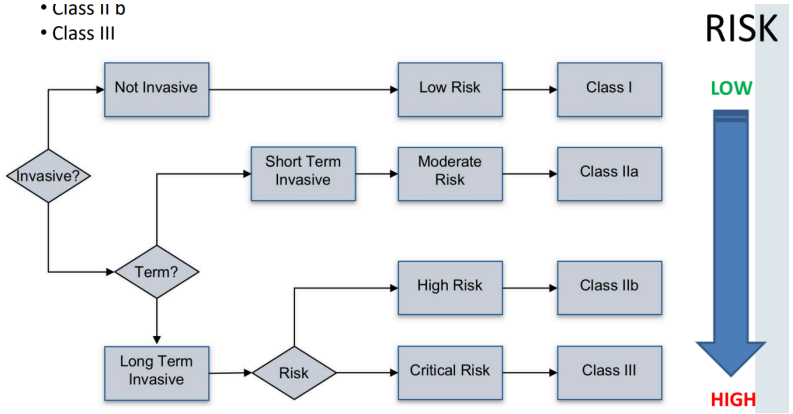
1. Classification of Medical Devices

- **Count**: 9
- **Dates**: April 2024, January 2024, September 2020, January 2021, April 2021, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
  1. *Which classification of biomedical devices is used in the EU? Write down 1-2 examples for each class and mention the parameters deciding which class a specific device belongs to.*
  2. *Criteria for classification of medical devices, examples for each class, and what risks are involved.*
  3. *Medical device classification: parameters for classification, examples, and related risks.*
- **Merged Questions:**
  - *What are the classifications of biomedical devices in the EU? Provide 1-2 examples for each class and explain the parameters that decide the classification.*
  - *Classification of Medical Devices: risks, examples, and what criteria are important.*

Classification of biomedical devices in the EU:

- Responsible organisation: European Medicines Agency (EMA)
- 4 Main categories: Class 1, Class 2a, Class 2b, Class 3
  - Biocompatibility is a requirement for 2b and 3
- Entscheidung nach folgendem Schema:



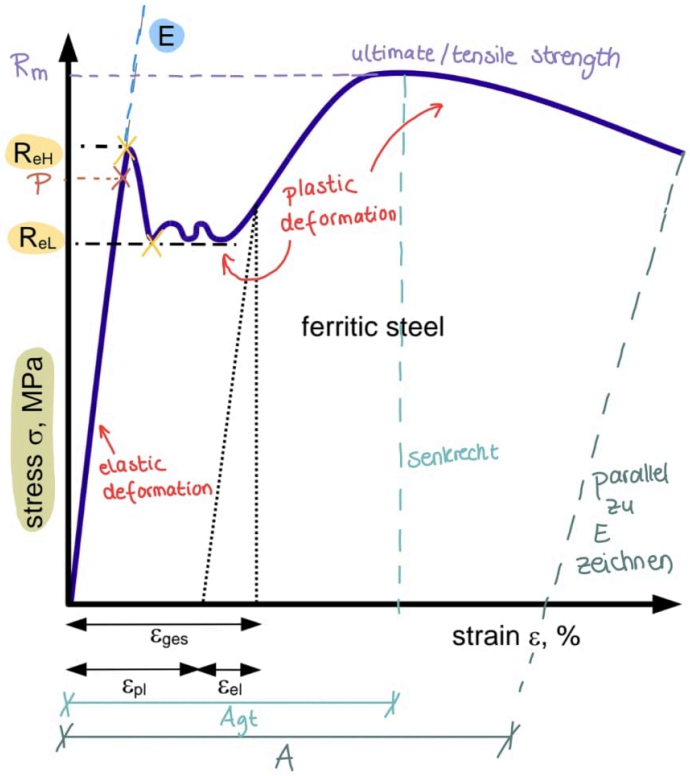
Parameters that decide classification

- Duration of host-MD contact, means intended for continuous use for specific time
  - Limited: less than 60 minutes
  - Prolonged: between 60 minutes and 30 days
  - Permanent: more than 30 days
- Invasiveness
  - non-invasive: doesnt involve skin break, no contact with mucous membrane (Schleimhaut) or internal body cavity other than through a natural or artificial body orifice (Körperöffnung)
  - invasive: generally surgery, breaking of skin or not natural entrance into body cavity
- Risk
  - low
  - moderate
  - high
  - critical

- **Examples**
    - Class 1: Hospital bed, arm sling, manual stethoscopes
    - Class 2a: Surgical gloves, soft contact lenses, hearing aids (Hörgeräte)
    - Class 2b: Long-term corrective contact lenses, orthopedic prostheses, breast implants (all non-degradable!)
    - Class 3: MD with contact to heart/ circulatory system/ brain/ nervous system, Degradable implants (eg degradable screw), bioactive medical devices (eg drug eluting stent)

2. Stress-Strain Curve

- **Count**: 7
- **Dates**: April 2024, January 2024, September 2020, January 2021, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
  1. *Draw a typical stress-strain curve for ferritic steel and highlight the essential parameters that can be obtained from it.*
  2. *Tensile curve: axes, important parameters (e.g., 0.2% yield strength, tensile `gth, elastic modulus).*
  3. *Explain important points of a strain-stress curve, including definitions of strength, stiffness, hardness, etc.*
- **Merged Questions:**
  - *Draw a typical stress-strain curve for ferritic steel and highlight key parameters (elastic modulus, tensile strength, yield strength, etc.).*
  - *Sketch a common stress-strain curve and mark important points.*



Mech. properties for metals originating from the engineering stress-strain curve in a uniaxial tensile test:

E = elastic modulus [GPa]
$\sigma_{y\varepsilon}$ = ε%-yield strength [MPa] → Y-Wert
P = proportional limit [MPa]
R_{eH}= upper yield point [MPa]
R_{eL} = lower yield point [MPa]
R_m = tensile strength [MPa]
A_{gt} = strain at maximum stress (total elongation before necking)[%]
A = plast. elongation at break [%]
Z = $(S_0-S_{min})/S_0$ = reduction in area [%]

Aufpassen beim Zeichnen:

- 0,2% yield strength wird parallel zum E-Modul eingezeichnet und nicht rechtwinklig!

Definitions:

- strength: resistance against plastic deformation/fracture (specific yield-strength)
- stiffness: resistance against elastic deformation (E-Modul bzw. young´s modulus)
- hardness: resistance against plastic deformation by indentation (keine eindeutige Einheit, kommt drauf an ob man Kratzhärte/ Eindringhärte/ Rückprallhärte/… misst)
- fracture toughness: resistance against crack-growth (K_c)

Formeln, falls wir was rechnen müssen (gilt nur für elastic deformation):

- σ [N/mm² = MPa] = E * ε
- ε [1]= ΔL/L0 (technical strain)
- σ = F/A

Rechenbeispiel Vorlesung:

Consider a cylindrical specimen of a steel alloy (see previous slide) 15mm in diameter and 75mm long that is pulled in tension.

