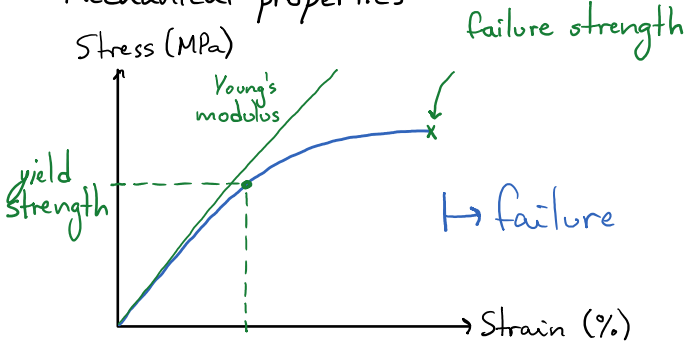
Biomaterials I

→ Definition:

- A non-viable material used in a medical device, intended to interact with biological systems
- A substance (other than a drug) or combination of substances, synthetic or natural, used to treat, augment or replace any tissue, organ, or function of the body

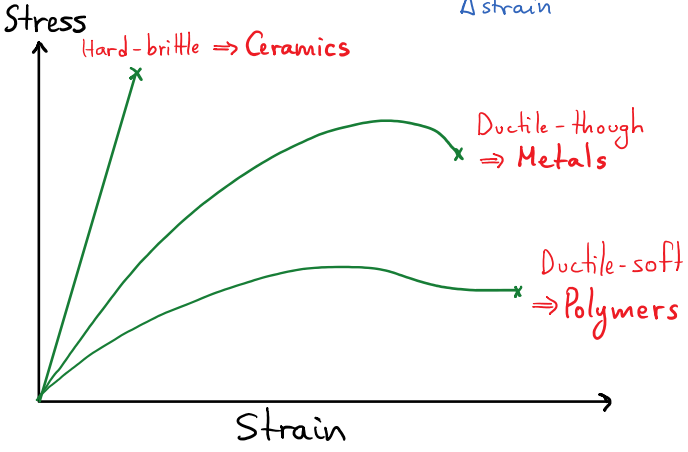
→ Mechanical properties



→ failure strength: Stress value where material breaks

→ Yield strength: Stress value where curve stops being linear

→ (Young's) modulus: slope of linear approximation (values before yield strength) $\frac{\Delta \text{stress}}{\Delta \text{strain}}$



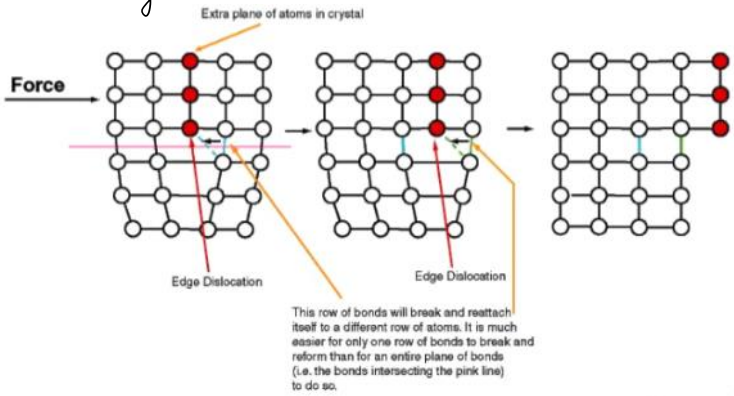
1. Metals

→ Properties:

- Shiny, opague, heavy
- Ductile, conductive
- Generally inert
- free electrons, close packing of atoms, atoms surrounded by a gas/sea of delocalized electrons

→ As a liquid metal cools down, crystallization starts at distinct regions and the borders define grains

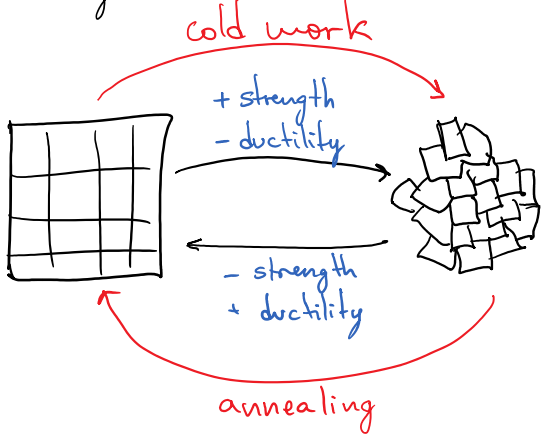
→ Ductility



→ Most common implant metals are alloyed

↳ improved strength and corrosion resistance

→ Annealing

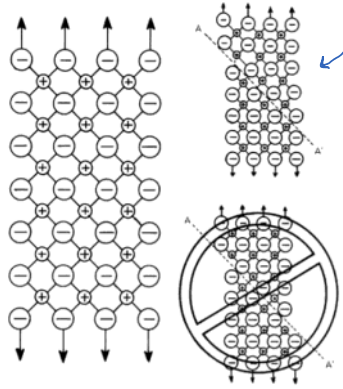


2. Ceramics

→ Properties

- Ionic bonds
- Corrosion resistant
- Electrically / Thermally insulating
- Strong, hard, wear-resistant
- Brittle → danger of catastrophic failure

→ Ionic bonds



alternating charge

↓

no slip dislocations

⇒ not ductile

→ The human body rejects metallic and synthetic polymeric materials by forming scar tissue

↳ bones normally have hydroxyapatite (HA)

hydrated calcium phosphate compound

↳ Larry L. Hench (inventor)

→ Bioglass: Type of ceramic (glass) that is composed by something similar to HA

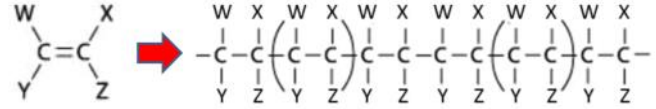
↳ first formulation of an artificial material that was found to chemically bond to bone.

3. Polymers

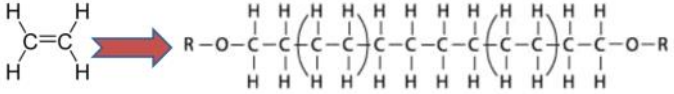
→ Properties:

- Flexible, tough
- Biocompatible
- Inert
- Largest range of properties
- Degradable
- Low friction
- Transparent

→ Covalent bond between mers:

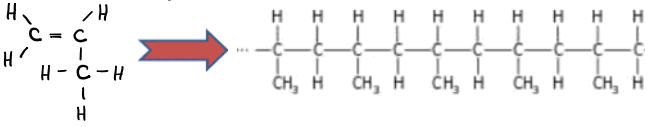


→ Poly (Ethylene)



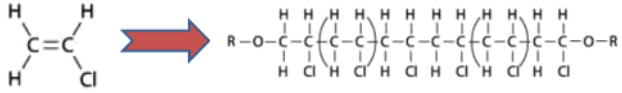
- Most widely produced
- Molecular weight → 3 Million Da
- Extremely high wear resistance
- Slippery, waxy, water-repellent surface

→ Poly (propylene)



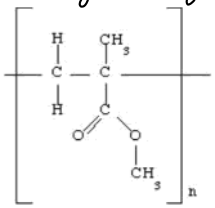
- 2nd most widely produced

→ Poly (vinyl-chloride)



- 3rd most widely produced

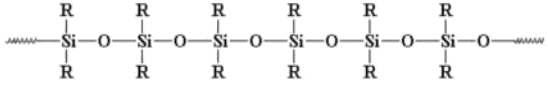
→ Poly (methyl methacrylate)



- High refractive index
- Easily processed
- Relatively inert
- Good mechanical properties
- Environmentally stable

↳ example: contact lenses

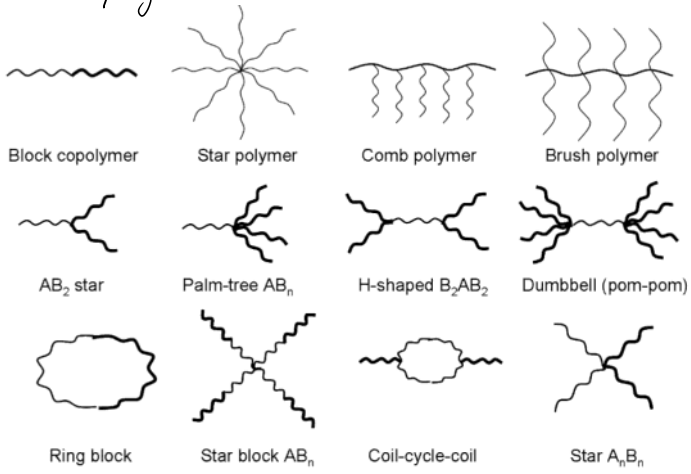
→ Polysiloxanes



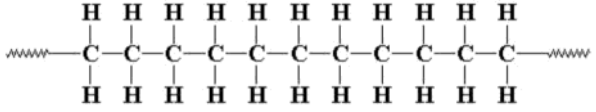
- Elastomers, sealants, coatings
- Very high oxygen permeability

example: breast implants, drug delivery

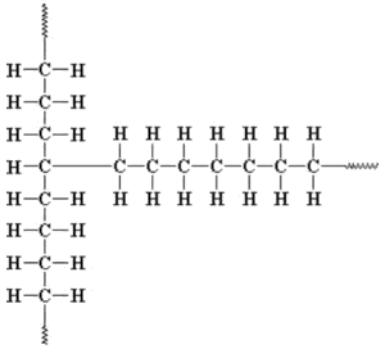
→ Co-polymers



- Linear polymer



- Branched polymer

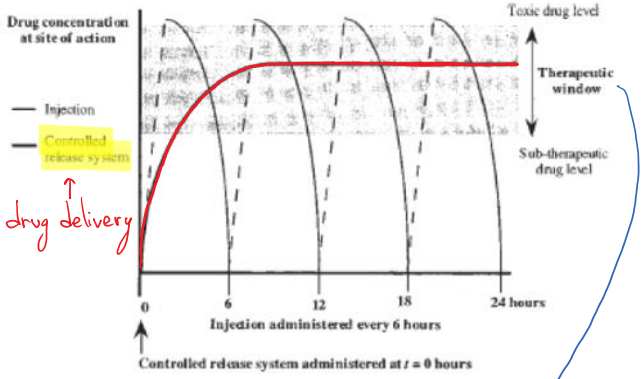


Material	Advantages	Disadvantages
Metals	Strong, Tough, Ductile, can be formed into complex shapes, Inert	Corrosion, stress shielding, wear debris, metal ion allergies
Ceramics	Biocompatible, low wear, microbial resistance, strong in compression, no corrosion	Expensive, difficult to machine and shape, brittle, prone to sudden catastrophic failure
Polymers	Easily formed into complex structure, degradability, flexibility, tunable properties,	Possible toxic degradation products, Properties change with sterilization, deform over time, Weaker properties than metals and ceramics

Biomaterials II

→ Drug delivery: Drug + Protection (→ Polymer etc.)

- Mantain therapeutic level of drug
- Protection of drug
- Protection of the patient (less side effects)
- Easy administration
- Implants don't need to be removed → biodegradable



Where we get the desired effects

→ Drug polarity

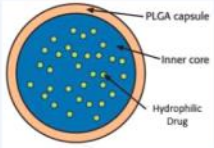
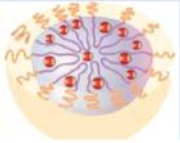
polar / hydrophilic vs. non-polar / hydrophobic

- Non-polar drugs best cross cell membranes
- Only polar drugs are soluble in water
- Many drugs are non-polar and have poor bioavailability without drug delivery systems

→ Partition coefficient, log(P)

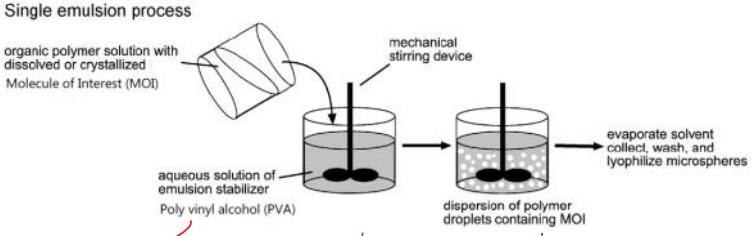
- $\log(P) := \frac{[\text{amount of drug dissolved in octanol}]}{[\text{amount of drug dissolved in water}]}$

$P > 1 \Rightarrow$ 10:1 organic:aqueous ↓ Polar (Hydrophobic)
$P = 0 \Rightarrow$ 1:1 organic:aqueous
$P < 1 \Rightarrow$ 1:10 organic:aqueous ↑ Polar (Hydrophilic)

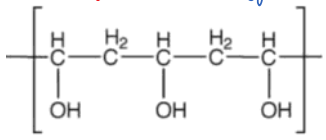
Drug	Polymer	Method
Hydrophobic	Hydrophobic	Single Emulsion 
Hydrophilic	Hydrophobic	Double Emulsion 
Hydrophobic	Hydrophilic/ Hydrophobic Block Co-Polymer	Self Asssembly 

1. Single Emulsion

- Hydrophobic polymer & drug
- "Oil in water"



Analogy: oil in water



- Poly vynil alcohol (polar / hydrophilic)

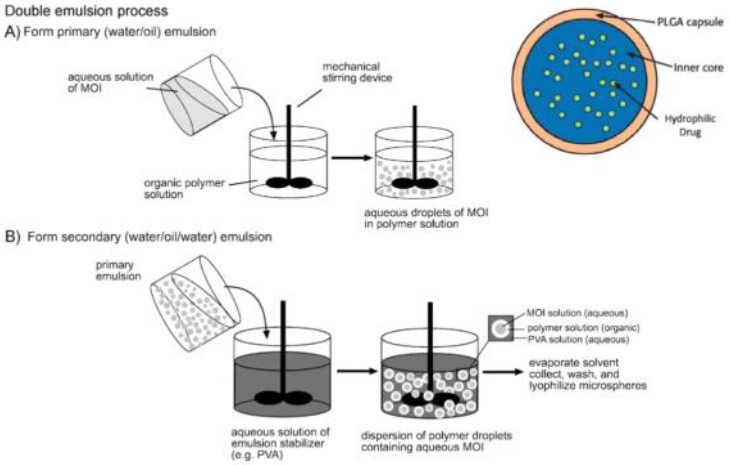
not to mix with our hydrophobic-hydrophobic nanoparticles, since PVA is only used as a solvent

- Polymer and drug mix well together (both hydrophobic)

⇒ just add their mixture into the solvent, shake to form droplets and remove solvent

2. Double Emulsion

- Hydrophobic polymer & hydrophilic drug
- "Water-oil-water" emulsion



- Polymer and drug don't mix well together

⇒ by adding dissolved drug into polymer solution we get droplets of aqueous solution of MOI.

