Continuous Sensing Mechanism for Knee Implants

Engs 89/90 Final Report for OrthoSensor Inc.

Published March 7th, 2012

THAYER SCHOOL OF ENGINEERING AT DARTMOUTH

ORTHOSENSOR

Group 23
Noah Bonnheim
Natalie Burkhard
Phillip Henson
Graham Keggi

II CONTINUOUS SENSING MECHANISM FOR KNEE IMPLANTS

I. Executive Summary

Total knee arthroplasty (TKA) is an effective and clinically successful solution for advanced osteoarthritis of the knee. There are more than 500,000 TKA procedures in the United States each year, with a five-year survivorship of 97.2%. However, treatment for failed implants can be a burden on both patients and the healthcare system, as revision surgeries can cost upwards of $100,000. This problem is likely to intensify because the number of patients requiring TKA and revision TKA is projected to grow by 673% and 601%, respectively, by the year 2030.

Infection is the most common cause of revision TKAs, accounting for 25.2% of revision surgeries between 2005 and 2006. Early diagnosis of infection is crucial to avoid revision surgery, but the multitude of complex clinical tests and the tendency of infections to mimic other conditions render early detection difficult. In fact, there currently exists no universal standard to diagnose infection in the early postoperative period. Many indicators for infection are recognized as both sensitive and specific via retrospective studies, but there is no system to continuously test for these indicators in a knee implant.

OrthoSensor, Inc. recognizes that there is a need for a continuous, implantable sensing modality for patients undergoing TKA in order to detect infection before revision surgery becomes necessary. Reducing the number of revision surgeries due to infection would alleviate the strain these procedures place on patients and the healthcare system. OrthoSensor's long-term goal is to develop a fully instrumented knee implant with real-time sensors to detect the onset of infection as well as monitor mechanical failures such as loosening and dislocation.

In support of OrthoSensor's goal, the team will provide the company with an infection sensor implementation plan that will involve: (1) identification of infection indicators and their respective sensing mechanisms, (2) design and fabrication of clinically relevant models for synovial fluid and the knee joint, (3) production of sensor output data for a range of healthy and infected synovial fluid conditions, and (4) establishment of threshold values for sensors that are sensitive and specific to infection.

Contents

II. Introduction

Infections are the primary cause of total knee arthroplasty (TKA) revision surgeries and place significant physical strains on patients, resource burdens on doctors, and financial drains on the healthcare system. Arthroplasty modifies the function or structure of a joint[1]. In a healthy knee, the joint is covered with cartilage and lubricated with synovial fluid (SF). TKA is performed to replace damaged knee components with plastic or metal parts with product lifetimes of 20-30 years[2]. The tibial and femoral bone heads are reshaped and replaced with metal surfaces that slide on a plastic cartilage replacement, thus eliminating bone spurs, reducing friction, alleviating pain, and restoring much joint functionality[3].

TKAs are clinically successful and cost-effective[4]. In 2005, 523,000 TKAs were performed in the United States with a success rate of 93%[5]. The success of TKAs has widened the base of recipients to include younger patients and has contributed to an unpredicted rise in procedure volume[6]. In 2002, the American Academy of Orthopedic Surgeons predicted that 474,000 TKAs would be performed each year by 2030[7]. This number was surpassed in 2005, is now expected to double by 2016, and could reach 3.48 million by 2030[8].

A proportional increase of revision TKAs has accompanied the rise in number of primary TKAs. The number of revision surgeries increased from 12,000 in 1990 to 60,000 in 2005[9]. Revision TKAs are a significant expense for the health system. In 2005, the average cost of a revision TKA ranged on average from $61,465 to $43,527 in the United States[10]. This is approximately twice the cost of a primary TKA, due to longer and more frequent hospital stays, longer operative times, implant and instrumentation costs, and higher blood loss[11].

Infection is the primary cause of revision TKAs, responsible for 25.2% of revision surgeries[12]. The average cost of a septic TKA revision is three to four times more than primary TKA cost as it requires complete prosthesis removal as opposed to single component revision and expensive antibiotics[13,14]. Revision surgeries put patients at risk and consume myriad human resources, and many may be avoidable. A technique to promptly detect an infection in a knee implant, and subsequently reduce the number of surgeries, has merit beyond that of pure economics.

OrthoSensor, Inc. develops orthopedic devices that monitor, assess, and deliver critical medical information using sensors, microelectronics, and wireless technology[15]. Currently, OrthoSensor plans to expand into instruments intended for long-term use[16]. Due to the rising need for total knee arthroplasty and the accompanying rise in joint revision surgeries, there exists a market for an intelligent implant that helps patients avoid revision surgery through early infection detection.

III. Problem Statement

There exists no non-invasive method to detect infection in the knee following total knee arthroplasty.

IV. Need Statement

There is a need for a continuous, implanted sensing modality sensitive and specific to infection to reduce the rate of revision surgeries due to infection.

V. Specifications and Constraints

A. Overview

Through specification matrices and discussions with OrthoSensor, we have concluded the following:

1) The entirety of the sensing package will be housed in the tibial tray, enabling implementation compatibility with existing OrthoSensor technology. A glass window will be hermetically sealed in the top surface of the tibial tray to permit optical access to synovial fluid.
2) The insert itself will undergo extrusion modifications to allow fluid flow to reach the glass surface. The proposed modification includes places two small holes in the central anterior and posterior locations of the insert. This will not compromise the mechanical stability of the knee implant (see **XI–A: Mechanical Analysis**).

A summary of major specifications, solutions, and binary achievement outcomes are tabulated below:

Table 1. *Final Specifications.*

Specification	Proposed Solution	Achieved in 89/90
Infection Indicators	Identify indicators that are sensitive, specific, testable, and able to be scaled down	Yes ✓
Fluid Contact	Fluid contact should not be a concern due to homogeneous nature of SF	Yes ✓
Sensitive and specific	Detects changes comparable to 200 WBC/μL or greater	Yes ✓
Quick: <72 hours	Detects changes in infection indicators in <8 hours	Yes ✓
Implantable	Small enough to be embedded in knee implant	Yes ✓
Safe	Worst case is neutral for patient (no change from implant without our device)	Yes ✓
Automatic/continuous	Long battery life and high sample rate	Existing Technology
Non-invasive	Transmits data wirelessly	Existing Technology

B. Indicator Specifications and Justifications

Our device senses clinically relevant indicators of infection. We chose to detect specific indicators on the basis of sensitivity (how well a binary test correctly identifies positives as such), specificity (how well a binary test correctly identifies negatives as such), testability (existence of a binary classification test), and the existence of a sensor at the desired scale (to allow our group to focus on finding infection rather than creating sensors). Based on these criteria, our sensing device was designed to detect pH, turbidity, and color. Indicator specifications, quantifications, and selection are summarized in **Tables 1** and **2** in **Appendix A**. **Table 3** in the **Appendix A** describes the specifications for the indicators. See **Table 4** for detailed explanations, quantifications, and cited references.

C. Device Location/Implementation Specifications and Justifications

The polyethylene tibial insert is snapped onto the titanium or cobalt-chrome tibial component, which is embedded in the tibia and often cemented in place. The femoral component articulates on the tibial insert and is cemented into the femur. The patellar button is often cemented onto the patella and is not always necessary. [17] Based on conversations with surgeons, literature research, discussions with OrthoSensor, and knowledge gained over the course of this project, the tibial tray was selected as the most feasible location for a sensing package, with slight modifications to the tibial insert to encourage synovial fluid contact with the tibial tray. See **Table 5** and **6** in **Appendix A** for sensing mechanism geometry specifications and justification.

For the sensing mechanism geometry, we designed a channel in the bottom surface of the tibial (material removed from the planar face). The channel has two access holes that lead to the top of the tibial insert to allow synovial fluid to enter the channel where our optics can access it. This middle area on the insert's top face is free of soft tissues and is bathed in well-mixed SF via motion of the adjacent articulating surfaces that prevents scar tissue accumulation[18]. See **Table 7** in **Appendix** A for mechanism location specifications and justifications.

The infection detection sensors will lie in the tibial tray "looking" up (through the glass window) into the channel on the bottom of the insert. The channel allows the color sensors and light sources to work in reflectance or direct transmittance, and it provides constant access to synovial fluid. See **Tables 8, 9, and 10** for specifications, justification, and selection matrix.

Synovial fluid permeates all surfaces of the prosthetic components and will thus fill the channel.[19] Also, replaced knees have no ACL and often no PCL, leaving the space between the condyles clear of soft tissue.[20] As an added consideration, the knee joint capsule is posteriorly tight but anteriorly loose, further implying the anterior middle area as the ideal location for our sensing mechanism. This space provides a volume of well-mixed SF, as the bearing surfaces articulate on the medial and lateral sides. This motion also protects t sensing mechanism from becoming clogged with scar tissue. Polyethylene does not attract or bind well with soft tissues in the knee joint, sealing it as our optimal location[21].

VI. Methodology

The general methodology of approach is outlined below. ENGS 89 was largely devoted to the development of the testing apparatus and proof of concept of the sensor technology for a clinically relevant model of SF in the knee. In ENGS 90, the test chamber was scaled down, the sensor location was refined, and clinical to the sensor output data using white blood cell solutions was established.

Model Fluid	•Clinically relevant synovial fluid model
Design Sensors	•Obtain optical sensor and other electronic components •Write code to control sensors and data collection
Proof of Concept	•Test sensors • Impose various fluid conditions; e.g. infections, color, turbidity, pH
Iteration	•Scale to proposed dimesions •Investigate novel sensing mechanisms •Establish infection parameters with respect to data output

VII. Deliverables

OrthoSensor has agreed upon the following deliverables for this project. All are complete.

1. *Final Report* (this document): Proposed sensing method; Sensor recommendations; Experimental procedures and clinical validations; Clinically relevant thresholds for infection indicators; Algorithm for interpreting thresholds for infection indicators
2. *DVD*: Apparatus and analytical software; Data and plots from experiments; CAD files for test chamber & prototypes
3. *Physical Devices*: Working prototypes; Test chambers
4. *Clinical Study*: Anticipated device use; Discussion of effectiveness, efficacy, and safety; Procedure to gain FDA approval; Recommended future studies; Recommended market strategy

VIII. Proof of Concept

The sensing mechanism uses optics to detect synovial fluid color and turbidity and a pH sensor to detect synovial fluid pH.

A literature search was conducted to characterize the motion and location of SF in the knee and synovial membrane within the joint capsule. Based on OrthoSensor's recommendation, a computational fluid dynamics (CFD) model that was built in GAMBIT and FLUENT (both ANSYS programs). Several models demonstrated that neither the femoral forces on the polyethylene insert nor tilting the tibial tray plane had significant effects on SF flow. Rather, the joint capsule's motion squeezes the synovial membrane of SF, and the resulting pressures drive SF motion. See **Figures 1** and **2** in **Appendix A** for the Gambit geometry used and a screenshot of a FLUENT simulation of a "tracker" (specially marked computational cells that allow fluid flow visualization). However, there currently exists no literature on dynamic SF pressures within the knee's synovial capsule and our group had no means to conduct in-vivo studies on synovial capsule pressures in healthy and infected human knees. We consulted with a GAMBIT and ANSYS Design Modeler and Senior Technical Services Engineer (and lecturing Dartmouth Professor), Chi-Yang Cheng, who advised that it did not appear feasible to make a simplified yet rigorous CFD model.

The proof of concept is thus the result of information culled from literature research and interviews with orthopedic surgeons. To ensure that the sensing mechanism will function accurately and reliably in the knee implant, it sensing must have access to approximately 10-25 mm^3 of synovial without contact with tissue. This constraint drove the decision to embed all electronics in the tibial tray and collect synovial fluid within the tibial insert.

IX. Clinical Study

We have outlined a clinical study to assist OrthoSensor after the conclusion of ENGS 89 and 90. It includes proposed solution methods as well as a description of how we anticipate the device to look and behave. The study also describes two design choices, pros and cons, and data interpretation and use. To ensure that the device's full capabilities are understood, we describe the anticipated device use and our clinical validation studies to demonstrate effectiveness as part of our proof of concept. We address our experimental assumptions and shortcomings and advise in-vivo studies to establish safety and efficacy with respect to our device.

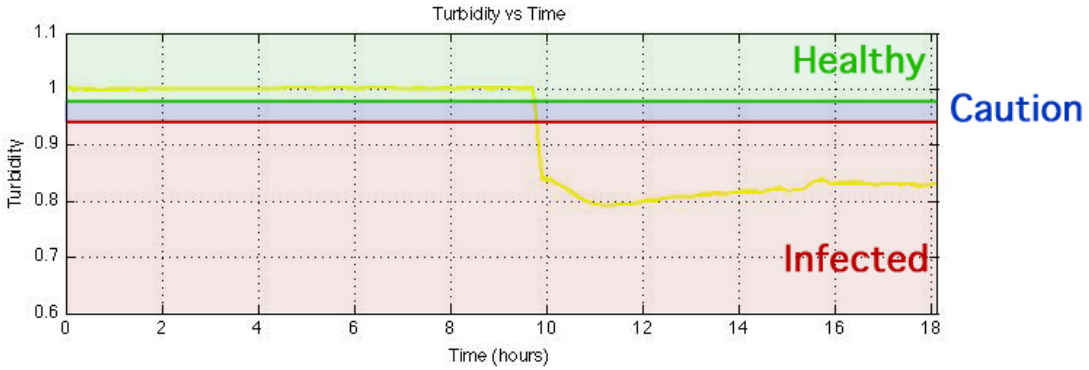
Also included in the clinical study are several design decisions OrthoSensor will need to make regarding our device. We provide recommendations on sensors and batteries as well as charging methods. In anticipation of the implemented device being ready for production, the clinical study outlines the FDA approval process and the associated costs based on the device's reception. We provide recommendations on comparable devices in the market to aid demonstration of similarity. We also propose a market strategy to introduce the implemented device to the biomedical device market, a strategy described later in this report.

The clinical study can be found in its entirety in **Appendix D**.

X. Summary: Data Interpretation and Use

Data the device generates is interpreted as follows: Infection indicator values are recorded at specific times and the data is transmitted wirelessly. This information is represented graphically below for turbidity. Note that Alpha = 1 – Turbidity.

Figure 2. *Example output data graph for turbidity.*



The bars drawn on the graph represent clinically relevant tolerances for turbidity, included in the chart below (see ***Table 2***). Each range of values for each infection indicator has a corresponding Data Score, ranging from 0-2. All values above the green line are considered "healthy" and correspond to an alpha value in [0, 0.03] or a turbidity value of [0.97, 1]. Values above the red line and below the green are alpha values in [0.03, 0.06] and correspond to turbidity values in [0.94, 0.97], and those below the red line are in the infected range.

Table 2. *Scores based on infection tolerances for indicators of infection*

Indicator		Healthy	Caution Advised	Infected
		Score: (0)	*Score: (1)*	*Score: (2)*
pH		7.23 - 7.39	7.18 - 7.23	0 - 7.18
Referenced Color	Red	244 – 255	230 - 244	0 - 230
	Green	240 – 255	210 - 240	0 - 210
	Blue	230 – 255	200 - 230	0 - 200
Color Corrected Turbidity		0.97 - 1.00	0.94 - 0.97	0 - 0.94

pH and Turbidity each have a data score of 0, 1 or 2 according to where the data falls in the given ranges. Color's data score is a 0, 1, or 2 based on the average data score among red, green, and blue, rounded to a 0, 1 or 2. If this system proves ineffective *in vivo* (our device does not detect infection as soon as it should), a more conservative system would assign a color data score based on the highest data score among red, green, and blue.

The device would then transmit a conglomerate score to the end user, a three-digit number such as "001" or "202". The end user would refer to the following chart, ***Table 3***, for the corresponding recommended course of action. These values are the result of experiment, literature research, and analysis rather than in-vivo trials, which are necessary to confirm the presence of infection in the future development of our novel device and discussed later in this clinical study. Scores consisting of varied orders of three-number combinations are viewed as equivalent (001 = 010 = 100).

***Table 3**. Interpretation of Data Scores for indicators of infection*

Infection Status	*Scores*	*Recommended Action*
Infected	222, 122, 022	Infection or failure likely. Medical attention highly recommended.
Caution Advised, II	111, 112, 002	Infection probable. Medical attention recommended.
Caution Advised, I	001, 011	Increase data delivery; download data more often. Infection possible.
Healthy	0	None.

In the post-operative period, a trend-fitting algorithm can use our device's outputs to detect trends or changes in the infection indicators enumerated above. A decreased pH, a trend away from clear toward strong colors, and an increased opacity or turbidity are all indicative of infection[22]. Part of the proposed clinical study will serve to define a clinically relevant length of time over which these trends occur to indicate infection. Ideally, the data would furnish analogous two charts as above. The post-operative state of a knee following surgery is highly patient specific due to the invasive nature of the operation as well as the differing amounts of blood, medicine, and other fluids in the joint, necessitating the use of trends and slopes rather than absolute numbers as in the long-term period.

