College of Engineering, Pune

(An Autonomous Institute of Government of Maharashtra)

Applied Science Department

CT16002 – Biology for Engineers

UNIT VI: Engineering perspectives of biological sciences

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1. Biology and engineering crosstalk
2. Optimization in biological systems
   A. At cell level: Hybridoma technology
   B. Optimization At tissue level: Plant Tissue Culture, Animal Tissue Culture;
   C. Tissue Engineering: Principles, methods and applications
3. Introduction to Biomimetics and Biomimicry, nanobiotechnology

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ENGINEERING PERSPECTIVES OF BIOLOGICAL SCIENCES

Bioengineering or Biomedical Engineering is a discipline that advances knowledge in engineering, biology, and medicine -- and improves human health through cross-disciplinary activities that integrate the engineering sciences with the biomedical sciences and clinical practice. Bioengineering/ Biomedical Engineering combines engineering expertise with medical needs for the enhancement of health care. It is a branch of engineering in which knowledge and skills from the existing methodologies in such fields as molecular biology, biochemistry, microbiology (study of microorganism), pharmacology (study of drugs and medicines), cytology (cell biology), immunology (study of immune system) and neuroscience (neurology) are utilized and applied to the design of medical devices, diagnostic equipment, biocompatible materials, and other important medical needs.

Bioengineering is not limited to the medical field. Bioengineers have the ability to exploit new opportunities and solve problems within the domain of complex systems. They have a great understanding of complexity within the living systems which can be applied to many fields including entrepreneurship. Those working within the bioengineering field are of service to people, work with living systems, and apply advanced technology to the complex problems of medical care.

Bioengineering may be categorized as:

- Biomedical engineering;
- Biomedical technology
- Biomedical Diagnosis
- Biomedical Therapy
- Biomechanics
- Biomaterials.
- Genetic engineering
- Cell engineering

Biomedical engineering (BME): By combining biology and medicine with engineering, biomedical engineers develop devices and procedures that solve medical and health - related problems. Biomedical engineers may be called upon to design i nstruments and devices, to bring together knowledge from many sources to develop new procedures, or to carry out research to acquire knowledge needed to solve problems. Many do research, along with life scientists, chemists, and medical scientists, to deve lop and evaluate systems and products for use in the fields of biology and health, such as artificial organs, prostheses (artificial devices that replace missing body parts), instrumentation, medical information systems, and health management and care deli very systems. Bioengineers design devices used in variety of medical procedures, such as the computers used to analyze blood or the laser systems used in corrective eye surgery. They develop artificial organs, imaging systems such as magnetic resonance, ul trasound, and x-ray, and devices for automating insulin injections or controlling body functions. Most engineers in this specialty require a sound background in one of the basic engineering specialties, such as mechanical or electronics engineering, in add ition to specialized biomedical training. Some specialties within bioengineering or biomedical engineering include biomaterials, biomechanics, medical imaging, rehabilitation engineering, and orthopedic engineering.

Examples of work done by biomedical engineers include:

• designing and constructing cardiac pacemakers, defibrillators, artificial kidneys, blood oxygenators, hearts, blood vessels, joints, arms, and legs.

• designing computer systems to monitor patients during surgery or in intensive care, or to monitor healthy persons in unusual environments, such as astronauts in space or underwater divers at great depth.

• designing and building sensors to measure blood chemistry, such as potassium, sodium, 0_2, CO_2, and pH.

• designing instruments and dev ices for therapeutic uses, such as a laser system for eye surgery or a device for automated delivery of insulin.

developing strategies for clinical decision making based on expert systems and artificial intelligence, such as acomputer -based system for sel ecting seat cushions for paralyzed patients orfor, managing the care of patients with severe burns or for diagnosing diseases.

• designing clinical laboratories and other units within the hospital and health care delivery system that utilize advanced tech nology. Examples would be a computerized analyzer for blood samples, ambulances for use in rural areas, or acardiac catheterization laboratory.

• designing, building and investigating medical imaging systems based on X -rays (computer assisted tomography), isotopes (position emission tomography), magnetic fields (magnetic resonance imaging), ultrasound, or newer modalities.

