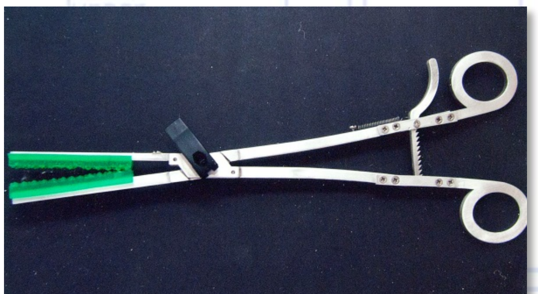
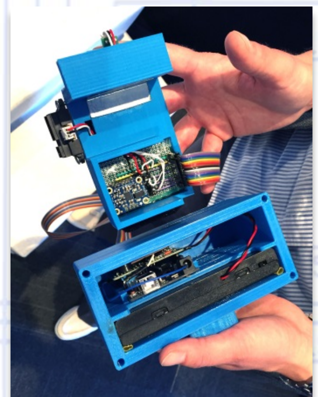
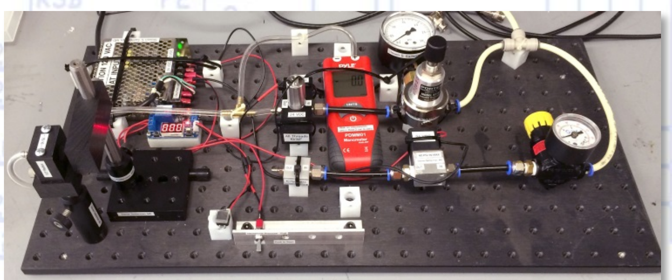
Introductory Medical Device Prototyping

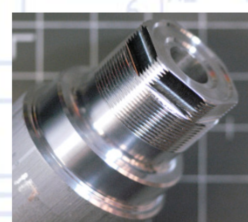
Biomaterials Part 1 - Overview

Prof. Steven S. Saliterman, http://saliterman.umn.edu/
Department of Biomedical Engineering, University of Minnesota









Topics

- Definition of a biomaterial.
- FDA medical device classes.
- Types of biomaterials.
  - Common concerns.
  - Materials from living systems.
  - Engineered natural materials.
  - “Intelligent” polymer systems & hydrogels
  - Synthetic materials:
    - Metals
    - Ceramics
    - Polymers (*Biomaterials Part 2* lecture)
- Adhesives and bone “cement.”
- FDA medical device categories.
- Examples of medical devices.

Definition of a Biomaterial

- "A *biomaterial* is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of *living systems*, the course of any *therapeutic* or *diagnostic* procedure."*
- Materials are part of a *medical device* and subject to the ISO 10993 requirements for medical devices, including *biocompatibility*.
- The FDA regulates medical devices in the United States, and divides devices into *Classes.*

*Elsevier Biomaterials Journal

FDA Medical Device Classes

Class I devices	Tongue depressors
	Bandages
	Gloves
	Bedpans
	Simple surgical devices
Class II devices	Wheelchairs
	X-ray machines
	MRI machines
	Surgical needles
	Catheters
	Diagnostic equipment
Class III devices	Heart valves
	Stents
	Implanted pacemakers
	Silicone implants
	Hip and bone implants

McKeen, L.W. in *Handbook of Polymer Applications in Medicine and Medical Devices*, 1st ed., Elsevier, William Andrew (2014).

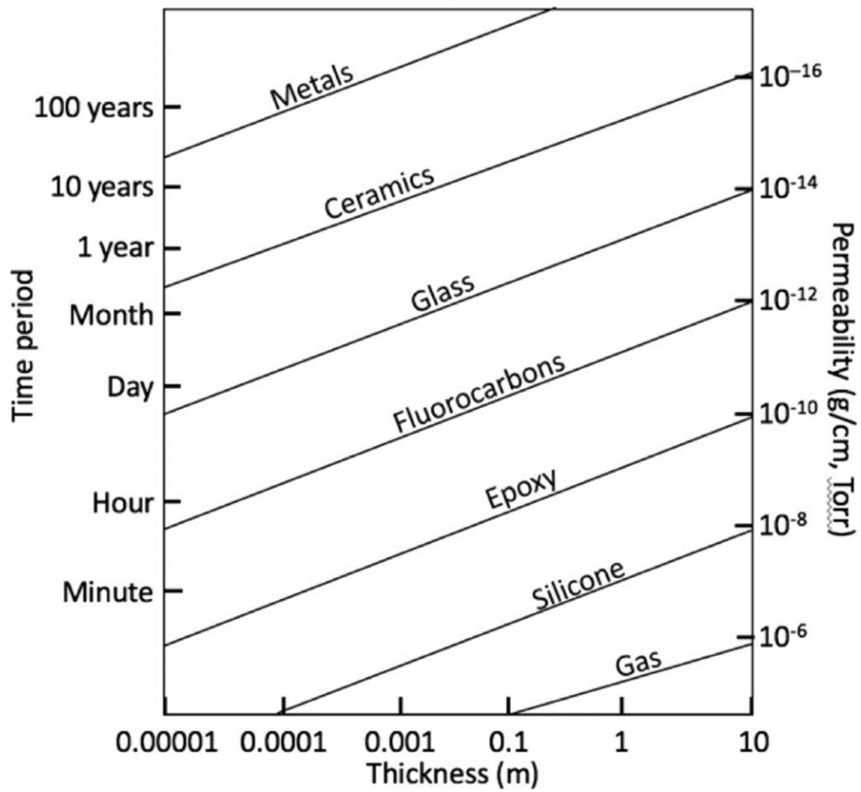
Types of Biomaterials

- Modified materials made from living systems:
  - Autograft, allograft or xenograft transplant materials.
  - Engineered natural materials.
- Synthetic materials made from:
  - Polymers
  - Ceramics
  - Metals

Some Common Concerns…

- Physical, mechanical, thermal and electrical properties.
- Machinability and moldability.
- Joining and welding.
- Porosity and pore morphology.
- Permeability.
- Degradation and degradation products.
- Biocompatibility (in vivo and in vitro).
- Sterilization

Permeability…



Joung, Y.-H. Development of implantable medical devices: from an engineering perspective. International neurourology journal 2013, 17(3), 98−106.

