Synoptic of an MS Thesis Prepared at Draper Laboratory:

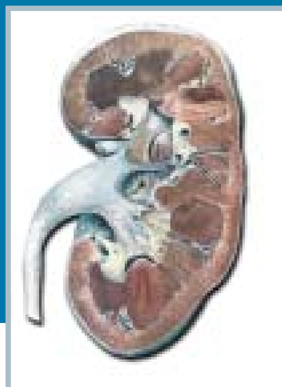
Preliminary Design of an Implantable Biosensor for the Detection and Differentiation of Acute Rejection, Vascular Occlusion, and Infection in the Liver or Kidney Transplant Graft

Megan M. Owens

Based on a thesis published by the Massachusetts Institute of Technology, Cambridge, MA.

ABSTRACT

Although organ transplant survival rates are encouraging from a historical perspective, they are not yet 100%. Patient death is unacceptable in a perfect world, highly undesirable in reality. Currently, ailment detection is by external symptom exhibition, a late-stage event. This is nonideal; earlier detection is preferable. Several common post-transplant complications evince similar and even identical symptoms, rendering doctors unable to diagnose with surety. In order to determine the correct ailment, a needle biopsy is performed and the results analyzed. Biopsy as a method of differentiation is flawed for several reasons, including time costliness, risk of complications, patient inconvenience, necessarily low number and frequency of sampling, and others. However, treatment regimens for different complications are specific and noninclusive. For example, if a doctor mistakenly prescribes immunosuppressive therapy to treat a case of supposed rejection when the ailment is truly infection, then the immune system will be crippled and the infection will worsen. A specialized sensor would be capable of eliminating ambiguities and would allow doctors to prescribe more rapidly an effective remedy with surety. The goal of this thesis is to present a preliminary design of an implantable sensor capable of detecting and distinguishing between liver or kidney graft acute immunorejection, vascular occlusion, and infection. These ailments may occur during the post-transplant critical period, the first month following surgery. Since the sensor resides within the organ of interest, it will allow the earliest possible detection of warning signs indicating an ailment. These warning signals are typically concentration surges or depletions of specific target molecules, most of which are cytokines. Since the sensor monitors the target concentrations in real-time, temporal profiles may be constructed correlating to ailment events. Currently, there is no product such as this available on the market. The proposed concept design consists of a sensing element, radio frequency telemetry system, data display, power system, and biocompatible packaging. The design combines the chemical sensor technology of the flexural plate-wave gravimetric sensor with implantable biosensor technology to yield a feasible solution to a significant clinical problem.



INTRODUCTION

While organ transplant survival rates have increased in recent history, they are not yet 100%. Currently, post-surgery ailment detection is through external symptom exhibition, a late-stage event, even though earlier detection is often critical to save the graft or even the patient. Several common post-transplant complications evince similar and even identical symptoms, rendering doctors unable to diagnose with surety. In order to determine the correct ailment, a needle biopsy is typically performed and the results are analyzed. Biopsy as a method of differentiation is flawed for several reasons, including risk of complications, time costliness, patient inconvenience, necessarily low number, and frequency of sampling. Treatment regimens for different ailments are mutually exclusive. For example, if a doctor mistakenly prescribes immunosuppressive therapy to treat a case of supposed rejection when the ailment is truly infection, then the immune system is crippled and the infection worsens.

A specialized sensor may eliminate ambiguities and allow doctors to rapidly prescribe an effective remedy with surety. *The thesis goal was to present a preliminary design of an implantable sensor capable of detecting and distinguishing between liver or kidney graft acute immunorejection, vascular occlusion, and infection*. These ailments can occur during the post-transplant "critical period," the first month following surgery. Since the sensor resides within the organ itself, warning signs are detected as early as possible. These signs are typically concentration surges or depletions of specific target molecules, most of which are cytokines. Since the sensor monitors a target molecule concentration in real time, a set of temporal profiles correlating to ailment events may be generated.

No equivalent, or even similar, product currently exists on the market; this allows a unique opportunity for exposure of technology. The design combines the chemical sensor technology of a flexural plate-wave gravimetric sensor with implantable biosensor technology, yielding a feasible solution to a significant clinical problem. The proposed concept design consists of a sensing element, radio frequency telemetry system, data display, power system, and biocompatible packaging. The internal sensor digitally emits target molecule concentration data to an external receiver once a day for 4 weeks. The information is received, processed, displayed, and stored. If target marker levels match those that correlate with a problem, both visual and audio alarms alert the medical team.

