Revolutionizing Prosthetics—Phase 3

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In early 2006, APL was awarded a contract to start the first phase of the Revolutionizing Prosthetics 2009 program, a multiyear, multimillion-dollar effort to develop an advanced upper-extremity prosthetic limb, the Modular Prosthetic Limb (MPL). This program's goal is to develop an advanced limb that would allow a prosthetic wearer to button a shirt, tune a radio, and feel the warmth of a loved one's hand; such a limb might even provide the warfighter with the opportunity to return to active duty. Currently in the third phase of Revolutionizing Prosthetics, APL is leading the Defense Advanced Research Projects Agency's effort to provide upper-extremity functionality to people who have no ability to control their native arms, such as amputees and those with high spinal cord injury or neurodegenerative diseases such as amyotrophic lateral sclerosis. Phase 3 of the program involves significant focus on clinical activities including maturing the MPL's robustness, submitting regulatory filings, designing and executing preclinical and clinical activities, and advancing cortical implant technology. Initial clinical activities during this third year of Phase 3 have involved a subject with tetraplegia using a brain computer interface to control the MPL. Further trials with this subject continue as the program team prepares for four additional subjects during Phase 3.

INTRODUCTION

Throughout history, the battlefield loss of limbs and/or motor function has been the major driving force for technological progress in the field of prosthetics. The existence of individuals with amputations or spinal cord injuries resulting from recent military operations, in addition to individuals in the general public with similar injuries and conditions, emphasizes the urgent need to accelerate the progress toward restoring lost function.

The Defense Advanced Research Projects Agency established and sponsored the Revolutionizing Prosthetics (RP) program to restore soldiers with upper-extremity injuries to preinjury levels of function and provide them the ability to return to activities of their choice either within the Armed Services or civilian society. The RP program envisions similar benefits to the general public.

The goal of prosthetics is defined as the design, manufacture, and fitting of artificial replacements for lost or dysfunctional limbs. The human upper extremity is a highly evolved structure that defines the unique human capability by enabling functional interaction with one's environment. Because of the sheer complexity of limbs, in terms of tissue composition and mechanical capabilities, the field of prosthetics encompasses one of the most diverse arrays of disciplines of any field in the medical sciences. Advances in prosthetics rely not only on traditional fields such as material sciences, power, and surgery but also increasingly on emerging areas such as neuroscience, tissue engineering, robotics, sensors, and nanotechnology. The driving goal of the RP program is to utilize and drive advances in these disparate areas for the benefit of the disabled soldier.

APL has a long history of addressing critical challenges for our nation. An experienced systems integrator, APL is well suited to bridge the gaps between academia and industry and help ensure that basic scientific discoveries are rapidly transitioned into the product development cycle. As in early phases of the RP program, APL continues to provide the systems integration and program management leadership to define the engineering approach and focus the efforts of the development activities and team member interactions. In this role, APL is responsible for translating the Defense Advanced Research Projects Agency's RP vision into a realizable design and for engaging the team members to address the critical technical barriers of chronic neural integration and direct neural sensory feedback.

PROGRAM OBJECTIVES

The RP Phase 3 (RP3 or Phase 3) program builds on the successes of the RP2009 program.[1] Specifically, RP3's goal is to use the Modular Prosthetic Limb (MPL) system[2] in conjunction with cortical implants for neural recording and stimulation to assist patients with high spinal cord injury, or tetraplegics, in performing activities of daily living. In addition, RP3 is evaluating wireless cortical implants and advanced neural signal-processing algorithms with an eye toward long-term use of these technologies in human subjects.

The primary objectives for Phase 3 are as follows:

1. **Closed-loop cortical control of the MPL:** Demonstrate closed-loop cortical control of a dexterous, multiple-degree-of-freedom prosthetic limb in human subjects. Having a closed loop in this context means enabling motion control by accessing neural signals in the motor cortex while simultaneously providing tactile and proprioceptive feedback through electrical stimulation of the somatosensory cortex.

2. **Development of wireless electrode arrays:** Develop a wireless architecture to support implantation of recording and stimulating electrode arrays suitable for long-term use in humans.

These two objectives involve a complex set of technical, clinical, programmatic, and regulatory challenges. To address these challenges and to accomplish these objectives, APL formed a world-class team. The University of Pittsburgh (Pitt) and the California Institute of Technology (Caltech) lead efforts to implant Utah Electrode Arrays (UEAs) in human subjects to demonstrate the ability to perform closed-loop cortical control. The University of Utah, with Blackrock Microsystems, is leading the development of wired and wireless electrode arrays. The University of Chicago, teamed with Northwestern University, is contributing research and development related to neural stimulation and support of the closed-loop cortical control. Hunter Defense Technologies is responsible for manufacturing enhancements to the MPL to meet Phase 3 objectives. APL is responsible for overall program management, integration of the technical and clinical activities, and overall systems integration.

The objectives of Phase 3 necessitate regulatory approval to ensure the safety and efficacy associated with the planned technology. Accordingly, identifying a regulatory pathway from today's state of the practice to the state of the art envisioned by this program is an extremely important element of the Phase 3 program plan. The extremely advanced technology associated with RP3 places achievement of program objectives at risk because of the regulatory challenges the program faces under traditional regulatory processes. Accordingly, the U.S. Food and Drug Administration (FDA) established a new program called the Innovation Pathway and selected RP3 as the pilot project. The Innovation Pathway, established for high-risk, advanced technology initiatives such as RP3, is intended to enable "in-stride" dialog between the technical stakeholders (the RP3 team in this case) and the FDA regarding safety and efficacy issues associated with advanced technology. The Innovation Pathway experience for RP3 has proven successful in terms of helping to shape the program's execution in a manner that addressed identified challenges earlier than would otherwise have been possible without the Innovation Pathway.

The major program and technical activities associated with RP3 are detailed in the following sections of this article.

CLINICAL ACTIVITIES—TOWARD RESTORING MOTOR CONTROL AND SENSORY FEEDBACK

Decades of neuroscience research has provided the foundation for today's understanding of cortical processing of information. Researchers have demonstrated the ability to decode signals from certain regions of the brain (Fig. 1), although much is still unknown. These decoded signals enable brain–computer interfaces, the likes of which include those that can control simple cursor movement on a computer screen to those that can control neuroprosthetic devices through thoughts alone.

