Checklist – WS 2013/14

- The following checklist about the subject matter shall help you to check your knowledge in biocompatible materials before registering for the written exam.
- No property values are to be known by heart for the exam, but you should have an idea about the magnitude in order to rank materials, if ever asked to do so, for a specific property (e.g., E-modulus, hardness, corrosion resistance, ...).
- No structural formula need to be known by heart.
- Further, the exact content of standards will not be asked. If necessary, you should be able to explain briefly how a specific mechanical test works (i.e. What kind of property is tested? What is needed to perform the experiment? What kind of result(s) do we get?)

Unit 1

- Definition of a biological system and biomaterials
- Interactions of a biological system and materials
- Steps in the selection process of a material for a specific application
- Definition of biocompatibility (and surface and structure compatibility)
- Compatibility of bone implants (according to Schenk)
- Material characteristics and factors influencing biocompatibility
- Definition of biofunctionality
    - examples of biofunctionality and corresponding requirements
    - Basic understanding of wear mechanisms

Unit 2

- Mechanical and physical properties
    - Basic understanding of *passivation, immunity* and *corrosion*; the underlying principle of passivation and corrosion, forms of corrosion in metals

Unit 3

- Mechanical and physical properties
    - degradation behavior of ceramics and polymers
    - Superelasticity
    - Behavior of materials towards external load
    - Hooke's law of elasticity and its application range
    - Aspects of stress-strain curves from tensile testing and corresponding material behavior
    - Stress raisers
- Basic knowledge of the significance of stiffness, creep, fatigue, toughness, ductility, indentation hardness and impact resistance

Unit 4

- Definition of Sterility, Sterility assurance level (SAL), D-value
- Materials, methods and requirements in terms of sterilization
- Different methods of sterilization (procedure, parameters and limitations)
- Packaging and monitoring
- Influence of sterilization packaging on properties of the device

Unit 5

- Implants definitions, requirements, objective and restrictions
- Implant property (biotolerant, bioinert, bioactive)
- Definition of Osteoconduction, Osteoinduction
- Determination of Biocompatibility
  - Definitions (Toxicants, Biological endpoint, ...)
  - *In vitro vs. in vivo* -systems
  - Sample preparation (biomaterial)
  - *In vitro* –systems (biological system: types, cultivation, preparation,..; tests and devices)

Unit 6

- Bone Tissue
- Tissue/Cell–Biomaterial–interaction
- Phagocytosis and Pinocytosis

Unit 7

- Surface properties
  - Factors influencing
  - Hydrophilicity, Hydrophobicity
  - Surface structures
  - Porosity, Roughness
- Surface modification (general principles)
- Surface structures and their characterization
- Contact angle (definition, significance, methods: Zisman, Vogler)
- Surface modification
  - Intention
  - Methods

Unit 8

- Natural Polymers
  - Cellulose
  - Alginate - hydrogels
  - Fibrin Sealants
  - Collagen
- Synthetic Polymers
  - Definitions; Polymer chemistry

Unit 9

- Synthetic Polymers
  - Classification
    - Thermoplastics (structure and properties) mechanical properties)
      - mechanical properties, permeability, optical properties
    - Elastomers (structure and properties)
    - Thermosets (structure and properties)

- Polyurethanes
- Silicones and Silicone Elastomers

Unit 10

- Silicones and Silicone Elastomers
- Biodegradable Polymers (Definitions, properties, applications, influencing factors, correlation mechanical properties bone/implant, mechanisms of degradation, problems)
- Polymers: different types, their properties and applications

Unit 11

- Bone cement
- Hydrogels
- Controlled Drug Delivery Systems

Unit 12

- Metallic biomaterials
  - Requirements, applications
  - Properties (influencing factor, problems)
  - Stainless steel (composition, properties)
  - Cobalt-based alloys (composition, properties)
  - Titanium and titanium-based alloys
- Ceramic biomaterials
  - Requirements, applications, properties
  - Classification
  - Aluminum oxides
  - Zirconium oxide
  - Calcium phosphates (porous, coatings, biodegradable types)
  - Bioactive glasses and glass-ceramics
- Carbons
- Anisotropic biocompatible fiber composites
- Implants of the musculoskeletal system
  - Ligaments and tendons

Unit 13

- Implants of the musculoskeletal system
  - Hip Joint Endoprosthesis
    - Requirements
    - different designs
      - THR (stem, head, acetabular cup)
      - BHR
      - BMHR
    - Materials
    - Resulting pairing
  - Knee Joint Endoprosthesis Systems

Biocompatible materials Checklist Ausarbeitung.
Unit 1

Definition of a biological system: A biological system is defined by a cell, or by an organized arrangement of cells that can reproduce, regenerate, repair itself by its own. It is an open-ended system. It has metabolic processes, it is a permanent exchange of energy, material and information. It is in direct and permanent contacte with its surrounding, that means it interacts and correlates continuously with its environment, it is temporarily in a dynamic, equilibrated state, and it adapts to the environment.

Definition of biomaterials: It is a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body.

Interaction of a biological system and materials:

- Bioerosion = Removal of matter from the surface of a biomaterial following implantation in the body without regard to the specific mechanism involved
- Biodegradation = Gradual breakdown of material by specific biological activity
- Biodeterioration = Process of change in characteristics of a substance, material or object that arise from its presence in a biological environment and which cause an undesirable reduction in overall quality

Steps in selection process of a material for a specific application:

- Translation: To express design requirements, limitations, objectives like mechanical and surface properties, field of application and duration, appropriate design and manufacturability
- Screening: To eliminate inappropriate materials
- Ranking: According to properties that meet requirements.
- Supporting Information: Consider limiting factors of top-ranked candidates like corrosion, wear, durability

Definition of biocompatibility: It describes the performance of a material in a specific application with an appropriate host response. It also describes the toxicology of the material. It is devided into:

- Structure compatibility: It describes the adaptation of the implant to the mechanical behaviour of the body tissue with the goal of "structural mimicry". It also includes the implant design and the microstructure.

- Surface compatibility: It describes the adaptation of chemical, physical, biological and morphological properties of the implant to the body tissue with the aim of clinically relevant and desired interactions.

- Toxicity: The degree to which a substance can harm humans or animals

→ Degrees:
- Acute: harmful effects through a single or short-term exposure
- Subchronic: toxic effects caused for more than one year but less than the lifetime of the exposed organism
- Chronic: the ability of a substance/mix of substances to cause harmful effects over an extended period (usually upon repeated or continous) exposure, sometimes lasting for the entire life of the organism.

→ Types:
- Cytotoxicity: damage to individual cells
- Immunogenicity: ability to provoke immune response (allergic reactions)
- Genotoxicity: property to alternate basepair sequence of the genom ⇒ mutation/cancer
- Mutagenicity: Mutation passed to the next gen.
- Carcinogenicity: directly involved in causing cancer.

Biocompatible materials Checklist Ausarbeitung
Unit 1

Compatibility of bone implants (Schenk):

- Incompatible: The implant disposes substances in toxic concentrations or antigens that cause immune response.
  Possible reactions:
  - allergy
  - antibody reactions
  - inflammation
  - necrosis
  - loosening

- Biocompatible: The implant disposes substances in non-toxic concentrations.
  Possible reactions:
  - encapsulation in connective tissue
  - low foreign-body reactions
    ↳ granulomatous inflammatory response. A characteristic feature is the formation of foreign body giant cells (collection of fused macrophages)

- Bioinert: The implant doesn't despose substances in toxic concentrations.

- Bioactive: positive interaction with tissue differentation
  Possible reactions: attachment/adhesion of bone along the interface between implant and tissue

- Inductive: Induction of heterotopic bone formation (= formation of bone where it is not normally found)

- Conductive: the material acts as a scaffold for bone deposition in an osteogene environment

Material characteristics and factors influencing biocompatibility:

Material characteristics:
- Bulk material: composition and micro-, nano-structure and morphology
- Crystallinity and crystallography (metals, polymers): degree of crystallinity + molecular symmetry
  - crystal structure
  - preferred orientations
  - grain size
- Elastic constants: including Young's modulus, shear and bulk moduli and Poisson's ratio
- Water content: hydrophobic/hydrophilic balance
- Porosity: macro, micro, nano
- Surface: chemical composition/gradients, molecular mobility on surface, topology, surface energy electrical and electronic properties
- Corrosion (metals): ion release profile, metal ion toxicity
- Degradation (polymers): degradation products, form and toxicity
- Accessory agents (polymers): Additives, catalysts, contaminants, products and toxicity
- Dissolution and degradation (ceramics): products and toxicity
- Wear: debris release profile

Factors:
- Quality and nature of clinical intervention
- Wide patient-to-patient variability: Depending on: age, sex, general health, current disease, physical mobility, lifestyle, pharmacological status
- Design of device
- Physical relationship between surface and body
- Presence or absence of micro-organisms
- Presence or absence of endotoxins

Bio-compatible materials Checklist Ausarbeitung
Unit 1

Definition of biofunctionality: Substitution of one or more functions in the biological system by the technical system

Examples of biofunctionality and corresponding requirements:

- Load transmission: It is the main function of implants used in the musculoskeletal system. Goals: support of bones, tendons, ligaments
  - Demands:
    - Sufficient stiffness, strength, toughness
    - good implant stabilisation in the tissue
    - sufficient fatigue resistance
    - surface conditions: regarding fatigue strength as well as stabilisation
  - Dimensioning & shaping:
    - Prevention of notch effects and stress concentration
    - Physiological load transmission into the bone
- Joint replacement:
  - Demands:
    - low friction + no wear
      ↳ because the coefficient of friction of cartilage in combination with the synovial fluid is very low ($\mu = 0.002$) => Goal: simulate it.
  - Dimensioning & shaping:
    - Combination of hard and soft materials (e.g. metal/ceramics + PE-UHMW)
      ↓ Ultra high molecular weight Polyethilen
  - Influences:
    - Chemical composition of the interfaces
    - Surface roughness
    - Lubrication
- Liquid transport: for cardiovascular transport of blood:
  - Demands:
    - Pumping in myocardial muscle
    - pipe as arteries/veins
    - controlling the flow directions as heart and venous valve
  - Dimensioning & shaping:
    - relative simple anfig. => different implants like pace maker, heart valves, blood vessels
    - however accurate replication is hard

- Optical and acoustical transmission:
  - Optical: - contact lenses
    ↳ Transmission and refraction of light
    - intraocular lenses
      ↳ replacement of the natural lenses in case of clouding
  - Acoustical: - cochlear implants
    ↳ 2 components: - external microphone + sound processor + transmitter system
    - implanted reciever + electrode system

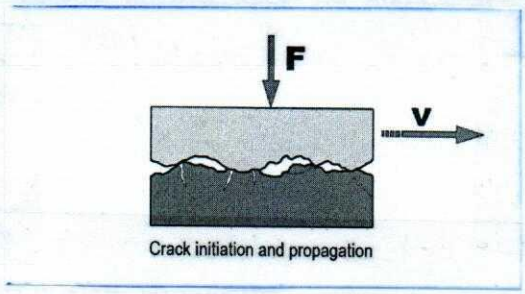
Basic understanding of wear mechanisms

- Wear phenomena are intimatelly linked to frictional processes
  ↳ if solid surfaces in relative motion are not separated
  ⇓
  wear can be expressed
  ↳ Solution: lubricantes

- In a tribological system different wear mechanisms can occure parallell
  ↳ consists of the surfaces of two components that are in moving contacht with one another and their surroundings.

- dominanting mechanism can change during load
- identification by wear particles and changes in surface topology

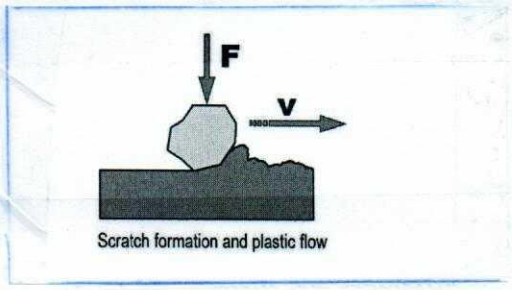
- main wear mechanisms:
  - Surface fatigue wear:
    - Usually associated with repeated stress cycling in rolling or sliding contact
    - strain near surface accumulates
    - cracks are initiated on weak, imperfect, damaged regions



Crack initiation and propagation

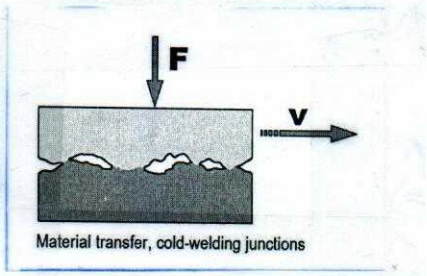
Biocompatible materials Checklist Ausarbeitung
Unit 1

- main wear mechanisms (Fortsetzung):
  - Abrasion wear:
    - Occurs in contact situations of direct physical contact
    - Different surfaces with considerably different hardness:
      - hard surface asperities press into softer surface
      - Plastic flow of softer surface occures
      - harder surface moves, ploughs and removes softer material as wear particle



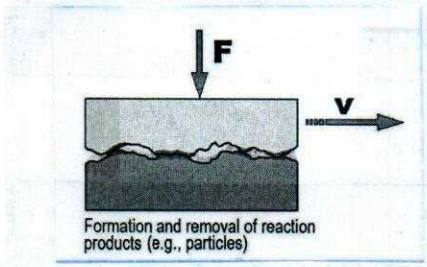
Scratch formation and plastic flow

  - Adhesive wear:
    - Material interactions play an important role:
      - Short range forces depending on nature of surface
    - occures quiet abruptly
    - "cold-welding" junctions



Material transfer, cold-welding junctions

  - Tribo-chemical wear:
    - System consists of: 2 surfaces and the environment
      - ↳ dynamic interaction of elements
    - continuous formation and removal of reaction products:
      - erosive-corrosive



Formation and removal of reaction products (e.g., particles)

Unit 2

- Mechanical and physical properties
  - Basic understanding of passivation and of the underlying principle:
    - Passivation: spontaneous formation or deliberate generation of shielding outer-layer of metals
    - Spontaneous formation = in oxigen or other corrosive environment, formation of a very thin oxide layer
      - → non-noble corrosion resistant metals: Cr, Al, Ni, Ti, Pb, Zn
    - Pilling-Bedworth-Ratio: describes the properties of the oxide-layer
      - → $PBV = \frac{V_{MeOxide}}{V_{Me}} = \frac{M_{MeOxide} \cdot \rho(Me)}{n \cdot M_{Me} \cdot \rho(MeOxide)}$

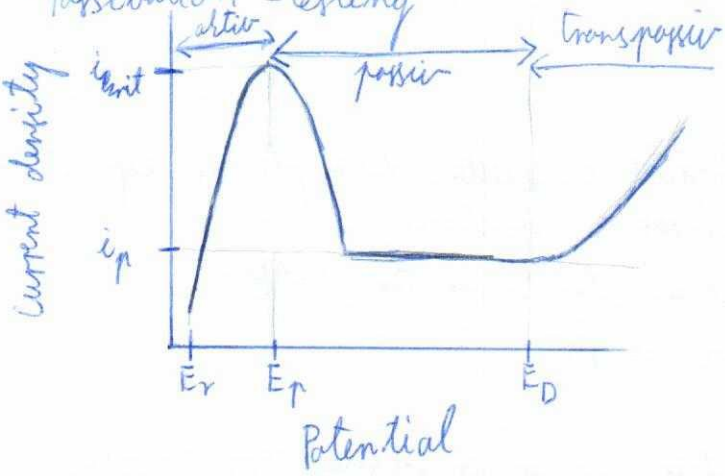
        n... number of metal atoms per oxide molecules
        V... Molar volume
        M... Molar or atomic mass
        ρ... density
      - → PBV < 1: porous and cracked oxide film (e.g. magnesium oxide)
        - Oxide is much smaller than metal ⇒ no passive layer ⇒ ∅ protection
      - → PBV > 3: chipping of the oxide layer (rust on iron)
        - Oxide is much bigger than metal ⇒ no passive layer ⇒ ∅ protection
      - → PBV = 1...3: formation of protecting, passive layer (Al, Ti, Cr on steel, tantalum)
    - Passivation methods:
      - Formation of oxide layers: often naturally/spontaneously
      - Conversion coating: conversion of metallic surfaces to "oxide-like", electrochemically passive states
        - oxide-like: because the structure is formed is complex, and includes -OH or -H subgroups as potentially crystalline
        - surface is a thin film (5-500 nm)
        - transparent or metallic colour

