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Review

Engineering and commercialization of human-device interfaces, from bone to brain☆,☆☆

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ABSTRACT

Cutting edge developments in engineering of tissues, implants and devices allow for guidance and control of specific physiological structure-function relationships. Yet the engineering of functionally appropriate human-device interfaces represents an intractable challenge in the field. This leading opinion review outlines a set of current approaches as well as hurdles to design of interfaces that modulate transfer of information, *i.a.* forces, electrical potentials, chemical gradients and haptotactic paths, between endogenous and engineered body parts or tissues. The compendium is designed to bridge across currently separated disciplines by highlighting specific commonalities between seemingly disparate systems, *e.g.* musculoskeletal and nervous systems. We focus on specific examples from our own laboratories, demonstrating that the seemingly disparate musculoskeletal and nervous systems share common paradigms which can be harnessed to inspire innovative interface design solutions. Functional barrier interfaces that control molecular and biophysical traffic between tissue compartments of joints are addressed in an example of the knee. Furthermore, we describe the engineering of gradients for interfaces between endogenous and engineered tissues as well as between electrodes that physically and electrochemically couple the nervous and musculoskeletal systems. Finally, to promote translation of newly developed technologies into products, protocols, and treatments that benefit the patients who need them most, regulatory and technical challenges and opportunities are addressed on hand from an example of an implant *cum* delivery device that can be used to heal soft and hard tissues, from brain to bone.

1. Introduction

Analogous to the survival of trees within the ecosystem of the Amazon rainforest, cellular survival in the complex ecosystem of the human tissues, organs, and organismal systems depends not only on **patent transport pathways** but also on the efficient transport of chemical, electrical, and biophysical information across interfaces bounding tissue compartments. Cutting edge rapid throughput imaging technologies, in combination with geo-navigational approaches to analyzing massive imaging data sets from human tissues, are enabling an epidemiological approach to understanding human health in context of organ and tissues' cellular inhabitants' health (Fig. 1) [1–4]. Equally critical, the maintenance of **functional barrier properties** at tissue compartment interfaces allows for control of the respective systems' steady state and dynamic equilibrium properties, where breaches at boundaries (interfaces) risk destabilizing those properties [2]. Coupled computational modeling and multimodal imaging approaches are enabling unprecedented understanding of

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☆ All investigations described herein that report on human subjects were carried out with informed consent and *per* respective Institutional Review Board guidelines.

☆☆ All experimental investigations described herein that report on data obtained from animals were carried out in accordance with animal care and use guidelines of the respective institutions where the studies were carried out.

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information transfer between and across different tissue compartments making up the complex biosystem of the human body [4,6,7]. While a number of studies have described the importance of the blood supply and vascularization for engineering tissues and next generation implants, engineering of interfaces represents a less explored yet equally important facet for success of human-device interfaces over time, providing the impetus for this review.

So much about the basic physiology of our own ecosystem remains unknown and needs to be addressed in order to engineer interfaces using top-down and bottom-up approaches. Indeed this is a grand challenge for development of next generation implants that integrate seamlessly between the device and the human ecosystem, between the organs and tissues comprising our bodies, and between these tissues and their cellular inhabitants. For example, every nonarticular surface of our bone is bounded by a soft tissue interface called the periosteum. Much like the blood-brain-barrier, the periosteum exhibits functional barrier properties and serves as a gatekeeper for transfer of information via all nonarticular outer surfaces of bone. Furthermore, the periosteum exhibits a remarkable capacity to respond to external stimuli to modulate its molecular permeability [8] as well as its mechanical properties [9], during and after trauma, the third leading cause of mortality in adults across age groups worldwide [10]. Stimuli-adaptive and responsive properties are defined as *smart properties* [8,11–14]. Periosteum's smart permeability properties emerge from spatiotemporal dynamics of molecular scale cell adhesion protein complexes called tight junctions [11,12]. Its smart mechanical properties emerge from spatial distribution and multiscale architectures of structural proteins including collagen and elastin making up the soft tissue sleeve and connecting it to bone, tendon and muscle [15,16]. Such smart properties provide inspiration for emulation when engineering functional tissue interfaces.

In that sense, engineering at the interface, and ultimately, the engineering of functional interfaces, itself serves as a portal to innovation. The challenge is to address multiscale mechano-, chemo- and electrophysiology from the organ to the molecular length scale and back again. Cutting edge developments in engineering of tissues, implants and devices allow for guidance and control of specific structure-function relationships. Yet the engineering of functionally appropriate interfaces represents a currently intractable challenge in the field.