RP3's program goals include developing an end-to-end system to capitalize on today's neuroscience understanding and enable tetraplegics to perform functions they would normally perform with functional natural limbs. Developing such a system requires several system components and subsystems, as shown in Fig. 2.

To achieve motor control of a neuroprosthetic, electrode arrays are implanted in the brain's cortex where they can access signals that would normally control a native limb. These motion intent signals are passed from the implanted arrays to a computer that decodes the intent (e.g., reach to this point in 3-D space, grasp an object such as a doorknob, and other similar actions people naturally perform). Despite the fact that tetraplegics cannot control their native limbs,
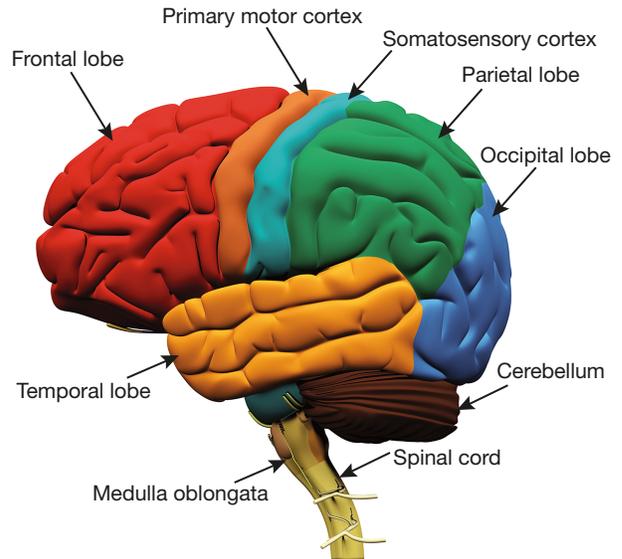
Figure 1. Regions of the brain. The brain exerts centralized control over the body by receiving and processing signals from throughout the body.

their brains still produce these intent signals. The MPL receives the decoded signals and translates these into commands to the motors built into the MPL. The process described thus far is referred to as "MPL motor control only" and represents the human subject research
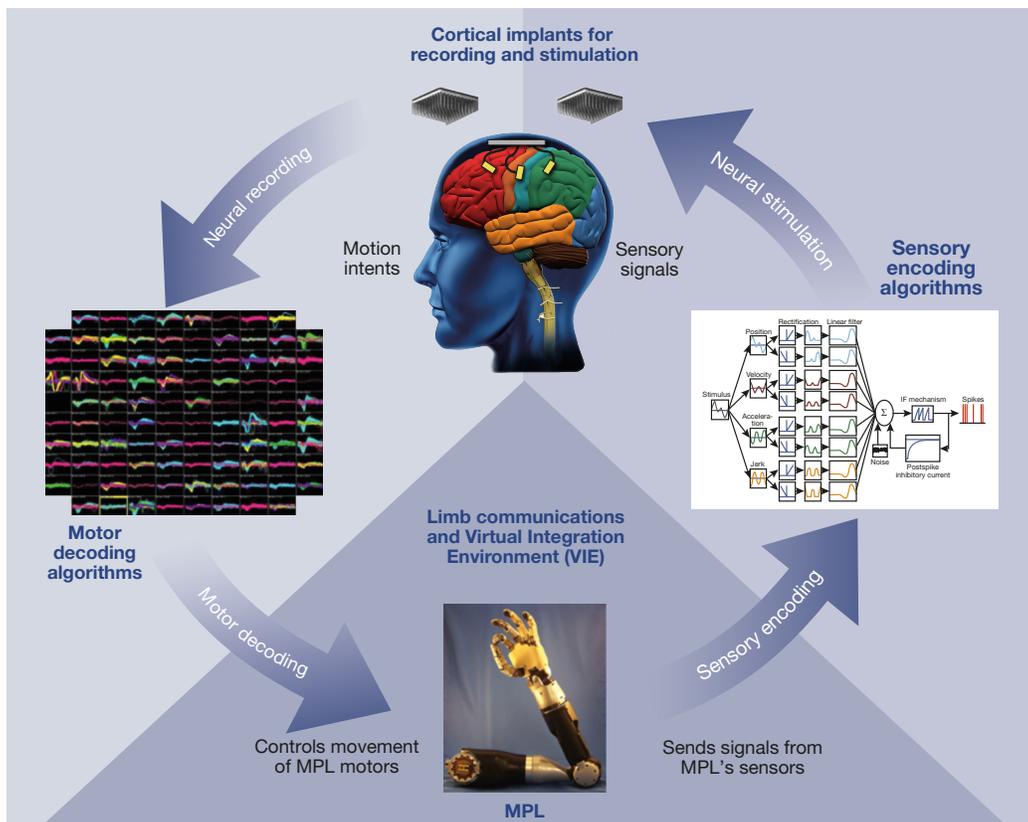
Figure 2. Notional system architecture.

planned at Pitt and Caltech for their respective first human subject studies.

Pitt's Patient 1 and Caltech's Patient 1 will both use visual feedback to "close the loop." In other words, their motor signals will position the arm based on their cortically generated intent signals, and they will use their eyes as visual feedback sensors to position the limb to accomplish the task they are attempting.