Materials from Living Systems

- Autograft
  - Graft of tissue from one point to another of the same individual's body
- Allograft
  - A tissue graft from a donor of the same species as the recipient but not genetically identical.
- Xenograft
  - A tissue graft or organ transplant from a donor of a different species from the recipient.

Some Natural Polymers as Biomaterials…

Material	Source	Property	Uses
Alginate	Algae (kelp)	Anionic polysaccharide, limited degradation, forms hydrogels	Wound dressing
Chitosan	Crustacean exoskeletons	Positively charged, enzymatic degradation, can form hydrogels	Hemostats, wound dressings
Silk	Synthesized by spider/silk worm	Slow degradation, reported biocompatibility issues	Sutures
Elastin	Animal tissues	Low solubility, reversible deformation, soluble precursor is tropelastin	Surgical mesh
Elastin-like Peptide	Synthetically produced	Highly repetitive amino acid motifs, reversible thermal phase transition	N/A
Collagen	Animal tissues, cell culture, fermentation	Abundant, triple helix structure, provide cell attachment sites	Dermal filler

Ratner, B.D., A.S. Hoffman, F.J. Schoen, J.E. Lemons, *Biomaterials Science*, Academic Press, New York (2013).

Material	Source	Property	Uses
Gelatin	Denatured collagen	Inexpensive form of collagen, used for cell attachment in culture	Gelfoam sterile sponge
Fibrin/ Fibrinogen	Animal tissues or plasma	Fibrin results from polymerization of fibrinogen with thrombin for clot formation	Fibrin sealant
Hyaluronic Acid	Animal tissues, bacterial fermentation	Lubricating polymer only non-sulfated glycosaminoglycans (GAG), negatively charged, hydrogels	Wound dressings, tissue engineering, bone grafts, drug del.
Heparin	Animal tissues/plasma	Anti-coagulant, negatively charged	Stent and catheter coatings
Chondroitin Sulfate	Animal tissues (sharks)	Major component of cartilage, negatively charged.	Nutritional supplements, wound dressings
Decellularized tissue	Animal tissues	Complex mixture of proteins/GAGs that retains tissue's ECM composition and structure.	Decellularized pulmonary artery patch

Ratner, B.D., A.S. Hoffman, F.J. Schoen, J.E. Lemons, *Biomaterials Science*, Academic Press, New York (2013).

Engineered Natural Materials

- Bone-Tissue
  - Direct injection of cells into the tissue of interest.
  - Implantation of cell-scaffold constructs (3D tissue structure).
  - Scaffold-based delivery of drugs and/or signaling molecules such as growth factors, capable of stimulating cell migration, growth, and differentiation.

J. Mitra, G. Tripathi, A. Sharma, B. Basu RSC Adv., 3 (2013), pp. 11073–11094

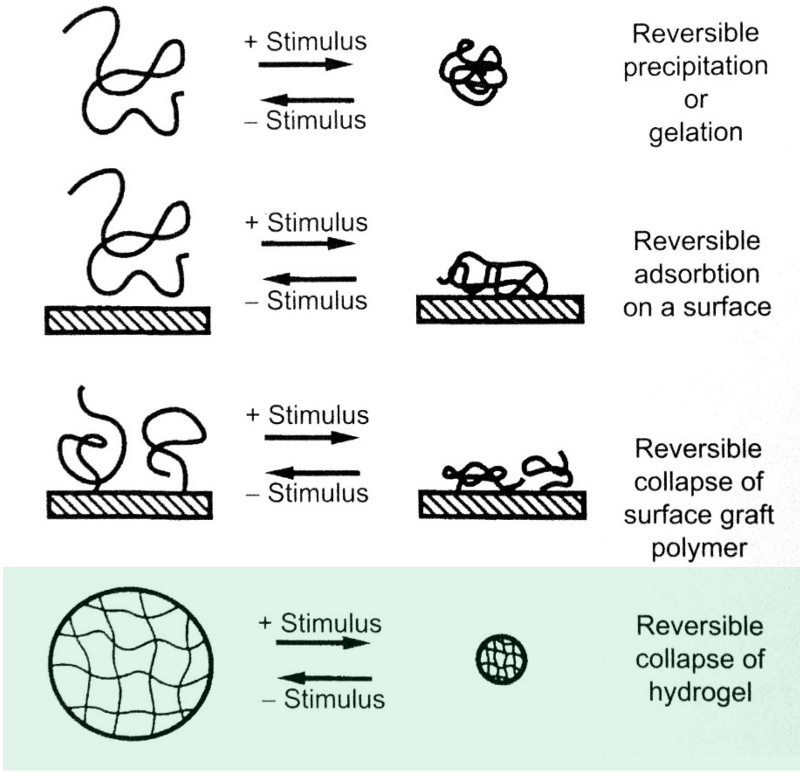
Scaffold Features…

- Biocompatible and bioresorbable constituents.
- Promotes the formation of the native anisotropic tissue structure.
- A highly porous structure with micro- and macro-porosity for the cell attachment, migration, bone growth, and vascularization.
  - Pore network promotes oxygen, nutrient and waste exchange.
  - A porous architecture can absorb impact energy.
  - Promotes osseointegration:
    - Pores smaller than 75 μm favor the formation of fibrous tissue.
    - Pores 75–100 μm support the formation of tissue with unmineralized osteoid.
    - Pores (>200 μm) facilitate enhanced bone ingrowth and vascularization.