XI. Work Done

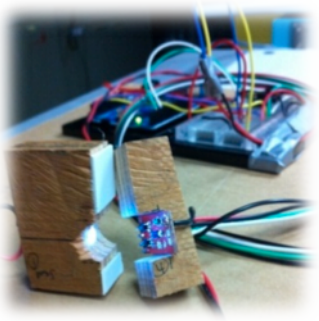
A. Mechanical Design

Sensor Location

Based on discussions with OrthoSensor, the sensing mechanism location is limited to the tibial tray. OrthoSensor indicated that placing sensing mechanisms in the tibial insert or in the femoral component would be excessively difficult due to problems with hermetically sealing the electronics and with integrating the electronics across three separate prosthetic components. OrthoSensor said, however, that there is considerable freedom within the tibial tray with regard to sensor type, size, and orientation. They explained that there is flexibility to place electronic components inside of the tibial tray and have already done extensive investigation into the hermetic sealing process and potential electronic architecture within the tray. They also said that they are comfortable placing a window in the top surface of the tibial tray, which complements this project's need for optical accessibility to synovial fluid.

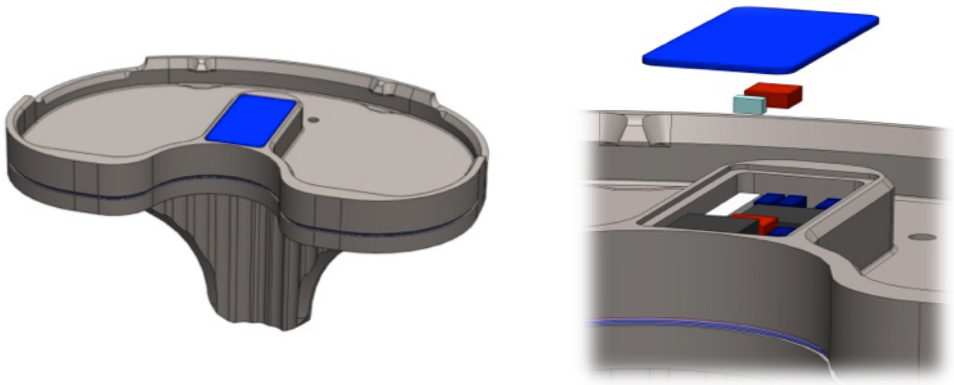
With the constraint that the entire sensing mechanism must be contained within the tibial tray, the challenge became how to detect changes in fluid color and turbidity using the reflection of light off the synovial fluid and tibial insert. This was a departure from the initial sensor proposal which had a color sensor mounted opposite of an LED, with synovial fluid flowing between the light source and color sensor. This early test-setup (pictures below) was based on fluid presence between the light source and color sensor, with the fluid acting as a light filter.

***Figures 3 and 4.** Images of the early test set-up. The clear plastic tube on the right contains infected bovine synovial fluid. A color sensor and LED were mounted opposite of one another.*



With the constraint that all of the sensors must be mounted in the tibial tray, the light source and the color sensor must be mounted adjacent to one another, each facing upwards from the window on the top surface of the tibial tray.

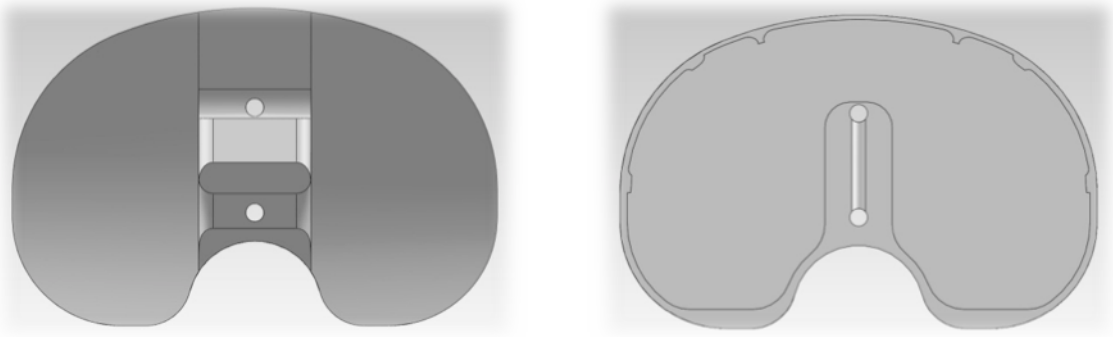
Figures 5 and 6. *CAD renderings of the proposed color sensor (red) and proposed light sensor (green) and their location adjacent to one another under a window in the tibial tray.*



Implementation of the Sensors in the Knee

For the sensors to work correctly, the top surface of the tibial tray must have access to the synovial fluid that lubricates the joint. Although the tibial insert sits directly on the top surface of the tibial tray, every component of the implant will come into contact with synovial fluid due to the kinematics of the knee. However, to ensure that the optical sensors have more than enough exposure to synovial fluid, we propose placing two small holes in the central anterior and posterior locations of the tibial insert that run from the top surface of the insert to the bottom. These holes will be connected by a small channel on the bottom surface of the insert to permit fluid flow.

Figures 7 and 8. *View of the top of the insert demonstrating the proposed hole location. View of the bottom of the insert demonstrating the channel.*



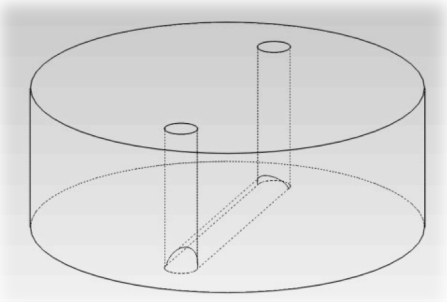
Test Setup

A test chamber was fabricated with the color sensor and the light source mounted adjacent to one another to test the ability of the sensors to detect color changes in synovial fluid using reflection.

Ultra-high molecular weight polyethylene (UHMWPE) was machined into a puck shape to represent the tibial insert. A ball-end mill was used to machine the cylindrical channel in the bottom surface of the insert. As

proposed for the actual insert, two holes were drilled through the puck (from the bottom surface to the top surface), originating at the end of the cylindrical channel.

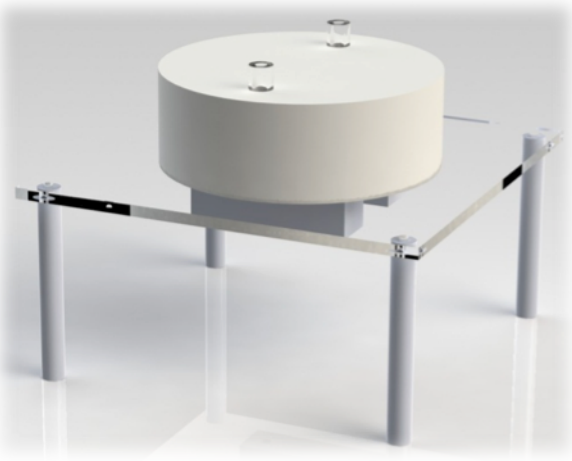
Figure 9. *Channel Extrusion*

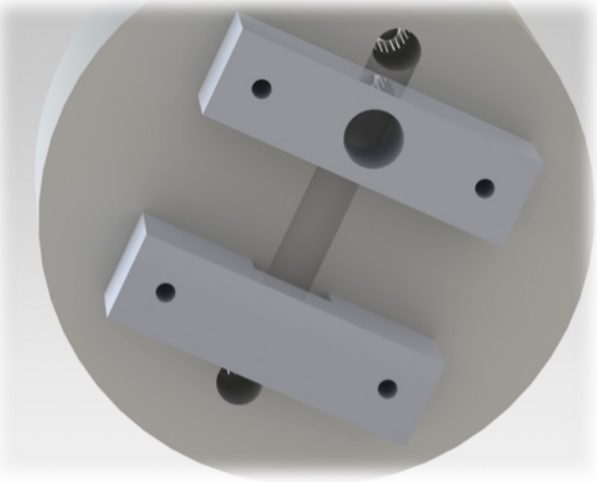


The bottom of the UHMWPE puck was then attached to a clear Plexiglas plane (representing the top surface of the tibial insert) with screws and silicone to create a fluid-tight seal. A color sensor and an LED were mounted on the Plexiglas plane across the channel.

Figure 10 (left): *An isometric view of the CAD model of the test setup. The white "puck" represents the tibial insert and the plexiglass plane it sits on represents the window in the top surface of the tibial tray.*

Figure 11 (right): *A view from the bottom, illustrating the channel in the bottom of the insert. Aluminum brackets hold the color sensor and light sensor in place across the channel.*





Bovine serum was poured into the top holes, allowing fluid to occupy the bottom channel. The serum was seeded with and infection and the entire test setup incubated while continuous color data was recorded.

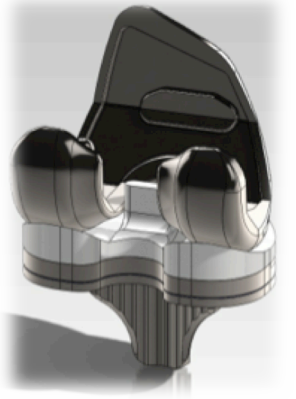
Mechanical Analysis

A mechanical analysis was performed of the modified implant geometry. The mechanical behavior of the implant with one central anterior hole and one central posterior hole was studied in order to determine if these holes would compromise the implant structure. Experimental mechanical testing with fabricated final prototypes will eventually be necessary to validate the mechanical behavior of the implant before clinical trials, but this step is well beyond the current state and scope of the project. A finite element analysis (FEA) of the implant, however, is an effective and reliable tool to provide a basic understanding of the mechanical behavior

of the tibial insert under various loading conditions. This FEA analysis provides a very general idea regarding the stress distribution in the tibial insert.

CAD files of the Stryker Scorpio tibial tray and femoral component were provided by OrthoSensor and the tibial insert was created using a physical Stryker Scorpio insert and SolidWorks CAD software.

Figure 12. *Full implant assembly*



Materials

OrthoSensor is developing their sensor using a Stryker Scorpio total knee revision system with an X3 Advanced Bearing tibial insert.[23] This insert (along with the vast majority of other bearing components used in orthopaedic implants) is made of ultra-high molecular weight polyethylene (UHMWPE).[24] UHMWPE was first introduced in an orthopaedic application in 1962 by Sir John Charnley and offers superior mechanical strength and wear reduction compared with conventional polyethylene. This increase in performance is primarily due to the high degree of cross-linking between the long hydrogen-carbon molecular chains of the polymer. The precise mechanical properties of the UHMWPE used in the X3 Advanced Bearing insert is proprietary information and Stryker refused to provide these values. However, UHMWPE is known to have the following mechanical properties:[25]

Property	Value
Poisson's Ratio	0.46
Modulus of Elasticity (MPa)	500*
Yield strength (MPa)	21**
Ultimate Tensile Strength (MPa)	39***

** The published values for modulus of elasticity range from 500 to 800 MPa. 500 MPa was used conservatively.*
*** The published values for yield strength range from 21-28 MPa. 21 MPa was used conservatively.*
**** The published values for ultimate tensile strength range from 39-48 MPa. 39 MPa was used conservatively.*

The femoral component of the Scorpio Stryker system is a cobalt-chromium (CoCr) alloy with the following material properties:[26]

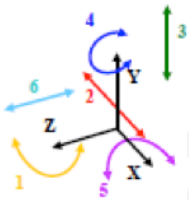
Property	Value
Poisson's Ratio	0.3
Modulus of Elasticity (GPa)	195

The FEA only involves determining the stress distribution within the UHMWPE insert, but determining the loading conditions requires finding a Hertzian contact area between the femoral component and the tibial insert (see ***Loading*** below). This requires knowledge of Poisson's ratio and modulus of elasticity for the Co-Cr component.

Fixtures

The bottom surface of the tibial insert was fixed in all six degrees-of-freedom.[27]

1. flexion/extension
2. anterior/posterior translation
3. traction/compression
4. internal/external rotation
5. varus/valgus
6. medial/lateral translation



Loading

A vertical load of 3200 N was applied to the tibial insert (this force represents a conservative estimate based on relevant literature regarding static knee joint loading).[28] This force was modeled as pressure evenly distributed between the medial and lateral contact areas of the insert.

Analysis was performed with the femoral component oriented at 15° (heel-strike), 45° (mid-stance) and 60° (toe-off) to represent the full gait cycle.

15°

45°

60°

The contact surface between the femoral component and the tibial insert was modeled as a sphere-sphere Hertzian contact surface. The contact surface was calculated using the equations shown in **Appendix A, Figure 6**[29]

With a constant load, this contact surface varies as the orientation of the femoral component changes because the radius of the femoral component is not constant as it rotates. The contact surface is an ellipse and it is often necessary to calculate a radius in two-dimensions (one for the two relevant cross sections of the femoral component). However, the Scorpio Stryker femoral component is flat on the bottom and it can be assumed that the width of the femoral component in each orientation is constant. Therefore the contact area can be represented as an ellipse with its major dimension being the width of the femoral component and its minor dimension being the radius of the contact circle. The calculated contact areas are:

Orientation	Contact Area (mm^2)
15°	61.54
45°	44.59
60°	40.38

Appendix A, Table 11 contains the sphere-sphere Hertzian contact surface calculations.

Results

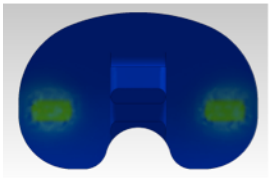
The maximum, average, and center stresses at the center of the top surface of the tibial insert are as follows:

Table 4. *Stresses on implant components*

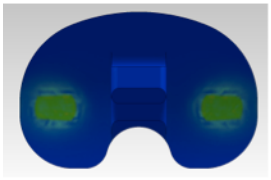
	15°		45°		60°	
	Original Insert	Modified Insert	Original Insert	Modified Insert	Original Insert	Modified Insert
Maximum Stress (MPa)	12.84	12.86	16.47	17	19.92	20.21
Average Stress (MPa)	1.214	1.124	1.383	1.223	1.525	1.26
Stress at Anterior Hole (MPa)	N/A	0.1502	N/A	0.1001	N/A	0.1186
Stress at Posterior Hole (MPa)	N/A	0.1513	N/A	0.0867	N/A	0.1196

Below are the stress distributions of the original and modified inserts at the three orientations of the gait cycle.

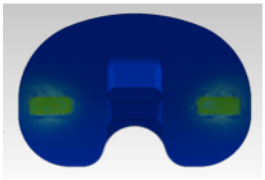
Figure 13. *Original Insert*



15° (Max = 12.84 MPa)

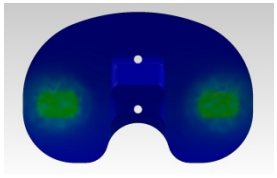


45° (Max = 16.47 MPa)

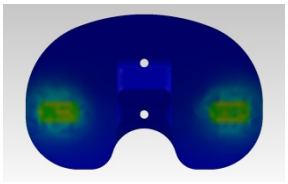


60° (Max = 19.92 MPa)

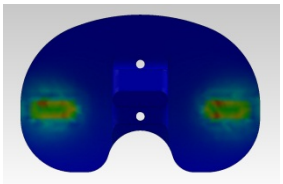
Figure 14. *Modified Insert*



15° (Max = 12.86 MPa)



45° (Max = 17 MPa)



60° (Max = 20.21 MPa)

Note: The stress gradients in the six images are not constant (eg. green for 15° does not correspond to the same stress magnitude as green for 45°. Note the labeled maximum stresses and the table values.)

See ***Figures 7 and 8*** in **Appendix A** for larger images of stress distributions.

These results indicate that adding an indent in the top center of the tibial insert does not compromise its mechanical behavior.

The ultimate accuracy (and therefore relevance) of this FEA, however, is limited by a number of factors. UHMWPE exhibits non-linear mechanical behavior under loading (UHMWPE is known to have nonlinear strain-rate sensitivity, creep, and relaxation behavior.)[30] SolidWorks is not equipped with a non-linear package and is limited to linear stress analysis. Material properties such as plasticity and hyperplasticity are therefore neglected, as are contact boundary nonlinearities. SolidWorks is not equipped with a dynamics package; while this FEA includes analysis of the insert in flexion and extension in the worst possible cases, the model neglects the true dynamic nature of the flexion and extension process. Important dynamic aspects such as steady-state harmonic analysis and random

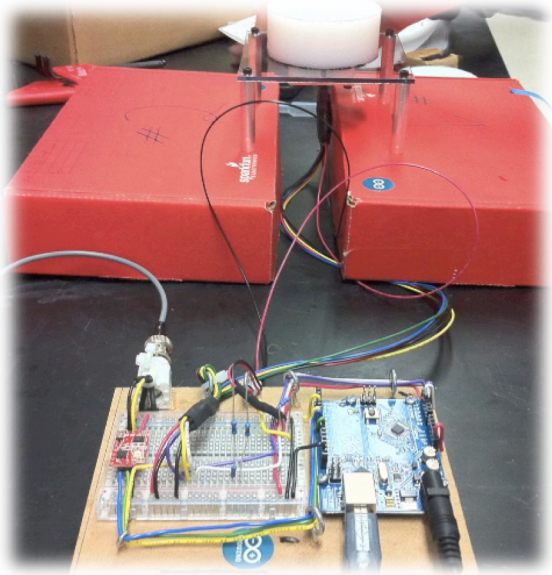
vibration effects are therefore neglected in this model. ABAQUS, which has the capability to analyze non-linear and dynamic systems, would provide a more robust and accurate FEA of the tibial insert. The complexity of an accurate ABAQUS FE model to integrate the non-linear and dynamical aspects of the tibial insert under loading is on the order magnitude of its own 89/90 project and likely unnecessary for this project's proof of concept. A SolidWorks static analysis of the worst possible cases in flexion and extension is adequate to demonstrate that the stresses in the center of the top surface of the insert are not significantly higher with the modified the geometry compared to the original insert.

