

Specific Aims

Even the most advanced prosthetic hand models have a limited range of motions that stem from coding with limited personalization and customizability. They are often not well integrated into the arm, and chafing, irritation, and misalignment can occur. An ideal prosthetic would be securely attached to the arm, capable of receiving signals from the nervous system, and have the ability to translate these signals into motions. In our novel prosthetic model, signals will be sensed using electrode microarrays, enhanced using amplifiers, and translated using tunable chips. These chips will be located in an electrical interface hub, a biocompatible-polymer coated titanium insert that is connected with stems to the arm bones. The prosthetic hand will attach to the hub. This model will be easily integrated and mimic natural hand motion.

Aim 1: Nerve sensing and signaling

Hypothesis: Signals from the brachial plexus nerve network can be detected using electrodes, amplified, and organized to mimic natural electrical impulses that translate to appendage motor control, such as the movement of individual fingers of the hand.

Method: A slanted electrode array will be inserted into the five peripheral nerve bundles in the brachial plexus nerve cluster, located under the clavicle. This will be achieved via microscope-assisted surgery, to avoid rupturing the blood vessels inside the nerve bundle. This type of electrode array has been clinically shown to detect signals from feline nervous system bundles. These signals, however, are weak and need to be enhanced using a high sensitivity electrical impulse amplifier, tuned for the human nervous system. Once amplified, the signal will travel down wires close to the surface of the skin. The wires will connect to a programmable hub and be translated to signals for fine motor control of a next generation prosthesis.

Aim 2: More mechanically intuitive and a wider range of prosthetic control

Hypothesis: Utilizing programmable signal recognition within the hub will allow for a vast number of natural nerve impulses to control the movements of a prosthetic hand.

Method: The tunability of the computer chip allows for signals received to be coded for different motions. When the patient attempts a motion the received signals can be coded to correlate to that motion. In this way, the movements will be more natural and intuitive than it is with current models. Because each movement will be correlated to a specific signal code, more movements can be coded than can in currently available models, which are created with set commands. Prior mapping of the nerve pathway is not needed using this method.

Aim 3: Osteointegration of the prosthetic and biocompatibility of the electrode array

Hypothesis: Sturdier attachments, biocompatible materials, and ease of access to parts would allow for desirable integration of the prosthetic into the arm.

Method: A bio-inert titanium hub will be mounted to the ulna and radius in a stem insertion method, similar to that of hip replacements. To ensure proper mobility of the ulna and radius, the stems will attach to the hub via ball-pivot mountings, and urethane bushings will be placed to ensure mechanical rigidity while allowing flexibility. A prosthetic robotic hand will be quick-release mounted to the hub, translating the signals coded from the hub directly to fine motor controls. The arm-side of the hub will have dual region coatings; one coating will be bioactive to promote skin healing around the hub-tissue interface, and the other coating, located further along the hub, will be bio-inert to reduce chances of infection and unwanted skin growth. This hub design would help to eliminate any skin to prosthetic interface, allowing for a more comfortable, stable fit than current prosthetics. The general concept of the electrode array has shown success in animal testing, and the addition of bioactive, conductive coatings will help to better integrate the array into the nervous system. The amplification unit and electrical leads coming from the unit will be mounted subcutaneously, and will be coated in bio-inert polymers to prevent an immune response.

The goals of this grant are to recognize and amplify nervous system signals, use these signals to create a wide range of mechanically intuitive movements, while maintaining both biocompatibility and stability in a novel prosthetic hand. This technology could eventually lead to advancements in the treatment of multiple types of injury, including spinal cord trauma.

DESIGN STRATEGY

Significance:

1. Current prosthetic models use unintuitive signals to create motions.

Many of the state of the art mechanical prosthetic limbs in today's market rely on using signaling from muscles that are not naturally associated with the motions the prosthetic will be performing. In the Touch Bionics "i-limb" product line, electrical signals are received from surviving muscular tissue via gold-plated electrodes and transmitted to a robotic appendage. To grasp with a robotic hand, for example, a certain combinations of muscles in the forearm need to contract. An amplifier then transmits the signals from the muscles to the robotic hand. The robotic hand is coded to interpret the signals and translate them to digital motion. While this method is effective, the motions are never going to be mechanically intuitive to the brain. Amputees are faced with using a limited number of muscles to control a wide range of motor functions. To overcome the issue of non-intuitive motor control a much broader sensor array would need to pick up a vast number of signals sent through the nervous system. We propose to use an array of sensors connected directly to the central nervous system (CNS) at the brachial plexus. This method will allow an amputee to use the motor signaling native to the body to control a prosthetic robotic limb.