Design Approach

The functions that the device must perform to solve the larger problem are: obtain information, transfer information, and be biocompatible. A set of actions fulfills each function.

Four basic events are necessary to obtain the desired information: (1) the target exists in the device environment; this is ensured by device placement; (2) the sample is filtered, which must occur to obtain a measurable sample; (3) the sample must contact the sensing element to allow the possibility of target binding; and (4) the sample minus the bound target returns to the environment; the unbound sample exits to allow the next assay.

Information is transferred by four consecutive actions: (1) the relevant target binding information is packaged in the form of a signal, (2) the signal is transferred through the host body, (3) the signal is received outside of the host, and (4) the data are displayed.

Biocompatibility is ensured by two requirements: the device does not harm the host, and the host does not harm the device. In order for the device to remain benign, it must elicit a minimum immunological host response, which depends on four conditions: (1) the device material in contact with the host, characterized by biomaterial-tissue interactions; (2) the device form, determined by the overall shape; (3) the amount of fluid leakage out of the device; and (4) the fixation firmness of the device within the surrounding tissue. Host harm to the device is governed by two conditions: (1) the amount of fluid leakage into the device; and (2) the extent of fibrous tissue capsule formation surrounding the device, which limits the measurable analyte level.

Issues

Location

In order to obtain pertinent information from the tissue environment, the sought targets must exist in the measurable environment. This criterion determines the device location. According to Steve Dawson, M.D.[1] and C.B. Carpenter, M.D.,[2] the cytokines and other analytes of interest reside in highest concentrations within the organ itself, not in the circulatory system. Dawson also revealed that a graft rejection, infection, or occlusion episode would result in comparable levels of targets throughout the organ body; one point within the organ would yield essentially identical target concentration readings as another arbitrary site within the same organ. This given, the site of implantation narrows from the entire host to the organ of interest. In order to simplify surgical implantation and minimize tissue damage due to the implantation procedure, the optimal placement position is just between the organ capsule and the organ body, within a tissue space roughly a few centimeters in width.

Sample Transport

So that the device may best measure the analytes in question, the sample must be filtered. Filtration disallows clumping of larger-scale molecules within the device at the sensing element surface. A dialysis membrane, selectively permeable to chemical species smaller than the desired targets, excludes larger molecules from analysis. As the sizes of the targets range from around 115 amino acids for interleukin-1 (IL-1) to 184 amino acids for IL-6, a dialysis membrane rejecting the flow of molecules below that range is ideal.[3]

Because the sensing element works by selectively binding the analyte, physical contact between the target and the sensing element surface is necessary. Diffusion into and out of the fluid chamber of the sensing element is the simplest solution to transport the analyte to the sensing surface. Simple diffusion also allows an exit path for the sensed sample. A diffusion model has been derived and its implications on sensor response time versus sensor lifetime have been discussed in the full text of the thesis.[4]

Sensor Response Time vs Sensing Surface Lifetime

Sensor response time and sensing element lifetime are mutually exclusive performance metrics; the optimization of one comes at the cost of the other. Both are associated with target diffusion through the semipermeable membrane and the fluid chamber space, followed by attachment to the detector surface. The relationship between these two parameters is explained with a simple fluid sampling model (Figure1).

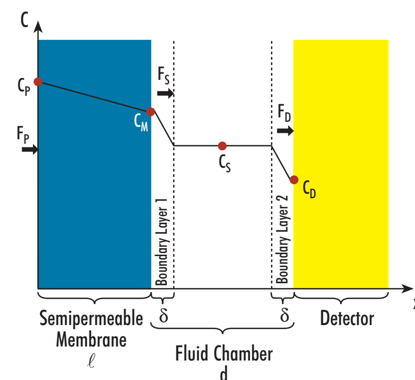


Figure 1. Sample transport model.

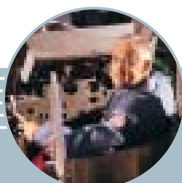
The sensor response time is the time it takes for a change in extracellular target concentration to indicate such at the system output. The response time, here, is simplified to be the time it takes for a concentration change within the body to result in a concentration change within a fluid layer of infinite thinness just above the coating surface of the sensing element. We also assume that once a target molecule reaches this boundary layer, it instantaneously binds to an available site on the coating. This is a valid approximation, as, in reality, this reaction is extremely rapid.

