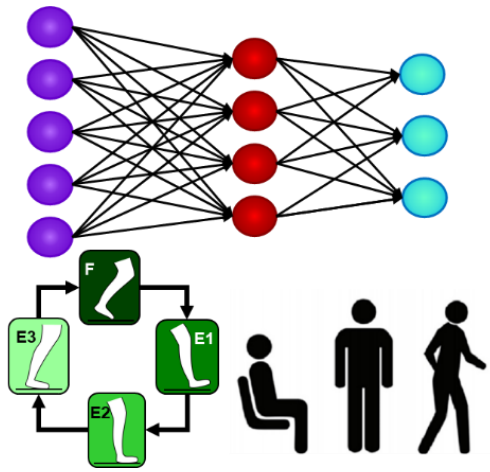
RESEARCH PROGRAM

The overall goal of my research is to improve the lives of people with disabilities using neural interfaces and prostheses. My research is highly interdisciplinary; I combine concepts from engineering, neuroscience, and computing science to advance neuroprosthetic technology and understanding. My research focus has 3 major thrusts: neural and artificial control of walking, implanted neural interfaces, and neuromodulation, utilizing my experience in both animal and human models. Much of my research also includes applying machine learning techniques to solve problems in neural engineering. The following research plans build on and branch out from my past and current research activities as outlined in my curriculum vitae. I outline immediate research questions in each thrust, as well as long-term research goals that build on the short-term objectives.

Control of Walking

Leg paralysis can be caused by many injuries or diseases including spinal cord injury (SCI), stroke, and traumatic brain injury, affecting millions of people in the US. Regaining the ability to walk is of high importance to people with paralysis. My research program focuses on both natural and artificial control of walking. My work is highly interdisciplinary and leverages state-of-the-art tools from machine learning, both to restore and understand walking. Much of my PhD work at the University of Alberta aimed to restore walking function in a model of SCI using a spinal cord implant called intraspinal microstimulation (ISMS). ISMS targets the motoneuron pools in the lumbar enlargement. Using small levels of current, ISMS can produce movements in individual muscles as well as multi-joint synergies. Control strategies for neurotechnologies such as ISMS need to predict and adapt to the user's intentions during walking in an intuitive manner for more seamless interaction between the device and user. I developed two controllers that utilized machine learning methods for use in a hemisection SCI model in anaesthetized cats. Both controllers used information from external sensors on one hindlimb to control the movements of the other hindlimb using ISMS. One controller used supervised machine learning to predict the speed of walking, and using that prediction adapted the control strategy during walking to improve walking at faster speeds. I also developed a controller that used reinforcement learning to learn predictions about the one limb and used those predictions to produce the stimulation output to move the other limb. This method of control is termed Pavlovian control due to its inspiration from classical conditioning, whereby predictions of a sensory stimulus (movements from one limb) were used to produce a fixed response (stimulation output). The Pavlovian controller did not need tuning of its settings between different cat experiments and with variable walking patterns, making it automatically adaptable to different subjects. While these controllers were developed for a model of hemisection SCI, they can be translated to restore walking in any type of hemiparalysis, such as after stroke, as well as for other neurotechnologies, prostheses, or orthoses.



Ex. Using machine learning to make predictions about the gait cycle and gait-type transitions

Research Plan

I plan to build on these control strategies in both short-term and long-term research plans that ultimately aim to restore or improve walking in people with stroke using an exoskeleton, as well as for controlling lower limb prostheses for amputees. My immediate research focus is to use supervised learning methods to predict different gait types such as walking, running, stand-to-sit transfers, stair climbing, slopes, etc. in healthy controls. I hypothesize that gait types, and the transitions between them, can be predicted using body-worn sensors such as insoles (forces), electromyography (EMG; muscle activity), and goniometers (limb position, joint angle). I will investigate how generalizable the gait-type predictions are across several people, including those that the model was not trained on. This research will also inform the key gait parameters for defining and transitioning to different gait types. The subsequent study will aim to predict gait types and transitions in people who suffered a stroke and have lower limb impairments. This study will identify the key gait parameters for defining and transitioning to different gait types in people with stroke, and how they differ from intact controls. Collectively, this work will lay the foundation for developing control strategies for assistive devices such as exoskeletons and electrical stimulation to improve walking after stroke. By using supervised learning to predict the gait type or transition, the control strategy can be adapted accordingly.