Pitt Patients 2 and 3 and Caltech Patient 2 will also use motor control and visual feedback; however, these patients are slated to also exploit the MPL's unique sensorization. These sensors, embedded into the MPL, will also be used, in conjunction with visual feedback, to close the loop. In other words, as shown in Fig. 2, sensors built into the MPL will generate signals such as contact or touch for these patients. Those sensor signals are encoded by computer algorithms, which will then feed into arrays implanted in the somatosensory region of the brain. These three patients, Pitt Patients 2 and 3 and Caltech Patient 2, will have the ability to not only position the MPL as needed but also rely on visual and/or somatosensory stimulation in a way that could potentially allow them to interact with the world in ways that have never been possible for tetraplegics.
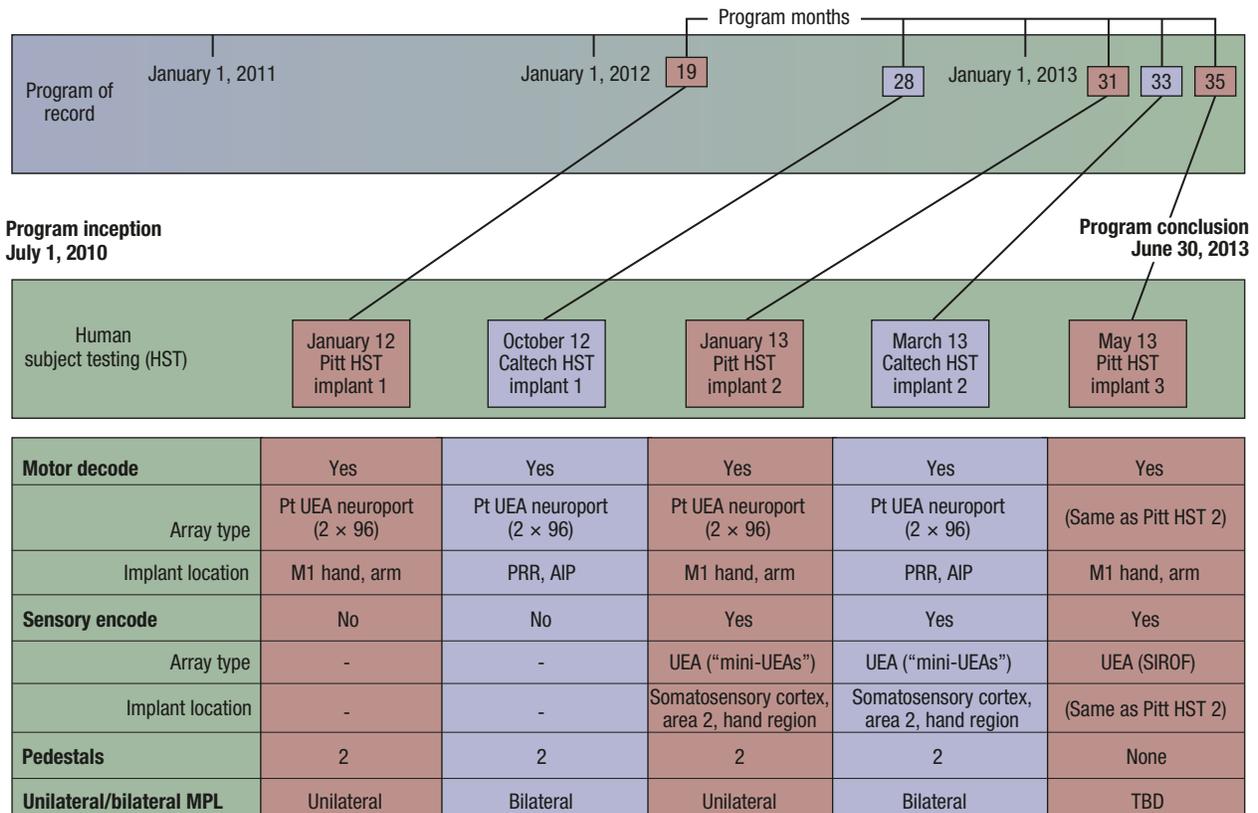
Figure 3 shows the progression of research activities planned for RP3, including the regions of the brain targeted, the neural array types planned, and the general objectives for each of the five subjects planned for the 3-year period of the RP3 program.

Clinical Evaluations

At the time of this writing, the Pitt Patient 1 human subject study is progressing. Pitt commenced this clinical human subject research on 10 February 2012, when they implanted their first patient, a subject with a neurodegenerative condition that prevents them from controlling their upper and lower extremities. The experience gained with this patient includes insight into the nature of human subject research with the MPL and a sense for how such a system can improve the lives of tetraplegics.

The research activities with Pitt Patient 1, described in more detail in Ref. 3, began within days after surgery. Once the patient's postoperative condition was evaluated and deemed stable, the research team began simple reach tasks with the MPL where the patient moved the limb to desired locations in 3-D space. Progressively, the Pitt research team challenged the patient to perform ever-more-complex tasks while the team tuned the neural decode algorithms and collected performance metrics (e.g., successful task completion, duration to successfully complete a task). Within approximately 6 months

	January 12 Pitt HST implant 1	October 12 Caltech HST implant 1	January 13 Pitt HST implant 2	March 13 Caltech HST implant 2	May 13 Pitt HST implant 3
Motor decode	Yes	Yes	Yes	Yes	Yes
Array type	Pt UEA neuroport (2 × 96)	Pt UEA neuroport (2 × 96)	Pt UEA neuroport (2 × 96)	Pt UEA neuroport (2 × 96)	(Same as Pitt HST 2)
Implant location	M1 hand, arm	PRR, AIP	M1 hand, arm	PRR, AIP	M1 hand, arm
Sensory encode	No	No	Yes	Yes	Yes
Array type	-	-	UEA ("mini-UEAs")	UEA ("mini-UEAs")	UEA (SIROF)
Implant location	-	-	Somatosensory cortex, area 2, hand region	Somatosensory cortex, area 2, hand region	(Same as Pitt HST 2)
Pedestals	2	2	2	2	None
Unilateral/bilateral MPL	Unilateral	Bilateral	Unilateral	Bilateral	TBD

Figure 3. RP3 research activities schedule and objectives. AIP, anterior intraparietal cortex; Pt, platinum; M1, primary motor cortex; PRR, parietal reach region; SIROF, sputtered iridium oxide film.

after surgery, the patient executed 10-degree-of-freedom movements of the arm and hand—the patient was able to perform standard clinical evaluation test tasks, such as the Action Research Arm Test, with a high degree of precision and successfully take part in more informal evaluations such as playing rock–paper–scissors with the research team. Increasingly, it has become evident that the future vision of a patient affected by tetraplegia performing some activities of daily living without the support of a caregiver is within sight.

