Biomedical Technology

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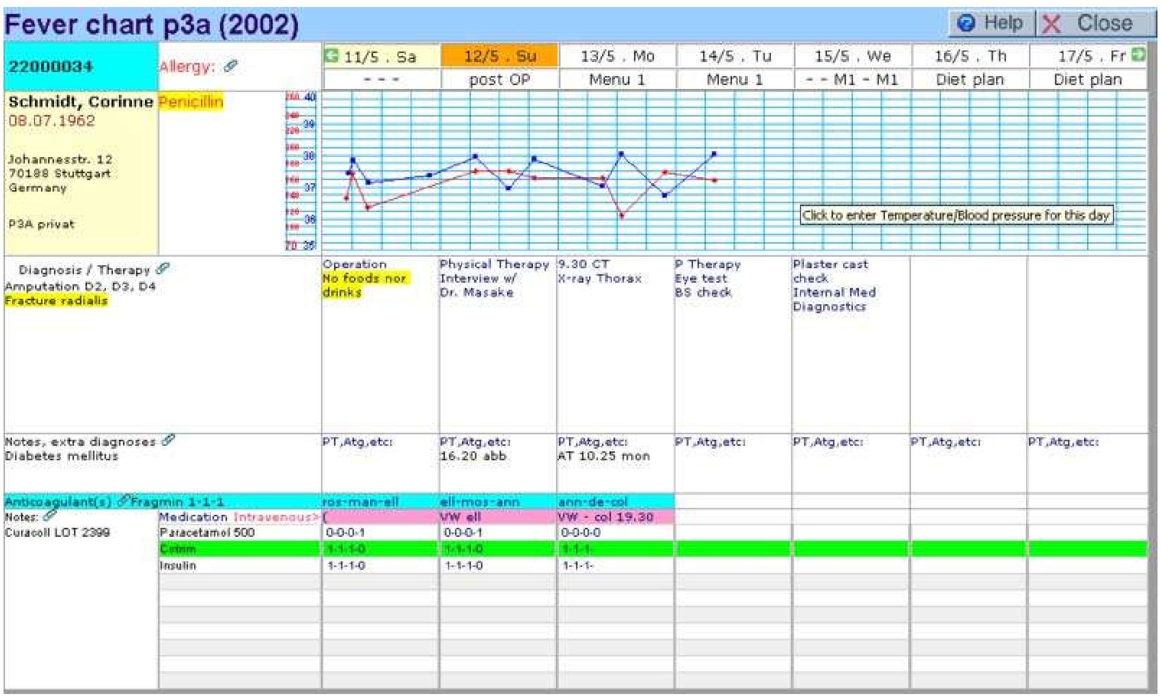
Health Informatics



Electronic patient chart from a health information system

Health informatics (also called **health care informatics**, **healthcare informatics**, **medical informatics**, **nursing informatics**, or **biomedical informatics**) is a discipline at the intersection of information science, computer science, and health care. It deals with the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health and biomedicine. Health informatics tools include not only computers but also clinical guidelines, formal medical terminologies, and information and communication systems. It is applied to the areas of nursing, clinical care, dentistry, pharmacy, public health, occupational therapy, and (bio)medical research.

- The international standards on the subject are covered by ICS 35.240.80 in which ISO 27799:2008 is one of the core components.
- Molecular bioinformatics and clinical informatics have converged into the field of translational bioinformatics.

History

Informatics were a central part of the Nazi health care system, which included Nazi eugenics as one of its fundamental principles. New systems and technology, like electronic punch card tabulating and sorting machines, and the science of medical statistics, were used to gather, sort, and analyze personal information on a vast scale unseen before in human history. The information was used to help find and eliminate the 'genetically inferior' through sterilization or wholesale murder. Many of the architects of these systems would go on to play a role in the post-war medical informatics field.

World wide use of technology in medicine began in the early 1950s with the rise of the computers. In 1949, Gustav Wager established the first professional organization for informatics in Germany. The prehistory, history, and future of medical information and health information technology are discussed in reference. Specialized university departments and Informatics training programs began during the 1960s in France, Germany, Belgium and The Netherlands. Medical informatics research units began to appear during the 1970s in Poland and in the U.S. Since then the development of high-quality health informatics research, education and infrastructure has been the goal of the U.S. and the European Union.

Early names for health informatics included medical computing, medical computer science, computer medicine, medical electronic data processing, medical automatic data processing, medical information processing, medical information science, medical software engineering, and medical computer technology.

The health informatics community is still growing, it is by no means a mature profession, but work in the UK by the voluntary registration body, the UK Council of Health Informatics Professions has suggested eight key constituencies within the domain - information management, knowledge management, portfolio/programme/project management, ICT, education and research, clinical informatics, health records(service and business-related), health informatics service management. These constituencies accommodate professionals in and for the NHS, in academia and commercial service and solution providers.

Since the 1970s the most prominent international coordinating body has been the International Medical Informatics Association (IMIA).

Medical informatics in the United States

Even though the idea of using computers in medicine sprouted as technology advanced in the early twentieth century, it was not until the 1950s that informatics made a realistic impact in the United States.

The earliest use of computation for medicine was for dental projects in the 1950s at the United States National Bureau of Standards by Robert Ledley.

The next step in the mid 1950s were the development of expert systems such as MYCIN and Internist-I. In 1965, the National Library of Medicine started to use MEDLINE and MEDLARS. At this time, Neil Pappalardo, Curtis Marble, and Robert Greenes developed MUMPS (Massachusetts General Hospital Utility Multi-Programming System) in Octo Barnett's Laboratory of Computer Science at Massachusetts General Hospital in Boston. In the 1970s and 1980s it was the most commonly used programming language for clinical applications. The MUMPS operating system was used to support MUMPS language specifications. As of 2004, a descendent of this system is being used in the United States Veterans Affairs hospital system. The VA has the largest enterprise-wide health information system that includes an electronic medical record, known as the Veterans Health Information Systems and Technology Architecture (VistA). A graphical user interface known as the Computerized Patient Record System (CPRS) allows health care providers to review and update a patient's electronic medical record at any of the VA's over 1,000 health care facilities.

In the 1970s a growing number of commercial vendors began to market practice management and electronic medical records systems. Although many products exist, only a small number of health practitioners use fully featured electronic health care records systems.

Homer R. Warner, one of the fathers of medical informatics, founded the Department of Medical Informatics at the University of Utah in 1968. The American Medical Informatics Association (AMIA) has an award named after him on application of informatics to medicine.

Current state of health informatics and policy initiatives

Americas

Argentina

Since 1997, the Buenos Aires Biomedical Informatics Group, a nonprofit group, represents the interests of a broad range of clinical and non-clinical professionals working within the Health Informatics sphere. Its purposes are:

- Promote the implementation of the computer tool in the healthcare activity, scientific research, health administration and in all areas related to health sciences and biomedical research.
- Support, promote and disseminate content related activities with the management of health information and tools they used to do under the name of Biomedical informatics.
- Promote cooperation and exchange of actions generated in the field of biomedical informatics, both in the public and private, national and international level.
- Interact with all scientists, recognized academic stimulating the creation of new instances that have the same goal and be inspired by the same purpose.
- To promote, organize, sponsor and participate in events and activities for training in computer and information and disseminating developments in this area that might be useful for team members and health related activities.

The Argentinian health system is very heterogeneous, because of that the informatics developments shows an heterogeneous stage. Lot of private Health Care center has develop system, as the German Hospital of Buenos Aires who was one of the first in develop the electronic health records system.

Brazil

The first applications of computers to medicine and healthcare in Brazil started around 1968, with the installation of the first mainframes in public university hospitals, and the use of programmable calculators in scientific research applications. Minicomputers, such as the IBM 1130 were installed in several universities, and the first applications were developed for them, such as the hospital census in the School of Medicine of Ribeirão Preto and patient master files, in the Hospital das Clínicas da Universidade de São Paulo, respectively at the cities of Ribeirão Preto and São Paulo campi of the University of São Paulo. In the 1970s, several Digital Corporation and Hewlett Packard minicomputers were acquired for public and Armed Forces hospitals, and more intensively used for intensive-care unit, cardiology diagnostics, patient monitoring amd other applications. In the early 1980s, with the arrival of cheaper microcomputers, a great upsurge of computer applications in health ensued, and in 1986 the Brazilian Society of Health Informatics was founded, the first Brazilian Congress of Health Informatics was held, and the first *Brazilian Journal of Health Informatics* was published.

Canada

Health Informatics projects in Canada are implemented provincially, with different provinces creating different systems. A national, federally-funded, not-for-profit organization called Canada Health Infoway was created in 2001 to foster the development and adoption of electronic health records across Canada. As of December 31, 2008 there were 276 EHR projects under way in Canadian hospitals, other health-care facilities, pharmacies and laboratories, with an investment value of $1.5-billion from Canada Health Infoway.

Provincial and territorial programmes include the following:

- **eHealth Ontario** was created as an Ontario provincial government agency in September 2008. It has been plagued by delays and its CEO was fired over a multimillion-dollar contracts scandal in 2009.
- **Alberta Netcare** was created in 2003 by the Government of Alberta. Today the netCARE portal is used daily by thousands of clinicians. It provides access to demographic data, prescribed/dispensed drugs, known allergies/intolerances, immunizations, laboratory test results, diagnostic imaging reports, the diabetes registry and other medical reports. netCARE interface capabilities are being included in electronic medical record products which are being funded by the provincial government.

United States

In 2004 the U.S. Department of Health and Human Services (HHS) formed the Office of the National Coordinator for Health Information Technology (ONCHIT). The mission of this office is widespread adoption of interoperable electronic health records (EHRs) in the US within 10 years.

The Certification Commission for Healthcare Information Technology (CCHIT), a private nonprofit group, was funded in 2005 by the U.S. Department of Health and Human Services to develop a set of standards for electronic health records (EHR) and supporting networks, and certify vendors who meet them. In July, 2006 CCHIT released its first list of 22 certified ambulatory EHR products, in two different announcements.

Europe

The European Union's Member States are committed to sharing their best practices and experiences to create a European eHealth Area, thereby improving access to and quality health care at the same time as stimulating growth in a promising new industrial sector. The European eHealth Action Plan plays a fundamental role in the European Union's strategy. Work on this initiative involves a collaborative approach among several parts of the Commission services. The European Institute for Health Records is involved in the promotion of high quality electronic health record systems in the European Union.

The NHS in England has contracted out to several vendors for a national health informatics system 'NPFIT' that originally divided the country into five regions and is to be united by a central electronic medical record system nicknamed "the spine". The project, in 2010, is seriously behind schedule and its scope and design are being revised in real time. In 2010 a wide consultation was launched as part of a wider 'Liberating the NHS' plan. Many organisations and bodies (look on their own websites, as most have made their responses public in detail for information) responded to the consultation and a new strategy is expected in the second quarter of 2011. The degree of computerisation in NHS secondary care was quite high before NPfIT and that programme has had the unfortunate effect of largely stalling further development of the installed base. Almost all general practices in England and Wales are computerised and patients have relatively extensive computerised primary care clinical records. Computerisation is the responsibility of individual practices and there is no single, standardised GP system. Interoperation between primary and secondary care systems is rather primitive. A focus on interworking (for interfacing and integration) standards is hoped will stimulate synergy between primary and secondary care in sharing necessary information to support the care of individuals. Scotland has an approach to central connection under way which is more advanced than the English one in some ways. Scotland has the GPASS system whose source code is owned by the State, and controlled and developed by NHS Scotland. GPASS was accepted in 1984. It has been provided free to all GPs in Scotland but has developed poorly. Discussion of open sourcing it as a remedy is occurring. The broad history of health informatics has been captured in the book UK Health Computing : Recollections and reflections, Hayes G, Barnett D (Eds.), BCS (May 2008) by those active in the field, predominantly members of BCS Health and its constituent groups. The book describes the path taken as ‘early development of health informatics was unorganized and idiosyncratic’. In the early -1950s it was prompted by those involved in NHS finance and only in the early 1960s did solutions including those in pathology (1960), radiotherapy (1962), immunization (1963), and primary care (1968) emerge. Many of these solutions, even in the early 1970s were developed in-house by pioneers in the field to meet their own requirements. In part this was due to some areas of health services (for example the immunization and vaccination of children) still being provided by Local Authorities. Interesting, this is a situation which the coalition government propose broadly to return to in the 2010 strategy Equity and Excellence: Liberating the NHS (July 2010); stating:

"We will put patients at the heart of the NHS, through an information revolution and greater choice and control’ with shared decision-making becoming the norm: ‘no decision about me without me’ and patients having access to the information they want, to make choices about their care. They will have increased control over their own care records."

These types of statements present a significant opportunity for health informaticians to come out of the back-office and take up a front-line role supporting clinical practice, and the business of care delivery. The UK health informatics community has long played a key role in international activity, joining TC4 of the International Federation of Information Processing (1969) which became IMIA (1979). Under the aegis of BCS Health, Cambridge was the host for the first EFMI Medical Informatics Europe (1974) conference and London was the location for IMIA’s tenth global congress (MEDINFO2001). In 2002, the idea of a profession of health informatics across the UK was first mooted and by 2004 a voluntary open register was established. The UK Council for Health Informatics Professions (UKCHIP) now has a formal Code of Professional Conduct, standards for expressing competences which are used for entry, confirmation of fitness to practice, re-grading and personal development. Consistent standards express competences of health informatics professionals in both domain-specific and generic informatics professional areas. The consistency is intended to apply in operational care delivery organizations, academia and the commercial service and solution providers. In

2011, self-assessment tools were introduced for use by any interested party. In addition, the principles and UKCHIP model are being considered internationally (as at 2011). UKCHIP certification is being considered for regulatory purposes. In conjunction with workforce development tools such as the NHS HI Career Framework it is possible for individuals to compare their skills against typical job roles, determine their professional level, and for employers to carry out detailed workforce analysis to meet the emerging requirements of the informatics strategies of all the home countries.

The European Commission's preference, as exemplified in the 5th Framework as well as currently pursued pilot projects, is for Free/Libre and Open Source Software (FLOSS) for healthcare.

Asia and Oceania

In Asia and Australia-New Zealand, the regional group called the Asia Pacific Association for Medical Informatics (APAMI) was established in 1994 and now consists of more than 15 member regions in the Asia Pacific Region.

Australia

The Australasian College of Health Informatics (ACHI) is the professional association for health informatics in the Asia-Pacific region. It represents the interests of a broad range of clinical and non-clinical professionals working within the health informatics sphere through a commitment to quality, standards and ethical practice. Founded in 2002, ACHI is increasingly valued for its thought leadership, its trusted advisors and national and international experts in Health Informatics. ACHI is an academic institutional member of the International Medical Informatics Association (IMIA) and a full member of the Australian Council of Professions. ACHI is a sponsor of the "e-Journal for Health Informatics", an indexed and peer-reviewed professional journal. ACHI has also supported the "Australian Health Informatics Education Council" (AHIEC) since its founding in 2009.

Although there are a number of health informatics organisations in Australia, the Health Informatics Society of Australia (HISA) is regarded as the major umbrella group and is a member of the International Medical Informatics Association (IMIA). Nursing informaticians were the driving force behind the formation of HISA, which is now a company limited by guarantee of the members. The membership comes from across the informatics spectrum that is from students to corporate affiliates. HISA has a number of branches (Queensland, New South Wales, Victoria and Western Australia) as well as special interest groups such as nursing (NIA), pathology, aged and community care, industry and medical imaging (Conrick, 2006).

China

Hong Kong

In Hong Kong a computerized patient record system called the Clinical Management System (CMS) has been developed by the Hospital Authority since 1994. This system has been deployed at all the sites of the Authority (40 hospitals and 120 clinics), and is used by all 30,000 clinical staff on a daily basis, with a daily transaction of up to 2 millions. The comprehensive records of 7 million patients are available on-line in the Electronic Patient Record (ePR), with data integrated from all sites. Since 2004 radiology image viewing has been added to the ePR, with radiography images from any HA site being available as part of the ePR.

The Hong Kong Hospital Authority placed particular attention to the governance of clinical systems development, with input from hundreds of clinicians being incorporated through a structured process. The Health Informatics Section in Hong Kong Hospital Authority has close relationship with Information Technology Department and clinicians to develop healthcare systems for the organization to support the service to all public hospitals and clinics in the region.

The Hong Kong Society of Medical Informatics (HKSMI) was established in 1987 to promote the use of information technology in healthcare. The eHealth Consortium has been formed to bring together clinicians from both the private and public sectors, medical informatics professionals and the IT industry to further promote IT in healthcare in Hong Kong.

India

Religare Technova IT solutions is attempting a new service to improve the healthcare information system in India

New Zealand

Health Informatics is taught at five New Zealand universities. The most mature and established is the Otago programme which has been offered for over a decade. Health Informatics New Zealand (HINZ) is the national organisation that advocates for Health Informatics.

Saudi Arabia

The Saudi Association for Health Information (SAHI) was established in 2006 to work under direct supervision of King Saud University for Health Sciences to practice public activities, develop theoretical and applicable knowledge, and provide scientific and applicable studies.

Health informatics law

Health informatics law deals with evolving and sometimes complex legal principles as they apply to information technology in health-related fields. It addresses the privacy, ethical and operational issues that invariably arise when electronic tools, information and media are used in health care delivery. Health Informatics Law also applies to all matters that involve information technology, health care and the interaction of information. It deals with the circumstances under which data and records are shared with other fields or areas that support and enhance patient care.

Clinical Informatics

Clinical Informatics is concerned with use information in health care by clinicians.

Clinical informaticians transform health care by analyzing, designing, implementing, and evaluating information and communication systems that enhance individual and population health outcomes, improve [patient] care, and strengthen the clinician-patient relationship. Clinical informaticians use their knowledge of patient care combined with their understanding of informatics concepts, methods, and health informatics tools to:

- assess information and knowledge needs of health care professionals and patients,
- characterize, evaluate, and refine clinical processes,
- develop, implement, and refine clinical decision support systems, and
- lead or participate in the procurement, customization, development, implementation, management, evaluation, and continuous improvement of clinical information systems.

Clinicians collaborate with other health care and information technology professionals to develop health informatics tools which promote patient care that is safe, efficient, effective, timely, patient-centered, and equitable.

Translational bioinformatics

With the completion of the human genome and the recent advent of high throughput sequencing and genome-wise association studies of single nucleotide polymorphisms, the fields of molecular bioinformatics, biostatistiques, statistical genetics and clinical informatics are converging into the emerging field of translational bioinformatics.

Chapter 2

Medical Research

Cell culture vials.

The University of Florida Cancer and Genetics Research Complex is one of the largest medical research facilities in the United States.

Biomedical research (or **experimental medicine**), in general simply known as **medical research**, is the basic research, applied research, or translational research conducted to aid and support the body of knowledge in the field of medicine. Medical research can be divided into two general categories: the evaluation of new treatments for both safety and efficacy in what are termed clinical trials, and all other research that contributes to the development of new treatments. The latter is termed preclinical research if its goal is specifically to elaborate knowledge for the development of new therapeutic strategies. A new paradigm to biomedical research is being termed translational research, which focuses on iterative feedback loops between the basic and clinical research domains to accelerate knowledge translation from the bedside to the bench, and back again.

The increased longevity of humans over the past century can be significantly attributed to advances resulting from medical research. Among the major benefits have been vaccines for measles and polio, insulin treatment for diabetes, classes of antibiotics for treating a host of maladies, medication for high blood pressure, improved treatments for AIDS, statins and other treatments for atherosclerosis, new surgical techniques such as microsurgery, and increasingly successful treatments for cancer. New, beneficial tests and treatments are expected as a result of the human genome project. Many challenges remain, however, including the appearance of antibiotic resistance and the obesity epidemic.

Most of the research in the field is pursued by biomedical scientists, however significant contributions are made by other biologists, as well as chemists and physicists.

Preclinical research

Preclinical research is research in basic science, which precedes the clinical trials, and is almost purely based on theory and animal experiments. Much of these experiments involve preclinical imaging modalities to aid *in vivo*, longitudinal studies.

New treatments come about as a result of other, earlier discoveries — often unconnected to each other, and in various fields. Sometimes the research is done for non-medical purposes, and only by accident contributes to the field of medicine (for example, the discovery of penicillin). Clinicians use these discoveries to create a treatment regimen, which is then tested in clinical trials.

Clinical trials

A clinical trial is a comparison test of a medication or other medical treatment, versus a placebo, other medications and devices, or the standard medical treatment for a patient's condition. Clinical trials vary greatly in size: from a single researcher in one hospital or clinic to an international multicenter trial with several hundred participating researchers on several continents. The number of patients tested can range from as few as a dozen to several thousands.

Every new drug formulation used in a clinical trial has to first undergo rigorous tests in a laboratory. Once the results from those tests confirm that the formulation is safe to be taken by humans, the drug is given to healthy volunteers in what are called Phase I clinical trials.

Funding

Research funding in many countries comes from research bodies which distribute money for equipment and salaries. In the UK, funding bodies such as the Medical Research Council derive their assets from UK tax payers, and distribute this to institutions in a competitive manner.

In the United States, the most recent data from 2003 suggest that about 94 billion dollars were provided for biomedical research in the United States. The National Institutes of Health and pharmaceutical companies collectively contribute 26.4 billion dollars and 27.0 billion dollars, respectively, which constitute 28% and 29% of the total, respectively. Other significant contributors include biotechnology companies (17.9 billion dollars, 19% of total), medical device companies (9.2 billion dollars, 10% of total), other federal sources, and state and local governments. Foundations and charities, led by the Bill and Melinda Gates Foundation, contributed about 3% of the funding.

In Australia, in 2000/01 (the most recent data available), about $1.7B was spent on biomedical research , with just under half ($800M, 47%) sourced from the Commonwealth government (all sources). About $540M came from business investments/funding and a further $220M from private or not-for-profit organisations (totalling 44%). The balance was from state and local governments. Since then there has been a significant in government funding through the National Health and Medical Research Council (NHMRC), whose expenditure on research was nearly $AUD700 million in 2008-09.

The enactment of orphan drug legislation in some countries has increased funding available to develop drugs meant to treat rare conditions, resulting in breakthroughs that previously were uneconomical to pursue.

Regulations and guidelines

Medical research is highly regulated. National regulatory authorities oversee and monitor medical research, such as for the development of new drugs. In the USA the Food and Drug Administration oversees new drug development, in Europe the European Medicines Agency and in Japan the Ministry of Health, Labour and Welfare (Japan). The World Medical Association develops the ethical standards for the medical profession, involved in medical research. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) works on the creation of rules and guidelines for the development of new medication, such as the guidelines for Good Clinical Practice (GCP). All ideas of regulation are based on a country's ethical standards code. This is why treatment of a particular disease in one country may not be allowed, but is in another.

Conflicts of interest

In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000, received 60% of the grants from pharmaceutical companies. In the U.S. researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.