Kumar, A. et al. Low temperature additive manufacturing of three dimensional scaffolds for bone-tissue engineering applications. Materials Science and Engineering. Volume 103, May 2016, pp. 1–39.

"Intelligent" Polymer Systems

- Potential Environmental Stimuli
  - Temperature
  - Ionic strength
  - Solvents
  - Light
  - Electric Fields
  - Mechanical stress
  - High Pressure
  - Sonic radiation
  - Magnetic fields
  - pH
  - Chemical agents
  - Enzyme substrates
  - Affinity ligands



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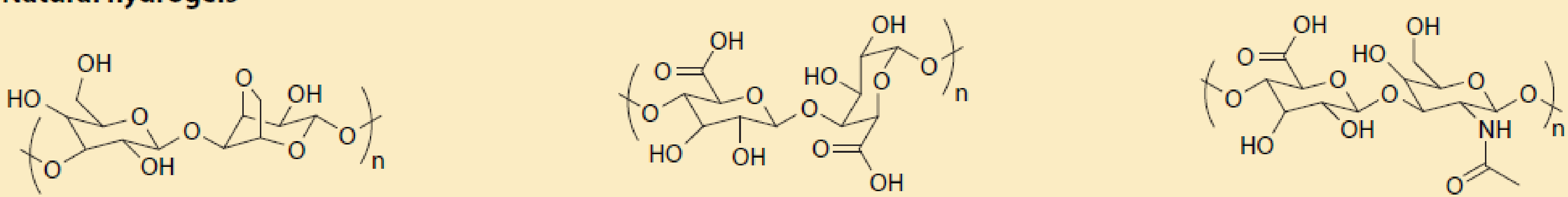
Natural Hydrogels…

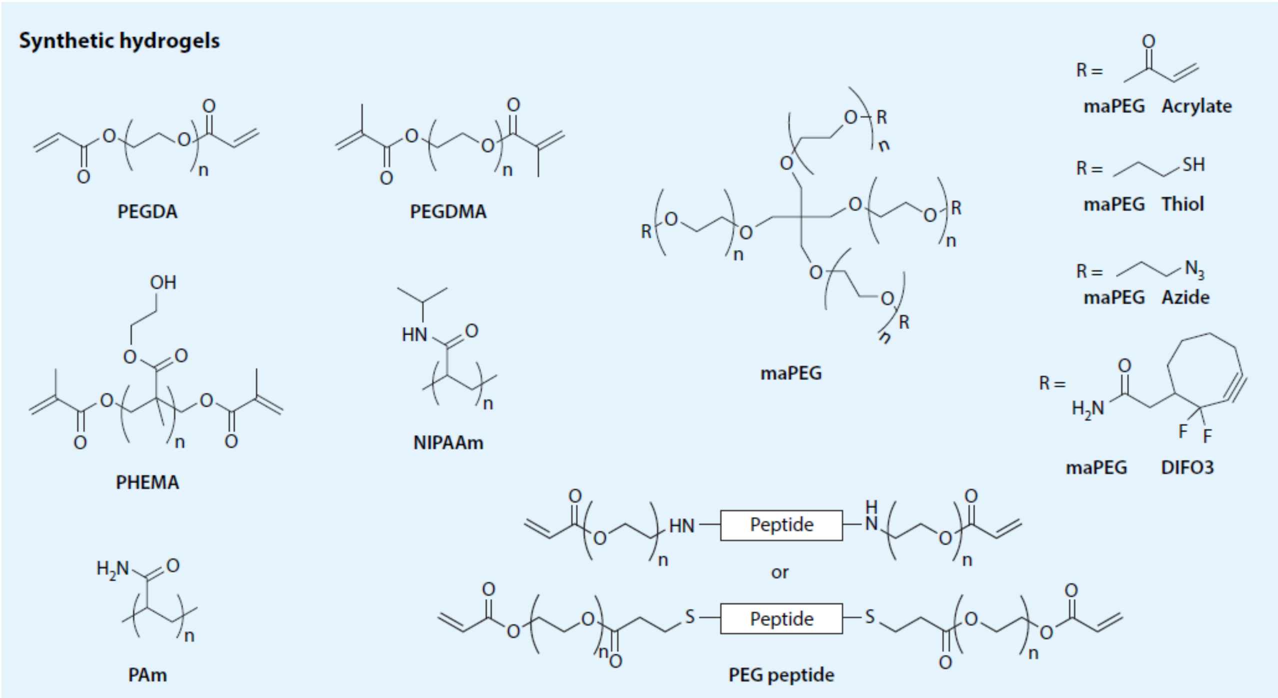
Natural hydrogels



Agarose | Alginate | **Hyaluronic Acid**

Bajaj, P. et al. 3D biofabrication strategies for tissue engineering and regenerative medicine. Annu. Rev. Biomed. Eng. 2014. 16:247–76

