Institute Lecture

# Integrated Medical Feedback Systems for Drug Delivery

**Adam Heller**
Dept. of Chemical Engineering, The University of Texas, Austin TX 78712

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*Drugs are now administered at frequencies and doses based on averages optimized for large populations. Because the optimal frequency and dose for an individual differs, transiently or permanently, from that of a population's average, the dosing is necessarily suboptimal. Feedback loop-based individualized integrated medical systems, comprising an implanted sensor, battery, amplifier, processor, and actuator are now in use in cardiac pacemakers and defibrillators. Drug-delivering medical feedback loops, comprising miniature sensors and drug pumps, would individualize, and thereby improve the effectiveness and safety of drugs. Their sensor would continuously or frequently monitor the effect of the drug and adjust, through a medical control algorithm, its flow to the minimum necessary for effectiveness, reducing thereby side effects and improving the success rate of experimental drugs. The pace of integration of the drug delivering feedback loops depends on the availability of proven miniature components and of medical control algorithms.* © 2005 American Institute of Chemical Engineers *AIChE J,* 51: 1054–1066, 2005

## Longevity and the Flow of Capital into Medical Devices

People, like cars, live longer when spare parts are available and require more spare parts as they age. This amplified loop underlies not only the longer lives of people, but also the growth of sales of medical devices. In the recent period of economic stagnation or downturn in many parts of the world, medical device sales grew at an annual rate of about 10% and in, 2003, a year of economic recovery, they accelerated to 13%, reaching about $200 billion/year. The rapidly growing segments of the medical device industry include diagnostic systems, structural and mechanical devices, drug delivering systems and electronic control systems. For each, annual sales exceeded $10 billion. Many people now consider access to medical devices, even devices that did not exist a decade ago, as a societal right. As their usage expands, their costs are dropping, and as the devices become more affordable, their usage expands. Medical devices have lowered the cost of health care by facilitating treatment of diseases and by preventing or alleviating diseases and their complications. Surgeries that were considered a decade ago as major and required extended hospitalization are now day surgeries.

Venture capital is flowing into companies developing new medical devices. Venture capitalists are obviously not adverse to risk-they live with it and thrive on it. Yet many consider the risks of investing in drug development as intractable. The difficulty of assessing risks of drug development is exemplified by the recent $50 billion loss suffered by investors in cyclooxidase-2 inhibitor producers Merck and Pfizer, after the two pharmaceutical manufacturers obtained unexpected adverse information about their products Vioxx™ and Celebrex.™ The preferred flow of capital, particularly of venture capital, into medical devices, feeds the industry's growth and further accelerates the introduction of new, better and more affordable devices.

## Integrated Medical Systems and Medical Feedback Loop

We are in the midst of a gradual process—not a revolution—in which devices, which I shall call *integrated medical systems,* are changing patient treatment, including the administration of drugs. The systems are likely to increase the rate of success of developmental drugs and reduce the side effects of available

A. Heller's e-mail address is heller@che.utexas.edu.
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drugs. Chemical engineers are particularly well trained in design, process control, materials, particularly polymers and their processing, and electrochemical power source engineering, all of essence in integrated medical systems. The feedback loops of the systems are related to the feedback loops controlling the operation of chemical plants. They are, however, wearable and much smaller than those controlling the plants. Examples of integrated medical systems already in use include the cardiac pacemaker and defibrillator. In the pacemaker, an oxygen sensor measures the partial pressure of $O_2$ in blood and feeds the information to an electrical pulse-delivering actuator, which paces the heart such that its rate is slow when $O_2$ consumption is low in a resting or sleeping wearer, but is rapid when $O_2$ consumption is high in an exercising wearer. In the defibrillator, a sensor detects a deviation from normal beating of the heart. It signals an actuator, which delivers a strong electrical pulse to the heart, restoring its normal beating.

In a future integrated medical system for diabetes management, a subcutaneously implanted glucose sensor-amplifier-transmitter will radio a signal to the receiver-processor-actuator of an insulin-pump when the glucose concentration is rising, or has already risen, above a physician-set limit, and the pump will deliver a medical algorithm-defined insulin dose. A related system could reduce the risks of cardiac arrhythmia- associated thrombosis and stroke. Here a pressure transducer would detect irregular pulse- frequency and pulse-shape, and small, incremental, medical algorithm-defined, doses of a blood clotting-inhibitor, like aspirin or coumadin, would be delivered to maintain the clotting-time in the range where the risks of thrombosis and stroke on one side, and of internal bleeding on the other, are small. Such a system would require the development of a yet unavailable implantable clotting-time monitor.

The first of the integrated drug-delivering feedback loops, considered here in detail, will be a diabetes management system. Its insulin pump is now available. Its integrated calibrator, built on *FreeStyle* ™, the painless, accurate and only 300 nL sample requiring blood glucose monitor of TheraSense (now Abbott Diabetes Care) is in use. Its implanted, miniature and reliable continuous glucose monitor, based on the electrical connection ("wiring") of glucose oxidase through an electron conducting hydrogel to a circuit, is likely to be available soon.

## Component Availability and Pace of the Introduction of Integrated Medical Systems

Neither entrepreneurs, nor established manufacturers, can afford the commitment of resources, or the undertaking of the risk, of developing more than one, or at most a few, components of a new integrated medical system. The entrepreneur or manufacturer-added component is usually system specific, for example, the glucose sensor of the diabetes management system. For the rest of the system, entrepreneurs and established manufacturers depend on purchased components. Their availability often defines the pace of integration. The dependence is analogous to that experienced in the evolution of silicon integrated circuits (ICs). The solid-state components of ICs were in use well before their integration. The components were integrated because many electronic systems had similar subsystems. For example, home entertainment systems, computers and communication systems had common memory, processors, clock and display-driving subsystems. Each of these became eventually an IC, then a block on a further integrated IC. The medical systems also share subsystems. For example, the drug metering subsystems comprise a battery, an actuator, a drug reservoir, a pump and implanted tubing. The subsystems of implanted insulin pumps for diabetes management and of pain-relieving drug pumps for chronic pain management are similar. The battery-amplifier-transmitter-antenna subsystem of the sensor-transmitter of the continuous glucose monitor, could also serve in monitors of pressure, flow, temperature or the concentrations of chemicals. The commonality of the subsystems is likely to increase the volume of their production and reduce their cost.

The early silicon integrated circuit manufacturers had to overcome extreme difficulties in controlling production yield and cost, reliability, reproducibility, and building customer confidence and demand. Only those companies that resisted premature over-integration survived. Road-maps, such as the map defined by Intel's Moore's Law, became standards of what is timely and what is premature. The integrated medical systems are introduced only as fast as the state of the development of their components or subsystems allows, and their developers are facing a similar issue, of distinguishing between the timely and the premature. The integration of components in subsystems requires proven miniature components, and integration of the subsystems in integrated disease management systems requires proven miniature subsystems. A diabetes management system, referred to as an "artificial pancreas", was proposed as early as 1972[1] and a feedback loop, controlling glycemia (blood glucose concentration), called the Biostator® GCIIS (Glucose Controlled Insulin Infusion System), was built in 1977 by the Ames Division of Miles Laboratories [2,3]. Although it yielded important information on algorithms for the controlling blood glucose concentration in diabetic people, it was not wearable and only a few hundred units were sold. Today, miniature processors, amplifiers and transmitters are available at low cost and miniature pumps, sensors, and actuators are becoming increasingly available. Their increasing availability converges with advances in process control and in medicine, on which the reported medical control algorithms for anesthesia[4] and the management of diseases, [5,6] particularly of diabetes,[7-15] were built.