• constructing and implementing mathematical/ computer models of physiological systems.

• designing and constructing biomaterials and de termining the mechanical, transport, and biocompatibility properties of implantable artificial materials.

• implementing new diagnostic procedures, especially those requiring engineering analyses to determine parameters that are not directly accessible to measurements, such as in the lungs or heart.

• investigating the biomechanics of injury and wound healing.

Specialty Areas

By combining biology and medicine with engineering, biomedical engineers develop devices and procedures that solve medical and healt h-related problems. Many do research, along with life scientists, chemists, and medical scientists, to develop and evaluate systems and products for use in the fields of biology and health, such as artificial organs, prostheses (artificial devices that rep lace missing body parts), instrumentation, medical information systems, and health management and care delivery systems. Some of the well established specialty areas within the field of biomedical engineering are bioinstrumentation, biomechanics, biomateri als, systems physiology, clinical engineering, and rehabilitation engineering.

Bioinstrumentation

Bioinstrumentation is the application of electronics and measurement principles and techniques to develop devices used in diagnosis and treatment of disease. Computers are becoming increasingly important in bioinstrumentation, from the microprocessor used to do a variety of small tasks in a single purpose instrument to the extensive computing power needed to process the large amount of information in a medical imaging system.

Biomechanics

Biomechanics is mechanics applied to biological or medical problems. It includes the study of motion, of material deformation, of flow within the body and in devices, and transport of chemical constituents across biological an d synthetic media and membranes. Efforts in biomechanics have developed the artificial heart and replacement heart valves, the artificial kidney, the artificial hip, as well as built a better understanding of the function of organs and musculoskeletal syst ems. Biomaterials describes both living tissue and materials used for implantation. Understanding the properties of the living material is vital in the design of implant materials. The selection of an appropriate material to place in the human body may be one of the most difficult tasks faced by the biomedical engineer. Certain metal alloys, ceramics, polymers, and composites have been used as implantable materials. Biomaterials must be nontoxic, noncarcinogenic, chemically inert, stable, and mechanically strong enough to withstand the repeated forces of a lifetime.

Systems Physiology

Systems physiology is the term used to describe that aspect of biomedical engineering in which engineering strategies, techniques and tools are used to gain a comprehensive and integrated understanding of the function of living organisms ranging from bacteria to humans. Modeling is used in the analysis of experimental data and in formulating mathematical descriptions of physiological events. In research, models are used in designing new experiments to refine our knowledge. Living systems have highly regulated feedback control systems which can be examined in this way. Examples are the biochemistry of metabolism and the control of limb movements.

Clinical Engineering

Clinical engineering is the application of technology for health care in hospitals. The clinical engineer is a member of the health care team along with physicians, nurses and other hospital staff. Clinical engineers are responsible for developing and maintaining computer databases of medical instrumentation and equipment records and for the purchase and use of sophisticated medical instruments. They may also work with physicians on projects to adapt instrumentation to the specific needs of the physician and the h ospital. This often involves the interface of instruments with computer systems and customized software for instrument control and data analysis. Clinical engineers feel the excitement of applying the latest technology to health care.

Rehabilitation Engineering

Rehabilitation engineering is a new and growing specialty area of biomedical engineering. Rehabilitation engineers expand capabilities and improve the quality of life for individuals with physical impairments. Because the products of their labor are so personal, often developed for particular individuals or small groups, the rehabilitation engineer often works directly with the disabled individual. These specialty areas frequently depend on each other. Often the bioengineer, or biomedical engineer, w ho works in an applied field will use knowledge gathered by bioengineers working in more basic areas. For example, the design of an artificial hip is greatly aided by a biomechanical study of the hip. The forces which are applied to the hip can be consider ed in the design and material selection for the prosthesis. Similarly, the design of systems to
electrically stimulate paralyzed muscle to move in a controlled way uses knowledge of the behavior of the human musculoskeletal system. The selection of appropr iate materials used in these devices falls within the realm of the biomaterials engineer. These are examples of the interactions among the specialty areas of biomedical engineering.