Biocompatible materials Checklist Ausarbeitung
Unit 2

- Passivation methods (Fortsetzung):
  - Formation of nitride layers: metallic devices, exposure to mineral acid (nitric-acid in H_2O) up to 30 mins

- Electropolishing:
  - Def: electrochemical process that removes the outermost surface layer of the metal
  - it is used to polish, passivate and deburr metal parts
  - Process:
    - Workpiece immersed in a temperature controlled bath of an electrolyte (concentrated acid solution)
    - Workpiece serves as the anode (+)
    - current passes from the anode, where metal on the surface is oxidized and dissolved in the electrolyte to the cathode (-)
    - at the cathode reduction reaction takes place, normally hydrogen is produced
  - Rough and protruding parts on the surface profile must dissolve faster than recess

- Passivation - testing



- Basic understanding of corrosion and the underlying principles and the forms of corrosion in metals
  - Corrosion: Physical interaction between a metal and its environment which results changes in the metal's properties.
    - ↳ These changes may lead to a significant functional impairment of the metal, the environment or the technical system which they form a part
  - The basic underlying reaction: Electron Transferring (Reduction-Oxidation-Reaction)
    - It increases the valence state of a metal
      - ↳ anode: $M \rightarrow M^{n+} + ne^-$
      - ↳ cathode: $M^{n+} + ne^- \rightarrow M$
  - Terms:
    - Corrosion damage: Corrosion phenomenon causing the impairment of the metal function, of the environment or of the technical system, of which they form a part
    - Corrosion failure: Corrosion damage characterized by the complete loss of operational capability of the technical system.
    - Corrosion resistance: Ability of a metal to maintain operational capability in a given corrosion system.
- Metals in human body:
  - "harboring" environment:
    - biological molecules disrupt the equilibrium of corrosion reaction
    - Proteins absorb on the surface
    - Change in PH
  - influence on mechanical properties:
    - change in visual appearance
    - loss of mechanical properties/functionality
    - change of mass
  - influence on biological systems:
    - irritates tissue + cell's behavior
    - change in cell metabolism
    - chemical environment changes (pH, oxygen partial pressure)
    - allergic reactions

Biocompatible materials Checklist Ausarbeitung
Unit 2

- Basic understanding of corrosion and the underlying principle and the forms of corrosion in metals (Fortsetzung):
  - Types:
    - Galvanic corrosion:
      - different metals and alloys have different electrode potentials
        ⇓
      - one acts as an anode the other as a cathode (in electrolyte)
      - anode dissolves into the electrolyte and deposit collects on the cathode (sacrificial anode)
      - electromechanical series:
        - anodic/less noble metals on the negative end of series (Zn, Al ..)
        - less noble metals are more likely to be attacked and corroded than noble/cathodic metals
    - Crevice corrosion:
      - one metal part + 2 connected environments
        - due to break down of passive layer by mechanical damage/structural defects/impurities
        - or local chemistry difference in a shielding area from that of the bulk fluid
      - chemistry inside ⇒ surface area inside will be an anode compared to outside
      - inside: oxidation $M \rightarrow M^{n+} + n \cdot e^-$
      - local chemical condition ⇒ passive layer reformation is hindered inside
    - Pitting corrosion:
      - localised corrosion in holes in metals
      - similar to crevice corrosion
      - difficult to detect
        ↳ too small/covered by corrosion products
    - Intergranular corrosion:
      - alloys, stainless steel
      - occures at grain boundaries which are depleted of corrosion-inhibiting elements
      - caused by: impurities/improper heat treatment/welding
      - stabilisation of stainless steel by adding Ti, niobium or tantalum ⇒ form carbids befor Cr

- Erosion corrosion:
  - removal of material by mechanical surface removal (= erosion) and corrosion
  - because of relative movements of single- and multiple-phase fluid/gas and solid material
    ↳ fluid and/or gas with abrasive particles
  - characterized by grooves, waves, rounded holes
  - usually directional pattern
- Stress corrosion cracking:
  - cracking caused by: tensile stress + corrosive environment + sensitive material against SCC
  - metal/alloy unattacked over most of its surface, while fine cracks progress through
  - appearance: brittle mechanical fracture
  - proceeds: perpendicular + to applied stress
- Microbiologically Influenced Corrosion:
  - Deterioration of metals by metabolic activity of microorganisms using constituents as energy source
  - In water/soil, pH 4-9, 0-50°C aerobic/anaerobic environment
  - mostly by dental implants
- Selective leaching:
  - involves: grain boundary depletion mechanisms
  - removal of one less noble element of alloy
    ↳ Demetalification: loss of self-healing property of passive layer

- <u>Basic understanding of immunity and the underlying principle:</u>

Immunity:
- after immersion in a corrosive environment, usually no corrosion reaction
- mostly noble metals

Biocompatible materials Checklist Ausarbeitung
Unit 3

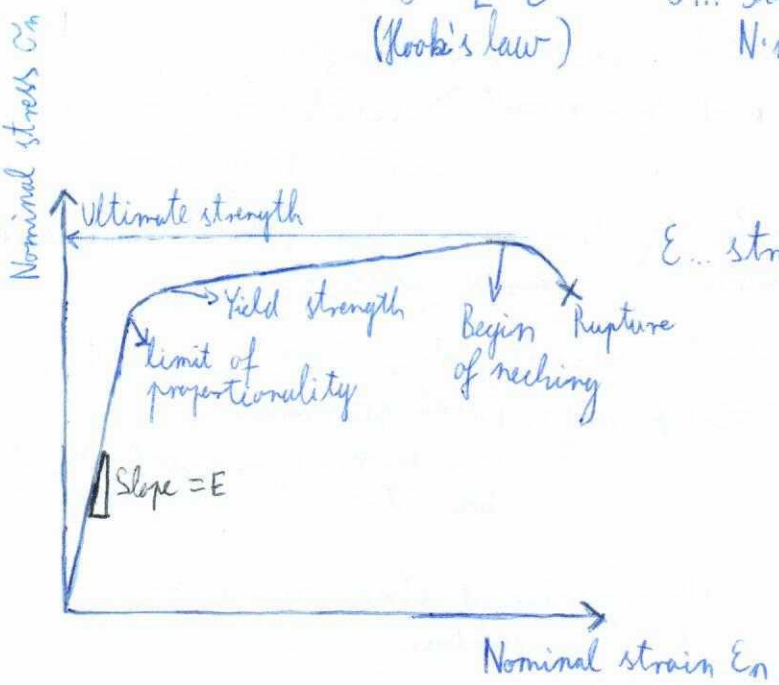
- Mechanical and physical properties:
  - degradation behavior of ceramics:
    - material imperfection => crack starting => abrupt failure
    - mostly almost entirely immune to corrosion
    - dissolving only in highly agressive environments (not in biological system)
    - smaller grain size in Total Hip Replacement => large avoidence of catastrophic fracture of ceramic head
  - Physical, mechanical issues:
    - chipping, during surgery/later impingements
    - increased range of motion => edge loading + striped wear
    - gait => cyclic micro-separation
    - Fretting corrosion
  - degradation behavior of polymers:
    - alteration of polymers by chemical reactions with their surroundings => => corrosion (like metals)
    - different physiochemical processes than in "common" corrosion processes
    - Rather in amorphous then in semicrystalline thermoplasts
      - ↳ heat softens the polymer
      - ↳ aging/degradation by physical/chemical/microbial agents
      - ↳ contact with specific chemical environment => accelerated brittle-crack formation
    - mechanical stress => activation of plastic => chemical reaction (reaction temperature is far below of the reaction temperature of unloaded plastics)
    - or mechanical stress => activation of plastic => interaction with contact fluid => weakening of intermolecular forces => deformation (with separation on micro- and macroscopic level at low stress)
    - Environmental stress cracking => brittle failure
    - stress concentration => micro-cavity formation
    - bulk polymers => ∅ chemical degradation
    - chemical environment => secondary linkage breaking
    - macro-cavity and craze formation/growing
    - premature initiation of cracking + embrittlement of plastics

- Superelasticity:
  - Nitinol: • (near) equiatomic intermetallic compound of Ti and Ni
    - ↳ there are almost the same amount of atoms of the two compounds
    - thermally / mechanically triggered solid-state transformation
      - ↳ Shape memory alloys undergo a phase transformation in their crystal structure when cooled from the stronger high temperature form (Austenite) to the weaker, low temp. form (Martensite)
  - Superelasticity: • stress-induced phase transformation
    - ↳ stress ⇒ stress-induced partial formation of Martensite above its normal temp. ⇒ change in Material to applied stress as a direct response
    - ↳ stress removed ⇒ material reverts to undeformed Austenite

- Behavior of materials towards external load
  - Elastic / Young's modulus: slope of the stress-strain curve in the elastic deformation range
    - ↳ the smaller the more elastic
    - ↳ $\sigma = E \cdot \varepsilon$ (Hooke's law)

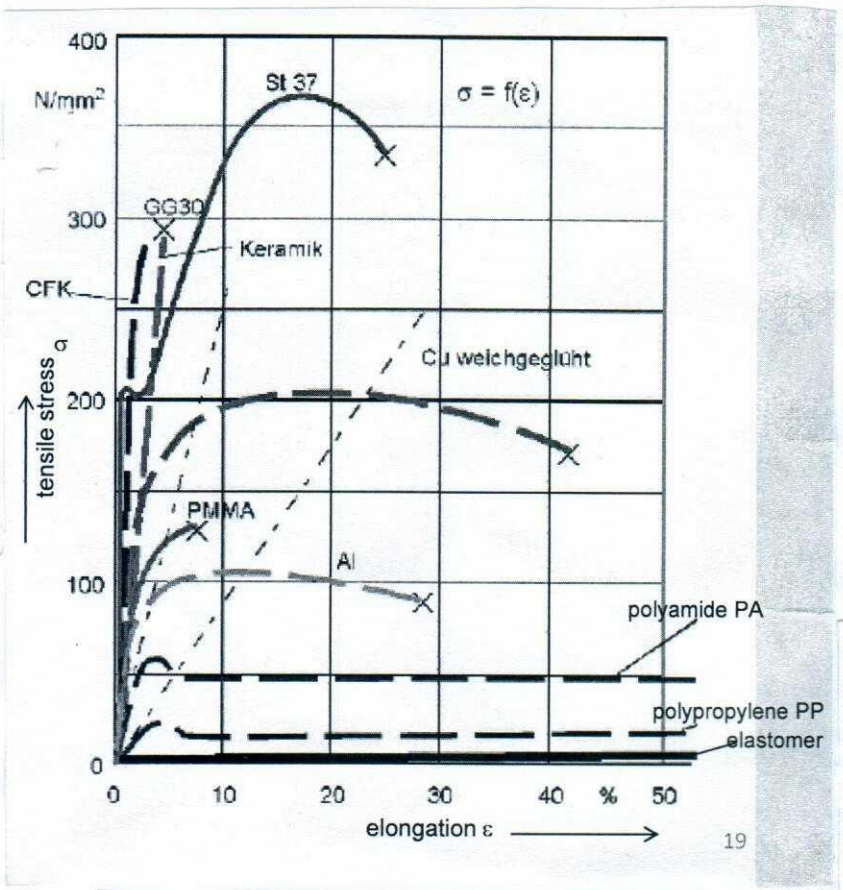
σ... Stress ... $\sigma = F/A$ ... F... force causing the deformation
$N \cdot mm^{-2}$ / Pa
A... Area to which the force is applied

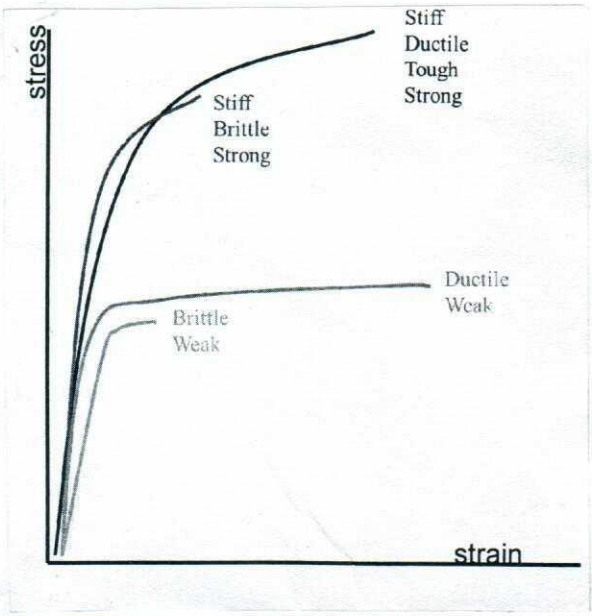
ε... strain ... $\varepsilon = \Delta l / l$ ... Δl... change in length
l ... initial length

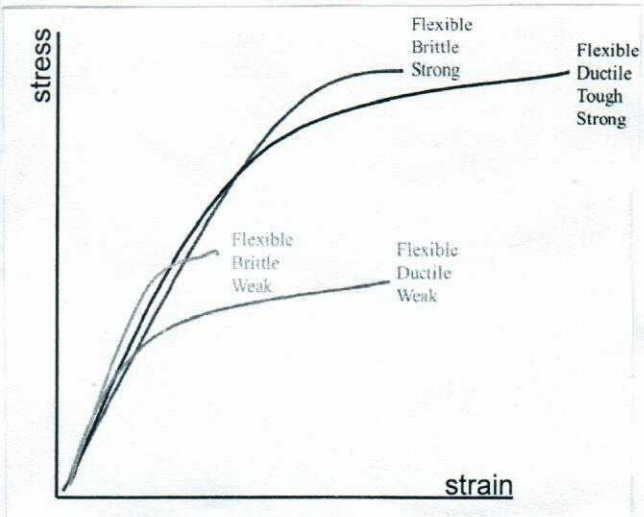


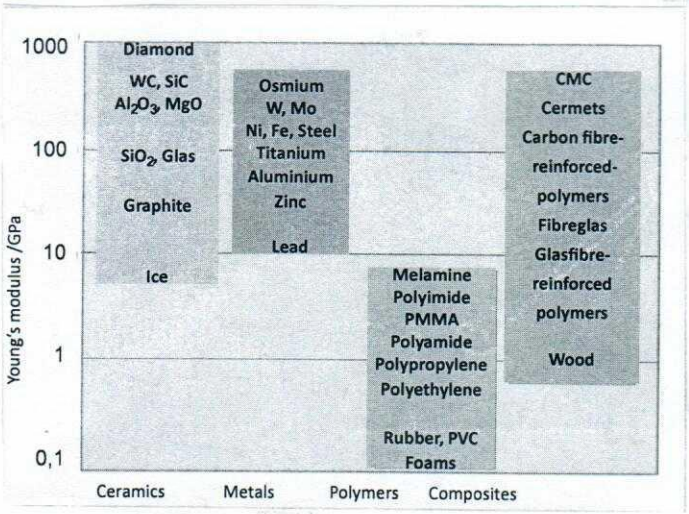
Biocompatible materials Checklist Ausarbeitung
Unit 3