## Anticipated Impact of the Integrated Medical Systems on the Success Rate of Developmental Drugs and on the Safety of Already Approved Drugs

Because of their feedback loops, the integrated medical systems are likely to improve the now low success rate of developmental drugs, as well as the safety of existing drugs. Drugs are labeled to show contraindications, the labels identifying groups of people who must not use the drug. However, users are often unaware that they belong to the excluded group, and pharmaceutical companies are not fully able, in spite of their best efforts, to identify all of the groups that must not use the full dose, or occasionally any, of a new drug, as has been the case for the cyclooxidase-2 inhibitors Vioxx™ and Celebrex™. Furthermore, members of the main user group differ, permanently or transiently, in the relative concentrations of the drug in the targeted organ and in the adversely affected organ. The metabolism of a drug is affected by many variables,

including exercise, age, sleep and meal habits and genetic make-up. Hence, useful drugs appear to be less safe than they would be if their effect was continuously or frequently monitored and its flow would be adjusted for efficacy to the necessary minimum by the feedback loop. The loop would tailor the dose to the individual, stopping delivery at the minimal effective dose, decreasing the likelihood of adverse effects. In the language of chemical engineering, the presently practiced nonrobust drug administration, without frequent monitoring and frequent adjustment of the drug influx, would be made more robust by the loop.

## Diabetes and TheraSense

According to the World Health Organization, diabetes affected in 2000, 177 million people or about 3% of the people of the world. [16] According to Butterfield,[17] there are 24,000 new cases of diabetes-caused blindness each year in the US. Diabetes accounts for 40% of the new dialysis patients and it is the most frequent cause of lower limb amputation. More than 56,000 limbs are lost to diabetes per year. The per capita medical expenditure incurred per diabetic person per year is about four times that for nondiabetic person. The annual cost of diabetes in the US is about $98 billion, and accounts for one of every four Medicare dollars.

The number of blood glucose analyses, performed by self-monitoring diabetic people, dwarfs the combined numbers all other chemical, biochemical, bacteriological and medical analyses. More than 6 billion glucose analyses are performed annually by self-monitoring diabetic people.

My son and senior partner, Ephraim Heller, and I founded TheraSense in 1994 to alleviate the pain and the suffering associated with diabetes. Our contributions to the technology of the company are described in its 51 issued US Patents (Table 1), the first 10 of which were licensed from the University of Texas and were assigned to E. Heller & Co., the predecessor of TheraSense.

The contributions to science were reported in about 100 peer reviewed publications, most from the University of Texas. In 2 years, by mid 1996, we demonstrated the feasibility of glucose analysis in a painlessly obtained 300 nL sample of blood, and by 1996 we also had a research prototype of a wearable continuous monitor of glucose, with a miniature subcutaneously implanted sensor. In mid 1996 TheraSense was capitalized by venture funds, and at the end of the year Ephraim and I hired Mark D. Lortz as the company's CEO. The US Food and Drug Administration approved the monitor, shown in Figure 1, in 2000.

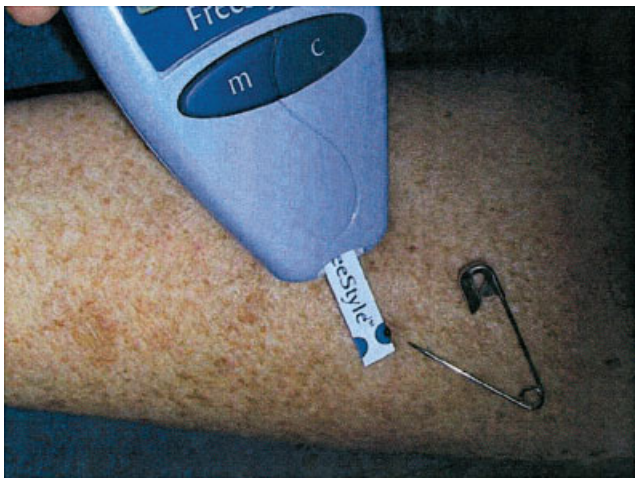


**Figure 1. The painless 300 nL blood sample utilizing thin-layer micro-coulometric blood glucose monitor for diabetes management, introduced in 2000.**

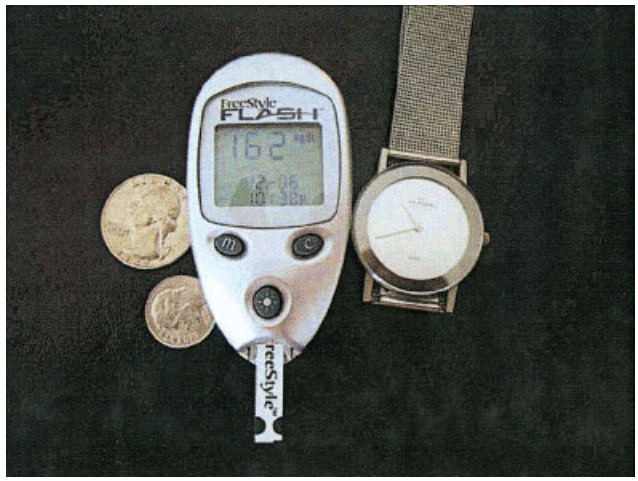


**Figure 2. *FreeStyle™ Flash*, the small painless glucose monitor of TheraSense/Abbott Diabetes Care.**

The company went public in the fall of 2001, raising $120 million. In 2002, after the painless blood glucose analyzer meaningfully improved the lives of many diabetic people and after the initial clinical trials of the continuous monitor were successful, Ephraim left TheraSense to found AngioScore, a company producing angioplastic balloons. By 2003, Therasense had a 7% market share in the $3 billion/year glucose monitoring market and was growing approximately at 2% per year. In 2004 the company was acquired by Abbott Laboratories for $1.2 billion. It is now the major component of Abbott Diabetes Care, is expanding rapidly, and is headed by Edward J. Fiorentino. It remains headquartered at the TheraSense campus in Alameda, CA, within a block of its original site. My work was completed, and I left the company in 2004.

## Accurate and Painless Monitoring of Glucose in 300 Nanoliters of Blood

The first product that TheraSense brought to diabetic people was an accurate and painless blood glucose monitor, *FreeStyle*™. [18] (Figures 1 and 2) The monitor serves also as the calibrator of the implanted, continuous glucose monitor (Figure 3). It requires only 300 nL of blood, a sample smaller than that taken by a mosquito. By greatly reducing the blood volume required for the analysis, we eliminated the pain associated with the piercing of the skin. The mass manufactured test strips comprise a microcell, in which glucose is selectively electrooxidized, and the completion of the oxidation is coulometrically monitored. The monitor is the first mass-produced ($>10^6$ units/day) submicroliter fluidic device. Its core is a fast and accurate thin layer microcoulometer, in which glucose is electrooxidized selectively in an enzyme-catalyzed process. The