⇒ Add this mix to emulsion stabilizer (PVA) to form these bigger droplets of polymer, drug and its solvent

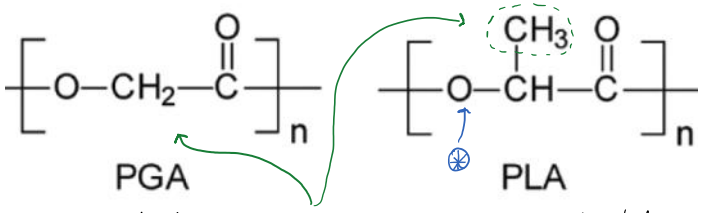
→ Polymer requirements for drug delivery

- Safe for clinical use
- Degradable (into non-toxic products)
- Tunable degradation rate (days - months)
- Biocompatible

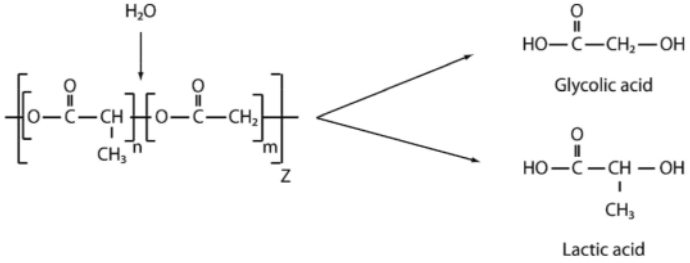
- Example: PLA and PGA ⇝ PLGA

→ PLA and PGA
↳ Poly lactic acid
↳ Poly glycolic acid

- Break down products are natural metabolites
hydrolisis
- Copolymers yield range of useful properties
- Very safe



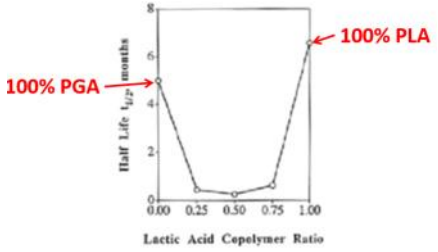
- PGA lacks one CH_3 group ⇒ more hydrophilic than PLA
- ⊛ The important oxygen where the water will attack ⇝ hydrolisis
- More hydrophilic ⇒ mixes better with water
  ⇒ hydrolisis happens faster
  ⇒ degrades faster
- PGA degrades faster than PLA
- PLGA ⇒ amorphous mixture of PLA & PGA



- Hydrolisis breaks PLGA into natural metabolites
- Amorphous materials make it easier for the water to enter in contrast to crystalline materials like PLA and PGA
  ⇒ PLGA degrades faster than PLA and PGA
- Degradation time

higher degradation time

PLGA → PGA → PLA

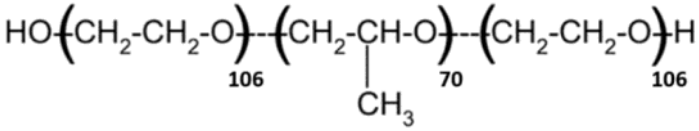


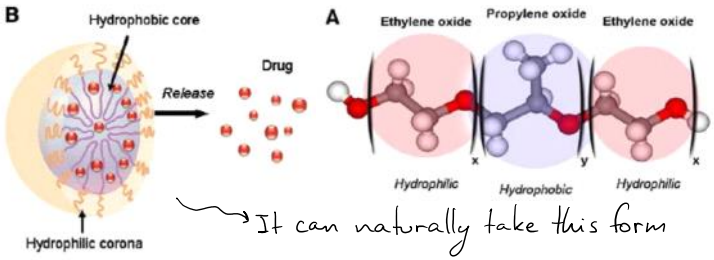
- Degradation rates

PLA		PGA	PLGA
12-16 months, (amorphous)	> 2 years (crystalline)	2-3 months (crystalline)	1-6 months (amorphous)

→ Self-assembly of Copolymers

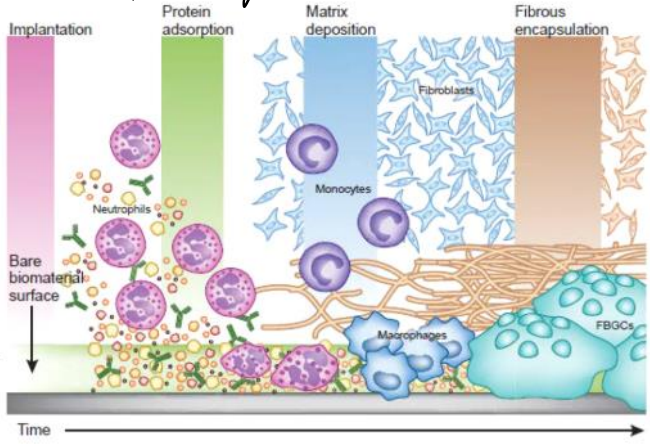
- Self-assembly: Formation of an organized structure from a disordered system of pre-existing components based on their local interactions
- Example: Pluronics (soft gel @ 37°C)

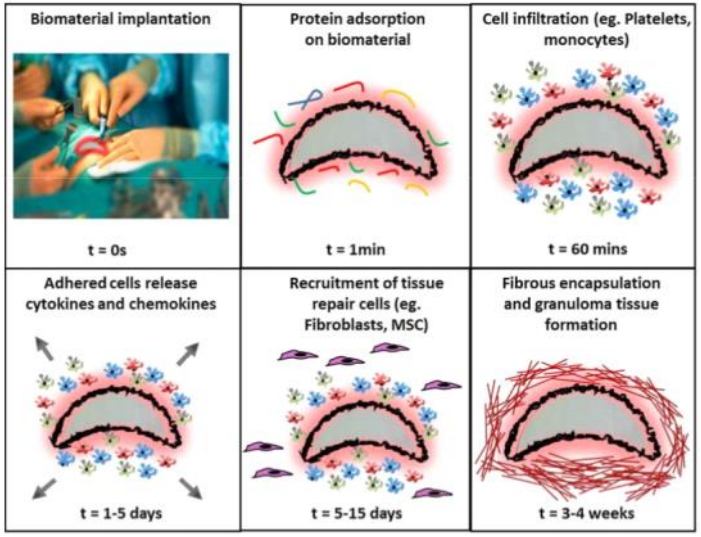




⇝ It can naturally take this form

→ Biocompatibility



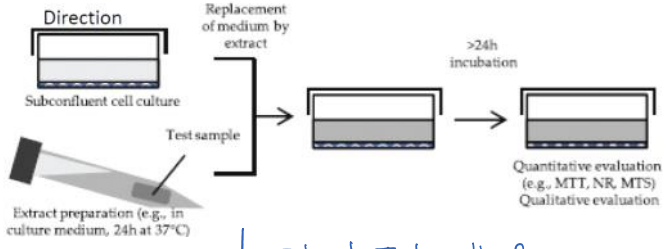


1. Protein absorption
2. Neutrophils → First contact
   ↳ produce cytokines
3. Macrophages and monocytes are attracted (also produce cytokines)
4. Recruitment of fibroblasts

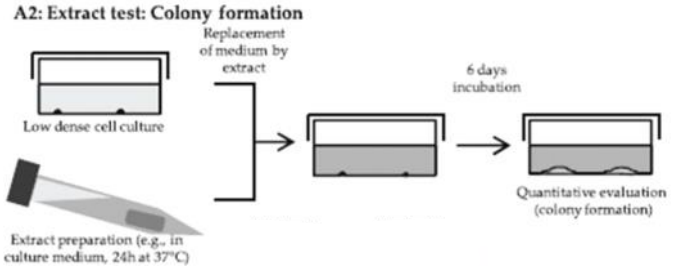
→ Test Biocompatibility

i) Extract Test

- Replace the medium by the extract to be tested on a flask with living cells
- Living cells are able to reduce tetrazole (yellow) to formazan (purple)
- Reduction of more than 30% ⇒ Toxic
- Alternatively one can observe colony formation (incubation of at least 6 days)



↳ Extract Test with formazan



↳ Colony formation

- **Limitation:** Difficult to find the right amount of sample to place on top
- Standard conditions for extract test

Extraction Vehicle (6 cm²/ml)

(a) culture medium with serum
(b) physiological saline buffer
(c) pure water or dimethyl sulfoxide (DMSO) \0.5%

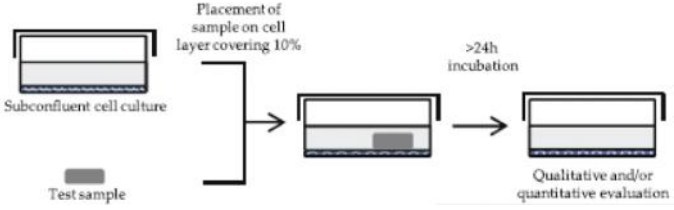
Possible Extraction Conditions

a) (24 ± 2) h at (37 ± 1) °C
b) (72 ± 2) h at (50 ± 2) °C
c) (24 ± 2) h at (70 ± 2) °C
d) (1 ± 0,2) h at (121 ± 2) °C

6mL medium per $25cm^2$ ⇒ 2.5cm height

ii) Direct Contact Test

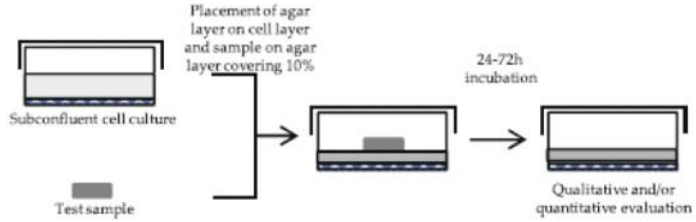
- Place sample directly on top of the living cells
- Material must cover 10% of area
- Live-Dead assay (green = alive, red = dead)
- **Limitation:** Some cells die because of the weight of the sample



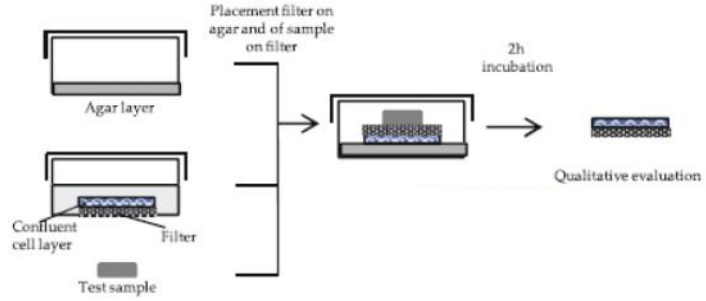
iii) Indirect Contact Test

- Same as direct contact test but with an agar layer between the cells and the sample → no direct contact of the cells with the sample

- **Limitations:** Not as effective as the direct contact test and can take very long

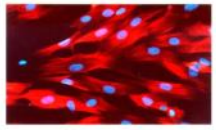
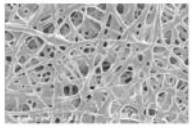
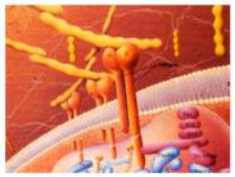


- Alternatively one can place a filter between the cell colony and the sample



Tissue Engineering I

→ **Goal:** Construction of living, functional components to regenerate malfunctioning tissues

CELLS	SCAFFOLD	BIOLOGICAL SIGNALS
		
Primary cells, stem cells, genetically manipulated	Bioactive, bioinert, resorpable…	Growth factors, Environmental proteins, Mechanical & Electrical signals…

1. Types of tissue

- **Connective** - Bone, cartilage, fat, fibrous tissue (Supporting)
- **Epithelium** - Lines the inner and outer surfaces of the body (Covering)
- **Nervous tissue** - Conducts electrical signals (Communicating)
- **Muscle** - Produces mechanical force by contracting (Moving)

2. Cell sources

→ **Autogenic/Autologous:** Cells from the patient
- No immunological response
- Scarce, Donor-Site morbidity
- Cells not very effective on old people

→ **Syngenetic:** Cells between two genetically identical individuals
- No rejection

→ **Allogeneic:** Cells from an unrelated human donor
- Chance of rejection, transfer of human diseases
- Available from younger donors

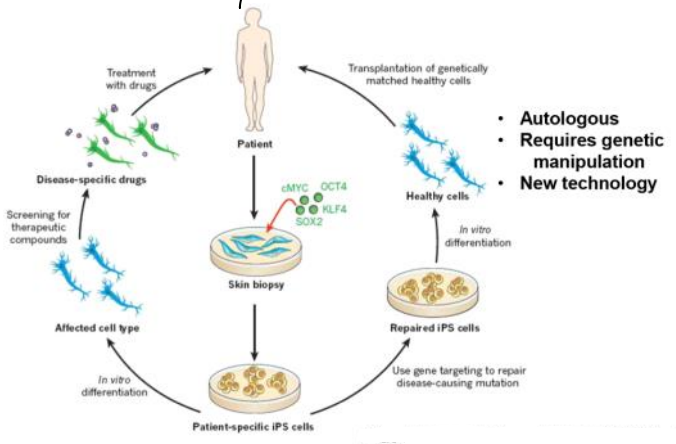
→ **Xenogeneic:** Cells from a different species (pig)
- Tissue needs to be decellularized
- Large chance of rejection
- Transfer of animal diseases to humans
- Unlimited supply from young animals

3. Differentiated vs. Stem cells

→ **Differentiated cells:** Have a specific function (they are specialized)
- Connective tissue - Fills space and provides structural support
- Epithelial cells - Lines cavities and surfaces, often with cilia, secretion, barrior functions
- Neuron - conducts electrical signals
- Muscle - Produce mechanical work
- Sensory cells - Detect external stimuli (light, sound, smells, tastes)
- Blood cells - Erythrocytes, leucocytes, lymphocytes

→ **Comparison**
- Primary cells (differentiated)
  - ↓ Low proliferation potential
  - ↓ Tendency to de-differentiate
  - ↓ Donor-Site Morbidity
- Stem cells
  - ↗ Adult, embryonic, induced pluripotent (iPS)
  - ↑ Can divide indefinitely
  - ↓ Scarce, ethical issues

→ **Induced Pluripotent Stem Cells**



4. Scaffolds

~100 μm

→ Network of large interconnective pores
- allows cells to migrate through the scaffold
- allows diffusion of nutrients
- allows growth of new blood vessels (angiogenesis)

* Mechanical stability (depending on what kind of tissue we want to create)

* Biocompatibility

→ Types of materials commonly used

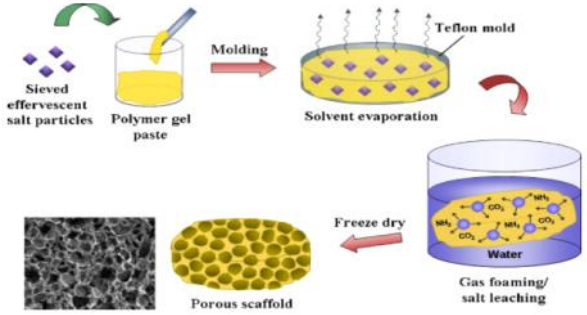
i) **Natural based polymers**
- Collagen, fibrin, hyaluronic acid

ii) **Synthetic polymers**
- PGA, PLA, PLGA, PEG (polyethylene glycol)

