Neural Engineering

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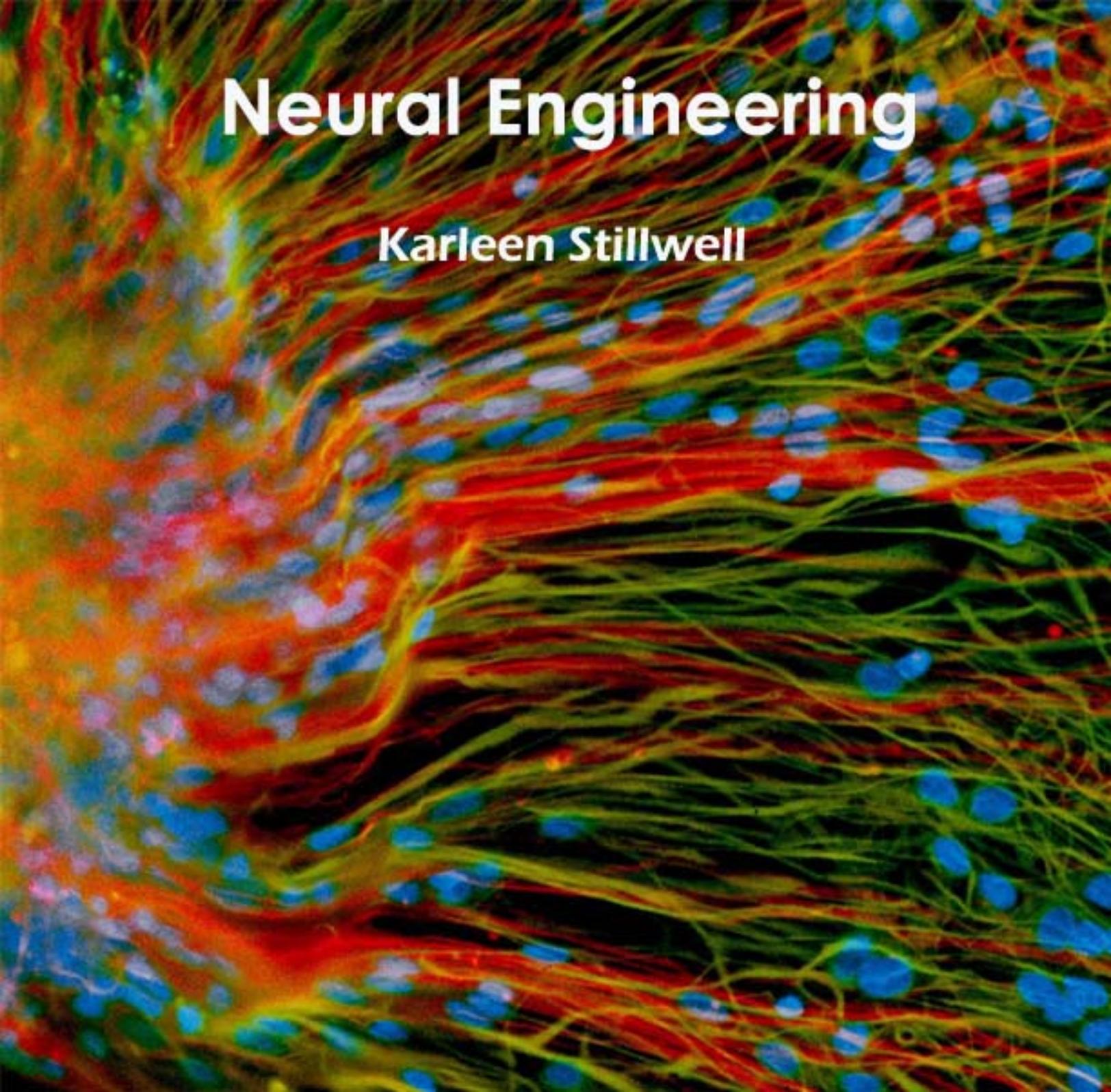
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Introduction

Neural engineering (also known as Neuroengineering) is a discipline within biomedical engineering that uses engineering techniques to understand, repair, replace, enhance, or otherwise exploit the properties of neural systems. Neural engineers are uniquely qualified to solve design problems at the interface of living neural tissue and non-living constructs.

Overview

This field of engineering draws on the fields of computational neuroscience, experimental neuroscience, clinical neurology, electrical engineering and signal processing of living neural tissue, and encompasses elements from robotics, cybernetics, computer engineering, neural tissue engineering, materials science, and nanotechnology.

Prominent goals in the field include restoration and augmentation of human function via direct interactions between the nervous system and artificial devices.

Much current research is focused on understanding the coding and processing of information in the sensory and motor systems, quantifying how this processing is altered in the pathological state, and how it can be manipulated through interactions with artificial devices including brain-computer interfaces and neuroprosthetics.

Other research concentrates more on investigation by experimentation, including the use of neural implants connected with external technology.

History

As neural engineering is a relatively new field, information and research relating to it is comparatively limited, although this is changing rapidly. The first journals specifically devoted to neural engineering, The Journal of Neural Engineering and The Journal of NeuroEngineering and Rehabilitation both emerged in 2004. International conferences on neural engineering have been held by the IEEE since 2003, most recently from 29 April until 2 May 2009 in Antalya, Turkey 4th Conference on Neural Engineering.

Chapter 1

Spinal Cord Stimulator

A **spinal cord stimulator** is a device used to exert pulsed electrical signals to the spinal cord to control chronic pain. Spinal cord stimulation (SCS), in the simplest form, consists of stimulating electrodes, implanted in the epidural space, an electrical pulse generator, implanted in the lower abdominal area or gluteal region, conducting wires connecting the electrodes to the generator, and the generator remote control. SCS has notable analgesic properties and, at the present, is used mostly in the treatment of failed back surgery syndrome, complex regional pain syndrome and refractory pain due to ischemia.

History

Electrotherapy of pain by neurostimulation began shortly after Melzack and Wall proposed the gate control theory in 1965. This theory proposed that nerves carrying painful peripheral stimuli and nerves carrying touch and vibratory sensation both terminate in the dorsal horn (the gate) of spinal cord. It was hypothesized that input to the latter could be manipulated to "close the gate" to the former. As an application of the gate control theory, Shealy et al. implanted the first spinal cord stimulator device directly on the dorsal column for the treatment of chronic pain and in 1971, Shimogi and colleagues first reported the analgesic properties of epidural spinal cord stimulation. Since then this technique has undergone numerous technical and clinical developments.

At this time neurostimulation for the treatment of pain is used with peripheral nerve stimulation, spinal cord stimulation, deep brain stimulation, and motor cortex stimulation.

Mechanism of action

The neurophysiologic mechanisms of action of spinal cord stimulation are not completely understood yet. Linderoth and others have noted that the mechanism of analgesia when SCS is applied in neuropathic pain states may be very different from that involved in analgesia due to limb ischemia. In neuropathic pain states, experimental evidence show

that SCS alters the local neurochemistry in dorsal horn, suppressing the hyperexcitability of the neurons. Specifically, there is some evidence for increased levels of GABA release, serotonin, and perhaps suppression of levels of some excitatory amino acids, including glutamate and aspartate. In the case of ischemic pain, analgesia seems to derive from restoration of the oxygen demand supply. This effect could be mediated by inhibition of the sympathetic system, although vasodilation is another possibility. It is also probable that a combination of the two abovementioned mechanisms is involved.

Technical consideration

Equipment

SCS, in simplest form, consists of a pulse generator with its remote controls, implanted stimulating electrodes and conducting wires connecting the electrodes to the generator.

Generator

The generator, implanted subcutaneously, could be a complete pulse generator module with its own battery or only a radio frequency (RF) receiver. The former case, usually called implantable pulse generator or IPG, has a battery of its own and could come with rechargeable battery which can be charged externally via a wireless power charger so that it does not need to be replaced surgically when it loses charge.

The RF receiver on the other hand is externally driven by a transmitter from which it gets its power and pulses. This external transmitter has a battery which can be easily replaced. RF receivers have traditionally been used for patients that require high power settings that would quickly deplete a primary-cell IPG.

The patient is also provided with a remote control to turn on and off the stimulator, and depending on the device and the surgeon's preference, can change the programming of the stimulation patterns. The surgeon has a programming device that could be used to modify a wide range of stimulation settings of the RF generator.

Various current, voltage and waveforms configurations are possible. SC stimulators come in constant current, variable voltage or constant voltage, variable current. A distinction is also made with respect to the number of independent power sources incorporated within the device. There are single source devices and multiple-source devices. Up to now, a maximum of 16-source devices are manufactured.

Electrodes

The electrodes, which consist of an array of leads, could be percutaneous type or paddle type. Percutaneous electrodes are easier to insert in comparison with paddle type, which are inserted via incision over spinal cord and laminectomy.

Insertion procedures and techniques

SCS procedure involves careful placement of electrodes in the epidural space, a trial period (which takes between 5–7 days), and, if the results of pain relieving was satisfactory in the trial period, anchoring the electrodes to the interspinal ligaments, positioning and implantation of the pulse generator, tunneling and connection of the connecting wires, programming the system for the special pattern of stimulation and performing required postoperative cares.

Selecting the level of stimulation

The representation of the dermatomal level in the dorsal columns of the spinal cord is much higher than the corresponding vertebral level. For instance, the sweet spot for sciatic pain (dermatomal level L5/S1) is around T10 nerve.

Electrodes selection

For the SCS to be effective, the area of paresthesia must overlap the area of pain. Selection of leads depends on which arrangement will give the best paresthesia coverage to the painful area. At present up to 16 electrodes can be stimulated by one system. A patient could have two octrodes (eight lead electrodes), which can be placed parallel to each other or at two different vertical sites. Four quatrodes (four lead electrodes) could be inserted to cover two different sites bilaterally or up to four sites vertically.

Generator implant

The IPG or the RF unit is usually implanted in the lower abdominal area or in the posterior superior gluteal region. It should be in a location that patients can access with their dominant hand for adjustment of their settings with the patient-held remote control. The decision to use a fully implantable IPG or an RF unit depends on several considerations. If the patient's pain pattern requires the use of many electrodes with high power settings, an RF unit should be used. The IPG battery life will largely depend on the power settings utilized, but the newer IPG units will generally last several years at average power settings.

Programming

Programming involves selecting the electrode stimulating configuration, adjusting the amplitude, width and frequency of electrical pulses. Amplitude indicates the intensity of stimulation. This is set within a range of 0–10 V according the type of electrode used and the type of nerves stimulated. Lower voltage is chosen for peripheral nerves and paddle type electrodes. Ideally paraesthesia should be felt between 2 and 4 V. Pulse width usually varies from 100 to 400 us. Widening the pulse width will also broaden the area of paraesthesia. Frequency of pulse wave is usually between 20 and 120 hertz. It is an individual preference: some patients choose low frequency beating sensation whereas others prefer high frequency buzzing.

Selection of lowest possible setting on all parameters is important in conserving battery life in non-rechargeable models of SCS. Cycling of stimulation is also employed to save battery life. Changing of stimulator program may have to be undertaken during the course of therapy and follow-up.

Patient selection

Appropriate patients for neurostimulation implants must meet the following criteria: the patient has a diagnosis amenable to this therapy, the patient has failed conservative therapy, significant psychological issues have been ruled out, and a trial has demonstrated pain relief. A trial period of stimulation over a period of 5–7 days should follow the psychiatric evaluation to demonstrate its effectiveness. This part of the protocol is important because of the cost of the equipment and the invasive nature of the procedure. The trial is considered successful if the patient achieves more than a 50% reduction in pain.

Indications

The most common use of SCS is failed back surgery syndrome (FBSS) in the United States and peripheral ischemic pain in Europe.

FBSS, classified as mixed pain syndrome (neuropathic and nociceptive), is the persistent or recurrent pain, mainly involving the lower back and/or legs after successful spinal surgery. It affects about 40% of patients who undergo spinal surgeries. Several studies showed overall efficacy of the SCS for FBSS.

SCS is also indicated in the treatment of inoperable ischemic limb pain. Furthermore, this technique is studied in various applications. For instance, it has been shown to modulate the function of sympathetic nervous system and increase norepinephrine release in refractory angina pectoris, decreasing the probability of angina attack. SCS units have been used to treat patients with frequent migraines. The electrodes are implanted in the bilateral suboccipital region.

Complications

Complications with SCS range from simple easily correctable problems to devastating paralysis, nerve injury and death. However, in a 7-year follow-up, the overall complication rate was 19.5%. The reported complications include infection, haematomas (subcutaneous or epidural), cerebrospinal fluid (CSF) leak, post dural puncture headache, discomfort at pulse generator site, seroma and transient paraplegia. Hardware-related complications such as electrode migration, fractured electrodes, and rotation of pulse generator are also reported.

Cost effectiveness

The cost effectiveness of spinal cord stimulation in the treatment of chronic back pain was evaluated by Kumar and colleagues in 2002. They examined 104 patients with failed back surgery syndrome. Of the 104 patients, 60 were implanted with a spinal cord stimulator. Both groups were monitored over a period of five years. The stimulation group annual cost was $29,000 versus $38,000 in the other group. 15% returned to work in the stimulation group versus 0% in the other group. The higher costs in the nonstimulator group were in the categories of medications, emergency center visits, x-rays, and ongoing physician visits.

Advantages and disadvantages

SCS is analgesia on demand. It is a useful option when other forms of therapy fail. It reduces pain medication and side effects. It is effective in about 50–70% cases. It is an invasive procedure, so it can have associated complications such as infection, bleeding, and dural puncture. It has the risk of disconnection or equipment failure.

SCS interaction with diathermy, pacemakers, MRI and therapeutic ultrasound can result in unexpected changes in stimulation, serious patient injury or death. It can also lead to failure of the device.

Future

SCS is finding its way to be applied to Parkinson's disease. More complex and power efficient microprocessor based equipments increasing the battery life could be developed. Closed loop bio-feedback systems which communicate and record neural responses following spinal cord stimulation could be applied and utilized In the future, it might be possible to combine SCS with implanted drug delivery systems to produce synergistic effects minimizing side effects and complications. Strong evidence is still lacking for SCS which may emerge in near future following robust research studies complimenting the rapid technological advances that is taking place in the field of SCS.

Chapter 2

Brain Implant

Brain implants, often referred to as **neural implants**, are technological devices that connect directly to a biological subject's brain - usually placed on the surface of the brain, or attached to the brain's cortex. A common purpose of modern brain implants and the focus of much current research is establishing a biomedical prosthesis circumventing areas in the brain that have become dysfunctional after a stroke or other head injuries. This includes sensory substitution, e.g. in vision. Other brain implants are used in animal experiments simply to record brain activity for scientific reasons. Some brain implants involve creating interfaces between neural systems and computer chips. This work is part of a wider research field called brain-computer interfaces. (Brain-computer interface research also includes technology such as EEG arrays that allow interface between mind and machine but do not require direct implantation of a device.)

Neural-implants such as deep brain stimulation and Vagus nerve stimulation are increasingly becoming routine for patients with Parkinson's disease and clinical depression respectively, proving themselves as a boon for people with diseases which were previously regarded as incurable.

Purpose

Brain implants electrically stimulate or block or record (or both record and stimulate simultaneously) from single neurons or groups of neurons (biological neural networks) in the brain. The blocking technique is called intra-abdominal vagal blocking. This can only be done where the functional associations of these neurons are approximately known. Because of the complexity of neural processing and the lack of access to action potential related signals using neuroimaging techniques, the application of brain implants has been seriously limited until recent advances in neurophysiology and computer processing power.

Research

Research in sensory substitution has made slow progress in recent years. Especially in vision, due to the knowledge of the working of the visual system, eye implants (often involving some brain implants or monitoring) have been applied with demonstrated success. For hearing, cochlear implants are used to stimulate the auditory nerve directly. The vestibulocochlear nerve is part of the peripheral nervous system, but the interface is similar to that of true brain implants.

Multiple projects have demonstrated success at recording from the brains of animals for long periods of time. As early as 1976, researchers at the NIH led by Edward Schmidt made action potential recordings of signals from Rhesus monkey motor cortexes using immovable "hatpin" electrodes, including recording from single neurons for over 30 days, and consistent recordings for greater than three years from the best electrodes.