Fields of research

Fields of biomedical research include:

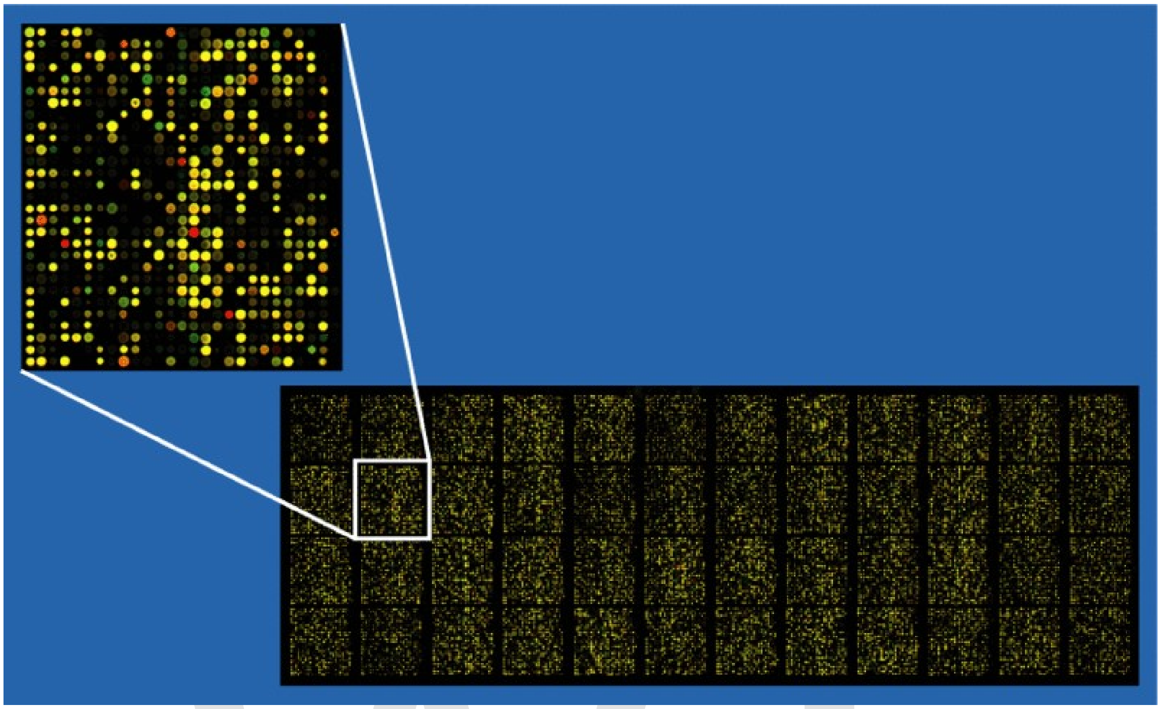
- Public Health
    - Epidemiology
    - Preventive medicine
    - Behavioral health
- Cancer
- Cellular biology
- Molecular biology
- Pharmacology
    - Psychopharmacology
- Neuroscience

- Aging
- Endocrinology
    - Neuroendocrinology
    - Diabetes
- Genetics
- Virology

Chapter 3

Biomedical Engineering

A JARVIK-7 artificial heart, an example of a biomedical engineering application of mechanical engineering with biocompatible materials for cardiothoracic surgery using an artificial organ.



Example of an approximately 40,000 probe spotted oligo microarray with enlarged inset to show detail.

Biomedical engineering is the application of engineering principles and techniques to the medical field. This field seeks to close the gap between **engineering** and **medicine**: It combines the design and problem solving skills of engineering with medical and biological sciences to improve healthcare diagnosis, monitoring and therapy.

Biomedical engineering has only recently emerged as its own discipline, compared to many other engineering fields; such an evolution is common as a new field transitions from being an interdisciplinary specialization among already-established fields, to being considered a field in itself. Much of the work in biomedical engineering consists of research and development, spanning a broad array of subfields (see below). Prominent biomedical engineering applications include the development of biocompatible prostheses, various diagnostic and therapeutic medical devices ranging from clinical equipment to micro-implants, common imaging equipment such as MRIs and EEGs, biotechnologies such as regenerative tissue growth, and pharmaceutical drugs and biopharmaceuticals.

Subdisciplines within biomedical engineering

Biomedical engineering is a highly interdisciplinary field, influenced by (and overlapping with) various other engineering and medical fields. This often happens with newer disciplines, as they gradually emerge in their own right after evolving from special applications of extant disciplines. Due to this diversity, it is typical for a biomedical engineer to focus on a particular subfield or group of related subfields. There are many different taxonomic breakdowns within BME, as well as varying views about how best to organize them and manage any internal overlap; the main U.S. organization devoted to BME divides the major specialty areas as follows:

- Biomechatronics
- Bioinstrumentation
- Biomaterials
- Biomechanics
- Bionics
- Cellular, Tissue, and Genetic Engineering
- Clinical Engineering
- Medical Imaging
- Orthopaedic Bioengineering
- Rehabilitation engineering
- Systems Physiology
- Bionanotechnology
- Neural Engineering

Sometimes, disciplines within BME are classified by their association(s) with other, more established engineering fields, which can include:

- Chemical engineering - often associated with biochemical, cellular, molecular and tissue engineering, biomaterials, and biotransport.
- Electrical engineering - often associated with bioelectrical and neural engineering, bioinstrumentation, biomedical imaging, and medical devices. This also tends to encompass Optics and Optical engineering - biomedical optics, imaging and related medical devices.
- Mechanical engineering - often associated with biomechanics, biotransport, medical devices, and modeling of biological systems, like soft tissue mechanics.

Biotechnology and pharmaceuticals

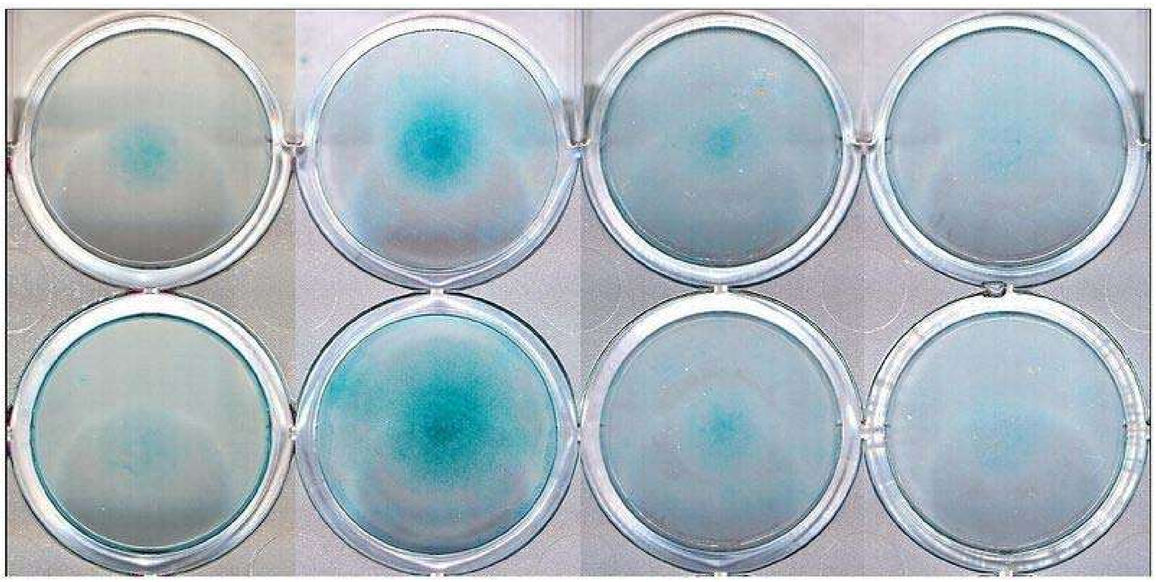
Biotechnology can be a somewhat ambiguous term, sometimes loosely used interchangeably with BME in general; however, it more typically denotes specific products which use "biological systems, living organisms, or derivatives thereof." Even some complex "medical devices" (see below) can reasonably be deemed "biotechnology" depending on the degree to which such elements are central to their principle of operation. Biologics/Biopharmaceuticals (e.g., vaccines, stored blood product), genetic engineering, and various agricultural applications are some major classes of biotechnology.

Pharmaceuticals are related to biotechnology in two indirect ways: 1) certain major types (e.g. biologics) fall under both categories, and 2) together they essentially comprise the "*non*-medical-device" set of BME applications. (The "Device - Bio/Chemical" spectrum is an imperfect dichotomy, but one regulators often use, at least as a starting point.)

Tissue engineering

Tissue engineering is a major segment of *Biotechnology*.

One of the goals of tissue engineering is to create artificial organs (via biological material) for patients that need organ transplants. Biomedical engineers are currently researching methods of creating such organs. Researchers have grown solid jawbones and tracheas from human stem cells towards this end. Several artificial urinary bladders actually have been grown in laboratories and transplanted successfully into human patients. Bioartificial organs, which use both synthetic and biological components, are also a focus area in research, such as with hepatic assist devices that use liver cells within an artificial bioreactor construct.



Micromass cultures of C3H-10T1/2 cells at varied oxygen tensions stained with Alcian blue.

Genetic Engineering

Genetic engineering, recombinant DNA technology, genetic modification/manipulation (GM) and gene splicing are terms that apply to the direct manipulation of an organism's genes. Genetic engineering is different from traditional breeding, where the organism's genes are manipulated indirectly. Genetic engineering uses the techniques of molecular cloning and transformation to alter the structure and characteristics of genes directly. Genetic engineering techniques have found success in numerous applications. Some examples are in improving crop technology, the manufacture of synthetic human insulin through the use of modified bacteria, the manufacture of erythropoietin in hamster ovary cells, and the production of new types of experimental mice such as the oncomouse (cancer mouse) for research.

Neural Engineering

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

Pharmaceutical engineering

Pharmaceutical Engineering is sometimes regarded as a branch of biomedical engineering, and sometimes a branch of chemical engineering; in practice, it is very much a hybrid sub-discipline (as many BME fields are). Aside from those pharmaceutical products directly incorporating biological agents or materials, even developing chemical drugs is considered to require substantial BME knowledge due to the physiological interactions inherent to such products' usage.

Medical devices

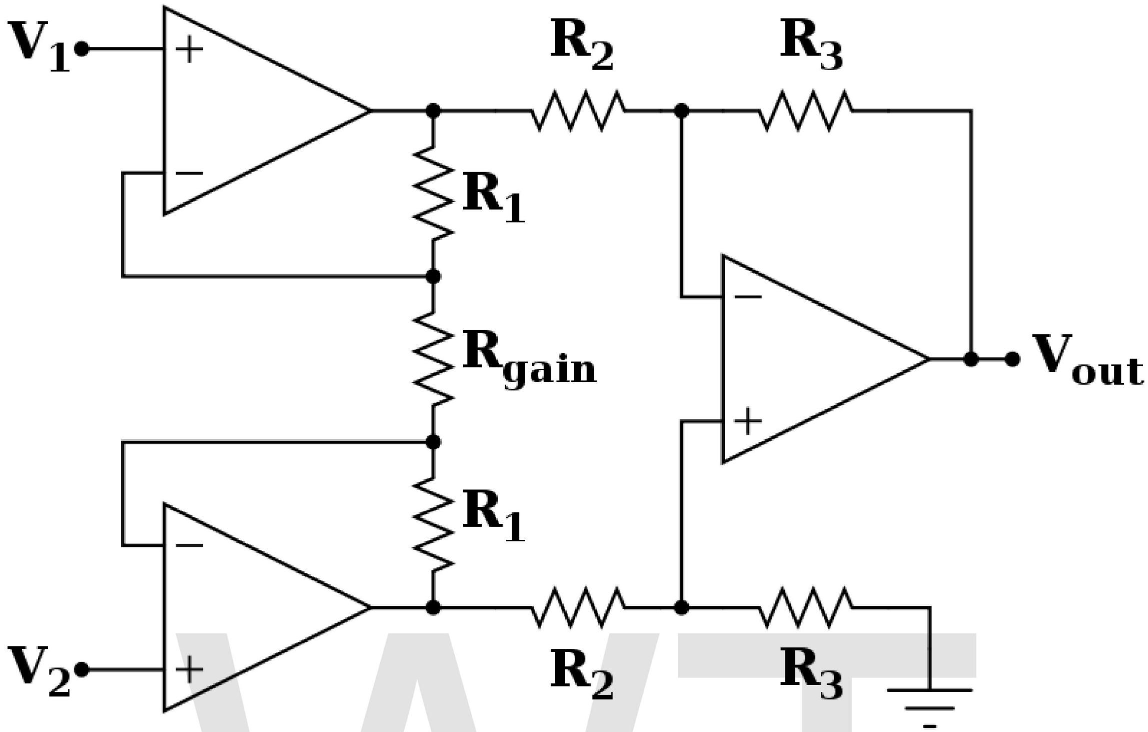
This is an *extremely broad category* -- essentially covering all health care products that do **not** achieve their intended results through predominantly chemical (e.g., pharmaceuticals) or biological (e.g., vaccines) means, and do not involve metabolism.

A medical device is intended for use in:

- the diagnosis of disease or other conditions, or
- in the cure, mitigation, treatment, or prevention of disease,

A pump for continuous subcutaneous insulin infusion, an example of a biomedical engineering application of electrical engineering to medical equipment.

Some examples include pacemakers, infusion pumps, the heart-lung machine, dialysis machines, artificial organs, implants, artificial limbs, corrective lenses, cochlear implants, ocular prosthetics, facial prosthetics, somato prosthetics, and dental implants.



Biomedical instrumentation amplifier schematic used in monitoring low voltage biological signals, an example of a biomedical engineering application of electronic engineering to electrophysiology.

Stereolithography is a practical example of *medical modeling* being used to create physical objects. Beyond modeling organs and the human body, emerging engineering techniques are also currently used in the research and development of new devices for innovative therapies, treatments, patient monitoring, and early diagnosis of complex diseases.

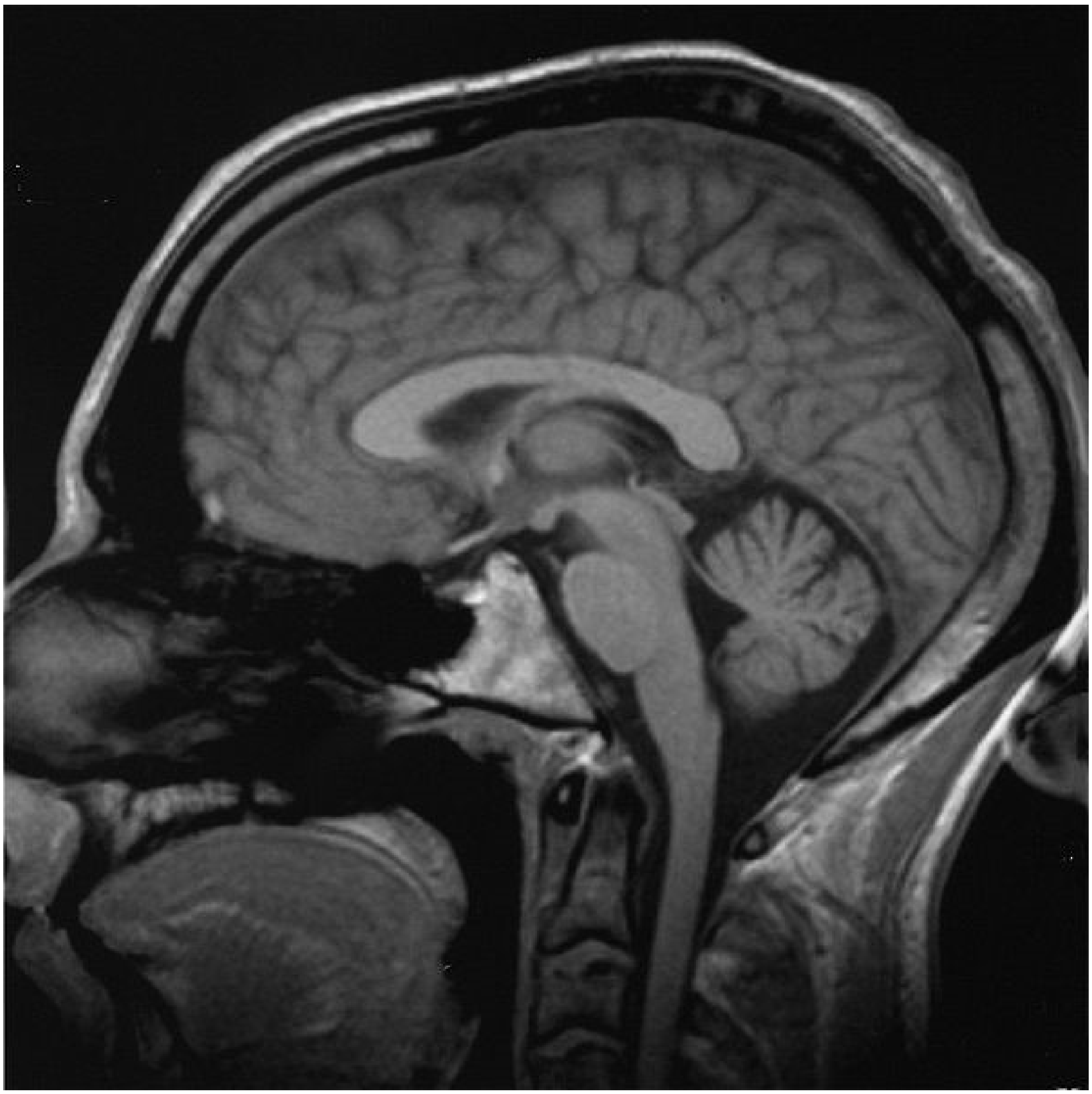
Medical devices are regulated and classified (in the US) as follows:

1. Class I devices present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Devices in this category include tongue depressors, bedpans, elastic bandages, examination gloves, and hand-held surgical instruments and other similar types of common equipment.
2. Class II devices are subject to special controls in addition to the general controls of Class I devices. Special controls may include special labeling requirements, mandatory performance standards, and postmarket surveillance. Devices in this class are typically non-invasive and include x-ray machines, PACS, powered wheelchairs, infusion pumps, and surgical drapes.
3. Class III devices generally require premarket approval (PMA) or premarket notification (510k), a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of Class I. Examples include replacement heart valves, hip and knee joint implants, silicone gel-filled breast

implants, implanted cerebellar stimulators, implantable pacemaker pulse generators and endosseous (intra-bone) implants.

Medical imaging

Medical/biomedical imaging is a major segment of medical devices. This area deals with enabling clinicians to directly or indirectly "view" things not visible in plain sight (such as due to their size, and/or location). This can involve utilizing ultrasound, magnetism, UV, other radiology, and other means.



An MRI scan of a human head, an example of a biomedical engineering application of electrical engineering to diagnostic imaging.

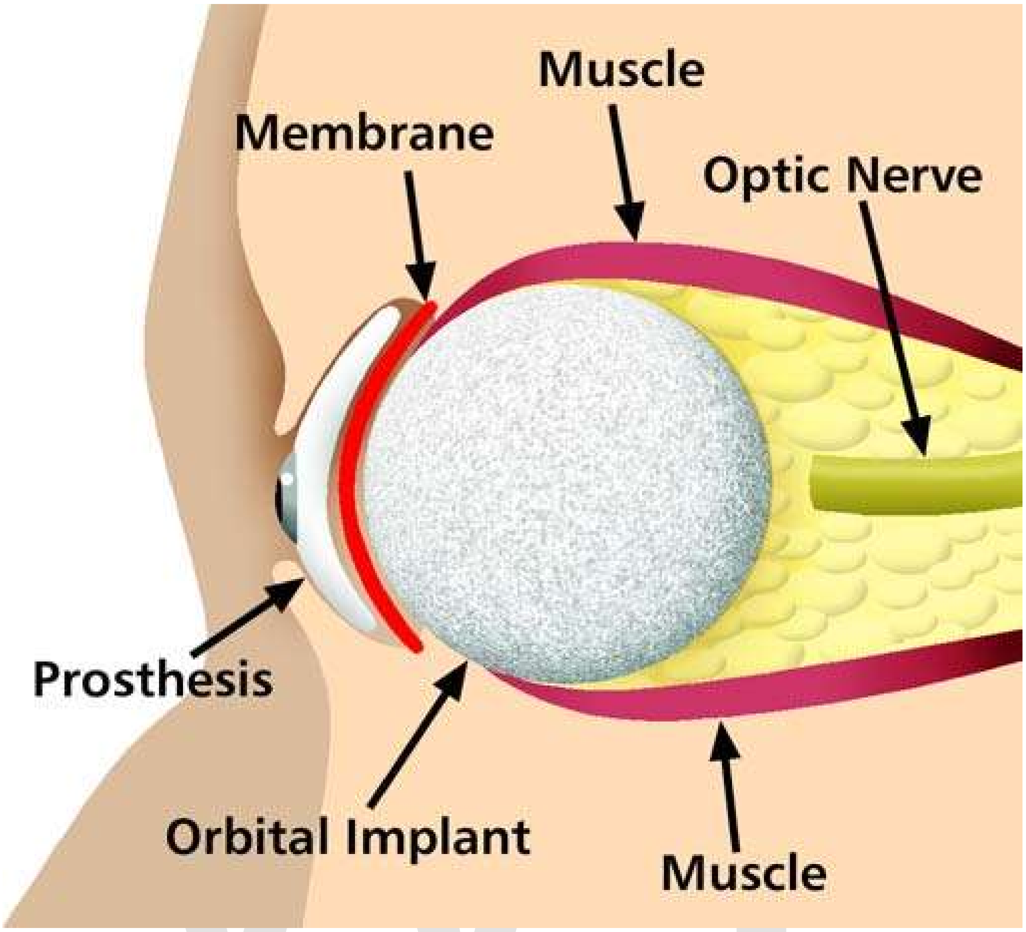
Imaging technologies are often essential to medical diagnosis, and are typically the most complex equipment found in a hospital including:

- Fluoroscopy
- Magnetic resonance imaging (MRI)
- Nuclear medicine
- Positron emission tomography (PET) PET scansPET-CT scans
- Projection radiography such as X-rays and CT scans
- Tomography
- Ultrasound
- Optical microscopy
- Electron microscopy

Implants

An implant is a kind of medical device made to replace and act as a missing biological structure (as compared with a transplant, which indicates transplanted biomedical tissue). The surface of implants that contact the body might be made of a biomedical material such as titanium, silicone or apatite depending on what is the most functional. In some cases implants contain electronics e.g. artificial pacemaker and cochlear implants. Some implants are bioactive, such as subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents.

Artificial limbs: The right arm is an example of a prosthesis, and the left arm is an example of myoelectric control.

