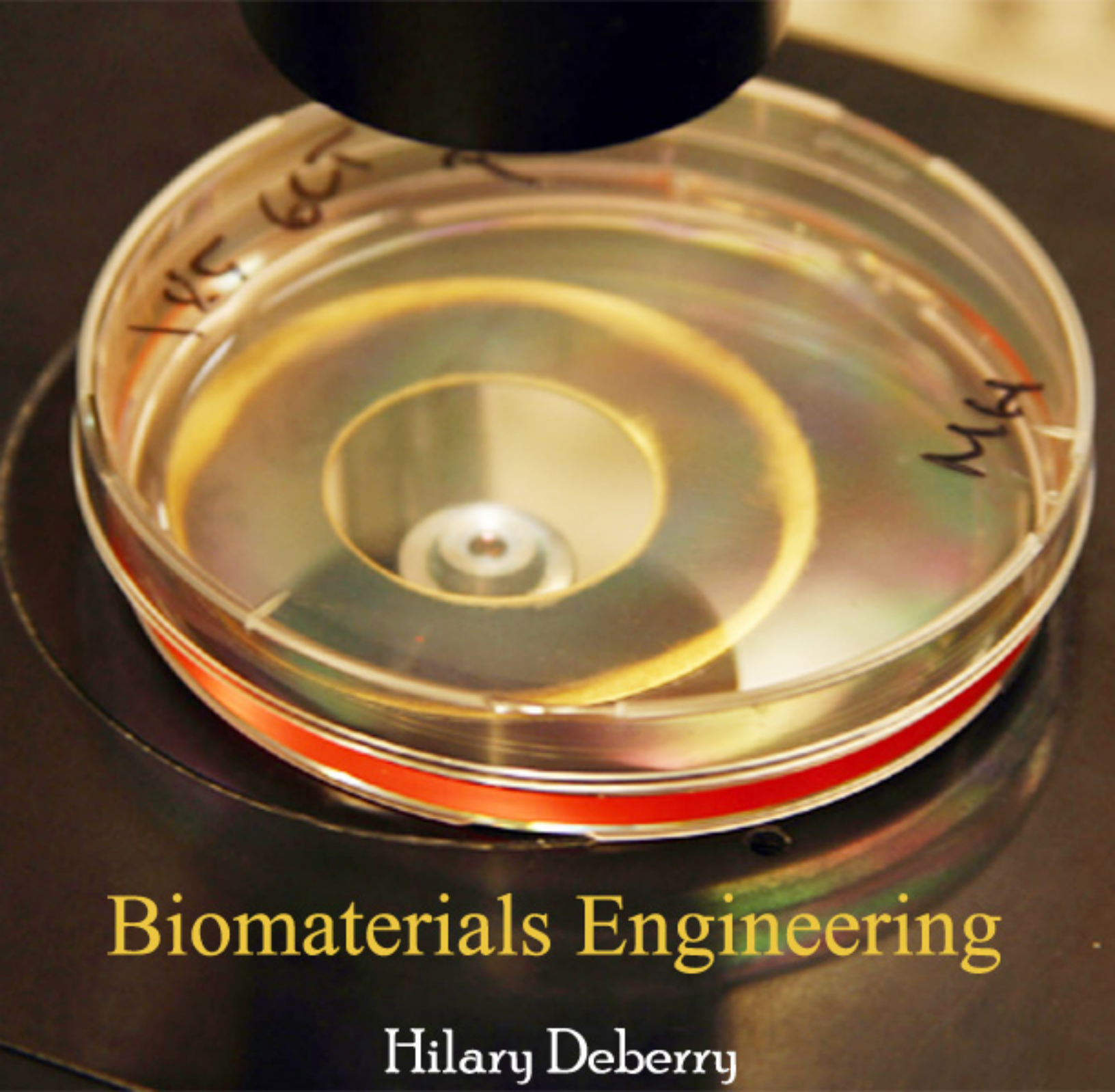

Biomaterials Engineering

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Chapter 1

Biomaterial

A biomaterial is any matter, surface, or construct that interacts with biological systems. The development of **biomaterials**, as a science, is about fifty years old. The study of biomaterials is called biomaterials science. It has experienced steady and strong growth over its history, with many companies investing large amounts of money into the development of new products. Biomaterials science encompasses elements of medicine, biology, chemistry, tissue engineering and materials science.

The iridescent nacre inside a nautilus shell.

Introduction

Biomaterials can generally be produced either in nature or synthesized in the laboratory using a variety of chemical approaches utilizing metallic components or ceramics. They are often used and/or adapted for a medical application, and thus comprises whole or part of a living structure or biomedical device which performs, augments, or replaces a natural function. Such functions may be benign, like being used for a heart valve, or may be bioactive with a more interactive functionality such as hydroxy-apatite coated hip implants. Biomaterials are also used every day in dental applications, surgery, and drug delivery. E.G. A construct with impregnated pharmaceutical products can be placed into the body, which permits the prolonged release of a drug over an extended period of time. A biomaterial may also be an autograft, allograft or xenograft used as a transplant material.

Materials scientists are currently paying more and more attention to the process inorganic crystallization within a largely organic matrix of naturally occurring compounds. This process typically generally occurs at ambient temperature and pressure. Interestingly, the vital organisms through which these crystalline minerals form are capable of consistently producing intricately complex structures. Understanding the processes in which living organisms are capable of regulating the growth of crystalline minerals such as silica could lead to significant scientific advances and novel synthesis techniques for nanoscale composite materials -- or nanocomposites.

Self-assembly

Self-assembly is the most common term in use in the modern scientific community to describe the spontaneous aggregation of particles (atoms, molecules, colloids, micelles, etc.) without the influence of any external forces. Large groups of such particles are known to assemble themselves into thermodynamically stable, structurally well-defined arrays, quite reminiscent of one of the 7 crystal systems found in metallurgy and mineralogy (e.g. face-centered cubic, body-centered cubic, etc.). The fundamental difference in equilibrium structure is in the spatial scale of the unit cell (or lattice parameter) in each particular case.

Molecular self-assembly is found widely in biological systems and provides the basis of a wide variety of complex biological structures. This includes an emerging class of mechanically superior biomaterials based on microstructural features and designs found in nature. Thus, self-assembly is also emerging as a new strategy in chemical synthesis and nanotechnology. Molecular crystals, liquid crystals, colloids, micelles, emulsions, phase-separated polymers, thin films and self-assembled monolayers all represent examples of the types of highly ordered structures which are obtained using these techniques. The distinguishing feature of these methods is self-organization.

Structural hierarchy

Nearly all materials could be seen as hierarchically structured, especially since the changes in spatial scale bring about different mechanisms of deformation and damage. However, in biological materials this hierarchical organization is inherent to the microstructure. One of the first examples of this, in the history of structural biology, is the early X-Ray scattering work on the hierarchical structure of hair and wool by Astbury and Woods. In bone, for example, collagen is the building block of the organic matrix—a triple helix with diameter of 1.5 nm. These tropocollagen molecules are intercalated with the mineral phase (hydroxyapatite, a calcium phosphate) forming fibrils that curl into helicoids of alternating directions. These "osteons" are the basic building blocks of bones, with the volume fraction distribution between organic and mineral phase being about 60/40. In another level of complexity, the hydroxyapatite crystals are platelets that have a diameter of approximately 70–100 nm and thickness of 1 nm. They originally nucleate at the gaps between collagen fibrils.

Similarly, the hierarchy of abalone shell begins at the nanolevel, with an organic layer having a thickness of 20–30 nm. This layer proceeds with single crystals of aragonite (a polymorph of $CaCO3$) consisting of "bricks" with dimensions of 0.5 and finishing with layers approximately 0.3 mm (mesostructure).

Crabs are arthropods whose carapace is made of a mineralized hard component (which exhibits brittle fracture) and a softer organic component composed primarily of chitin. The brittle component is arranged in a helical pattern. Each of these mineral ‘rods’ (1 μm diameter) contains chitin–protein fibrils with approximately 60 nm diameter. These fibrils are made of 3 nm diameter canals which link the interior and exterior of the shell.

Applications

Biomaterials are used in:

- Joint replacements
- Bone plates
- Bone cement
- Artificial ligaments and tendons
- Dental implants for tooth fixation
- Blood vessel prostheses
- Heart valves
- Skin repair devices (artificial tissue)
- Cochlear replacements
- Contact lenses
- Breast implants

Biomaterials must be compatible with the body, and there are often issues of biocompatibility which must be resolved before a product can be placed on the market and used in a clinical setting. Because of this, biomaterials are usually subjected to the

same requirements of those undergone by new drug therapies. All manufacturing companies are also required to ensure traceability of all of their products so that if a defective product is discovered, others in the same batch may be traced.

Heart valves

In the United States, 45% of the 250,000 valve replacement procedures performed annually involve a mechanical valve implant. The most widely used valve is a bileaflet disc heart valve, or St. Jude valve. The mechanics involve two semicircular discs moving back and forth, with both allowing the flow of blood as well as the ability to form a seal against backflow. The valve is coated with pyrolytic carbon, and secured to the surrounding tissue with a mesh of woven fabric called Dacron™ (du Pont's trade name for polyethylene terephthalate). The mesh allows for the body's tissue to grow while incorporating the valve.

Skin repair

Most of the time "artificial" tissue is grown from the patients own cells. However, when the damage is so extreme that it is impossible to use the patient's own cells, artificial tissue cells are grown. The difficulty is in finding a scaffold that the cells can grow and organize on. The characteristics of the scaffold must be that it is biocompatible, cells can adhere to the scaffold, mechanically strong and biodegradable. One successful scaffold is a copolymer of lactic acid and glycolic acid.

Compatibility

Biocompatibility is related to the behavior of biomaterials in various environments under various chemical and physical conditions. The term may refer to specific properties of a material without specifying where or how the material is to be used. For example, a material may elicit little or no immune response in a given organism, and may or may not able to integrate with a particular cell type or tissue). The ambiguity of the term reflects the ongoing development of insights into how biomaterials interact with the human body and eventually how those interactions determine the clinical success of a medical device (such as pacemaker or hip replacement. Modern medical devices and prostheses are often made of more than one material—so it might not always be sufficient to talk about the biocompatibility of a specific material.

Also, a material should not be toxic unless specifically engineered to be so—like "smart" drug delivery systems that target cancer cells and destroy them. Understanding of the anatomy and physiology of the action site is essential for a biomaterial to be effective. An additional factor is the dependence on specific anatomical sites of implantation. It is thus important, during design, to ensure that the implement will fit complementarily and have a beneficial effect with the specific anatomical area of action.

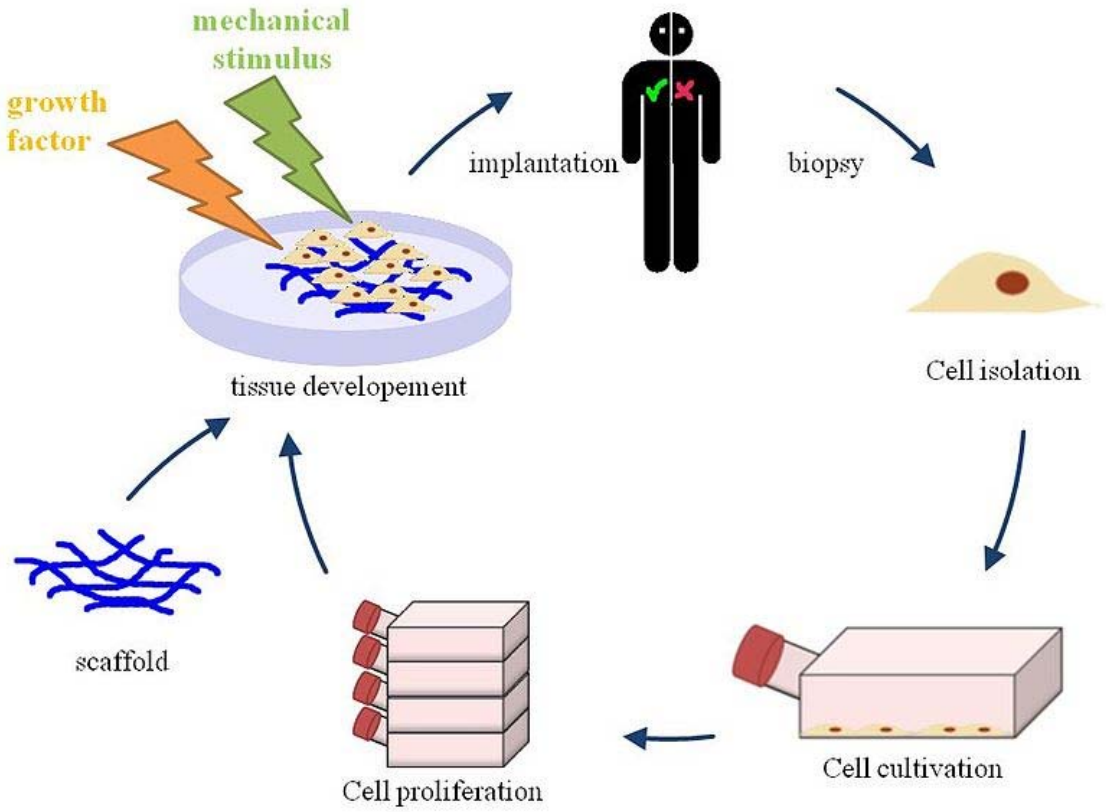
Biopolymers

Biopolymers are polymers produced by living organisms. Cellulose and starch, proteins and peptides, and DNA and RNA are all examples of biopolymers, in which the monomeric units, respectively, are sugars, amino acids, and nucleotides. Cellulose is both the most common biopolymer and the most common organic compound on Earth. About 33% of all plant matter is cellulose.

Some biopolymers are biodegradable. That is, they are broken down into CO_2 and water by microorganisms. In addition, some of these biodegradable biopolymers are compostable. That is, they can be put into an industrial composting process and will break down by 90% within 6 months. Biopolymers that do this can be marked with a 'compostable' symbol, under European Standard EN 13432 (2000). Packaging marked with this symbol can be put into industrial composting processes and will break down within 6 months (or less). An example of a compostable polymer is PLA film under 20 μm thick: films which are thicker than that do not qualify as compostable, even though they are biodegradable. A home composting logo may soon be established: this will enable consumers to dispose of packaging directly onto their own compost heap.

Chapter 2

Tissue Engineering

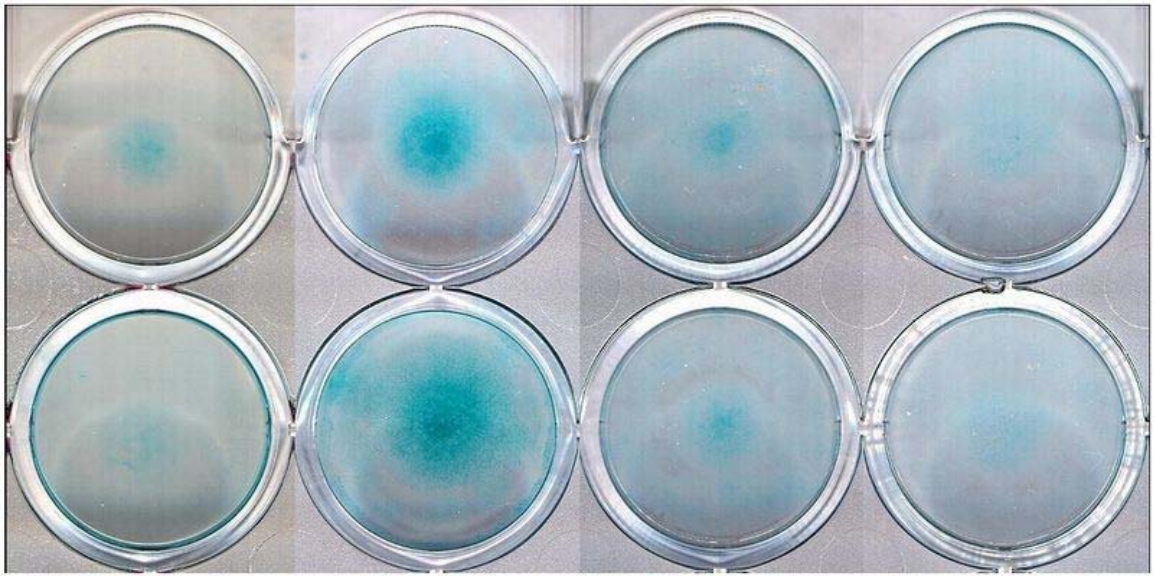


Principle of tissue engineering

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

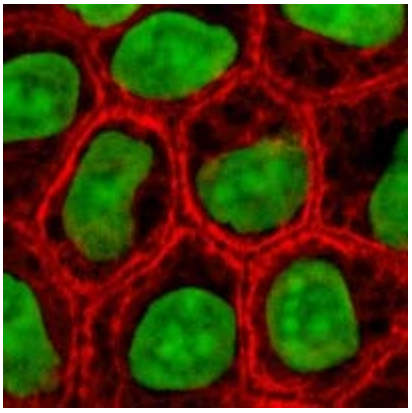
laboratory-grown tissues destined for transplantation. The continued success of tissue engineering, and the eventual development of true human replacement parts, will grow from the convergence of engineering and basic research advances in tissue, matrix, growth factor, stem cell, and developmental biology, 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.