The "hatpin" electrodes were made of pure iridium and insulated with Parylene-c, materials that are currently used in the Cyberkinetics implementation of the Utah array. These same electrodes, or derivations thereof using the same biocompatible electrode materials, are currently used in visual prosthetics laboratories, laboratories studying the neural basis of learning, and motor prosthetics approaches other than the Cyberkinetics probes.
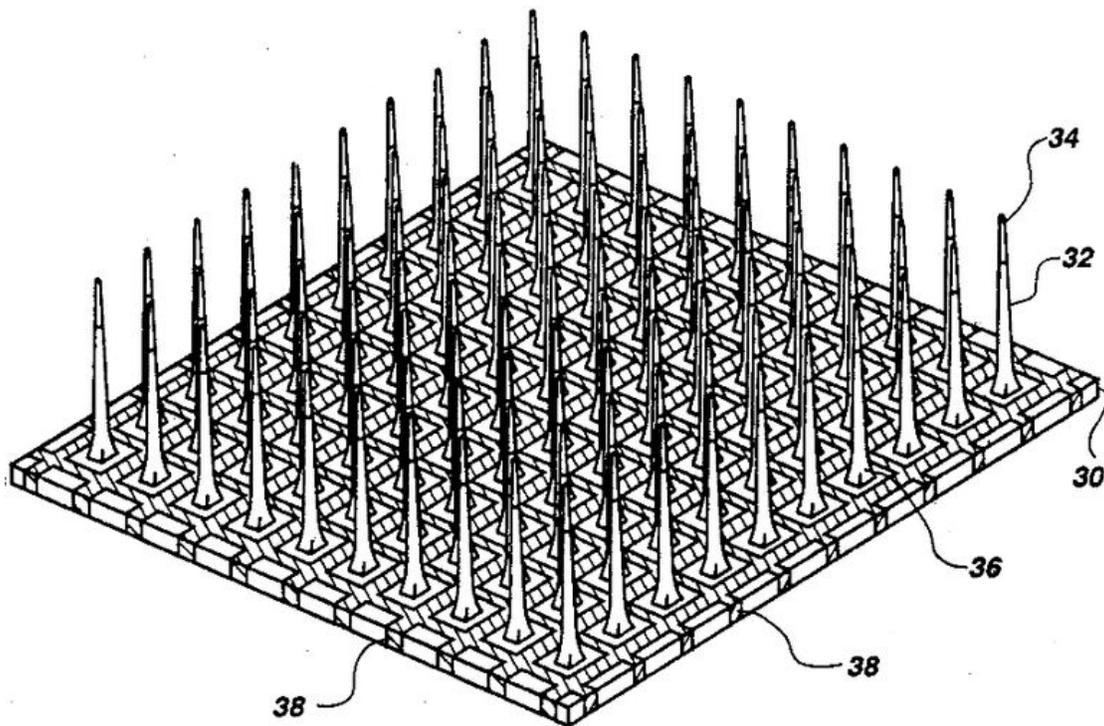
Schematic of the "Utah" Electrode Array

A competing series of electrodes and projects is sold by Plexon including Plextrode Series of Electrodes. These are variously the "Michigan Probes", the microwire arrays first used at MIT, and the FMAs from MicroProbe that emerged from the visual prosthetic project collaboration between Phil Troyk, David Bradley, and Martin Bak.

Other laboratory groups produce their own implants to provide unique capabilities not available from the commercial products.

Breakthroughs include studies of the process of functional brain re-wiring throughout the learning of a sensory discrimination, control of physical devices by rat brains, monkeys over robotic arms, remote control of mechanical devices by monkeys and humans, remote control over the movements of roaches, electronic-based neuron transistors for leeches, the first reported use of the Utah Array in a human for bidirectional signalling. Currently a number of groups are conducting preliminary motor prosthetic implants in humans. These studies are presently limited to several months by the longevity of the implants.

Rehabilitation

Brain pacemakers have been in use since 1997 to ease the symptoms of such diseases as epilepsy, Parkinson's Disease, dystonia and recently depression.

Current brain implants are made from a variety of materials such as tungsten, silicon, platinum-iridium, or even stainless steel. Future brain implants may make use of more exotic materials such as nanoscale carbon fibers (nanotubes), and polycarbonate urethane.

Historical research on brain implants

In 1870, Eduard Hitzig and Gustav Fritsch demonstrated that electrical stimulation of the brains of dogs could produce movements. Robert Bartholow showed the same to be true for humans in 1874. By the start of the 20th century Fedor Krause began to systematically map human brain areas, using patients that had undergone brain surgery.

Prominent research was conducted in the 1950s. Robert G. Heath experimented with aggressive mental patients, aiming to influence his subjects' moods through electrical stimulation.

Yale University physiologist Jose Delgado demonstrated limited control of animal and human subjects' behaviours using electronic stimulation. He invented the *stimoceiver* or *transdermal stimulator* a device implanted in the brain to transmit electrical impulses that modify basic behaviours such as aggression or sensations of pleasure.

Delgado was later to write a popular book on mind control, called "Physical Control of the Mind", where he stated: "*the feasibility of remote control of activities in several species of animals has been demonstrated [...] The ultimate objective of this research is to provide an understanding of the mechanisms involved in the directional control of animals and to provide practical systems suitable for human application.*"

In the 1950s, the CIA also funded research into mind control techniques, through programs such as MKULTRA. Perhaps because he received funding for some research through the US Office of Naval Research, it has been suggested (but not proven) that Delgado also received backing through the CIA. He denied this claim in a 2005 article in *Scientific American* describing it only as a speculation by conspiracy-theorists. He stated that his research was only progressively scientifically-motivated to understand how the brain works.

Ethical considerations

Whilst deep brain stimulation is increasingly becoming routine for patients with Parkinson's disease, there may be some behavioural side effects. Reports in the literature describe the possibility of apathy, hallucinations, compulsive gambling, hypersexuality, cognitive dysfunction, and depression. However, these may be temporary and related to correct placement and calibration of the stimulator and so are potentially reversible.

Some transhumanists, such as Raymond Kurzweil and Kevin Warwick, see brain implants as part of a next step for humans in progress and evolution, where as others, especially bioconservatives, view them as unnatural, with humankind losing essential human qualities. It raises controversy similar to other forms of human enhancement. For instance, it is argued that implants would technically change people into cybernetic organisms (cyborgs). Some people fear implants may be used for mind control, *e.g.* to change human perception of reality.

Chapter 3

Neurotechnology

Neurotechnology is any technology that has a fundamental influence on how people understand the brain and various aspects of consciousness, thought, and higher order activities in the brain. It also includes technologies that are designed to improve and repair brain function and allow researchers and clinicians to visualize the brain.

Background

The field of neurotechnology has been around for nearly half a century but has only reached maturity in the last twenty years. Advents of brain imaging revolutionized the field and gave rise to a whole new shift in research that could now directly monitor the brain's activities during experiments. The field of neurotechnology is incredibly relevant to society, though its presence is so commonplace that many do not realize its ubiquity. From pharmaceutical drugs to brain scanning, neurotechnology affects nearly all industrialized people either directly or indirectly, be it from drugs for depression, sleep, ADD, or anti-neurotics to cancer scanning, stroke rehabilitation, and much more. Its potentials reach nearly all aspects of daily life, and as the field's depth increases modern societies will be able to harness and control more of what the brain does and how it influences lifestyles and personalities. It is important to note that there are many technologies that are taken for granted that could apply in the field. Games like BrainAge, and programs like FastForWord are methods for improvement of brain function and therefore apply as well. In addition, numerous pharmaceutical companies develop many new and useful functional drugs that can help improve function and restore normality in a person's life. Currently, modern science can image nearly all aspects of the brain as well as control a degree of the function of the brain. It can help control depression, over-activation, sleep deprivation, and many other conditions. Therapeutically it can help improve stroke victims' motor coordination, improve brain function, reduce epileptic episodes, improve patients with degenerative motor diseases (Parkinson's Disease, Huntington's Disease, ALS), and can even help alleviate phantom pain perception. Advances in the field promise many new enhancements and

rehabilitations for patients suffering from neurological problems. The neurotechnology revolution has given rise to the Decade of the Mind initiative, which was started in 2007. It also offers the possibility of revealing the mechanisms by which mind and consciousness emerge from the brain.

Current technologies

Imaging

Magnetic resonance imaging (MRI) is used for scanning the brain for topological and landmark structure in the brain, but can also be used for imaging activation in the brain. While detail about how MRI works is reserved for the actual MRI article, the uses of MRI are far reaching in the study of neuroscience. It is a cornerstone technology in studying the mind, especially with the advent of functional MRI (fMRI). Functional MRI measures the oxygen levels in the brain upon activation (higher oxygen content = neural activation) and allows researchers to understand what loci are responsible for activation under a given stimulus. This technology is a large improvement to single cell or loci activation by means of exposing the brain and contact stimulation. Functional MRI allows researchers to draw associative relationships between different loci and regions of the brain and provides a large amount of knowledge in establishing new landmarks and loci in the brain.

Computed tomography (CT) is another technology used for scanning the brain. It has been used since the 1970s and is another tool used by neuroscientists to track brain structure and activation. While many of the functions of CT scans are now done using MRI, CT can still be used as the mode by which brain activation and brain injury are detected. Using an X-ray, researchers can detect radioactive markers in the brain that indicate brain activation as a tool to establish relationships in the brain as well as detect many injuries/diseases that can cause lasting damage to the brain such as aneurysms, degeneration, and cancer.

Positron emission tomography (PET) is another imaging technology that aids researchers. Instead of using magnetic resonance or X-rays, PET scans rely on positron emitting markers that are bound to a biologically relevant marker such as glucose. The more activation in the brain the more that region requires nutrients, so higher activation appears more brightly on an image of the brain. PET scans are becoming more frequently used by researchers because PET scans are activated due to metabolism whereas MRI is activated on a more physiological basis (sugar activation versus oxygen activation).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is essentially direct magnetic stimulation to the brain. Because electric currents and magnetic fields are intrinsically related, by stimulating the brain with magnetic pulses it is possible to interfere with specific loci in the brain to produce a predictable effect. This field of study is currently receiving a large

amount of attention due to the potential benefits that could come out of better understanding this technology.

Cranial surface measurements

Electroencephalography (EEG) is a method of measuring brainwave activity non-invasively. A number of electrodes are placed around the head and scalp and electrical signals are measured. Typically EEGs are used when dealing with sleep, as there are characteristic wave patterns associated with different stages of sleep. Clinically EEGs are used to study epilepsy as well as stroke and tumor presence in the brain. EEGs are a different method to understand the electrical signaling in the brain during activation.

Magnetoencephalography (MEG) is another method of measuring activity in the brain by measuring the magnetic fields that arise from electrical currents in the brain. The benefit to using MEG instead of EEG is that these fields are highly localized and give rise to better understanding of how specific loci react to stimulation or if these regions over-activate (as in epileptic seizures).

Implant technologies

Neurodevices are any devices used to monitor or regulate brain activity. Currently there are a few available for clinical use as a treatment for Parkinson's disease. The most common neurodevices are deep brain stimulators (DBS) that are used to give electrical stimulation to areas stricken by inactivity. Parkinson's disease is known to be caused by an inactivation of the basal ganglia (nuclei) and recently DBS has become the more preferred form of treatment for Parkinson's disease, although current research questions the efficiency of DBS for movement disorders.

Neuromodulation is a relatively new field that combines the use of neurodevices and neurochemistry. The basis of this field is that the brain can be regulated using a number of different factors (metabolic, electrical stimulation, physiological) and that all these can be modulated by devices implanted in the neural network. While currently this field is still in the researcher phase, it represents a new type of technological integration in the field of neurotechnology.

Gene/cell therapy

Cell therapy is a field devoted to improving cells via genetic enhancement. Currently there are many researchers investigating the ability for programmed regeneration and genetic influencing in the brain. Using viral or nanoparticle vectors (a "carrier" for the gene of interest), scientists are finding new ways to manipulate and improve the brain's capacity, overall health, and resistance to disease. Researchers have begun looking at uses for stem cells in the brain, which recently have been found in a few loci. A large number of studies are being done to determine if this form of therapy could be used in a large scale.

Pharmaceuticals

Pharmaceuticals play a vital role in maintaining stable brain chemistry, and are the most commonly used neurotechnology by the general public and medicine. Drugs like sertraline, methylphenidate, and zolpidem act as chemical modulators in the brain, and they allow for normal activity in many people whose brains cannot act normally under physiological conditions. While pharmaceuticals are usually not mentioned and have their own field, the role of pharmaceuticals is perhaps the most far-reaching and commonplace in modern society.

How these help study the brain

Magnetic resonance imaging is a vital tool in neurological research in showing activation in the brain as well as providing a comprehensive image of the brain being studied. While MRIs are used clinically for showing brain size, it still has relevance in the study of brains because it can be used to determine extent of injuries or deformation. These can have a significant effect on personality, sense perception, memory, higher order thinking, movement, and spatial understanding. However, current research tends to focus more so on fMRI or real-time functional MRI (rtfMRI). These two methods allow the scientist or the participant, respectively, to view activation in the brain. This is incredibly vital in understanding how a person thinks and how their brain reacts to a person's environment, as well as understanding how the brain works under various stressors or dysfunctions. Real-time functional MRI is a revolutionary tool available to neurologists and neuroscientists because patients can see how their brain reacts to stressors and can perceive visual feedback. CT scans are very similar to MRI in their academic use because they can be used to image the brain upon injury, but they are more limited in perceptual feedback. CTs are generally used in clinical studies far more than in academic studies, and are found far more often in a hospital than a research facility. PET scans are also finding more relevance in academia because they can be used to observe metabolic uptake of neurons, giving researchers a wider perspective about neural activity in the brain for a given condition. Combinations of these methods can provide researchers with knowledge of both physiological and metabolic behaviors of loci in the brain and can be used to explain activation and deactivation of parts of the brain under specific conditions.

Transcranial magnetic stimulation is a relatively new method of studying how the brain functions and is used in many research labs focused on behavioral disorders and hallucinations. What makes TMS research so interesting in the neuroscience community is that it can target specific regions of the brain and shut them down or activate temporarily; thereby changing the way the brain behaves. Personality disorders can stem from a variety of external factors, but when the disorder stems from the circuitry of the brain TMS can be used to deactivate the circuitry. This can give rise to a number of responses, ranging from "normality" to something more unexpected, but current research is based on the theory that use of TMS could radically change treatment and perhaps act as a cure for personality disorders and hallucinations. Currently, repetitive transcranial magnetic stimulation (rTMS) is being researched to see if this deactivation effect can be made more permanent in patients suffering from these disorders. Some techniques

combine TMS and another scanning method such as EEG to get additional information about brain activity such as cortical response.

Both EEG and MEG are currently being used to study the brain's activity under different conditions. Each uses similar principles but allows researchers to examine individual regions of the brain, allowing isolation and potentially specific classification of active regions. As mentioned above, EEG is very useful in analysis of immobile patients, typically during the sleep cycle. While there are other types of research that utilize EEG, EEG has been fundamental in understanding the resting brain during sleep. There are other potential uses for EEG and MEG such as charting rehabilitation and improvement after trauma as well as testing neural conductivity in specific regions of epileptics or patients with personality disorders.

Neuromodulation can involve numerous technologies combined or used independently to achieve a desired effect in the brain. Gene and cell therapy are becoming more prevalent in research and clinical trials and these technologies could help stunt or even reverse disease progression in the central nervous system. Deep brain stimulation is currently used in many patients with movement disorders and is used to improve the quality of life in patients. While deep brain stimulation is a method to study how the brain functions per se, it provides both surgeons and neurologists important information about how the brain works when certain small regions of the basal ganglia (nuclei) are stimulated by electrical currents.

Future technologies

The future of neurotechnologies lies in how they are fundamentally applied, and not so much on what new versions will be developed. Current technologies give a large amount of insight into the mind and how the brain functions, but basic research is still needed to demonstrate the more applied functions of these technologies. Currently, rtfMRI is being researched as a method for pain therapy. deCharms et al. have shown that there is a significant improvement in the way people perceive pain if they are made aware of how their brain is functioning while in pain. By providing direct and understandable feedback, researchers can help patients with chronic pain decrease their symptoms. This new type of bio/mechanical-feedback is a new development in pain therapy. Functional MRI is also being considered for a number of more applicable uses outside of the clinic. Research has been done on testing the efficiency of mapping the brain in the case when someone lies as a new way to detect lying. Along the same vein, EEG has been considered for use in lie detection as well. TMS is being used in a variety of potential therapies for patients with personality disorders, epilepsy, PTSD, migraine, and other brain-firing disorders, but has been found to have varying clinical success for each condition. The end result of such research would be to develop a method to alter the brain's perception and firing and train patients' brains to rewire permanently under inhibiting conditions. In addition, PET scans have been found to be 93% accurate in detecting Alzheimer's disease nearly 3 years before conventional diagnosis, indicating that PET scanning is becoming more useful in both the laboratory and the clinic.

Stem cell technologies are always salient both in the minds of the general public and scientists because of their large potential. Recent advances in stem cell research have allowed researchers to ethically pursue studies in nearly every facet of the body, which includes the brain. Research has shown that while most of the brain does not regenerated and is typically a very difficult environment to foster regeneration, there are portions of the brain with regenerative capabilities (specifically the hippocampus and the olfactory bulbs). Much of the research in central nervous system regeneration is how to overcome this poor regenerative quality of the brain. It is important to note that there are therapies that improve cognition and increase the amount of neural pathways, but this does not mean that there is a proliferation of neural cells in the brain. Rather, it is called a plastic rewiring of the brain (*plastic* because it indicates malleability) and is considered a vital part of growth. Nevertheless, many problems in patients stem from death of neurons in the brain, and researchers in the field are striving to produce technologies that enable regeneration in patients with stroke, Parkinson's diseases, severe trauma, and Alzheimer's disease, as well as many others. While still in fledgling stages of development, researchers have recently begun making very interesting progress in attempting to treat these diseases. Researchers have recently successfully produced dopaminergic neurons for transplant in patients with Parkinson's diseases with the hopes that they will be able to move again with a more steady supply of dopamine. Many researchers are building scaffolds that could be transplanted into a patient with spinal cord trauma to present an environment that promotes growth of axons (portions of the cell attributed with transmission of electrical signals) so that patients unable to move or feel might be able to do so again. The potentials are wide-ranging, but it is important to note that many of these therapies are still in the laboratory phase and are slowly being adapted in the clinic. Some scientists remain skeptical with the development of the field, and warn that there is a much larger chance that electrical prosthesis will be developed to solve clinical problems such as hearing loss or paralysis before cell therapy is used in a clinic.