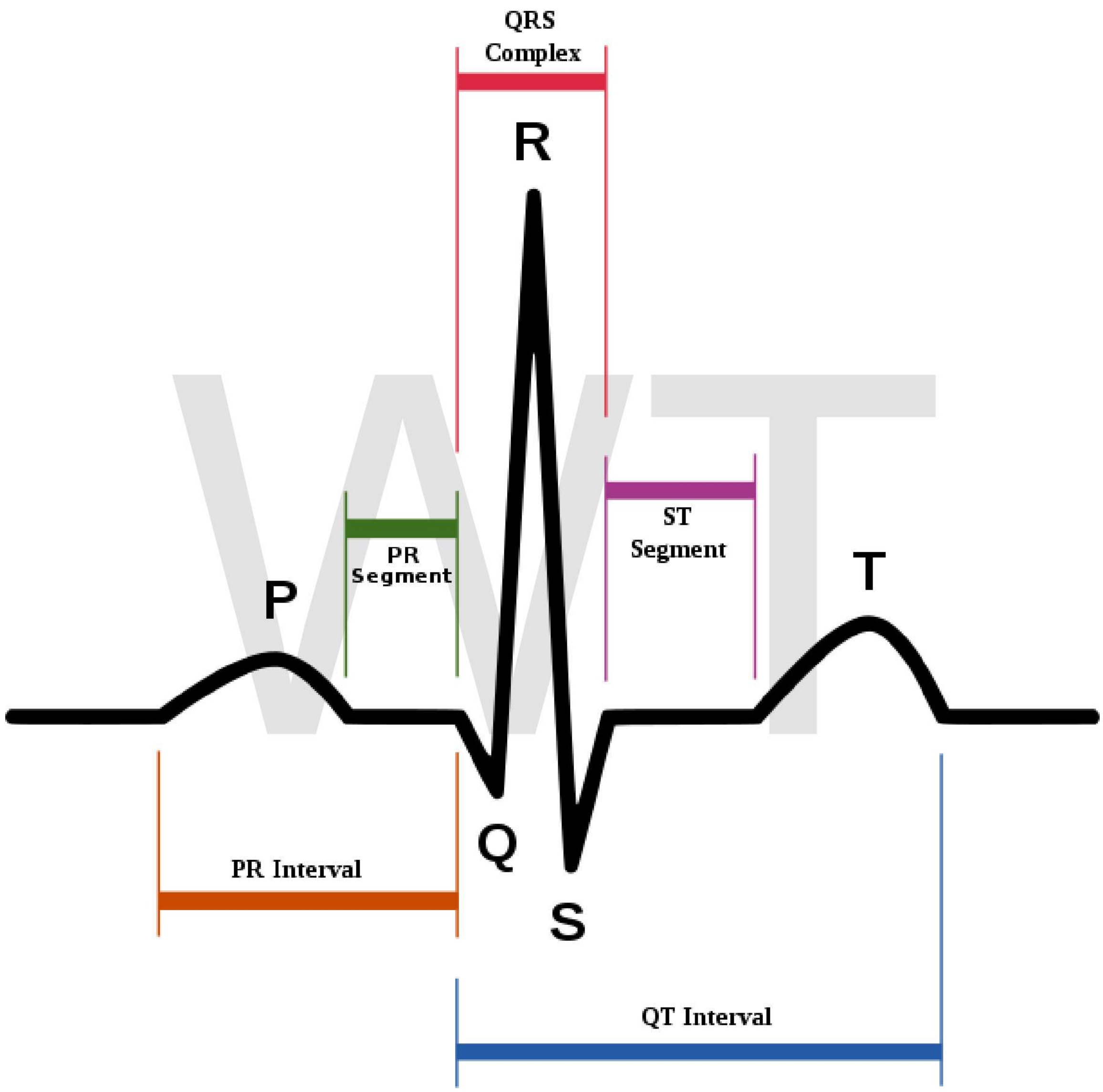


A prosthetic eye, an example of a biomedical engineering application of mechanical engineering and biocompatible materials to ophthalmology.

Clinical engineering

Clinical engineering is the branch of biomedical engineering dealing with the actual implementation of medical equipment and technologies in hospitals or other clinical settings. Major roles of clinical engineers include training and supervising biomedical equipment technicians (BMETs), selecting technological products/services and logistically managing their implementation, working with governmental regulators on inspections/audits, and serving as technological consultants for other hospital staff (e.g. physicians, administrators, I.T., etc.). Clinical engineers also advise and collaborate with medical device producers regarding prospective design improvements based on clinical experiences, as well as monitor the progression of the state-of-the-art so as to redirect procurement patterns accordingly.

Their inherent focus on *practical* implementation of technology has tended to keep them oriented more towards *incremental*-level redesigns and reconfigurations, as opposed to revolutionary research & development or ideas that would be many years from clinical adoption; however, there is a growing effort to expand this time-horizon over which clinical engineers can influence the trajectory of biomedical innovation. In their various roles, they form a "bridge" between the primary designers and the end-users, by combining the perspectives of being both 1) close to the point-of-use, while 2) trained in product and process engineering. Clinical Engineering departments will sometimes hire not just biomedical engineers, but also industrial/systems engineers to help address operations research/optimization, human factors, cost analysis, etc.



Schematic representation of a normal ECG trace showing *sinus rhythm;* an example of widely-used clinical medical equipment (operates by applying electronic engineering to electrophysiology and medical diagnosis.

A point of reference for clinical engineers would be the catalogue published by The American Society for Hospital Engineering in the Hospital Engineering Reference Series called Maintenance Management for Medical Equipment

Regulatory issues

Regulatory issues are of particular concern to a biomedical engineer; it is among the most heavily-regulated fields of engineering, and practicing biomedical engineers must routinely consult and cooperate with regulatory law attorneys and other experts. The Food and Drug Administration (FDA) is the principal healthcare regulatory authority in the United States, having jurisdiction over medical *devices, drugs, biologics, and combination* products. The paramount objectives driving policy decisions by the FDA are **safety** and **efficacy** of healthcare products.

In addition, because biomedical engineers often develop devices and technologies for "consumer" use, such as physical therapy devices (which are also "medical" devices), these may also be governed in some respects by the Consumer Product Safety Commission. The greatest hurdles tend to be 510K "clearance" (typically for Class 2 devices) or pre-market "approval" (typically for drugs and class 3 devices).

Implants, such as artificial hip joints, are generally extensively regulated due to the invasive nature of such devices.

Most countries have their own particular mechanisms for regulation, with varying formulations and degrees of restrictiveness. In most European countries, more discretion rests with the prescribing doctor, while the regulations chiefly assure that the product operates as expected. In European Union nations, the national governments license certifying agencies, which are for-profit companies. Technical committees of engineers write recommendations which incorporate public comments, and these can be adopted as regulations by the European Union. These recommendations vary by the type of device, and specify tests for safety and efficacy. Once a prototype has passed the tests at a certification lab, and that model is being constructed under the control of a certified quality system, the device is entitled to bear a CE mark, indicating that the device is believed to be safe and reliable when used as directed.

The different regulatory arrangements sometimes result in particular technologies being developed first for either the U.S. or in Europe depending on the more favorable form of regulation. While nations often strive for substantive harmony to facilitate cross-national distribution, philosophical differences about the *optimal extent* of regulation can be a hindrance; more restrictive regulations seem appealing on an intuitive level, but critics decry the tradeoff cost in terms of slowing access to life-saving developments.

Training and certification

Education

Biomedical engineers require considerable knowledge of both engineering and biology, and typically have a Master's (M.S., M.S.E., or M.Eng.) or a Doctoral (Ph.D.) degree in BME or another branch of engineering with considerable potential for BME overlap. As interest in BME is increasing, many engineering colleges now have a Biomedical Engineering Department or Program, with offerings ranging from the undergraduate (B.S. or B.S.E.) to the doctoral levels. As noted above, biomedical engineering has only recently been emerging as *its own discipline* rather than a cross-disciplinary hybrid specialization of other disciplines; now, BME programs of study at all levels are becoming more widespread, including the Bachelor of Science in Biomedical Engineering which actually includes so much biological science content that many students use it as a "pre-med" major in preparation for medical school. The number of biomedical engineers is expected to rise as both a cause and effect of improvements in medical technology.

In the U.S., an increasing number of undergraduate programs are also becoming recognized by ABET as accredited bioengineering/biomedical engineering programs. Over 65 programs are currently accredited by ABET.

As with many degrees, the reputation and ranking of a program may factor into the desirability of a degree holder for either employment or graduate admission. The reputation of many undergraduate degrees are also linked to the institution's graduate or research programs, which have some tangible factors for rating, such as research funding and volume, publications and citations. With BME specifically, the ranking of a university's hospital and medical school can also be a significant factor in the perceived prestige of its BME department/program.

Graduate education is a particularly important aspect in BME. While many engineering fields (such as mechanical or electrical engineering) do not need graduate-level training to obtain an entry-level job in their field, the majority of BME positions do prefer or even require them. Since most BME-related professions involve scientific research, such as in pharmaceutical and medical device development, graduate education is almost a requirement (as undergraduate degrees typically do not involve sufficient research training and experience). This can be either a **Masters** or **Doctoral** level degree; while in certain specialties a Ph.D. is notably more common than in others, it is hardly ever the majority (except in academia). In fact, the perceived need for some kind of graduate credential is so strong that some undergraduate BME programs will actively discourage students from majoring in BME without an expressed intention to also obtain a masters degree or apply to medical school afterwards.

Graduate programs in BME, like in other scientific fields, are highly varied, and particular programs may emphasize certain aspects within the field. They may also feature extensive collaborative efforts with programs in other fields (such as the University's Medical School or other engineering divisions), owing again to the interdisciplinary nature of BME. M.S. and Ph.D. programs will typically require applicants to have an undergraduate degree in BME, or *another engineering* discipline (plus certain life science coursework), or *life science* (plus certain engineering coursework).

Education in BME also varies greatly around the world. By virtue of its extensive biotechnology sector, its numerous major universities, and relatively few internal barriers, the U.S. has progressed a great deal in its development of BME education and training opportunities. Europe, which also has a large biotechnology sector and an impressive education system, has encountered trouble in creating uniform standards as the European community attempts to supplant some of the national jurisdictional barriers that still exist. Recently, initiatives such as BIOMEDEA have sprung up to develop BME-related education and professional standards. Other countries, such as Australia, are recognizing and moving to correct deficiencies in their BME education. Also, as high technology endeavors are usually marks of developed nations, some areas of the world are prone to slower development in education, including in BME.

Licensure/Certification

Engineering licensure in the US is largely optional, and rarely specified by branch/discipline. As with other learned professions, each state has certain (fairly similar) requirements for becoming licensed as a registered professional engineer (PE), but in practice such a license is not required to practice in the majority of situations (due to an exception known as the private industry exemption, which effectively applies to the vast majority of American engineers). This is notably not the case in many other countries, where a license is as legally necessary to practice engineering as it is for law or medicine.

Biomedical engineering is regulated in some countries, such as Australia, but registration is typically only recommended and not required.

In the UK, mechanical engineers working in the areas of Medical Engineering, Bioengineering or Biomedical engineering can gain Chartered Engineer status through the Institution of Mechanical Engineers. The Institution also runs the Engineering in Medicine and Health Division.

The Fundamentals of Engineering exam - the first (and more general) of two licensure examinations for most U.S. jurisdictions—does now cover biology (although technically not BME). For the second exam, called Part 2 or the Professional Engineering exam, candidates may select a particular engineering discipline's content to be tested on; there is currently not an option for BME with this, meaning that any biomedical engineers seeking a license must prepare to take this examination in another category (which does not affect the actual license, since most jurisdictions do not recognize discipline specialties anyway). However, the Biomedical Engineering Society (BMES) is, as of 2009, exploring the possibility of seeking to implement a BME-specific version of this exam to facilitate biomedical engineers pursuing licensure.

Beyond governmental registration, certain private-sector professional/industrial organizations also offer certifications with varying degrees of prominence. One such example is the Certified Clinical Engineer (CCE) certification for Clinical engineers.

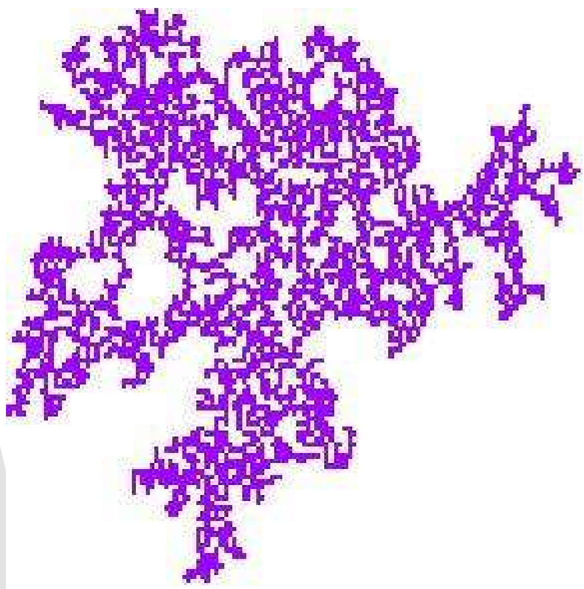
Founding figures

- Leslie Geddes (deceased)- Professor Emeritus at Purdue University, electrical engineer, inventor and educator of over 2000 biomedical engineers, received a National Medal of Technology in 2006 from President George Bush for his more than 50 years of contributions that have spawned innovations ranging from burn treatments to miniature defibrillators, ligament repair to tiny blood pressure monitors for premature infants, as well as a new method for performing cardiopulmonary resuscitation (CPR).
- Y. C. Fung - professor emeritus at the University of California, San Diego, considered by many to be the founder of modern Biomechanics
- Robert Langer - Institute Professor at MIT, runs the largest BME laboratory in the world, pioneer in drug delivery and tissue engineering
- Herbert Lissner (deceased) - Professor of Engineering Mechanics at Wayne State University. Initiated studies on blunt head trauma and injury thresholds beginning in 1939 in collaboration with Dr. E.S. Gurdjian, a neurosurgeon at Wayne State's School of Medicine. Individual for whom the American Society of Mechanical Engineers' top award in Biomedical Engineering, the Herbert R. Lissner Medal, is named.
- Nicholas A. Peppas - Chaired Professor in Engineering, University of Texas at Austin, pioneer in drug delivery, biomaterials, hydrogels and nanobiotechnology.
- Otto Schmitt (deceased) - biophysicist with significant contributions to BME, working with biomimetics

- Ascher Shapiro (deceased) - Institute Professor at MIT, contributed to the development of the BME field, medical devices (e.g. intra-aortic balloons)
- John G. Webster - Professor Emeritus at the University of Wisconsin–Madison, a pioneer in the field of instrumentation amplifiers for the recording of electrophysiological signals
- Robert Plonsey - Professor Emeritus at Duke University, pioneer of electrophysiology
- U. A. Whitaker (deceased) - provider of The Whitaker Foundation, which supported research and education in BME by providing over $700 million to various universities, helping to create 30 BME programs and helping finance the construction of 13 buildings
- Frederick Thurstone (deceased) - Professor Emeritus at Duke University, pioneer of diagnostic ultrasound
- Kenneth R. Diller - Chaired and Endowed Professor in Engineering, University of Texas at Austin. Founded the BME department at UT Austin. Pioneer in bioheat transfer, mass transfer, and biotransport
- Alfred E. Mann - Physicist, entrepreneur and philanthropist. A pioneer in the field of Biomedical Engineering.
- Forrest Bird - aviator and pioneer in the invention of mechanical ventilators
- Willem Johan Kolff (deceased) - pioneer of hemodialysis as well as in the field of artificial organs
- Medical device

Chapter 4

Biological Engineering



Modeling of the spread of disease using Cellular Automata and Nearest Neighbor Interactions

Biological engineering, **biotechnological engineering** or **bioengineering** (including **biological systems engineering**) is the application of concepts and methods of physics, chemistry, and mathematics to solve problems in life sciences, using engineering's own analytical and synthetic methodologies. In this context, while traditional engineering applies physical and mathematical sciences to analyze, design and manufacture inanimate tools, structures and processes, bioengineering uses the same sciences to study many aspects of living organisms. Usually it is used to analyze and solve problems related to human health.

Biological engineering is a science-based discipline founded upon the biological sciences in the same way that chemical engineering, electrical engineering, and mechanical engineering are based upon chemistry, electricity and magnetism and statics, respectively.

Biological engineering can be differentiated from its roots of pure biology or classical engineering in the following way. Biological studies often follow a reductionist approach in viewing a system on its smallest possible scale which naturally leads toward tools such as functional genomics. Engineering approaches, using classical design perspectives, are constructionist, building new devices, approaches, and technologies from component concepts. Biological engineering utilizes both of these methods in concert relying on reductionist approaches to define the fundamental units which are then commingled to generate something new. Although engineered biological systems have been used to manipulate information, construct materials, process chemicals, produce energy, provide food, and help maintain or enhance human health and our environment, our ability to quickly and reliably engineer biological systems that behave as expected remains less well developed than our mastery over mechanical and electrical systems.

The differentiation between biological engineering and overlap with Biomedical Engineering can be unclear, as many universities now use the terms "bioengineering" and "biomedical engineering" interchangeably . Some contend that Biological Engineering (like biotechnology) has a broader base which spans molecular methods (tends to emphasize the using of biological substances - applying engineering principles to molecular biology, biochemistry, microbiology, pharmacology, protein chemistry, cytology, immunology, neurobiology and neuroscience, cellular and tissue based methods (including devices and sensors), whole organisms (plants, animals), and up increasing length scales to ecosystems. Neither biological engineering nor biomedical engineering is wholly contained within the other, as there are non-biological products for medical needs and biological products for non-medical needs.

ABET , the U.S.-based accreditation board for engineering B.S. programs, makes a distinction between Biomedical Engineering and Biological Engineering; however, the differences are quite small. Biomedical engineers must have life science courses that include human physiology and have experience in performing measurements on living systems while biological engineers must have life science courses (which may or may not include physiology) and experience in making measurements not specifically on living systems. Foundational engineering courses are often the same and include thermodynamics, fluid and mechanical dynamics, kinetics, electronics, and materials properties.

The word bioengineering was coined by British scientist and broadcaster Heinz Wolff in 1954. The term bioengineering is also used to describe the use of vegetation in civil engineering construction. The term bioengineering may also be applied to environmental modifications such as surface soil protection, slope stabilisation, watercourse and shoreline protection, windbreaks, vegetation barriers including noise barriers and visual screens, and the ecological enhancement of an area. The first biological engineering program was created at Mississippi State University in 1967, making it the first biological engineering curriculum in the United States. More recent programs have been launched at MIT and Utah State University .

Biological Engineers or *bioengineers* are engineers who use the principles of biology and the tools of engineering to create usable, tangible products. Biological Engineering employs knowledge and expertise from a number of pure and applied sciences, such as mass and heat transfer, kinetics, biocatalysts, biomechanics, bioinformatics, separation and purification processes, bioreactor design, surface science, fluid mechanics, thermodynamics, and polymer science. It is used in the design of medical devices, diagnostic equipment, biocompatible materials, renewable bioenergy, ecological engineering, and other areas that improve the living standards of societies.

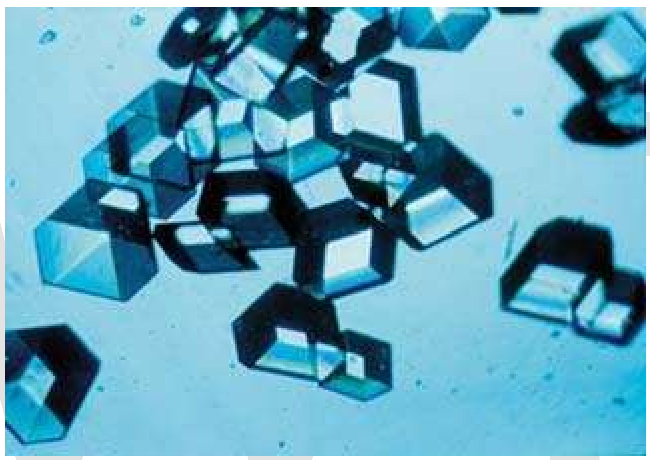
In general, biological engineers attempt to either mimic biological systems in order to create products or modify and control biological systems so that they can replace, augment, or sustain chemical and mechanical processes. Bioengineers can apply their expertise to other applications of engineering and biotechnology, including genetic modification of plants and microorganisms, bioprocess engineering, and biocatalysis.

Because other engineering disciplines also address living organisms (e.g., prosthetics in mechanical engineering), the term biological engineering can be applied more broadly to include agricultural engineering and biotechnology. In fact, many old agricultural engineering departments in universities over the world have rebranded themselves as **agricultural and biological engineering** or **agricultural and biosystems engineering**. Biological engineering is also called bioengineering by some colleges and Biomedical engineering is called Bioengineering by others, and is a rapidly developing field with fluid categorization. The Main Fields of Bioengineering may be categorised as:

- **Bioprocess Engineering**: Bioprocess Design, Biocatalysis, Bioseparation, Bioinformatics, Bioenergy
- **Genetic Engineering**: Synthetic Biology, Horizontal gene transfer.
- **Cellular Engineering**: Cell Engineering, Tissue Culture Engineering, Metabolic engineering.
- **Biomedical Engineering**: Biomedical technology, Biomedical Diagnostics, Biomedical Therapy, Biomechanics, Biomaterials.

Chapter 5

Biotechnology



Insulin crystals.

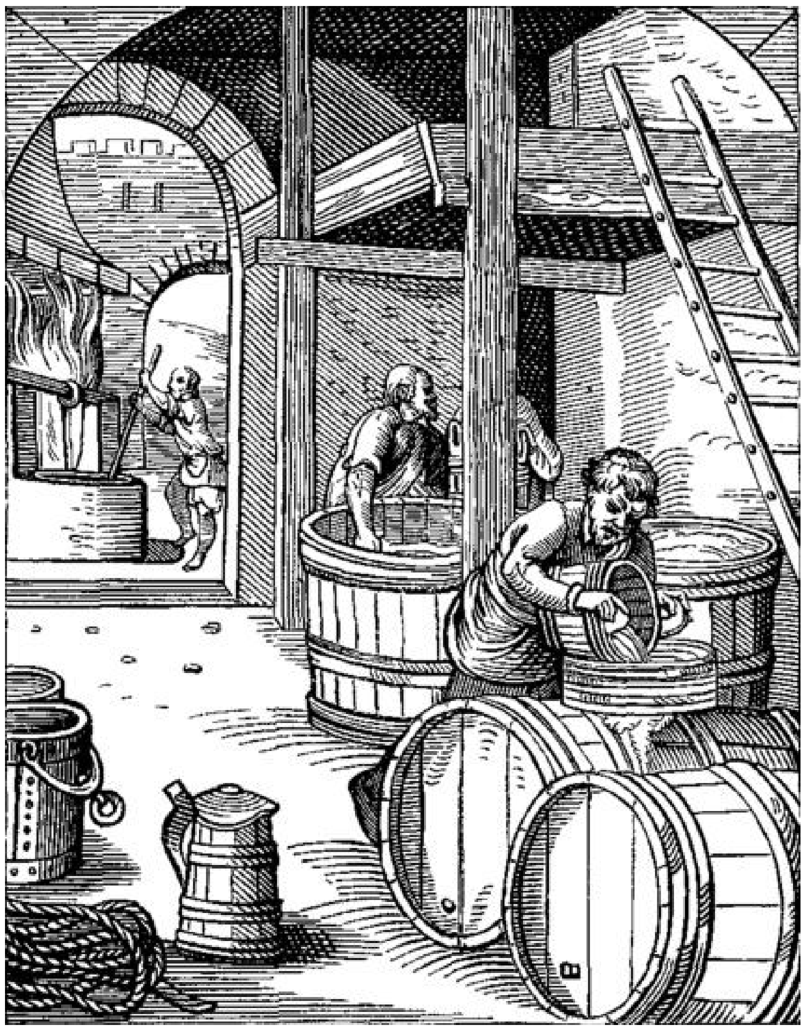
Biotechnology is a field of applied biology that involves the use of living organisms and bioprocesses in engineering, technology, medicine and other fields requiring bioproducts. Biotechnology also utilizes these products for manufacturing purpose. Modern use of similar terms includes genetic engineering as well as cell- and tissue culture technologies. The concept encompasses a wide range of procedures (and history) for modifying living organisms according to human purposes - going back to domestication of animals, cultivation of plants, and "improvements" to these through breeding programs that employ artificial selection and hybridization. By comparison to biotechnology, bioengineering is generally thought of as a related field with its emphasis more on higher systems approaches (not necessarily altering or using biological materials *directly*) for interfacing with and utilizing living things. The United Nations Convention on Biological Diversity defines biotechnology as:

"Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."

