Biomedical Engineering

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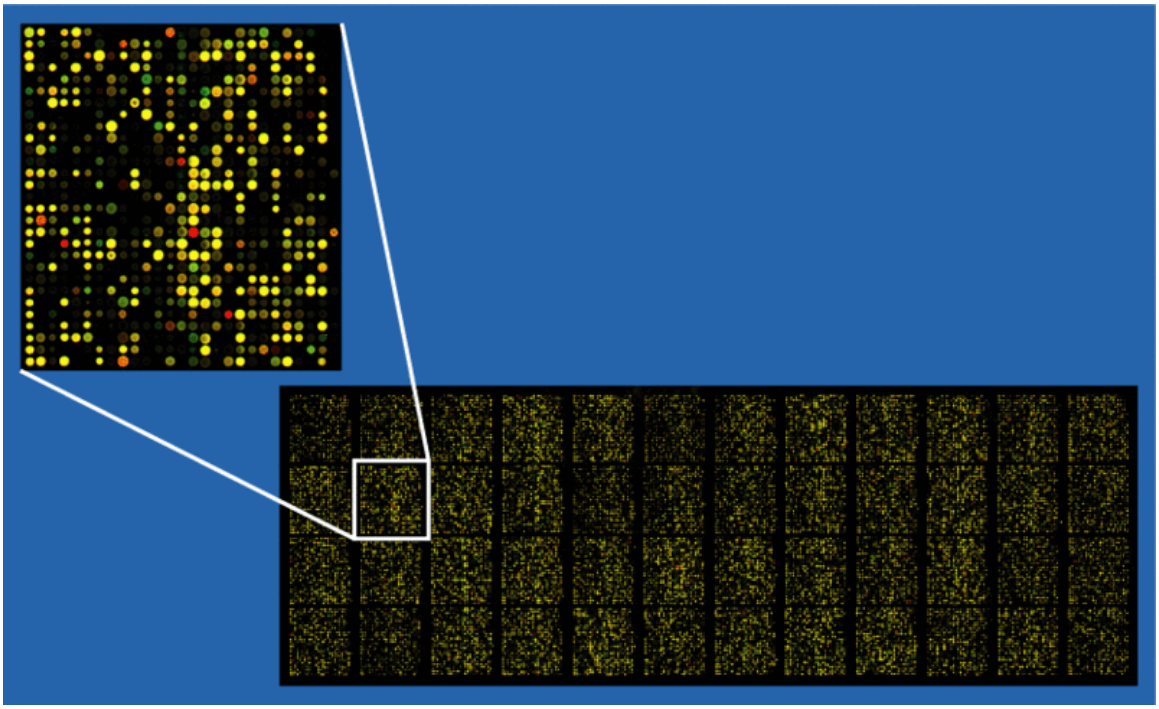
Chapter 1

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

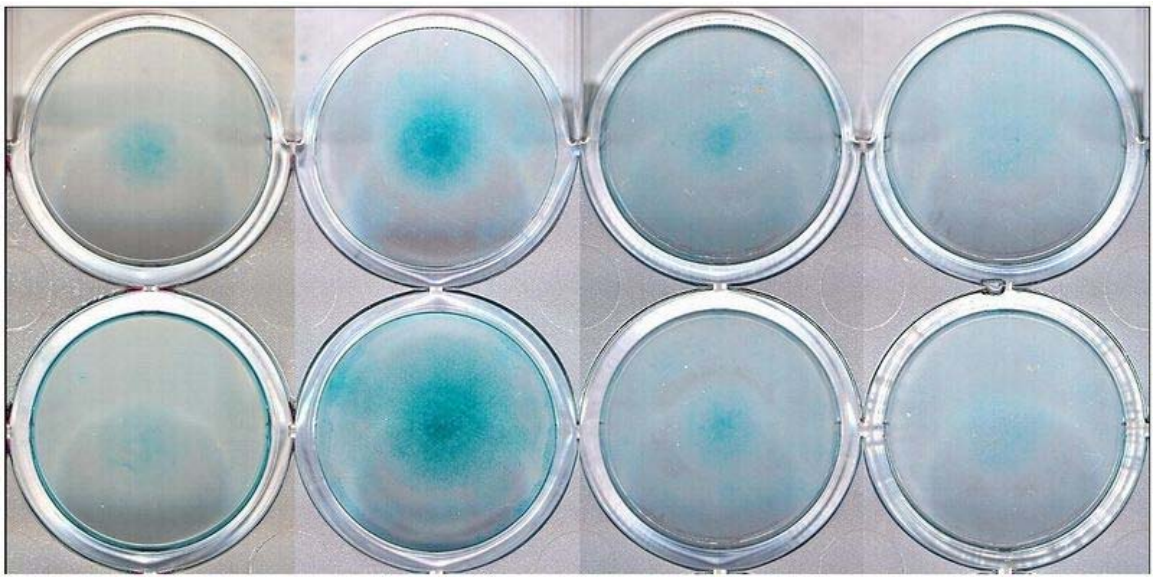
Biotechnology can be a somewhat ambiguous term, sometimes loosely used interchangeably with BME in general; however, it more typically denotes specific products which use "biological systems, living organisms, or derivatives thereof." Even some complex "medical devices" (see below) can reasonably be 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 (not a medical application per se), 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

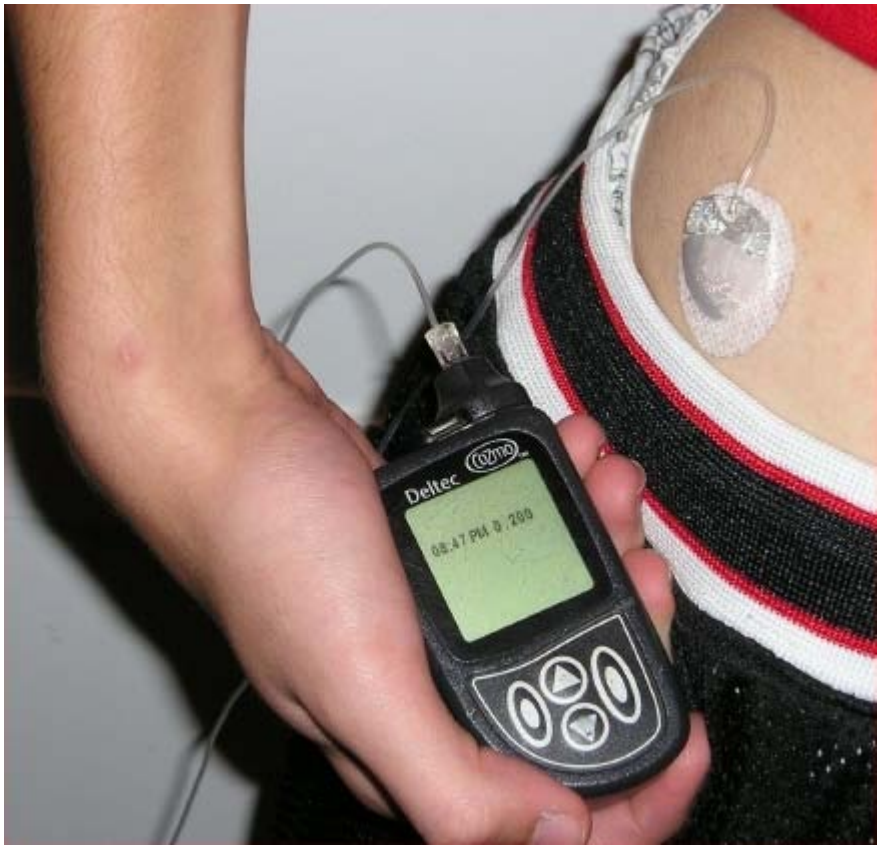
Pharmaceutical Engineering is sometimes regarded as a branch of biomedical engineering, and sometimes a branch of chemical engineering; in practice, it is very much a hybrid sub-discipline (as many BME fields are). Aside from those pharmaceutical products directly incorporating biological agents or materials, 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.

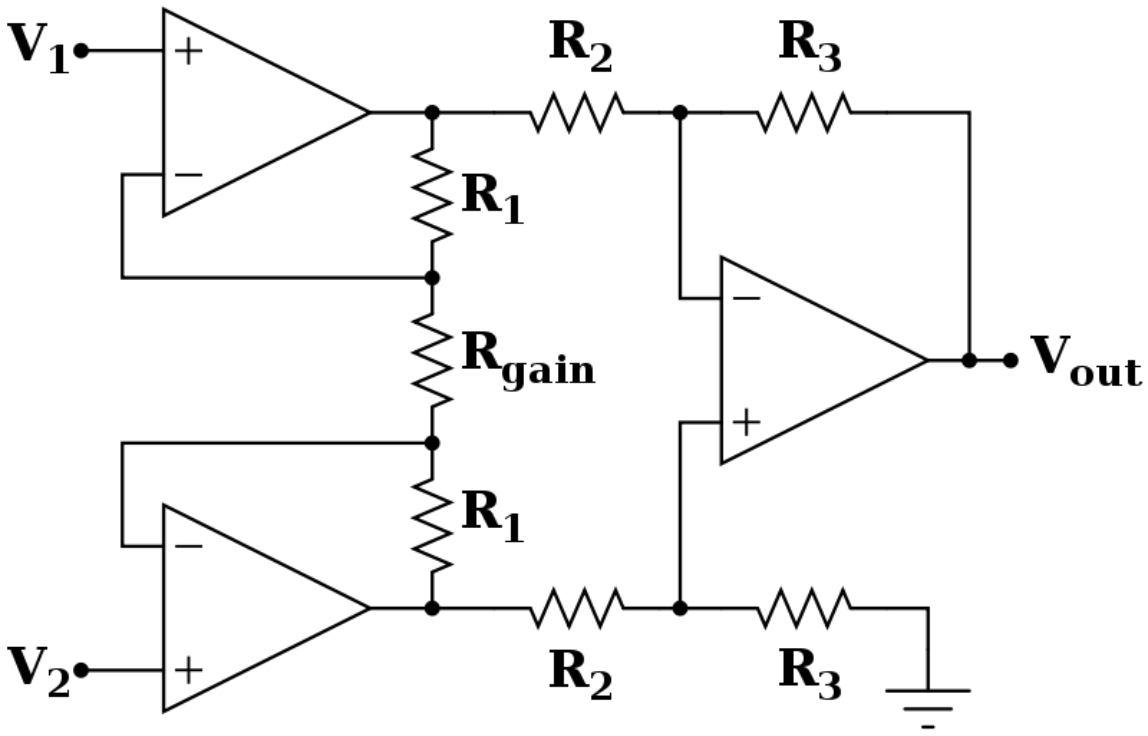
A medical device is intended for use in:

- 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.

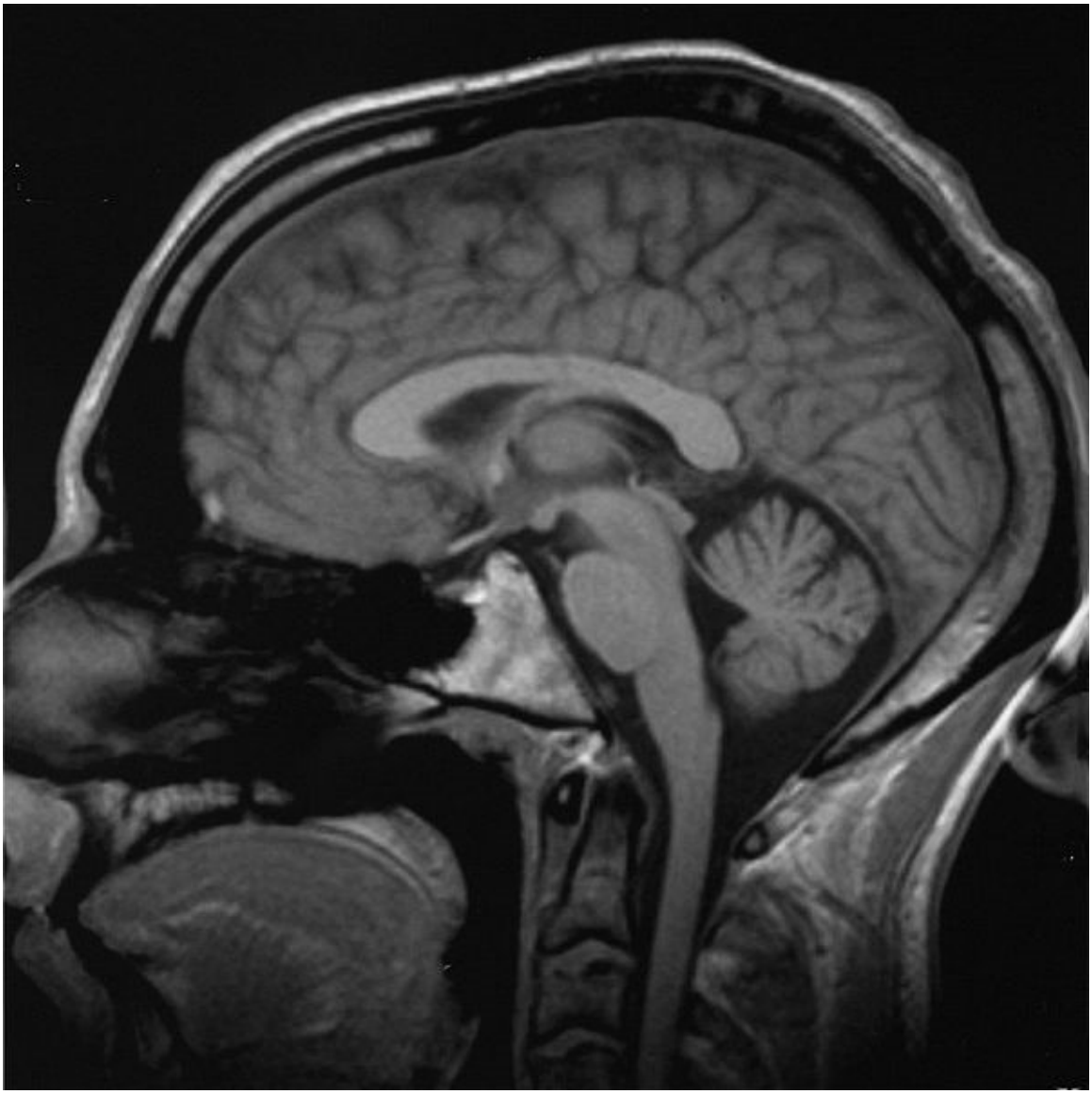
Medical devices are regulated and classified (in the US) as follows:

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.

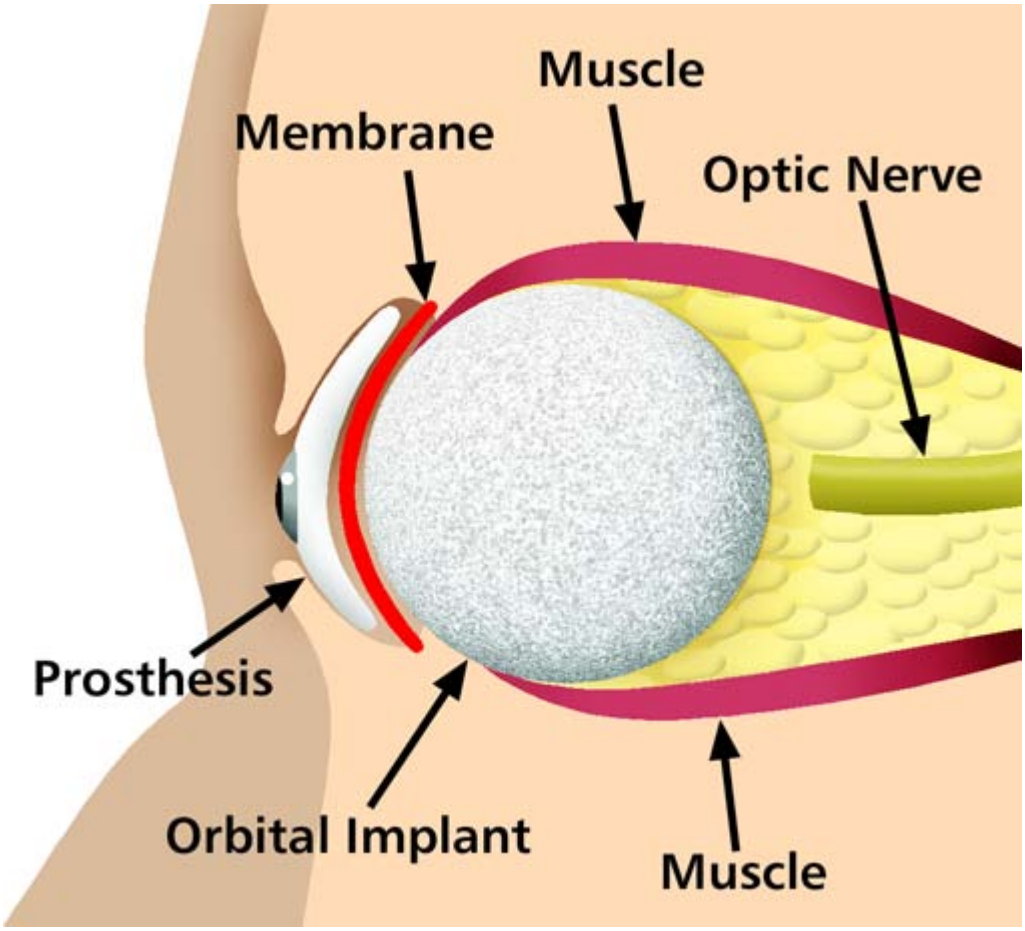
Imaging technologies are often essential to medical diagnosis, and are typically the most complex equipment found in a hospital including:

- 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.



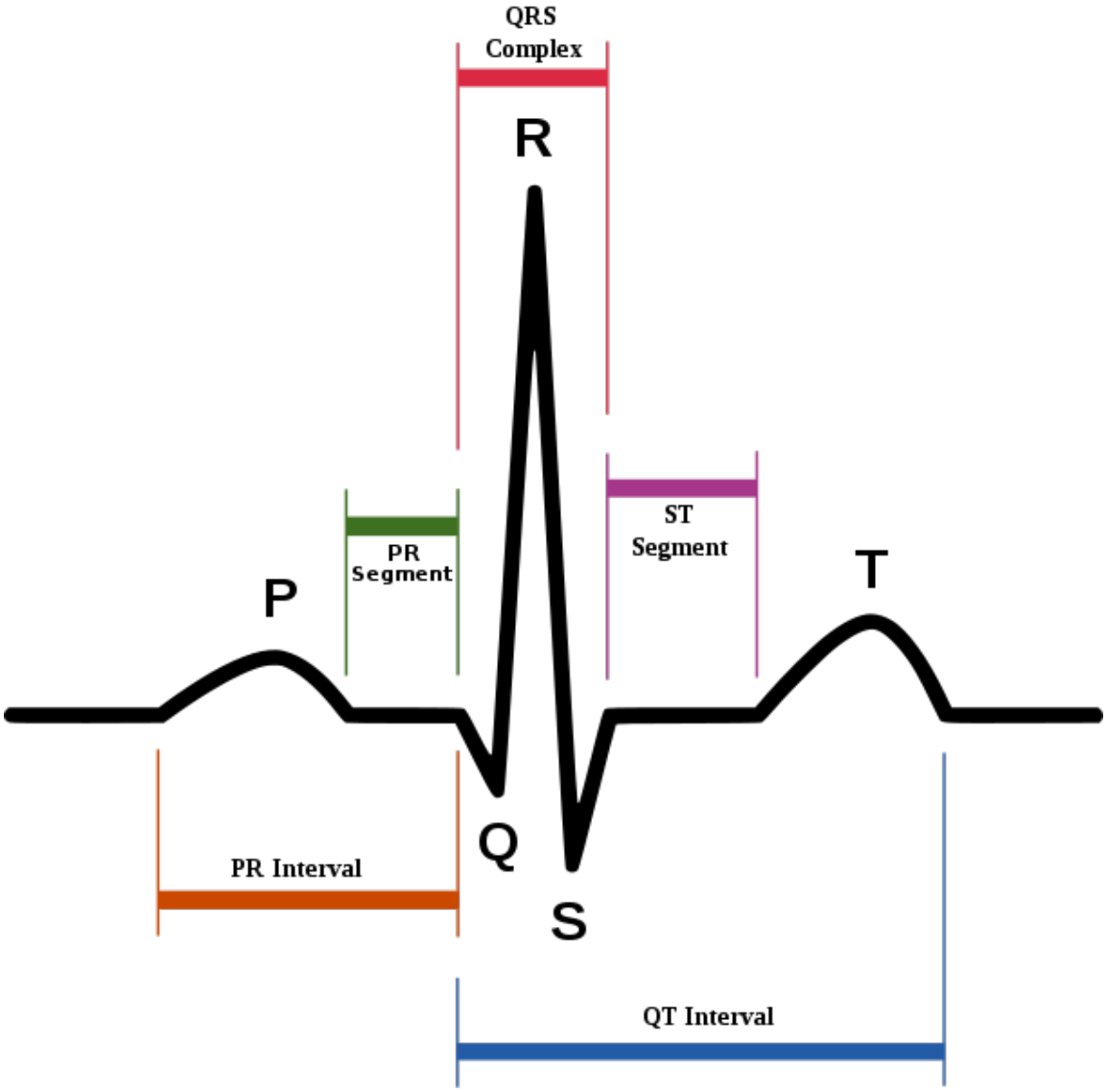
A prosthetic eye, an example of a biomedical engineering application of mechanical engineering and biocompatible materials to ophthalmology.

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.



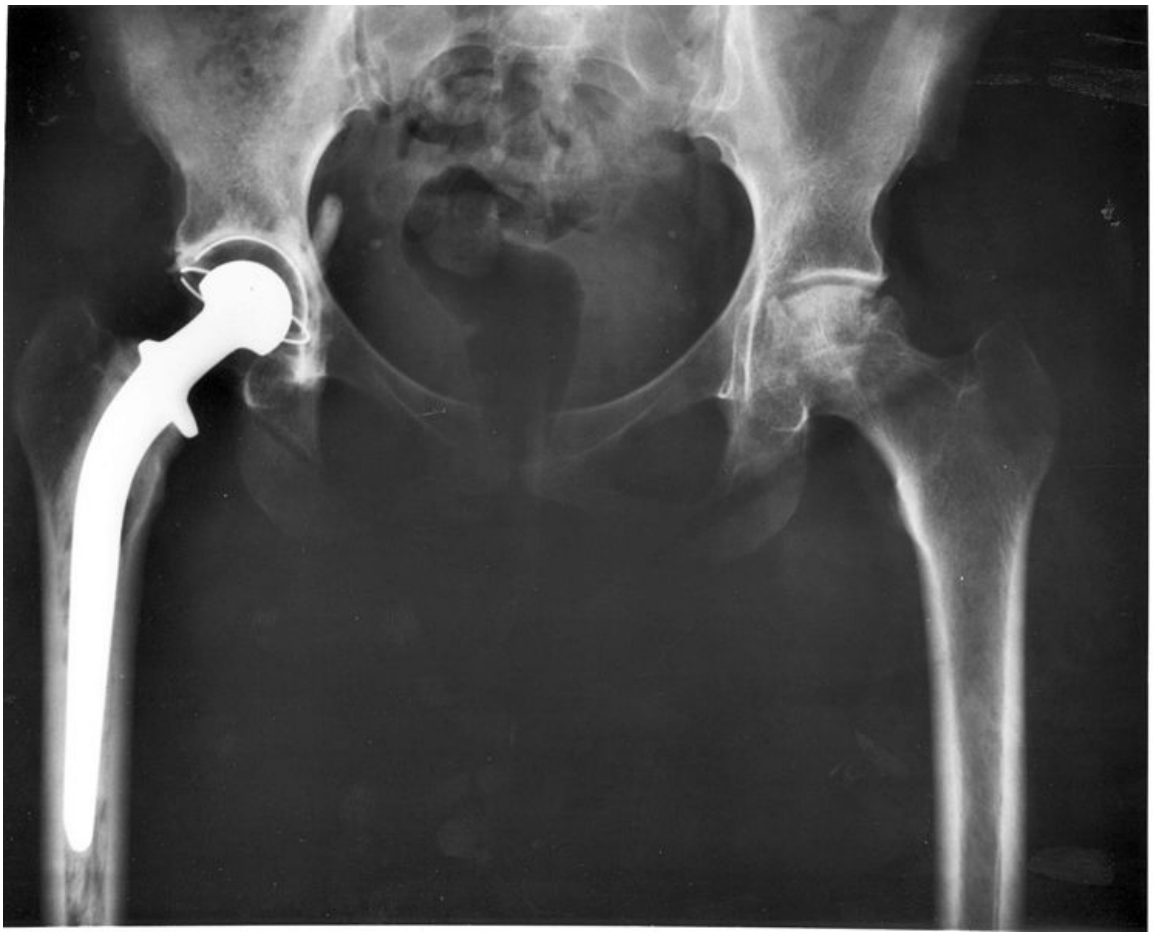
Schematic representation of a normal ECG trace showing *sinus rhythm;* an example of widely-used clinical medical equipment (operates by applying electronic engineering to electrophysiology and medical diagnosis.

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.

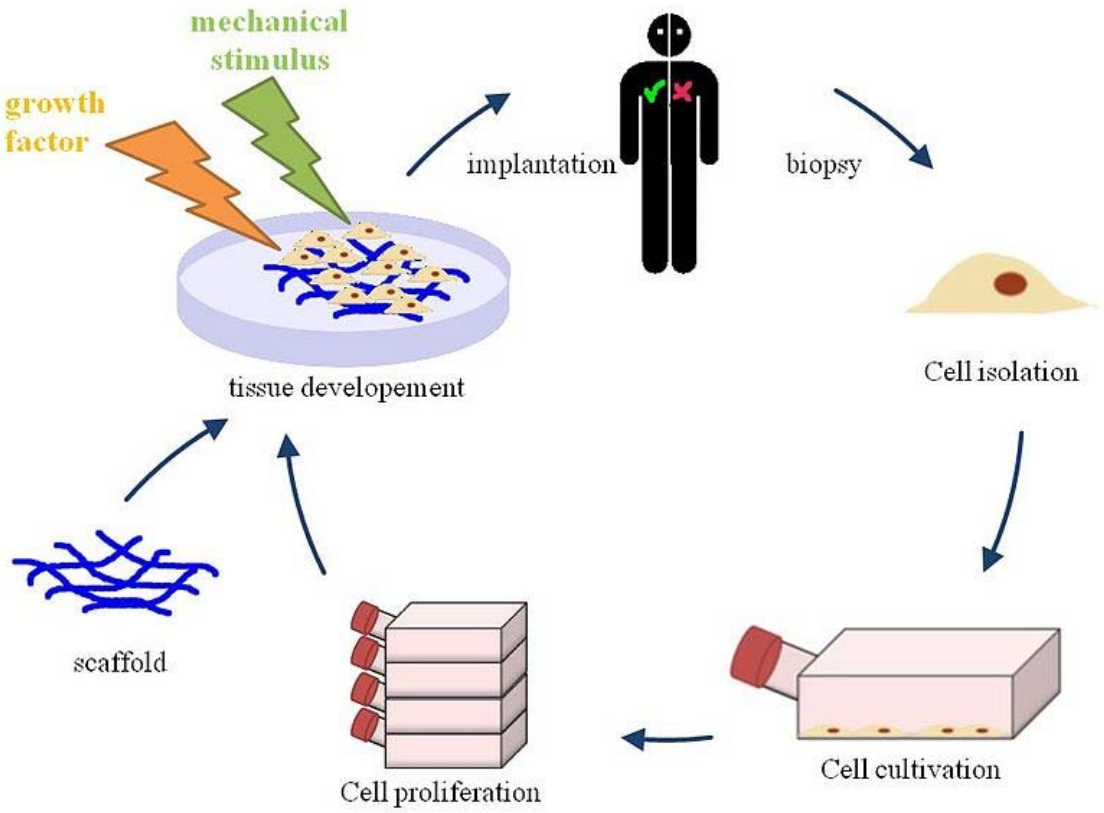
Founding figures

- 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 2

Tissue Engineering

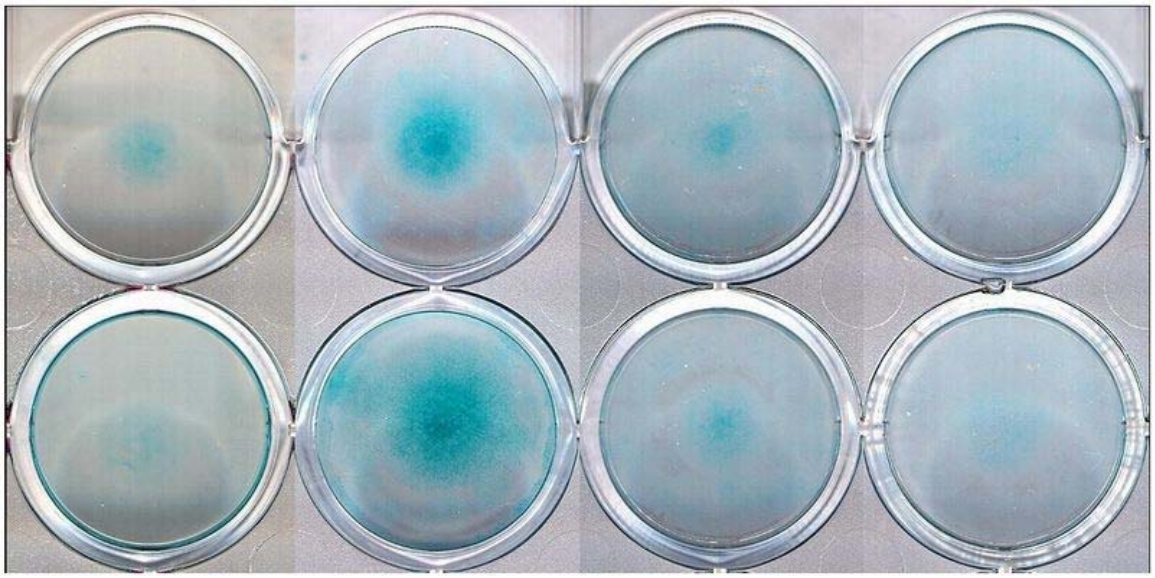


Principle of tissue engineering

Tissue engineering was once categorized as a sub-field of bio materials, but having grown in scope and importance it can be considered as a field in its own right. It is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physio-chemical factors to improve or replace biological functions. While most definitions of tissue engineering cover a broad range of applications, in practice the term is closely associated with applications that repair or replace portions of or whole tissues (i.e., bone, cartilage, blood vessels, bladder, skin etc.). Often, the tissues involved require certain mechanical and structural properties for proper functioning. The

term has also been applied to efforts to perform specific biochemical functions using cells within an artificially-created support system (e.g. an artificial pancreas, or a bio artificial liver). The term **regenerative medicine** is often used synonymously with tissue engineering, although those involved in regenerative medicine place more emphasis on the use of stem cells to produce tissues.