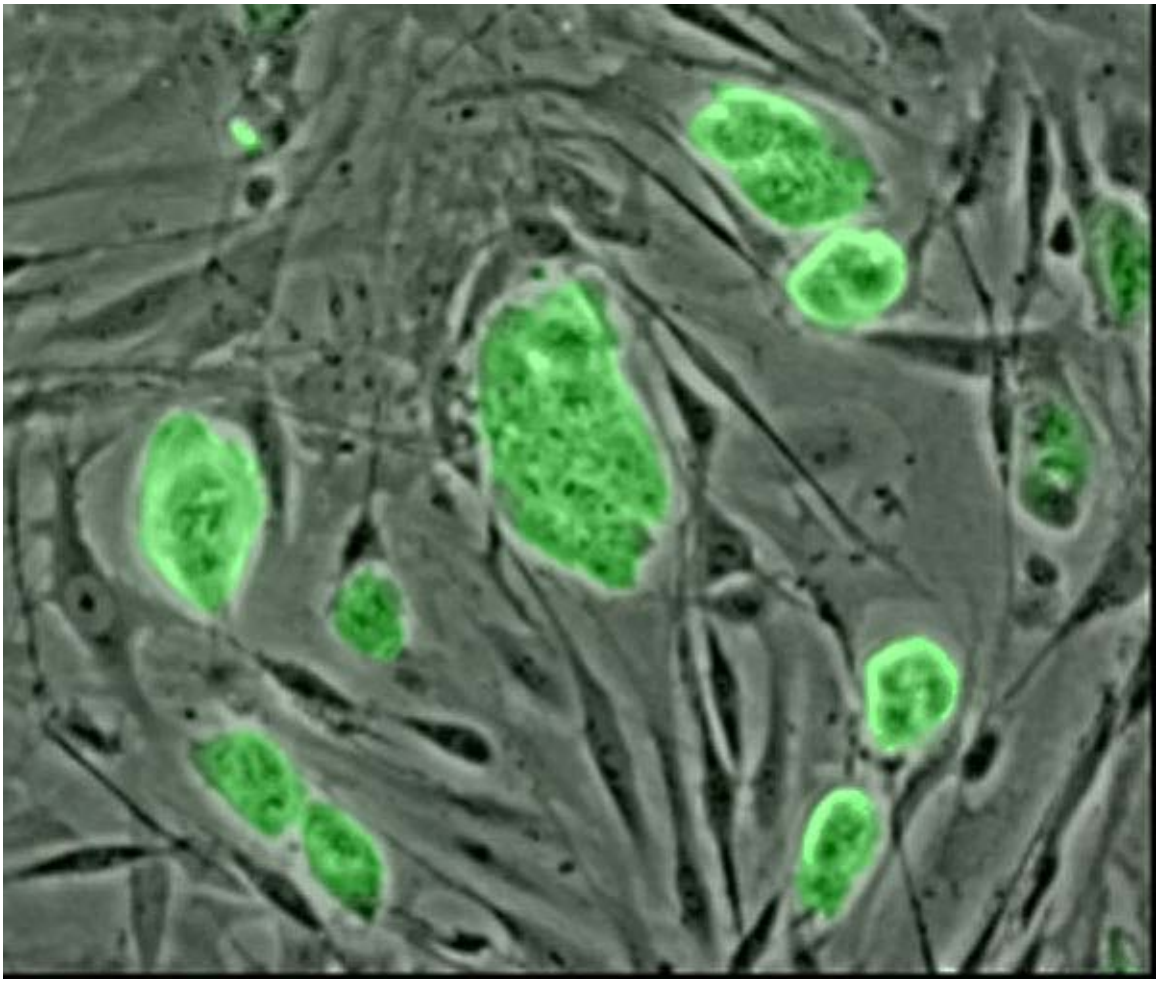
Extraction

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.

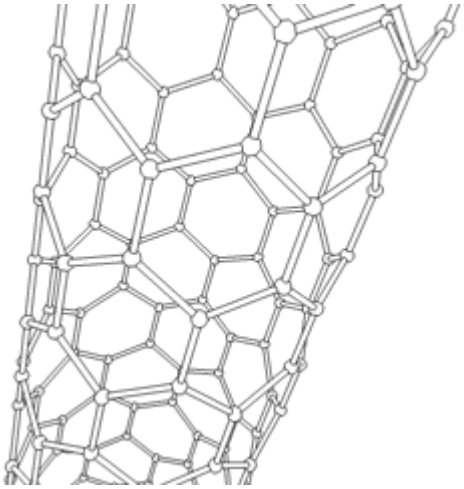
- **Secondary** cells are from a cell bank.

- **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



Rotating Carbon nanotube shows its 3D structure. 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.

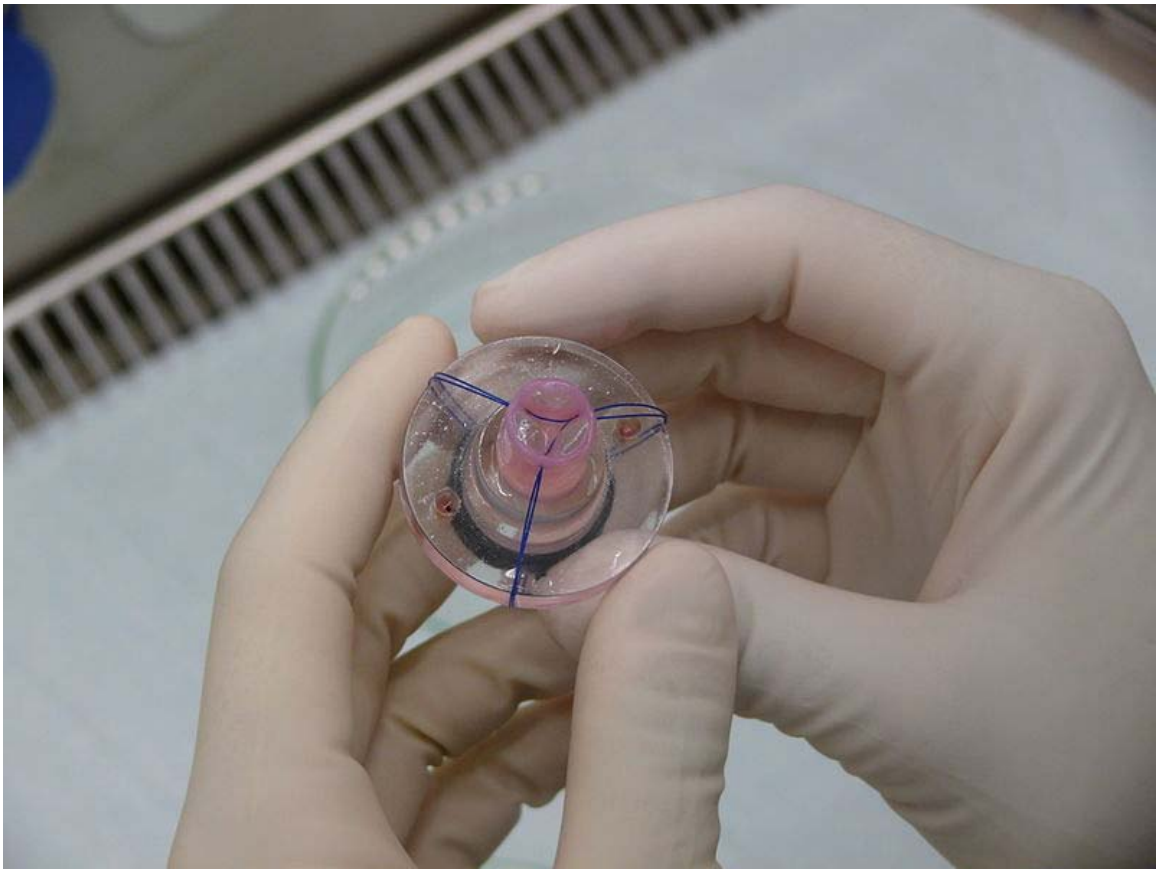
New biomaterials have been engineered to have ideal properties and functional customization: injectability, synthetic manufacture, biocompatibility, non-immunogenicity, transparency, nano-scale fibers, low concentration, resorption rates, etc. PuraMatrix, originating from the MIT labs of Zhang, Rich, 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.

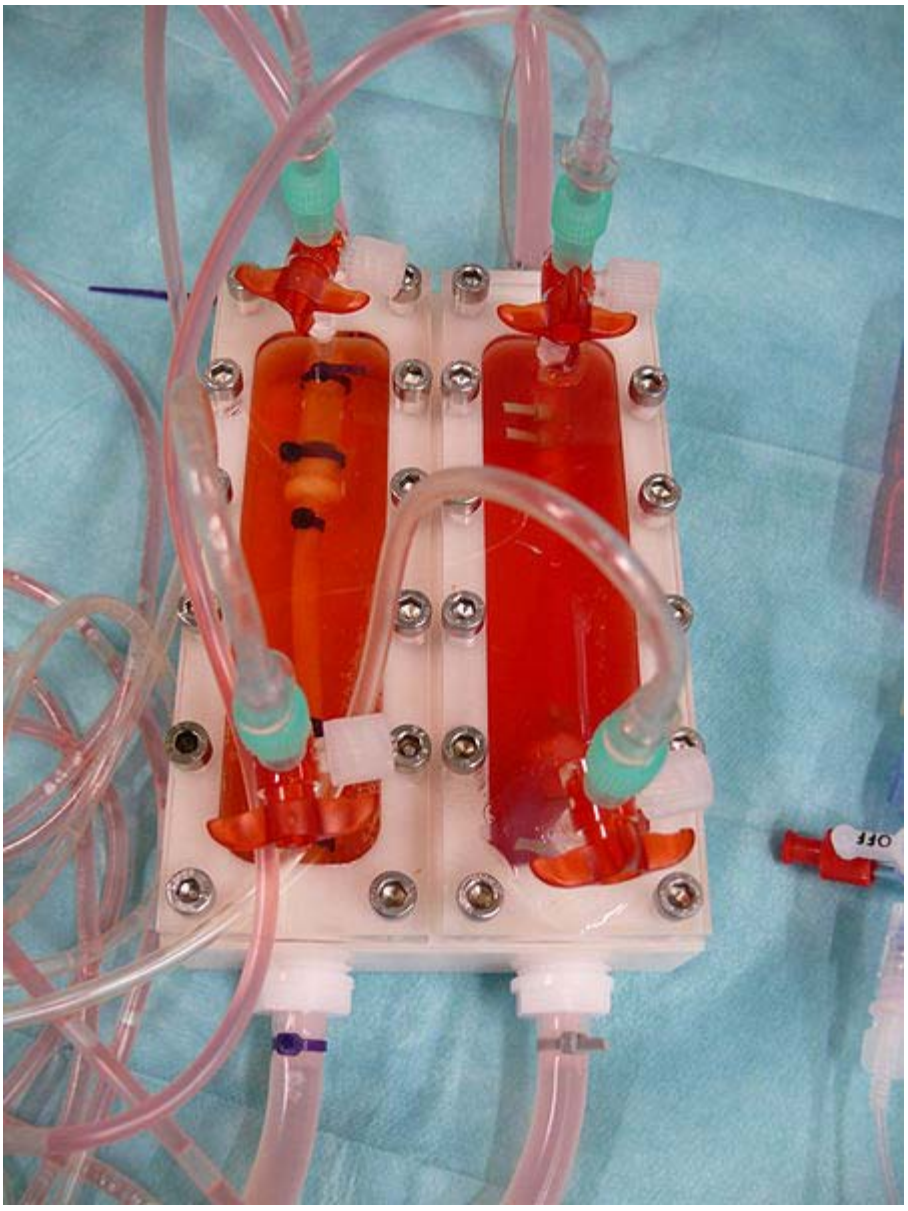
It might be possible to print organs, or possibly entire organisms. A recent innovative method of construction uses an ink-jet mechanism to print precise layers of cells in a matrix of thermoreversable gel. Endothelial cells, the cells that line blood vessels, have been printed in a set of stacked rings.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

Biomineralization

Calcitic skeletal parts of belemnites (Jurassic of Wyoming).

Biomineralization is the process by which living organisms produce minerals, often to harden or stiffen existing tissues. Such tissues are called mineralized tissues. It is an extremely widespread phenomenon; all six taxonomic kingdoms contain members that are able to form minerals, and over 60 different minerals have been identified in

organisms.Examples include silicates in algae and diatoms, carbonates in invertebrates, and calcium phosphates and carbonates in vertebrates. These minerals often form structural features such as sea shells and the bone in mammals and birds. Organisms have been producing mineralised skeletons for the past 550 million years. Other examples include copper, iron and gold deposits involving bacteria. Biologically-formed minerals often have special uses such as magnetic sensors in magnetotactic bacteria (Fe_3O_4), gravity sensing devices ($CaCO_3$, $CaSO_4$, $BaSO_4$) and iron storage and mobilization ($Fe_2O_3 \cdot H_2O$ in the protein ferritin).

In terms of taxonomic distribution, the most common biominerals are the phosphate and carbonate salts of calcium that are used in conjunction with organic polymers such as collagen and chitin to give structural support to bones and shells. The structures of these biocomposite materials are highly controlled from the nanometer to the macroscopic level, resulting in complex architectures that provide multifunctional properties. Because this range of control over mineral growth is desirable for materials engineering applications, there is significant interest in understanding and elucidating the mechanisms of biologically controlled biomineralization.

Biological roles

Biominerals perform a variety of roles in organisms, the most important being support, defence and feeding.

Biology

If present on a super-cellular scale, biominerals are usually deposited by a dedicated organ, which is often defined very early in the embryological development. This organ will contain an organic matrix which facilitates and directs the deposition of crystals. The matrix may be collagen, as in deuterostomes, or based on chitin or other polysaccharides, as in molluscs.

Shell formation in molluscs

The mollusc shell is a biogenic composite material that has been the subject of much interest in materials science because of its unusual properties and its model character for biomineralization. Molluscan shells consist of 95-99% calcium carbonate by weight, while an organic component makes up the remaining 1-5%. The resulting composite has a fracture toughness ~3000 times greater than that of the crystals themselves. In the biomineralization of the mollusc shell, specialized proteins are responsible for directing crystal nucleation, phase, morphology, and growths dynamics and ultimately give the shell its remarkable mechanical strength. The application of biomimetic principles elucidated from mollusc shell assembly and structure may help in fabricating new composite materials with enhanced optical, electronic, or structural properties.

Chemistry

Because extracellular iron is strongly involved in inducing calcification, its control is essential in developing shells; the gene *ferritin* plays an important role in controlling the distribution of iron.

Evolution

In most lineages, biomineralization first occurred in the Cambrian or Ordovician periods. Organisms used whichever form of calcium carbonate was more stable in the water column at the point in time when they became biomineralized, and stuck with that form for the remainder of their biological history. The stability is dependant on the Ca/Mg ratio of seawater, which is thought to be controlled primarily by the rate of sea floor spreading, although atmospheric CO_2 levels may also play a role.

Biomineralization evolved multiple times, independently – but interestingly, many of the same processes are used in unrelated lineages, which suggests that biomineralization machinery was assembled from pre-existing "off-the-shelf" components already used for other purposes in the organism. Although the biomachinery facilitating biomineralization is complex – involving signalling transmitters, inhibitors, and transcription factors – many elements of this 'toolkit' are shared between phyla as diverse as corals, molluscs and vertebrates. The shared components tend to perform quite fundamental tasks, such as designating which cells will be used to create the minerals; whereas genes controlling more finely tuned aspects that occur later in the biomineralization process – such as the precise alignment and structure of the crystals produced – tend to be uniquely evolved in different lineages. This suggests that Precambrian organisms were employing the same elements, albeit for a different purpose — perhaps to *avoid* the inadvertent precipitation of calcium carbonate from the supersaturated Proterozoic oceans. Certainly, forms of mucus that are involved in inducing mineralization in most metazoan lineages appear to have performed such an anticalcifatory function in the ancestral state. Further, certain proteins that would originally have been involved in maintaining calcium concentrations within cells are homologous to all metazoans, and appear to have been co-opted into biomineralization after the divergence of the metazoan lineages. The *galaxins* are one probable example of a gene being co-opted from a different ancestral purpose into controlling biomineralization, in this case being 'switched' to this purpose in the Triassic scleractinian corals; the role performed appears to be functionally identical to the unrelated pearlin gene in molluscs. Carbonic anhydrase serves a role in mineralization in sponges, as well as metazoans, implying an ancestral role. Far from being a rare trait that evolved a few times and remained stagnant, biomineralization pathways in fact evolved many times and are still evolving rapidly today; even within a single genus it is possible to detect great variation within a single gene family.

The homology of biomineralization pathways is underlined by a remarkable experiment whereby the nacreous layer of a molluscan shell was implanted into a human tooth, and rather than experiencing an immune response, the molluscan nacre was incorporated into

the host bone matrix. This points to the exaptation of an original biomineralization pathway.

The most ancient example of biomineralization, dating back 2 billion years, is the deposition of magnetite, which is observed in some bacteria, as well as the teeth of chitons and the brains of vertebrates; it is possible that this pathway, which performed a magentosensory role in the common ancestor of all bilaterians, was duplicated and modified in the Cambrian to form the basis for calcium-based biomineralization pathways. Iron is stored in close proximity to magnetite-coated chiton teeth, so that the teeth can be renewed as they wear. Not only is there a marked similarity between the magnetite deposition process and enamel deposition in vertebrates, but some vertebrates even have comparable iron storage facilities near their teeth.

Type of mineralization	Examples of organisms
Calcium carbonate (calcite or aragonite)	• foraminifera • coccolithophores • calcareous sponge spicules • corals • Archaeocyatha • bryozoans • brachiopod and mollusc shells • Echinoderms
Silica	• radiolarians • diatoms • most sponge spicules
Apatite (phosphate carbonate)	• enamel (Vertebrate teeth) • Vertebrate bone • conodonts

Potential applications

Most traditional approaches to synthesis of nanoscale materials are energy inefficient, requiring stringent conditions (e.g., high temperature, pressure or pH) and often produce toxic byproducts. Furthermore, the quantities produced are small, and the resultant material is usually irreproducible because of the difficulties in controlling agglomeration. In contrast, materials produced by organisms have properties that usually surpass those of analogous synthetically manufactured materials with similar phase composition. Biological materials are assembled in aqueous environments under mild conditions by using macromolecules. Organic macromolecules collect and transport raw materials and assemble these substrates and into short- and long-range ordered composites with consistency and uniformity. The aim of biomimetics is to mimic the natural way of producing minerals such as apatites. Many man-made crystals require elevated temperatures and strong chemical solutions whereas the organisms have long been able to

lay down elaborate mineral structures at ambient temperatures. Often the mineral phases are not pure but are made as composites which entail an organic part, often protein, which takes part in and controls the biomineralisation. These composites are often not only as hard as the pure mineral but also tougher, as at last, the micro-environment controls biomineralisation.

Astrobiology

It has been suggested that biominerals could be important indicators of extraterrestrial life and thus could play an important role in the search for past or present life on Mars. Furthermore, organic components (biosignatures) that are often associated with biominerals are believed to play crucial roles in both pre-biotic and biotic reactions.

Chapter 4

Bioglass & Bioactive Glass

Bioglass

Bioglass is a commercially available family of bioactive glasses, composed of SiO_2, Na_2O, CaO and P_2O_5 in specific proportions. The proportions differ from the traditional soda-lime glasses in low amount of silica (less than 60 mol.%), high amount of sodium and calcium, and high calcium/phosphorus ratio.

High ratio of calcium to phosphorus promotes formation of apatite crystals; calcium and silica ions can act as crystallization nuclei.

Bioglasses have different formulations. Some bind to soft tissues and bone (e.g. 45S5), some only to bone (e.g. 5S4.3 or Ceravital), some do not form a bond at all and after implantation get encapsulated with nonadhering fibrous tissue, and others are completely resorbed within few weeks. Fine powders resorb faster than bulk materials. A thin layer of apatite forms on the glass-tissue interface, facilitating strong bond to the bone. Some formulations can facilitate growth of osteoblasts through the material. Generally, there are four classes of bioglasses:

- 35-60 mol.% SiO_2, 10-50 mol.% CaO, 5-40 mol.% Na_2O: bioactive, bonds to bone, some formulations bond to soft tissues
- <35 mol.% SiO_2: non glass-forming
- >50 mol.% SiO_2, <10 mol.% CaO, <35 mol.% Na_2O: bioactive, resorption within 10–30 days
- >65 mol.% SiO_2: non-bioactive, nearly inert, gets encapsulated with fibrous tissue

Some CaO can be replaced with MgO and some Na_2O with K_2O without much effect to bone bonding. Some CaO can be replaced with CaF_2 without altering bone bonding, this however modifies the dissolution rate of the glass. B_2O_3 or Al_2O_3 may be added for easier

material processing, however these influence the bone bonding; alumina inhibits bonding and its content is therefore restricted to small levels of about 1-1.5%.