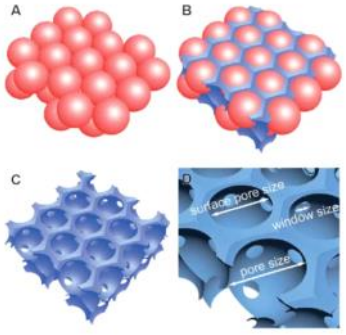
→ **Methods for creating scaffolds**

i) **Porogen Leaching Method**
- Use gas foaming/particulate leaching
- Sieved effervescent salt particles are dispersed in polymer gel paste
- Cast on a teflon mold for solvent evaporation

- immersed in water for gas foaming or salt leaching

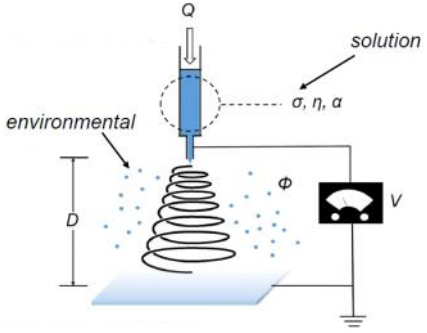


ii) Reverse Opal Method



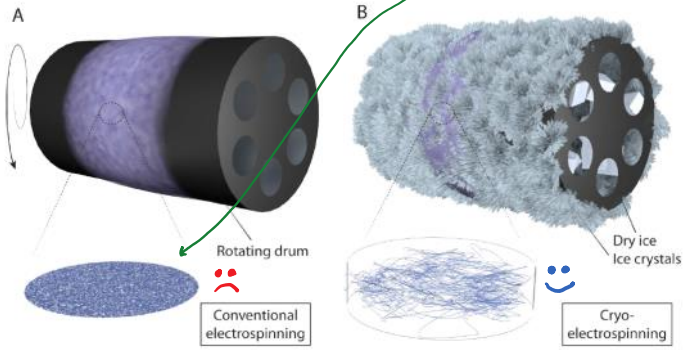
- Similar to 1.
- More control over pore size compared to 1.

iii) Electrospinning

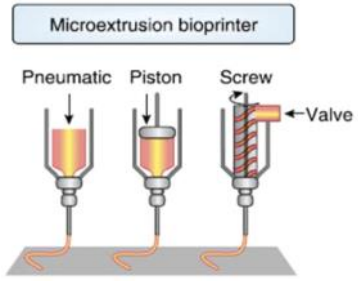


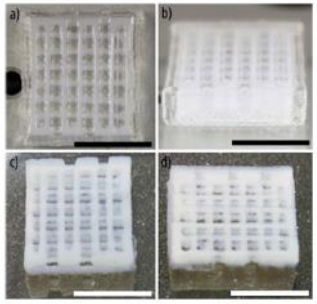
- Produce a fibrous like structure
- PLGA is dissolved in a solvent and extruded on high voltage (electrostatic repulsion stretches the droplet which extends to a fiber)
- One can change density, orientation of the fiber by manipulating the electric field

- disadvantage: We end up with a dense mat
- Cryo-electrospinning



iv) 3D Bioprinting

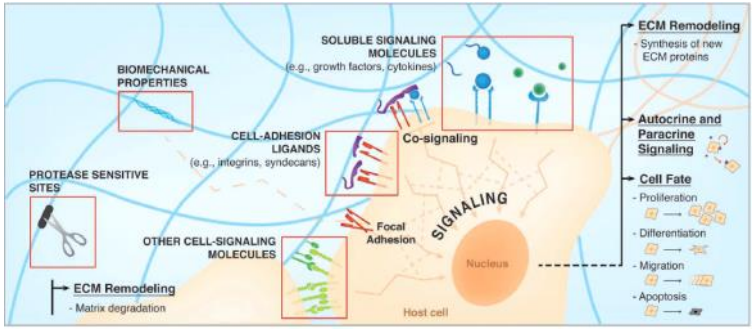




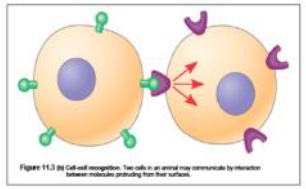
→ Resorbable scaffolds
- Scaffold is eventually 100% dissolved
- Dissolution products are safely metabolized
- Degradation of scaffolds matches rates of growth

5. Cell signals

→ How cells interact with the environment

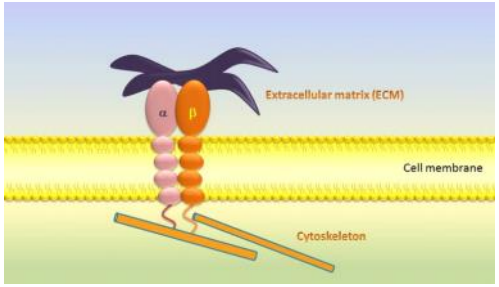


i. Cell-Cell Adhesions (Cadherins)



- Cell adhesion molecule
- Bind cells with each other

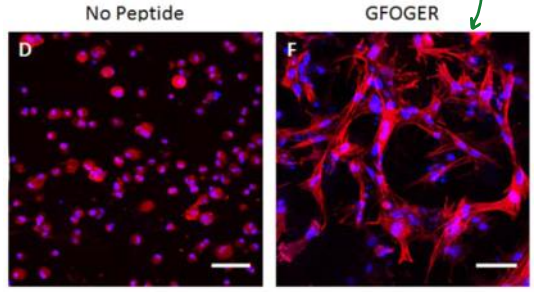
ii) Cell-Matrix Adhesions (Integrins)



- Activate signal transduction pathways that mediate cellular signals → allows rapid and flexible responses to events at the cell surface (coagulation etc.)

→ Put this cool stuff inside your scaffold to help cells grow better and make them happy as hell

See? Happy fuckers right there

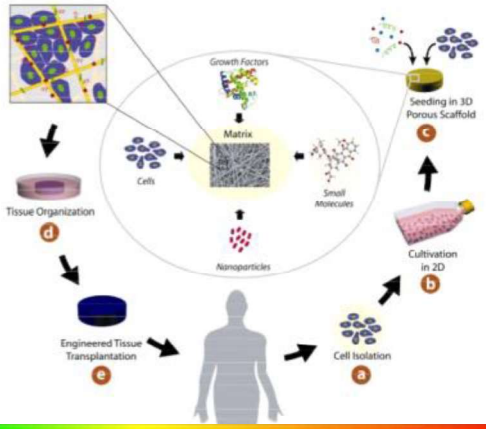


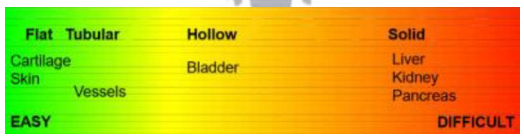
iii) Soluble Growth Factors

- **Autocrine factors:** Produced by cells and active on the same cell
- **Paracrine factors:** Produced by cells and active on their neighbors

Tissue Engineering II

→ Tissue Engineering Paradigm

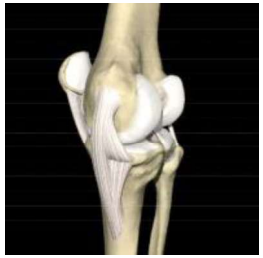


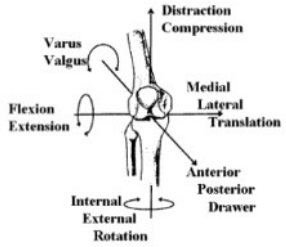


↳ ≈ 2D ⇒ "easy" ≈ 3D ⇒ "difficult" ↲

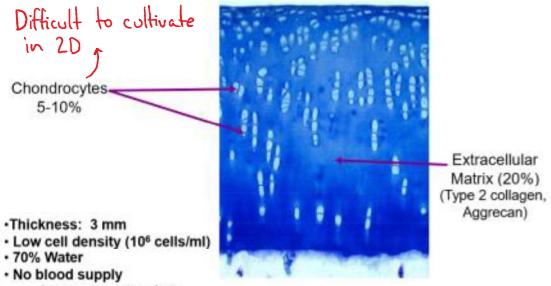
1. Cartilage Engineering

→ Cartilage lines joints and provides low friction surfaces

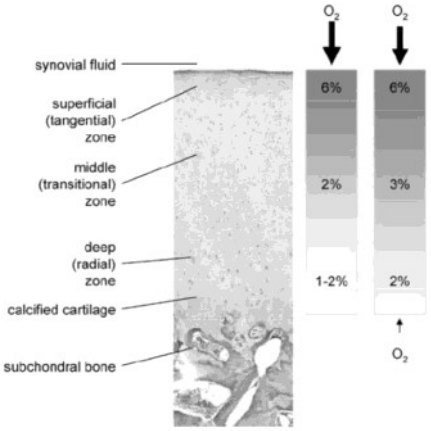




Difficult to cultivate in 2D ↴



→ No oxygen, glucose etc.

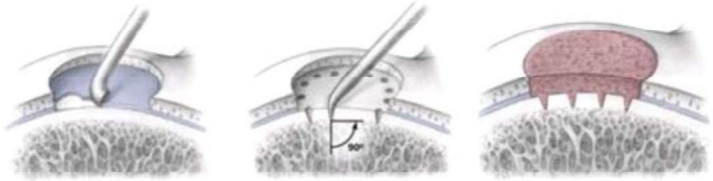


i) **Mosaicplasty**: Extraction of osteochondral plugs which are then inserted into the cartilage lesion

↳ Donor Site Morbidity

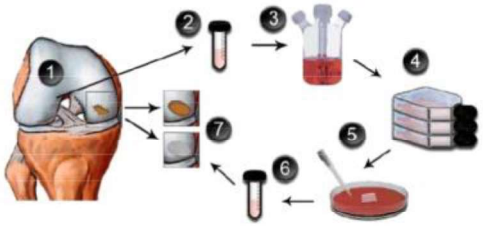
ii) **Microfracture: Poor man's cell therapy**: Clean lesion, make holes → causes bleeding and clot formation

- Difficult to get approval
- High failure rate (50-80%)



iii) **Autologous Chondrocyte Implantation**:

A cartilage biopsy is taken (1) and cells isolated (2/3). The cells are grown in the lab until 12 x 10^6 cells are available (4). Cells are seeded onto a scaffold (5) and the scaffold is placed in the lesion (7).



2 surgeries
extract implant

→ Current strategies:

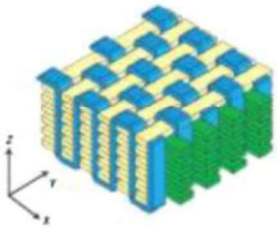
i) **Fibrin injection**

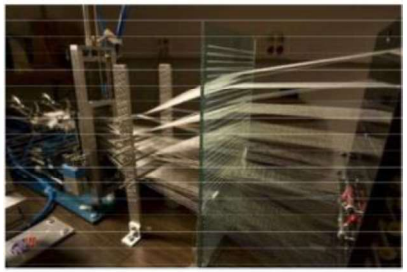
- Fibrin is a hydrated mesh which form during blood clotting via the polymerization of fibrinogen and thrombin
- Injectable, space-filling, sticky
- Hydrogel polymerizes in 10 seconds

↑ Defects are perfectly filled
↓ Tissue is very weak in tension
↓ Made from human blood ⇒ disease transmission

ii) **Woven Cartilage**

- 3D composite structure
- Fiber → Polyglycolic acid yarn (≈ 104μm diameter)
- Hydrogel → Fibrin seeded with chondrocytes

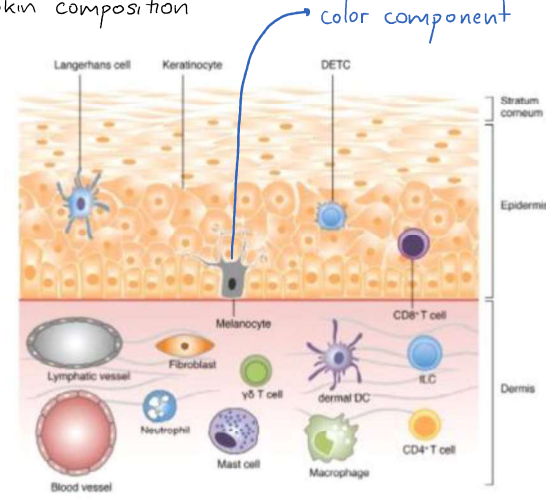




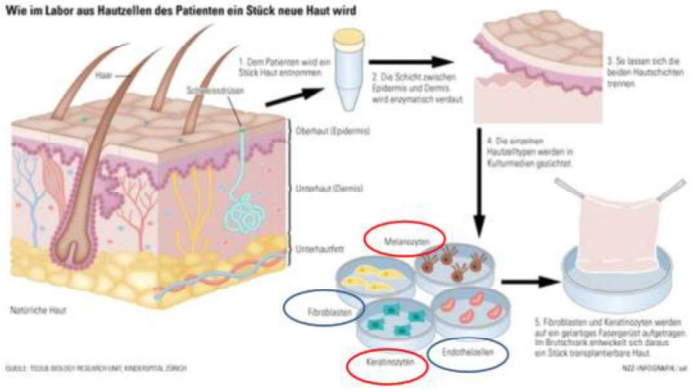
- Woven material show similar properties to native articular cartilage

2. Skin Engineering

→ Skin composition

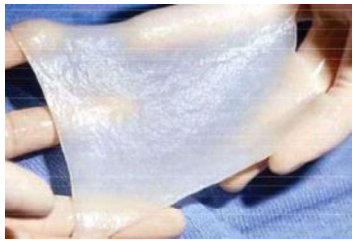


→ Skin Tissue Engineering



→ Used cells:

- Endothelial cells
- Fibroblasts
- Keratinocytes
- Melanocytes
- Stem cells



Collagen gel + these listed cells ↵

→ Vasculature to connect the graft to the patient

↳ capillary veins/arteries

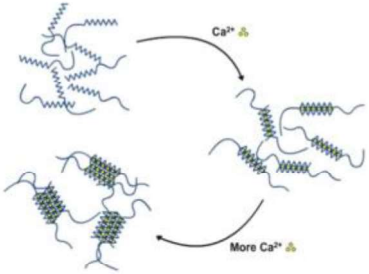
3. Pancreas Engineering

→ Goal is to replace non-functioning Islets of Langerhans, which can sense glucose levels and secrete insulin

→ Donor islets are embedded in a sheet to prevent host rejection

- Sheet is thin → oxygen diffusion

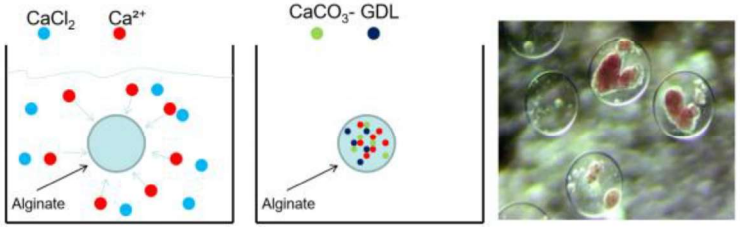
→ **Alginate** is used to protect and encapsulate the islets



→ Alginate forms a sheet in the presence of Ca^{2+} ions

→ 2 Gelation methods

- $CaCl_2$: fast, uncontrolled non-homogeneous, hard shell softer core
- $CaCO_3$-GDL (D-(+)-glucono-δ-lactone): time-controlled, homogeneous structures



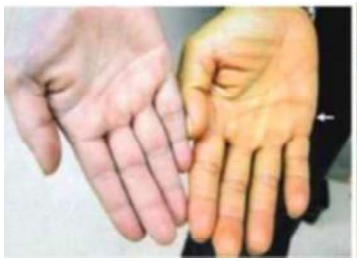
4. Liver Engineering

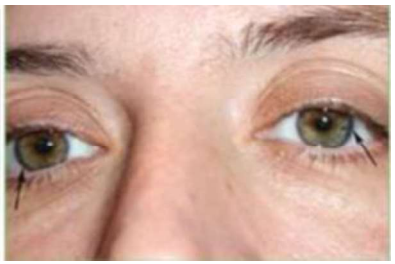
→ Control of fats, amino acids, glucose
→ Glycogen storage
→ Decomposition of red blood cells
→ Detoxication of poisons, drugs, insecticides
→ Production of bile, enzymes, hormones, blood clotting and plasma proteins
→ Fighting infections
→ We can live up to 24 hours without a liver :-
→ **Liver Disease**

- Often begins in the periportal region (vein-organ connection) → highest toxin levels
- Caused by viruses, analgesic medications, alcohol, ischemic insult and extensive liver resections for trauma or cancer

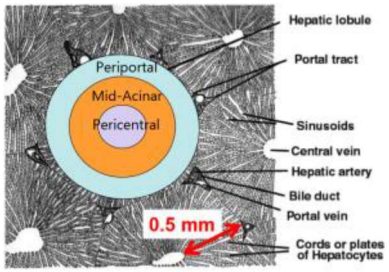
→ Indications of liver disease

- Yellow Skin (Jaundice): Accumulation of bilirubin, a yellow breakdown product normally excreted in bile or urine.
- Aside from the skin, the discoloration can also affect the nails and eyes.