In other term "Application of scientific and technical advances in life science to develop commercial products" is biotechnology.

Biotechnology draws on the pure biological sciences (genetics, microbiology, animal cell culture, molecular biology, biochemistry, embryology, cell biology) and in many instances is also dependent on knowledge and methods from outside the sphere of biology (chemical engineering, bioprocess engineering, information technology, biorobotics). Conversely, modern biological sciences (including even concepts such as molecular ecology) are intimately entwined and dependent on the methods developed through biotechnology and what is commonly thought of as the life sciences industry.

History



Brewing was an early application of biotechnology

Biotechnology is not limited to medical/health applications (*unlike* Biomedical Engineering, which includes much biotechnology). Although not normally thought of as biotechnology, agriculture clearly fits the broad definition of "*using a biotechnological* *system to make products*" such that the cultivation of plants may be viewed as the earliest biotechnological enterprise. Agriculture has been theorized to have become the dominant way of producing food since the Neolithic Revolution. The processes and methods of agriculture have been refined by other mechanical and biological sciences since its inception. Through early biotechnology, farmers were able to select the best suited crops, having the highest yields, to produce enough food to support a growing population. Other uses of biotechnology were required as the crops and fields became increasingly large and difficult to maintain. Specific organisms and organism by-products were used to fertilize, restore nitrogen, and control pests. Throughout the use of agriculture, farmers have inadvertently altered the genetics of their crops through introducing them to new environments and breeding them with other plants—one of the first forms of biotechnology. Cultures such as those in Mesopotamia, Egypt, and India developed the process of brewing beer. It is still done by the same basic method of using malted grains (containing enzymes) to convert starch from grains into sugar and then adding specific yeasts to produce beer. In this process the carbohydrates in the grains were broken down into alcohols such as ethanol. Ancient Indians also used the juices of the plant Ephedra vulgaris and used to call it Soma. Later other cultures produced the process of Lactic acid fermentation which allowed the fermentation and preservation of other forms of food. Fermentation was also used in this time period to produce leavened bread. Although the process of fermentation was not fully understood until Pasteur's work in 1857, it is still the first use of biotechnology to convert a food source into another form.

For thousands of years, humans have used selective breeding to improve production of crops and livestock to use them for food. In selective breeding, organisms with desirable characteristics are mated to produce offspring with the same characteristics. For example, this technique was used with corn to produce the largest and sweetest crops.

In the early twentieth century scientists gained a greater understanding of microbiology and explored ways of manufacturing specific products. In 1917, Chaim Weizmann first used a pure microbiological culture in an industrial process, that of manufacturing corn starch using *Clostridium acetobutylicum,* to produce acetone, which the United Kingdom desperately needed to manufacture explosives during World War I.

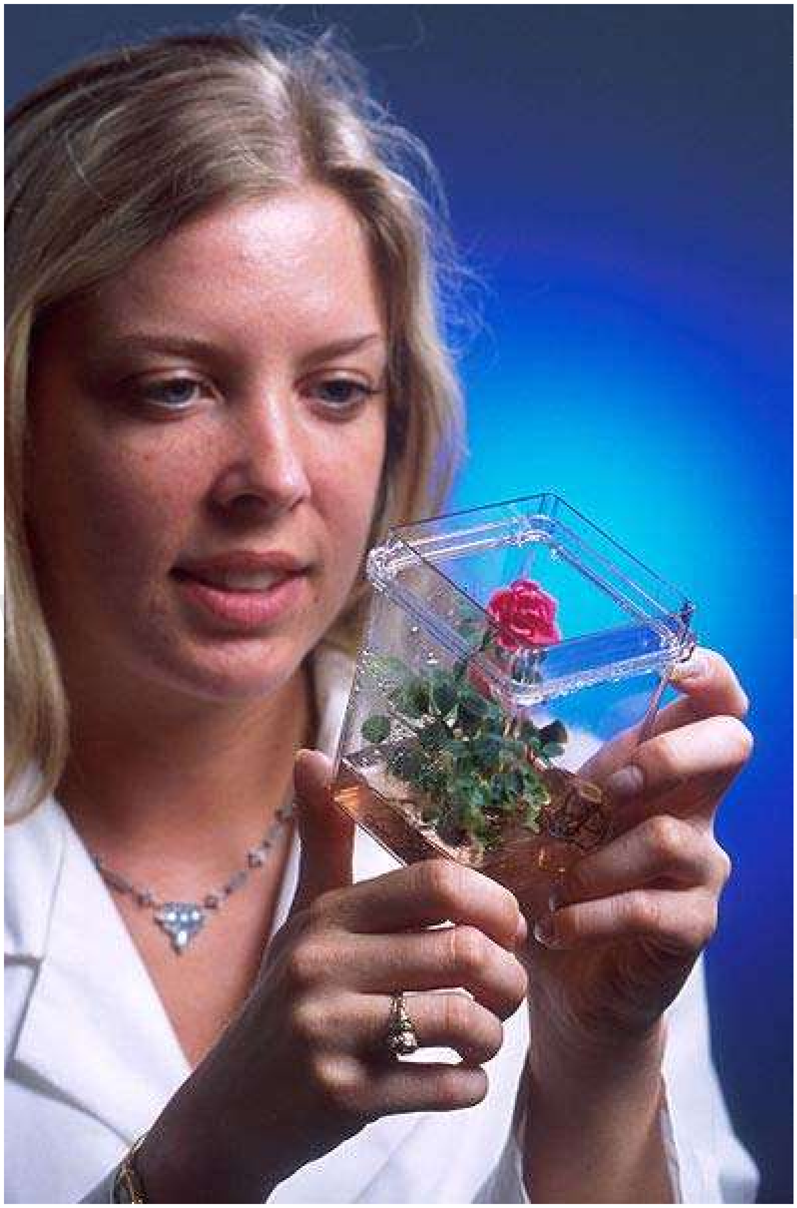
Biotechnology has also led to the development of antibiotics. In 1928, Alexander Fleming discovered the mold Penicillium. His work led to the purification of the antibiotic by Howard Florey, Ernst Boris Chain and Norman Heatley penicillin. In 1940, penicillin became available for medicinal use to treat bacterial infections in humans.

The field of modern biotechnology is thought to have largely begun on June 16, 1980, when the United States Supreme Court ruled that a genetically modified microorganism could be patented in the case of *Diamond v. Chakrabarty*. Indian-born Ananda Chakrabarty, working for General Electric, had developed a bacterium (derived from the *Pseudomonas* genus) capable of breaking down crude oil, which he proposed to use in treating oil spills.

Revenue in the industry is expected to grow by 12.9% in 2008. Another factor influencing the biotechnology sector's success is improved intellectual property rights legislation—and enforcement—worldwide, as well as strengthened demand for medical and pharmaceutical products to cope with an ageing, and ailing, U.S. population.

Rising demand for biofuels is expected to be good news for the biotechnology sector, with the Department of Energy estimating ethanol usage could reduce U.S. petroleum-derived fuel consumption by up to 30% by 2030. The biotechnology sector has allowed the U.S. farming industry to rapidly increase its supply of corn and soybeans—the main inputs into biofuels—by developing genetically modified seeds which are resistant to pests and drought. By boosting farm productivity, biotechnology plays a crucial role in ensuring that biofuel production targets are met.

Applications



A rose plant that began as cells grown in a tissue culture

Biotechnology has applications in four major industrial areas, including health care (medical), crop production and agriculture, non food (industrial) uses of crops and other products (e.g. biodegradable plastics, vegetable oil, biofuels), and environmental uses.

For example, one application of biotechnology is the directed use of organisms for the manufacture of organic products (examples include beer and milk products). Another example is using naturally present bacteria by the mining industry in bioleaching. Biotechnology is also used to recycle, treat waste, clean up sites contaminated by industrial activities (bioremediation), and also to produce biological weapons.

A series of derived terms have been coined to identify several branches of biotechnology, for example:

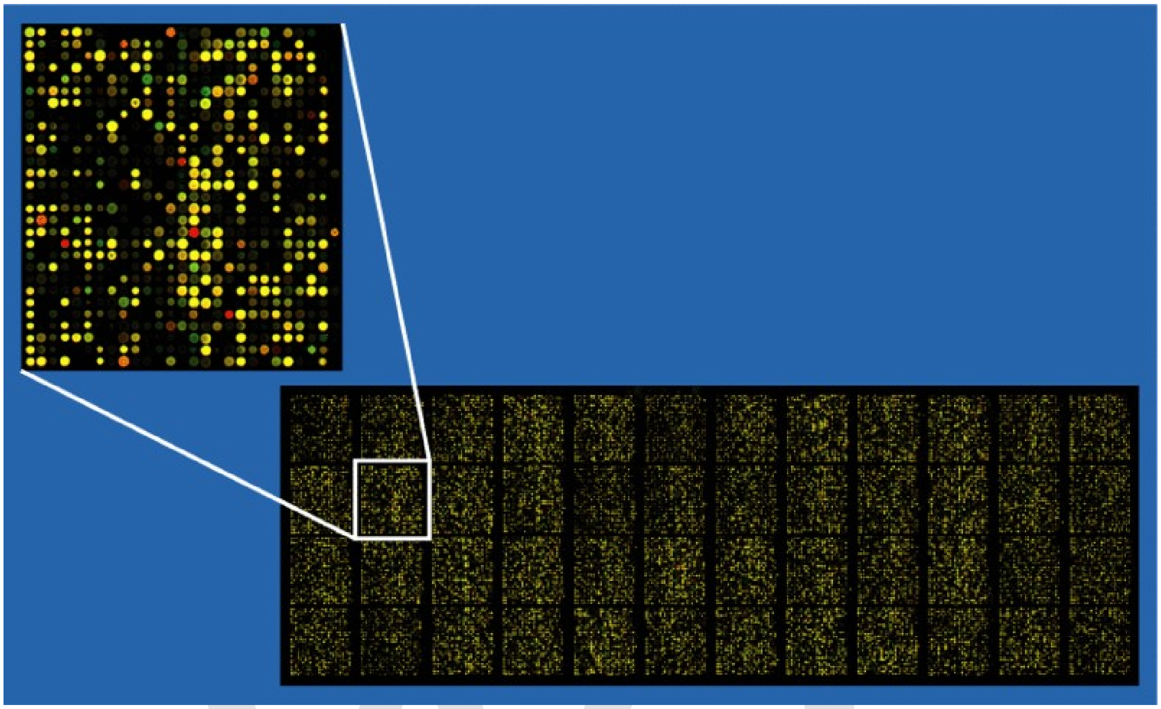
- **Bioinformatics** is an interdisciplinary field which addresses biological problems using computational techniques, and makes the rapid organization and analysis of biological data possible. The field may also be referred to as *computational biology*, and can be defined as, "conceptualizing biology in terms of molecules and then applying informatics techniques to understand and organize the information associated with these molecules, on a large scale." Bioinformatics plays a key role in various areas, such as functional genomics, structural genomics, and proteomics, and forms a key component in the biotechnology and pharmaceutical sector.
- **Blue biotechnology** is a term that has been used to describe the marine and aquatic applications of biotechnology, but its use is relatively rare.
- **Green biotechnology** is biotechnology applied to agricultural processes. An example would be the selection and domestication of plants via micropropagation. Another example is the designing of transgenic plants to grow under specific environments in the presence (or absence) of chemicals. One hope is that green biotechnology might produce more environmentally friendly solutions than traditional industrial agriculture. An example of this is the engineering of a plant to express a pesticide, thereby ending the need of external application of pesticides. An example of this would be Bt corn. Whether or not green biotechnology products such as this are ultimately more environmentally friendly is a topic of considerable debate.
- **Red biotechnology** is applied to medical processes. Some examples are the designing of organisms to produce antibiotics, and the engineering of genetic cures through genetic manipulation.
- **White biotechnology**, also known as industrial biotechnology, is biotechnology applied to industrial processes. An example is the designing of an organism to produce a useful chemical. Another example is the using of enzymes as industrial catalysts to either produce valuable chemicals or destroy hazardous/polluting chemicals. White biotechnology tends to consume less in resources than traditional processes used to produce industrial goods. The investment and economic output of all of these types of applied biotechnologies is termed as **bioeconomy**.

Medicine

In medicine, modern biotechnology finds promising applications in such areas as

- drug production
- pharmacogenomics
- gene therapy
- genetic testing: techniques in molecular biology detect genetic diseases. To test the developing fetus for Down syndrome, Amniocentesis and chorionic villus sampling can be used.

Pharmacogenomics



DNA Microarray chip – Some can do as many as a million blood tests at once

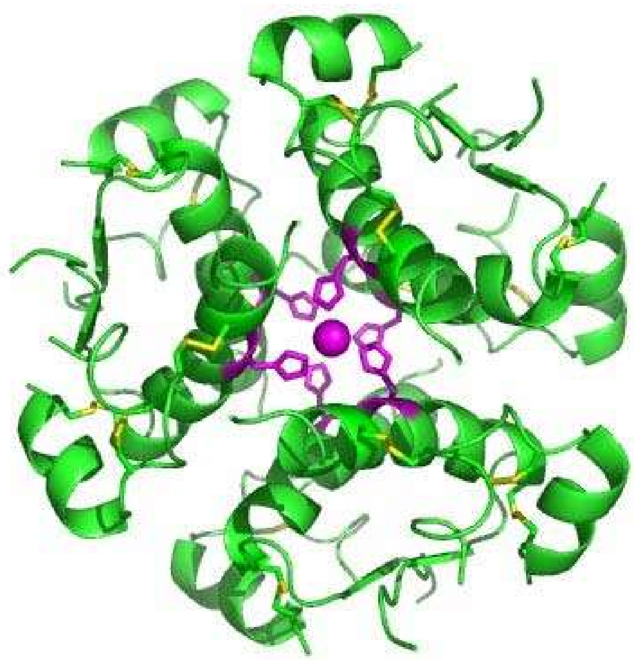
Pharmacogenomics is the study of how the genetic inheritance of an individual affects his/her body's response to drugs. It is a coined word derived from the words "pharmacology" and "genomics". It is hence the study of the relationship between pharmaceuticals and genetics. The vision of pharmacogenomics is to be able to design and produce drugs that are adapted to each person's genetic makeup.

Pharmacogenomics results in the following benefits:

1. Development of tailor-made medicines. Using pharmacogenomics, pharmaceutical companies can create drugs based on the proteins, enzymes and RNA molecules that are associated with specific genes and diseases. These tailor-made drugs promise not only to maximize therapeutic effects but also to decrease damage to nearby healthy cells.
2. More accurate methods of determining appropriate drug dosages. Knowing a patient's genetics will enable doctors to determine how well his/ her body can process and metabolize a medicine. This will maximize the value of the medicine and decrease the likelihood of overdose.
3. Improvements in the drug discovery and approval process. The discovery of potential therapies will be made easier using genome targets. Genes have been associated with numerous diseases and disorders. With modern biotechnology, these genes can be used as targets for the development of effective new therapies, which could significantly shorten the drug discovery process.

4. Better vaccines. Safer vaccines can be designed and produced by organisms transformed by means of genetic engineering. These vaccines will elicit the immune response without the attendant risks of infection. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of pathogen at once.

Pharmaceutical products



Computer-generated image of insulin hexamers highlighting the threefold symmetry, the zinc ions holding it together, and the histidine residues involved in zinc binding.

Most traditional pharmaceutical drugs are relatively simple molecules that have been found primarily through trial and error to treat the symptoms of a disease or illness. Biopharmaceuticals are large biological molecules known as proteins and these usually target the underlying mechanisms and pathways of a malady (but not always, as is the case with using insulin to treat type 1 diabetes mellitus, as that treatment merely addresses the symptoms of the disease, not the underlying cause which is autoimmunity); it is a relatively young industry. They can deal with targets in humans that may not be accessible with traditional medicines. A patient typically is dosed with a small molecule *via* a tablet while a large molecule is typically injected.

Small molecules are manufactured by chemistry but larger molecules are created by living cells such as those found in the human body: for example, bacteria cells, yeast cells, animal or plant cells.

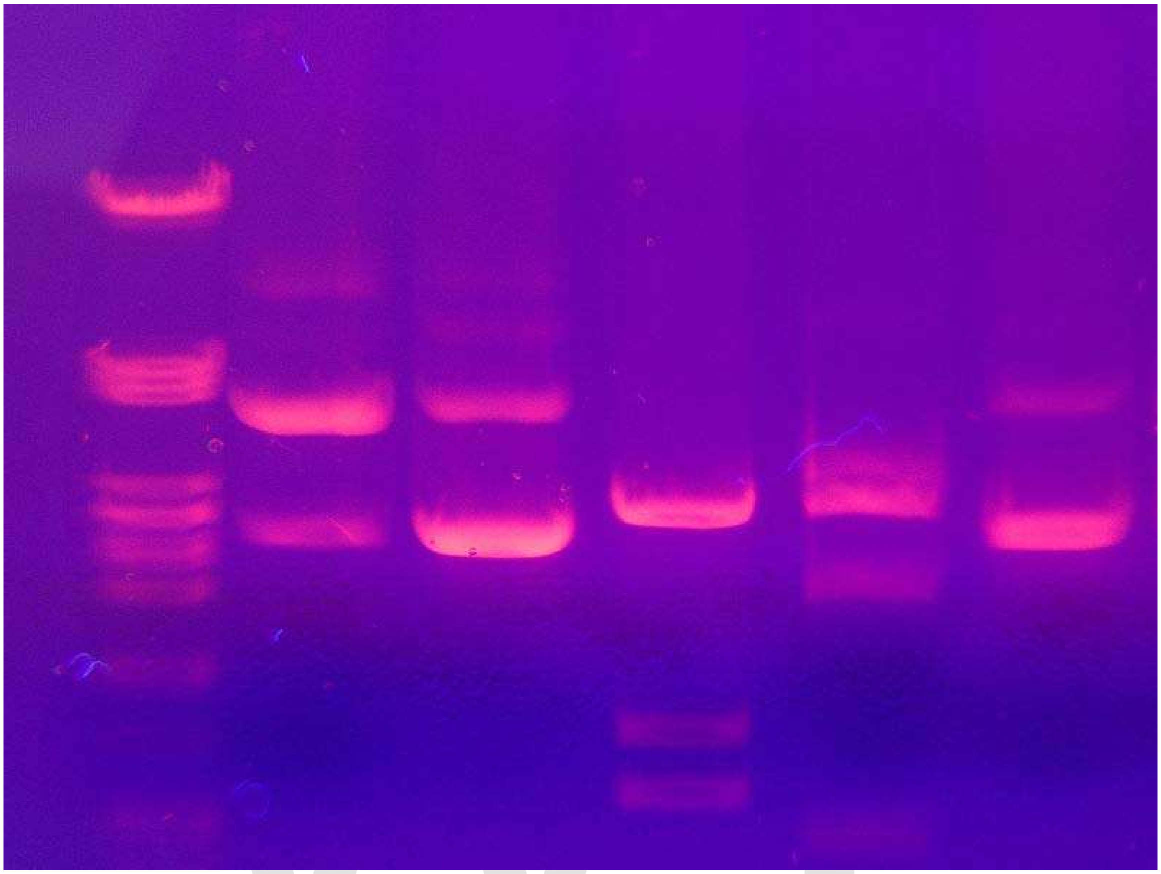
Modern biotechnology is often associated with the use of genetically altered microorganisms such as *E. coli* or yeast for the production of substances like synthetic insulin or antibiotics. It can also refer to transgenic animals or transgenic plants, such as Bt corn. Genetically altered mammalian cells, such as Chinese Hamster Ovary (CHO) cells, are also used to manufacture certain pharmaceuticals. Another promising new biotechnology application is the development of plant-made pharmaceuticals.

Biotechnology is also commonly associated with landmark breakthroughs in new medical therapies to treat hepatitis B, hepatitis C, cancers, arthritis, haemophilia, bone fractures, multiple sclerosis, and cardiovascular disorders. The biotechnology industry has also been instrumental in developing molecular diagnostic devices that can be used to define the target patient population for a given biopharmaceutical. Herceptin, for example, was the first drug approved for use with a matching diagnostic test and is used to treat breast cancer in women whose cancer cells express the protein HER2.

Modern biotechnology can be used to manufacture existing medicines relatively easily and cheaply. The first genetically engineered products were medicines designed to treat human diseases. To cite one example, in 1978 Genentech developed synthetic humanized insulin by joining its gene with a plasmid vector inserted into the bacterium *Escherichia coli*. Insulin, widely used for the treatment of diabetes, was previously extracted from the pancreas of abattoir animals (cattle and/or pigs). The resulting genetically engineered bacterium enabled the production of vast quantities of synthetic human insulin at relatively low cost. According to a 2003 study undertaken by the International Diabetes Federation (IDF) on the access to and availability of insulin in its member countries, synthetic 'human' insulin is considerably more expensive in most countries where both synthetic 'human' and animal insulin are commercially available: e.g. within European countries the average price of synthetic 'human' insulin was twice as high as the price of pork insulin. Yet in its position statement, the IDF writes that "there is no overwhelming evidence to prefer one species of insulin over another" and "[modern, highly purified] animal insulins remain a perfectly acceptable alternative.

Modern biotechnology has evolved, making it possible to produce more easily and relatively cheaply human growth hormone, clotting factors for hemophiliacs, fertility drugs, erythropoietin and other drugs. Most drugs today are based on about 500 molecular targets. Genomic knowledge of the genes involved in diseases, disease pathways, and drug-response sites are expected to lead to the discovery of thousands more new targets.

Genetic testing



Gel electrophoresis

Genetic testing involves the direct examination of the DNA molecule itself. A scientist scans a patient's DNA sample for mutated sequences.

There are two major types of gene tests. In the first type, a researcher may design short pieces of DNA ("probes") whose sequences are complementary to the mutated sequences. These probes will seek their complement among the base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and flag the mutation. In the second type, a researcher may conduct the gene test by comparing the sequence of DNA bases in a patient's gene to disease in healthy individuals or their progeny.