Phosphate-free glasses also exhibit bioactivity. The role of the phosphate is only in aiding of nucleation of apatite on the surface; phosphate ions adsorbed from the organism itself can play the same role.

Bioglasses are divided to two categories:

- **Class A** bioglasses are osteoproductive. They bind with both soft tissues and bone. The HCA layer forms within several hours.
- **Class B** bioglasses are osteoconductive. Bond to soft tissues is not facilitated. The HCA layer takes one to several days to form.

Composition of bioglasses and glass-ceramics (wt.%)

glass	**SiO_2**	**P_2O_5**	**CaO**	**$Ca(PO_3)_2$**	**CaF_2**	**Na_2O**	**others**	**properties**
Bioglass 42S5.6	*42.1*	*2.6*	*29.0*			*26.3*		*mol.%*
Bioglass 46S5.2	*46.1*	*2.6*	*26.9*			*24.4*		*mol.%*; best tissue bonding of Bioglass formulas
Bioglass 49S4.9	*49.1*	*2.6*	*25.3*			*23.8*		*mol.%*
Bioglass 52S4.6	*52.1*	*2.6*	*23.8*			*21.5*		*mol.%*
Bioglass 55S4.3	*55.1*	*2.6*	*22.2*			*20.1*		*mol.%*
Bioglass 60S3.8	*60.1*	*2.6*	*19.6*			*17.7*		*mol.%*; no phosphate film formed
Bioglass 45S5	45	6	24.5			24.5		the original Bioglass formulation; binds with bone and soft tissues
Bioglass 45S5F	45	6	12.25		12.25	24.5		
Bioglass 45S5.4F	45	6	14.7		9.8	24.5		
Bioglass 40S5B5	40	6	24.5			24.5	5 B_2O_3	

Bioglass 52S4.6	52	6	21			21		
Bioglass 55S4.3	55	6	19.5			19.5		
Bioglass 8625	?	?	?			?	Fe_2O_3	highly biocompatible, does not bind with tissues, fibrous encapsulation; absorbs infrared radiation, can be laser-sealed, used for RFID tag encapsulation
Ceravital KGC	46.2		20.2	25.5		4.8	2.9 MgO, 0.4 K_2O	
Ceravital KGS	46		33	16		5		
Ceravital KGy213	38		31	13.5		4	7 Al_2O_3, 6.5 Ta_2O_5/TiO_2	
Ceravital bioactive	40-50	10-15	30-35			5-10	2.5-5 MgO, 0.5-3 K_2O	
Ceravital nonbioactie	30-35	7.5-12	25-30			3.5-7.5	1-2.5 MgO, 0.5-2 K_2O, 5.0-15.0 Al_2O_3, 5-15 Ta_2O_5, 1.0-5.0 TiO_2	
A-W GC (Cerabone)	34.2	16.3	44.9		0.5		4.6 MgO	Oxyfluoroapatite/Wollastonite glass-ceramic; high strength, used to replace parts of bones;

	interfacial apatite forms quickly and the bond is stronger than the bone itself.
Bioverit	bioactive, machinable glass-ceramics containing apatite and phlogophite, used as artificial vertebra

Bioglass 45S5

Bioglass 45S5, one of the most important formulations, is composed of SiO_2, Na_2O, CaO and P_2O_5. Professor Larry Hench developed Bioglass at the University of Florida in the late 1960s. He was challenged by a MASH army officer to develop a material to help regenerate bone, as many Vietnam war veterans suffered badly from bone damage, such that most of them injured in this way lost their limbs.

The composition was originally selected because of being roughly eutectic.

The 45S5 name signifies glass with 45 wt.% of SiO_2 and 5:1 ratio of CaO to P_2O_5. Lower Ca/P ratios do not bond to bone.

The key composition features of Bioglass is that it contains less than 60 mol% SiO_2, high Na_2O and CaO contents, high CaO/P_2O_5 ratio, which makes Bioglass highly reactive to aqueous medium and bioactive.

High bioactivity is the main advantage of Bioglass, while its disadvantages includes mechanical weakness, low fracture resistance due to amorphous 2-dimensional glass network. The bending strength of most Bioglass is in the range of 40–60 MPa, which is not enough for load-bearing application. Its Young's modulus is 30–35 GPa, very close to that of cortical bone, which can be an advantage. Bioglass implants can be used in non-load-bearing applications, for buried implants loaded slightly or compressively. Bioglass can be also used as a bioactive component in composite materials or as powder.

The first successful surgical use of Bioglass 45S5 was in replacement of ossicles in middle ear, as a treatment of conductive hearing loss. The advantage of 45S5 is in no tendency to form fibrous tissue. Other uses are in cones for implantation into the jaw

following a tooth extraction. Composite materials made of Bioglass 45S5 and patient's own bone can be used for bone reconstruction.

Bioglass is comparatively soft in comparison to other glasses. It can be machined, preferably with diamond tools, or ground to powder. Bioglass has to be stored in a dry environment, as it readily absorbs moisture and reacts with it.

Bioglass 45S5 is manufactured by conventional glass-making technology, using platinum or platinum alloy crucibles to avoid contamination. Contaminants would interfere with the chemical reactivity in organism. Annealing is a crucial step in forming bulk parts, due to high thermal expansion of the material.

Heat treatment of Bioglass reduces the volatile alkali metal oxide content and precipitates apatite crystals in the glass matrix. The resulting glass-ceramic material, named **Ceravital**, has higher mechanical strength and lower bioactivity.

Bioglass 8625

Bioglass 8625, also called **Schott 8625**, is a soda-lime glass used for encapsulation of implanted devices. The most common use of Bioglass 8625 is in the housings of RFID transponders for use in human and animal microchip implants. It is patented and manufactured by Schott AG. Bioglass 8625 is also used for some piercings.

Bioglass 8625 does not bond to tissue or bone, it is held in place by fibrous tissue encapsulation. After implantation, a calcium-rich layer forms on the interface between the glass and the tissue. Without additional antimigration coating it is subject to migration in the tissue. The antimigration coating is a material that bonds to both the glass and the tissue. Parylene, usually parylene type C, is often used as such material.

Bioglass 8625 has a significant content of iron, which provides infrared light absorption and allows sealing by a light source, e.g. a Nd:YAG laser or a mercury-vapor lamp. The content of Fe_2O_3 yields high absorption with maximum at 1100 nm, and gives the glass a green tint. The use of infrared radiation instead of flame or contact heating helps preventing contamination of the device.

After implantation, the glass reacts with the environment in two phases, in the span of about two weeks. In the first phase, alkali metal ions are leached from the glass and replaced with hydrogen ions; small amount of calcium ions also diffuses from the material. During the second phase, the Si-O-Si bonds in the silica matrix undergo hydrolysis, yielding a gel-like surface layer rich on Si-O-H groups. A calcium phosphate-rich passivation layer gradually forms over the surface of the glass, preventing further leaching.

Bioglass 8625 is extensively tested in a series of studies since the 1970s. It is used in microchips for tracking of many kinds of animals, and recently in some human implants.

The U.S. Food and Drug Administration (FDA) approved use of Bioglass 8625 in humans in 1994.

Bioactive Glass

Bioactive glasses are a group of surface reactive glass-ceramic biomaterials and include the original bioactive glass, Bioglass. The biocompatibility of these glasses has led them to be investigated extensively for use as implant materials in the human body to repair and replace diseased or damaged bone.

History

Larry Hench and colleagues at the University of Florida first developed these materials in the late 1960s and they have been further developed by his research team at the Imperial College London and other researchers worldwide.

Compositions

There have been many variations on the original composition which was Food and Drug Administration (FDA) approved and termed Bioglass. This composition is known as 45S5. Other compositions are in the list below.

- **45S5:** 46.1 mol% SiO_2, 26.9 mol% CaO, 24.4 mol% Na_2O and 2.5 mol% P_2O_5. Bioglass
- **58S:** 60 mol% SiO_2, 36 mol% CaO and 4 mol% P_2O_5.
- **S70C30:** 70 mol% SiO_2, 30 mol% CaO.

Mechanism of bioactivity

The underlying mechanisms that enable bioactive glasses to act as materials for bone repair have been investigated since the first work of Hench et al. at the University of Florida. Early attention was paid to changes in the bioactive glass surface. Five inorganic reaction stages are commonly thought to occur when a bioactive glass is immersed in a physiological environment: 1) Ion exchange in which modifier cations (mostly Na^+) in the glass exchange with hydronium ions in the external solution, 2) Hydrolysis in which Si-O-Si bridges are broken, forming Si-OH silanol groups, and the glass network is disrupted, 3) Condensation of silanols in which the disrupted glass network changes its morphology to form a gel-like surface layer, depleted in sodium and calcium ions 4) Precipitation in which an amorphous calcium phosphate layer is deposited on the gel, and 5) Mineralization in which the calcium phosphate layer gradually transforms into crystalline hydroxyapatite, that mimics the mineral phase naturally contained with vertebrate bones. Later, it was discovered that the morphology of the gel surface layer was a key component in determining the bioactive response. This was supported by studies on bioactive glasses derived from sol-gel processing. Such glasses could contain significantly higher concentrations of SiO_2 than traditional melt-derived bioactive glasses

and still maintain bioactivity (i.e., the ability to form a mineralized hydroxyapatite layer on the surface). The inherent porosity of the sol-gel-derived material was cited as a possible explanation for why bioactivity was retained, and often enhanced with respect to the melt-derived glass.

Subsequent advances in DNA microarray technology enabled an entirely new perspective on the mechanisms of bioactivity in bioactive glasses. Previously, it was known that a complex interplay existed between bioactive glasses and the molecular biology of the implant host, but the available tools did not provide a sufficient quantity of information to develop a holistic picture. Using DNA microarrays, researchers are now able to identify entire classes of genes that are regulated by the dissolution products of bioactive glasses, resulting in the so-called "genetic theory" of bioactive glasses. The first microarray studies on bioactive glasses demonstrated that genes associated with osteoblast growth and differentiation, maintenance of extracellular matrix, and promotion of cell-cell and cell-matrix adhesion were up-regulated by conditioned cell culture media containing the dissolution products of bioactive glass.

Structure

Solid state NMR spectroscopy has been very useful in elucidating the structure of amorphous solids. Bioactive glasses have been studied by ^{29}Si and ^{31}P solid state MAS NMR spectroscopy. The chemical shift from MAS NMR is indicative of the type of chemical species present in the glass. The ^{29}Si MAS NMR spectroscopy showed that Bioglass 45S5 was a Q2 type-structure with a small amount of Q3 and Q1; i.e., silicate chains with a few crosslinks. The ^{31}P MAS NMR revealed Q0 species; i.e., PO_4^{3-}; subsequent MAS NMR and IR-Raman spectroscopy measurements have highlighted a small percentage of phosphate crosslinked to the silicate network, through P-O-Si bonds.

Medical applications

Bioactive glasses have many applications but these are primarily in the areas of bone repair and bone regeneration via tissue engineering:

- Synthetic bone graft materials for general orthopaedic, craniofacial (bones of the skull and face), maxillofacial and periodontal (the bone structure that supports teeth) repair. These are available to surgeons in a particulate form
- Cochlear implants
- Bone tissue engineering scaffolds. These are being investigated in many forms, in particular as porous (contains pores into which cells can grow and fluids can travel) 3-dimensional scaffolds
- Treating dentine hypersensitivity and promoting enamel remineralization

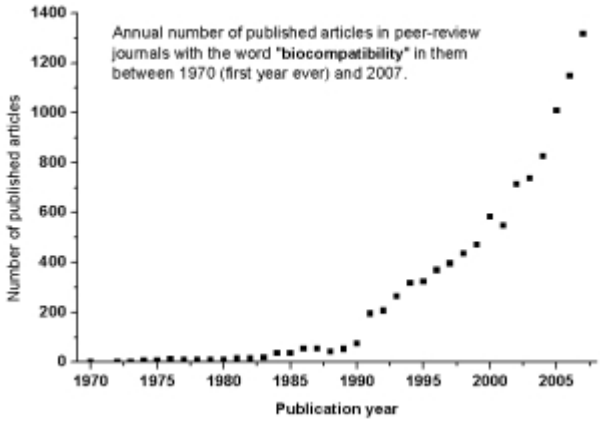
Chapter 5

Biocompatibility & Biopolymer

Biocompatibility

Biocompatibility is related to the behavior of biomaterials in various contexts. The term may refer to specific properties of a material without specifying where or how the material is used (for example, that it elicits little or no immune response in a given organism, or is able to integrate with a particular cell type or tissue), or to more empirical clinical success of a whole device in which the material or materials feature. The ambiguity of the term reflects the ongoing development of insights into how biomaterials interact with the human body and eventually how those interactions determine the clinical success of a medical device (such as pacemaker, hip replacement or stent). Modern medical devices and prostheses are often made of more than one material so it might not always be sufficient to talk about the biocompatibility of a specific material.

Indeed, since the immune response and repair functions in the body are so complicated it is not adequate to describe the biocompatibility of a single material in relation to a single cell type or tissue. Sometimes one hears of biocompatibility testing that is a large battery of in vitro test that is used in accordance with ISO 10993 (or other similar standards) to determine if a certain material (or rather biomedical product) is biocompatible. These tests do not determine the biocompatibility of a material, but they constitute an important step towards the animal testing and finally clinical trials that will determine the biocompatibility of the material in a given application, and thus medical devices such as implants or drug delivery devices.



The word *biocompatibility* seems have been mentioned for the first time in peer-review journals and meetings in 1970 by RJ Hegyeli (Amer Chem Soc Annual Meeting abstract) and CA Homsy et al. (J Macromol Sci Chem A4:3,615, 1970). It took almost two decades before it began to be commonly used in scientific literature.

Recently Williams (again) has been trying to re-evaluate the current knowledge status regarding what factors determine clinical success. Doing so notes that an implant may not always have to be positively bioactive but it must not do any harm (either locally or systematically) (Williams, 2008).

Five definitions of biocompatibility

1. "The ability of a material to perform with an appropriate host response in a specific application", Williams' definition.
2. "The quality of not having toxic or injurious effects on biological systems".
3. "Comparison of the tissue response produced through the close association of the implanted candidate material to its implant site within the host animal to that tissue response recognised and established as suitable with control materials" - ASTM
4. "Refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy".
5. "Biocompatibility is the capability of a prosthesis implanted in the body to exist in harmony with tissue without causing deleterious changes".

Comments on the above five definitions

1. This is also referred to as the Williams' definition. It was defined in the European Society for Biomaterials Consensus Conference I and can more easily be found in "The Williams dictionary of Biomaterials".
2. The Dorland Medical definition not recommended according to Williams Dictionary since it only defines biocompatibility as the absence of host response

and does not include any desired or positive interactions between the host tissue and the biomaterials.
3. The ASTM is not recommended according to Williams Dictionary since it only refers to local tissue responses, in animal models.
4. The fourth is an expansion or rather more precise version of the first definition noting both that low toxicity and the one should be aware of the different demands between various medical applications of the same material.

All these definitions deal with materials and not with devices. This is a drawback since many medical devices are made of more than one material. Much of the pre-clinical testing of the materials is not conducted on the devices but rather the material itself. But at some stage the testing will have to include the device since the shape, geometry and surface treatment etc. of the device will also affect its biocompatibility.

Biocompatible

In the literature, one quite often stumbles upon the adjective form: biocompatible. However, according to Williams' definition, this does not make any sense because biocompatibility is contextual, i.e. much more than just the material itself will determine the clinical outcome of the medical device of which the biomaterial is a part. This also points to one of the weaknesses with the current definition because a medical device usually is made of more than one material.

Suggested sub-definitions

The scope of the first definition is so wide that D Williams tried to find suitable subgroups of applications in order to be able to make more narrow definitions. In the MDT article from 2003 the chosen supgroups and their definitions were:

Biocompatibility of long-term implanted devices
: The biocompatibility of a long-term implantable medical device refers to the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host

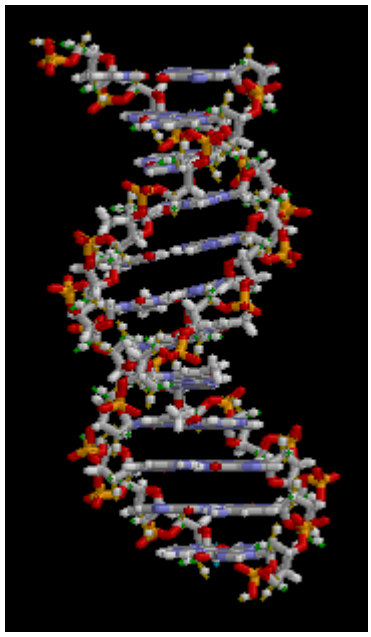
Biocompatibility of short-term implantable devices
: The biocompatibility of a medical device that is intentionally placed within the cardiovascular system for transient diagnostic or therapeutic purposes refers to the ability of the device to carry out its intended function within flowing blood, with minimal interaction between device and blood that adversely affects device performance, and without inducing uncontrolled activation of cellular or plasma protein cascades.

Biocompatibility of tissue-engineering products
: The biocompatibility of a scaffold or matrix for a tissue-engineering products refers to the ability to perform as a substrate that will support the appropriate cellular activity, including the facilitation of molecular and mechanical signalling systems, in order to optimise tissue regeneration, without eliciting any undesirable

effects in those cells, or inducing any undesirable local or systemic responses in the eventual host.

In these definitions the notion of biocompatibility is related to devices rather than to materials as compared to top three definitions. There was a consensus conference on biomaterial definitions in Sorrento September 15–16, 2005.

Biopolymer



In this microstructure of of DNA is a pair of **biopolymers**, Polynucleotides, forming the double helix found in DNA

Biopolymers are polymers produced by living organisms. Since they are polymers, Biopolymers contain monomeric units that are covalently bonded to form larger structures. There are three main classes of biopolymers based on the differing monomeric units used and the structure of the biopolymer formed. Polynucleotides long polymers which are composed of 13 or more nucleotide monomers, Polypeptides short polymers of amino acids, and Polysaccharides which are often linear bonded polymeric carbohydrate structures.

Cellulose is the most common organic compound and biopolymer on Earth. About 33 percent of all plant matter is cellulose. The cellulose content of cotton is 90 percent and that of wood is 50 percent.