Overview



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

A commonly applied definition of tissue engineering, as stated by Langer and Vacanti, is "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ". Tissue engineering has also been defined as "understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use." A further description goes on to say that an "underlying supposition of tissue engineering is that the employment of natural biology of the system will allow for greater success in developing therapeutic strategies aimed at the replacement, repair, maintenance, and/or enhancement of tissue function."

Powerful developments in the multidisciplinary field of tissue engineering have yielded a novel set of tissue replacement parts and implementation strategies. Scientific advances in biomaterials, stem cells, growth and differentiation factors, and biomimetic environments have created unique opportunities to fabricate tissues in the laboratory from combinations of engineered extracellular matrices ("scaffolds"), cells, and biologically active molecules. Among the major challenges now facing tissue engineering is the need for more complex functionality, as well as both functional and biomechanical stability in laboratory-grown tissues destined for transplantation. The continued success of tissue engineering, and the eventual development of true human replacement parts, will grow

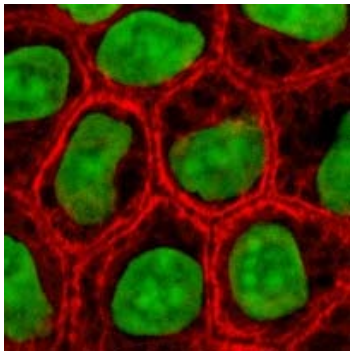
from the convergence of engineering and basic research advances in tissue, matrix, growth factor, stem cell, and developmental biology, as well as materials science and bio informatics.

In 2003, the NSF published a report entitled "The Emergence of Tissue Engineering as a Research Field" , which gives a thorough description of the history of this field.

Examples

- Tissue engineered autologous heartvalves and vessels - workgroup of Dr.med.S.Jockenhoevel at the Department of Applied Medical Engineering (RWTH-Aachen University,Germany)
- In vitro meat — Edible artificial animal muscle tissue cultured *in vitro*.
- Bioartificial liver device — several research efforts have produced hepatic assist devices utilizing living hepatocytes.
- Artificial pancreas — research involves using islet cells to produce and regulate insulin, particularly in cases of diabetes.
- Artificial bladders — Anthony Atala (Wake Forest University) has successfully implanted artificially grown bladders into seven out of approximately 20 human test subjects as part of a long-term experiment.
- Cartilage — lab-grown tissue was successfully used to repair knee cartilage.
- Doris Taylor's heart in a jar
- Tissue-engineered airway
- Artificial skin constructed from human skin cells embedded in collagen
- Artificial bone marrow
- Artificial bone
- Artificial penis

Cells as building blocks



Stained cells in culture

Tissue engineering utilizes living cells as engineering materials. Examples include using living fibroblasts in skin replacement or repair, cartilage repaired with living chondrocytes, or other types of cells used in other ways.

Cells became available as engineering materials when scientists at Geron Corp. discovered how to extend telomeres in 1998, producing immortalized cell lines. Before this, laboratory cultures of healthy, noncancerous mammalian cells would only divide a fixed number of times, up to the Hayflick limit.

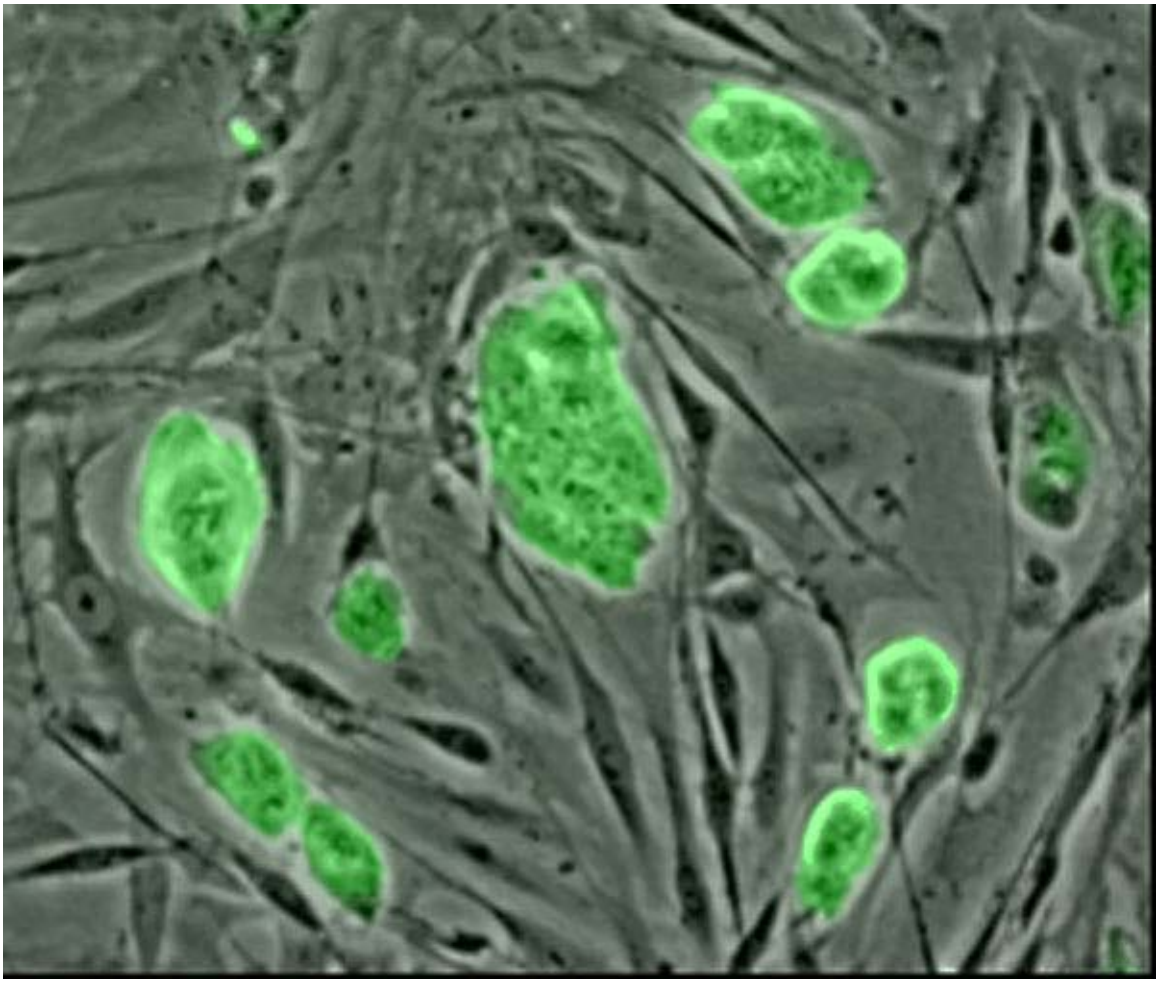
Extraction

From fluid tissues such as blood, cells are extracted by bulk methods, usually centrifugation or apheresis. From solid tissues, extraction is more difficult. Usually the tissue is minced, and then digested with the enzymes trypsin or collagenase to remove the extracellular matrix that holds the cells. After that, the cells are free floating, and extracted using centrifugation or apheresis.
Digestion with trypsin is very dependent on temperature. Higher temperatures digest the matrix faster, but create more damage. Collagenase is less temperature dependent, and damages fewer cells, but takes longer and is a more expensive reagent.

Types of cells

Cells are often categorized by their source:

- **Autologous** cells are obtained from the same individual to which they will be reimplanted. Autologous cells have the fewest problems with rejection and pathogen transmission, however in some cases might not be available. For example in genetic disease suitable autologous cells are not available. Also very ill or elderly persons, as well as patients suffering from severe burns, may not have sufficient quantities of autologous cells to establish useful cell lines. Moreover since this category of cells needs to be harvested from the patient, there are also some concerns related to the necessity of performing such surgical operations that might lead to donor site infection or chronic pain. Autologous cells also must be cultured from samples before they can be used: this takes time, so autologous solutions may not be very quick. Recently there has been a trend towards the use of mesenchymal stem cells from bone marrow and fat. These cells can differentiate into a variety of tissue types, including bone, cartilage, fat, and nerve. A large number of cells can be easily and quickly isolated from fat, thus opening the potential for large numbers of cells to be quickly and easily obtained.



Mouse embryonic stem cells. **More lab photos**

- **Allogeneic** cells come from the body of a donor of the same species. While there are some ethical constraints to the use of human cells for *in vitro* studies, the employment of dermal fibroblasts from human foreskin has been demonstrated to be immunologically safe and thus a viable choice for tissue engineering of skin.

- **Xenogenic** cells are these isolated from individuals of another species. In particular animal cells have been used quite extensively in experiments aimed at the construction of cardiovascular implants.

- **Syngenic** or **isogenic** cells are isolated from genetically identical organisms, such as twins, clones, or highly inbred research animal models.

- **Primary** cells are from an organism.

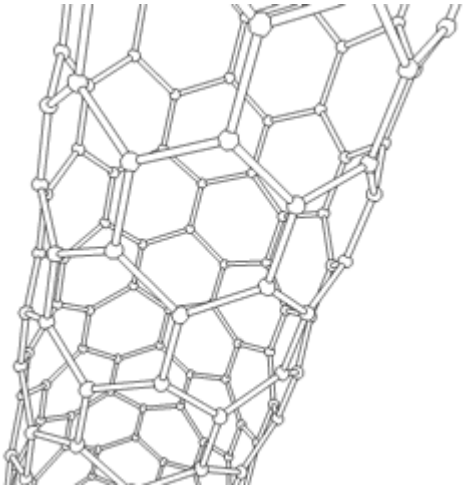
- **Secondary** cells are from a cell bank.

- **Stem cells** are undifferentiated cells with the ability to divide in culture and give rise to different forms of specialized cells. According to their source stem cells are divided into "adult" and "embryonic" stem cells, the first class being multipotent and the latter mostly pluripotent; some cells are totipotent, in the earliest stages of the embryo. While there is still a large ethical debate related with the use of embryonic stem cells, it is thought that stem cells may be useful for the repair of diseased or damaged tissues, or may be used to grow new organs.

Scaffolds

Cells are often implanted or 'seeded' into an artificial structure capable of supporting three-dimensional tissue formation. These structures, typically called scaffolds, are often critical, both *ex vivo* as well as *in vivo*, to recapitulating the *in vivo* milieu and allowing cells to influence their own microenvironments. Scaffolds usually serve at least one of the following purposes:

- Allow cell attachment and migration
- Deliver and retain cells and biochemical factors
- Enable diffusion of vital cell nutrients and expressed products
- Exert certain mechanical and biological influences to modify the behaviour of the cell phase



Carbon nanotubes are among the numerous candidates for tissue engineering scaffolds since they are biocompatible, resistant to biodegradation and can be functionalized with biomolecules. However, the possibility of toxicity with non-biodegradable nano-materials is not fully understood.

To achieve the goal of tissue reconstruction, scaffolds must meet some specific requirements. A high porosity and an adequate pore size are necessary to facilitate cell seeding and diffusion throughout the whole structure of both cells and nutrients. Biodegradability is often an essential factor since scaffolds should preferably be absorbed by the surrounding tissues without the necessity of a surgical removal. The rate at which

degradation occurs has to coincide as much as possible with the rate of tissue formation: this means that while cells are fabricating their own natural matrix structure around themselves, the scaffold is able to provide structural integrity within the body and eventually it will break down leaving the neotissue, newly formed tissue which will take over the mechanical load. Injectability is also important for clinical uses. Recent research on organ printing is showing how crucial a good control of the 3D environment is to insure reproducibility of experiments and offer better results.

Materials

Many different materials (natural and synthetic, biodegradable and permanent) have been investigated. Most of these materials have been known in the medical field before the advent of tissue engineering as a research topic, being already employed as bioresorbable sutures. Examples of these materials are collagen and some polyesters.

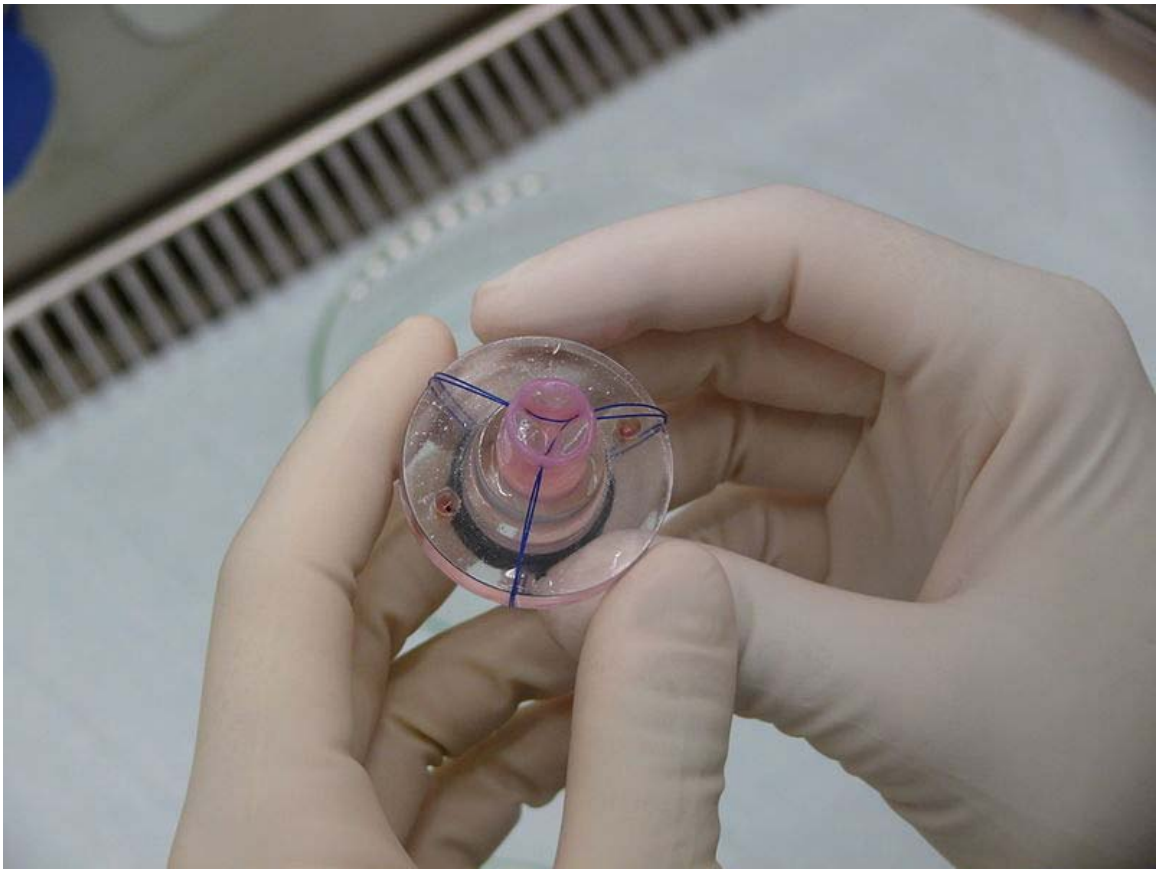
New biomaterials have been engineered to have ideal properties and functional customization: injectability, synthetic manufacture, biocompatibility, non-immunogenicity, transparency, nano-scale fibers, low concentration, resorption rates, etc. PuraMatrix, originating from the MIT labs of Zhang, Rich, Grodzinsky and Langer is one of these new biomimetic scaffold families which has now been commercialized and is impacting clinical tissue engineering.

A commonly used synthetic material is PLA - polylactic acid. This is a polyester which degrades within the human body to form lactic acid, a naturally occurring chemical which is easily removed from the body. Similar materials are polyglycolic acid (PGA) and polycaprolactone (PCL): their degradation mechanism is similar to that of PLA, but they exhibit respectively a faster and a slower rate of degradation compared to PLA.

Scaffolds may also be constructed from natural materials: in particular different derivatives of the extracellular matrix have been studied to evaluate their ability to support cell growth. Proteic materials, such as collagen or fibrin, and polysaccharidic materials, like chitosan or glycosaminoglycans (GAGs), have all proved suitable in terms of cell compatibility, but some issues with potential immunogenicity still remains. Among GAGs hyaluronic acid, possibly in combination with cross linking agents (e.g. glutaraldehyde, water soluble carbodiimide, etc...), is one of the possible choices as scaffold material. Functionalized groups of scaffolds may be useful in the delivery of small molecules (drugs) to specific tissues. Another form of scaffold under investigation is decellularised tissue extracts whereby the remaining cellular remnants/extracellular matrices act as the scaffold.

Synthesis

tissue engineered vascular graft



tissue engineered heart valve

A number of different methods have been described in literature for preparing porous structures to be employed as tissue engineering scaffolds. Each of these techniques presents its own advantages, but none are free of drawbacks.

- **Nanofiber Self-Assembly**: Molecular self-assembly is one of the few methods for creating biomaterials with properties similar in scale and chemistry to that of the natural in vivo extracellular matrix (ECM). Moreover, these hydrogel scaffolds have shown superiority in in vivo toxicology and biocompatibility compared to traditional macroscaffolds and animal-derived materials.

- **Textile technologies**: These techniques include all the approaches that have been successfully employed for the preparation of non-woven meshes of different polymers. In particular, non-woven polyglycolide structures have been tested for tissue engineering applications: such fibrous structures have been found useful to grow different types of cells. The principal drawbacks are related to the difficulties in obtaining high porosity and regular pore size.

- **Solvent Casting & Particulate Leaching (SCPL)**: This approach allows for the preparation of porous structures with regular porosity, but with a limited thickness. First, the polymer is dissolved into a suitable organic solvent (e.g.

polylactic acid could be dissolved into dichloromethane), then the solution is cast into a mold filled with porogen particles. Such porogen can be an inorganic salt like sodium chloride, crystals of saccharose, gelatin spheres or paraffin spheres. The size of the porogen particles will affect the size of the scaffold pores, while the polymer to porogen ratio is directly correlated to the amount of porosity of the final structure. After the polymer solution has been cast the solvent is allowed to fully evaporate, then the composite structure in the mold is immersed in a bath of a liquid suitable for dissolving the porogen: water in the case of sodium chloride, saccharose and gelatin or an aliphatic solvent like hexane for use with paraffin. Once the porogen has been fully dissolved, a porous structure is obtained. Other than the small thickness range that can be obtained, another drawback of SCPL lies in its use of organic solvents which must be fully removed to avoid any possible damage to the cells seeded on the scaffold.

- **Gas Foaming**: To overcome the need to use organic solvents and solid porogens, a technique using gas as a porogen has been developed. First, disc-shaped structures made of the desired polymer are prepared by means of compression molding using a heated mold. The discs are then placed in a chamber where they are exposed to high pressure CO_2 for several days. The pressure inside the chamber is gradually restored to atmospheric levels. During this procedure the pores are formed by the carbon dioxide molecules that abandon the polymer, resulting in a sponge-like structure. The main problems resulting from such a technique are caused by the excessive heat used during compression molding (which prohibits the incorporation of any temperature labile material into the polymer matrix) and by the fact that the pores do not form an interconnected structure.

- **Emulsification/Freeze-drying**: This technique does not require the use of a solid porogen like SCPL. First, a synthetic polymer is dissolved into a suitable solvent (e.g. polylactic acid in dichloromethane) then water is added to the polymeric solution and the two liquids are mixed in order to obtain an emulsion. Before the two phases can separate, the emulsion is cast into a mold and quickly frozen by means of immersion into liquid nitrogen. The frozen emulsion is subsequently freeze-dried to remove the dispersed water and the solvent, thus leaving a solidified, porous polymeric structure. While emulsification and freeze-drying allow for a faster preparation when compared to SCPL (since it does not require a time consuming leaching step), it still requires the use of solvents. Moreover, pore size is relatively small and porosity is often irregular. Freeze-drying by itself is also a commonly employed technique for the fabrication of scaffolds. In particular, it is used to prepare collagen sponges: collagen is dissolved into acidic solutions of acetic acid or hydrochloric acid that are cast into a mold, frozen with liquid nitrogen and then lyophilized.

- **Thermally Induced Phase Separation (TIPS)**: Similar to the previous technique, this phase separation procedure requires the use of a solvent with a low melting point that is easy to sublime. For example dioxane could be used to

dissolve polylactic acid, then phase separation is induced through the addition of a small quantity of water: a polymer-rich and a polymer-poor phase are formed. Following cooling below the solvent melting point and some days of vacuum-drying to sublime the solvent, a porous scaffold is obtained. Liquid-liquid phase separation presents the same drawbacks of emulsification/freeze-drying.

- **Electrospinning**: A highly versatile technique that can be used to produce continuous fibers from submicron to nanometer diameters. In a typical electrospinning set-up, a solution is fed through a spinneret and a high voltage is applied to the tip. The buildup of electrostatic repulsion within the charged solution, causes it to eject a thin fibrous stream. A mounted collector plate or rod with an opposite or grounded charge draws in the continuous fibers, which arrive to form a highly porous network. The primary advantages of this technique are its simplicity and ease of variation. At a laboratory level, a typical electrospinning set-up only requires a high voltage power supply (up to 30 kV), a syringe, a flat tip needle and a conducting collector. By modifying variables such as the distance to collector, magnitude of applied voltage, or solution flow rate—researchers can dramatically change the overall scaffold architecture.

- **CAD/CAM Technologies**: Because most of the above techniques are limited when it comes to the control of porosity and pore size, computer assisted design and manufacturing techniques have been introduced to tissue engineering. First, a three-dimensional structure is designed using CAD software, then the scaffold is realized by using ink-jet printing of polymer powders or through Fused Deposition Modeling of a polymer melt.

Assembly methods

One of the continuing, persistent problems with tissue engineering is mass transport limitations. Engineered tissues generally lack an initial blood supply, thus making it difficult for any implanted cells to obtain sufficient oxygen and nutrients to survive, and/or function properly.

Self-assembly may play an important role here, both from the perspective of encapsulating cells and proteins, as well as creating scaffolds on the right physical scale for engineered tissue constructs and cellular ingrowth.

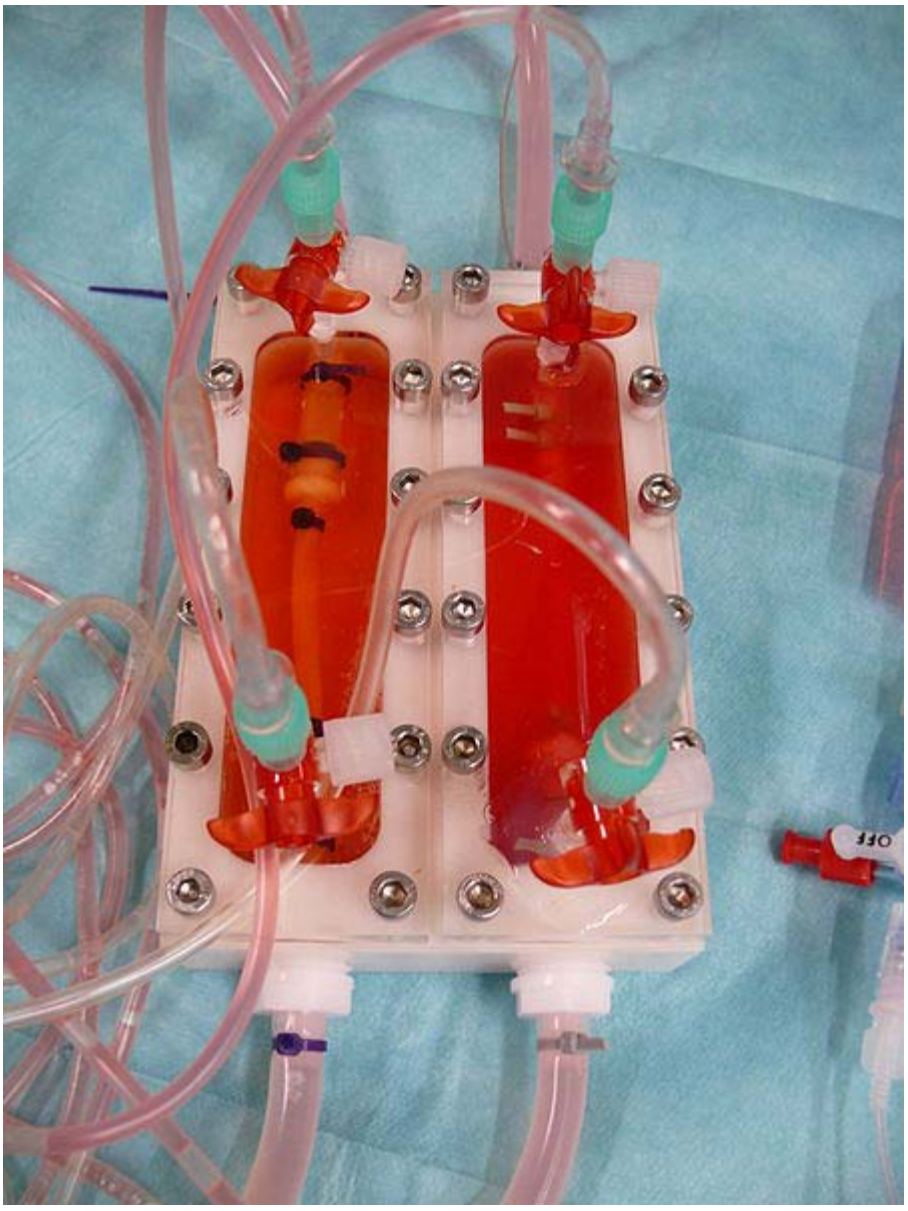
It might be possible to print organs, or possibly entire organisms. A recent innovative method of construction uses an ink-jet mechanism to print precise layers of cells in a matrix of thermoreversable gel. Endothelial cells, the cells that line blood vessels, have been printed in a set of stacked rings. When incubated, these fused into a tube.