Major Advances in Bioengineering

Artificial Joints

In 1994, a National Ins titutes of Health Consensus Panel declared that total hip replacement (THR) is one of the most successful surgical procedures, providing immediate and substantial improvement in a patient's pain, mobility, and quality of life. THR involves removing diseased or damaged bone in the upper end of the thigh bone (femur) and the section of the lower pelvis into which the femur fits. The bone is then replaced with prosthesis, usually made of a metal alloy or polyethelene (plastic) components. Successful replacement of deteriorated, arthritic, and severely injured hips has contributed to enhanced mobility and comfortable, independent living for many people who would otherwise be substantially disabled.

Magnetic Resonance Imaging (MRI)

In 1952, the Nobel Prize in Physics was awarded for the discovery of nuclear magnetic resonance, which laid the groundwork for one of the most unique and important inventions in medical imaging since the discovery of the X-ray. Magnetic resonance imaging (MRI) is a method of looking inside the body without using surgery, harmful dyes or radiation. The method uses magnetism and radio waves to produce clear pictures of the human anatomy. Although MRI is used for medical diagnosis, it uses a physics phenomenon discovered in the 1930s in which magnetic fields and radio waves, both harmless to humans, cause atoms to give off tiny radio signals. Different kinds of animal tissue emit response signals of differing length e.g. response signals between cancerous and non -cancerous tissue, and among the response times of other kinds of diseased tissue.

Heart Pacemaker

The invention and development of the heart pacemaker illustrates the merging of medicine and engineering. The device is a result of the collective efforts and collaboration of people and organizations from both engineering and medicine, and both public and private institutions. The pacemaker was the first electronic device ever surgically implanted inside a human. First developed in the 1960s, pacemaker typically refers to a small, batt ery-powered device that helps the heart beat in a regular rhythm. Small electrical charges travel to one or multiple electrodes placed next to the heart muscle. Originally pacemakers sent one steady beat to the heart through a single electrode. Today's pac emakers can sense when a heart needs help and delivers just the right amount and duration of impulse ---sometimes through multiple electrodes - --that maintain steady heart rate, even during physical activity. While most pacemakers today
are permanent implan ts, some are used as temporary therapy for recovering heart patients.

Arthroscopy

Arthroscopy is a surgical procedure orthopedic surgeons use to visualize, diagnose and treat problems inside a joint. The word arthroscopy comes from two Greek words, "arthr o" (joint) and "skopein" (look), and literally means "to look within the joint." In an arthroscopic examination, an orthopedic surgeon makes a small incision in the patient's skin and then inserts pencil -sized instruments that contain a small lens and ligh ting system to magnify and illuminate the structures inside the joint. Light is transmitted through fiber optics to the end of the arthroscope that is inserted into the joint. By attaching the arthroscope to a miniature television camera, the surgeon is ab le to see the interior of the joint through this very small incision. The camera attached to the arthroscope displays the image of the joint on a television screen, allowing the surgeon to look, for example, throughout the knee -- at cartilage and ligament s, and under the kneecap. The surgeon can determine the amount or type of injury, and then repair or correct the problem, if necessary.

Angioplasty

Insertion of a catheter into a patient's coronary artery and inflated a tiny balloon, opening a blockage and restoring blood flow to a human heart is known as coronary angioplasty. It accounts a most common medical intervention in the world. Although this procedure was first envisioned as simply an alternative to open heart bypass surgery in only a handful of patients, today angioplasty accounts for more than half of the treatments for coronary artery disease. Biomedical engineering and advances in technology have not only optimized basic balloon angioplasty, but also added the use of stents, lasers and other interventional devices that restore normal blood flow while minimizing damage to the heart muscle.

Bioengineered Skin

The burgeoning field of tissue engineering promises to be one of the most significant biomedical areas of the new century. The hope is that, eventually, whole organs could be manufactured to replace those that are injured or diseased. The field's first contribution to health care took a big step toward fulfilling these promises by producing artificial version of the body's largest organ, skin. Skin is a difficult organ to transplant because of its inherently strong immune defense system. Nevertheless, it has a relatively simple structure, making it a good testing ground for the talents of tissue engineers. Patients can have skin made to order that combines collagen as a binder with living human cells. This is placed onto a wound, usually a chronic ulcer or a burn, and its cells become activated and gradually integrate with those of the patient.