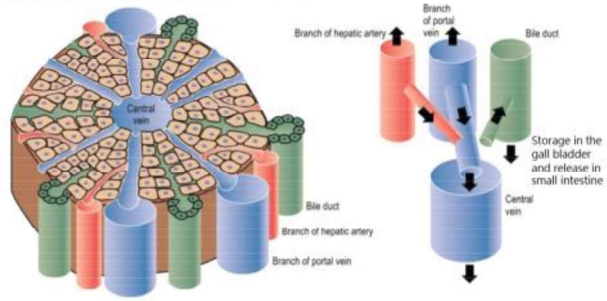




→ Liver's functional sub-unit: Acinus

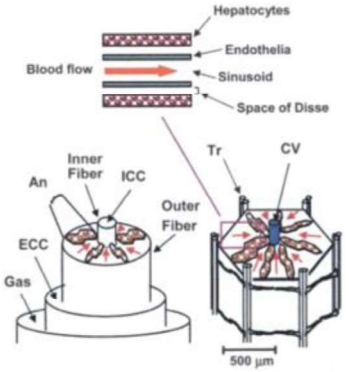


- Blood flows from the periportal vein to the central vein at about $0.01\ cm \cdot s^{-1}$



→ Multi-coaxial Hollow Fiber Bioreactor

- Bioreactor mimics the liver acinus generating a radial flow from ECC to ICC according to



$$Q_r = A \cdot L_p \cdot \Delta P$$

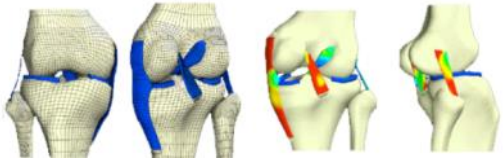
A = Surface area
L_p = hydraulic permeability
ΔP = Pressure difference

→ Problems

- Transmission of disease from the donor hepatocytes
- Foreign proteins
- Toxins from patient's plasma kills donor hepatocytes
- $300'000

Classic Biomechanics

→ Movement science → study of the mechanics of a living body



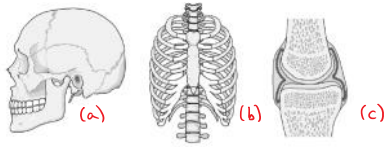
→ **Skeletal System**: design goal is survival
- Energetic efficiency
- Power (fight / flight, Darwinian competition)
- Avoid damage, quick and effective repair

→ **Operating principle (categories)**:
- Kinematic mechanisms ⇝ jointed bones
- Dynamic actuators ⇝ muscles and tendons

1. Kinematic Mechanisms

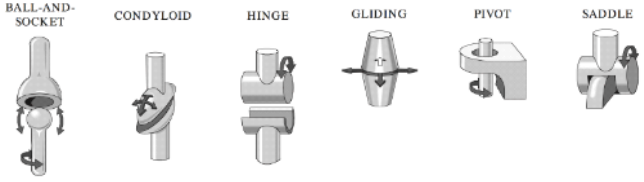
→ Jointed bones

→ The bones can be attached to each other at
- i.) fibrous (a)
- ii.) cartilaginous (b)
- iii) synovial joints (c)

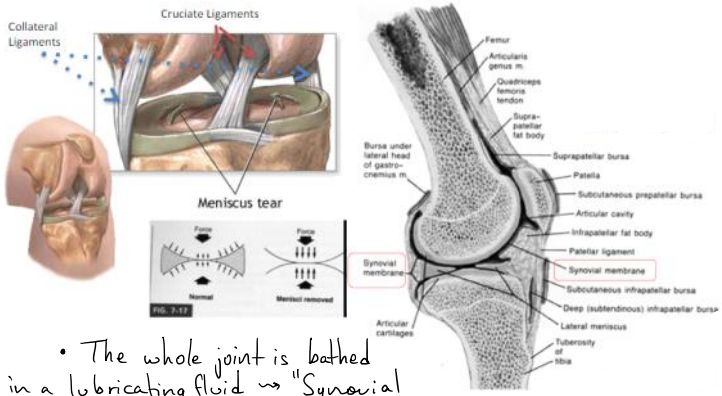


→ A synovial joint is bathed in the lubricating fluid which is encapsulated by the synovial capsule.

- Can be classified into one of six types, depending on the structure and motion type of the joint



→ Example: Human knee (synovial joint)

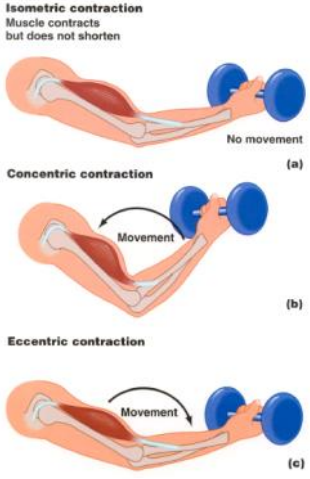


- The whole joint is bathed in a lubricating fluid ⇝ "Synovial fluid" inside the "synovial capsule"

2. Dynamic actuators

→ Effective muscle recruitment depends on the goal
- **Repetitive movements**: walking, running etc
  Survival when food is scarce
- **Power movements**: Power maximization → running
  Survival against threats
- **Constrains**:
  * Avoid overload (cartilage, tendon, muscle etc)
  * Keep joints stable
  Survival by avoiding injury

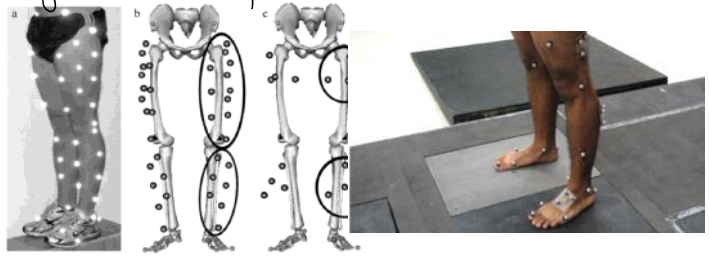
→ Muscle Function



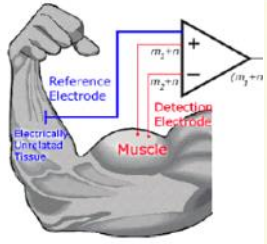
- **Stabilise** a joint (force applied without movement)
  Isometric (co-) contraction
  (muscle remains the same length)
- **Move** a joint
  Concentric (co-) contraction
  (muscle shortens)
- **Dampen** a movement
  Eccentric (co-) contraction
  (muscle fibers lengthen as they contract)

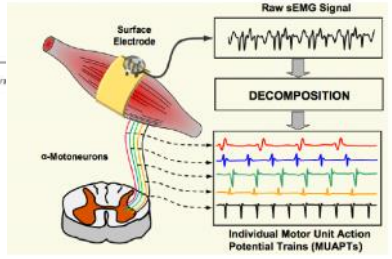
→ Movement Science

- **Force Plates**: Force plates for a precise localisation of external forces (ground reaction force) on the body
- **Motion Capture**: Process of recording the movement of people or objects by using markers around a joint, for example



- **Electromyography (EMG)**: Measure the muscle's activation by detecting electrical potentials generated
  → It is not possible to tell the force being made using only EMG → just a rough idea of force





Muscuskeletal Tissue

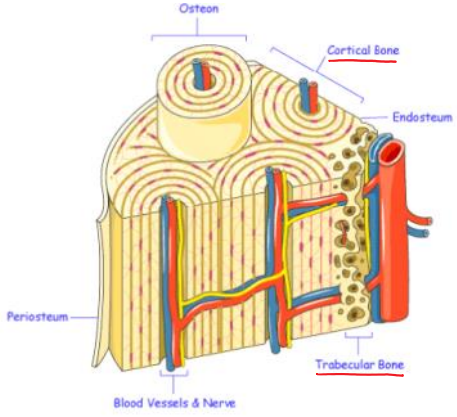
For an Engineer	For a Tissue
• Segments	• Bones
• Joints/Bearing Surfaces	• Muscles and Tendons
• Actuators/Springs/Dampers	• Cartilage, Fibrocartilage and Ligaments

→ Function

- **Mechanical**: Structural support for movement and protect internal organs
- **Biological**: Provide an environment for marrow (where blood cells are produced)
- **Biochemical/Metabollic**: Storage for minerals (Ca)

→ Two types of tissue

- **Cortical**: Hard, compact, smooth outer layer
- **Trabecular**: Spongy inner layer → lighter and lense dense than compact bone

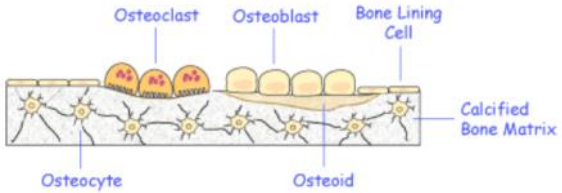


→ Composition

1. Nonmineral matrix: mostly **collagen** (↗ Type-I (94%)) with some non-collagenous proteins (osteoid)
2. Inorganic mineral salts deposited within the collagen matrix (Calcium)
3. Cells (osteoblast/osteocytes, osteoclasts)

→ Types of cells

- **Osteoblasts**: deposits bone matrix (osteoid) that mineralises
- **Osteocytes**: Osteoblasts that get trapped after mineralisation ('sense' mechanical load)
- **Osteoclasts**: Break down bone matrix

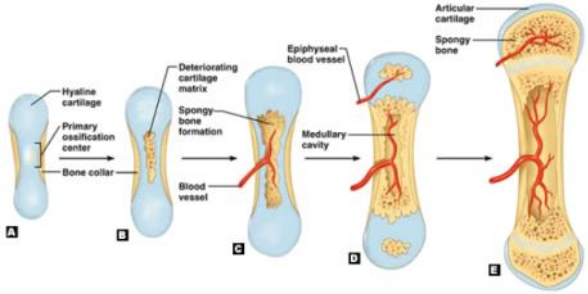


→ Bone Tissue Formation (Osteogenesis)

- Bone formation occurs by two processes

i.) **Intra-membranous ossification**: Replacement of connective tissue membrane sheets with bone tissue
⇒ formation of flat bones (e.g. skull, clavicle, mandible)

ii.) **Endochondral ossification**: Replacement of a hyaline cartilage model with bone tissue (e.g. femur, tibia, humerus)



- Long bones continue to grow throughout the entire childhood due to continued endochondral bone formation at both ends of the bone
- Hyaline cartilage is made out of Type-II Collagen (resistance to tensile forces) and Aggrecan (large proteoglycan made of long sugar chains that attract water → support compressive loads)

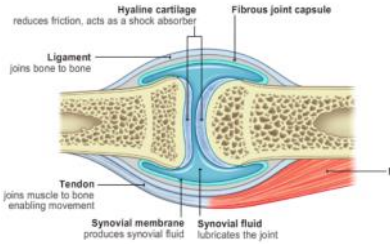
→ Articular Cartilage

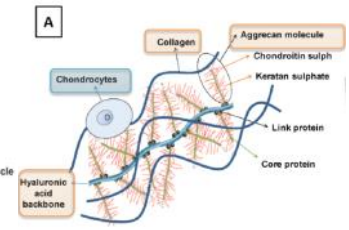
- The mechanical function of articular cartilage as a connective tissue is to articulate joints.
- Articular cartilage is hyaline cartilage on the articular surfaces of bones

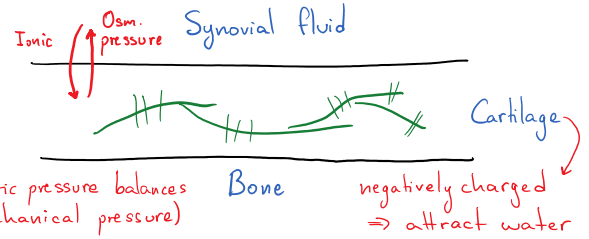
⇒ Formed of fibrils (Type-II Collagen), proteoglycan complexes of aggrecan and hyaluronan and chondrocyte cells.