Tissue culture

In many cases, creation of functional tissues and biological structures *in vitro* requires extensive culturing to promote survival, growth and inducement of functionality. In

general, the basic requirements of cells must be maintained in culture, which include oxygen, pH, humidity, temperature, nutrients and osmotic pressure maintenance.

Tissue engineered cultures also present additional problems in maintaining culture conditions. In standard cell culture, diffusion is often the sole means of nutrient and metabolite transport. However, as a culture becomes larger and more complex, such as the case with engineered organs and whole tissues, other mechanisms must be employed to maintain the culture, such as the creation of capillary networks within the tissue.



bioreactor for cultivation of vascular grafts

Another issue with tissue culture is introducing the proper factors or stimuli required to induce functionality. In many cases, simple maintenance culture is not sufficient. Growth

factors, hormones, specific metabolites or nutrients, chemical and physical stimuli are sometimes required. For example, certain cells respond to changes in oxygen tension as part of their normal development, such as chondrocytes, which must adapt to low oxygen conditions or hypoxia during skeletal development. Others, such as endothelial cells, respond to shear stress from fluid flow, which is encountered in blood vessels. Mechanical stimuli, such as pressure pulses seem to be beneficial to all kind of cardiovascular tissue such as heart valves, blood vessels or pericardium.

Bioreactors

A bioreactor in tissue engineering, as opposed to industrial bioreactors, is a device that attends to simulate a physiological environment in order to promote cell or tissue growth in vivo. A physiological environment can consist of many different parameters such as temperature and oxygen or carbon dioxide concentration, but can extend to all kinds of biological, chemical or mechanical stimuli. Therefore, there are systems that may include the application of forces or stresses to the tissue or even of electrical current in two- or three-dimensional setups.

In academic and industry research facilities, it is typical for bioreactors to be developed to replicate the specific physiological environment of the tissue being grown (e.g., flex and fluid shearing for heart valve growth). Several general-use and application-specific bioreactors are also commercially available, and may provide static chemical stimulation or combination of chemical and mechanical stimulation.

Chapter 3

Medical Device

A **medical device** is a product which is used for medical purposes in patients, in diagnosis, therapy or surgery. Whereas *medicinal products* (also called *pharmaceuticals*) achieve their principal action by pharmacological, metabolic or immunological means. *Medical devices* act by other means like physical, mechanical, physico-chemical or chemical means. *Medical devices* are included in the category: *Medical technology*.

Medical devices include a wide range of products varying in complexity and application. Examples include tongue depressors, medical thermometers, blood sugar meters, total artificial hearts, fibrin scaffolds, stents and X-ray machines.

The global market of medical devices reached roughly 209 billion US Dollar in 2006 and is expected to grow with an average annual rate of 6 - 9% through 2010.

Definitions

European Union legal framework and definition

Based on the "New Approach", rules relating to the safety and performance of medical devices were harmonised in the EU in the 1990s. The "New Approach", defined in a European Council Resolution of May 1985, represents an innovative way of technical harmonisation. It aims to remove technical barriers to trade and dispel the consequent uncertainty for economic operators allowing for the free movement of goods inside the EU.

The core legal framework consists of 3 directives:

- Directive 90/385/EEC regarding active implantable medical devices;
- Directive 93/42/EEC regarding medical devices;
- Directive 98/79/EC regarding in vitro diagnostic medical devices.

They aim at ensuring a high level of protection of human health and safety and the good functioning of the Single Market. These 3 main directives have been supplemented over

time by several modifying and implementing directives, including the last technical revision brought about by Directive 2007/47 EC.

Directive 2007/47/ec defines a medical device as: *"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings. Devices are to be used for the purpose of:*

- Diagnosis, prevention, monitoring, treatment or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap.
- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception

This includes devices that do not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

The government of each Member State is required to appoint a **Competent Authority** responsible for medical devices. The Competent Authority (CA) is a body with authority to act on behalf of the government of the Member State to ensure that the requirements of the Medical Device Directives are transposed into National Law and are applied. The Competent Authority reports to the Minister of Health in the Member State. • The Competent Authority in one Member State does not have jurisdiction in any other Member State, but they do exchange information and try to reach common positions.

In UK the Medicines and Healthcare products Regulatory Agency (MHRA) acts as a CA, in Italy it is the Ministero Salute (Ministry of Health)

Medical devices must not be mistaken with medicinal products. In the EU, all medical devices must be identified with the CE mark.

Definition in USA by the Food and Drug Administration

Medical Device Definition

A device is:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

-recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

-intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

-intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Definition in Canada by the Food and Drugs Act

The term medical devices, as defined in the Food and Drugs Act, covers a wide range of health or medical instruments used in the treatment, mitigation, diagnosis or prevention of a disease or abnormal physical condition. Health Canada reviews medical devices to assess their safety, effectiveness and quality before being authorized for sale in Canada.

Classification

The regulatory authorities recognize different classes of medical devices, based on their design complexity, their use characteristics, and their potential for harm if misused. Each country or region defines these categories in different ways. The authorities also recognize that some devices are provided in combination with drugs, and regulation of these combination products takes this factor into consideration.

Canada

The Medical Devices Bureau of Health Canada has recognized four classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device. Class I devices present the lowest potential risk and do not require a licence. Class II devices require the manufacturer's declaration of device safety and effectiveness, whereas Class III and IV devices present a greater potential risk and are subject to in-depth scrutiny. . A guidance document for device classification is published by Heath Canada .

Canadian classes of medical devices generally correspond to the European Council Directive 93/42/EEC (MDD) devices as follows: Class IV (Canada) generally corresponds to Class III (ECD), Class III (Canada) generally corresponds to Class IIb (ECD), Class II (Canada) generally corresponds to Class IIa (ECD), and Class I (Canada) generally corresponds to Class I (ECD) . Examples are surgical instruments (Class I); contact lenses, ultrasound scanners (Class II); orthopedic implants, hemodialysis machines (Class III); and cardiac pacemakers (Class IV) .

United States

The Food and Drug Administration has recognized three classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device. The

classification procedures are described in the Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860).

Class I: General controls

Class I devices are subject to the least regulatory control. Class I devices are subject to "General Controls" as are Class II and Class III devices. General controls include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices. Class I devices are not intended for use in supporting or sustaining life or to be of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury. Most Class I devices are exempt from the premarket notification and/or good manufacturing practices regulation. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Class II: General controls with special controls

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. A few Class II devices are exempt from the premarket notification. Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance. Devices in Class II are held to a higher level of assurance than Class I devices, and are designed to perform as indicated without causing injury or harm to patient or user. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

Class III: General controls and premarket approval

A Class III device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices. Such a device needs premarket approval, a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of Class I. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Examples of Class III devices which currently require a premarket notification include implantable pacemaker, pulse generators, HIV diagnostic tests, automated external defibrillators, and endosseous implants.

European Union (EU) and European Free Trade Association (EFTA)

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC. There are basically four classes, ranging from low risk to high risk.

- Class I (including Is & Im)
- Class IIa
- Class IIb
- Class III

The authorization of medical devices is guaranteed by a Declaration of Conformity. This declaration is issued by the manufacturer itself, but for products in Class Is, Im, IIa, IIb or III, it must be verified by a Certificate of Conformity issued by a Notified Body. A Notified Body is a public or private organisation that has been accredited to validate the compliance of the device to the European Directive. Medical devices that pertain to class I (on condition they do not need to be sterilised or are not used to measure a function) can be put on the market purely by self-certification.

The European classification depends on rules that involve the medical device's duration of body contact, its invasive character, its use of an energy source, its effect on the central circulation or nervous system, its diagnostic impact or its incorporation of a medicinal product.

Certified medical devices should have the CE mark on the packaging, insert leaflets, etc.. These packagings should also show harmonised pictograms and EN standardised logos to indicate essential features such as instructions for use, expiry date, manufacturer, sterile, don't reuse, etc.

Radio-frequency identification

Medical devices incorporating RFID

In 2004, the FDA authorized marketing of two different types of medical devices that incorporate radio-frequency identification, or RFID. The first type is the SurgiChip tag, an external surgical marker that is intended to minimize the likelihood of wrong-site, wrong-procedure and wrong-patient surgeries. The tag consists of a label with passive transponder, along with a printer, an encoder and a RFID reader. The tag is labeled and encoded with the patient's name and the details of the planned surgery, and then placed in the patient's chart. On the day of surgery, the adhesive-backed tag is placed on the patient's body near the surgical site. In the operating room the tag is scanned and the information is verified with the patient's chart. Just before surgery, the tag is removed and placed back in the chart.

The second type of RFID medical device is the implantable radiofrequency transponder system for patient identification and health information. One example of this type of medical device is the VeriChip, which includes a passive implanted transponder, inserter and scanner. The chip stores a unique electronic identification code that can be used to access patient identification and corresponding health information in a database. The chip itself does not store health information or a patient's name.

Practical and information security considerations

Companies developing RFID-containing medical devices must consider product development issues common to other medical devices that come into contact with the body, are implanted in the body, or use computer software. For example, as part of product development, a company must implement controls and conduct testing on issues such as product performance, sterility, adverse tissue reactions, migration of the implanted transponder, electromagnetic interference, and software validation.

Medical devices that use RFID technology to store, access, and/or transfer patient information also raise significant issues regarding information security. The FDA defines "information security" as the process of preventing the modification, misuse or denial of use, or the unauthorized use of that information. At its core, this means ensuring the privacy of patient information.

Four components of information security

The FDA has recommended that a company's specifications for implantable RFID-containing medical devices address the following four components of information security: confidentiality, integrity, availability and accountability (CIAA).

- Confidentiality means data and information are disclosed only to authorized persons, entities and processes at authorized times and in the authorized manner. This ensures that no unauthorized users have access to the information.

- Integrity means data and information are accurate and complete, and the accuracy and completeness are preserved. This ensures that the information is correct and has not been improperly modified.

- Availability means data, information and information systems are accessible and usable on a timely basis in the required manner. This ensures that the information will be available when needed.

- Accountability is the application of identification and authentication to ensure that the prescribed access process is followed by an authorized user.

Although the FDA made these recommendations in the context of implantable RFID-containing medical devices, these principles are relevant to all uses of RFID in connection with pharmaceuticals and medical devices.

List of medical devices

High-risk devices

High-risk devices are life supports, critical monitoring, energy emitting and other devices whose failure or misuse is reasonably likely to seriously injure patient or staff. Examples include:

- Anesthesia units
- Anesthesia ventilators
- Apnea monitors
- Argon enhanced coagulation units
- Aspirators
- Auto transfusion units
- Cardiac defibrillator, external or internal
- Electrosurgical units
- External pacemaker
- Fetal monitors
- Heart-lung machine
- Incubators
- Infusion pump
- Invasive blood pressure units
- Pulse oximeters
- Radiation-therapy machines
- Ventilator
- Stent

An example of the stent used in an EVAR procedure

Medium-risk devices

These are devices including many diagnostic instruments whose misuse, failure or absence (e.g. out of service) with no replacement available would have a significant impact on patient care, but would not be likely to cause direct serious injury. Examples include:

- ECG
- EEG
- Treadmills
- Ultrasound sensors

- Phototherapy units
- Endoscopes
- Human-implantable RFID chips
- Surgical drill and saws
- Laparoscopic insufflators
- Phonocardiographs
- radiant warmers (adult)
- Zoophagous agents (e.g., medicinal leeches; medicinal maggots)
- Lytic bacteriophages

Low-risk devices

Devices in this category are those whose failure or misuse is unlikely to result in serious consequences. Examples include:

- Electronic thermometer,
- Breast pumps
- Surgical microscope
- Ultrasonic nebulizers
- Sphygmomanometers
- Surgical table
- Surgical lights.
- Temperature monitor
- Aspirators
- X-ray diagnostic equipment
- Lensometer
- keratometer

Standardization and regulatory concerns

The ISO standards for medical devices are covered by ICS 11.100.20 and 11.040.01 . The quality and risk management regarding the topic for regulatory purposes is convened by ISO 13485 and ISO 14971. Further standards are IEC 60601-1, for electrical devices (mains-powered as well as battery powered) and IEC 62304 for medical software. The US FDA also published a series of guidances for industry regarding this topic against 21 CFR Subchapter H—Medical Devices.

Starting in the late 1980s the FDA increased its involvement in reviewing the development of medical device software. The precipitant for change was a radiation therapy device (Therac-25) that overdosed patients because of software coding errors. FDA is now focused on regulatory oversight on medical device software development process and system-level testing.

A 2011 study by Dr. Diana Zuckerman and Paul Brown of the National Research Center for Women and Families, and Dr. Steven Nissen of the Cleveland Clinic, published in the Archives of Internal Medicine, showed that most medical devices recalled in the last five

years for “serious health problems or death” had been previously approved by the FDA using the less stringent, and cheaper, 501(k) process. In a few cases the devices had been deemed so low-risk that they did not need FDA regulation. Of the 113 devices recalled, 35 were for cardiovacular issues. This may lead to a reevaluation of FDA procedures and better oversight.

Packaging standards

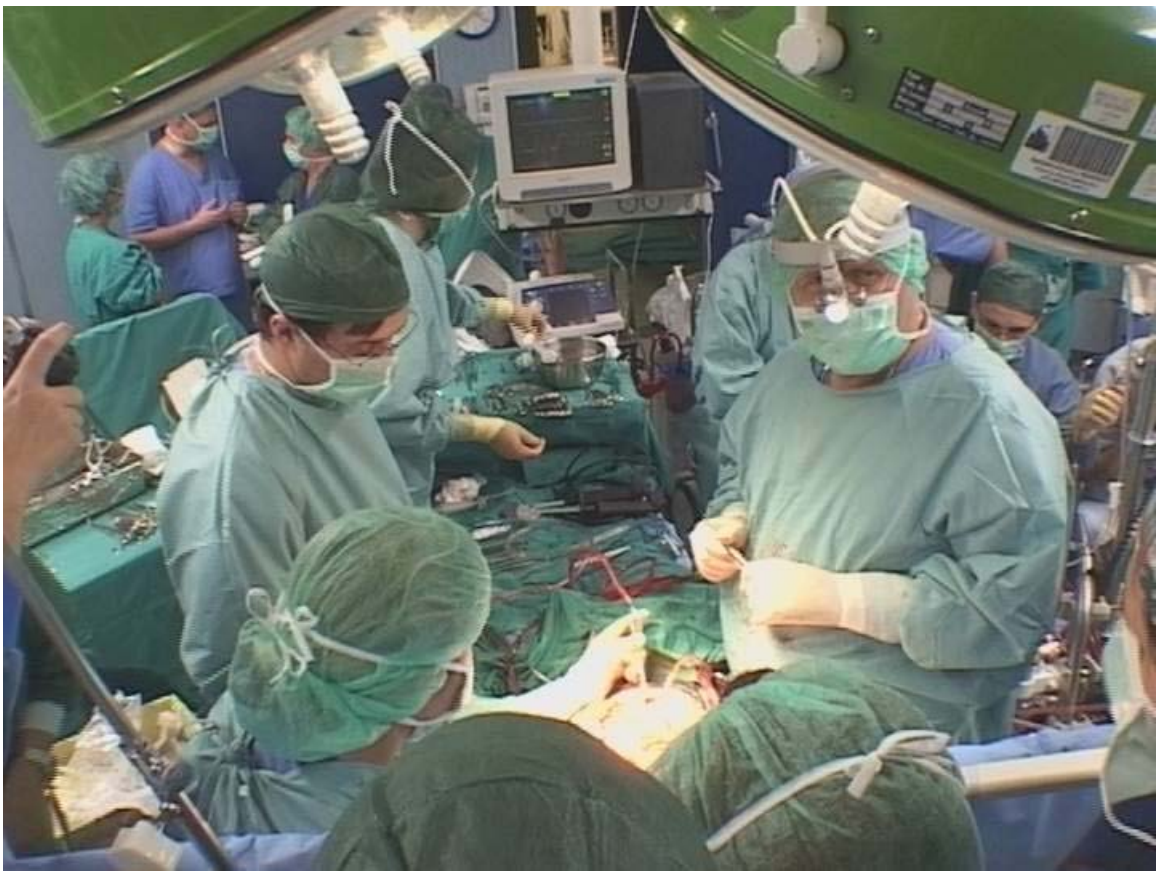
Medical device packaging is highly regulated. Often medical devices and products are sterilized in the package. The sterility must be maintained throughout distribution to allow immediate use by physicians. A series of special packaging tests is used to measure the ability of the package to maintain sterility. Relevant standards include: ASTM D1585- Guide for Integrity Testing of Porous Medical Packages, ASTM F2097- Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products , EN 868 Packaging materials and systems for medical devices which are to be sterilized. General requirements and test methods, ISO 11607 Packaging for terminally sterilized medical devices, and others.

Package testing needs to conducted and documented to ensure that packages meet regulations and all end-use requirements. Manufacturing processes need to be controlled and validated to ensure consistent performance.

Chapter 4

Medical Equipment and Medical Technology

Medical equipment



Medical equipment

Innovations in medical technology - starting from the ancients and till date - have produced numerous appliances and instruments that have been essential in diagnosis, treatment, prevention and rehabilitation. Modern medicine requires and utilizes numerous

such instruments that can be as simple as a scalpel or sutures to as complex as a respirator or a dialyser.

Field such as pediatrics, geriatrics, community medicine, food and nutrition, etc. do not require special instruments.

Functions

Medical equipment is designed to aid in the diagnosis, monitoring or treatment of medical conditions. These devices are usually designed with rigorous safety standards. The *medical equipment* is included in the category *Medical technology*.

There are several basic types:

- Diagnostic equipment includes medical imaging machines, used to aid in diagnosis. Examples are ultrasound and MRI machines, PET and CT scanners, and x-ray machines.
- Therapeutic equipment includes infusion pumps, medical lasers and LASIK surgical machines.
- Life support equipment is used to *maintain* a patient's bodily function. This includes medical ventilators, anaesthetic machines, heart-lung machines, ECMO, and dialysis machines.
- Medical monitors allow medical staff to measure a patient's medical state. Monitors may measure patient vital signs and other parameters including ECG, EEG, blood pressure, and dissolved gases in the blood.
- Medical laboratory equipment automates or helps analyze blood, urine and genes.
- Diagnostic Medical Equipment may also be used in the home for certain purposes, e.g. for the control of diabetes mellitus

A biomedical equipment technician (BMET) is a vital component of the healthcare delivery system. Employed primarily by hospitals, BMETs are the people responsible for maintaining a facility's medical equipment.

Inventions

- 1895, X-ray, by Wilhelm Röntgen
- 1903, electrocardiograph, by Willem Einthoven
- 1956, endoscope, by Basil Hirschowitz
- 1958, ultrasound scan, by Ian Donald
- 1973, CT (CAT) scan, by Godfrey Hounsfield and Allan Cormack
- 1982, artificial heart, by Robert Jarvik

Notable medical equipment companies

- Cameron Health
- Cardinal Health, Columbus, Ohio

- Boston Scientific
- Beckman Coulter
- Dräger
- GE Healthcare
- Getinge Group
- Heine Optotechnik
- Johnson & Johnson
- MAQUET
- Medtronic
- Mindray
- Philips
- REXMED
- St. Jude Medical
- Siemens AG

Medical technology

Medical technology encompasses a wide range of healthcare products and, in one form or another, is used to diagnose, monitor or treat diseases or medical conditions affecting humans. Such technologies (applications of medical science) are intended to improve the quality of healthcare delivered and patient outcomes through earlier diagnosis, less invasive treatment options and reductions in hospital stays and rehabilitation times.

Health technology is:

Any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes the pharmaceuticals, devices, procedures and organizational systems used in health care.

Definition

Medical technology extends and improves life. It alleviates pain, injury and handicap. Its role in healthcare is essential. Incessant medical technology innovation enhances the quality and effectiveness of care. Billions of patients worldwide depend on medical technology at home, at the doctor's, at hospital and in nursing homes. Wheelchairs, pacemakers, orthopedic shoes, spectacles and contact lenses, insulin pens, hip prostheses, condoms, oxygen masks, dental floss, MRI scanners, pregnancy tests, surgical instruments, bandages, syringes, life-support machines: more than 500,000 products (10,000 generic groups) are available today. Medical technology represents only 6,3% of total healthcare expenditure in Europe - a modest share if you consider the benefits for every member of society.
— **Eucomed**.

Allied professions

The term **medical technology** may also refer to the duties performed by clinical laboratory professionals in various settings within the public and private sectors. The work of these professionals encompass clinical applications of chemistry, genetics, hematology, immunohematology (blood banking), immunology, microbiology, serology, urinalysis and miscellaneous body fluid analysis. These professionals may be referred to as Medical Technologists (MT) and Medical Laboratory Technologists.

Chapter 5

Medical Imaging

Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology). Although imaging of removed organs and tissues can be performed for medical reasons, such procedures are not usually referred to as medical imaging, but rather are a part of pathology.

As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), nuclear medicine, investigative radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Measurement and recording techniques which are not primarily designed to produce images, such as electroencephalography (EEG), magnetoencephalography (MEG), Electrocardiography (EKG) and others, but which produce data susceptible to be represented as maps (i.e. containing positional information), can be seen as forms of medical imaging.

Up until 2010, 5 billion medical imaging studies had been conducted worldwide. Radiation exposure from medical imaging in 2006 made up about 50% of total ionizing radiation exposure in the United States.

Overview

In the clinical context, "invisible light" medical imaging is generally equated to radiology or "clinical imaging" and the medical practitioner responsible for interpreting (and sometimes acquiring) the images is a radiologist. "Visible light" medical imaging involves digital video or still pictures that can be seen without special equipment. Dermatology and wound care are two modalities that utilize visible light imagery. Diagnostic radiography designates the technical aspects of medical imaging and in particular the acquisition of medical images. The *radiographer* or *radiologic technologist* is usually responsible for acquiring medical images of diagnostic quality, although some radiological interventions are performed by radiologists. While radiology is an evaluation of anatomy, nuclear medicine provides functional assessment.

As a field of scientific investigation, medical imaging constitutes a sub-discipline of biomedical engineering, medical physics or medicine depending on the context: Research and development in the area of instrumentation, image acquisition (e.g. radiography), modelling and quantification are usually the preserve of biomedical engineering, medical physics and computer science; Research into the application and interpretation of medical images is usually the preserve of radiology and the medical sub-discipline relevant to medical condition or area of medical science (neuroscience, cardiology, psychiatry, psychology, etc.) under investigation. Many of the techniques developed for medical imaging also have scientific and industrial applications.

Medical imaging is often perceived to designate the set of techniques that noninvasively produce images of the internal aspect of the body. In this restricted sense, medical imaging can be seen as the solution of mathematical inverse problems. This means that cause (the properties of living tissue) is inferred from effect (the observed signal). In the case of ultrasonography the probe consists of ultrasonic pressure waves and echoes inside the tissue show the internal structure. In the case of projection radiography, the probe is X-ray radiation which is absorbed at different rates in different tissue types such as bone, muscle and fat.

The term noninvasive is a term based on the fact that following medical imaging modalities do not penetrate the skin physically. But on the electromagnetic and radiation level, they are quite invasive. From the high energy photons in X-Ray Computed Tomography, to the 2+ Tesla coils of an MRI device, these modalities alter the physical and chemical environment of the body in order to obtain data.

Imaging technology

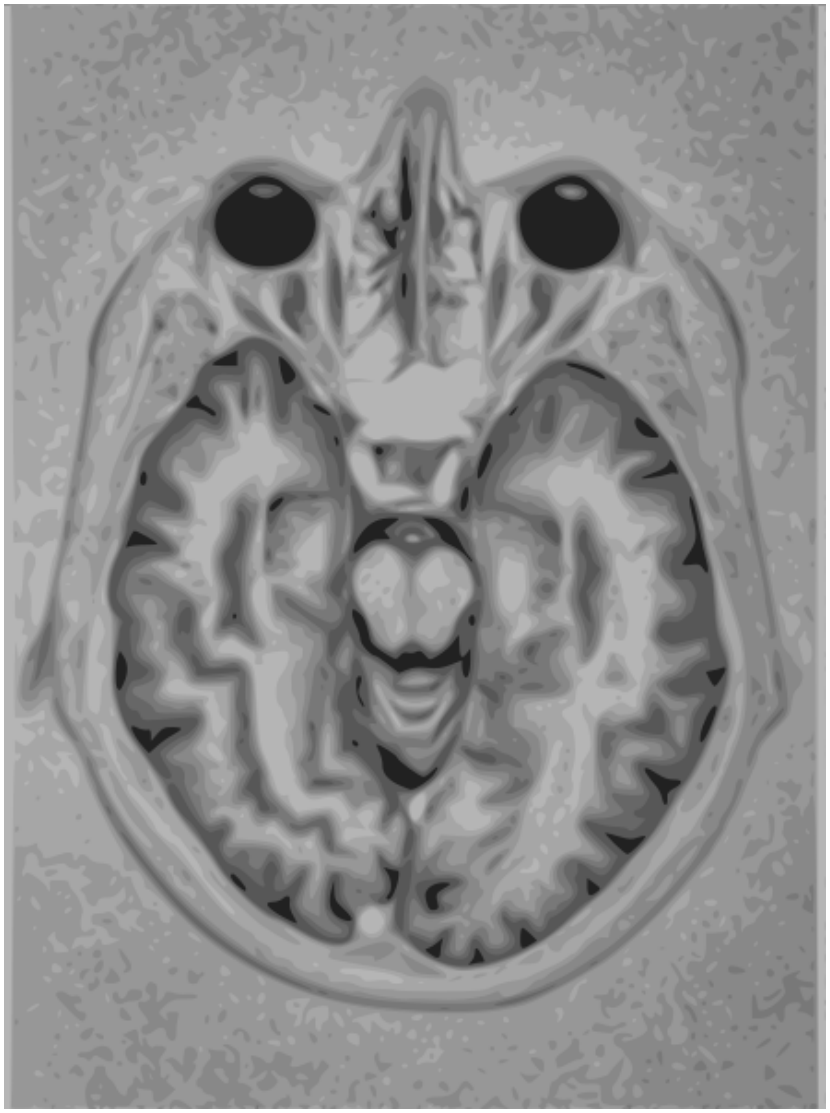
Radiography

Two forms of radiographic images are in use in medical imaging; projection radiography and fluoroscopy, with the latter being useful for catheter guidance. These 2D techniques are still in wide use despite the advance of 3D tomography due to the low cost, high resolution, and depending on application, lower radiation dosages. This imaging modality utilizes a wide beam of x rays for image acquisition and is the first imaging technique available in modern medicine.

- *Fluoroscopy* produces real-time images of internal structures of the body in a similar fashion to radiography, but employs a constant input of x-rays, at a lower dose rate. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest. Early on this was a fluorescing screen, which gave way to an Image Amplifier (IA) which was a large vacuum tube that had the receiving end coated with cesium iodide, and a mirror at the opposite end. Eventually the mirror was replaced with a TV camera.

- *Projectional radiographs*, more commonly known as x-rays, are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. With the use of radio-opaque contrast media, such as barium, they can also be used to visualize the structure of the stomach and intestines - this can help diagnose ulcers or certain types of colon cancer.

Magnetic resonance imaging (MRI)



A brain MRI representation

A magnetic resonance imaging instrument (MRI scanner), or "nuclear magnetic resonance (NMR) imaging" scanner as it was originally known, uses powerful magnets to polarise and excite hydrogen nuclei (single proton) in water molecules in human tissue, producing a detectable signal which is spatially encoded, resulting in images of the body. The MRI machine emits an RF (radio frequency) pulse that specifically binds only to hydrogen. The system sends the pulse to the area of the body to be examined. The pulse

makes the protons in that area absorb the energy needed to make them spin in a different direction. This is the “resonance” part of MRI. The RF pulse makes them (only the one or two extra unmatched protons per million) spin at a specific frequency, in a specific direction. The particular frequency of resonance is called the Larmour frequency and is calculated based on the particular tissue being imaged and the strength of the main magnetic field. MRI uses three electromagnetic fields: a very strong (on the order of units of teslas) static magnetic field to polarize the hydrogen nuclei, called the static field; a weaker time-varying (on the order of 1 kHz) field(s) for spatial encoding, called the gradient field(s); and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

Like CT, MRI traditionally creates a two dimensional image of a thin "slice" of the body and is therefore considered a tomographic imaging technique. Modern MRI instruments are capable of producing images in the form of 3D blocks, which may be considered a generalisation of the single-slice, tomographic, concept. Unlike CT, MRI does not involve the use of ionizing radiation and is therefore not associated with the same health hazards. For example, because MRI has only been in use since the early 1980s, there are no known long-term effects of exposure to strong static fields (this is the subject of some debate) and therefore there is no limit to the number of scans to which an individual can be subjected, in contrast with X-ray and CT. However, there are well-identified health risks associated with tissue heating from exposure to the RF field and the presence of implanted devices in the body, such as pace makers. These risks are strictly controlled as part of the design of the instrument and the scanning protocols used.