Kidney Dialysis

Considerable human population on the Earth currently lives with chronic kidney failure resulting from disease, birth defect or injury. Virtually all these patients would die if not for the aid of ongoing kidney dialysis. Kidney dialysis artificially filters and removes waste products and excess water from blood, a process normally performed by the kidneys. Although often referred to as an artificial kidney, kidney dialysis is not a cure. The procedure can, however, give damaged kidneys a rest and a chance to recover normal function, or be used until the patient receives a transplant. For many patients, kidney dialysis is a way of life. Kidney dialysis was first developed by a Dutch physician, Willem Kolff, M.D., Ph.D. In the early 1940s, he began searching for a way to use dialysis, the process by which particles pass through a membrane, to treat patients with kidney failure. A sever shortage of materials due to the war forced Kolff to improvise, especially when it came to a suitable membrane, the key component to the filtering process.

Today, research to find more efficient, low -cost methods of treatment remains a priority for biomedical engineers. Current efforts include not only improving the components of dialysis, such as better dialysates and membranes, but also developing alternati ves to dialysis, such as a true artificial kidney, xenotransplantation and replacement kidneys through tissue engineering.

Heart-lung Machine

One of the truly revolutionary pieces of medical equipment has been the invention and development of the heart -lung machine. Before its introduction to medicine in the 1950s, heart surgery was unheard of; there was no way to keep a patient alive while working on the heart. During an open -heart surgery, such as bypass surgery, the heart -lung machine takes over the functions of the heart and lungs and allows a surgeon to carefully stop the heart while the rest of the patient’s body continues to receive oxygen -rich blood. The surgeon can then perform delicate work on the heart without interference from bleeding or the heart’s pumping motion. Once the procedure is over, the surgeon restarts the heart and disconnects the heart -lung machine.

A typical biomedical engineering department does the corrective and preventive maintenance on the medical devices used by the hospital , except for those covered by a warranty or maintenance agreement with an external company. All newly acquired equipment is also fully tested. That is, every line of software is executed, or every possible setting is exercised and verified. Most devices ar e intentionally simplified in some way to make the testing process less expensive, yet accurate. Many biomedical devices need to be sterilized. This creates a unique set of problems, since most sterilization techniques can cause damage to machinery and materials. Most medical devices are either inherently safe, or have added devices and systems so that they can sense their failure and shut down into an unusable, thus very safe state. A typical, basic requirement is that no single failure should cause the therapy to become unsafe at any point during its life -cycle.

TISSUE ENGINEERING

Tissue engineering 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. 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, etc.). 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.

Stem cells are cells found in most, if not all, multi- cellular organism. They are characterized by the ability to renew themselves through mitotic cell division and differentiating into a diverse range of specialized cell types. The two broad types of mammalian stem cells are: **embryonic stem cells** that are isolated from the inner cell mass of blastocysts, and **adult stem cells** that are found in adult tissues.

Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.

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 bioinformatics.

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

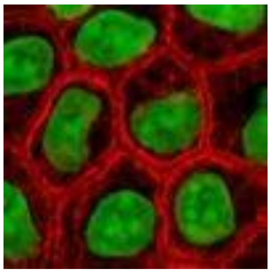
Examples

- 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

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 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.

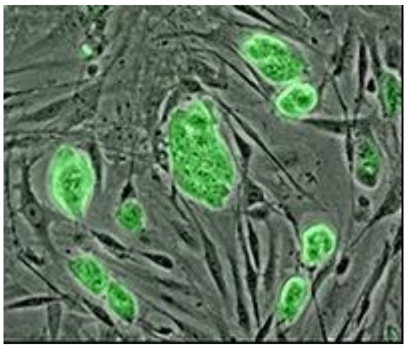
Types of cells

Cells are often categorized by their source:

- **Autologous** cells are obtained from the same individual to which they will be reimplanted. The distiguishing features of Autologous cells are:
    1. They have the very few 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.