Although Pitt Patient 1's performance is not definitively representative of the performance of the four remaining patients planned for RP3, the types of experimental paradigms and the analysis procedures are reflective of what can be expected for the future planned patients, particularly Caltech Patient 1 who, like Pitt Patient 1, involves MPL motor control only. The remaining Pitt and Caltech patients, however, add the complexity of stimulation, which imparts the requirement of additional hardware (cortical implants and external stimulation signal-processing computers) and additional experimental paradigms to assess the performance associated with stimulation.

ENABLING TECHNOLOGIES AND DESIGN

The five major subsystem elements depicted and highlighted in blue in Fig. 2 represent the key enabling technologies associated with the closed-loop cortical control system targeted by this program: the MPL, sensory encoding algorithms, cortical implants, the Virtual Integration Environment (VIE), and motor control algorithms. The motor control algorithms subsystem element is discussed elsewhere;[4,5] the following discusses the other four key subsystem elements in relation to RP3.

MPL Phase 3 Design Improvements

At the outset of RP Phase 3, it was clear that, in order to meet programmatic goals of performing five human subject research trials each lasting a year in a clinical setting and/or at the subject's home at distant-to-APL sites (i.e., Pittsburgh and California) within time and budgetary constraints, the MPL system that existed at the end of the second phase of the program in mid-2010 required a number of key design modifications. At the hardware level, these design modifications ranged from complete redesign to incremental improvements focusing on increasing reliability, maintainability, and functionality. At the software level, efforts focused on increasing the breadth and capabilities of the overall software architecture through incremental improvements to the existing code base as well as systematic additions of unfinished or unrealized functionality. The five MPL systems developed for Phase 3 were built in a tiered fashion, with Serial Number (SN) 1 completed in

December 2010, SNs 2 and 3 completed in May 2011, and SNs 4 and 5 completed in January 2012. SNs 1–3 are right-handed systems while SNs 4 and 5 are left-handed systems; the RP3 requirements for left and right handedness stemmed from the program's objective of demonstrating bilateral control by a human.

Key MPL Mechanical and Electrical Hardware Design Updates

Wrist

As with other components of the MPL that existed at the end of Phase 2, for Phase 3, the wrist needed enhancements to improve its reliability, availability, and maintainability. For Phase 3, Kinea Design (which, during the second year of Phase 3, was purchased by Hunter Defense Technologies) assumed the role of wrist developer to lead this redesign effort. With the existing wrist design in such an immature state, the wrist subsystem was the highest-risk developmental item for the program from an MPL standpoint because it was the first build of Kinea's design.

As designed, the wrist has three controllable degrees of freedom: rotation (±90°), deviation (–15°/+45°), and flexion (±60°). Each drive can output 8 N·m of torque in a stall condition, which corresponds to approximately 15 lb. of resistive curl and 1.65 N·m at ~120°/s at the palm. Custom service loops (a service loop is an extra electrical assembly added to improve serviceability, movement, or accessibility) allow for passing of power and communication from the forearm, through the wrist, and down to the palm. The total weight of the wrist system is 1.1 lb. in a volume approximated by a cylinder of 5-cm diameter and 10.5-cm height. Conforming to the MPL's modular design philosophy, the wrist assembly can be swapped between the left- and right-handed MPL systems with only minor software configuration parameter changes. The wrist subsystem uses a brushless DC motor packaged intimately with a custom integrated motor controller, the wrist motor controller, which is a smaller variant of the large motor controllers (LMCs) used in the shoulder, humeral rotator, and elbow. This intricate packaging required replacing the magnetic ring used for the relative position sensor with simpler Hall effect devices, making the wrist's actual motor control scheme similar to that of the small motor controllers used in the fingers.

Thumb

The thumb mechanical and electrical hardware was successfully designed and integrated during Phase 2 activities, but programmatic shifts resulted in a subsystem that lacked the maturity to meet the Phase 3 requirements for preclinical and clinical testing. As a result, resolution was required for many of the thumb's fabrication issues, performance tweaks, and tolerance adjustments necessary for optimum performance. Phase 3 thumb re-engineering efforts focused on sev-

eral improvements including designing novel means of passing power, ground, and communication lines throughout the confined space of the thumb, reducing electromechanical complexity, redesigning factors associated with tolerance stack-up issues within the multi-stage planetary gearboxes of the thumb, and redesigning passive compliance elements to ensure the most efficient torque transmission with minimal lash and losses.

Palm

The Phase 2 palm was characterized by very complex and time-consuming assembly. Accordingly, the redesign for RP3 decreases the assembly complexity, minimizes the number of parts, and reduces the fabrication complexity of the primary endoskeleton. Repositioning certain electronic boards to the palmar side of the palm enables better access for servicing, and custom-designed flex service loops for the finger busses greatly improves serviceability and packaging within the allowable volume.