Novel drug delivery systems are being researched in order to improve the lives of those who struggle with brain disorders that might not be treated with stem cells, modulation, or rehabilitation. Pharmaceuticals play a very important role in society, and the brain has a very selective barrier that prevents some drugs from going from the blood to the brain. There are some diseases of the brain such as meningitis that require doctors to directly inject medicine into the spinal cord because the drug cannot cross the blood-brain barrier. Research is being conducted to investigate new methods of targeting the brain using the blood supply, as it is much easier to inject into the blood than the spine. New technologies such as nanotechnology are being researched for selective drug delivery, but these technologies have problems as with any other. One of the major setbacks is that when a particle is too large, the patient's liver will take up the particle and degrade it for excretion, but if the particle is too small there will not be enough drug in the particle to take effect. In addition, the size of the capillary pore is important because too large a particle might not fit or even plug up the hole, preventing adequate supply of the drug to the brain. Other research is involved in integrating a protein device between the layers to create a free-flowing gate that is unimpeded by the limitations of the body. Another direction is receptor-mediated transport, where receptors in the brain used to transport

nutrients are manipulated to transport drugs across the blood-brain barrier. Some have even suggested that focused ultrasound opens the blood-brain barrier momentarily and allows free passage of chemicals into the brain. Ultimately the goal for drug delivery is to develop a method that maximizes the amount of drug in the loci with as little degraded in the blood stream as possible.

Neuromodulation is a technology currently used for patients with movement disorders, although research is currently being done to apply this technology to other disorders. Recently, a study was done on if DBS could improve depression with positive results, indicating that this technology might have potential as a therapy for multiple disorders in the brain. DBS is limited by its high cost however, and in developing countries the availability of DBS is very limited. A new version of DBS is under investigation and has developed into the novel field, optogenetics. Optogenetics is the combination of deep brain stimulation with fiber optics and gene therapy. Essentially, the fiber optic cables are designed to light up under electrical stimulation, and a protein would be added to a neuron via gene therapy to excite it under light stimuli. So by combining these three independent fields, a surgeon could excite a single and specific neuron in order to help treat a patient with some disorder. Neuromodulation offers a wide degree of therapy for many patients, but due to the nature of the disorders it is currently used to treat its effects are often temporary. Future goals in the field hope to alleviate that problem by increasing the years of effect until DBS can be used for the remainder of the patient's life. Another use for neuromodulation would be in building neuro-interface prosthetic devices that would allow quadriplegics the ability to maneuver a cursor on a screen with their thoughts, thereby increasing their ability to interact with others around them. By understanding the motor cortex and understanding how the brain signals motion, it is possible to emulate this response on a computer screen.

Ethics

Stem cells

The ethical debate about use of embryonic stem cells has stirred controversy both in the United States and abroad; although more recently these debates have lessened due to modern advances in creating induced pluripotent stem cells from adult cells. The greatest advantage for use of embryonic stem cells is the fact that they can differentiate (become) nearly any type of cell provided the right conditions and signals. However, recent advances by Shinya Yamanaka et al. have found ways to create pluripotent cells without the use of such controversial cell cultures. Using the patient's own cells and re-differentiating them into the desired cell type bypasses not only the fear of patient rejection of the cells but also gives researchers a more ethical (and larger) supply of available cells. Induced pluripotent cells are by no means perfect though, they still have the potential to form teratomas, or benign (though they can be potentially malignant in effect) tumors, and tend to have poor survivability *in vivo* (in the living body) on damaged tissue. Much of the ethics concerning use of stem cells has subsided from the embryonic/adult stem cell debate due to its rendered moot, but now societies find themselves debating whether or not this technology can be ethically used. Enhancements

of traits, use of animals for tissue scaffolding, and even arguments for moral degeneration have been made with the fears that if this technology reaches its full potential a new paradigm shift will occur in human behavior.

Military application

New neurotechnologies have always garnered the appeal of governments, from lie detection technology and virtual reality to rehabilitation and understanding the psyche. Due to the Iraq War and War on Terror, American soldiers coming back from Iraq and Afghanistan are reported to have percentages up to 12% with PTSD. There are many researchers hoping to improve these peoples' conditions by implementing new strategies for recovery. By combining pharmaceuticals and neurotechnologies, some researchers how found ways to low the fear response and theorize that it may be applicable to PTSD. Virtual reality is also a technology that has found a large amount of attention in the military. If improved upon, it would be possible to train soldiers in complex situations in times of peace in order to better prepare and train a modern army.

Privacy

Finally, when these technologies are being developed society must understand that these neurotechnologies could reveal the one thing that people can always keep secret, what they are thinking. While there are large amounts of benefits associated with these technologies, it is necessary for scientists and policy makers alike to consider implications about "cognitive liberty." This term is important in many ethical circles concerned with the state and goals of progress in the field of neurotechnology. Current improvements such as "brain fingerprinting" or lie detection using EEG or fMRI could give rise to a set fixure of loci/emotional relationships in the brain, although these technologies are still years away from full application. It is important to consider how all these neurotechnologies might affect the future of society, and it is suggested that political, scientific, and civil debates are heard about the implementation of these newer technologies that potentially offer a new wealth of once-private information. Some ethicists are also concerned with the use of TMS and fear that the technique could be used to alter patients in ways that are undesired by the patient.

Chapter 4

Neuroprosthetics

Neuroprosthetics (also called **neural prosthetics**) is a discipline related to neuroscience and biomedical engineering concerned with developing neural prostheses. Neural prostheses are a series of devices that can substitute a motor, sensory or cognitive modality that might have been damaged as a result of an injury or a disease. Cochlear implants provide an example of such devices. These devices substitute the functions performed by the ear drum and Stapes, while simulating the frequency analysis performed in the cochlea. A microphone on an external unit gathers the sound and processes it; the processed signal is then transferred to an implanted unit that stimulates the auditory nerves through a microelectrode array.

The development of such devices has had a profound impact on the quality of human life, and research in this field intends to resolve disabilities.

There is another side to the application of neural prostheses. These implantable devices can also be used in animal experiments as a tool for neuroscientists to develop a better understanding of how the brain works. Wireless electrical recording from the brain of awake, freely behaving animals can open many important doors into understanding how the brain handles different functions. Accurately probing and recording the electrical signals in the brain would help better understand the relationship among a local population of neurons that are responsible for a specific function. In order to substitute sensory, motor or cognitive modalities, we need to first understand which part of the brain is responsible for those modalities and how those functions are performed. Neuroprosthetics and neuro science have a very intertwined relationship. Neuroprostheses contribute to better understanding of the neural system and this better understanding helps develop better, more application-specific neural prostheses.

There are many challenges which must be overcome in order to develop these devices. Any implanted device has to be very small to be to minimally invasive, especially in the brain, eye or cochlea. Also this implant would have to communicate with the outside world wirelessly. This bidirectional wireless communication requires a high bandwidth

for real-time data transmission; this is a great challenge considering that this data link has to operate through the skin. The minimal size of the implant means no battery can be embedded in the implant. Instead, the implant works on wireless power transmission through the skin. This is just as challenging as the data transmission. The tissue surrounding the implant is usually very sensitive to temperature rise so the implant must have very low power consumption in order to assure it won't harm the tissue. Another very important issue is the bio compatibility of the material that the implants are coated with. The more biocompatible these materials are, the less tissue reaction they will cause thus resulting less implant risk and longer implant period.

Gradually as these devices become safer and the our understanding of how the brain works enhances the use of these devices will become more and more common and help people with severe disabilities live a normal life. The neuroprosthetic seeing the most widespread use is the cochlear implant, with approximately 100,000 in use worldwide as of 2006.

Today, the use of cochlear implants and pacemakers has become an undeniable fact of life. The future holds an exciting prospect for the every day use of a variety of neural prostheses.

History

The first cochlear implant dates back to 1957. Other landmarks include the first motor prosthesis for foot drop in hemiplegia in 1961, the first auditory brainstem implant in 1977 and a peripheral nerve bridge implanted into spinal cord of adult rat in 1981. Paraplegics were helped in standing with a lumbar anterior root implant (1988) and in walking with Functional Electrical Stimulation (FES).

Regarding the development of electrodes implanted in the brain, an early difficulty was reliably locating the electrodes, originally done by inserting the electrodes with needles and breaking off the needles at the desired depth. Recent systems utilize more advanced probes, such as those used in deep brain stimulation to alleviate the symptoms of Parkinson's Disease. The problem with either approach is that the brain floats free in the skull while the probe does not, and relatively minor impacts, such as a low speed car accident, are potentially damaging. Some researchers, such as Kensall Wise at the University of Michigan, have proposed tethering 'electrodes to be mounted on the exterior surface of the brain' to the inner surface of the skull. However, even if successful, tethering would not resolve the problem in devices meant to be inserted deep into the brain, such as in the case of deep brain stimulation (DBS).

Sensory prosthetics

Visual prosthetics

A visual prosthesis can create a sense of image by electrically stimulating neurons in the visual system. A camera would wirelessly transmit to an implant, the implant would map

the image across an array of electrodes. The array of electrodes has to effectively stimulate 600-1000 locations, stimulating these optic neurons in the retina thus will create an image. The stimulation can also be done anywhere along the optic signal's path way. The optical nerve can be stimulated in order to create an image, or the visual cortex can be stimulated, although clinical tests have proven most successful for retinal implants.

A visual prosthesis system consists of an external (or implantable) imaging system which acquires and processes the video. Power and data will be transmitted to the implant wirelessly by the external unit. The implant uses the received power/data to convert the digital data to an analog output which will be delivered to the nerve via micro electrodes.

Photoreceptors are the specialized neurons that convert photons into electrical signals. They are part of the retina, a multilayer neural structure about 200 um thick that lines the back of the eye. The processed signal is sent to the brain through the optical nerve. If any part of this path way is damaged blindness can occur.

Blindness can result from damage to the optical pathway (cornea, aqueous humor, crystalline lens, and vitreous). This can happen as a result of accident or disease. The two most common retinal degenerative diseases that result in blindness secondary to photoreceptor loss is age related macular degeneration (AMD) and retinitis pigmentosa (RP).

The first clinical trial of a permanently implanted retinal prosthesis was a device with a passive microphotodiod array with 3500 elements. This trial was implemented at Optobionics, Inc., in 2000. In 2002, Second Sight Medical Products, Inc. (Sylmar, CA) began a trial with a prototype epiretinal implant with 16 electrodes. The subjects were six individuals with bare light perception secondary to RP. The subjects demonstrated their ability to distinguish between three common objects (plate, cup, and knife) at levels statistically above chance. An active sub retinal device developed by Retina Implant GMbH (Reutlingen, Germany) began clinical trials in 2006. An IC with 1500 microphotodiods was implanted under the retina. The microphotodiods serve to modulate current pulses based on the amount of light incident on the photo diode.

The seminal experimental work towards the development of visual prostheses was done by cortical stimulation using a grid of large surface electrodes. In 1968 Giles Brindley implanted an 80 electrode device on the visual cortical surface of a 52-year-old blind woman. As a result of the stimulation the patient was able to see phosphenes in 40 different positions of the visual field. This experiment showed that an implanted electrical stimulator device could restore some degree of vision. Recent efforts in visual cortex prosthesis have evaluated efficacy of visual cortex stimulation in a non-human primate. In this experiment after a training and mapping process the monkey is able to perform the same visual saccade task with both light and electrical stimulation.

The requirements for a high resolution retinal prosthesis should follow from the needs and desires of blind individuals who will benefit from the device. Interactions with theses

patients indicate that mobility without a cane, face recognition and reading are the main necessary enabling capabilities.

The results and implications of fully-functional visual prostheses are exciting. However, the challenges are grave. In order for a good quality image to be mapped in the retina a high number of micro-scale electrode arrays are needed. Also, the image quality is dependent on how much information can be sent over the wireless link. Also this high amount of information must be received and processed by the implant without much power dissipation which can damage the tissue. The size of the implant is also of great concern. Any implant would be preferred to be minimally invasive.

With this new technology, several scientists, including Karin Moxon at Drexel, John Chapin at SUNY, and Miguel Nicolelis at Duke University, started research on the design of a sophisticated visual prosthesis. Other scientists have disagreed with the focus of their research, arguing that the basic research and design of the densely populated microscopic wire was not sophisticated enough to proceed.

Auditory prosthetics

Cochlear implants (CIs), auditory brain stem implants (ABIs), and auditory midbrain implants (AMIs) are the three main categories for auditory prostheses. CI electrode arrays are implanted in the cochlea, ABI electrode arrays stimulate the cochlear nucleus complex in the lower brain stem, and AMIs stimulates auditory neurons in the inferior colliculus. Cochlear implants have been very successful among these three categories. Today Advanced Bionics and Medtronic are the major commercial providers of cochlea implants.

In contrast to traditional hearing aids that amplify sound and send it through the external ear, cochlear implants acquire and process the sound and convert it into electrical energy for subsequent delivery to the auditory nerve. The microphone of the CI system receives sound from the external environment and sends it to processor. The processor digitizes the sound and filters it into separate frequency bands that are sent to the appropriate tonotonic region in the cochlea that approximately corresponds to those frequencies.

In 1957, French researchers A. Djourno and C. Eyries, with the help of D. Kayser, provided the first detailed description of directly stimulation the auditory nerve in a human subject. The individuals described hearing chirping sounds during simulation. In 1972, the first portable cochlear implant system in an adult was implanted at the House Ear Clinic. The U.S. Food and Drug Administration (FDA) formally approved the marketing of the House-3M cochlear implant in November 1984.

Improved performance in cochlea implants not only depends on understanding the physical and biophysical limitations of implant stimulation but also on an understanding of the brain's pattern processing requirements. Modern signal processing represents the most important speech information while also providing the brain the pattern recognition information that it needs. Pattern recognition in the brain is more effective than

algorithmic preprocessing at identifying important features in speech. A combination of engineering, signal processing, biophysics, and cognitive neuroscience was necessary to produce the right balance of technology to maximize the performance of auditory prosthesis.

Since the early 2000s FDA has been involved in a clinical trial of device termed the "Hybrid" by Cochlear Corporation. This trial is aimed at examining the usefulness of cochlea implantation in patients with residual low-frequency hearing. The "Hybrid" utilizes a shorter electrode than the standard cochlea implant, since the electrode is shorter it stimulates the basil region of the cochlea and hence the high-frequency tonotopic region. In theory these devices would benefit patients with significant low-frequency residual hearing who have lost perception in the speech frequency range and hence have decreased discrimination scores.

Prosthetics for pain relief

The SCS (Spinal Cord Stimulator) device has two main components: an electrode and a generator. The technical goal of SCS for neuropathic pain is to mask the area of a patient's pain with a stimulation induced tingling, known as "paresthesia", because this overlap is necessary (but not sufficient) to achieve pain relief. Paresthesia coverage depends upon which afferent nerves are stimulated. The most easily recruited by a dorsal midline electrode, close to the pial surface of spinal cord, are the large dorsal column afferents, which produce broad paresthesia covering segments caudally.

In ancient times the electrogenic fish was used as a shocker to subside pain. Healers had developed specific and detailed techniques to exploit the generative qualities of the fish to treat various types of pain, including headache. Because of the awkwardness of using a living shock generator, a fair level skill was required to deliver the therapy to the target for the proper amount of time. (Including keeping the fish alive as long as possible) Electro analgesia was the first deliberate application of electricity. By the nineteenth century, most western physicians were offering their patients electrotherapy delivered by portable generator. In the mid-1960s, however, three things converged to insure the future of electro stimulation.

1. Pacemaker technology, which had it start in 1950, became available.

2. Melzack and Wall published their gate control theory of pain, which proposed that the transmission of pain could be blocked by stimulation of large afferent fibers.

3. Pioneering physicians became interested in stimulating the nervous system to relieve patients from pain.

The design options for electrodes include their size, shape, arrangement, number, and assignment of contacts and how the electrode is implanted. The design option for the pulse generator include the power source, target anatomic placement location, current or voltage source, pulse rate, pulse width, and number of independent channels.

Programming options are very numerous (a four-contact electrode offers 50 functional bipolar combinations). The current devices use computerized equipment to find the best options for use. This reprogramming option compensates for postural changes, electrode migration, changes in pain location, and suboptimal electrode placement.

Motor prosthetics

Devices which support the function of autonomous nervous system include the implant for bladder control. In the somatic nervous system attempts to aid conscious control of movement include Functional electrical stimulation and the lumbar anterior root stimulator.

Bladder control implants

Where a spinal cord lesion leads to paraplegia, patients have difficulty emptying their bladders and this can cause infection. From 1969 onwards Brindley developed the sacral anterior root stimulator, with successful human trials from the early 1980s onwards. This device is implanted over the sacral anterior root ganglia of the spinal cord; controlled by an external transmitter, it delivers intermittent stimulation which improves bladder emptying. It also assists in defecation and enables male patients to have a sustained full erection.

The related procedure of sacral nerve stimulation is for the control of incontinence in able-bodied patients.

Motor prosthetics for conscious control of movement

Researchers are attempting to build motor neuroprosthetics that will help restore movement and the ability to communicate with the outside world to persons with motor disabilities such as tetraplegia or amyotrophic lateral sclerosis.

To capture electrical signals from the brain, scientists have developed microelectrode arrays smaller than a square centimeter that can be implanted in the skull to record electrical activity, transducing recorded information through a thin cable. After decades of research in monkeys, neuroscientists have been able to decode neuronal signals into movements. Completing the translation, researchers have built interfaces that allow patients to move computer cursors, and they are beginning to build robotic limbs and exoskeletons that patients can control by thinking about movement.

The technology behind motor neuroprostheses is still in its infancy. Investigators and study participants continue to experiment with different ways of using the prostheses. Having a patient think about clenching a fist, for example, produces a different result than having him or her think about tapping a finger. The filters used in the prostheses are also being fine-tuned, and in the future, doctors hope to create an implant capable of transmitting signals from inside the skull wirelessly, as opposed to through a cable.

Preliminary clinical trials suggest that the devices are safe and that they have the potential to be effective. Some patients have worn the devices for over two years with few, if any, ill effects.