2. Current models are not structurally secure and have a limited range of motions.

Nearly all modern prosthetics rely on straps, suction cups, or elastic materials to remain affixed in place (see Figure 1). These methods leave the prosthetics prone to loosening with normal use, and can lead to temporary loss of function due to misalignment and tissue irritation in the mounting location. In addition, to suboptimal mounting conditions, current sensors used for robotic prosthetics have limited inputs, meaning there is limited control over prosthetics. The processors used in the prosthetics are capable of handling a wide array of input commands from a limited number of sources, but the non-intuitive nature of the limited inputs, as previously mentioned, put a soft cap on the number of motions the prosthetics can achieve. We hypothesize that the attachment of a rigid mounting system directly to the bone will provide a more stable mounting for the prosthetic. This mounting system will incorporate a microcomputer to translate signals from the nerve sensing array to a robotic prosthetic.



Figure 1 - Female subject with a current upper arm prosthetic limb [1]

Innovation:

1. A biocompatible polymer coated microelectrode array and amplifier can use CNS impulses, as opposed to muscle contractions, to control a robotic hand.

Five slanted microelectrode arrays, inserted into each of the brachial plexus nerves using microsurgery, will penetrate many of the nerve fascicles within. Inside these fascicles lie thousands of axons, with which the electrodes of the array will come into contact. While this insertion will disrupt normal cell function, it has been shown that nerve cells heal and regenerate function over time. A conductive, biocompatible polymer coating will promote this healing while maintaining signal detection. These electrical signals will be amplified to a higher voltage by an amplifier approximately 5 cm downstream from the arrays; this serves to counter any drop in signal strength along the wires. The amplifier and wires will be encased in a fashion similar to how pacemakers,

in a bioinert container. The amplifier and wires will be located close to the surface of the skin for ease of access. While the polymers, slanted microelectrode array, amplifier, and amplifier casing are existing technologies and have shown promising results in research, this combination as well as the application is a novel procedure.

2. A polymer coated hub with stems and a tunable chip will create a structurally stable and personalizable prosthetic.

The hub will detect signals from the microelectrode array and amplifier system. Implantation of the titanium hub stems into the radius and ulna bones will increase the structural stability of the prosthetic. Biocompatible coatings and oxidizing of the stems will improve interactions with the body. Specifically located polymer coatings of the hub will promote or inhibit skin growth at the skin-hub interface to increase comfort and decrease infection. Once we implant this biocompatible system, a programmable computer chip can translate the signals into motions. These motions, derived from natural CNS signals, will be more intuitive and have a wider range of possible motions than current pre-programmed prosthetics. While these polymers, stems, and tunable chips are existing technologies, researchers have never combined them in a design similar to this novel prosthetic attachment method.

Approach:

In Aim 1, we will implant a slanted microelectrode array and amplifier into primates to detect and increase the strength of natural signals from the brachial plexus nerves. In Aim 2, we will translate these signals into motions and record them using available microchip technology. We will then compare the number of motions coded to those of preprogrammed prosthetics. For Aim 3, primates without hands will be necessary. We will implant the hub into the radius and ulna bones of primates for increased structural stability of the prosthetic. Through this biocompatible system, natural signals can be detected and translated into intuitive motions of a prosthetic hand.

Aim 1: Detecting and enhancing natural signals from the brachial plexus nerves using a slanted microelectrode array and amplifier implanted using microsurgery.

Hypothesis: Signals from the brachial plexus nerve network can be detected using electrodes, amplified, and organized to mimic natural electrical impulses that translate to appendage motor control, such as the movement of individual fingers of the hand.

Method: A slanted electrode array will be surgically inserted into the five peripheral nerve bundles of the brachial plexus nerve cluster, located under the clavicle. The electrodes will detect and transfer weak electrical impulses from the CNS, which must then be enhanced using a high sensitivity electrical impulse amplifier. Once amplified, the signal will travel down wires coated in a bio-inert polymer to a programmable hub and be translated to signals for fine motor control of a next generation prosthesis.

1A. An array of electrodes of varying length can be inserted into each of the five brachial plexus nerves to detect impulses from the brain.