Synthetic Hydrogels…



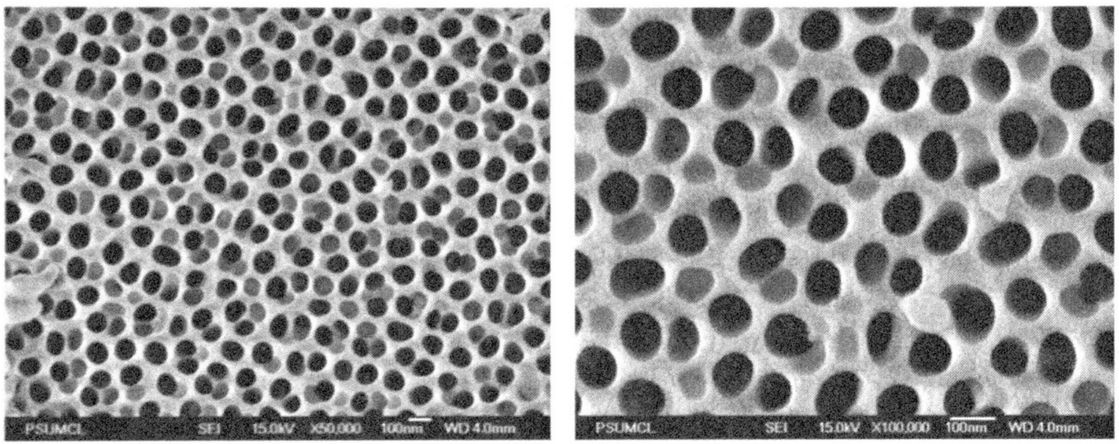
DIFO3, difluorinated cyclooctyne; HA, hyaluronic acid; maPEG, multiarm PEG; NIPAAm, *N*- isopropyl acrylamide; PAm, poly(acrylamide); PEG, poly(ethylene glycol); PEGDA, PEG-diacrylate; PEGDMA, PEG-dimethacrylate; PHEMA, poly(2-hydroxy ethyl methacrylate).

Bajaj, P. et al. 3D biofabrication strategies for tissue engineering and regenerative medicine. Annu. Rev. Biomed. Eng. 2014. 16:247–76

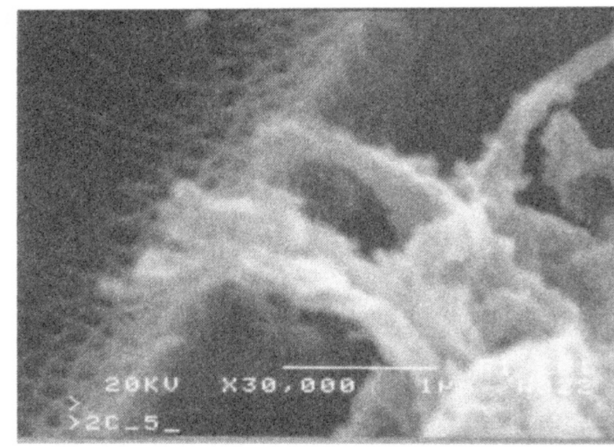
Ceramics

- Natural & synthetic hydroxyapatites.
  - The mineral in bone and dentin is a poorly-crystalline analog of the geologic mineral hydroxylapatite.
  - Ionic substitutions can change its properties.
  - HAP ceramics allow bone growth on the surface, allowing osteointegration.
  - Bioresorbable
- Alumina ceramics
  - Aluminum oxide Al_2O_3 – inert and resistive to corrosion in-vivo.
  - It is non-bioresorbable, and the body treats it as a foreign body and creates a fibrous encapsulation around it. Engineering of the interface can present this.
  - Used for femoral heads in hip replacements and wear heads in knee replacements.
  - Low wear on opposing UHMWPE plastic surfaces. High density increase strength.
- Zirconia ceramics
  - Zirconium oxide ZrO_2. Stabilized with Y_2O_3 for medical devices.
  - Used in oxygen sensors and fuel cell membranes – oxygen moves freely through the crystal at high temperatures.
  - Low electronic conductivity.

Alumina…



Nanoporous alumna fabricated by anodization



Osteoblast interaction with the nanoporous surface.

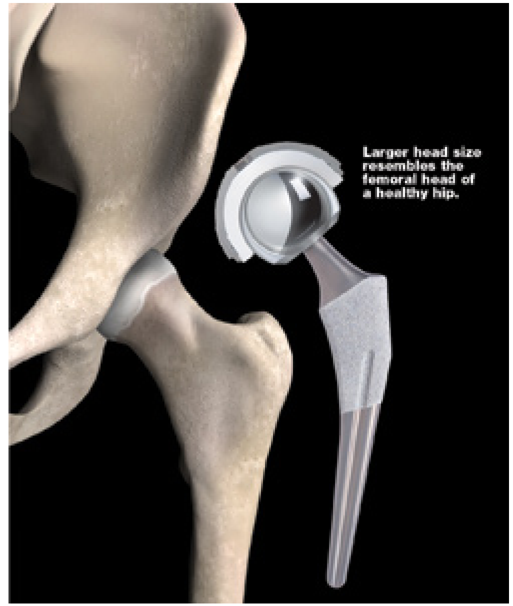
Ratner, B.D., A.S. Hoffman, F.J. Schoen, J.E. Lemons, *Biomaterials Science*, Academic Press, New York (2013).