Prior to these advancements, Philip Kennedy (Emory and Georgia Tech) had an operable if somewhat primitive system which allowed an individual with paralysis to spell words by modulating their brain activity. Kennedy's device used two neurotrophic electrodes: the first was implanted in an intact motor cortical region (e.g. finger representation area) and was used to move a cursor among a group of letters. The second was implanted in a different motor region and was used to indicate the selection.

Developments continue in replacing lost arms with cybernetic replacements by using nerves normally connected to the pectoralis muscles. These arms allow a slightly limited range of motion, and reportedly are slated to feature sensors for detecting pressure and temperature.

Dr. Todd Kuiken at Northwestern University and Rehabilitation Institute of Chicago has developed a method called targeted reinnervation for an amputee to control motorized prosthetic devices and to regain sensory feedback.

Sensory/motor prosthetics

In 2002 an array of 100 electrodes was implanted directly into the median nerve fibers of the scientist Kevin Warwick. The recorded signals were used to control a robot arm developed by Warwick's colleague, Peter Kyberd and was able to mimic the actions of Warwick's own arm. Additionally, a form of sensory feedback was provided via the implant by passing small electrical currents into the nerve. This caused a contraction of the first lumbrical muscle of the hand and it was this movement that was perceived.

Cognitive prostheses

Cognitive prostheses seek to restore cognitive function to individuals with brain tissue loss due to injury, disease, or stroke by performing the function of the damaged tissue with integrated circuits. The theory of localization states that brain functions are localized to a specific portion of the brain. However, recent studies on brain plasticity suggest that the brain is capable of rewiring itself so that an area of the brain traditionally associated with a particular function (i.e. auditory cortex) can perform functions associated with another portion of the brain. (i.e. auditory cortex processing visual information). Implants could take advantage of brain plasticity to restore cognitive function even if the native tissue has been destroyed.

Applications

Alzheimer's Disease

Alzheimer's Disease is projected to affect more than 107 million people worldwide by the year 2050. Due to increased life spans, more and more people are being affected by Alzheimer's disease. Alzheimer's disease renders individuals incapable of supporting themselves. Many of the more severe cases of Alzheimer's patients end up in nursing homes. Even a small measure of success by cognitive implants would help keep Alzheimer's patients out of nursing homes.

Hippocampal Deficits

Dr. Theodore Berger at the University of Southern California is developing a prosthetic for treatments of hippocampal detriments including Alzheimer's. Degenerative hippocampal neurons are the root cause of the memory disorders that accompany Alzheimer's disease. Also, hippocampal pyramidal cells are extremely sensitive to even brief periods of anoxia, like those that occur during stroke. Loss of hippocampal neurons in the dentate gyrus, an area associated with new memory formation has been attributed to blunt head trauma. Hippocampal dysfunction has also been linked to epileptic activity. This demonstrates the wide scope of neural damage and neurodegenerative disease conditions for which a hippocampal prosthesis would be clinically relevant.

Traumatic Brain Injury

More than 1.4 million people in the United States suffer traumatic brain injury. Orthosis for TBI patients to control limb movement via devices that read neurons in brain, calculate limb trajectory, and stimulate needed motor pools to make movement. (Anderson Paper, Cole at NIH - specifically "Computer software as an orthosis for Brain Injury",

Parkinson's Disease

Nearly 1 million people in the United States are affected by Parkinson's Disease. Deep Brain Stimulation relieves symptoms of Parkinson's Disease for numerous patients. Parkinson's Disease patients could benefit from a cortical device that mimics the natural signals needed to promote dopamine production. Another possible avenue for mitigation of PD is a device that supplements dopamine when given specific neuronal inputs which would let the body regulate dopamine levels with its intrinsic sensors.

Speech Deficits

Approximately 7.5 million people in the United States have trouble speaking. Many of these can be attributed to aphasias. The success of cochlear implants suggest that cortical implants to the speech areas of the brain can be developed to improve speech in such patients.

Paralysis

According to the Christopher and Dana Reeve Foundation's Paralysis Resource Center, approximately 6 million people are living with paralysis in the United States. Paralysis results from many sources, stroke, traumatic brain injury, neurodegenerative diseases like multiple sclerosis and Lou Gehrig's Disease, and congenital sources. Many patients would benefit from a prosthetic device that controls limb movement via devices that read neurons in brain, calculate limb trajectory, and stimulate the needed motor pools to make movement. This technology is being developed at the Andersen Lab, located at the California Institute of Technology. The goal is to develop a device to enable locked in patients, those without the ability to move or speak, to communicate with others.

Societal Impact/Market Information

Nearly 1 million people in the United States are affected by Parkinson's Disease.

Alzheimer's Disease is projected to affect more than 107 million people worldwide by the year 2050.

Just these two diseases indicate that there is already a large market for cognitive neural prosthetics, with more potential markestspace revealed in traumatic brain injury and speech problems (particularly damage to Broca's or Wernicke's areas).

More than 1.4 million people in the United States suffer traumatic brain injury.

Approximately 7.5 million people in the United States have trouble speaking. Many of these can be attributed to aphasias.

More than 6.5 million people in the United States have suffered stroke.

Obstacles

Mathematical Modeling

Accurate characterization of the nonlinear input/output (I/O) parameters of the normally functioning tissue to be replaced is paramount to designing a prosthetic that mimics normal biologic synaptic signals. Mathematical modeling of these signals is a complex task "because of the nonlinear dynamics inherent in the cellular/molecular mechanisms comprising neurons and their synaptic connections." The output of nearly all brain neurons are dependent on which post-synaptic inputs are active and in what order the inputs are received. (spatial and temporal properties, respectively).

Once the I/O parameters are modeled mathematically, integrated circuits are designed to mimic the normal biologic signals. For the prosthetic to perform like normal tissue, it must process the input signals, a process known as transformation, in the same way as normal tissue.

Size

Implantable devices must be very small to be implanted directly in the brain, roughly the size of a quarter. One of the example of microimplantable electrode array is the Utah array.

Wireless Controlling Devices can be mounted outside of the skull and should be smaller than a pager.

Power Consumption

Power consumption drives battery size. Optimization of the implanted circuits reduces power needs. Implanted devices currently need on-board power sources. Once the battery runs out, surgery is needed to replace the unit. Longer battery life correlates to fewer surgeries needed to replace batteries. One option that could be used in the medical field to recharge implant batteries without surgery or wires is being used in powered toothbrushes. These devices make of inductive coupling to recharge batteries. Another strategy is to convert electromagnetic energy into electrical energy, as in radio frequency identification tags.

Bio Compatibility

Cognitive prostheses are implanted directly in the brain, so biocompatibility is very important obstacle to overcome. Materials used in the housing of the device, the electrode material (such as iridium oxide), and electrode insulation must be chosen for long term implantation. Subject to Standards: ISO 14708-3 2008-11-15, Implants for Surgery - Active implantable medical devices Part 3: Implantable neurostimulators.

Crossing the Blood Brain Barrier can introduce pathogens or other materials that may cause an immune response. The brain has its own immune system that acts differently than the immune system of the rest of the body.

Questions to answer:How does this affect material choice? Does the brain have unique phages that act differently and may affect materials thought to be bio compatible in other areas of the body?

Data Transmission

Wireless Transmission is being developed to allow continuous recording of neuronal signals of individuals in their daily life. This allows physicians and clinicians to capture more data, ensuring that short term events like epileptic seizures can be recorded, allowing better treatment and characterization of neural disease.

A small, light weight device has been developed that allows constant recording of primate brain neurons at Stanford University. This technology also enables neuroscientists to study the brain outside of the controlled environment of a lab.

Methods of data transmission must be robust and secure. Neurosecurity is a new issue. Makers of cognitive implants must prevent unwanted downloading of information or thoughts from and uploading of detrimental data to the device that may interrupt function.

Correct Implantation

Implantation of the device presents many problems. First, the correct presynaptic inputs must be wired to the correct postsynaptic inputs on the device. Secondly, the outputs from the device must be targeted correctly on the desired tissue. Thirdly, the brain must learn how to use the implant. Various studies in brain plasticity (int link) suggest that this may be possible through exercises designed with proper motivation.

Current Developments

Andersen Lab

The Andersen Lab builds on research done previously by Musallam and show that high-level cognitive signals in the post parietal cortex, or PPC, can be used to decode the target position of reaching motions. Signals like these could be used to directly control a prosthetic device. Functionally speaking, the PPC is situated between sensory and motor areas in the brain. It is involved in converting sensory inputs into plans for action, a phenomenon known as sensory – motor integration.

Within the PPC is an area known as the post parietal reach region, or PRR for short. This area has been shown to be most active when an individual is planning and executing a movement. The PRR receives direct visual information, indicating that vision may be the primary sensory input. The PRR encodes the targets for reaching in visual coordinates relative to the current direction of gaze AKA retinal coordinates. Because it is coding the goal of the movement and not all the different variables required for the limb to contact the target, the planning signals of the PRR are considered cognitive in nature. Decoding these signals is important to help paralyzed patients, especially those with damage to areas of the brain that calculate limb movement variables, or relay this information to motor neurons. Perhaps the most astonishing possibility is utilizing these signals to provide 'locked in' individuals, those without the ability to move or speak, an avenue of communication.

First, Andersen and colleagues placed electrode arrays onto the dorsal premotor cortex, the PRR, and medial interparietal area (MIP) of monkeys to record signals made by these regions while the monkeys looked at a computer screen. After the monkeys touched a central cue spot on the screen and looked at a central fixation point (red), another cue (green) popped up briefly then disappeared. The monkeys were given a juice reward if they reached to where the newly vanished target was at the end of a short memory period, about 1.5 seconds. The recordings were made when the monkeys were planning movement, but sitting motionless in the dark absent of eye movements, ensuring that motor and sensory information were not influencing the planning activity.

Next, the researchers conducted brain-control trials using neural activity data recorded from 2 tenths of a second to 1 second of the memory period to decode the intended reach destination. A brain-machine interface used the decoded data to move a cursor to the spot on the screen where the monkeys planned to move, without using their limbs. Monkeys were rewarded with juice if the correct target was decoded and the cue was flashed again, providing visual reinforcement. After a month or two of training, the monkeys were much better at hitting the target. This learning is a testament to the brain's natural plasticity, and creates an opportunity for patients to improve how they operate the prosthesis with training. Each time the patient uses the prosthetic system, the brain could automatically make subtle adjustments to the input signal recorded by the system.

Finally, the researchers used reach trials to decode intentions in healthy monkeys. However, paralyzed patients cannot perform reach trials for the scientists to record reach intention data. Adaptive databases overcome this scenario. Each time a reach decoding is successful, it is added to the database. If the number of database entries is kept constant, one trial, (a less successful one) must be deleted. Eventually the database will contain only successful decodes, making the system work better each time the patient uses it. This suggests a FIFO, or first-in, first-out, setup. The oldest data drops out first. Initially filling the database will be difficult, but with rigorous training and many trials, the system will be able to accurately discern the user's intentions. This process, along with the brain's plasticity, should enable people to control a myriad of prostheses, and perhaps even motorized wheel chairs. Furthermore, in the future precision devices such as surgical tools could be controlled directly by the brain instead of controls manipulated by the motor system.

Hippocampal Prosthetic

Dr. Theodore Berger's research lab at the University of Southern California seeks to develop models of mammalian neural systems, currently the hippocampus, essential for learning and memory. The goal is to make an implantable device that replicates the way living hippocampal neurons behave and exchange electrical signals. If successful, it would be a large step towards a biomedical solution for Alzheimer's symptoms. Complications from brain injury to motor areas of the brain like reduced coordination could be improved. Speech and language problems caused by stroke could be reversed. To accomplish this, the device will listen for neuronal signals going to the hippocampus with implanted electrode arrays, calculate what the outgoing response of normal hippocampus neurons would be, and then to stimulate neurons in other parts of the brain, hopefully just like the tissue did before damage or degeneration.

Technologies Involved

Local Field Potentials

Local field potentials (LFPs) are electrophysiological signals that are related to the sum of all dendritic synaptic activity within a volume of tissue. Recent studies suggest goals

and expected value are high-level cognitive functions that can be used for neural cognitive prostheses.

- explain how they are used
- how they are better than other methods

Automated Movable Electrical Probes

One hurdle to overcome is the long term implantation of electrodes. If the electrodes are moved by physical shock or the brain moves in relation to electrode position, the electrodes could be recording different nerves. Adjustment to electrodes is necessary to maintain an optimal signal. Individually adjusting multi electrode arrays is a very tedious and time consuming process. Development of automatically adjusting electrodes would mitigate this problem. Anderson's group is currently collaborating with Yu-Chong Tai's lab and the Burdick lab (all at Cal Tech) to make such a system that uses electrolysis-based actuators to independently adjust electrodes in a chronically implanted array of electrodes.

MRI

Used for imaging to determine correct positionings

Imaged Guided Surgical Techniques

Image-Guided Surgery is used to precisely position brain implants.

Future Directions

Self-charging implants that use bioenergy to recharge would eliminate the need for costly and risky surgeries to change implant batteries.

Memory/Brain off-loading and subsequent uploading to learn new information quickly. Researchers at the Georgia Institute of Technology are researching mammalian memory cells to determine exactly how we learn. The techniques used in the Potter Lab can be used to study and enhance the activities of neural prosthetics devices.

Controlling complex machinery with thoughts instead of converting motor movements into commands for machines would allow greater accuracy and enable users to distance themselves from hazardous environments.

Other future directions include devices to maintain focus, to stabilize/induce mood, to help patients with damaged cortices feel and express emotions, and to enable true telepathic communication, not simply picking up visual/auditory cues and guessing emotional state or subject of thought from context.

Chapter 5

Neural Ensemble

A **neural ensemble** is a population of nervous system cells (or cultured neurons) involved in a particular neural computation.

Background

The concept of neural ensemble dates back to the work of Charles Sherrington who described the functioning of the CNS as the system of reflex arcs, each composed of interconnected excitatory and inhibitory neurons. In Sherrington's scheme, α-motoneurons are the final common path of a number of neural circuits of different complexity: motoneurons integrate a large number of inputs and send their final output to muscles.

Donald Hebb theoretically developed the concept of neural ensemble in his famous book "The Organization of Behavior" (1949). He defined "cell assembly" as "a diffuse structure comprising cells in the cortex and diencephalon, capable of acting briefly as a closed system, delivering facilitation to other such systems". Hebb suggested that, depending on functional requirements, individual brain cells could participate in different cell assemblies and be involved in multiple computations.

In the 1980s, Apostolos Georgopoulos and his colleagues Ron Kettner, Andrew Schwartz, and Kenneth Johnson formulated a population vector hypothesis to explain how populations of motor cortex neurons encode movement direction. This hypothesis was based on the observation that individual neurons tended to discharge more for movements in particular directions, the so-called *preferred directions* for individual neurons. In the population vector model, individual neurons 'vote' for their preferred directions using their firing rate. The final vote is calculated by vectorial summation of individual preferred directions weighted by neuronal rates. This model proved to be successful in description of motor-cortex encoding of reach direction, and it was also capable to predict new effects. For example, Georgopoulos' population vector accurately

described mental rotations made by the monkeys that were trained to translate locations of visual stimuli into spatially shifted locations of reach targets.

Encoding

Neuronal ensembles encode information in a way somewhat similar to the principle operation - multiple edits by many participants. Neuroscientists have discovered that individual neurons are very noisy. For example, by examining the activity of only a single neuron in the visual cortex, it is very difficult to reconstruct the visual scene that the owner of the brain is looking at. Like a single participant, an individual neuron does not 'know' everything and is likely to make mistakes. This problem is solved by the brain having billions of neurons. Information processing by the brain is population processing, and it is also distributed - in many cases each neuron knows a little bit about everything, and the more neurons participate in a job, the more precise the information encoding. In the distributed processing scheme, individual neurons may exhibit neuronal noise, but the population as a whole averages this noise out.

An alternative to the ensemble hypothesis is the theory that there exist highly specialized neurons that serve as the mechanism of neuronal encoding. In the visual system, such cells are often referred to as grandmother cells because they would respond in very specific circumstances--such as when a person gazes at a photo of their grandmother. Neuroscientists have indeed found that some neurons provide better information than the others, and a population of such expert neurons has an improved signal to noise ratio. However, the basic principle of ensemble encoding holds: large neuronal populations do better than single neurons.

The emergence of specific neural assemblies is thought to provide the functional elements of brain activity that execute the basic operations of informational processing.

Neuronal code or the 'language' that neuronal ensembles speak is very far from being understood. Currently, there are two main theories about neuronal code. The *rate encoding theory* states that individual neurons encode behaviorally significant parameters by their average firing rates, and the precise time of the occurrences of neuronal spikes is not important. The *temporal encoding theory*, on the contrary, states that precise timing of neuronal spikes is an important encoding mechanism.

Neuronal oscillations that synchronize activity of the neurons in an ensemble appear to be an important encoding mechanism. For example, oscillations have been suggested to underlie visual feature binding (Gray, Singer and others). In additions, sleep stages and waking are associated with distinct oscillatory patterns.

Location and function

Relatively simple neuronal ensembles operate in the spinal cord where they control basic automatisms such as monosynaptic tendon reflex and reciprocal innervation of muscles. These include both excitatory and inhibitory neurons. Central pattern generations that

reside in the spinal cord are more complex ensembles for coordination of limb movements during locomotion. Neural ensembles of the higher brain structures such as the cerebral cortex, basal ganglia and cerebellum are not completely understood, despite the vast literature on the neuroanatomy of these regions.