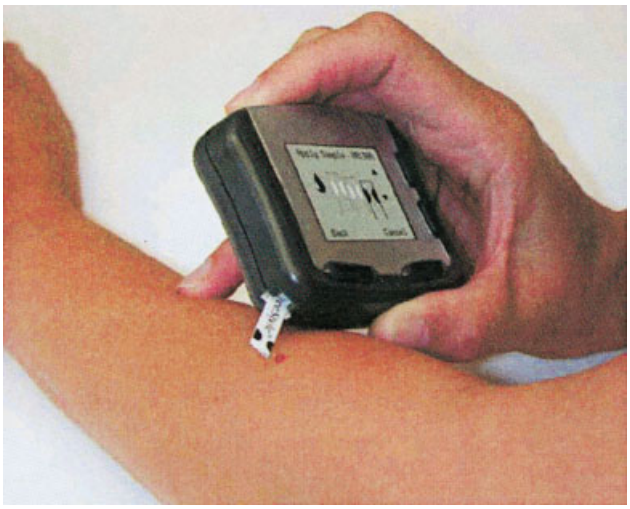

**Figure 3. The integrated RF-receiver-display-calibrator of the investigational continuous glucose monitor of TheraSense/Abbott Diabetes Care.**

The picture shows the calibration process, performed on capillary blood, using the integrated glucose meter. (From Ben Feldman, Abbott Diabetes Care, Diabetes Technology Meeting, Philadelphia, PA October 29, 2004).

coulometer measures the charge produced upon the electrooxidation of the glucose in a 50 $\mu$m thick blood film. Because of the short diffusion length, the oxidation takes only a few seconds, and because the outcome of coulometry does not depend on kinetic parameters like temperature, viscosity or enzyme activity, the assay is accurate. A computerized, PDA-like, communicating version of the painless 300 nL microcoulometric blood glucose monitor was introduced in 2002, and a miniature version, the world's smallest blood glucose monitor (Figure 2), was introduced in 2003. Because the monitor is not only painless and small, but also accurate, it will be part of the integrated RF receiver-display-calibration unit (Figure 3) of the continuous monitor (Figure 3).

## Continuous Monitoring of Glucose with a Miniature, Subcutaneously Implanted Sensor

Diabetic people are concerned about extreme hypoglycemia, which can result in coma and even in death. To reduce the risk, they maintain higher than normal blood glucose concentrations. Maintenance of glucose concentrations higher than those recommended for prolonged periods increases the risk of diabetes complications, including circulatory disease, leading to loss of limbs, kidney failure, rethinopathy and neuropathy. The 1983 – 1993 Diabetes Control and Complications Trial of the NIH/National Institute of Diabetes and Digestive and Kidney Diseases established that by keeping their blood glucose concentration close to normal, through frequent monitoring and insulin injection, diabetic people drastically reduce the risk and the progression of diabetes complications.[20] Ideally, diabetic people would monitor their glucose concentration continuously.

At the University of Texas in Austin, later at TheraSense, we undertook the development of an accurate, reliable, miniature, continuous amperometric glucose sensor based on the electrical wiring of glucose oxidase. We built,[21-23], optimized for stability, [24] tested in the dog[25], in the rat [26-30], in my son Ephraim, (who was at the time the President of TheraSense) and in myself, then in collaboration with Prof. Philip J. Raskin MD, in volunteers admitted to the Clinical Research Center of the University of Texas Southwestern Medical Center, and in a mobile, very active young Type 1 diabetic chimpanzee (Figure 4)[19] the research prototype of our wired glucose oxidase sensor. The results were so encouraging that TheraSense undertook a large and costly project to engineer, clinically evaluate and manufacture the system.

The engineered system of TheraSense (Figure 5) has physician-set hypoglycemic (low sugar) and hyperglycemic (high sugar) alarms, warning not only of actual, but also of impending hypoglycemia or hyperglycemia. Like the earlier research version, it is based on the electrical "wiring" of glucose oxidase.[31-33] Its core component is a miniature subcutaneously implanted amperometric glucose sensor, printed on a plastic strip, which is nearly painlessly replaced by the user every 3 days. Its other components are a mechanical, spring-loaded inserter; a battery-powered amplifier-transmitter, with leads contacting the implanted sensor; and a battery powered integrated calibrator-receiver- processor- display, carried in the pocket or purse, shown in Figure 3. It displays the glucose concentration and the direction of its change.

## The Science: Making Water an Electron Conductor and the Electrical Wiring of Enzymes

In 1987 Yinon Degani and I, working at Bell Laboratories, discovered that the protein of the enzyme glucose oxidase (GOx), which like all other proteins is an electronic insulator, can be converted into an electron conductor.[34,35] GOx catalyzes the oxidation of glucose by oxygen to gluconolactone. It has deeply buried flavin adenine dinucleotide ($FAD/FADH_2$) redox centers. Because they are surrounded by an electrically insulating protein, they are not electrooxidized or electroreduced on an electrode. To make the protein conduct electrons, we bound to it fast redox centers, which exchanged electrons when approaching each other. The redox centers of the now electronically conductive GOx were reduced by glucose to $FADH_2$ (Eq.

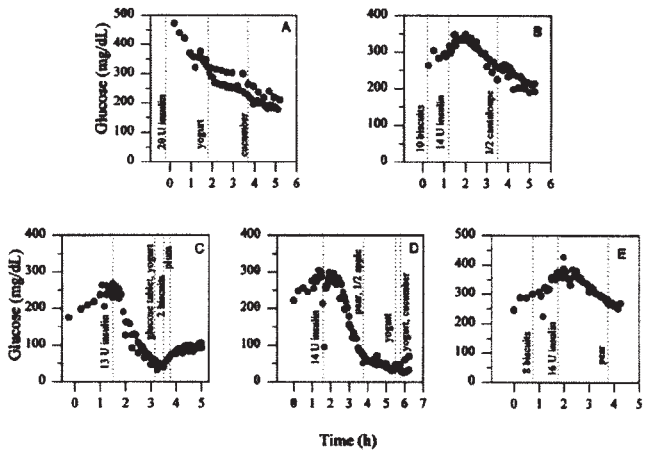


**Figure 4. Results of blood glucose assays [● ]and the readings of the subcutaneously implanted monitor implanted in a type 1 brittle diabetic chimpanzee [○]. [19]**

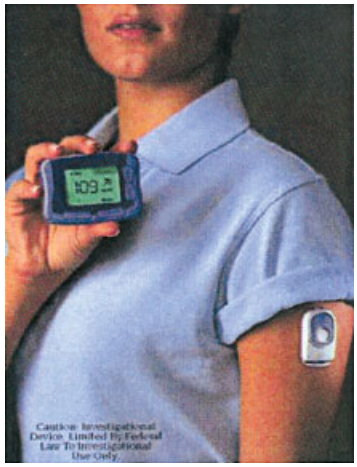

**Figure 5. The investigational subcutaneously implanted continuous blood glucose monitor of TheraSense, based on the electrical wiring of the enzyme glucose oxidase. From Ben Feldman, Therasense (now Abbott Diabetes Care) Diabetes Technology Meeting, November 6-8, 2003, San Francisco, CA.**