→ **Collagen**: resistance to tensile forces

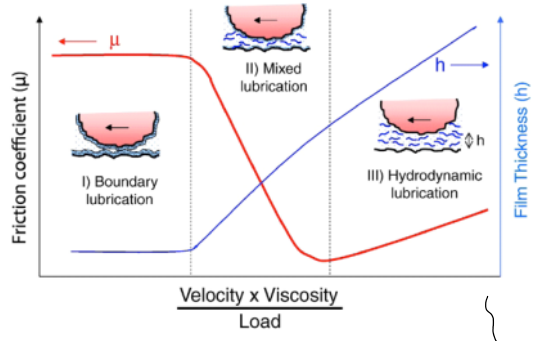
→ **Aggrecan**: Attract water to support compressive loads







- Hydrodynamic lubrification: As joint speed and viscosity of the synovial liquid increases, the amount of fluid drawn into the joint space increases → Creates a fluid boundary layer that lowers friction

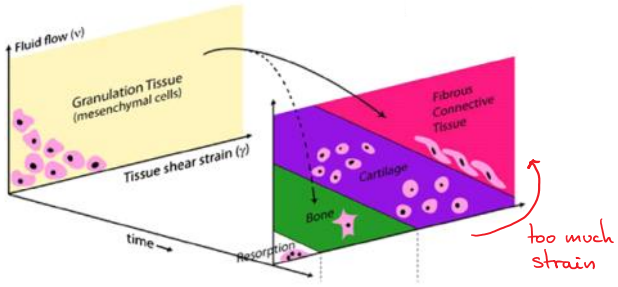


	Normal	Non-inflammatory	Inflammatory	Septic
Volume (ml)	<3.5	>3.5	>3.5	>3.5
Viscosity	**0.1 - 0.2**	**0.1 - 0.2**	**<0.05**	**Mixed**
Clarity	Clear	Clear	Cloudy	Opaque
Color	Colorless/straw	Straw/yellow	Yellow	Mixed

$$\frac{dp}{dx} = \frac{6V\eta(h-h^*)}{h^3}$$

→ Damage of Articular Cartilage

- Normal joint surface movement and loading is key to joint health.
- Too much shearing motions on the cartilage can induce **fibrocartilage** formation



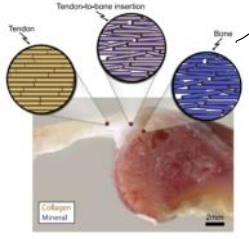
→ Fibrocartilage

- Can support both compressive and shear forces
- Contains Type-II Collagen and Aggrecan just like conventional cartilages **but also Type-I Collagen**
- Naturally found in the menisci and labrum (tissue found in basically all ball-and-socket joints)

Bone: Type-I Collagen (osteoid)
Cartilage: Type-II Collagen + Aggrecan
Fibrocartilage: Type-I and II Collagens + Aggrecan

→ Ligaments

- Connects bones to bones (joint stability)
- Mainly composed of Type-I Collagen and fibrocartilage
- Limit the mobility of joint articulation or movements altogether

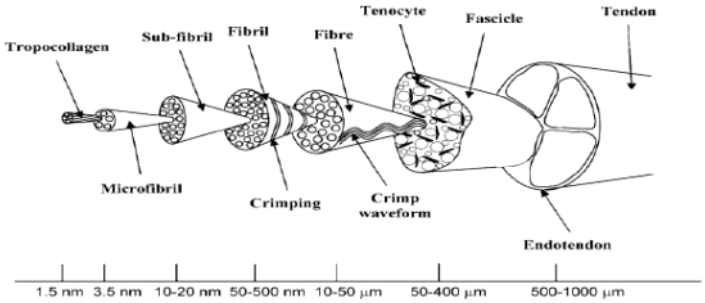


→ steep gradients of mineralized Type-I Collagen on the transition between ligament and bone

High mineral (bone) → None (ligament)

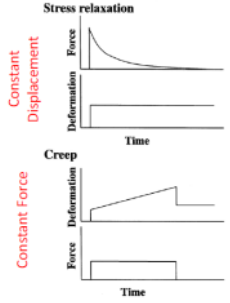
→ Tendons

- Fibrous collagen tissue that connects bones to muscles

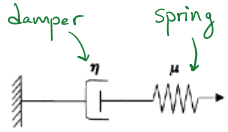


→ Viscoelasticity

- Elastic → collagen. Viscoelastic → collagen + proteoglycans
- Muscles and tendons are damping for movement



Maxwell Model



Muscle

→ 3 types of muscles

- **Skeletal/striated** → voluntary
- **Cardiac** } involuntary
- **Smooth** }

→ Sliding Filament Theory

- Describes the process for muscle contraction

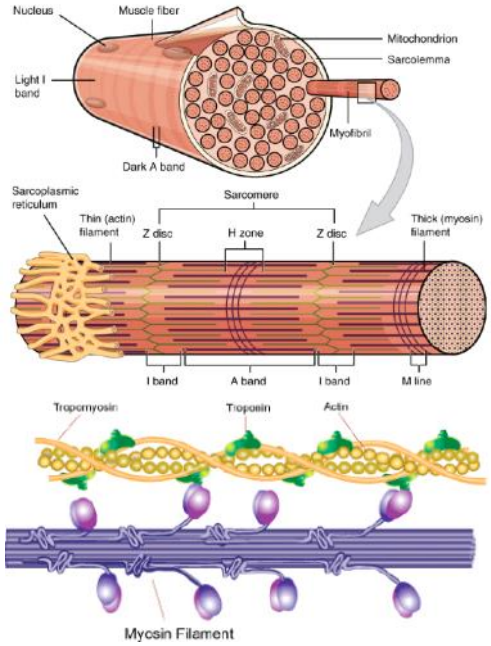
i) Incoming action potential depolarizes inner portion of the muscle fiber

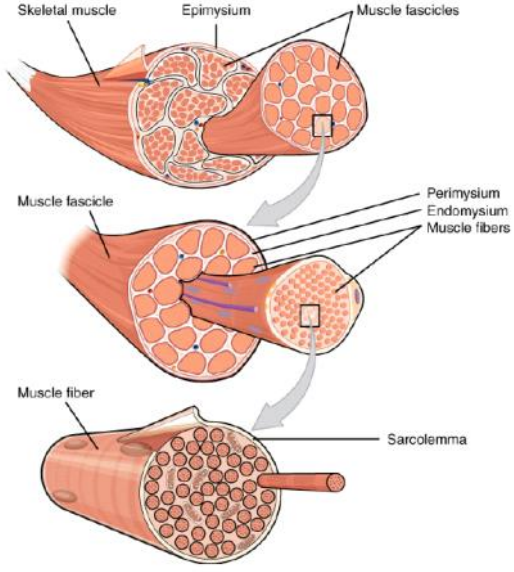
ii) This depolarization activates voltage-dependent calcium channels near the **Sarcoplasmatic Reticulum**

iii) This makes the Sarcoplasmatic Reticulum to release calcium ions (Ca^{2+})

iv) Calcium atoms bind to troponin on the myofibrils
⇒ This makes tropomyosin to unblock the binding sites for myosin on the thin filaments

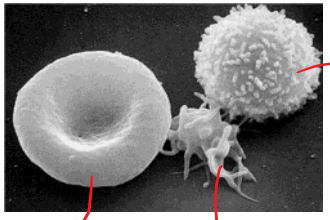
v) Myosin binds to actin on the thin filament and, when releasing its bound ADP, pulls the ends of the muscle unit → Sarcomere shortening





The Heart

→ The circulatory system delivers nutrients (e.g. glucose and O_2) and hormones throughout the body, removes waste products from tissues (e.g. CO_2) and provides a mechanism for regulating temperature and removing heat generated by the metabolic activities of the body's internal organs.

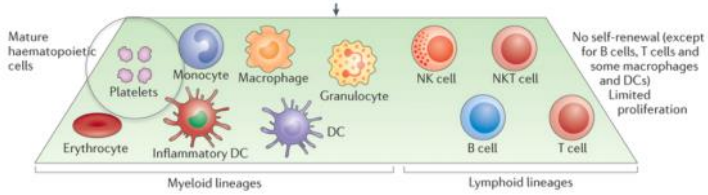


→ Leukocytes (white blood cells) ≈ 0.15 %

(Hematocytes)

Erythrocytes (red blood cells) ≈ 95 %

Platelets ≈ 5 %

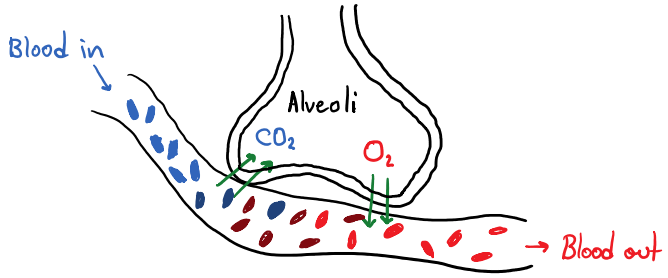


→ Erythrocytes (red blood cells): Responsible for transporting blood gases (mainly O_2)

→ Leukocytes (white blood cells): Endow the human body with the ability to identify and dispose of foreign substances

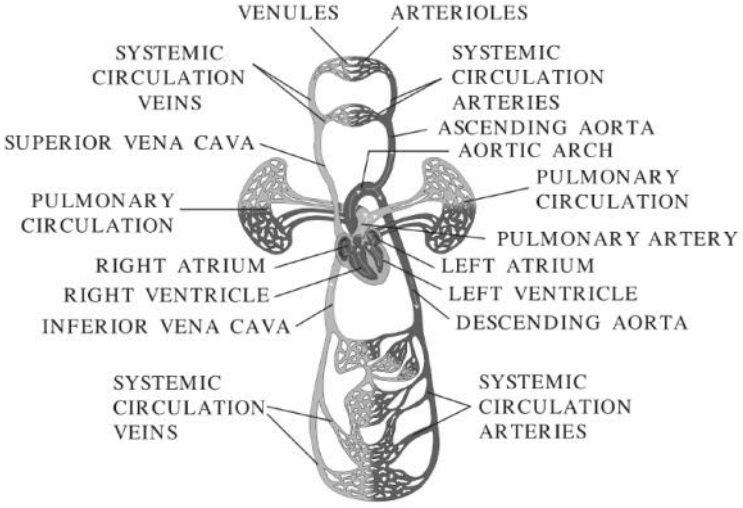
- agranulocytes → lymphocytes, monocytes } identify
- granulocytes → neutrophils, basophils, esinophils } dispose

→ Platelets: Participate in the blood-clotting process

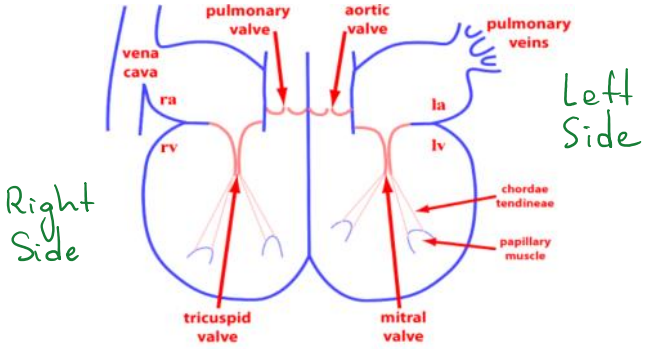


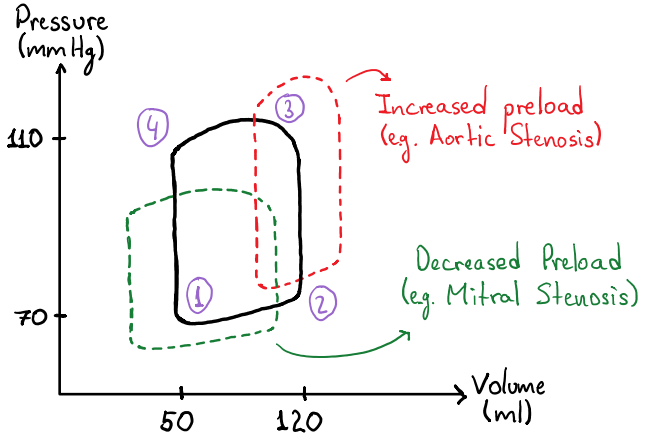
→ Cardiovascular System and the Heart:

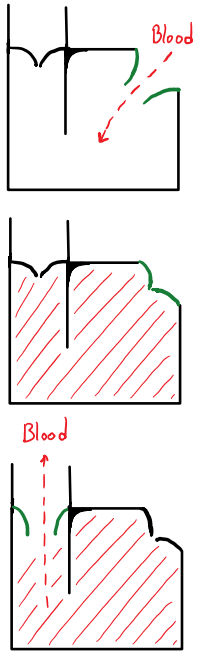
- **Veins:** blood vessels that carry blood toward the heart (normally deoxygenated blood)
- **Arteries:** blood vessels that carry blood away from the heart (normally oxygenated blood)
- The pulmonary artery is the only artery that carries deoxygenated blood and the pulmonary vein is the only vein that carries oxygenated blood.



- the right side of the heart is the pulmonary circuit pump → CO_2 unloaded and O_2 loaded
- the left side of the heart is the systemic circuit pump. Pumps blood to the tissues, delivering O_2 and nutrients and picking up CO_2 and wastes







① Beginning of Diastole
Opening of Mitral valve

≈ 480 ms

② End Diastolic Volume (EDV)
Closure of Mitral valve

≈ 270 ms

③ Beginning of Systole
Opening of aortic valve

④ End Systolic Volume (ESV)
Closure of aortic valve

Tot ≈ 750 ms

→ **Stroke-Volume (SV)** = Amount of blood pumped in one heart beat

EDV ≈ 140 ml
ESV ≈ 70 ml
} SV = EDV − ESV ≈ 70 ml

→ **Cardiac Ejection Ratio** = The ratio between the stroke volume (SV) and the end-diastolic-volume (EDV)

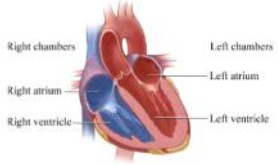
- 0.5 - 0.75 ⇒ normal
- 0.4 - 0.5 ⇒ mild cardiac damage
- 0.25 - 0.4 ⇒ moderate heart damage
- < 0.25 ⇒ severe heart damage

→ **Cardia Output (CO)**: How much blood is pumped out per unit time ⇒ flow

CO = Heartrate × SV = Heartrate × (EDV − ESV)

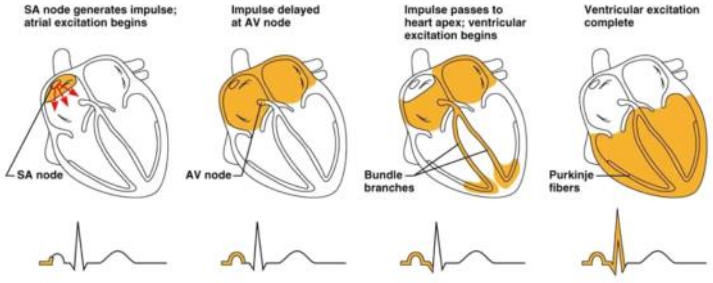
→ **Chamber volumes at rest** (in total ≈ 350 ml)

- Left atrium: 45 ml
- Right atrium: 63 ml
- Left ventricle: 100 ml
- Right ventricle: 130 ml