Microelectrode arrays have the ability to detect and stimulate signals, which has been successfully tested in cat sciatic nerves [2]. We will test this stainless steel microelectrode array in monkey brachial plexus nerves, implanting one array in each of the five nerves (see Figure 2). The array will be 4 mm by 4 mm, and the 100 electrodes on it will range from 0.5 to 1.5 mm in length along one axis (see Figure 2). This slanted array design will ensure a range of probe depths, so that axons in different locations within the bundle

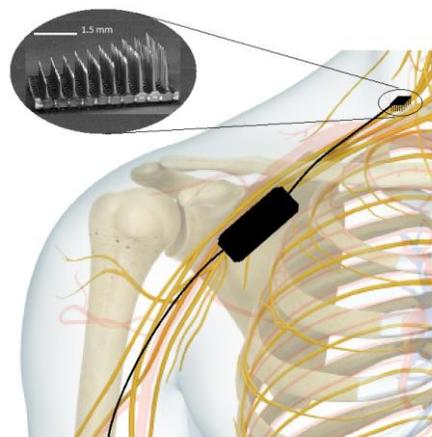


Figure 2 - Image of the gradient length electrode array [2]

will be in contact with the probes. Recordings of voltage signals during various activities are expected to be approximately 20 mV [2]. Previous research has shown that as axons and their surroundings heal from insertion of microelectrode arrays, allowing signals to be detected clearly with minimal background after approximately 1 month [2].

1B. The electrode array will be inserted into the nerves through microsurgery, and a silicone cuff will ensure a secure connection.

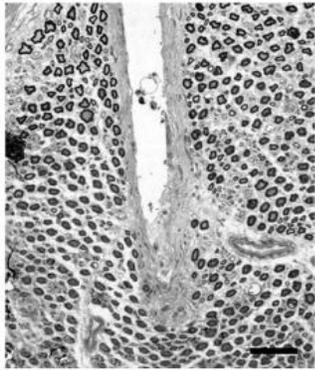


Figure 3 – One electrode from an implanted array surrounded by axons in a fascicle [2]

The surgical manipulation of individual axons, whose diameters may be smaller than a micron, is not feasible with current medical technology [3]. Instead, we will insert the electrode array into a peripheral nerve. Once the 0.5-1.5 mm long probes break through the wall of the nerve bundle, the majority of them will pierce the fascicles held within. Inside the fascicles, the tips of the coated probes will lie amongst thousands of axons, where they can receive electronic impulses from the central nervous system (see Figure 3). Following a procedure similar to that of Branner et al., we will insert the electrode array into the nerve using a pneumatically actuated impulse inserter. A custom fit silicone cuff will be used to secure the array to the nerve bundle while healing takes place. The customized silicone cuff will prevent the newly inserted array from detaching from the nerve, and also prevents excessive connective tissue growth, which can disrupt signaling [4], or cause the array to become dislodged from the nerve..

1C. Minimal signal strength from the nervous system needs to be amplified close to the array site in order to ensure signal propagation.

The average signal strength of a nerve impulse is approximately 20 mV [5]. A shift in potassium and chloride ions causes the electrical impulse, much of which is likely to be lost through the array itself. Using 40 gauge (0.08 mm diameter, appropriate for the scale of the array) coated copper wire as an example, a wire of one half-meter length will experience a voltage drop of 15-50% from the array to the end destination of the prosthetic hub. An amplifier placed within 5 cm of the array will convert a signal as small as 20 μ V into a signal greater than 100 mV at the end destination. Researchers have already developed and proven such an amplifier, albeit in a different configuration [6]. We will remove items from this configuration, such as an integrated nerve cuff, wireless transmitters, etc., in order to reduce power draw. A single CR2477 coin style battery can power the current model for half a year of continuous use, but a modified model for use with our array has the potential to last substantially longer. The amplifier will lie under the skin for ease of minor surgical access during battery changes. The amplifier itself will have a 0.2 mm polytetrafluoroethylene (PTFE) skin to avoid any electrical interference or biocompatibility issues. This will be revisited in section 3B. Wires leaving the amplifier will be bundled into a single subcutaneous loom running to the prosthetic attachment location.

