

Review

In Vivo Chemical Sensing—Opportunities and Challenges

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Advances in science and engineering bring us closer to the day when sophisticated mechanical devices will be available to replace damaged or malfunctioning human organs. Prototype optoelectronic devices are being evaluated as replacements for damaged retinas (1–3) and tremendous strides have been made in the development of cochlear implants to enhance certain types of hearing disorders (4–5).

Many organs targeted for bionic replacement utilize the human body's exquisite chemical sensing capabilities. Artificial organs must possess equally reliable chemical sensing technologies in order to mimic critical organ functions. *In vivo* chemical sensors must operate reliably, rapidly, and selectively over extended periods under harsh conditions. Proper organ function demands both temporal and spatial analytical information that can only be provided by a dedicated chemical sensing unit linked intimately with the bionic device.

One example is the development of an artificial pancreas. In the early 1960's, Leland Clark first demonstrated the glucose biosensor (6) and subsequently the artificial pancreas was proposed as a means for controlling glycemia. The basic idea is to implant an insulin delivery system along with a continuously operating glucose sensor. The sensor supplies real-time blood glucose information to a microprocessor-controlled insulin delivery pump so that the ideal amount of insulin is administered in real-time. Professor Clark's vision sparked considerable research activity over the subsequent four decades.

And yet today, the artificial pancreas has not been realized. Over the years, excellent pump technology has been developed and indwelling insulin-delivery pumps are now available. In addition, elaborate algorithms have been proposed for controlling insulin delivery on the basis of real-time glucose concentration information. Unfortunately, the necessary glucose sensing technology is not yet available. The lack of a reliable, *in vivo* glucose sensor is currently the single biggest impediment to the development of an artificial pancreas.

Three general approaches are possible for continuous chemical sensing within the human body. First, individual chemical sensors can be implanted within the body and used to probe the surrounding chemical environment. Alternatively, an automated sampling device can be used to collect a representative sample from within the body and then a device located outside the body analyzes this sample. Finally, the necessary chemical information can be obtained noninvasively by analyzing light that is transmitted through the body. Each approach offers unique opportunities and challenges.

To date there is no commercially available implantable chemical sensing device (for glucose or any other analyte) that is capable of long-term operation within the human body. Researchers in the field generally use one year as a benchmark for the period that an implant must operate in order to be practical from a medical standpoint. Although various laboratories have described prototype glucose biosensors that func-

tion continuously for several months within animal models (7,8), none of these devices performs over an entire year with sufficient robustness and reliability for routine clinical applications. Presently, it is not yet possible to manufacture chemical sensors of any type for long-term implantation. In fact, the feasibility of short-term sensor implants (*i.e.*, three to seven days) has only recently been demonstrated (9–12) and further research is required before such devices will be commonplace (13, 14).

Chemical sensors implanted within the human body must accommodate a changing and hostile environment. Long-term implants must be biocompatible, that is they must be able to function accurately in spite of biologic responses designed to isolate the implant. Both chemical and physical strategies are under development to minimize the extent of such biologic responses and enhance the biocompatibility of implanted chemical sensors (15–17). *In situ* calibration, reagent stability, and toxicity are other critical issues for long-term implants.

The immense challenges associated with operating a chemical sensor continuously under *in vivo* conditions and recent advances in sampling schemes have driven interest in alternative configurations where a sample is first removed from the body and then analyzed automatically. The key is to collect clinically relevant samples in a painless and non-intrusive manner. For example, numerous procedures have been reported for collecting small volumes of interstitial fluid, and the corresponding glucose concentration in these samples can be related to blood glucose, thereby providing the information necessary for glycemic control (18–22). Such sensing configurations are termed minimally invasive when the procedure used to collect the sample is both painless and non-intrusive. Although possible for short-term discrete measurements, minimally invasive strategies are questionable for long-term applications given the inconveniences associated with physically handling clinical samples.

Noninvasive analytical measurements involve passing a harmless band of light through the body and then extracting the analytical information from the resulting spectra. Nothing is placed inside the body and there is no need to acquire a sample for the analysis. Hence, issues of biocompatibility and sample handling are irrelevant. Pulse oximetry is an example of a noninvasive measurement scheme that provides *in vivo* chemical information (blood oxygen saturation) in a continuous, sample-free, and painless manner (23). The key is to use a region of the electromagnetic spectrum that can propagate through the human body and that contains chemical information. Near infrared spectroscopy meets these requirements, as human tissue is relatively transparent to wavelengths of light from 0.6 to 2.5 microns and spectroscopic patterns between 0.6 and 2.5 microns are unique for many molecular species. In fact, many substances can be distinguished and quantified by near infrared light, including proteins, glucose, cholesterol, and urea (24–26). Success requires that the optical information be collected with a sufficiently high signal-to-noise ratio so that molecular information can be reliably distinguished from the underlying noise and matrix variation.

Regardless of the approach, considerable research is needed to overcome the many challenges faced when attempting to monitor *in vivo* levels of selected chemical species both continuously and over extended periods. Advances in materials and instrumentation will be necessary to address critical issues of biocompatibility and measurement signal-to-noise ratios. Perhaps completely new directions are warranted, such as the use of nano-fabrication and micro-machines to construct tiny, implantable analytical laboratories where sample collection is automated and the required analytical chemistry is performed within a sealed and controlled environment. For all these approaches, implanted sensors, minimally invasive devices, noninvasive measurement schemes, or implanted laboratories, unique methods must be developed to link the collected chemical information to the functioning element of the artificial organ. Success will offer mechanical cures for many diseases.

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