Because CT and MRI are sensitive to different tissue properties, the appearance of the images obtained with the two techniques differ markedly. In CT, X-rays must be blocked by some form of dense tissue to create an image, so the image quality when looking at soft tissues will be poor. In MRI, while any nucleus with a net nuclear spin can be used, the proton of the hydrogen atom remains the most widely used, especially in the clinical setting, because it is so ubiquitous and returns a large signal. This nucleus, present in water molecules, allows the excellent soft-tissue contrast achievable with MRI.

Nuclear medicine

Nuclear medicine encompasses both diagnostic imaging and treatment of disease, and may also be referred to as molecular medicine or molecular imaging & therapeutics. Nuclear medicine uses certain properties of isotopes and the energetic particles emitted from radioactive material to diagnose or treat various pathology. Different from the typical concept of anatomic radiology, nuclear medicine enables assessment of physiology. This function-based approach to medical evaluation has useful applications in most subspecialties, notably oncology, neurology, and cardiology. *Gamma cameras* are used in e.g. scintigraphy, SPECT and PET to detect regions of biologic activity that may be associated with disease. Relatively short lived isotope, such as ^{123}I is administered to the patient. Isotopes are often preferentially absorbed by biologically active tissue in the body, and can be used to identify tumors or fracture points in bone.

Images are acquired after collimated photons are detected by a crystal that gives off a light signal, which is in turn amplified and converted into count data.

- *Scintigraphy* ("scint") is a form of diagnostic test wherein radioisotopes are taken internally, for example intravenously or orally. Then, gamma cameras capture and form two-dimensional images from the radiation emitted by the radiopharmaceuticals.
- *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. A dual detector head gamma camera combined with a CT scanner, which provides localization of functional SPECT data, is termed a SPECT/CT camera, and has shown utility in advancing the field of molecular imaging. In most other medical imaging modalities, energy is passed through the body and the reaction or result is read by detectors. In SPECT imaging, the patient is injected with a radioisotope, most commonly Thallium 201TI, Technetium 99mTC, Iodine 123I, and Gallium 67Ga

. The radioactive gamma rays are emitted through the body as the natural decaying process of these isotopes takes place. The emissions of the gamma rays are captured by detectors that surround the body. This essentially means that the human is now the source of the radioactivity, rather than the medical imaging devices such as X-Ray, CT, or Ultrasound.

- *Positron emission tomography* (PET) uses coincidence detection to image functional processes. Short-lived positron emitting isotope, such as ^{18}F, is incorporated with an organic substance such as glucose, creating F18-fluorodeoxyglucose, which can be used as a marker of metabolic utilization. Images of activity distribution throughout the body can show rapidly growing tissue, like tumor, metastasis, or infection. PET images can be viewed in comparison to computed tomography scans to determine an anatomic correlate. Modern scanners combine PET with a CT, or even MRI, to optimize the image reconstruction involved with positron imaging. This is performed on the same equipment without physically moving the patient off of the gantry. The resultant hybrid of functional and anatomic imaging information is a useful tool in non-invasive diagnosis and patient management.

Photo acoustic imaging

Photoacoustic imaging is a recently developed hybrid biomedical imaging modality based on the photoacoustic effect. It combines the advantages of optical absorption contrast with ultrasonic spatial resolution for deep imaging in (optical) diffusive or quasi-diffusive regime. Recent studies have shown that photoacoustic imaging can be used in vivo for tumor angiogenesis monitoring, blood oxygenation mapping, functional brain imaging, and skin melanoma detection, etc.

Breast Thermography

Digital infrared imaging thermography is based on the principle that metabolic activity and vascular circulation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Cancerous tumors require an ever-increasing supply of nutrients and therefore increase circulation to their cells by holding open existing blood vessels, opening dormant vessels, and creating new ones (neoangiogenesis). This process frequently results in an increase in regional surface temperatures of the breast. Digital infrared imaging uses extremely sensitive medical infrared cameras and sophisticated computers to detect, analyze, and produce high-resolution diagnostic images of these temperature variations. Because of DII's sensitivity, these temperature variations may be among the earliest signs of breast cancer and/or a pre-cancerous state of the breast.

Tomography

Tomography is the method of imaging a single plane, or slice, of an object resulting in a tomogram. There are several forms of tomography:

- Linear tomography: This is the most basic form of tomography. The X-ray tube moved from point "A" to point "B" above the patient, while the cassette holder (or "bucky") moves simultaneously under the patient from point "B" to point "A." The fulcrum, or pivot point, is set to the area of interest. In this manner, the points above and below the focal plane are blurred out, just as the background is blurred when panning a camera during exposure. No longer carried out and replaced by computed tomography.
- Poly tomography: This was a complex form of tomography. With this technique, a number of geometrical movements were programmed, such as hypocycloidic, circular, figure 8, and elliptical. Philips Medical Systems produced one such device called the 'Polytome.' This unit was still in use into the 1990s, as its resulting images for small or difficult physiology, such as the inner ear, was still difficult to image with CTs at that time. As the resolution of CTs got better, this procedure was taken over by the CT.
- Zonography: This is a variant of linear tomography, where a limited arc of movement is used. It is still used in some centres for visualising the kidney during an intravenous urogram (IVU).
- Orthopantomography (OPT or OPG): The only common tomographic examination in use. This makes use of a complex movement to allow the radiographic examination of the mandible, as if it were a flat bone. It is often referred to as a "Panorex", but this is incorrect, as it is a trademark of a specific company.
- Computed Tomography (CT), or Computed Axial Tomography (CAT: A CT scan, also known as a CAT scan), is a helical tomography (latest generation), which traditionally produces a 2D image of the structures in a thin section of the body. It uses X-rays. It has a greater ionizing radiation dose burden than projection radiography; repeated scans must be limited to avoid health effects. CT

is based on the same principles as X-Ray projections but in this case, the patient is enclosed in a surrounding ring of detectors assigned with 500-1000 scintillation detectors.

This being the fourth-generation X-Ray CT scanner geometry. Previously in older generation scanners, the X-Ray beam was paired by a translating source and detector.

Ultrasound

Ultrasound representation of Urinary bladder (black butterfly-like shape) and hyperplastic prostate

Medical ultrasonography uses high frequency broadband sound waves in the megahertz range that are reflected by tissue to varying degrees to produce (up to 3D) images. This is

commonly associated with imaging the fetus in pregnant women. Uses of ultrasound are much broader, however. Other important uses include imaging the abdominal organs, heart, breast, muscles, tendons, arteries and veins. While it may provide less anatomical detail than techniques such as CT or MRI, it has several advantages which make it ideal in numerous situations, in particular that it studies the function of moving structures in real-time, emits no ionizing radiation, and contains speckle that can be used in elastography. Ultrasound is also used as a popular research tool for capturing raw data, that can be made available through an Ultrasound research interface, for the purpose of tissue characterization and implementation of new image processing techniques. The concepts of ultrasound differ from other medical imaging modalities in the fact that it is operated by the transmission and receipt of sound waves. The high frequency sound waves are sent into the tissue and depending on the composition of the different tissues; the signal will be attenuated and returned at separate intervals. A path of reflected sound waves in a multilayered structure can be defined by an input acoustic impedance(Ultrasound sound wave) and the Reflection and transmission coefficients of the relative structures . It is very safe to use and does not appear to cause any adverse effects, although information on this is not well documented. It is also relatively inexpensive and quick to perform. Ultrasound scanners can be taken to critically ill patients in intensive care units, avoiding the danger caused while moving the patient to the radiology department. The real time moving image obtained can be used to guide drainage and biopsy procedures. Doppler capabilities on modern scanners allow the blood flow in arteries and veins to be assessed.

Medical imaging topics

Maximizing imaging procedure use

The amount of data obtained in a single MR or CT scan is very extensive. Some of the data that radiologists discard could save patients time and money, while reducing their exposure to radiation and risk of complications from invasive procedures.

Creation of three-dimensional images

Recently, techniques have been developed to enable CT, MRI and ultrasound scanning software to produce 3D images for the physician. Traditionally CT and MRI scans produced 2D static output on film. To produce 3D images, many scans are made, then combined by computers to produce a 3D model, which can then be manipulated by the physician. 3D ultrasounds are produced using a somewhat similar technique. In diagnosing disease of the viscera of abdomen,ultrasound is particularly sensitive on imaging of biliary tract,urinary tract and female reproductive organs (ovary,fallopian tubes). As for example,diagnosis of gall stone by dilatation of common bile duct and stone in common bile duct . With the ability to visualize important structures in great detail, 3D visualization methods are a valuable resource for the diagnosis and surgical treatment of many pathologies. It was a key resource for the famous, but ultimately unsuccessful attempt by Singaporean surgeons to separate Iranian twins Ladan and Laleh

Bijani in 2003. The 3D equipment was used previously for similar operations with great success.

Other proposed or developed techniques include:

- Diffuse optical tomography
- Elastography
- Electrical impedance tomography
- Optoacoustic imaging
- Ophthalmology
    - A-scan
    - B-scan
    - Corneal topography
    - Optical coherence tomography
    - Scanning laser ophthalmoscopy

Some of these techniques are still at a research stage and not yet used in clinical routines.

Compression of medical images

Medical imaging techniques produce very large amounts of data, especially from CT, MRI and PET modalities. As a result, storage and communications of electronic image data are prohibitive without the use of compression. JPEG 2000 is the state-of-the-art image compression DICOM standard for storage and transmission of medical images. The cost and feasibility of accessing large image data sets over low or various bandwidths are further addressed by use of another DICOM standard, called JPIP, to enable efficient streaming of the JPEG 2000 compressed image data.

Non-diagnostic imaging

Neuroimaging has also been used in experimental circumstances to allow people (especially disabled persons) to control outside devices, acting as a brain computer interface.

Archiving and recording

Used primarily in ultrasound imaging, capturing the image a medical imaging device is required for archiving and telemedicine applications. In most scenarios, a frame grabber is used in order to capture the video signal from the medical device and relay it to a computer for further processing and operations.

Open source software for medical image analysis

Several open source software packages are available for performing analysis of medical images:

- ImageJ
- 3D Slicer
- ITK
- OsiriX
- GemIdent
- MicroDicom
- FreeSurfer

Use in pharmaceutical clinical trials

Medical imaging has become a major tool in clinical trials since it enables rapid diagnosis with visualization and quantitative assessment.

A typical clinical trial goes through multiple phases and can take up to eight years. Clinical endpoints or outcomes are used to determine whether the therapy is safe and effective. Once a patient reaches the endpoint, he/she is generally excluded from further experimental interaction. Trials that rely solely on clinical endpoints are very costly as they have long durations and tend to need large number of patients.

In contrast to clinical endpoints, surrogate endpoints have been shown to cut down the time required to confirm whether a drug has clinical benefits. Imaging biomarkers (a characteristic that is objectively measured by an imaging technique, which is used as an indicator of pharmacological response to a therapy) and surrogate endpoints have shown to facilitate the use of small group sizes, obtaining quick results with good statistical power.

Imaging is able to reveal subtle change that is indicative of the progression of therapy that may be missed out by more subjective, traditional approaches. Statistical bias is reduced as the findings are evaluated without any direct patient contact.

For example, measurement of tumour shrinkage is a commonly used surrogate endpoint in solid tumour response evaluation. This allows for faster and more objective assessment of the effects of anticancer drugs. In evaluating the extent of Alzheimer's disease, it is still prevalent to use behavioural and cognitive tests. MRI scans on the entire brain can accurately pinpoint hippocampal atrophy rate while PET scans is able to measure the brain's metabolic activity by measuring regional glucose metabolism.

An imaging-based trial will usually be made up of three components:

1. A realistic imaging protocol. The protocol is an outline that standardizes (as far as practically possible) the way in which the images are acquired using the various modalities (PET, SPECT, CT, MRI). It covers the specifics in which images are to be stored, processed and evaluated.
2. An imaging centre that is responsible for collecting the images, perform quality control and provide tools for data storage, distribution and analysis. It is important for images acquired at different time points are displayed in a standardised format

to maintain the reliability of the evaluation. Certain specialised imaging contract research organizations provide to end medical imaging services, from protocol design and site management through to data quality assurance and image analysis.

3. Clinical sites that recruit patients to generate the images to send back to the imaging centre.

Chapter 6

Clinical Engineering

Clinical engineering is a specialty within Biomedical engineering responsible primarily for applying and implementing medical technology to optimize healthcare delivery. Roles of clinical engineers include training and supervising biomedical equipment technicians (BMETs), working with governmental regulators on hospital inspections/audits, and serving as technological consultants for other hospital staff (i.e. physicians, administrators, I.T., etc.). Clinical engineers also advise medical device producers regarding prospective design improvements based on clinical experiences, as well as monitor the progression of the state-of-the-art in order to redirect hospital 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" R&D or cutting-edge ideas that would be many years from clinical adoptability; however, there is nonetheless an effort to expand this time-horizon over which clinical engineers can influence the trajectory of biomedical innovation. In their various roles, they form a sort of "bridge" between product originators and end-users, by combining the perspectives of being both close to the point-of-use ("front lines"), while also trained in product and process design. Clinical Engineering departments at large hospitals will sometimes hire not just biomedical engineers, but also industrial/systems engineers to help address operations research, human factors, cost analyses, safety, etc.

History

While some trace its roots back to the 1940s, the actual term "clinical engineering" was first used in 1969. The first explicit published reference to the term "clinical engineering" appears in a paper published in 1969 by Landoll and Caceres. Cesar A. Caceres, a cardiologist, is generally credited with coining the term "clinical engineering." Of course, the broader field of "biomedical engineering" has a relatively recent history as well. The first modern professional intersociety engineering meeting to be focused on the application of engineering in medicine was probably held in 1948, according to the Alliance for Engineering in Medicine and Biology

The general notion of the application of engineering to medicine can be traced back centuries; for example, Stephen Hales's work in the early 18th century which led to the invention of a ventilator and the discovery of blood pressure certainly involved the application of engineering techniques to medicine .

The recent history of this sub-discipline is somewhat erratic. In the early 1970s, clinical engineering was thought to be a field that would require many new professionals. Estimates for the US ranged as high as 5,000 to 8,000 clinical engineers, or five to ten clinical engineers for every 250,000 of population, or one clinical engineer per 250 hospital beds..

The history of its formal credentialization and accreditation procedures has also been somewhat unstable. The International Certification Commission for Clinical Engineers (ICC) was formed under the sponsorship of the Association for the Advancement of Medical Instrumentation (AAMI) in the early 1970s, to provide a formal certification process for clinical engineers. A similar certification program was formed by academic institutions offering graduate degrees in clinical engineering as the American Board of Clinical Engineering (ABCE). In 1979, the ABCE agreed to dissolve, and those certified under its program were accepted into the ICC certification program. By 1985, only 350 clinical engineers had become certified. Finally, in 1999, AAMI after lengthy deliberation, and analysis of a 1998 survey demonstrating that there was not a viable market for its certification program decided to suspend that program, no longer accepting any new applicants as of July 1999.

The new, current Clinical Engineering Certification (CCE) program was started in 2002 under the sponsorship of the American College of Clinical Engineering (ACCE), and is administered by the ACCE Healthcare Technology Foundation. In 2004, the first year that the certification process was actually underway, 112 individuals were granted certification based upon their previous ICC certification, and three individuals were awarded the new certification. By the time of the publication of the 2006-2007 AHTF Annual Report (approx. June 30, 2007), a total of 147 individuals were included in the ranks of HTF certified clinical engineers.

Clinical engineering in India

Healthcare has increasingly become technology driven and requires trained manpower to keep pace with the growing demand for professionals in the field. An M-Tech Clinical Engineering course was initiated by Indian Institute of Technology Madras (IITM), Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum and Christian Medical College, Vellore (CMC), to address the country's need of human resource development. This was aimed for indigenous Biomedical Device Development as well as Technology management, and thereby contribute to the overall development of healthcare delivery in the country. During the course, students of engineering are given an insight into biology, medicine, relevant electronic background, clinical practices, device development and even management aspects. Additionally, students are paired with clinical doctors from CMC and SCTIMST to get hands-on experience during internships.

An important aspect of this training is simultaneous, long term and detailed exposure to clinical environment as well as to medical device development activity. This is aimed at making students understand the process of identifying 'unmet clinical need' and thus, contributing to the development of new medical devices in the country. A unique feature of the course is clinical attachment which exposes the students to the clinical environment. The program also trains engineers to manage and ensure safe and effective use of technology in heath care delivery points. The minimum essential qualification for joining this course is bachelors degree in any discipline of engineering except civil engineering and a valid GATE score in their respective fields.

The Definition

A **Clinical engineer** is defined by ACCE as "a professional who supports and advances patient care by applying engineering and managerial skills to healthcare technology." This definition was first adopted by the ACCE Board of Directors on May 13, 1991. Clinical Engineering is also recognized by the Biomedical Engineering Society (BMES), the major professional organization for biomedical engineering, as being a branch within Biomedical Engineering.

There are at least two issues with the ACCE definition that cause some confusion. First, it is phrased so broadly that it's not readily evident that "clinical engineer" is but one subset of "biomedical engineer." Many times the terms actually get used interchangeably: some hospitals refer to their relevant departments as "Clinical Engineering" departments, while others call them "Biomedical Engineering" departments. Indeed, as noted above, the *technicians* are almost universally referred to as "biomedical equipment technicians," regardless of the name of the department that they might work under. However, the term "biomedical engineer" is generally thought to be more all-encompassing, including engineers who work in the primary design of medical devices for manufacturers, or in original R&D, or in academia—whereas clinical engineers generally work in hospitals solving problems that are very close to where equipment is actually used in a patient care setting. The clinical engineers in some countries such as India are trained to innovate and find technological solutions for the clinical needs.. The other issue not evident from the ACCE definition is the appropriate educational background for a clinical engineer. Generally, the expectation of the certification program is that an applicant for certification as a clinical engineer will hold an accredited bachelor's degree in engineering (or at least engineering technology).

The future

The management of healthcare technology is becoming increasingly complex. The driving factors and opportunities presented are examined in The Future of Clinical Engineering, published in the IEEE EMBS magazine in 2003.

Eligibility Requirements

To be eligible for certification in clinical engineering (CCE), a candidate must hold appropriate professional or educational credentials (an accredited engineering or possibly engineering-technology degree) have certain relevant experience, and pass an examination. The Examination for Certification in Clinical Engineering involves a written examination composed of a maximum of 150 multiple-choice objective questions with a testing time of three (3) hours, and a separate oral exam.. Particular weight is given to applicants for CE certification (CCE) who are already licensed as registered Professional Engineers (PE) -- which itself has extensive requirements (including an accredited engineering degree and engineering experience).

Chapter 7

Prosthesis

A man with two prosthetic arms playing table football.

In medicine, a **prosthesis**, **prosthetic**, or **prosthetic limb** is an artificial device extension that replaces a missing body part. It is part of the field of biomechatronics, the science of using mechanical devices with human muscle, skeleton, and nervous systems to assist or enhance motor control lost by trauma, disease, or defect. Prostheses are typically used to replace parts lost by injury (traumatic) or missing from birth (congenital) or to supplement defective body parts. Inside the body, artificial heart valves are in common

use with artificial hearts and lungs seeing less common use but under active technology development. Other medical devices and aids that can be considered prosthetics include hearing aids, artificial eyes, palatal obturator, gastric bands, and dentures.

Prosthetics are specifically *not* orthotics, although given certain circumstances a prosthetic might end up performing some or all of the same functionary benefits as an orthotic. Prostheses (or "A" prosthesis) are technically the complete finished item. For instance, a C-Leg knee alone is *not* a prosthesis, but only a prosthetic *part*. The complete prosthesis would consist of the stump attachment system - usually a "socket", and all the attachment hardware parts all the way down to and including the foot. Keep this in mind as often nomenclature is interchanged.

History

Prosthetic toe from ancient Egypt

Prosthetics have been mentioned throughout history. Egyptians were the early pioneers of the idea. Roman bronze crowns have also been found, but their use could have been more aesthetic than medical. The first recorded mention of a prosthetic was done by the historian Herodotus, who tells the story of a Hegistratus, a Persian soldier, who cut off his own foot to escape his captors and replaced it with a wooden one. Pliny the Elder also recorded that a Roman general who had his arm cut off had an iron one made to hold his shield up when he returned to battle. A famous and quite refined historical prosthetic arm was that of Götz von Berlichingen, made in the beginning of the 16th century. Around the same time, François de la Noue is also reported to have had an iron hand, as is, in the

17th century, René-Robert Cavalier de la Salle. During the Dark Ages, prosthetics remained quite basic in form. Debilitated knights would be fitted with prosthetics so they could be fitted with a shield. Only the wealthy were able to afford anything that would assist in daily function. During the Renaissance, prosthetics also underwent a rebirth. Prosthetics development using iron, steel, copper, and wood started. Functional prosthetics began to make an appearance in the 1500s. Gotz von Berlichingen, a German mercenary, developed a pair of iron hands that could be moved by relaxing a series of releases and springs. Record written by an Italian surgeon also notes the existence of amputee who had an arm that allowed him to remove his hat, open his purse, and sign his name. Improvement in amputation surgery and prosthetic design came at the hands of Ambroise Paré. Among his inventions was an above-knee device that was a kneeling peg leg and foot prosthesis that had a fixed position, adjustable harness, and knee lock control. The functionality of his advancements showed what future prosthetics would function.

Other major improvements before the modern era:

- Pieter Verduyn - First nonlocking below-knee (BK) prosthesis.
- James Potts - Prosthesis made of a wooden shank and socket, a steel knee joint and an articulated foot that was controlled by catgut tendons from the knee to the ankle. Came to be known as “Anglesey Leg” or “Selpho Leg.”
- Sir James Syme - A new method of ankle amputation that did not involve amputating at the thigh.
- Benjamin Palmer - Improved upon the Selpho leg. Added an anterior spring and concealed tendons to simulate natural-looking movement.
- Dubois Parmlee – Created prosthetic with a suction socket, polycentric knee, and multi-articulated foot.
- Marcel Desoutter & Charles Desoutter – First aluminum prosthesis

At the end of World War II, the NAS (National Academy of Sciences) began to advocate better research and development of prosthetics. Through government funding, a research and development program was developed within the Army, Navy, Air Force, and the Veterans Administration.

The following organizations have been created to help and inform the general publics about prosthetics:

- American Orthotics and Prosthetic Association, American Board for Certification in Prosthetics and Orthotics, American Academy of Orthotics and Prosthetics – These three groups work together to take responsibility for the academic side of orthotics and prosthetics and provide certification of individuals and facilities working with orthotics and prosthetics.
- The International Society for Prosthetics and Orthotics – Founded in 1970 and headquartered in Copenhagen, this association helps with the progression in research and clinical practice worldwide. They hold an international conference every three years and publish their own technical journal.

- Association of Children's Orthotic-Prosthetic Clinics – The organization was started in 1950s to advocate research and development of children's prosthetics. They meet annually and have their own publication.
- Amputee Coalition of America – The organization was created in 1990 to improve the lives of amputees. Advocate the improvement of amputee lifestyle through education and also have their own publication, inMotion.

Lower extremity prosthetics

Lower extremity prosthetics describes artificially replaced limbs located at the hip level or lower. The two main subcategories of lower extremity prosthetic devices are 1.trans-tibial (any amputation transecting the tibia bone or a congenital anomaly resulting in a tibial deficiency) and 2.trans-femoral (any amputation transecting the femur bone or a congenital anomaly resulting in a femural deficiency). In the prosthetic industry a trans-tibial prosthetic leg is often referred to as a "BK" or below the knee prosthesis while the trans-femoral prosthetic leg is often referred to as an "AK" or above the knee prosthesis.

Other, less prevalent lower extremity cases include the following:

1. Hip disarticulations - This usually refers to when an amputee or congenitally challenged patient has either an amputation or anomaly at or in close proximity to the hip joint.
2. Knee disarticulations - This usually refers to an amputation through the knee disarticulating the femur from the tibia.
3. Symes - This is an ankle disarticulation while preserving the heel pad.

Lower extremity modern history

Socket technology for lower extremity limbs saw a revolution of advancement during the 1980s when Sabolich Prosthetics, John Sabolich C.P.O., invented the Contoured Adducted Trochanteric-Controlled Alignment Method (CATCAM) socket, later to evolve into the Sabolich Socket. The advancement was due to the difference in the socket to patient contact model. Prior, sockets were made in the shape of a square bucket with no specialized containment for either the patient's bony prominences' or muscular tissue. Sabolich's design held the patient's limb like a glove, locking it into place and distributing the weight evenly over the existing limb as well as the bone structure of the patient. This was the first instance of ischial containment and led to an extreme advancement in patient accomplishment. Because of Sabolich's dedication to research and development in lower extremity prosthetics, Sabolich Prosthetics saw the first above the knee prosthetic patients walk and run step over step with both one leg and two legs missing, walking down stairs, suction sockets, modern plastic and bio elastic sockets, sense of feel technology, and numerous other inventions in the prosthetic field.

The first microprocessor-controlled prosthetic knees became available in the early 1990s. The Intelligent Prosthesis was first commercially available microprocessor controlled prosthetic knee. It was released by Chas. A. Blatchford & Sons, Ltd., of Great Britain, in

1993 and made walking with the prosthesis feel and look more natural. An improved version was released in 1995 by the name Intelligent Prosthesis Plus. Blatchford released another prosthesis, the Adaptive Prosthesis, in 1998. The Adaptive Prosthesis utilized hydraulic controls, pneumatic controls, and a microprocessor to provide the amputee with a gait that was more responsive to changes in walking speed.

C-Leg knee prosthesis

Two different models of the C-Leg prosthesis

The Otto Bock Orthopedic Industry introduced the **C-Leg** during the World Congress on Orthopedics in Nuremberg in 1997. The company began marketing the C-Leg in the United States in 1999. Other microprocessor-controlled knee prostheses include Ossur's Rheo Knee, released in 2005, the Power Knee by Ossur, introduced in 2006, the Plié Knee from Freedom Innovations and DAW Industries' Self Learning Knee (SLK).

The idea was originally developed by Kelly James, a Canadian engineer, at the University of Alberta. The C-Leg uses hydraulic cylinders to control the flexing of the knee. Sensors send signals to the microprocessor that analyzes these signals, and communicates what resistance the hydraulic cylinders should supply. C-Leg is an abbreviation of 3C100, the model number of the original prosthesis, but has continued to be applied to all Otto Bock microprocessor-controlled knee prostheses. The C-Leg functions through various technological devices incorporated into the components of the prosthesis. The C-Leg uses a knee-angle sensor to measure the angular position and angular velocity of the flexing joint. Measurements are taken up to fifty times a second. The knee-angle sensor is located directly at the axis of rotation of the knee.

Moment sensors are located in the tube adapter at the base of the C-Leg. These moment sensors use multiple strain gauges to determine where the force is being applied to the knee, from the foot, and the magnitude of that force.

The C-Leg controls the resistance to rotation and extension of the knee using a hydraulic cylinder. Small valves control the amount of hydraulic fluid that can pass into and out of

the cylinder, thus regulating the extension and compression of a piston connected to the upper section of the knee. The microprocessor receives signals from its sensors to determine the type of motion being employed by the amputee. The microprocessor then signals the hydraulic cylinder to act accordingly. The microprocessor also records information concerning the motion of the amputee that can be downloaded onto a computer and analyzed. This information allows the user to make better use of the prosthetic.

The C-Leg is powered by a lithium-ion battery housed inside the prosthesis below the knee joint. (cell is actually located within the axis of the joint) On a full charge, the C-leg can operate for up to 45 hours, depending on the intensity of use. A charging port located on the front of the knee joint can be connected to a charging cable plugged directly into a standard outlet. A "pigtail" charging port adapter permits the relocation of the charging port to a location more accessible when the prosthesis has a cosmetic cover applied. The charger cord has lights that allow the user to observe the level of charge when connected to the knee. A 12 volt car charger adapter can also be purchased.

