required, but also the possible development of self-adapting materials to mimic biological analogues.

Nature has creatively produced a broad range of functionally disparate materials (*diversity*) using a limited number of (*universal*) constituents, rather than inventing new building blocks. Such multiscale hierarchical systems simply cannot be analysed or predicted at a single scale. The so-called *universality–diversity paradigm* (15, 16) presents an alternative approach; it shifts the focus from individual component analysis towards the analysis of fundamental elements, hierarchical organization and functional mechanisms (sometimes referred to as *emergent* properties, a concept common in the scope of systems biology). Yet again, the whole is greater than the sum of its parts.

But how can we (a) determine what function is required and (b) reduce the number of potential material candidates for our need? Two main approaches can be considered in materials research to deal with this complexity and understand and engineer biological systems: firstly, via a bottom-up approach, identify fundamental building blocks and study their structure, interactions and properties at all relevant scales, from Ångstrom- to macro-level (from a single peptide to the collagen fibre); secondly, via a high-throughput approach, study the biological roles of a material system as a whole (combining the best of holistic and reductionist approaches; see Further Reading).

Within the first perspective, investing in the relation between universal structures and corresponding functions is similar to the field of proteomics (study of the function and structure of proteins) and interactomics (study of the web of interactions between biological molecules in a cell) (17–19), but extended beyond the confines of a cell and tissue to interactions and properties of materials. Observation and extraction of the general underlying principles (e.g. physical, chemical, optical, electronic, thermal, mechanical, etc.) of the structure–function relationship, using both experiments and theory, is required to make them available as concepts useful in materials science and engineering

beyond biological occurrence, so that they should theoretically hold for similar synthetic material systems (20). But biological systems present inevitable complexity, introducing constraints in materials interactions analysis. Fields such as biomimetics attempt to exploit the structure and function (including the complexity) of such biological systems, applying principles of biology to synthetic systems for the design and engineering of material systems (20, 21).

Continuing this line of thought – applying biological 'tricks' to synthetic systems – we find that the problem quickly becomes intractable, as the sheer number of possible material–material interactions is unbounded. Moreover, unlike the biological limitation to available amino acids and ambient environmental conditions, in biomaterial research the complexity is further increased by the number of controls and variables produced by engineers (either by necessity or by choice).

The second approach mentioned above, the use of high-throughput combinatorial methods, may open up new possibilities. High-throughput-based methods allow simultaneous synthesis/processing and evaluating of a multitude of system variations (e.g. material, molecular) (22) to isolate desired behaviour/responses. Such methods have been commonly used in pharmacology for drug discovery (23), for the successful genetic screening of fruit flies and zebra fish (23) and for various applications in systems biology (24), to mention a few examples. Building on these past successes (also including proteomics or genomics (25, 26)), modern approaches have accelerated the discovery process and analytical methods, and have likewise extended insights and potential applications. Far from autonomous improvement, successful studies rely on technological advances in many fields, as every step involved in this approach requires high-throughput methods; from synthesis characterization (e.g. from a chemical or structural perspective) to analysis and characterization of the desired outcome (at cellular or tissue level) (27).

The screening process is relatively simple: when the desired performance is attained (based on a variety of metrics), a suitable material or system candidate can be defined, and subsequently iterated. The better candidates can then be investigated in more detail, to determine the relation between 'universal' material components and observed biological response, such as the relationship between surface chemistry or topology and a biological phenomenon of interest such as cell differentiation. The pathways and mechanisms thus unravelled may serve as a basis for further material refinement and development. An advantage is that no theoretical background of complex biological processes is required to screen for performance of material systems – only the results drive the screening process. Critical performance metrics and material properties may unexpectedly emerge upon characterization and analysis of successful outcomes, leading to new insights and target parameters. Such holistic screening of systems, together with reductionist characterization of the phenomenon, can be beneficial both for finding new systems and determining the mechanisms involved, providing a self-optimizing protocol for delineating material system characteristics and performance, beyond the scope of any one-off system investigation. High-throughput screening of a material property within a specific application can lead to unexpected findings, or even properties that could not have arisen naturally, which can in turn lead to optimized design of new materials.

