Structural Tissue Interfaces: Enabling and Enhancing Continual Maintenance and Adaptation to Mechanical and Biologic Factors

TASK GROUP DESCRIPTION

Background

Successful implantation of devices that employ a direct structural interface with native tissues and organs requires the development of an intimate and symbiotic relationship enabling effective transmission of both mechanical and biologic signals. Furthermore, these mechanical and biologic signals serve as important regulators of the structure and function of the interface tissues. As a result, long-term incorporation and maintenance of an effective structural tissue interface will depend on the delivery of “just the right” signals.

From a design optimization perspective, an approach to the development of robust tissue interfaces would include the fabrication of implants that mimic the structure, mechanical properties, and biologic behavior of native tissue. An alternative strategy might include the design of an implant with generic properties that can rapidly adapt to the local environment (mechanical and biologic) by remodeling its structure and material properties. Clearly, these strategies are interrelated and depend on the creation of local niches inducing normal behavior of cells, matrices, and bioregulatory factors.

Initial Challenges to Consider

- Despite the recognized need for the creation of optimized local mechanical conditions, the characteristics of mechanical signals required for tissue maintenance remain incompletely understood. What are the critical mechanical conditions that regulate cell behavior at the interface? What are the mechanisms that enable the transduction and response to these mechanical signals?
- Long-term maintenance of a structural tissue interface requires the creation of a biodynamic interaction between the implant surface and the native tissue. What are the morphologic, architectural, and biomaterial features that promote the creation of this biodynamic interface?
- The strategies to create lasting interfaces might include the use of engineered materials that are inert or degradeable and induce effective tissue ongrowth or replacement, or the use of biologically based biomaterials that become incorporated and inherently part of the native tissue composite. What are the critical design features and parameters that would enable long-term incorporation and function at the tissue interface?

Initial References

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TASK GROUP SUMMARY

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Summary

Every prosthetic device—whether inside or outside the body, permanent or temporary, and regardless of the material it is made out of—will at some point abut the body's native tissue. This interface, in order to be smart, must enable the device to work with the body in order to allow the prosthetic to function as a living part of the system.

At the Keck *Futures Initiative* Conference in November, task group 6 faced the challenge of defining the characteristics of such a smart structural interface and

identifying the gaps in current knowledge and technology that must be closed before a smart interface can be achieved.

The first order of business was to define the problem. Everyone agreed that a smart interface needs to be adaptable within the body’s changing milieu, and capable of remodeling so that it does not degrade and can continue to adapt. The interface also must be stable and able to withstand different stresses and situations. But these descriptions seemed too vague, so the group finally settled on a more specific statement:

> The challenge is to develop a durable structural interface with native tissues and organs that promotes a seamless and interdependent relationship enabling effective transmission of mechanical and biologic factors and signals.

The group identified the three key characteristics a smart interface must have as durability, seamlessness, and interdependence with surrounding tissues. A **durable** interface was defined as stable, functioning continuously for the lifetime of the prosthesis’s purpose (e.g., as long as its user is alive for a permanent implant, or until the purpose of the prosthesis has been served).

A **seamless** interface, as envisioned by group 6, would enable a natural transition between the prosthetic device and the body’s native tissue. This transition would most likely require a mechanical and/or biological gradient and be able to withstand different functional stresses at different size scales. The seamless interface connects a prosthesis to the body naturally from a cellular level through a macroscopic scale. In other words, there is no boundary (encapsulation) tissue separating the implant from native tissue.

And finally, a smart structural interface must be **interdependent** with the tissues surrounding it. The interface must be able to adapt to the ever-changing environment of the body—remodeling, self-healing, and growing, if necessary. This interdependent interface must also allow the prosthesis to communicate with the body and use the body's resources—a concept the group called "biopermissive." A biopermissive interface would allow bidirectional biological signaling (mechanical, chemical, and electrical), and it would use the body's nutrients, resources, and waste disposal mechanisms (for both metabolic and wear waste).

In order to illustrate these abstract ideas, the group chose a model system for which to design an intelligent interface: an osseointegrated prosthetic limb that joins with the bone, muscle, tendons, and nerves in the body, and protrudes through the skin. The three essential characteristics—durability, seamlessness, and interdependence—present unique challenges when discussing bone, muscle, nerve, etc.

Durability for all the individual interfaces (skin, bone, and nerve) means that the prosthetic interface must be stable and robust, lasting for the lifetime of the user. In the case of the nerve interface, "durable" must include stable signaling that does not change over time.