The C-Leg provides certain advantages over conventional mechanical knee prostheses. It provides an approximation to an amputee's natural gait. The C-Leg allows amputees to walk at near walking speed. Variations in speed are also possible and are taken into account by sensors and communicated to the microprocessor, which adjusts to these changes accordingly. It also enables the amputees to walk down stairs with a step-over-step approach, rather than the one step at a time approach used with mechanical knees. The C-Leg's ability to respond to sensor readings can help amputees recover from stumbles without the knee buckling. However, the C-Leg has some significant drawbacks that impair its use. The C-Leg is susceptible to water damage and thus great care must be taken to ensure that the prosthesis remains dry. Otto Bock recommends that each amputee use the C-Leg for up to two months before the system can fully become accustomed to the individual's unique gait. Becoming accustomed to the C-Leg is especially difficult when walking downhill, and amputees should seek help while becoming familiar with the system to avoid injury.

A wide range of amputees can make use of the C-Leg; however, some people are more suited to this prosthesis than others. The C-Leg is designed for use on people who have undergone transfemoral amputation, or amputation above the knee. The C-Leg can be used by amputees with either single or bilateral limb amputations. In the case of bilateral amputations, the application of C-Legs must be closely monitored. In some cases, those who have undergone hip disarticulation amputations can be candidates for a C-Leg. The prosthesis is recommended for amputees that vary their walking speeds and can reach over 3 miles per hour; however, it cannot be used for running. The C-Leg is practical for upwards of 3 miles daily, and can be used on uneven ground, slopes, or stairs. Active amputees, such as bikers and rollerbladers may find the C-Leg suited to their needs.

Certain physical requirements must be met for C-Leg use. The amputee must have satisfactory cardiovascular and pulmonary health. The balance and strength of the

amputee must be sufficient to take strides while using prosthesis. The C-Leg is designed to support amputees weighing up to 275 pounds.

Robotic prostheses

In order for a robotic prosthetic limb to work, it must have several components to integrate it into the body's function: Biosensors detect signals from the user's nervous or muscular systems. It then relays this information to a controller located inside the device, and processes feedback from the limb and actuator (e.g., position, force) and sends it to the controller. Examples include wires that detect electrical activity on the skin, needle electrodes implanted in muscle, or solid-state electrode arrays with nerves growing through them. One type of these biosensors are employed in myoelectric prosthesis.

Mechanical sensors process aspects affecting the device (e.g., limb position, applied force, load) and relay this information to the biosensor or controller. Examples include force meters and accelerometers.

The controller is connected to the user's nerve and muscular systems and the device itself. It sends intention commands from the user to the actuators of the device, and interprets feedback from the mechanical and biosensors to the user. The controller is also responsible for the monitoring and control of the movements of the device.

An actuator mimics the actions of a muscle in producing force and movement. Examples include a motor that aids or replaces original muscle tissue.

Cosmesis

Cosmetic prosthesis has long been used to disguise injuries and disfigurements. With advances in modern technology, cosmesis, the creation of lifelike limbs made from silicone or PVC has been made possible. Such prosthetics, such as artificial hands, can now be made to mimic the appearance of real hands, complete with freckles, veins, hair, fingerprints and even tattoos. Custom-made cosmeses are generally more expensive (costing thousands of US dollars, depending on the level of detail), while standard cosmeses come ready-made in various sizes, although they are often not as realistic as their custom-made counterparts. Another option is the custom-made silicone cover, which can be made to match a person's skin tone but not details such as freckles or wrinkles. Cosmeses are attached to the body in any number of ways, using an adhesive, suction, form-fitting, stretchable skin, or a skin sleeve.

Cognition

Unlike neuromotor prostheses, neurocognitive prostheses would sense or modulate neural function in order to physically reconstitute or augment cognitive processes such as executive function, attention, language, and memory. No neurocognitive prostheses are currently available but the development of implantable neurocognitive brain-computer interfaces has been proposed to help treat conditions such as stroke, traumatic brain

injury, cerebral palsy, autism, and Alzheimer's disease. The recent field of Assistive Technology for Cognition concerns the development of technologies to augment human cognition. Scheduling devices such as Neuropage remind users with memory impairments when to perform certain activities, such as visiting the doctor. Micro-prompting devices such as PEAT, AbleLink and Guide have been used to aid users with memory and executive function problems perform activities of daily living.

Prosthetic enhancement

In addition to the standard artificial limb for everyday use, many amputees or congenital patients have special limbs and devices to aid in the participation of sports and recreational activities.

Within science fiction, and, more recently, within the scientific community, there has been consideration given to using advanced prostheses to replace healthy body parts with artificial mechanisms and systems to improve function. The morality and desirability of such technologies are being debated. Body parts such as legs, arms, hands, feet, and others can be replaced.

The first experiment with a healthy individual appears to have been that by the British scientist Kevin Warwick. In 2002, an implant was interfaced directly into Warwick's nervous system. The electrode array, which contained around a hundred electrodes, was placed in the median nerve. The signals produced were detailed enough that a robot arm was able to mimic the actions of Warwick's own arm and provide a form of touch feedback again via the implant.

In 2008, Oscar Pistorius was briefly ruled ineligible for the 2008 Summer Olympics due to an alleged mechanical advantage over runners who have ankles.

In early 2008, Oscar Pistorius, the "Blade Runner" of South Africa, was briefly ruled ineligible to compete in the 2008 Summer Olympics because his prosthetic limbs were said to give him an unfair advantage over runners who had ankles. One researcher found that his limbs used twenty-five percent less energy than those of an able-bodied runner moving at the same speed. This ruling was overturned on appeal, with the appellate court stating that the overall set of advantages and disadvantages of Pistorius' limbs had not been considered. Pistorius did not qualify for the South African team for the Olympics, but went on to sweep the 2008 Summer Paralympics, and has been ruled eligible to qualify for any future Olympics.

The "Luke arm" is an advanced prosthesis currently under trials as of 2008.

Types

A United States Marine with bilateral prosthetic legs leads a formation run.

There are four main types of artificial limbs. These include the transtibial, transfemoral, transradial, and transhumeral prostheses. The type of prosthesis depends on what part of the limb is missing.

Transtibial prosthesis

A transtibial prosthesis is an artificial limb that replaces a leg missing below the knee. Transtibial amputees are usually able to regain normal movement more readily than someone with a transfemoral amputation, due in large part to retaining the knee, which allows for easier movement. In the prosthetic industry a trans-tibial prosthetic leg is often referred to as a "BK" or below the knee prosthesis.

Transfemoral prosthesis

A transfemoral prosthesis is an artificial limb that replaces a leg missing above the knee. Transfemoral amputees can have a very difficult time regaining normal movement. In general, a transfemoral amputee must use approximately 80% more energy to walk than a person with two whole legs. This is due to the complexities in movement associated with the knee. In newer and more improved designs, after employing hydraulics, carbon fibre, mechanical linkages, motors, computer microprocessors, and innovative combinations of these technologies to give more control to the user. In the prosthetic industry a trans-femoral prosthetic leg is often referred to as an "AK" or above the knee prosthesis.

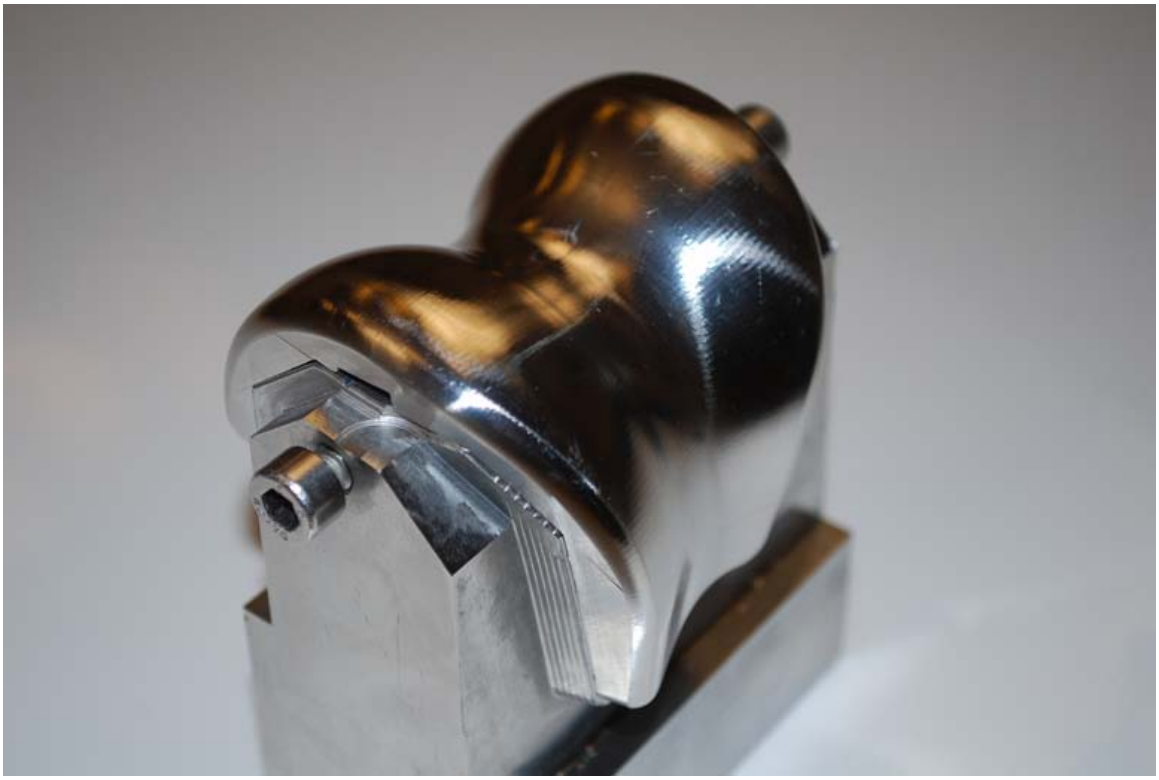
Transradial prosthesis

A transradial prosthesis is an artificial limb that replaces an arm missing below the elbow. Two main types of prosthetics are available. Cable operated limbs work by attaching a harness and cable around the opposite shoulder of the damaged arm. The other form of prosthetics available are myoelectric arms. These work by sensing, via electrodes, when the muscles in the upper arm moves, causing an artificial hand to open or close. In the prosthetic industry a trans-radial prosthetic arm is often referred to as a "BE" or below elbow prosthesis.

Transhumeral prosthesis

A transhumeral prosthesis is an artificial limb that replaces an arm missing above the elbow. Transhumeral amputees experience some of the same problems as transfemoral amputees, due to the similar complexities associated with the movement of the elbow. This makes mimicking the correct motion with an artificial limb very difficult. In the prosthetic industry a trans-humeral prosthesis is often referred to as a "AE" or above the elbow prothesis.

Current technology/manufacturing



Knee prosthesis manufactured using WorkNC Computer Aided Manufacturing software.

In recent years there have been significant advancements in artificial limbs. New plastics and other materials, such as carbon fiber, have allowed artificial limbs to be stronger and lighter, limiting the amount of extra energy necessary to operate the limb. This is especially important for transfemoral amputees. Additional materials have allowed artificial limbs to look much more realistic, which is important to transradial and transhumeral amputees because they are more likely to have the artificial limb exposed.

In addition to new materials, the use of electronics has become very common in artificial limbs. Myoelectric limbs, which control the limbs by converting muscle movements to electrical signals, have become much more common than cable operated limbs. Myoelectric signals are picked up by electrodes, the signal gets integrated and once it exceeds a certain threshold, the prosthetic limb control signal is triggered which is why inherently, all myoelectric controls lag. Conversely, cable control is immediate and physical, and through that offers a certain degree of direct force feedback that myoelectric control does not. Computers are also used extensively in the manufacturing of limbs. Computer Aided Design and Computer Aided Manufacturing are often used to assist in the design and manufacture of artificial limbs.

Most modern artificial limbs are attached to the stump of the amputee by belts and cuffs or by suction. The stump either directly fits into a socket on the prosthetic, or - more commonly today - a liner is used that then is fixed to the socket either by vacuum

(suction sockets) or a pin lock. Liners are soft and by that, they can create a far better suction fit than hard sockets. Silicone liners can be obtained in standard sizes, mostly with a circular (round) cross section, but for any other stump shape, custom liners can be made. The socket is custom made to fit the residual limb and to distribute the forces of the artificial limb across the area of the stump (rather than just one small spot), which helps reduce wear on the stump. The custom socket is created by taking a plaster cast of the stump or, more commonly today, of the liner worn over the stump, and then making a mold from the plaster cast. Newer methods include laser guided measuring which can be input directly to a computer allowing for a more sophisticated design.

One problems with the stump and socket attachment is that a bad fit will reduce the area of contact between the stump and socket or liner, and increase pockets between stump skin and socket or liner. Pressure then is higher, which can be painful. Air pockets can allow sweat to accumulate that can soften the skin. Ultimately, this is a frequent cause for itchy skin rashes. Further down the road, it can cause breakdown of the skin.

Artificial limbs are typically manufactured using the following steps:

1. Measurement of the stump
2. Measurement of the body to determine the size required for the artificial limb
3. Fitting of a silicone liner
4. Creation of a model of the liner worn over the stump
5. Formation of thermoplastic sheet around the model – This is then used to test the fit of the prosthetic
6. Formation of permanent socket
7. Formation of plastic parts of the artificial limb – Different methods are used, including vacuum forming and injection molding
8. Creation of metal parts of the artificial limb using die casting
9. Assembly of entire limb

Body-powered arms

Current body powered arms contain sockets that are built from hard epoxy or carbon fiber. Wrist units are either screw-on connectors featuring the UNF 1/2-20 thread (USA) or quick release connector, of which there are different models. Terminal devices contain a range of hooks, hands or other devices. Hands require a large activation force, which is often uncomfortable. Hooks require a much lower force. Hosmer and Otto Bock are major commercial hook providers. Mechanical hands are sold by Hosmer and Otto Bock as well; the Becker Hand is still manufactured by the Becker family. Prosthetic hands may be fitted with standard stock or custom made cosmetic looking silicone gloves. But regular work gloves may be worn as well. Other terminal devices include the V2P Prehensor, a versatile robust gripper that allows customers to modify aspects of it, Texas Assist Devices (with a whole assortment of tools) and TRS that offers a range of terminal devices for sports. Cable harnesses can be built using aircraft steel cables, ball hinges and self lubricating cable sheaths. Current high tech allows body powered arms to weigh around half to only a third of the weight that a myoelectric arm has.

Actor Owen Wilson gripping the myoelectric prosthetic arm of a United States Marine

Myoelectric

A **myoelectric prosthesis** uses electromyography signals or potentials from voluntarily contracted muscles within a person's residual limb on the surface of the skin to control the movements of the prosthesis, such as elbow flexion/extension, wrist supination/pronation (rotation) or hand opening/closing of the fingers. A prosthesis of this type utilizes the residual neuro-muscular system of the human body to control the functions of an electric powered prosthetic hand, wrist or elbow. This is as opposed to an electric switch prosthesis, which requires straps and/or cables actuated by body movements to actuate or operate switches that control the movements of a prosthesis or one that is totally mechanical. It is not clear whether those few prostheses that provide

feedback signals to those muscles are also myoelectric in nature. It has a self suspending socket with pick up electrodes placed over flexors and extensors for the movement of flexion and extension respectively.

The first commercial myoelectric arm was developed in 1964 by the Central Prosthetic Research Institute of the USSR, and distributed by the Hangar Limb Factory of the UK.

Robotic limbs

Advancements in the processors used in myoelectric arms has allowed for artificial limbs to make gains in fine tuned control of the prosthetic. The Boston Digital Arm is a recent artificial limb that has taken advantage of these more advanced processors. The arm allows movement in five axes and allows the arm to be programmed for a more customized feel. Raymond Edwards, Limbless Association Acting CEO, was the first amputee to be fitted with the i-LIMB by the National Health Service in the UK. The hand, manufactured by "Touch Bionics" of Scotland (a Livingston company), went on sale on 18 July 2007 in Britain. It was named alongside the Super Hadron Collider in Time magazine's top fifty innovations. Another robotic hand is the RSLSteeper bebionic

Another neural prosthetic is Johns Hopkins University Applied Physics Laboratory Proto 1. Besides the Proto 1, the university also finished the Proto 2 in 2010.

Robotic legs exist too: the Argo Medical Technologies ReWalk is an example or a recent robotic leg, targeted to replace the wheelchair. It is marketed as a "robotic pants".

Targeted muscle reinnervation (TMR) is a technique in which motor nerves which previously controlled muscles on an amputated limb are surgically rerouted such that they reinnervate a small region of a large, intact muscle, such as the pectoralis major. As a result, when a patient thinks about moving the thumb of his missing hand, a small area of muscle on his chest will contract instead. By placing sensors over the reinervated muscle, these contractions can be made to control movement of an appropriate part of the robotic prosthesis.

An emerging variant of this technique is called targeted sensory reinnervation (TSR). This procedure is similar to TMR, except that sensory nerves are surgically rerouted to skin on the chest, rather than motor nerves rerouted to muscle. The patient then feels any sensory stimulus on that area of the chest, such as pressure or temperature, as if it were occurring on the area of the amputated limb which the nerve originally innervated. In the future, artificial limbs could be built with sensors on fingertips or other important areas. When a stimulus, such as pressure or temperature, activated these sensors, an electrical signal would be sent to an actuator, which would produce a similar stimulus on the "rewired" area of chest skin. The user would then feel that stimulus as if it were occurring on an appropriate part of the artificial limb.

Recently, robotic limbs have improved in their ability to take signals from the human brain and translate those signals into motion in the artificial limb. DARPA, the

Pentagon's research division, is working to make even more advancements in this area. Their desire is to create an artificial limb that ties directly into the nervous system.

Direct bone attachment / osseointegration

Osseointegration is a new method of attaching the artificial limb to the body. This method is also sometimes referred to as exoprosthesis (attaching an artificial limb to the bone), or endo-exoprosthesis.

The stump and socket method can cause significant pain in the amputee, which is why the direct bone attachment has been explored extensively. The method works by inserting a titanium bolt into the bone at the end of the stump. After several months the bone attaches itself to the titanium bolt and an abutment is attached to the titanium bolt. The abutment extends out of the stump and the artificial limb is then attached to the abutment. Some of the benefits of this method include the following:

- Better muscle control of the prosthetic.
- The ability to wear the prosthetic for an extended period of time; with the stump and socket method this is not possible.
- The ability for transfemoral amputees to drive a car.

The main disadvantage of this method is that amputees with the direct bone attachment cannot have large impacts on the limb, such as those experienced during jogging, because of the potential for the bone to break.

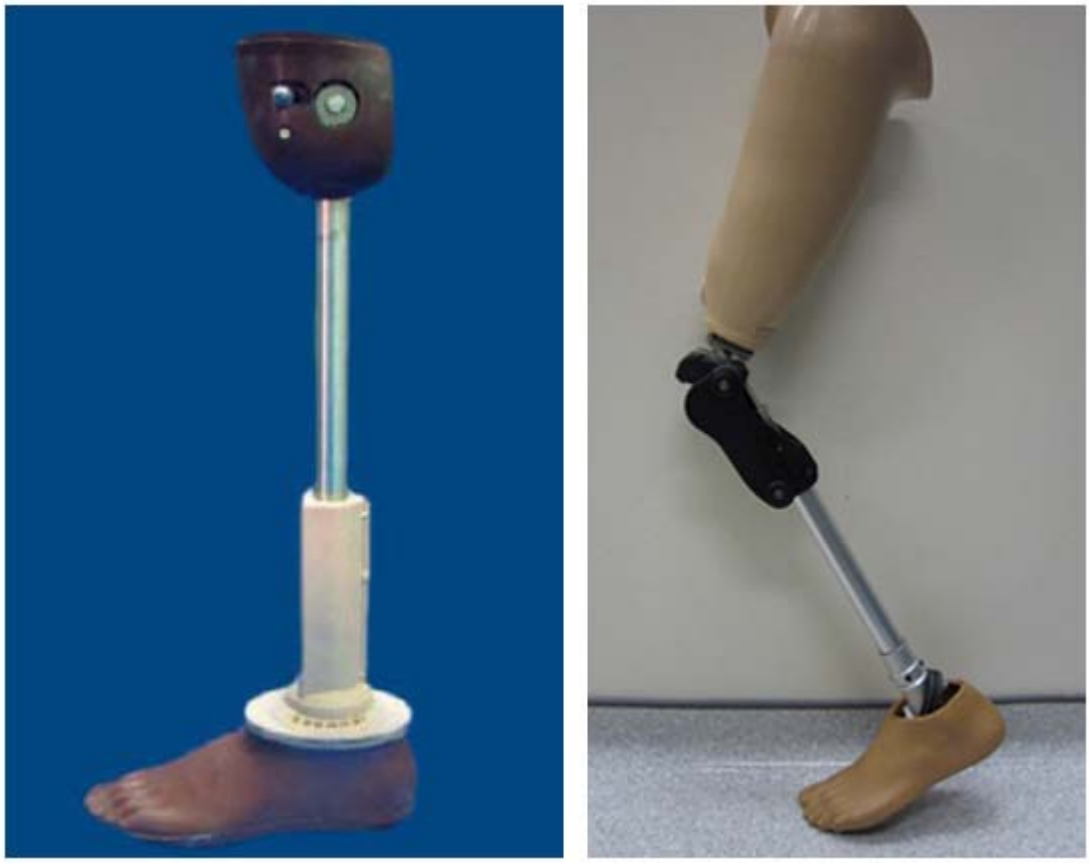
Cost

Transradial and transtibial prostheses typically cost between US $6,000 and $8,000. Transfemoral and transhumeral prosthetics cost approximately twice as much with a range of $10,000 to $15,000 and can sometimes reach costs of $35,000. The cost of an artificial limb does recur because artificial limbs are usually replaced every 3–4 years due to wear and tear. In addition, if the socket has fit issues, the socket must be replaced within several months. If height is an issue components can be changed, such as the pylons.

Low cost above knee prostheses often provide only basic structural support with limited function. This function is often achieved with crude, non-articulating, unstable, or manually locking knee joints. A limited number of organizations, such as the International Committee of the Red Cross (ICRC), create devices for developing countries. Their device which is manufactured by CR Equipments is a single-axis, manually operated locking polymer prosthetic knee joint.

Table. List of knee joint technologies based on the literature review.

Name of technology (country of origin)	Brief description	Highest level of evidence
ICRC knee (Switzerlan)	Single-axis with manual lock	Independent field
ATLAS knee (UK)	Weigh-activated friction	Independent field
POF/OTRC knee (US)	Single-axis with ext. assist	Field
DAV/Seattle knee (US)	Compliant polycentric	Field
LEGS M1 knee (US)	Four-bar	Field
JaipurKnee (US)	Four-bar	Field
LCKnee (Canada)	Single-axis with automatic lock	Field
None provided (Nepal)	Single-axis	Field
None provided (New Zealand)	Roto-molded single-axis	Field
None provided (India)	Six-bar with squatting	Technical development
Friction knee (US)	Weigh-activated friction	Technical development
Wedgelock knee (Australia)	Weigh-activated friction	Technical development
SATHI friction knee (India)	Weigh-activated friction	Limited data available



Low Cost Above Knee Prosthetic Limbs: ICRC Knee (left) and LC Knee (right)

There is currently an open Prosthetics design forum known as the "Open Prosthetics Project". The group employs collaborators and volunteers to advance Prosthetics technology while attempting to lower the costs of these necessary devices.

A plan for a low-cost artificial leg, designed by Sébastien Dubois, was featured at the 2007 International Design Exhibition and award show in Copenhagen, Denmark, where it won the Index: Award. It would be able to create an energy-return prosthetic leg for US $8.00, composed primarily of fiberglass.

Prior to the 1980s, foot prostheses merely restored basic walking capabilities. These early devices can be characterized by a simple artificial attachment connecting one's residual limb to the ground.

The introduction of the Seattle Foot (Seattle Limb Systems) in 1981 revolutionized the field, bringing the concept of an Energy Storing Prosthetic Foot (ESPF) to the fore. Other companies soon followed suit, and before long, there were multiple models of energy storing prostheses on the market. Each model utilized some variation of a compressible heel. The heel is compressed during initial ground contact, storing energy which is then returned during the latter phase of ground contact to help propel the body forward.

Since then, the foot prosthetics industry has been dominated by steady, small improvements in performance, comfort, and marketability. *Jaipur Foot*, an artificial limb from Jaipur, India, costs about US$ 40.

Design considerations

There are multiple factors to consider when designing a transtibial prosthesis. Manufacturers must make choices about their priorities regarding these factors.

Performance

Nonetheless, there are certain elements of foot mechanics that are invaluable for the athlete, and these are the focus of today's high-tech prosthetics companies:

- Energy storage and return – storage of energy acquired through ground contact and utilization of that stored energy for propulsion
- Energy absorption – minimizing the effect of high impact on the musculoskeletal system
- Ground compliance – stability independent of terrain type and angle
- Rotation – ease of changing direction
- Weight – maximizing comfort, balance and speed
- Suspension - how the socket will join and fit to the limb

Other

The buyer is also concerned with numerous other factors:

- Cosmetics
- Cost
- Ease of use
- Size availability

Emerging technology

Most companies choose to focus on two areas of performance: energy capabilities and ground compliance. Two particular models exemplify the innovation in these areas: the Elite foot (Endolite) and the Venture foot (College Park Industries).

The Elite foot relies on a polymeric material with a very specific set of elasticity and resistance requirements in order to optimize energy storage and return. It also uses an unprecedented three-pronged foot, which allegedly allows the foot to closely mold to the contours of any surface.

In contrast, the Venture foot retains the common one-point contact with the ground, but seeks to maximize performance (in both energy and compliance) with a complex metal heel component. This heel is equipped not just with a standard compressible foam piece,

but also hinges which allow rotation on three different axes, allegedly yielding superior comfort (ground compliance) and a more precise mimicry of native foot biomechanics (energy capabilities).

Many other foot prostheses employ other useful innovative technology and designs. No one foot is perfect for all transtibial amputees. Hopefully, however, each amputee can find a foot that is best for his or her particular pattern of physical activity.

Chapter 8

Bioheat Transfer

Bioheat transfer is the study of heat transfer in biological systems. In simpler terms, it is the study of how heat moves from one compartment, be it within the body or external to the body, to another compartment in the body. Bioheat transfer has its foundations in the engineering discipline of heat transfer and is itself a subfield of biomedical engineering or bioengineering. In addition, computational techniques to model various bioheat transfer scenarios are widely employed and hold an important place in developing devices and protocols for the medical community.

Constitutive Values

Because modeling bioheat transfer is of the utmost importance in proper device or heating protocol design, constitutive values of various tissues of the body had to be measured early on in the history of bioheat transfer.

Of particular importance were the values of specific gravity, specific heat, thermal conductivity for the various tissues in the body e.g. skin, fat, muscle, bone, and blood. Today, such values can be easily found in various handbooks and study publications such as the CRC Handbook of Mechanical Engineering (2nd Ed.) or the Report of the task group on reference man (1975).

To illustrate the detailed knowledge that is required by the bioheat transfer community, The CRC Handbook of Mechanical Engineering includes a nearly 2 page table of value for thermal conductivity of various organs including but not limited to: kidney, aorta, arterial plaque, blood, liver, spleen, heart, muscle and tumor.

Because of the importance of blood perfusion on thermal equilibria in the body, blood perfusion values were also pursued early in the history of the field. The CRC Handbook of Mechanical Engineering's chapter on Bioheat Transfer includes a nearly 6 page table of blood perfusion values for a similar variety of tissues as the table for thermal conductivity. Greater discussion on the effect of blood perfusion on heat transfer is given in Section 2.

The Cardiovascular System

The cardiovascular system is the key system by which heat is distributed throughout the body. The blood serves as the vehicle to transport heat from the areas of high heat to areas of lower heat. In general this transfer takes place in the direction from body core to extremities such as the limbs and head. In the case where the extremities are hotter than the core body temperature, perfusion would serve to transport heat from the extremity back towards the body core. Whether or not the core temperature rises depends on many factors such as the duration of elevated local temperature at the extremity, temperature difference between extremity and core, volume of blood heated above core temperature, and the rate of blood perfusion. This same moderating phenomena of blood perfusion can be applied to local heat transfer problems e.g. heating of a tumor.

Ablative Surgical Procedures

Ablative surgical techniques generally employ some method of energy deposition which destroys cells and tissue with a concomitant increase in temperature at the targeted site. Bioheat transport equations can be applied to the process of energy deposition into the tissue as well as the subsequent conduction/convection heat transport to cells neighboring the targeted site to predict a temperature history and distribution. Such a model could be used to select the most appropriate protocol for the surgery.