In spite of the discussed intrinsic biological complexity, recent advances in (biological) material sciences have been considerable. Continuous refinement of techniques is 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, modelling and simulation – has transformed investigative approaches of materials systems. The motivation has come from a vast assortment of disciplines: for example medicine (physiological properties of tissues for prosthetic devices, replacement materials and tissue engineering), biology (material aspects of adaptation, evolution, functionality, etc.) and materials science (thermal and electrical properties of nanosystems, functional performance of microscale devices, etc.). The potential reward and challenge of understanding biological materials elicits contributions from biologists, chemists and engineers alike. Further progress is hindered, however, by a 'divide and conquer' approach, and instead dictates a convergence of scientific disciplines under a common banner – and this is what is known as *materiomics*.

1.4. Emergence of materiomics

Traditionally, materials science, in its broadest sense, has been divided into distinct research areas based on classes of structures, length scales and varying functionalities (structural, thermal, electronic, etc.). Disparate disciplinary affiliations coexist, such as the specialities of ceramics and polymers, the fields of nano- and microtechnology, or the area of bioactive materials, for specific applications. In Nature, however, reciprocal refinement (i.e. 'evolution') has led to a balance between chemistry, materials, structure and required function. From this perspective, the disciplinary boundaries in material sciences should be razed, and the merger (or *convergence*) of different disciplines is inevitable. The rich history, experience and unique perspectives of distinct fields promote progress in this inherently interdisciplinary venture (Figure 1.3). Unsurprisingly, combining the widespread knowledge of materials scientists with the detailed understanding of biological systems and structures built over years by biologists holds great promise.

The emerging field of materiomics works from this philosophy of convergence and is characterized by an approach that considers all mechanisms of a material system across multiple scales. Materiomics – the transparent combination of 'material' with '-omics' – is most simply defined as the holistic study of materials systems. It approaches biological materials science (systems with or without synthetic components) through the integration of natural functions and biological processes ('living' interactions) with traditional materials science perspectives (physical properties, chemical components, hierarchical structures, mechanical behaviour, etc.). The suffix -omics, as in fields such as proteomics or metabolomics, emphasizes the complexity of such work; by definition it refers to 'all constituents considered collectively'. Genomics, for instance, is defined as the study of the human genome referring to all the genes of the considered organism and not just a small subset of genes that determines the observed phenotype. Equally, materiomics entails much more than the commonly used approach of piece-wise unravelling the

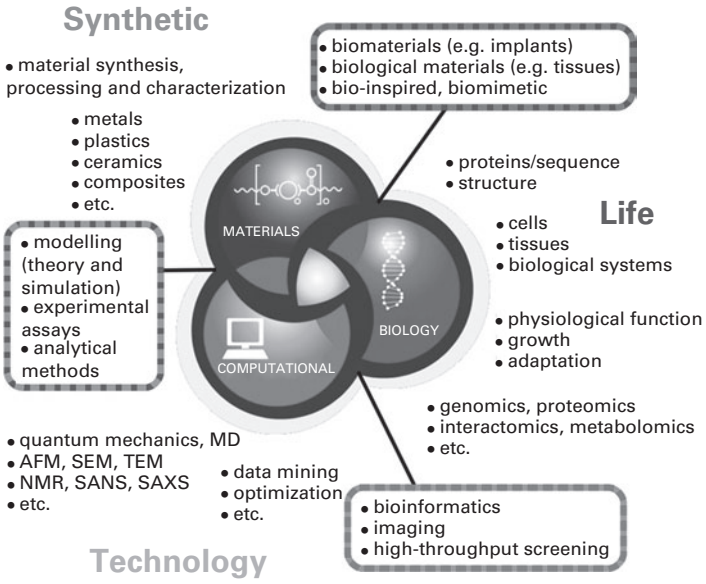

Figure 1.3 **Materiomics – the convergence of disparate fields**. The interface of materials science ('synthetic') and biology ('life') has been successful in the development of biomaterials, but recent technological advances allow for a truly integrated and holistic multidisciplinary approach. While some biological materials have been investigated from a materials science approach, and some material developments have been inspired by Nature, complete understanding requires convergence of each knowledge base and toolset. For example, 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 lies at the apex of these information streams, attempting to reconcile biological function with material interactions and properties.

properties and behaviour of a material. It entails the study of all possible functionalities and properties. For example, the process of bone tissue growth on a calcium phosphate scaffold under controlled conditions is a materials science and biological problem (albeit nontrivial). Understanding how bone tissue can be grown on *any* arbitrary material platform is a materiomics problem. At the juncture is the emergence of the *materiome*, which can be thought of as the abstract collection of all material behaviours, functions and interactions with all potential material systems and environmental conditions.