2. These cells can differentiate into a variety of tissue types, including bone, cartilage, fat, and nerve.
3. 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. Several companies have been founded to capitalize on this technology, the most successful at this time being Cytori Therapeutics.



Mouse embryonic stem cells.

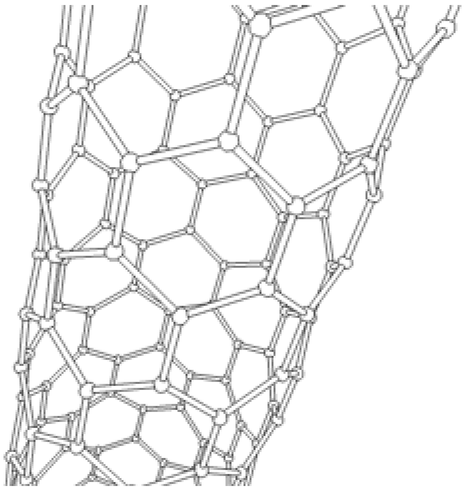
- **Allogenic** cells come from the body of a donor of the same species. While there are some ethical constraints to the use of human cells for *in vitro* studies, the employment of dermal fibroblasts from human foreskin has been demonstrated to be immunologically safe and thus a viable choice for tissue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



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. The purposes served by the scaffolds are:

- 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

This rotating Carbon nanotube shows its 3D structure. Carbon nanotubes are

1. Among the numerous candidates for tissue engineering scaffolds
2. They are biocompatible
3. Resistant to biodegradation
4. Can be functionalized with biomolecules.
5. However, the possibility of toxicity with non-biodegradable nano-materials is not fully understood.

Also the requirements of an ideal scaffold are:

- 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.

Materials: They are usually functionally customized and the ideal properties are:

a. injectability,
b. synthetic manufacture
c. biocompatibility
d. non-immunogenicity

e. transparency
f. nano-scale fibers
g. low concentration
h. desired resorption rates

The different types of materials:

1. **Natural or constructed from natural materials** - different derivatives of the extracellular matrix. Proteic materials, such as collagen or fibrin, and polysaccharidic materials, like chitosan or glycosaminoglycans (GAGs), are all 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...), bioresorbable sutures like collagen
2. **Synthetic** – PuraMatrix, 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; polyglycolic acid (PGA) and polycaprolactone (PCL): their degradation mechanism is similar to that of PLA, but slightly slower.

The materials can be biodegradable or non-biodegradable.

Synthesis

A number of different methods has 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 is devoid of drawbacks.

- **Nanofiber Self-Assembly**: Molecular self-assembly is the method to create biomaterials with properties similar in scale and chemistry to that of the natural in vivo extracellular matrix (ECM). The polymers are immerced in the hydrogels and assemble on their own thus known as self assembly. These are hydrogel scaffolds, superior in vivo toxicology and biocompatibility.

- **Textile technologies**: these techniques include the preparation of non-woven meshes of different polymers. e.g. non-woven polyglycolide structures. Such fibrous structures are useful to grow different types of cells. The drawbacks - difficulties of obtaining high porosity and regular pore size.

- **Solvent Casting & Particulate Leaching (SCPL)**: the preparation of porous structures with regular porosity, but with a limited thickness.
  1. the polymer is dissolved into a suitable organic solvent (e.g. polylactic acid could be dissolved into dichloromethane),
  2. the solution is cast into a mold filled with porogen particles of inorganic salt like sodium chloride, crystals of saccharose, gelatin spheres or paraffin spheres. The size of the porogen particles and the polymer to porogen ratio is directly correlated to the amount of porosity of the final structure.
  3. The solvent is allowed to fully evaporate,
  4. the composite structure in the mold is immersed in a bath of a liquid suitable for dissolving the porogen. Once the porogen has been fully dissolved a porous structure is obtained.