Aspects of stress-strain curves from tensile testing and corresponding material behavior:









- Stress raisers:
  - in implants:
    - geometric discontinuities (e.g. sharp corners, screw holes)
    - cracks
    - inclusions (e.g. blowholes)
  - Maximum stress: $\sigma = \sigma_0 \left(1 + 2 \cdot \sqrt{\frac{D}{r}}\right)$

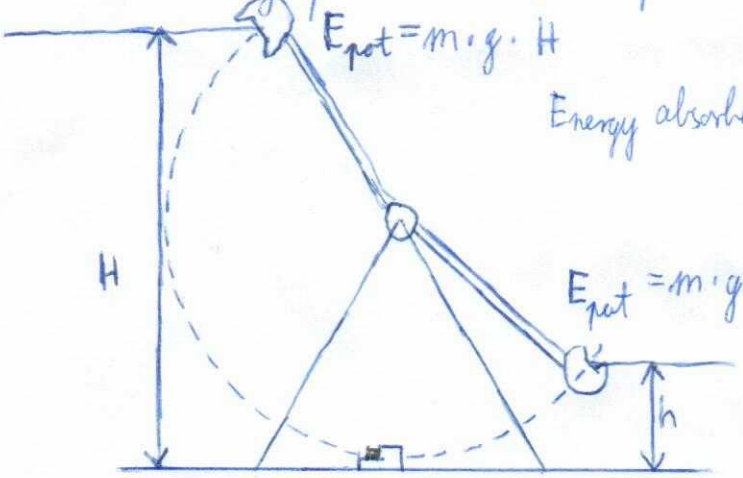
    σ_0... uniform stress applied to the material sample

    D... depth of the notch from the free surface

    r... radius of curvature of the notch tip

Stress distribution is not uniform

- Charpy impact test: performed on notched and un-notched specimens, to evaluate toughness behavior of plastic under impact loading

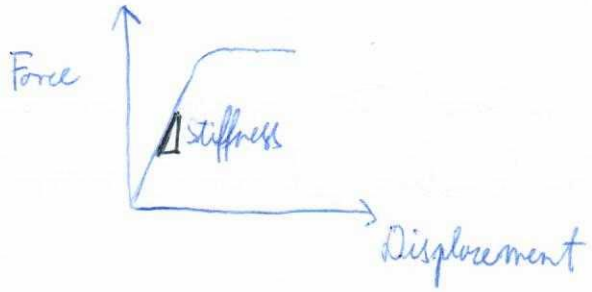


Energy absorbed/Notch impact energy:

$KV = m \cdot g \cdot H - m \cdot g \cdot h$

Biocompatible materials Checklist Ausarbeitung:
Unit 3

- Basic knowledge of the significance of stiffness, creep, fatigue, toughness, ductility, indentation, hardness and impact resistance:
  - Stiffness: The material and structural stiffness determines both
    - how much something deforms under load
    - how it shares (transfers) part of the load to other materials/structures with which it is in contact.



  - creep: (Also cold flow) is the tendency of a solid material to move slowly/deform permanently under the influence of mechanical stresses.
    - Inlike brittle fracture, creep deformation does not occure suddenly upon the application of stress. Instead, strain accumulates as a result of long-term stress.
  - fatigue: Progressive and localized structural damage that occures when materials are subjected to cyclic loading
    - fatigue life = # of cycles needed to reach catastrophic failure
      - ↳ stages:
        - crack initiation: development of permanent damage via micro-structural changes.
        - Initiation of microscopic cracks: they join together and propagate through the material perpendicular to the stress
        - growth/coalescence of microscopic flaws into dominant cracks
        - stable propagation of dominant cracks
        - finale fracture
    - can lead to component failure at markedly lower stress than under static load conditions

- fatigue (Fortsetzung): • rupture: brittle-like or ductile
  - brittle-like → granular/shiny appearence
  - ductile → fibrous/dull appearence
  - smooth/burnished crack propagation
  - Small punch test

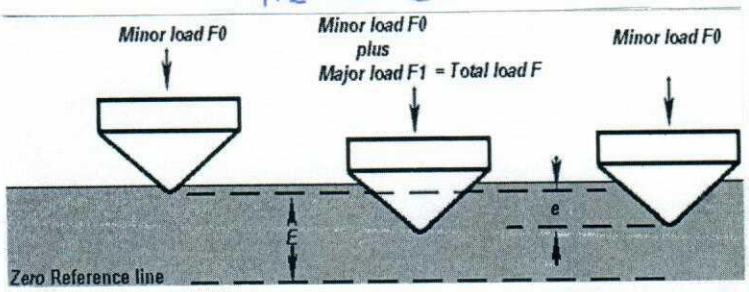
- toughness: The ability of a material to absorb energy and deform plastically without fracturing

- ductility: The ability of a material to undergo permanent deformation through elongation/bending at room temperature without fracturing

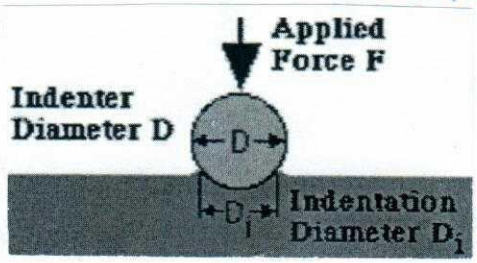
- hardness: Property of a material to resist plastic deformation, bending scratching, abrasion or cutting
  - Types of measurements:
    - Rebound hardness
      - → height of a diamant-tip, rebouncing from a material after release of a certain height
      - → related to elasticity
    - Scratch hardness
      - → resistance to plastic deformation/fracture due to friction applied by a sharp object
      - → harder material scratches softer
      - → Mohs scale
      - → Coatings: force that needed to destroy a dense film
    - Indentation hardness
      - → resistance to deformation against a compressive load, applied by a sharp object.
      - → typical tests: Rockwell, Vickers, Shore, Brinell

Biocompatible materials Checklist Ausarbeitung
Unit 3

- hardness (Fortsetzung): • materials with high hardness are:
  - often brittle
  - break brittle and do not form plastically
  - often not tough => do not compensate high stresses by plastic deformation
  - often more resistant against wear
- best combination: bulk material with high toughness + strength and surface material with high hardness
- Tests:
  - Rockwell: • Intender: diamond cone / steel ball
    - $HR = E - e$



  - Brinell: • Intender: ball with 10 mm diameter (D)
    - $HBW = 0.102 \cdot \frac{2F}{\pi \cdot D \cdot (D - \sqrt{D^2 - d^2})}$



load for 10 – 15 s (– 30 s)
• Standard format: 345 HBW 10/3000
↳ load in kg
↳ 10 mm
Wolfram ball (HBS => steel)

  - Vickers: Intender: diamond, square-based pyramide
    - similar to Brinell
    - $HV = 0.102 \cdot \frac{1.8544 F}{d^2}$
    - $t = 10 - 15 s$
    - Standard format: 300 HV 30/20
      - result
      - loading time
      - load in kgf

- Impact resistance: It decreases with decreasing elasticity => stiffer materials have less impact resistance

Unit 4

- Definition of sterility, Sterility assurance level (SAL), D-Value:
  - Sterility = absence of viable contaminating microorganisms including higly resistant bacterial endospores.
    - can only be considered in terms of probability, cannot be proven empirically
  - Sterility assurance = to protect a sterile product throughout its manufacturing life
  - SAL = . probability to detect a viable germ
    - describes efficacy of a sterilization process

    OR

    the probability that a given sterilization process has failed to destroy all of the microorganisms
  - D-Value = the time that is required at a certain temperature to kill 90% of the organisms being tested
- Materials, methods and requirements in terms of sterilization:
  - Material requirements:
    - cleanable
    - Drying behavior
    - Accessibility of the entire surface for the sterilizing agent
  - Method requirements:
    - material specific
    - need to be compatible with specific material properties (temp, irradiation, stress-cracking resistance) and design
    - maintain dimensional accuracy of a material, workpiece and its joints (welded/glued joint)
    - appropriate packaging
    - possibility of multiple sterilization
    - sterilization testing (chemical, bio-indicators), quality testing
    - no formation and release of toxic substances due to the sterilization process

Biocompatible materials healthcare engineering
Unit 4

- Different methods of sterilization (procedure, parameters, requirements
  - Hot sterilization:
    - Steam:
      - Parameters:
        - Time
        - Temperature
        - pressure

        } each can be manipulated
        - cycle requirements can vary significant depending on load type

      - Applications:
        - gravity:
          - most common and basic sterilization cycle
          - steam is pumped into a chamber containing air
          - density of steam < air => steam displaces air without mechanical assistance -> by gravity, air is forced through a drain vent

          for: glassware, unwrapped goods, waste, redbags, vented containers

        - Pre-/Post-Vacuum:
          - air is removed from chamber and load with a series of vacuum and pressure pulses
          - steam also penetrates porous areas of the load

          for: wrapped goods, packs, cages, porous materials, redbags

      - Procedure:
        - saturated steam at T ≥ 115°C and overpressure
        - common used clinical combination: 5 min at 134°C or 20 min at 121°C
        - ISO 11138: purity, maximum ion content of the steam, number of arrangement of the bio-indicators

      - Requirements:
        - absence of air (by fractionation)
        - Temp. profile
        - conditions of saturated steam

- Steam (Fortsetzung):
  - Usage:
    - in hospitals:
      - metallic surgical instruments
      - heat-resistant surgical supplies
      - stainless steel sutures
  - Limitations:
    - heat resistance
      ↳ some plastics melt at the temperature range applied
    - low heat conductivity / large devices
      ↳ heat requires extra time to reach centre of a device
    - moisture-sensitive substances
    - sharp instruments become dull

- Dry heat sterilization:
  - Prozedure:
    - dry heat at $T \geq 160°C$
    - mechanism: coagulation of proteins (de-naturation) and oxidative demage
    - needs higher temp and longer exposure time than steam sterilization
      - 160°C for 2 h, 170°C for 1 h
      - positive pressure for sterile integrity
    - convection:
      - by gravity: density of hot air < cool air ⇒ hot air will rise
      - mechanical convection
  - Applications:
    - No toxic residues
    - Usful for materials:
      - high temp resistance
      - not sterilisable by steam (e.g: hygroscopic powders)
  - Limitations:
    - Not suitable for: towels / papers / fabric → burnable
    - liquids in sealed container → burst

Biocompatible materials checklist Ausarbeitung
Unit 4

- Different methods of sterilization (procedure, parameters and limitations) (Fortsetzung):
  - Cold Sterilization:
    - Gas Sterilization:
      - Ethylene oxide (EO, EtO, C_2H_4O)
        - Procedure:
          - EO is flammable => mix with N_2 or CO_2
          - vessel evacuated = air removed
          - steam moisture introduced (>30% humidity)
          - gas injected (600 - 1200 mg/l)
          - T = 40 - 50°C for sufficient time to reach required SAL
          - re-evacuate chamber = remove EO
          - overpressure
            - -> 6% EO + 94% CO_2 at 1,7 bar
            - -> gas-mix not explosive
            - -> CO_2 affects desorption procedure positively

          underpressure (below atmospheric pressure)
            - -> 100% EO

        - Properties:
          - Toxic, irritating, carcinogenic, extremely flammable
          - strong microbicidal, virucidal, fungicidal, sporicidal effect
          - desorption time depends on material, temp, EO-concentration (min. desorption time = longest desorption time of the material)
          - highly diffusive: penetrates well through textiles, paper, some plastics (packaging)

        - Limitations:
          - handling
          - Time of desorption

        - Applications:
          - Surgical sutures, (Non-)Absorbable meshes
          - intraocular lenses
          - ligament/Tendon repair devices
          - vascular grafts/stents coated with bioactive compounds

- Formaldehyde (CH_2O)
  - Procedure: • Water vapor in combination with active diffusion by pressure changing (fractionated vacuum)
    → low-temp steam + formaldehyde ster. process
    - high humidity
    - 5 – 15 mg/l
    - removal of residues (rinsing with water vapour)
      → steam wash
    - sterilization temp: 50 - 80°C
  - Limitations:
    - less diffuse → insufficient penet
    - (• thermal sensitivity of material)

- Irradiation:
  - Types: e⁻-radiation: high dose rate, low penetration depth
    γ-radiation: high penetration depth, low dose rate
    ↳ also high density/metallic components are penetrated
  - Procedure: • radiation interacts and destroys DNA/cell membrane of microorganisms and deactivates them
    - radiation energy:
      - e⁻-radiation: cathode rays, under vacuum, 2 electrodes + high voltage
      - γ-radiation: by radioactive sources like ^{60}Co, ^{137}Cs
  - Pros:
    - Efficient + easy control
    - High penetration depth
      ↳ sterilization inside the package without high temp
    - No residue of ster. agent
    - Ster of components with complex geometries
  - Cons:
    - physical/chemical damages in the material
    - high costs

Biocompatible materials checklist Ausarbeitung
Unit 4

- Irradiation (Fortsetzung):
  - UV-radiation:
    - desinfection of rooms, rinsing water for desinfection machines, endoscopes, water
    - highest effectiveness: $\lambda \approx 254$ nm
    - UV-dose = intensity · exposure time
    - dose to kill micro-organisms/viruses:
      2,2–5 mW·s/cm² for Staphylococcus aureus
      34 mW·s/cm² for Hepatitis virus
  - Limitations:
    - low penetration depth => only surface sterilization

- Plasma-sterilization:
  - Temperature range: 37–60 °C, low pressure
  - typically hidrogen peroxide vapours that are converted in gas plasma
    - → generation of free radicals => reaction with molecules
    - → essential in the metabolism and reproduction of micro-organisms
  - Suitable in case of:
    - heat/moisture sensitive devices
    - No toxic residues
  - Limitations:
    - Free radicals can influence molecular structure of Polymers

- Sterile filteration
  - Retention of micro-organisms on the surface of filter material
  - Filter materials for the sterilization of liquids/gases are membrane filters made of cellulose derivates/synthetic polimers
  - Pore diameter: depending on the organism that is needed to be separated (usually 0,45 µm – 0,1 µm)
  - Limitations: too small organisms (e.g. Mycoplasma, Spirochaete)
    deformable (∅ membrane)

- Packaging and monitoring:
  - Stridization indicators:
    - upon exposure to sterilization procedure -> colour change
    - don't prove that the enclosed items are sterile

- Methods of monitoring sterilization processes:
  - Physical
  - Chemical
  - Biological
  - ISO11140 chemical indicators:
    - Class 1: Process indicators: for use with individual units
    - class 2: indicators for use in specific tests: used in spec. test procedures
    - Class 3: Single variable indicators: to react to one of the critical variables
    - Class 4: multi-variable indicators: to react to two or more of the critical variables
    - Class 5: Integrating indicators: to react to all critical variables
    - Class 6: Emulating indicators: cycle verification indicators

- Transdermal drug-delivery patches:
  - Liner: protects the adhesive and drug formulation during storage. Removed prior to use
  - Backings: outermost layer of the patch

- Influence of sterilization packaging on properties of the device:
  - Gamma radiation induces:
    - crosslinking or initiation of material degradation
    - oxidation of macro-radicals, that are persistant even years after irradiation

- class I: gas-permeable packaging
- class II: barrier packaging using multilayer polymer film barriers
- class III: ——— " ——— a combination of aluminium foil and multilayer polymer films