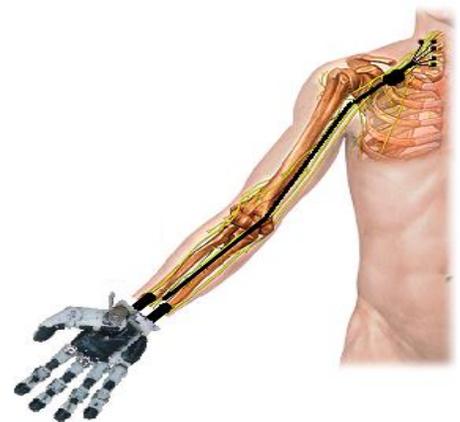


Figure 4 - Full connection of array, amplifier, hub, and robotic hand [5]

Aim 2: The prosthetic will utilize a wider range of mechanically intuitive motions once signals are translated and tuned.

Hypothesis: Utilizing programmable signal recognition within the hub will allow for a vast number of natural nerve impulses to control the movements of a prosthetic hand.

Method: Signals sent from the amplifier will be interpreted by a microprocessor for custom configurations (see Figure 4). The tunability of this microprocessor will allow the received signals to code for different motions. Because each movement will be correlated to a specific signal code, more movements can be coded than can in currently available models, which are created with set commands.

2A. Signals sent from the amplifier will be interpreted by a microprocessor for custom configurations.

The prosthetic mounting location (hub) will contain a programmable complementary metal-oxide semiconductor (CMOS), similar to the BIOS of a conventional computer. By testing the on/off status of the multiple leads coming from the amplifier, researchers in conjunction with software programmers will be able to translate the sequence of independent nerve signals into actual motor functions. Researchers will continuously collect data transferred from the amplifiers in real time, and compare it to the actual hand gestures of the primate subjects. This will allow researchers to record a database of signal vs. motion measurements for each subject. We will analyze the data and program the processor accordingly.

2B. A larger range of intuitive motions will be programmed for this prosthetic in comparison to current models.

The custom programmable nature of the novel implant allows for a wider range of motions than a conventional prosthetic, where the subject must learn a limited series of unintuitive motions to cause the mechanical hand to perform the desired action. A library of signals can be compiled for use when coding the mechanical hand's motions. Our goal is to detect nearly all of the nerve impulses that control the natural motions of the hand, enabling a prosthetic robotic hand to intuitively mimic any natural motion.

Aim 3: Specific materials and polymer coatings will enhance the biocompatibility of the electrode array system and the hub system, causing osteointegration and reducing rejection of implanted parts.

Hypothesis: Sturdier attachments, biocompatible materials, and ease of access to parts will allow for desirable integration of the prosthetic into the arm.

Method: The mobility and coatings of the stems and hub will make them biocompatible. The stems will be coated with polymers and oxygenated, increasing osteointegration. The hub will have skin growth promoting and inhibiting regions, so that the hub will have controlled integration with the body at the arm-hub interface. The microelectrode array will have a conductive, biocompatible coating to decrease rejection while maintaining signal detection. The wires and amplifier will be coated with bio-inert materials. This system will create a comfortable prosthetic, and reduce rejection.

3A. The electrodes in the array will be coated with a polypyrrole and silk fibroin mixture to facilitate cell growth and biointegration.

While researchers have shown that nerves can recover and function normally after the implantation of the microelectrode array, polymer coatings can increase this biocompatibility and aid in signal detection. A composite polypyrrole and silk fibroin (PPY SF) fiber has highly conductive properties, 0.38-0.42 S/cm [7], and facilitates cell growth [8]. We will coat the arrays with approximately 15 μm of PPY SF before implantation. Three of the monkeys will receive arrays with no coatings, to serve as a control group. A comparative test of the amplitude of the signal will determine the functionality of the coated array.

3B. The amplifier will be coated with polytetrafluoroethylene sheets to prevent contact dermatitis or any other immune response.

A rare but considerable problem with implanted electronic devices, such as pacemakers or an implantable defibrillator, is contact dermatitis. An allergic reaction to a component of the device (titanium and nickel being the most common allergens) typically causes this irritation and swelling of the skin surrounding an implanted

device [9]. In order to avoid this potential problem with the amplification device in the novel prosthetic, a similar solution to that used with irritating pacemakers will be utilized. Doctors at Nagoya University Hospital in Japan have discovered that coating the pacemaker of a patient, who had repeatedly had inflammation and necrosis of the tissue surrounding the implantation site, with 0.2 mm PTFE sheets eliminated tissue irritation [9]. Prior to implantation and testing in primates, we will encase the functioning amplifier in PTFE sheets, so as to not trigger an immune or allergic response.