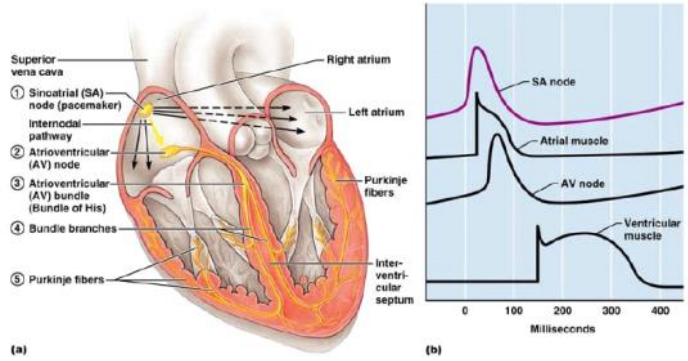


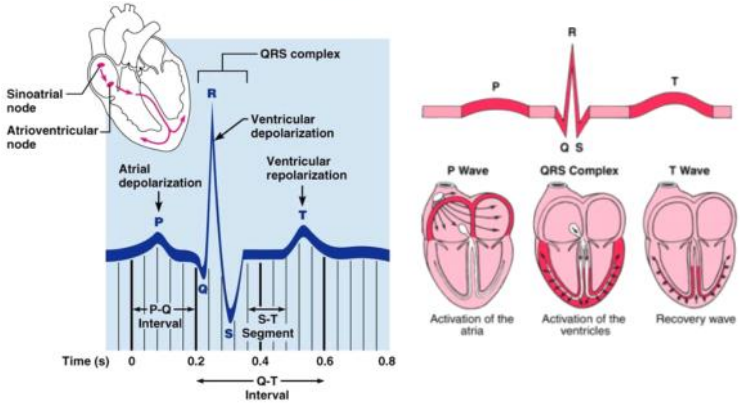
→ **Cardiac Polarisation Wave**: Generation and propagation of electrical signals inside the heart

- Cardiac cells are linked and tightly coupled so action potentials can spread
- Process of a heart beat can be divided in four basic steps:
  - i) Depolarisation (recovery/reset)
  - ii) SA node (initiates the wave)
  - iii) AV node (passes the wave from atria to ventricles)
  - iv) Perkinje fibers (accelerate propagation through ventricles)

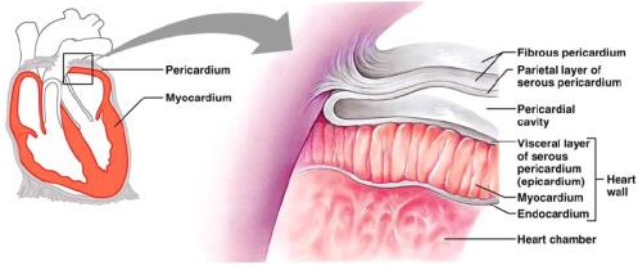


- The activation wave front moves across the atria (at around 1 m·s⁻¹) which contracts when depolarised. This contraction (atrial systole) moves blood to the ventricles. The wave front then moves to the atrioventricular (AV) node, where it slows down (to about 0.05 m·s⁻¹) to allow time for the ventricles to fill. After leaving the AV node, the wave progresses to specialised, conduction tissue (Purkinje system) which spreads the wave to a whole collection of cells in the ventricle (at about 3 m·s⁻¹). This results in the simultaneous contraction of the ventricles (ventricular systole)





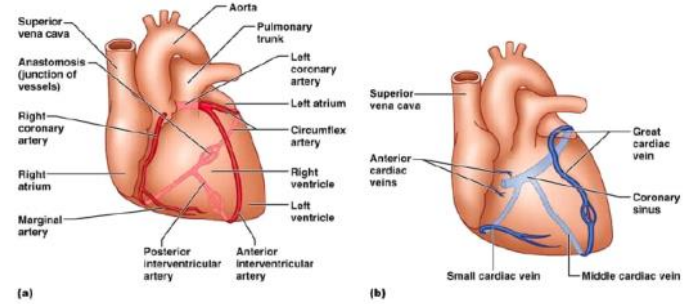
→ **Structure of the Heart**



- Myocardium is mainly cardiac muscle
- Epicardium, Myocardium, Endocardium

→ **Coronary Circulation**

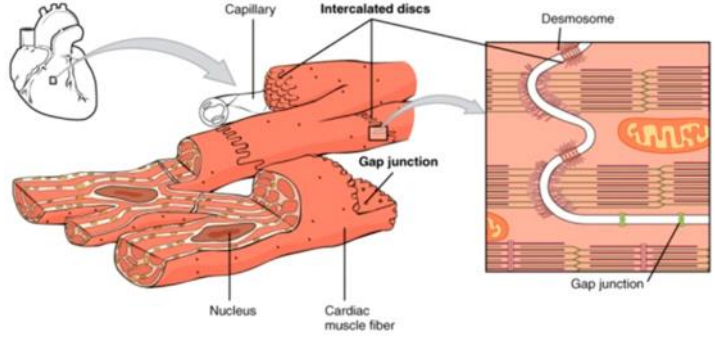
- The heart receives no nourishment from the blood as it passes through the chamber → Coronary circulation provides the blood supply for the heart cells
- In a myocardial infarction, there is prolonged coronary blockage that leads to cell death



→ **Cardiac Muscle**

- Cardiac muscle is striated and contraction occurs via the sliding filament mechanism
- The cells are short, fat, branched and interconnected by **intercalated discs** (different to skeletal muscle)
  - ↳ joins muscle cells to make them work as a single functional organ or **Syncytium**

(not like skeletal muscle where they are "activated" separately)



- The intercalated disks contain three types of cell junctions
  - * Actin anchoring sites to interconnect the cells and transmit contraction forces → **Fascia adherens**
  - * filament binding sites that stop separating during contraction, joining cells together → **Desmosomes**
  - * **Gap junctions**

• **Gap junctions** allow potentials to spread between cardiac cells by permitting the passage of ions (Ca^{2+}) between cells, producing depolarization of the heart muscle
↳ Syncytium

• Some cardiac cells are self-excitable or **autorythmic**
These cells generate an action potential that spreads through the myocardium, causing the heart to contract as a single unit

However, the refractory period of an autorythmic contraction is relatively high (5 to 10 seconds) so the cells wait for the sinoatrial (SA) node to fire an impulse (much faster)

• Still, the refractory period is high compared to skeletal muscle, which prevents tetanic contractions of the heart

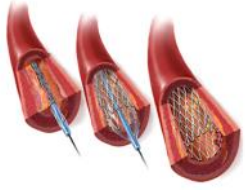
→ Coronary Artery Occlusion and Stenting

• A **stent** is a small mesh tube that's used to treat narrowed or weakened arteries

• A stent is placed in an artery as part of a procedure calle **percutaneous coronary intervention** (PCI) or **angioplasty**

• PCI/angioplasty restores blood flow through narrow or blocked arteries. The stent helps support the inner wall

• Types of stents:

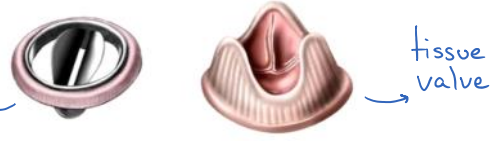


1. Metal mesh
↳ most common type
2. Fabric
↳ also called **stent grafts**

• Some stents are coated with medicine that is slowly released into the artery → **drug-eluting stents**
↳ medicine helps preventing the arteries from becoming blocked again → a common complication in 30-50% of operations

→ Heart Valve Replacement

• Aortic valve replacement is a procedure in which a patient's failing aortic valve is replaced with an artificial heart valve



• Two types of replacement valves

1. **Mechanical valve**: long-lasting artificial valves which generally present a one-surgery solution
But there is an increased risk of blood clots ⇒ recipients must take anticoagulant drugs for the rest of their lives

2. **Tissue valve**: Made from animal tissue. The tissue is treated to prevent rejection and calcification.
These types of valves usually "wear-out" and become leaky (inadequate "long term tissue integration") → mechanical valves?

• Functional requirements of heart valve prostheses

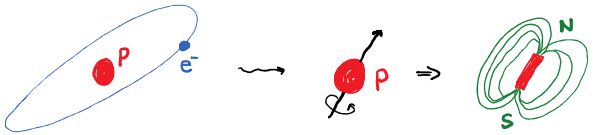
The functioning of natural heart valves is characterized by many advantages:

1. **Minimal regurgitation** – This means that the amount of blood lost upstream as the valve closes is small (5 ml or less).
2. **Minimal transvalvular pressure gradient** – Natural heart valves have a low transvalvular pressure gradient as they present little obstruction to the flow through themselves, normally less than 16 mmHg. A desirable characteristic of heart valve prostheses is that their transvalvular pressure gradient is as small as possible.
3. **Non-thrombogenic** – As natural heart valves are lined with an endothelium continuous with the endothelium lining the heart chambers they are not normally thrombogenic. A desirable characteristic of heart valve prostheses is that they are non or minimally thrombogenic.
4. **Self-repairing** – Although of limited extent compared to well vascularised tissue (e.g. muscle), the valve leaflets do retain some capacity for repair due to the presence of regenerative cells (e.g. fibroblasts) in the connective tissue from which the leaflets are composed. As the human heart beats approximately 3.4x109 times during a typical human lifespan this limited but nevertheless present repair capacity is critically important. No heart valve prostheses can currently self-repair but replacement tissues grown using stem cell technology may eventually offer such capabilities.
5. **Non-damaging to blood cells.**

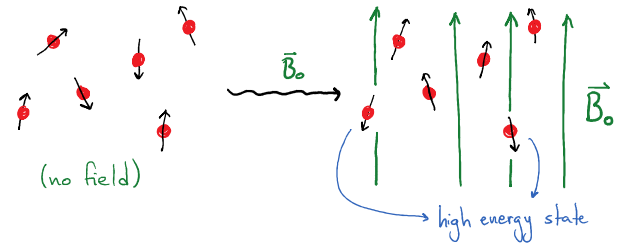
Magnetic Resonance Imaging

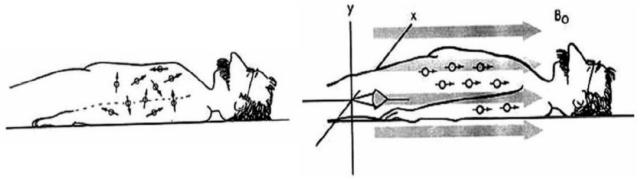
→ MRI examines the magnetic properties of atomic nuclei

- Certain atomic nuclei (Those with **odd atomic mass**) possess a quantum quantity called "spin"
- Since it has charge, and spin, it possesses a small magnetic field
- The magnetic field is greater in protons (^1H → good, since we have a lot of water in our bodies)

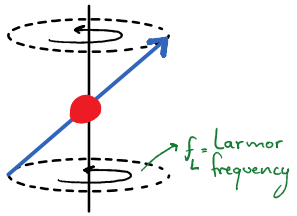


- In the presence of a magnetic field, the protons will shift and align themselves parallel (low energy state) or anti-parallel (high energy state) to the applied field B_0





- Protons are not completely aligned. They spin like a gyroscope with a given frequency → **Larmor frequency**



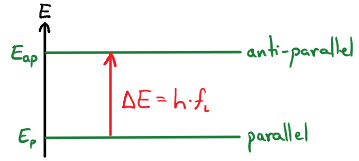
- The Larmor frequency f_L of a sample is directly proportional to the applied magnetic field B_0.

$$f_L = \gamma_0 \cdot B_0$$

Gyromagnetic ratio ($MHz \cdot T^{-1}$)

- The gyromagnetic ratio of hydrogen is $\approx 43\ MHz \cdot T^{-1}$
  This frequency corresponds to **radio frequencies**

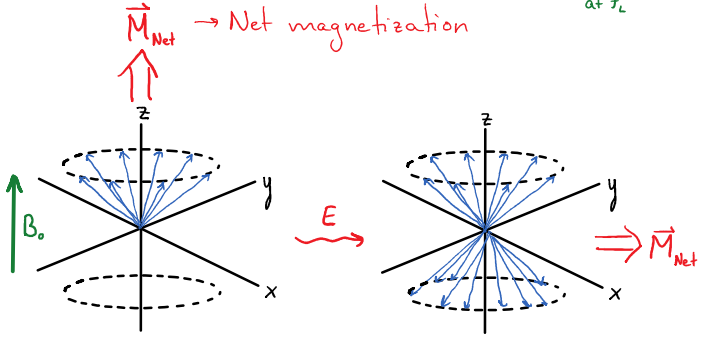
- If we give the right amount of energy to a proton, we can make it go from the parallel to the anti-parallel state



$$E = h \cdot f_L$$

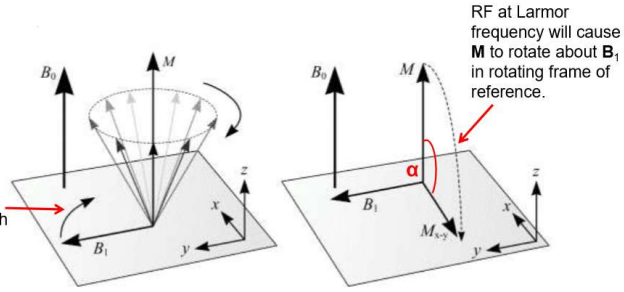
Planck's constant

- We can see what happens with net magnetization when we give this energy with a radio-frequency (RF) pulse at f_L



Net magnetization in the same direction as the applied field B_0 (number of anti-parallel states is negligible)

Net magnetization perpendicular to the applied field B_0 → in this case somewhere in the xy-plane



- After changing the net magnetization direction (using the RF pulse) by exciting half of the protons to the anti-parallel state, the protons start losing energy again by going back to the parallel state
  ↳ give energy to the surroundings

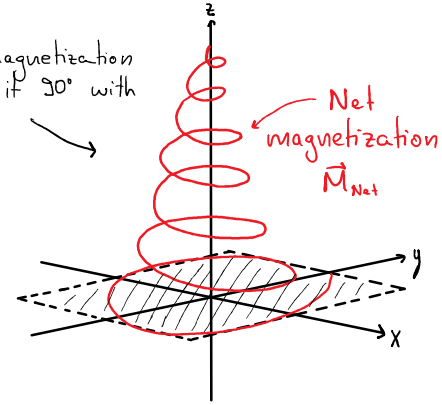
- Actually, the number of anti-parallel induced states depends on the duration of the RF pulse (at f_L)

$$\alpha = 2\pi\gamma\left(\frac{B_1}{2}\right)t_p$$

flip angle; duration of the RF pulse; Gyromagnetic ratio

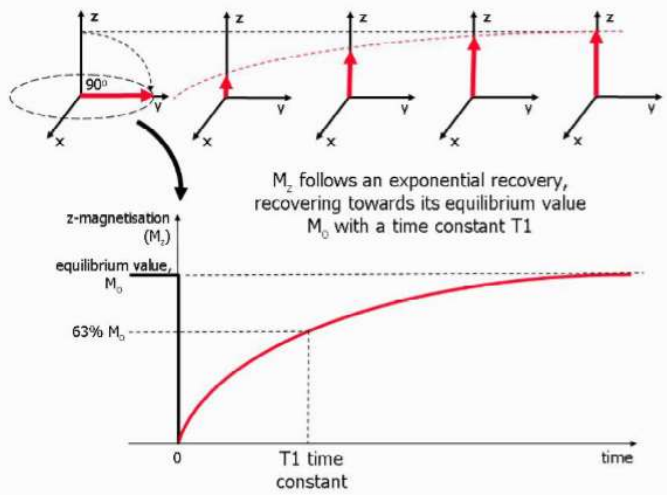
- This relaxation of the net magnetization decays exponentially → **Frequency induced decay (FID)**