1), and were electrooxidized at electrodes (Eq. 2). Thus, the electrooxidation of glucose was

$$\text{GOx-FAD} + \text{glucose} \rightarrow \text{GOx-FADH}_2 + \text{gluconolactone} \quad (1)$$

$$\text{GOx-FADH}_2 \rightarrow \text{GOx-FAD} + 2\text{H}^+ + 2\text{e}^- \quad (2)$$

catalyzed by the modified enzyme, and its turnover translated the glucose flux to an electrical current.[34,35] To devote my work to the interfacing of enzymes and circuits, I moved to the University of Texas, where we developed, between 1988 and 2004, a series of electron conducting redox hydrogels, which electrically wired the reaction of enzymes to electrodes.[36-53] Because of the small entropy of mixing of the macromolecular enzymes and their wires, they phase-separated. The separation was prevented by forming electrostatic adducts of the polyanionic enzymes and wires, which we designed to be polycations.[47,54,55] Following the crosslinking of the electrostatic adducts on the electrodes, the now nonleachable redox centers of the 3-dimensional (3-D) hydrogel-enzyme matrix were reversibly electroreduced and electrooxidized. This extended the electrocatalysis from the 2-D planes of electrode surfaces to the 3-D volumes of the electron conducting wired enzyme gels.[31,32,37,38,51] The enzyme wiring hydrogels were highly permeable to water-soluble salts and also to water-soluble reactants and products, like glucose and gluconolactone. With more enzyme molecules turning over and delivering electrons in the 3-D gel than at the 2-D electrode surface, the reaction rates per unit electrode area, or current densities, increased to about 1 mA $cm^{-2}$.[32,36,37,45,46,51-53,56,57]

Figure 6 shows the elementary steps of electron transfer, underlying the electronic conductivity of the redox hydrogels.[41,46,49,58] The electrons propagate through collisions of electron rich (reduced) and electron deficient (oxidized) redox centers, tethered to the backbones of polymers.[41,46,52,53,57] High apparent electron diffusion coefficients are reached when the structures of the pendant reduced and oxidized complexes are similar, so there is little or no spatial reorganization of atoms when an electron is exchanged between a reduced and an oxidized center. [59] Long and flexible tethers increase the rate of effective electron transferring collisions and thereby the apparent electron diffusion coefficients.[52,53,57] When the tethers are long and flexible, the amplitudes of the redox centers are large, and the electrons diffuse as rapidly as their charge-balancing ions.

Because of the 3-dimensionality of the catalytic hydrogel films on the electrodes, the number of electrically connected redox enzyme molecules per unit area can be large enough for the reaction rates, meaning the currents, to be mass transport limited rather than being limited by electrode kinetics. When this is the case, the fluxes, and, therefore, the concentrations, of glucose of other substrates of redox enzymes are selectively transduced to electrical currents.[31,32] While the transduction of biochemical fluxes to electrical currents has been practiced for many years,[60,61] it required use of water-soluble, and, therefore, water-extracted, electron carrying redox couples, which diffused between the enzyme and the electrode. The wiring of enzymes obviated the need for such water-extracted diffusional electron carriers, and made the wired enzyme electrodes useful in flow systems[62] and *in vivo*.[21,23,25,27,28,30,33]

## In-vivo Calibration and Validation of Accuracy

In integrated medical systems the sensors must be well calibrated. They must either maintain their *ex vivo* calibration after implantation, or must be conveniently and rapidly calibrated *in vivo*. Validation of their calibration *in vivo* also requires either the maintenance of their *ex vivo* pre-calibration, or easy confirmation of their accuracy after *in vivo* calibration. Any calibration requires at least two data points, as well as knowledge of the function connecting the points. In the case of

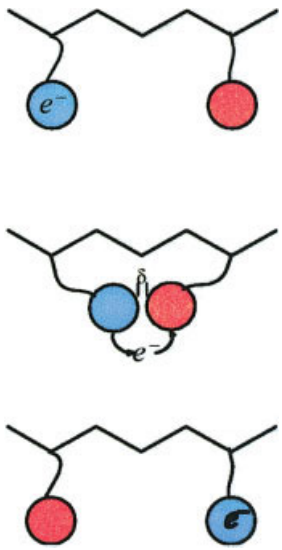


**Figure 6. Electron conduction in redox hydrogels results in electron transfer between reduced and oxidized redox centers tethered to the backbone of polymers.**

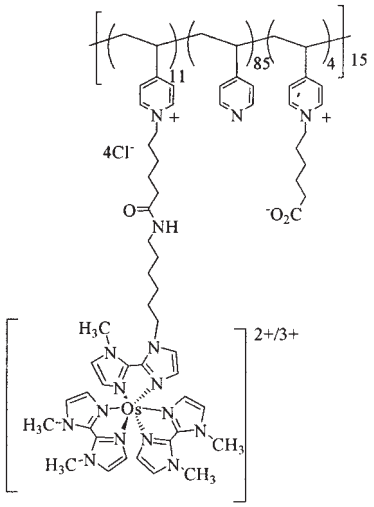

**Figure 7. A "wire" of glucose oxidase, enabling the electrooxidation of glucose at - 0.1 V vs. Ag/AgCl at a current density of 1.3 mA $cm^{-2}$.**

The $5.8 \times 10^{-6}$ cm $^{-2}$ s $^{-1}$ apparent electron diffusion coefficient in the hydrogel formed of the crosslinked polymer approaches the diffusion coefficient of ions, when these are about as large as the redox complexes, in water. The mers are randomly distributed in the polymer. [52]

the implanted glucose sensor, calibration would require at least two measurements, separated by a time interval in which the glucose concentration changes substantially. However, if it is true that the signal is nil when there is no glucose in the solution, then the null point is valid for the calibration. In this special case, a single analysis of the glucose concentration in a withdrawn blood sample, for example, with the calibrator integrated in the receiver-processor (Figure 3), suffices for the calibration. If the system is already calibrated, the assay of one blood sample suffices for the validation of its performance.[21,23,27,28] If a one-point calibration were not feasible, the diabetic user would have to obtain a blood sample when his/her blood glucose concentration was low, then a second point when it was high. The two events would be temporally separated in an unpredictable manner, making the calibration difficult.

In the amperometric monitoring of glucose *in vivo*, the calibration is particularly simple when at zero glucose concentration the current is nil, and the signal increases linearly with the concentration of glucose. This condition is met when the output of the sensor does not vary with the concentration of any biological constituent other than glucose. The near perfect selectivity for glucose can be achieved through design of the wire of glucose oxidase. [21-23,27,28,45,63,64]

In our preferred gels, the redox centers are $Os^{2+}/Os^{3+}$ complexes, tethered to modified poly-4-vinylpyridine backbones.[46,49,51,65] A redox polymer, optimized for the electrooxidation of glucose, [52,57,66] is shown in Figure 7. The -0.26 V vs. Ag/AgCl potential of its tris-*N,N*'-dialkyl-2,2'-diimidazole $Os^{2+/3+}$ redox complex is tailored, by the design of its ligands, to provide for rapid glucose electrooxidation of the $FADH_2$ centers of glucose oxidase at a potential, as reducing as - 0.1 V vs. Ag/AgCl. At such a reducing potential the easy to oxidize constituents of the subcutaneous interstitial fluid, like urate and acetaminophen (Tylenol$^{TM}$), are not electrooxidized, and the measured current represents exclusively the electrooxidation of glucose. Additionally, fast electron diffusion is provided by the 13 atom long tether linking the redox complex to the polymer backbone, and the charge of is adjusted by quaternizing backbone pyridines with alkyl-carboxylate functions. The apparent electron diffusion coefficient of the crosslinked film of this polymer is $6 \times 10^{-6}$ $cm^2$ $s^{-1}$, [52,57] the highest for a redox hydrogel.