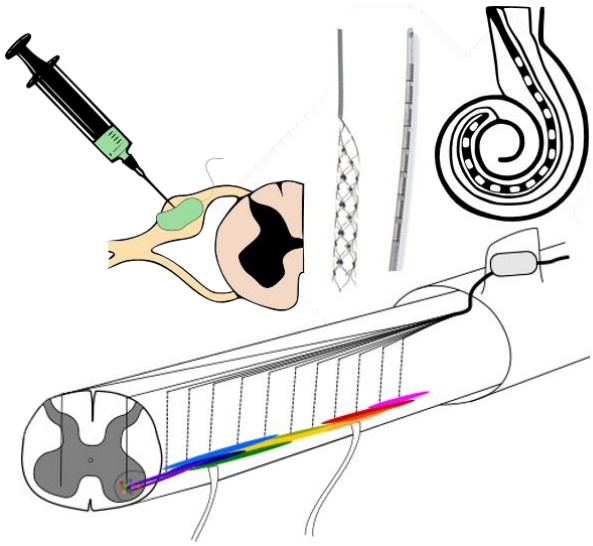
I also aim to expand the use of the Pavlovian controller to be used to control lower limb prostheses for amputees and exoskeletons for people with paralysis. The Pavlovian controller can be easily modified to include different feedback signals (such as EMG, forces, joint angles, and cameras), and it has phenomenal online adaptation capabilities. This makes it an ideal controller to translate to existing devices and has the potential to make a large clinical impact.

Overall, this research thrust combines machine learning algorithms to predict gait types and transitions and adapt control strategies to improve walking using several assistive devices. This work is highly interdisciplinary and incorporates skills and knowledge in biomedical engineering, computing science, rehabilitation, and neuroscience. I will also seek out collaborations with experts in computational modeling because many of these algorithms could benefit from testing in a simulated environment prior to online testing. Furthermore, this research thrust also has applications for assisting veterans who have acquired injuries, as well as in robotics, making it attractive to funding agencies such as the NIH, DARPA, and DOD.

Implanted Neural Interfaces

Implanted neural interfaces can be used throughout the body to restore functions lost after injury or disease. There are technological and biological barriers that must be overcome for devices to be successful and remain effective for the lifetime of the user, including but not limited to lead wire damage, corrosion, and rejection. Functional *in vivo* testing of implanted neural interfaces is key to assessing their performance prior to clinical implantation. During my PhD, I collaborated on a study investigating the safety of ISMS implants in minipigs. We implanted and stimulated through ISMS microwires into the spinal cords of pigs with an intact spinal cord intraoperatively. We removed the electrodes and tracked their recovery and any functional deficits following the procedure for 4 weeks. My role was to assist with the surgical procedure (under aseptic conditions), remove the spine hardware and close the incision, care for the animals during their recovery, and analyze gait data recorded during the post-operative assessments. This work showed that there

were initially functional deficits in balance and gait following the procedure (which included a 2-level laminectomy), but the pigs were fully recovered by the end of the 4 weeks. This work paves the way for intraoperative testing in humans to determine a functional map of the human spinal cord for the ultimate goal of translating ISMS to people with SCI.



Ex. Implanted neural interfaces I have used in vivo: Injectrode, epidural spinal cord stimulation, cochlear implant, and intraspinal microstimulation. First-in-human trial starting with the Stentrode.

