INTELLIGENT SURFACES IN BIOTECHNOLOGY

SCIENTIFIC AND ENGINEERING CONCEPTS, ENABLING TECHNOLOGIES, AND TRANSLATION TO BIO-ORIENTED APPLICATIONS

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FOREWORD

THE BORDER BETWEEN LIVING AND NONLIVING

The interface between the living and the nonliving—between cells or tissues, and materials—is, and has been for many decades, an area of science and technology where there are more questions than answers. Materials science—and particularly materials by design—is difficult; understanding "life" is even more difficult. The interface between materials and life compounds the two difficulties but adds a further, complicating twist: Biology and biochemistry at the interface with synthetic materials is—almost by definition—abnormal, and it is not even clear how much of what we know of "normal biology" can be applied in this region. Molecules normally found in interfaces *in vivo*, whatever they might be, are missing; proteins adsorb to synthetic interfaces, assume abnormal configurations, denature, and trigger the complex cascades that lead to inflammation, clotting, and bacterial attachment. It is a very important area and a very difficult one. A small area of interface with the wrong properties can trigger a large biological response.

THE PROBLEMS OF STATIC SOLUTIONS TO DYNAMIC PROBLEMS

One of the difficult problems of biointerfacial science is that most materials are static, and all of biology (over some scale of time) is dynamic. Bone and teeth remodel; cells divide, function, age, and die; skin sheds. Many synthetic materials used in biology, by contrast, are static. In some circumstances, the nonadaptive character of materials seems not to be a problem. For example, we assume—for convenience—that cells grown in plastic dishes recapitulate many of the characteristics of the same types of cells in tissue. We also know, however, that replacement of a hip joint by a construct of metal and polyethylene is good for only, perhaps, two decades and then must be replaced. We understand some of the mechanisms of failure of the synthetic joint but not others.

A concept that seems very attractive in attacking the problem of biointerfaces is that of "adaptive," or "intelligent," or "self-healing" materials. The goal is the development of materials that somehow replicate and mimic the ability of tissues and biological materials to adapt and renew. There is, however, an essential difference between "dynamic" materials and biological systems. The former are typically designed to respond to changes in environmental conditions by a change in structure and properties, and operate at, or close to, equilibrium. The latter are dissipative: Remodeling of bone involves the dissolution of existing bone by osteoclasts and redeposition of new bone by osteoblasts; both require ATP and metabolism. We do not, at the moment, know how to build dissipative biomimetic materials and structures that exist in a stable, out-of-equilibrium state, and the question is, thus, "how far can one go in building a biocompatible interface between synthetic and biological systems using the currently available tools of materials science?"

One interesting class of materials that is designed to be out of equilibrium, but is not truly dynamic in the sense of biological tissues and structures, is that intended for biodegradation and for applications such as drug delivery. These systems, rather than operating on the basis of remodeling requiring the production of ATP through metabolism, are designed to be out of equilibrium on the basis of a reactive structure. Poly(lactic acid) (PLA), for example, is thermodynamically unstable with respect to lactic acid in biological fluids, and the interface between PLA and tissue or blood is constantly renewed by hydrolysis and erosion of the polymer. In other materials and structures, the tendency of the interface to initiate unwanted biochemical processes can sometimes be accommodated by other forms of energy dissipation: For example, the tendency of a metal stent to initiate clotting in the blood passing over it is at least partially mitigated by fluid shear from this blood (which sweeps away clots) and by the slower, but also dissipative, processes that allow epithelial cells to cover the material of the stent.

WHAT IS IT THAT MAKES FOR COMPATIBILITY?

So, what makes for biological compatibility? In general, the answer is "We do not know." Although we accept cells growing in culture dishes as being useful models for studies in cell biology, we know that these cells are not fully normal; we believe (but in general cannot prove) that the compromise between the biologically abnormal environment of the culture dish, and the convenience and acceptable expense of the culture dish, justifies the use of plasticware in cell biology. In research biology, many compromises are easy to accommodate because the consequences of failure are either small or hidden. *In vivo*, and especially in humans, the stakes are much higher, and biomaterials science is still severely limited by fundamental issues in compatibility. The field still needs new ideas.