The drawback of SCPL - 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 necessity to use organic solvents and solid porogens a technique using gas as a porogen has been developed.
  1. disc shaped structures made of the desired polymer are prepared by means of compression molding using a heated mold.
  2. The discs are then placed in a chamber where are exposed to high pressure CO_2 for several days.
  3. 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 drawbacks: prohibits the incorporation of any temperature labile material into the polymer matrix; the pores do not form an interconnected structure.

- **Emulsification/Freeze-drying**: this technique does not require the use of a solid porogen like SCPL.
  1. a synthetic polymer is dissolved into a suitable solvent (e.g. polylactic acid in dichloromethane),
  2. water is added to the polymeric solution
  3. the two liquids are mixed in order to obtain an emulsion.
  4. the emulsion is cast into a mold
  5. quickly frozen by means of immersion into liquid nitrogen.
  6. The frozen emulsion is subsequently freeze-dried to remove the dispersed water and the solvent, thus leaving a solidified, porous polymeric structure.

  Drawbacks -it still requires the use of solvents, pore size is relatively small and porosity is often irregular.)

- **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.

- **CAD/CAM Technologies**: since most of the above described approaches 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

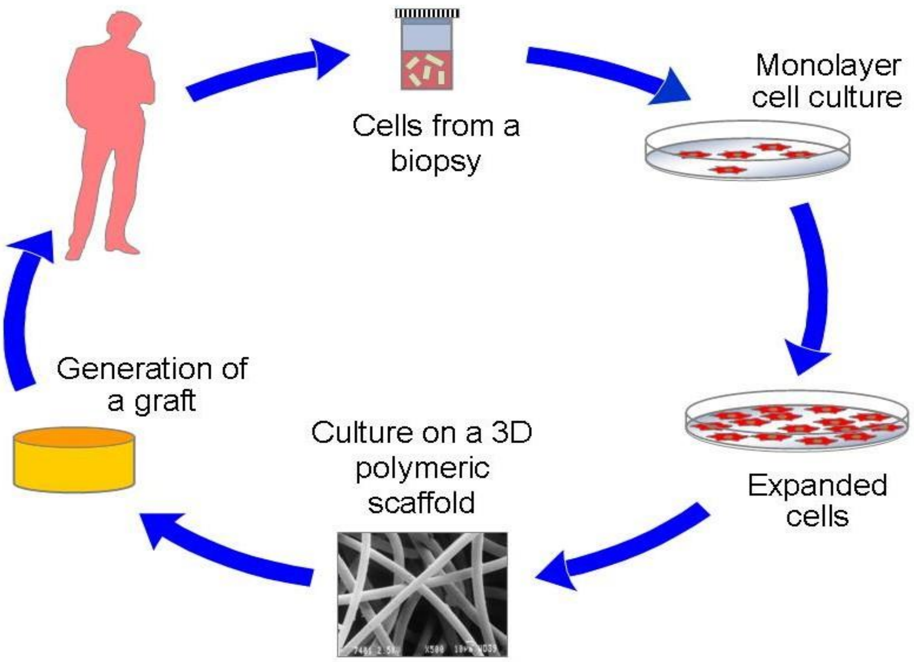
In many cases, creation of functional tissues and biological structures *in vitro* requires extensive culturing to promote survival, growth and inducement of functionality. In general, the basic requirements of cells must be maintained in culture, which include oxygen, pH, humidity, temperature, nutrients 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.

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.

Basic principle of Tissue engineering is illustrated in the following figure. Cells can be isolated from the patient’s body, and expanded in a petridish in laboratory. Once we have enough number of cells, they can be seeded on a polymeric scaffold material, and cultured in vitro in a bioreactor or incubator. When the construct is matured enough, then it can be implanted in the area of defect in patient’s body.

Basic principles of Tissue engineering



The application of the principles & methods of engineering & life sciences towards the fundamental understanding of structure, function & relationships in normal & pathological mammalian tissue & the development of biological substitutes to restore, maintain & improve tissue function.