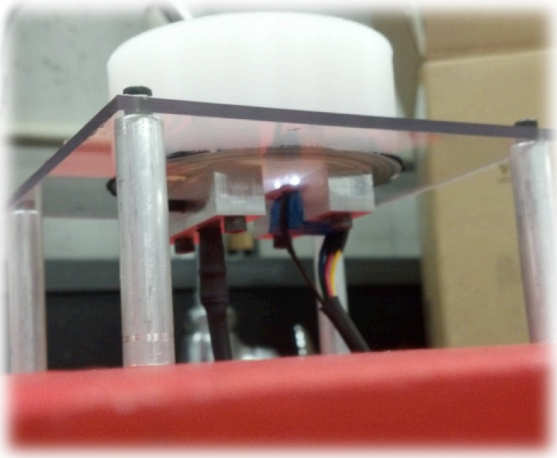
B. Electronics Design and Implementation

Sensing System Overview

We have developed a sensing package to monitor and record changing properties of synovial fluid as an infection develops. The core of the system is a microprocessor based data collection unit that we have programmed to collect and store the sensor values. The microprocessor directs the sensors to take a sample, saves the sample to memory, and times the samples for optimal resolution based on expected total experiment duration. After the experiment has concluded the data can be downloaded to MatLab and processed with scripts we have developed to extract relevant patterns and important features.

In general, a sample of inoculated synovial fluid (diluted bovine serum) is placed in the test chamber, the sensors are attached to the chamber and/or immersed in the fluid, the entire apparatus is placed in an incubator set to 37C, and the unit is directed to begin taking samples. The current sensors include a subtractive color optical sensor and a pH probe, which allows monitoring of turbidity, particulate color, composite color, and pH. Our final experimental setup is pictured below (see A**ppendix A: Figures 3 - 5** for the first iteration of our setup).





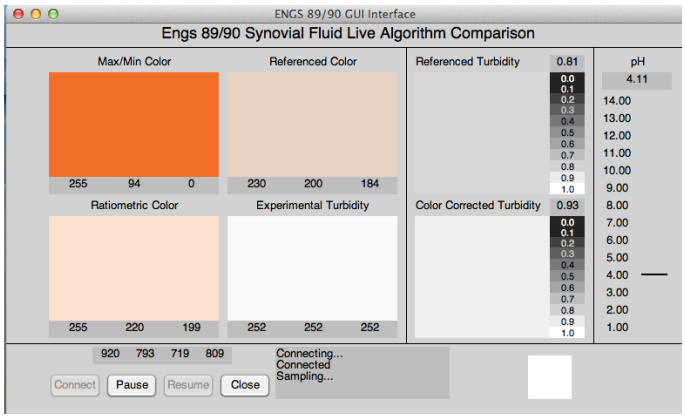
Figures 15 and 16. *Final experimental setup. Note sensor location on right is indicated by glowing LED*

Optical Sensor

The sensor, the ADJD-S311-CR999 by Avago Technologies, is a self-contained digital unit with external dimensions of 2.2mm x 2.2mm x 0.76mm. The small form factor will facilitate easy installation in the confined space within the implant. Additionally, the 9mW active power usage and 5μW sleep mode draw will ensure that the overall system will have good battery performance. Internally, the sensor functions in three stages: capacitors that function as an analog integrator, an integrator with a variable time window, and a 10-bit analog to digital converter (ADC). Gain is set by selecting the number of capacitors and the window of integration such that the maximum expected intensity of light registers near the high range of the ADC (1023).

The calibration algorithms use the capacitor selection option to balance the four channels to each read the same value under white light. The four channels are: Red (645±20nm), Green (542±35nm), Blue (460±25nm), and clear (400-700nm). Once the capacitors are set, the gain is found by using a binary search to set the data to 1000 out of 1023 to ensure the best possible resolution. The sampling algorithm illuminates the fluid with an LED, takes 64 samples in rapid succession and averages them to reduce noise before disabling the LED and returning the value, which is saved to the EEPROM. We created a graphical user interface to display color output from our sensors, shown below in ***Figure 17*** (see **Appendix C** for additional information regarding optics).

Figure 17. *Live Color Algorithm GUI*



pH Sensor

The sensor is a combination of an electrostatic probe by Atlas Scientific and a circuit board by SparkFun electronics to read solution pH and take temperature dependent readings. The probe is not suitable for implantation, however it will be sufficient to gather data about how pH changes during the development of the infection in the fluid. There are MEMs implantable pH sensors that are available in bulk or through agreements with distributors that we do not have access to, that would be available in a final design. The software has been developed to calibrate and operate the pH probe however there hasn't yet been an experiment run with the pH probe installed. It is important to note here that the size of the pH sensor has prevented us from being able to use it in our final, scaled-down test chamber, but several options exist for small scale measurements.

C. Biological Modeling

In testing our sensors, we sought to achieve the most clinically relevant model possible. From published data, we determined relevant substances to simulate a synovial fluid infection in the knee, tabulated below.

Table 5. *Biological parameters and our selected experimental models*

Parameters (*In Vivo*)	Experimental Analog	Justification
Synovial Fluid	**Bovine Serum**	Current ISO standards in wear testing [31,32]
Bacterial Organism	***Escherichia Coli***	Effective model for knee infection organisms[33,34]
Physical/Chemical Characteristics	**Color, turbidity, & pH**	State of the art for joint aspiration infection indicators[35,36]
Infection Propagation	**Incubation and WBC analysis**	Need to establish clinical relevance to indicator detection

D. Experimentation

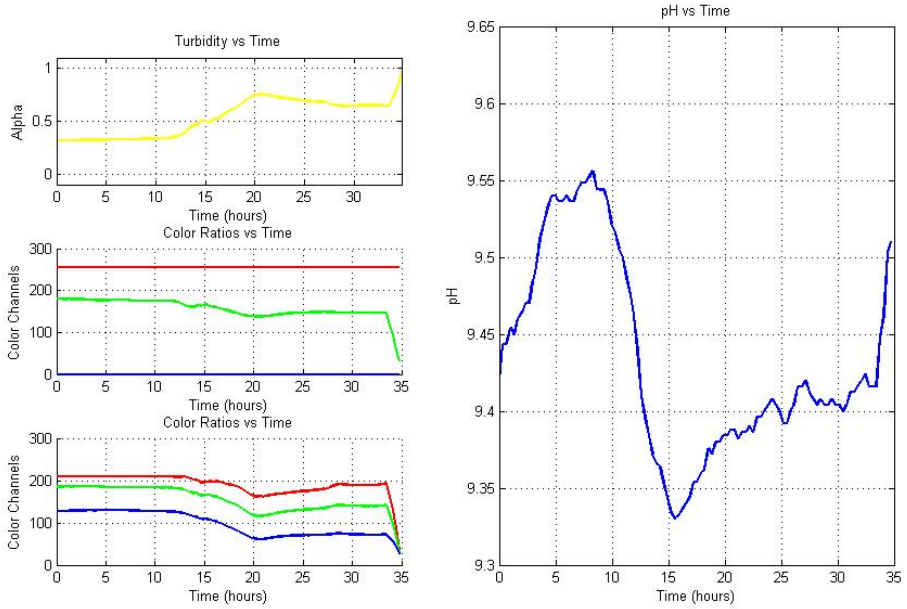
Incubation

Materials and Methods

In our incubation experiments, we used both bovine calf serum (Sigma Aldrich, St. Louis, MO) and fetal bovine serum (HyClone, Thermo Scientific, Logan, UT). Lab strain *E.coli* was available in the biotechnology teaching labs within the Thayer School of Engineering. Bacteria was grown in a liquid culture overnight, and then quantified with a spectrophotometer to ensure optimal growth (an optical density of between 1 and 2 for a wavelength of 600 nm)[37]. For testing using the final iteration of our test chamber, an aliquot of the liquid culture (~350 µL) was diluted in 2 mL bovine serum and injected into the chamber. Our experimental setup was portable, so once the sensors were prepared to take data, we completely enclosed the equipment within a 37 °C incubator. Most infection runs were between 18 and 36 hours, however the bacteria generally propagated within the first 5-15 hours of the incubation.

Results

Figure 18. *Sample output following an infection run*



The graphs in Figure 18 represent a typical output from our sensors following an incubation run. Note the infection taking off around 12.5 hours, which is reflected by the turbidity increase, color channel changes, and pH decreases. In addition, all three parameters appear to drift back towards the starting conditions and approach some equilibrium value. The exact mechanism for this is unclear, but we suspect that the bacteria have run out of nutrients and start to die out. Additionally some sedimentation of suspended particles may be contributing to the drift.

White Blood Cell Correlation

Materials and Methods

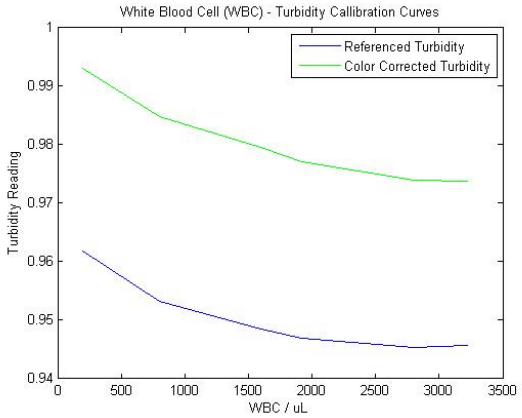
We purchased bovine blood to use in experiments designed to mimic the immediate post-operative environment of the synovium. However, the blood also provided a source of white blood cells, which are produced in the knee during an immune response and are often counted as part of a clinical procedure to diagnose infection. In fact, there is a clinically acknowledged threshold of 3,000 WBC/µL above which infection is likely. We sought to give more relevance to the turbidity data our sensors were generating, so we designed an experiment to correlate a concentration of white blood cells with the numbers from the output of our sensors. In addition to bovine blood, we

obtained chemicals to help isolate and purify the white blood cells, a centrifuge, and a hemocytometer (microscope with ruled slide for cell counting). The general protocol is as follows (full protocol in **Appendix B**):

1. Isolate WBCs from whole bovine blood
2. Resuspend WBCs in bovine serum
3. Quantify WBCs using hemocytometer
4. Measure turbidity while varying WBC concentration

Results

***Figure 19**: Correlation between turbidity readings and WBC concentration. Note color corrected turbidity is higher since the red light absorbed by the color registers incorrectly as being absorption across all channels. The color corrected turbidity accounts for absorption of individual channels by color and only looks at absorption across all channels.*



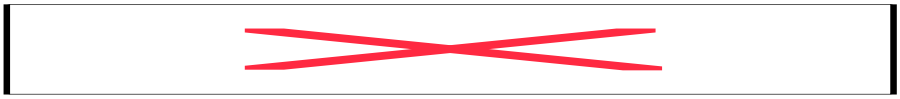
In order to determine the sensitivity of our system, we were interested in detecting turbidity at low concentrations of WBCs, at or under the clinically reported threshold for infection. We were able to detect subtle changes in turbidity at concentrations as low as 200 WBC/µL, and as expected observed a decrease in turbidity reading as the WBC concentration increased (**Figure 19**). It is important to note that *in vivo*, there will be more activity in the synovial fluid with the propagation of bacteria, wear particles or tissue fragments. However, we wanted to establish a low end detection range to show the high degree of sensitivity of our sensing system.

E. Additional Analyses

Implementation Analysis

In order to communicate the data to a physician the device must have some manner of downloading data. We have identified a low-cost, ultra-low power, commercially available technology that can meet that need. The CC2540 Bluetooth® Low-Energy v4.0 chipset by Texas Instruments retails for $20 in a 6mm x 6mm system-on-a-chip. It provides a 30nA standby current, 100m range drawing 24mA for 0.6ms, and can solve this problem very easily.

The battery could be Quallion medical grade Li-Ion battery that is designed to last 25 years in the body, is made of bio-safe sealed materials, provides 20mAh of power, and only self-discharges 14% in 3.5 years. Using the battery and radio above along with the sensor package drawing 2uA in standby and 21mA during a 1 second sample, we see that device can operate for:



Using data from the above mentioned devices we find that we can run the sensor package for 1 year, sampling once per day and transmitting the results all from a single battery charged before implantation.

Sensor System Constraints

The sensor system must operate for up to 25 years in a human body with minimal risk of failure. Therefore it is subject to a number of constraints. The components must each have a mean-time-between-failure (MTBF) that is sufficiently high that when combined as a system the device's MTBF is larger than 100,000 hours. Additionally, the system must have components that are designed to function correctly at 37°C for 10+ years. This is especially an issue for batteries whose capacity declines sharply with age. The system must fit within the knee implant without causing mechanical weakening. In order to prevent interference with bodily functions the sensors shouldn't release any significant energy into the surrounding tissue (heat, laser light, radiation, etc) that affects normal processes.

Failure Modes: Safety and Reliability

A good design is safe and reliable[38]. We are consistently aware of safety and reliability concerns throughout all aspects of development. Important factors to keep in mind include use/misuse, codes and standards, and hazards (acute, ergonomic, and environmental). **Table 6** below outlines some examples of risk assessment that we applied to our design. Another important consideration is reliability. A design is reliable if: (1) it fails infrequently, (2) fails in such a way to be easily detected and repaired, and (3) fails in a safe manner. **Table 7** below provides examples of Failure Mode, Effects and Criticality Analysis (FMECA).

Table 6. *Risk Assessment Examples*

Design Under Evaluation	Nature of Hazard	Assessment				
Polyethylene insert	Misuse such as running may induce excessive wear	LO	FE	DPH	NP	HRN
		1	.1	2	1	0.2
		Degree of Risk: Acceptable				
Data transfer	Misuse such as neglecting to transfer data daily	LO	FE	DPH	NP	HRN
		2	1	2	1	4
		Degree of Risk: Very Low				
Location of sensor	Cutting into polyethylene insert may create pinch points	LO	FE	DPH	NP	HRN
		1	5	.5	1	2.5
		Degree of Risk: Very Low				
Electronics stability	Impact to knee may damage electronics	LO	FE	DPH	NP	HRN
		1	.1	1	1	.1
		Degree of Risk: Acceptable				

Table 7. *FMECA Examples*

Function	Failure Mode	Effects	Cause	Control Method	RPN			Total	Action Plan
					Severity	Occurrence	Control	RPN Score	
LED sensor	Sensing cavity clogs	LED light cannot penetrate – data output unusual	Build-up of particles (wear or biological)	Subcutaneous cleaning	4	6	6	216	**Mandatory**: Design sensor location as to minimize potential occurrence
LED sensor	LED blows out	Data stops collecting	Defective LED	-	3	1	10	30	No action required
Power supply (e.g. battery)	Battery loses charge	Data stops collecting	Battery not replaced or charged as necessary	-	2	3	4	24	No action required
Electronics	Circuit fails to draw current	Sensors cannot operate	Loosening of wire connection	-	5	2	3	30	No action required

XII. Economic Analysis

A. Budget / Expenses to Date

Item	Cost
Electronics (Arduino, Optics, pH)	($367.34)
Test Chamber Materials	($27.39)
Bovine Calf Serum and Magnesium Hydroxide	($59.40)
Fetal Bovine Serum	($122.00)
Bovine Blood	($134.36)
Misc (Food coloring, paint, etc)	($9.48)
Nano-Mesh pH Sensors	($160.00)
Total Spent	**($879.97)**
Budget	**$1,000.00**
Remaining	**$120.03**

B. Discussion and Analysis

A detailed discussion and analysis regarding the impact expected for this device in the medical implant market is included in the Clinical Study found in **Appendix D**. In summary, we expect that the rising number of TKA procedures coupled with the high cost of procedures will encourage use of OrthoSensor's instrumented knee replacement, which will be both a better implant and drive long term savings for insurance providers. Even with an implant price increase of nearly 40%, we have calculated that we will remain a viable option in the marketplace. However, we anticipate adding only ~$250 to the total cost of the implant if one accounts for parts and R&D costs. If our implant is successful, it would save $2,800 per implant over its lifetime.

C. Final R&D and FDA Trials

OrthoSensor would need to conduct additional research and development to finalize the interface between their ASIC and the delivered sensors. As well as face the multi-million dollar fixed cost of the ASIC design as mentioned above. Beyond that the standard costs of R&D for a knee implant would apply. This is discussed in detail in the Clinical Study found in **Appendix D**.