To ensure that the sensing element coating remains viable throughout the product lifetime, L_P, the coating lifetime, L_C, must be quantified in the context of typical target molecule concentration levels. The coating lifetime must equal or exceed the product lifetime

$$L_C \geq L_P$$

Although the sensing surface is coated for multiple targets, this discussion pertains only to the limiting target, identified experimentally, and its specific antibody coating. Because this target is present in the extracellular milieu in higher concentrations than any of the other targets in the trial, these coating binding sites are those most quickly exhausted, hence, the limiting factor.

The model is divided into six sections: (1) the ambient environment of the patient, (2) the semipermeable membrane through which the target passes, (3) the first boundary layer



of the fluid chamber inside the sensor body, (4) the central layer of the fluid chamber, (5) the second boundary layer of the fluid chamber, and (6) the detector surface. There are four target concentration levels: (1) that of the ambient environment, C_P; (2) that of the first boundary layer, C_M; (3) that of the central layer, C_S; and (4) that of the second boundary layer, C_D. The thickness of the semipermeable membrane is given as ℓ, and that of the fluid chamber as d. The thickness of each boundary layer is δ. The distance through the semipermeable membrane and fluid chamber is measured in the x-coordinate as is illustrated in Figure 1. The model includes target concentration fluxes F_P, F_S, and F_D, also shown (Figure 1). We assume that the outer boundary of the membrane is kept at steady-state concentration, C_P, and that the inner boundary remains at C_M. The initial concentration of the inner boundary is C_0.

If the coating is a monolayer of N target binding sites, the coating lifetime, L_C, is the time it takes to bind every available site. This time is deduced from the rate at which targets attach to the coating, the concentration flux, F_D

$$L_C = \frac{N}{A_T F_D} \tag{1}$$

where A_T is the total binding area. This is the sensing element surface, the coated surface area, approximately 1 mm × 1 mm, or 1×10^{-6} m^2. The attachment frequency, ν_a, an area-normalized rate, is

$$\nu_a = \left(\frac{N}{A_T L_C}\right)\left(\frac{A}{1}\right) = F_D A \tag{2}$$

where A is the area of one binding site, and the number 1 represents one target. The inverse of this frequency is simply the coating lifetime

$$L_C = \frac{1}{\nu_a} \tag{3}$$

To gauge the coating lifetime, A and F_D must be estimated.

F_D is the rate at which target molecules attach to the coating, per area. This rate is a function of the target concentration just above the coating, C_D, the total number of binding sites, N, the number of molecules already attached, m_A, and some diffusion constant at the sensing element surface, D_D

$$\frac{dm_A}{dt} = C_D\left(\frac{N - m_A}{N}\right)D_D \tag{4}$$

The concentration C_D may be estimated as the number of molecules in the layer as a function of time divided by the number of binding sites times the area of a single site

$$C_D = \frac{m(t)}{NA} \tag{5}$$

This concentration may also be calculated from the equation above if the initial concentration at the inner boundary of the membrane, C_0, is known. The initial value, C_0, is assumed to be zero.

Consider the size of a representative target, IL-6, composed of 184 amino acids. While an amino acid count does not directly correlate to the molecular path length due to tertiary interactions, an upper-bound length value generously assumes that the molecule does not fold and that its entire length contacts the coating surface. In order to transform this length into an area, we again exaggerate, assuming the width is equal to the length. Amino acids are attached to one another by peptide bonds, carbon to nitrogen single-bond interactions, for which the bond length is 0.132 nm.[5] Then, the path length of IL-6 is 24.288 nm, yielding an estimated area, A, of about 6×10^{-16} m^2 per molecule. As an aside: given A and A_T, the number of binding sites, N, might be estimated

$$N = \left(\frac{1}{A}\right)(A_T) \tag{6}$$

about 1.7×10^9 molecules.

Three transport mechanisms control target attachment at the detector, and hence, the response time and the lifetime. These are: (1) the diffusion of molecules through the semipermeable membrane, (2) the diffusion of molecules through changing concentrations in the fluid chamber, and (3) the attachment of molecules to the detector surface. The first event is likely the rate limiter; its effects on the binding rate are greater than the effects of diffusion in the fluid chamber or attachment to the detector.

