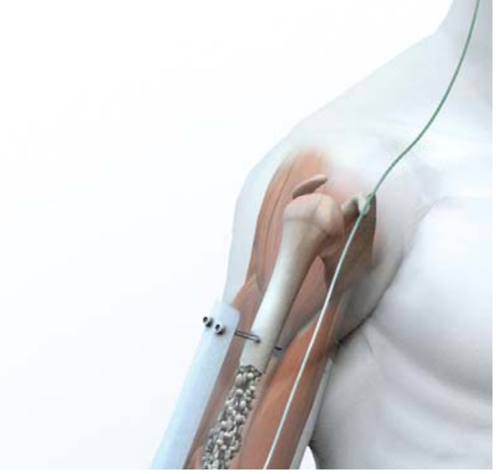

# THE CENTER FOR RESTORATIVE AND REGENERATIVE MEDICINE

The biohybrid limb is conceptualized as consisting of biological tissues and non-biological materials. Conceptualizing a limb as a biohybrid organ frees researchers and clinicians from constraints imposed by biological tissue and biomaterials, respectively. Cover and inside cover artwork by Bryan Christie Design.

**Left** The Center for Restorative and Regenerative Medicine is a Center of Excellence of the Department of Veterans Affairs Rehabilitation Research and Development Service.
**Right** Brown University is the major academic collaborator with the Providence VA Medical Center.

# BLURRING THE LINE BETWEEN MAN AND MACHINE

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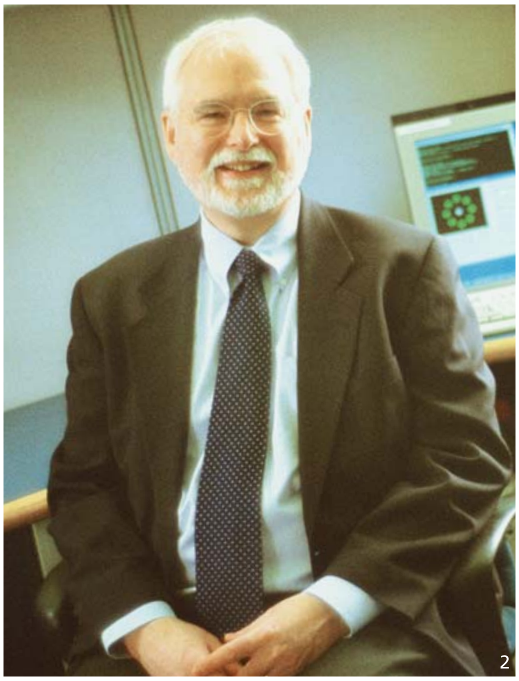
The Center for Restorative and Regenerative Medicine is a collaboration between the Providence VA Medical Center and Brown University. The mission of the Center is to improve function for individuals with limb trauma by developing technologically advanced solutions for the restoration of limb function. To achieve this goal, the Center brings to bear state-of-the-art techniques in tissue engineering, orthopaedics, neurotechnology, prosthetic design, and rehabilitation. These are complementary techniques and they converge in the concept of the biohybrid limb – composed of both biological and non-biological materials – enabling us to envision solutions that transcend the limitations of biological tissue or prosthetic materials alone.

Biohybrid structures are composed of both biological tissue and non-biological components. Examples in current clinical use are joint replacements, in which metal implants are integrated directly into bone. Biohybrid structures often have unique physical and physiological properties resulting from the integration of tissues and materials that require full understanding before they can be most effectively utilized in the clinical setting. Biohybrid limb research integrates independent developments in regenerative medicine, neurotechnology, prosthetics, and orthopedics to maximize limb function.

Long term goals of the Center are to:

- develop biomimetic prostheses.
- optimize the human-prosthesis interface with neural control devices, osseointegrated fixation, and lengthening of short residual limbs.
- explore regenerative medicine techniques for tissue restoration.
- develop advanced rehabilitation strategies for both physical and emotional injuries.

The phoenix is emblematic of the goals of the Center for Restorative and Regenerative Medicine. A mythical symbol that appears in many cultures as the representation of regeneration, restored function and new beginnings, the phoenix emerges from a crucible of fire that represents the hope of tempering and strengthening. This phoenix is reminiscent of the Department of Veterans Affairs eagle. It is rendered in brown, red, and white, the colors of Brown University, the Center's major academic partner.