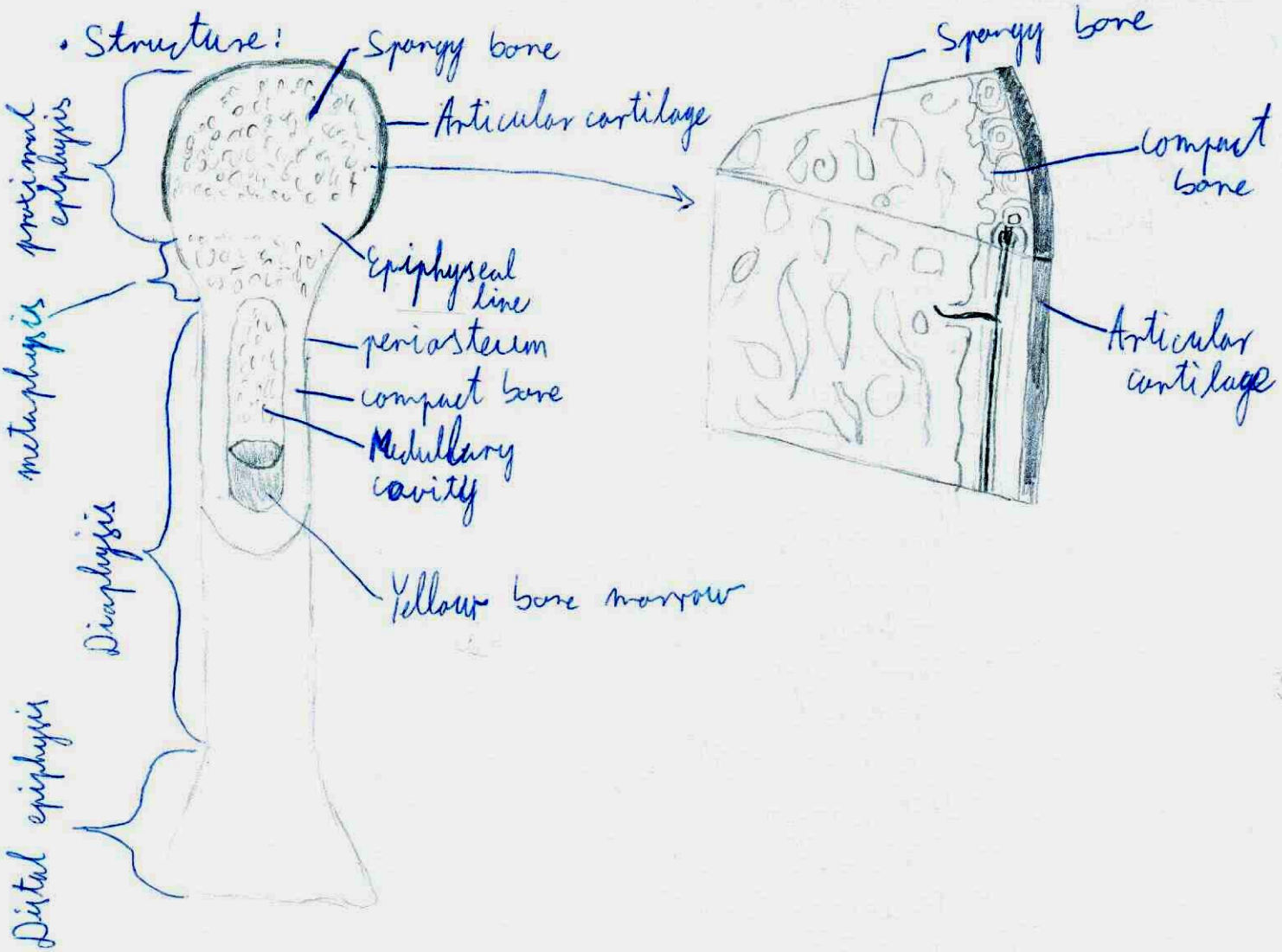
Oxidation level in γ-sterilized PE components: class III lowest class I highest

Biocompatible materials Checklist Ausarbeitung
Unit 6

• Bone Tissue:

- Classification:
  - Macroscopic
    - location
      - axial
      - cranial
      - appendicular
    - shape
      - long bones
        - most bones of limbs
        - fingers
      - short bones
        - skull
        - iliac crest
      - flat bones
        - skull
      - sesamoid bones
        - patella
      - pneumatised bones
      - irregular bones
        - spine
        - pelvis
  - histologic
    - woven (immature) bone
    - lamellar (mature) bone
  - structure
    - compact (cortical) bone
    - trabecular (cancellous or spongy) bone

- Structure:



- Construction:
  - Compact bone:
    - Osteons: 250μm thick, 1-5 cm long
    - Inner and outer circumferential lamellae
    - Mechanical properties:
      - Compressive strength: 170MPa
      - Tensile strength: 104-121MPa
      - Shear strength: 52MPa
  - Collagen:
    - Bone strength: mainly determined by tissue mass and stiffness, which is determined by the mineral phase
    - Bone toughness: collagen matrix contributes mainly to bone toughness
  - Spongy bone: similar composition and aggregation to compact bone, but different porosity.

Biocompatible materials Checklist Ausarbeitung
Unit 6

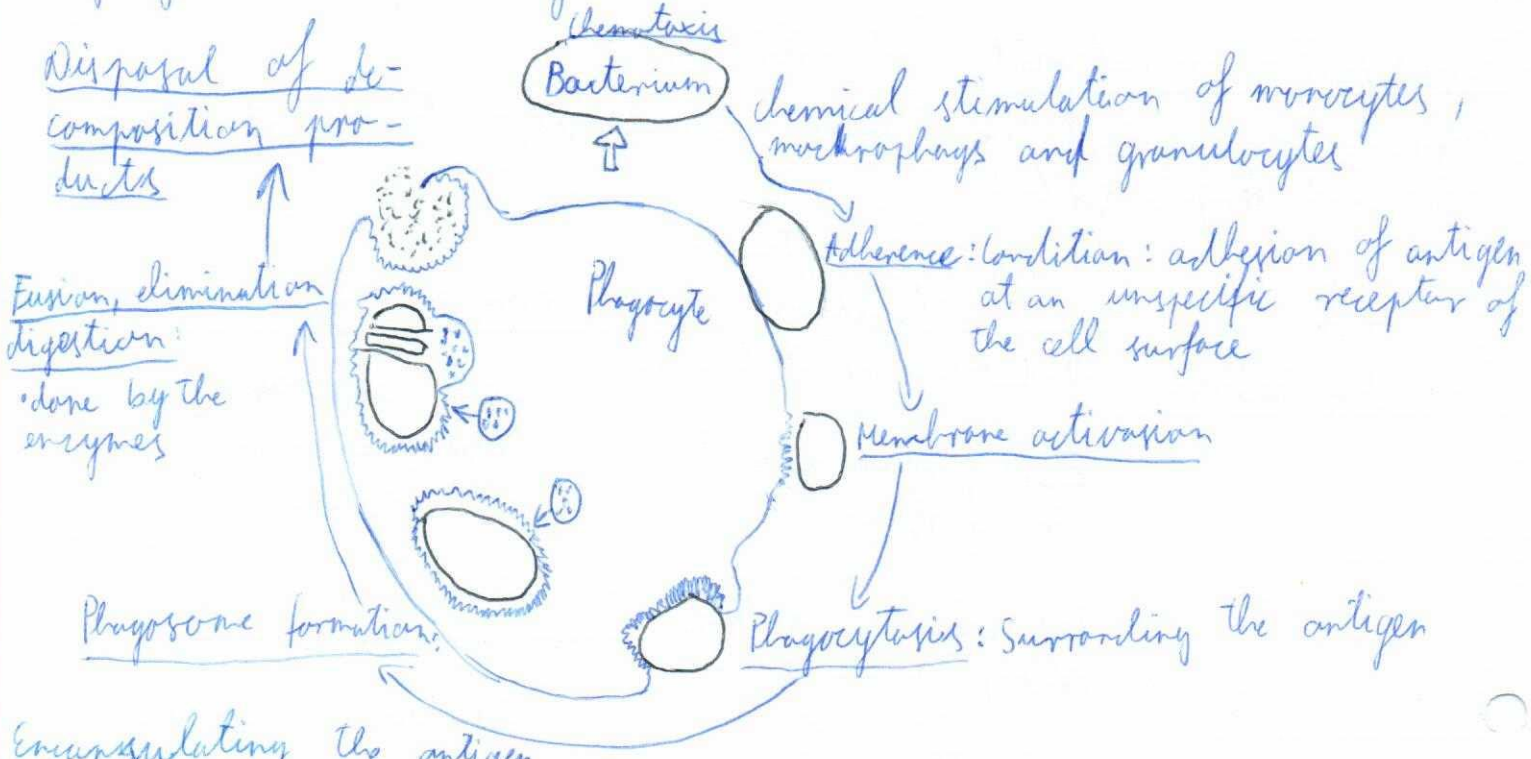
- Tissue / Cell - Biomaterial - interaction:
  - Events occure at the tissue-biomaterial-interface at varying time and length scale:

Time scale	Tissue-Biomaterial-interaction	Length scale
Fraction of a second	Water-surface interaction	Sub cellular Nano/micrometer <10 µm
Seconds	ECM protein adsorption an surface	
	Intracellular protein adsorption an surface	
Hours	Cell adhesion	Cellular micrometer 10 - 100 µm
	Spreading	
	Migration / Differentation	
Days	Cellular functions	Supra cellular macroscopic >100 µm
	Integration to tissue	

- Cell behavior/function (such as adhesion, cell morphology, migration orientation, and differentation) are influenced by biomaterial surface topography and chemistry
  → important design considerations during the development of an implant to improve integration and compatibility

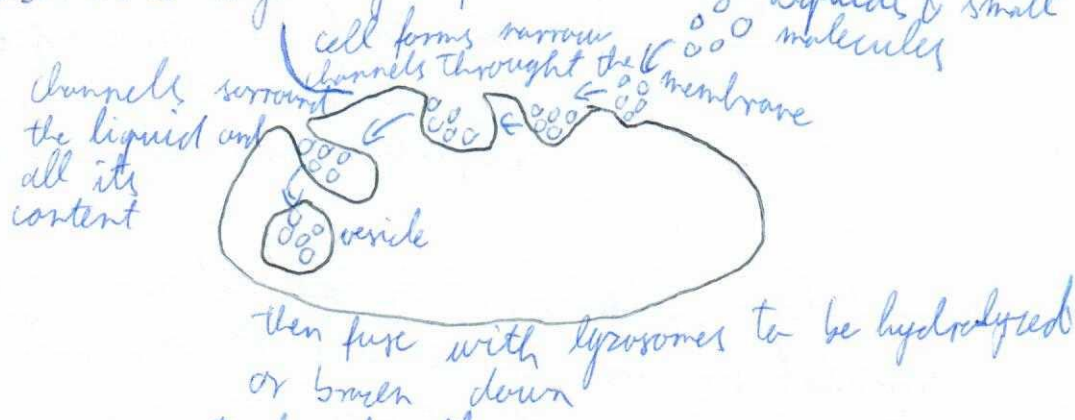
- Condition filming: it is belived that the condition film deposited on the biomaterial is responsible for the afibrilar interfacial zone host response
  ↳ thickness and appearence varies, forms regardless the material
- bone formation in the periprosthetic regions occurs in two directions of a titanium screw (from implant is 30% faster)

• Phagocytosis and Pinocytosis:



Encapsulating the antigen in a vacuole (phagosome)
- merging with granule that are filled with enzymes
- evacuation of the enzymes in the phagosomes

• Pinocytosis:
- Assimilation of dissolved molecules/liquids:
  - Proteins, Dextran
  - Primarily used for absorption of extracellular fluids
  - Cell-drinking
- Fuse with lyzosomes to hydrolyze particles
- Non-specific



• pinocytosis and phagocytosis part of endocytosis:
- cell absorbs molecules by engulfing them (substances that are important for cell)

Biocompatible materials Checklist Aufarbeitung
Unit 7

- Surface properties:
  - The surface region of a material is known to be uniquely reactive.
    - ↳ reason: Two dimensional crystal lattice illustrating bonding orbitals:
      - atoms in the center (bulk): crystal binding sites are associated
      - at planar exterior surface: one binding is unfilled
      - single atom at the top: 3 unfilled valences

- Surfaces readily contaminate:
  - ultra-high vacuum conditions can retard contamination
  - medical devices are used in conditions of athmospheric pressure
  - packaging can also induce contamination
- The surface of material is different from the bulk
- Hydrophilicity/Hydrophobicity:
  - ↓ Describes tendency to interact with, attracted to or dissolved by water/other polar substances
  - ↳ Substances that do not dissolve in/interact with water. It is the degree of being repelled from water/other polar substances
  - Proteins act as intermediate to enable the bonding of hidrophilic molecules onto hydrophobic surfaces.

- Surface structure:
  - different chemical composition:
    - selected elements/functional groups determine surface properties or properties of the interface in a certain environment
    - compositionally/structurally inhomogeneous => surface gradient (inhomogeneous in depth)
  - crystalline/amorphous surface:
    - degree of structural order in a solid
    - also determines bulk properties: hardness, diffusion, density
  - overcoat -> coating surface has different composition than bulk

- Porosity:
  - a measure of void spaces in a material, and is the ratio of the volume of voids over the total volume of the substance or a mixture of substances
  - morphological property => independent of material
  - To create: salt leaching / gas foaming / phase separation / freeze-drying / sintering -> depending on material

- Roughness:
  - A measure of the finely spaced surface irregularities

- Surface modification (general principles):
  - To be considered:
    - Thin surfaces
    - Delamination resistance
    - Surface rearrangement
    - Surface analysis
    - Commerciality

  - Thin surfaces:
    - as thin as possible => otherwise change in mechanical and functional properties / subjected to delamination
    - Ideally 3-10 Å:
      - In practice: thicker => ensure uniformity
      - thin layers are subjected to surface reversal and mechanical erosion
      - Some coatings: intrinsically specific thickness
    - Minimum thickness to garantee:
      - uniformity
      - durability
      - functionality

  - Delamination resistance:
    - Achieved by:
      - covalently bond the modified region to the substrate
      - intermixing components of substrate and the surface film at an interfacial zone
      - Intercorporating compatibilizing ("primer") layer
      - Intercorporating appropriate functional groups for strong intermolecular adhesion between substrate and overlayer

Biocompatible materials Checklist Ausarbeitung
Unit 7

- Surface modification (general principles) (Fortsetzung):
  - Surface rearrangement/"surface segregation":
    - Mobility-related alteration in surface structure and chemistry
    - Occurs readily as a result of:
      - diffusion/translation of surface atoms/molecules in respons to the external environment
      - newly formed surface chemistry can migrate from the surface into the bulk, or molecules from the bulk can diffuse to cover the surface
    - Driving force is thermodynamic - to minimize the interfacial energy → in any case sufficient atomic/molecular mobility must exist (to perform rearrangement in reasonable time scale)
    - Surface reversal can be prevented/inhibited by:
      - cross-linking
      - sterically blocking the ability of surface structures to move
      - incorporating a rigid, impermeable layer between substrate material and surface modification/environment
  - Surface analysis:
    - Thin layers
    - Methods often not sensitive enough
    - Contaminants are introduced easily
    - Monitoring reaction ⇒ ensure that intended surface is indeed formed
  - Commercialility:
    - production of mass products
    - too complex modifications might be too difficult/expensive to commercialize
    - minimizing the steps in surface modification process
    - design ~~of~~ each step should be insensitive to changes in reaction condition