D. Future Financial Liability

Implant failure or side effects are very serious concerns, not only for physicians and patients but also for the company that manufactures the implant. A detailed discussion on this topic may be found in the Clinical Study in **Appendix D**. In summary, This implant is no more likely to fail than other implants and should follow standard industry practice

E. Market Entry Strategy

In order to reach the target market of global primary implants, it may be beneficial to start in the US two stage septic revision market. Every year there are approximately 14,000 revisions due to septic infection of the primary implant.[39] These revision typically involve a surgery to remove the infected implant, a spacer made of an anti-biotic impregnated bone cement that fills the gap left by the removed implant, and a second surgery 6-12 months later to remove the spacer and install the revision implant. The role of the temporary spacer is to deliver medicine directly to the infection site, allow the patient to walk with crutches while the infection heals, and to maintain the soft tissue integrity during the interim period.

This spacer presents an opportunity to quickly break into a market with fewer constraints and develop brand identity as well as provide data on performance before entering the highly competitive primary implant market. The device would only have to perform for a maximum of 1 year; this alleviates the tight restrictions of battery life and component longevity. The data provided by the device would allow the physician to monitor the infection as it clears and proceed with the revision surgery sooner than would otherwise be possible. The patient data over time would be combined to develop a detailed model of infection behavior, which would yield highly accurate trigger points of a developing infection.

Most design details could be testing in a known environment and examined for physician/patient feedback. Additionally, with the current solution physicians make a mold of the primary implant, pour the bone cement, and allow the mixture to set. With our sensors pre-set into a small rectangle of bone cement with the required channel geometry set into the bottom all that would be required is that our device be dropped into the mold prior to pouring the rest of the cement. The cement would bond with our device, ensuring mechanical stability, and form the completed custom spacer. New spacer material designs in Germany gained 14% market share within the first year, using this as a basis estimate, we are looking at 2,000 devices in the first year.[40] Once the device is on the market, the FDA approval process for a primary instrumented knee becomes much shorter, the brand is known in the medical community, and all potentially design features have had a chance to be tested.

XIII. Client Relations

There has been sufficient contact with the industry-based sponsor through weekly group emails, and individual members often additional emails to gather information or introduce ideas. Approximately every two weeks or so we hold a teleconference with Leon Radziemski and/or Marc Stein. Teleconferences entail an update on individual and group progress and an exchange of ideas regarding the project's trajectory. Our sponsors have been clear in their objectives and very responsive, and we have established the previously stated deliverables with them.

The client is pleased with the progress thus far. During a recent teleconference, Marc Stein stated, "You guys have done some really excellent work here; I'm highly pleased with the progress you all have made." The relationship between our sponsors and our group is open and conducive to allowing us to respond to their expectations.

Our faculty advisor is Dr. Michael Mayor, with whom we did not set a rigid schedule for meetings. Instead, we send group emails often, have teleconferences when necessary, and have met several times at critical points. Individual group members often send additional emails with questions and updates.

Appendix A: Tables and Figures

Table 1: Summary of Indicator Specifications and Quantifications

Specifications	Justification	Indicator	Quantification	
			Healthy	Infected
Sensitivity vs. Specificity	Indication of infection or healthiness	pH	7.23±0.09, 7.30±0.09	7.06±0.12
		Glucose	<10 mg/100 mL	>20 mg/100 mL
		ESR	75±30 mm/hr	80±29 mm/hr
		SF-WBC	13-180 cells/μL	300+ cells/μL
		Turbidity	clear, 5-50 NTU	cloudy, ~500 NTU
		Volume	0.5-3.5 mL	0.55-71 mL
		Color	clear to 632 nm light	opaque/yellow, absorbs light red
		C-Proteins	<10 mg/L	>10 mg/L
		Gram Stains	Blue, 99% specific	Pink, 7% sensitive
		Temperature	T±ΔTN	T±ΔTI
		Clotting	Firm	Friable
		Viscosity	Baseline	0.1*Baseline
Testability	Need to quantify the indicator within the knee implant		No differential (measurements external to the knee) required	
			Indicator measurements can be read to the tolerances above	
Sensor Existence	More time and cost efficient to work with existing sensors on the scale we need		Scale: Must fit inside knee implant components	

Table 2: Selection of Indicators

Indicators	*Appears in infected knees*	*Doesn't appear in healthy knees*	Testability	Sensor Existence	Fraction	Normalized with Geometric Mean
	Sensitive	Specific				
WEIGHT	2	1.5	1	2		
pH	2	2	2	2	1.0	1.90
Glucose	1	2	1	2	0.8	1.47
ESR	2	1	0	0	0.4	0.81
SF-WBC	2	2	2	0	0.7	1.32
Turbidity	2	2	2	2	1.0	1.90
Volume	1	2	0	0	0.4	0.73
Color	2	2	2	2	1.0	1.90
C-Proteins	1	1	2	0	0.4	0.81
Gram Stains	0	2	1	0	0.3	0.59
Temperature	1	1	2	2	0.7	1.39
Clotting	0	2	0	0	0.2	0.44
Viscosity	0	2	0	0	0.2	0.44

Table 3: Represents a description of the specifications for the infection indicators.

Specification	Description
Sensitivity	$Sensitivity = \frac{number\ of\ true\ postives}{number\ of\ true\ positives + number\ of\ false\ \ negatives}$ The indicator must appear in a nonzero number of infected knees, and a binary classification test must exist. The indicator has high sensitivity if a negative result from the binary classification test suggests the absence of infection. Sensitivity above 80% received the highest score; 60-80% received the middle score; below 60% received the lowest.
Specificity	$Specificity = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ \ positives}$ The indicator must not appear in all healthy knees, and a binary classification test must exist. If an indicator has high specificity, a positive result from the binary classification test means high probability of infection. Specificity above 80% received the highest score; 60-80% received the middle score; below 60% received the lowest.
Testability	The indicator must have a binary classification test. The test must have clear delineations between a healthy as opposed to an infected knee. The indicator is testable if it is feasible to quantify it and specify ranges for healthy and infected. In addition, the conduction of this test must have practical feasibility and be measurable within the volume of the knee implant components. It also must not impact a patient's health negatively or obstruct normal daily activities.
Sensor Exists at Desired Scale	The sensing method must be sufficiently small to reside within the knee implant parts (in addition to OrthoSensor's components) without compromising the implant's structural integrity (see "Size" specification under "Sensing Methods Specifications"). The existence of a sensor at this scale will increase the time and cost efficiency of our project.

Table 4: Specifications and Quantifications Describing Infection Indicators

pH

Sensitivity:	A lowered pH below healthy is a statistically significant indicator of infection (p=0.006) [41] Normal-traumatic has mean difference 0.209 with p<0.001, Normal-osteoarthritic has mean difference 0.219 with p<0.002; p = probability of chance occurrence[42]
Specificity:	pH in the healthy range is a statistically significant indicator of no infection (p=0.006)[43]
Binary Classification Test:	Healthy knee: 7.23±0.09 (uninfected revision TKA), 7.30±0.09 (primary TKA) [44] Infected knee: 7.06±0.12 (infected revision TKA) [45]
Testability:	Requires periodic calibration to body norm.
Existence of Sensor at Scale:	Yes: Implantable pH Microsensor[46], Micro Electro-Mechanical Sensor (MEMS) PH and Temperature, Electro-Static PH Sensor

Glucose

Sensitivity:	Only 20% of infected knees will demonstrate a change in glucose levels.[47]
Specificity:	84% of infected knees were identified as such[48]. However, "healthy" glucose level does not necessarily indicate a healthy knee, especially in diabetics[49].
Binary Classification Test:	Healthy knee: <10 mg/100 mL Infected knee: >20 mg
Testability:	Requires differential with blood glucose levels[50]. Impractical within knee implant.
Existence of Sensor at Scale:	Yes: Continuous implantable blood glucose monitor available[51,52].

Erythrocyte Sedimentation Rate (ESR)

Sensitivity:	100% for ESR ≥ 38 mm/hour[53]
Specificity:	12% for ESR ≥ 38 mm/hour[54]
Binary Classification Test:	Healthy knee: 75±30 mm/hr Infected knee: 80±29 mm/hr[55]
Testability:	Can be evaluated with automated analyzer. Requires use of gravity; impractical within knee implant. Needs to be repeated after several weeks or months to verify results[56].
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Synovial Fluid White Blood Cell Count (SF-WBC)

Sensitivity:	84% for WBC count ≥ 27,800 cell/μL[57]
Specificity:	99% for WBC count ≥ 27,800 cell/μL[58]
Binary Classification Test:	Healthy knee: 4,200 ± 5,700 cells/μL Infected knee: 92,600 ± 127,000 cells/μL[59]
Testability:	Can test for it with Wright's stain[60], but impractical within the knee implant.
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Turbidity[61]

Sensitivity:	Infected knees will demonstrate a change in turbidity (elevated from healthy range).
Specificity:	Healthy knees will only demonstrate turbidity in the healthy range.
Binary Classification Test:	See Appendix: Figure 2.
Testability:	No reference or calibration required.
Existence of Sensor at Scale:	Yes: Laser Diode, Light Emitting Diode

Volume

Sensitivity:	Not characteristic of all infected knees[62].
Specificity:	If change in volume is present, the knee is infected. Healthy knees are not swollen[63].
Binary Classification Test:	Healthy knee: 0.5-3.5 mL Infected knee: 0.55-71 mL
Testability:	Difficult to test without retrieving all synovial fluid from the knee. Impractical within knee implant. Only qualitative visual tests possible.
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Color

Sensitivity:	Infected knees will demonstrate color change.
Specificity:	Healthy knees will not demonstrate color change (typically clear; can read a newspaper through it) [64,65].
Binary Classification Test:	Healthy knee: clear to 632 nm light Infected knee: opaque/yellow, absorbs light red
Testability:	No differential or calibration required.
Existence of Sensor at Scale:	Yes: Laser Diode, Light Emitting Diode

C-reactive Proteins (CRP)

Sensitivity:	52% of infected knees will have a decrease in C-Protein presence below the healthy level[66].
Specificity:	56% of infected are identifiable as such[67]. Healthy knees will not have a decrease in C-Protein presence below the healthy level.
Binary Classification Test:	Healthy knee: <10 mg/L Infected knee: >10 mg/L
Testability:	Blood test is difficult and impractical within knee implant[68].
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Gram Stains

Sensitivity:	Not all infected knees will have a presence of bacteria or fungi.
Specificity:	If organisms are present, the knee is infected.
Binary Classification Test:	Healthy knee: Blue, 99% specific Infected knee: Pink, 7% sensitive
Testability:	Difficult to test without creating a culture and retrieving fluid from the knee. Impractical within knee implant[69].
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Temperature

Sensitivity:	Not characteristic of all infected knees.
Specificity:	Healthy knees can exhibit changes in temperature.
Binary Classification Test:	Healthy knee: $T \pm \Delta T_N$ (patient specific) Infected knee: $T \pm \Delta T_I$ (patient specific)
Testability:	Requires frequent calibration to body norm. Differential preferred to isolate factors not related to infection.
Existence of Sensor at Scale:	Yes: Micro Electro-Mechanical Sensor (MEMS) Temperature, Thermocouple, Thermistor

Clotting

Sensitivity:	Not characteristic of all infected knees: noninflammatory infected knees maintain firm mucin clots while septic or inflammatory infections have friable mucin clots.
Specificity:	All healthy knees have firm mucin clots.
Binary Classification Test:	Healthy knee: Firm Infected knee: Friable
Testability:	Difficult to test: qualitative, requires applying pressure or friction[70]. Impractical within knee implant.
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Viscosity

Sensitivity:	Not all infected knees will demonstrate a change in viscosity.
Specificity:	If a difference exists, there is a statistically significant correlation ($p<0.05$) of healthy and infected synovial fluid viscosity changes[71].
Binary Classification Test:	Healthy knee: Baseline (patient specific, decreases with patient age), very viscous; Intrinsic viscosity = 69.3±4.2 Infected knee: 0.1*Baseline (time sensitive differential required), greatly reduced viscosity; Intrinsic viscosity = 32.5±1.7[72]
Testability:	Difficult to test without using gravity and fluid retrieval from knee[73], chemical reaction with acetic acid (Mucin clot), or qualitative 'feel' (Thumb) test[74]. Impractical within knee implant.
Existence of Sensor at Scale:	No sensor exists at scale necessary.

Table 5. Sensing Mechanism Component Specifications and Justifications.

Specification	Justification
Patient Safety	Implementation into the chosen implant component must not cause harm or discomfort to the patient.
Implant Safety	Implementation into the chosen implant component must not degrade the stability of the implant through, but not limited to, loosening, excessive wear, mechanical weakening or other effects that could increase the likelihood of implant failure.
Ease of Replacement or Maintenance	Should our sensing mechanism fail, the chosen implant component must be able to be easily removed or modified, thereby not increasing the likelihood of highly invasive surgery (removing implants from bones).
Cost	The cost of implementation into the chosen implant component as well as the cost of replacing the component must not add a prohibitive expense to the existing implant cost; otherwise it will not be economically viable. See Sensing Method Specifications for details.
Ease of Implementation	The chosen implant component must not require excessively difficult procedures to modify. The component must also have enough volume to accommodate our sensing mechanism.
Measurement Accuracy	The chosen implant component must have sufficient access to non-stagnant synovial fluid.
Patient Independent	The chosen implant component must not require the sensing mechanism to become patient specific or require excessively difficult calibration. For instance, if a component of the knee implant varies greatly in geometry from patient to patient, this makes it more difficult to implement our sensing mechanism into it.

Table 6: Detailed Quantifications and Justification for Sensing Mechanism Component

	Weight	Polyethylene Insert/ Spacer	Tibial Tray/ Component	Femoral Component	Patellar Button/Component
Patient Safety	Patient safety is of the utmost importance to us, as the entire goal of the project is to eliminate risky and expensive surgery.	No anticipated concerns.	No anticipated concerns.	No anticipated concerns.	No anticipated concerns.
Implant Safety	The implant safety is important; however, as the geometry will have minimal impact on the overall component geometry, the implant is unlikely to fail any faster.	No anticipated concerns.	No anticipated concerns.	No anticipated concerns.	Component is so small that a large portion of the component would consist of our sensing mechanism and would compromise the mechanical integrity.
Ease/ Necessity of Maintenance	If the sensing mechanism fails, the component on which it is located should be easy to access.	Easy to access; simply snaps into place.	Very invasive to access or replace; either cemented in place or bone has grown into implant.	Very invasive to access or replace; either cemented in place or bone has grown into implant.	Invasive to access or replace; either cemented in place or bone has grown into implant.

Cost	Cost is an issue, but anticipated additional costs for implant design modifications is small.	Plastic insert is much cheaper to remove than the others and cheaper to replace than the metal tibial or femoral components.	Expensive to replace or remove. More costly to alter metal than plastic.	Expensive to replace or remove. More costly to alter metal than plastic.	Cheapest to replace but difficult to remove (cemented in place).
Ease of Implementation	Must have enough volume to contain our sensing mechanism and be easy to modify.	Large enough to accommodate parts; has nice planar faces to use.	Large enough to accommodate parts; has nice planar faces to use.	Not many flat areas to use, would have to put much of mechanism inside bone.	Too small to contain our sensing mechanism and its power source.
Measurement Accuracy	The component must facilitate, not impede, sensing mechanisms and have access to non-stagnant synovial fluid.	Has as much access to synovial fluid as any other component.	Has as much access to synovial fluid as any other component.	Rubs against the patellar component; could impede accurate measurement.	Rubs against the femoral component; could impede accurate measurement.
Patient Independent	The geometry must not require the sensing mechanism to be additionally patient specific.	Fitted to patient but varies little.	Fitted to patient but varies little.	Fitted to patient but varies little.	Not all patients need a patellar button.

Table 7. Sensing Mechanism Location Specifications and Justifications.

Specification	Justification
Accuracy of Infection Indicator Measurement	The chosen implant location must have sufficient access to non-stagnant synovial fluid; maximizing fluid contact will aid our sensors' performance. Mixing should occur nearby to ensure the sensors have access to infected fluid.
Minimal non-Fluid Contact	The sensing mechanism location should not often come into contact with hard surfaces (increased friction and wear) or soft surfaces such as tissues that may alter or impede the performance of our sensors.
Ease of Access	Emergency cleansing/clearing of channel must be accessible with needle aspiration.
Ease of Implementation	The sensing mechanism location must not necessitate excessively difficult procedures to implement the sensing mechanism geometry into the implant geometry.
Patient Safety	The sensing mechanism location must not cause harm or discomfort to the patient or obstruct synovial fluid flow within the joint.
Implant Safety	The sensing mechanism location must not degrade the stability of the implant through, but not limited to, loosening, excessive wear, mechanical weakening or other effects that could increase the likelihood of implant failure.
Cost	Cost of altering the given component or replacing it should the mechanism fail.

Table 8: Sensing Mechanism Geometry Specifications and Justifications.