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**(DIRECTOR, CRRM NEUROTECHNOLOGY PROGRAM)**

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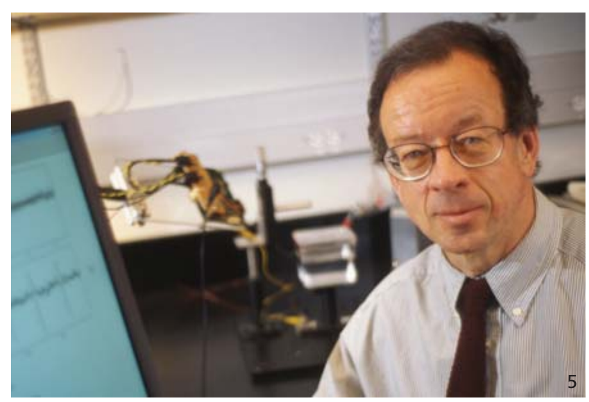

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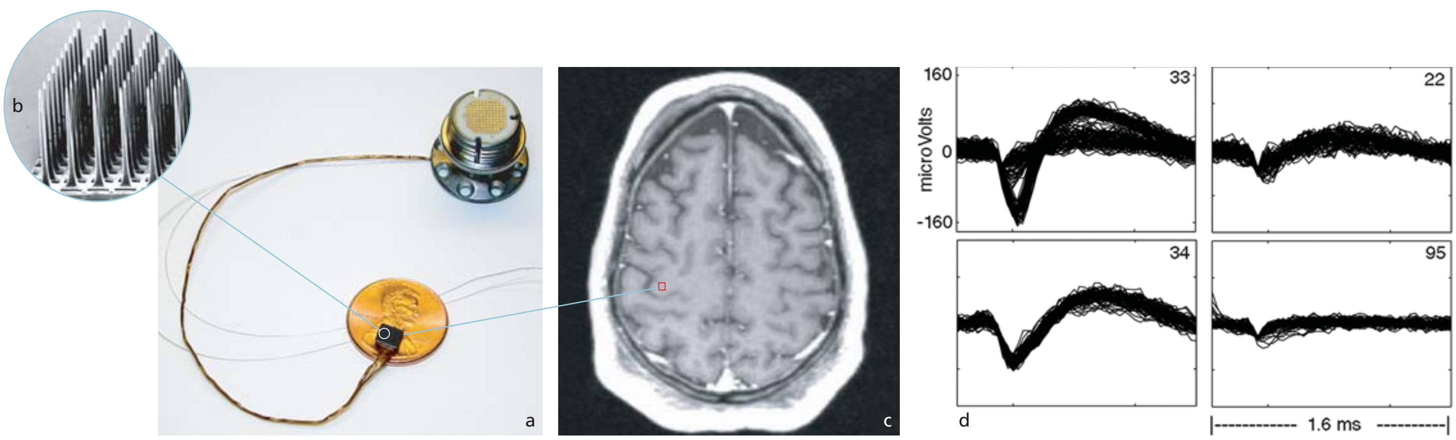
# NEUROTECHNOLOGY




Advances in microelectronic devices and our understanding of neural plasticity suggest that linkages will be made between nerve tissue and robotic prostheses in the foreseeable future. Our investigations focus on the use of microelectronic devices and the development of mathematical algorithms to translate complex patterns of neural activity into control outputs for prosthetic devices.

In the human nervous system, sensory and motor information are represented in patterns of electrical impulses (neuronal action potentials), often called spikes. Research into these patterns has paved the way for the development of closed-loop neuromotor prostheses (NMPs), which have the potential to enable bidirectional interaction between the human nervous system and external devices. The emerging technology of NMPs combines cutting-edge biomedicine, neuroscience, mathematics, computer science, and engineering. This type of interface transcends earlier controllers because it is based on neural spiking, a source of information-rich, rapid, complex control signals from the nervous system. NMPs promise an entirely new paradigm for building bionic systems that can restore lost neurological functions.

The application of NMP technology has the potential to restore lost neurologic function to disabled people and to provide relatively precise control of physical devices, including prosthetic limbs or semiautonomous robots. Our research will develop the key elements of advanced NMP technology with integrated microscale signal processors, innovative broadband optical telemetry and powering, and miniaturized processors. In addition, we are working on new mathematical models for representing and decoding human neural coding to allow two-way communication between machines and the nervous system. We are using this technology to establish the nature of control signals required for humans to control complex devices. These neural control signals have already been successfully used by persons with tetraplegia to control a computer for spelling, running software and assistive devices. These same signals could also command motion of paralyzed muscles or the actions of prosthetic limbs or electric wheelchairs. Our goal is to develop both control algorithms and user interfaces that would enable human performance of robot navigation tasks or other complex interactions under neural control, and to apply these advances to robotic limbs.