- Surface structures and their characterization:
  - to be considered:
    - Sample should resemble as closely as possible the material / device being subjected to implantation
    - Methods have the potential to alter the surface
    - More than one method should be used
    - Analyzing methods easily "damage" polymeric / organic materials (compared to metals / ceramics / glasses / carbons)
    - Polymeric systems exhibit greater surface molecular mobility than inorganic systems.
    - Due to high surface energy, inorganic materials are contaminated more rapidly than polymeric materials.
    - Electrically conductive metals / carbons are often easier to characterize than isolators (using electron / X-ray / ion interaction method)

- Contact angle (definition, significance, methods: Zisman, Vogler):
  - Def: Contact angle represents the balance between the attractive forces of molecules within the liquid (cohesive force) and the attractive forces of the liquid molecules with the molecules that make up the solid surface (adhesive force)
    - Equilibrium at energetic minimum
    - Young's equation: $\cos\Theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}}$

      Θ: contact angle

      γ_{SV}: solid / vapor interfacial energy / solid surface free energy

      γ_{SL}: solid / liquid interfacial energy

      γ_{LV}: liquid / vapor —— " —— / liquid surface tension

      unknown

  - Significance:
    - Super hydrophobic: $\Theta > 140° \Rightarrow \emptyset$ wetting, water drips of strongly
    - Hydrophobic: $\Theta = 80° - 140° \Rightarrow$ bad wetting, water drips of
    - normal state: $\Theta = 10° - 80° \Rightarrow$ surface wetting: moderate – well
    - Hydrophilic: $\Theta = 0° - 10° \Rightarrow$ total wetting, water spreads on the surface
    - It characterizes surface topology / roughness / cleanliness
    - helps to quantify contamination / surface chemical heterogeneity
    - describes the effect of surface treatments / surfactants and other solutes

Biocompatible materials Checklist Ausarbeitung
Unit 7

- Contact angle (definition, significance, methods: Zisman, Vogler) (Fortsetzung):
  - Methods:
    - Zisman:
      - measures the critical surface tension γ_{cr}
      - Empirical rule
      - Permits a critical surface tension value, an approximation to the solid surface tension
        - when a liquid spreads freely on a certain surface => => its surface tension is $\leq$ surface energy of that surface
        - is a characteristic property of any given solid
        - any liquid with $\gamma_L < \gamma_{cr}$ will wet the surface
          ↳ value of the surface tension of a liquid that barely spreads on the material analyzed (assumption: $\gamma_{cr} \approx \gamma_S$)
    - Vogler:
      - uses the water adhesion tension τ^0
      - Hydrophilicity can be quantified by determining $\tau^0 (= \gamma_{LV} \cdot \cos\theta)$
      - Relation between aqueous adhesion tension and contact angle of the liquid drop:
        - Hydrophobic: $\theta > 65^\circ$
          ↳ surface: support protein adsorption in energetically favorable hydrophobic interactions but may induce strongly irreversible adsorption and denature the protein's native conformation – results in denaturation and loss of bioactivity
        - Hydrophilic: $\theta < 65^\circ$
          ↳ surface: have polar functional groups and electrical charges, and therefore, high surface energy, resulting in attachment with proteins that bind to surface less tightly because of attractions with surrounding water molecules
      - surface that very hydrophilic/phobic => inhibit cell attachment
      - surface with moderate wettability: protein adsorption without conformation change
        - positive cell attachment + growth

- Surface modification:
  - Intention:
    - modify blood compatibility
    - influence cell adhesion and growth
    - control protein adsorption
    - improve lubricity
    - improve wear resistance and corrosion resistance
    - alter transport properties
    - modify electrical characteristics
    - create surface texture, roughness
  - Methods:
    - chemical surface reaction:
      - reaction performed with surface atoms/molecules, but no overcoating with new layer
      - Specific: change only one functional group into an other with a high yield and few side reactions
      - Non-specific: leave a distribution of different functional groups at the surface
    - Radiation grafting and photografting
      - three types of reaction can be used:
        - ionizing radiation sources (Co-60 γ-rad.)
        - UV radiation
        - high energy electron beams
      - How does it work:
        1, radiation breaks chemical bonds
        2, formation of free radicals/peroxides/other reactive species
        3, reactive surface groups are exposed to a monomer
        4, monomer reacts with free radicals
        5, propagates as a free radical chain reaction, incorporating other monomers into a surface grafted polymer
    - Conversion coating:
      - goal: modify the surface of a metal into a dense oxide-rich layer
      - why:
        - to import corrosion protection → chemically passive state
        - enhance adhesivity
        - may enhance lubricity to metals
        - relevant for most musculoskeletal load-bearing surgical implants
      - how:
        - steel: treatment with phosphoric/chromic acid → phosphated/chromated
        - aluminium: electrochemically anodized in chromic/oxalic/sulfuric acid electrolytes
        - Titanium(-alloys): electrochemically anodized, electro-polishing

Biocompatible materials checklist Ausarbeitung
Unit 7

- Surface modification (Fortsetzung):
  - Methods (Fortsetzung):
    - Ion beam implantation:
      - injects accelerated ions with energies ranging from 10^1 to 10^6 eV into the surface zone of a material
      - usually implanted into metals/ceramics/glasses (= inorganics)
      - ions are formed from most atoms
    - Plasma treatment
      - advantages:
        - can be operated at controllable low pressure
        - has efficient ionization mechanism
        - spatially uniform and conformal => penetrating nature of low pressure gaseous environment => complex geometric shapes can be treated
        - Free of voids an pinholes
        - Plasma-deposited polymeric films can be placed upon almost any solid substrate and exhibit adhesion to the substrate
        - Unique film chemistries can be produced
        - excelent barrier film (⇐ pinhole-free and dense cross-linked nature)
        - show low level of leachables
        - easily prepared
        - surface is steral after treatment
      - disadvantages:
        - chemistry produced can be ill defined
        - apparatus can be expensive
        - uniform reaction with larg narrow pores => difficult to achieve
        - contamination
    - Silanization (specific chemical surface reaction):
      - used to modify hidroxylated/amine-rich surfaces (e.g: glass, silicon)
      - simple, high stability => covalent and/or cross-linked structure
      - increases contact angle (especially alkyl/fluoroalky silanes)
      - types of surface film structure:
        - catallyzed by traces of water => single layer
        - higher amount of water => thicker silane layer can be formed

- Self-Assembled Monolayers (SAM)
  - surface coating films
  - form as highly ordered structures on specific substrates =>
    => 2-dimensional crystals
    - N-alkyl silanes on hydroxylated surfaces (silica, glass, alumina)
    - Alkane thiols and dithiols on some metals (gold, silver, copper)
    - amines and alcohols on platinum
  - Strong exothermic adsorption of anchoring chemical group to surface => chemisorption driving force to fill every site on surface and displace contaminants
- Physical adsorption
  - Adhesion of atoms/ions/biomolecules/molecules of gas/liquid/dissolved solids onto another solid state
  - No chemical bonding => physisorption
  - substrate needs functional groups to interact with coating =>
    => strong adsorption
  - immobilizing a bioactive compound by:
    - electrostatic interactions
    - ligand receptor pairing

      ⇓

      drug delivery applications -> simple reversible
- Surface micro- and Nanopatterning (Topography modification)
  - conventional photolithography:

    1, liquid photoresist on substrate

    2, spin-coating: spin substrate => uniformly thick layer

    3, pre-bake: thermal treatment of photoresist => desorb solvent

    4, Exposed to a pattern (mask) of light => photochemical reaction =>
    => photoresist change => become soluble/insoluble (positive/negative photoresist) in developer solution

    5 post ~~x~~bake exposure: thermal treatment => strengthen/smoothen structural profile

    6. a, Develop: developer removes soluble parts, then hard-bake => dry + stable

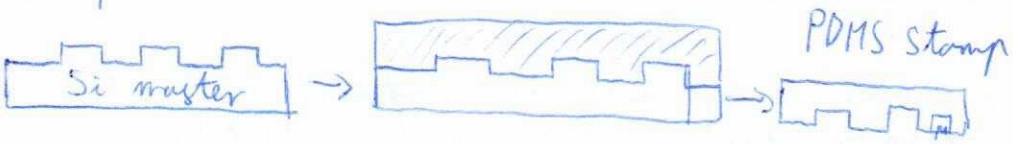
    b, Etch: liquid/plasma agent removes substrate, that are not protected

    c, Strip: removal of photo-resist

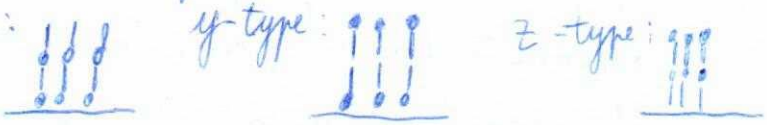
Biocompatible materials Checklist Ausarbeitung

Unit 7

- Surface modification (Fortsetzung):
  - Method (Fortsetzung):
    - Chemical Patterns - Microcontact printing:
      - created by chemical molecules
      - PDMS stamp with pattern dipped into solution with desired molecules (e.g. proteins)
      - molecules are transferred on biomaterial by printing the stamp



    - Langmuir-Blodgett (LB) Film deposition:
      - covers surface with highly ordered layer of amphiphiles (like lipids)
      - on water-air interface: head in water, tail in air
      - substrate immersed in solution with molecules
      - remove slowly by lifting up
      - multilayers: x-type: y-type: z-type:



Unit 8

- Natural polymers:
  - Cellulose:
    - Structural components of the cell walls of plants and algae
    - Consists of β(1->4)-linked D-Glucose units
    - well tolarated by tissue
    - non-toxic
    } => good biocompatibility
    - Application:
      - coating materials for drugs
      - additives of pharmaceutical products
      - blood coagulant
      - supports immobilized enzymes
      - artificial kidney membrane
      - wound care
      - implant material
      - scaffold in tissue engineering

- produced by bacteria (Gluconacetobacter xylinus)
  - high quality cellulose
  - organized as twisting ribbons of microfibrillar bundles
  - chemically same as from plant
    - ↳ but the cellulose nano-fibers are 100 times smaller than that of plants cellulose

- Alginate - hydrogels:
  - Application:
    - wound healing
    - drug delivery
    - tissue engineering
  - Structure:
    - 3-D cross-linked networks composed of hydrophilic copolymers with high water content (dispersion medium)
    - ratio of guluronate (G) and mannuronate (M) varies depending on the natural source
  - Extraction:
    - extracted from brown algae by treatment with aqueous alkali solutions (e.g. NaOH)
    - extract filtered/precipitated by adding $CaCl_2$
    - treatment with dilute HCl => transformation into alginic acid
    - purification: conversion into water-soluble sodium alginate powder
  - Bacterial biosynthesis: more defined chemical/physical properties
    - by Azotobacter and Pseudomonas

- Hydrogel formation and properties:
  - physicochemical properties dependent on:
    - cross-linking type
    - —— " —— density
    - molecular weight + chemical composition of the polymers

- Cross-linking types:
  - Ionic cross-linking:
    - combination with ionic cross-linking agents (e.g. Ca^{2+})
    - bind solely to guluronate blocks
      - ↳ structure allows high degree of coordination of divalent ions

Biocompatible materials Checklist Ausarbeitung
Unit 8

- Natural polymers (Fortsetzung):
  - Alginate - hydrogels (Fortsetzung):
    - Cross - linking types (Fortsetzung):
      - Covalent cross - linking:
        - improve physical gel properties
        - with e.g. poly(ethylene glycol-)-diamines
        - degradation rate/mechanical stiffness controlled by multi-functional cross - linking molecules
        - alginate + methacrylate + cross-linked by lasercexposure => clear, flexible hydrogel => sealing for corneal perforation
        - cross-linking agents are often toxic
      - Thermal gelatition: · Thermo sensitive hydrogels
        - response to temperature changes -> adjustable swelling => modulation of drug release on-demand
        - e.g. PNIPAAm
      - Cell cross-linking / cell - interactive alginate
        - gel modified with cell adhesion ligands
        - cell bind multiple polymer chains => long distance, reversible network formation, Ø chemical agents
  - Fibrin Sealants:
    - physiological 2-component adhesive
    - mimic final step of blood coagulation cascade
    - forms stable, physiological fibrin clot
    - assists hemostasis + wound healing
    - to replace sutures
    - Components: Component 1: Fibrinogen + Factor XIII + Aprotinin
      Component 2: Thrombinin + $CaCl_2$
    - Not able to: · Stop arterial bleeding
      - Stop severe venous bleeding
      - Replace surgical hemostatic techniques like ligations, clips, electrocoagulation
      - Replace sutures

- Collagen:
  - Most abundant structural protein component of the extracellular matrix (ECM)
  - various connective tissue in mammals
  - Provides insoluble fibres and microfibrils
  - Key role:
    - scaffold for cell attachment + migration
    - mechanical properties
    - specific info for cell
  - Arrangment of fibrils depends on functionality:
    - Tendon: parallell aligned collagen bundles => optimized force transmission
    - Skin: flat formation => tear strength
    - Sclera of eyes: plane network
    - Vitreaous humor: 3D-network, translucent
  - Isolation:
    - soluble collagen:
      - by enzymatic cleavage of telopeptides
        ↳ intermolecular crosslinks
      - Dispersion of collagen molecules + collagen aggregates in aqueous buffer solution
      - under certain conditions: fibril formation
    - Collagen fibrils:
      - removal of non-collagen components from tissue containing collagen
      - saline solution + skin/tendons => extraction
      - removing collagen molecules, that are not integrated yet
  - Application:
    - Drug delivery:
      - Shields in opthalmology
      - Sponges for burns and wounds
      - mini-pellets and tablets for protein delivery
      - collagen + liposomes => gel for sustained drug delivery
      - transdermal drug delivery
    - Barrier membrane:
      - Films of 0,01-0,5 mm thickness
      - biodegradable
      - from Atelocollagen (telepeptide-free
      - slow release profile

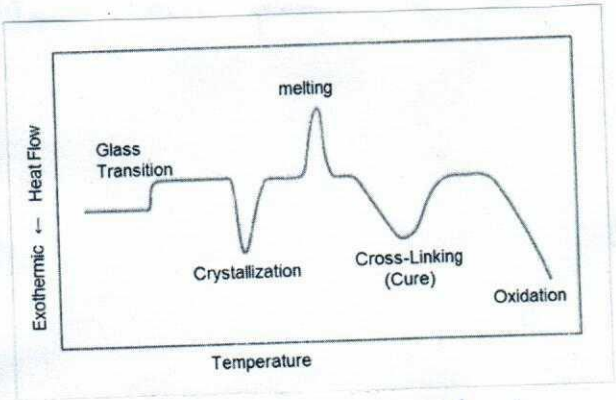
Biocompatible materials Checklist Ausarbeitung
Unit 9

- **Synthetic polymers:**
  - **Polymer chemistry:**
    - chain growth polymerization:
      - unsaturated (with double/triple bonds) monomer adds onto active site of polymer and regenerates active site
      - Initiation of growing: free radicals / carbocations (cationic) / carbanions (anionic) / organometallic complex (coordination)
    - Step-growth polymerization: multi-/bi-functional monomers forming a dimer, trimer
    - condensation: monomers with min 2 functional groups, polymer and low molecular weight product
    - addition: different monomers with functional groups and double bonds react by hydrogen transfer, no atom/molecular loss
  - Homopolymer = contains single type of unit
  - Copolymer = mixture of repeating subunits
    - Alternating copolymer: A B AB ABAB ....
    - Periodic copolymers: $(ABAAABBAB)_n$
    - Statistical copolymers: statistical sequence of different subunits depending on sterical factors and availability ABAAABBAB
    - Block copolymers: contains blocks of homopolymeric subunits AAABBBAAA

- **Classification:**
  - **Thermoplastics:**
    - Properties: high molar mass macromolecules
      - form an entanglement network
      - not cross-linked, but associated through intermolecular forces (Hydrogen bonds, Van-der Waals)
      - meltable / moldable
      - Soluble
      - At room temp: Soft to tough, ductile to brittle