Real-time decoding

After the techniques of multielectrode recordings were introduced , the task of real-time decoding of information from large neuronal ensembles became feasible. If, as Georgopoulos showed, just a few primary motor neurons could accurately predict hand motion in two planes, reconstruction of the movement of an entire limb should be possible with enough simultaneous recordings. In parallel, with the introduction of an enormous Neuroscience boost from DARPA, several lab groups used millions of dollars to make brain-machine interfaces. Of these groups, two were successful in experiments showing that animals could control external interfaces with models based on their neural activity, and that once control was shifted from the hand to the brain-model, animals could learn to control it better. These two groups are led by John Donoghue and Miguel Nicolelis, and both are involved in towards human trials with their methods. The success of both groups followed the funding thrust from DARPA.

John Donoghue formed the company Cyberkinetics to facilitate commercialization of brain-machine interfaces. They bought the Utah array from Richard Normann. Along with colleagues Hatsopoulos, Paninski, Fellows and Serruya, they first showed that neural ensembles could be used to control external interfaces by having a monkey control a cursor on a computer screen with its mind (2002).

Miguel Nicolelis worked with John Chapin, Johan Wessberg, Mark Laubach, Jose Carmena, Mikhail Lebedev, Antonio Pereira, Jr., Sidarta Ribeiro and other colleagues showed that activity of large neural ensembles can predict arm position. This work made possible creation of brain-machine interfaces - electronic devices that read arm movement intentions and translate them into movements of artificial actuators. Carmena et al. (2003) programmed the neural coding in a brain-machine interface allowed a monkey to control reaching and grasping movements by a robotic arm, and Lebedev et al. (2005) argued that brain networks reorganize to create a new representation of the robotic appendage in addition to the representation of the animal's own limbs.

In addition to the studies by Nicolelis and Donoghue, the groups of Andrew Schwartz and Richard Andersen are developing decoding algorithms that reconstruct behavioral parameters from neuronal ensemble activity. For example Andrew Schwartz uses population vector algorithms that he previously developed with Apostolos Georgopoulos.

Demonstrations of decoding of neuronal ensemble activity can be subdivided into two major classes: off-line decoding and on-line (real time) decoding. In the off-line decoding, investigators apply different algorithms to previously recorded data. Time considerations are usually not an issue in these studies: a sophisticated decoding algorithm can run for many hours on a computer cluster to reconstruct a 10-minute data
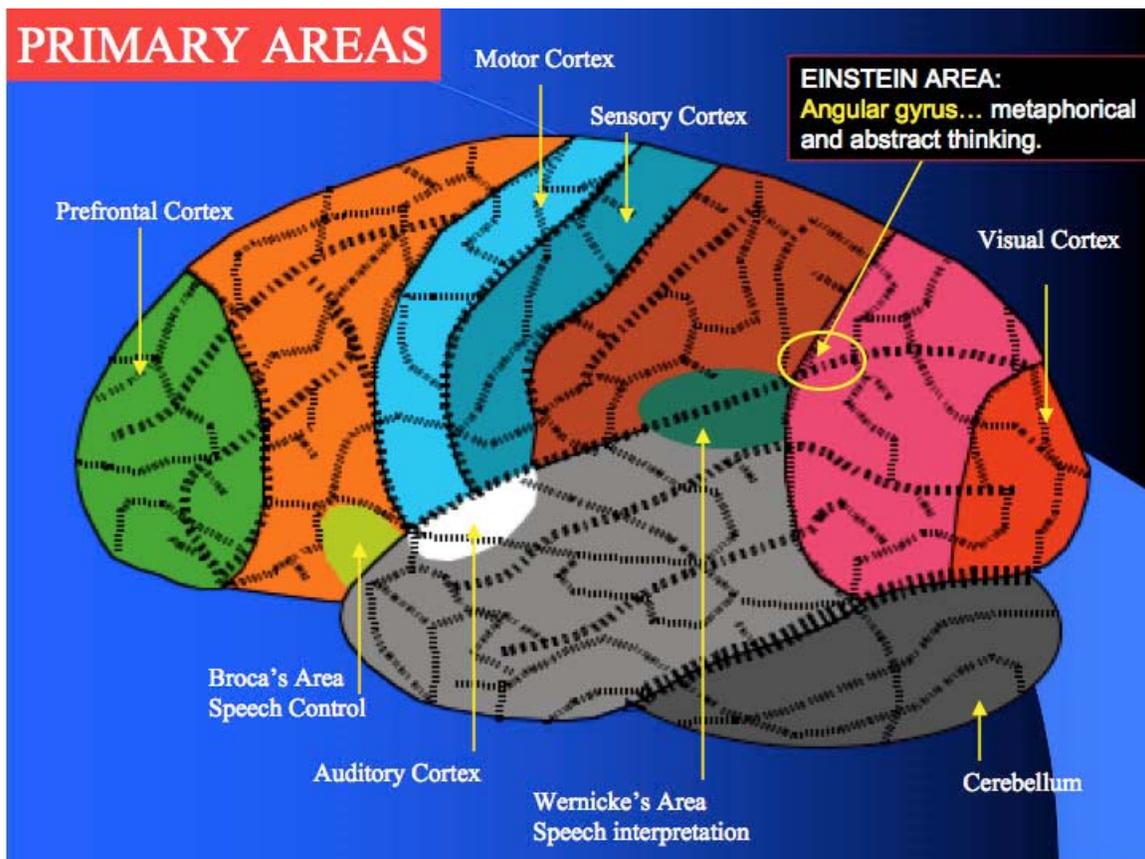
piece. On-line algorithms decode (and, importantly, predict) behavioral parameters in real time. Moreover, the subject may receive a feedback about the results of decoding — the so-called closed loop mode as opposed to the open loop mode in which the subject does not receive any feedback.

Interestingly, as Hebb predicted, individual neurons in the population can contribute information about different parameters. For example, Miguel Nicolelis and colleagues reported that individual neurons simultaneously encoded arm position, velocity and hand gripping force when the monkeys performed reaching and grasping movements. Mikhail Lebedev, Steven Wise and their colleagues reported prefrontal cortex neurons that simultaneously encoded spatial locations that the monkeys attended to and those that they stored in short-term memory. Both attended and remembered locations could be decoded when these neurons were considered as population.

To address the question of how many neurons are needed to obtain an accurate read-out from the population activity, Mark Laubach in Nicolelis lab used neuron-dropping analysis. In this analysis, he measured neuronal read-out quality as a function of the number of neurons in the population. Read-out quality increased with the number of neurons -- initially very notably, but then substantially larger neuronal quantities were needed to improve the read-out.

Chapter 6

Neuroplasticity

PRIMARY AREAS

Motor Cortex

Sensory Cortex

EINSTEIN AREA:
Angular gyrus... metaphorical and abstract thinking.

Prefrontal Cortex

Visual Cortex

Broca's Area
Speech Control

Auditory Cortex

Wernicke's Area
Speech interpretation

Cerebellum

Neuroplasticity challenges the idea that brain functions are fixed in certain locations.

Neuroplasticity (also known as **cortical re-mapping**) refers to the ability of the human brain to change as a result of one's experience, that the brain is 'plastic' and 'malleable'.

The discovery of this feature of the brain is rather modern; the previous belief amongst scientists was that the brain does not change after the critical period of infancy.

The brain consists of nerve cells (or "neurons") and glial cells which are interconnected, and learning may happen through change in the strength of the connections, by adding or removing connections, and by the formation of new cells. "Plasticity" relates to learning by adding or removing connections, or adding cells.

During the 20th century, the consensus was that lower brain and neocortical areas were immutable in structure after childhood, meaning learning only happens by changing of connection strength, whereas areas related to memory formation, such as the hippocampus and dentate gyrus, where new neurons continue to be produced into adulthood, were highly plastic. This belief is being challenged by new findings, suggesting all areas of the brain are plastic even after childhood.

Hubel and Wiesel had demonstrated that ocular dominance columns in the lowest neocortical visual area, V1, were largely immutable after the critical period in development. Critical periods also were studied with respect to language; the resulting data suggested that sensory pathways were fixed after the critical period. However, studies determined that environmental changes could alter behavior and cognition by modifying connections between existing neurons and via neurogenesis in the hippocampus and other parts of the brain, including the cerebellum.

Decades of research have now shown that substantial changes occur in the lowest neocortical processing areas, and that these changes can profoundly alter the pattern of neuronal activation in response to experience. According to the theory of neuroplasticity, experience can actually change both the brain's physical structure (anatomy) and functional organization (physiology) from top to bottom. Neuroscientists are presently engaged in a reconciliation of critical period studies demonstrating the immutability of the brain after development with the more recent research showing how the brain can, and does, change.

Etymology

This idea was first proposed in 1890 by William James in *The Principles of Psychology*, though the idea was largely neglected for the next fifty years. The first person to use the term *neural plasticity* appears to have been the Polish neuroscientist Jerzy Konorski.

Neurobiology

One of the fundamental principles of how neuroplasticity functions is linked to the concept of synaptic pruning, the idea that individual connections within the brain are constantly being removed or recreated, largely dependent upon how they are used. This concept is captured in the aphorism, "neurons that fire together, wire together"/"neurons that fire apart, wire apart." If there are two nearby neurons that often produce an impulse simultaneously, their cortical maps may become one. This idea also works in the opposite

way, i.e. that neurons which do not regularly produce simultaneous impulses will form different maps.

Cortical maps

Cortical organization, especially for the sensory systems, is often described in terms of maps. For example, sensory information from the foot projects to one cortical site and the projections from the hand target in another site. As the result of this somatotopic organization of sensory inputs to the cortex, cortical representation of the body resembles a map (or homunculus).

In the late 1970s and early 1980s, several groups began exploring the impacts of removing portions of the sensory inputs. Michael Merzenich and Jon Kaas and Doug Rasmusson used the cortical map as their dependent variable. They found—and this has been since corroborated by a wide range of labs—that if the cortical map is deprived of its input it will become activated at a later time in response to other, usually adjacent inputs. At least in the somatic sensory system, in which this phenomenon has been most thoroughly investigated, JT Wall and J Xu have traced the mechanisms underlying this plasticity. Re-organization is not cortically emergent, but occurs at every level in the processing hierarchy; this produces the map changes observed in the cerebral cortex.

Merzenich and William Jenkins (1990) initiated studies relating sensory experience, without pathological perturbation, to cortically observed plasticity in the primate somatosensory system, with the finding that sensory sites activated in an attended operant behavior increase in their cortical representation. Shortly thereafter, Ford Ebner and colleagues (1994) made similar efforts in the rodent whisker barrel cortex (also somatic sensory system). These two groups largely diverged over the years. The rodent whisker barrel efforts became a focus for Ebner, Matthew Diamond, Michael Armstrong-James, Robert Sachdev, Kevin Fox and great inroads were made in identifying the locus of change as being at cortical synapses expressing NMDA receptors, and in implicating cholinergic inputs as necessary for normal expression. However, the rodent studies were poorly focused on the behavioral end, and Ron Frostig and Daniel Polley (1999, 2004) identified behavioral manipulations as causing a substantial impact on the cortical plasticity in that system.

Merzenich and DT Blake (2002, 2005, 2006) went on to use cortical implants to study the evolution of plasticity in both the somatosensory and auditory systems. Both systems show similar changes with respect to behavior. When a stimulus is cognitively associated with reinforcement, its cortical representation is strengthened and enlarged. In some cases, cortical representations can increase two to threefold in 1–2 days at the time at which a new sensory motor behavior is first acquired, and changes are largely finished within at most a few weeks. Control studies show that these changes are not caused by sensory experience alone: they require learning about the sensory experience, and are strongest for the stimuli that are associated with reward, and occur with equal ease in operant and classical conditioning behaviors.

An interesting phenomenon involving cortical maps is the incidence of phantom limbs. This is most commonly described in people that have undergone amputations in hands, arms, and legs, but it is not limited to extremities. The phantom limb feeling, which is thought to result from disorganization in the brain map and the inability to receive input from the targeted area, may be annoying or painful. Incidentally, it is more common after unexpected losses than planned amputations. There is a high correlation with the extent of physical remapping and the extent of phantom pain. As it fades, it is a fascinating functional example of new neural connections in the human adult brain.

The concept of plasticity can be applied to molecular as well as to environmental events The phenomenon itself is complex and can involve many levels of organization. To some extent the term itself has lost its explanatory value because almost any changes in brain activity can be attributed to some sort of "plasticity". For example, the term is used prevalently in studies of axon guidance during development, short-term visual adaptation to motion or contours, maturation of cortical maps, recovery after amputation or stroke, and changes that occur in normal learning in the adult. Plasticity in more recent writing is frequently described as a property of the central nervous system with the term reorganization used to introduce the specific types of changes observed including axonal sprouting, long-term potentiation or the expression of plasticity related genomic responses Pinaud.

Norman Doidge, following the lead of Michael Merzenich, separates manifestations of neuroplasticity into adaptations that have positive or negative behavioral consequences. For example, if an organism can recover after a stroke to normal levels of performance, that adaptiveness could be considered an example of "positive plasticity". An excessive level of neuronal growth leading to spasticity or tonic paralysis, or an excessive release of neurotransmitters in response to injury which could kill nerve cells; this would have to be considered a "negative" plasticity. In addition, drug addiction and obsessive-compulsive disorder are deemed examples of "negative plasticity" by Dr. Doidge, as the synaptic rewiring resulting in these behaviors is also highly maladaptive.

A 2005 study found that the effects of neuroplasticity occur even more rapidly than previously expected. Medical students' brains were imaged during the period when they were studying for their exams. In a matter of months, the students' gray matter increased significantly in the posterior and lateral parietal cortex.

History

Proposal

Until around the 1970s, an accepted idea across neuroscience was that the nervous system was essentially fixed throughout adulthood, both in terms of brain functions, as well as the idea that it was impossible for new neurones to develop after birth.

The idea that the brain and its functions are not fixed throughout adulthood was first proposed in 1890 by William James in The Principles of Psychology, though the idea was largely neglected.

Research and discovery

In 1923, Karl Lashley conducted experiments on rhesus monkeys which demonstrated changes in neuronal pathways, which he concluded to be evidence of plasticity, although despite this, as well as further examples of research suggesting this, the idea of neuroplasticity was not widely accepted by neuroscientists. However, more significant evidence began to be produced in the 1960s and after, notably from scientists including Paul Bach-y-Rita, Michael Merzenich along with Jon Kaas, as well as several others.

In the 1960s, Paul Bach-y-Rita invented a device that allowed blind people to read, perceive shadows, and distinguish between close and distant objects. This "machine was one of the first and boldest applications of neuroplasticity." The patient sat in an electrically stimulated chair that had a large camera behind it which scanned the area, sending electrical signals of the image to four hundred vibrating stimulators on the chair against the patient's skin. The six subjects of the experiment were eventually able to recognize a picture of the supermodel Twiggy.

It must be emphasized that these people were congenitally blind and had previously not been able to see. Bach-y-Rita believed in sensory substitution; if one sense is damaged, your other senses can sometimes take over. He thought skin and its touch receptors could act as a retina (using one sense for another). In order for the brain to interpret tactile information and convert it into visual information, it has to learn something new and adapt to the new signals. The brain's capacity to adapt implied that it possessed plasticity. He thought, "We see with our brains, not with our eyes."

A tragic stroke that left his father paralyzed inspired Bach-y-Rita to study brain rehabilitation. His brother, a physician, worked tirelessly to develop therapeutic measures which were so successful that the father recovered complete functionality by age 68 and was able to live a normal, active life which even included mountain climbing. "His father's story was firsthand evidence that a 'late recovery' could occur even with a massive lesion in an elderly person." He found more evidence of this possible brain reorganization with Shepherd Ivory Franz's work. One study involved stroke patients who were able to recover through the use of brain stimulating exercises after having been paralyzed for years. "Franz understood the importance of interesting, motivating rehabilitation: 'Under conditions of interest, such as that of competition, the resulting movement may be much more efficiently carried out than in the dull, routine training in the laboratory'(Franz, 1921, pg.93)." This notion has led to motivational rehabilitation programs that are used today.

Michael Merzenich is a neuroscientist who has been one of the pioneers of brain plasticity for over three decades. He has made some of "the most ambitious claims for the field - that brain exercises may be as useful as drugs to treat diseases as severe as

schizophrenia - that plasticity exists from cradle to the grave, and that radical improvements in cognitive functioning - how we learn, think, perceive, and remember are possible even in the elderly." Merzenich's work was affected by a crucial discovery made by David Hubel and Torsten Wiesel in their work with kittens. The experiment involved sewing one eye shut and recording the cortical brain maps. Hubel and Wiesel saw that the portion of the kitten's brain associated with the shut eye was not idle, as expected. Instead, it processed visual information from the open eye. It was"… as though the brain didn't want to waste any 'cortical real estate' and had found a way to rewire itself."

This implied brain plasticity during the critical period. However, Merzenich argued that brain plasticity could occur beyond the critical period. His first encounter with adult plasticity came when he was engaged in a postdoctoral study with Clinton Woosley. The experiment was based on observation of what occurred in the brain when one peripheral nerve was cut and subsequently regenerated. The two scientists micromapped the hand maps of monkey brains before and after cutting a peripheral nerve and sewing the ends together. Afterwards, the hand map in the brain that was expected to be jumbled was nearly normal. This was a substantial breakthrough. Merzenich asserted that "if the brain map could normalize its structure in response to abnormal input, the prevailing view that we are born with a hardwired system had to be wrong. The brain had to be plastic."

Applications and examples

Treatment of brain damage

A surprising consequence of neuroplasticity is that the brain activity associated with a given function can move to a different location; this can result from normal experience and also occurs in the process of recovery from brain injury. Neuroplasticity is the fundamental issue that supports the scientific basis for treatment of acquired brain injury with goal-directed experiential therapeutic programs in the context of rehabilitation approaches to the functional consequences of the injury.