Specification	Justification
Patient Safety	The sensing mechanism geometry must not cause harm or discomfort to the patient or obstruct synovial fluid flow within the joint.
Implant Safety	The sensing mechanism geometry must not degrade the stability of the implant through, but not limited to, loosening, excessive wear, mechanical weakening or other effects that could increase the likelihood of implant failure.
Ease/Necessity of Maintenance	Should the sensing mechanism collect debris (thus obstructing the sensing mechanism), clearing the geometry must not require surgery or anything more invasive than needle aspiration of the joint.
Cost	Cost includes cost of geometry implementation and any necessary accompanying maintenance mechanisms. The sensor must not add a prohibitive expense to the existing implant cost; otherwise it will not be economically viable. See Sensing Method Specifications for details.
Ease of Implementation	The sensing mechanism geometry must not require excessively difficult procedures to implement into the implant geometry.
Measurement Accuracy	The sensing mechanism geometry must not impede our sensing mechanisms' measurement of infection indicators. This includes but is not limited to allowing sensor access to non-stagnant synovial fluid and providing a controlled environment in which the sensing mechanism can function as intended.
Patient Independent	The sensing mechanism geometry must not require the sensing mechanism to become patient specific or require excessively difficult calibration.

Table 9: Detailed Quantifications and Justification for Sensing Mechanism Geometry

	Weight	Planar	Indent	Channel
Patient Safety	Patient safety is of the utmost importance to us, as the entire goal of the project is to eliminate risky and expensive surgery.	Poses no anticipated issues.	Poses no anticipated issues. Too small to collect much if any debris.	Poses no anticipated issues. Too small to collect much if any debris.
Implant Safety	The implant safety is important, because if it fails the patient will require surgery; however, as the geometry will have minimal impact on the overall implant geometry, the implant is unlikely to fail any faster.	Poses no anticipated issues. Outer geometry appears unchanged from control implant.	Poses limited if any issues. Any extruded cut into a geometry poses some mechanical compromise, although the indent does not need to be very big at all.	Long channel through the implant geometry poses a mechanical compromise.
Ease/ Necessity of Maintenance	If maintenance is required, it should be easy to administer.	No change to external geometry; nothing to maintain.	An open, short indent is easy to aspirate and clear completely.	A long, thin channel is difficult to aspirate and clear completely.
Cost	Cost is an issue, but anticipated additional costs for implant design modifications is small.	The planar face should is simple, requires a boundary between the LED and sensing mechanism, and needs one large window.	The indent requires no boundary but does need two opposing windows.	The channel will have to be long to go through the entire component and may require dual sensing mechanisms to function as intended.
Ease of Implementation	Additional machining on the implant is minimal, so is not a large consideration.	A planar face is easiest to machine.	Indents are easy to machine.	Channels are hardest to machine.

Measurement Accuracy	The geometry must facilitate, not impede, sensing mechanisms.	Sensors will see most free mixing of synovial fluid, but optics will rely on reflection off the nearest biological surface, which varies in color and distance by patient and time. In addition, sensors are most likely to touch/see the synovial capsule.	Sensing will see much free mixing of synovial fluid, and optics can use direct sensing. Highly unlikely the sensors will see/touch any tissues.	Sensing will see much free mixing of synovial fluid, and optics can use direct sensing. Highly unlikely the sensors will see/touch any tissues.
Patient Independent	The geometry must not require the sensing mechanism to be additionally patient specific.	Optics will rely on reflection off nearest biological structure which is patient specific in color and identification.	Control space is provided for sensors; patient independent.	Control space is provided for sensors; patient independent.

Table 10: Selection of Sensing Mechanism Geometry

	Weight	Planar	Indent	Channel
Patient Safety	4	2	2	2
Implant Safety	2	2	1	1
Ease of Maintenance	3	2	0	1
Cost	1	2	2	1
Ease of Implementation	1	2	1	1
Measurement Accuracy	4	0	1	2
Patient Independent	4	0	2	2
Fraction	**38**	**0.58**	**0.66**	**0.82**
Weighted with Geomean	**0.68**	**0.85**	**0.97**	**1.20**

Figure 1: Gambit mesh of tibial insert channel.

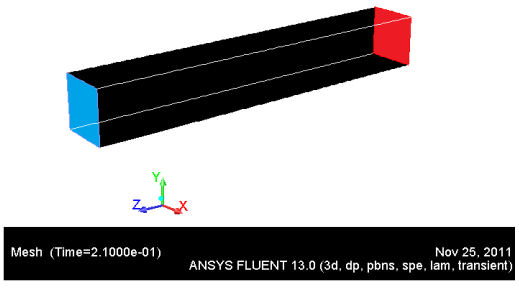
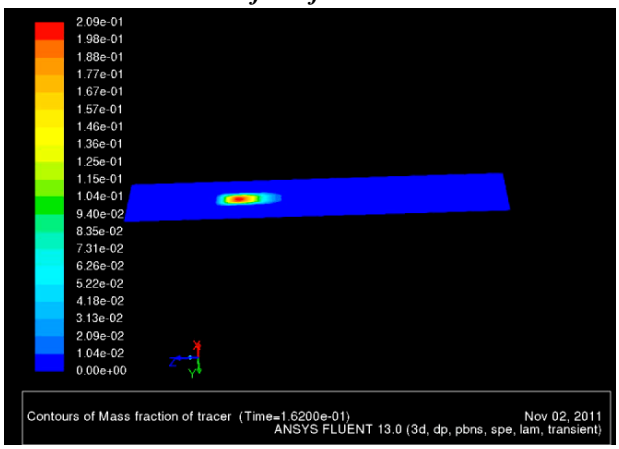
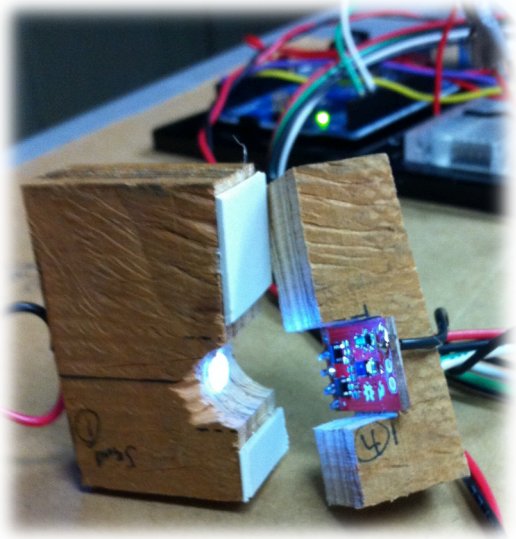


Figure 2: Fluent simulation screenshot visualizing fluid flow.

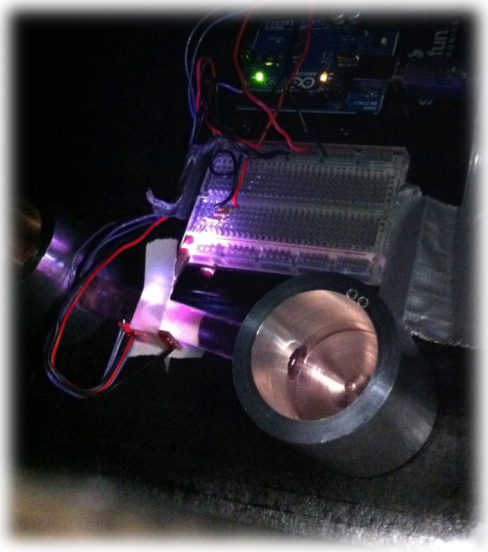


Figures 3-5 (Clockwise from top left): Preliminary experimental setup

Sensor/LED Mount



Running



Full Setup w/ Fluid

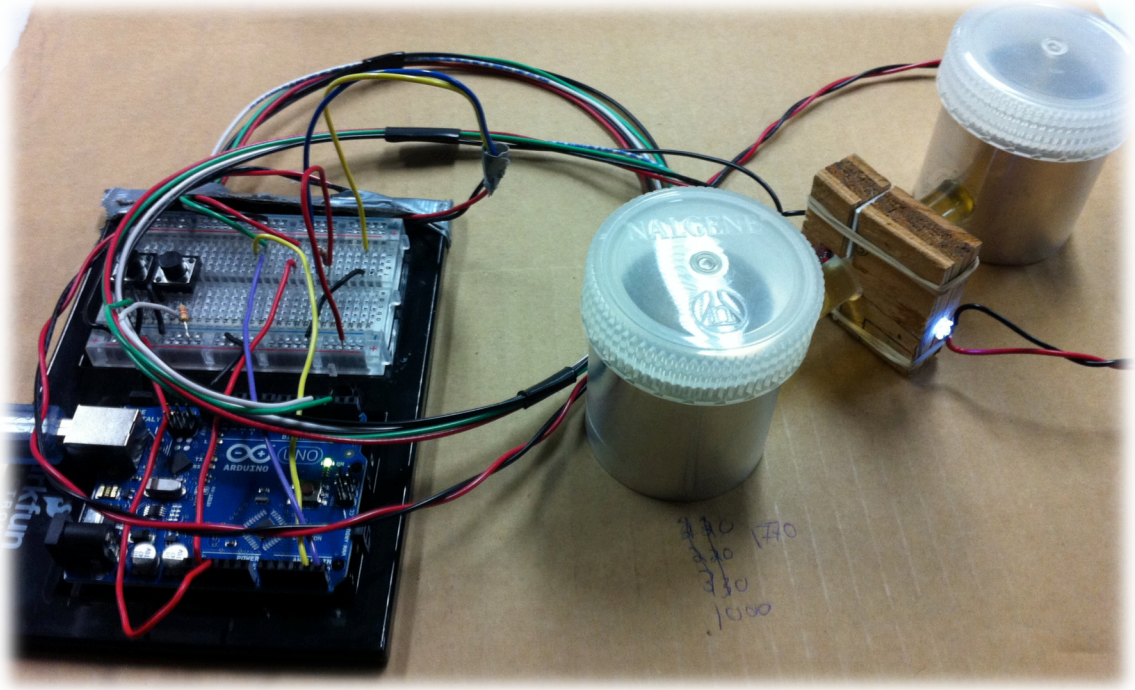


Figure 6: Hertzian Contact Surface Equations

$$a = 3\left(\frac{PR}{4E}\right)^{\frac{1}{2}}$$

a = Radius of Contact Circle, P = load

$$\frac{1}{R} = relative\ curvature = \left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

$$R_1 = radius\ of\ femoral\ component,\quad R_2 = radius\ of\ insert$$

$$\frac{1}{E} = combined\ elastic\ modulus = \frac{1-v_1^2}{E_1} + \frac{1-v_2^2}{E_2}$$

$$E_1 = elastic\ modulus\ of\ femoral\ component,$$
$$E_2 = elastic\ modulus\ of\ insert$$

$$v_1 = Poisson's\ ratio\ of\ femoral\ compnent,\quad v_2 = Poisson's ratio\ of\ insert$$

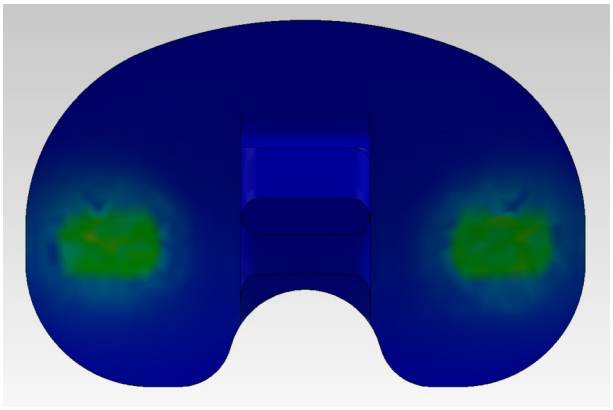
Table 11. Hertzian Contact Surface Calculations

15°					
Force = 1600 N					
Material 1 (femoral component)		**Material 2 (tibial insert)**		**Output**	
R_1 (m)	0.0242908	**R_2 (m)**	0.0343592	**R (m)**	0.0828946
E_1 (Pa)	1.95E+11	**E_2 (Pa)**	500000000	**E (Pa)**	632324425
υ_1	0.3	**υ_2**	0.46	**a (m)**	0.0053983
45°					
Force = 1600 N					
Material 1 (femoral component)		**Material 2 (tibial insert)**		**Output**	
R_1 (m)	0.022108	**R_2 (m)**	0.0343592	**R (m)**	0.0620027
E_1 (Pa)	1.95E+11	**E_2 (Pa)**	500000000	**E (Pa)**	632324425
υ_1	0.3	**υ_2**	0.46	**a (m)**	0.0049002
60°					
Force = 1600 N					
Material 1 (femoral component)		**Material 2 (tibial insert)**		**Output**	
R_1 (m)	0.0202344	**R_2 (m)**	0.0343592	**R (m)**	0.049221
E_1 (Pa)	1.95E+11	**E_2 (Pa)**	500000000	**E (Pa)**	632324425
υ_1	0.3	**υ_2**	0.46	**a (m)**	0.0045373

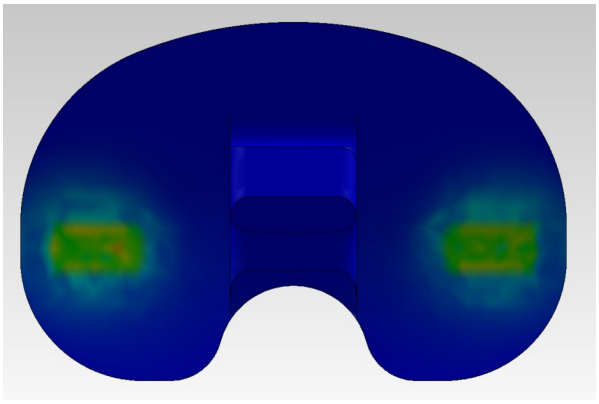
***Figure 7**: Stress distributions in original inserts*

Original Insert

15 Degrees



45 Degrees



60 Degrees

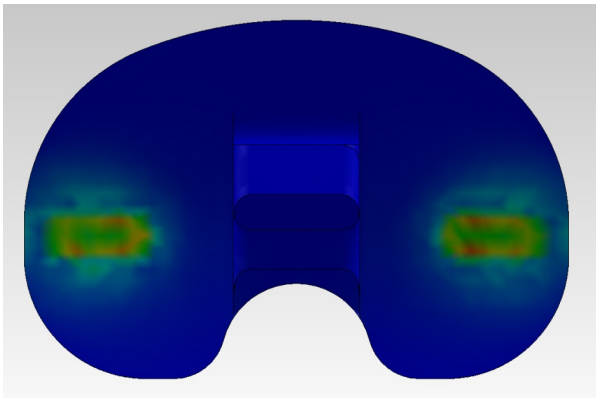
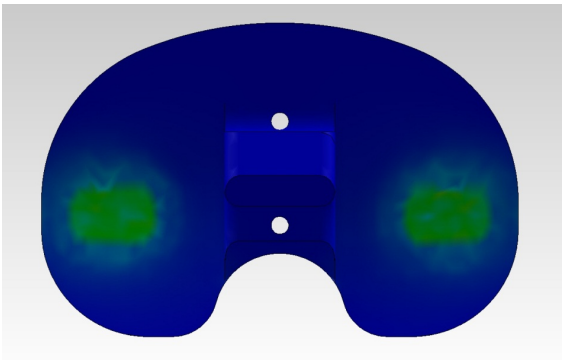
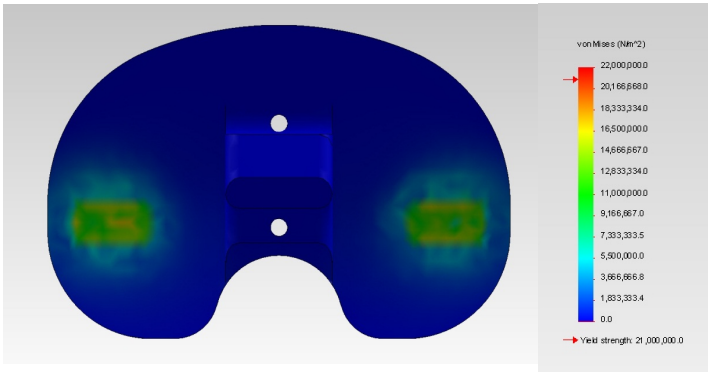


Figure 8: *Stress distributions in modified inserts*
Modified Insert

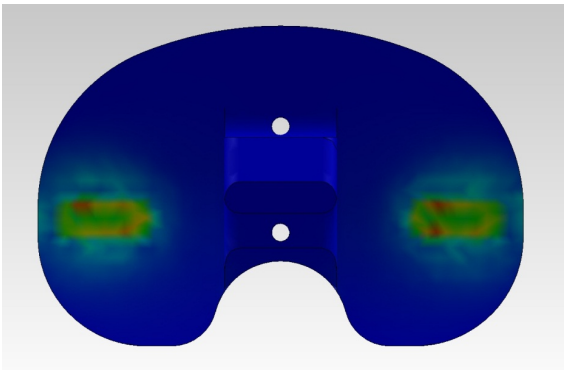
15 Degrees



45 Degrees



60 Degrees



Appendix B: Experimental Protocols

Incubation

Equipment

- Electronics (Sparkfun)
  - Color Light Sensor Evaluation Board (SEN-10701)
  - Arduino and Breadboard Holder (DEV-10059)
  - Breadboard Clear Self-Adhesive (PRT-0567)
  - Arduino Uno SMD (DEV-10356)
  - FTDI Basic Breakout – 3.3V (DEV-09873)
  - 9V DC 650mA Wall Adapter Power Supply – Retail (RLT – 10273)
- Test chamber
- Micropipettes