Selected MPL Software Updates

Given the complexity of the MPL system with its multiple points of failure, an automated way to detect anomalies and feed them back through the system is paramount, particularly in light of the Phase 3 objective to increase the reliability, serviceability, robustness, and diagnostic/error reporting capabilities of the MPL system. Accordingly, the development team incorporated algorithms to detect communication failures, overheat conditions, sensor failures, memory errors, and others performance anomalies. The MPL's processing system propagates these detected anomalies through the limb system to provide fast detection of problem nodes to the researchers using the MPL.
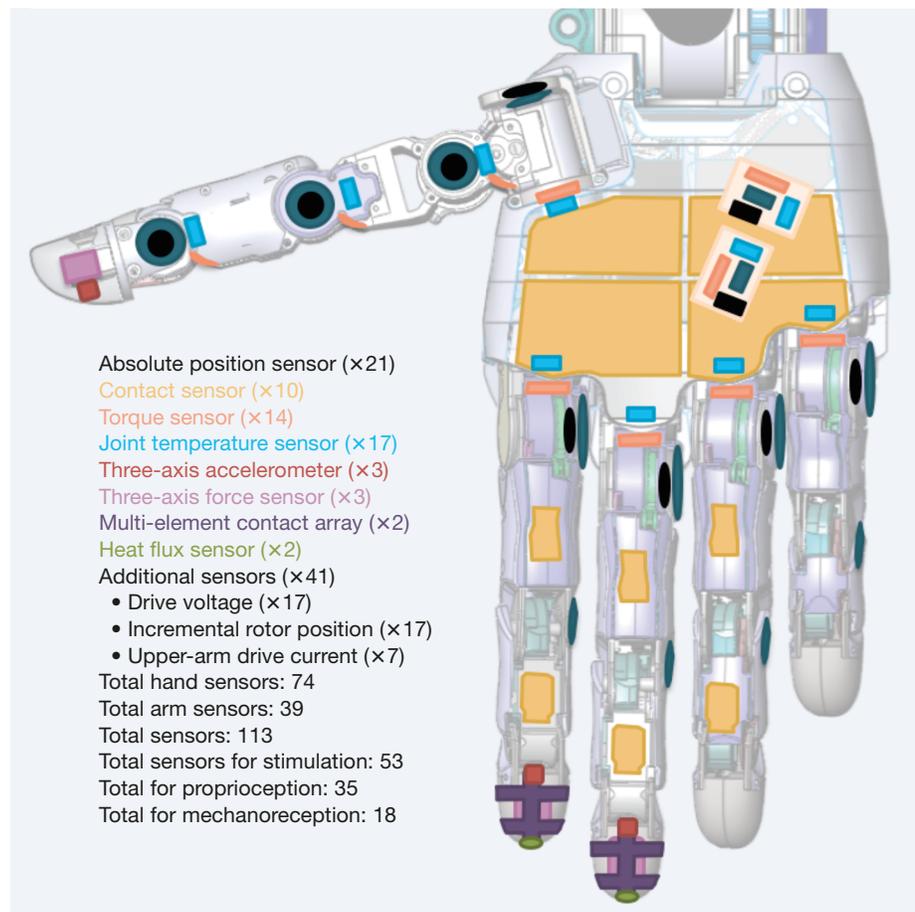
During Phase 3 of the program, the development team produced the wrist motor controller software as a variant of the LMC. In addition, the development team made several improvements to the LMC software to increase

reliability and decrease system lag. Improvements include streamlining the local controls code and fine tuning control gains to give optimal response for total system lag, resulting in more natural limb control.

Finally, the Phase 3 MPL development team integrated a full sensor suite, originally designed during Phase 2, into the MPL system. This sensorization includes the addition of fingertip sensor nodes to the tips of the index and middle fingers as well as the thumb to provide three-axis force and three-axis vibration measurements. The sensor integration includes polyvinylidene fluoride-based contact sensors in the MPL's palm shell and the underbelly of the three long fingers. The combination of these sensors, in addition to the joint-level torque sensors, provides tactile feedback to the patient using the limb.

This sensorization of the limb defines the uniqueness of the MPL—it is highly sensorized relative to other prosthetics and establishes the MPL as an essential platform to investigate advancements in neural stimulation (Fig. 4).

Additional software updates to the MPL included significant improvements to the control algorithms, which

Absolute position sensor (×21)
Contact sensor (×10)
Torque sensor (×14)
Joint temperature sensor (×17)
Three-axis accelerometer (×3)
Three-axis force sensor (×3)
Multi-element contact array (×2)
Heat flux sensor (×2)
Additional sensors (×41)
 • Drive voltage (×17)
 • Incremental rotor position (×17)
 • Upper-arm drive current (×7)
Total hand sensors: 74
Total arm sensors: 39
Total sensors: 113
Total sensors for stimulation: 53
Total for proprioception: 35
Total for mechanoreception: 18

Figure 4. The MPL includes more than 100 sensors used for control of the limb and feedback to the MPL user.

are essential to the dexterity and intuitive control of the MPL. These control algorithms, coupled with the electromechanical components of the MPL, enable gross limb positioning and fine motor manipulation. Empirical observations emanating from preclinical and clinical testing at Pitt and Caltech induced much of the design refinements of these controls algorithms developed during Phase 3.

As the research team gained more experience using the MPL's control strategy, the development team inserted additional functionality into the control algorithms in a number of areas including the following: dynamic joint control, implementation of multiple workspace limits, keep-out regions to protect users or fixtures in the limb's workspace, and control strategies favoring minimizing wrist deflection instead of minimizing overall joint velocities, which helps to ensure the greatest range of orientation possible from wherever the hand currently is located.

Phase 3 also saw the redesign and integration of an improved algorithm to perform preprogrammed grasp motions, known as the reduced order control mode. The reduced order control mode allows a user with limited ability to control individual fingers to be able to perform coordinated grasp motions. This requires a lower amount of cognitive loading on the users while enabling them to perform many of their day-to-day tasks. The revised system supports storage on the computer interface (or optionally within the limb controller itself) of up to 256 different coordinated finger positions ("waypoints") that make up a single motion. This capability allows the user to simultaneously control up to 16 grasps or partial grasps at once, combining and fading between these, depending on the user's preferred grasp configuration for a given particular task.

Virtual Integration Environment

As shown in Fig. 2, the VIE provides the limb communication mechanism and serves as an integration and training tool for patients and clinical researchers using the MPL. The VIE is a virtual reality framework that has been developed for use in training and evaluation of neural decoding algorithms and, as a low-cost, versatile limb simulator, serves an integral role in the development, integration, and evaluation of neural decoding algorithms.

The VIE graphically and physically simulates the MPL and everyday objects and can be used in situations where the MPL is not available for use (Fig. 5). The VIE uses accurate, real-time, physics-based modeling of the everyday objects as virtual objects and simulates physical interactions of the object with the virtual MPL (vMPL) that include contact, grasping and fingertip force, and actions such as grasping, transporting, and repositioning of objects. Furthermore, the use of computational

mechanics software in the VIE allows simulation of dynamic forces of the real world, including the effects of gravity, momentum, and motion.

As a framework, the VIE provides the tools necessary to rapidly develop new scenarios, incorporate new virtual objects, and apply properties to and interact with these virtual objects (Fig. 6). The scenarios are created by importing computer-aided design models or artists' renderings of objects into the VIE environment and linking them to physical models and operational scripts. Figure 6 shows two different training scenarios developed in the VIE framework. The first is a table tennis scenario, where the patient plays table tennis against a computer opponent. The second is a catch scenario, where the patient can develop endpoint control acumen while trying to catch balls and avoid traps.