The adult brain is not "hard-wired" with fixed and immutable neuronal circuits. There are many instances of cortical and subcortical rewiring of neuronal circuits in response to training as well as in response to injury. There is solid evidence that neurogenesis (birth of brain cells) occurs in the adult, mammalian brain—and such changes can persist well into old age. The evidence for neurogenesis is mainly restricted to the hippocampus and olfactory bulb, but current research has revealed that other parts of the brain, including the cerebellum, may be involved as well.

In the rest of the brain, neurons can die, but they cannot be created. However, there is now ample evidence for the active, experience-dependent re-organization of the synaptic networks of the brain involving multiple inter-related structures including the cerebral cortex. The specific details of how this process occurs at the molecular and ultrastructural levels are topics of active neuroscience research. The manner in which experience can influence the synaptic organization of the brain is also the basis for a number of theories of brain function including the general theory of mind and epistemology referred to as

Neural Darwinism and developed by immunologist Nobel laureate Gerald Edelman. The concept of neuroplasticity is also central to theories of memory and learning that are associated with experience-driven alteration of synaptic structure and function in studies of classical conditioning in invertebrate animal models such as Aplysia. This latter program of neuroscience research has emanated from the ground-breaking work of another Nobel laureate, Eric Kandel, and his colleagues at Columbia University College of Physicians and Surgeons.

Paul Bach-y-Rita, deceased in 2006, was the "father of sensory substitution and brain plasticity." In working with a patient whose vestibular system had been damaged he developed BrainPort, a machine that "replaces her vestibular apparatus and [will] send balance signals to her brain from her tongue." After she had used this machine for some time it was no longer necessary, as she regained the ability to function normally. Her balancing act days were over.

Plasticity is the major explanation for the phenomena. Because her vestibular system was "disorganized" and sending random rather than coherent signals, the apparatus found new pathways around the damaged or blocked neural pathways, helping to reinforce the signals that were sent by remaining healthy tissues. Bach-y-Rita explained plasticity by saying, "If you are driving from here to Milwaukee and the main bridge goes out, first you are paralyzed. Then you take old secondary roads through the farmland. Then you use these roads more; you find shorter paths to use to get where you want to go, and you start to get there faster. These "secondary" neural pathways are "unmasked" or exposed and strengthened as they are used. The "unmasking" process is generally thought to be one of the principal ways in which the plastic brain reorganizes itself."

Randy Nudo's group found that if a small stroke (an infarction) is induced by impedance of blood flow to a portion of a monkey's motor cortex, the part of the body that responds by movement will move when areas adjacent to the damaged brain area are stimulated. In one study, intracortical microstimulation (ICMS) mapping techniques were used in nine normal monkeys. Some underwent ischemic infarction procedures and the others, ICMS procedures. The monkeys with ischemic infarctions retained more finger flexion during food retrieval and after several months this deficit returned to preoperative levels. With respect to the distal forelimb representation, "postinfarction mapping procedures revealed that movement representations underwent reorganization throughout the adjacent, undamaged cortex." Understanding of interaction between the damaged and undamaged areas provides a basis for better treatment plans in stroke patients. Current research includes the tracking of changes that occur in the motor areas of the cerebral cortex as a result of a stroke. Thus, events that occur in the reorganization process of the brain can be ascertained. Nudo is also involved in studying the treatment plans that may enhance recovery from strokes, such as physiotherapy, pharmacotherapy and electrical stimulation therapy.

Jon Kaas, a professor at Vanderbilt University, has been able to show "how somatosensory area 3b and ventroposterior (VP) nucleus of the thalamus are affected by long standing unilateral dorsal column lesions at cervical levels in macaque monkeys."

Adult brains have the ability to change as a result of injury but the extent of the reorganization depends on the extent of the injury. His recent research focuses on the somatosensory system, which involves a sense of the body and its movements using many senses. Usually when people damage the somatosensory cortex, impairment of the body perceptions are experienced. He is trying to see how these systems (somatosensory, cognitive, motor systems) are plastic as a result of injury.

One of the most recent applications of neuroplasticity involves work done by a team of doctors and researchers at Emory University, specifically Dr. Donald Stein (who has been in the field for over three decades) and Dr. David Wright. This is the first treatment in 40 years that has significant results in treating traumatic brain injuries while also incurring no known side effects and being cheap to administer. Dr. Stein noticed that female mice seemed to recover from brain injuries better than male mice. Also in females, he noticed that at certain points in the estrus cycle females recovered even more. After lots of research, they attributed this difference due to the levels of progesterone. The highest level of progesterone present led to the fastest recovery of brain injury in these mice.

They developed a treatment that includes increased levels of progesterone injections to give to brain injured patients. "Administration of progesterone after traumatic brain injury (TBI) and stroke reduces edema, inflammation, and neuronal cell death, and enhance spatial reference memory and sensory motor recovery." In their clinical trials, they had a group of severely injured patients that after the three days of progesterone injections there was a 60% reduction in mortality. Sam* was in a horrific car accident that left him with marginal brain activity; according to the doctors, he was one point away from being brain dead. His parents decided to have him participate in Dr. Stein's clinical trial and he was given the three-day progesterone treatment. Three years after the accident, he had achieved an inspiring recovery with no brain complications and the ability to live a healthy, normal life.

Stein has done some studies in which beneficial effects have been seen to be similar in aged rats to those seen in youthful rats. As there are physiological differences in the two age groups, the model was tweaked for the elderly animals by reducing their stress levels with increased physical contact. During surgery, anesthesia was kept at a higher oxygen level with lower overall isoflurane percentage and "the aged animals were give subcutaneous lactated ringers solution post-surgery to replace fluids lost through increased bleeding." The promising results of progesterone treatments "could have a significant impact on the clinical management of TBI." These treatments have been shown to work on human patients who receive treatment soon after the TBI. However, Dr. Stein now focuses his research on those persons who have longstanding traumatic brain injury in order to determine if progesterone treatments will assist them in the recovery of lost functions as well.

Treatment of learning difficulties

Michael Merzenich developed a series of "plasticity-based computer programs known as Fast ForWord ." FastForWord offers seven brain exercises to help with the language and

learning deficits of dyslexia. In a recent study, experimental training was done in adults to see if it would help to counteract the negative plasticity that results from age-related cognitive decline (ARCD). The ET design included six exercises designed to reverse the dysfunctions caused by ARCD in cognition, memory, motor control, and so on . After use of the ET program for 8–10 weeks, there was a "significant increase in task-specific performance." The data collected from the study indicated that a brain plasticity-based program could notably improve cognitive function and memory in adults with ARCD.

Brain plasticity during operation of brain-machine interfaces

Brain-machine interface (BMI) is a rapidly developing field of neuroscience. According to the results obtained by Mikhail Lebedev, Miguel Nicolelis and their colleagues, operation of BMIs results in incorporation of artificial actuators into brain representations. The scientists showed that modifications in neuronal representation of the monkey's hand and the actuator that was controlled by the monkey brain occurred in multiple cortical areas while the monkey operated a BMI. In these single day experiments, monkeys initially moved the actuator by pushing a joystick. After mapping out the motor neuron ensembles, control of the actuator was switched to the model of the ensembles so that the brain activity, and not the hand, directly controlled the actuator. The activity of individual neurons and neuronal populations became less representative of the animal's hand movements while representing the movements of the actuator. Presumably as a result of this adaptation, the animals could eventually stop moving their hands yet continue to operate the actuator. Thus, during BMI control, cortical ensembles plastically adapt, within tens of minutes, to represent behaviorally significant motor parameters, even if these are not associated with movements of the animal's own limb.

Active laboratory groups include those of John Donoghue at Brown, Richard Andersen at Caltech, Krishna Shenoy at Stanford, Nicholas Hatsopoulos of University of Chicago, Andy Schwartz at University of Pittsburgh, Sandro Mussa-Ivaldi at Northwestern and Miguel Nicolelis at Duke. Donoghue and Nicolelis' groups have independently shown that animals can control external interfaces in tasks requiring feedback, with models based on activity of cortical neurons, and that animals can adaptively change their minds to make the models work better. Donoghue's group took the implants from Richard Normann's lab at Utah (the "Utah" array), and improved it by changing the insulation from polyimide to parylene-c, and commercialized it through the company Cyberkinetics. These efforts are the leading candidate for the first human trials on a broad scale for motor cortical implants to help quadriplegic or locked-in patients communicate with the outside world.

Phantom limbs
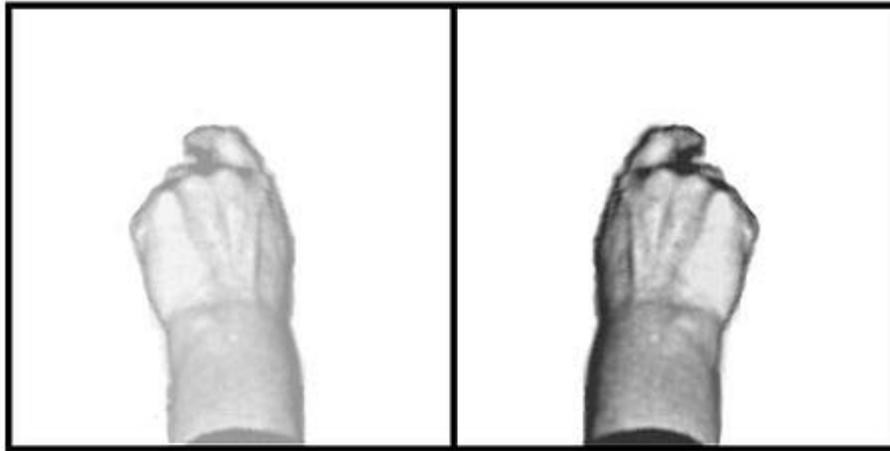
A diagrammatic explanation of the mirror box. The patient places the good limb into one side of the box (in this case the right hand) and the amputated limb into the other side. Due to the mirror, the patient sees a reflection of the good hand where the missing limb would be (indicated in lower contrast). The patient thus receives artificial visual feedback that the "resurrected" limb is now moving when they move the good hand.

Phantom limbs are phenomena in which a person continues to feel pain or sensation within a part of their body which has been amputated. An explanation for this refers to the concept of neuroplasticity, as the cortical maps of the removed limbs are believed to have become engaged with the area around them in the postcentral gyrus. This results in activity within the surrounding area of the cortex being misinterpreted by the area of the cortex formerly responsible for the amputated limb. Pain is often experienced due to the

association of this area with the pain that may have been experienced by the limb before it was amputated. Much of this was discovered by neuroscientist Vilayanur S. Ramachandran, who also developed a method of treatment for it called a mirror box, again using neuroplasticity to remove the association of the limb with the surrounding cortex by providing visual feedback to make it appear that the limb is responding.

Meditation

A number of studies have linked meditation practice to differences in cortical thickness or density of gray matter. One of the most well-known studies to demonstrate this was led by Sara Lazar, from Harvard University, in 2000. Richard Davidson, a neuroscientist at the University of Wisconsin, has led experiments in cooperation with the Dalai Lama on effects of meditation on the brain. His results suggest that long-term, or short-term practice of meditation results in different levels of activity in brain regions associated with such qualities as attention, anxiety, depression, fear, anger, the ability of the body to heal itself, and so on. These functional changes may be caused by changes in the physical structure of the brain.

Fitness and Exercise

"In the study, scientists had two groups of mice swim a water maze and in a separate trial had them endure an unpleasant stimulus to see how quickly they would learn to move away from it. For the next four weeks they allowed one group of mice to run inside their rodent wheels, an activity most mice enjoy, while requiring the other group to push harder on minitreadmills at a speed and duration controlled by the scientists. They then tested both groups again to track their learning skills and memory. Both groups of mice performed admirably in the water maze, bettering their performances from the earlier trial. But only the treadmill runners were better in the avoidance task, a skill that, according to brain scientists, demands a more complicated cognitive response.

The mice who raced on the treadmills showed evidence of molecular changes in several portions of their brains when viewed under a microscope, while the voluntary wheel-runners had changes in only one area. "Our results support the notion that different forms of exercise induce neuroplasticity changes in different brain regions," Chauying J. Jen, a professor of physiology and an author of the study, says."

Chapter 7

Cultured Neuronal Network

A **cultured neuronal network** is a cell culture of neurons that is used as a model to study the central nervous system, especially the brain. Often, cultured neuronal networks are connected to an input/output device such as a multi-electrode array (MEA), thus allowing two-way communication between the researcher and the network. This model has proved to be an invaluable tool to scientists studying the underlying principles behind neuronal learning, memory, plasticity, connectivity, and information processing.

Cultured neurons are often connected via computer to a real or simulated robotic component, creating a hybrot or animat, respectively. Researchers can then thoroughly study learning and plasticity in a realistic context, where the neuronal networks are able to interact with their environment and receive at least some artificial sensory feedback. One example of this can be seen in the Multielectrode Array Art (MEART) system developed by the Potter Research Group at the Georgia Institute of Technology in collaboration with the Symbi-oticA Research Group at the University of Western Australia. Another example can be seen in the neurally controlled animat.

Use as a Model

Advantages

The use of cultured neuronal networks as a model for their *in vivo* counterparts has been an indispensable resource for decades. It allows researchers to investigate neuronal activity in a much more controlled environment than would be possible in a live organism. Through this mechanism researchers have gleaned important information about the mechanisms behind learning and memory.

A cultured neuronal network allows researchers to observe neuronal activity from several vantage points. Electrophysiological recording and stimulation can take place either across the network or locally via an MEA, and the network development can be visually observed using microscopy techniques. Moreover, chemical analysis of the neurons and their environment is more easily accomplished than in an *in vivo* setting.

Disadvantages

Cultured neuronal networks are by definition disembodied cultures of neurons. Thus by being outside their natural environment, the neurons are influenced in ways that are not biologically normal. Foremost among these abnormalities is the fact that the neurons are usually harvested as neural stem cells from an embryo and are therefore disrupted at a critical stage in network development. When the neurons are suspended in solution and subsequently dispensed, the connections previously made are destroyed and new ones formed. Ultimately, the connectivity (and consequently the functionality) of the tissue is changed from what the original template suggested.

Another disadvantage lies in the fact that the cultured neurons lack a body and are thus severed from sensory input as well as the ability to express behavior – a crucial characteristic in learning and memory experiments. It is believed that such sensory deprivation has adverse effects on the development of these cultures and may result in abnormal patterns of behavior throughout the network.

Cultured networks on traditional MEAs are flat, single-layer sheets of cells with connectivity only two dimensions. Most *in vivo* neuronal systems, to the contrary, are large three-dimensional structures with much greater interconnectivity. This remains one of the most striking differences between the model and the reality, and this fact probably plays a large role in skewing some of the conclusions derived from experiments based on this model.

Growing a Neuronal Network

Neurons Used

Because of their wide availability, neuronal networks are typically cultured from dissociated rat neurons. Studies commonly employ rat cortical, hippocampal, and spinal neurons, although lab mouse neurons have also been used. Currently, relatively little research has been conducted on growing primate or other animal neuronal networks. Harvesting neural stem cells requires sacrificing the developing fetus, a process considered too costly to perform on many mammals that are valuable in other studies.

One study, however, did make use of human neural stem cells grown into a network to control a robotic actuator. These cells were acquired from a fetus that spontaneously aborted after ten weeks in gestation

Long-Term Culture

One of the most formidable problems associated with cultured neuronal networks is their lack of longevity. Like most cell cultures, neuron cultures are highly susceptible to infection. They are also susceptible to hyperosmolality from medium evaporation. The long timelines associated with studying neuronal plasticity (usually on the scale of months) makes extending the lifespan of neurons *in vitro* paramount.

One solution to this problem involves growing cells on an MEA inside a sealed chamber. This chamber serves as a non-humidified incubator that is enclosed by a fluorinated ethylene propylene (FEP) membrane that is permeable to select gases (i.e. gases necessary for metabolism) but impermeable to water and microbes. Other solutions entail an incubator with an impermeable membrane that has a specific mix of gases (air with 5% CO_2 is typical) sealed inside.

Multi-electrode Arrays (MEAs)

A multi-electrode array (MEA), also commonly called a microelectrode array, is a patterned array of electrodes laid out in a transparent substrate used for communication with neurons in contact with it. The communication can be, and usually is, bidirectional; researchers can both record electrophysiological data from a live network and stimulate it with a number of patterns.

This device has been an essential biosensor for more than thirty years. It has been used not only in the study of neuronal plasticity and information processing but also in drug and toxin effects on neurons. Additionally, when coupled with a sealed incubation chamber this device greatly reduces the risk of culture contamination by nearly eliminating the need to expose it to air.

Currently, commonly used MEAs have relatively poor spatial resolution. They employ approximately sixty electrodes for recording and stimulation in varying patterns in a dish with a typical culture of 50,000 cells or more (or a density of 5,000 cells/mm^2). It follows that each electrode in the array services a large cluster of neurons and cannot provide resolute information regarding signal origin and destination; such MEAs are only capable of region-specific data acquisition and stimulation.

Ideally it would be possible to record and stimulate from a single or a few neurons at a time. Indeed, companies such as Axion Biosystems are working to provide MEAs with much higher spatial resolution to this end (a maximum of 768 input/output electrodes). Another study investigates establishing a stable one-to-one connection between neurons and electrodes. The goal was to meet the ideal interface situation by establishing a correspondence with every neuron in the network. They do so by caging individual neurons while still allowing the axons and dendrites to extend and make connections. Neurons are contained within ''neurocages'', and the device itself is referred to as the caged neuron MEA or neurochip.

Other research suggests alternative techniques to stimulating neurons *in vitro*. One study investigates the use of a laser beam to free caged compounds such as neurotransmitters and neuromodulators. A laser beam with wavelength in the UV spectrum would have extremely high spatial accuracy and, by releasing the caged compounds, could be used to influence a very select set of neurons.