… Symposium on Tissue Engineering (1988)

Defect	Organ	Function
Mechanical	Cartilage	Resist compression
Metabolites	Liver	Nitrogen metabolism
Synthetic	Pancreas	Insulin production
Communication	Nerve	Coordination
Combination	Skin	prevents water loss immunologic barrier

Biomimicry, Biomimetics, Biologically Inspired Design : much more than inspiration

There are many human inventions which were inspired by observations of the living (and non-living) systems that surround us. The systematic study of the systems of nature with the aim of helping engineers has started to receive greater interest since the 60s: terms such as bionics and biomimetics were created to refer to these approaches aiming specifically at using the knowledge gathered from living systems to improve human-created technology. The idea behind these two terms was that copying or mimicking some function, some characteristic of the natural systems would be useful for improving technical systems. The publication of the book "Biomimicry, Innovation inspired by Nature" in 1997 by the American science writer and lecturer Janine Benyus gave a new impulsion for the so-called biologically inspired approach or biomimicry which is defined as "a new science that studies nature's models and then imitates or takes inspiration from these designs and processes to solve human problems" **[1]**.

Numerous associations of biomimicry practitioners and people interested in the approach were created: BIOKON (Germany), the Biomimicry Institute (co-founded in the US by Benyus), Biomimicry Europa (Belgium and France), Biomimicry NL (Netherlands), Biomimicry IL (Israel), Biomimicry UK. In France, a dedicated research center is being built in the town of Senlis (CEEBIOS). And the number of publications on the biomimicry / biomimetic field keeps growing **[2]**.

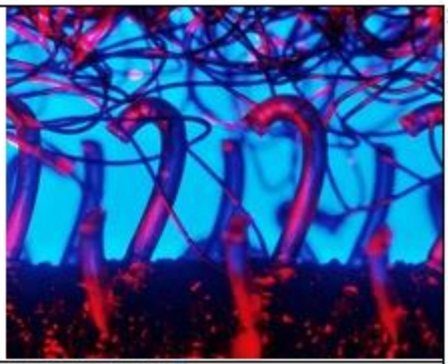
This article presents some examples of biologically inspired products and recent developments and also some perspectives about the use of biological inspiration in innovative design.

Some "successful" examples

There are numerous publications related to biologically inspired developments. The two books of Y. Bar-Cohen **[3,4]** for example, give a wide set of examples spanning different technological fields in which biological inspiration has been applied to. The most emblematic examples, gathered from literature on biological inspiration are:

1) George de Mestral's Velcro®

George de Mestral, a swiss engineer, observed that the seeds of burdock plant got caught in his dog's fur **[5]**, being easily removed with a light force. He analyzed these seeds and attributed the gripping to the tiny hooks that cover the seeds surface. Velcro was then created as a two sided zip, which contains in one side stiff hooks (as in the burdock seeds) and on the other loops to which the hooks get attached. The name Velcro came from the contraction of the words *velour* (velvet) and *crochet* (hook) **[6]**.

	
Burdock Plant, CC- Zephyris http://en.wikipedia.org/wiki/File:Bur_Macro_BlackBg.jpg	Velcro Micrograph CC – Natural Philo http://en.wikipedia.org/wiki/File:Micrograph_of_hook_and_loop_fastener,(Velcro_like).jpg

2) Self-cleaning surfaces

Lotus-leaves have long been recognized as a symbol of purity, as it grows in muddy environments and always stay clean. Two German researchers, Barthlott & Neinhuis, while doing some studies on plants surfaces, unveiled the mechanism that allowed these plants to stay clean. They discovered that leaves such as the lotus, had a rough surface covered with a hydrophobic coating **[7]**. This allowed the development of microstructured hydrophobic coatings being employed as paints for rendering surfaces self-cleaning (ex. Lotusan, developed by Sto AG)**[8]**.

	
Lotus leaf CC – Claire Houck	Lotusan – Sto AG

3) Eastgate Center

The Eastgate Center, in Zimbabwe, was projected by the Zimbabwean architect Mick Pearce. He drew its inspiration from the termite mounds of southern Africa termite mounds, which were believed to provide ventilation and temperature control for the colony. The ventilation system of the building was built using two models of termite mound ventilation: the thermosiphon and the induced flow, and steady temperatures are achieved without massive energy consumption for air conditioning. However, Turner and Soar **[9]** pointed out that “there is no evidence that termites regulate nest temperature” and the ventilation has no or little to do with the temperature regulation. This shows that even *not fully understood* biological phenomena can lead to interesting biologically inspired developments.