As a surrogate for the physical MPL, the vMPL in the VIE simulates the same functionality as the MPL. In this manner, the VIE provides a single logical interface to the researcher for both a virtual and physical MPL, executes movement using the same control paradigms, and provides realistic visual and percept feedback from both systems. In virtual mode, the VIE accepts motion intents, executes high-level control algorithms, and simulates MPL motion in a virtual world using a commercially developed software. Output from the simulation provides feedback of joint positions to the high-level controls, virtual object states (world state) to task control, and simulated percepts to a percept encoder. In MPL interface mode, the VIE accepts motion intents, translates and forwards them to the MPL, receives percepts from the MPL, and forwards the percepts to the neural encoders. If a physical MPL is available, the VIE also provides a built-in test interface, displaying MPL status on a separate console.

The VIE is implemented as a low-cost PC test bed and has 3-D display capability that supports active 3-D rendering using commercial 3-D displays and glasses such that virtual scenarios can be deployed as immer-
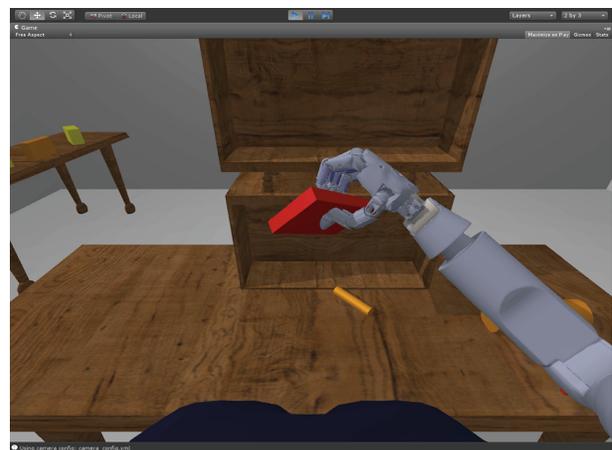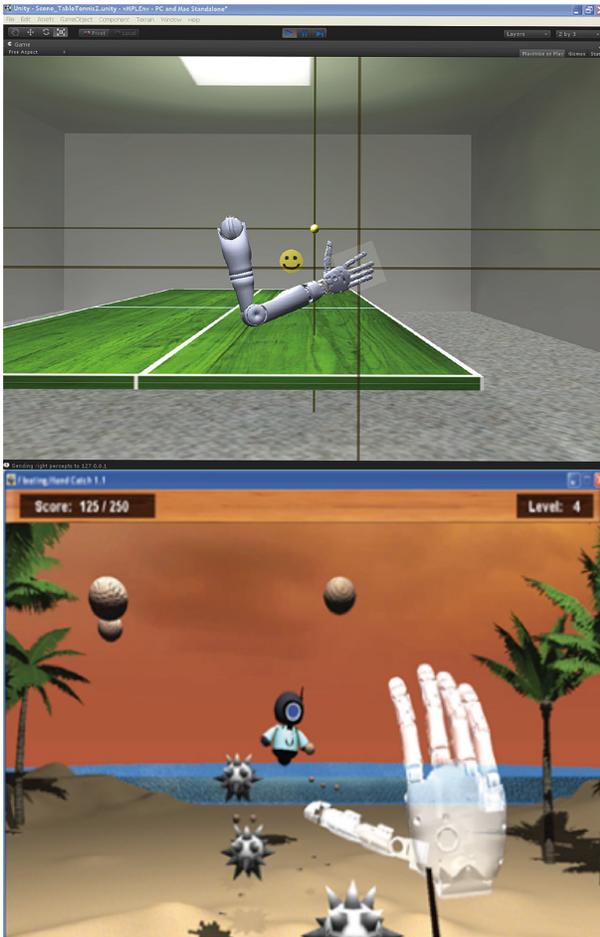

Figure 5. The vMPL grasping an object in the virtual world.

Figure 6. The vMPL playing table tennis against an artificial intelligence opponent and a patient catching balls and avoiding traps.

sive environments if desired. Researchers at Pitt and Caltech are currently using the VIE to develop neural decoding and control algorithms as part of the RP3 program. These teams have successfully developed training scenarios specific to their experimental paradigms and have effectively used the VIE to collect data and refine neural control algorithms.

Sensory Encoding Algorithms

The RP3 goal of achieving sensory feedback via cortical stimulation brings about challenges to the existing state-of-the-art neuroscience research knowledge, as well as regulatory challenges. Addressing the regulatory challenges requires the execution of preclinical studies involving human surrogates to generate appropriate regulatory documentation containing safety and efficacy data of concern to the FDA. Some of the required safety and efficacy data required for RP3 are available via references to previous studies with similar devices implanted in similar cortical locations. Other aspects of the RP3 objectives, particularly cortical stimulation, required the production of new data to prove safety and efficacy.

Accordingly, the RP3 team deliberately designed and executed preclinical studies using system components and procedures that were identical or similar to those planned for the human subject studies. This approach not only helps provide the necessary safety and efficacy data for regulatory bodies, but it also provides clinicians and research staff with a dry run prior to the human subject study.

In terms of state-of-the-art knowledge regarding the neuroscience of stimulation, it is well accepted that, in order for an upper-extremity prosthesis to be truly effective, rich sensory feedback must be delivered to the prosthesis user in a timely manner. Rich sensory feedback implies feedback from a variety of sources as opposed to just one (typically visual feedback). To this end, the RP3 stimulation team developed sensory encoding algorithms to map mechanically elicited tactile and proprioceptive percepts to electrically elicited percepts. These maps, extracted from the data, serve as the basis for generalized "sensory algorithms" that will be translated to the human experiments in which a human subject's intended movements are decoded to actuate the MPL, which in turn interacts with the environment and relays precious sensory information back to the patient, thus allowing a more efficacious use of the MPL than possible with motor control alone.