Innovation and successful (predictive) biomaterial design involves a rigorous understanding of the properties and mechanisms of biological matter. Thus, even without the widespread adoption of the term 'materiomics' attempts are currently being made to combine the fields of biology and materials science, resulting in progress in research on complex biological and synthetic material systems. Although biological materials may appear irreducibly complex, researchers in biomaterial synthesis and self-assembly are far from idle. Several spin-off research areas have emerged to satisfy the needs of materials research driven by this new approach. Some of these are biologically 'themed'

interdisciplinary research areas, such as bioinformatics, nanobiology or systems biology (see Figure 1.3). Through the merging of technologies, processes and devices, new pathways and opportunities are created that would be inaccessible to any single discipline or knowledge base.

The knowledge and advanced technology acquired over the years by material scientists has allowed the production of large material libraries ('living' and/or synthetic) with diverse chemical properties (28). These include libraries based on block copolymer chemistry (29, 30), or click-chemistry (31–34) or surface topography, as well the protein databank archives (http://www.rcsb.org/). The assembly of such libraries is obviously crucial for progress in the materiomics approach; however, the existence of material *data* should be distinguished from material *knowledge*. While assembly of material libraries is important (and necessary), without associated understanding of material function it is akin to filling a library with books, yet being unable to read a single word. The assembly of materials represents only the first steps in materiomics-based material development, just as determining the genome sequence is the first step in unlocking the power of the genetic code. The analysis of material properties with respect to their biological and functional influence is the variable to address, as inspired by nature, where the structure and function of a system are intimately interlinked. Equally, slight alterations in underlying chemistry of a biological system may have great influence on its resulting functional properties, and may serve to inspire or guide further materials development.

1.5 Conclusion and book outline

The field of materials research for biomedical and clinical applications has witnessed exciting developments over the past several years: a materiomics approach has been undertaken and is forecast to guide the field to progress faster and more efficiently. From the materiomics perspective, biomedical materials research must rely on a holistic approach to investigate biological material systems. As most material properties are strongly dependent on the scale of observation, integration of multiscale experimental and simulation analyses is the key to improve our systematic understanding of how structure and properties are linked. Different scientific fields, with their distinct knowledge and methodologies must converge.

As we have said, at the interface of living and non-living materials, the whole is greater than the sum of its parts. Understanding of such complex systems, therefore, requires more than the summation of disciplinary contributions – fields and techniques must be integrated in a cohesive and synergistic manner. Further streamlining of the process from material banking to assay development, high-content imaging and data mining will ensure that the *materiomics* approach becomes available for the biomaterial research community.

A key challenge is to extend physiochemical metrics, using insights based on the material properties (discussed further in **Chapter 2**) and mechanical function in a biological context, across the molecular, cellular and tissue scales. Seamless integration of

synthetic components requires both the development of *de novo* materials (**Chapter 3**) and efficient means to synthesize functional systems (**Chapter 4**). Assessing success requires the integration of advanced biological assays (**Chapter 5**), high-content image processing (**Chapter 6**) and bioinformatics (**Chapter 7**), to evaluate, monitor and predict mechanisms associated with materials and the structures composed of these materials.

Although complete understanding of a material system (biological or synthetic) is theoretically desirable, advances and immediate applications can be developed in a continuously refined and self-regulating cycle. Lacking a complete picture from genetic transcription to tissue function has not impeded advances in and use of the mechanisms and interactions we know (fairly) well (see **Chapter 8** on upscaling, and **Chapter 9** on clinical translation). The study of hierarchical material structures and their effect on molecular and microscopic properties, by making use of structure–process–property relations in a biological context, provides a basis for understanding complex systems by translating material concepts from biology intended for non-biomedical applications (**Chapter 10**). Engineering hubris and ingenuity, combined with clinical need, have laid the groundwork for future refinement. But the inverse problem remains: that is, can we introduce and exploit biological processes (such as healing or growth) seamlessly within a synthetic system, subtly eliminating the distinction between 'material' and 'tissue'? This book is a guide through this materiomics approach to biomaterial research, from material properties to clinical translation.

Further reading

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