Metals

- Gold, Silver and Platinum
- Tantalum
- Stainless steel
- Titanium (Ti) and alloys such as Nitinol (NiTi)
- Ni-free Co-Cr-Mo alloys
- Mg alloys
- Bulk metallic glasses (BMGs)

Titanium Implants…

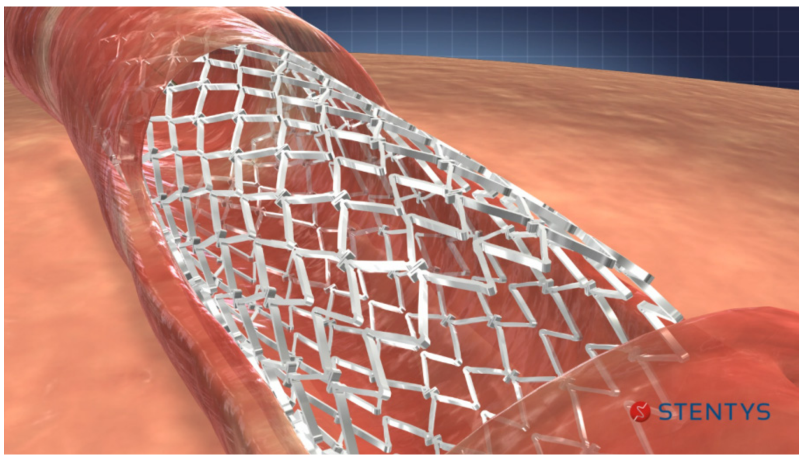
- Pelvis and hip reconstruction.

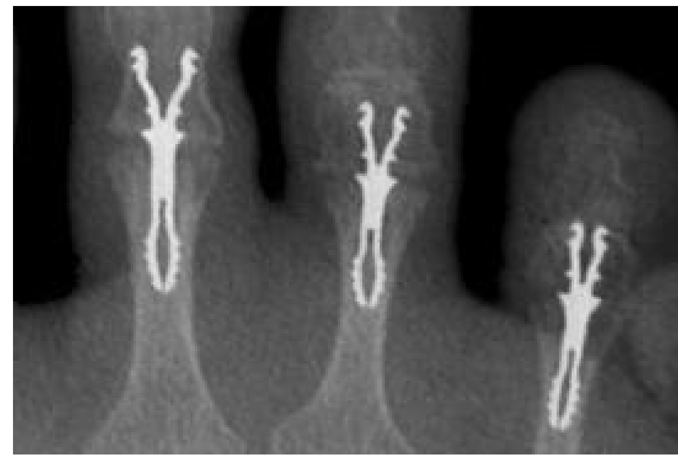


(Left) Image Courtesy of Alphaform and EOS
(Right) Images courtesy of Tube Hollows International

Nitinol Implants…

- Stentys vascular stent and BioMedical Enterprises HammerLock nitinol intramedullary fixation system.





(Left) Image Courtesy of Stentys.
(Right) Images courtesy of BioMedical Enterprises

Stainless Steel Products…

- Surgical instruments and laparoscopic trocar.

(Left) Image Courtesy of WiseGeek.com
(Right) Image courtesy of BRD

Comparison of Metallic Implant Materials…

	Stainless steels	Cobalt-base alloys	Ti and Ti-base alloys
Grade	Austenitic stainless steel	Cobalt–chromium alloy	α–β alloy
Composition	Fe Cr (17–20) Ni (12–14) Mo (2–4)	Co Cr (19–30) Mo (0–10) Ni (0–37)	Ti Al (6) V (4) Nb (7)
Young's modulus (GPa)	200	230	106
Tensile strength (MPa)	540–1,000	900–1,540	900
Advantages	Cost, availability, processing	Wear resistance, corrosion resistance, fatigue strength	Biocompatibility, corrosion, minimum modulus, fatigue strength
Disadvantages	Long-term behaviour, high modulus	High modulus, biocompatibility	Lower wear resistance, low shear strength
Uses	Temporary devices (fracture plates, screws, hip nails); used for total hip replacement	Dentistry castings, prostheses stems, load-bearing components in total joint replacement	Used in THRs with modular femoral heads; long-term permanent devices (nails, pacemakers)

Davis JR (2003) *Handbook of materials for medical devices*. ASM International, Materials Park, OH

Polymers

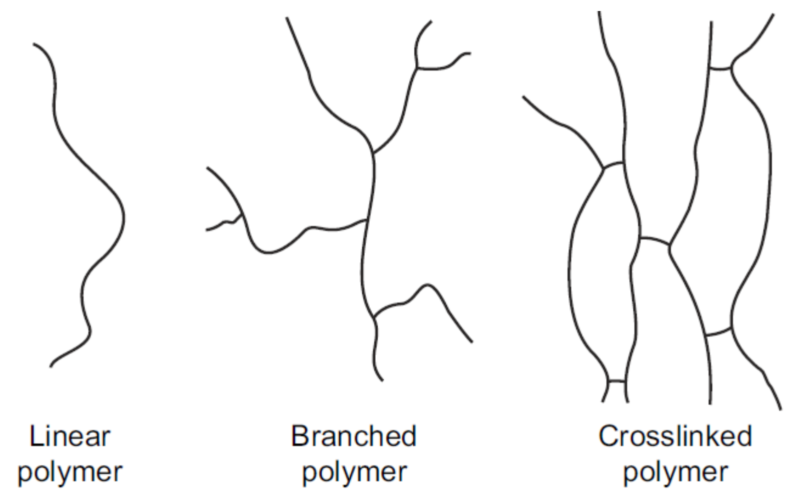
- Polymers are generally lightweight, inexpensive, easily mass produced, fracture tolerant, pliable and many are biocompatible.
- They may have certain favorable mechanical, electrical, optical, thermodynamic, kinetic and heat transport properties.
- They can undergo surface modification and functionalization, and are useful in microstructures (bioMEMS).
- They may be dielectric, electrically conducting, ion-conducting, ferroelectric, piezoelectric or photoelectric.
- May be used as coatings.