(1) Determine its elongation when a load of 20kN is applied. → $\Delta L = ?$

(2) Determine the applied stress and its relation (in percent) to the 0,2% yield strength

$r = 7{,}5 \cdot 10^{-3}\,m \qquad L = 75 \cdot 10^{-3}\,m \qquad E = 200\ GPa$ (siehe letzte Folie)

1) $\sigma = E \cdot \varepsilon$

$\sigma = \frac{F}{A}$

$\varepsilon = \frac{\Delta L}{L} \Leftrightarrow \Delta L = \varepsilon \cdot L = \frac{\sigma}{E} \cdot L = \frac{F}{A \cdot E} \cdot L = \frac{F}{r^2 \cdot \pi \cdot E} \cdot L = \Delta L$

Werte einsetzen:

$$\Delta L = \frac{F \cdot L}{r^2 \cdot \pi \cdot E} = \frac{\overbrace{20 \cdot 10^{3}}^{N} \cdot \overbrace{75 \cdot 10^{-3}}^{m}}{\underbrace{(7{,}5 \cdot 10^{-3})^2}_{m} \cdot \pi \cdot \underbrace{200 \cdot 10^{9}}_{Pa}} = 42\,\mu m = 42 \cdot 10^{-6}$$

2) $\sigma = \frac{F}{A} = \frac{F}{r^2 \cdot \pi}$

$= \frac{20 \cdot 10^3}{(7{,}5 \cdot 10^{-3})^2 \cdot \pi} = \frac{20 \cdot 10^9}{(7{,}5)^2 \cdot \pi} = 113\ MPa$ → Stress

How close to 0,2% yield strength?

0,2% → 390 MPa = $\sigma_{0,2\%}$

$\frac{\sigma}{\sigma_{1,002}} = \frac{113}{390} = 29\%$

3. Wound Healing Stages

- **Count**: 6
- **Dates**: April 2024, January 2024, September 2020, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
  1. *What are the 4 phases of a normal wound healing process? How can wound dressings help in healing a skin wound?*
  2. *Explain the stages of wound healing and their significance in biomedical applications.*
- **Merged Questions:**
  - *What are the 4 phases of a normal wound healing process? How can wound dressings help in healing?*
  - *Differences between long bone fracture healing and cranial fracture healing.*

4 Phasen (ich denke Phase, Timeframe, Function reicht)

TABLE I. Phases of the normal wound-healing process

Phase	Timeframe	Cells involved	Function	Cellular and biophysical events
Haemostasis	Immediate	Platelets (also called thrombocytes and involved in blood clotting)	Clotting	» Vascular constriction » Platelet aggregation, degranulation, and fibrin formation (thrombus)
Inflammation	Day 1-4	» Monocytes » Lymphocytes » Neutrophils » Macrophages	Phagocytosis (ingestion of bacteria)	» Neutrophil infiltration » Monocyte infiltration, and differentiation of macrophages » Lymphocyte infiltration
Proliferation	Day 4-21	» Macrophages » Lymphocytes » Angiocytes » Neutrophils » Fibroblasts » Keratinocytes	» Re-establishment of skin function » Wound bed filling » Wound closure Granulation tissue	» Re-epithelialisation » Angiogenesis (growth of new capillaries) » Collagen synthesis
Remodelling	Day 21-year 2	Fibrocytes	» Develop tensile strength	» Collagen remodelling » Vascular maturation and regression

How can wound dressing help, significance:

- absorbs excess of exudate (Ausschwitzungen, Exsudate)
- maintains moist environment
- removes necrotic materials (abgestorbene Zellen)
- promotes healing
- preserve integrity of underlying granulation tissue
- protect from infection or penetration of contamination
- maintain temperature, gazes exchange
- non-adherent to the wound bed (haftet nicht auf Wundbett)
- fibre and toxin free
- do not hurt when changing
- comfortable
- inexpensive

→ important choice since wrong selection can delay wound healing

Differences long bone / cranial fracture healing

- **Long Bone Healing:**
  - Follows **endochondral ossification**.
  - Involves the formation of a cartilage intermediate at the fracture site, which is later replaced by bone.
  - Phases:
    1. **Inflammation**: Hematoma formation and inflammatory cell infiltration.
    2. **Soft Callus Formation**: Cartilage forms within the fracture gap.
    3. **Hard Callus Formation**: Cartilage is replaced by woven bone.
    4. **Remodeling**: Woven bone is replaced by lamellar bone.
  - Requires stabilization due to mechanical loading.
- **Cranial Bone Healing:**
  - Predominantly through **intramembranous ossification**.
  - Bone forms directly from osteoblasts without a cartilage intermediate.
  - Phases:
    1. **Inflammation**: Similar hematoma and inflammatory response.
    2. **Direct Bone Formation**: Osteoblasts form bone at the fracture site.
    3. **Remodeling**: Bone matures but lacks weight-bearing mechanical adaptation.
  - Stabilization is less critical as cranial bones do not bear weight.

Aspect	Long Bone Healing	Cranial Bone Healing
Bone Type	Cortical and trabecular, weight-bearing	Flat bones, protective
Healing Process	Endochondral ossification (via cartilage)	Intramembranous ossification (direct bone)
Phases	Inflammation → Soft callus → Hard callus → Remodeling	Inflammation → Direct bone formation → Remodeling
Role of Periosteum	Significant for osteogenesis and blood supply	Less pronounced
Vascularization	Rich, critical for healing	Less vascularized but sufficient
Stabilization	Essential due to mechanical stress	Less critical, non-weight-bearing
Time & Focus	Longer, weight-bearing recovery	Faster, focus on brain protection and aesthetics

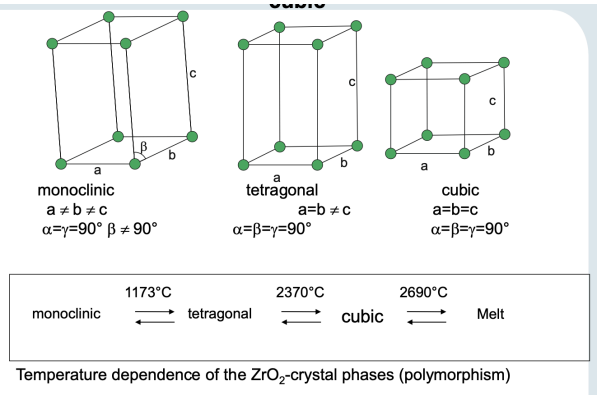
4. Zirconia (Transformation Strengthening)

- **Count**: 6
- **Dates**: January 2024, April 2021, September 2020, WhatsApp summary (10.12.21)
- **Variations**:
  1. *Phase transformation of zirconia: What mechanism strengthens it?*
  2. *Transformation strengthening of zirconia: Physical formulas, fracture mechanics, and mechanical values*
- **Merged Questions:**
  - *Explain the strengthening mechanism in tetragonal zirconium. How does it make the material tougher?*
  - *What induces the transformation in zirconia, and what formulas describe it?*

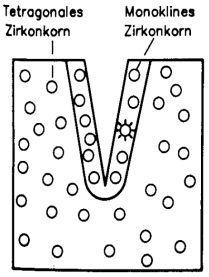
General use:

The most important fields of application are the production of refractory materials (for example, high-temperature crucibles, investment casting for titanium casting) or, in connection with aluminum oxide, the production of grinding wheels. Zirconia proves itself in cutting tools of all kinds, from kitchen knives to high-speed cutting in industrial applications.

Use dental:
Due to the very high strength and fracture toughness, zirconia is a widely used framework material (crown copings, bridge frameworks, abutments) in dentistry.
Zirconia is processed by CAD/CAM techniques (milling) and additive manufacturing, respectively.