"INTELLIGENCE" IN SURFACES AND INTERFACES

Can one make "intelligent" or "adaptive" surfaces for use in biomaterials science and bioengineering? The answer is clearly "yes," but with clear caveats.

Artificial hips and knees do not fully replicate natural structures; artificial lenses allow sight but have limitations; artificial teeth work well but not perfectly; surfaces in contact with blood often remove platelets and initiate clotting. Almost all synthetic materials, over time, induce some level of inflammation and fibrosis. The successes of biomaterials science in producing acceptable solutions to the problem of biocompatibility have been remarkable, but there remains enormous opportunity for improvement. One possible direction is toward intelligent surfaces and interfaces.

"Intelligence," in this sense, is a word that is used flexibly. An "intelligent material" is one whose structure—in a particular environment—can change in a way that autonomously optimizes its performance in some application. An "intelligent child" might be one who plays Bach by the age of five. The same word "intelligent" is used in both sentences, but with very different meanings. Materials cannot have "intention," and do not sense, control, and change even as a so-called intelligent machine might. The difference between "intelligence" and "adaptability" as applied in materials science might not be important; but since the current generation of "intelligent materials" is very close to the starting point in moving from completely inert, static structures to structures optimized for performance in complex biological environments, and capable of responding to changes in them, keeping the difference between intelligence and adaptability in mind is useful in understanding how large the gap between capability and ultimate need, and how great the opportunity for new science, is in this area.

MATERIALS BY DESIGN: REDUCTIONIST SCIENCE, OR EMPIRICISM AND ENGINEERING?

In searching for solutions to difficult problems, there are always the "top-down" and "bottom-up" approaches. In one, one hopes to understand the fundamental mechanisms by which synthetic materials and biological molecules and systems interact and use that understanding in the rational design of synthetic materials having intended properties. In the second, one relies more on intuition (sometimes guided by knowledge from other areas) and empiricism to develop useful technology, even if the outcome is that the technology is not completely understood. "Biointerfaces" are still closer to empiricism than to fundamental science. Even in what appears to be the simplest cases—for example, the adsorption of proteins on the surfaces of polymers and self-assembled monolayers—and although there are quite useful empirical solutions to the design of, for example, nonabsorbing surfaces, the mechanistic basis for their activity is still not completely understood. In more complex cases—for example, the design of nonclotting surfaces for contact with blood—there is still an enormous amount to be learned even about the steps that initiate clotting.

TRADING INFORMATION ACROSS A BORDER

One of the most challenging of problems in the interfacial science of biomaterials is that of sensing or actuation. "Information" in synthetic systems is typically carried in the form of electrical current or voltage in electrically conducting wires, or as light. Information in biological systems generally takes the form of molecules interacting with receptors, or of concentration gradients in ions (or of electrochemical potentials due to these gradients) across cell membranes. It remains a challenging problem to translate between these two fundamentally different currencies. The problem is particularly difficult when the biological signal to be detected is itself problematic. "Biomarkers" for use in the diagnosis and management of disease represent a specific example of high current interest. It is unquestionably correct that biomarkers exist for some diseases: For example, the concentrations of glucose and of glycosylated hemoglobin in blood are both biomarkers relevant to the management of diabetes. For many diseases, however, the basic biology of biomarkers remains uncertain or unvalidated: The recent example of prostate-specific antigen (PSA), which has gone from "biomarker for early prostate cancer" to "clinically marginally useful, or perhaps harmful, bioanalysis" over a 20-year period, is an example. Although the field of biomarkers will certainly advance in the next years, the basic philosophy of early detection and management of disease through simple analyses (or even through a more complex recognition of patterns in multiple analyses) is still a work in progress. That uncertainty aside, however, building the technological base that allows the design and fabrication of the interfaces between electronic or photonic systems and biological systems will clearly be useful, in research and ultimately in the clinic, and remains a complex and challenging problem.

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