Biopolymers versus polymers

A major but defining difference between polymers and biopolymers can be found in their structures. Polymers, including **biopolymers**, are made of repetitive units called

monomers. Biopolymers often have a well defined structure, though this is not a defining characteristic (example:ligno-cellulose): The exact chemical composition and the sequence in which these units are arranged is called the primary structure, in the case of proteins. Many biopolymers spontaneously fold into characteristic compact shapes, which determine their biological functions and depend in a complicated way on their primary structures. Structural biology is the study of the structural properties of the biopolymers. In contrast most **synthetic polymers** have much simpler and more random (or stochastic) structures. This fact leads to a molecular mass distribution that is missing in biopolymers. In fact, as their synthesis is controlled by a template directed process in most in vivo systems all biopolymers of a type (say one specific protein) are all alike: they all contain the similar sequences and numbers of monomers and thus all have the same mass. This phenomenon is called monodispersity in contrast to the polydispersity encountered in synthetic polymers. As a result biopolymers have a polydispersity index of 1.

Conventions and nomenclature

Polypeptides

The convention for a polypeptide is to list its constituent amino acid residues as they occur from the amino terminus to the carboxylic acid terminus. The amino acid residues are always joined by peptide bonds. Protein, though used colloquially to refer to any polypeptide, refers to larger or fully functional forms and can consist of several polypeptide chains as well as single chains. Proteins can also be modified to include non-peptide components, such as saccharide chains and lipids.

Nucleic acids

The convention for a nucleic acid sequence is to list the nucleotides as they occur from the 5' end to the 3' end of the polymer chain, where 5' and 3' refer to the numbering of carbons around the ribose ring which participate in forming the phosphate diester linkages of the chain. Such a sequence is called the primary structure of the biopolymer.

Sugars

Sugar-based biopolymers are often difficult with regards to convention. Sugar polymers can be linear or branched are typically joined with glycosidic bonds. However, the exact placement of the linkage can vary and the orientation of the linking functional groups is also important, resulting in α- and β-glycosidic bonds with numbering definitive of the linking carbons' location in the ring. In addition, many saccharide units can undergo various chemical modification, such as amination, and can even form parts of other molecules, such as glycoproteins.

Structural characterization

There are a number of biophysical techniques for determining sequence information. Protein sequence can be determined by Edman degradation, in which the N-terminal residues are hydrolyzed from the chain one at a time, derivatized, and then identified. Mass spectrometer techniques can also be used. Nucleic acid sequence can be determined using gel electrophoresis and capillary electrophoresis. Lastly, mechanical properties of these biopolymers can often be measured using optical tweezers or atomic force microscopy. Dual polarisation interferometry can be used to measure the conformational changes or self assembly of these materials when stimulated by pH, temperature, ionic strength or other binding partners.

Biopolymers as materials

Some biopolymers- such as polylactic acid (PLA), naturally occurring zein, and poly-3-hydroxybutyrate can be used as plastics, replacing the need for polystyrene or polyethylene based plastics.

Some plastics are now referred to as being 'degradable', 'oxy-degradable' or 'UV-degradable'. This means that they break down when exposed to light or air, but these plastics are still primarily (as much as 98 per cent) oil-based and are not currently certified as 'biodegradable' under the European Union directive on Packaging and Packaging Waste (94/62/EC). Biopolymers, however, will break down and some are suitable for domestic composting.

Biopolymers (also called renewable polymers) are produced from biomass for use in the packaging industry. Biomass comes from crops such as sugar beet, potatoes or wheat: when used to produce biopolymers, these are classified as non food crops. These can be converted in the following pathways:

Sugar beet > Glyconic acid > Polyglonic acid

Starch > (fermentation) > Lactic acid > Polylactic acid (PLA)

Biomass > (fermentation) > Bioethanol > Ethene > Polyethylene

Many types of packaging can be made from biopolymers: food trays, blown starch pellets for shipping fragile goods, thin films for wrapping.

Environmental Impacts of Biopolymers

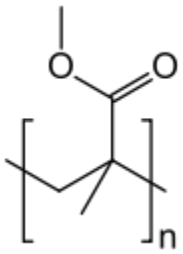
Biopolymers can be sustainable, carbon neutral and are always renewable, because they are made from plant materials which can be grown year on year indefinitely. These plant materials come from agricultural non food crops. Therefore, the use of biopolymers would create a sustainable industry. In contrast, the feedstocks for polymers derived from petrochemicals will eventually run out. In addition, biopolymers have the potential to cut

carbon emissions and reduce CO_2 quantities in the atmosphere: this is because the CO_2 released when they degrade can be reabsorbed by crops grown to replace them: this makes them close to carbon neutral.

Biopolymers are biodegradable, and some are also compostable. Some biopolymers are biodegradable: they are broken down into CO_2 and water by microorganisms. Some of these biodegradable biopolymers are compostable: they can be put into an industrial composting process and will break down by 90% within six months. Biopolymers that do this can be marked with a 'compostable' symbol, under European Standard EN 13432 (2000). Packaging marked with this symbol can be put into industrial composting processes and will break down within six months or less. An example of a compostable polymer is PLA film under 20µm thick: films which are thicker than that do not qualify as compostable, even though they are biodegradable. In Europe there is a home composting standard and associated logo that enables consumers to identify and dispose of packaging in their compost heap.

Chapter 6

Poly(Methyl Methacrylate)

Poly(methyl methacrylate)	
	
IUPAC name Poly(methyl 2-methylpropenoate)	
Other names Poly(methyl methacrylate) (PMMA) methyl methacrylate resin	
Identifiers	
CAS number	9011-14-7
Properties	
Molecular formula	$(C_5O_2H_8)_n$
Molar mass	varies
Density	1.18 g/cm^3
Melting point	160 °C (320 °F)
Boiling point	200.0 °C (392.0 °F)
Refractive index (n_D)	1.4914 at 587.6 nm.

Poly(methyl methacrylate) (**PMMA**) is a transparent thermoplastic, often used as a light or shatter-resistant alternative to glass. It is sometimes called **acrylic glass**. Chemically, it is the synthetic polymer of methyl methacrylate. The material was developed in 1928 in various laboratories, and was first brought to market in 1933 by Rohm and Haas Company, under the trademark **Plexiglas**. It has since been sold under many different names including Lucite and Perspex.

PMMA is an economical alternative to polycarbonate (PC) when extreme strength is not necessary. Additionally, PMMA does not contain the potentially harmful bisphenol-A subunits found in polycarbonate. It is often preferred because of its moderate properties, easy handling and processing, and low cost, but behaves in a brittle manner when loaded, especially under an impact force, and is more prone to scratching compared to glass.

History

The first acrylic acid was created in 1843. Methacrylic acid, derived from acrylic acid, was formulated in 1865. The reaction between methacrylic acid and methanol results in the ester methyl methacrylate. The German chemists Fittig and Paul discovered in 1877 the polymerization process that turns methyl methacrylate into polymethyl methacrylate. In 1933 the German chemist Otto Röhm patented and registered the brand name PLEXIGLAS. In 1936 the first commercially viable production of acrylic safety glass began. During World War II acrylic glass was used for submarine periscopes, windshields, canopies, and gun turrets for airplanes.

Names

PMMA has been sold under a variety of brand names and generic names. It is often generically called acrylic glass, although it is chemically unrelated to glass. It is sometimes called simply **acrylic**, although *acrylic* can also refer to other polymers or copolymers containing polyacrylonitrile. Other notable trade names include:

- Plexiglas
- Altuglas (Arkema)
- Lucite
- Perspex
- Perclax
- Optix (Plaskolite)

Synthesis

PMMA is routinely produced by emulsion polymerization, solution polymerization and bulk polymerization. Generally radical initiation is used (including living polymerization methods), but anionic polymerization of PMMA can also be performed. To produce 1 kg (2.2 lb) of PMMA, about 2 kg (4.4 lb) of petroleum is needed.

Processing

The glass transition temperature of PMMA ranges from 85 to 165 °C (185 to 329 °F); the range is so wide because of the vast number of commercial compositions. The forming temperature starts at the glass transition temperature and goes up from there. All common molding processes may be used, including injection molding, compression molding and extrusion. The highest quality PMMA sheets are produced by cell casting, but in this case, the polymerization and molding steps occur concurrently. The strength of the

material is higher than molding grades owing to its extremely high molecular mass. Rubber toughening has been used to increase the strength of PMMA owing to its brittle behavior in response to applied loads.

Handling, cutting, and joining

PMMA can be joined using cyanoacrylate cement, more commonly known as superglue, with heat (melting), or by using solvents such as di- or trichloromethane to dissolve the plastic at the joint which then fuses and sets, forming an almost invisible weld. Scratches may easily be removed by polishing or by heating the surface of the material.

Laser cutting may be used to form intricate designs from PMMA sheets. PMMA vaporizes to gaseous compounds (including its monomers) upon laser cutting, so a very clean cut is made, and cutting is performed very easily. However, the pulsed lasercutting introduces a high internal stresses along the cut edge, which when exposed to solvents produces undesirable "stress-crazing" at the cut edge and several millimetres deep. Even ammonium-based glass-cleaner and almost everything short of soap-and-water produces similar undesirable crazing, sometimes over the entire surface of the cut parts, at great distances from the stressed edge. Annealing the PMMA sheet/parts is therefore an obligatory post-processing step when intending to chemically bond lasercut parts together. This involves heating the parts in an air circulating oven from room temperature up to 90 degrees C (at a rate of no more than 18 degrees per hour) down to room temperature (at a rate of no more than 12 degrees per hour). Temperature should be maintained as follows: One hour for 3mm thickness, two hours for up to 6mm thickness, four hours for up to 12mm thickness, and six hours for up to 20mm thickness. A rapid annealing cycle is reliable for thin sheets and involves placing them in a pre-heated oven to 80 degrees C for one hour, then removing parts from oven and allowing to cool to room temperature. This added time component should be factored into the whole fabrication process, and the alternative Zero-rake sawcutting technique may provide better cost-effectiveness, unless complex non-straight line edges are required. In this respect PMMA has an advantage over competing polymers such as polystyrene and polycarbonate, which require higher laser powers and give more messy and charred laser cuts.

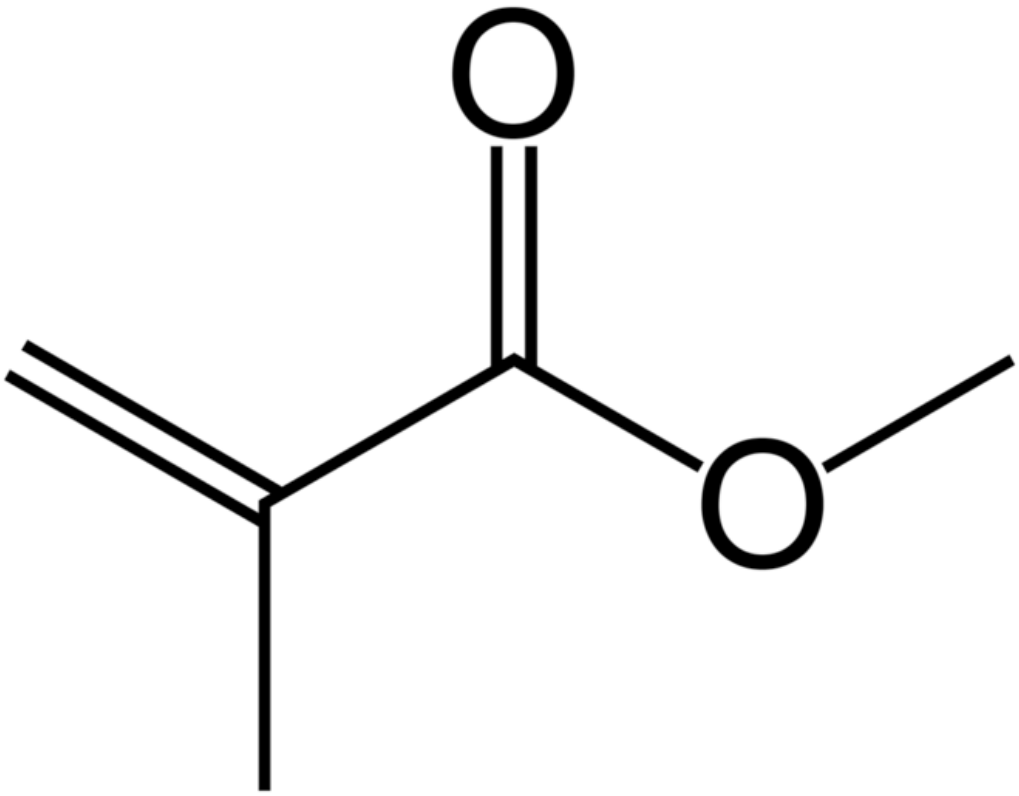
In the majority of applications, it will not shatter. Rather, it breaks into large dull pieces. Since PMMA is softer and more easily scratched than glass, scratch-resistant coatings are often added to PMMA sheets to protect it (as well as possible other functions).

Acrylate resin casting

Illustrative and secure bromine chemical sample used for teaching. The sample vial of corrosive and poisonous liquid has been cast into an acrylic plastic cube

Methyl methacrylate "synthetic resin" for casting (simply the bulk liquid chemical) may be used in conjunction with a polymerization catalyst such as MEKP, to produce hardened transparent PMMA in any shape, from a mold. Objects like insects or coins, or even dangerous chemicals in breakable quartz ampules, may be embedded in such "cast" blocks, for display and safe handling.

Properties



Skeletal structure of methyl methacrylate, the monomer that makes up PMMA

PMMA is a strong and lightweight material. It has a density of 1.17–1.20 g/cm^3, which is less than half that of glass. It also has good impact strength, higher than both glass and polystyrene; however, PMMA's impact strength is still significantly lower than polycarbonate and some engineered polymers. PMMA ignites at 460 °C (860 °F) and burns, forming carbon dioxide, water, carbon monoxide and low molecular weight compounds, including formaldehyde.

PMMA transmits up to 92% of visible light (3 mm thickness), and gives a reflection of about 4% from each of its surfaces on account of its refractive index (1.4914 at 587.6 nm). It filters ultraviolet (UV) light at wavelengths below about 300 nm (similar to ordinary window glass). Some manufacturers add coatings or additives to PMMA to improve absorption in the 300–400 nm range. PMMA passes infrared light of up to 2800 nm and blocks IR of longer wavelengths up to 25000 nm. Colored PMMA varieities allow specific IR wavelengths to pass while blocking visible light (for remote control or heat sensor applications, for example).

PMMA swells and dissolves in many organic solvents; it also has poor resistance to many other chemicals on account of its easily hydrolyzed ester groups. Nevertheless, its environmental stability is superior to most other plastics such as polystyrene and polyethylene, and PMMA is therefore often the material of choice for outdoor applications.

PMMA as maximum water absorption ratio of 0.3–0.4% by weight. Tensile strength decreases with increased water absorption. Its coefficient of thermal expansion is relatively high as $(5–10)\times10^{-5}$ /K.

Modification of properties

Pure poly(methyl methacrylate) homopolymer is rarely sold as an end product, since it is not optimized for most applications. Rather, modified formulations with varying amounts of other comonomers, additives, and fillers are created for uses where specific properties are required. For example,

- A small amount of acrylate comonomers are routinely used in PMMA grades destined for heat processing, since this stabilizes the polymer to depolymerization ("unzipping") during processing.
- Comonomers such as butyl acrylate are often added to improve impact strength.
- Comonomers such as methacrylic acid can be added to increase the glass transition temperature of the polymer for higher temperature use such as in lighting applications.
- Plasticizers may be added to improve processing properties, lower the glass transition temperature, or improve impact properties.
- Dyes may be added to give color for decorative applications, or to protect against (or filter) UV light.
- Fillers may be added to improve cost-effectiveness.

Poly(methyl acrylate)

The polymer of methyl acrylate, PMA or poly(methyl acrylate), is similar to poly(methyl methacrylate), except for the lack of methyl groups on the backbone carbon chain. PMA is a soft white rubbery material that is softer than PMMA because its long polymer chains are thinner and smoother and can more easily slide past each other.

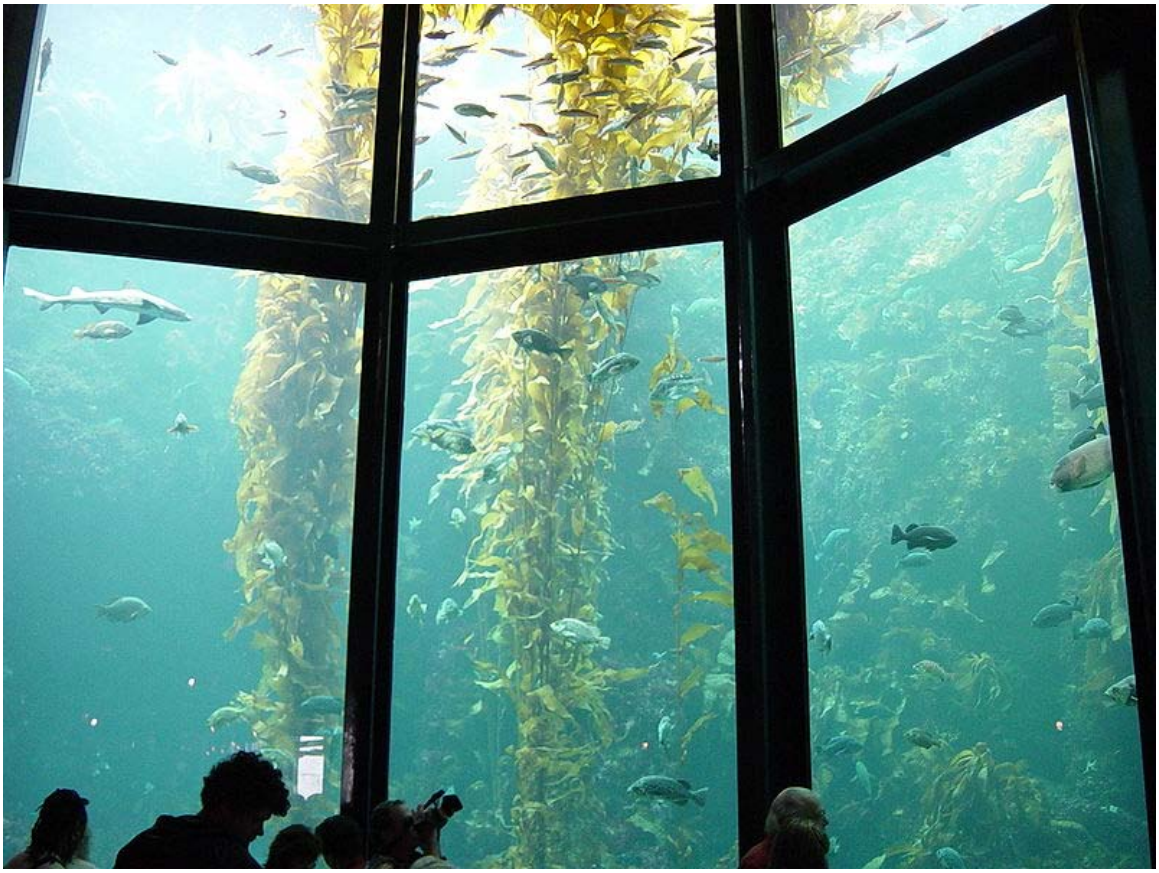
Uses

PMMA is a versatile material and has been used in a wide range of fields and applications.