Various modalities of energy deposition include: radio frequency, laser, high intensity focused ultrasound, etc. These modalities are commonly used in the minimally invasive surgical treatment of cancer. One common type is radiofrequency ablation, a type of hyperthermia therapy.

Cryosurgical Procedures

Cryosugery is a technique which employs the use of low temperatures to destroy cells. The mechanism of death is usually by plasma membrane and protein disruption via physical and osmotic damage when ice crystals form within the cytoplasm of the cell. Bioheat transport equations can also be used to model this process.

Therapeutic Hyperthermia & Hypothermia

Heat can be used not only to destroy cells, but also to aid in the recovery of cells and tissues. Such use of heat is sometimes called therapeutic hyperthermia, perhaps to distinguish it from malignant hyperthermia.

An example of therpeutic hyperthermia is the ThermaCare HeatWrap by Procter & Gamble. The application of heat to injured tissues works to heal target tissues by a temperature dependent vasodilation. This vasodilation increases the mass transport of wastes and nutrients from and to the site of injury. Because damaged tissue is more metabolically active the enhanced mass transport can facilitate more rapid healing.

Hypothermia
Heat transfer is not only study of raising temperatures, but also reducing them. It is commonly understood that lower temperatures help to preserve living or "once living" tissue. For example, foods stored in refrigerators last longer because the metabolic processes of cellular decay and bacterial growth are slowed due to the lower free energy (e.g. heat) in the refrigerator. This principle is often applied in surgical wards to individuals who experience head trauma.

In cases of head trauma, it is common procedure to reduce the body temperature to about 32°C (90°F) which is about 5°C (8.5°F) lower than normal core temperature of 37°C (98.5°F). This presents a good example of how bioheat transfer engineers can contribute to medical treatments. Such a situation would be broken down first into a system, which in this case would include the entire surface of the body. Assuming the individual is submerged in cold water up to the neck and ears, or otherwise surrounded by an environment that can be modeled as a temperature sink, the engineering would model the body as a composite system composed od skin, fast, muscle bone and possibly organs depending on how complex the model must be. The head could be considered a separate system connected to the body via a third major system, the vasculature. The vasculature would bring cooled blood from the submerged body to the brain where there would be some amount of conductive and convection heat transfer based on the passage of blood through the vessels cooling the vessel via forced convection and the subsequent cooling of the brain via conduction between blood vessel and brain tissue. Each of these heat transfer processes i.e. water to body, body to vasculature, and vasculature to brain would require knowledge of the thermal conductivity, specific heat, density, blood perfusion rate, and diameter of blood vessel at the least to predict the temperature history at any point within the body e.g. to know when the temperature at the center of the head trauma reaches 32°C.

Such application of hypothermia is also employed during open heart surgery where perfusion to the body and brain must stop while cardiac output is rerouted through a heart lung machine. Furthermore, biomedical engineerings who specialize in bioheat transfer are able to design such medical devices to perform within a specified range of temperatures and rates of cooling.

Cryopreservation

- Tissue banking
- Blood
- Transplant organs

Bioheat Models

- Pennes' Bioheat Equation

Training

Most people in that work in the field of bioheat transfer can be considered biomedical engineers. A number of universities grant bachelors degrees in biomedical engineering and bioengineering, but due to the large variety of sub-fields in biomedical engineering the training that undergraduate students receive varies greatly from program to program. Most engineers who have expertise in bioheat transfer received training from academic research labs either as undergraduates or as graduate students.

- Undergraduate degree programs
- Graduate degree programs

Chapter 9

Artificial Pancreas

The **artificial pancreas** is a technology in development to help people with diabetes automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.

There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production which is the motivation to develop a substitute. While the current state of insulin replacement therapy is appreciated for its life-saving capability, the task of manually managing the blood sugar level with insulin alone is arduous and inadequate.

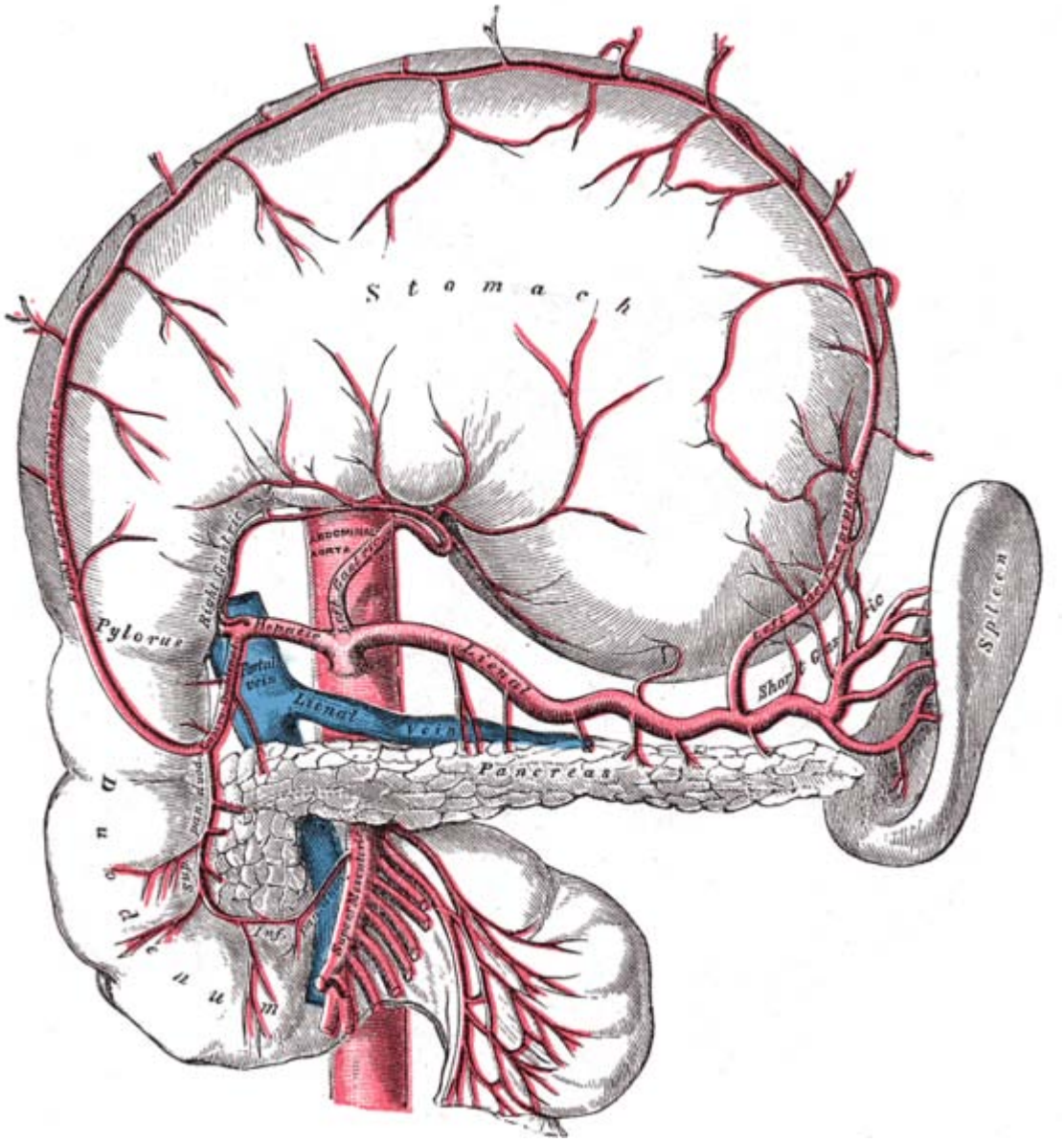
The goal of the artificial pancreas is threefold:

1. to improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and
2. to ease the burden of therapy for the insulin-dependent.
3. to mimic normal stimulation of the liver by the pancreas.

Different approaches under consideration include:

- the medical equipment approach -- using an insulin pump under closed loop control using real-time data from a continuous blood glucose sensor.
- the bioengineering approach -- the development of a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.
- the stimulation of the liver through delivery of pulses of insulin as seen in normal pancreatic insulin stimulation of hepatic tissues.
- the gene therapy approach -- the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells.

Background in endocrine physiology



The pancreas (below the stomach and above the duodenum) releases endocrine hormones (insulin, amylin, and glucagon) into the portal vein, where it flows directly to the liver.

The pancreas produces three hormones that are important to glycemic control:

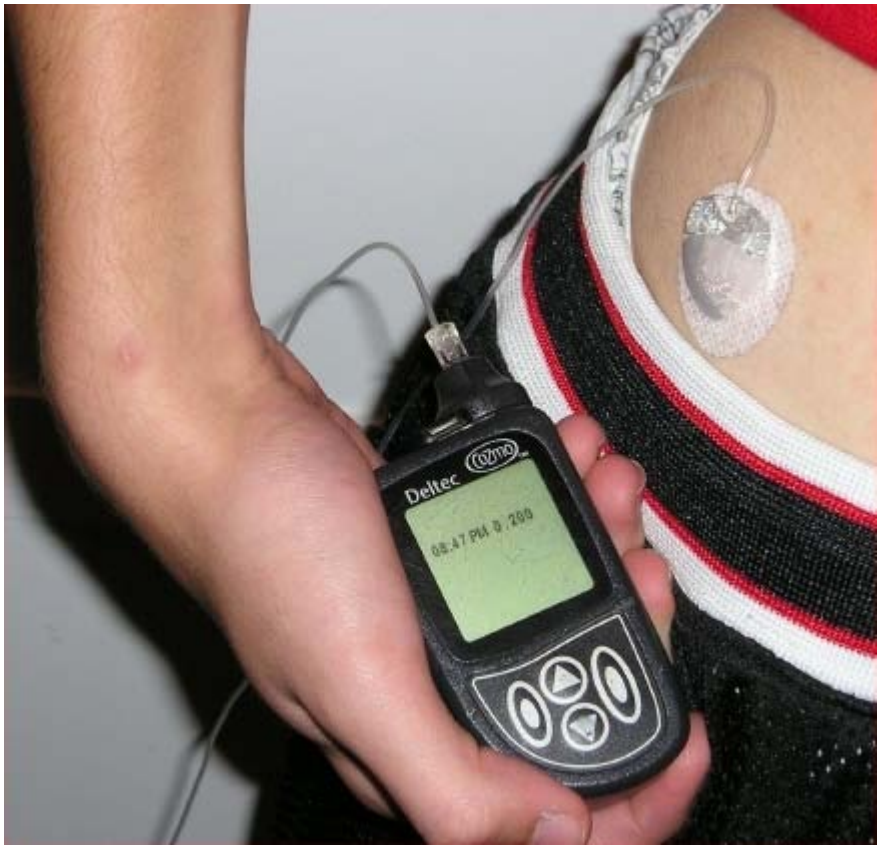
- insulin, which lowers blood glucose;
- amylin, which slows digestion and slows the rate of glucose entering the bloodstream, and temporarily suppresses release of glucagon;
- and glucagon, which raises the blood glucose.

Upon digestion of carbohydrates, glucose levels in the blood will begin to rise. As the blood and glucose flow into the pancreas, insulin and amylin are cosecreted by the pancreatic beta cells directly into the bloodstream in response to elevated blood glucose levels. In the presence of glucose these insulin responses are almost exclusively delivered in boluses every 4 to 6 minutes. Insulin causes blood glucose to be removed from the bloodstream and stored in the liver and muscle cells. Notice as the blood sugar goes higher, additional insulin will bring the blood sugar back down in a classic negative feedback loop. As insulin is released from the beta cells, amylin is also released into the bloodstream. Amylin slows gastric emptying, and also inhibits the release of glucagon from the pancreatic alpha cells. The effect of amylin is to spread out the blood glucose peak after eating, reducing the quantity of insulin needed. As the blood sugar level comes back toward normal, the beta cells will stop spurting insulin and amylin. As the glucose level approaches a low mark, the pancreatic alpha cells will release glucagon directly into the bloodstream. Glucagon causes the liver to release stored glucose back into the bloodstream. Notice that increased glucagon will increase blood glucose levels to produce a positive error in the negative feedback loop. Together, the three endocrine hormones work as a system to maintain the blood glucose level between high and low boundaries. By delivering the insulin in boluses as presented by a non-diabetic pancreas, the goal of an artificial pancreas can be achieved.

When the beta cell produces insulin from proinsulin, a connecting peptide (or C-peptide) is also manufactured and released into the bloodstream. Absence of C-peptide in the blood indicates that insulin has not been released from the pancreas, and this fact confirms the diagnosis of diabetes type 1. C-peptide was believed to be only a by-product of natural insulin production, however recent studies suggest that C-peptide exerts beneficial therapeutic effects on diabetic nociceptive neuropathy.

Ideally, to replicate the natural function of the pancreas as closely as possible, an artificial pancreas might someday replace all of the beneficial endocrine functions lost, including the delivery of insulin, amylin, glucagon, and C-peptide.

Background in insulin therapy



The Insulin pump is used to automatically deliver basal insulin continuously, and bolus insulin at meal times by pressing the buttons. Before meals, a blood glucose value is entered into the pump to calculate the correction bolus to bring the blood glucose level back to the target value.

In insulin-dependent persons, blood glucose levels have been roughly controlled using insulin alone. The number of grams of carbohydrate is estimated by measuring foods, and the measurement is used to determine the amount of insulin necessary to *cover* the meal. The calculation is based on a simple *open-loop model*: an insulin to carbohydrate ratio (adjusted based on past success) is multiplied by the grams of carbohydrate to calculate the units of insulin needed. That quantity of insulin is then adjusted based on a pre-meal blood glucose measurement (insulin bolus increased for a high blood sugar or insulin bolus delayed and reduced for a low blood sugar). Insulin is injected or infused under the skin, and enters the bloodstream in approximately 15 minutes. After the insulin has acted in the bloodstream, the blood glucose level can be tested again and then adjusted with injection of more insulin, or eating more carbohydrates, until balance is restored. Assuming the design requirement is to truly mimic normal pancreatic delivery of insulin to the liver in order to achieve proper hepatic stimulation, and to cause normal insulin induced functions, until another system is available to deliver portal vein concentrations of insulin, a intravenous infusion device will be needed.

There are notable differences with insulin replacement compared to the function of pancreatic insulin delivery:

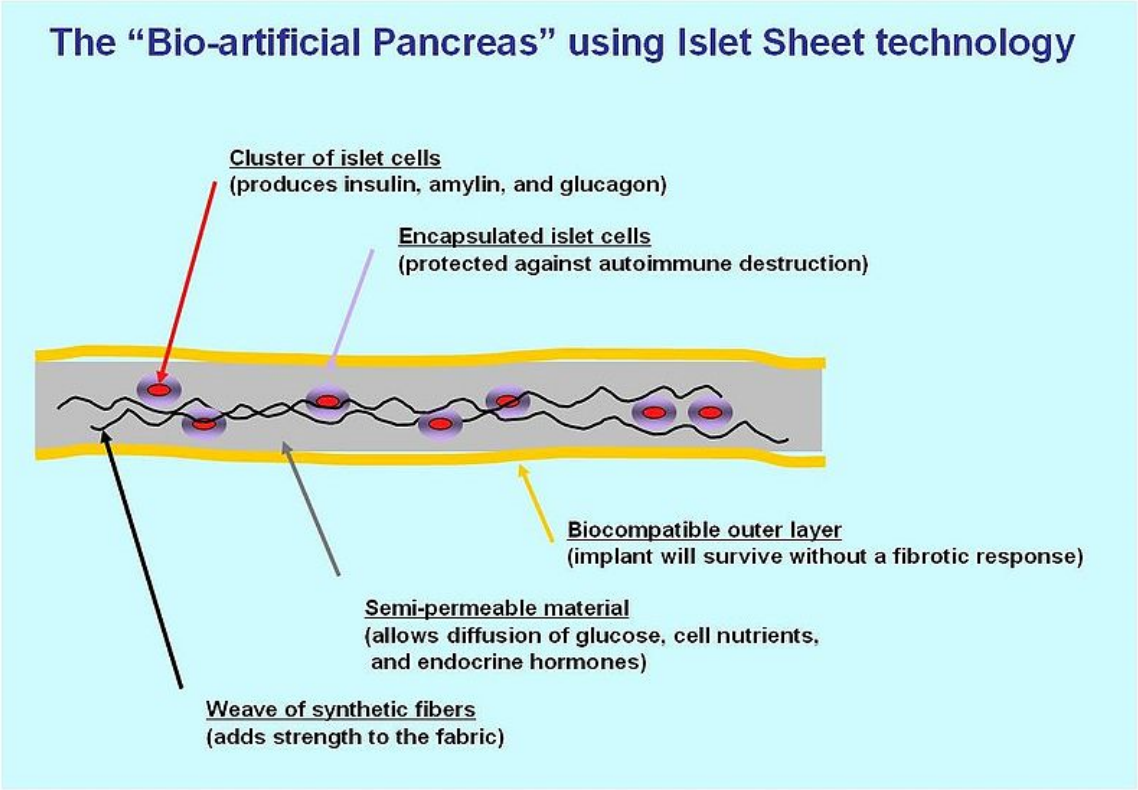
1. the insulin dose is predicted based on measured food (where accuracy of measured carbohydrate is difficult) whereas pancreatic insulin is released in proportional response to actual blood glucose levels;
2. pancreatic insulin is released into to the portal vein, where it flows almost directly to the liver, which is the major organ for storing glycogen (50% of insulin produced is used by the liver);
3. pancreatic insulin is pulsatile which helps maintain the insulin sensitivity of hepatic tissues;
4. injected insulin is delivered subcutaneously (under the skin) but not directly to the bloodstream, so there is a delay before injected insulin begins to reduce blood glucose (although this can be compensated by injecting insulin 15 minutes before eating);
5. insulin which is not delivered intravenously cannot achieve normal momentary concentrations in the portal vein which connects the pancreas to the liver;
6. replacement insulin therapy does not include amylin (although Symlin is now available for use), which can reduce the insulin need by 50%;
7. replacement insulin is dosed as a best compromise between aggressive use for lowering the blood sugar when eating but also conservative use to avoid a post-prandial low blood sugar due to excess insulin, whereas pancreatic function releases insulin aggressively and later includes automatic release of glucagon at the end of an insulin cycle to manage the blood sugar level and avoid hypoglycemia.

An insulin pump to infuse a rapid-acting insulin is the first step in simulating the function of the pancreas. The pump can accurately deliver small increments of insulin compared to an injection, and its electronic controls permit shaping a bolus over time to match the insulin profile required for a given situation. The insulin pump is controlled by the pump user to bolus manually based on a recent blood glucose measurement and an estimate of the grams of carbohydrate consumed. This predictive approach is said to be *open-loop.* Once a bolus has been calculated and delivered, the pump continues to deliver its basal rate insulin in the manner that has been programmed into the pump controls based on the predicted insulin requirements of its user.

While insulin replacement is appreciated as a life saving therapy, its practical use in controlling blood glucose levels sufficiently to avoid the long term complications associated with hyperglycemia is not ideal. Also, it is generally agreed that even with very tight glucose control, there are a significant number of patients who go on to develop all of the life impacting complications of diabetes. Thus, the goal of the Artificial Pancreas should be to normalize carbohydrate and lipid metabolism at a minimum.

Approaches to an Artificial Pancreas

Bioengineering approach



The Bio-artificial pancreas: this diagram shows a cross section of bio-engineered tissue with encapsulated islet cells which deliver endocrine hormones in response to glucose.

A biological approach to the artificial pancreas is to implant bioengineered tissue containing islet cells, which would secrete the amount of insulin, amylin, and glucagon needed in response to sensed glucose.

When islet cells have been transplanted via the Edmonton protocol, insulin production (and glycemic control) was restored at the expense of immunosuppression. Encapsulation of the islet cells in a protective coating has been developed to block the immune response to transplanted cells, which relieves the burden of immunosuppression and benefits the longevity of the transplant.

One concept of the bio-artificial pancreas uses encapsulated islet cells to build an *islet sheet* which can be surgically implanted to function as an artificial pancreas.

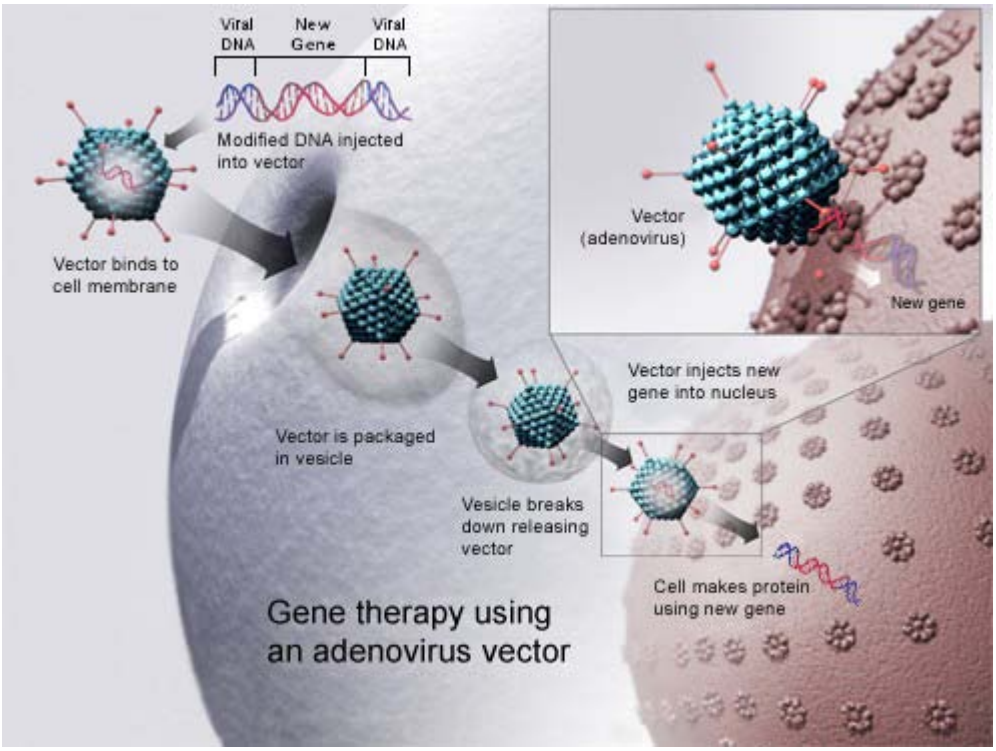
This islet sheet design consists of:

- an inner mesh of fibers to provide strength for the islet sheet;

- islet cells, encapsulated to avoid triggering a proliferating immune response, adhered to the mesh fibers;
- a semi-permeable protective layer around the sheet, to allow the diffusion of nutrients and secreted hormones;
- a protective coating, to prevent a foreign body response resulting in a fibrotic reaction which walls off the sheet and causes failure of the islet cells.

Islet sheet research is pressing forward with large animal studies at the present, with plans for human clinical trials within a few years.

Gene therapy approach



Gene therapy: Designing a viral vector to deliberately infect cells with DNA to carry on the viral production of insulin in response to the blood sugar level.

Technology for gene therapy is advancing rapidly such that there are multiple pathways possible to support endocrine function, with potential to practically cure diabetes.

- Gene therapy can be used to **manufacture insulin directly**: an oral medication, consisting of viral vectors containing the insulin sequence, is digested and delivers its genes to the upper intestines. Those intestinal cells will then behave like any viral infected cell, and will reproduce the insulin protein. The virus can be controlled to infect only the cells which respond to the presence of glucose, such that insulin is produced only in the presence of high glucose levels. Due to the limited numbers of vectors delivered, very few intestinal cells would actually be impacted and would die off naturally in a few days. Therefore by varying the

amount of oral medication used, the amount of insulin created by gene therapy can be increased or decreased as needed. As the insulin producing intestinal cells die off, they are boosted by additional oral medications.

- Gene therapy might eventually be used to **cure the cause of beta cell destruction**, thereby curing the new diabetes patient before the beta cell destruction is complete and irreversible.
- Gene therapy can be used to **turn duodenum cells and duodenum adult stem cells into beta cells** which produce insulin and amylin naturally. By delivering beta cell DNA to the intestine cells in the duodenum, a few intestine cells will turn into beta cells, and subsequently adult stem cells will develop into beta cells. This makes the supply of beta cells in the duodenum self replenishing, and the beta cells will produce insulin in proportional response to carbohydrates consumed.

Medical equipment approach

Development of Continuous Blood Glucose Monitoring

Technology for continuous blood glucose monitoring supports the mission of the artificial pancreas by:

1. automatically providing a blood glucose reading every few minutes without finger sticks from the user,
2. monitoring trends pertaining to rising and falling blood sugars, which is helpful in the prediction of blood glucose levels in the immediate future,
3. comparing blood sugar levels and predictions against a high blood sugar threshold, and then prompting the user that a correction bolus from an insulin pump is needed immediately,
4. comparing blood sugar levels and predictions against a low blood sugar threshold, and then prompting the user to reduce the basal insulin from the pump or to eat something.

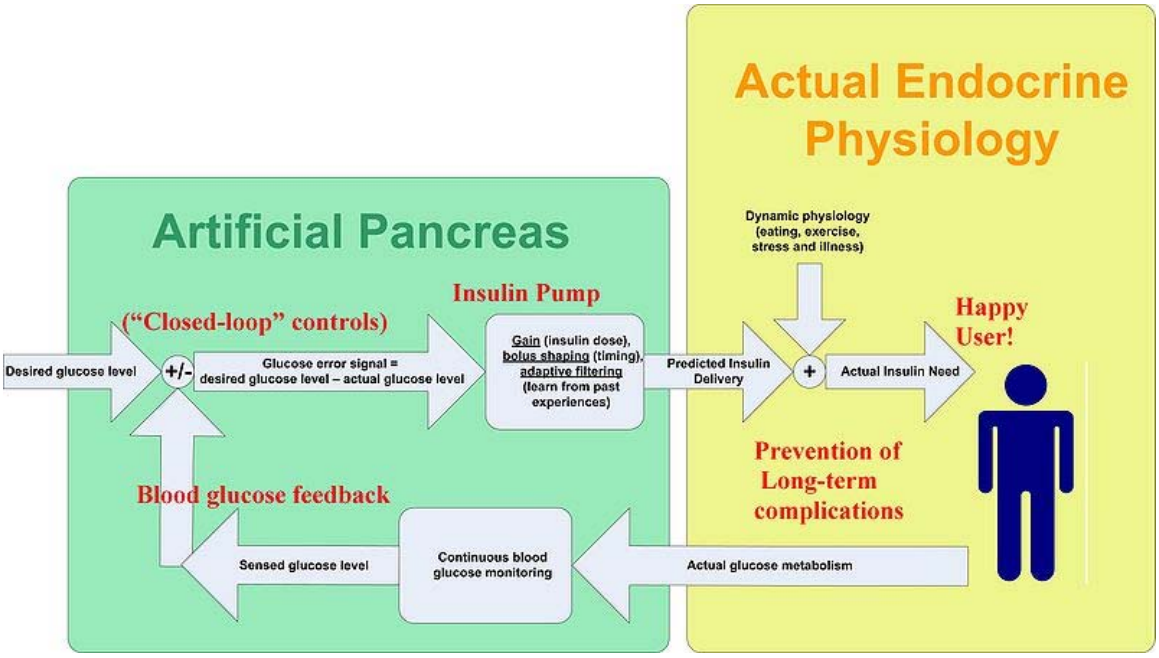
These capabilities suggest that a stream of real-time data can be used to "close the loop" and control the insulin pump directly.

Some issues with the present performance of continuous sensing technology suggest that additional study is needed for application to the artificial pancreas:

1. continuous sensors require calibration a few times a day, by performing a manual blood glucose test with a finger stick, and then entering the blood glucose data into the continuous system for a sensor correction,
2. continuous sensors are measuring interstitial glucose, so there is a time delay between the sensor data and the true blood glucose,
3. automatic control removes the intellect of the user, which can be an additional safeguard when the data is subject to error and must be verified before taking action.

As the state of the art for blood glucose monitoring continues to advance, so does the promise of the artificial pancreas.

Feedback of real-time blood glucose data to an insulin pump for basal control



The medical equipment approach to an artificial pancreas: automatic control of an insulin pump with feedback from a continuous blood glucose sensor.