As was previously stated, we assume that once a target exists in the concentration C_D, it immediately binds to an available site. Then, the flux out of the secondary boundary layer and onto the coating is the change in concentration through the second layer over the distance between these concentrations, δ, multiplied by the fluid diffusion constant, D

$$F_D = -D\frac{\partial C}{\partial x} \cong -D\frac{C_D - C_S}{\delta} \tag{7}$$

Likewise, the flux out of the first boundary layer and into the central layer is calculated

$$F_S = -D\frac{\partial C}{\partial x} \cong -D\frac{C_S - C_M}{\delta} \tag{8}$$

These two equations tie C_D to C_M through C_S, which is an initial concentration, C_0, plus the change in fluxes at the boundary layers, over the distance, multiplied by elapsed time, t

$$C_S = C_0 + \left(\frac{F_S - F_D}{d}\right)t \tag{9}$$

Following this approach, the fluid chamber might be deconstructed into infinite layers of differing concentrations, each with its own flux governed by the differential $-D(\partial C/\partial x)$. Each layer concentration might be linked to its neighboring layers' values as is done above. In this fashion, a more realistic model might be constructed. For the current purpose, the simple model is sufficient.

Relating the concentrations or the fluxes spanning the dialysis membrane requires more elaborate calculation. The membrane is the dominant consideration. Accordingly, the fluid chamber is assumed to be infinitely thin, so as not to affect target flux onto the detector. This assumes that the first boundary layer concentration, C_M, is one and the same as the second boundary layer concentration, C_D. First, the target concentration within the membrane as a function of distance and time is solved for the time period between initial and steady state. The concentration at a distance, x, at time, t, is

described.[6] Second, the total amount of the target entering the membrane during the time from initial time to steady-state, as well as the amount entering after steady-state, may also be found, as may the total target content within the membrane at any time t. Third, the rate at which the target leaves the membrane is $-D(\partial C/\partial x)_{x=\ell}$, by using the concentration equation above. This expression is integrated with respect to time to yield the total amount of target passing through the membrane in time t.[6] If the sheet $-\ell<x<\ell$ is initially at C_0 and the target enters at constant flux $F_P = F_S$ over unit area of surface (in other words, $D(\partial C/\partial x) = FP$, $x=\ell$), then the difference in concentration after time t is[6]

$$C-C_0=C_P-C_M=\frac{F_P\ell}{D_M}\left[\frac{D_M t}{\ell^2}+\frac{3x^2-\ell^2}{6\ell^2}-\frac{2}{\pi^2}\right.$$
$$\left.\left[\left(-e^{\frac{-D_M\pi^2 t}{\ell^2}}\cos\frac{\pi x}{\ell}\right)+\left(\frac{1}{4}e^{\frac{-4D_M\pi^2 t}{\ell^2}}\cos\frac{2\pi x}{\ell}\right)\right]\right] \tag{10}$$

Once an estimate for F_D is elucidated, the expressions may be evaluated in cascade; the variables link the equations, as is more fully described in the complete thesis. Target attachment to the sensor is, therefore, correlated with entrance through the membrane, and sensor response time and lifetime are quantifiable.

The sensor response time and the coating lifetime are directly related to the flux F_D. A high flux rate results in rapid depletion of available binding sites, and hence, a short lifetime. Since the flux F_D may be described, using the interrelating equations above, as a function of the flux into the sensor F_P, a high F_D also indicates a fast response time. A low flux, on the other hand, implies a long coating lifetime and a slow response time.

The flux F_D is linked to the diffusion gradient that exists through the semipermeable membrane and fluid chamber space. The larger the gradient, the higher the flux, and vice versa. This diffusion gradient depends on two variables. The first is the difference in concentration value between the external environment and the boundary layer neighboring the detector, C_P - C_D. The second variable is the distance separating these concentrations, $\ell + \delta$. The gradient is given as a particular relationship between the two, $\partial C/\partial x$. The largest gradient is produced with a large difference in concentration over a small distance, whereas the smallest gradient is yielded by a small change in concentration over a large distance.

This linkage, of concentration and distance to the diffusion gradient to the flux into the detector, guides any sensor design for which response time and lifetime ought to be optimized. To do so, without increasing the sensing element or membrane area, the concentration gradient and the fluid path distance should be defined accordingly. While the concentration in the patient, C_P, is an independent variable, the porosity of the membrane is a specification that may be altered to increase or decrease the ratio between C_P and C_D, existing at any given C_P. In this manner, the concentration gradient is somewhat controllable given different values of C_P. Sensing element sensitivity may also be relevant to C_D. Sensitivity is a measure of how much target must bind in order to yield a detectable response. If the detector has high sensitivity, less target need attach in order to produce a response, and hence, C_D need not be large.