Transparent glass substitute

Close-up of pressure sphere of Bathyscaphe Trieste, with single conical window of PMMA (Plexiglas) set into sphere hull. The very small black circle (smaller than the man's head) is the inner side of the plastic "window," and is only a few inches in diameter. The larger circular clear black area represents the larger outer-side of the thick one-piece plastic cone "window."

B-17G Plexiglass bombardier nose compartment. Note the pilot cockpit above and behind



10 meter deep Monterey Bay Aquarium tank has acrylic windows up to 13 inches thick to withstand the water pressure

- PMMA acrylic glass is commonly used for constructing residential and commercial aquariums. Designers started building big aquariums when poly(methyl methacrylate) could be used. The spectacular size of both flat panels and tunnels in aquariums such as Monterey Bay, Tokyo Sea Life Park, Osaka, Nagoya, Georgia and Dubai Aquariums were made possible with the introduction of acrylic.
- PMMA was used for the window of the bathyscaphe Trieste for all of its dives, including the record-setting dive to the bottom of the Challenger deep in the Mariana Trench in 1960. The conical window set into the 12.7 cm thick wall of the sphere (small end inward) was required to withstand ~ 1100 atmospheres of pressure at the bottom.
- Acrylic is used for viewing ports and even complete pressure hulls of submersibles, such as the Alicia submarine's viewing sphere.
- PMMA is used in the lenses of exterior lights of automobiles.
- The spectator protection in ice hockey rinks is made from PMMA.
- It is used in motorcycle helmet visors
- Historically, PMMA was an important improvement in the design of aircraft windows, making possible such iconic designs as the bombadier's transparent nose compartment in the Boeing B-17 Flying Fortress.

- Polycast acrylic sheet is the most widely used material in aircraft transparencies (windows). In applications where the aircraft is pressurized, stretched acrylic is used. Only in the most advanced modern fighter jets, such as the F-22 Raptor, has traditional acrylic been replaced by polycarbonate (Lexan).
- Police vehicles for riot control often have the regular glass replaced with acrylic to protect the occupants from thrown objects.
- In some Motor racing championships the glass windows in the cars are replaced with acrylic to prevent glass shattering on the driver and track during a crash. They also help to save some weight making the car lighter and faster.
- Acrylic is an important material in the making of certain lighthouse lenses.
- Acrylic is also used to make infra-red receptors tamper-proof. Infra red radiation can travel through acrylic material, but its use prevents physical damage to the sensor.

Daylight redirection

- Laser cut acrylic panels have been used to redirect sunlight into a light pipe and, from there, to spread it into a room. Their developers Veronica Garcia Hansen, Ken Yeang, and Ian Edmonds were awarded the Far East Economic Review Innovation Award in bronze for this technology in 2003.
- Attenuation being quite strong for distances over one meter (more than 90% intensity loss for a 3000 K source), acrylic broadband light guides are then dedicated mostly to decorative uses.
- Pairs of acrylic sheets with a layer of microreplicated prisms between the sheets can have reflective and refractive properties that let them redirect part of incoming sunlight in dependence on its angle of incidence. Such panels act as miniature light shelves. Such panels have been commercialized for purposes of daylighting, to be used as a window or a canopy such that sunlight descending from the sky is directed to the ceiling or into the room rather than to the floor. This can lead to a higher illumination of the back part of a room, in particular when combined with a white ceiling, while having a slight impact on the view to the outside compared to normal glazing.

Medical technologies and implants

- PMMA has a good degree of compatibility with human tissue, and can be used for replacement intraocular lenses in the eye when the original lens has been removed in the treatment of cataracts. This compatibility was discovered in WWII RAF pilots, whose eyes had been riddled with PMMA splinters coming from the side windows of their Supermarine Spitfire fighters - the plastic scarcely caused any rejection, compared to glass splinters coming from aircraft such as the Hawker Hurricane. Historically, hard contact lenses were frequently made of this material. Soft contact lenses are often made of a related polymer, where acrylate monomers containing one or more hydroxyl groups make them hydrophilic.
- In orthopedic surgery, PMMA bone cement is used to affix implants and to remodel lost bone. It is supplied as a powder with liquid methyl methacrylate

(MMA). When mixed these yield a dough-like cement that gradually hardens. Surgeons can judge the curing of the PMMA bone cement by pressing their thumb on it. Although PMMA is biologically compatible, MMA is considered to be an irritant and a possible carcinogen. PMMA has also been linked to cardiopulmonary events in the operating room due to hypotension. Bone cement acts like a grout and not so much like a glue in arthroplasty. Although sticky, it does not bond to either the bone or the implant, it primarily fills the spaces between the prosthesis and the bone preventing motion. A big disadvantage to this bone cement is that it heats to quite a high temperature while setting, potentially 82.5 deg C and because of this, thermal necrosis of neighboring tissue can potentially result. A careful balance of initiators and monomers is needed to reduce the rate of polymerisation, and thus the heat generated. A major consideration when using PMMA cement is the effect of stress shielding. Since PMMA has a Young's modulus greater than that of natural bone, the stresses are loaded into the cement and so the bone no longer receives the mechanical signals to continue bone remodeling and so resorption will occur.

- Dentures are often made of PMMA, and can be color-matched to the patient's teeth & gum tissue. PMMA is also used in the production of ocular prostheses.
- In cosmetic surgery, tiny PMMA microspheres suspended in some biological fluid are injected under the skin to reduce wrinkles or scars permanently.
- A large majority of white Dental filling materials (i.e. composites) have PMMA as their main organic component.
- Emerging biotechnology and Biomedical research uses PMMA to create microfluidic lab-on-a-chip devices, which require 100 micrometre-wide geometries for routing liquids. These small geometries are amenable to using PMMA in a biochip fabrication process and offers moderate biocompatibility.
- Bioprocess chromatography columns use cast acrylic tubes as an alternative to glass and stainless steel. These are pressure rated and satisfy stringent requirements of materials for biocompatibility, toxicity and extractables.

Artistic and aesthetic uses

- Acrylic paint essentially consists of PMMA suspended in water; however since PMMA is hydrophobic, a substance with both hydrophobic and hydrophilic groups needs to be added to facilitate the suspension.
- Modern furniture makers, especially in the 1960s and 1970s, seeking to give their products a space age aesthetic, incorporated Lucite and other PMMA products into their designs, especially office chairs. Many other products (for example, guitars) are sometimes made with acrylic glass to make the commonly opaque objects translucent.
- Perspex has been used as a surface to paint on, for example by Salvador Dalí.
- Diasec is a process which uses acrylic glass as a substitute for normal glass in picture framing. This is done for its relatively low cost, light weight, shatter-resistance, aesthetics and because it can be ordered in larger sizes than standard picture framing glass.

- From approximately the 1960s onward, sculptors and glass artists such as Leroy Lamis began using acrylics, especially taking advantage of the material's flexibility, light weight, cost and its capacity to refract and filter light.
- In the 1950s and 1960s, Lucite was an extremely popular material for jewelry, with several companies specialized in creating high-quality pieces from this material. Lucite beads and ornaments are still sold by jewelry suppliers.

Other uses

High heel shoes made of Lucite

An electric bass guitar with its body made out of perspex

- Sheets of PMMA are commonly used in the sign industry to make flat cut out letters in thicknesses typically varying from 3 to 25 millimeters (0.1 to 1.0 in). These letters may be used alone to represent a company's name and/or logo, or they may be a component of channel letters which are neon or LED illuminated. Acrylic's attractiveness, durability and resistance to warping make it an ideal interior and exterior sign material. Acrylic is also used extensively throughout the sign industry as a component of wall signs where it may be a backplate, painted on the surface or the backside, a faceplate with additional raised lettering or even photographic images printed directly to it, or a spacer to separate sign components. One of the most popular sheets is a non-glare, translucent which is sold in 1.6 millimeters (0.06 in) or 3 millimeters (0.12 in) in thicknesses.
- PMMA was used in laserdisc optical media. (CDs and DVDs use both acrylic and polycarbonate for higher impact resistance.)
- It is used as a light guide for the backlights in TFT-LCDs.
- Plastic optical fiber used for short distance communication is made from PMMA, and perfluorinated PMMA, clad with fluorinated PMMA, in situations where its flexibility and cheaper installation costs outweigh its poor heat tolerance and higher attenuation over glass fiber.
- PMMA, in a purified form, is used as the matrix in laser dye-doped solid-state gain media for solid state dye lasers.
- In semiconductor research and industry, PMMA aids as a resist in the electron beam lithography process. A solution consisting of the polymer in a solvent is used to spin coat silicon and other semiconducting and semi-insulating wafers with a thin film. Patterns on this can be made by an electron beam (using an

electron microscope), deep UV light (shorter wavelength than the standard photolithography process), or X-rays. Exposure to these creates chain scission or (de-cross-linking) within the PMMA, allowing for the selective removal of exposed areas by a chemical developer, making it a positive photoresist. PMMA's advantage is that it allows for extremely high resolution (nanoscale) patterns to be made. It is an invaluable tool in nanotechnology. Smooth (Ref: M. Lapczyna, M. Stuke, Appl. Phys. A 66, 473–475 (1998), "Direct fabrication of micro mesas by VUV laser ablation of polymers:PMMA (polymethylmethacrylate)"), PMMA surface can be easily nanostructured by treatment in oxygen radio-frequency plasma and nanostructured PMMA surface can be easily smoothed by vacuum ultraviolet (VUV) irradiation.

- PMMA is used as a shield to stop beta radiation emitted from radioisotopes.
- Small strips of PMMA are used as dosimeter devices during the Gamma Irradiation process. The optical density of PMMA changes as the Gamma dose increases and can be measured with a spectrophotometer.
- Recently a blacklight-reactive tattoo ink using PMMA microcapsules was developed. This ink is reportedly safe for use, and claims to be Food and Drug Administration (FDA) approved for use on wildlife that may enter the food supply.
- PMMA can be used as a dispersant for ceramic powders to stabilize colloidal suspensions in non-aqueous mediums.
- PMMA has also been used extensively as a hybrid rocket fuel.
- In the 1960s, luthier Dan Armstrong developed a line of electric guitars and basses whose bodies were made completely of acrylic. These instruments were marketed under the Ampeg brand. Ibanez and B.C. Rich have also made acrylic guitars.
- Ludwig-Musser makes a line of acrylic drums called Vistalites, well known as being used by Led Zeppelin drummer John Bonham.
- Artificial fingernails are made of acrylic.
- Some modern briar, and occasionally meerschaum, tobacco pipes sport stems made of Lucite, although the vast majority of stems for such pipes are still made with the traditional vulcanized rubber.

Chapter 7

Nickel Titanium

Nickel titanium, also known as **nitinol**, is a metal alloy of nickel and titanium, where the two elements are present in roughly equal atomic percentages.

Nitinol alloys exhibit two closely related and unique properties: shape memory and superelasticity (also called pseudoelasticity). Shape memory refers to the ability of nitinol to undergo deformation at one temperature, then recover its original, undeformed shape upon heating above its "transformation temperature". Superelasticity occurs at a narrow temperature range just above its transformation temperature; in this case, no heating is necessary to cause the undeformed shape to recover, and the material exhibits enormous elasticity, some 10-30 times that of ordinary metal.

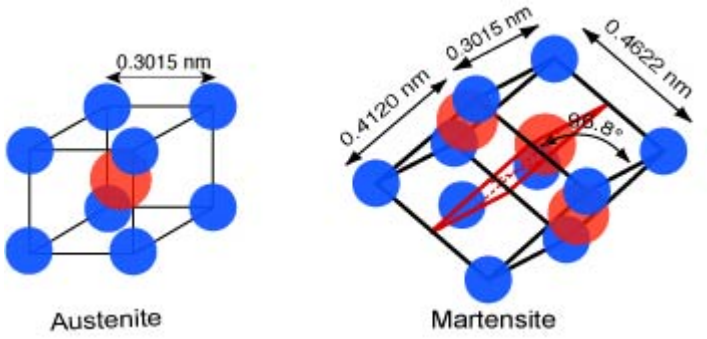
History

The term nitinol is derived from its composition and its place of discovery: (Nickel Titanium Naval Ordnance Laboratory). William J. Buehler along with Frederick Wang, discovered its properties during research at the Naval Ordnance Laboratory in 1962.

While the potential applications for nitinol were realized immediately, practical efforts to commercialize the alloy didn't take place until a decade later. This delay was largely because of the extraordinary difficulty of melting, processing and machining the alloy. Even these efforts encountered financial challenges that weren't really overcome until the 1990s, when these practical difficulties finally began to be resolved.

The discovery of the shape-memory effect in general dates back to 1932 when Swedish researcher Arne Olander first observed the property in gold-cadmium alloys. The same effect was observed in Cu-Zn in the early 1950s.

How it works



Austenite and Martensite structures of the NiTi compound.

Nitinol's unusual properties are derived from a reversible, solid state phase transformation known as a martensitic transformation.

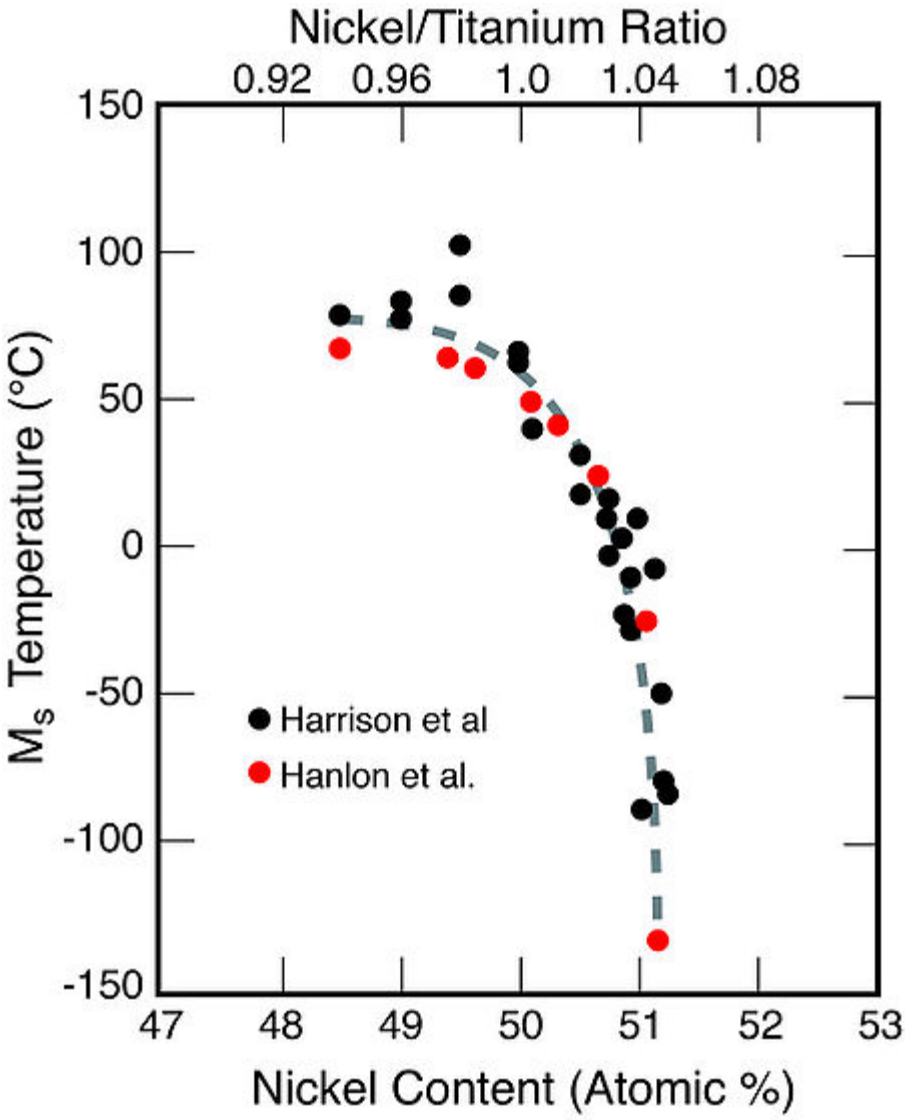
At high temperatures, nitinol assumes an interpenetrating simple cubic crystal structure referred to as austenite (also known as the parent phase). At low temperatures, nitinol spontaneously transforms to a more complicated “monoclinic” crystal structure known as martensite. The temperature at which austenite transforms to martensite is generally referred to as the transformation temperature. More specifically, there are four transition temperatures. When the alloy is fully austenite, martensite begins to form as the alloy cools at the so-called martensite start, or M_s temperature, and the temperature at which the transformation is complete is called the martensite finish, or M_f temperature. When the alloy is fully martensite and is subjected to heating, austenite starts to form at the A_s temperature, and finishes at the A_f temperature.

Crucial to nitinol’s properties are two key aspects of this phase transformation. First is that the transformation is “reversible,” meaning that heating above the transformation temperature will revert the crystal structure to the simpler austenite phase. Upon heating, however, there is a slight upward shift in the temperatures, now beginning at the A_s temperature, and finishing at the A_f temperature. The second key point is that the transformation in both directions is instantaneous.

Martensite's crystal structure (known as a monoclinic, or B19' structure) has the unique ability to undergo limited deformation in some ways without breaking atomic bonds. This type of deformation is known as twinning, which consists of the rearrangement of atomic planes without causing slip, or permanent deformation. It is able to undergo about 6-8% strain in this manner. When martensite is reverted to Austenite by heating, the original austenitic structure is restored, regardless of whether the martensite phase was deformed. Thus the name "shape memory" refers to the fact that the shape of the high temperature austenite phase is "remembered," even though the alloy is severely deformed at a lower temperature.

A great deal of force can be produced by preventing the reversion of deformed martensite to austenite - in many cases, more than 100,000 psi. One of the reasons that nitinol works

so hard to return its original shape is that it is not just an ordinary metal alloy, but what is known as an intermetallic compound. In an ordinary alloy, the constituents are randomly positioned on the crystal lattice; in an ordered intermetallic compound, the atoms (in this case, nickel and titanium) have very specific locations in the lattice. The fact that nitinol is an intermetallic is largely responsible for the difficulty in fabricating devices made from the alloy.



The effect of nitinol composition on the M_s temperature.

The scenario described above (cooling austenite to form martensite, deforming the martensite, then heating to revert to austenite, thus returning the original, undeformed shape) is known as the thermal shape memory effect. A second effect, called superelasticity or pseudoelasticity is also observed in nitinol. This effect is the direct

result of the fact that martensite can be formed by applying a stress as well as by cooling. Thus in a certain temperature range, one can apply a stress to austenite, causing martensite to form while at the same time changing shape. In this case, as soon as the stress is removed, the nitinol will spontaneously return to its original shape. In this mode of use, nitinol behaves like a super spring, possessing an elastic range some 10 to 30 times greater than that of a normal spring material. There are, however, constraints: the effect is only observed some 0-40 degrees C above the A_f temperature.