Materials

- Bovine Calf Serum, untreated (Sigma-Aldrich 310093-25G)
- Liquid culture *E.coli* with optical density between 1 and 2 at 600 nm

Procedure

1. Prepare test environment
   a. Connect electronics to test chamber
   b. Power the electronics
   c. Initialize sensors
2. Test infected BCS
   a. Using the micropipette, add 350 µL of the liquid culture to 2 mL diluted bovine serum (1:3 with DI water) and mix.
   b. Introduce with pipette to test chamber, taking care not to create bubbles within the chamber
   c. Place entire setup in 37°C environment and incubate for at least 18 hours while continuously sensing data

Cleaning/Disposal

- Non-infected BCS can be washed down the drain.
- Infected BCS must be dumped into a 10% bleach solution and sit for 30 minutes before being washed down the drain with water.
- Test chamber should be soaked for at least 30 minutes in a 10% bleach solution

WBC Correlation

Equipment

- Electronics and test chamber from **Infection Protocol**
- Micropipettes
- Centrifuge
- Hemocytometer
- Two 50mL centrifuge tubes

Materials

- Bovine blood, defibrinated (Quattro, 910)
- Bovine Calf Serum, untreated (Sigma-Aldrich, 310093-25G)
- 90 mL .17 M NH_4Cl
- ~100 mL 1x PBS

Procedure

5. Isolate WBCs from whole bovine blood[75]
    a. Add 5 mL blood to each of two 50 mL centrifuge tubes
    b. Add 45 mL room temperature .17 M NH_4Cl to each tube to lyse red blood cells
    c. Incubate for a maximum of 5 minutes on rotator
    d. Centrifuge for 5 minutes at 2000 RPM
    e. Aspirate supernatant and resuspend each pellet in ~ 50mL cold 1x PBS
    f. Centrifuge for 5 minutes at 2000 RPM
    g. Aspirate supernatant and remaining is WBC pellet
    h. Resuspend WBCs by filling volume to 45 mL with BCS in each tube
6. Quantify WBCs using hemocytometer[76,77]
    a. Fill counting chamber on hemocytometer slide and wait 2-3 minutes for cells to settle
    b. Focus on four outer corner areas (each should have 16 small squares) at 10x or 100x power
    c. Count cells in four squares, including those overlapping the left and top edges, but NOT those overlapping the right and bottom edges
    d. The concentration of WBCs in the sample can be calculated as follows:

$$C = \text{Total number WBCs counted} \text{Proportion of Chamber Counted} \times \text{Volume of Chamber}$$

    For this particular procedure, the "proportion of chamber counted" = 4 and the "volume of chamber" = 0.1 μL.

7. Measure turbidity while varying WBC concentration
    a. From resulting quantification of WBCs, dilute or concentrate appropriately to desired experimental concentration (for our purposes, we concentrated our sample to around 3,000 WBC/μL – the current clinical threshold for infection in synovial fluid)
    b. Setup test chamber with WBC solution (~2-3 μL) and begin taking real time turbidity data. Record value once equilibrium is reached
    c. Consistently step down in concentration by diluting the WBC solution with bovine serum, until device is no longer sensitive to changes.

Cleaning/Disposal

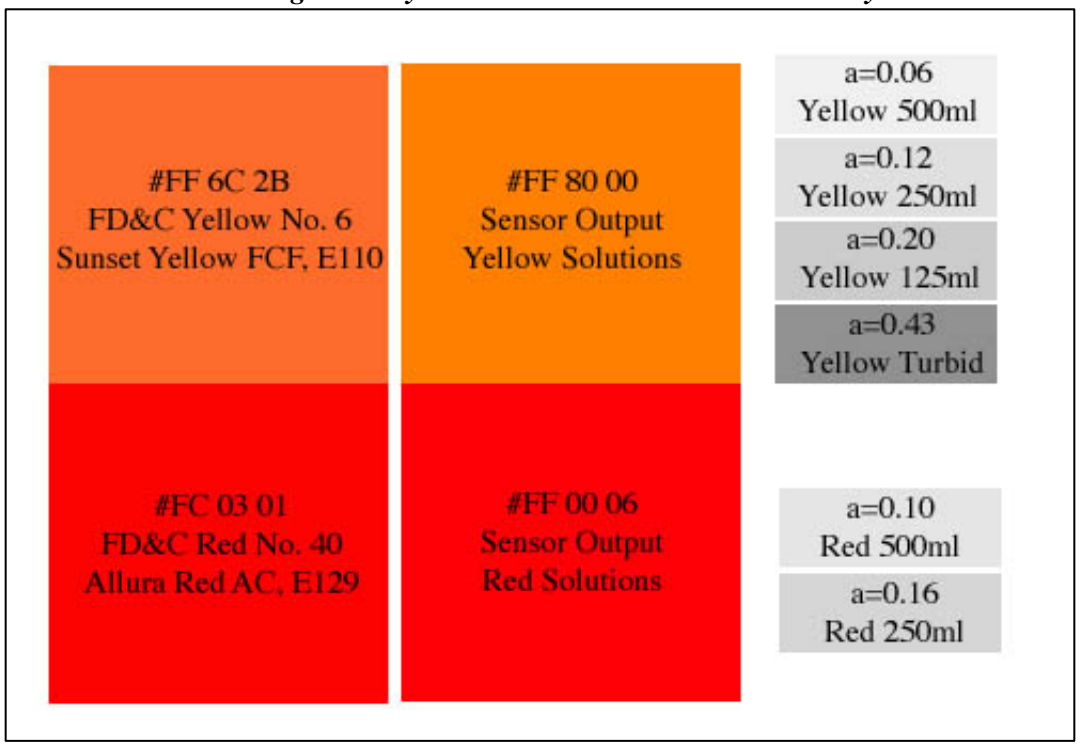
- Add 10% bleach solution and sit for 30 minutes before being washed down the drain with excess water.

Appendix C: Additional Information

Preliminary Processed Data Results (Optics)

Algorithm output color and turbidity data is on right, color of dye on left. For clarity, a=1.00 indicates that no light passes the fluid, a=0.00 indicates perfect transmission. Colors codes are 3 2-digit hexidecimal values #Red Green Blue and range from 00-FF (0-255 in decimal).

Figure 9: Dye color vs Sensed Color – w/ Turbidity



Note: The 4 yellow solutions of different concentrations and turbidities returned very slightly different colors but are essentially visually indistinguishable. Same applies for the Red solutions.

Table 12: Returned values for color and turbidity

Solution	Red	Green	Blue	Alpha (a)
Yellow 500ml	0xFF	0x73	0x00	0.06
Yellow 250ml	0xFF	0x87	0x00	0.12
Yellow 250ml Turbid	0xFF	0x70	0x00	0.43
Yellow 125ml	0xFF	0x8B	0x00	0.20
Red 500ml	0xFF	0x00	0x0C	0.10
Red 250ml	0xFF	0x00	0x06	0.16
Calibration Reference	**0xFF**	**0xFF**	**0xFF**	0.00

Algorithms (Optics)

The following symbols are used:

$$data\ R\ G\ B\ C$$

$$C_o = Calibrated\ Clear\ Value$$

The transparency is computed from the know reference value for clear water and the relative ration of the current reading from the clear channel (total transmitted) subtracted from 1 such that a high value means light blocked.

$$\alpha = 1 - \left(\frac{C}{C_o}\right)$$

The particulate color algorithm first scales the lowest channel (relative to the other 2) to 0 and scales the highest channel to 255 and then places the middle channel in the appropriate range. This at first seems like the color will always have 1 channel pegged at 255 and another at 0 which is correct, however this still yields valid colors and covers a wide spectrum of possible colors.

$$lower = \min(R,G,B)$$

$$R_{rel} = R - lower, G_{rel} = G - lower, B_{rel} = B - lower$$

$$norm = \max(R_{rel}, G_{rel}, B_{rel})$$

$$color = \frac{255}{norm}\left[R_{rel}, G_{rel}, B_{rel}\right]$$

The composite color algorithm compares the returned color values to the calibration values and determines a color that is more akin to the visible color, which includes the alpha as well.

$$\{R,G,B,C\}_o = calibrated\ values$$

$$adj = 1 - \frac{C}{C_o}$$

$$color = \frac{255}{adj}\left[\frac{R}{R_o}, \frac{G}{G_o}, \frac{B}{B_o}\right]$$

Data Averages (Optics)

Solution	Red Avg.	Green Avg.	Blue Avg.	Clear Avg.
Yellow 500ml	897	859	828	944
Yellow 250ml	875	805	726	881
Yellow 250ml Turbid	761	678	613	761
Yellow 125ml	845	733	598	798
Red 500ml	876	788	792	903
Red 250ml	854	717	720	844
Calibration Reference	915	903	912	997

Appendix D: Clinical Study

I. Introduction: Reducing Total Knee Revision Surgery

Total knee arthroplasty (TKA) is an effective and clinically successful solution for advanced osteoarthritis of the knee[78,79,80]. Arthroplasty is a procedure that modifies the function or structure of a joint[81]. In a healthy knee, the joint is covered with cartilage and lubricated with synovial fluid (SF). Degenerative diseases, such as osteoarthritis (OA), rheumatoid arthritis (RA), or post-traumatic arthritis, can disrupt this harmony[82].

There are more than 500,000 TKA procedures in the United States each year, with a five-year survivorship of 97.2%[83.84]. However, treatment for failed implants often poses a burden on both patients and the healthcare system, as revision surgeries can cost upwards of $100,000[85]. This problem is likely to intensify as the number of patients requiring TKA and revision TKA is projected to grow by 673% and 601%, respectively, by the year 2030[86].

Infection is the most common cause of revision TKAs, accounting for 25.2% of revision surgeries between 2005 and 2006[87]. Early diagnosis of infection is crucial to avoid revision surgery, but the multitude of complex clinical tests and the tendency of infections to mimic other conditions render early detection difficult[88]. In fact, there currently exists no universal standard to diagnose infection in the early postoperative period[89]. Many indicators for infection are recognized as both sensitive and specific via retrospective studies, but there is no system to continuously test for these indicators in a knee implant.

OrthoSensor, Inc. recognizes that there is a need for a continuous, implantable sensing modality for patients undergoing TKA in order to detect infection before revision surgery becomes necessary. Reducing the number of revision surgeries due to infection would alleviate the strain these procedures place on patients and the healthcare system. OrthoSensor's long-term goal is to develop a fully instrumented knee implant with real-time sensors to detect the onset of infection as well as monitor mechanical failures such as loosening and dislocation.

In support of OrthoSensor's goal, the team has provided the company with an infection sensor implementation plan that will involve: (1) identification of infection indicators and their respective sensing mechanisms, (2) design and fabrication of clinically relevant models for synovial fluid (SF) and the knee joint, (3) production of sensor output data for a range of healthy and infected SF conditions, and (4) establishment of threshold values for sensors that are sensitive and specific to infection.

II. Preliminary Results

A. Overview of Proposed Solution Methods

Our novel device is an implantable sensing mechanism that continuously measures the in-vivo values of pH, particulate color, composite color, and turbidity of synovial fluid (SF) in a knee implant. As OrthoSensor plans to integrate our novel device into their sensing mechanism packet, the Application Specific Integrated Circuit (ASIC), our device is currently tailored to fit the Stryker Scorpio Triathlon size 3, although its design is easily modified for any knee implant that does not have an internal stabilizing post.

We are proposing a Treatment Clinical Trial to evaluate the safety and efficacy of our novel device that is intended to detect infection in knee implants to reduce knee revision surgery. The

clinical trial proposed is designed to test the following hypothesis: by monitoring the pH, particulate color, composite color, and turbidity, our device can detect infection before knee revision surgery becomes necessary. Early diagnosis of deep infection is imperative to salvage the prosthesis with debridement and retention, otherwise prosthesis removal is required.[90]

B. Anticipated Device Use

There are two general time dependent situations in which our device is may function: post-operative and long-term. The post-operative time period begins immediately after operation and lasts approximately eight weeks after surgery. The length of this period is highly patient specific and ends when the indicator values match those expected of the long-term period. The long-term time period is the remainder of the implant or patient lifespan.

Our device produces data by taking samples at specified increments of time. The data can be used in its given form, as an absolute number that occurs at a specific time. Alternatively, the change in the data over time can be calculated to give a slope. The former case is useful for the long-term period, while the latter will be useful for the post-operative period.

Tabulated later in this report are infection indicator ranges that allow quantification of the infected or uninfected state of the knee. Trends or slopes for the expected change in the infection indicators are not included in this report but are rather goals in one of the recommended future studies involving this device. Until clinical data is available to define the amount of time over which a specified differential in pH, color, or turbidity occurs to constitute an infection, our device is not prepared to operate in the post-operative period. Discussion of the clinical study necessary to use our device in the post-operative period occurs later in this report.

C. Infection Indicators

Our device detects information concerning three clinically relevant indicators of infection in SF: pH, color, and turbidity. These indicators of infection were selected on the basis of sensitivity, specificity, the existence of a binary classification test, testability, and the existence of an implantable sensor at scale.

In the long-term period, as the knee replenishes its SF and the values of pH, color, and turbidity return to normal ranges, the absolute numbers our device generates can be used to detect infection. Healthy SF pH is 7.30 ± 0.09[91]; infected SF pH is lowered to 7.06 ± 0.12[92]. Healthy knees will not demonstrate color change (typically clear; one can read a newspaper through it)[93,94] while infected SF may be brown, red, yellow, and so forth. Increased turbidity is indicative of osteolysis or the presence of other abnormal particulates in the synovial capsule.

Our device delivers data for interpretation according to Table 1. Each range of values for each infection indicator has a corresponding Data Score, ranging from 0-2. Example data for turbidity is depicted below. All values above the green line are considered “healthy” and correspond to an alpha value in [0, 0.03] or a turbidity value of [0.97, 1]. Values above the red line and below the green are alpha values in [0.03, 0.06] and correspond to turbidity values in [0.94,0.97], and those below the red line are in the infected range.

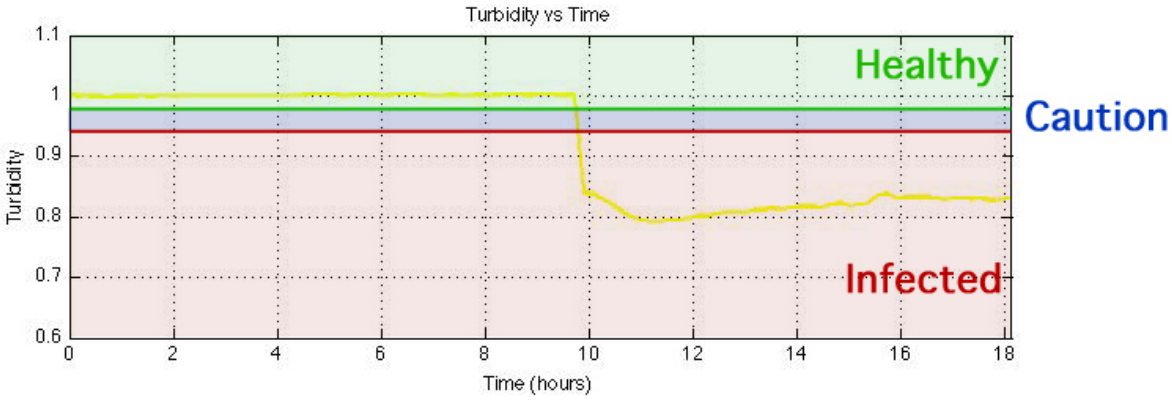


Table 1. Infection Indicator Values

Indicator		Healthy Data Score: (0)	Caution Advised Data Score: (1)	Infected Data Score: (2)
pH		7.23 - 7.39	7.18 - 7.23	0 - 7.18
Referenced Color	Red	244 – 255	230 - 244	0 - 230
	Green	240 – 255	210 - 240	0 - 210
	Blue	230 – 255	200 - 230	0 - 200
Color Corrected Turbidity		0.97 - 1.00	0.94 - 0.97	0 - 0.94

pH and Turbidity each have a data score of 0, 1 or 2 according to where the data falls in the given ranges. Color's data score is a 0, 1, or 2 based on the average data score among red, green, and blue, rounded to a 0, 1 or 2. If this system proves ineffective in-vivo (our device does not detect infection as soon as it should), a more conservative system would assign a color data score based on the highest data score among red, green, and blue.