In this design, the concentration difference must be low, so as not to extinguish the binding sites too quickly. Lower porosities decrease C_D and increase the detector lifetime, yet also decrease the response time. The thickness of the membrane, ℓ, as well as the height of the fluid chamber, δ, might both be reduced, decreasing the response time, but also decreasing the coating lifetime. Once preliminary measurements are taken, a compromise between sensor response time and detector lifetime may be established and these two metrics may be defined.

Telemetry

To transport data out of the body, the information must first be translated into an electrical signal. The sensing element detects the change in mass of the sensing surface, due to the attached target, as a shift in the frequency of the surface, and this shift is quantified in electrical terms by a small internal electric circuit. The signal could be transferred from the body by many methods, including ultrasound, radio, or optics, but, for this application, radio transmission is preferred because of the medium and the distance that the signal must propagate. The circuit outputs the electrical signal as a current with a certain magnitude and amplitude, which is fed into an a magnetic coil. The current in the coil generates a magnetic dipole field that transmits the signal from the device through the tissue. Reception occurs outside the host body, where another magnetic coil is used to pick up the signal present in the field. The signal is thereafter processed by external circuitry to yield a measured target concentration value. As measurements are made, values are stored and displayed as a concentration profile versus time.

The optimal operating frequency is chosen by considering the signal depth of penetration at different frequencies. These calculations depend on the transmission material's properties, as depth of penetration is given by

$$h=\sqrt{\frac{\rho}{\pi\mu f}} \tag{11}$$

where ρ is the tissue resistivity, μ is the magnetic permeability of the tissue, and f is the operating frequency.[7] The results of calculation, in the range of a patient's body thickness measured from anterior to posterior, are given in Figure 2.

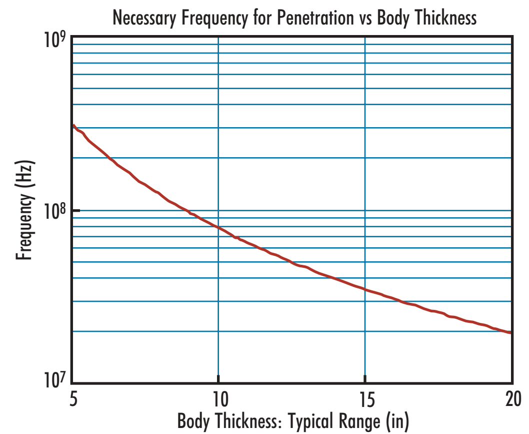


Figure 2. Necessary frequency for penetration vs body thickness.

Design guidelines suggest that the actual distance the signal must travel should be much less than the depth of penetration. Assume for the sake of simplicity that the sensor, mounted on the anterior surface of the kidney or liver, is halfway through the body thickness. Then, the actual distance is half the body thickness. Though the upper bound body thickness value measures at about 10 in, the expected travel distance is 5 in. Multiplying by a safety factor of 2, we choose a frequency based on a 10-in travel distance, or a 20-in body thickness. This corresponds to a frequency of about 20 MHz. While lower frequencies would penetrate even further through the tissue, 20 MHz is chosen as a compromise between the advantages of both low- and high-frequency operation, elaborated in the full work. Therefore, the first-pass operating frequency is defined as 20 MHz.

Biocompatibility

The device will minimally harm the patient if the immunological response is minimized. This depends on the material, shape, fixation, and leakage of the device. The material chosen to construct the device housing is polyethylene; this material has previously proved positive results in chronic biomaterial studies.[8] The shape of the device also contributes to the immunological response. Less angular shapes reduce the host response, so surfaces should transition smoothly; large radii should be applied to all surface meeting planes. Device fixation plays an important role as well, as loose coupling between the device and the surrounding tissue allows more movement and increased friction, which may result in particulate debris formation from the biomaterial surface. The presence of particulate debris leads to macrophage and foreign body giant cell activation: an onslaught by the immune response. A porous coating on the main body of the housing will allow device fixation by tissue ingrowth and resulting mechanical interdigitation. Coating the porous layer itself with a chemical that encourages tissue ingrowth, such as fibronectin, will further increase adherence. Any fluids that may leak out of the device are potentially hazardous as well. Foreign fluid in the extracellular milieu will, like debris, result in immune cell recruitment. A robust gasketing scheme will minimize fluid leakage. So that the host does not impair the device function, the formation of a fibrous tissue capsule should be discouraged. To this end, it is again suggested that the housing be coated with a porous material in order to allow mechanical stabilization. So that fluid may diffuse in and out of the semipermeable membrane freely without obstruction from proteins adhered on the device surface surrounding the opening, these areas should be coated with phosphorylcholine heads. The cell membrane mimic-coating will discourage protein adsorption around the area of diffusion. The host system may also interfere with sensing if body fluid leaks into the housing; the gasketing, previously mentioned, will eliminate this issue.