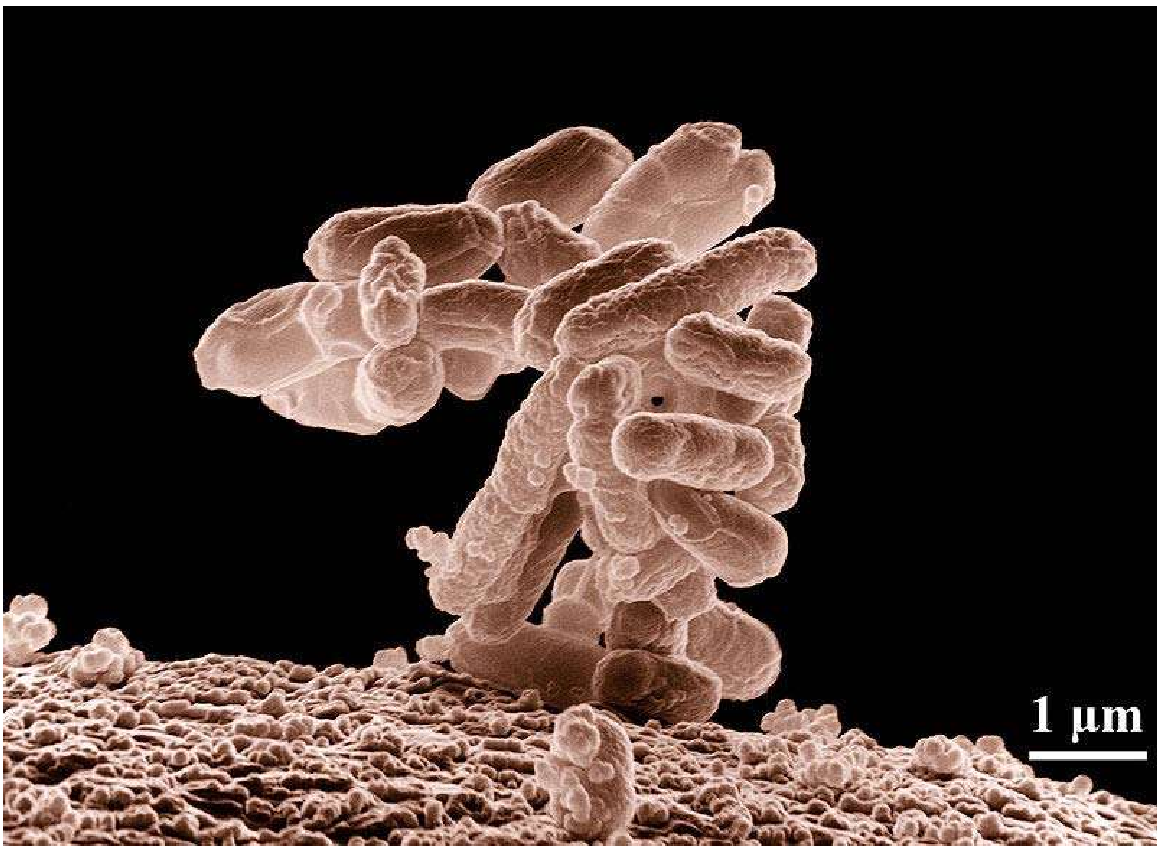
Genetic testing is now used for:

- Carrier screening, or the identification of unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to manifest;
- Confirmational diagnosis of symptomatic individuals;
- Determining sex;
- Forensic/identity testing;
- Newborn screening;

- Prenatal diagnostic screening;
- Presymptomatic testing for estimating the risk of developing adult-onset cancers;
- Presymptomatic testing for predicting adult-onset disorders.

Some genetic tests are already available, although most of them are used in developed countries. The tests currently available can detect mutations associated with rare genetic disorders like cystic fibrosis, sickle cell anemia, and Huntington's disease. Recently, tests have been developed to detect mutation for a handful of more complex conditions such as breast, ovarian, and colon cancers. However, gene tests may not detect every mutation associated with a particular condition because many are as yet undiscovered, and the ones they do detect may present different risks to different people and populations.

Controversial questions



The bacterium *Escherichia coli* is routinely genetically engineered.

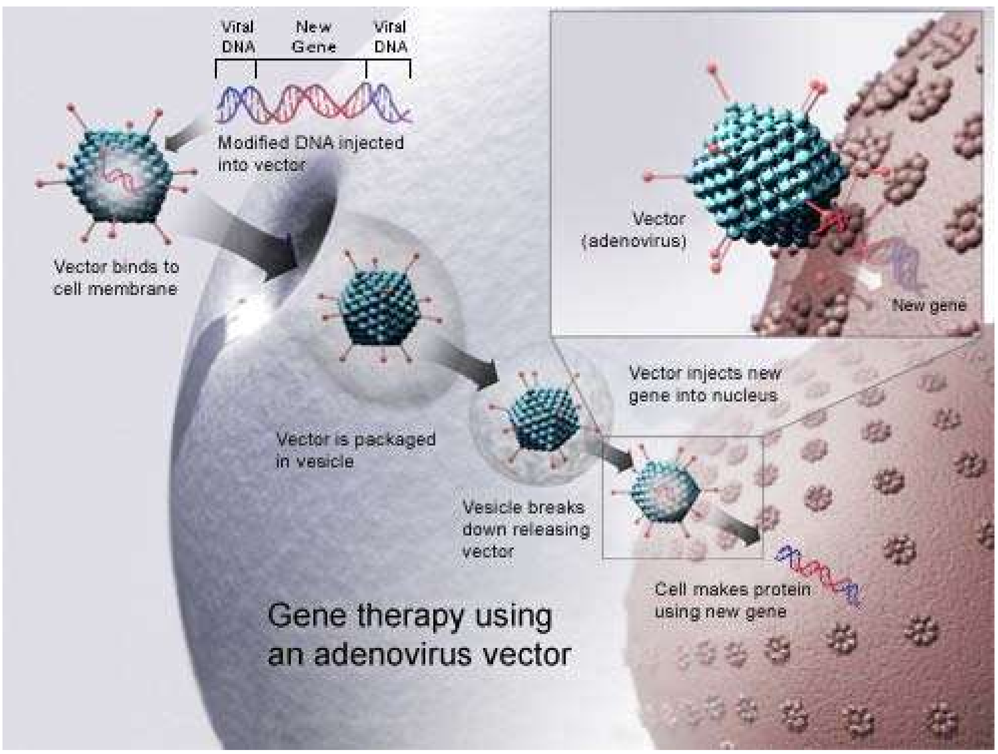
The absence of privacy and anti-discrimination legal protections in most countries can lead to discrimination in employment or insurance or other use of personal genetic information. This raises questions such as whether genetic privacy is different from medical privacy.

1. Reproductive issues. These include the use of genetic information in reproductive decision-making and the possibility of genetically altering reproductive cells that

may be passed on to future generations. For example, germline therapy changes the genetic make-up of an individual's descendants. Thus, any error in technology or judgment may have far-reaching consequences (though the same can also happen through natural reproduction). Ethical issues like designed babies and human cloning have also given rise to controversies between and among scientists and bioethicists, especially in the light of past abuses with eugenics.

2. Clinical issues. These center on the capabilities and limitations of doctors and other health-service providers, people identified with genetic conditions, and the general public in dealing with genetic information.
3. Effects on social institutions. Genetic tests reveal information about individuals and their families. Thus, test results can affect the dynamics within social institutions, particularly the family.
4. Conceptual and philosophical implications regarding human responsibility, free will vis-à-vis genetic determinism, and the concepts of health and disease.

Gene therapy



Gene therapy using an Adenovirus vector. A new gene is inserted into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.

Gene therapy may be used for treating, or even curing, genetic and acquired diseases like cancer and AIDS by using normal genes to supplement or replace defective genes or to bolster a normal function such as immunity. It can be used to target somatic (i.e., body) or gametes (i.e., egg and sperm) cells. In somatic gene therapy, the genome of the recipient is changed, but this change is not passed along to the next generation. In contrast, in germline gene therapy, the egg and sperm cells of the parents are changed for the purpose of passing on the changes to their offspring.

There are basically two ways of implementing a gene therapy treatment:

1. *Ex vivo*, which means “outside the body” – Cells from the patient’s blood or bone marrow are removed and grown in the laboratory. They are then exposed to a virus carrying the desired gene. The virus enters the cells, and the desired gene becomes part of the DNA of the cells. The cells are allowed to grow in the laboratory before being returned to the patient by injection into a vein.
2. *In vivo*, which means “inside the body” – No cells are removed from the patient’s body. Instead, vectors are used to deliver the desired gene to cells in the patient’s body.

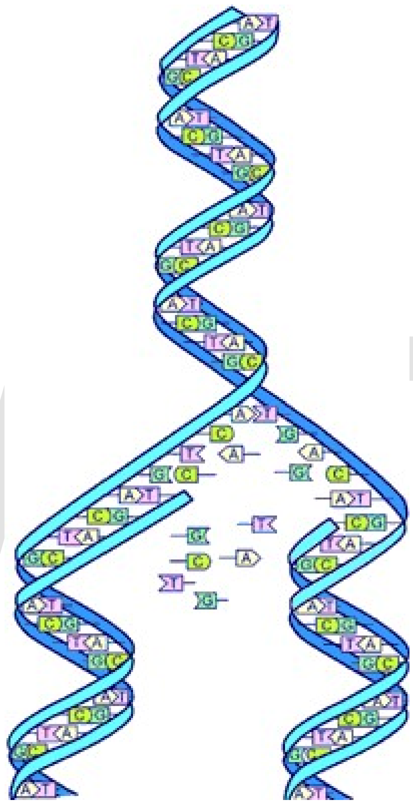
As of June 2001, more than 500 clinical gene-therapy trials involving about 3,500 patients have been identified worldwide. Around 78% of these are in the United States, with Europe having 18%. These trials focus on various types of cancer, although other multigenic diseases are being studied as well. Recently, two children born with severe combined immunodeficiency disorder (“SCID”) were reported to have been cured after being given genetically engineered cells.

Gene therapy faces many obstacles before it can become a practical approach for treating disease. At least four of these obstacles are as follows:

1. *Gene delivery tools*. Genes are inserted into the body using gene carriers called vectors. The most common vectors now are viruses, which have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists manipulate the genome of the virus by removing the disease-causing genes and inserting the therapeutic genes. However, while viruses are effective, they can introduce problems like toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, in order for gene therapy to provide permanent therapeutic effects, the introduced gene needs to be integrated within the host cell's genome. Some viral vectors effect this in a random fashion, which can introduce other problems such as disruption of an endogenous host gene.
2. *High costs*. Since gene therapy is relatively new and at an experimental stage, it is an expensive treatment to undertake. This explains why current studies are focused on illnesses commonly found in developed countries, where more people can afford to pay for treatment. It may take decades before developing countries can take advantage of this technology.
3. *Limited knowledge of the functions of genes*. Scientists currently know the functions of only a few genes. Hence, gene therapy can address only some genes that cause a particular disease. Worse, it is not known exactly whether genes have more than one function, which creates uncertainty as to whether replacing such genes is indeed desirable.

4. *Multigene disorders and effect of environment*. Most genetic disorders involve more than one gene. Moreover, most diseases involve the interaction of several genes and the environment. For example, many people with cancer not only inherit the disease gene for the disorder, but may have also failed to inherit specific tumor suppressor genes. Diet, exercise, smoking and other environmental factors may have also contributed to their disease.

Human Genome Project



DNA Replication image from the Human Genome Project (HGP)

The Human Genome Project is an initiative of the U.S. Department of Energy ("DOE") that aims to generate a high-quality reference sequence for the entire human genome and identify all the human genes.

The DOE and its predecessor agencies were assigned by the U.S. Congress to develop new energy resources and technologies and to pursue a deeper understanding of potential health and environmental risks posed by their production and use. In 1986, the DOE announced its Human Genome Initiative. Shortly thereafter, the DOE and National Institutes of Health developed a plan for a joint Human Genome Project ("HGP"), which officially began in 1990.

The HGP was originally planned to last 15 years. However, rapid technological advances and worldwide participation accelerated the completion date to 2003 (making it a 13 year project). Already it has enabled gene hunters to pinpoint genes associated with more than 30 disorders.

Cloning

Cloning involves the removal of the nucleus from one cell and its placement in an unfertilized egg cell whose nucleus has either been deactivated or removed.

There are two types of cloning:

1. Reproductive cloning. After a few divisions, the egg cell is placed into a uterus where it is allowed to develop into a fetus that is genetically identical to the donor of the original nucleus.
2. Therapeutic cloning. The egg is placed into a Petri dish where it develops into embryonic stem cells, which have shown potentials for treating several ailments.

In February 1997, cloning became the focus of media attention when Ian Wilmut and his colleagues at the Roslin Institute announced the successful cloning of a sheep, named Dolly, from the mammary glands of an adult female. The cloning of Dolly made it apparent to many that the techniques used to produce her could someday be used to clone human beings. This stirred a lot of controversy because of its ethical implications.

Agriculture

Crop yield

Using the techniques of modern biotechnology, one or two genes (Smartstax from Monsanto in collaboration with Dow AgroSciences will use 8, starting in 2010) may be transferred to a highly developed crop variety to impart a new character that would increase its yield. However, while increases in crop yield are the most obvious applications of modern biotechnology in agriculture, it is also the most difficult one. Current genetic engineering techniques work best for effects that are controlled by a single gene. Many of the genetic characteristics associated with yield (e.g., enhanced growth) are controlled by a large number of genes, each of which has a minimal effect on the overall yield. There is, therefore, much scientific work to be done in this area.

Reduced vulnerability of crops to environmental stresses

Crops containing genes that will enable them to withstand biotic and abiotic stresses may be developed. For example, drought and excessively salty soil are two important limiting factors in crop productivity. Biotechnologists are studying plants that can cope with these extreme conditions in the hope of finding the genes that enable them to do so and eventually transferring these genes to the more desirable crops. One of the latest developments is the identification of a plant gene, At-DBF2, from Arabidopsis thaliana, a tiny weed that is often used for plant research because it is very easy to grow and its genetic code is well mapped out. When this gene was inserted into tomato and tobacco cells, the cells were able to withstand environmental stresses like salt, drought, cold and heat, far more than ordinary cells. If these preliminary results prove successful in larger trials, then At-DBF2 genes can help in engineering crops that can better withstand harsh environments. Researchers have also created transgenic rice plants that are resistant to rice yellow mottle virus (RYMV). In Africa, this virus destroys majority of the rice crops and makes the surviving plants more susceptible to fungal infections.

Increased nutritional qualities

Proteins in foods may be modified to increase their nutritional qualities. Proteins in legumes and cereals may be transformed to provide the amino acids needed by human beings for a balanced diet. A good example is the work of Professors Ingo Potrykus and Peter Beyer in creating Golden rice (discussed below).

Improved taste, texture or appearance of food

Modern biotechnology can be used to slow down the process of spoilage so that fruit can ripen longer on the plant and then be transported to the consumer with a still reasonable shelf life. This alters the taste, texture and appearance of the fruit. More importantly, it could expand the market for farmers in developing countries due to the reduction in spoilage. However, there is sometimes a lack of understanding by researchers in developed countries about the actual needs of prospective beneficiaries in developing countries. For example, engineering soybeans to resist spoilage makes them less suitable for producing tempeh which is a significant source of protein that depends on fermentation. The use of modified soybeans results in a lumpy texture that is less palatable and less convenient when cooking.

The first genetically modified food product was a tomato which was transformed to delay its ripening. Researchers in Indonesia, Malaysia, Thailand, Philippines and Vietnam are currently working on delayed-ripening papaya in collaboration with the University of Nottingham and Zeneca.

Biotechnology in cheese production: enzymes produced by micro-organisms provide an alternative to animal rennet – a cheese coagulant – and an alternative supply for cheese makers. This also eliminates possible public concerns with animal-derived material, although there are currently no plans to develop synthetic milk, thus making this argument less compelling. Enzymes offer an animal-friendly alternative to animal rennet. While providing comparable quality, they are theoretically also less expensive.

About 85 million tons of wheat flour is used every year to bake bread. By adding an enzyme called maltogenic amylase to the flour, bread stays fresher longer. Assuming that 10–15% of bread is thrown away as stale, if it could be made to stay fresh another 5–7 days then perhaps 2 million tons of flour per year would be saved. Other enzymes can cause bread to expand to make a lighter loaf, or alter the loaf in a range of ways.

Reduced dependence on fertilizers, pesticides and other agrochemicals

Most of the current commercial applications of modern biotechnology in agriculture are on reducing the dependence of farmers on agrochemicals. For example, *Bacillus thuringiensis* (Bt) is a soil bacterium that produces a protein with insecticidal qualities. Traditionally, a fermentation process has been used to produce an insecticidal spray from these bacteria. In this form, the Bt toxin occurs as an inactive protoxin, which requires digestion by an insect to be effective. There are several Bt toxins and each one is specific to certain target insects. Crop plants have now been engineered to contain and express the genes for Bt toxin, which they produce in its active form. When a susceptible insect ingests the transgenic crop cultivar expressing the Bt protein, it stops feeding and soon thereafter dies as a result of the Bt toxin binding to its gut wall. Bt corn is now commercially available in a number of countries to control corn borer (a lepidopteran insect), which is otherwise controlled by spraying (a more difficult process).

Crops have also been genetically engineered to acquire tolerance to broad-spectrum herbicide. The lack of herbicides with broad-spectrum activity and no crop injury was a consistent limitation in crop weed management. Multiple applications of numerous herbicides were routinely used to control a wide range of weed species detrimental to agronomic crops. Weed management tended to rely on preemergence—that is, herbicide applications were sprayed in response to expected weed infestations rather than in response to actual weeds present. Mechanical cultivation and hand weeding were often necessary to control weeds not controlled by herbicide applications. The introduction of herbicide-tolerant crops has the potential of reducing the number of herbicide active ingredients used for weed management, reducing the number of herbicide applications made during a season, and increasing yield due to improved weed management and less crop injury. Transgenic crops that express tolerance to glyphosate, glufosinate and bromoxynil have been developed. These herbicides can now be sprayed on transgenic crops without inflicting damage on the crops while killing nearby weeds.

From 1996 to 2001, herbicide tolerance was the most dominant trait introduced to commercially available transgenic crops, followed by insect resistance. In 2001, herbicide tolerance deployed in soybean, corn and cotton accounted for 77% of the 626,000 square kilometres planted to transgenic crops; Bt crops accounted for 15%; and "stacked genes" for herbicide tolerance and insect resistance used in both cotton and corn accounted for 8%.

Production of novel substances in crop plants

Biotechnology is being applied for novel uses other than food. For example, oilseed can be modified to produce fatty acids for detergents, substitute fuels and petrochemicals. Potatoes, tomatoes, rice tobacco, lettuce, safflowers, and other plants have been genetically engineered to produce insulin and certain vaccines. If future clinical trials prove successful, the advantages of edible vaccines would be enormous, especially for developing countries. The transgenic plants may be grown locally and cheaply. Homegrown vaccines would also avoid logistical and economic problems posed by having to transport traditional preparations over long distances and keeping them cold while in transit. And since they are edible, they will not need syringes, which are not only an additional expense in the traditional vaccine preparations but also a source of infections if contaminated. In the case of insulin grown in transgenic plants, it is well-established that the gastrointestinal system breaks the protein down therefore this could not currently be administered as an edible protein. However, it might be produced at significantly lower cost than insulin produced in costly bioreactors. For example, Calgary, Canada-based SemBioSys Genetics, Inc. reports that its safflower-produced insulin will reduce unit costs by over 25% or more and approximates a reduction in the capital costs associated with building a commercial-scale insulin manufacturing facility of over $100 million, compared to traditional biomanufacturing facilities.

Animal Biotechnology

In animals, biotechnology techniques are being used to improve genetics and for pharmaceutical or industrial applications. Molecular biology techniques can help drive breeding programs by directing selection of superior animals. Animal cloning, through somatic cell nuclear transfer (SCNT), allows for genetic replication of selected animals. Genetic engineering, using recombinant DNA, alters the genetic makeup of the animal for selected purposes, including producing therapeutic proteins in cows and goats. There is a genetically altered salmon with an increased growth rate being considered for FDA approval.

Criticism

There is another side to the agricultural biotechnology issue. It includes increased herbicide usage and resultant herbicide resistance, "super weeds," residues on and in food crops, genetic contamination of non-GM crops which hurt organic and conventional farmers, etc.

Biological engineering

Biotechnological engineering or biological engineering is a branch of engineering that focuses on biotechnologies and biological science. It includes different disciplines such as biochemical engineering, biomedical engineering, bio-process engineering, biosystem engineering and so on. Because of the novelty of the field, the definition of a bioengineer is still undefined. However, in general it is an integrated approach of fundamental biological sciences and traditional engineering principles.

Biotechnologists are often employed to scale up bio processes from the laboratory scale to the manufacturing scale. Moreover, as with most engineers, they often deal with management, economic and legal issues. Since patents and regulation (e.g., U.S. Food and Drug Administration regulation in the U.S.) are very important issues for biotech enterprises, bioengineers are often required to have knowledge related to these issues.

The increasing number of biotech enterprises is likely to create a need for bioengineers in the years to come. Many universities throughout the world are now providing programs in bioengineering and biotechnology (as independent programs or specialty programs within more established engineering fields).

Bioremediation and biodegradation

Biotechnology is being used to engineer and adapt organisms especially microorganisms in an effort to find sustainable ways to clean up contaminated environments. The elimination of a wide range of pollutants and wastes from the environment is an absolute requirement to promote a sustainable development of our society with low environmental impact. Biological processes play a major role in the removal of contaminants and biotechnology is taking advantage of the astonishing catabolic versatility of microorganisms to degrade/convert such compounds. New methodological breakthroughs in sequencing, genomics, proteomics, bioinformatics and imaging are producing vast amounts of information. In the field of Environmental Microbiology, genome-based global studies open a new era providing unprecedented *in silico* views of metabolic and regulatory networks, as well as clues to the evolution of degradation pathways and to the molecular adaptation strategies to changing environmental conditions. Functional genomic and metagenomic approaches are increasing our understanding of the relative importance of different pathways and regulatory networks to carbon flux in particular environments and for particular compounds and they will certainly accelerate the development of bioremediation technologies and biotransformation processes.

Marine environments are especially vulnerable since oil spills of coastal regions and the open sea are poorly containable and mitigation is difficult. In addition to pollution through human activities, millions of tons of petroleum enter the marine environment every year from natural seepages. Despite its toxicity, a considerable fraction of petroleum oil entering marine systems is eliminated by the hydrocarbon-degrading activities of microbial communities, in particular by a remarkable recently discovered group of specialists, the so-called hydrocarbonoclastic bacteria (HCCB).

Biotechnology regulations

The National Institute of Health was the first federal agency to assume regulatory responsibility in the United States. The Recombinant DNA Advisory Committee of the NIH published guidelines for working with recombinant DNA and recombinant organisms in the laboratory. Nowadays, the agencies that are responsible for the biotechnology regulation are: US Department of Agriculture (USDA) that regulates plant pests and medical preparation from living organisms, Environmental Protection Agency (EPA) that regulates pesticides and herbicides, and the Food and Drug Administration (FDA) which ensures that the food and drug products are safe and effective

Education

In 1988, after prompting from the United States Congress, the National Institute of General Medical Sciences (National Institutes of Health) instituted a funding mechanism for biotechnology training. Universities nationwide compete for these funds to establish Biotechnology Training Programs (BTPs). Each successful application is generally funded for five years then must be competitively renewed. Graduate students in turn compete for acceptance into a BTP; if accepted then stipend, tuition and health insurance support is provided for two or three years during the course of their PhD thesis work. Nineteen institutions offer NIGMS supported BTPs. Biotechnology training is also offered at the undergraduate level and in community colleges.

Chapter 6

Cloning

The sea anemone, *Anthopleura elegantissima* in process of cloning

Cloning in biology is the process of producing similar populations of genetically identical individuals that occurs in nature when organisms such as bacteria, insects or plants reproduce asexually. Cloning in biotechnology refers to processes used to create copies of DNA fragments (molecular cloning), cells (cell cloning), or organisms. The term also refers to the production of multiple copies of a product such as digital media or software.

The term *clone* is derived from *κλῶνος*, the Greek word for "trunk, branch", referring to the process whereby a new plant can be created from a twig. In horticulture, the spelling *clon* was used until the twentieth century; the final *e* came into use to indicate the vowel is a "long o" instead of a "short o". Since the term entered the popular lexicon in a more general context, the spelling *clone* has been used exclusively.