My postdoctoral work at the Bionics Institute in Australia consisted of chronic experiments using cochlear implants in rats, guinea pigs, and cats. I evaluated different electrode coating materials using electrochemical methods *in vivo* to determine their performance and reliability for chronic stimulation. I was also responsible for electrochemical testing for high charge density stimulation trials, which were designed to investigate stimulation safety limits for cochlear stimulation.

During my postdoctoral work at the University of Pittsburgh and now at Carnegie Mellon University, I am using an injectable electrode (Injectrode) to stimulate the lumbar dorsal root ganglion (DRG) in cats. DRG stimulation is a method that uses electrical stimulation for the treatment of chronic pain. The Injectrode is a polymer that cures inside the body minutes after injection and has the potential to reduce the surgical time and trauma for implanting electrodes. I am comparing the recruitment properties of the Injectrode with a clinical-like stainless steel electrode in acute, and soon to be chronic experiments in cats. I am also performing *in vivo* electrochemical testing to further characterize the behaviour of the Injectrode for electrical stimulation. Additionally, we are currently starting experiments investigating the mechanisms of DRG stimulation on pain relief in rats in collaboration with Abbott Laboratories.

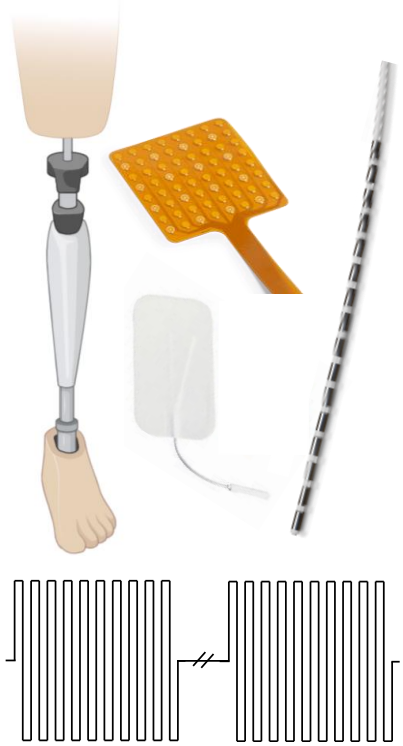
I am also a part of the research team conducting the first-in-human testing of the Stentrode brain-computer interface (BCI) in the United States in people with amyotrophic lateral sclerosis (ALS). The Stentrode is a stent-mounted electrode array implanted into the superior sagittal sinus adjacent to the primary motor cortex. The Stentrode records motor neural activity, which is then used to control a computer cursor and keyboard for performing activities of daily living. This work is in collaboration with Mount Sinai Hospital (New York) and Synchron (New York and Melbourne). My role in this study is to investigate the effects of vibrotactile somatosensory feedback on neural activity. *In vivo* and first-in-human testing of implanted neural interfaces is highly collaborative work, as it requires cooperation between engineers, neuroscientists, surgeons, and biologists. As both an engineer and neuroscientist, I am capable leading these efforts and working with device engineers to test and improve innovative and novel implantable devices, as well as to conduct high-impact and high-quality studies to ensure their translation.

Research Plan

I will continue to build relationships with industry partners and lead the research efforts to test novel electrode materials and implantable devices in acute and chronic *in vivo* experiments. Much of this work can be done in rats, but I also have experience working in cat, guinea pig, and pig models. Specifically, I will lead functional testing including measuring recruitment properties, electrochemical performance, and assessing material integrity and imaging. This work will not only systematically evaluate the viability of materials and devices for chronic use, but also investigate the mechanisms of action of the therapy. From my experience, I can direct the design and verification efforts for applications in ISMS, functional electrical stimulation (FES), epidural spinal cord stimulation (eSCS), and DRG stimulation. I will form relationships with researchers within the Department of Biomedical Engineering, as well as with Neurosurgery, Health and Kinesiology, and other departments to identify potential collaborators. I have a strong network from my previous and current research that I can use as a springboard for identifying collaborators. My long-term goal is to translate one or more materials or technologies for use in clinical implants, using the acute and chronic animal and first-in-human studies as the foundation for that work. I will attain funding through the industrial partners, as well as through the NIH and NSF.