Surgical Considerations

Sensor implantation may occur either prior to organ implantation or during transplantation surgery. By choosing one of these times to implant, the procedure is minimally-invasive, as insertion is opportunistic. Since organ transplant recipients are the target users, and since the sensor is to be used up to 1 month post-transplant, one of these two times is only rational.

Because a surgeon may choose to implant the device during transplantation surgery, the method of implantation must be easy. Ease of implantation may be described as the surgeon making five or less separate movements to install the sensor. This is within reason, as the site of implantation (Figure 4), the anterior side of the organ capsule, is readily exposed following a kidney or liver transplant. Because the implantation site is shallow and the sensor housing is porous and coated with adhesion-encouraging agents, no mechanical anchorage is necessary. The surgeon must only make a small slit in the organ capsule, slip the sensor inside, and then may or may not choose to suture the capsule. Since the incision length need not be greater than the sensor diameter, suture may not be necessary. When inserting the sensor, the surgeon should take care to orient the device with the top facing the anterior position; this will set the direction of magnetic radiation and, hence, the orientation of the receiver. The sensor implantation method should also be swift. This is defined as 3 min or less. Given the events in the implantation sequence, this should not be a troublesome requirement for an experienced surgeon.

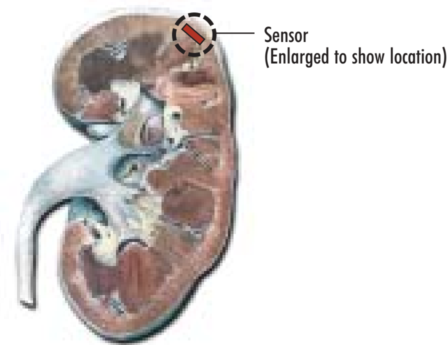


Figure 3. Probable sensor location in the kidney.

Conceptual Design

The interior sensor system should be organized so that all components fit into the smallest space with minimum physical and electrical interference.

The housing is constructed from two injection-molded pieces, allowing ease of manufacturing and assembly. The assembly of the inner components is first accomplished, followed by capping with the top and bottom housing and the application of sealant. The housings form a shape with a definite top and bottom to facilitate proper orientation during sensor implantation. The edges are rounded to ease tissue aggravation.

The semipermeable membrane is stretched over an opening in the top housing and is in direct contact with the environment. The sensing element surface is placed as near to the interior surface of the semipermeable membrane as is possible, without actual physical contact; such contact and resultant friction could possibly dislodge relevant portions of the molecular coating, rendering the sensing element inaccurate and ineffective. A finite distance is then left between the two surfaces, leaving a fluid chamber.

The sensing element couples directly to the circuit board. Minimum wiring distance reduces the possibility of connection failure, which could be due to sensor component vibration from normal operation or patient movement. Minimal overall space constraint is also a consideration. For the same reasons, the internal power source directly abuts the opposite side of the circuit board. The transmitter antenna loop is oriented parallel to the receiver coil, while the battery remains outside the transmitter loop. Wiring and circuitry components on both sides of the board are encased in an encapsulant.

The shapes and placements of the components in this conceptual model are not to be construed as exact and final. As is evident, this simple model does not show gasketing, encapsulant, sealant, nor the porous external coating. (See Figures 4 and 5.)

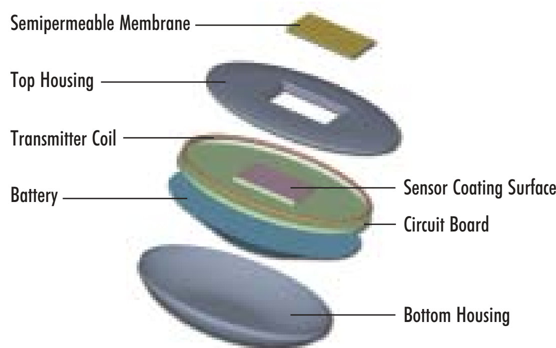


Figure 4. Design concept, exploded view.