The first step in controlling an insulin pump based on continuous blood glucose data is to automatically control the basal rate of the insulin pump. When a bolus has not recently been performed, the pump can manage the blood glucose level by adjusting the basal rate as needed:

- when the blood sugar is increasing, a small correction bolus can be automatically delivered and a higher basal rate can be set;
- when the blood sugar is decreasing, the basal rate can be halted to deny the quantity of insulin needed to bring the blood glucose level back up until the basal rate can be continued at a new lower rate;
- and with adaptive filtering techniques, the pump can "learn" the unique basal rates for the person as a function of the time of day.

When controlling the basal rate alone, the closed loop can still correct a meal bolus error that was too large or small for the food consumed by:

- recognizing an imbalance between the bolus "insulin on board" and the level of blood glucose,
- automatically bolusing to correct a shortage of insulin,

- automatically reducing or interrupting the basal rate to correct an abundance of insulin,
- and using adaptive filtering techniques to "learn" the carbohydrate to insulin ratios for each meal bolus.

First clinical tests: implantable insulin pumps and continuous glucose sensors

In France, a human clinical trial of an artificial pancreas is underway. The system is fully automated by combining Medtronic MiniMed's long-term glucose sensor and its implantable insulin pump. A summary of the project shows promise as well as some present limitations:

- The implantable sensor is inserted into a neck vein leading to the heart.
- The sensor is connected, via an electrical-type wire under the skin, to the implantable insulin pump: as blood sugar levels fluctuate, a signal tells the pump how much insulin to deliver.
- The sensor accurately measured glucose in 95% of cases when compared with values obtained by fingersticks.
- The blood glucose levels were maintained in the normal range more than 50% of the time in the patients using the pump connected to the sensor.
- Events of hypoglycemia dropped to less than 5%.
- While implantable insulin pumps work for an average of eight years before they have to be changed, the sensors stop working after an average of nine months,
- The mathematical programs that calculate just how much insulin should be delivered at different parts of the day also needs to be refined.

Insulin and amylin combination

When **pramlintide** (brand name Symlin or synthetic amylin) is used in combination with insulin, the benefits for post-prandial glycemic control are substantial.

Pramlintide is a relatively new treatment for diabetes. The treatment involves:

- a separate injection of pramlintide before a meal,
- a reduction in insulin bolus by 50% for that meal.

Pramlintide can be infused using an insulin pump. At the present time, the mixing of pramlintide and insulin in the same cartridge is not an approved practice, so two infusion pumps are used simultaneously. Since insulin and amylin are co-secreted by the pancreatic beta cells in response to raising blood glucose levels, using pramlintide and insulin together more closely duplicates the function of the pancreas.

Symlin has potential to support the artificial pancreas project because:

- Insulin and pramlintide may in the future be automatically infused together

    - at a mixture from a single automatic insulin pump, or
    - two infusion pumps could be used automatically with the insulin pump acting as master and the simlin pump acting as slave, or
    - a dual system in one pump machine (two cartridges, a dual infusion set tube, and two subcutaneous insertions);
- because it improves post prandial glycemic excursions relative to insulin alone, this supports the possible use of an automatic bolus with less impact due to the delay of the insulin bolus;
- and because it simply duplicates the natural pancreas function, the full benefits of which are not fully understood.

Feedback of real-time blood glucose data to an insulin pump for bolus control

The ability of the electronic controls of the infusion pump, particularly in the bolus shaping capability, suggests that the control algorithm may replicate the function of the healthy pancreas in a more copycat fashion. At present, the insulin bolus is a predictive dose based on what is about to be eaten, and then infused completely. Even with the benefit of the closed-loop control of the basal insulin, the standard bolus is still a "guess and then fix it later" approach. Compare to the pancreatic physiology, where insulin and amylin are released from the beta cells in pulses almost directly to the liver in response to the immediate blood glucose level. The natural release from the beta cells is a closed loop response to sensed glucose, and the shape of the insulin delivery is adaptable and appropriate to the food eaten and the body's present metabolic capability.

As technology for continuous blood glucose monitoring improves, the integrated components will support a typical application of control theory by employing the proportional, integral, and derivative control algorithm. This will make it feasible to infuse an *adaptive bolus* that changes its shape and integral dose based on the measured performance of the bolus in progress, depending on:

- **the rate of glucose increase** (i.e the derivative function would deliver more insulin for a rapid increase in blood sugar);
- **the peak of the glucose curve** (i.e. the proportional function would deliver more insulin for a higher peak in the blood sugar); and
- **the duration of elevated glucose** (i.e. the integral function would deliver more insulin for a long duration of high blood sugar).

The adaptive bolus could start with an assumption of a typical proportions and a bolus shape like the *combination bolus*. This could include:

1. a prebolus of pramlintide (optional perhaps, but resolves issue with insulin timing)
2. initiation of a combination bolus with the initial spike sized in proportion to the present blood glucose level and trends in the change of blood glucose level,

3. modification to the square wave portion of the bolus, increasing or extending if blood sugar is increasing, and decreasing or limiting in duration when blood sugar is decreasing.

The benefits of an automatic bolus delivery might include:

- increased accuracy in the total insulin delivered relative to what was needed,
- freedom to the user of the artificial pancreas,
- elimination of glycemic excursions due to user error (such as forgetting to bolus in conventional pump therapy),
- adaptability to changes in digestion of carbohydrates based on food choices,
- adaptability to variable metabolic needs due to stress, illness, or exercise.

Glucagon combination

The purpose of glucagon is to raise blood sugar, primarily by promoting release of stored glucose in the liver. Human glucagon has been synthesized by recombinant DNA technology and is available in a dry powder form in the glucagon rescue kit. Glucagon injection pens are also sometimes provided to diabetics in the UK along with insulin. This is useful for rescue of unconscious diabetics from a severe state of hypoglycemia.

In healthy pancreatic function, glucagon production is initially suppressed by beta cell production of insulin and amylin when blood sugar is high, and then is later produced by low or falling blood sugar. The natural pancreatic function uses glucagon at the end of an insulin cycle to release glucose from the liver, with two advantages:

1. to prevent low blood sugar, and
2. to speed the overall insulin action by cancelling the insulin tail.

If an artificial pancreas was to simulate the natural endocrine pancreas to the maximum extent, then insulin and amylin would be used at the beginning of an insulin cycle and glucagon would be used at the end of the insulin cycle. Research with diabetic pigs given insulin-glucagon combination via separate subcutaneous infusion pumps demonstrated closed loop control without incidence of hypoglycemia. While the copycat endocrine function including glucagon seems desirable, the benefits relative to the cost and complexity of an artificial pancreas without glucagon are not yet known.

Initiatives around the globe

In the United States in 2006, the Juvenile Diabetes Research Foundation (JDRF) launched a multi-year initiative to help accelerate the availability of an artificial pancreas to people with diabetes. The overall goal of the Artificial Pancreas Project is to accelerate the development, regulatory approval, and acceptance of continuous glucose monitoring and artificial pancreas technology in the shortest possible timeframe. The long term goal is for broad patient access and a thriving competitive market for these devices and products.

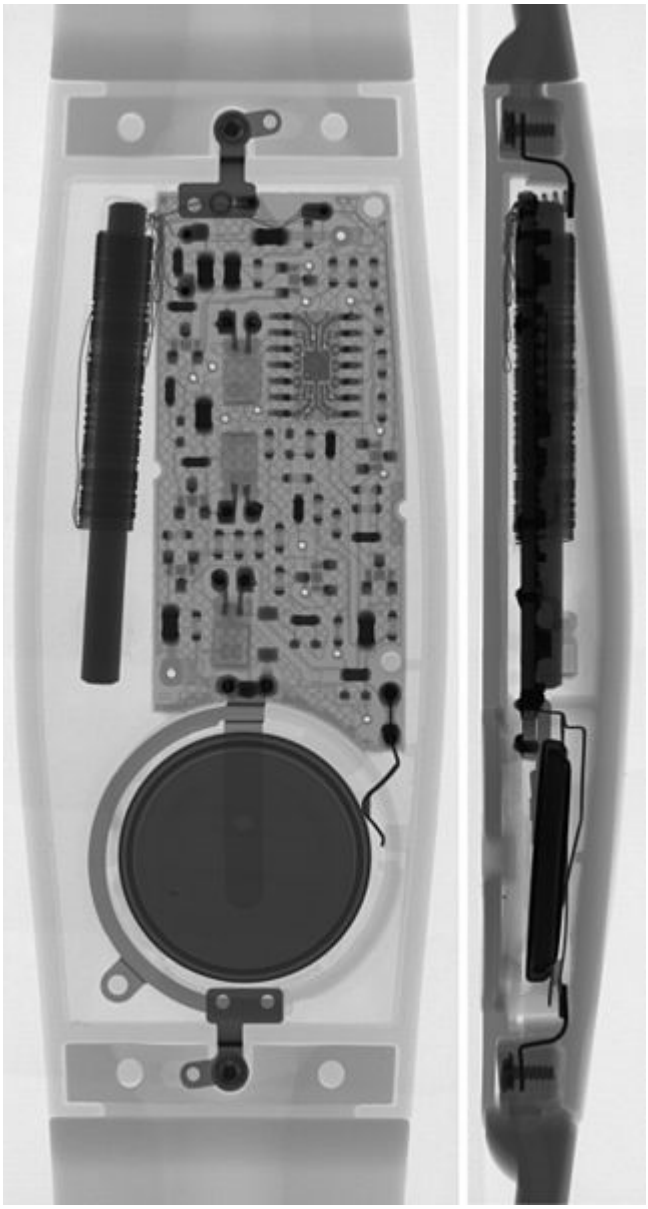
JDRF's role in quickening the development and availability of the Artificial Pancreas consists of funding research in order to look over the outcomes of patients using the Artificial Pancreas, keeping close contact with the Food and Drug Administration so that the standards of the patient are met, advocating for health care coverage of technologies such as the Artificial Pancreas and working to ensure clinical acceptance of technologies such as the Artificial Pancreas.

Chapter 10

Heart Rate Monitor and Needle Remover

Heart rate monitor

Photo of a heart rate monitor showing chest strap and watch



X-ray image of a chest strap (left: frontal view; right: side view). Visible is the circuit board, the antenna for data transfer and the battery.

Photo of a strapless heart rate monitor

A **heart rate monitor** is a personal monitoring device which allows a subject to measure his or her heart rate in real time or record his or her heart rate for later study. Early models consisted of a monitoring box with a set of electrode leads which attached to the chest.

The first wireless EKG Heart rate monitor was invented in 1977 as a training aid for the Finnish National Cross Country Ski team and as 'intensity training' became a popular concept in athletic circles in the mid-80s, retail sales of wireless personal heart monitors started from 1983.

Modern heart rate monitors usually comprise two elements: a chest strap transmitter and a wrist receiver or mobile phone (which usually doubles as a watch or phone). In early plastic straps water or liquid was required to get good performance. Later units have used conductive smart fabric with built in microprocessors which analyse the EKG signal to determine heart rate.

Strapless heart rate monitors now allow the user to just touch two sensors on a wristwatch display for a few seconds to view their heart rate. These are popular for their comfort and ease of use though they don't give as much detail as monitors which use a chest strap.

More advanced models will offer measurements of heart rate variability, activity, and breathing rate to assess parameters relating to a subject's fitness.

Another style of heart rate monitor replaces the plastic around-the-chest strap with fabric sensors - the most common of these is a sports bra for women which includes sensors in the fabric.

In old versions, when a heart beat is detected a radio signal is transmitted, which the receiver uses to determine the current heart rate. This signal can be a simple radio pulse or a unique coded signal from the chest strap (such as Bluetooth, ANT, or other low-power radio link); the latter prevents one user's receiver from using signals from other nearby transmitters (known as cross-talk interference).

Newer versions include a microprocessor which is continuously monitoring the EKG and calculating the heart rate, and other parameters. These may include accelerometers which can detect speed and distance eliminating the need for foot worn devices.

There are a wide number of receiver designs, with various features. These include average heart rate over exercise period, time in a specific heart rate zone, calories burned, breathing rate, built in speed and distance, and detailed logging that can be downloaded to a computer.

Needle remover

a wall-mounted sharps container

Needle removers are devices that physically remove a needle from a syringe. In developing countries, there is still a need for improvements in needle safety in hospital settings as most of the needle removal processes are done manually and under severe risk of hazard from needles puncturing skin and allowing infection. These countries cannot afford needles with individual safety devices attached, so needle-removers must be used to remove the needle from the syringe. This lowers possible pathogen spread by preventing the reuse of the syringes, reducing incidents of accidental needle-sticks, and facilitating syringe disposal.

Background

In developing countries, most hospitals are lacking in needle safety. In regions surveyed by the World Health Organization (WHO), the reported number of needle-stick injuries in developing world countries ranged from .93 to 4.68 injuries per person and per year, which is five times higher than in industrialized nations (Department of Essential Health Technology, 2004). Needle-stick injuries are further complicated by disease transmission,

such as Hepatitis B, Hepatitis C and HIV. In Ghana, a study of 803 schoolchildren revealed that 61.2% had at least one marker of hepatitis B virus (Sagoe-Moses et al., 2001). As a result, health care workers (HCWs), patients, and the community in developing nations are at an increased risk of contracting blood-borne pathogens via the reuse and improper disposal of needles, and accidental needle-sticks (Harner, 2004).

Before needle safety regulations, HCWs were on their own to avoid accidental needle-sticks and safely disposal of needles. However, in the U.S., after the Needlestick Safety Act signed in 2000 and the 2001 Bloodborne Pathogens Standard, the burden was no longer on HCWs. Both of these regulations mandated the use of safety devices and needle-removers with any sharps or needles (Jagger, 2003, 27-28). As a result, there was a large increase in research, development, and marketing of needle safety devices and needle-remover. In most hospital and medical settings in the U.S., needle safety regulations are maintained through individual needle safety devices and needle disposal boxes.

Existing solutions

One of the most common causes of needle-stick injuries, which the Needlestick Act and Bloodborne Pathogens Standard were attempting to decrease, was two-handed recapping (Wilburn, 2004). As a result, a one-handed capping mechanism was added to insulin and tuberculin syringes. The cap is attached to the syringe via a hinge, which allows the cap to be snapped onto the needle using one hand. The disadvantage to the hinge system is that the cap can get caught by jewelry and clothing, can get bumped when used, and the fixed position can be a hindrance during low angle injection. So Becton Dickinson (BD) has recently come out with a variation on this safety: instead of a hinge, the device slides over the needle and fully covers the tip of the needle, so accidental needle-sticks do not occur (Becton, Dickinson, and Company, 2004, BD SafetyGlide).

However, the rest of the world does not have similar needle and syringe regulations. For instance, the WHO is only able to regulate vaccinations in developing countries by ensuring that all vaccination syringes sent to these countries have autodisable features, since the major concern is the reuse of contaminated needles and syringes. These autodisable features allow the syringes to only be used once, so they cannot be reused. These mechanisms could be teeth that interlock to prevent the plunger from being pulled back for another use or a bag prefilled with the vaccine to stop reuse. For example, the SoloShot has a metal clip that locks the plunger down after one use (International Council of Nurses, 2005). The BD Uniject is a prefilled vaccine syringe that uses a plastic bulb instead of a plunger and has a disc valve to prevent reuse (Becton, Dickinson, and Company, 2005).

Still, over 90% of syringes worldwide do not have autodisable features (Harner, 2004). Individual protection devices are expensive, and regular needles are much more prevalent. Consequently, many developing world countries use needle-removers to reduce the risk of disease transmission via these exposed.

Benefits of needle-removers

Needle-removers minimize the occurrence of accidental needle-sticks because they allow immediate removal and containment of the needles, especially if the device is near the area of use. Reuse of syringes is prevented because the needle-remover physically separates the needle from the syringe, making the syringe useless. They also improve waste disposal by decreasing both the amount of infectious waste and the amount of safety boxes needed for the waste, since safety boxes can pack syringes 20-60% more compactly without the needles (Harner, 2004). Additionally, these devices are cost-efficient since one device can handle several hundred needles. Many developing world countries do not have the resources to afford auto-disable syringes, so with needle-removers, the hospitals can continue to use cheap syringes, while only paying a one-time fee to buy a needle-remover that has a life-span of about 200-500 needles (Harner, 2004).

Social and ethical implications

A significant ethical issue for the project is whether or not the needle-remover will cause more harm than its potential benefits. Engineers are obliged to use their skills and knowledge to improve the safety, health, and welfare of the public (Biomedical Engineering Society, 2004). The main concern is for the operator of the device; no engineer should create a device that could injure the operator. Another concern is that children may gain access to the device and accidentally hurt themselves. If a device design could potentially cause either of these problems, the team would be ethically obligated to reexamine that design, and it would either have to be improved or abandoned. When the device functions effectively and safely, it will serve to protect the welfare of the community. In developing countries, the risk of disease transmission is elevated due to the high percentage of needle-stick injuries, which is a result of inadequate needle collection devices (Department of Essential Health Technology, 2004). Increased pathogen transmission also occurs from the reuse of contaminated needles when supplies are low (Sagoe-Moses et al., 2001). The device will prevent reuse of needles and facilitate needle collection and disposal, and thus will improve the health and safety of hospital workers and the community.

The social and economic effects of the device also need to be recognized. In developing countries, the lack of proper needle collection devices leads to an increase in the number of occupational needle-sticks by HCWs via contaminated needles. Occupational needle-sticks account for 40%-65% of Hepatitis B and C infections in HCWs (Prüss-Üstün, Rapiti, and Hutin, 2003). As a result, more HCWs have to undergo postexposure testing and treatment, both of which cost money for the hospitals and the countries. There is also the manpower cost associated with losing trained HCWs to infections acquired on the job. With fewer than 10 doctors for every 100,000 individuals in sub-Saharan nations, any loss of hospital staff puts a strain of hospital resources. In addition, developing countries have made significant investments in training their HCWs, which is lost when occupational needle-sticks cause HCWs to leave the medical field (Sagoe-Moses et al., 2001).

The economic considerations are not just limited to costs associated with HCWs. Due to the high cost of needle-disposal containers and the fact that the containers usually have to be shipped overseas, unsafe and dangerous substitutes are used instead. This practice can potentially lead to needle-sticks by HCWs and individuals in the community, as well as needle reuse by members of the community, which can increase the potential spread of diseases.

Possible designs

The easiest needle-removers to operate are electrically powered, and either melt the needle or cut the needles at multiple sections. One patented design involves a syringe falling down into a chamber where powered moveable blades advance the syringe onto fixed blades on the opposite side, at which point the syringe is cut with a shearing motion at multiple points (Garvis and Beer, 1974). There are other patents that use electricity between electrodes or between rotating gears to short-circuit the needle and melt it off the syringe (Ch'ing-Lung, 1986; Hashimoto, 1990). A more complex design involves a hammer mill and grinder to break up and grind up the plastic and metal parts of the syringes, after which, the pieces are heated and cooled. The end result is metal particles encapsulated in a piece of plastic (Wallace et al., 1991).

However, electricity in developing countries is not a dependable source, so hand-powered needle-cutters would be preferred. Some designs use the squeezing force from a hand to force one or two blades to shear across each other and hence cut the needle between the blades (Choksi et al., 1981; Harner, 2004). There are other designs in which a twisting motion brings a shearing blade in contact with the needle and thus cuts it (W. Thead, D. Thead, and Evans, 2000). Another design has a stationary outer surface that the syringe body rests against and a cylindrical inner cutting body with a bore for the needle to pass through. A lever rotates the inner body, which shears the needle from the syringe and dumps the needle into a container (Johan and Morner, 1972). A crank system can be used to power a similar design, which also uses a cylindrical inner body. However instead of cutting the needle, the device pulls the needle completely out of the syringe, which deforms the needle, and dumps it into a container (Samuel, 2004). A more complicated design actually pulls the needle and collar from the barrel of the syringe without a rotational motion: the downward motion of putting the syringe into the device powers two arms to pull the needle off the syringe. The interesting aspect of this device is that it appears to be one-handed (Atsumi, 1996). Another one-handed device uses a downward motion to cause rotating gears to unscrew the needle and collar from the syringe (Thead and Evans, 1991). This design is very complex to implement, so an improvement of this design involves pegs that grip and rotate the needle collar instead of gears. The downward force is transferred into moving the pegs in helical slots, which causes the collar to rotate and the needle to be removed from the syringe (Han, 1994).

In 2006 a cheap and simple solution utilizing old cola or beer cans to dispose needles and specially developed lid to safely seal them has been developed. One click and the can is permanently sealed by the safely seal. The snap-lock seals the two parts together without using glue or tools. The 'collar' of the cap is protecting the user during the needle

separation process. The insertion hole is designed to separate needle and syringe at the point of use. No finger can pass through the opening. Each can securely contains 150-200 used needles (Business Ideas Forum, 2007).

Commercial models

There are several electrically powered needle-removers on the market now. The Disintegrator Needle Destruction Device, offered by American Scientific Resources (ASFX), uses plasma arch technology to destroy the needle, kill pathogens and blunt the syringe. Designed to be used with only one hand, this device completely eliminates the sharp. One model from Techno Fab uses a regular electrical short-circuit to melt the needle, while another needle-remover uses a plasma arc to melt the needle. A unique needle-remover design is the Needle Remover Device, designed by the Program for Appropriate Technology in Health (PATH). It uses two handles that are squeezed together to slide two circular blades across each other, which cuts the hub from the syringe. It is also reusable, and its target cost is about $15 (Harner, 2004). Another needle-removers currently on the market is Advanced Care Products's Clip&Stor, which uses a hand-powered clipper action to remove the needle (Advanced Care Products, 2005). The cost of the Clip&Stor is about seven dollars. There is also the BD Hub Cutter, which uses a squeezing hand motion to cut the syringe. The edges of the squeezable parts have blades that do the actual cutting. However, unlike a regular needle-remover, the BD Hub Cutter cuts the syringe at the hub so the needle is completely separated from the syringe. As a result, the risk of a contaminated puncture is completely eliminated because no needle shards remain on the syringe. The Hub Cutter is not reusable though, and disposal of the whole unit must occur (Becton, Dickinson, and Company, 2004). The cost of the Hub Cutter is about four dollars (Department of Essential Health Technology, 2004).

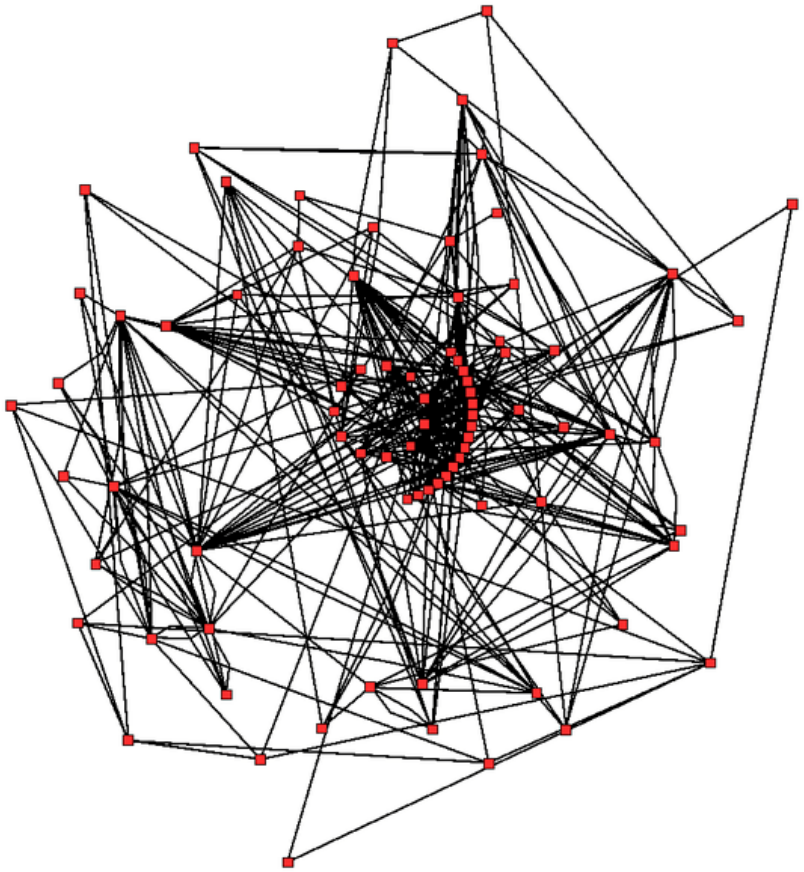
Limitations

Most of these current needle-removers require the use of two hands; one to hold the needle in place and the other to activate the mechanism. This form of operation can cause problems because if hospital personnel are busy, especially in a developing world country, they may not have the time or hands needed to operate the device. As a result, the needle will remain exposed on the syringe, posing a risk to both HCWs and patients.

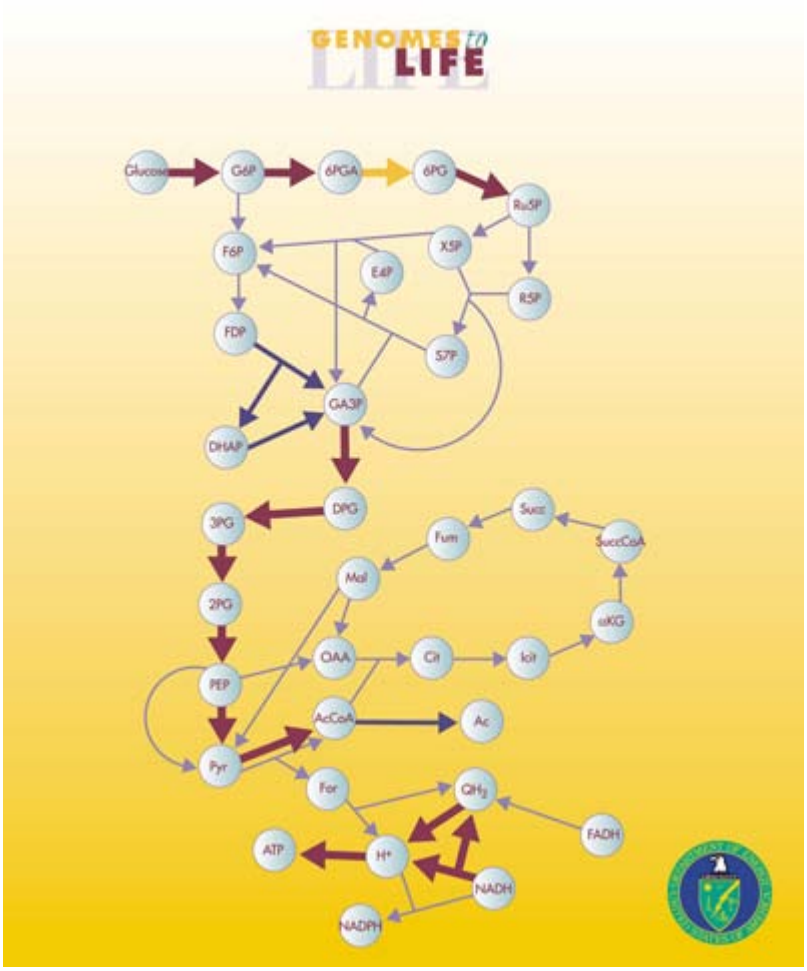
Furthermore, many of these existing needle-removers do not make use of cheap and readily available materials, like used motor oil jugs, for containers, which raises the price of the device and requires that the hospital continuously buys more containers from the company. A typical 3-gallon Bemis sharps container with a rotating lid costs about $8 without including shipping costs (GRP & Associates, 2005). If these containers must be shipped overseas, the price of the device can far exceed the available resources of many hospitals in developing countries, which causes them not to buy needle-removers.

Chapter 11

Metabolic Network Modelling



Metabolic network showing interactions between enzymes and metabolites in the *Arabidopsis thaliana* citric acid cycle. Enzymes and metabolites are the red dots and interactions between them are the lines.



Metabolic Network Model for Escherichia coli.

Metabolic network reconstruction and simulation allows for an in depth insight into comprehending the molecular mechanisms of a particular organism, especially correlating the genome with molecular physiology (Francke, Siezen, and Teusink 2005). A reconstruction breaks down metabolic pathways into their respective reactions and enzymes, and analyzes them within the perspective of the entire network. Examples of various metabolic pathways include glycolysis, Krebs cycle, pentose phosphate pathway. In simplified terms, a reconstruction involves collecting all of the relevant metabolic information of an organism and then compiling it in a way that makes sense for various types of analyses to be performed. The correlation between the genome and metabolism is made by searching gene databases, such as KEGG , GeneDB , for particular genes by inputting enzyme or protein names. For example, a search can be conducted based on the protein name or the EC number (a number that represents the catalytic function of the enzyme of interest) in order to find the associated gene (Francke *et al.* 2005).