	
Termite mound, Lichfield Naitional Park CC- David King http://www.asknature.org/strategy/0b6de7e76091446430d275b2c52473dd	Eastgate Centre CC- David Brazier http://en.wikipedia.org/wiki/File:Eastgate_Centre,_Harare,_Zimbabwe.jpg

4) Flectofin®

Flectofin® is the result of collaboration between German engineers, architects and botanists. Reducing complexity of deployable systems in architecture is a challenge for architects, as in general deployability is achieved using “rigid elements connected with technical hinges” **[10]**. In Nature, this property is achieved using different mechanisms, such as the elastic deformations in plants. This was the starting point of a screening process for finding plants movements that would be useful for technical applications. The bird of paradise flower petals movements were identified as a torsional buckling mechanism, known to engineers, but usually considered as a failure mode, to be prevented. The plants movements showed how to use this mechanism, which was abstracted in a “thin shell element attached to a beam” **[11]**. Further studies on the materials properties and simulations allowed the development of Flectofin, described as a façade shading system formed by bending lamellas that is also adaptable to curved geometries.

	
Bird-of-paradise flower CC- Camila Freitas	Flectofin CC- Simons Schleicher, ITKE, University of Stuttgart

5) Nature-inspired algorithms for optimization

Steer, Wirth and Halgamuge, in a review about these algorithms **[12]** propose that natural systems may exhibit behavior that is optimum-seeking, which could be used in artificial applications, while others act like "methaphor" inspiring, providing a framework for problem understanding and for the production of solutions. Their review included the following examples of nature-inspired algorithms :

- Evolutionary algorithms, inspired by the Darwin's theory of Evolution by Natural Selection ("evolutionary operation", "genetic algorithms", "evolution strategies" and "evolutionary programming").
- Particle Swarm Optimization, inspired by social behavior in nature.
- Ant Colony Optimization, inspired by the "recruitment strategy of ants which use chemical markers to mark the source of a rich food source".
- Artificial Neural Networks, inspired by the central nervous system of many organisms.

These examples show that the biologically inspired designs are rarely a copy of the inspiring natural system, they in fact involve an interaction between the knowledge from biology and the technical knowledge: normally observing the biological systems allow an activation of knowledge that would not otherwise be activated: for example, who would think that roughness could produce self-cleaning surfaces? Or that a materials failure mode could be the key for improving deployability?

Including biological inspiration in R&D

The growing number of publications involving biomimetics in different scientific fields and the innovations some of them brought, attracted the interest of many companies, seeking to be more innovative.

The first and more classic use of the biological knowledge in companies can be as a means of stimulating idea generation. Asking engineers: "how our problem is solved in nature?", can stimulate them to analogically generate new ideas for their problems. Nevertheless, the examples mentioned above highlight that only the analogy may not be sufficient for finding the disruptive path: some further research in the biological knowledge may be necessary. For example, in the flectofin case, a screening process of different plants mechanisms was necessary, in the Eastgate centre, the two ventilation mechanisms needed to be uncovered.

As a consequence, engineers may require an easy access to the biological knowledge, which will allow them to lately contact specialists. This access can be achieved by using databases containing biological phenomena, such as Asknature.org **[13]** or by searching in biological literature, as proposed in the Natural Language Approach **[14]**. There are also computational tools being developed for facilitating the transfer between the biological knowledge and the technical knowledge **[15]**. Therefore, the encounters between engineers and specialists may produce some interesting mutual inspirational interactions: engineers will propose biologists new questions about their work and biologists may propose new interpretations or regards about engineers' problems. These questions are currently being studied at the chair "Design Theory and Methods for Innovation", with the C-K theory as a framework for understanding the different roles of biological knowledge in the biologically inspired design process and for demonstrating that biomimetics indeed allows designers to go beyond mimicking or inspiration.

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