Temperature dependence of the ZrO_2-crystal phases (polymorphism)



- Stress-induced phase-transformation from the tetragonal into the monoclinic phase
- Increase in volume of the ZrO_2-crystals by ca. 3%
- Closes crack notch and therefore prevents crack growth → high fracture toughness

the largest defect and the toughness of the ceramic material, since according to linear elastic fracture mechanics (see Sec. 3.4.1), the macroscopic stress σ is related to the stress intensity factor K, the form factor f and the defect size a:

$$\sigma = \frac{K}{f \sqrt{\pi \cdot a}} \qquad \text{Equ. (40)}$$

The critical stress σ_c is therefore related to the critical stress intensity factor K_c (fracture toughness) and the defect size a:

$$\sigma_c = \frac{K_c}{f \sqrt{\pi \cdot a}} \qquad \text{Equ. (41)}$$

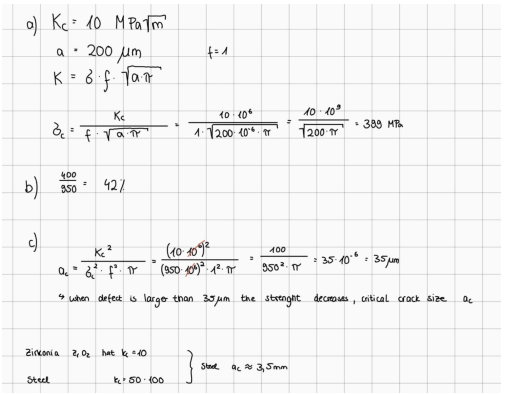
This means that the macroscopic strength (e.g. the bending strength as listed in Table 6-4) not only depends on the toughness of the material, but also on the maximum defect size, which is mainly influenced by the choice of the raw material and the specific processing conditions. We can view above equation also from another side, by requiring a certain bending strength value σ_b with a given toughness K_c and checking the related maximum defect size a_m which is allowed in the sample:

$$a_m = \frac{K_c^2}{f^2 \cdot \sigma_b^2 \cdot \pi} \qquad \text{Equ. (42)}$$

Beispiel Vorlesung:

By falling down, Mr. Z. loses one of his teeth. The missing tooth is replaced by the dentist through a zirconia ceramic bridge (K_{IC} = 10MPa m$^{1/2}$). When inserting the bridge, careless handling of the drill results in a notch (crack) with a crack length of 200µm at a mechanically loaded point.

(a) Calculate at which stress on the bridge fracture mechanical failure occurs. Take a form factor of f = 1.
(b) By what percentage is the strength of the cracked bridge reduced compared to undamaged zirconia (strength R_m = 950MPa)?
(c) How long can a crack be at the most so that the strength of the bridge does not fall below a value of 950MPa?

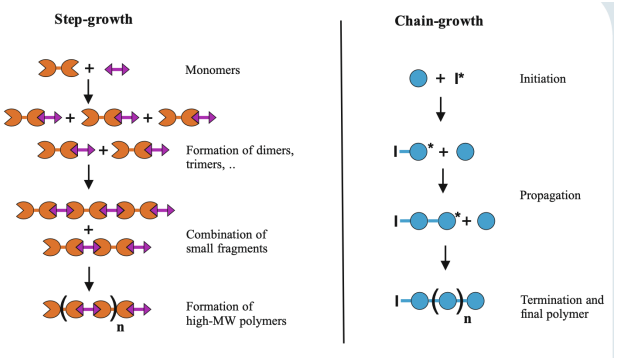


Mechanical values: Kc = 10 MPa $\sqrt{m}$

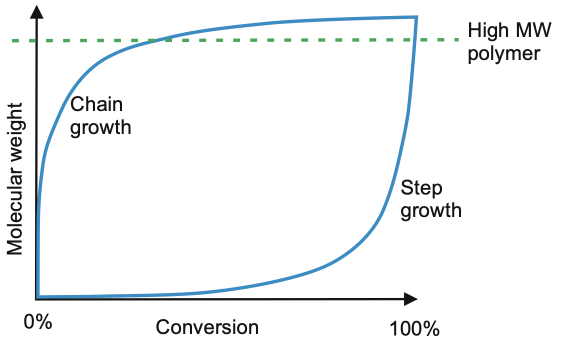
By adding rare earth oxides to the pure zirconia (e.g. 3 mol% of Y_2O_3), the tetragonal phase can be stabilized at room temperature.

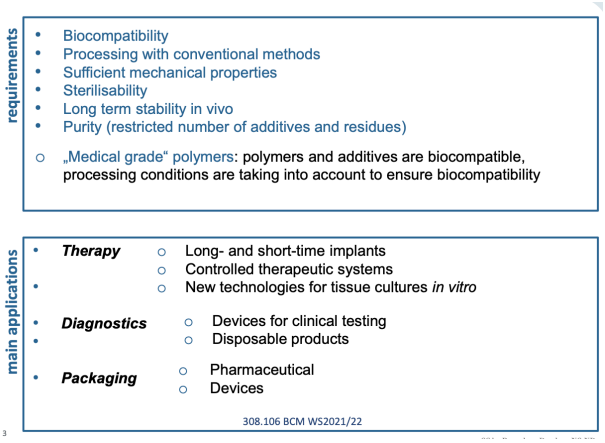
5. Polymers

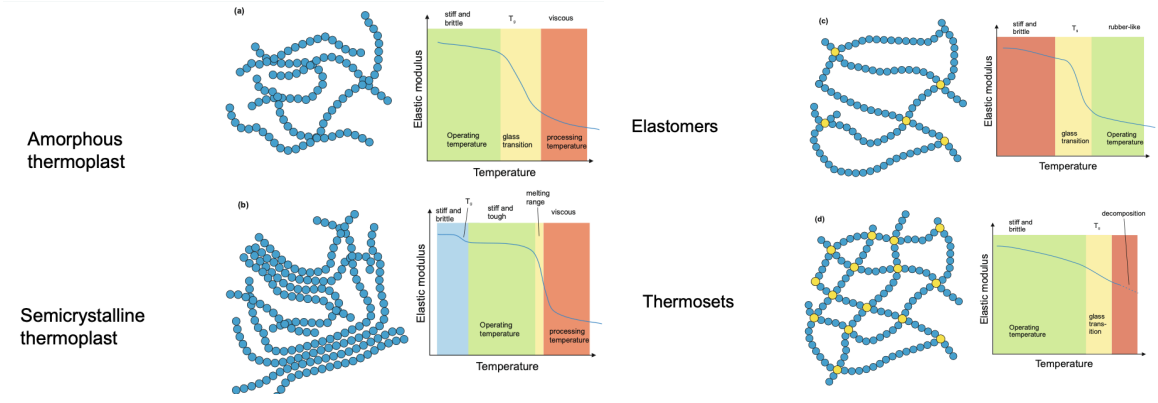
- **Count**: 6
- **Dates**: April 2024, January 2024, September 2020, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
    1. *What are the differences between chain growth and step growth polymerization? Provide the molecular weight-conversion diagram.*
    2. *Polymers: Types, bonds, morphology, and why thermoplastics have low melting points*
- **Merged Questions:**
    - *What are the differences between chain growth and step growth polymerization? Provide molecular weight-conversion diagrams.*
    - *Why are thermoplastics' melting points low? Classify polymers based on bonds and structure.*



Chain Growth Polymerization	Step Growth Polymerization
addition of monomer to a growing chain with a reactive terminus → growth only at one end of chain	reaction can occur between any pair of molecular species → growth throughout the matrix
monomer concentration decreases steadily as reaction time increases and remains even at long reaction times	rapid loss of monomers, in favor of low oligomers
molar mass initially increases rapidly, doesn't change much as reaction proceeds	oligomers steadily increase in size, molar mass increases slowly, long times required to obtain long chains
after termination reaction chains are not active	living polymer – ends remain active
initiator required	no initiator required







yellow dots = covalent bonds (cross-links) chemical bond's

thermoplastic = only weak bond's (bsp van der vaals force)