Neuromodulation

Neuromodulation is the alteration of neural activity using electrical stimulation. It is commonly used for chronic pain treatment and for reducing tremors using deep brain stimulation. I am part of a team at the University of Pittsburgh that is using eSCS to restore sensation in the phantom limb of lower-limb amputees. Specifically, I am looking at the reflex responses evoked in muscles during sensory restoration stimulation during walking. eSCS for sensory restoration has also been shown to reduce phantom limb pain. I am also interested in non-invasive neuromodulation methods because they are more easily tested and translated to clinical applications. Recently, I wrote a pilot grant that was successfully funded through the National Center of Neuromodulation for Rehabilitation (NM4R) and the NIH to use transcutaneous spinal cord stimulation (tSCS) to reduce phantom limb pain in lower-limb amputees. tSCS uses surface electrodes over the spine to deliver a novel stimulation waveform that enables targeting the same structures as eSCS (the dorsal roots) and has been shown to improve mobility and reduce spasticity in people with SCI. In my pilot study, I will determine if spinal reflex modulation is altered after limb amputation, and if tSCS can be used to restore normal reflex modulation and reduce phantom limb pain. This pilot grant also covers the exploration of using machine learning classification methods to determine if a biomarker of phantom limb pain is present in EMG of the residual limb. I have used similar



Ex. Using neuromodulation and high-density EMG to improve lives of amputees

classification methods on neural activity recorded from the ventral roots of neonatal mice during my PhD. The current work utilizes high-density EMG recordings to capture the unique musculature of the residual limb. Predictions of phantom limb pain episodes from EMG could potentially be used as a feedback signal for a neuromodulation technique to treat the phantom limb pain before it occurs.

I am also conducting experiments comparing the recruitment properties of different waveforms that are commonly used for tSCS. Many research groups deliver tSCS at 30-50 Hz, while others also include a 10 kHz carrier frequency. The high frequency stimulation is hypothesized to reduce focal pain from the stimulation due to blocking of local cutaneous afferents. This allows the stimulation current to be increased (up to 180 mA) to target the deep spinal structures with less discomfort. I hypothesize that the 10 kHz stimulation is not as capable of targeting the dorsal roots and will have a higher threshold for inducing reflex responses than traditional stimulation. This work will increase the understanding of how tSCS excites the spinal cord and help determine which stimulation parameters are most useful for neuromodulation applications.

Research Plan

My immediate research plan is to build on the results obtained from the pilot study investigating the use of tSCS as a method for reducing phantom limb pain in a larger clinical trial. The trial will include control groups and limit the cause of amputation to traumatic injury. I will also investigate whether tSCS can improve balance and gait stability lower limb amputees, because they are at a greater risk of falling due to lack of sensation as well as impaired spinal cord reflex modulation. Long term, I will expand this work to include people with diabetic neuropathy with and without an amputation, since diabetic neuropathy is the leading cause for lower limb amputation. I hypothesize that tSCS can reduce phantom limb pain and improve balance and gait function in lower limb amputees and people with neuropathy. I will also explore the changes in the spinal cord that result from such extreme insults to the peripheral nerves, which will increase our understanding of phantom limb pain and neuropathy and how they can affect the central nervous system. Furthermore, I also plan to explore the use of tSCS for improving walking and reducing spasticity after stroke, since it has shown great success in people with SCI. Longer term, this work could be combined with the exoskeleton and control strategies research described above. This research thrust has the potential to attract funding from the DOD and DARPA, particularly because much of the work involves amputees. I will also seek funding from the NIH and the American Diabetes Association.

Collectively, my former, current, and future research plans span the entire spectrum of translating neurotechnologies and rehabilitation interventions by combining my expertise in engineering, neuroscience, and machine learning.