Net magnetization after flipping it 90° with a RF pulse



- There are two reading possibilities. Or we read the change of the z-component of M_{Net} (M_z) or the change of the xy-component of M_{Net} (M_{xy})

→ Decay of M_z (T_1)



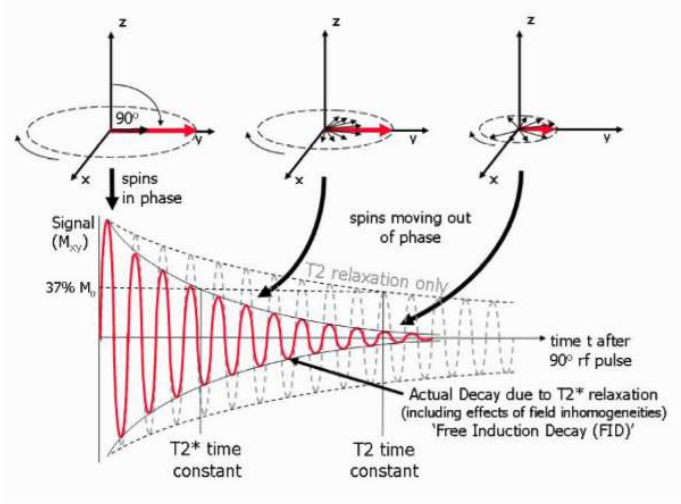
- The time constant T_1 (T_1 = "spin lattice recovery time") can be calculated with

$$M_z = M\left(1 - e^{-\frac{t}{T_1}}\right)$$

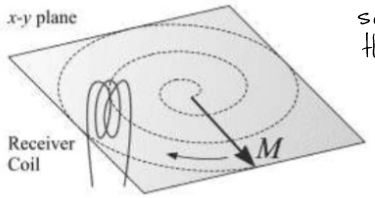
→ Decay M_{xy} (T_2)

- Time constant T_2 follows the same idea as T_1

$$M_{xy'} = M_{xy} e^{-\frac{t}{T_2}}$$



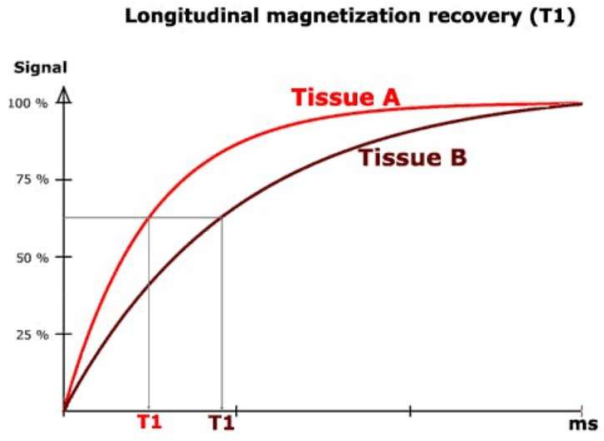
- Since M_z and M_{xy} are time changing magnetic fields, we can use Faraday's law to measure it (Faraday: time changing magnetic fields induce a current in a coil)



- Receiver coil is the same coil used to generate the RF pulse

- The idea is tha T_1 and T_2 are affected by temperature and viscosity of the tissue

⇒ Different tissues will have different T_1/T_2 times



Tissue	T_1 (ms)	T_2 (ms)
Cerebrospinal fluid	2,000	1,000
Fat	160	100
Gray matter	520	95
Malignant tumor	800	200
Typical edema or infarction	600	150
White matter	380	85

→ Spatial Localisation

- The problem is that if we use a constant B field through the entire body and send a RF pulse, all the protons of the entire body will get excited (anti-parallel state) ⇒ We will not be able to differentiate the decay time for each specific point of the body (no spatial localisation)

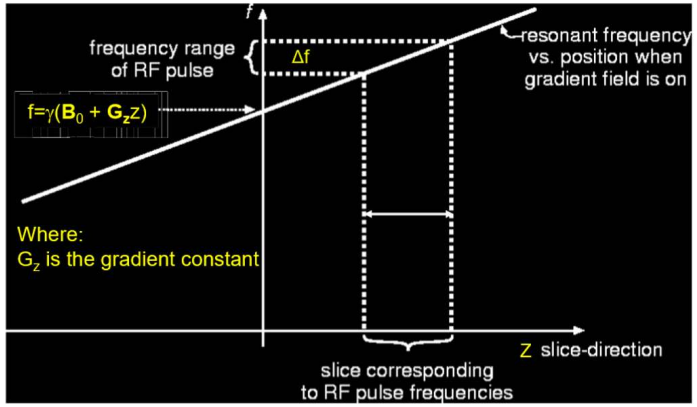
- As seen before, the energy of the RF is given by the Larmor frequency, which in contrast is proportional to the applied field

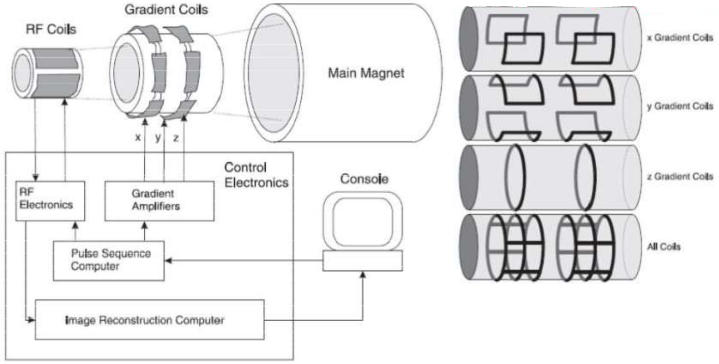
$$E = hf_L \quad \text{and} \quad f_L = \gamma_0 B_0 \Rightarrow E = h\gamma_0 B_0$$

⇒ If we create a magnetic field gradient in the z-direction, we can induce a net magnetization in one specific z-position by applying its z-dependent RF pulse.

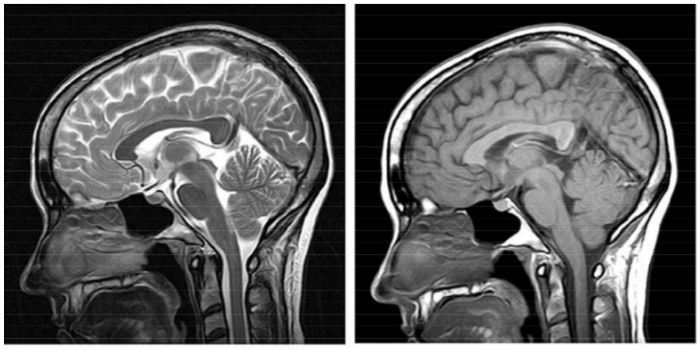
- Now we can induce (and read) a net magnetization on a specific z-position

- This solves the problem for the z-direction but not for the xy-directions ⇒ Add a magnetic field gradient in the x and the y-direction





- Examples of T_1 and T_2 imaging

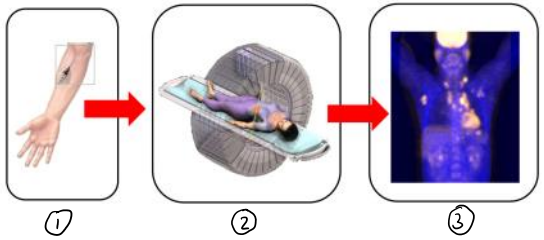


*T*2W *T*1W

- MRI is very useful to detect tumors and other anomalies, since these anomalies tend to be very rich in water content ⇒ good contrast on the T_1/T_2 image.

Radiation Imaging

→ Basic principles of radiation imaging

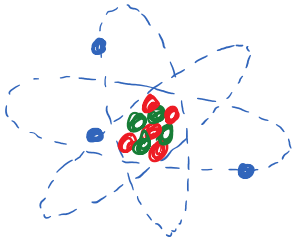


① ② ③

① Inject tracer with radiation
② Sense photon emission caused by decay of radiation
③ Construct image from all collected data

→ **Tracer**: Chemical compounds in which one or more atoms have been replaced by a radioisotope
atom with unstable nucleous ↵

• Example: Glucose is metabolized by cancerous tumors. ⇒ Glucose linked with a radioactive tracer will reveal the tumor's location

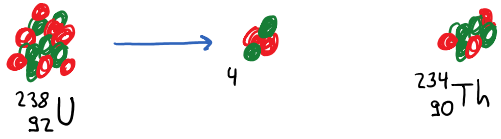


● = electron (9.1×10^{-31} kg)
● = Proton
● = Neutron
} (1.6×10^{-27} kg)

• short range nuclear force between protons and neutrons is far greater than electromagnetic force of repulsion between positively charged protons

→ Radiation theory: 3 types of radiation

1. **Alpha radiation**: decay via emission of an α-particle (^4_2He)



$$\Rightarrow \quad {}^{m}_{\ell}X \longrightarrow {}^{m-4}_{\ell-2}Y + {}^{4}_{2}\alpha$$

2.1 **Beta (-) radiation**: One neutron is transformed into a proton, an electron and a neutrino

$${}^{1}_{0}n \longrightarrow {}^{1}_{1}p + {}^{0}_{-1}e + \bar{\nu}$$ ⇝ neutrino
↳ electron gets emitted

• The energy released cannot be explained by the kinetic energy of the daughter particle

⇝ The energy is carried by the neutrino (zero charge, negligible mass, difficult to detect

$$\Rightarrow \quad {}^{m}_{\ell}X \longrightarrow {}^{m}_{\ell+1}Y + {}^{0}_{-1}e + \bar{\nu}$$

2.2 **Beta(+) radiation**: One proton is transformed

• Positron decay → produces a different element by decreasing the atomic number by 1

$${}^{1}_{1}p \longrightarrow {}^{1}_{0}n + {}^{0}_{1}e + \bar{\nu}$$ ⇝ neutrino
↳ positron gets emitted

$$\Rightarrow \quad {}^{m}_{\ell}X \longrightarrow {}^{m}_{\ell-1}Y + {}^{0}_{1}e + \bar{\nu}$$

3. **Gamma radiation**: Emission of a photon in a very high energetic state

• β decays (negatron or positron) are normally accompanied by a gamma decay
• Following β decay, proton and neutrons residing in the nucleous are left in high energy states
• Photons of energy (γ-rays) are emitted to achieve a more stable configuration

$$\Rightarrow \quad {}^{m}_{\ell}X \longrightarrow {}^{m}_{\ell-1}Y^{*} + {}^{0}_{-1}e + \bar{\nu}$$
$${}^{m}_{\ell-1}Y^{*} \longrightarrow {}^{m}_{\ell-1}Y + \gamma$$

* = denotes excited state
↳ here β(-)

→ **Mass units**:

• **Gram atomic mass (gm)**: Weight in grams of an isotope which is equivalent to its atomic mass

⇝ There are 6.023×10^{23} atoms in one gm

$^{12}_{6}C \rightarrow \frac{12}{6.023\times10^{23}} = 1.99\times10^{-23}$ gm → mass in gm of carbon 12

• **atomic mass unit (AMU)**: mass in gm of one atomic unit

$$AMU = \frac{1.99\times10^{-23}}{12} = 1.66\times10^{-24} \text{ gm}$$

→ **Energy**: Einstein's equation $E = mc^2$

• Energy of one amu:

$E = mc^2 = 1.49\times10^{-3}$ gm·cm²·s⁻¹ → [erg]

⇒ 1 amu = 1.49×10^{-3} ergs

1 eV = 1.6×10^{-12} ergs
1 amu = 1.49×10^{-3} ergs
⇒ 1 amu = 931.5 MeV

• released energy in α-decay: Conservation of mass and energy

$$M_X \longrightarrow M_Y + \Delta m \quad \Rightarrow \quad E = \Delta m\, c^2$$
E [MeV] = 931.5 Δm [amu] ↵

Example: $^{226}_{88}Ra \longrightarrow {}^{222}_{86}Rn + {}^{4}_{2}\alpha$

226.025406 amu = 222.017574 amu + 4.002603 amu + Δm
Δm = 0.005229 amu ⇒ E = 931.5 Δm ≈ 4.87 MeV

→ **Radioactive decay**: Unaffected by change in temperature, pressure or chemical combination.

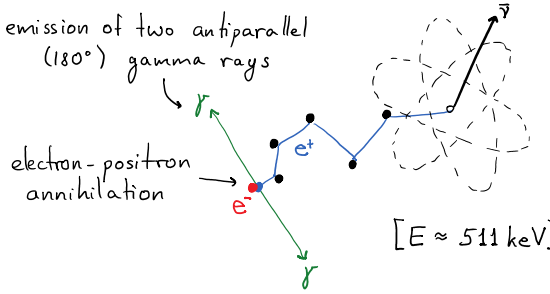
• The rate of decay (λ) remains constant with the same number of disintegrations occuring per unit time.

• **Half-time $T_{1/2}$**: Time required for half of the nuclei to decay

$$\frac{dN}{dt} = \lambda N \Rightarrow \boxed{N = N_0 e^{-\lambda t}}$$

• for $T_{1/2} \Rightarrow \frac{N_0}{2} = N_0 e^{-\lambda T_{1/2}} \Rightarrow T_{1/2} = \frac{\ln(2)}{\lambda} \approx \frac{0.693}{\lambda}$

→ **Positron-electron annihilation**: On a $\beta+$ decay, positrons are emitted and travel just a few mm into the skin before recombining with an electron and emitting γ-rays (annihilation)



→ **Instrumentation / Gamma imaging**: Use gamma decay happening inside of the patient's body to scan for malicious tumors etc.

• **Scintillation**: When a material (usually zinc sulfide and sodium iodide) emits a flash of light when struck by ionizing radiation (γ-rays)

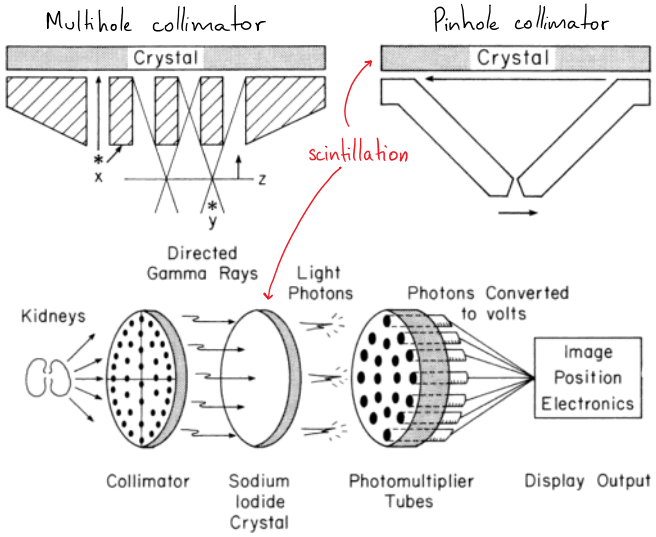
γ-rays from the annihilation process

amount of light emitted $\propto$ energy of the photons

• **Photomultiplier**: Measure intensity of light (by intensifying it) and convert it to an electrical impulse

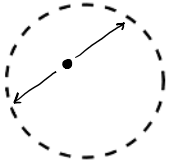
! Scintillation + Photomultiplier gives only the energy of the incident radiation and activity of a specific radionuclide but no spatial information! Spatial information achieved with collimation.