	Structure	Appearance	Behaviour when heated up	Behaviour when treated with solvents
Termoplastics	linear or branched macromolecules	**Semicrystalline**: soft to hard solids, tough due to plastic flow, opaque due to scattering at inner interfaces, only thin films are transparent; **amorphous**: transparent, hard and rather brittle (if not toughened)	softening, becoming clear during melting, forming thin filaments during melting, weldable	**semicryst**.: swellable, in cold solvents not easily soluble. Becomes soluble at higher temperatures. **Amorph**.: Generally easily soluble after previous swelling in certain organic solvents
Thermosets	tightly cross-linked macromolecules	hard, brittle, transparent when not filled	Remain hard, maintain shape up to the temperature of decomposition	insoluble; no or almost no swelling
Elastomers (Rubbers)	(mostly) looesely cross-linked macromolecules	soft and flexible	flexible, but no plastic flow up to temperature of decomposition	insoluble, but easily swellable due to loose network

Low melting point because of: heterogenous nature of semi-crystalline thermoplastic polymers

6. Ceramics and Glass Ceramics

- **Count**: 6
- **Dates**: January 2024, April 2021, September 2020, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
  1. *What are ceramics, glasses, and glass ceramics? Compare their properties and applications.*
  2. *Advantages and disadvantages of ceramics in dental applications*
- **Merged Questions:**

Ceramics are materials that are based on a chemical bond between a semi-metal or metal (e.g., Si, Al, Zr, ..) and a non-metal (usually oxygen, nitrogen or carbon). The dominant bonding type in ceramics is the covalent bond. In addition, ionic bonds play a role. Ceramics are either entirely polycrystalline, or there is a *crystalline phase* (at least 30% of the overall volume), which is embedded in an amorphous (glassy) matrix.

Glasses are also compounds of (semi) metals with non-metallic elements (oxygen is especially important). In contrast to ceramics, glasses are *completely amorphous*. Thus, there is no long-range order governing the internal structure of the material. There is only a short range order whose character is defined by the type of bond between the constituent elements

Glass ceramics are materials in which, starting from a molten glass, a crystalline phase emerges in a glassy matrix. By a suitable temperature treatment *controlled crystallization* takes place, leading to a multi-phase material with an amorphous (glassy) and crystalline phase (ceramic).

Applications:

Table 6-1: Use of glasses and ceramics in biomedical engineering.

Inorganic glasses	eyeglasses, diagnostic instruments, chemical ware, thermometers, tissue culture flasks, fiber optics for endoscopy
Insoluble porous glasses	Carriers for enzymes, antibodies and antigens
Ceramics and glass ceramics	
Aluminium oxide [Al_2O_3]	Femoral head, implant, facial surgery, middle ear implant
Zirconium oxide [ZrO_2]	Femoral head, dental restorations and implants
Hydroxyapatite [$Ca_5(PO_4)_3(OH)$]	Orthopaedic implant, bone replacement, dental implant, implants in ears and vertebras
Glass ceramics	Dental restorations, ceramic veneering of metallic restorations
Bioactive glass	Middle ear and facial surgery, bone replacement, tooth pastes

Advantages & Disadvantages (general):

+ strong covalent bonds → low chemical reactivity, good corrosion resistance and biocompatibility
+ Ceramics are a constitutive element of biological hard tissues like dentin and bone → compatible with physiological processes in living organisms and in consequence are well suited as (biodegradable) materials
+ mechanically hard and strong as well as temperature resistant → good compressive strength values
- rather low fracture toughness of ceramics due to dominance of covalent bonds → most applications involve large tensile or bending stresses

Adjust translucency by adapting the particle (or grain) size as well as the refractive index of the involved constituents

More specific for dental applications:

Benefits:
- good corrosion resistance
- Very good esthetics (colour, translucency, …)
- Good biocompatibility
- X-ray opacity can be easily adjusted
- High strength values when properly processed (little defects)
- Electrically non-conductive → no galvanic elements
- Low thermal conductivity compared to metals

Drawbacks:
- Complex processing
- Low fracture toughness compared to metals → sensitive towards defects. Reason: no plastic deformation

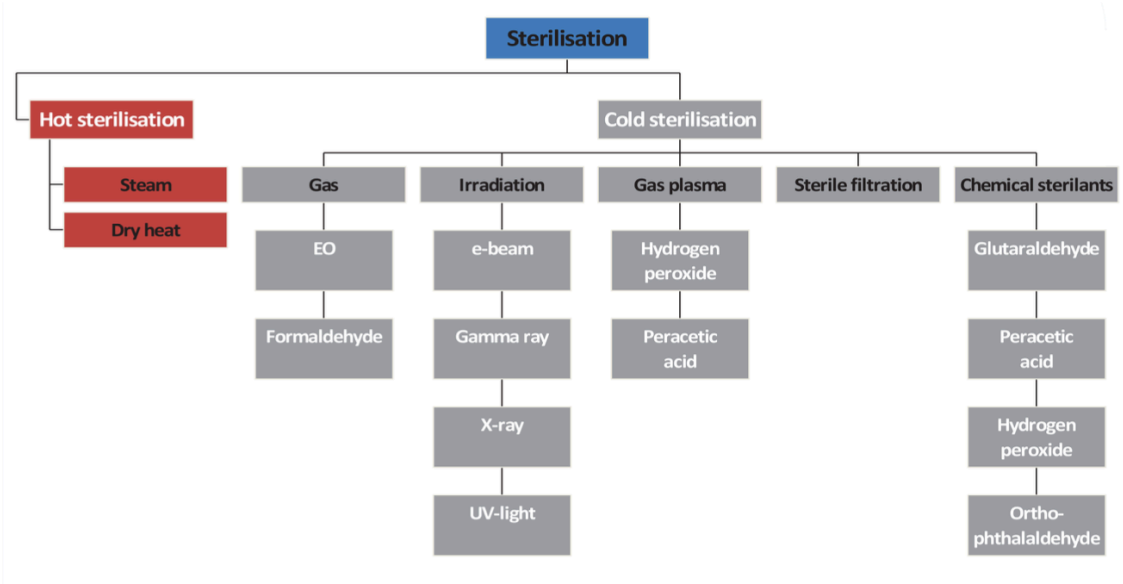
High-strength ceramics

Parameter for obtaining high-strength ceramics:

- **Small grain size**
  (a high number of grain boundaries constitute a large number of obstacles for crack growth → heterogeneity)
  can be reached by using nano-scale powders and low sintering temperatures
  P**roblem**:
  - multiple scattering events, and thus poor translucency
  - lower solid loading and therefore large shrinkage/warpage
- **Low porosity** (few defects, which are ideally as small as possible)
  can be reached by applying high sintering temperature
  (problem: grain growth)
  residual porosity is highly depending on how raw materials are processed (dispersion, pressing parameters, …)
- **Incorporation of crack stoppers** (e.g. fibres → more heterogeneity, lithium disilicate glass ceramics)
- **Transformation strengthening/toughening** (e.g. zirconia)

7. Sterilization Methods

- **Count**: 5
- **Dates**: September 2020, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
  1. *All sterilization methods with a short explanation.*
  2. *Gas sterilization (e.g., EO): Mechanism, materials suitable for it, and its pros and cons*
- **Merged Questions:**
  - *Explain all sterilization methods, including gas sterilization (e.g., EO), steam, and radiation. Mention pros, cons, and viable materials.*
  - *What is SAL, and how is sterilization effectiveness measured?*



Gas sterilisation

- Gas sterilization is realized by a microbiocidal gas or gas mixture
- Suitable for sterilisation of **thermosensitive materials** and components or materials sensitive to radiation (plastics, optics, electrics)
- Medical device is exposed to the reactive gas in high concentration
- Load need to be packed in foils and films permeable to gas
- Importance to validate the absence of remaining gases at the end of the process (long desorption)

Irradiation

- Serilisation of products within their packaging (in case of high-energy radiation)
- At room temperature
- No toxic residues

Chemical sterilisation

- Sterilisation with aqueous solutions is rather a disinfection process than sterilisation process
- Often the microorganisms are only harmed and they can no longer provoke any infections
- However, especially bacterial spores are rarely eliminated by this method
- Different treatments can be combined in order to increase effectiveness.