3C. The wires connecting the array to the amplifier, and the amplifier to the hub, will be coated in an insulating, bio-inert polymer.

Copper wire will connect the array to the amplifier (40 gauge), as well as the amplifier to the hub (36 gauge). We will coat the copper wire with a thin layer of polypropylene to protect the metal from the liquid and dissolved salts in the body, as well as provide the necessary electrical insulation. Polypropylene is a soft, flexible, and bio-inert material that the body will not “see,” and therefore will not trigger an immune system response [10]. The bundle of insulated wires will be implanted close to the surface of the skin for easy access in the event of damage or routine maintenance.

3D. A peripheral mounting hub will encase the translational circuitry and allow for easy attachment of a prosthetic appendage.

A titanium hub, as shown in Figure 5, containing the circuitry described in section 2A will be designed on a per-case basis to ensure proper fit. The hub face (away from the body) will consist of a titanium hollow elliptical disk with multiple contact points for signal transmission to a robotic hand. The rear of the disk will have a magnetic port to receive the leads from the amplifier, and a separate input port to accommodate programming of the circuitry. The circuits will translate signals received from the leads, and transmit them to the robotic hand contact points in a sequence that will be uniform to all robotic prosthetics utilizing the hub design described herein; that is, the signal for movement of a particular joint will be in a uniform location across all hubs of this design, eliminating the need to code the robotic hands separately. The rear side of the hub will also have semispherical divots, generating an attachment location for the stems to be inserted into the ulna and radius. These divots will contain semi-rigid polyurethane bushings to allow for circular rotation in the natural plane of the radius and ulna while limiting motion deviating from a proper alignment of the arm to prosthetic. This will allow for preservation of some degree of forearm control. A bio-inert silicone sleeve will cover the bushings to avoid contact irritation between the skin and urethane bushings.



Figure 5 - Initial design of the prosthetic processing hub

3E. Bioactive stem coatings will be utilized for optimal osteointegration of the mounting hub.

The titanium stems inserted into the radius and ulna will have a 21.45% titanium, 1.80% aluminum, 52.85% oxygen, 16.64% phosphorus, 0.31% carbon, 6.94% calcium coating via electrolysis [11]. Uncoated titanium stems will be tested as a control. While titanium is generally bio-inert, the coating described will provide a bioactive surface for osteogenesis, increasing the structural integration of the stems while decreasing the chance of rejection. Similar to the methods utilized in hip replacement, researchers will insert the stems into the cleaved

ends of the ulna and radius. Initially all stems will need to be custom fabricated to fit the primate's exact bone formation. Primates will be used for this testing, and will be sacrificed after 12 weeks to determine the level of osteointegration.

3F. The biocompatible, antibacterial, skin-growth promoting area of the hub close to the arm followed by the bio-inert area of the hub can be created using PCL and PTFE coatings, respectively.

Current prosthetic models often result in irritating interfaces between the material and the skin. It is essential that the skin-hub interface be comfortable and not prone to infection. Polycaprolactone (PCL) facilitates the growth of skin and, when combined with 1% chlorhexidine diacetate, promotes anti-bacterial qualities [12]. A 70% PCL-acetic acid coating and an oxygenated surface with 50% porosity provide an area for the skin to grow, while inhibiting the growth of bacteria [12]. Research has shown that this combination results in only 10% fewer viable cells *in vivo* when compared to *in vitro* cultures and 71% fewer bacteria. A PTFE coating following the PCL coating will distinguish the bio-inert area of the prosthetic and the end of the biocompatible skin-hub interface [13]. These coatings combined form a comfortable, biocompatible, antibacterial section of the titanium hub close to the arm followed by a bio-inert section.

Potential Pitfalls and Solutions:

1a. A potential pitfall would be if the microelectrode array does not function as well in primates as it has been shown to in other animal studies. Either it cannot detect signal well enough, does not penetrate deep enough, or does not promote healing and/or causes damage.

Solution: Longer, thinner microelectrodes can increase the range of detectable axons while causing less damage. While the polymer coating will promote healing, different polymers can be experimented with if healing is not satisfactory.

2a. A potential pitfall would be if when tuning the chip, the signals cannot easily be sorted, meaning codes for movements are not distinct.

Solution: Unnecessary motions can be sacrificed for more desired motions. While the number of motions would be fewer than ideal, there exists a potential for significantly more than pre-programmed prosthetics and these motions would still utilize naturally, more intuitive signals.