Molecular cloning

Molecular cloning refers to the process of making multiple molecules. Cloning is commonly used to amplify DNA fragments containing whole genes, but it can also be used to amplify any DNA sequence such as promoters, non-coding sequences and randomly fragmented DNA. It is used in a wide array of biological experiments and practical applications ranging from genetic fingerprinting to large scale protein production. Occasionally, the term cloning is misleadingly used to refer to the identification of the chromosomal location of a gene associated with a particular phenotype of interest, such as in positional cloning. In practice, localization of the gene to a chromosome or genomic region does not necessarily enable one to isolate or amplify the relevant genomic sequence. To amplify any DNA sequence in a living organism, that sequence must be linked to an origin of replication, which is a sequence of DNA capable of directing the propagation of itself and any linked sequence. However, a number of other features are needed and a variety of specialised cloning vectors (small piece of DNA into which a foreign DNA fragment can be inserted) exist that allow protein expression, tagging, single stranded RNA and DNA production and a host of other manipulations.

Cloning of any DNA fragment essentially involves four steps

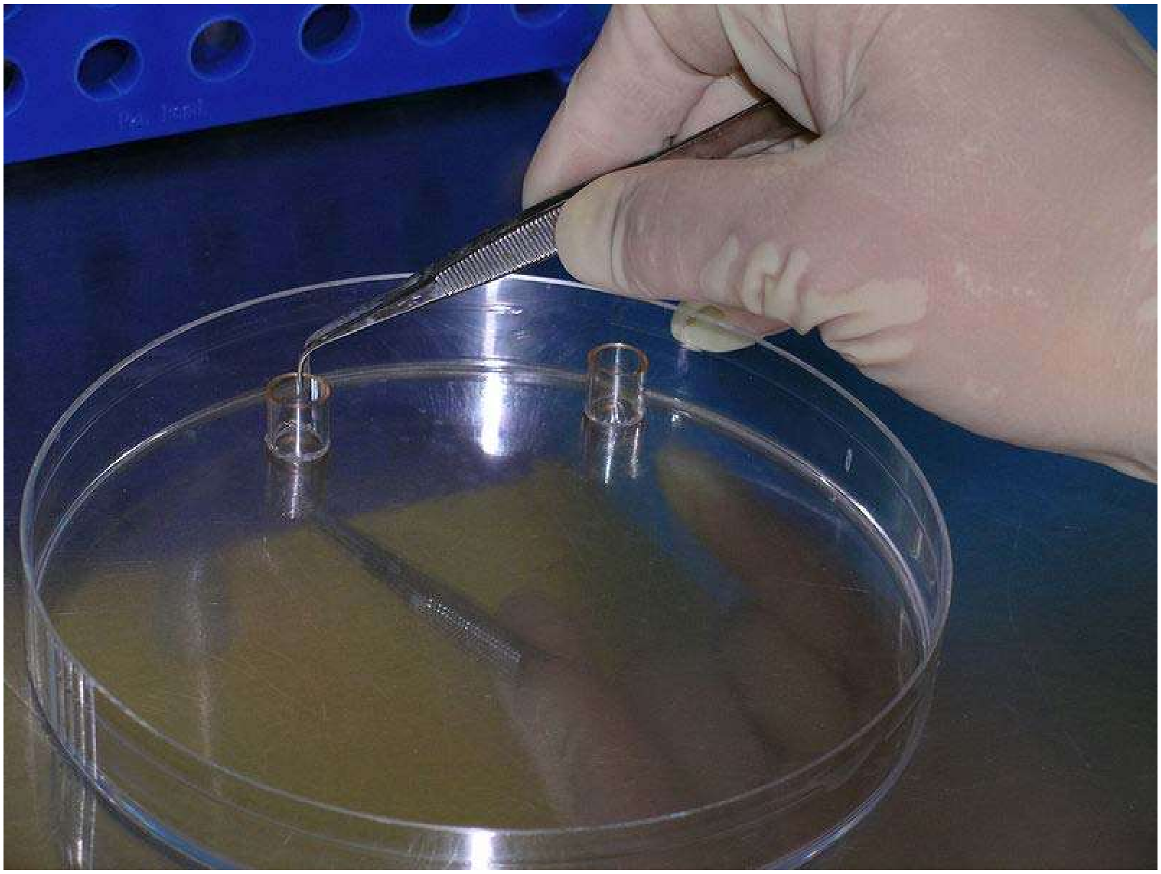
1. fragmentation - breaking apart a strand of DNA
2. ligation - gluing together pieces of DNA in a desired sequence
3. transfection - inserting the newly formed pieces of DNA into cells
4. screening/selection - selecting out the cells that were successfully transfected with the new DNA

Although these steps are invariable among cloning procedures a number of alternative routes can be selected, these are summarized as a 'cloning strategy'.

Initially, the DNA of interest needs to be isolated to provide a DNA segment of suitable size. Subsequently, a ligation procedure is used where the amplified fragment is inserted into a vector (piece of DNA). The vector (which is frequently circular) is linearised using restriction enzymes, and incubated with the fragment of interest under appropriate conditions with an enzyme called DNA ligase. Following ligation the vector with the insert of interest is transfected into cells. A number of alternative techniques are available, such as chemical sensitivation of cells, electroporation, optical injection and biolistics. Finally, the transfected cells are cultured. As the aforementioned procedures are of particularly low efficiency, there is a need to identify the cells that have been successfully transfected with the vector construct containing the desired insertion sequence in the required orientation. Modern cloning vectors include selectable antibiotic resistance markers, which allow only cells in which the vector has been transfected, to grow. Additionally, the cloning vectors may contain colour selection markers, which provide blue/white screening (??-factor complementation) on X-gal medium. Nevertheless, these selection steps do not absolutely guarantee that the DNA insert is present in the cells obtained. Further investigation of the resulting colonies must be required to confirm that cloning was successful. This may be accomplished by means of PCR, restriction fragment analysis and/or DNA sequencing.

Cellular cloning

Unicellular organisms



Cloning cell-line colonies using cloning rings

Cloning a cell means to derive a population of cells from a single cell. In the case of unicellular organisms such as bacteria and yeast, this process is remarkably simple and essentially only requires the inoculation of the appropriate medium. However, in the case of cell cultures from multi-cellular organisms, cell cloning is an arduous task as these cells will not readily grow in standard media.

A useful tissue culture technique used to clone distinct lineages of cell lines involves the use of cloning rings (cylinders). According to this technique, a single-cell suspension of cells that have been exposed to a mutagenic agent or drug used to drive selection is plated at high dilution to create isolated colonies; each arising from a single and potentially clonal distinct cell. At an early growth stage when colonies consist of only a few of cells, sterile polystyrene rings (cloning rings), which have been dipped in grease are placed over an individual colony and a small amount of trypsin is added. Cloned cells are collected from inside the ring and transferred to a new vessel for further growth.

Cloning in stem cell research

Somatic cell nuclear transfer, known as SCNT, can also be used to create embryos for research or therapeutic purposes. The most likely purpose for this is to produce embryos for use in stem cell research. This process is also called "research cloning" or "therapeutic cloning." The goal is not to create cloned human beings (called "reproductive cloning"), but rather to harvest stem cells that can be used to study human development and to potentially treat disease. While a clonal human blastocyst has been created, stem cell lines are yet to be isolated from a clonal source.

Organism cloning

Organism cloning (also called reproductive cloning) refers to the procedure of creating a new multicellular organism, genetically identical to another. In essence this form of cloning is an asexual method of reproduction, where fertilization or inter-gamete contact does not take place. Asexual reproduction is a naturally occurring phenomenon in many species, including most plants and some insects. Scientists have made some major achievements with cloning, including the asexual reproduction of sheep and cows. There is a lot of ethical debate over whether or not cloning should be used. However, cloning, or asexual propagation, has been common practice in the horticultural world for hundreds of years.

Horticultural

The term *clone* is used in horticulture to refer to descendants of a single plant which were produced by vegetative reproduction or apomixis. Many horticultural plant cultivars are clones, having been derived from a single individual, multiplied by some process other than sexual reproduction. As an example, some European cultivars of grapes represent clones that have been propagated for over two millennia. Other examples are potato and banana. Grafting can be regarded as cloning, since all the shoots and branches coming from the graft are genetically a clone of a single individual, but this particular kind of cloning has not come under ethical scrutiny and is generally treated as an entirely different kind of operation.

Many trees, shrubs, vines, ferns and other herbaceous perennials form clonal colonies. Parts of a large clonal colony often become detached from the parent, termed fragmentation, to form separate individuals. Some plants also form seeds is asexually, termed apomixis, e.g. dandelion.

Parthenogenesis

Clonal derivation exists in nature in some animal species and is referred to as parthenogenesis (reproduction of an organism by itself without a mate). This is an asexual form of reproduction that is only found in females of some insects, crustaceans and lizards. The growth and development occurs without fertilization by a male. In plants, parthenogenesis means the development of an embryo from an unfertilized egg cell, and is a component process of apomixis. In species that use the XY sex-determination system, the offspring will always be female. An example is the "Little Fire Ant" (*Wasmannia auropunctata*), which is native to Central and South America but has spread throughout many tropical environments.

Artificial cloning of organisms

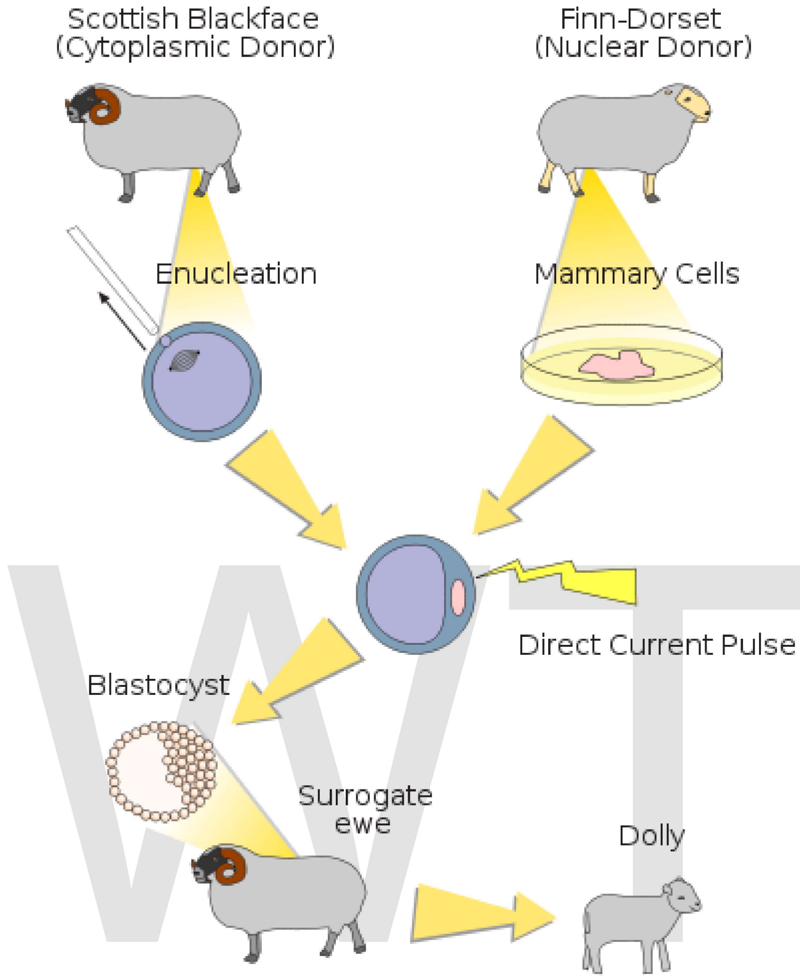
Artificial cloning of organisms may also be called *reproductive cloning*.

Methods

Reproductive cloning generally uses "somatic cell nuclear transfer" (SCNT) to create animals that are genetically identical. This process entails the transfer of a nucleus from a donor adult cell (somatic cell) to an egg that has no nucleus. If the egg begins to divide normally it is transferred into the uterus of the surrogate mother. Such clones are not strictly identical since the somatic cells may contain mutations in their nuclear DNA. Additionally, the mitochondria in the cytoplasm also contains DNA and during SCNT this DNA is wholly from the donor egg, thus the mitochondrial genome is not the same as that of the nucleus donor cell from which it was produced. This may have important implications for cross-species nuclear transfer in which nuclear-mitochondrial incompatibilities may lead to death.

Artificial *embryo splitting* or *embryo twinning* may also be used as a method of cloning, where an embryo is split in the maturation before embryo transfer. It is optimally performed at the 6- to 8-cell stage, where it can be used as an expansion of IVF to increase the number of available embryos. If both embryos are successful, it gives rise to monozygotic (identical) twins.

Dolly the Sheep



Dolly, a Finn-Dorset ewe, was the first mammal to have been successfully cloned from an adult cell. She was cloned at the Roslin Institute in Scotland and lived there from her birth in 1996 until her death in 2003 when she was six. Her stuffed remains were placed at Edinburgh's Royal Museum, part of the National Museums of Scotland.

Dolly was publicly significant because the effort showed that the genetic material from a specific adult cell, programmed to express only a distinct subset of its genes, can be reprogrammed to grow an entirely new organism. Before this demonstration, it had been shown by John Gurdon that nuclei from differentiated cells could give rise to an entire organism after transplantation into an enucleated egg. However, this concept was not yet demonstrated in a mamallian system.

Cloning Dolly the sheep had a low success rate per fertilized egg; she was born after 237 eggs were used to create 29 embryos, which only produced three lambs at birth, only one of which lived. Seventy calves have been created and one third of them died young;

Prometea took 277 attempts. Notably, although the first clones were frogs, no adult cloned frog has yet been produced from a somatic adult nucleus donor cell.

There were early claims that Dolly the Sheep had pathologies resembling accelerated aging. Scientists speculated that Dolly's death in 2003 was related to the shortening of telomeres, DNA-protein complexes that protect the end of linear chromosomes. However, other researchers, including Ian Wilmut who led the team that successfully cloned Dolly, argue that Dolly's early death due to respiratory infection was unrelated to deficiencies with the cloning process.

Water buffalo

On September 15, 2007, the Philippines announced its development of Southeast Asia's first cloned water buffalo. The Philippine Council for Agriculture, Forestry and Natural Resources Research and Development (PCARRD), under the Department of Science and Technology in Los Baños, Laguna approved this project.

Species cloned

The modern cloning techniques involving nuclear transfer have been successfully performed on several species. Landmark experiments in chronological order:

- Tadpole: (1952) Many scientists questioned whether cloning had actually occurred and unpublished experiments by other labs were not able to reproduce the reported results.
- Carp: (1963) In China, embryologist Tong Dizhou produced the world's first cloned fish by inserting the DNA from a cell of a male carp into an egg from a female carp. He published the findings in a Chinese science journal.
- Mice: (1986) A mouse was the first mammal successfully cloned from an early embryonic cell. Soviet scientists Chaylakhyan, Veprencev, Sviridova, and Nikitin had the mouse "Masha" cloned. Research was published in the magazine "Biofizika" volume XXXII, issue 5 of 1987.
- Sheep: (1996) From early embryonic cells by Steen Willadsen. Megan and Morag cloned from differentiated embryonic cells in June 1995 and Dolly the sheep from a somatic cell in 1997.
- Rhesus Monkey: Tetra (January 2000) from embryo splitting
- Gaur: (2001) was the first endangered species cloned.
- Cattle: Alpha and Beta (males, 2001) and (2005) Brazil
- Cat: CopyCat "CC" (female, late 2001), Little Nicky, 2004, was the first cat cloned for commercial reasons
- Dog: Snuppy, a male Afghan hound was the first cloned dog (2005).
- Rat: Ralph, the first cloned rat (2003)
- Mule: Idaho Gem, a john mule born 4 May 2003, was the first horse-family clone.
- Horse: Prometea, a Haflinger female born 28 May 2003, was the first horse clone.

- Water Buffalo: Samrupa was the first cloned water buffalo. It was born on February 6, 2009, at India's Karnal National Diary Research Institute but died five days later due to lung infection.
- Camel: (2009) Injaz, is the first cloned camel.

Human cloning

Human cloning is the creation of a genetically identical copy of an existing or previously existing human. The term is generally used to refer to *artificial* human cloning; human clones in the form of identical twins are commonplace, with their cloning occurring during the natural process of reproduction. There are two commonly discussed types of human cloning: therapeutic cloning and reproductive cloning. Therapeutic cloning involves cloning adult cells for use in medicine and is an active area of research. Reproductive cloning would involve making cloned humans. A third type of cloning called replacement cloning is a theoretical possibility, and would be a combination of therapeutic and reproductive cloning. Replacement cloning would entail the replacement of an extensively damaged, failed, or failing body through cloning followed by whole or partial brain transplant.

The various forms of human cloning are controversial. There have been numerous demands for all progress in the human cloning field to be halted. Most scientific, governmental and religious organizations oppose reproductive cloning. The American Association for the Advancement of Science (AAAS) and other scientific organizations have made public statements suggesting that human reproductive cloning be banned until safety issues are resolved. Serious ethical concerns have been raised by the future possibility of harvesting organs from clones. Some people have considered the idea of growing organs separately from a human organism - in doing this, a new organ supply could be established without the moral implications of harvesting them from humans. Research is also being done on the idea of growing organs that are biologically acceptable to the human body inside of other organisms, such as pigs or cows, then transplanting them to humans, a form of xenotransplantation.

The first hybrid human clone was created in November 1998, by American Cell Technologies. It was created from a man's leg cell, and a cow's egg whose DNA was removed. It was destroyed after 12 days. Since a normal embryo implants at 14 days, Dr Robert Lanza, ACT's director of tissue engineering, told the Daily Mail newspaper that the embryo could not be seen as a person before 14 days. While making an embryo, which may have resulted in a complete human had it been allowed to come to term, according to ACT: "[ACT's] aim was 'therapeutic cloning' not 'reproductive cloning'"

On January, 2008, Wood and Andrew French, Stemagen's chief scientific officer in California, announced that they successfully created the first 5 mature human embryos using DNA from adult skin cells, aiming to provide a source of viable embryonic stem cells. Dr. Samuel Wood and a colleague donated skin cells, and DNA from those cells was transferred to human eggs. It is not clear if the embryos produced would have been capable of further development, but Dr. Wood stated that if that were possible, using the technology for reproductive cloning would be both unethical and illegal. The 5 cloned embryos, created in Stemagen Corporation lab, in La Jolla, were destroyed.

Ethical issues of cloning

Because of recent technological advancements, the cloning of animals (and potentially humans) has been an issue. The Catholic Church and many religious organizations oppose all forms of cloning, on the grounds that life begins at conception. Judaism does not equate life with conception and, though some question the wisdom of cloning, Orthodox rabbis generally find no firm reason in Jewish law and ethics to object to cloning. From the standpoint of classical liberalism, concerns also exist regarding the protection of the identity of the individual and the right to protect one's genetic identity.

Gregory Stock is a scientist and outspoken critic against restrictions on cloning research. Bioethicist Gregory Pence also attacks the idea of criminalizing attempts to clone humans.

The social implications of an artificial human production scheme were famously explored in Aldous Huxley's novel *Brave New World.*

On December 28, 2006, the U.S. Food and Drug Administration (FDA) approved the consumption of meat and other products from cloned animals. Cloned-animal products were said to be virtually indistinguishable from the non-cloned animals. Furthermore, companies would not be required to provide labels informing the consumer that the meat comes from a cloned animal.

Critics have raised objections to the FDA's approval of cloned-animal products for human consumption, arguing that the FDA's research was inadequate, inappropriately limited, and of questionable scientific validity. Several consumer-advocate groups are working to encourage a tracking program that would allow consumers to become more aware of cloned-animal products within their food.

Joseph Mendelson, legal director of the Center for Food Safety, said that cloned food still should be labeled since safety and ethical issues about it remain questionable.

Carol Tucker Foreman, director of food policy at the Consumer Federation of America, stated that FDA does not consider the fact that the results of some studies revealed that cloned animals have increased rates of mortality and deformity at birth.

Cloning extinct and endangered species

Cloning, or more precisely, the reconstruction of functional DNA from extinct species has, for decades, been a dream of some scientists. The possible implications of this were dramatized in the best-selling novel by Michael Crichton and high budget Hollywood thriller *Jurassic Park*. In real life, one of the most anticipated targets for cloning was once the Woolly Mammoth, but attempts to extract DNA from frozen mammoths have been unsuccessful, though a joint Russo-Japanese team is currently working toward this goal. And in January 2011, it was reported by Yomiuri Shimbun that a team of scientists headed by Akira Iritani of Kyoto University had built upon research by Dr. Wakayama, saying that they will extract DNA from a mammoth carcass that had been preserved in a Russian laboratory and insert it into the egg cells of an African elephant in hopes of producing a mammoth embryo. The researchers said they hoped to produce a baby mammoth within six years.

In 2001, a cow named Bessie gave birth to a cloned Asian gaur, an endangered species, but the calf died after two days. In 2003, a banteng was successfully cloned, followed by three African wildcats from a thawed frozen embryo. These successes provided hope that similar techniques (using surrogate mothers of another species) might be used to clone extinct species. Anticipating this possibility, tissue samples from the last *bucardo* (Pyrenean Ibex) were frozen in liquid nitrogen immediately after it died in 2000. Researchers are also considering cloning endangered species such as the giant panda, ocelot, and cheetah. The "Frozen Zoo" at the San Diego Zoo now stores frozen tissue from the world's rarest and most endangered species.

In 2002, geneticists at the Australian Museum announced that they had replicated DNA of the Thylacine (Tasmanian Tiger), extinct about 65 years previous, using polymerase chain reaction. However, on February 15, 2005 the museum announced that it was stopping the project after tests showed the specimens' DNA had been too badly degraded by the (ethanol) preservative. On 15 May 2005 it was announced that the Thylacine project would be revived, with new participation from researchers in New South Wales and Victoria.

In January 2009, for the first time, an extinct animal, the Pyrenean ibex mentioned above was cloned, at the Centre of Food Technology and Research of Aragon, using the preserved DNA of the skin samples from 2001 and domestic goat egg-cells. (The ibex died shortly after birth due to physical defects in its lungs.) One of the continuing obstacles in the attempt to clone extinct species is the need for nearly perfect DNA. Cloning from a single specimen could not create a viable breeding population in sexually reproducing animals. Furthermore, even if males and females were to be cloned, the question would remain open whether they would be viable at all in the absence of parents that could teach or show them their natural behavior.

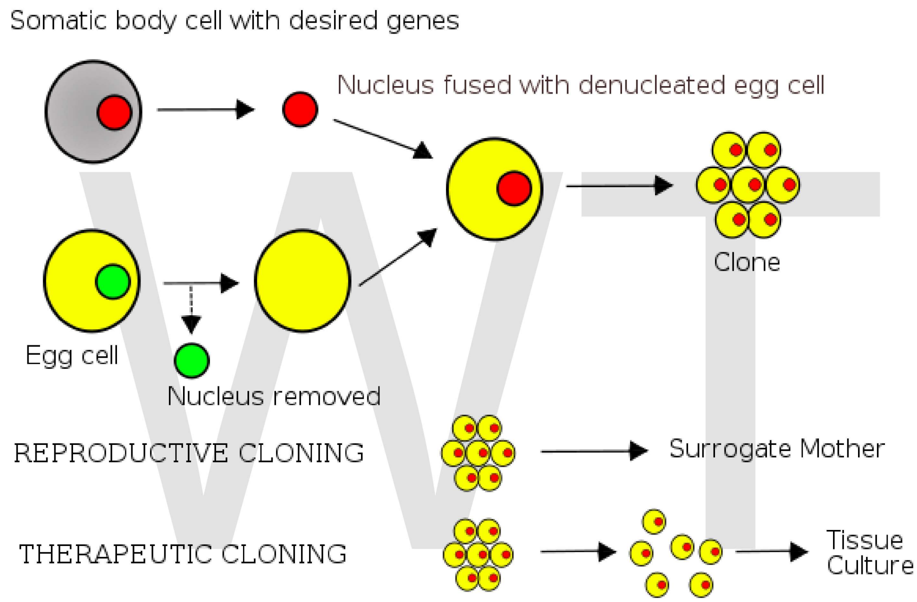
Cloning endangered species is a highly ideological issue. Many conservation biologists and environmentalists vehemently oppose cloning endangered species — mainly because they think it may deter donations to help preserve natural habitat and wild animal populations. The "rule-of-thumb" in animal conservation is that, if it is still feasible to conserve habitat and viable wild populations, breeding in captivity should not be undertaken in isolation.