Sterility assurance level

Heat Sterilisation Methods

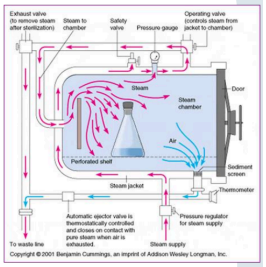
Steam

- Heating: increasing of temperature – increasing of pressure due to expansion of air and increase in water vapour pressure
- Sterilisation: system must maintain T and p until sterilisation period is completed
- Cooling: After sterilisation procedure - Air cooling

Advantages:
- low cost
- non-toxic

Limitations:
- heat resistance
  - e.g. some plastics melt at the temperature range applied
- low heat conductivity or large devices
  - heat requires extra time to reach centre of a device
- moisture-sensitive substances

Autoclave



common used clinical combination, either/or:
- 5 min at 134 °C
- **20 min at 121 °C**

Heat Sterilisation Methods

Steam

Relies on 3 parameters:
- **Time**
- **Temperature**
- **Pressure**

} each parameter can be manipulated

} cycle requirement can vary significantly depending on load type

Steam can be applied differently, depending on the load:

Gravity:
- most common and basic sterilisation cycle
- steam is pumped into the chamber containing air
- as steam has lower density than air, steam displaces air in the chamber without mechanical assistance → **by gravity**, air is forced through a drain vent

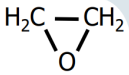
– Glassware, unwrapped goods, vented containers, bio-hazardous waste

Pre-Vacuum and/or Post-Vacuum:
- air is removed mechanically from chamber and load with a series of vacuum and pressure pulses
- steam also penetrates porous areas of the load (that couldn´t be reached with gravity displacement)

– Wrapped goods, packs, cages, porous materials

Gas Sterilisation

- **Ethylene oxide (EO, EtO, C_2H_4O)**
  - pure EO is flammable, often used as mixture with N_2 or CO_2
  - vessel is evacuated (air removed)
  - steam moisture introduced (>40 % humidity)
  - gas(-mixture) injected, 600-1200 mg/l
  - T = 40-50°C for sufficient time to achieve required SAL
  - chamber is re-evacuated to remove adsorbed EO



Properties
- toxic, irritating, carcinogenic, extremely flammable
- strong microbicidal, virucidal, fungicidal and sporicidal effect
- desorption time depends on material, temperature and EO concentration
  - min. desorption time is determined by material with longest desorption time
- highly diffusive: penetrates well, migrates through textiles, paper and some plastics (e.g. some packaging material)

Limitations
- Handling
- Time of desorption

Applications:
- Surgical sutures, Absorbable and non-absorbable meshes
- Intraocular lenses
- Ligament and tendon repair devices
- Vascular grafts and stents coated with bioactive compounds

Irradiation Sterilisation

- **E beam/X-ray- and Gamma radiation**

- Difference in penetrating power:
  - e⁻-radiation: high dose rate, with low penetration depth;
  - γ-radiation: high penetration depth at low dose rate; also products of high density, and metallic components are penetrated
- Mechanism: radiation interacts and destroys DNA and cell membrane of microorganisms and deactivates them

- **Advantages:**
  - Efficient and easy to control
  - High penetration depth
  - Medical devices can be sterilized within packaging without increasing temperatures
  - No residues of the sterilising agent
  - Sterilisation of components of complex geometries possible
- **Disadvantages:**
  - physical or chemical changes in the material,
  - **Polymer chain scission (post-irradiation aging)**
  - high costs

Gas Plasma Sterilisation

Plasma Sterilisation

Plasma is the fourth state of matter (solid, liquid, gas, and plasma) and is created when a gas is heated sufficiently or exposed to a strong electromagnetic field -> **ionized gas**

- **Low-temperature plasma sterilisation**
  - Temperature range 37-60°C, low pressure
  - typically hydrogen peroxide vapours that are converted in gas plasma
    - generation of free radicals that react with molecules (kill via oxidation)
    - essential in the metabolism and reproduction of micro-organisms

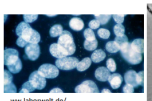
- **Advantages**
  - Suitable for heat and moisture sensitive devices
  - No toxic residues
  - Short aeration time

- **Limitations**
  - Free radicals can influence molecular structure of Polymers

Sterilisation by Filtration

- Retention of micro-organisms on the surface of filter materials
- Filter materials for the sterilisation of liquids and gases are membrane filters made of cellulose derivates or synthetic polymers (PC, PSU, PTFE ...)
- Pore diameter: depending on microorganisms that need to be separated from 0.45 µm – 0.1 µm

Limitations:
Cannot filter some microorganisms such as:
- Mycoplasma: deformable, due to lack of cell wall
- Spirochaete: diameter of 0.1-0.6 µm and length of 5-250 µm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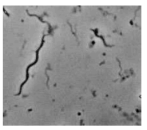
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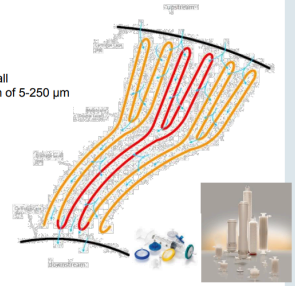
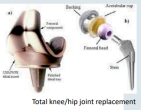


Sterilisation by radiation – Material changes

Sterilisation by irradiation and Polymers


Total knee/hip joint replacement

Two direct consequences of this bond scission are a:
decrease in molecular weight and the formation of **cross-linking between** polymer chains.

lead to significant **changes in the surface and sub-surface structure** of the material and a loss of desirable mechanical properties, resulting in poor clinical performance

Aging has been attributed to the reaction between oxygen and long-lived free radicals present in the irradiated sample → **affect longevity of the biomaterials**

POST-IRRADIATION AGING

8. Fracture Toughness

- **Count**: 4
- **Dates**: April 2024, January 2024, WhatsApp summary (10.12.21)
- **Variations**:
  1. *How is the stress intensity factor K influenced by acting stress, defect size, and form factor?*
  2. *Fracture mechanics: Formula for critical defect size, Kc values for steel vs. ceramics.*
- **Merged Questions:**
  - *How is the stress intensity factor* K *influenced by stress* σ*, defect size* a*, and form factor* f*? How does the critical defect size* a_c *depend on the fracture toughness* K_c*?*
  - *Give and explain the formula for fracture mechanics of ceramics. What are typical* K_c *values for different materials?*

Formeln:

the largest defect and the toughness of the ceramic material, since according to linear elastic fracture mechanics (see Sec. 3.4.1), the macroscopic stress σ is related to the stress intensity factor K, the form factor f and the defect size a:

$$\sigma = \frac{K}{f \sqrt{\pi \cdot a}} \qquad \text{Equ. (40)}$$

The critical stress σ_c is therefore related to the critical stress intensity factor K_c (fracture toughness) and the defect size a:

$$\sigma_c = \frac{K_c}{f \sqrt{\pi \cdot a}} \qquad \text{Equ. (41)}$$

This means that the macroscopic strength (e.g. the bending strength as listed in Table 6-4) not only depends on the toughness of the material, but also on the maximum defect size, which is mainly influenced by the choice of the raw material and the specific processing conditions. We can view above equation also from another side, by requiring a certain bending strength value σ_b with a given toughness K_c and checking the related maximum defect size a_m which is allowed in the sample:

$$a_m = \frac{K_c^2}{f^2 \cdot \sigma_b^2 \cdot \pi} \qquad \text{Equ. (42)}$$

$$K = \sigma * f * \sqrt{a * \pi}$$

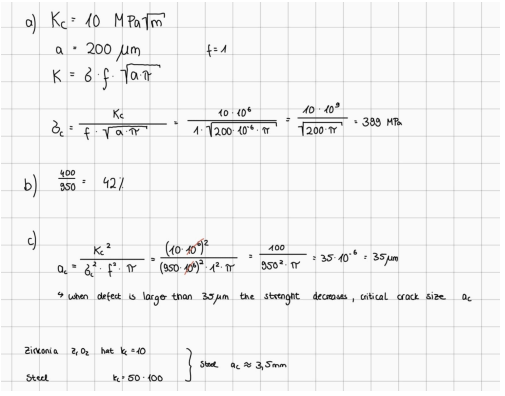
critical defect size $a_c = \frac{K_c^2}{\sigma_c^2 * f^2 * \pi}$