Nitinol is typically composed of approximately 50 to 51% nickel by atomic percent (55 to 56% weight percent). Making small changes in the composition can change the transition temperature of the alloy significantly. One can control the A_f temperature in nitinol to some extent, but convenient superelastic temperature ranges are from about -20 degrees to +60 degrees C.

One often-encountered complication regarding nitinol is the so-called R-Phase. The R-Phase is another martensitic phase that competes with the martensite phase mentioned above. Because it does not offer the large memory effects of the martensite phase, it is, more often than not, an annoyance.

Making nitinol and nitinol devices

Nitinol is exceedingly difficult to make due to the exceptionally tight compositional control required, and the tremendous reactivity of titanium. Every atom of titanium that combines with oxygen or carbon is an atom that is robbed from the NiTi lattice, thus shifting the composition and making the transformation temperature that much colder. There are two primary melting methods used today:

- Vacuum Arc Remelting: This is done by striking an electrical arc between the raw material and a water-cooled copper strike plate. Melting is done in a high vacuum, and the mold itself is water cooled copper, so no carbon is introduced during melting.

- Vacuum Induction Melting: This is done by using alternating magnetic fields to heat the raw materials in a crucible (generally carbon). This is also done in a high vacuum, but carbon is introduced during the process.

While both methods have advantages, there are no substantive data showing that material from one process is better than the other. Other methods are also used on a boutique scale, including plasma arc melting, induction skull melting, and e-beam melting. Physical vapor deposition is also used on a laboratory scale.

Hot working of nitinol is relatively easy, but cold working is difficult because the enormous elasticity of the alloy increases die or roll contact, leading to tremendous frictional resistance and tool wear. For similar reasons, machining is extremely difficult—to make things worse, the thermal conductivity of nitinol is poor, so heat is

difficult to remove. Grinding (abrasive cutting), Electrical discharge machining (EDM) and laser cutting are all relatively easy.

Heat treating nitinol is delicate and critical. It is the essential tool in fine-tuning the transformation temperature. Aging time and temperature controls the precipitation of various Ni-rich phases, and thus controls how much nickel resides on the NiTi lattice; by depleting the matrix of nickel, aging increases the transformation temperature. The combination of heat treatment and cold working is essential in controlling the properties of nitinol.

Hot topics

Fatigue failures of nitinol devices are a constant subject of discussion. Because it is the material of choice for applications requiring enormous flexibility and motion (e.g., peripheral stents and heart valves), it is necessarily exposed to much greater fatigue strains than are other metals. While the strain controlled fatigue performance of nitinol is superior to all other known metals, fatigue failures have been observed in the most demanding applications. There is a great deal of effort underway trying to better understand and define the durability limits of nitinol.

Nitinol is half nickel, and thus there has been a great deal of concern in the medical industry regarding the release of nickel, a known allergen and possible carcinogen. (Nickel is also present in substantial amounts in stainless steel and cobalt-chrome alloys.) When properly treated (via electropolishing and/or passivation), nitinol forms a very stable protective TiO_2 layer that acts as a very effective and self-healing barrier against ion exchange. It has been repeatedly shown that nitinol releases nickel at a slower pace than stainless steel, for example. With that said, very early medical devices were made without electropolishing, and corrosion was observed. Today's nitinol vascular self-expandable metallic stents, for example, show no evidence of corrosion or nickel release, and the outcomes in patients with and without nickel allergies are indistinguishable.

There are constant and long-running discussions regarding inclusions in nitinol, both TiC and Ti_2NiO_x. All metals contain inclusions, and nitinol cannot be melted without inclusions—they are omnipresent. The size, distribution and type of inclusions can be controlled to some extent. Theoretically, smaller, rounder and few inclusions should lead to increased fatigue durability. All studies done to date, however, have failed to show measurable differences.

A major limitation to further use of nitinol has been its difficulty to weld, both to itself and other materials. In the past ten years, laser welding nitinol to itself has become a relatively routine process. More recently, strong joints between NiTi wires and stainless steel wires have been made using nickel filler. More research is ongoing into other processes and other metals nitinol can be welded to.

Applications

There are four commonly used types of applications for nitinol.

- Free Recovery: nitinol is deformed at a low temperature, and heated to recover its original shape.
- Constrained Recovery: The same, except that recovery is rigidly prevented, and thus a stress is generated.
- Work Production: Here the alloy is allowed to recover, but to do so it must act against a force (thus doing work).
- Superelasticity: As discussed above, here the nitinol acts as a super spring.

In 1989 a survey was conducted in the United States and Canada that involved seven organizations. The survey focused on predicting the future technology, market, and applications of SMA's. The companies predicted the following uses of nitinol in a decreasing order of importance: (1) Couplings, (2) Biomedical and medical, (3) Toys, demonstration, novelty items, (4) Actuators, (5) Heat Engines, (6) Sensors, (7) Cryogenically activated die and bubble memory sockets, and finally (8) lifting devices.

- In colorectal surgery , the material is used in devices for reconnecting the intestine after removing the pathology.
- In dentistry, the material is used in orthodontics for brackets and wires connecting the teeth. Once the SMA is placed in the mouth its temperature rises to ambient body temperature. This causes the nitinol to contract back to its original shape applying a constant force to move the teeth. These SMA wires don't need to be retightened as often as they can contract as the teeth move unlike conventional stainless steel wires. Additionally, nitinol can be used in endodontics, where nitinol files are used to clean and shape the root canals during the root canal procedure.
- Due to the fact it can change shapes it is also used as a golf club insert.
- Another significant application of nitinol in medicine is in stents: A collapsed stent can be inserted into a vein and heated (returning to its original expanded shape) helping to improve blood flow. Also, as a replacement for sutures where nitinol wire can be weaved through two structures then allowed to transform into its preformed shape which should hold the structures in place.
- Nitinol is highly biocompatible and has properties suitable for use in orthopaedic implants.
- Nitinol is also popular in extremely resilient glasses frames. It is also used in some mechanical watch springs.
- It can be used as a temperature control system; as it changes shape, it can activate a switch or a variable resistor to control the temperature.
- It is used in cell-phone technology as a retractible antenna, or microphone boom, due to its highly flexible & mechanical memory nature.
- It is used in some novelty products, such as self-bending spoons which can be used by amateur and stage magicians to demonstrate "psychic" powers or as a

practical joke, as the spoon will bend itself when used to stir tea, coffee, or any other warm liquid.

- It can also be used as wires which are used to locate and mark breast tumours so that following surgery can be more exact.
- Nickel titanium can be used to make the underwires for underwire bras.

Chapter 8

Hydroxylapatite & Bone Cement

Hydroxylapatite

Hydroxylapatite	
 Hydroxylapatite crystals on matrix	
General	
Category	Phosphate mineral
Chemical formula	$Ca_5(PO_4)_3(OH)$
Crystal symmetry	Hexagonal 6/m - dipyramidal
Unit cell	a = 9.41 Å, c = 6.88 Å; Z = 2
Identification	
Molar mass	502.31 gm
Color	Colorless, White, Gray, Yellow, Yellowish green
Crystal habit	As tabular crystals and as stalagmites, nodules, in crystalline

	to massive crusts
Crystal system	Hexagonal
Cleavage	Poor on {0001} and {1010}
Fracture	Conchoidal
Tenacity	Brittle
Mohs scale hardness	5
Luster	Vitreous to subresinous, earthy
Streak	White
Diaphaneity	Transparent to translucent
Specific gravity	3.14 - 3.21 measured, 3.16 calculated
Optical properties	Uniaxial (-)
Refractive index	$n_\omega = 1.651$ $n_\varepsilon = 1.644$
Birefringence	$\delta = 0.007$

Hydroxylapatite, also called **hydroxyapatite** (HA), is a naturally occurring mineral form of calcium apatite with the formula $Ca_5(PO_4)_3(OH)$, but is usually written $Ca_{10}(PO_4)_6(OH)_2$ to denote that the crystal unit cell comprises two entities. Hydroxylapatite is the hydroxyl endmember of the complex apatite group. The OH^- ion can be replaced by fluoride, chloride or carbonate, producing fluorapatite or chlorapatite. It crystallizes in the hexagonal crystal system. It has a specific gravity of 3.08 and is 5 on the Mohs hardness scale. Pure hydroxylapatite powder is white. Naturally occurring apatites can, however, also have brown, yellow, or green colorations, comparable to the discolorations of dental fluorosis.

Up to fifty percent of bone is made up of a modified form of the inorganic mineral hydroxylapatite (known as bone mineral). Carbonated calcium-deficient hydroxylapatite is the main mineral of which dental enamel and dentin are comprised. Hydroxylapatite crystals are also found in the small calcifications (within the pineal gland and other structures) known as corpora arenacea or 'brain sand'.

Medical uses

Flexible hydrogel-HA composite, which has a mineral-to-organic matrix ratio approximating that of human bone.

Hydroxylapatite can be found in teeth and bones within the human body. Thus, it is commonly used as a filler to replace amputated bone or as a coating to promote bone ingrowth into prosthetic implants. Although many other phases exist with similar or even identical chemical makeup, the body responds much differently to them. Coral skeletons can be transformed into hydroxylapatite by high temperatures; their porous structure allows relatively rapid ingrowth at the expense of initial mechanical strength. The high temperature also burns away any organic molecules such as proteins, preventing an immune response and rejection.

Many modern implants, e.g. hip replacements and dental implants, are coated with hydroxylapatite. It has been suggested that this may promote osseointegration.

Porous Hydroxlyapatite implants are used for local drug delivery in bone.

Supplement

Microcrystalline hydroxylapatite (MH) is marketed as a "bone-building" supplement with superior absorption in comparison to calcium. It is a second-generation calcium supplement derived from bovine bone. In the 1980s, bone meal calcium supplements were found to be contaminated with heavy metals, and although the manufacturers' claim their MH is free from contaminants, people are advised to avoid it because it has not been well-tested. However, the limited tests seem to show positive results. A 1995 randomized placebo-controlled study of 40 people in Europe found that it was more effective than calcium carbonate in slowing bone loss. A 2007 randomized double-blind controlled study of an MH supplement called the Bone Builder found significant positive effects in bone mineral density (BMD) compared to placebo. Hydroxylapatite has been used by Noel Fitzpatrick to facilitate bionic development in animals, by coating steel rods in

hydroxylapatite to encourage natural growth of skin around it. As a component of nanocomposites, hydroxylapatite is finding uses as a potential new bone replacement materials.

Chromatography

The mechanism of hydroxylapatite (HA) chromatography is complicated and has been described as "mixed-mode" ion exchange. It involves nonspecific interactions between positively charged calcium ions and negatively charged phosphate ions on the stationary phase HA resin with protein negatively charged carboxyl groups and positively charged amino groups. It may be difficult to predict the effectiveness of HA chromatography based on physical and chemical properties of the desired protein to be purified. For elution, a buffer with increasing phosphate concentration is typically used.

Use in archaeology

In archaeology, hydroxylapatite from human and animal remains is analysed in order to reconstruct ancient diets. The mineral fractions of bone and teeth act as a reservoir of trace elements, including strontium. It has been established that the ratio of strontium to calcium in bone hydroxylapatite broadly reflects an animal's diet during the period before its death when the bone was being formed (5–10 years in the case of human remains), or in the case of dental mineral in childhood. In either case analysis of Sr/Ca ratios allows an individual's diet to be classified as carnivorous, herbivorous or omnivorous and either predominantly marine or terrestrially based. However the difficulty of compensating for post-mortem contamination of archaeological samples through interaction with groundwater continues to cast doubt on the reliability of the method. Stable isotope analysis is considered a more viable alternative, although strontium and other trace mineral analyses of dental samples are commonly used in situations where this is impossible because the collagen content of the bone has completely decayed (i.e. for palaeolithic samples).

Bone Cement

Bone cements have been used very successfully to anchor artificial joints (hip joints, knee joints, shoulder and elbow joints) for more than half a century. Artificial joints (referred to as prostheses) are anchored with bone cement. The bone cement fills the free space between the prosthesis and the bone and plays the important role of an elastic zone. This is necessary because the human hip is acted on by approximately 10-12 times the body weight and therefore the bone cement must absorb the forces acting on the hips to ensure that the artificial implant remains in place over the long term.

Bone cement chemically is nothing more than Plexiglas (i.e. polymethyl methacrylate or PMMA). PMMA was used clinically for the first time in the 1940s in plastic surgery to close gaps in the skull. Comprehensive clinical tests of the compatibility bone cements with the body were conducted before their use in surgery. The excellent tissue

compatibility of PMMA allowed bone cements to be used for anchorage of head prostheses in the 1950s.

Today several million procedures of this type are conducted every year all over the world and more than half of them routinely use bone cements - and the proportion is increasing. Bone cement is considered a reliable anchorage material with its ease of use in clinical practice and particularly because of its proven long survival rate with cemented-in prostheses. Hip and knee registers for artificial joint replacements such as those in Sweden and Norway clearly demonstrate the advantages of cemented-in anchorage. A similar endoprosthesis is expected to be introduced in Germany in 2009.

Composition

Bone cements are provided as two-component materials. Bone cements consist of a powder (i.e., pre-polymerized PMMA and or PMMA or MMA co-polymer beads and or amorphous powder, radio-opacifer, initiator) and a liquid (MMA monomer, stabilizer, inhibitor). The two components are mixed and a free radical polymerization occurs of the monomer when the initiator is mixed with the accelerator. The bone cement viscosity changes over time from a runny liquid into a dough like state that can be safely applied and then finally hardens into solid hardened material. The set time can be tailored to help the physician safely apply the bone cement into the bone bed to either anchor metal or plastic prosthetic device to bone or used alone in the spine to treat osteoporotic compression fractures.

During the exothermic free-radical polymerization process of the cement heats up. This polymerization heat reaches temperatures of around 82-86°C in the body. This temperature is superior to the critical level for the protein denaturation in the body. The cause of the low polymerization temperature in the body is the relatively thin cement coating, which should not exceed 5 mm, and the temperature dissipation via the large prosthesis surface and the flow of blood.

The individual components of the bone cement are also known in the area of dental filler materials. Acrylate-based plastics are also used in these applications. While the individual components are not always perfectly safe as pharmaceutical additives and active substances per se, as bone cement the individual substances are either converted or fully enclosed in the cement matrix during the polymerization phase from the increase in viscosity to curing. From current knowledge, cured bone cement can now be classified as safe, as originally demonstrated during the early studies on compatibility with the body conducted in the 1950s.

More recently bone cement has been use in the spine in either vertebroplasty or kyphoplasty procedures.

Important information for the use of bone cement

What is referred to as bone cement syndrome is described in the literature. For a long time it was believed that the incompletely converted monomer released from bone cement was the cause of circulation reactions and embolism. However, it is now known that this monomer (residual monomer) is metabolized by the respiratory chain and split into carbon dioxide and water and excreted. Embolisms can always occur during anchorage of artificial joints when material is inserted into the previously cleared thigh bone cavity. The result is intramedullary pressure increase, which can be regulated by the anesthetist.

If the patient is known to have any allergies to constituents of the bone cement, according to current knowledge bone cement should not be used to anchor the prosthesis. Anchorage without cement - cement-free implant placement - is the alternative.

Revisions

Revision is the replacement of a prosthesis. This means that a prosthesis previously implanted in the body is removed and replaced by a new prosthesis. Compared to the initial operation revisions are often more complex and more difficult, because every revision involves the loss of healthy bone substance. Revision operations are also more expensive for a satisfactory result. The most important goal is therefore to avoid revisions by using a good surgical procedure and using products with good (long-term) results.

Unfortunately, it is not always possible to avoid revisions. There can also be different reasons for revisions and there is a distinction between septic or aseptic revision. If it is necessary to replace an implant without confirmation of an infection - i.e. aseptic - now the cement is not necessarily removed completely. However, if the implant has loosened for septic reasons, the cement must be fully removed. In the current state of knowledge it is easier to remove cement than to release a well-anchored cement-free prosthesis from the bone site. Ultimately it is important for the stability of the revised prosthesis to detect possible loosening of the initial implant early to be able to retain as much healthy bone as possible.

A prosthesis fixed with bone cement offers very high primary stability combined with fast remobilization of patients. The cemented-in prosthesis can be fully loaded very soon after the operation. The necessary rehabilitation is comparatively simple for patients who have had a cemented-in prosthesis implanted. The joints can be loaded again very soon after the operation, but the use of crutches is still required for a reasonable period for safety reasons.

Bone cement has proven particularly useful because specific active substances, e.g. antibiotics, can be added to the powder component. The active substances are released locally after implant placement of the new joint, i.e. in the immediate vicinity of the new prosthesis and have been confirmed to reduce the danger of infection. The antibiotics act against bacteria precisely at the site where they are required in the open wound without

subjecting the body in general to unnecessarily high antibiotic levels. This makes bone cement a modern drug delivery system that delivers the required drugs directly to the surgical site. The important factor is not how much active substance is in the cement matrix but how much of the active substance is actually released locally. Too much active substance in the bone cement would actually be detrimental, because the mechanical stability of the fixed prosthesis is weakened by a high proportion of active substance in the cement. The local active substance levels of industrially manufactured bone cements that are formed by the use of bone cements that contain active substances are approximate (assuming that there is no incompatibility) and are significantly below the clinical routine dosages for systemic single injections.

Chapter 9

Bionics

Bionics (also known as **biomimicry**, **biomimetics**, **bio-inspiration**, **biognosis**, and close to **bionical creativity engineering**) is the application of biological methods and systems found in nature to the study and design of engineering systems and modern technology.

The word *bionic* was coined by Jack E. Steele in 1958, possibly originating from the Greek word βίον, *bíon*, ("bee-on"), meaning 'unit of life' and the suffix -ic, meaning 'like' or 'in the manner of', hence 'like life'. Some dictionaries, however, explain the word as being formed as a portmanteau from ***bio****logy* + *electro****nics***. It was popularized by the 1970s television series *The Six Million Dollar Man* and *The Bionic Woman*, which were influenced by Steele's work, and feature humans given superhuman powers by electromechanical implants.

The transfer of technology between lifeforms and manufactures is, according to proponents of bionic technology, desirable because evolutionary pressure typically forces living organisms, including fauna and flora, to become highly optimized and efficient. A classical example is the development of dirt- and water-repellent paint (coating) from the observation that the surface of the lotus flower plant is practically unsticky for anything (the lotus effect).

The term "biomimetic" is preferred when reference is made to chemical reactions. In that domain, biomimetic chemistry refers to reactions that, in nature, involve biological macromolecules (for example, enzymes or nucleic acids) whose chemistry can be replicated using much smaller molecules *in vitro*.

Examples of bionics in engineering include the hulls of boats imitating the thick skin of dolphins; sonar, radar, and medical ultrasound imaging imitating the echolocation of bats.

In the field of computer science, the study of bionics has produced artificial neurons, artificial neural networks, and swarm intelligence. Evolutionary computation was also

motivated by bionics ideas but it took the idea further by simulating evolution in silico and producing well-optimized solutions that had never appeared in nature.