Polymer Structure…

- Polymers are a class of macromolecules consisting of regularly repeating chemical units joined to form a chain molecule.
- Monomers refer to either the repeating chemical unit or the small molecule which polymerizes to give the polymer. (Polymerization is the process of reacting monomers to form polymers.)
- Homopolymers consist of the same type of repeating unit,
- Copolymers consist of two (typically) or more types on monomers in differing ratios.
- Molecular structures may be linear, branched or networks.

Properties…

- For any given polymer there are multiple grades determined by size, structure, and additives.
  - Structures included linear, branched and cross linked:



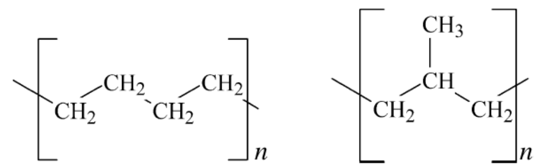
McKeen, L.W. in *Handbook of Polymer Applications in Medicine and Medical Devices*, 1st ed., Elsevier, William Andrew (2014).

Structure and Characteristics…

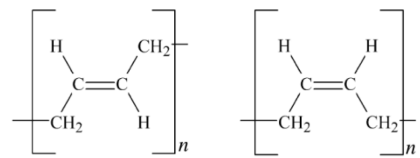
- Thermoplastics
  - Linear or branched molecules.
  - Soften and melt when heated and may be used for molding.
  - The molten state consists of a tangle mass of molecules. Upon cooling they may form a glass below the glass transition temperature (Tg), or may crystallize.
- Rubbers or elastomers
  - Network polymers that are lightly crosslinked and may be reversibly stretched.
  - The crosslinks prevent the molecules from coming apart during stretching and prevent flow when the material is heated.
- Thermosets
  - Network polymers that are heavily crosslinked and rigid.
  - They flow initially, but once cooled, cure and retain their shape.
  - These include epoxy resins and the phenol- or urea-formaldehyde resins.

Isomers…

- Compounds with the same molecular formula but a different arrangement of atoms.
  - Structural:



  - Geometric:



trans-isomer *cis*-isomer

  - Stereoisomers – syndiotactic, isotactic and atactic.

McKeen, L.W. in *Handbook of Polymer Applications in Medicine and Medical Devices*, 1st ed., Elsevier, William Andrew (2014).

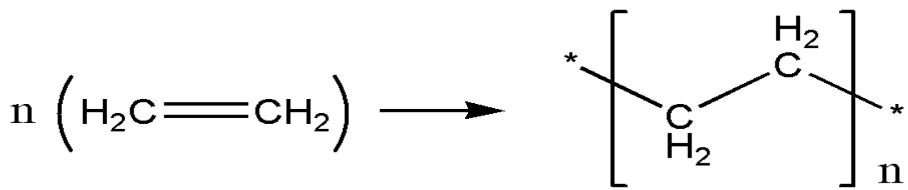
Additives…

- Reinforcing fillers – glass and carbon
- Particulate fillers – glass spheres, mineral powders, colors and extenders.
- Release agents –lubricants, liquids and powders (micro-powders of a fluoropolymer, silicon resins or waxes).
- Slip additives (altering the COF– e.g. PTFE).
- Catalysts
- Impact modifiers and tougheners.
- Others – radiation stabilizers, optical brighteners, plasticizer, coupling agents, thermal stabilizers and antistats.

McKeen, L.W. in *Handbook of Polymer Applications in Medicine and Medical Devices*, 1st ed., Elsevier, William Andrew (2014).

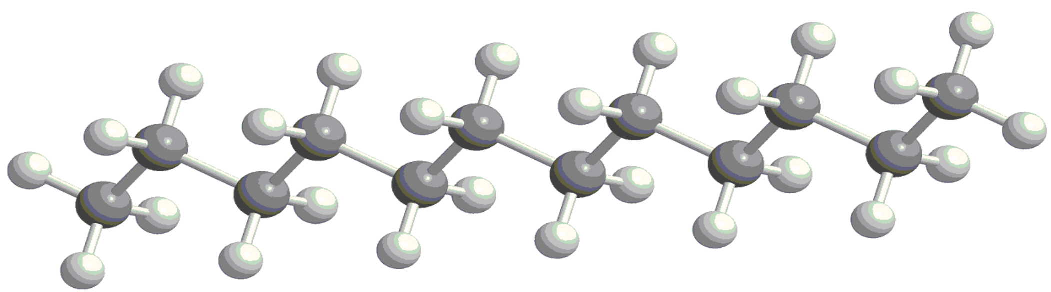
Polymerization…

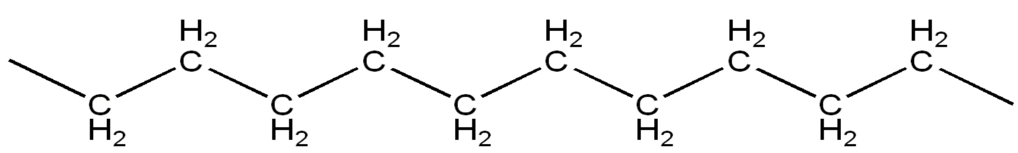
- In the simplest examples the chemical repeating unit contains the same group of atoms as the monomer, such as in the polymerization of ethylene into polyethylene.
- For addition polymerization to occur there must be a reactive double or triple bond.