Kc Values: steel = 50-100 MPa $\sqrt{m}$, ceramic = 10 MPa $\sqrt{m}$

Beispiel Vorlesung:

By falling down, Mr. Z. loses one of his teeth. The missing tooth is replaced by the dentist through a zirconia ceramic bridge (K_{IC} = 10MPa $m^{1/2}$). When inserting the bridge, careless handling of the drill results in a notch (crack) with a crack length of 200µm at a mechanically loaded point.

(a) Calculate at which stress on the bridge fracture mechanical failure occurs. Take a form factor of f = 1.
(b) By what percentage is the strength of the cracked bridge reduced compared to undamaged zirconia (strength R_m = 950MPa)?
(c) How long can a crack be at the most so that the strength of the bridge does not fall below a value of 950MPa?



9. Biocompatibility Matrix

- **Count**: 3
- **Dates**: January 2024, September 2020, Biocompatible materials (27.01.2020)
- **Variations**:
  1. *What information is contained in a biocompatibility matrix?*
  2. *Where can you look up required tests for a medical device?*
- **Merged Questions:**
  - *What is the biocompatibility matrix? What factors should be considered (e.g., application time, carcinogenicity, etc.)?*
  - *Overview of ISO standards and biocompatibility testing.*

Materials Biocompatibility Matrix ISO 10993

The Materials Biocompatibility Matrix indicates which tests need to be performed depending on the following criteria:

1) **Contact duration**
- < 24 h
- 24h - 30 d
- > 30 d

2) **Body contact**:
- Surface Devices
  - Skin
  - Mucosal membrane
  - Breached or compromised surfaces
- Externally communicating devices
  - Blood path/indirect
  - Tissue/Bone/Dentin
  - Circulating Blood
- Implant Devices
  - Tissue/Bone
  - Blood

DEVICE CATEGORIES			BIOLOGICAL EFFECT												
BODY CONTACT		**CONTACT DURATION** **A** = Limited (≤24 Hours) **B** = Prolonged (24 Hours - 30 Days) **C** = Permanent (>30 Days)	Cytotoxicity	Sensitization	Irritation/Intracutaneous	Acute Systemic Toxicity	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental	Biodegradation
SURFACE DEVICES	Skin	A	x	x	x									
		B	x	x	x									
		C	x	x	x									
	Mucosal Membrane	A	x	x	x									
		B	x	x	x	o	o		o					
		C	x	x	x	o	x	x	o		o			
	Breached or Compromised Surfaces	A	x	x	x	o								
		B	x	x	x	o	o		o					
		C	x	x	x	o	x	x	o		o			
EXTERNALLY COMMUNICATING DEVICES	Blood Path, Indirect	A	x	x	x	x				x				
		B	x	x	x	x	o			x				
		C	x	x	o	x	x	x	o	x	o	o		
	Tissue/Bone/Dentin Communicating[1]	A	x	x	x	o								
		B	x	x	x	x	x	x	x					
		C	x	x	x	x	x	x	x		o	o		
	Circulating Blood	A	x	x	x	x		o[2]		x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	o	o		
IMPLANT DEVICES	Tissue/Bone	A	x	x	x	o								
		B	x	x	x	x	x	x	x					
		C	x	x	x	x	x	x	x		o	o		
	Blood	A	x	x	x	x	x		x	x				
		B	x	x	x	x	x	x	x	x				
		C	x	x	x	x	x	x	x	x	o	o		

x – Tests per ISO 10993-1
o – Additional tests that may be applicable in the U.S.

10. Titanium

- **Count**: 3
- **Dates**: April 2024, September 2020, WhatsApp summary (10.12.21)
- **Variations**:
  1. *What are the benefits and drawbacks of using titanium as a biomaterial?*
  2. *Why is titanium considered biocompatible?*
- **Merged Questions:**
  - *What are the benefits and drawbacks of using titanium as a biomaterial? Why is CP-titanium used instead of Ti-6AL-4V?*
  - *What makes titanium so biocompatible?*

- Benefit:
  - Excellent biocompatibility due to stable TiO_2-coating on surface
  - High strength and stiffness, rather low weight

- Drawbacks and challenges:
  - Pure titanium has hexagonal crystal structure (α-phase) at room temperature → low ductility
  - Very sensitive to oxygen, hydrogen and nitrogen (embrittlement) → difficult to process metal (problems with casting, welding, …)

Titanium grades:

- **Commercially pure titanium**: excellent biocompatibility due to lack of alloying elements, limited strength
- **Alpha and near-alpha Ti-alloys**: single phase, but strengthened by solid solution strengthening (Al as α-stabilizer)
- **Alpha-beta alloys**: yields best mechanical properties, uses α- and β-stabilizers (e.g. Al for α and V for β). Certain criticism regarding Al and V.
- **Beta titanium alloys**: β-phase ductile and therefore suitable for cold-working. Not extensively used for biomedical applications

Use of titanium in biomedical engineering:
• Total Hip Replacement
• Screws and fixation devices
• Cranio-facial surgery (meshes, screws, ..)
• Osteosynthesis (plates, screws, …)
• Dental implants

Ti-6AL-4V (6%Al, 4%V)
Al as well as V are of some concern regarding negatively influencing biocompatibility. This is the reason for using cpTi for certain applications, or replacing at least the potentially cytotoxic V with the more biocompatible Nb.

For biomedical applications, the following grades of titanium are used: Commercially pure titanium (cpTi) provides **excellent biocompatibility** due to lack of alloying elements. Many strengthening mechanisms cannot be used in pure metals, causing a limited strength for cpTi.

11. Hydrogels

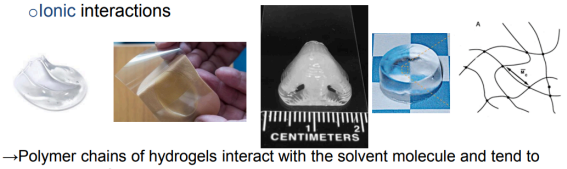
- **Count**: 3
- **Dates**: April 2024, January 2021, WhatsApp summary (10.12.21)
- **Variations**:
  1. *What is the definition of a hydrogel and its important feature?*
  2. *Applications of hydrogels in medical fields.*
- **Merged Questions:**
  - *What is the definition of a hydrogel? Name important parameters, properties, and applications.*
  - *Describe the process of making a hydrogel and compare hydrogels with other polymers.*

Hydrogel

Hydrogels - properties

Definition:

•3D network of hydrophilic polymers, either
- ○Covalent bonds produced by reaction of one or more copolymers
- ○Physical cross-links from entanglements, hydrogen bonds or strong van der Waals interactions between chains, OR
- ○Ionic interactions



→Polymer chains of hydrogels interact with the solvent molecule and tend to **expand** to the fully solvated state