**Above** (a) The BrainGate sensor, resting on a US penny, is connected by a 13-cm ribbon cable to the percutaneous titanium pedestal. (b) Its 100-electrode sensor, (c) is positioned in the right precentral gyrus, (d) where it records brain activity.

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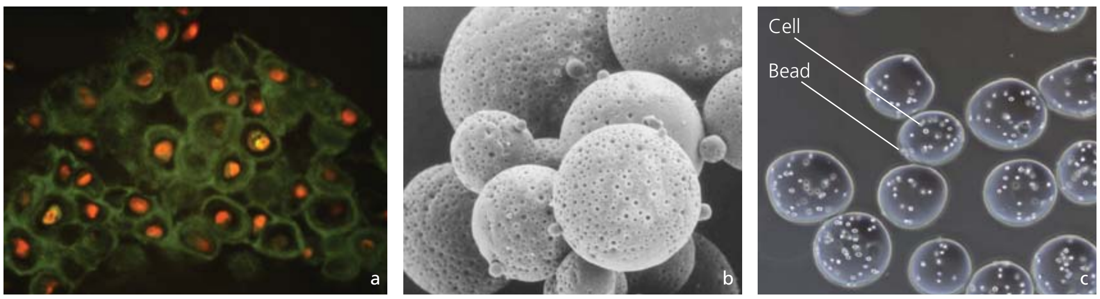
# REGENERATIVE MEDICINE



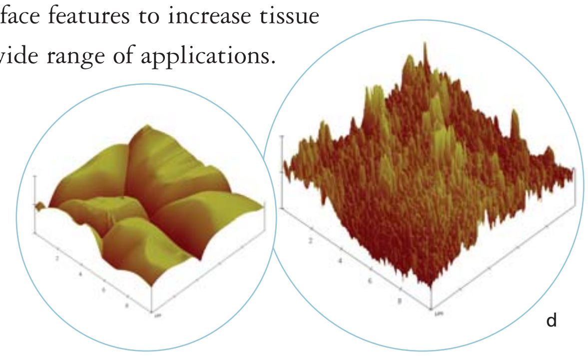

The engineering of biological tissue may be able to restore function lost to trauma or disease. Tissue engineering is accomplished by a combination of cell-based and materials approaches and by delivery of growth factor proteins that guide the differentiation of stem cells to differentiated, mature cells capable of skeletal functions.

**CELL-BASED TISSUE ENGINEERING** We are investigating two areas of skeletal biology related to tissue engineering. One set of studies is exploring physicochemical signaling and protein expression in bone cells, especially the response to oxygen gradients. A second set of studies is engineering a transplantable biocomposite cartilage replacement. A stem cell population has been identified in joint lining tissues (synovium) that can be differentiated into cartilage cells by exposure to specific sequences of growth factors. These techniques will have a range of applications including repairing, rather than replacing, damaged joints and accelerating the repair of bone injuries.

**POLYMER-ENCAPSULATED GROWTH FACTORS** Growth factors are proteins involved in cell growth, repair and differentiation. One promising approach to growth factor delivery is encapsulation in bioerodible nano- or microspheres, which provide sequential release of growth factors to optimize tissue repair. We have fabricated polymer microspheres in our laboratory to encapsulate and release a wide variety of growth factors (including insulin, IL-2, IL-12, growth hormone, FGF2, and TGF-ß1) while maintaining greater than 90% bioactivity. These microspheres will become part of a scaffold that will support and enhance cell growth.

**IMMUNOISOLATED CELL THERAPY** Immunoisolated cell therapy is another approach to the delivery of growth factors. In this approach, living cells that have been genetically modified to constitutively produce growth factors are encapsulated within biodegradable polymer capsules. Systems are under development which would permit release from the capsules to be chemically switched on or off after implantation. This approach to drug delivery is highly appealing because it delivers freshly synthesized, biologically active growth factors for release at consistent dose levels.