- Initiation requires an activated species such as a free radical to attack and open the double bond forming a new activated species.

- Propagation occurs by adding one monomer after the next, with each monomer undergoing activation allowing addition of a subsequent monomer.
- Termination occurs by a variety of specific chain-terminating reactions.





Polyethyelene

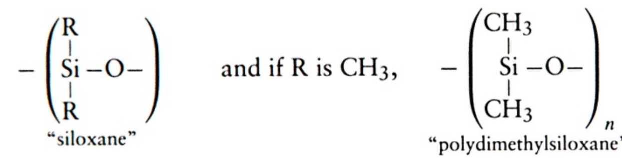
Polymerization Techniques…

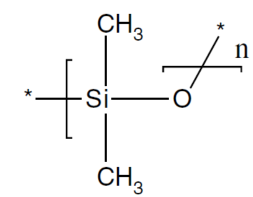
- Step-growth polymerization
  - Joining together of smaller molecules that contain two reactive group. Chains increase in size by either the addition of a monomer to either end, or by joining together smaller chains.
- Condensation polymers
  - Common condensation reactions of organic chemistry, including amidation and esterification. Polycarbonates and polyurethanes for example are produced in this manner.

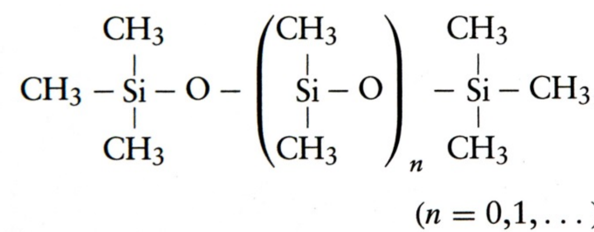
- Photopolymerization
  - Based on UV curing occurs between 225 and 550 nm. Free radical and cationic curing mechanisms may be utilized.
  - When the photoinitiator is exposed to UV, they break down leaving components with an unpaired electron, or free radicals.
  - Propagation occurs with addition of monomers, and transfer of the free radical down the propagating chain to continue the process of addition of monomers.
  - Termination occurs when the growing chain stops.
    - Acrylates are associated with free radical polymerization.
    - Structural polymers and environmentally-sensitive hydrogels may be photopolymerized through optically transparent lab-on-a-chip devices for in-situ fabrication.

Silcones…

- Poly(dimethyl siloxane) and Trimethylsilyloxy end-blocked polydimethylsiloxanes.
  - “Siloxane” is the basic repeating unit, and “R” can be substitute by methyl, phenyl, vinyl and trifluoropropyl groups.
  - Silicones have excellent biocompatibility and biodurability.
  - Flexible, but lower tensile strength or tear resistance compared to polyurethanes.
  - Degrade in strongly acidic or basic environments.
  - Like all hydrophobic materials they become quickly coated with proteins when placed in tissue contact.

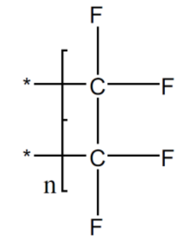


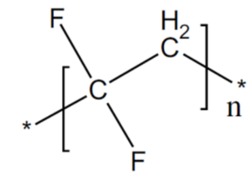




Fluorinated Biomaterials…

- Poly(tetrafluoroethylene) (PTFE, Teflon)
  - High chemical resistance, low and high temperature capability, low friction, and good electrical and thermal insulator.
  - Various forms are used in vascular grafts, tubing, catheters, introducers, issue repair meshes, sutures, coatings and other implants.
- Poly(vinylidene fluoride) (PVDF)
  - Soluble in highly polar solvents.
  - High dielectric constant, piezoelectric forms.
- Fluorinated Ethylene Propylene (FEP)
  - Improves the melt-processability of PTFE.
- Generic Equivalents (ePTFE, Gore-Tex™)
  - PTFE film extrusion useful for high-flow grafts and dialysis access.
  - Porosity for tissue ingrowth and "stabilizing" coagulation.
- Perfluorocarbon liquids.
  - Oxygen carrying blood substitutes.





Adhesives & Bone "Cement"

- Uses:
  - Joining plastic parts to metal and joining most other dissimilar materials requires using an adhesive.
  - Pressure sensitive adhesives (PSAs) and soft skin adhesives (SSAs) can be used for wearable monitoring devices, wound care products, medical device attachments, external prosthetic devices and specialty cosmetic applications.
- Requirements:
  - Must have the correct mechanical, physical and chemical properties.
  - Degree of adhesion varies with application.
  - Must be biocompatible if part of a medical device.
  - Be able to withstand sterilization processes.
  - Rapid and safe application, and quick curing if used in manufacturing.

- Examples:
  - Dymax Corp. 215-CTH-UR-SC, an LED-curable adhesive for assembling catheters made with Nylon 12 and polyether block amide (PEBA).
    - Useful for balloon-to-lumen bonding, hub-to-lumen bonding, marker bands and manifold bond joints. Recommended bondable substrates include Nylon 12, polycarbonate, polyethylene terephthalate (PET), PVC, ABS and PEBA.
  - Henkel Corp. Loctite 4902 and 4903
    - Both cyanoacrylates bond reliably to plastics, rubber, metals. Loctite 770 or 7701 primers can be used to enhance bond strength on hard-to-bond substrates, such as polyethylene or polypropylene.
  - Bluestar Silicones:
    - Silbione HC2 2022 is for wound care applications.
    - Silbione RT Gel 4642 is formulated for wearable devices, scar management and transdermal drug delivery applications.