Key accomplishments associated with this cortical stimulation research include the following:

- **Characterization of safe and effective stimulation pulse characteristics**: The Chicago team defined charge-balanced, biphasic, and interpulse interval durations and amplitude attributes.

- **Contact detection and pressure and location discrimination**: The experimental setup was developed to ascertain whether a nonhuman primate (NHP) perceives contact, successfully discriminates between two pressures of different intensities, and successfully discriminates between two stimuli delivered in two different physical hand locations. Briefly, independently of whether the percepts are delivered mechanically or electrically, the NHP is trained to saccade in one of two directions depending on whether a contact is perceived or not (contact detection), the first contact is perceived as of higher pressure than the second (pressure discrimination), and the first contact is perceived at the left of the second contact location (location discrimination).

- Preliminary results have shown the effectiveness of the electrical stimulation and the interchangeability between the mechanical and electrical stimuli. More details about the experiments can be found in Ref. 6. These results led to the development of the first somatosensory prosthesis.

- **The first somatosensory prosthesis:** In the experimental setup built to demonstrate the first somatosensory prosthesis, the tactile stimulator makes contact with an MPL finger.[3] The MPL fingertip sensor node detects contact and transfers force information to the sensory algorithm, which converts the measured force into electrical signal pulse trains of appropriate intensity delivered to the NHP's somatosensory cortex. The NHP saccades appropriately and can be considered to have perceived that contact was made with its own hand. This demonstration represents a breakthrough in what could possibly be achieved with human patients affected by tetraplegia. In fact, while the NHP *can* perceive contact with its own hand, people with tetraplegia often lack required sensory afferents, therefore preventing sensory information from being perceived. Other studies have shown the importance of providing sensory feedback specifically from the fingertips.[7]

At the time of this writing, the RP3 stimulation team continues to collect data to characterize the full range of contact pressure that can be discriminated and determine whether and how stimulation type (mechanical or electrical) could affect that discrimination. Plans are being developed to quantify differences in mechanical and electrical percepts delivered to humans and NHPs. Should humans not be able to discriminate between electrically and mechanically generated percepts, this would have huge ramifications for the field of neuroprosthetics. It would highlight that humans can recover tactile sensory capabilities in the upper extremities, even if affected by tetraplegia. Further, such findings would imply that as far as the patients are concerned, they wouldn't be able to say whether their real hand or their MPL had made contact with an object—a great advancement in quality of life for those who traditionally had no measure of hope for such a breakthrough.

Cortical Implant Technology

Current state-of-the-practice cortical interfaces, though very capable devices, still present several limitations given the nature of the RP3 objectives. Specifically, these devices require one or more skull-penetrating pedestals to route wires to/from the implanted arrays to the external environment for processing and analysis. These pedestals impart surgical and infection risks, and the wires themselves could induce mechanical stresses on the surrounding tissues or be subject to mechanical stress from those tissues that diminish the signal transmissibility to the implanted arrays. In long-duration human research trials, these pedestal- and wire-related factors become regulatory challenges to safety and efficacy. Accordingly, the RP3 devices team focused on two key strategies: (*i*) use previously FDA-approved or -cleared technologies to the extent feasible while focus-

ing on accomplishing the device-related goals and (*ii*) reduce (or eliminate altogether) the number of pedestals protruding from patient's scalp.

In terms of using previously approved or cleared technologies, RP3 used the UEA as the basis for neural implant technology for preclinical and clinical RP3 testing. The UEA, which consists of a 10 × 10 array of 1.5-mm-long silicon electrodes with platinum tips, was previously premarket cleared [510(k)] by the FDA for less than 30-day (acute) monitoring or recording of brain activity. Through an approved Investigational Device Exemption, the FDA granted RP3 permission to use these UEAs for chronic implantation (more than 30 days). Additionally, RP3 sought and received 510(k) clearance for acute use of a device similar to the UEA but with tips made of SIROF instead of platinum for recording neural signals only. The next steps in this regulatory process will include clearing this device for (acute) stimulation as well as recording, using FDA regulations and leveraging the SIROF UEA as the predicate biocompatible device. Once these clearances are granted, we will collect more data from the safety experiments being conducted at the University of Chicago (see the *Sensory Encoding Algorithms* section) to support an FDA filing requesting approval to extend the implant duration of the stimulation arrays to 1 year. These efforts are being made to meet the program-driven requirement of conducting year-long cortical closed-loop human subject research trials involving the use of implant arrays capable of recording and stimulating neural signals.

To address RP3's goal of reducing or eliminating skull-penetrating electrodes, the devices team pursued two technologies: active arrays and a fully implantable neural cortical system (INCS).

Active Arrays

As mentioned earlier, today's implanted neural arrays use large numbers of wires to transmit the signals from the brain to the external world. To reduce the number of wires, the RP3 devices team pursued an approach that amplifies, digitizes, and multiplexes the neural signals directly on the array itself. With the signals multiplexed, the number of wires needed to carry the signal to/from the brain can be reduced. Reducing the number of wires means fewer pedestals are required to move more signals in/out of the brain. Working with the University of Utah and Blackrock Microsystems, RP3 developed a flip-chip bonded application specific integrated circuit that adheres to the back of a UEA through the use of an interposer module known as the redistribution layer. The resulting configuration reduces the number of output wires from 22 to 16 in the new design. This device is then encapsulated into a package to prevent harmful interaction between the device and the tissues. The device's exposed electrode tips enable recording of surrounding neurons.

To test the integrity of the encapsulated package, these devices were soak tested in hot (57°C) baths of agarose (also known as accelerated aging tests) over a period of up to 10 months (equivalent to more than 3 years of actual longevity) during which these arrays exhibited excellent performance after this environmental exposure. However, the arrays then proved to be less reliable when used in physical media that more closely mimic human cortical tissue. The main reason for these failures seems to have lain in the encapsulation method used. The team is currently in the process of testing a new batch of active arrays with an extra encapsulation layer to protect the electronics from harmful (to the device) ions found in the baths and in cortical tissue that are corrosive to metals.