Here, leaders in the development of mechanically, electrically, chemically, and biologically functional interfaces, use examples from their respective labs to illustrate hurdles and innovative solutions for the design of interfaces that modulate transfer of information between endogenous and engineered body parts or tissues. In this context, information is used as a general term for the transfer of *i.a.* forces or stresses, electrical potentials, chemical gradients and haptotactic paths. As noted in the following **sections**, myriad “weakest links” exist between engineered systems and endogenous tissues, which themselves exhibit profoundly disparate mechanical, chemical, and electrical properties. In parallel, cutting edge technological approaches are described to overcome current hurdles. “Weakest links” within organs are outlined in **Functional Barrier Interfaces in the Knee**. Those between endogenous and engineered tissues are described conceptually in **Gradients to Link Disparate Tissues**, and those between electrodes that physically and electrochemically couple the nervous and musculoskeletal systems are captured in detail in **Engineering Mechanically Functional Interfaces in the Brain: Overcoming Strain Gradients**. Finally, the challenges of moving so-called combination products smoothly through the regulatory agencies as well as traversing the “valley of death” on the commercialization path toward clinical implementation serve as the weakest links in translating engineered interface innovations to commercially viable clinical devices, as described based on an example class of interface products (surgical membranes) in **Translation and Bridge to the Future**.

2. Functional barrier interfaces in the knee

Human physiology provides exquisite examples of the importance of functional barriers. In particular, the substructures comprising an anatomical joint link the structure-function relationships enabling mobility of the individual to those underlying the exquisite flexibility and resilience of the joint, to those of the tissues making up the joint and the cells that inhabit its respective tissues. The currently intractable challenge of connecting between these length scales, and over the time scale of the growing and then aging individual, in health and disease, may be solved in the near future through coupling of cutting edge, seamless imaging methods and computational models of virtual physiological systems (Fig. 2) [3,6,7,17,18]. Such approaches are key to understanding conundrums related to biomaterials, pharmaceuticals and multiscale physiology. For example, how do chondrocytes in avascular cartilage receive their nutrition? Do popular, over the counter oral supplements such as chondroitin sulphate reach the cells in the cartilage of the knee when ingested orally by aging adults who suffer from knee pain associated with osteoarthritis? If I want to design a material that couples between vascular bone tissue and avascular cartilage, how can I harness movement to do facilitate transport? How do I couple the musculoskeletal and nervous systems which have such different mechanical, electrical and chemical properties? The list of questions is infinite but an understanding of complex biosystems will pave the path toward greater understanding and discovery.

New high resolution episcopic blockface imaging methods [19,20] in combination with multibeam scanning electron microscopy [3,4], *in vivo* computed tomography and high resolution magnetic resonance imaging methods [19,20] enable elucidation of structure and function from nanometers to centimeters, in a longitudinal manner (over time). Going forward, in combination with coupled, multiscale and multiphysics computational models (*in silico* models), it will be possible to predict complex biosystems behavior and to prioritize future experiments based on parametric sweeps that determine system variables exerting dominant influence on outcome measures of interest [7]. While the integration of biophysical and biochemical cues is perhaps most obvious in tissues of the musculoskeletal or circulatory systems with their obvious motility and pumping functions, every tissue of the human body exhibits *i.a.* molecular sieving, electrophoretic and osmotic pressure gradients.

As an example, expanding to address osteoarthritis, the largest cause of disability in the aging population, pairing of *in vivo* and *in silico* models not only provides an integrative approach to mechanical modeling of interfaces, but also traverses numerous length and time scales [1,2,17,18]. Coupled models enable integrative study of all interfaces, including biological and non-biological, in device design and evaluation while bridging length and time scales. Cutting-edge imaging modalities enable seamless study of complex systems from a single cell to a whole joint and allow for characterization of interface barrier properties and their degradation with age and disease (Fig. 2). Episcopic and magnetic resonance imaging lend themselves for the study of organismal systems, and will pave the way for virtual physiome models including cellular to organ scale detail, with high spatial and temporal resolution [3,21,22]. This allows one to account for the vascular system as an interfacing organ between the musculoskeletal and other organ systems in the body. Of particular note, it also enables inclusion of the lymphatic system which drains and recycles interstitial fluid that bathes the