Network Behavior

Spontaneous Network Activity

Spontaneous network bursts are a commonplace feature of neuronal networks both *in vitro* and *in vivo*. *In vitro*, this activity is particularly important in studies on learning and plasticity. Such experiments look intensely at the network-wide activity both before and after experiments in order to discern any changes that might implicate plasticity or even learning. However, confounding this experimental technique is the fact that normal neuronal development induces change in array-wide bursts that could easily skew data. *In vivo*, however, it has been suggested that these network bursts may form the basis for memories.

Depending on experimental perspective, network-wide bursts can be viewed either positively or negatively. In a pathological sense, spontaneous network activity can be attributed to the disembodiment of the neurons; one study saw a marked difference between array-wide firing frequency in cultures that received continuous input versus those that did not. To eliminate abhorrent activity, researchers commonly use magnesium or synaptic blockers to quiet the network. However, this approach has great costs; quieted networks have little capacity for plasticity due to a diminished ability to create action potentials. A different and perhaps more effective approach is the use of low frequency stimulation that emulates sensory background activity.

In a different light, network bursts can be thought of as benign and even good. Any given network demonstrates non-random, structured bursts. Some studies have suggested that these bursts represent information carriers, expression of memory, a means for the network to form appropriate connections, and learning when their pattern changes.

Array-Wide Burst Stability

Stegenga et al. set out to establish the stability of spontaneous network bursts as a function of time. They saw bursts throughout the lifetime of the cell cultures, beginning at 4–7 days *in vitro* (DIV) and continuing until culture death. They gathered network burst profiles (BPs) through a mathematical observation of array-wide spiking rate (AWSR), which is the summation of action potentials over all electrodes in an MEA. This analysis yielded the conclusion that, in their culture of Wistar rat neocortical cells, the AWSR has long rise and fall times during early development and sharper, more intense profiles after approximately 25 DIV. However, the use of BPs has an inherent shortcoming; BPs are an average of all network activity over time, and therefore only contain temporal information. In order to attain data about the spatial pattern of network

activity they developed what they call phase profiles (PPs), which contain electrode specific data.

Data was gathered using these PPs on timescales of milliseconds up through days. . Their goal was to establish the stability of network burst profiles on the timescale of minutes to hours and to establish stability or developmental changes over the course of days. In summary, they were successful in demonstrating stability over minutes to hours, but the PPs gathered over the course of days displayed significant variability. These finding imply that studies of plasticity of neurons can only be conducted over the course of minutes or hours without bias in network activity introduced by normal development .

Learning vs. Plasticity

There is much controversy in the field of neuroscience surrounding whether or not a cultured neuronal network can learn. A crucial step in finding the answer to this problem lies in establishing the difference between learning and plasticity. One definition suggests that learning is "the acquisition of novel behavior through experience". Corollary to this argument is the necessity for interaction with the environment around it, something that cultured neurons are virtually incapable of without sensory systems. Plasticity, on the other hand, is simply the reshaping of an existing network by changing connections between neurons: formation and elimination of synapses or extension and retraction of neurites and dendritic spines. But these two definitions are not mutually exclusive; in order for learning to take place, plasticity must also take place.

In order to establish learning in a cultured network, researchers have attempted to re-embody the dissociated neuronal networks in either simulated or real environments. Through this method the networks are able to interact with their environment and, therefore, have the opportunity to learn in a more realistic setting. Other studies have attempted to imprint signal patterns onto the networks via artificial stimulation. This can be done by inducing network bursts or by inputing specific patterns to the neurons, from which the network is expected to derive some meaning (as in experiments with animats, where an arbitrary signal to the network indicates that the simulated animal has run into a wall or is moving in a direction, etc.). The latter technique attempts to take advantage of the inherent ability of neuronal networks to make sense of patterns. However, experiments have had limited success in demonstrating a definition of learning that is widely agreed upon. Nevertheless, plasticity in neuronal networks is a phenomenon that is well-established in the neuroscience community, and one that is thought to play a very large role in learning.

Chapter 8

Artificial Neural Network

An **artificial neural network (ANN)**, usually called **neural network (NN)**, is a mathematical model or computational model that is inspired by the structure and/or functional aspects of biological neural networks. A neural network consists of an interconnected group of artificial neurons, and it processes information using a connectionist approach to computation. In most cases an ANN is an adaptive system that changes its structure based on external or internal information that flows through the network during the learning phase. Modern neural networks are non-linear statistical data modeling tools. They are usually used to model complex relationships between inputs and outputs or to find patterns in data.
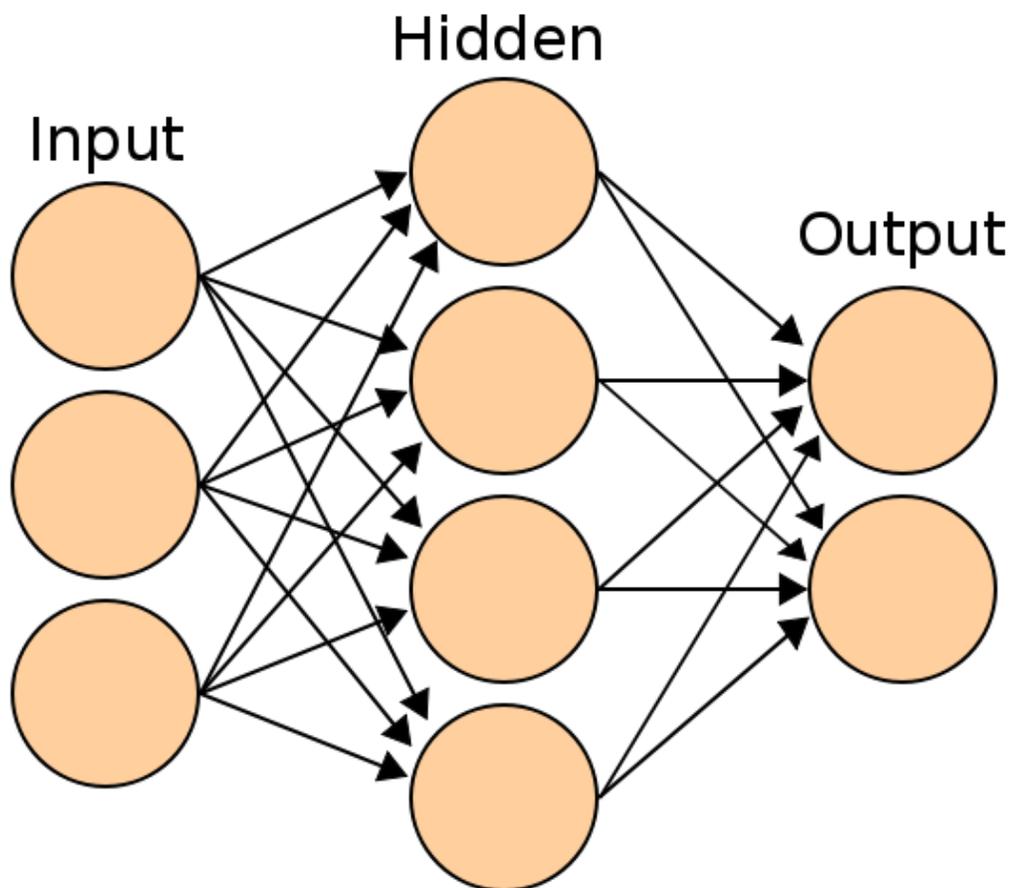
An artificial neural network is an interconnected group of nodes, akin to the vast network of neurons in the human brain.

Background

The original inspiration for the term *Artificial Neural Network* came from examination of central nervous systems and their neurons, axons, dendrites, and synapses, which constitute the processing elements of biological neural networks investigated by neuroscience. In an artificial neural network, simple artificial nodes, variously called "neurons", "neurodes", "processing elements" (PEs) or "units", are connected together to form a network of nodes mimicking the biological neural networks — hence the term "artificial neural network".

Because neuroscience is still full of unanswered questions, and since there are many levels of abstraction and therefore many ways to take inspiration from the brain, there is no single formal definition of what an artificial neural network is. Generally, it involves a network of simple processing elements that exhibit complex global behavior determined by connections between processing elements and element parameters. While an artificial neural network does not have to be adaptive per se, its practical use comes with algorithms designed to alter the strength (weights) of the connections in the network to produce a desired signal flow.

These networks are also similar to the biological neural networks in the sense that functions are performed collectively and in parallel by the units, rather than there being a clear delineation of subtasks to which various units are assigned. Currently, the term Artificial Neural Network (ANN) tends to refer mostly to neural network models employed in statistics, cognitive psychology and artificial intelligence. Neural network models designed with emulation of the central nervous system (CNS) in mind are a subject of theoretical neuroscience and computational neuroscience.

In modern software implementations of artificial neural networks, the approach inspired by biology has been largely abandoned for a more practical approach based on statistics and signal processing. In some of these systems, neural networks or parts of neural networks (such as artificial neurons) are used as components in larger systems that combine both adaptive and non-adaptive elements. While the more general approach of such adaptive systems is more suitable for real-world problem solving, it has far less to do with the traditional artificial intelligence connectionist models. What they do have in common, however, is the principle of non-linear, distributed, parallel and local processing and adaptation.

Models

Neural network models in artificial intelligence are usually referred to as artificial neural networks (ANNs); these are essentially simple mathematical models defining a function $f : X \rightarrow Y$ or a distribution over X or both X and Y, but sometimes models are also intimately associated with a particular learning algorithm or learning rule. A common use of the phrase ANN model really means the definition of a *class* of such functions (where members of the class are obtained by varying parameters, connection weights, or specifics of the architecture such as the number of neurons or their connectivity).

Network function

The word *network* in the term 'artificial neural network' refers to the inter–connections between the neurons in the different layers of each system. The most basic system has three layers. The first layer has input neurons, which send data via synapses to the second layer of neurons, and then via more synapses to the third layer of output neurons. More complex systems will have more layers of neurons with some having increased layers of input neurons and output neurons. The synapses store parameters called "weights" that manipulate the data in the calculations.

The layers network through the mathematics of the system algorithms. The network function $f(x)$ is defined as a composition of other functions $g_i(x)$, which can further be defined as a composition of other functions. This can be conveniently represented as a network structure, with arrows depicting the dependencies between variables. A widely used type of composition is the *nonlinear weighted sum*, where $f(x)=K\left(\sum_i w_i g_i(x)\right)$, where K (commonly referred to as the activation function) is some predefined function, such as the hyperbolic tangent. It will be convenient for the following to refer to a collection of functions g_i as simply a vector $g=(g_1, g_2, ..., g_n)$.
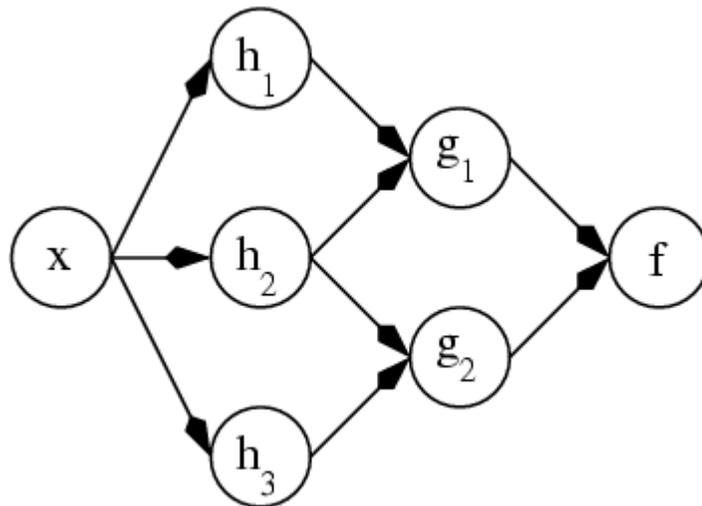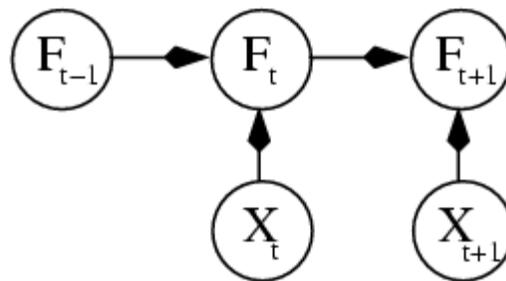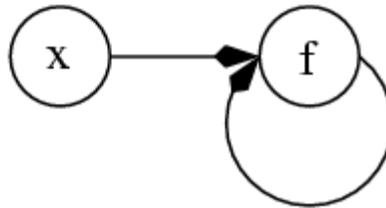

ANN dependency graph

This figure depicts such a decomposition of f, with dependencies between variables indicated by arrows. These can be interpreted in two ways.

The first view is the functional view: the input x is transformed into a 3-dimensional vector h, which is then transformed into a 2-dimensional vector g, which is finally transformed into f. This view is most commonly encountered in the context of optimization.

The second view is the probabilistic view: the random variable $F=f(G)$ depends upon the random variable $G=g(H)$, which depends upon $H=h(X)$, which depends upon the random variable X. This view is most commonly encountered in the context of graphical models.

The two views are largely equivalent. In either case, for this particular network architecture, the components of individual layers are independent of each other (e.g., the components of g are independent of each other given their input h). This naturally enables a degree of parallelism in the implementation.

Recurrent ANN dependency graph

Networks such as the previous one are commonly called feedforward, because their graph is a directed acyclic graph. Networks with cycles are commonly called recurrent. Such networks are commonly depicted in the manner shown at the top of the figure, where f is shown as being dependent upon itself. However, an implied temporal dependence is not shown. ANN depends on three basic critareas:

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- Interconnection between different Layers of Neurons;
- Learning process of ANN;
- Activation Function;
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Interconnection shows the relationship between single layer ,multiple layers of input output parameters of Neurons it shows the relationship of One to Many .it means same input can perform many outputs for different layer of architecture.

Learning

What has attracted the most interest in neural networks is the possibility of *learning*. Given a specific *task* to solve, and a *class* of functions, F, learning means using a set of *observations* to find $f^* \in F$ which solves the task in some *optimal* sense.

This entails defining a cost function $C : F \to \mathbb{R}$ such that, for the optimal solution f^*, $C(f^*) \leq C(f) \forall f \in F$ (i.e., no solution has a cost less than the cost of the optimal solution).

The cost function C is an important concept in learning, as it is a measure of how far away a particular solution is from an optimal solution to the problem to be solved. Learning algorithms search through the solution space to find a function that has the smallest possible cost.

For applications where the solution is dependent on some data, the cost must necessarily be a *function of the observations*, otherwise we would not be modelling anything related to the data. It is frequently defined as a statistic to which only approximations can be made. As a simple example, consider the problem of finding the model f, which minimizes $C = E\left[(f(x) - y)^2\right]$, for data pairs (x, y) drawn from some distribution $\mathcal{D}$. In practical situations we would only have N samples from $\mathcal{D}$ and thus, for the above example, we would only minimize $\hat{C} = \frac{1}{N} \sum_{i=1}^{N} (f(x_i) - y_i)^2$. Thus, the cost is minimized over a sample of the data rather than the entire data set.

When $N \to \infty$ some form of online machine learning must be used, where the cost is partially minimized as each new example is seen. While online machine learning is often used when $\mathcal{D}$ is fixed, it is most useful in the case where the distribution changes slowly over time. In neural network methods, some form of online machine learning is frequently used for finite datasets.

Choosing a cost function

While it is possible to define some arbitrary, ad hoc cost function, frequently a particular cost will be used, either because it has desirable properties (such as convexity) or because it arises naturally from a particular formulation of the problem (e.g., in a probabilistic formulation the posterior probability of the model can be used as an inverse cost). Ultimately, the cost function will depend on the desired task. An overview of the three main categories of learning tasks is provided below.

Learning paradigms

There are three major learning paradigms, each corresponding to a particular abstract learning task. These are supervised learning, unsupervised learning and reinforcement learning.

Supervised learning

In supervised learning, we are given a set of example pairs $(x,y), x \in X, y \in Y$ and the aim is to find a function $f: X \to Y$ in the allowed class of functions that matches the examples. In other words, we wish to *infer* the mapping implied by the data; the cost function is related to the mismatch between our mapping and the data and it implicitly contains prior knowledge about the problem domain.

A commonly used cost is the mean-squared error, which tries to minimize the average squared error between the network's output, f(x), and the target value y over all the example pairs. When one tries to minimize this cost using gradient descent for the class of neural networks called multilayer perceptrons, one obtains the common and well-known backpropagation algorithm for training neural networks.

Tasks that fall within the paradigm of supervised learning are pattern recognition (also known as classification) and regression (also known as function approximation). The supervised learning paradigm is also applicable to sequential data (e.g., for speech and gesture recognition). This can be thought of as learning with a "teacher," in the form of a function that provides continuous feedback on the quality of solutions obtained thus far.

Basically supervised learning are classified in two types. These are error connection gradient descent and stochastic.

Error connection gradient descent are also classified into least mean square and backpropagation.

Unsupervised learning

In unsupervised learning, some data x is given and the cost function to be minimized, that can be any function of the data x and the network's output, f.

The cost function is dependent on the task (what we are trying to model) and our *a priori* assumptions (the implicit properties of our model, its parameters and the observed variables).

As a trivial example, consider the model $f(x) = a$, where a is a constant and the cost $C = E[(x - f(x))^2]$. Minimizing this cost will give us a value of a that is equal to the mean of the data. The cost function can be much more complicated. Its form depends on the application: for example, in compression it could be related to the mutual information between x and y, whereas in statistical modeling, it could be related to the posterior probability of the model given the data. (Note that in both of those examples those quantities would be maximized rather than minimized).

Tasks that fall within the paradigm of unsupervised learning are in general estimation problems; the applications include clustering, the estimation of statistical distributions, compression and filtering.