Implantable Neural Cortical System

As noted, use of active arrays reduced the number of wires that route signals from the brain and thus the number of pedestals required. Reducing the number of pedestals required marks a first step toward removing the patient pedestals altogether and a significant achievement in terms of the risk associated with pedestals. The next step undertaken by the device development team was to be achieved by routing the small number of wires subcutaneously from the brain implants to a chest-implanted battery-powered module that could wirelessly transfer information into and out of the body. This module allows an external user to configure appropriate parameters in the module and on the chips as well as to receive neuronal information that can be decoded into movements for the MPL. This module, known as the INCS, is inductively powered and, according to preliminary data, lasts approximately 8 h on a full charge. Because of the design maturity of the INCS relative to the RP3 timeline, the INCS will not be used in human subject research as part of RP3. The design of this wireless capability, however, achieves the stated RP3 goal of developing a wireless architecture to support implantation of recording and stimulating electrode arrays suitable for chronic use in humans. RP3 will look to future programs to take this technology into human subject trials.

Programmable Stimulator

In addition to monitoring and recording neural activity, one of the main thrusts of this phase of the RP program has been on cortical stimulation. This required the development of passive UEAs with lower impedances as well as external devices capable of delivering tunable current pulses and quickly switching between recording and stimulating modalities. This led to the development of arrays with SIROF electrode tips and the CereStim M96 and the CereStim Switch devices. The SIROF-tipped electrodes allow impedances to be reduced significantly compared with platinum tips. This allows lower currents to be delivered with the same efficacy or alternatively same currents to be more efficacious. The CereStim M96 is capable of adjusting the amplitude of the biphasic current pulses, the duration of the pulses, the delay between the cathodic and anodic phases, which directly supports the stimulation research for the second through fifth human subjects planned for RP3. Additionally, the programmable stimulator supports stimulation of both microelectrodes, such as those used in these studies and which require low currents but high charge densities, and electrocorticographical surface electrodes, which required higher currents but lower densities for the stimulation pulses that are spread across a wider area.

TRANSITION AND COMMERCIALIZATION ACTIVITIES

A major objective of the RP3 program is to leverage the 7-year investment by the Defense Advanced Research Projects Agency to stimulate commercial use of the RP technology. Because the population of upper-extremity amputees is very small (fewer than 300 for veterans of Operation Iraqi Freedom and Operation Enduring Freedom), commercial transition is extremely challenging. While expansion of the program to include individuals that can no longer use their native limbs increases the potential number of beneficiaries, it also elevates the regulatory barriers. To mitigate this risk, APL is working closely with the FDA to identify testing requirements as part of the Innovation Pathway program. The Innovation Pathway was established by FDA to shorten the overall time and cost to develop new medical devices. Through interactions with the FDA, we have significantly reduced cost and schedule risk to the program by engaging FDA reviewers and technical experts earlier in the review process. This engagement has already facilitated approval of two Investigational Device Exemptions, with several additional Investigational Device Exemptions in process. As the program moves forward, the Innovation Pathway should also help us to identify needs for clinical data required to support the ultimate goal of a market application for a neurally controlled prosthetic limb.

Technologies from RP3 are also being incorporated for nonmedical use. Hunter Defense Technologies has adopted key components of the MPL for use in military robotics. Motors that drive the MPL have been adapted for applications such as explosive ordinance disposal and are able to lift heavier loads and function in harsh environments. Increasing the dexterity of mobile robotic systems will help to protect soldiers by reducing the need for them to work in dangerous areas. Production of military versions of RP technology will also drive improve-

ments and production volume that will ultimately increase reliability and decrease cost. APL is using expertise developed in RP to help the Navy develop an Advanced Explosive Ordinance Disposal Robotic System that will incorporate an open architecture. A goal of the Advanced Explosive Ordinance Disposal Robotic System is to promote innovative approaches that will decrease the time to develop new systems and ultimately reduce the life-cycle costs.

SUMMARY

The MPL is a highly advanced robotic prosthetic upper extremity capable of gross movements and highly dexterous fine manipulation. Coupled with neural control algorithms, the MPL enables users to intuitively perform limb movements through thought control. With these characteristics, the MPL serves as the cornerstone for the RP program. Aided by the FDA's unique Innovation Pathway program, the third phase of RP has achieved significant accomplishments with the first of five human subject research trials involving tetraplegics. The remaining year of the program promises even more achievements as the RP3 team targets trials involving

somatosensory feedback that will provide the targeted human subject population the ability to interact with the world in ways that have never before been possible. These advancements will truly change the lives of these people and society at large.

REFERENCES

[1]Smith, D. G., and Bigelow, J. D., "Biomedicine: Revolutionizing Prosthetics—Guest Editors' Introduction," *Johns Hopkins APL Tech. Dig.* **30**(3), 182–185 (2011).
[2]Johannes, M. S., Bigelow, J. D., Burck, J. M., Harshbarger, S. D., Kozlowski, M. V., and Van Doren, T., "An Overview of the Developmental Process for the Modular Prosthetic Limb," *Johns Hopkins APL Tech. Dig.* **30**(3), 207–216 (2011).
[3]Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., et al., "High-Performance Neuroprosthetic Control by an Individual with Tetraplegia," *Lancet* **381**(9866), 557–564 (2013).
[4]Harris, A., Katyal, K., Para, M., and Thomas, J., "Revolutionizing Prosthetics Software Technology," in *Proc. 2011 IEEE International Conf. on Systems, Man, and Cybernetics (SMC)*, Anchorage, AK, pp. 2877–2884 (2011).
[5]Bridges, M., Para, M., and Mashner, M., "Control System Architecture for the Modular Prosthetic Limb," *Johns Hopkins APL Tech. Dig.* **30**(3), 217–222 (2011).
[6]Berg, J. A., Dammann, J. F. III, Tenore, F., Tabot, G., Boback, J. L., et al., "Behavioral Demonstration of a Somatosensory Prosthesis," *IEEE Trans. Neural Syst. Rehabil. Eng.* (in press).
[7]Johansson, R. S., and Flanagan, J. R., "Coding and Use of Tactile Signals from the Fingertips in Object Manipulation Tasks," *Nat. Rev. Neurosci.* **10**(5), 345–359 (2009).

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