In a 2006 review, David Ehrenfeld concluded that cloning in animal conservation is an experimental technology that, at its state in 2006, could not be expected to work except by pure chance and utterly failed a cost-benefit analysis. Furthermore, he said, it is likely to siphon funds from established and working projects and does not address any of the issues underlying animal extinction (such as habitat destruction, hunting or other overexploitation, and an impoverished gene pool). While cloning technologies are well-established and used on a regular basis in plant conservation, care must be taken to ensure genetic diversity. He concluded:

Vertebrate cloning poses little risk to the environment, but it can consume scarce conservation resources, and its chances of success in preserving species seem poor. To date, the conservation benefits of transgenics and vertebrate cloning remain entirely theoretical, but many of the risks are known and documented. Conservation biologists should devote their research and energies to the established methods of conservation, none of which require transgenics or vertebrate cloning.

Chapter 7

Somatic Cell Nuclear Transfer



Somatic cell nuclear transfer can create clones for both reproductive and therapeutic purposes. The diagram depicts the removal of the donor nucleus for schematic purposes; in practice usually the whole donor cell is transferred.

In genetics and developmental biology, **somatic cell nuclear transfer** (**SCNT**) is a laboratory technique for creating a clonal embryo, using an ovum with a donor nucleus. It can be used in embryonic stem cell research, or, potentially, in regenerative medicine where it is sometimes referred to as "**therapeutic cloning**". It can also be used as the first step in the process of reproductive cloning.

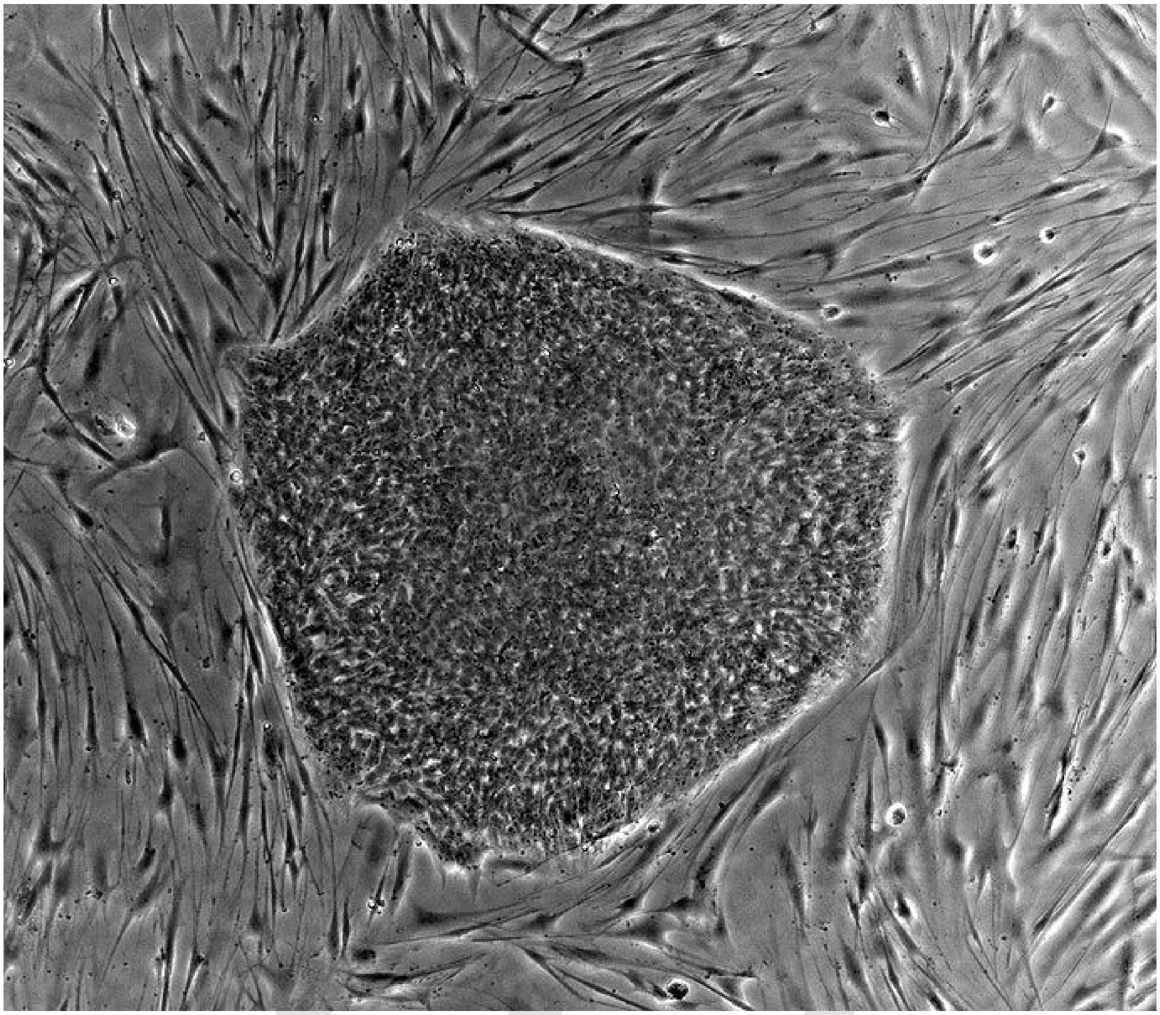
The process

In SCNT the nucleus, which contains the organism's DNA, of a somatic cell (a body cell other than a sperm or egg cell) is removed and the rest of the cell discarded. At the same time, the nucleus of an egg cell is removed. The nucleus of the somatic cell is then inserted into the denucleated egg cell. After being inserted into the egg, the somatic cell nucleus is reprogrammed by the host cell. The egg, now containing the nucleus of a somatic cell, is stimulated with a shock and will begin to divide. After many mitotic divisions in culture, this single cell forms a blastocyst (an early stage embryo with about 100 cells) with almost identical DNA to the original organism. The technique of transferring a nucleus from a somatic cell into an egg that produced Dolly was an extension of experiments that had been ongoing for over 40 years. In the simplest terms, the technique used to produce Dolly the sheep - somatic cell nuclear transplantation cloning - involves removing the nucleus of an egg and replacing it with the diploid nucleus of a somatic cell.

SCNT in stem cell research

Some researchers use SCNT in stem cell research. The aim of carrying out this procedure is to obtain stem cells that are genetically matched to the donor organism. Presently, no human stem cell lines have been derived from SCNT research.

Embryonic stem cells are new, unspecialized cells that are able to be produced into a specialized cell that can replace another cell that has been lost in the body.



Human Embryonic Stem cell colony on mouse embryonic fibroblast feeder layer.

A potential use of genetically-customized stem cells would be to create cell lines that have genes linked to the particular disease. For example, if a person with Parkinson's disease donated his or her somatic cells, then the stem cells resulting from SCNT would have genes that contribute to Parkinson's disease. In this scenario, the disease specific stem cell lines would be studied in order to better understand the disease.

In another scenario, genetically-customized stem cell lines would be generated for cell-based therapies to transplant to the patient. The resulting cells would be genetically identical to the somatic cell donor, thus avoiding any complications from immune system rejection.

Only a handful of the labs in the world are currently using SCNT techniques in human stem cell research. In the United States, scientists at the Harvard Stem Cell Institute, the University of California San Francisco, Stemagen (La Jolla, CA) and possibly Advanced Cell Technology are currently researching a technique to use somatic cell nuclear transfer to produce embryonic stem cells. In the United Kingdom, the Human Fertilisation and

Embryology Authority has granted permission to research groups at the Roslin Institute and the Newcastle Centre for Life. SCNT may also be occurring in China.

In 2005, a South Korean research team led by Professor Hwang Woo-suk, published claims to have derived stem cell lines via SCNT, but supported those claims with fabricated data. Recent evidence has proved that he in fact created a stem cell line from a parthenote.

The impetus for SCNT-based stem cell research has been decreased by the development and improvement of alternative methods of generating stem cells. Methods to reprogram normal body cells into pluripotent stem cells were developed in humans in 2007. The following year, this method achieved a key goal of SCNT-based stem cell research: the derivation of pluripotent stem cell lines that have all genes linked to various diseases. Some scientists working on SCNT-based stem cell research have recently moved to the new methods of induced pluripotent stem cells.

SCNT in reproductive cloning

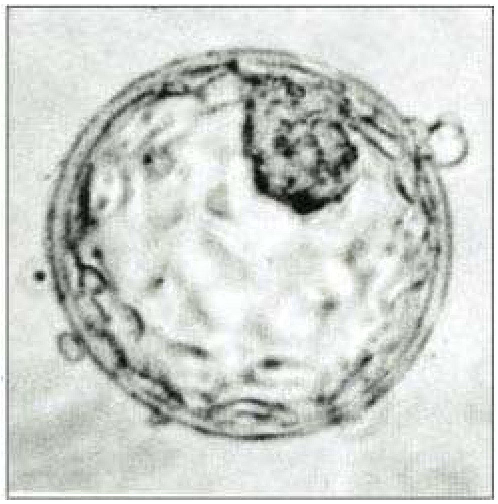
This technique is currently the basis for cloning animals (such as the famous Dolly the sheep), and in theory could be used to clone humans. However, most researchers believe that in the foreseeable future it will not be possible to use this technique to produce a human clone that will develop to term. However, it is still a possibility and can become more probable in the future as it will probably need a few more adjustments to work for humans.

Limitations

Stresses placed on both the egg cell and the introduced nucleus are enormous, leading to a high loss in resulting cells. For example, Dolly the sheep was born after 277 eggs were used for SCNT, which created 29 viable embryos. Only three of these embryos survived until birth, and only one survived to adulthood. As the procedure currently cannot be automated, but has to be performed manually under a microscope, SCNT is very resource intensive. The biochemistry involved in reprogramming the differentiated somatic cell nucleus and activating the recipient egg is also far from understood.

In SCNT, not all of the donor cell's genetic information is transferred, as the donor cell's mitochondria that contain their own mitochondrial DNA are left behind. The resulting hybrid cells retain those mitochondrial structures which originally belonged to the egg. As a consequence, clones such as Dolly that are born from SCNT are not perfect copies of the donor of the nucleus.

Controversy



Human Blastocyst, showing the inner cell mass (top, right).

Proposals to use nucleus transfer techniques in human stem cell research raise a set of concerns beyond the moral status of any created embryo. These have led to some individuals and organizations who are *not* opposed to human embryonic stem cell research to be concerned about, or opposed to, SCNT research.

One concern is that blastula creation in SCNT-based human stem cell research will lead to the reproductive cloning of humans. Both processes use the same first step: the creation of a nuclear transferred embryo, most likely via SCNT. Those who hold this concern often advocate for strong regulation of SCNT to preclude implantation of any derived products for the intention of human reproduction, or its prohibition.

A second important concern is the appropriate source of the eggs that are needed. SCNT requires human eggs, which can only be obtained from women. The most common source of these eggs today are eggs that are produced and in excess of the clinical need during IVF treatment. This is a minimally invasive procedure, but it does carry some health risks, such as ovarian hyperstimulation syndrome, and in very rare instances even death.

One vision for successful stem cell therapies is to create custom stem cell lines for patients. Each custom stem cell line would consist of a collection of identical stem cells each carrying the patient's own DNA, thus reducing or eliminating any problems with rejection when the stem cells were transplanted for treatment. For example, to treat a man with Parkinson's disease, a cell nucleus from one of his cells would be transplanted by SCNT into an egg cell from an egg donor, creating a unique lineage of stem cells almost identical to the patient's own cells. (There would be differences. For example, the mitochondrial DNA would be the same as that of the egg donor. In comparison, his own cells would carry the mitochondrial DNA of his mother.)

Potentially millions of patients could benefit from stem cell therapy, and each patient would require a large number of donated eggs in order to successfully create a single custom therapeutic stem cell line. Such large numbers of donated eggs would exceed the number of eggs currently left over and available from couples trying to have children through assisted reproductive technology. Therefore, healthy young women would need to be induced to sell eggs to be used in the creation of custom stem cell lines that could then be purchased by the medical industry and sold to patients. It is so far unclear where all these eggs would come from. The sale of human eggs is normally referred to as a "donation", but women who donate their eggs are often paid thousands of dollars.

Stem cell experts consider it unlikely that such large numbers of human egg donations would occur in developed country because of the unknown long-term public health effects of treating large numbers of healthy young women with heavy doses of hormones in order to induce hyperovulation (ovulating several eggs at once). Although such treatments have been performed for several decades now, the long-term effects have not been studied or declared safe to use on a large scale on otherwise healthy women. Longer-term treatments with much lower doses of hormones are known to increase the rate of cancer decades later. Whether hormone treatments to induce hyperovulation could have similar effects is unknown. There are also ethical questions surrounding paying for eggs. In general, marketing body parts is considered unethical and is banned in most countries. Human eggs have been a notable exception to this rule for some time.

To address the problem of creating a human egg market, some stem cell researchers are investigating the possibility of creating artificial eggs. If successful, human egg donations would not be needed to create custom stem cell lines. However, this technology may be a long way off.

Policies regarding human SCNT

SCNT involving human cells is currently legal for research purposes in the United Kingdom, having been incorporated into the Human Fertilisation and Embryology Act 1990 in 2001. Permission must be obtained from the Human Fertilisation and Embryology Authority in order to perform or attempt SCNT.

In the United States, the practice remains legal, as it has not been addressed by federal law. However, in 2002, a moratorium on United States federal funding for SCNT prohibits funding the practice for the purposes of research. Thus, though legal, SCNT cannot be federally funded. In 2003, the United Nations adopted a proposal submitted by Costa Rica, calling on member states to "prohibit all forms of human cloning in as much as they are incompatible with human dignity and the protection of human life." This phrase may include SCNT, depending on interpretation.

The Council of Europe's *Convention on Human Rights and Biomedicine* and its *Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Being* appear to ban SCNT of human beings. Of the

Council's 45 member states, the *Convention* has been signed by 31 and ratified by 18. The *Additional Protocol* has been signed by 29 member nations and ratified by 14.

The UN is currently against all forms of human cloning.

Chapter 8

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 9

Brain–Computer Interface

A **brain–computer interface** (**BCI**), sometimes called a **direct neural interface** or a **brain–machine interface** (**BMI**), is a direct communication pathway between the brain and an external device. BCIs are often aimed at assisting, augmenting or repairing human cognitive or sensory-motor functions.

Research on BCIs began in the 1970s at the University of California Los Angeles (UCLA) under a grant from the National Science Foundation, followed by a contract from DARPA. The papers published after this research also mark the first appearance of the expression *brain–computer interface* in scientific literature.

The field of BCI research and development has since focused primarily on neuroprosthetics applications that aim at restoring damaged hearing, sight and movement. Thanks to the remarkable cortical plasticity of the brain, signals from implanted prostheses can, after adaptation, be handled by the brain like natural sensor or effector channels. Following years of animal experimentation, the first neuroprosthetic devices implanted in humans appeared in the mid-nineties.

BCI versus neuroprosthetics

Neuroprosthetics is an area of neuroscience concerned with neural prostheses—using artificial devices to replace the function of impaired nervous systems and brain related problems or sensory organs. The most widely used neuroprosthetic device is the cochlear implant, which, as of 2006, has been implanted in approximately 100,000 people worldwide. There are also several neuroprosthetic devices that aim to restore vision, including retinal implants.

The differences between BCIs and neuroprosthetics are mostly in the ways the terms are used: neuroprosthetics typically connect the nervous system to a device, whereas BCIs usually connect the brain (or nervous system) with a computer system. Practical neuroprosthetics can be linked to any part of the nervous system—for example, peripheral nerves—while the term "BCI" usually designates a narrower class of systems which interface with the central nervous system.

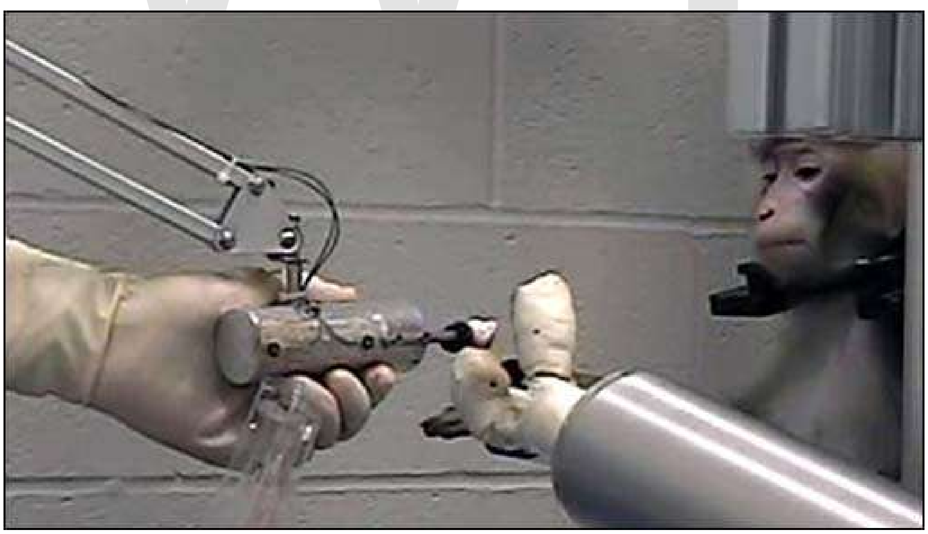
The terms are sometimes used interchangeably. Neuroprosthetics and BCIs seek to achieve the same aims, such as restoring sight, hearing, movement, ability to communicate, and even cognitive function. Both use similar experimental methods and surgical techniques.

Animal BCI research

Rats implanted with BCIs in Theodore Berger's experiments

Several laboratories have managed to record signals from monkey and rat cerebral cortices in order to operate BCIs to carry out movement. Monkeys have navigated computer cursors on screen and commanded robotic arms to perform simple tasks simply by thinking about the task and without any motor output. In May 2008 photographs that showed a monkey operating a robotic arm with its mind at the Pittsburgh University Medical Center were published in a number of well known science journals and magazines. Other research on cats has decoded visual signals.

Early work



Monkey operating a robotic arm with brain–computer interfacing

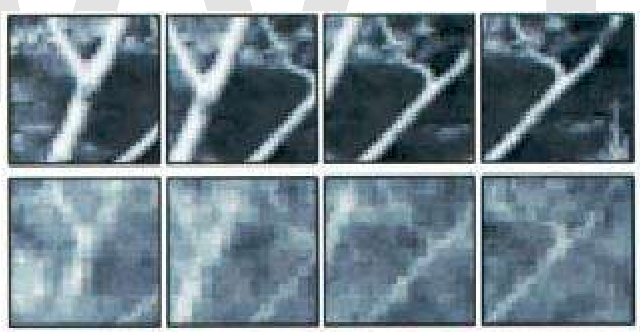
The operant conditioning studies of Fetz and colleagues first showed that monkeys could learn to control the deflection of a biofeedback meter arm with neural activity. Such work in the 1970s established that monkeys could quickly learn to voluntarily control the firing rates of individual and multiple neurons in the primary motor cortex if they were rewarded for generating appropriate patterns of neural activity.

Studies that developed algorithms to reconstruct movements from motor cortex neurons, which control movement, date back to the 1970s. In the 1980s, Apostolos Georgopoulos at Johns Hopkins University found a mathematical relationship between the electrical responses of single motor-cortex neurons in rhesus macaque monkeys and the direction that monkeys moved their arms (based on a cosine function). He also found that dispersed groups of neurons in different areas of the brain collectively controlled motor commands but was only able to record the firings of neurons in one area at a time because of technical limitations imposed by his equipment.

There has been rapid development in BCIs since the mid-1990s. Several groups have been able to capture complex brain motor centre signals using recordings from neural ensembles (groups of neurons) and use these to control external devices, including research groups led by Richard Andersen, John Donoghue, Phillip Kennedy, Miguel Nicolelis, and Andrew Schwartz.

Prominent research successes

Phillip Kennedy and colleagues built the first intracortical brain–computer interface by implanting neurotrophic-cone electrodes into monkeys.



Yang Dan and colleagues' recordings of cat vision using a BCI implanted in the lateral geniculate nucleus (top row: original image; bottom row: recording)

In 1999, researchers led by Yang Dan at University of California, Berkeley decoded neuronal firings to reproduce images seen by cats. The team used an array of electrodes embedded in the thalamus (which integrates all of the brain's sensory input) of sharp-eyed cats. Researchers targeted 177 brain cells in the thalamus lateral geniculate nucleus area, which decodes signals from the retina. The cats were shown eight short movies, and their neuron firings were recorded. Using mathematical filters, the researchers decoded the signals to generate movies of what the cats saw and were able to reconstruct recognizable scenes and moving objects. Similar results in humans have been since then achieved by researchers in Japan (see below).

Miguel Nicolelis has been a prominent proponent of using multiple electrodes spread over a greater area of the brain to obtain neuronal signals to drive a BCI. Such neural ensembles are said to reduce the variability in output produced by single electrodes, which could make it difficult to operate a BCI.

After conducting initial studies in rats during the 1990s, Nicolelis and his colleagues developed BCIs that decoded brain activity in owl monkeys and used the devices to reproduce monkey movements in robotic arms. Monkeys have advanced reaching and grasping abilities and good hand manipulation skills, making them ideal test subjects for this kind of work.

By 2000, the group succeeded in building a BCI that reproduced owl monkey movements while the monkey operated a joystick or reached for food. The BCI operated in real time and could also control a separate robot remotely over Internet protocol. But the monkeys could not see the arm moving and did not receive any feedback, a so-called open-loop BCI.