The device would then transmit a conglomerate score to the end user, a three-digit number such as "001" or "202". The end user would refer to the following chart, Table 2 for the corresponding recommended course of action. These values are the result of experiment, literature research, and analysis rather than in-vivo trials, which are necessary to confirm the presence of infection in the future development of our novel device and discussed later in this clinical study.

Table 2. Infection Indicator Value Interpretation

Infection Status	Scores	Recommended Action
Infected	222, 122, 022	Infection or failure likely. Medical attention highly recommended.

Caution Advised, II	111, 112, 002	Infection probable. Medical attention recommended.
Caution Advised, I	001, 011	Increase data delivery; download data more often[1]. Infection possible.
Healthy	000	None.

Scores consisting of varied orders of three-number combinations are viewed as equivalent (001 = 010 = 100).

In the post-operative period, a trend-fitting algorithm can use our device's outputs to detect trends or changes in the infection indicators enumerated above. A decreased pH, a trend away from clear toward strong colors, and increased opacity or turbidity are all trends indicative of infection[95]. Part of the proposed clinical study will serve to define a clinically relevant length of time over which these trends occur to indicate infection. Ideally, the data would furnish analogous two charts as above. The post-operative state of a knee following surgery is highly patient specific due to the invasive nature of the operation as well as the differing amounts of blood, medicine, and other fluids in the joint, necessitating the use of trends and slopes rather than absolute numbers as in the long-term period.

D. Sensing Methods

The device detects pH using a pH probe, and it detects particulate color, composite color, and turbidity using a Light Emitting Diode (LED) and a Micro Electro-Mechanical Sensor (MEMS) device. The LED shines light through the SF, and the MEMs device detects the reflected light in terms of color and intensity, which produces the color and turbidity data. These methods of detecting the selected infection indicators were selected on the basis of small size, low cost, high patient and implant safety, high mechanical Mean Time Before Failure (MTBF), high electrical MTBF, no signal interference, low detection time, possibility of digitization of data, low power draw, and minimal required re-calibration. We utilize a CMOS IC with integrated RGB filters and a clear channel (Avago ADJD-S311-CR999) to detect the changes in light composition by wavelength and overall intensity, the sensor has 10-bits of resolution per channel and can be tuned to respond to intensities as low as 0.007mW/cm^2 and as high as 6.7mW/cm^2. Acidity is sensed using an electrostatic temperature compensation probe by Atlas Scientific with an accuracy of ±0.01pH. The data is recorded using an ATmega328 microprocessor with built in EEPROM for saving data.

The core of the system is a microprocessor-based data collection unit that is programmed to collect and store the sensor values of the infection indicators. The microprocessor directs the sensors to take a sample, saves the sample to memory, and times the samples for optimal resolution based on expected total experiment duration. After the experiment has concluded, the data can be downloaded to MatLab and processed with scripts developed to extract relevant patterns and features. When the device is implemented into OrthoSensor's ASIC, it will be programmed to take data at flexible intervals, with more frequent samples taken during the high

[1] Frequency of data delivery is charging/power management scheme dependent. Currently, the power management allows data delivery up to every 5-10 minutes. If the user charges the device regularly, then the power management allows data delivery such that the device is not depleted by the next recharge . If the user charges the device infrequently or the device is self-powered (microthermal or peizoelectrics) then the sample rate should be increased until it reflects the average power production of the unit.

risk post-operative period and less frequent sampling during the low risk long term period to reflect the corresponding time-dependent vulnerability of the knee to infection. The data delivery system thus determines the sampling rate (sampling faster than data will be delivered wastes battery), and both are dependent on the MTBF of the battery chosen for implementation.

The device will be chargeable via a common external inductive charging device to achieve short-distance energy transfer.

E. Implementation

Our device is located within the tibial tray of the knee implant and requires a channel through the tibial insert. Depicted below in Figures 1-4 are various views of one of our final device designs. The design depicted has three channels. The design not shown has only one channel.

Both designs will function in the knee implant and feature a hemispherical cylindrical channel cut into the UHMWPE such that it faces the tibial insert. This channel through the tibial insert allows SF to accumulate above our device, which resides below this channel in the tibial tray under a Plexiglas window and interacts with the SF directly or through the Plexiglas. Our sensors are validated for no-mixing situations.

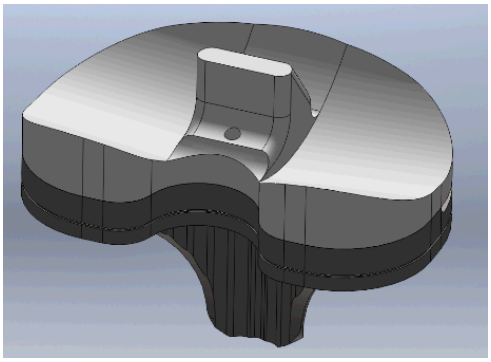


Figure 1. Triple Channel Design, top view.

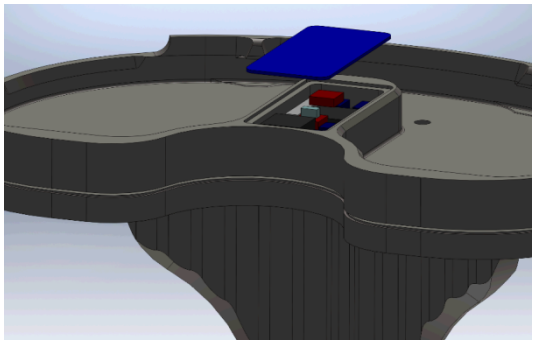


Figure 2. Tray, components housing.

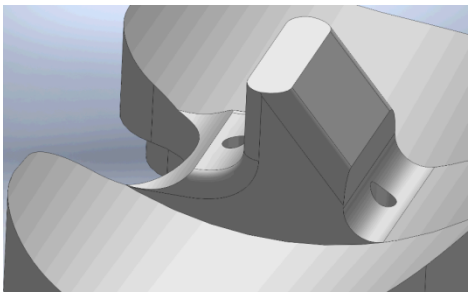


Figure 3. Insert; top view of channels.

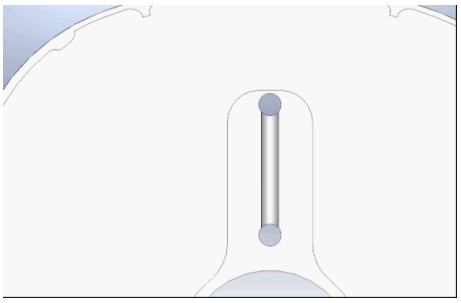


Figure 4. Insert; bottom view.

The Triple Channel design features a horizontal channel with two vertical channels of slightly larger diameter at either end. These two channels allow SF to enter the single horizontal channel freely from the top of the tibial insert in addition to seeping in from the sides. This encourages greater interaction with the larger volume of synovial fluid in the joint capsule and anticipated quicker infection detection than in the Single Channel design.

The Single Channel design features the single horizontal channel from the Triple Channel design between the insert and the tray. The human body produces SF to fill any cavities in the joint capsule, which will include our channel. The only difference between the two designs is the Single Channel design does not have a vertical channel at either end of the horizontal channel.

A final design should be selected according to the following criteria provided in Table 3 below. Both designs would ultimately work but pose difference benefits or disadvantages.

Table 3. Design Advantages and Possible Issues.

Design	Single Channel.	Triple Channel.
Possible advantages	• Nearly impossible to clog • Fewer alterations made to UHMWPE insert • More mechanically sound	• Easy to unclog with needle aspiration if necessary • Encourages high degree of mixing • Allows sensors access to large particles
Possible issues	• Impossible to unclog without surgery • Won't allow sensors access to large particles • Mixing will take longer	• More likely to clog • More alterations made to UHMWPE insert • Less mechanically sound

In summary, the Single Channel design is very unlikely to cease proper function although its infection detection time may be much longer than that for the Triple Channel design. The Triple Channel design is easy to unclog and will have a quicker response time.

F. Data Interpretation and Use

Our device is capable of generating data as a function of time as shown below in Figure 5. This data may be used as discussed earlier in Section II. C. as trends (after clinical data is gathered and validated) or absolute numbers.

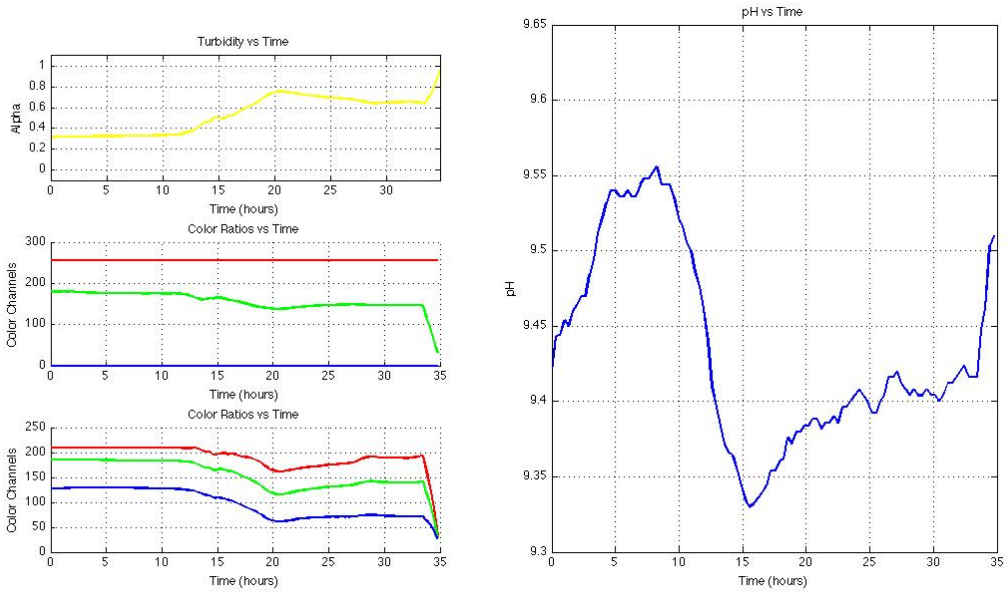


Figure 5. Device Data Output Example.

The discussion presented in Section II. C. also describes the recommended actions for different ranges of infection indicator values our device delivers, and the Further Studies describe how to establish clinically relevant trends indicative of infection. Our device delivers data in the following form (see Figure 6 below).

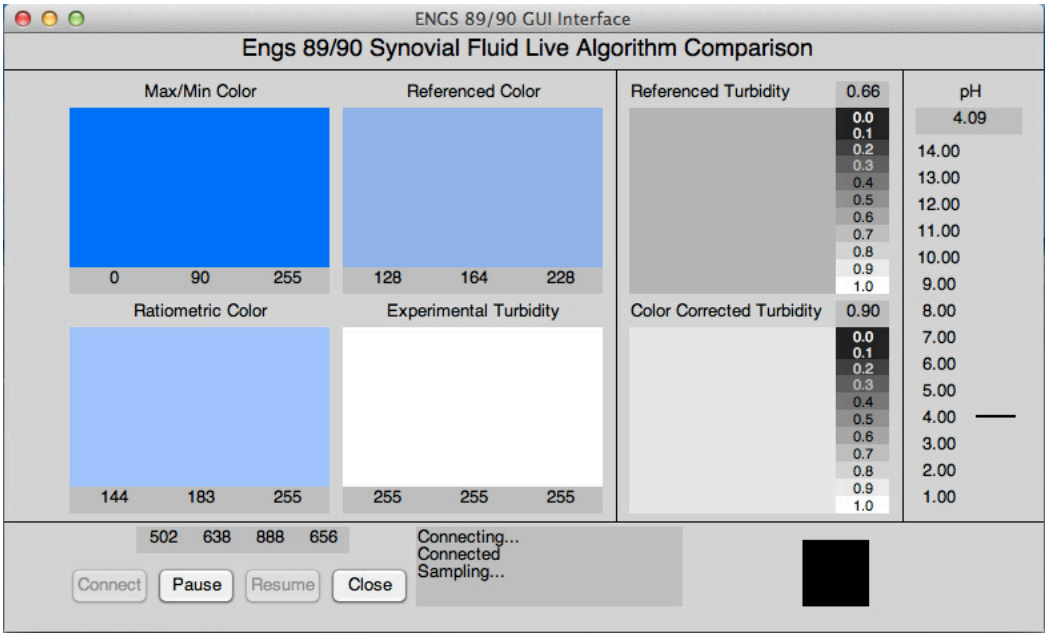


Figure 6. Live Algorithm Comparison, GUI Screenshot.

As shown, the device delivers a set of data points for color, turbidity, and pH as a function of time. A trend fitting algorithm can identify trends/slopes indicative of infection, and the binary classification tests can resolve absolute numbers into statements of infection presence or absence. In addition to early detection of infection, the data our device generates will also fill the following voids in existing clinical literature:

1. pH, color, and turbidity values in SF as a knee heals "ideally" (without infection)
2. pH, color, and turbidity values in SF as a knee heals "unideally" (with infection); may also allow further specification within this study for different infection types
3. pH, color, and turbidity values may help identify SF composition post-operatively

III. Discussion

A. Improvement over Prior Art

We have identified a list of parameters validated for sensitivity and specificity to infection. There exists prior art that involves sensing modalities in knee implants, which are enumerated below in Table 4 along with a justification that our project does not fall within their scope and thus is a separate and novel entity. In addition, our client has filed a patent on a sensing method for biological activity, but the sensor has not achieved full development or production thus far, and it is assumed permissible for our work to operate under that patent.

Table 4. Prior Art.

Author	Title	Justification
William Martin Roche *Filed*: 10/22/09	"Detection, Prevention and Treatment of Infections in Implantable Devices."[96]	The patent applicant is the CEO of OrthoSensor. The claims include a biological sensor to detect one of pH, temperature, viscosity or blood flow but do not mention use of optics as a measure of turbidity or the use of multiple indicators for infection.

Boyd McCutchen Evans *Filed*: 8/25/04 *Issued*: 8/29/06	"In-vivo orthopedic implant diagnostic device for sensing load, wear, and infection."[97]	This patent mentions using a chemical sensor as means for detecting infection, but we have found that an optical sensor would be a more efficient sensing modality.
Ray C. Wasielewski *Filed*: 08/03/07	"Smart Joint Implant Sensors."[98]	This patent describes a plurality of sensors but does not include mention of an optical sensor for turbidity.
Milton Nance Ericson *Filed*: 10/26/05	"Method and apparatus for orthopedic implant assessment."[99]	This patent describes the use of optical techniques to detect infection, but does not indicate the importance of sensor location and interaction with synovial fluid in the knee.
Darren Wilson et al. *Filed*: 9/31/07	"Medical Device."[100]	This patent involves sensors in joint implants to detect chemical changes, but does not address optical properties of synovial fluid.
Yen-Shuo Liao *Filed*: 3/31/04 *Issued*: 3/13/07	"Joint endoprosthesis with ambient condition sensing."[101]	This patent's claims are very general in regards to the parameters being detected. It describes a method to sense ambient temperature in the vicinity of a joint but does not specify the need for synovial fluid contact or the importance of detecting indicators for infection.

Currently, the gold standard for diagnosis of infection is the triple test. Knee joint aspiration, ESR and CRP are routine procedures in all suspected cases of infected TKR. An abnormal finding in two out of these three is suspicious for infection. Knee joint aspiration is another common procedure with the patient off antibiotics for 7-10 days to avoid false-negatives[102]. The issue with the triple test or aspiration is that both require the patient to suspect infection and seek medical attention, at which point the infection may have progressed past the point where avoiding surgery is possible.

We define success as a lowered total knee revision rate due to infection, and we believe our device is capable of achieving this feat.

B. Safety

The results from a finite element analysis conducted in SolidWorks has shown that our device will not negatively impact implant functionality. It must be noted, however, that implementation is not possible as proposed if the implant has an internal stabilizing post. OrthoSensor, Inc. currently plans to use our device in the Stryker Scorpio Triathlon Size 3 which has no such post, and our device is easily modifiable for other sizes and styles. The implant functionality is not compromised under the imposition of conditions necessary for our device, and our mechanism poses no factors of risk to the patient.

Our device contains no unusual use of materials; all are widely accepted for use in implanted medical devices. Our device will be hermetically sealed; thus, the patient is exposed to only Plexiglas, the same material of which bone cement is composed.

Our sensors pose no safety concerns either. The LED emits <50mcd (1mW laser = 180mcd), and its dispersion pattern places the radiated energy within biological tissue limits. It must be noted that any optical radiation degrades the polyethylene spacer material and shortens overall lifespan, but the radiation is so minimal we anticipate no concerns. The MEMs device is a passive sensor and does not require direct connect with tissue or fluids, thus posing no risks to the patient. In addition, it does not require a cavity to operate nor does it induce vibrations; therefore it poses no threat to the implant functionality either. In terms of device malfunction, the worst case is the

device generates no data or the patient receives unwarranted medical attention in the form of a hospital checkup.