3f. A potential pitfall would be if the bacterial infections occur, even with a decrease in bacterial growth in comparison to uncoated hubs.

Solution: Other antibiotic materials can be used or antibiotics can be taken to decrease infection in the early stages of implantation.

Summary of Goals and Innovation

We will implant a bioactively coated nerve impulse-sensing array into the brachial plexus of primate subjects. A computer will read the amplified signals from the subjects to ensure that the arrangement of the amplifier and array are functioning properly. The subjects' hand movements will be recorded and compared to the electrical impulses sent from the amplifier. These impulses will be translated to determine the accuracy of the readings compared to the subjects' motions. These primates will be sacrificed after 8 weeks to determine the degree of biocompatibility achieved through the coatings of the arrays and amplifier. Further tests will be conducted to determine the ideal coating to be used on the stems of the hub assembly. Mechanical properties such as degree of osteointegration and structural rigidity will be examined in sacrificed primates 12 weeks after implantation. Finally, we will incorporate all of the aforementioned methods to implant test primates with fully functional bio-controlled implants, as a model for human applications.

References:

1. Kuiken, T. A., Miller, L. A., Lipschutz, R. D., Lock, B. A., Stubblefield, K., Marasco, P. D., ... & Dumanian, G. A. (2007). Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study. *The Lancet*, 369(9559), 371-380.
2. Branner, A., Stein, R. B., Fernandez, E., Aoyagi, Y., & Normann, R. A. (2004). Long-term stimulation and recording with a penetrating microelectrode array in cat sciatic nerve. *Biomedical Engineering, IEEE Transactions on*, 51(1), 146-157.
3. Sretavan, D. W., Chang, W., Hawkes, E., Keller, C., & Kliot, M. (2005). Microscale surgery on single axons. *Neurosurgery*, 57(4), 635-646.
4. Branner, A., Stein, R. B., Fernandez, E., Aoyagi, Y., & Normann, R. A. (2004). Long-term stimulation and recording with a penetrating microelectrode array in cat sciatic nerve. *Biomedical Engineering, IEEE Transactions on*, 51(1), 146-157.
5. Pratt, Charlotte W. "Chapter 9: Membrane Transport." *Essential Biochemistry*. 3rd ed. Hoboken, NJ: John Wiley & Sons, 2014. N. pag. Print.
6. Nielsen, J. H., & Bruun, E. (2006). An implantable CMOS front-end system for nerve-signal sensors. *Analog Integrated Circuits and Signal Processing*, 46(1), 7-15.
7. Xia, Youyi, and Yun Lu. "Fabrication and properties of conductive conjugated polymers/silk fibroin composite fibers." *Composites Science and Technology* 68.6 (2008): 1471-1479.
8. Collier, J. H., Camp, J. P., Hudson, T. W., & Schmidt, C. E. (2000). Synthesis and characterization of polypyrrole-hyaluronic acid composite biomaterials for tissue engineering applications. *Journal of biomedical materials research*, 50(4), 574-584.
9. Tamenishi, A., Usui, A., Oshima, H., & Ueda, Y. (2008). Entirely polytetrafluoroethylene coating for pacemaker system contact dermatitis. *Interactive CardioVascular and Thoracic Surgery*, 7(2), 275-277.
10. Mano, J. F., Sousa, R. A., Boesel, L. F., Neves, N. M., & Reis, R. L. (2004). Bioinert, biodegradable and injectable polymeric matrix composites for hard tissue replacement: state of the art and recent developments. *Composites Science and Technology*, 64(6), 789-817.
11. Schrader, C., J. Bossert, U. Finger, A. Henning, A. Huppner, KD Jandt, M. Pfister, J. Schmidt, and S. Zankovych. "Development of Biofunctional Coatings on Titanium Implants to Improve Biocompatibility and Osteoinductivity." *International Conference on Phenomena in Ionized Gases* 29 (2009): 16-21. Print.
12. Smith, C. M., Roy, T. D., Bhalkikar, A., Li, B., Hickman, J. J., & Church, K. H. (2009). Engineering a titanium and polycaprolactone construct for a biocompatible interface between the body and artificial limb. *Tissue Engineering Part A*, 16(2), 717-724.
13. Karwoski, T., & Matsuzawa, Y. (1988). U.S. Patent No. 4,718,907. Washington, DC: U.S. Patent and Trademark Office.