→Crosslink structure works as **retractive** force to pull back polymer chain inside

Important feature:
Are able to retain a large quantity of water within their structure **without dissolving** (up to 99% of H_2O dry weight) -> reason why they are highly biocompatible

Hydrogel

Hydrogels - Classification

Various classifications: source, method of preparation, component, ionic charge, physical structure, crosslink, function, etc…

•Source:
○Natural (Polysaccharide, agar, agarose, alginate. Polypeptides, collagen, fibrin vs Synthetic (PEG (poly(ethylene glycol)), PAA (poly(acrylic acid))…

•Method of preparation:
- ○Crosslink of polymer
- ○Simultaneous polymerization

•Component:
○Homopolymer hydrogels: cross-linked networks of one type of hydrophilic monomer unit
○Copolymer hydrogels: cross-linking of two comonomer units, at least one is hydrophilic (swellability)
○Multipolymer hydrogels: three or more comonomers

•Ionic charge:
○neutral, anionic, cationic, ampholytic (having both positive and negative charges)

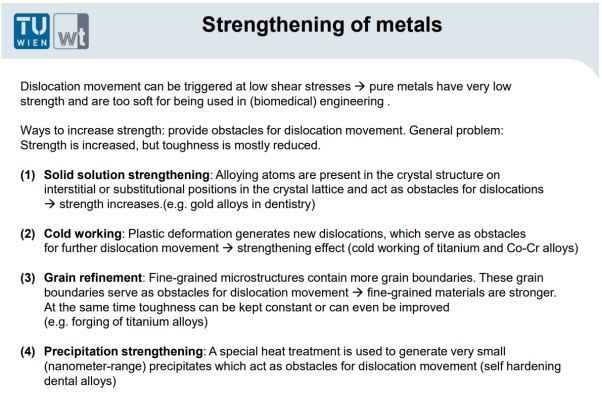
Hydrogels - Applications

•Medical application
- ○Lubricant
  - ○dry surfaces of catheters, drainage tubes, exhibit high friction coefficients (injure surrounding tissue)
- ○Blood-contacting hydrogels
  - ○Nonionic hydrogels, prepared from polyvinylalcohol, pHEMA, and polyethyleneglycol (PEG)
  - ○heparin-based hydrogels
- ○Contact lenses
  - ○Soft contact lenses
- ○Wound dressings need to have
  - ○Flexibility, strength, non-immunogenicity, permeability of water and metabolites, barrier effect
    - ○Hydrogels possess all of these characteristics except of mechanical strength → creation of composite blends

•Pharmaceutical application
- ○Drug Delivery System (DDS)

12. Strengthening Methods (Metals and Ceramics)

- **Count**: 3
- **Dates**: January 2021, Biocompatible materials (27.01.2020), WhatsApp summary (10.12.21)
- **Variations**:
    1. *What mechanisms can increase the strength of ceramics or metals?*
    2. *Tetragonal zirconium: Why does it make ceramics stronger?*



Strengthening of metals

Dislocation movement can be triggered at low shear stresses → pure metals have very low strength and are too soft for being used in (biomedical) engineering .

Ways to increase strength: provide obstacles for dislocation movement. General problem: Strength is increased, but toughness is mostly reduced.

(1) **Solid solution strengthening**: Alloying atoms are present in the crystal structure on interstitial or substitutional positions in the crystal lattice and act as obstacles for dislocations → strength increases.(e.g. gold alloys in dentistry)

(2) **Cold working**: Plastic deformation generates new dislocations, which serve as obstacles for further dislocation movement → strengthening effect (cold working of titanium and Co-Cr alloys)

(3) **Grain refinement**: Fine-grained microstructures contain more grain boundaries. These grain boundaries serve as obstacles for dislocation movement → fine-grained materials are stronger. At the same time toughness can be kept constant or can even be improved (e.g. forging of titanium alloys)

(4) **Precipitation strengthening**: A special heat treatment is used to generate very small (nanometer-range) precipitates which act as obstacles for dislocation movement (self hardening dental alloys)

Ceramic: Transformation strengthening (siehe Frage 4 Zirkonia)

13. Foreign Body Reaction

- **Merged Questions:**
  - *What are the stages of a foreign body reaction? How can surface properties (hydrophilic/phobic) influence it?*
  - *How can foreign body reactions be controlled or mitigated?*
- **Count:** 3 times
- **Dates:** WhatsApp Group Summary, Miscellaneous

Biomaterials response to host body

The FBR involves many complex molecular and cellular players but can be broadly categorized into five sequential phases:

(i) Blood-biomaterial interaction

(ii) Acute inflammation

(iii) Chronic inflammation

(iv) Foreign body giant cell formation

(v) Encapsulation

Besides their *in vivo* functionality, biomaterials also require characteristics that allow **their integration into the intended tissue without eliciting an overshooting foreign body reaction** (FBR).

The host response to implants is essentially an **inflammatory response** that continues as long as there is a foreign body present to which to respond.

1) Hydration of Surface

Hydrophilicity

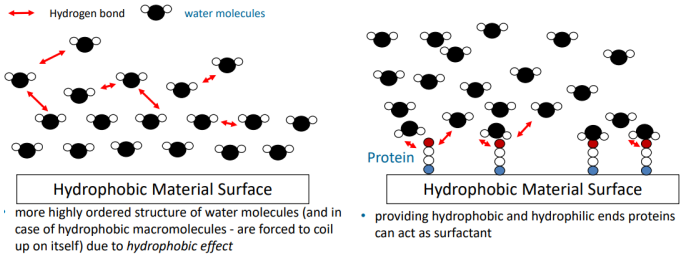
Describes tendency to interact with, be attracted to or dissolved by water or other polar substances

Hydrophobicity

Substances that do not interact or dissolve in water, degree of being repelled from water or other non-polar substances

Hydrophobicity ↔ hydrophilicity

Proteins act as intermediate to enable the bonding of hydrophilic molecules onto hydrophobic surfaces



- more highly ordered structure of water molecules (and in case of hydrophobic macromolecules - are forced to coil up on itself) due to *hydrophobic effect*
- providing hydrophobic and hydrophilic ends proteins can act as surfactant

Material characteristics that can influence biocompatibility & the host response

- Bulk material
- Crystallinity and crystallography
- Elastic constants
- Water content
- Macro-, micro-, nano-porosity
- Surface
- Corrosion
- Degradation
- Accessory agents
- Dissolution and Degradation
- Wear

Factors that influence biocompatibility & the host response

- Quality and nature of clinical intervention
- Wide patient-to-patient variability
  - age, sex, general health, concurrent disease, physical mobility, lifestyle features, pharmacological status
- Design of the device
- Physical relationship between surface and body (inappropriate fixation)
- Presence or absence of micro-organisms/endotoxins
- Anatomical location
  - Tissues are known to have limited regenerative potential (cartilage, nerves, muscles….) -> nondividing cells

The affinity of the molecules of water to the surface of a materials depends on **its surface hydration.** Materials that exhibit a strong surface hydration, will be able to form rapidly a layer of tightly bound molecules of water on its surface. In such dense layer, the hydrogen interaction between the molecules of water will be so strong that it will repulse other surrounding molecules like proteins {Chen, 2010 #7}.

Such materials exhibit a bioactivity which is called **non-fouling or anti-fouling,** meaning that no protein or really low amount of protein can adsorb to its surface. For materials with strong surface hydration, the molecules of water will have to be expulsed from the surface of the implant to permit non-specific adsorption of proteins.