We anticipate several modes of failure. Should the channel clog with blood or other particulates, the device will deliver data with very high turbidity and caution the patient to seek medical attention. The channel is positioned in such a way that relatively noninvasive needle aspiration is all that is required to clear all debris and resume normal function. Whether the channel clogging is indicative of infection of not, medical attention is good as the knee should never contain sizeable particulates.

C. Proof of Concept

We have validated our device in a laboratory setting and maintained the clinically relevant aspects of the in-vivo situation. Our test chamber is pictured below in Figure 5. We have constructed several iterations of test chambers and have consequently excluded channel or chamber size effects on device function. The chambers on either end of the channel simulate the relatively larger volume of SF in front or behind the knee. The dimensions of the channel depicted reflect the scale recommended in the final design.

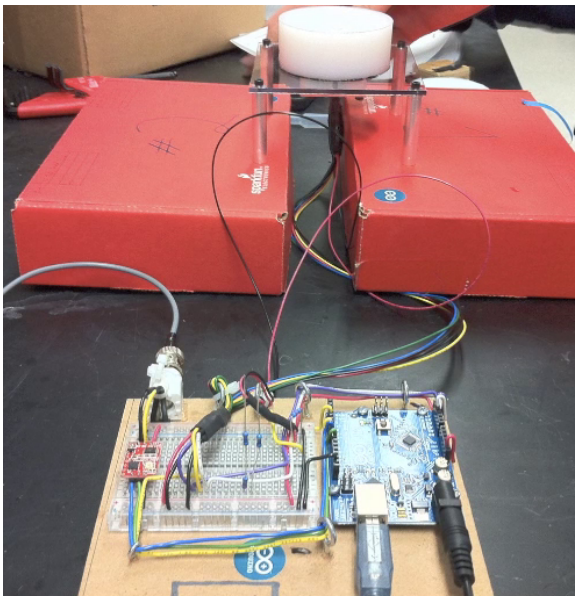


Figure 5. Experimental Test Chamber.

The LED shines light through fluid onto our Ultra High Weight Molecular Polyethylene (UHMWPE) tibial insert back into the fluid (bovine serum, a clinically relevant substitute for human synovial fluid[103,104]). The MEMs detects this light and generates color and turbidity data. The entire test chamber was enclosed in a dark volume to exclude extraneous light.

The pH probe was simply dipped into the serum and left in constant contact. The ISO standards for simulating SF in polyethylene wear testing recommend using calf serum diluted with deionized water to a protein concentration of 17 g/L[105]. For our purposes in measuring changes in the pH, color, and turbidity of sterile and infected SF, the calf serum is an appropriate model. The infected serum was diluted with water and bleached before disposal. Lastly, the fluid was shielded from all external light to simulate the optical conditions inside the joint.

The sensor must have access to enough SF to shine the LED through it or reflect it back to the receiver. The pH sensor requires nearly constant access to SF. Our device thus requires SF to fill

the channel in the tibial insert. As the body generates fluid to fill the space in the joint cavity, this specification is met.

An infection typically consists of {3,000-75,000 WBC/uL + 1,100 Bacteria/uL + Cellular waste particles/debris} whereas a healthy knee contains {200 WBC/uL + nothing}. As our sensors are validated to the sensitivity level of the healthy knee with 200 WBC/uL only and zero mixing, we are able to detect any deviation from healthy according to the resultant data. Deviation from this healthy baseline will trigger at different times based on the speed of the infection propagation but will always catch the infections in the early, easily treatable stages.

We have been using *E.coli* as a model for infection (which could be caused by a variety of bacteria *in vivo*) due to its availability and analogous behavior to pathogenic bacteria in synovial fluid. We incubate *E.coli* overnight and the following day use a spectrophotometer to quantify bacteria concentration in the liquid culture. We can then add a known concentration of bacteria to our test chamber, and based on the output of our sensors adjust the dilution of the liquid culture to achieve infection faster (increase concentration of added bacteria) or prolong the infection (decrease concentration of added bacteria). We have tried to keep our infections in the 10-20 hour range to allow for maximum data collection. Infection process *in vivo* can last 24-48 hours, but we propose that if our sensors are sensitive to changes in infection parameters for a shorter time scale, they will remain sensitive as that time increases.

D. Efficacy

As described above in the Proof of Concept section, we have validated the effectiveness of our device and must now prove its efficacy. In practice, our device is capable of detecting absolute values of and changes in pH, particulate color, composite color, and turbidity. However, experiments inherently differ from in-vivo studies; here, we discuss our experimental shortcomings.

1. Our channel and chambers do mimic the proposed geometry in knee implants but are approximations to the actual dynamics in a human knee.
2. OrthoSensor will ultimately select the sensors to implement into their ASIC; however, as long as these sensors measure the same indicators to the same precision as the sensors we selected, we anticipate no problems.
3. Our experiments used bovine serum instead of human SF. Although serum is a clinically relevant substitute, our device has not yet been tested with human SF.

To provide proof of efficacy with respect to our experimental shortcomings, we recommend continuing further studies to fine-tune and establish in-vivo tolerances on what constitutes an infection (we have provided in this report a baseline valid within the limits of our experiments) and establish indicator values (either absolute values of or changes in) what warrants medical attention.

IV. Further Studies

A. Design and Further Testing

OrthoSensor will finalize the design of our device. This includes the selection of the sensing components, the interface between their ASIC and the sensors, and any modifications to enable the device to operate in another knee implant type.

Further studies must define or clarify the following aspects of our device:

1. Select a proposed device design (single horizontal channel or accompanied by two vertical channels) or modify either to produce a different design. To compare our proposed designs, we recommend testing the two devices clinically and then in-vivo to compare their likelihood of clogging as well as their disparity in response time to infection. If either device fails to meet the performance required, design compromise between the two is encouraged.
2. Select a battery with a MTBF that can accommodate the minimum and maximum expected sampling frequency (should not be higher than the data delivery frequency). The suggested sampling frequency is given in Section II. C. and must be validated in-vivo. If the sampling frequency does not provide data quickly enough to alert the patients of infection in time to avoid revision surgery, the sampling frequency should be increased.
3. Fine-tune the values given as boundaries for our Data Score system discussed in Section II. C. If a Data Score (e.g., 022, 011) generates too many false positives, move it a lower Infection Status to assign it a less proactive Recommended Action. If a Data Score warrants less medical attention than is necessary to reduce revision surgery for that set of infection indicator values, move the Data Score to a higher Infection Status to assign it a more proactive Recommended Action.
4. Define values for infection indicator trends that constitute infection. This includes defining the time scale over which the trend must appear to constitute an infection. This necessitates an in-vivo study to pull a trend out from data while ignoring noise. Accompanying this effort, creation and implementation of a trend-fitting algorithm in parallel will be necessary to identify the trend.

Animal testing on sheep, pigs, cows, horses, or goats could prove valuable as they all have SF that exhibits a change in color from transparent and colorless to yellow[106], a decreased pH[107], an increased turbidity,[108] and an increased volume[109] when infected. Animal testing is a possibility as a preliminary measure but inadvisable as the risk benefit would not justify the cost. Our device will not heighten the chance of infection as discussed in the section on safety above, so we recommend human testing.

The risk is deemed low as the worst case outcome associated with our device is the sensing mechanism could fail to generate useful data. If it generated a false positive, the patient would receive unnecessary medical attention. If the device did not register an infection, the patient would endure no additional harm as compared with a patient who did not have our device implanted.

Approximately one-third of infections occur in the first three months after surgery and the other two-thirds after 3 months.[110,111] However, the artificial joint can become infected many years after operation,[112] so the recommended order of magnitude for the length of in-vivo testing is on the order of years rather than months.

Before reaching clinical trials, further FDA testing is necessary to complete the approvals process:

1. Biomaterials testing as described in the International Organization for Standardization (ISO) standard ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."
2. 10 million cycle ASTM F1800 fatigue testing of the tibial base plate
3. ASTM F1715 or ISO 14243-1, and ASTM F 2025 or ISO 14243-2 testing of the polymer insert for wear
4. Shear fatigue testing of the tibial post

5. Full property characterization as per "Data Requirements for Ultrahigh Molecular Weight Polyethylene (UHMWPe) Used in Orthopedic Devices, dated March 28, 1995."
6. Range of motion data on the tibiofemoral interface and constraint data involving the lateral stability of the patellofemoral joint
7. Complete report of the contact surface area between the femoral and tibial components at several different positions of flexion and extension
8. Analysis as per Guidance "Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement, dated April 28, 1994".[113]

B. Approval Process

Ideally, the device would fall under the category of a 510(k). OrthoSensor would apply for a ruling of equivalency from the FDA on the basis of similarity of this implantable device to an existing implantable device currently in use in the marketplace. Examples are described in Section III. A. In addition, our device uses no novel materials and has many references that may serve as precedents. If our device meets the criteria of being "substantially similar" to an existing product, the approval process could utilize the 510(k) pre-approval process that requires a fee of $5,000 and 3-6 months to approve.[114] An example of a well-established device in the marketplace with similar construction, materials, risk factors, and purpose is the intelligent hip-joint prosthesis available from Fraunhofer-Institut Photonische Mikrosysteme in Germany.[115]

If the implant does not meet those criteria, or the 510(k) process is revoked after review due to a recent failure of an implant the process approved[116], then it will have to follow the 2-year, $250,000-$500,000 fee, Class IIb (Special Controls) pre-market approval (PMA) system.[117] The total process will require $5 Million to $300 Million depending on the device complexity and any issues that arise and require further study.[118] The PMA system consists of three stages:

1. Stage 1: The device is studied in a small number of individuals with a two-year follow-up to assess device safety.
2. Stage 2: If stage 1 is successful, the device is studied in a larger number of individuals to develop statistical power in the patient population.
3. Stage 3: If stage 2 is successful, patients are recruited from a number of different centers to test the device and demonstrate an equivalent level of safety and efficacy past the primary sponsor.

The timeline is thus approval process dependent.

V. Recommended Market Introduction

Novel medical devices often take years to gain approval, let alone gain the confidence and acceptance of the medical community necessary for the device to become ubiquitous. In addition, enlisting patients in which the device is tested is difficult, especially for a device such as our sensing mechanism which requires a long period of study and a large number of patients due to the nature of synovial fluid infections: not all patients develop them nor can one depend on them to develop an infection in a short amount of time.

To expedite the in-vivo testing and thus the approval process, we suggest the following strategy for introduction of our sensing mechanism in OrthoSensor's instrumented implant:

1. Introduce the instrumented implant as a monitor for patients whose implants have failed. These patients have a spacer put in their knee during the interim period, and the spacer is left there for a length of time ranging from 6 weeks to a year. These patients are often very highly monitored, and having the infection sensor in there would save doctors the trouble of constant needle aspiration and the patient a large number of check-ups. Our sensing mechanism would allow the patient to rather correspond with the doctor by phone or email as to the status of their implant's data output, a non-invasive and independent process. This would help gather data for the in-vivo validation process to refine the infection indicator calibration values as well as satisfy conditions to demonstrate safety and efficacy.
2. After the medical community has gained confidence in the instrumented implant, its function may then be advertised for use in revision implants rather than solely in a temporary antibiotic spacer.
3. After the medical community has gained confidence in the instrumented implant for long-term use, its function may then be advertised for use in primary implants in addition to revision implants or antibiotic spacers.

Introducing the instrumented implant into the medical device market in this fashion would thus make its introduction gradual and alleviate the difficulty of finding patients in whom to collect the in-vivo safety and efficacy data, as the interim patients would return their antibiotic spacers with the device in them to receive their revision implant in return. These factors, we believe, would bolster the device's chances for success in the long-term.

VI. Anticipated Costs and Liability

A. R&D Costs

Our device implements optical monitoring sensors in the $5 range, pH sensors in the $10 range, wireless transmitters (~$50-$100), and power modules (~50-$100) for a total of ~$200. The ASIC that controls the sensors and transmitters is produced with an estimated fixed cost of ~$11 Million and recurring cost of $3 per unit.[119] The project sponsor, OrthoSensor Inc., recently entered an agreement with Stryker, which has a 19.5% market share in total knee implants.[120] As the technology largely entails adding sensors to existing implants, we will work off the premise that Stryker would add the technology to as many implants as possible to reduce the overall implant cost and create a market advantage. If the intelligent knee implant remains on the market as a Stryker device we can expect total lifetime sales of 1.7 Million implants (based on a 10% Annual Growth Rate derived from the 20 year 670% increase discussed previously). Using these numbers, and the assumption that the other implant costs are similar to current systems, we determine the total increase in cost to be roughly $250 per unit. We see that that R&D budget is approximately 6.3% of sales, which amounts to ~$50 Million dollars annually for Stryker, which is much larger than the largest expected cost, the ASIC, at $11 Million. See Figures 6 and 7 below.

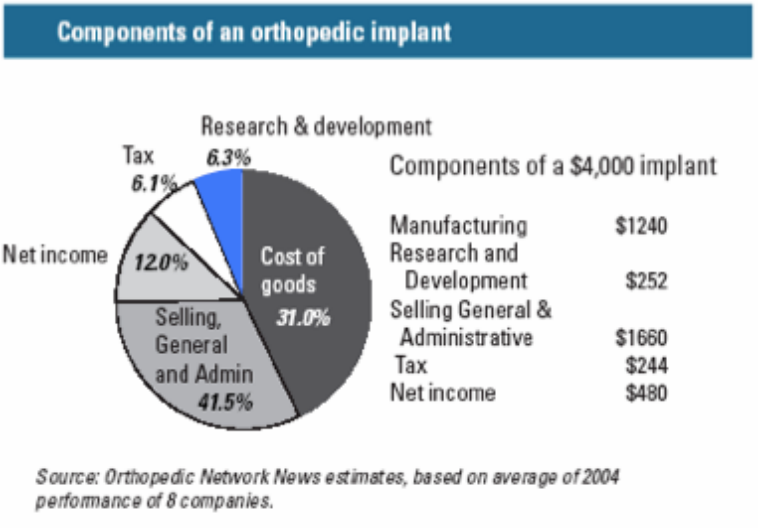


Figure 6. Components of an Orthopedic Implant.

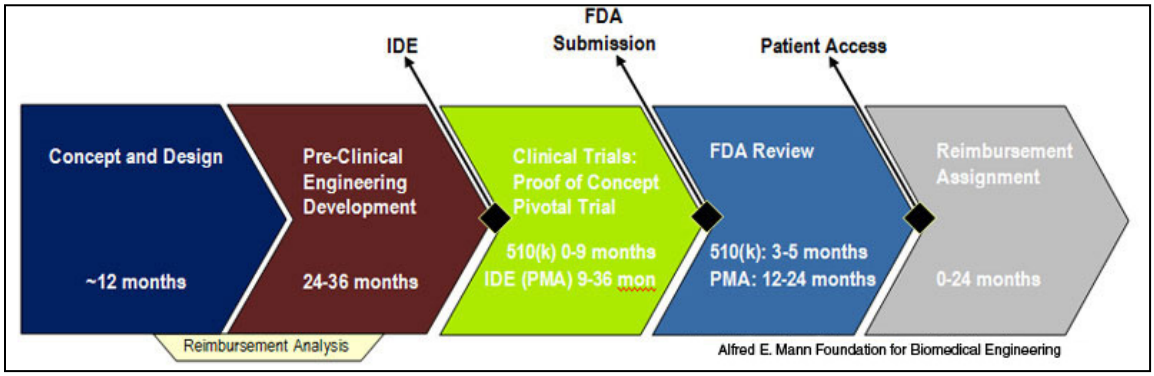


Figure 7. FDA Approval Process.

B. Approval Costs

Approval costs are dependent on whether the device is permitted approval under the 510(k) or requires a PMA study. See Section IV. C. for discussion.

C. Liability

Implant failure or side effects are very serious concerns, not only for physicians and patients but also for the company that manufactures the implant. The recent Zimmer Durom Cup hip replacement litigation, which has stemmed from a higher than expected failure rate of 20% instead of the industry average of 5.7%, has cost the parent company upwards of $1 Billion USD in liability payouts to patients with defective implants.[121] Industry practice has been to set aside a preventative fund that grows annually to buy down the risk involved, as time passes more implants are installed which increases liability in the event of a defect but the fund is worth more due to the power of compound interest. This implant is no more likely to fail than other implants and should follow standard industry practice.

VII. Conclusion

Infection is the primary cause of revision TKAs, responsible for about 25.2% of revision surgeries[122], and there currently exists no universal standard for proactive detection and treatment. Septic revision surgery is extremely expensive: the average cost of a septic TKA revision is three to four times more than primary TKA cost. Septic revision is typically comprehensive in nature (complete prosthesis removal as opposed to single component revision) and requires expensive antibiotics[123,124].

Revision TKA surgeries pose not only an economic but also a social burden. Revision surgeries put patients at risk and consume myriad human resources, and many may be avoidable. A technique to promptly detect an infection in a knee implant, and subsequently reduce the number of surgeries, has merit beyond that of pure economics. Our device is intended to reduce the number of total knee revision surgeries via early detection of infection in synovial fluid in the knee.

Our device's focus is to provide early measurement of specific variables allowing an appropriate early intervention in face of the indication of infection.

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