- Structure:
  - Types:
    - amorphous:
      - Ø long-range order
      - glass transation
      - Ø melting, soften
      - transparent, often brittle
    - semi-crystalline:
      - amorphous + crystalline phases
        ↳ also periodic, repeating spatial units
      - glass transation
      - melting
      - translucent, often ductile

- Amorphous phase:
  - lower density
  - contains:
    - all structural irregulatories of polymer chain
      ↳ crosslinks, branching points
    - Catalyst residuals
    - oxidation takes place
    - Additives (= stabilizers: e.g: vitamin E plasticizer)
    - Entanglements (= physical crosslinks)
    - non-ordered polymer chain segments

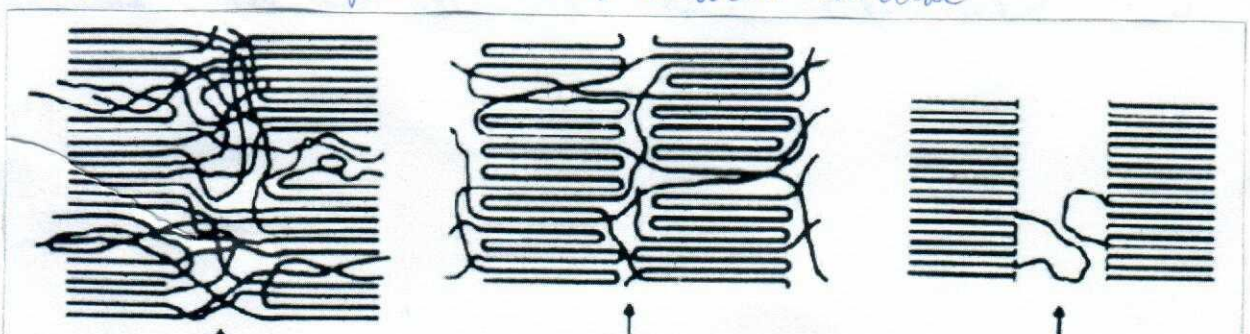


- Glass transition (T_g):
  - only the amorphous part
  - reversible (by supercooling)
  - No phase transition (like melting/sublimation)
  - Increased chain segment mobility ⇒ increase in heat capacity
  - transition: $T > T_g$ ⇒ soft and rubbery polymer
    $T < T_g$ ⇒ stiff polymer

- Melting (T_m):
  - only semi-crystallines melt (→ crystalline part can melt)
  - T_m, point at which the majority of the crystalline regions have melted → reflects thickness and perfectness of crystals
  - Reversible (endothermic phase transition)
  - Area underneath the melting peak is proportional to crystallinity

Biocompatible materials Checklist Ausarbeitung Unit 9

- Synthetic polymers (Fortsetzung):
  - Thermoplastics (Fortsetzung):
    - Difference in mechanical properties:
      - $T < T_g$ - thermoplastics hard and brittle
      - $T > T_g$ - amorphous thermoplastic: soften, start to flow (but not melting)
        - semicrystalline thermoplastics: strong intermolecular forces => prevented softening
    - Semi-crystalline polymers:
      - Thermal properties (T_g, T_m, crystallization, %X) determine application (%X → degree of crystallinity)
      - Crystallinity + crystalline structure influences the mechanical properties
      - chains with reasonable structural regularity => crystallize (but not complete => amorphous regions between crystals)
      - crystallization from melt: characterized by the conformation of the individual molecular chains and their organization relative to one another
        - chain folding => regular 3D array of molecular segments => lamellae formation
        - lamellae => supermolecular spherical structure formation
        - spherulites: semi-crystalline structure
          - tangentially arranged macromolecular structures
          - composed by highley ordered lamellae with diameter $\leq 0{,}3$ nm
          - amorphous segments between lamellae
    - Model for non-crystalline areas between lamellae



All chains run from one crystalline to other (unlikely)

Single chains run from crystalline to other + amorphous part between (very likely)

Single folded chains run back to original crystalline (possible in some cases)

- Tie-molecules:
  - molecules that bridges crystal lamellae, joins at least 2 different lamellae
  - crutial for stress-transfer between lamellae
  - high elongation at break => toughness + impact resistance
  - good resistance to slow crack growth + environmental stress cracking
  - polymers with higher molar mass are more likely to form inter-crystalline linkages
  - degradation of Tie-molecules + increase in crystallinity => material embrittlement + mechanical integrity loss

- Mechanical properties:
  - it depends on the used material
  - principles:
    - contact lens -> soft + elastic
    - Acetabular cup -> hard + tough, no creep
    - Pumping bladder of artificial heart -> elastic + tough
    - blood bag -> strong + flexible
    - ultrasound coupling gel -> soft + deformable
    - tendon prothesis -> extremly strong + flexible

- Permeability:
  - it is question of engineering -> depends on polymer and function (along with permeation)

- No permeation:
  - high density + cross linking, ionic/crystalline polymers
  - For water => hydrophobic polymers
  - For hydrophobic molecules => hydrophilic polymers

- To enhance permeation:
  - For water => hydrophilic/amorphous lightly cross-linked polymers
  - [illegible]

- Tuning permeation from high to low:
  - copolymerization of hydrophilic with hydrophobic prononer
  - interpenetrating network of hydrophilic + hydrophobic polymers

Biocompatible materials Checklist Ausarbeitung
Unit 9

- Synthetic polymers (Fortsetzung):
  - Thermoplastics (Fortsetzung):
    - Optical properties:
      - important in ophthalmologic applications
      - optical clarity important for:
        - contact lenses
        - artificial corneas
        - intraocular lenses
      - optical clarity achieved by:
        - using amorphous polymers => low/zero crystallinity
        - polymers with phase-separated domains in ≤ 100 nm size range => no visible light scattering
    - Refractive index (n):
      - n↑ => thickness of lens ↓
      - e.g.: PMMA $n = 1{,}49$
        Silicone $n = 1{,}41 - 1{,}46$
        ⋮

- Elastomers (Rubber):
  - Types:
    - cross-linked rubber:
      - covalently bond
      - (mostly) loosely cross-linked
      - 3D cross-linked network
      - displays rubber-like elasticity
      - amorphous
      - application $T > T_g$ => segmental motion -> stress removed => => return to original shape
    - Thermoplastic elastomers:
      - ionomers:
        - composed of ionomer molecules
          ↳ small but significant proportion of units have ionizible/ionic groups (or both)
        - is copolymer => contains nonionic and ionic components (ionic ≤ 15%)
      - Block copolymers:

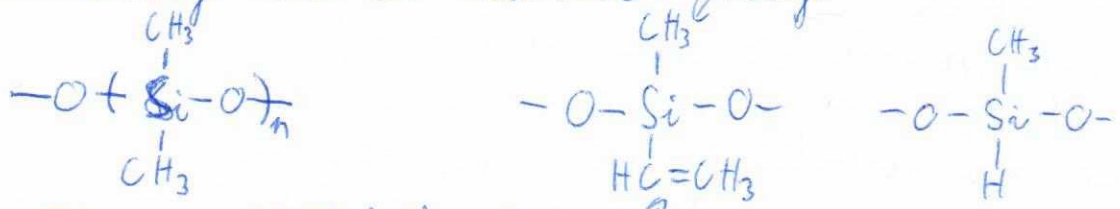
- Thermosets:
  - tightly cross-linked 3D network
  - pre-polymers irreversibly cured ⇐ initiated by heat/catalyst/irradiation
  - molded into final shape (gel point)
  - properties:
    - high mechanical/physical strength
    - high stress/load supported
    - suitable for high temperature applications (sterilization)
    - insoluble
    - Ø swelling
    - high creepresistance
    - poor elongation/elasticity

- Polyurethanes:
  - excelent mechanical properties: tough and flexible
    - tough ← highly H-bonded crystalline segments
    - flexible → amorphous soft segment
  - chemically stable
  - phase-separated domains ≈ 100nm in size
  - microfilamentous polyurethanes need to be stressed to exhibit biodegradability
  - degradation: as surface cracking + loss of ultimate mechanical properties
    - reasons:
      - oxidation of soft segment → particularly soft segments
      - enzymatic degradation of urethane linkage
      - hydrolysis of polyester soft segments

Biocompatible materials Checklist Ausarbeitung
Unit 9

• Silicone and silicone elastomers:

• commonly used in medicine:



PDMS (Polydimethylsiloxane)
- → most widely used
- → viscous liquid / grease-like jellies (depending on synthesis condition)
- → cross linking ⇒ forming true gel / elastomers

• Properties:
- chemically stable
- non-toxic
- good mechanical properties
- moderate cost
- fabrication in many shapes
- successfully application in medicine / biology

• Applications:
- medical grade tubing
- shunts
- catheters
- breast / penile implant

• -O-Si-O- bond:
- strong and mobile ⇒ chemical inertness + flexibility
- quite polar (but shielded by CH_3-groups) ⇒ would lead to intermolecular interactions
- low rotation barriers
- chemical / thermal stability ⇒ stable in body
- outstanding resistance to aging

- low critical surface tension of wetting ⇒ highly hydrophobic
- low T_g(PDMS) = −127 °C ⇒
  - highly permeable to O/N/H_2O-vapor
  - highly compressive
  - low flow activation energy
  - uniform properties over wide temp. range

- non-toxic, little tissue reactivity, moderate biocompatibility, resistant to biodegradation
- high tear strength, elastic, gaspermeable
- moderate cost

- Elastomer filler: • reduces silicone's stickiness
  - hardness + mechanical strength ↑
  - barium sulfate: radiopacity ↑

- Fumed silica: improve mechanical properties of cross-linked silicones
  - → amorphous
  - → small, spheroid silica particles (10 nm)
  - → high surface area: 100 - 400 m^2/g
  - → fuse irreversibility: • semi-molten → creating aggregates
    - • cool → aggregates from agglomerates
  - → incorporation of filler prior to cross-linking
  - → large surface area ⇒ adsorption
  - → H-bonds between filler and silicone polymer:
    - • viscosity ↑ (already high)
    - • silane treatment of filler ⇒ reinforcing properties ↑

- Cross-linking:
  - with radicals: • requires vinyl-group on polymer chain
    - • used for high-consistency silicone rubbers (HCR)
    - • used in: • extrusion
      - • injection molding
    - • peroxide added before processing
    - • peroxide's volatile residues ⇒ voids
    - • peroxide's residues + high temp. ⇒ depolymerization
  - by condensation: • chain ends blocked with 2 acetoxy functional groups as liquid product
    - • requires: moisture → diffuse into the mat.
    - • by-product: acetic acid
  - by addition: • vinyl endblocked polymers with Si-H
    - • catalyzed by: Pt/Rh (organic metal complexes)
    - • Ø by-products
    - • Ø shrinkage

Biocompatible materials Checklist Ausarbeitung
Unit 9

- Sythetic polymers (Fortsetzung):
  - Silicone and silicone elastomers (Fortsetzung):
    - Silicone elastomers:
      - Thermosetting materials => must be formed into shape before cure
      - Costing extrusion + shaping => depends on viscosity of feedstock
      - High consistency rubber (HCR)
        - high molecular weight silicone polymers
        - high tear strength
        - high tensile elongation
      - Liquid silicone rubber (LSR)
        - lower molecular weight silicone polymer/silica blend
        - used in injection molding

      cured by exposure to heat

      - Room temperature vulcanizing (RTV) elastomer
        - Variation of LSR -> viscosity↓, inhibitor↓
        - 2-parts: used for laboratory trials, dental impression molding
        - 1-part: ready to use as adhesive -> condensation reaction on moisture
    - Silicone gels:
      - lightly cross-linked elastomers
      - polymer network swollen with silicone fluids => controls consistency of material
      - Ø silica or other fillers
      - Used as breast/testicular/soft tissue implant for augmentation/restoration
      - before curing filled into shell
    - Application: orthopedic: finger joints
      - medical grade tubing/shunts/drains/catheters
      - aesthetic implants
      - contact lenses/special dressings/air/blood filter membrane/tissue expanders/artificial dermises/esophaguses/intra-ocular lenses/artificial cornea

- Biodegradable polymers:
  - Definitions:
    - Biodegradation: chemical process resulting in the cleavage of covalent bonds. a biological agent (enzyme, cell, microorganism) is causing the chemical degradation of the device
    - Bioerosion: physical change in size/shape/mass of device, without regard to a specific mechanism involved => "bio" refers that erosion occures under physiological conditions

!!! erosion can occure in the absence of degradation, and degradation can occure in the absence of erosion!!!

- Bioabsorption, Bioresorption: not clearly defined
  - refers to polymer/degradation products are removed by cellular activity

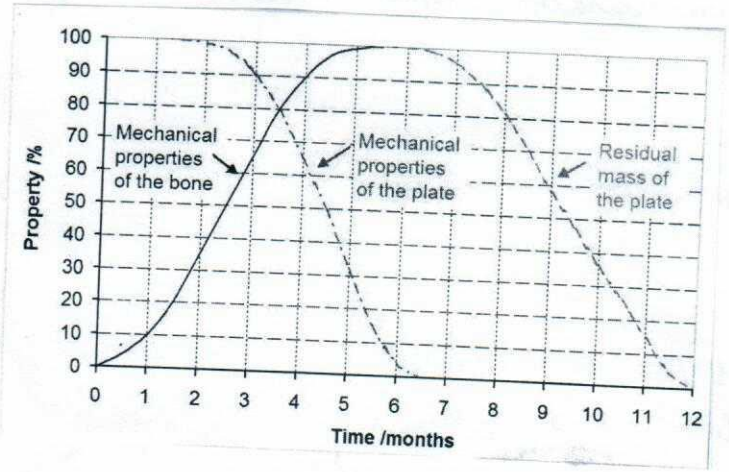
- capable of being decomposed in the human body
  - by macrophages/enzymes/hydrolysis
  - within days to several years

- Application:
  - orthopedics (screws, plates)
  - stents
  - drug delivery systems
  - scaffolds/tissue engineering
  - suture materials/adhesives

- Properties:
  - Biocompatibility (influenced by: composition, crystallinity, release of oligomers/residual monomers, degradation products and design, implant design, surface properties)
  - Biofunctionality (influenced by: physical/mechanical/biological properties during degradation)
  - Processability (influenced by: thermal stability, melting/dissolving behavior)
  - Sterilizability (influenced by: irradiation -> chemical stability, thermal/chemical sterilization)
  - storage (influenced by: aging, adsorption of water)

Biocompatible materials Checklist Ausarbeitung
Unit 9

- Biodegradable polymers (Fortsetzung):
  - Correlation mechanical properties bone/implant:
    - fracture => internal fixation
    - bone regains stability
    - implant mechanical properties ↓ => implant transfers load to the bone increasing gradually
    - after complete recovery: entire load on bone
    - mass loss of implant start



  - Mechanisms of degradation:
    - Aim: • degradation products should be integrated into body's metabolism
      ⇓
      molar mass < 40000 – 50000 g/mol => excretion/secretion in kidney, liver, lung, skin, intestine
    - Methods:
      - Polymer dissociation: • irradiation/thermal/mechanical processes => degradation
        • cleavage of covalent bonds
        • results in radical formation => additional disintegration
      - Hydrolysis: • in case of hydrolytic instable bonds (e.g.: ester, amide groups)
        • inversion of polycondensation
        • controlled by diffusion of H_2O molecules
        • catalysts: temperature, acid, base, enzymes
      - Enzymatic degradation: • at specific groups identified by enzymes
        • hydrolitic, oxidative or chain scission
        • high molecular weight enzyme => ∅ diffusion into polymer => surface degradation