The wiring of GOx with this polymer allows glucose electrooxidation current densities as high as $1.1 \times 10^{-3}$ A $cm^{-2}$.[57,67] Because electrooxidation and electroreduction currents as small as $10^{-10}$. Amperes (A) can be monitored with simple and inexpensive potentiostats, glucose-sensing microelectrodes can be built [68,69] by coating the 7 $\mu$m dia. tips of carbon fibers with the wired GOx hydrogel. The high current density also underlies the feasibility of miniaturization of the subcutaneously implanted glucose sensing electrodes. The research prototypes of the implanted sensors (Figure 8) were made of 250 $\mu$m dia. polyimide insulated gold wires. Their wired GOx electrocatalyst was coated with a glucose transport limiting film to extend their linear range to the required 2-30 mM encountered in diabetes, [21,22] then over-coated with a bioinert film, which reduced biofouling and the recruitment of glucose-consuming and oxidant-generating neutrophils.[70,71] To stabilize the implanted electrocatalytic hydrogels during their intended 3 day continuous operation against being sheared off in contracting muscles, the gels were crosslinked to form a tough, leather-like film.[65] The counter-reference electrode was an on-the-skin, standard EKG Ag/AgCl electrode. The TheraSense-engineered implanted sensor, which incorporates the

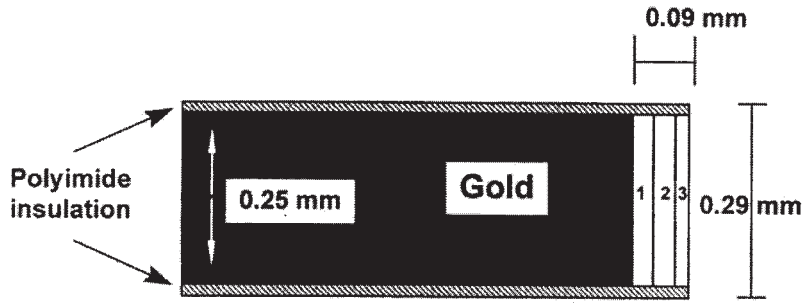


**Figure 8. Structure of the 2000 version of the continuously glucose monitoring subcutaneously implanted "wired" GOx electrodes.**

(1) Wired GOx sensing layer.(2) Glucose transport controlling membrane, and (3) Bioinert poly(ethylene glycol) film. [22,23]

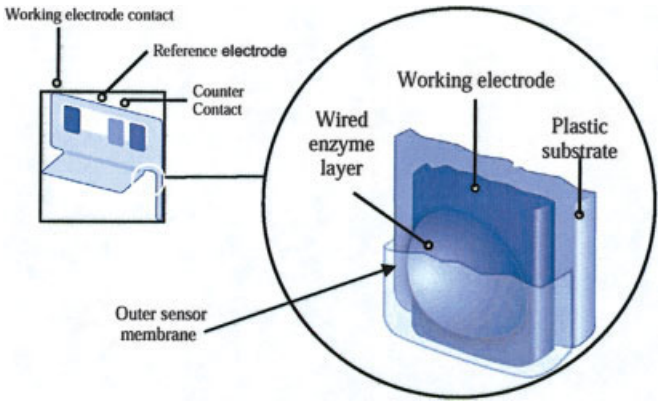


**Figure 9. The implanted unit of the continuous glucose monitor of TheraSense/Abbott Diabetes Care, replaced by the user every 3 days: from Ben Feldman, Abbott Diabetes Care, presented at the Diabetes Technology Meeting, Philadelphia on October 29, 2004.**

counter-reference electrode and is designed for mass manufacture at low cost, is shown in Figure 9.

## Integrated Therapeutic Systems

The combination of the administration of a drug by its pumping, as needed, into the subcutaneous tissue, with continuous or frequent monitoring of the drug-affected physiological parameter by an implanted sensor should prevent transient under-dosing and over-dosing. The doses and their timing would be tailored to the individual, whose instantaneous physiology rarely matches that of the population's average. The effectiveness of the administered doses is ascertained now by the sensor. The risk of side effects is reduced, because the administration of the drug is promptly halted at the effective dose threshold. Figure 10 shows a foreseen integrated therapeutic system for optimal dosing and timing of the delivery of a drug, such as fast-acting insulin in diabetes, or a fast-acting anti-hypertensive drug for cerebrovascular protection and renoprotection. It consists of two patches on the skin. One is an implanted sensor-amplifier-transmitter, similar to the just discussed continuous glucose monitor, replaced by the user every few days. The other, also replaced by the user every few days, delivers a solution of the drug and comprises a calibrator, an RF receiver, a drug reservoir, a pump, a battery and a miniature subcutaneously implanted drug inlet. The future drug delivering skin patch is shown in Figure 11. The RF-transmitted signal from sensor-amplifier-transmitter patch is received by the receiver patch and is translated, through a medical algorithm, to a series of timed micro-doses of the drug.

## The Size and Integration Limiting Component: The Power Source

I expressed a view that integrated medical systems will be introduced as soon as most of their component subsystems become available. In mobile electronic systems the largest and heaviest component is always the battery. This is so in a flashlight, a wristwatch, a music player, a laptop computer or a cardiac pacemaker or defibrillator. In the integrated drug delivery systems the size and weight defining component will also be the battery, except when the drug-solution must be highly diluted. To be useful, the battery must cost the user less than about \$1, so as not to affect excessively the ~ \$3/day intended cost of the disposable parts. Miniaturization of the battery requires not only that the intrinsic energy density of its reactive chemicals be high: it also requires replacement of its expensive to miniaturize stainless steel case and seal. Simple to miniaturize, low cost packaging requires safer chemicals than those of today's high energy density batteries (Table 2), which contain corrosive, reactive or toxic matter.

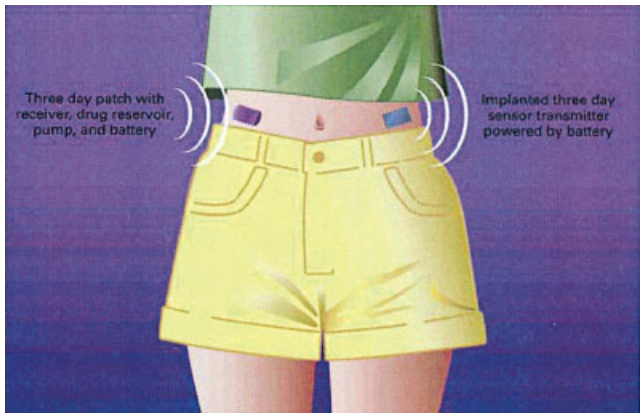


**Figure 10. Future integrated medical system comprising two communicating patches on the skin, one monitoring the drug-corrected physiological function, the other delivering the drug.**

Air-cathode based batteries, among which the $Zn/KOH/O_2$ battery is most widely used, have a high energy density (Table 2), but zinc-air batteries of volumes less than about 80 $mm^3$ are not available. The battery contains KOH. It is frequently swallowed and occasionally chewed on by children. Other high energy batteries contain Li, which reacts with water, potentially violently. For these reasons, batteries are packaged in strong stainless steel cans, with special seals. The strong cans greatly reduce the energy density when the battery is miniaturized.