**NANOSTRUCTURED BIOMATERIALS** Nanomaterials are materials with one dimension less than 100 nm. Nanostructured materials hold promise for numerous tissue engineering applications. Nanomaterials have unique, tailorable surface energy properties that control cell interactions resulting in tissue growth and repair. The goal of Center research in this arena is to manipulate traditional materials used as implants to possess biologically inspired nanometer surface features to increase tissue growth for a wide range of applications.



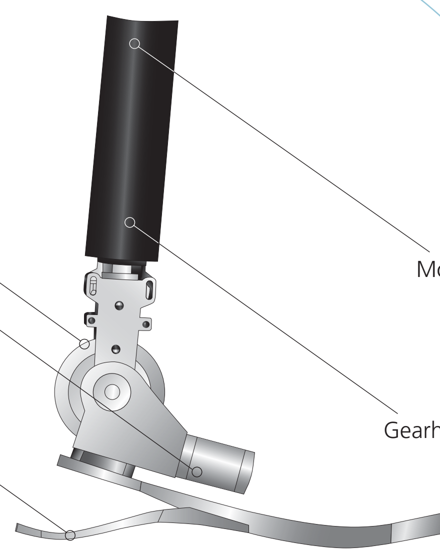

**Above** (a) Green fluorescence reveals deposition of extracellular matrix. (b) Biodegradable polymer beads release growth factor proteins according to an optimum time schedule. (c) Cells transfected with genes regulating the synthesis of growth factors are encapsulated in polymer beads. (d) Nano-surfaces increase tissue growth. Pictured at left is a traditional implant and pictured at right is a nano-implant surface.

**1. HUGH M. HERR, PH.D.**

MIT Associate Professor, Media Arts and Sciences, MIT-Harvard Division of Health Sciences and Technology, NEC Career Development Professor of Media Arts and Sciences, Director, MIT Media Laboratory Biomechatronics Group

Biohybrid limb research is producing significant advances in lower extremity prosthetics. Biomimetic control, muscle-like actuation, and neuro-sensors will allow leg amputees to experience improved responsiveness to their actions and wishes. The ultimate goal of this research is to restore amputee limb function to near normal levels.

# BIOMIMETIC PROSTHESES




Our goal is to design an ankle-foot prosthesis that would mimic a normal walking gait and simulate natural joint function. We have conducted extensive studies of the human ankle to model its kinematics in order to provide the design specifications of this biomimetic ankle-foot prosthesis.

Creating prostheses that simulate the dynamics of joint impedance and allow users to control motive force and joint position is of critical importance if prostheses are to truly mimic biologic function. Many currently available ankle-foot prostheses employ passive-spring mechanisms that do not simulate natural joint kinematics. They do not respond to sensory feedback from the user, nor do they provide energy for forward progression. As a consequence, traversing uneven terrain, running, and climbing are almost impossible for amputees using prostheses, while even normal walking and changes in gait speed or direction create problems with balance and cause high energy expenditure and fatigue.

Biomimetic limb research seeks to simulate normal joint function and mimic two-way communication between the prosthetic limb and the nervous system.

The ankle-foot system will consist of four main mechanical elements: a motor, transmission, series springs, and leaf-spring foot. The leaf-spring provides shock absorption and energy storage. The high-power output motor with transmission and series springs will be combined into a rotary series elastic actuator (SEA) to mimic the behavior of the human ankle joint. Previously developed for legged robots, SEAs provide precise force control by controlling the extent to which the series spring is compressed. SEAs can limit maximum force in order to avoid harm to the human user, making them a good choice for rehabilitation applications.

**Above** Schematic view of the biomimetic ankle for a below-knee prosthesis.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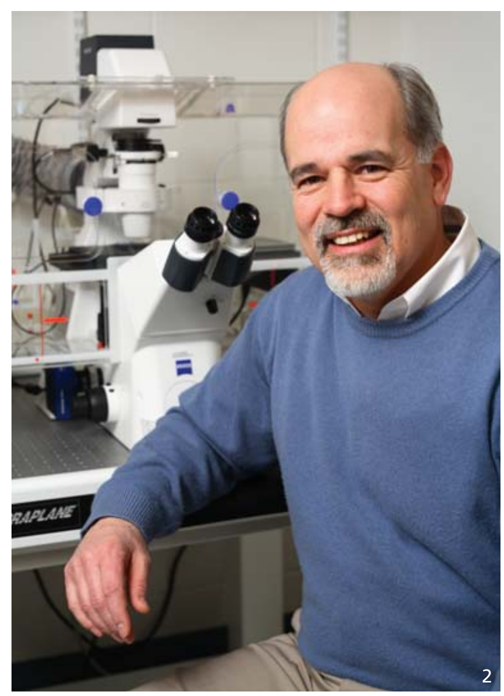