- Dissociation of polymer - polymer complexes (PPC):
  - occurs via salvation of macromolecular components
  - until the gain of free energy becomes higher than the energy of intermolecular cooperative interaction between the two polymers

- Problems:
  - Bulk degradation: slow degrading surface as semipermeable membrane =>
    => degradation products not removable from bulk =>
    => catalyst for further degradation
    ↳ autocatalytic process inside: chain scission

  - Burst release & pH profile:
    - PLA degradation by hydrolysis
    - thick walls => high concentration of degradation products =>
      => carboxylic end group formation => catalyst => surface layer holds back degradation products => faster degradation inside => sudden release of high concentration of degradation products => inflammation

  - Crystallites:
    - crystalline parts are more stable against hydrolysis than amorphous => faster amorphous degradation => implant crystallites remain in tissue => tissue irritation/ /inflammation
    - lowered crystallinity by racemic poly-D,L-lactide

- Polymers:
  - Ultra high molecular weight PE (UHMW-PE):
    - Application: • hip/knee/spine implants
    - Properties: • low coefficient of friction
      • low static friction => low initial load
      • high wear strength
      • fatigue strength + toughness
      • good long-time strength
      • chemically stable aliphatic chains
      • electrically neutral
      • bulk material in the surrounding tissue => low immune reaction
      • hardly any in growth of tissue

Biocompatible materials Checklist Ausarbeitung

Unit 9

- Polymers (Fortsetzung):
  - Polyetheretherketone (PEEK):
    - Application:
      - bone fixation
      - dentistry -> removable dental prothesis
        - Metal-free clasp denature
        - crown
    - Properties:
      - E-modulus resembles that of a bone (by composites -> tailorable)
      - radiolucent/radiopaque (with $BaSO_4$ powder or tantalum wires)
      - Ø corrosion, high wear resistance
      - hardly changes after (repeated) sterilization procedures
      - metal-free, no allergy-free solution
      - high strength-to-weight-ratio
      - reduced heat/electrical conductivity
  - Polypropylene (PP):
    - Application:
      - components for blood oxygenators + kidney dialisis
      - finger joint prothesis
      - heart valves
      - sutures
      - syringes
      - packaging
    - Properties:
      - Semi-crystalline
      - density $\rho = 0{,}895 - 0{,}915\ g/cm^3$
      - T_m and crystallinity depends on tacticity
        - ↳ commercial iPP $T_m = 160 - 165°C$
      - higher stiffness/hardness/strength than PE, but lower than PA
      - lower water adsorption
  - Polyethylene terepthalate (PET):
    - Application:
      - Artificial blood vessels
      - replacement of tendon/ligaments
      - Sutures, fabric knits, weaves, velours
    - Properties: physical properties depend on degree of crystallinity (30-40%) ↳ depends on processing
      - Crystallization of PET < polyacetal (POM) or HDPE
      - $T_m(PET) = 260°C$, density $\rho = 1{,}38\ g/cm^3$
      - extrusion + rapid quenching => amorphous materials
      - high mechanical strength + good chemical stability
      - made by transesterification reaction between ethylene glycol and dimethyl terephthalate

- Polyvinylchloride (PVC):
  - Application:
    - Extracorporeal blood vessels
    - blood bags + bags for IV solutions
    - medical disposables (e.g. endotracheal tubes)
  - Properties:
    - good strength/flexibility/crystal clarity + low cost
    - pure HMW-PVC: hard, brittle
    - amorphous
    - $T_g = 79°C$
    - add plasticizers => achieve desirable softness/flexibility
      - ↳ problem: leaching
- Polycarbonate (PC):
  - Application:
    - Components for blood oxygenators + kidney dialysis devices
    - unbreakable sterile bottles
    - packaging
    - tubes
    - syringes
  - Properties:
    - Density $\rho = 1,2 - 1,22\ g/cm^3$
    - amorphous
    - $T_g = 147°C$
    - high strength/impact strength/hardness/stiffness
    - highly transparent
    - problem: presence of Bisphenol A (BPA) (essential ingredient to make PC)
- Polyamide (PA):
  - Application:
    - component for kidney dialysis devices
    - heart mitral valves
    - catheter tubes
    - anti-embolism stockings
    - sutures
    - syringes
  - Properties:
    - macromolecule with amide-bonds
    - Density $\rho = 1 - 1,14\ g/cm^3$
    - varying subunits with aliphatic/(semi-)aromatic main chain
    - homopolymers (PA6, PA66), copolymers (PA6/66)
    - Typically: semi-crystalline, available amorphous types
    - $T_g = 37 - 60°C$, $T_m = 170 - 290°C$ (depending on subunit)
- Polyoxymethylene (POM):
  - Application:
    - Components for bone cement mixer
    - mainly used extracorporeally
    - powder inhaler
    - insulin pen

    } functional/mechanical components with high dimensional precision + stability
  - Properties:
    - highly crystalline: 75-85%
    - Density $\rho = 1,39 - 1,42\ g/cm^3$
    - high strength/stiffness/hardness/toughness
    - low water adsorption, chemical + hydrolysis resistance
    - $T_m = 175 - 178°C$
    - good long-term behavior + low fatigue under mechanical stress

Biocompatible materials Checklist Ausarbeitung
Unit 9

- Polymers (Fortsetzung):
  - Polymethyl methacrylate (PMMA):
    - Application:
      - Bone cement
      - intraocular lenses + hard contact lenses
      - artificial teeth and dentures
      - diagnostics
      - dental filling materials
    - Properties:
      - Density $\rho = 1{,}19\ g/cm^3$
      - amorphous
      - high optical clarity/transparency
      - good resistance to chemicals/bodily fluids
      - $T_g = 45-115°C$ (depending on tacticity)
      - high heat deflection temperature
      - high UV transmittance
  - Polyurethan (PUR):
    - Application:
      - vascular graft prostheses
      - coating for artificial blood vessels
      - artificial heart valve
      - dialysis membrane
      - infusion tubes
      - peristaltic pump materials
      - wound dressing
    - Properties:
      - excellent mechanical properties: tough + flexible
      - chemically stable
      - processability
      - change LMW-components/oligomerics => property tailoring
  - Fluoropolymers (PTFE + others):
    - Application:
      - Vascular prothesis
      - Filter membranes
      - Artificial heart valves
      - ePTFE: vascular prostheses, hernia meshes + other when tissue ingrowth needed
      - (drug eluting) coatings
    - Properties:
      - chemically inert, highly hydrophobic, low thrombogenecity, minimal inflammatory stimulation, $\rho(PTFE) = 2{,}1-2{,}3\ g/cm^3$
      - PTFE: + insoluble, decomposes before melting
      - ePTFE: expanded form of PTFE, highly porous
      - FEP: fluorinated ethylene propylene, insoluble, $T_m \approx 260°C$
      - Teflon AF: amorphous fluoroplastic (optical clarity, strength), soluble in prefluorinated solvents, high gas permeability/compressibility/creep resistance

- Polysulfone (PSU):
  - Application: dialysis membrane (pore size down to 40nm)
  - Properties:
    - Rigid
    - high strength
    - transparent
    - temperature resistance $T_g \approx 185°C$
    - high dimensional stability & hydrolysis

Unit 10

- Bone cement:
  - Def: Synthetic, self-curing (in-/organic material used to fill up a cavity or to create a mechanical fixation.
    - → usually polymethyl methacrylate or copolymers
    - → possible source of released reagents => local/systemic toxicity
  - Application:
    - Bone filling
    - hip/knee endoprosthesefixation
    - vertebroplasty
  - Aim: rapid restoration of the structural support
  - Types:
    - non-degradable
      - polymer basis
      - for long-term fixation
      - 2 components:
        - Powder
          - → polymer (PMMA pearls 5-100 µm)
          - → initiator (polymerization initiation)
          - → BPO
          - → radiopacifier
          - → antibiotics
        - Liquid
          - → monomer (MMA = methyl methacrylate)
          - → activator (activates initiator)
          - → inhibitor (prevents premature polymerization)
      - After mixing: exothermic polymerization (temp. rise: peak 56°C up to 90°C)
      - during polymerization of MMA to PMMA, the pearls bonded into a dough-like mass
    - degradable
      - calcium-phosphate basis
      - temporary fixation
      - healing progression → bone takes over supporting function

Biocompatible materials Checklist Ausarbeitung
Unit 10

- Bone cement (Fortsetzung):
  - Curing procedure:
    - phases:
      - mixing:
        - shortly before implantation, in a ratio of 2:1 (Powder: liquid)
        - vacuum mixing: porosity ↓, mechanical strength ↑
      - waiting:
        - for 10-12 mins still sticky dough
        - liquid monomer is cytotoxic ⇒ after mixing 4-5 min waiting before application
      - application
      - setting: cement sets + hardens depending on temperature
  - Final properties depend on mixing technique/application/composition
    - Porosity
    - Temperature
    - Humidity
    - Ratio powder/liquid
    - Powder and monomer composition
    - Powder particle size distribution
    - Molar mass
  - Disadvantages:
    - Exothermic polymerization up to 90°C
    - Reaction shrinkage (-22% Vol)
    - Reaction depends on temperature + moisture
    - Residual monomer
      - ↳ Allergic
      - ↳ toxic
      - ↳ can lead to chronic damage
    - Difficult reoperation

- Hydrogels:
  - 3D network of hydrophilic polymers
    - with covalent bonds produced by reaction of one or more copolymers
    - or with physical cross-links from entanglements/hydrogen bonds/strong Van der Walls interactions between chains/crystallities
  - are able to retain a large quantity of water within their structure without dissolving
  - counterbalance of:
    - hydrogel polymer chains interact with solvent and expand to fully solvated state
    - crosslink structure ⇒ retractive force ⇒ pull back chain

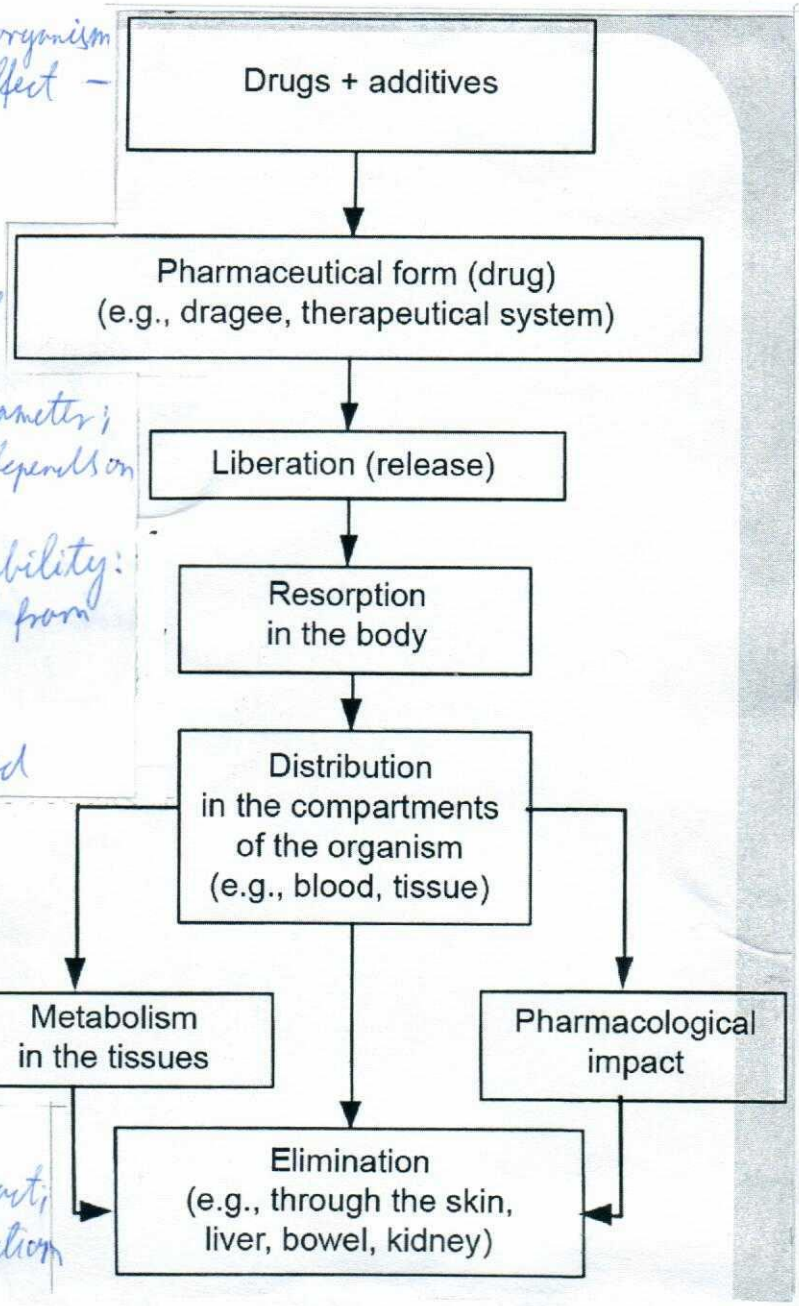
- Classification:
  - source: natural / synthetic
    - ↳ coating for catheters
    - ↳ contact lenses
  - Preparation method: polymer crosslink / simultaneous polymerization
  - components:
    - Homopolymer hydrogel: 1 type of hydrophilic monomer unit in a cross-linked network
    - Copolymer hydrogel: 2 cross-linked comonomer unit
      - ↳ min. one is hydrophilic
    - Multipolymer hydrogel: 3+ comonomer units
    - Interpenetrating polymeric hydrogels:
      preparing first network → network swollen in monomer ⇒ ⇒ reaction ⇒ formation of second network
  - ionic charge: neutral / anionic / cationic / amphalytic
    - ↳ both ⊕ and ⊖
  - physical structure: amorphous / semicrystalline / hydrogen bonds + complexation structures
    - ↳ dense regions of ordered macromolecular chains (crystallines)
    - ↳ randomly arranged macromolecular chains
  - crosslink: covalent bonds / intermolecular forces
  - function: stimuli responsive / biodegradable / superabsorbent
- Properties:
  - permeability of target (molecules / oxygen)
  - swelling behaviour:
    - water content $= \frac{\text{weight of water}}{\text{weight of water + weight of dry gel}} \cdot 100$
    - swelling ratio $= \frac{\text{weight of swollen gel}}{\text{weight of dry gel}}$
  - elastic nature ⇒ minimize irritation of tissue
  - low interfacial tension between hydrogel surface and aqueous solutions ⇒ minimize protein adsorption / cell adhesion

Biocompatible materials Checklist Nachbearbeitung
Unit 10

- Hydrogels (Fortsetzung):
  - Preparation:
    - Irradiation: electron beams / γ-rays / UV-light => polymer chain excitation => cross-link production
    - Chemical reactions:
      - polymerizable cross-linking agent => simultanious copolymerization reaction between 1+ monomers
      - cross-linking agent: • di- or tri-functional
        • polymer with reactive functional groups in side chain / chain end
    - physical association: intermolecular forces => physical cross-linking
  - Tailoring properties:
    - neutral type: available hydrophilic / hydrophobic groups
      ↳ mechanical strength ↑
      ↳ swelling ↑
    - acidic / anionic: minimize calcification
    - basic / cationic: acquire charge => permeability of anions ↑
  - Application:
    - lubricant
      - dry surfaces of catheters / surgical latex gloves / drainage tubes (they have a high friction coefficient)
    - blood containing hydrogels
      - nonionic hydrogels
      - heparin-based hydrogels
    - Contact lenses:
      - soft contact lenses
    - Wound dressing:
      ↳ need to be flexible, strong, non-immunogenic, permeable for water + metabolities, barrier effect
      ⇓
      hydrogels have all these except mechanical strength => composite blends
    - Drug delivery

• Drug delivery systems:

Active substance: interacts with organism + pharmacological effect –



Dosage form: pharmaceutical ready for use, it contains active substance + excipients with no pharmacological effect.