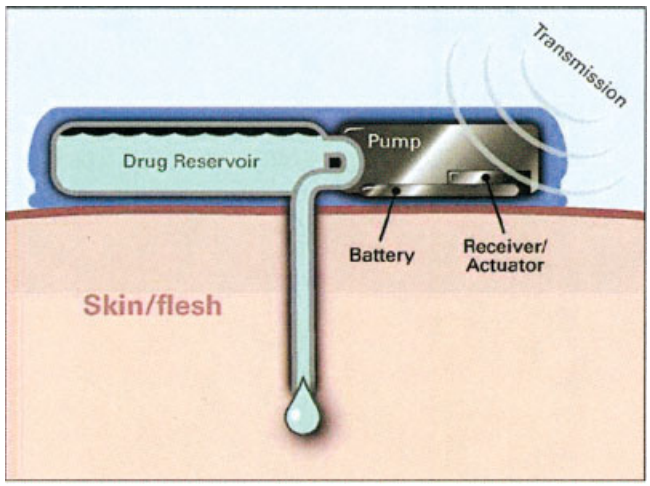


**Figure 11. Elements of a yet unavailable RF-connected drug-delivering skin patch.**

**Table 1. The Technology of TheraSense: Issued US Patents**

| Inventors | Title | Patent No. | Yr |
|---|---|---|---|
| Gregg BA, Heller A | Enzyme electrodes | *5,262,035* | 1993 |
| Heller A, Maidan R | Interferant eliminating biosensors | *5,262,305* | 1993 |
| Gregg BA, Heller A, Kerner W, Pishko MV, Katakis I | Enzyme electrodes | *5,264,104* | 1993 |
| Gregg BA, Heller A, Kerner W, Pishko MV, Katakis I | Enzyme electrodes | *5,264,105* | 1993 |
| Gregg BA, Heller A | Electrode and method for the detection of hydrogen peroxide | *5,320,725* | 1994 |
| Heller A, Maidan R | Interferent eliminating biosensors | *5,356,786* | 1994 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *5,593,852* | 1997 |
| Heller A, Vreeke MS | Soybean peroxidase electrochemical sensor | *5,665,222* | 1997 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *5,965,380* | 1999 |
| Heller A, Vreeke MS | Electrochemical analyte sensors using thermostable peroxidase | *5,972,199* | 1999 |
| Heller A, Pishko MV | Electrochemical analyte measurement system | *6,083,710* | 2000 |
| Say J, Tomasco MF, Heller A, Gal Y, Aria B, Heller E, Plante PJ, Vreeke MS | Process for producing an electrochemical biosensor | *6,103,033* | 2000 |
| Heller A, Feldman BJ, Say J, Vreeke MS | Method of using a small volume in vitro analyte sensor | *6,120,676* | 2000 |
| Heller A, Pishko MV | Electrochemical analyte measurement system | *6,121,009* | 2000 |
| Say J, Tomasco MF, Heller A, Gal Y, Aria B, Heller E, Plante PJ, Vreeke MS | Electrochemical analyte | *6,134,461* | 2000 |
| Heller A, Feldman BJ, Say J, Vreeke MS | Small volume in vitro analyte sensor | *6,143,164* | 2000 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *6,162,611* | 2000 |
| Say J, Tomasco MF, Heller A, Gal Y, Aria B, Heller E, Plante PJ, Vreeke MS, Friedman KA, Colman FC | Analyte monitoring device and methods of use | *6,175,752 B1* | 2001 |
| Heller A, Yarnitzky C | Potentiometric sensors for analytic determination | *6,251,260* | 2001 |
| Heller A, Campbell CN | Electrochemical affinity assay | *6,281,006* | 2001 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *6,284,478* | 2001 |
| Heller A | Biological fuel cell and method | *6,294,281* | 2001 |
| Feldman BJ, Heller A, Heller E, Mao F, Vivolo JA, Funderburk JV, Colman FC, Krishman R | Small volume in vitro analyte sensor with diffusible or non-leachable redox mediator | *6,299,757* | 2001 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *6,329,161* | 2001 |
| Feldman BJ, Heller A, Heller E, Mao F, Vivolo JA, Funderburk JV, Colman FC, Krishman R | Small volume in vitro analyte sensor with diffusible or non-leachable redox mediator | *6,338,790* | 2002 |
| Feldman BJ, Heller A, Heller E, Mao F, Vivolo JA, Funderburk JV, Colman FC, Krishman R | Small volume in vitro analyte sensor with diffusible or non-leachable redox mediator | *6,461,496* | 2002 |
| Say J, Tomasco MF, Heller A, Gal Y, Aria B, Heller E, Plante PJ, Vreeke MS | Electrochemical analyte sensor | *6,484,046* | 2002 |
| Heller A, Pishko MV | Subcutaneous glucose electrode | *6,514,718* | 2003 |
| Heller A | Biological fuel cell and method | *6,531,239* | 2003 |
| Heller A, Feldman BJ, Say J, Vreeke MS | Small volume in vitro analyte sensor | *6,551,494 B1* | 2003 |
| Heller A, Drucker SH, Jin RY, Funderburk JV | Analyte monitoring device and methods of use | *6,560,471* | 2003 |
| Say J, Tomasco MF, Heller A, Gal Y, Aria B, Heller E, Plante PJ, Vreeke MS, Friedman KA, Colman FC | Analyte monitoring device and methods of use | *6,565,509* | 2003 |
| Heller A, Feldman BJ, Say J, Vreeke MS | Small volume in vitro analyte sensor | *6,575,101* | 2003 |
| Heller A, Campbell CN | An electrochemical affinity assay system for detection of ligand–ligand receptor binding | *6,576,461* | 2003 |
| Bonnecaze R, Freeland AC | Blood analyte monitoring through subcutaneous measurement | *6,579,690* | 2003 |
| Buse JB, Moses AC | Small volume in vitro analyte sensor with diffusible or non-leachable redox mediator | *6,591,125* | 2003 |
| Feldman BJ, Heller A, Heller E, Mao F, Vivolo JA, Funderburk JV, Colman FC, Krishman R | Method of using a small volume in vitro analyte sensor with diffusible or non-leachable redox mediator | *6,592,745* | 2003 |
| Mao F, Heller A | Polymeric transition metal complexes and uses thereof | *6,605,200* | 2003 |
| Mao F, Heller A | Transition metal complexes with bidentate ligand having an imidazole ring and sensor constructed therewith | *6,605,201* | 2003 |
| Heller A, Feldman BJ, Say J, Vreeke MS | Integrated lancing and measurement device and analyte measuring methods | *6,607,658* | 2003 |
| Liamos CT, Vivolo JA, Colman FC | Small volume in vitro analyte sensor and methods | *6,616,819* | 2003 |
| Feldman BJ, Heller A, Heller E, Vivolo JA, Funderburk JV, Colman FC, Krishman R | Method of manufacturing small volume in vitro analyte sensor | *6,618,934* | 2003 |
| Heller A, Say J, Funderburk JV | Reusable ceramic skin-piercing device | *6,623,501* | 2003 |
| Heller A, de Lumley-Woodyear T, Georgiou G, Freeman A | Rapid amperometric verification of PCR amplification of DNA | *6,638,716* | 2003 |
| Say J, Sakslund H, Tomasco MF, Audett JD, Yamasaki D, Heller A | Mass transport limited in vivo analyte sensor | *6,654,625* | 2003 |
| Mao F, Heller A | Transition metal complexes with (pyridyl)imidazole ligands and sensors using said complexes | *6,676,816* | 2004 |
| Heller A, Kenausis GL, Chen Q, Vreeke MS | Electrochemical analyte sensors using thermostable soybean peroxidase | *6,689,265* | 2004 |
| Heller A, Chen T, Friedman KA | Electrodes with multilayer membranes and methods of making the electrodes | *6,746,582 B2* | 2004 |
| Levaughn RW, Flynn SJ, Kennedy GE, Lipoma MV | Lancing device and method of sample collection | *6,749,618* | 2004 |
| Liamos CT, Feldman BJ, Funderburk JV, Krishman R, Plante PJ, Vivolo JA, Jin RY, Cloud MS | Small volume in vitro analyte sensor and methods | *6,749,740* | 2004 |