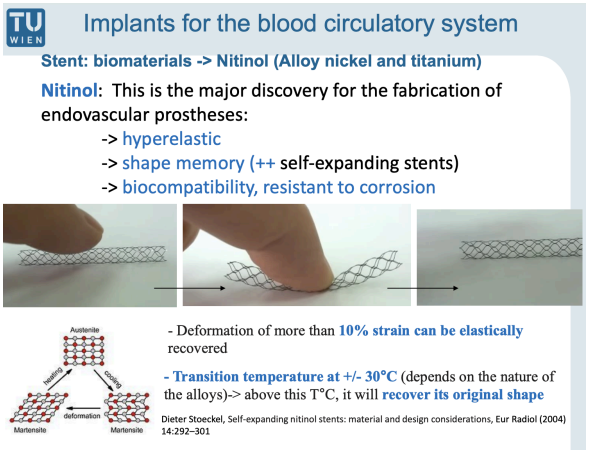
Many implant´s surface properties can play a role in the strength of this surface hydration:

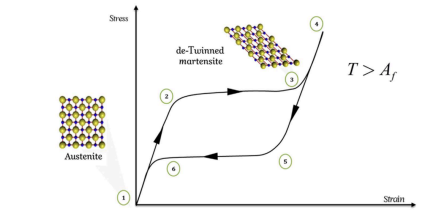
- ➔ Surface wettability
- ➔ Surface topography
- ➔ Surface charge
- ➔ Surface chemistry …

Known polymers which have non-fouling effect due to high surface hydration are **hydrophilic materials** like PEG (polyethylene glycol), some polysaccharides, etc…

Miscellaneous:

nitinol: Stress strain, Explanation of transformation phases

- Stents
- Tools for minimal-invasive surgery
- Wires for orthodontics
- Tools for root canal removal in dentistry
- 

- 

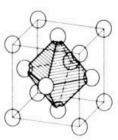
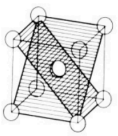
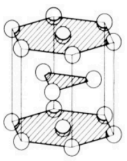
Superelasticity
- Stress-induced phase transformation austenite → martensite
- Diffusionless phase change → fast
- 1→2: elastic deformation; 2→3: austenite to martensite; 3→4: elastic deformation of martensite; 4→5: elastic release; 5→6: martensite to austenite
- Big benefit: up to 11% quasi-elastic deformation
- Resistance against kinking

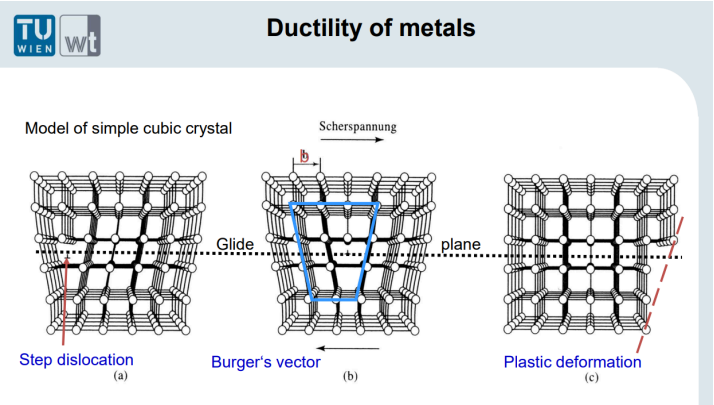
types of bonds

- siehe andere Zusammenfassung

Metal lattice structures and ductility.

- Unit cells of most important lattice structures of metals and corresponding densely packed planes (glide planes)

Gitter	kubisch flächenzentriert	kubisch raumzentriert	hexagonal
E-Zelle und Gleitebenen			
Gleitebenen	4	6 [1]	1
Gleitmöglichkeiten	12	12	3
Kaltformbarkeit	sehr gut	gut	gering
Metalle	Al, γ-Fe, Cu, Pb	α-Fe, Cr, Mo, V	Mg, Zn, Ti



- Shear stress auf metal cube → Step dislocation of atoms
- Der **Burgers-Vektor** beschreibt die Größe und Richtung der Verschiebung der Atome entlang der Gleitebene
- Die Bewegung von Versetzungen durch das Kristallgitter erlaubt Metallen, sich unter Belastung zu dehnen, ohne sofort zu brechen
- Nach wiederholtem Gleiten der Atomebenen entlang der Gleitebene ist das Kristallgitter dauerhaft verformt. (Schritt 3, Plastic deformation)
- Die Fähigkeit zur plastischen Verformung hängt von der Beweglichkeit der Versetzungen ab. Materialien mit einer hohen Versetzungsdichte und einfacher Bewegung zeigen größere Duktilität

Packaging functions for biomedical devices

- Packaging performs 3 functions:
  - protection
  - utility
  - communication

- **Protection**
- protect against **contamination:** → contributes to limited shelf life
  - not only occurs during fabrication and sterilization of devices but also introduced during packaging, transport and storage
- From environment and vice versa
  - Maintain sterility throughout its entire life, incl: sterilisation, shipping, storage, handling, and use.
  - Protection from shock and vibration, crushing, puncturing, tearing, bursting, splitting, pinholing, humidity, heat,…

In vitro testing methods for biomaterials (e.g., direct/indirect contact, extract tests).

Use of fillers in photopolymerization.

Biodegradation

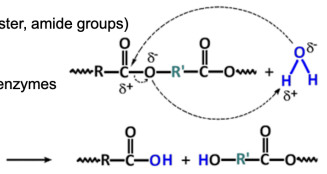
Definition: chemical process resulting in the cleavage of covalent bonds; a biological agent (enzyme, cell, or microorganism) is causing the chemical degradation of the implanted device

4 mechanisms of degradation with brief examples?

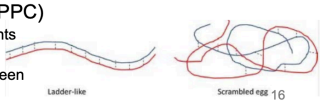
Mechanisms of degradation

- Polymer dissolution
- Hydrolysis
- Enzymatic degradation
- Dissociation of Polymer-polymer-complexes

- Polymer dissolution
  - Cleavage of covalent bonds
  - Degradation due to thermal or mechanical processes
  - Destruction of the entire polymer backbone
- Hydrolysis
  - In case of hydrolytic instable bonds (e.g. ester, amide groups)
  - Inversion of polycondensation
  - Controlled by diffusion of water molecules
  - Catalysed by temperature, acids, base or enzymes



- Enzymatic degradation
  - Takes place at specific groups identified by enzymes
  - Hydrolytic, oxidative or chain scission
  - High molecular weight enzymes do not diffuse into polymer → surface degradation
- Dissociation of polymer-polymer complexes (PPC)
  - occurs via solvation of the macromolecular components
  - until the gain of free energy becomes higher than the energy of intermolecular cooperative interaction between the two polymers



Mechanisms for higher toughness

Toughening mechanisms

(T1) The yield stress will be high in all those materials that are characterized by **strong physical bonds**. Such bonds allow the individual atoms or molecules to slide, thereby dissipating energy. The higher the stress level at which this slipping occurs, the higher the dissipated energy will be.

(T2) The deformation volume can be increased if the material has a high degree of **heterogeneity**: Heterogeneities can be crystalline interfaces, but also fibers or particles, where the crack gets stuck during growth. Heterogeneities can also serve as nucleation sites for new cracks which increase the dissipation volume.

(T3) Another very efficient approach to increase the deformation volume is the use of materials with pronounced **strain hardening**. In materials with pronounced strengthening potential, the flow stress increases steadily with increasing elongation. This leads to a increasingly growing plastic zone and in further consequence to a larger deformation volume.

(T4) In order to obtain a high elongation at break, **physical bonds** are highly beneficial on the one hand. On the other hand, the internal **crystalline structure** is crucial for allowing atom layers to move relatively to each other.

Ashby maps

Ashby maps