Liberation/release: pharmaceutical parameter; solubility (rate) can be controlled; depends on temperature + perfusion

Resorption of body surface; bioavailability: quantity of active substance resorbed from dosage form per time

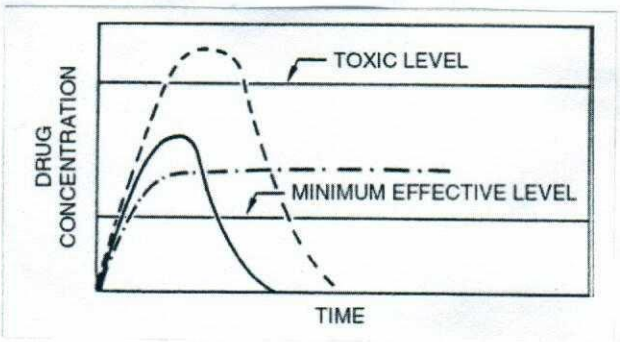
Distribution: blood supply required

Elimination: complete processes of termination of pharmacological impact, by chemical conversion or extraction (metabolism)

• Aim: controlled release of the drug with constant rate
↳ supply : elimination = 1

⇓

Result: • equal drug level in plasma and tissue over a defined period
• lat less amount of needed drug, than by conventional methods
• reduction of adverse reactions
• increased safety



Biocompatible materials checklist Ausarbeitung
Unit 10

- **Drug delivery systems (Fortsetzung):**
  - Types:
    - Membrane-controlled reservoir device
      - active agent in the core ("reservoire") surrounded by a thin polymer membrane
      - release: diffusion through rate-controlling membrane
      - influence on diffusion coefficient:
        - molar mass ↑ => d.c. ↓
        - crosslink density ↑ => ↓
        - main chain stiffness => ↓
        - molecule interactions => ↓
        - crystallinity ↑ => ↓
        - plasticizer content ↑ => ↑
        - filler content ↑ => ↑
    - Monolithic devices (Matrix-type devices):
      - active agent uniformly dispersed/dissolved in polymer matrix
      - release: controlled by diffusion from matrix
        - non-porous matrix => diffusion along/between polymer segments
        - No zero-order release kinetics with typical geometries
          - ↳ fast release at surface
          - ↳ retarded release from volume
      - matrix is inert
        - ↳ non-swelling/fully swollen
        - ↳ non-degradable
      - diffusion dependent on solubility of agent in polymer
        - ↳ agent is below its solubility => dissolved in polymer
        - ↳ — " — well above — " — => dispersed — " —
      - geometry influences release rate
  - chemically controlled drug delivery devices:
    - Backbones with pendent drugs (degradable)
      - carriers
      - active substance bond to main chain/backbone
      - differentiating between main/side-chain bound agents
      - high drug content (≤80 mass-%) => higher therapeutic efficiency
        - longer action duration
        - higher specificity

- Osmotic-controlled system:
  - Parts: • strong waterpermeable membrane
    - flexible membrane impermeable to water/drug
  - contact with body fluids:
    - body fluid diffuses through strong membrane (salt concentration in device > body) => reservoire pressure ↑ => drug release
- Swelling-controlled systems (hydrogels):
  - Types: rapidly swelling, diffusion-controlled
    - slowly swelling, swelling-controlled
  - preparation:
    - swelling in drug solution => carefully drying
    - dried polymer: glassy state
    - active agent: dispersed, forms nonporous films/discs/spheres
  - drug release: simultaneous rate process dependent
    ↳ water migration into => polymer chain hydrates + relaxes => drug dissolution => drug diffusion outward

Biocompatible materials checklist Ausarbeitung
Unit 11

Metallic biomaterials:

- Requirements:
  - mechanical strength:
    - permanent load transmission between implant and tissue
    - implant stiffness ≈ bone stiffness
  - Adequate wear behaviour
  - corrosion resistance: prevention of corrosion by electrochemical stable materials
  - biocompatibility:
    - ∅ demage of surrounding tissue
    - structure / surface compatibility
- Application:
  - stents
  - heart valves
  - orthopedic hips/knees
  - oral / maxillofacial implants
- Properties (influencing factors, problems):
  - → chemical and crystallographic identities of the phases present in the microstructure
  - → relative amounts, distribution and orientation of these phases
  - → adaptable by:
    - changing of composition
    - alloying
    - manufacturing method
    - thermal treatment
- Metals and Ceramics have higher mechanical properties than compact bone ⇒ possible stress shielding
- Fatigue endurance limit: amplitude of cyclic stress without fatigue failure
- Cold-worked state: mechanical stress to cause plastic deformation to metal below recrystallization temp.

- Stainless steel:
  - composition:
    - carbon (< 0,030%)
    - iron (60-65%)
    - chromium (17-20%)
    - nickel (12-14%)
  - Properties:
    - chromium => forms a strongly adherent oxide => corrosion-resistance
    - Molybdenum => crevice corrosion resistance ↑
    - nickel => stabilizes stronger austenitic phase
    - carbon => corrosion resistance improvement

- cobalt-based alloys:
  - ASTM F75: Co-Cr-Mo cast alloy
  - ASTM F799: modified F75
    - ↳ mechanically processed by hot forging
    - different microstructure => doubled fatigue, yield, ultimate tensile strength
  - ASTM F90: Co-Cr-W-Ni
    - ↳ improves machinability + fabrication
    - Annealed state: mechanical properties similar to F75
    - in cold-worked state: up to 44%, properties double
  - ASTM F562, MP35N:
    - primarily Co + Ni with significant amount of Cr + Mo
    - processed by thermal treatment + cold working => produces controlled microstructure and alloy with high-strength
    - one of the strongest alloys

Biocompatible materials Checklist Ausarbeitung
Unit 11

- Metallic biomaterials (Fortsetzung):

  - Titanium and titanium based alloys:
    - CP Ti: ASTM F65: • cp = comercially pure
      - O, C, N etc. content of cp Ti affects: • yield, • tensile, • fatigue — strength
    - Ti-6Al-4V: ASTM F136: • Al stabilized alpha phase (HCP, hexagonal closed packed)
      - V stabilized beta phase (BBC, body-centered cubic)
      - properties depend on treatment
    - Ni-Ti alloy: shape memory effect
    - [illegible]

- Ceramic biomaterials:
  - Properties: • difficult to shear plastically due to ionic nature of the bonding
    - non ductile
    - almost 0 creep at room temp.
    - generally hard
    - Ø plastic deformation ⇒ susceptible to notches/cracks
      - crack initiation ⇒ fracture
    - refractory inorganic compounds made from metals and non-metals like O, N, C, S
    - polycrystalline compounds
    - resistant against: • microbial attack
      - pH change
      - solvent condition
      - temperature
    - small changes in composition ⇒ affects if ceramics are bioinert/resorbable or bioactive

- Application and classification:
  - ceramics, glasses, glass-ceramics: eyeglasses, fiber optics for endoscopy, diagnostic instruments
  - insoluble porous glasses: carrier for enzymes/antibodies/antigen
  - bioceramics:
    - Aluminium oxide Al_2O_3: femoral head, dental implant, facial surgery, middle ear implant
    - Zirconium oxide ZrO_2: femoral head
    - Hydroxylapatite: orthopedic implants, bone replacement, dental implant, implants in ears/vertebras
    - Bioactive glass: middle ear + facial surgery, dental implant, bone replacement, vertebra implant, orthopedic implant
  - generally: repair/replace of skeletal hard connective tissue
- Aluminium oxides:
  - high density and purity
  - strength, fatigue resistance and fracture toughness depends on porosity and grain size
    - grain size $> 17\,\mu m \Rightarrow$ mechanical properties $\downarrow$ by 20%
    - grain size $< 4\,\mu m \Rightarrow$ low friction + wear
  - excelent corrosion resistance, good biocompatibility, high wear resistance, high strength, high hardness, low friction and wear
- Zirconium oxide:
  - Polymorphism (monoclinic, tetragonal, cubic)
  - stress + moisture $\Rightarrow$ possible weakening
  - Y_2O_3 used to stabalized cubic Zr
  - lower e-modulus and higher strength $\Rightarrow$ potential advantages
  - finer grain size + $\emptyset$ porosity

Biocompatible materials checklist Ausarbeitung
Unit 11

- Ceramic biomaterials (Fortsetzung):

- Calcium phosphate:
  - porous: · chemical composition is similar to bone => good biocompatibility
    - Applications: · bone tissue regeneration
      · cell proliferation
      · drug delivery

- coatings: · on metallic implants
  - properties influenced by:
    - thickness: influences coating adhesion
    - crystalinity: affects dissolution + biological behavior
    - biodegradation: affected by phase purity, chemical purity, porosity, crystallinity
    - adhesion strength
    - osseointegration = living bone and surface of implant show direct functional and structural connection

- biodegradable: · Resorption caused by:
  - Physiochemical dissolution: depends on solubility and local pH
  - Physical decomposition: into small particles by chemical attack of grain boundaries
  - Biological factors: phagocytosis, causes decrease in local pH concentration

- Bioactive glasses and glass-ceramics:
  - shows time-dependent kinetic modification of the surface, occurs upon implantation - forms biologically active carbonated HA layer => interaction with tissue
  - brittle => ∅ load-bearing application
  - application:
    - middle ear surgery
    - vertebral surgery
    - bone cement
    - coatings

- Carbons:
  - pyrolytic carbon for implant fabrication
  - mechanical properties dependent on density

- Anisotropic biocompatible fiber composites:
  - biomaterials functionality should resemple the functionality of the anisotropic structure of the tissue => only way to mimic is using composites
  - Anisotropy = mechanical properties dependent on spacial order
    topology
    position
  - flexo elasticity = elastic behavior of implant adapted to elastic behavior of tissue

- Fibers:
  - more effective than particles
    ↳ are isotropic
  - can reach same or higher stiffness/strength than metals
  - load-bearing part of device
  - determine mechanical properties of composite
  - radiolucency: ∅ shielding effect

- Matrix:
  - fibers embedded in matrix => fiber architecture is retained in case of exterior load
  - underpinning fibers during shear/compressive load
  - force transmission
  - strength during load is perpendicular to fiber directions
  - protection of fiber against agressive media
  - protection of tissue against fiber particle

Biocompatible materials Checklist Ausarbeitung:
Unit 11

- Anisotropic biocompatible fiber composites:
  - Wetting and adhesion:
    - complete wetting ⇒ ideal adhesion
      ↳ depends on:
        - surface energy of matrix and fiber
        - processing procedure
  - Adhesion determines:
    - failure behavior
    - ultimate strength and fracture toughness
    - elastic and fatigue behavior
  - Adhesion depends on:
    - mechanical anchoring
      ↳ improved by wetted surface ↑
    - coupling agent
    - intermolecular forces

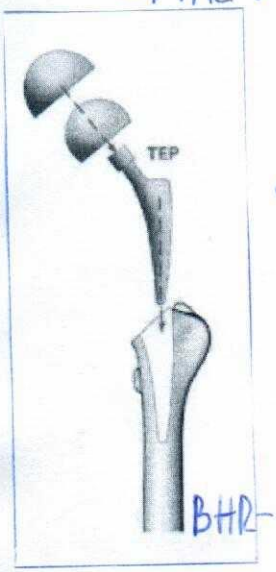
Bio-compatible materials Checklist Ausarbeitung
Unit 12

- Implants of the musculoskeletal system:
  - Artificial ligaments and tendons:
    - Requirements:
      - biocompatibility
      - durability
        - → sufficient fatigue strength
        - → fixation with resistance to slipping under cyclic load
        - → abraision resistance
  - Synthetic replacement systems:
    - Silver wires and silk sutures
    - PP and PA fibers
    - → unsatisfactory long term outcome

      ⇓

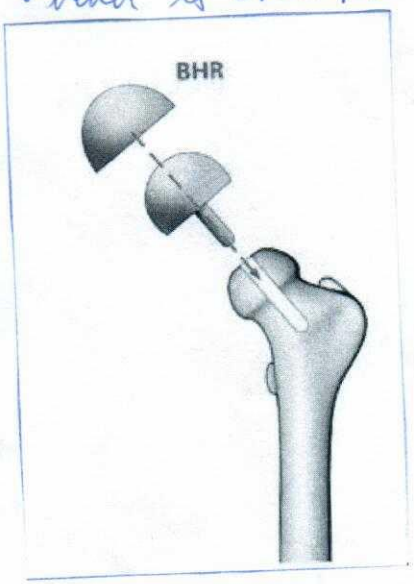
      instead development of materials that should act as a scaffold/matrix on which a new ligament can regrow.
  - Hip joint endoprathesis:
    - Requirements:
      - economic specification: acceptable processing costs
      - material specification:
        - wear resistance + low friction
        - sufficient static/dynamic strength
        - stiffness adapted to bones
        - good damping properties
        - high toughness
        - narrow property tolerances
      - construction specification:
        - easy implantation/reoperation
        - optimum biomechanical fixation on the bone
        - adaptability on different patients

- different designs:
  - THR: - femoral head and neck are resected to allow the insertation of a stem into the femoral dedullary canal

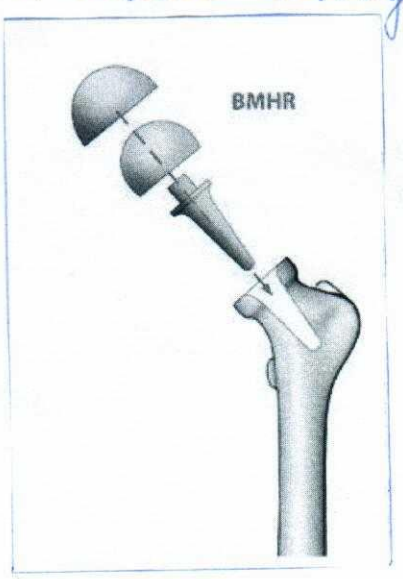


  - 3 parts: - Stem: fitted into the femur and provides stability
    - head: replaces the head of the femur
    - acetabular cup: fitted into the pelvis, replaces the worn surface

BHR - Birmingham hip resurfacing:
- removal of diseased surface only
- femoral head and neck preserved
- head is crowned with a metal cup



- BMHR - Birmingham mid head resection:
  - head is resected through the middle



Biocompatible materials checklist Ausarbeitung
Unit 12

- Implants of the musculoskeletal system (Fortsetzung):
  - Hip joint endoprothesis (Fortsetzung):
    - Materials:
      - Stem:
        - Ti alloys (biocompatible)
        - CoCr alloys (high corrosion resistance)
        - Stainless steel
      - head:
        - CoCr alloys
        - ceramic materials: aluminium/zirconium oxide
        - oxinium (Zr+Nb alloy)
      - acetabular cup:
        - metal (Ti/CoCr alloys)
        - polymer
        - ceramic
    - Resulting pairing:
      - Metal-on-metal:
        - cup + head: CoCr
        - stem: Ti
        - Problems: metallosis, corrosion, wear particles
      - Ceramics-polymer:
        - head: ceramic
        - cup: polymer
        - lower coefficient of friction
      - Ceramics-on-ceramics:
        - cup + head: Alumina/Zirconia or composite
        - problems:
          - implant breaks
          - total failure
          - squeezing
      - Metal-polymer:
        - Ball -> metal -
        - cup: sandwich of polymer + metal
      - Ceramic-metal-polymer:
        - head: ceramic
        - cup: sandwich of ceramic + metal
          - ceramic + polymer + metal

- Knee joint endoprothesis systems:
  - Two types: - total
    - uncompromental