- Dow Corning :
  - Silastic® Medical Adhesive Silicone, Type A for bonding elastomers, synthetics, and metals for part fabrication and medical devices.
  - Pressure sensitive adhesives (PSAs) and soft skin adhesives (SSAs) for drug delivery and skin attachment.
- Bone Cement:
  - Polymethyl methacrylate (PMMA), is widely used for implant fixation in various Orthopaedic and trauma surgery.
  - PMMA acts as a space-filler that creates a tight space which holds the implant against the bone. Bone cements have no intrinsic adhesive properties, but they rely instead on close mechanical interlock between the irregular bone surface and the prosthesis. (Vaisha R.J., Bone cement . Clin Orthopedic Trauma. 2013 Dec; 4(4): 157–163.)

- Dymax UV curable adhesive being used to connect PEBA tubing with a Nylon part.

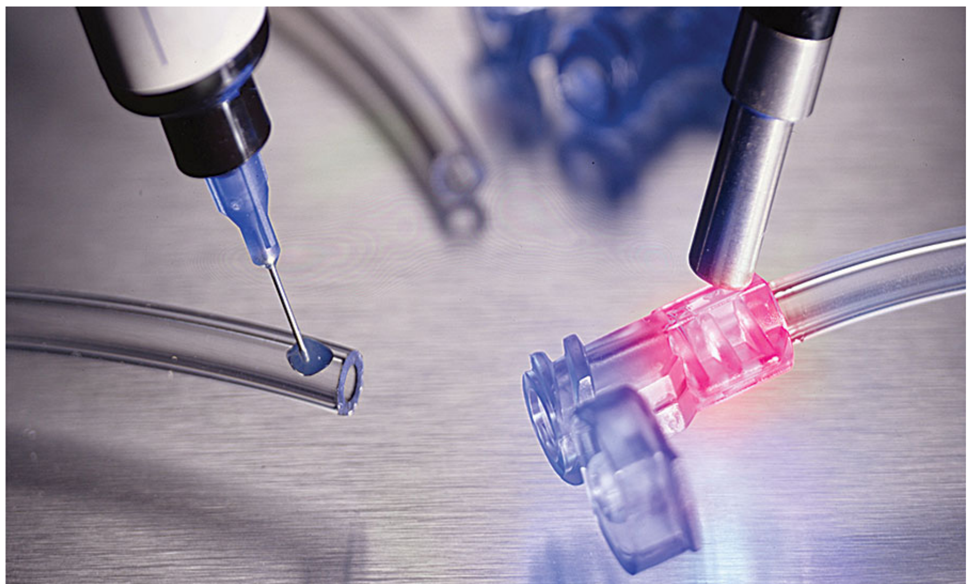
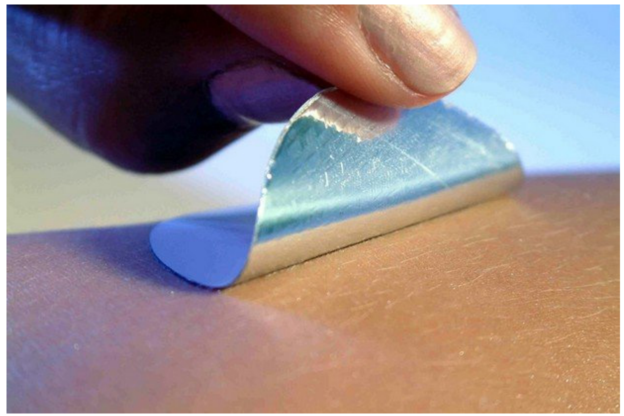


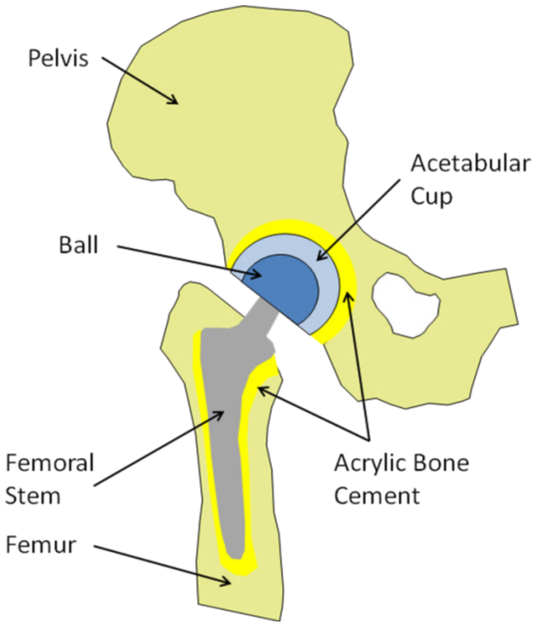
Image courtesy of *Assembly* Magazine April 2, 2015

- Skin application adhesives.



Images courtesy Dow Corning

- Bone cement.



Nicholas Dunne and R.W. Ormsby. MWCNT used in orthopaedic bone cements, in Naraghi, M. *Carbon Nanotubules – Growth and Application,* In-Tech (2011).

Summary

- Definition of a biomaterial.
- FDA medical device classes.
- Types of biomaterials.
  - Common concerns.
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