Beginning steps of a reconstruction

Resources

Below is more detailed description of a few gene/enzyme/reaction/pathway databases that are crucial to a metabolic reconstruction:

- **Kyoto Encyclopedia of Genes and Genomes (KEGG)**: This is a bioinformatics database containing information on genes, proteins, reactions, and pathways. The 'KEGG Organisms' section, which is divided into eukaryotes and prokaryotes, encompasses many organisms for which gene and DNA information can be searched by typing in the enzyme of choice. This resource can be extremely useful when building the association between metabolism enzymes, reactions and genes.

- **BioCyc, EcoCyc, and MetaCyc**: BioCyc is a collection of 1,000 pathway/genome databases (as of Oct 2010), with each database dedicated to one organism. For example, EcoCyc is a highly detailed bioinformatics database on the genome and metabolic reconstruction of *Escherichia coli*, including thorough descriptions of *E. coli* signaling pathways and regulatory network. The EcoCyc database can serve as a paradigm and model for any reconstruction. Additionally, MetaCyc, an encyclopedia of experimentally defined metabolic pathways and enzymes, contains 1,500 metabolic pathways and 8,700 metabolic reactions (Oct 2010).

- **Pathway Tools** : A bioinformatics software package that assists in the construction of pathway/genome databases such as EcoCyc (Karp 2010). Developed by Peter Karp and associates at the SRI International Bioinformatics Group, Pathway Tools comprises several separate units. First, PathoLogic takes an annotated genome for an organism and infers probable metabolic pathways to produce a new pathway/genome database. This can be followed by application of the Pathway Hole Filler, which predicts likely genes to fill "holes" (missing steps) in predicted pathways. Afterward, the Pathway Tools Navigator and Editor functions let users visualize, analyze, access and update the database. Thus, using PathoLogic and encyclopedias like MetaCyc, an initial fast reconstruction can be developed automatically, and then using the other units of Pathway Tools, a very detailed manual update, curation and verification step can be carried out (SRI 2005).

- **ERGO**: ERGO integrates data from every level including genomic, biochemical data, literature, and high-throughput analysis into a comprehensive user friendly network of metabolic and nonmetabolic pathways.

- **metaTIGER** : is a collection of metabolic profiles and phylogenomic information on a taxonomically diverse range of eukaryotes. Phylogenomic information is provided by 2,257 large phylogenetic trees which can be interactively explored.

High-throughput tree analysis can also be carried out to identify trees of interest, e.g. trees containing horizontal gene transfers. metaTIGER also provides novel facilities for viewing and comparing the metabolic profiles.

- **ENZYME**: This is an enzyme nomenclature database (part of the ExPASY proteonomics server of the Swiss Institute of Bioinformatics). After searching for a particular enzyme on the database, this resource gives you the reaction that is catalyzed. Additionally, ENZYME has direct links to various other gene/enzyme/medical literature databases such as KEGG, BRENDA, PUBMED, and PUMA2 to name a few.

- **BRENDA**: A comprehensive enzyme database, BRENDA, allows you to search for an enzyme by name or EC number. You can also search for an organism and find all the relevant enzyme information. Moreover, when an enzyme search is carried out, BRENDA provides a list of all organisms containing the particular enzyme of interest.

- **PUBMED**: This is an online library developed by the National Center for Biotechnology Information, which contains a massive collection of medical journals. Using the link provided by ENZYME, the search can be directed towards the organism of interest, thus recovering literature on the enzyme and its use inside of the organism.

- **Model SEED** : This is an online resource for the analysis, comparison, reconstruction, and curation of genome-scale metabolic models (Henry et al. 2010). Users can submit genome sequences to the RAST annotation system, and the resulting annotation can be automatically piped into the Model SEED to produce a draft metabolic model. The Model SEED automatically constructs a network of metabolic reactions, gene-protein-reaction associations for each reaction, and a biomass composition reaction for each genome to produce a model of microbial metabolism that can be simulated using Flux Balance Analysis.

Next steps of the reconstruction

After the initial stages of the reconstruction, a systematic verification is made in order to make sure no inconsistencies are present and that all the entries listed are correct and accurate (Francke *et al.* 2005). Furthermore, previous literature can be researched in order to support any information obtained from one of the many metabolic reaction and genome databases. This provides an added level of assurance for the reconstruction that the enzyme and the reaction it catalyzes do actually occur in the organism.

Any new reactions not present in the databases need to be added to the reconstruction. The presence or absence of certain reactions of the metabolism will affect the amount of reactants/products that are present for other reactions within the particular pathway. This is because products in one reaction go on to become the reactants for another reaction, i.e. products of one reaction can combine with other proteins or compounds to form new

proteins/compounds in the presence of different enzymes or catalysts (Francke *et al.* 2005).

Francke *et al.* (2005) provide an excellent example as to why the verification step of the project needs to be performed in significant detail. During a metabolic network reconstruction of *Lactobacillus plantarum*, the model showed that succinyl-CoA was one of the reactants for a reaction that was a part of the biosynthesis of methionine. However, an understanding of the physiology of the organism would have revealed that due to an incomplete tricarboxylic acid pathway, *Lactobacillus plantarum* does not actually produce succinyl-CoA, and the correct reactant for that part of the reaction was acetyl-CoA.

Therefore, systematic verification of the initial reconstruction will bring to light several inconsistencies that can adversely affect the final interpretation of the reconstruction, which is to accurately comprehend the molecular mechanisms of the organism. Furthermore, the simulation step also ensures that all the reactions present in the reconstruction are properly balanced. To sum up, a reconstruction that is fully accurate can lead to greater insight about understanding the functioning of the organism of interest (Francke *et al.* 2005).

Advantages of a reconstruction

- Several inconsistencies exist between gene, enzyme, and reaction databases and published literature sources regarding the metabolic information of an organism. A reconstruction is a systematic verification and compilation of data from various sources that takes into account all of the discrepancies.
- A reconstruction combines the relevant metabolic and genomic information of an organism.
- A reconstruction also allows for metabolic comparisons to be performed between various organisms of the same species as well as between different organisms.

Metabolic network simulation

A metabolic network can be broken down into a stoichiometric matrix where the rows represent the compounds of the reactions, while the columns of the matrix correspond to the reactions themselves. Stoichiometry is a quantitative relationship between substrates of a chemical reaction (Merriam 2002). In order to deduce what the metabolic network suggests, recent research has centered on two approaches; namely extreme pathways and elementary mode analysis (Papin, Stelling, Price, Klamt, Schuster, and Palsson 2004).

Extreme Pathways

Price, Reed, Papin, Wiback and Palsson (2003) use a method of singular value decomposition (SVD) of extreme pathways in order to understand regulation of a human red blood cell metabolism. Extreme pathways are convex basis vectors that consist of steady state functions of a metabolic network (Papin, Price, and Palsson 2002). For any

particular metabolic network, there is always a unique set of extreme pathways available (Papin *et al.* 2004). Furthermore, Price *et al.* (2003) define a constraint-based approach, where through the help of constraints like mass balance and maximum reaction rates, it is possible to develop a 'solution space' where all the feasible options fall within. Then, using a kinetic model approach, a single solution that falls within the extreme pathway solution space can be determined (Price *et al.* 2003). Therefore, in their study, Price *et al.* (2003) use both constraint and kinetic approaches to understand the human red blood cell metabolism. In conclusion, using extreme pathways, the regulatory mechanisms of a metabolic network can be studied in further detail.

Elementary mode analysis

Elementary mode analysis closely matches the approach used by extreme pathways. Similar to extreme pathways, there is always a unique set of elementary modes available for a particular metabolic network (Papin *et al.* 2004). These are the smallest sub-networks that allow a metabolic reconstruction network to function in steady state (Schuster, Fell, and Dandekar 2000; Stelling, Klamt, Bettenbrock, Schuster, and Gilles 2002). According to Stelling *et al.* (2002), elementary modes can be used to understand cellular objectives for the overall metabolic network. Furthermore, elementary mode analysis takes into account stoichiometrics and thermodynamics when evaluating whether a particular metabolic route or network is feasible and likely for a set of proteins/enzymes (Schuster *et al.* 2000).

Minimal metabolic behaviors (MMBs)

Recently, Larhlimi and Bockmayr (2009) presented a new approach called "minimal metabolic behaviors" for the analysis of metabolic networks. Like elementary modes or extreme pathways, these are uniquely determined by the network, and yield a complete description of the flux cone. However, the new description is much more compact. In contrast with elementary modes and extreme pathways, which use an inner description based on generating vectors of the flux cone, MMBs are using an outer description of the flux cone. This approach is based on sets of non-negativity constraints. These can be identified with irreversible reactions, and thus have a direct biochemical interpretation. One can characterize a metabolic network by MMBs and the reversible metabolic space.

Flux balance analysis

A different technique to simulate the metabolic network is to perform flux balance analysis. This method uses linear programming, but in contrast to elementary mode analysis and extreme pathways, only a single solution results in the end. Linear programming is usually used to obtain the maximum potential of the objective function that you are looking at, and therefore, when using flux balance analysis, a single solution is found to the optimization problem (Stelling *et al.* 2002). In a flux balance analysis approach, exchange fluxes are assigned to those metabolites that enter or leave the particular network only. Those metabolites that are consumed within the network are not

assigned any exchange flux value. Also, the exchange fluxes along with the enzymes can have constraints ranging from a negative to positive value (ex: -10 to 10).

Furthermore, this particular approach can accurately define if the reaction stoichiometry is in line with predictions by providing fluxes for the balanced reactions. Also, flux balance analysis can highlight the most effective and efficient pathway through the network in order to achieve a particular objective function. In addition, gene knockout studies can be performed using flux balance analysis. The enzyme that correlates to the gene that needs to be removed is given a constraint value of 0. Then, the reaction that the particular enzyme catalyzes is completely removed from the analysis.

Dynamic simulation and parameter estimation

In order to perform a dynamic simulation with such a network it is necessary to construct an ordinary differential equation system that describes the rates of change in each metabolite's concentration or amount. To this end, a rate law, i.e., a kinetic equation is required for each reaction. Often these rate laws contain kinetic parameters with uncertain values. In many cases it is desired to estimate these parameter values with respect to given time-series data of metabolite concentrations. The system is then supposed to reproduce the given data. For this purpose the distance between the given data set and the result of the simulation, i.e., the numerically or in few cases analytically obtained solution of the differential equation system is computed. The values of the parameters are then estimated to minimize this distance (Dräger *et al.* 2009). One step further, it may be desired to estimate the mathematical structure of the differential equation system because the real rate laws are not known for the reactions within the system under study. To this end, the program SBMLsqueezer allows automatic creation of appropriate rate laws for all reactions with the network.

Conclusion

In conclusion, metabolic network reconstruction and simulation can be effectively used to understand how an organism or parasite functions inside of the host cell. For example, if the parasite serves to compromise the immune system by lysing macrophages, then the goal of metabolic reconstruction/simulation would be to determine the metabolites that are essential to the organism's proliferation inside of macrophages. If the proliferation cycle is inhibited, then the parasite would not continue to evade the host's immune system. A reconstruction model serves as a first step to deciphering the complicated mechanisms surrounding disease. The next step would be to use the predictions and postulates generated from a reconstruction model and apply it to drug delivery and drug-engineering techniques.

Currently, many tropical diseases affecting third world nations are very inadequately characterized, and thus poorly understood. Therefore, a metabolic reconstruction and simulation of the parasites that cause the tropical diseases would aid in developing new and innovative cures and treatments.

Chapter 12

Sensory Substitution

Sensory substitution means to transform the characteristics of one sensory modality into stimuli of another sensory modality. It is hoped that sensory substitution systems can help handicapped people by restoring their ability to perceive a certain defective sensory modality by using sensory information from a functioning sensory modality. A sensory substitution system consists of three parts: a sensor, a coupling system, and a stimulator. The sensor records stimuli and gives them to a coupling system which interprets these signals and transmits them to a stimulator. In case the sensor obtains signals of a kind not originally available to the bearer it is a case of sensory augmentation. Sensory substitution concerns human perception and the plasticity of the human brain; and therefore, allows us to study these aspects of neuroscience more through neuroimaging.

History

Sensory Substitution was introduced in the '60s by Paul Bach-y-Rita as a means of using one sensory modality, mainly tactition, to gain environmental information to be used by another sensory modality, mainly vision. The first sensory substitution system was developed by Bach-y-Rita et al. as a means of brain plasticity in congenitally blind individuals. After this historic invention, sensory substitution has been the basis of many studies investigating perceptive and cognitive neuroscience. Since then, sensory substitution has contributed to the study of brain function, human cognition and rehabilitation.

Physiology of sensory substitution

When a person becomes blind or deaf they generally do not lose the ability to hear or see, they simply lose their ability to transmit the sensory signals from the periphery (retina for visions and cochlea for hearing) to brain. Since the vision processing pathways are still intact, a person who has lost the ability to retrieve data from the retina can still see subjective images by using data gathered from other sensory modalities such as touch or audition.

In a regular visual system, the data collected by the retina is converted into an electrical stimulus in the optic nerve and relayed to the brain, which re-creates the image and perceives it. Because it is the brain that is responsible for the final perception, sensory substitution is possible. During sensory substitution an intact sensory modality relays information to the visual perception areas of the brain so that the person can perceive to see. With sensory substitution, information gained from one sensory modality can reach brain structures physiologically related to other sensory modalities. Touch-to-visual sensory substitution transfers information from touch receptors to the visual cortex for interpretation and perception. For example, through fMRI, we can determine which parts of the brain are activated during sensory perception. In blind persons, we can see that while they are only receiving tactile information, their visual cortex is also activated as they perceive to *see* objects. We can also have touch to touch sensory substitution where information from touch receptors of one region can be used to perceive touch in another region. For example, in one experiment by Bach-y-Rita, he was able to restore the touch perception in a patient who lost peripheral sensation from leprosy.

Technological support

In order to have sensory substitution and stimulate the brain without intact sensory organs to relay the information, it is also possible to develop machines that do the signal transduction. This brain–machine interface is where external signals are collected and transduced into electrical signals for the brain to interpret. Generally a camera or a microphone is used to collect visual or auditory stimuli that are used to replace lost sensory information. The visual or auditory data collected from the sensors is transduced into tactile stimuli that are then relayed to the brain for visual and auditory perception. This type of sensory substitution is only possible due to the plasticity of the brain.

Brain plasticity

Brain plasticity is the brain's ability to adapt to the complete absence or the deterioration of a sense. Sensory substitution is therefore most likely explained through the study of brain plasticity. Cortical re-mapping or reorganization takes place when the brain experiences some sort of deterioration. This is an evolutionary mechanism that allows people with the deprivation of a sense to adapt and compensate by using other senses. Functional imaging of congenitally blind patients showed a cross-modal recruitment of the occipital cortex during the realization perceptual tasks such as Braille reading, tactile perception, tactual object recognition, sound localization, and sound discrimination. This shows that blind people can use their occipital lobe, generally used for vision, to perceive objects though the use of other sensory modalities, which would explain their oft-displayed propensity towards increased strength of the other senses.

Perception versus sensing

While talking about the physiological aspects of sensory substitution, it is essential to distinguish between sensing and perceiving. The general question posed by this differentiation is: Are blind people seeing or perceiving to see by putting together

different sensory data? While sensation comes in one modality – visual, auditory, tactile etc. – perception due to sensory substitution is not one modality but a result of cross-modal interactions. Therefore, we can say that while sensory substitution for vision induces visual-like perception in sighted individual, it induces auditory or tactile perception in blind individuals. In short, blind people *perceive* to see through touch and audition with sensory substitution.

Different applications of sensory substitution

Applications are not restricted to handicapped persons, but also include artistic presentations, games, and augmented reality. Some examples are substitution of visual stimuli to audio or tactile, and of audio stimuli to tactile. Some of the most popular are probably Paul Bach-y-Rita's Tactile Vision Sensory Substitution (TVSS), developed with Carter Collins at Smith-Kettlewell Institute and Peter Meijer's Seeing with Sound approach (The vOICe). Technical developments, such as miniaturization and electrical stimulation help the advance of sensory substitution devices.

In sensory substitution systems, we generally have sensors that collect the data from the external environment. This data is then relayed to a coupling system that interprets and transduces the information and then replays it to a stimulator. This stimulator ultimately stimulates a functioning sensory modality. After training, people learn to use the information gained from this stimulation to experience a perception of the sensation they lack instead of the actually stimulated sensation. For example, a leprosy patient, whose perception of peripheral touch was restored, was equipped with a glove containing artificial contact sensors coupled to skin sensory receptors on the forehead (which was stimulated). After training and acclimation, the patient was able to experience data from the glove as if it was originating in the fingertips while ignoring the sensations in the forehead.

Tactile sensory substitution systems

To understand **tactile sensory substitution** it is essential to understand some basic physiology of the tactile receptors of the skin. There are six basic types of tactile receptors: Pacinian corpuscle, Meissner's corpuscle, Ruffini endings, Merkel nerve endings, free nerve endings, and tactile disks. These receptors are mainly characterized by their ability to adapt to stimuli and their thresholds. Because of the relative high thresholds of most these receptors and their rapid adaptation to stimulus, the human body requires rapidly changing tactile stimulation systems.

There have been two different types of stimulators: electrotactile or vibrotactile. Electrotactile stimulators use direct electrical stimulation of the nerve ending in the skin to initiate the action potentials; the sensation triggered, burn, itch, pain, pressure etc. depends on the stimulating voltage. Vibrotactile stimulators use pressure and the properties of the mechanoreceptors of the skin to initiate action potentials. There are advantages and disadvantages for both these stimulation systems. With the electrotactile stimulating systems a lot of factors effect the sensation triggered: stimulating voltage,

current, waveform, electrode size, material, contact force, skin location, thickness and hydration. Electrotactile stimulation may involve the direct stimulation of the nerves (percutaneous), or through the skin (transcutaneous). Percutaneous application causes additional distress to the patient, and is a major disadvantage of this approach. Furthermore, stimulation of the skin without insertion leads to the need for high voltage stimulation because of the high impedance of the dry skin, unless the tongue is used as a receptor, which requires only about 3% as much voltage. This latter technique is undergoing clinical trials for various applications. Alternatively, the roof of the mouth has been proposed as another area where low currents can be felt.

Electrostatic arrays are explored as human-computer interaction devices for touch screens. These are based on a phenomenon called electrovibration, which allows microamperre-level currents to be felt as roughness on a surface.

Vibrotactile systems use the properties of mechanoreceptors in the skin so they have fewer parameters that need to be monitored as compared to electrotactile stimulation. However, vibrotactile stimulation systems need to account for the rapid adaptation of the tactile sense.

Another important aspect of tactile sensory substitution systems is the location of the tactile stimulation. Tactile receptors are abundant on the fingertips, face, and tongue while sparse on the back, legs and arms. It is essential to take into account the spatial resolution of the receptor as it has a major effect on the resolution of the sensory substitution.

Below you can find some descriptions of current tactile substitution systems.

Tactile–visual substitution

One of the earliest and most well known form of sensory substitution devices was Paul Bach-y-Rita's TVSS that converted the image from a video camera into a tactile image and coupled it to the tactile receptors on the back of his blind subject. Recently, several new systems have been developed that interface the tactile image to tactile receptors on different areas of the body such as the on the chest, brow, fingertip, abdomen, and forehead. The tactile image is produced by hundreds of activators placed on the person. The activators are solenoids of one millimeter diameter. In experiments, blind (or blindfolded) subjects equipped with the TVSS can learn to detect shapes and to orient themselves. In the case of simple geometric shapes, it took around 50 trials to achieve 100 percent correct recognition. To identify objects in different orientations requires several hours of learning.

A system using the tongue as the human-machine interface is most practical. The tongue-machine interface is both protected by the closed mouth and the saliva in the mouth provides a good electrolytic environment that ensures good electrode contact. Results from a study by Bach-y-Rita et al. show that electrotactile stimulation of the tongue required 3% of the voltage required to stimulate the finger. Also, since it is more practical

to wear an orthodontic retainer holding the stimulation system than an apparatus strapped to other parts of the body, the tongue-machine interface is more popular among TVSS systems.

This tongue TVSS system works by delivering electrotactile stimuli to the dorsum of the tongue via a flexible electrode array placed in the mouth. This electrode array is connected to a Tongue Display Unit [TDU] via a ribbon cable passing out of the mouth. A video camera records a picture, transfers it to the TDU for conversion into a tactile image. The tactile image is then projected onto the tongue via the ribbon cable where the tongue's receptors pick up the signal. After training, subjects are able to associate certain types of stimuli to certain types of visual images. In this way, tactile sensation can be used for visual perception.

Sensory substitutions have also been successful with the emergence of wearable haptic actuators like vibrotactile motors, solenoids, peltier diodes, etc. At the Center for Cognitive Ubiquitous Computing @ Arizona State University researchers have developed technologies that enable people who are blind to perceive social situational information using wearable vibrotactile belts (Haptic Belt) and gloves (VibroGlove). Both technologies use miniature cameras that are mounted on a pair of glasses worn by the user who is blind. The Haptic Belt provides vibrations that convey the direction and distance at which a person is standing in front of a user, while the VibroGlove uses spatio-temporal mapping of vibration patterns to convey facial expressions of the interaction partner.

Tactile–auditory substitution

While there are no tactile-auditory substitution system currently available, recent experiments by Schurmann et al. show that tactile senses can activate the human auditory cortex. Currently vibrotactile stimuli can be used to facilitate hearing in normal and hearing-impaired people. To test for the auditory areas activated by touch, Schurmann et al. tested subjects while stimulating their fingers and palms with vibration bursts and their finger tips with tactile pressure. They found that tactile stimulation of the fingers lead to activation of the auditory belt area, which suggests that there is a relationship between audition and tactition. Therefore, future research can be done to investigate the likelihood of a tactile-auditory sensory substitution system. Full normal hearing range of nine octaves is delivered via 216 electrodes to sequential touch nerve zones, next to the spine. Inventor is incorporating a nonprofit organization in August 2010, to build prototypes for 'proof of concept' considerations.

Tactile–vestibular substitution

Some people with balance disorders or adverse reactions to antibiotics suffer from bilateral vestibular damage (BVD). They experience difficulty maintaining posture, unstable gait, and oscillopsia. Tyler et al. studied the restitution of postural control through a tactile for vestibular sensory substitution. Because BVD patients cannot integrate visual and tactile cues, they have a lot of difficulty standing. Using a head-

mounted accelerometer and a brain-machine interface that employs electrotactile stimulation on the tongue, information about head-body orientation was relayed to the patient so that a new source of data is available to orient themselves and maintain good posture.

Tactile–tactile substitution to restore peripheral sensation

Touch to touch sensory substitution is where information from touch receptors of one region can be used to perceive touch in another. For example, in one experiment by Bach-y-Rita, the touch perception was restored in a patient who lost peripheral sensation from leprosy. For example, this leprosy patient was equipped with a glove containing artificial contact sensors coupled to skin sensory receptors on the forehead (which was stimulated). After training and acclimation, the patient was able to experience data from the glove as if it was originating in the fingertips while ignoring the sensations in the forehead. After two days of training one of the leprosy subjects reported "the wonderful sensation of touching his wife, which he had been unable to experience for 20 years."

Tactile feedback system for prosthetic limbs

The development of new technologies has now made it plausible to provide patients with prosthetic arms with tactile and kinesthetic sensibilities. While this is not purely a sensory substitution system, it uses the same principles to restore perception of senses. Some tactile feedback methods of restoring a perception of touch to amputees would be direct or micro stimulation of the tactile nerve afferents.

Other applications of sensory substitution systems can be seen in function robotic prostheses for patients with high level quadriplegia. These robotic arms have several mechanisms of slip detection, vibration and texture detection that they relay to the patient through feedback. After more research and development, the information from these arms can be used by patients to perceive that they are holding and manipulating objects while their robotic arm actually accomplishes the task.

Auditory sensory substitution systems

Auditory sensory substitution systems like the tactile sensory substitution systems aim to use one sensory modality to compensate for the lack of another sensory modality in order to gain a perception of one that is lacking. With auditory sensory substitution, we use visual or tactile sensors to detect and store information about the external environment. This information is then transduced by brain-machine interfaces into auditory signals that are then relayed via the auditory receptors to the brain.

Auditory vision substitution

Auditory vision substitution aims to use the sense of hearing to convey visual information to the blind.

The vOICe

The vOICe vision technology is one of several approaches towards sensory substitution (vision substitution) for the blind that aims to provide synthetic vision to the user by means of a non-invasive visual prosthesis. The vOICe converts live camera views from a video camera into soundscapes. This system uses general video to audio mapping by associating height to pitch and brightness with loudness in a left-to-right scan of any video frame. Views are typically refreshed about once per second with a typical image resolution of up to 60 x 60 pixels as can be proven by spectrographic analysis. Neuroscience and psychology research indicate recruitment of relevant brain areas in seeing with sound, as well as functional improvement through training. The ultimate goal is to provide synthetic vision with truly visual sensations by exploiting the neural plasticity of the human brain. Neuroscience research has shown that the visual cortex of even adult blind people can become responsive to sound, and “seeing with sound” might reinforce this in a visual sense with live video from a head-mounted camera encoded in sound. The extent to which cortical plasticity indeed allows for functionally relevant rewiring or remapping of the human brain is still largely unknown and is being investigated in an open collaboration with research partners around the world.

PSVA

Another successful visual-to-auditory sensory substitution device is the Prosthesis Substituting Vision for Audition (PSVA). This system utilizes a head-mounted TV camera that allows real-time, online translation of visual patterns into sound. While the patient moves around, the device captures visual frames at a high frequency and generates the corresponding complex sounds that allow recognition. Visual stimuli are transduced into auditory stimuli with the use of a system that uses pixel to frequency relationship and couples a rough model of the human retina with an inverse model of the cochlea.

The Vibe

The sound produced by this software is a mixture of sinusoidal sounds produced by virtual "sources", corresponding each to a "receptive field" in the image. Each receptive field is a set of localized pixels. The sound's amplitude is determined by the mean luminosity of the pixels of the corresponding receptive field. The frequency and the inter-aural disparity are determined by the center of gravity of the co-ordinates of the receptive field's pixels in the image.

Other systems

Other approaches to the substitution of hearing for vision use binaural directional cues, much as natural human echolocation does. An example of the latter approach is the "SeeHear" chip from Caltech.

Other visual-auditory substitution devices deviate from the vOICe's greyscale mapping of images. Zach Capalbo's Kromophone uses a basic color spectrum correlating to different sounds and timbres to give users perceptual information beyond the vOICe's capabilities.

Nervous system implants

By means of stimulating electrodes implanted into the human nervous system, it is possible to apply current pulses to be learned and reliably recognized by the recipient. It has been shown successfully in experimentation, by Kevin Warwick, that signals can be employed from force/touch indicators on a robot hand as a means of communication.

Criticism

It has been argued that the term "substitution" is misleading, as it is merely an "addition" or "supplementation" not a substitution of a sensory modality.

Sensory Augmentation

Building upon the research conducted on sensory substition, investigations into the possibility of *augmenting* the body's sensory apparatus are now beginning. The intention is to extend the body's ability to sense aspects of the environment that are not normally perceivable by the body in its natural state.

Active work in this direction is being conducted by, among others, the e-sense project of the Open University and Edinburgh University, and the feelSpace project of the University of Osnabrück.

The findings of research into sensory augmentation (as well as sensory substitution in general) that investigate the emergence of perceptual experience (qualia) from the activity of neurons have implications for the understanding of consciousness.

Magnetic Perception

In 2005, the feelSpace group conducted a study of sensory augmentation with a vibrotactile magnetic compass belt worn around the waist. In this study, the participants were provided with the direction of magnetic north as a vibration on their waist.

Significant performance improvements in navigational tests were observed (over and above those experienced by control subjects during the same period with the same training) and, for half of the participants, the perception of the belt's vibration underwent a profound change from simple tactile innervation to approach a genuine and direct sense of allocentric orientation: in other words, could *perceive* north as an entity distinct from the vibrating transducer on the waist, like one perceives a glass on a table as an entity distinct from the impact of reflected photons on the retina. Further, tests of the influence of the belt information on the rotational nystagmus effect suggested that, after training, the processing of the belt information became subcognitive.