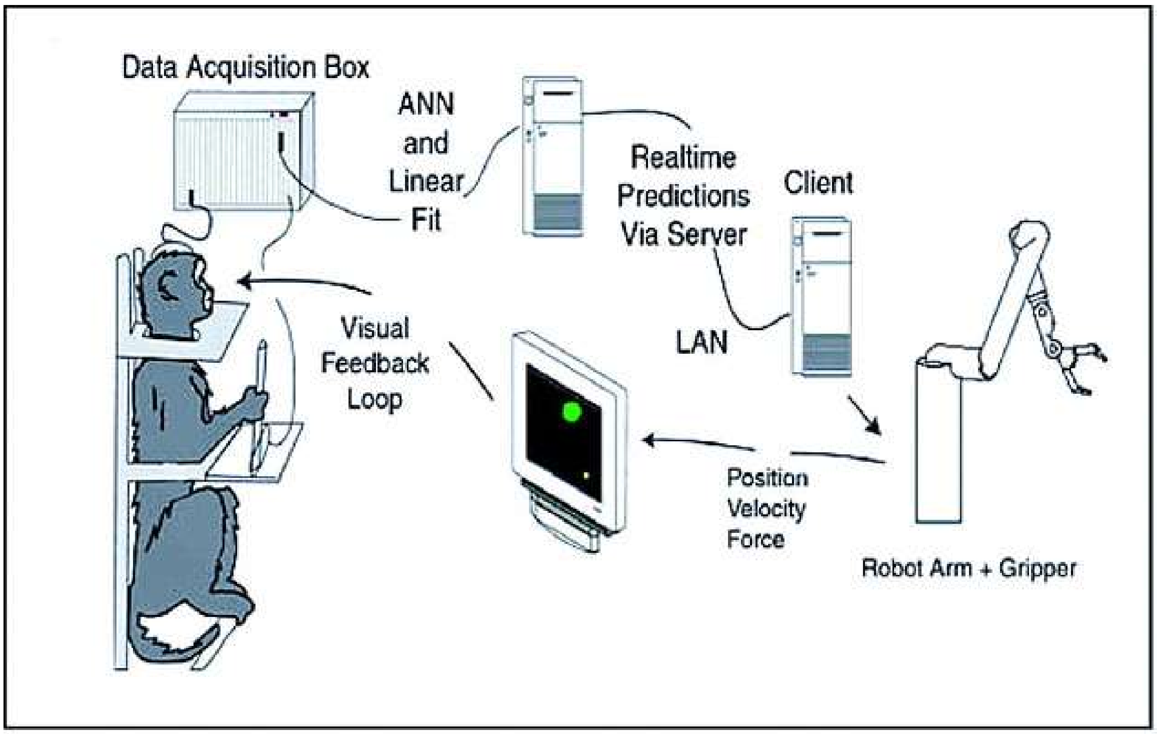


Diagram of the BCI developed by Miguel Nicolelis and colleagues for use on Rhesus monkeys

Later experiments by Nicolelis using rhesus monkeys succeeded in closing the feedback loop and reproduced monkey reaching and grasping movements in a robot arm. With their deeply cleft and furrowed brains, rhesus monkeys are considered to be better models for human neurophysiology than owl monkeys. The monkeys were trained to reach and grasp objects on a computer screen by manipulating a joystick while corresponding movements by a robot arm were hidden. The monkeys were later shown the robot directly and learned to control it by viewing its movements. The BCI used velocity predictions to control reaching movements and simultaneously predicted hand gripping force.

Other labs that develop BCIs and algorithms that decode neuron signals include John Donoghue from Brown University, Andrew Schwartz from the University of Pittsburgh and Richard Andersen from Caltech. These researchers were able to produce working BCIs even though they recorded signals from far fewer neurons than Nicolelis (15–30 neurons versus 50–200 neurons).

Donoghue's group reported training rhesus monkeys to use a BCI to track visual targets on a computer screen with or without assistance of a joystick (closed-loop BCI). Schwartz's group created a BCI for three-dimensional tracking in virtual reality and also reproduced BCI control in a robotic arm. The group created headlines when they demonstrated that a monkey could feed itself pieces of zucchini using a robotic arm controlled by the animal's own brain signals.

Andersen's group used recordings of premovement activity from the posterior parietal cortex in their BCI, including signals created when experimental animals anticipated receiving a reward.

In addition to predicting kinematic and kinetic parameters of limb movements, BCIs that predict electromyographic or electrical activity of muscles are being developed. Such BCIs could be used to restore mobility in paralyzed limbs by electrically stimulating muscles.

Miguel Nicolelis *et al.* 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. 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.* 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.

The biggest impediment of BCI technology at present is the lack of a sensor modality that provides safe, accurate, and robust access to brain signals. It is conceivable or even likely that such a sensor will be developed within the next twenty years. The use of such a sensor should greatly expand the range of communication functions that can be provided using a BCI.

Development and implementation of a Brain–Computer Interface (BCI) system is complex and time consuming. In response to this problem, Dr. Gerwin Schalk has been developing a general-purpose system for BCI research, called BCI2000. BCI2000 has been in development since 2000 in a project led by the Brain–Computer Interface R&D

Program at the Wadsworth Center of the New York State Department of Health in Albany, New York, USA.

A new 'wireless' approach uses light-gated ion channels such as Channelrhodopsin to control the activity of genetically defined subsets of neurons in vivo. In the context of a simple learning task, illumination of transfected cells in the somatosensory cortex influenced the decision making process of freely moving mice.

Human BCI research

Invasive BCIs

Invasive BCI research has targeted repairing damaged sight and providing new functionality to persons with paralysis. Invasive BCIs are implanted directly into the grey matter of the brain during neurosurgery. As they rest in the grey matter, invasive devices produce the highest quality signals of BCI devices but are prone to scar-tissue build-up, causing the signal to become weaker or even lost as the body reacts to a foreign object in the brain.

Jens Naumann, a man with acquired blindness, being interviewed about his vision BCI on CBS's The Early Show

In *vision science*, direct brain implants have been used to treat non-congenital (acquired) blindness. One of the first scientists to come up with a working brain interface to restore sight was private researcher William Dobelle.

Dobelle's first prototype was implanted into "Jerry", a man blinded in adulthood, in 1978. A single-array BCI containing 68 electrodes was implanted onto Jerry's visual cortex and succeeded in producing phosphenes, the sensation of seeing light. The system included cameras mounted on glasses to send signals to the implant. Initially, the implant allowed Jerry to see shades of grey in a limited field of vision at a low frame-rate. This also required him to be hooked up to a two-ton mainframe, but shrinking electronics and faster computers made his artificial eye more portable and now enable him to perform simple tasks unassisted.

Dummy unit illustrating the design of a BrainGate interface

In 2002, Jens Naumann, also blinded in adulthood, became the first in a series of 16 paying patients to receive Dobelle's second generation implant, marking one of the earliest commercial uses of BCIs. The second generation device used a more sophisticated implant enabling better mapping of phosphenes into coherent vision. Phosphenes are spread out across the visual field in what researchers call the starry-night effect. Immediately after his implant, Jens was able to use his imperfectly restored vision to drive slowly around the parking area of the research institute.

BCIs focusing on *motor neuroprosthetics* aim to either restore movement in individuals with paralysis or provide devices to assist them, such as interfaces with computers or robot arms.

Researchers at Emory University in Atlanta led by Philip Kennedy and Roy Bakay were first to install a brain implant in a human that produced signals of high enough quality to simulate movement. Their patient, Johnny Ray (1944–2002), suffered from 'locked-in syndrome' after suffering a brain-stem stroke in 1997. Ray's implant was installed in 1998 and he lived long enough to start working with the implant, eventually learning to control a computer cursor; he died in 2002 of a brain aneurysm.

Tetraplegic Matt Nagle became the first person to control an artificial hand using a BCI in 2005 as part of the first nine-month human trial of Cyberkinetics Neurotechnology's BrainGate chip-implant. Implanted in Nagle's right precentral gyrus (area of the motor cortex for arm movement), the 96-electrode BrainGate implant allowed Nagle to control a robotic arm by thinking about moving his hand as well as a computer cursor, lights and TV. One year later, professor Jonathan Wolpaw received the prize of the Altran Foundation for Innovation to develop a Brain Computer Interface with electrodes located on the surface of the skull, instead of directly in the brain.

Partially-invasive BCIs

Partially invasive BCI devices are implanted inside the skull but rest outside the brain rather than within the grey matter. They produce better resolution signals than non-invasive BCIs where the bone tissue of the cranium deflects and deforms signals and have a lower risk of forming scar-tissue in the brain than fully-invasive BCIs.

Electrocorticography (ECoG) measures the electrical activity of the brain taken from beneath the skull in a similar way to non-invasive electroencephalography (see below), but the electrodes are embedded in a thin plastic pad that is placed above the cortex, beneath the dura mater. ECoG technologies were first trialed in humans in 2004 by Eric Leuthardt and Daniel Moran from Washington University in St Louis. In a later trial, the researchers enabled a teenage boy to play Space Invaders using his ECoG implant. This research indicates that control is rapid, requires minimal training, and may be an ideal tradeoff with regards to signal fidelity and level of invasiveness.

(Note: These electrodes were not implanted in the patients for BCI experiments. The patient was suffering from severe epilepsy and had the electrodes temporarily implanted to help his physicians localize seizure foci; the researchers simply took advantage of this.)

Light Reactive Imaging BCI devices are still in the realm of theory. These would involve implanting a laser inside the skull. The laser would be trained on a single neuron and the neuron's reflectance measured by a separate sensor. When the neuron fires, the laser light pattern and wavelengths it reflects would change slightly. This would allow researchers to monitor single neurons but require less contact with tissue and reduce the risk of scar-tissue build-up.

This signal can be either subdural or epidural, but is not taken from within the brain parenchyma itself. It has not been studied extensively until recently due to the limited access of subjects. Currently, the only manner to acquire the signal for study is through the use of patients requiring invasive monitoring for localization and resection of an epileptogenic focus.

ECoG is a very promising intermediate BCI modality because it has higher spatial resolution, better signal-to-noise ratio, wider frequency range, and lesser training requirements than scalp-recorded EEG, and at the same time has lower technical difficulty, lower clinical risk, and probably superior long-term stability than intracortical single-neuron recording. This feature profile and recent evidence of the high level of control with minimal training requirements shows potential for real world application for people with motor disabilities.

Non-invasive BCIs

As well as invasive experiments, there have also been experiments in humans using non-invasive neuroimaging technologies as interfaces. Signals recorded in this way have been used to power muscle implants and restore partial movement in an experimental volunteer. Although they are easy to wear, non-invasive implants produce poor signal resolution because the skull dampens signals, dispersing and blurring the electromagnetic waves created by the neurons. Although the waves can still be detected it is more difficult to determine the area of the brain that created them or the actions of individual neurons.

EEG

Recordings of brainwaves produced by an electroencephalogram

Electroencephalography (EEG) is the most studied potential non-invasive interface, mainly due to its fine temporal resolution, ease of use, portability and low set-up cost. But as well as the technology's susceptibility to noise, another substantial barrier to using EEG as a brain–computer interface is the extensive training required before users can work the technology. For example, in experiments beginning in the mid-1990s, Niels Birbaumer of the University of Tübingen in Germany trained severely paralysed people to self-regulate the *slow cortical potentials* in their EEG to such an extent that these signals could be used as a binary signal to control a computer cursor. (Birbaumer had earlier trained epileptics to prevent impending fits by controlling this low voltage wave.) The experiment saw ten patients trained to move a computer cursor by controlling their brainwaves. The process was slow, requiring more than an hour for patients to write 100 characters with the cursor, while training often took many months.

Another research parameter is the type of waves measured. Birbaumer's later research with Jonathan Wolpaw at New York State University has focused on developing technology that would allow users to choose the brain signals they found easiest to operate a BCI, including *mu* and *beta* rhythms.

A further parameter is the method of feedback used and this is shown in studies of P300 signals. Patterns of P300 waves are generated involuntarily (stimulus-feedback) when people see something they recognize and may allow BCIs to decode categories of thoughts without training patients first. By contrast, the biofeedback methods described above require learning to control brainwaves so the resulting brain activity can be detected.

Lawrence Farwell and Emanuel Donchin developed an EEG-based brain–computer interface in the 1980s. Their "mental prosthesis" used the P300 brainwave response to allow subjects, including one paralyzed Locked-In syndrome patient, to communicate words, letters, and simple commands to a computer and thereby to speak through a speech synthesizer driven by the computer. A number of similar devices have been developed since then. In 2000, for example, research by Jessica Bayliss at the University of Rochester showed that volunteers wearing virtual reality helmets could control elements in a virtual world using their P300 EEG readings, including turning lights on and off and bringing a mock-up car to a stop.

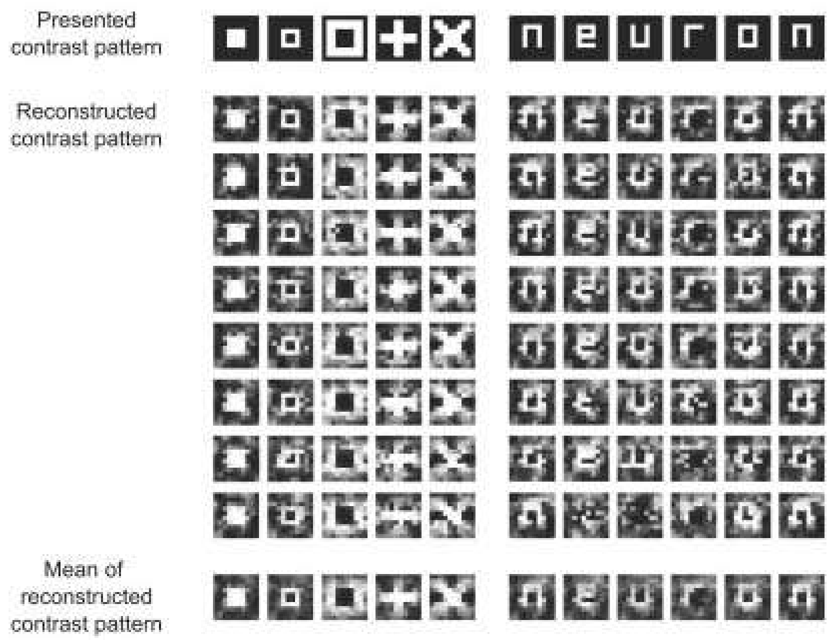
In the early 90s Babak Taheri, at UC DAVIS demonstrated the first single and also multichannel dry active electrode arrays using micro-machining. The single channel dry EEG electrode construction and results were published in 1994. The arrayed electrode was also demonstrated to perform well compared to Ag/AgCl electrodes. The device consisted of four sites of sensors with integrated electronics to reduce noise by impedance matching. The advantages of such electrodes are: (1) no electrolyte used, (2) no skin preparation, (3) significantly reduced sensor size, and (4) compatibility with EEG monitoring systems. The active electrode array is an integrated system made of an array of capacitive sensors with local integrated circuitry housed in a package with batteries to power the circuitry. This level of integration was required to achieve the functional performance obtained by the electrode. The electrode was tested on an electrical test bench and on human subjects in four modalities of EEG activity, namely: (1) spontaneous EEG, (2) sensory event-related potentials, (3) brain stem potentials, and (4) cognitive event-related potentials. The performance of the dry electrode compared favorably with that of the standard wet Ag/AgCl electrodes in terms of skin preparation, no gel requirements (dry), and higher signal-to-noise ratio. In 1999, researchers at Case Western Reserve University led by Hunter Peckham, used 64-electrode EEG skullcap to return limited hand movements to quadriplegic Jim Jatich. As Jatich concentrated on simple but opposite concepts like up and down, his beta-rhythm EEG output was analysed using software to identify patterns in the noise. A basic pattern was identified and used to control a switch: Above average activity was set to on, below average off. As well as enabling Jatich to control a computer cursor the signals were also used to drive the nerve controllers embedded in his hands, restoring some movement.

Electronic neural networks have been deployed which shift the learning phase from the user to the computer. Experiments by scientists at the Fraunhofer Society in 2004 using neural networks led to noticeable improvements within 30 minutes of training.

Experiments by Eduardo Miranda aim to use EEG recordings of mental activity associated with music to allow the disabled to express themselves musically through an encephalophone.

The Emotiv company has been selling a commercial video game controller, known as the Epoc, since December 2009. The Epoc uses electromagnetic sensors.

MEG and MRI



ATR Labs' reconstruction of human vision using fMRI (top row: original image; bottom row: reconstruction from mean of combined readings)

Magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) have both been used successfully as non-invasive BCIs. In a widely reported experiment, fMRI allowed two users being scanned to play Pong in real-time by altering their haemodynamic response or brain blood flow through biofeedback techniques.

fMRI measurements of haemodynamic responses in real time have also been used to control robot arms with a seven second delay between thought and movement.

More recently, research developed in the Advanced Telecommunications Research (ATR) Computational Neuroscience Laboratories in Kyoto, Japan allowed the scientists to reconstruct images directly from the brain and display them on a computer. The article announcing these achievements was the cover story of the journal Neuron of 10 December 2008, While the early results are limited to black and white images of 10x10 squares (pixels), according to the researchers further development of the technology may make it possible to achieve color images, and even view or record dreams.

Commercialization and companies

John Donoghue and fellow researchers founded Cyberkinetics. The company markets its electrode arrays under the BrainGate product name and has set the development of practical BCIs for humans as its major goal. The BrainGate is based on the Utah Array developed by Dick Normann.

Philip Kennedy founded Neural Signals in 1987 to develop BCIs that would allow paralysed patients to communicate with the outside world and control external devices. As well as an invasive BCI, the company also sells an implant to restore speech. Neural Signals' Brain Communicator BCI device uses glass cones containing microelectrodes coated with proteins to encourage the electrodes to bind to neurons.

Although 16 paying patients were treated using William Dobelle's vision BCI, new implants ceased within a year of Dobelle's death in 2004. A company controlled by Dobelle, Avery Biomedical Devices, and Stony Brook University are continuing development of the implant, which has not yet received Food and Drug Administration approval in the United States for human implantation.

Ambient, at a TI developers conference in early 2008, demoed a product they have in development call The Audeo. The Audeo is being developed to create a human–computer interface for communication without the need of physical motor control or speech production. Using signal processing, unpronounced speech representing the thought of the mind can be translated from intercepted neurological signals.

Mindball is a product developed and commercialized by Interactive Productline in which players compete to control a ball's movement across a table by becoming more relaxed and focused. Interactive Productline is a Swedish company whose objective is to develop and sell easy understandable EEG products that train the ability to relax and focus.

An Austrian company, Guger Technologies, g.tec, has been offering Brain Computer Interface systems since 1999. The company provides base BCI models as development platforms for the research community to build upon, including the P300 Speller, Motor Imagery, and mu-rhythm. They commercialized a Steady State Visual Evoked Potiential BCI solution in 2008 with 4 degrees of machine control.

A Spanish company, Starlab, has entered this market in 2009 with a wireless 4-channel system called Enobio. Designed for research purposes the system provides a platform for application development.

There are three main consumer-devices commercial-competitors in this area (launch date mentioned in brackets) which have launched such devices primarily for gaming- and PC-users:

- Neural Impulse Actuator (April, 2008)
- Emotiv Systems (December, 2009)

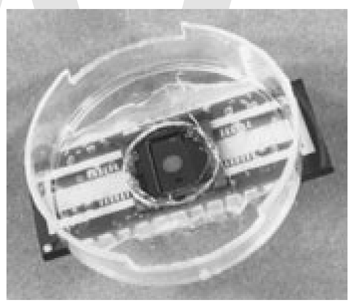
- NeuroSky (MindSet – June, 2009; Uncle Milton Force Trainer – Fall 2009, Mattel MindFlex – Summer, 2009)

Synthetic telepathy

Research is ongoing into synthetic or computer-mediated telepathy which would allow user-to-user communication through analysis of neural signals. The research aims to detect and analyze the word-specific neural signals, using EEG, which occur before speech is vocalized, and to see if the patterns are generalizable. As of 2009, the research is focused on military uses.

Cell-culture BCIs

Researchers have built devices to interface with neural cells and entire neural networks in cultures outside animals. As well as furthering research on animal implantable devices, experiments on cultured neural tissue have focused on building problem-solving networks, constructing basic computers and manipulating robotic devices. Research into techniques for stimulating and recording from individual neurons grown on semiconductor chips is sometimes referred to as neuroelectronics or neurochips.



World first: Neurochip developed by Caltech researchers Jerome Pine and Michael Maher

Development of the first working neurochip was claimed by a Caltech team led by Jerome Pine and Michael Maher in 1997. The Caltech chip had room for 16 neurons.

In 2003, a team led by Theodore Berger at the University of Southern California started work on a neurochip designed to function as an artificial or prosthetic hippocampus. The neurochip was designed to function in rat brains and is intended as a prototype for the eventual development of higher-brain prosthesis. The hippocampus was chosen because it is thought to be the most ordered and structured part of the brain and is the most studied area. Its function is to encode experiences for storage as long-term memories elsewhere in the brain.

Thomas DeMarse at the University of Florida used a culture of 25,000 neurons taken from a rat's brain to fly a F-22 fighter jet aircraft simulator. After collection, the cortical neurons were cultured in a petri dish and rapidly began to reconnect themselves to form a living neural network. The cells were arranged over a grid of 60 electrodes and used to control the pitch and yaw functions of the simulator. The study's focus was on understanding how the human brain performs and learns computational tasks at a cellular level.

Ethical considerations

There has not been a vigorous debate about the ethical implications of BCIs, even though there are several commercially available systems such as brain pacemakers used to treat neurological conditions, and could theoretically be used to modify other behaviours.

Important topics in the neuroethical debate are:

- obtaining informed consent from people who have difficulty communicating,
- risk/benefit analysis,
- shared responsibility of BCI teams (e.g. how to ensure that responsible group decisions can be made),
- the consequences of BCI technology for the quality of life of patients and their families,
- side-effects (e.g. neurofeedback of sensorimotor rhythm training is reported to affect sleep quality),
- personal responsibility and its possible constraints (e.g. who is responsible for erroneous actions with a neuroprosthesis),
- issues concerning personality and personhood and its possible alteration,
- therapeutic applications and their possible exceedance,
- questions of research ethics that arise when progressing from animal experimentation to application in human subjects,
- mind-reading and privacy,
- mind-control,
- selective enhancement and social stratification, and
- communication to the media.

Emory University neuroscience professor Michael Crutcher has expressed concern about BCIs, specifically ear and eye implants: "If only the rich can afford it, it puts everyone else at a disadvantage." Clausen concluded in 2009 that “BCIs pose ethical challenges, but these are conceptually similar to those that bioethicists have addressed for other realms of therapy”. Moreover, he suggests that bioethics is well-prepared to deal with the issues that arise with BCI technologies. Haselager and colleagues pointed out that expectations of BCI efficacy and value play a great role in ethical analysis and the way BCI scientists should approach media. Furthermore, standard protocols can be implemented to ensure ethically sound informed-consent procedures with locked-in patients.

Researchers are well aware that sound ethical guidelines, appropriately moderated enthusiasm in media coverage and education about BCI systems will be of utmost importance for the societal acceptance of this technology. Thus, recently more effort is made inside the BCI community to create consensus on ethical guidelines for BCI research, development and dissemination.

BCI based toys

Recently a number of companies have scaled back medical grade EEG technology (and in one case, NeuroSky, rebuilt the technology from the ground up) to create inexpensive BCIs. This technology has been built into toys and gaming devices; some of these toys have been extremely commercially successful like the NeuroSky and Mattel MindFlex.

- In 2006 Sony patented a neural interface system allowing radio waves to affect signals in the neural cortex.
- In 2007 NeuroSky released the first affordable consumer based EEG along with the game NeuroBoy. This was also the first large scale EEG device to use dry sensor technology.
- In 2008 OCZ Technology developed device for use in video games relying primarily on electromyography.
- In 2008 the Final Fantasy developer Square Enix announced that it was partnering with NeuroSky to create a game, Judecca.
- In 2009 Mattel partnered with NeuroSky to release the Mindflex, a game that used an EEG to steer a ball through an obstacle course. By far the best selling consumer based EEG to date.
- In 2009 Uncle Milton Industries partnered with NeuroSky to release the Star Wars Force Trainer, a game designed to create the illusion of possessing the force.
- In 2009 Emotiv released the EPOC, a 14 channel EEG device. The EPOC is the first commercial BCI to use dry sensor technology, which can be dampened with a saline solution for a better connection.
- In 2010 NeuroSky added an electromyography function for recognising eye blink to the MindSet.

Chapter 10

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.