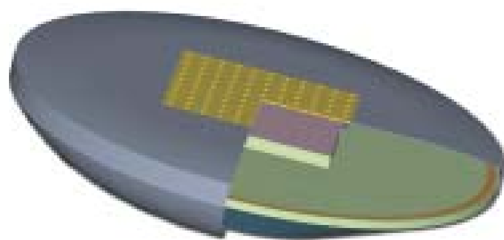


Figure 5. Design concept, cutaway view.

Conclusion

This thesis presented a medical problem for which there is no currently implemented solution: the delayed and nonideal method for positive identification of acute rejection, infection, and vascular occlusion in the transplanted kidney and liver. In the full document, issues of interest with respect to the problem were explored: kidney and liver anatomy, the history of transplantation surgery, post-operative complications of transplantation surgery, immunology events, a literature review of chemical correlates associated with ailments, biomaterial-tissue interaction events, a literature review of biomaterials, biosensor benchmarking, analysis of the sensor, and biotelemetry. Also, a design methodology was described and its results were given. Finally, a preliminary design was presented as a feasible solution to the problem posed. This synopsis is a general overview of the complete work.

In brief, the design describes a noninvasive, chronically-implantable biosensor able to detect concentration levels of cytokines or other chemical species indicative of acute rejection, infection, or vascular occlusion. The sensor is designed for long-term biocompatibility, as retrieval is not anticipated. The transducer element is the flexural plate-wave sensor, which may be coated with antibody for virtually any chemical species. The detected levels are transmitted via radio telemetry to an external receiver, where the data are displayed and stored.

Further work is necessary in order to yield a product. A prototype should be constructed, based on the given theoretical design, in order to obtain experimental design parameter values, which may vary from theory due to unforeseen factors. Biocompatibility should be tested in order to best predict long-term in vivo performance and stability. A cost analysis should be undertaken to prove that the concept is monetarily attractive to potential developers. Finally, a manufacturing plan should be constructed to allow timely and efficient product production and implementation.

The concepts developed in the thesis and the further work, once it is accomplished, will develop the implantable organ biosensor, a product necessary to solve a serious problem facing organ transplant recipients today.

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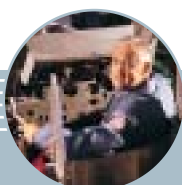
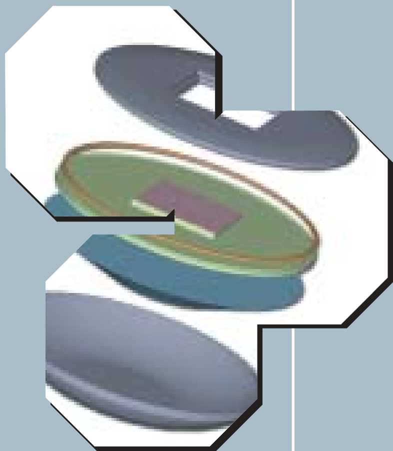
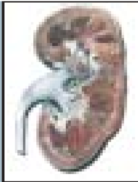




Megan M. Owens



Biography

Megan M. Owens mowens@draper.com

is currently a Member of the Technical Staff in the Electronics Packaging and Prototyping Group at Draper Laboratory. A former Draper Fellow, she has investigated the parylene deposition process for the heterogeneous integration process, solved chemical sensor design issues, aided in choosing components for implementing the SOA vacuum system, investigated laser micromachining of silicon, produced generic interposers for rapid prototype of chip scale packages, and implemented various hybrid electronics packaging process improvements. Current tasks include establishing a holographic interferometry capability for package strain analysis, designing a new package for the nonvolatile residue (sensor) chemical sensor, and optimizing the laser process for formation of MCM-D deep vias. Ms. Owens is a member of ASME and an associate member of Sigma Xi, Scientific Research Society. She received a BS in Mechanical Engineering from MIT. Her thesis was based on a Draper, CIMIT, and MIT interest: Preliminary Investigation of an Automated, Ultrasound-Guided Phlebotomy and Intravenous Line Insertion Device (1998). She obtained an MS in Mechanical Engineering from MIT (2000).