2

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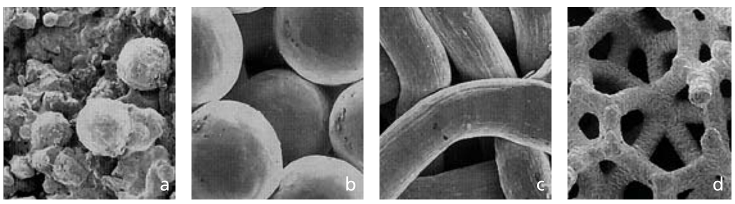
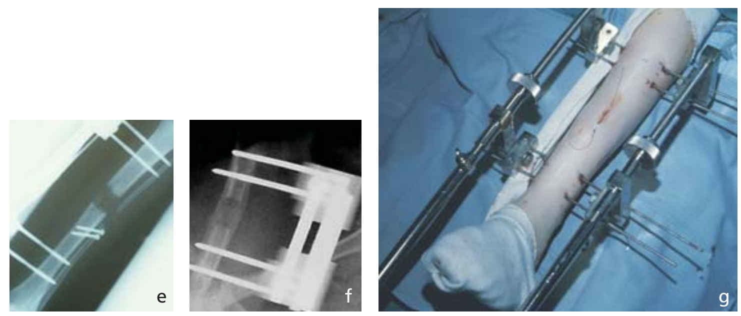
# THE HUMAN-PROSTHETIC INTERFACE




**OSSEOINTEGRATION** One example of a novel biohybrid structure is an osseointegrated transcutaneous implant to create an improved interface between a residual limb after amputation and a biomimetic prosthetic limb. The technique of osseointegration is a promising method of fixing a prosthesis directly to bone. Much like hip replacements, this technique integrates titanium implants with bone; however, the implants extend from the bone, exiting through the skin to create an anchor for the prosthetic limb. This method bypasses skin contact with the prosthesis, reducing pain. The technique has raised concerns, however, because it destroys the barrier function provided by skin, which prevents contamination of the internal environment by the external environment. When pathways develop around the implant through the soft tissues, infection and metal corrosion can result, which in turn can lead to additional loss of bone in residual limbs. These concerns have focused our attention on the interface of soft tissue – particularly skin – with the implant. Our research goal is to develop an environmental seal, integrating skin and dermis with the metal implant by promoting adhesion to, or growth into, porous prosthetic surfaces.

To that end, we are studying osseointegrated transcutaneous implants with both materials and tissue engineering approaches. We are determining optimum surface characteristics for the attachment of soft tissues and are developing finite element models to understand the mechanics of the skin-prosthesis interface.



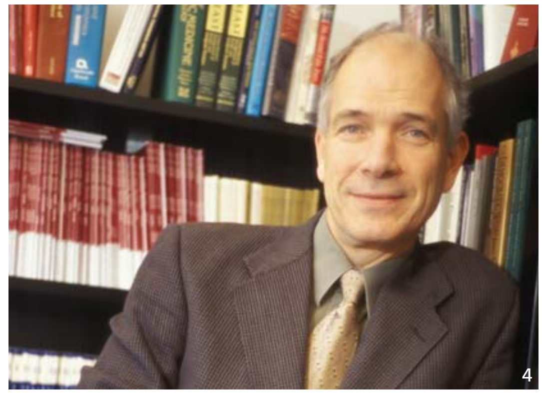

**LIMB LENGTHENING** A serious problem for traumatic amputees is short residual limbs. For example, short residual proximal tibias may not allow for fitting with a below-knee prosthesis and may force the user to function as an above-knee amputee. Often, the higher amputation requires a heavier, less functional, and thus more awkward, proximal prosthesis, which increases the energy cost of movement.

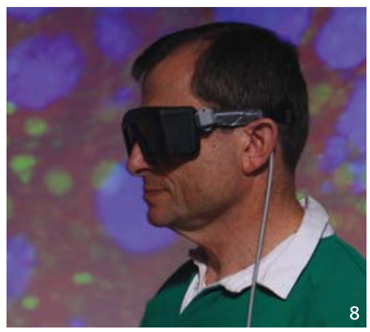
One solution is to lengthen a short residual limb by surgically lengthening bone. This is accomplished by creating an osteotomy and separating the bone ends by gradual distraction, a process called *distraction osteogenesis*. Delayed bone healing is a complication of distraction osteogenesis and can retard restoration of limb function. Our investigations have therefore focused on techniques of accelerating or augmenting bone healing.