Seamlessness and interdependence, however, are related to one another and require a more complex description. Skin, bone, and nerve interfaces in the osseointegrated prosthetic limb require different considerations. For skin a seamless interface must allow both a mechanical and biological gradient to exist, so that the skin will adhere to the protruding prosthesis even through subtle movements, and so that the skin will grow with it, treating it as part of the body, and allowing signals to pass between the prosthesis and native tissue. An analog system already exists in fingernails, the tooth-gum interface, and horns and tusks in animals. The challenge is to understand the signaling that happens at these natural interfaces so that it can be replicated in an artificial interface, thus enabling interdependence between the skin and the prosthesis. A truly seamless, interdependent interface at the skin would control infection, allow re-epithelization of the skin and remodeling of the prosthesis by taking advantage of nutrients in the body, and perhaps even enable vascularization of the prosthesis.

The bone interface also must have a mechanical gradient, able to evenly distribute stresses. In order to be seamless and interdependent, bone tissue must be integrated into the device (osseointegration), much in the way that bone remodels itself in the presence of orthopedic implants like artificial hips. In order for this to be a successful integration, the geometry and topology of the surface must be designed to work with the body and have a smooth mechanical gradient at many different size scales. The biopermissive interface must also enable remodeling of both the bone and prosthesis, through biological signaling and interdependent use of synthetic and biologic resources.

A seamless and interdependent nerve interface is perhaps the biggest challenge in a smart osseointegrated prosthetic limb. Seamless and interdependence of the nerve interface are reflected in two aspects of the interface with the nervous system. The first aspect involves the local molecular signals and pathways that control the interface with the engineered system. In the most biomimetic system the nerves would form synaptic connections to the device. This requires several incompletely understood signals to form the connection and an even less understood continual set of signals to maintain the connection indefinitely. The device also needs to match the mechanical characteristics of the nerve. In the inflammation cascade the device should not promote a long-term fibrous capsule that separates the device form the nerves. The presence of the device cannot disrupt the ionic balance of the local environment, which could affect the function of the nerves. The second aspect of the neural interface is signaling from information flow. In the example of an osseointegrated prosthetic, the nerve interface needs to extract information from the electroactivity of the nerves to interpret user intention and it needs to produce artificial activity to communicate sensory information to the user. There are thousands of axons within a single peripheral nerve. Communicating individually with each of these fibers, routing this information to a processor to interpret the information, and sending information to the interface are all challenges to be addressed.

So how will scientists create these durable, seamless, and interdependent interfaces between prostheses and native tissues? The group identified the gaps in current knowledge and research tools to acquire the knowledge that must be closed before such an interface can be designed.

Most importantly, in order for an interface to allow a prosthesis to virtually become part of the body, we must understand the multitude of interdependent systems that exist within the body. This includes cellular signaling, nutrient delivery and waste disposal, immune response, and the nervous system, among others. Although we understand much about how these systems function normally or in the presence of foreign bodies, such as an implanted prosthesis, their relationships with one another in the presence of implantable prostheses remain poorly understood. In order to design an interface that will function as a part of the body, we need to understand how native systems interrelate and influence one another in the presence of said prosthesis.

A specific challenge within this systemic approach is understanding mechanotransduction. How do external stimuli impact cellular activity? Evidence suggests that mechanotransduction, heat, and other factors play a much greater role in gene and subsequent protein expression patterns than originally believed. In order to create a biopermissive interface that allows signaling for nutrient exchange, waste disposal, or immune response, we need to develop a greater understanding of all of the factors involved in gene expression and how those factors might influence one another in a multifactorial environment.

In order to acquire such knowledge certain technological hurdles must be overcome. Models must be developed that take into account multiple biological systems so that interfaces can be evaluated in a realistic environment, such as the 3-D liver system known as “liver on a chip.” Developing in vitro assays, in vivo model systems, and computational or virtual analyses using high-resolution imaging techniques, metabolic imaging, and appropriate algorithms will do much to promote our understanding of structural interfaces between man and machine.

Once biologically relevant in vitro systems are developed, high-throughput testing methods will need to be employed. In this way many different structural interfaces can be tested in a variety of scenarios by nondestructive means.

Task group 6 concluded that in order to develop these technologies and acquire systems-level knowledge, collaboration across diverse fields will be necessary. Chemists, structural and molecular biologists, and macromolecular scientists will have to share their expertise in order to understand what will be required to create a truly biopermissive interface.

Even after the ideal interface has been successfully defined, technological hurdles remain to actually building a living system. The interface will have to utilize biological substrates and integrate biological and synthetic materials, such as proteins and synthetic by-products. The actual fabrication and assembly methods will have to be able to simultaneously handle different size scales from nano through macro, and incorporate varying moduli and porosity into the device and interface.

Although these hurdles are significant, if they are overcome, the benefit to society would be enormous. Based on the osseointegration model alone, there are myriad of new or improved applications for smart interfaces—in-dwelling catheters, feeding tubes, and joint replacements. When these and other challenges are faced, almost any prosthesis will become a living part of the body.