Current research at the University of Texas is aimed at reducing the size of the electrochemical power source of the disposable skin patches of the drug-delivering feedback loops. For the drug-delivering receiver-processor-micro-pump-drug reservoir package, in which most of the power and energy are consumed by the micro-pump, we are considering a metal-air battery, with a nontoxic, noncorrosive pH 5 citrate buffer electrolyte. As yet, we do not have an adequately performing metal anode, but we do have a good air-cathode, its electrocatalyst based on the wiring of the enzyme laccase. [53,72-74] The

**Table 2. Comparison of the Characteristics of the Proposed "Wired" Laccase Metal-Air Battery and of Available Batteries**

| Cell | Whr/kg | Whr/L | W/kg | W/L |
|---|---|---|---|---|
| Li-$MnO_2$ | 300 | 800 | 300 | 1000 |
| Li-$SOCl_2$ | 740 | 1,300 | 1,500 | 2,500 |
| Alkaline Zn-Air | 460 | 1,500 | 5 | 15 |
| Proposed Laccase Metal-Air | 600 | 4,000 | 20 | 50 |

wired laccase cathode[53] is greatly superior (Figure 12) to the acid electrolyte platinum or platinum alloy cathode,[75] and is also superior to the manganese-dioxide activated carbon catalyst cathode[76] in alkaline solutions. $O_2$ is electroreduced to water with the wired laccase electrocatalyst at a true surface area-based current density of 0.5 mA $cm^{-2}$ and at 37°C at a polarization (potential vs the reversible potential of the $O_2/H_2O$ half cell in the same electrolyte) of only -0.06 V, one-fifth of the -0.40 V polarization of smooth platinum, when the platinum resides in its best electrolyte, 0.5 M $H_2SO_4$. Also, at pH 5 the solubility of $O_2$ is twice that in strong acids and the limiting current density is doubled.[53]

The noncorrosive electrolyte, and the absence of other hazardous matter, should allow containment of the battery constituents in an inexpensive, simple to miniaturize plastic bag. The energy density would be higher than that of any of the other nonrechargeable batteries. (cf. Table 2) The package would comprise an $O_2$ and water impermeable metallized (for example, aluminized) polymer for storage, which would be stripped off prior to use to expose a heat-sealed $O_2$-permeable sac (for example, of a silicone elastomer), containing the wired laccase air cathode, the metal anode and the pH 5 citrate buffer electrolyte.

The wire of the $O_2$ reducing enzyme, laccase, is shown in Figure 13. Like the wire of glucose oxidase (Figure 7) it has a poly-4-vinylpyridine backbone, to which the tris-2,2'-bipyridine complexed $Os^{2+/3+}$ redox centers are tethered with long and flexible chains to increase the electron diffusivity. The

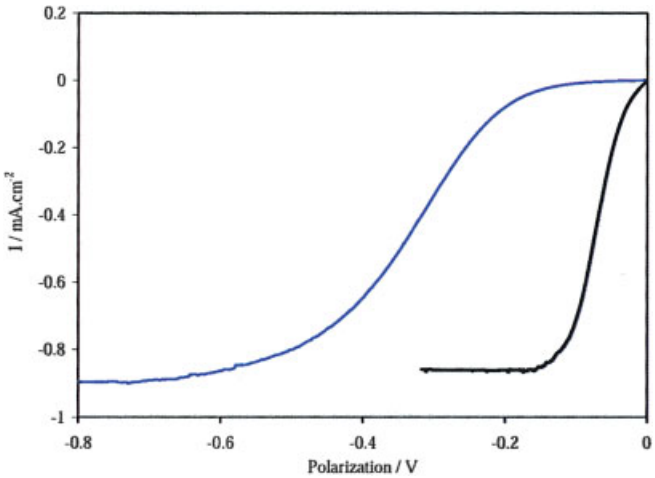


**Figure 12. Voltage (polarization) losses in the electroreduction of $O_2$ to $H_2O$ for solid smooth platinum in 0.5 M $H_2SO_4$ (blue curve), and for the wired laccase coated smooth vitreous carbon electrode.**

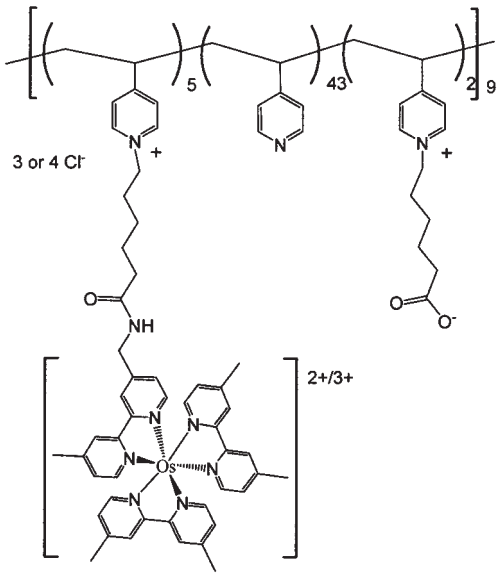


**Figure 13. The wire electrically connecting the enzyme laccase to the carbon cathode.**

Wired laccase is superior to platinum in the four-electron electrocatalytic reduction of $O_2$ to water. The mers are randomly distributed in the polymer. [53]

redox potential of the cathodic wire is tailored by its tris-bipyridine complex of $Os^{2+/3+}$, to be 0.8 V more oxidizing than that of the anodic wire, having *N,N'*-dialkyl-2,2'-diimidazole ligands.

We are also working on a second miniature power source, a miniature glucose $O^2$ biofuel cell intended to power the sensor-amplifier-transmitter skin patch.[53,77-83] Nearly all the power of the sensor-amplifier-transmitter is consumed by the transmitter. A biofuel cell supplying continuously $\sim 3\ \mu W$ for a few days would suffice to power the disposable sensor-patch of a system in which the output of the sensor is transmitted once every 2 min, and the receiver is located at a distance of about 20 cm. (Figure 10). Because glucose and $O_2$ are present in the subcutaneous fluid, and because of the specificity of enzyme-based electrodes for their reactants, the implanted biofuel cell would consist merely of two printed carbon lines, one a wired glucose anode, the other a wired bilirubin oxidase $O_2$ cathode, overcoated with a bioinert, crosslinked poly(ethylene glycol) film. (Figure 14)[83] Bilirubin oxidase is, like laccase, a blue copper enzyme with four $Cu^{+/2+}$ reaction centers, but unlike laccase it is active at the physiological pH range of 7.2-7.4 and 0.14 M NaCl concentration.[84,85]

The biofuel cell would enable the design of a low cost disposable skin patch comprising the sensor-amplifier-transmitter. The printed electrodes of the cell would be added as shown in Figure 14 to the sensor flag-pole of the implanted unit of this continuous sensor (Figure 9 left). The need for the nondisposable part of the sensor-amplifier-transmitter patch (Figure 5), containing the battery and the electronics, would be obviated. The one-part disposable flag-like patch would comprise the glucose sensor and the biofuel cell printed on its pole, an amplifier- transmitter silicon chip and also a printed wire antenna.