It is estimated by Julian Vincent, professor of biomimetics at the University of Bath's department of mechanical engineering (Biomimetics group), that "at present there is only a 10% overlap between biology and technology in terms of the mechanisms used".

History

The name biomimetics was coined by Otto Schmitt in the 1950s. The term bionics was coined by Jack E. Steele in 1958 while working at the *Aeronautics Division House* at Wright-Patterson Air Force Base in Dayton, Ohio. However, terms like biomimicry or biomimetics are more preferred in the technology world in efforts to avoid confusion between the medical term bionics. Coincidentally, Martin Caidin used the word for his 1972 novel *Cyborg*, which inspired the series *The Six Million Dollar Man*. Caidin was a long-time aviation industry writer before turning to fiction full time.

Methods

Velcro was inspired by the tiny hooks found on the surface of burs.

Often, the study of bionics emphasizes implementing a function found in nature rather than just imitating biological structures. For example, in computer science, cybernetics tries to model the feedback and control mechanisms that are inherent in intelligent

behavior, while artificial intelligence tries to model the intelligent function regardless of the particular way it can be achieved.

The conscious copying of examples and mechanisms from natural organisms and ecologies is a form of applied case-based reasoning, treating nature itself as a database of solutions that already work. Proponents argue that the selective pressure placed on all natural life forms minimizes and removes failures.

Although almost all engineering could be said to be a form of biomimicry, the modern origins of this field are usually attributed to Buckminster Fuller and its later codification as a house or field of study to Janine Benyus.

Roughly, we can distinguish three biological levels in the fauna or flora, after which technology can be modeled:

- Mimicking natural **methods of manufacture**
- Imitating **mechanisms** found in nature (velcro)
- Studying **organizational principles from the social behaviour of organisms**, such as the flocking behaviour of birds, optimization of ant foraging and bee foraging, and the swarm intelligence (SI)-based behaviour of a school of fish.

Examples

- Velcro is the most famous example of biomimetics. In 1948, the Swiss engineer George de Mestral was cleaning his dog of burrs picked up on a walk when he realized how the hooks of the burrs clung to the fur.

- The horn-shaped, saw-tooth design for lumberjack blades used at the turn of the 19th century to cut down trees when it was still done by hand was modeled after observations of a wood-burrowing beetle. It revolutionized the industry because the blades worked so much faster at felling trees.

- Cat's eye reflectors were invented by Percy Shaw in 1935 after studying the mechanism of cat eyes. He had found that cats had a system of reflecting cells, known as tapetum lucidum, which was capable of reflecting the tiniest bit of light.

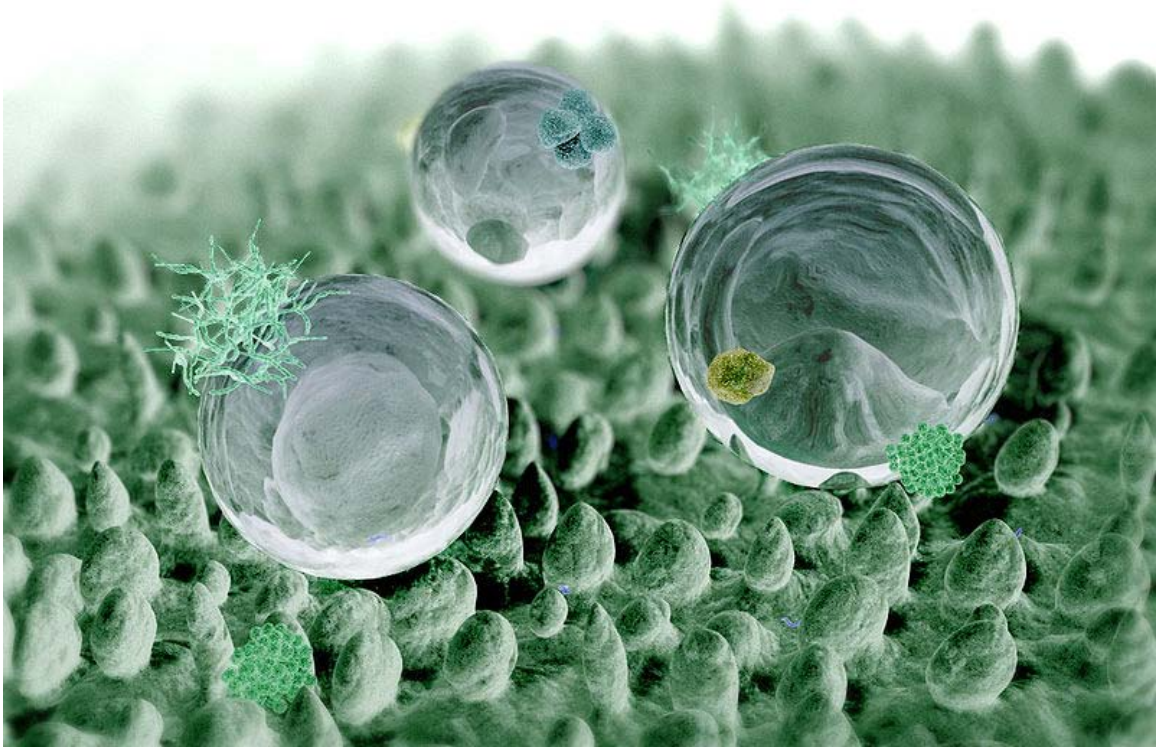
- Leonardo da Vinci's flying machines and ships are early examples of drawing from nature in engineering.

- Resilin is a replacement for rubber that has been created by studying the material also found in anthropods.

- Julian Vincent drew from the study of pinecones when he developed in 2004 "smart" clothing that adapts to changing temperatures. "I wanted a nonliving system which would respond to changes in moisture by changing shape", he said. "There are several such systems in plants, but most are very small — the pinecone

is the largest and therefore the easiest to work on". Pinecones respond to higher humidity by opening their scales (to disperse their seeds). The "smart" fabric does the same thing, opening up when the wearer is warm and sweating, and shutting tight when cold.

- "Morphing aircraft wings" that change shape according to the speed and duration of flight were designed in 2004 by biomimetic scientists from Penn State University. The morphing wings were inspired by different bird species that have differently shaped wings according to the speed at which they fly. In order to change the shape and underlying structure of the aircraft wings, the researchers needed to make the overlying skin also be able to change, which their design does by covering the wings with fish-inspired scales that could slide over each other. In some respects this is a refinement of the swing-wing design.



Lotus leaf surface, rendered: microscopic view

- Some paints and roof tiles have been engineered to be self-cleaning by copying the mechanism from the Nelumbo lotus.

- Cholesteric liquid crystals (CLCs) are the thin-film material often used to fabricate fish tank thermometers or mood rings, that change color with temperature changes. They change color because their molecules are arranged in a helical or chiral arrangement and with temperature the pitch of that helical

structure changes, reflecting different wavelengths of light. Chiral Photonics, Inc. has abstracted the self-assembled structure of the organic CLCs to produce analogous optical devices using tiny lengths of inorganic, twisted glass fiber.

- Nanostructures and physical mechanisms that produce the shining color of butterfly wings were reproduced in silico by Greg Parker, professor of Electronics and Computer Science at the University of Southampton and research student Luca Plattner in the field of photonics, which is electronics using photons as the information carrier instead of electrons.

- The wing structure of the blue morpho butterfly was studied and the way it reflects light was mimicked to create an RFID tag that can be read through water and on metal.

- The wing structure of butterflies has also inspired the creation of new nanosensors to detect explosives.

- Neuromorphic chips, silicon retinae or cochleae, has wiring that is modelled after real neural networks. *S.a.:* connectivity.

- Synthetic or "robotic" vegetation, which aids in conservation and restoration, are machines designed to mimic many of the functions of living vegetation.

- Medical adhesives involving glue and tiny nano-hairs are being developed based on the physical structures found in the feet of geckos.

- Computer viruses also show troubling similarities with biological viruses in their way to curb program-oriented information towards self-reproduction and dissemination.

- The cooling system of the Eastgate Centre building, in Harare was modeled after a termite mound to achieve very efficient passive cooling.

- Through the field of bionics, new aircraft designs with far greater agility and other advantages may be created. This has been described by Geoff Spedding and Anders Hedenström in an article in Journal of Experimental Biology. Similar statements were also made by John Videler and Eize Stamhuis in their book Avian Flight and in the article they present in Science about LEVs. John Videler and Eize Stamhuis have since worked out real-life improvements to airplane wings, using bionics research. This research in bionics may also be used to create more efficient helicopters or miniature UAVs. This latter was stated by Bret Tobalske in an article in Science about Hummingbirds. Bret Tobalske has thus now started work on creating these miniature UAVs which may be used for espionage. UC Berkeley as well as ESA have finally also been working in a similar direction and created the Robofly (a miniature UAV)and the Entomopter (a UAV which can walk, crawl and fly).

Specific uses of the term

In medicine

Bionics is a term which refers to the flow of concepts from biology to engineering and vice versa. Hence, there are two slightly different points of view regarding the meaning of the word.

In medicine, **bionics** means the replacement or enhancement of organs or other body parts by mechanical versions. Bionic implants differ from mere prostheses by mimicking the original function very closely, or even surpassing it.

Bionics' German equivalent, *Bionik*, always adheres to the broader meaning, in that it tries to develop engineering solutions from biological models. This approach is motivated by the fact that biological solutions will usually be optimized by evolutionary forces.

While the technologies that make bionic implants possible are still in a very early stage, a few bionic items already exist, the best known being the cochlear implant, a device for deaf people. By 2004 fully functional artificial hearts were developed. Significant further progress is expected to take place with the advent of nanotechnologies. A well known example of a proposed nanodevice is a respirocyte, an artificial red cell, designed (though not built yet) by Robert Freitas.

Kwabena Boahen from Ghana was a professor in the Department of Bioengineering at the **University of Pennsylvania**. During his eight years at Penn, he developed a silicon retina that was able to process images in the same manner as a living retina. He confirmed the results by comparing the electrical signals from his silicon retina to the electrical signals produced by a salamander eye while the two retinas were looking at the same image.

In 2007 the Scottish company Touch Bionics launched the first commercially available bionic hand, named "i-Limb Hand". According to the firm, by May 2010 it has been fitted to more than 1,200 patients worldwide.

The Nichi-In group is working on bimomimicking scaffolds in tissue engineering, stem cells and regenerative medicine have given a detailed classification on biomimetics in medicine.

Politics

A political form of biomimicry is bioregional democracy, wherein political borders conform to natural ecoregions rather than human cultures or the outcomes of prior conflicts.

Critics of these approaches often argue that ecological selection itself is a poor model of minimizing manufacturing complexity or conflict, and that the free market relies on

conscious cooperation, agreement, and standards as much as on efficiency – more analogous to sexual selection. Charles Darwin himself contended that both were balanced in natural selection – although his contemporaries often avoided frank talk about sex, or any suggestion that free market success was based on persuasion, not value.

Advocates, especially in the anti-globalization movement, argue that the mating-like processes of standardization, financing and marketing, are already examples of runaway evolution – rendering a system that appeals to the consumer but which is inefficient at use of energy and raw materials. Biomimicry, they argue, is an effective strategy to restore basic efficiency.

Biomimicry is also the second principle of Natural Capitalism.

Other uses

Business biomimetics is the latest development in the application of biomimetics. Specifically it applies principles and practice from biological systems to business strategy, process, organisation design and strategic thinking. It has been successfully used by a range of industries in FMCG, defence, central government, packaging and business services. Based on the work by Phil Richardson at the University of Bath the approach was launched at the House of Lords in May 2009.

In a more specific meaning, it is a creativity technique that tries to use biological prototypes to get ideas for engineering solutions. This approach is motivated by the fact that biological organisms and their organs have been well optimized by evolution. In chemistry, a **biomimetic synthesis** is a man-made chemical synthesis inspired by biochemical processes.Example-Dr Atul Kumar group has reported biomimetic synthesis using Human Heamoglobin catalysed sulfoxidation reaction. " Another, more recent meaning of the term bionics refers to merging organism and machine. This approach results in a hybrid system combining biological and engineering parts, which can also be referred as a cybernetic organism (cyborg). Practical realization of this was demonstrated in Kevin Warwick's implant experiments bringing about ultrasound input via his own nervous system.

Chapter 10

Synthetic Biodegradable Polymer

Many opportunities exist for the application of **synthetic biodegradable polymers** in the biomedical area particularly in the fields of tissue engineering and controlled drug delivery. Degradation is important in biomedicine for many reasons. Degradation of the polymeric implant means surgical intervention may not required for removal at the end of its functional life, eliminating the need for a second surgery. In tissue engineering, biodegradable polymers can be designed such to approximate tissues, providing a polymer scaffold that can withstand mechanical stresses, provide a suitable surface for cell attachment and growth, and degrade at a rate that allows the load to be transferred to the new tissue. In the field of controlled drug delivery, biodegradable polymers offer tremendous potential either as a drug delivery system alone or in conjunction to functioning as a medical device.

In the development of applications of biodegradable polymers, the chemistry of some polymers including synthesis and degradation is reviewed below. A description of how properties can be controlled by proper synthetic controls such as copolymer composition, special requirements for processing and handling, and some of the commercial devices based on these materials are discussed.

Polymer chemistry and material selection

Some biodegradable polymers, their properties and degradation times can be found in Table 2 in this document.

When investigating the selection of the polymer for biomedical applications, important criteria to consider are;

- The mechanical properties must match the application and remain sufficiently strong until the surrounding tissue has healed.
- The degradation time must match the time required.

- It does not invoke a toxic response.
- It is metabolized in the body after fulfilling its purpose.
- It is easily processable in the final product form with an acceptable shelf life and easily sterilized.

Mechanical performance of a biodegradable polymer depends on various factors which include monomer selection, initiator selection, process conditions and the presence of additives. These factors influence the polymers crystallinity, melt and glass transition temperatures and molecular weight. Each of these factors needs to be assessed on how they affect the biodegradation of the polymer. Biodegradation can be accomplished by synthesizing polymers with hydrolytically unstable linkages in the backbone. This is commonly achieved by the use of chemical functional groups such as esters, anhydrides, orthoesters and amides. Most biodegradable polymers are synthesized by ring opening polymerization.

Processing

Biodegradable polymers can be melt processed by conventional means such as compression or injection molding. Special consideration must be given to the need to exclude moisture from the material. Care must be taken to dry the polymers before processing to exclude humidity. As most biodegradable polymers have been synthesized by ring opening polymerization, a thermodynamic equilibrium exists between the forward polymerization reaction and the reverse reaction that results in monomer formation. Care needs to be taken to avoid an excessively high processing temperature that may result in monomer formation during the molding and extrusion process.

Degradation

Once implanted, a biodegradable device should maintain its mechanical properties until it is no longer needed and then be absorbed by the body leaving no trace. The backbone of the polymer is hydrolytically unstable. That is, the polymer is unstable in a water based environment. This is the prevailing mechanism for the polymers degradation. This occurs in two stages.

1. Water penetrates the bulk of the device, attacking the chemical bonds in the amorphous phase and converting long polymer chains into shorter water-soluble fragments. This causes a reduction in molecular weight without the loss of physical properties as the polymer is still held together by the crystalline regions. Water penetrates the device leading to metabolization of the fragments and bulk erosion.

2. Surface erosion of the polymer occurs when the rate at which the water penetrating the device is slower than the rate of conversion of the polymer into water soluble materials.

Biomedical engineers can tailor a polymer to slowly degrade and transfer stress at the appropriate rate to surrounding tissues as they heal by balancing the chemical stability of

the polymer backbone, the geometry of the device, and the presence of catalysts, additives or plasticisers.

Applications

As previously mentioned, biodegradable polymers are used commercially in both the tissue engineering and drug delivery field of biomedicine. Specific applications include.

- Sutures
- Dental devices
- Orthopedic fixation devices
- Tissue engineering scaffolds
- Biodegradable vascular stents

Chapter 11

Biofuel

Information on pump regarding ethanol fuel blend up to 10%, California

Bus run on biodiesel

Biofuels are a wide range of fuels which are in some way derived from biomass. The term covers solid biomass, liquid fuels and various biogases. Biofuels are gaining increased public and scientific attention, driven by factors such as oil price spikes, the need for increased energy security, and concern over greenhouse gas emissions from fossil fuels.

Bioethanol is an alcohol made by fermenting the sugar components of plant materials and it is made mostly from sugar and starch crops. With advanced technology being developed, cellulosic biomass, such as trees and grasses, are also used as feedstocks for ethanol production. Ethanol can be used as a fuel for vehicles in its pure form, but it is usually used as a gasoline additive to increase octane and improve vehicle emissions. Bioethanol is widely used in the USA and in Brazil.

Biodiesel is made from vegetable oils, animal fats or recycled greases. Biodiesel can be used as a fuel for vehicles in its pure form, but it is usually used as a diesel additive to reduce levels of particulates, carbon monoxide, and hydrocarbons from diesel-powered vehicles. Biodiesel is produced from oils or fats using transesterification and is the most common biofuel in Europe.

Biofuels provided 1.8% of the world's transport fuel in 2008. Investment into biofuels production capacity exceeded $4 billion worldwide in 2007 and is growing.

Liquid fuels for transportation

Most transportation fuels are liquids, because vehicles usually require high energy density, as occurs in liquids and solids. High power density can be provided most

inexpensively by an internal combustion engine; these engines require clean burning fuels, to keep the engine clean and minimize air pollution.

The fuels that are easiest to burn cleanly are typically liquids and gases. Thus liquids (and gases that can be stored in liquid form) meet the requirements of being both portable and clean burning. Also, liquids and gases can be pumped, which means handling is easily mechanized, and thus less laborious.

First generation biofuels

'First-generation' or conventional biofuels are biofuels made from sugar, starch, and vegetable oil.

Bioalcohols

Neat ethanol on the left (A), gasoline on the right (G) at a filling station in Brazil

Biologically produced alcohols, most commonly ethanol, and less commonly propanol and butanol, are produced by the action of microorganisms and enzymes through the fermentation of sugars or starches (easiest), or cellulose (which is more difficult). Biobutanol (also called biogasoline) is often claimed to provide a direct replacement for gasoline, because it can be used directly in a gasoline engine (in a similar way to biodiesel in diesel engines).

Ethanol fuel is the most common biofuel worldwide, particularly in Brazil. Alcohol fuels are produced by fermentation of sugars derived from wheat, corn, sugar beets, sugar cane, molasses and any sugar or starch that alcoholic beverages can be made from (like potato and fruit waste, etc.). The ethanol production methods used are enzyme digestion (to release sugars from stored starches), fermentation of the sugars, distillation and drying. The distillation process requires significant energy input for heat (often unsustainable natural gas fossil fuel, but cellulosic biomass such as bagasse, the waste left after sugar cane is pressed to extract its juice, can also be used more sustainably).