Some of these techniques include the use of biomimetic scaffolds, growth factors, demineralized bone matrix, gene therapy, and interaction with physical stimuli, including mechanical, ultrasound, and electrical energy. While the biology of distraction osteogenesis has been fairly well explored, no paradigm exists for augmented distraction. Therefore we are examining the effects of growth factors and physical stimuli on vascularization and the synthesis of cartilage and bone extracellular matrix using biological, radiographic, and biomechanical measurements of consolidation. These tissue engineering strategies hold the promise of accelerating the rate of elongation, maximizing the length of regenerated bone, and diminishing osteoporosis and refracture.

**Above** (a-d) Examples of porous coated orthopaedics implants. (a) plasma spray, (b) porous surface, (c ) fibre metal, and (d) porous tantalum structure. Images courtesy of J.Dennis Bobyn, Ph.D., Jo Miller Orthopaedic Research Laboratory, Montreal General Hospital, McGill University. (e) Gaps in lengthened bone showing gain in length. (f) Reconstitution of the periosteum and early calcification in the distraction gap. (g) Leg positioned in fixators during distraction osteogenesis.



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Chief, Substance Abuse Programs, Providence VA Medical Center

**4. VINCENT MOR, PH.D.**

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**5. LINDA RESNIK, PH.D.**

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Research Health Scientist, Providence VA Medical Center

**6. M. TRACIE SHEA, PH.D.** (Not pictured)

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Psychologist, PTSD Clinic, Providence VA Medical Center

**7. WILLIAM S. UNGER, PH.D.**

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**8. ANDRIES VAN DAM, PH.D.**

Thomas J. Watson Jr. University Professor of Technology and Education, Department of Computer Science, Brown University

**9. AMINADAV ZAKAI, M.D.**

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Medical Director, PTSD Clinic, Providence VA Medical Center

# ADVANCED REHABILITATION


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One of the innovative aspects of our Center is a holistic approach that integrates rehabilitation of physical and emotional injuries. Consistent with the technological focus of the Center, we are exploring virtual immersive environments and motion analysis as techniques to diagnose and treat these injuries.

## ASSESSING REHABILITATION OUTCOMES

Our goals are to design and test therapeutic solutions, define functional demands, and prepare injured individuals for return to functional activities and full participation in society. To that end, we are developing assessment tools that measure functional deficits and are responsive to change on an individual level. We are also assessing the effectiveness of current interventions in clinical practice and exploring quality of life and mobility tests in patients with lower extremity amputations and advanced prostheses. An emphasis of our outcomes assessment research is the exploration of self-report and physical performance tests to determine which tests best reflect improvements in physical capabilities and how physical function can be measured with most validity.

**ADVANCED REHABILITATION** Virtual immersive environments (virtual reality) can be used to expose individuals to challenging visual, auditory, vestibular, tactile, and other sensory experiences in safe, structured settings in order to diagnose and treat both physical and emotional conditions. We are integrating virtual reality and motion analysis facilities to explore individual reactions to stress, simulate vocational environments, and enhance high-performance training by both assessing and training capabilities, especially as related to spatial navigation and mobility.

Our motion analysis techniques will permit definition of vocational requirements, enhance the design of prostheses and rehabilitation regimens to meet those requirements, and test individual capabilities.

**BEHAVIORAL MEDICINE** Virtual reality immersive environments can be used to both diagnose and treat Post Traumatic Stress Disorder (PTSD). We are combining immersive environments with advanced biofeedback using wireless sensors to study PTSD profiles by measuring psychophysiologic arousal following acute stress.

Virtual reality systems consist of PC-based programs, head-mounted displays or high-resolution wall displays (CAVE) with 3-dimensional spatial audio and head-and-limb tracking systems, vibration platforms, and scent machines designed to create an immersive experience representative of that encountered in combat.

**Above** (a) Rehabilitation and assessment of lower limb prosthetics. (b) A virtual reality motion detection system (CAREN). Image Courtesy of MOTEK. (c) Virtual immersive environment for physical and behavior rehabilitation.

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## BIOMIMETIC PROSTHESES AND THE HUMAN PROSTHETIC INTERFACE

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