Experimental miniature biofuel cells[53,77-79,83,86,87] consisting of two wired enzyme coated 7 $\mu$m dia., 2 cm long carbon fibers

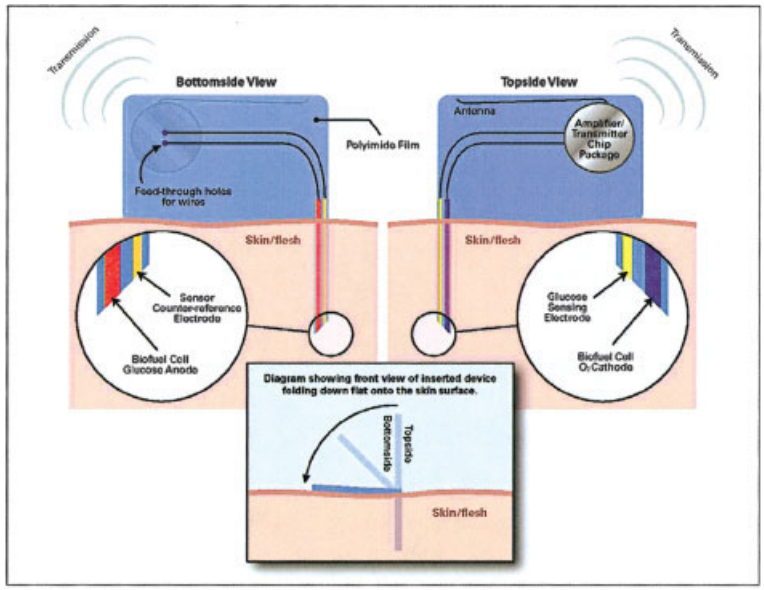


**Figure 14. Foreseen integration and miniaturization of the sensor-amplifier-transmitter of the disposable continuously glucose monitoring skin patch.**

are now in hand. The anode fiber is coated with the wired glucose oxidase glucose oxidation catalyst and the cathode fiber with the wired bilirubin oxidase, or laccase, $O_2$-reduction catalyst.

Unlike platinum group metal catalysts, enzymes are specific for their reactants. While $H_2$ is oxidized and $O_2$ is reduced on platinum, the oxidation of glucose at the wired laccase or bilirubin oxidase cathode and the reduction of $O_2$ at the wired glucose oxidase anode are avoided, even though the potential of the cathode is highly oxidizing and that of the anode is highly reducing. For this reason, unlike in other liquid electrolyte fuel cells, the anode and the cathode can reside in the same compartment. Other fuel cells, utilizing platinum group metal catalysts, like the $H_2/O_2$ cell or the methanol/air cell, depend on costly ion-conducting membranes to prevent hydrogen or methanol from crossing over to the cathode compartment, and $O_2$ from crossing over to the anode compartment. In the absence of a membrane, $H_2$ or methanol would be oxidized at the cathode and $O_2$ would be reduced at the anode, decreasing the power output, often to nil. Furthermore, an $H_2/O_2$ or methanol-air cell requires a container, a seal for sealing the container, a membrane, a membrane seal, a contained electrolyte, an anode, a cathode, a fuel container, and plumbing to connect the fuel container to the anode. In contrast, the miniature biofuel cell functioning in a living organisms has only two parts, the anode and the cathode. The volume of our biofuel cells is 0.005 $mm^3$, about $1/1000^{th}$ of the volume of the smallest battery now manufactured, and about $1/10{,}000^{th}$ of the volume of the smallest previously reported fuel cell. They produce in 1 week ~1 joule, about 100 times more electrical energy than the highest energy density Zn-AgO or Zn-$O_2$ battery could produce, were it possible to miniaturize the battery. [83] One of the miniature glucose-$O_2$ cells now operates optimally at a voltage as high as at 0.88 V. [53] Another miniature glucose-$O_2$ biofuel cell operates for 1 week at 37°C in a pH 7.2 physiological buffer solution, and for a day in a grape (its sap is rich in glucose). [79] The power curve for the cell operating in the grape is seen in Figure 15. The cell is, however, still unstable in serum.[82]

## Conclusion

Disease is a process requiring control. There is a self evident need to simultaneously optimize the treatment of disease for optimal outcome, least pain, least mental anguish, least loss of productivity and least cost. The necessary knowledge and components for the optimization, particularly through integrated medical systems, are becoming available. Chemical Engineers

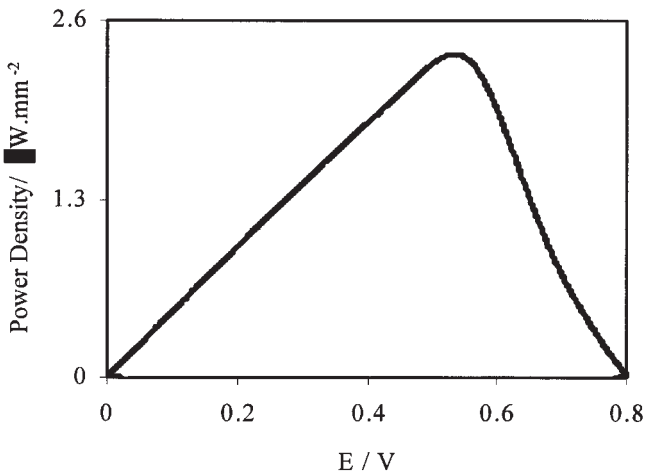


**Figure 15. Dependence of the power density of a miniature glucose-$O_2$ biofuel cell operating in a grape on the cell's operating voltage.**

The cell consists of two 7 $\mu$m diameter, 2 cm long, carbon fibers coated with 3 $\mu$m thick "wired" enzyme hydrogels. The cell generates ~3 $\mu$W, enough to power the sensor-amplifier-transmitter. The footprint of the fibers is 0.53 $mm^2$ and their combined volume is 0.0052 $mm^3$.

will have an eminent role in the control of disease through the integrated medical systems. Their knowledge of design, process control, materials, particularly sophisticated polymers, transport, fluids, electrochemical power sources and sensors is highly relevant.

The pharmaceutical industry and ventures feeding into it are struggling with a massive loss of drug candidates. Manufacturers of drugs also face risks of late discovery of side effects, as seen recently when investors in COX-2 producing companies lost about $ 50 billion. Drugs have been optimized for averaged patient populations. Any individual patient is likely to differ, transiently or permanently from this average. Differences defining an individual (for example, genetic makeup, weight, age) and her or his lifestyle (for example, exercise, meal habits, sleeping habits) lead to transient or regular differences in the concentrations of the drug in the target organ and in an adversely affected organ. Therapeutic feedback loops, conceptually similar to those applied by chemical engineers in process control in chemical producing plants, but small enough to be wearable, will tailor, however, the administration of the drug to the individual patient.

The first of these loops is likely to be an integrated diabetes management system, continuously monitoring the glucose concentration and administering small doses of insulin.

The foreseen individualized drug administration systems, which are likely to consist of disposable patches on the skin, share common subsystems. Examples of these include the small integrated drug-reservoir-RF-receiver-actuator-drug pump, with a subcutaneous fluid-feeder; a subcutaneous sensor introducer; and an amplifier-processor-transmitter of the sensor. The availability of the common subsystems, and of application-specific sensors, medical control algorithms and fast-acting versions of established drugs define the pace of introduction of the individualized integrated therapeutic systems.

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