Ethanol can be used in petrol engines as a replacement for gasoline; it can be mixed with gasoline to any percentage. Most existing car petrol engines can run on blends of up to 15% bioethanol with petroleum/gasoline. Ethanol has a smaller energy density than gasoline, which means it takes more fuel (volume and mass) to produce the same amount of work. An advantage of ethanol (CH3CH2OH) is that it has a higher octane rating than ethanol-free gasoline available at roadside gas stations which allows an increase of an engine's compression ratio for increased thermal efficiency. In high altitude (thin air) locations, some states mandate a mix of gasoline and ethanol as a winter oxidizer to reduce atmospheric pollution emissions.

Ethanol is also used to fuel bioethanol fireplaces. As they do not require a chimney and are "flueless", bio ethanol fires are extremely useful for new build homes and apartments without a flue. The downside to these fireplaces, is that the heat output is slightly less than electric and gas fires.

In the current alcohol-from-corn production model in the United States, considering the total energy consumed by farm equipment, cultivation, planting, fertilizers, pesticides, herbicides, and fungicides made from petroleum, irrigation systems, harvesting, transport of feedstock to processing plants, fermentation, distillation, drying, transport to fuel terminals and retail pumps, and lower ethanol fuel energy content, the net energy content value added and delivered to consumers is very small. And, the net benefit (all things considered) does little to reduce imported oil and fossil fuels required to produce the ethanol.

Although ethanol-from-corn and other food stocks has implications both in terms of world food prices and limited, yet positive energy yield (in terms of energy delivered to customer/fossil fuels used), the technology has led to the development of cellulosic ethanol. According to a joint research agenda conducted through the U.S. Department of Energy, the fossil energy ratios (FER) for cellulosic ethanol, corn ethanol, and gasoline are 10.3, 1.36, and 0.81, respectively.

Many car manufacturers are now producing flexible-fuel vehicles (FFV's), which can safely run on any combination of bioethanol and petrol, up to 100% bioethanol. They dynamically sense exhaust oxygen content, and adjust the engine's computer systems, spark, and fuel injection accordingly. This adds to the initial cost and ongoing increased vehicle maintenance. As with all vehicles, efficiency falls and pollution emissions increase when FFV system maintenance is needed (regardless of the fuel mix being

used), but is not performed. FFV internal combustion engines are becoming increasingly complex, as are multiple-propulsion-system FFV hybrid vehicles, which impacts cost, maintenance, reliability, and useful lifetime longevity.

Even dry ethanol has roughly one-third lower energy content per unit of volume compared to gasoline, so larger / heavier fuel tanks are required to travel the same distance, or more fuel stops are required. With large current unsustainable, non-scalable subsidies, ethanol fuel still costs much more per distance traveled than current high gasoline prices in the United States.

Methanol is currently produced from natural gas, a non-renewable fossil fuel. It can also be produced from biomass as biomethanol. The methanol economy is an interesting alternative to get to the hydrogen economy, compared to today's hydrogen production from natural gas. But this process is not the state-of-the-art clean solar thermal energy process where hydrogen production is directly produced from water.

Butanol is formed by ABE fermentation (acetone, butanol, ethanol) and experimental modifications of the process show potentially high net energy gains with butanol as the only liquid product. Butanol will produce more energy and allegedly can be burned "straight" in existing gasoline engines (without modification to the engine or car), and is less corrosive and less water soluble than ethanol, and could be distributed via existing infrastructures. DuPont and BP are working together to help develop Butanol. E. coli have also been successfully engineered to produce Butanol by hijacking their amino acid metabolism.

Fermentation is not the only route to forming biofuels or bioalcohols. One can obtain methanol, ethanol, butanol or mixed alcohol fuels through pyrolysis of biomass including agricultural waste or algal biomass. The most exciting of these pyrolysis alcoholic fuels is the pyrolysis biobutanol. The product can be made with limited water use and most places in the world.

Biodiesel

In some countries biodiesel is less expensive than conventional diesel.

Biodiesel is the most common biofuel in Europe. It is produced from oils or fats using transesterification and is a liquid similar in composition to fossil/mineral diesel. Chemically, it consists mostly of fatty acid methyl (or ethyl) esters (FAMEs). Feedstocks for biodiesel include animal fats, vegetable oils, soy, rapeseed, jatropha, mahua, mustard, flax, sunflower, palm oil, hemp, field pennycress, pongamia pinnata and algae. Pure biodiesel (B100) is the lowest emission diesel fuel. Although liquefied petroleum gas and hydrogen have cleaner combustion, they are used to fuel much less efficient petrol engines and are not as widely available.

Biodiesel can be used in any diesel engine when mixed with mineral diesel. In some countries manufacturers cover their diesel engines under warranty for B100 use, although Volkswagen of Germany, for example, asks drivers to check by telephone with the VW environmental services department before switching to B100. B100 may become more viscous at lower temperatures, depending on the feedstock used. In most cases, biodiesel is compatible with diesel engines from 1994 onwards, which use 'Viton' (by DuPont) synthetic rubber in their mechanical fuel injection systems.

Electronically controlled 'common rail' and 'unit injector' type systems from the late 1990s onwards may only use biodiesel blended with conventional diesel fuel. These engines have finely metered and atomized multi-stage injection systems that are very sensitive to the viscosity of the fuel. Many current generation diesel engines are made so that they can run on B100 without altering the engine itself, although this depends on the fuel rail design. Since biodiesel is an effective solvent and cleans residues deposited by mineral diesel, engine filters may need to be replaced more often, as the biofuel dissolves old deposits in the fuel tank and pipes. It also effectively cleans the engine combustion chamber of carbon deposits, helping to maintain efficiency. In many European countries, a 5% biodiesel blend is widely used and is available at thousands of gas stations. Biodiesel is also an *oxygenated fuel*, meaning that it contains a reduced amount of carbon and higher hydrogen and oxygen content than fossil diesel. This improves the combustion of fossil diesel and reduces the particulate emissions from un-burnt carbon.

Biodiesel is also safe to handle and transport because it is as biodegradable as sugar, 10 times less toxic than table salt, and has a high flash point of about 300 F (148 C) compared to petroleum diesel fuel, which has a flash point of 125 F (52 C).

In the USA, more than 80% of commercial trucks and city buses run on diesel. The emerging US biodiesel market is estimated to have grown 200% from 2004 to 2005. "By the end of 2006 biodiesel production was estimated to increase fourfold [from 2004] to more than 1 billion gallons".

Green diesel

Green diesel, also known as renewable diesel, is a form of diesel fuel which is derived from renewable feedstock rather than the fossil feedstock used in most diesel fuels. Green diesel feedstock can be sourced from a variety of oils including canola, algae, jatropha and salicornia in addition to tallow. Green diesel uses traditional fractional distillation to process the oils, not to be confused with biodiesel which is chemically quite different and processed using transesterification.

“Green Diesel” as commonly known in Ireland should not be confused with dyed green diesel sold at a lower tax rate for agriculture purposes, using the dye allows custom officers to determine if a person is using the cheaper diesel in higher taxed applications such as commercial haulage or cars.

Vegetable oil

Filtered waste vegetable oil

Straight unmodified edible vegetable oil is generally not used as fuel, but lower quality oil can and has been used for this purpose. Used vegetable oil is increasingly being processed into biodiesel, or (more rarely) cleaned of water and particulates and used as a fuel.

Also here, as with 100% biodiesel (B100), to ensure that the fuel injectors atomize the vegetable oil in the correct pattern for efficient combustion, vegetable oil fuel must be heated to reduce its viscosity to that of diesel, either by electric coils or heat exchangers. This is easier in warm or temperate climates. Big corporations like MAN B&W Diesel, Wärtsilä, and Deutz AG as well as a number of smaller companies such as Elsbett offer engines that are compatible with straight vegetable oil, without the need for after-market modifications.

Vegetable oil can also be used in many older diesel engines that do not use common rail or unit injection electronic diesel injection systems. Due to the design of the combustion chambers in indirect injection engines, these are the best engines for use with vegetable oil. This system allows the relatively larger oil molecules more time to burn. Some older engines, especially Mercedes are driven experimentally by enthusiasts without any conversion, a handful of drivers have experienced limited success with earlier pre-"Pumpe Duse" VW TDI engines and other similar engines with direct injection. Several

companies like Elsbett or Wolf have developed professional conversion kits and successfully installed hundreds of them over the last decades.

Oils and fats can be hydrogenated to give a diesel substitute. The resulting product is a straight chain hydrocarbon with a high cetane number, low in aromatics and sulfur and does not contain oxygen. Hydrogenated oils can be blended with diesel in all proportions Hydrogenated oils have several advantages over biodiesel, including good performance at low temperatures, no storage stability problems and no susceptibility to microbial attack.

Bioethers

Bio ethers (also referred to as fuel ethers or oxygenated fuels) are cost-effective compounds that act as octane rating enhancers. They also enhance engine performance, whilst significantly reducing engine wear and toxic exhaust emissions. Greatly reducing the amount of ground-level ozone, they contribute to the quality of the air we breathe.

Biogas

Pipes carrying biogas

Biogas is methane produced by the process of anaerobic digestion of organic material by anaerobes. It can be produced either from biodegradable waste materials or by the use of energy crops fed into anaerobic digesters to supplement gas yields. The solid byproduct, digestate, can be used as a biofuel or a fertilizer.

- Biogas can be recovered from mechanical biological treatment waste processing systems.

Note:Landfill gas is a less clean form of biogas which is produced in landfills through naturally occurring anaerobic digestion. If it escapes into the atmosphere it is a potential greenhouse gas.

- Farmers can produce biogas from manure from their cows by using an anaerobic digester (AD).

Syngas

Syngas, a mixture of carbon monoxide and hydrogen, is produced by partial combustion of biomass, that is, combustion with an amount of oxygen that is not sufficient to convert the biomass completely to carbon dioxide and water. Before partial combustion the biomass is dried, and sometimes pyrolysed. The resulting gas mixture, syngas, is more efficient than direct combustion of the original biofuel; more of the energy contained in the fuel is extracted.

- Syngas may be burned directly in internal combustion engines or turbines. The wood gas generator is a wood-fueled gasification reactor mounted on an internal combustion engine.
- Syngas can be used to produce methanol, DME and hydrogen, or converted via the Fischer-Tropsch process to produce a diesel substitute, or a mixture of alcohols that can be blended into gasoline. Gasification normally relies on temperatures >700°C.
- Lower temperature gasification is desirable when co-producing biochar but results in a Syngas polluted with tar.

Solid biofuels

Examples include wood, sawdust, grass cuttings, domestic refuse, charcoal, agricultural waste, non-food energy crops, and dried manure.

When raw biomass is already in a suitable form (such as firewood), it can burn directly in a stove or furnace to provide heat or raise steam. When raw biomass is in an inconvenient form (such as sawdust, wood chips, grass, urban waste wood, agricultural residues), the typical process is to densify the biomass. This process includes grinding the raw biomass to an appropriate particulate size (known as hogfuel), which depending on the densification type can be from 1 to 3 cm (1 in), which is then concentrated into a fuel product. The current types of processes are wood pellet, cube, or puck. The pellet process is most common in Europe and is typically a pure wood product. The other types of densification are larger in size compared to a pellet and are compatible with a broad range of input feedstocks. The resulting densified fuel is easier to transport and feed into thermal generation systems such as boilers.

A problem with the combustion of raw biomass is that it emits considerable amounts of pollutants such as particulates and PAHs (polycyclic aromatic hydrocarbons). Even modern pellet boilers generate much more pollutants than oil or natural gas boilers.

Pellets made from agricultural residues are usually worse than wood pellets, producing much larger emissions of dioxins and chlorophenols.

Notwithstanding the above noted study, numerous studies have shown that biomass fuels have significantly less impact on the environment than fossil based fuels. Of note is the U.S. Department of Energy Laboratory, Operated by Midwest Research Institute Biomass Power and Conventional Fossil Systems with and without CO2 Sequestration – Comparing the Energy Balance, Greenhouse Gas Emissions and Economics Study. Power generation emits significant amounts of greenhouse gases (GHGs), mainly carbon dioxide (CO_2). Sequestering CO_2 from the power plant flue gas can significantly reduce the GHGs from the power plant itself, but this is not the total picture. CO_2 capture and sequestration consumes additional energy, thus lowering the plant's fuel-to-electricity efficiency. To compensate for this, more fossil fuel must be procured and consumed to make up for lost capacity.

Taking this into consideration, the global warming potential (GWP), which is a combination of CO_2, methane (CH_4), and nitrous oxide (N_2O) emissions, and energy balance of the system need to be examined using a life cycle assessment. This takes into account the upstream processes which remain constant after CO_2 sequestration as well as the steps required for additional power generation. firing biomass instead of coal led to a 148% reduction in GWP.

A derivative of solid biofuel is biochar, which is produced by biomass pyrolysis. Bio-char made from agricultural waste can substitute for wood charcoal. As wood stock becomes scarce this alternative is gaining ground. In eastern Democratic Republic of Congo, for example, biomass briquettes are being marketed as an alternative to charcoal in order to protect Virunga National Park from deforestation associated with charcoal production.

Advanced biofuels

Advanced biofuels can refer to any biofuel made by a novel method and/or that gives a better product than current biofuels. Second, third, and fourth generation biofuels are also called advanced biofuels.

Second generation biofuels

Supporters of biofuels claim that a more viable solution is to increase political and industrial support for, and rapidity of, second-generation biofuel implementation from non-food crops. These include waste biomass, the stalks of wheat, corn, wood, and special-energy-or-biomass crops (e.g. Miscanthus). Some second generation (2G) biofuels use biomass to liquid technology, including cellulosic biofuels. Many second generation biofuels are under development such as biohydrogen, biomethanol, DMF, BioDME, Fischer-Tropsch diesel, biohydrogen diesel, mixed alcohols and wood diesel.

Cellulosic ethanol production uses non-food crops or inedible waste products and does not divert food away from the animal or human food chain. Lignocellulose is the "woody" structural material of plants. This feedstock is abundant and diverse, and in some cases (like citrus peels or sawdust) it is in itself a significant disposal problem.

Producing ethanol from cellulose is a difficult technical problem to solve. In nature, ruminant livestock (like cattle) eat grass and then use slow enzymatic digestive processes to break it into glucose (sugar). In cellulosic ethanol laboratories, various experimental processes are being developed to do the same thing, and then the sugars released can be fermented to make ethanol fuel. In 2009 scientists reported developing, using "synthetic biology", "15 new highly stable fungal enzyme catalysts that efficiently break down cellulose into sugars at high temperatures", adding to the 10 previously known. The use of high temperatures, has been identified as an important factor in improving the overall economic feasibility of the biofuel industry and the identification of enzymes that are stable and can operate efficiently at extreme temperatures is an area of active research. In addition, research conducted at TU Delft by Jack Pronk has shown that elephant yeast, when slightly modified can also create ethanol from non-edible ground sources (e.g. straw).

The recent discovery of the fungus Gliocladium roseum points toward the production of so-called myco-diesel from cellulose. This organism was recently discovered in the rainforests of northern Patagonia and has the unique capability of converting cellulose into medium length hydrocarbons typically found in diesel fuel. Scientists also work on experimental recombinant DNA genetic engineering organisms that could increase biofuel potential.

Scientists working in New Zealand have developed a technology to use industrial waste gases from steel mills as a feedstock for a microbial fermentation process to produce ethanol.

Third generation biofuels

Algae fuel, also called oilgae or third generation biofuel, is a biofuel from algae. Algae are low-input, high-yield feedstocks to produce biofuels. Based on laboratory experiments, it is claimed that algae can produce up to 30 times more energy per acre than land crops such as soybeans, but these yields have yet to be produced commercially. With the higher prices of fossil fuels (petroleum), there is much interest in algaculture (farming algae). One advantage of many biofuels over most other fuel types is that they are biodegradable, and so relatively harmless to the environment if spilled. Algae fuel still has its difficulties though, for instance to produce algae fuels it must be mixed uniformly, which, if done by agitation, could affect biomass growth.

The United States Department of Energy estimates that if algae fuel replaced all the petroleum fuel in the United States, it would require only 15,000 square miles (38,849 square kilometers), which is roughly the size of Maryland, or less than one seventh the amount of land devoted to corn in 2000.

Algae, such as *Botryococcus braunii* and *Chlorella vulgaris* are relatively easy to grow, but the algal oil is hard to extract. There are several approaches, some of which work better than others. Macroalgae (seaweed) also have a great potential for bioethanol and biogas production.

Ethanol from living algae

Most biofuel production comes from harvesting organic matter and then converting it to fuel but an alternative approach relies on the fact that some algae naturally produce ethanol and this can be collected without killing the algae. The ethanol evaporates and then can be condensed and collected. The company Algenol is trying to commercialize this process.

Distillates

However, if biocatalytic cracking and traditional fractional distillation are used to process properly prepared algal biomass, i.e. biocrude, then distillates can be produced, such as jet fuel, gasoline, diesel and others.

Fourth generation biofuels

A number of companies are pursuing advanced "bio-chemical" and "thermo-chemical" processes that produce "drop in" fuels like "green gasoline," "green diesel," and "green aviation fuel." While there is no one established definition of "fourth-generation biofuels," some have referred to it as the biofuels created from processes other than first generation ethanol and biodiesel, second generation cellulosic ethanol, and third generation algae biofuel. Some fourth generation technology pathways include: pyrolysis, gasification, upgrading, solar-to-fuel, and genetic manipulation of organisms to secrete hydrocarbons.

- GreenFuel Technologies Corporation developed a patented bioreactor system that uses nontoxic photosynthetic algae to take in smokestacks flue gases and produce biofuels such as biodiesel, biogas and a dry fuel comparable to coal.
- With thermal depolymerization of biological waste one can extract methane and other oils similar to petroleum.

Hydrocarbon plants or petroleum plants are plants which produce terpenoids as secondary metabolites that can be converted to gasoline-like fuels. Latex producing members of the Euphorbiaceae such as *Euphorbia lathyris* and *E. tirucalli* and members of Apocynaceae have been studied for their potential energy uses.

Biofuels by region

There are international organizations such as IEA Bioenergy, established in 1978 by the OECD International Energy Agency (IEA), with the aim of improving cooperation and information exchange between countries that have national programs in bioenergy

research, development and deployment. The U.N. International Biofuels Forum is formed by Brazil, China, India, South Africa, the United States and the European Commission. The world leaders in biofuel development and use are Brazil, United States, France, Sweden and Germany. Russia also has 22% of worlds forest and is a big biomass (solid biofuels) supplier. In 2010, Russian pulp and paper maker, Vyborgskaya Cellulose, said they would be producing pellets that can be used in heat and electricity generation from its plant in Vyborg by the end of the year. The plant will eventually produce about 900,000 tons of pellets per year, making it the largest in the world once operational.

Issues with biofuel production and use

There are various social, economic, environmental and technical issues with biofuel production and use, which have been discussed in the popular media and scientific journals. These include: the effect of moderating oil prices, the "food vs fuel" debate, poverty reduction potential, carbon emissions levels, sustainable biofuel production, deforestation and soil erosion, loss of biodiversity, impact on water resources, as well as energy balance and efficiency.