Reinforcement learning

In reinforcement learning, data x are usually not given, but generated by an agent's interactions with the environment. At each point in time t, the agent performs an action y_t and the environment generates an observation x_t and an instantaneous cost c_t, according to some (usually unknown) dynamics. The aim is to discover a *policy* for selecting actions that minimizes some measure of a long-term cost; i.e., the expected cumulative cost. The environment's dynamics and the long-term cost for each policy are usually unknown, but can be estimated.

More formally, the environment is modeled as a Markov decision process (MDP) with states $s_1,...,s_n \in S$ and actions $a_1,...,a_m \in A$ with the following probability distributions: the instantaneous cost distribution $P(c_t|s_t)$, the observation distribution $P(x_t|s_t)$ and the transition $P(s_{t+1}|s_t,a_t)$, while a policy is defined as conditional distribution over actions given the observations. Taken together, the two define a Markov chain (MC). The aim is to discover the policy that minimizes the cost; i.e., the MC for which the cost is minimal.

ANNs are frequently used in reinforcement learning as part of the overall algorithm.

Tasks that fall within the paradigm of reinforcement learning are control problems, games and other sequential decision making tasks.

Learning algorithms

Training a neural network model essentially means selecting one model from the set of allowed models (or, in a Bayesian framework, determining a distribution over the set of allowed models) that minimizes the cost criterion. There are numerous algorithms available for training neural network models; most of them can be viewed as a straightforward application of optimization theory and statistical estimation. Recent developments in this field use particle swarm optimization and other swarm intelligence techniques.

Most of the algorithms used in training artificial neural networks employ some form of gradient descent. This is done by simply taking the derivative of the cost function with respect to the network parameters and then changing those parameters in a gradient-related direction.

Evolutionary methods, simulated annealing, expectation-maximization and non-parametric methods are some commonly used methods for training neural networks.

Temporal perceptual learning relies on finding temporal relationships in sensory signal streams. In an environment, statistically salient temporal correlations can be found by monitoring the arrival times of sensory signals. This is done by the perceptual network.

Employing artificial neural networks

Perhaps the greatest advantage of ANNs is their ability to be used as an arbitrary function approximation mechanism that 'learns' from observed data. However, using them is not so straightforward and a relatively good understanding of the underlying theory is essential.

- Choice of model: This will depend on the data representation and the application. Overly complex models tend to lead to problems with learning.
- Learning algorithm: There are numerous trade-offs between learning algorithms. Almost any algorithm will work well with the *correct hyperparameters* for training on a particular fixed data set. However selecting and tuning an algorithm for training on unseen data requires a significant amount of experimentation.
- Robustness: If the model, cost function and learning algorithm are selected appropriately the resulting ANN can be extremely robust.

With the correct implementation, ANNs can be used naturally in online learning and large data set applications. Their simple implementation and the existence of mostly local dependencies exhibited in the structure allows for fast, parallel implementations in hardware.

Applications

The utility of artificial neural network models lies in the fact that they can be used to infer a function from observations. This is particularly useful in applications where the complexity of the data or task makes the design of such a function by hand impractical.

Real-life applications

The tasks artificial neural networks are applied to tend to fall within the following broad categories:

- Function approximation, or regression analysis, including time series prediction, fitness approximation and modeling.
- Classification, including pattern and sequence recognition, novelty detection and sequential decision making.
- Data processing, including filtering, clustering, blind source separation and compression.
- Robotics, including directing manipulators, Computer numerical control.

Application areas include system identification and control (vehicle control, process control), quantum chemistry, game-playing and decision making (backgammon, chess, racing), pattern recognition (radar systems, face identification, object recognition and more), sequence recognition (gesture, speech, handwritten text recognition), medical diagnosis, financial applications (automated trading systems), data mining (or knowledge discovery in databases, "KDD"), visualization and e-mail spam filtering.

Neural networks and neuroscience

Theoretical and computational neuroscience is the field concerned with the theoretical analysis and computational modeling of biological neural systems. Since neural systems are intimately related to cognitive processes and behavior, the field is closely related to cognitive and behavioral modeling.

The aim of the field is to create models of biological neural systems in order to understand how biological systems work. To gain this understanding, neuroscientists strive to make a link between observed biological processes (data), biologically plausible mechanisms for neural processing and learning (biological neural network models) and theory (statistical learning theory and information theory).

Types of models

Many models are used in the field defined at different levels of abstraction and modeling different aspects of neural systems. They range from models of the short-term behavior of individual neurons, models of how the dynamics of neural circuitry arise from interactions between individual neurons and finally to models of how behavior can arise from abstract neural modules that represent complete subsystems. These include models of the long-term, and short-term plasticity, of neural systems and their relations to learning and memory from the individual neuron to the system level.

Current research

While initial research had been concerned mostly with the electrical characteristics of neurons, a particularly important part of the investigation in recent years has been the exploration of the role of neuromodulators such as dopamine, acetylcholine, and serotonin on behavior and learning.

Biophysical models, such as BCM theory, have been important in understanding mechanisms for synaptic plasticity, and have had applications in both computer science and neuroscience. Research is ongoing in understanding the computational algorithms used in the brain, with some recent biological evidence for radial basis networks and neural backpropagation as mechanisms for processing data.

Computational devices have been created in CMOS for both biophysical simulation and neuromorphic computing. More recent efforts show promise for creating nanodevices for very large scale principal components analyses and convolution. If successful, these effort could usher in a new era of neural computing that is a step beyond digital computing, because it depends on learning rather than programming and because it is fundamentally analog rather than digital even though the first instantiations may in fact be with CMOS digital devices.

Neural network software

Neural network software is used to simulate, research, develop and apply artificial neural networks, biological neural networks and in some cases a wider array of adaptive systems.

Types of artificial neural networks

Artificial neural network types vary from those with only one or two layers of single direction logic, to complicated multi–input many directional feedback loop and layers. On the whole, these systems use algorithms in their programming to determine control and organization of their functions. Some may be as simple, one neuron layer with an input and an output, and others can mimic complex systems such as dANN, which can mimic chromosomal DNA through sizes at cellular level, into artificial organisms and simulate reproduction, mutation and population sizes.

Most systems use "weights" to change the parameters of the throughput and the varying connections to the neurons. Artificial neural networks can be autonomous and learn by input from outside "teachers" or even self-teaching from written in rules.

Theoretical properties

Computational power

The multi-layer perceptron (MLP) is a universal function approximator, as proven by the Cybenko theorem. However, the proof is not constructive regarding the number of neurons required or the settings of the weights.

Work by Hava Siegelmann and Eduardo D. Sontag has provided a proof that a specific recurrent architecture with rational valued weights (as opposed to full precision real number-valued weights) has the full power of a Universal Turing Machine using a finite number of neurons and standard linear connections. They have further shown that the use of irrational values for weights results in a machine with super-Turing power.

Capacity

Artificial neural network models have a property called 'capacity', which roughly corresponds to their ability to model any given function. It is related to the amount of information that can be stored in the network and to the notion of complexity.

Convergence

Nothing can be said in general about convergence since it depends on a number of factors. Firstly, there may exist many local minima. This depends on the cost function and the model. Secondly, the optimization method used might not be guaranteed to converge when far away from a local minimum. Thirdly, for a very large amount of data

or parameters, some methods become impractical. In general, it has been found that theoretical guarantees regarding convergence are an unreliable guide to practical application.

Generalization and statistics

In applications where the goal is to create a system that generalizes well in unseen examples, the problem of over-training has emerged. This arises in convoluted or over-specified systems when the capacity of the network significantly exceeds the needed free parameters. There are two schools of thought for avoiding this problem: The first is to use cross-validation and similar techniques to check for the presence of overtraining and optimally select hyperparameters such as to minimize the generalization error. The second is to use some form of *regularization*. This is a concept that emerges naturally in a probabilistic (Bayesian) framework, where the regularization can be performed by selecting a larger prior probability over simpler models; but also in statistical learning theory, where the goal is to minimize over two quantities: the 'empirical risk' and the 'structural risk', which roughly corresponds to the error over the training set and the predicted error in unseen data due to overfitting.
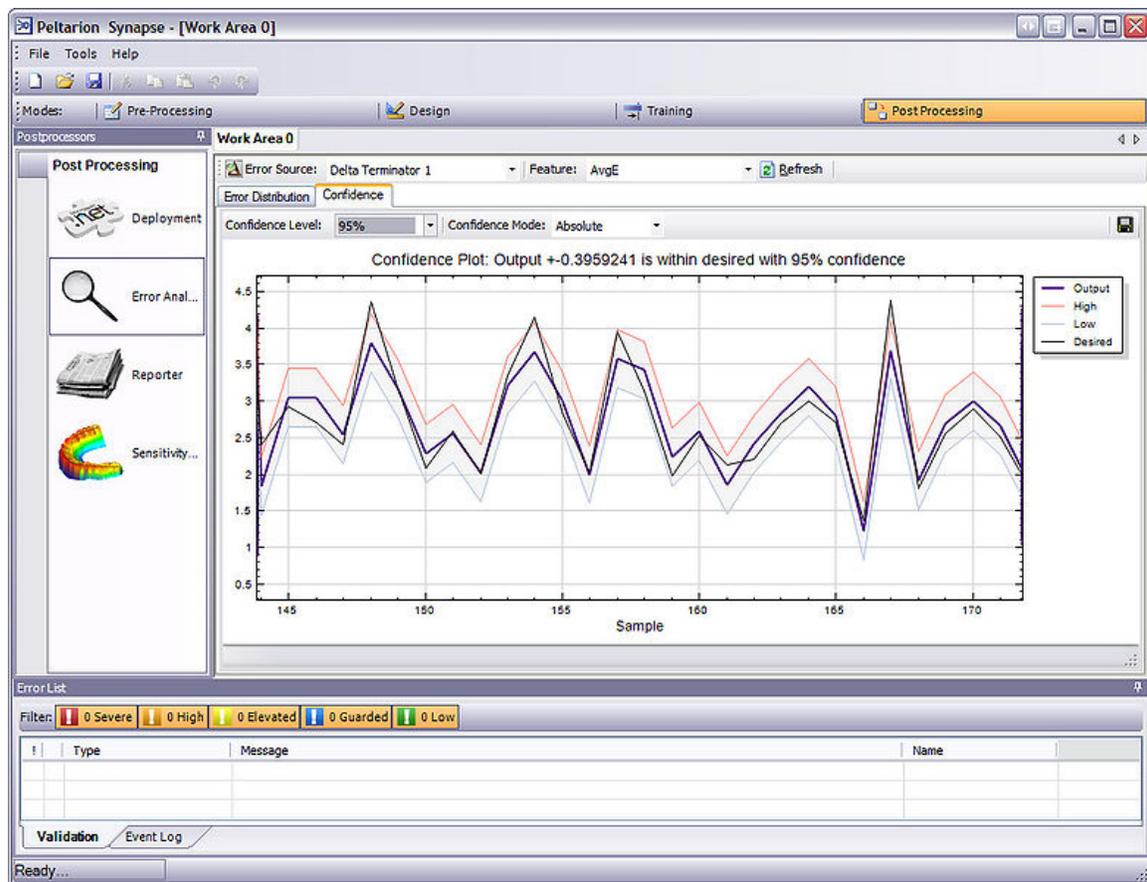
Confidence analysis of a neural network

Supervised neural networks that use an MSE cost function can use formal statistical methods to determine the confidence of the trained model. The MSE on a validation set can be used as an estimate for variance. This value can then be used to calculate the confidence interval of the output of the network, assuming a normal distribution. A confidence analysis made this way is statistically valid as long as the output probability distribution stays the same and the network is not modified.

By assigning a softmax activation function on the output layer of the neural network (or a softmax component in a component-based neural network) for categorical target variables, the outputs can be interpreted as posterior probabilities. This is very useful in classification as it gives a certainty measure on classifications.

The softmax activation function is:

$$y_i = \frac{e^{x_i}}{\sum_{j=1}^{c} e^{x_j}}$$

Dynamic properties

Various techniques originally developed for studying disordered magnetic systems (i.e., the spin glass) have been successfully applied to simple neural network architectures, such as the Hopfield network. Influential work by E. Gardner and B. Derrida has revealed many interesting properties about perceptrons with real-valued synaptic weights, while later work by W. Krauth and M. Mezard has extended these principles to binary-valued synapses.

Criticism

A common criticism of artificial neural networks, particularly in robotics, is that they require a large diversity of training for real-world operation. Dean Pomerleau, in his research presented in the paper "Knowledge-based Training of Artificial Neural Networks for Autonomous Robot Driving," uses a neural network to train a robotic vehicle to drive on multiple types of roads (single lane, multi-lane, dirt, etc.). A large amount of his research is devoted to (1) extrapolating multiple training scenarios from a single training experience, and (2) preserving past training diversity so that the system does not become overtrained (if, for example, it is presented with a series of right turns – it should not learn to always turn right). These issues are common in neural networks that must decide from amongst a wide variety of responses.

A. K. Dewdney, a former *Scientific American* columnist, wrote in 1997, "Although neural nets do solve a few toy problems, their powers of computation are so limited that I am surprised anyone takes them seriously as a general problem-solving tool." (Dewdney, p. 82)

Arguments for Dewdney's position are that to implement large and effective software neural networks, much processing and storage resources need to be committed. While the

brain has hardware tailored to the task of processing signals through a graph of neurons, simulating even a most simplified form on Von Neumann technology may compel a NN designer to fill many millions of database rows for its connections - which can lead to abusive RAM and HD necessities. Furthermore, the designer of NN systems will often need to simulate the transmission of signals through many of these connections and their associated neurons - which must often be matched with incredible amounts of CPU processing power and time. While neural networks often yield *effective* programs, they too often do so at the cost of time and money *efficiency*.

Arguments against Dewdney's position are that neural nets have been successfully used to solve many complex and diverse tasks, ranging from autonomously flying aircraft to detecting credit card fraud. Technology writer Roger Bridgman commented on Dewdney's statements about neural nets:

Neural networks, for instance, are in the dock not only because they have been hyped to high heaven, (what hasn't?) but also because you could create a successful net without understanding how it worked: the bunch of numbers that captures its behaviour would in all probability be "an opaque, unreadable table...valueless as a scientific resource". In spite of his emphatic declaration that science is not technology, Dewdney seems here to pillory neural nets as bad science when most of those devising them are just trying to be good engineers. An unreadable table that a useful machine could read would still be well worth having.
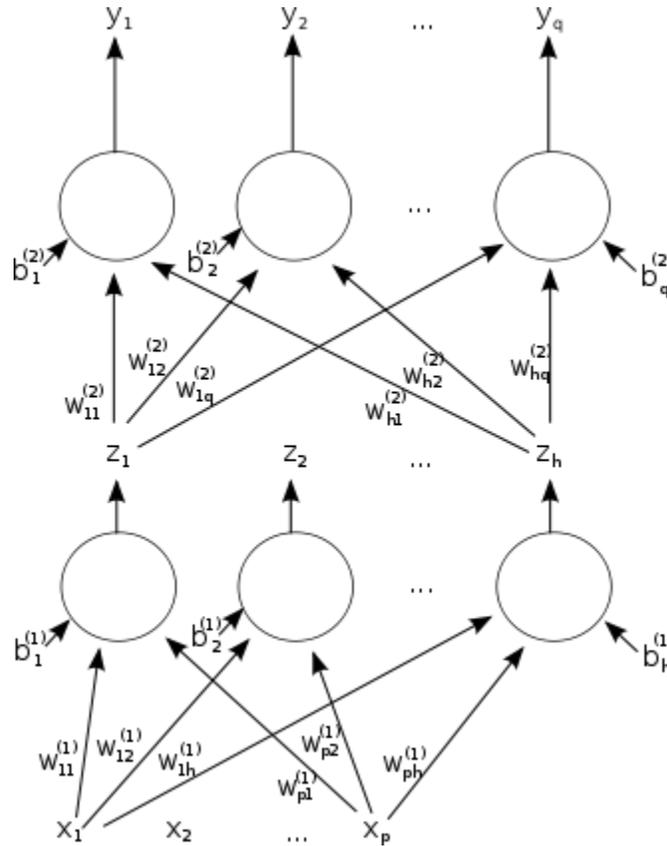
Some other criticisms came from believers of hybrid models (combining neural networks and symbolic approaches). They advocate the intermix of these two approaches and believe that hybrid models can better capture the mechanisms of the human mind (Sun and Bookman 1994).

Gallery
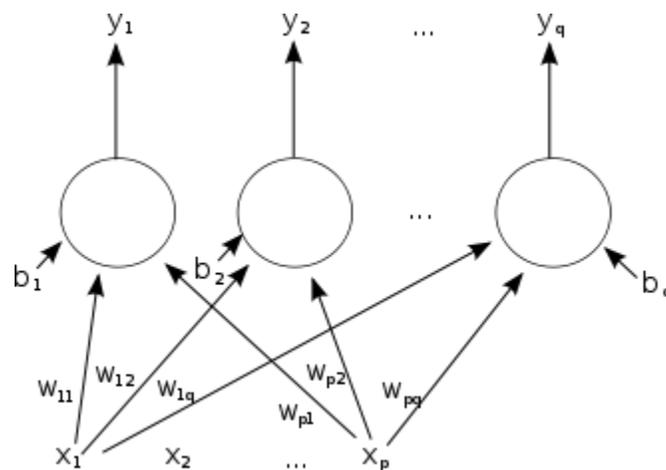
A single-layer feedforward artificial neural network. Arrows originating from x_2 are omitted for clarity. There are p inputs to this network and q outputs. There is no

activation function (or equivalently, the activation function is $g(x)=x$). In this system, the value of the qth output, y_q would be calculated as $y_q=\sum(x_i * w_{iq})$

A two-layer feedforward artificial neural network.