• **Collimation**: Device that filters a stream of rays so that mostly those traveling parallel to a specified direction are allowed through

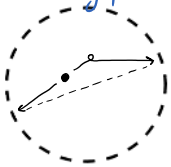


→ **Error sources positron emission tomography**

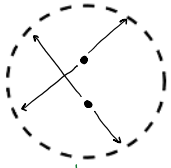
true incidence → Ideal



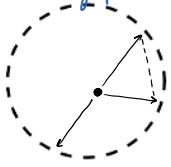
scattering process



concurrent events



secondary photon

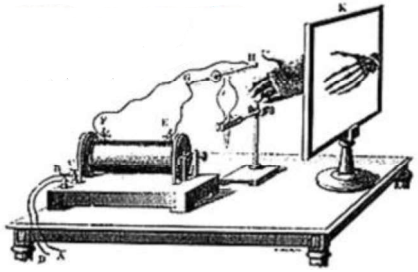


↳ not a big problem. We can just drop this reading, since there are millions happening each second

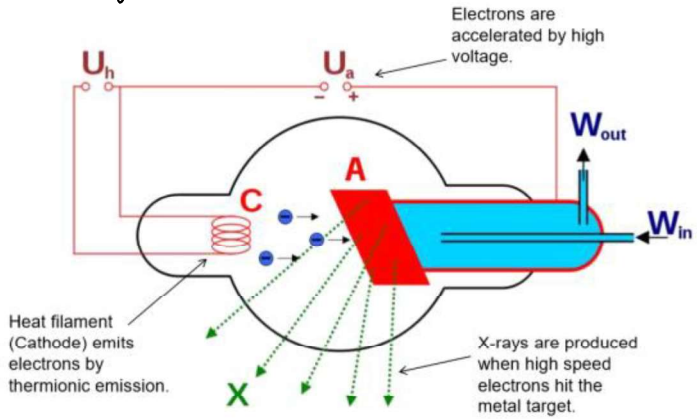
Radiographic Imaging

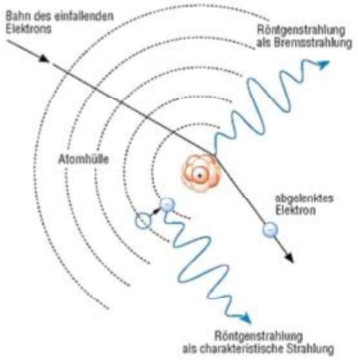
→ Externally produced radiation passing through tissue is used to generate images.

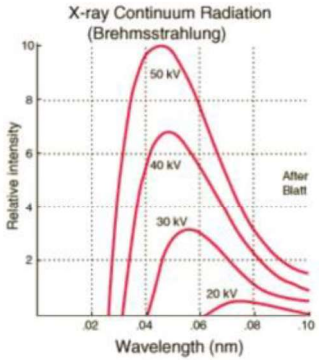
→ Wilhem-Konrad Röntgen: X-Rays
- high voltage generated by coil applied across a vacuum tube
- Radiation induced is visualized on a fluorescent screen



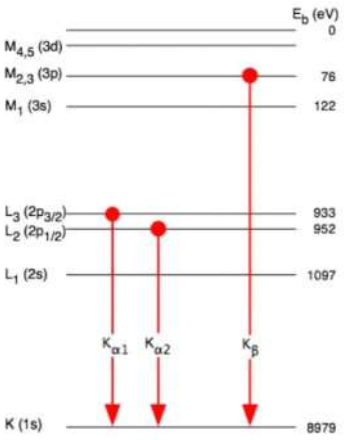
→ X-Ray Tube

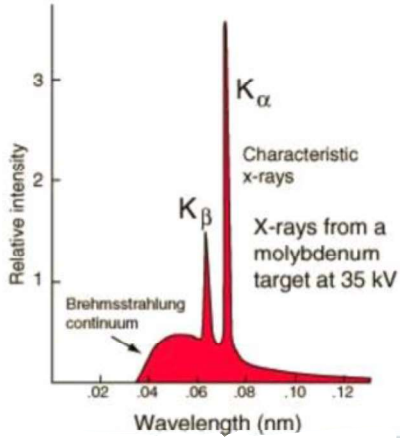




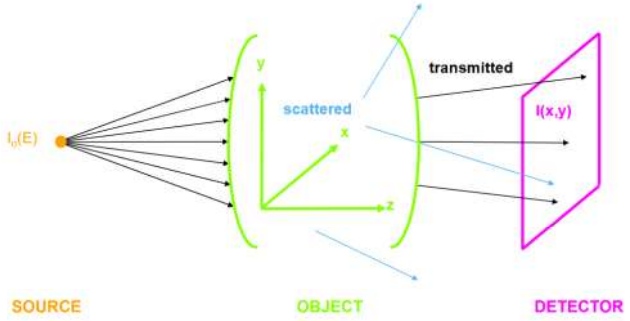


- Interatomic energy transfer

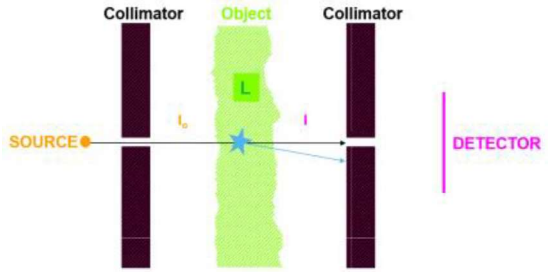




→ Physics of X-Rays



- Rays are scattered when hitting the object
- Collimator filters scattered rays



- For the intensity on the detector

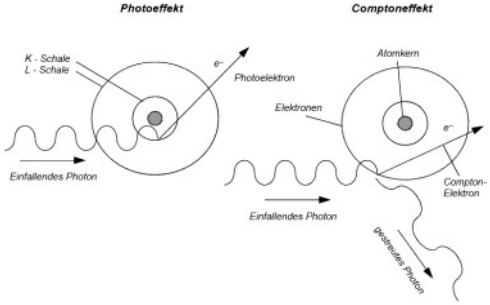
$$I_{Det} = I_0 e^{-\mu L} \quad \Rightarrow \quad \mu = \frac{1}{L} \ln\left(\frac{I_0}{I_{Det}}\right)$$

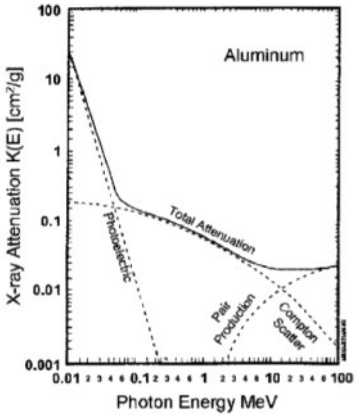
- μ = linear attenuation

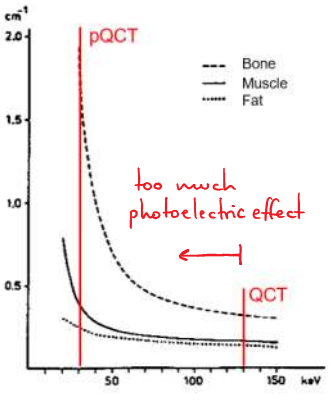
homogeneous	non-homogeneous
$I = I_0 e^{-\mu L}$	$I = I_0 e^{-\int \mu(z) dz}$
$\mu = \frac{1}{L} \ln\left(\frac{I_0}{I}\right)$	$\mu = ?$ ↘

it is not possible to find all values of $\mu(z)$ just by using the initial and final intensities in the case of a non-homogeneous material

- X-Ray imaging is based on rays and the calculated attenuation
- Attenuation depends on the energy of the used rays, since there are many different photo-effects happening





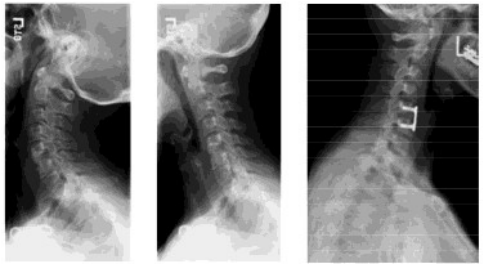


- Attenuation values start to stabilize at ≈ 140 keV (where rays are dominated by the Compton effect)

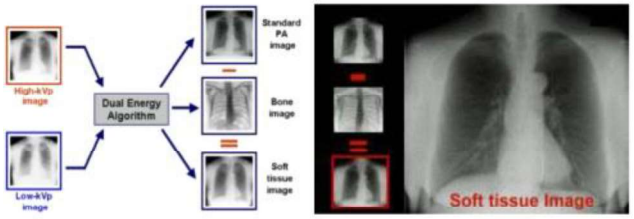
These are the energies we work with

→ X-ray Radiography

- Radiography relies upon differential attenuation of X-rays
- Advantages:
  i) High resolution image
  ii) Rapid acquisition
  iii) Low dose
- Disadvantages
  i) No depth information
  ii) Difficult to distinguish between materials of similar density

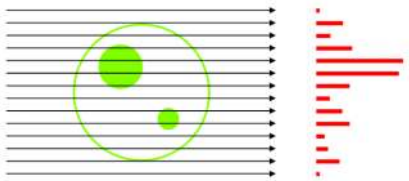


- Since different energies result in different values for the attenuation, we can combine images that come from these different energies

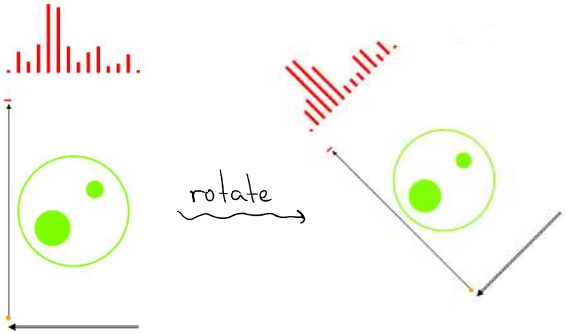


→ Computed Tomography Measurement

- Unwanted structures are not blurred but rather a 2D image is reconstructed from its 1D projections



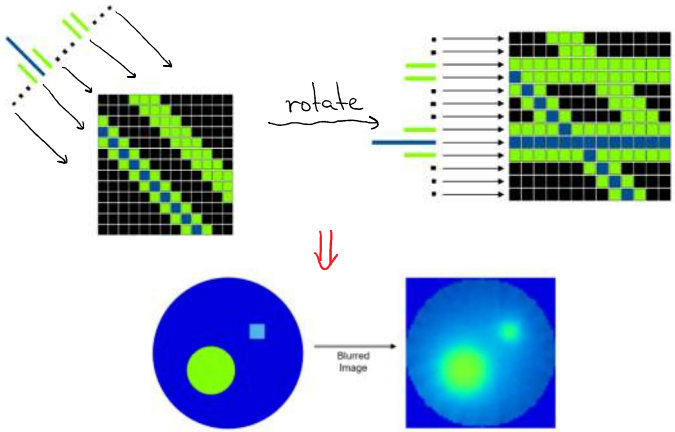
- All projections recorded digitally for angles varying between 0° and 180° describe the data set needed for the image reconstruction



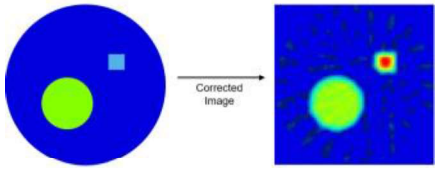
→ CT Reconstruction

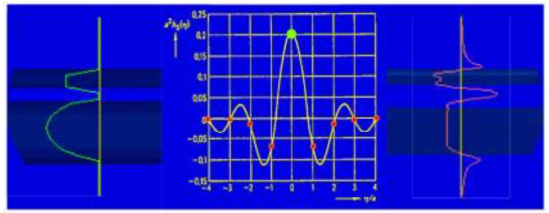
- Iterative reconstruction (ART): image estimation, error minimization
- Direct reconstruction: Backprojection

→ Direct Reconstruction



- By using a Shepp and Logan filter we can correct a little bit the final image (instead of direct backprojection)



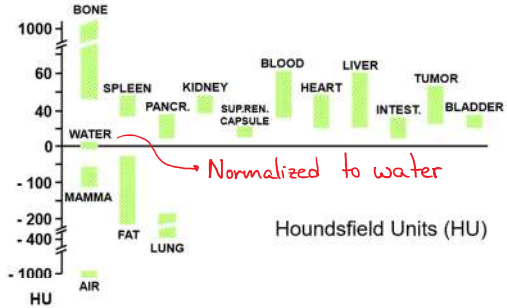


↳ Direct Filtered ↲

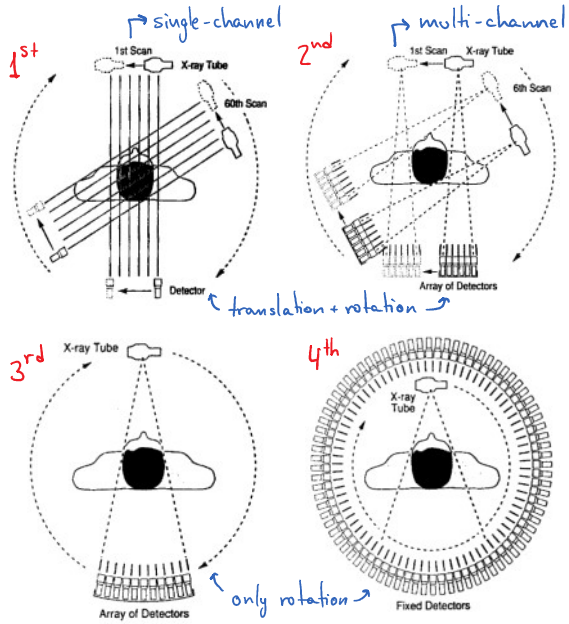
→ Image Representation

- After reconstruction an image represents a matrix of linear attenuation coefficients
- Values are normally shown in Hounsfield Units (HU)

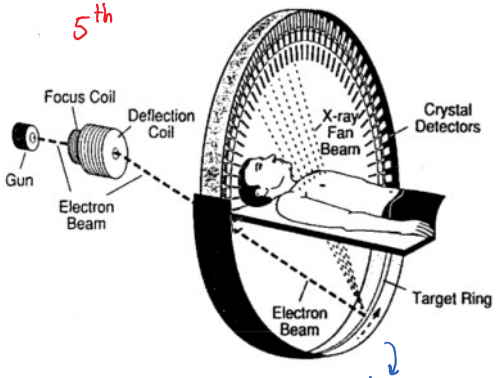
Range from -1000 (air) to +3000 (compact bone) ↲



Normalized to water



5th

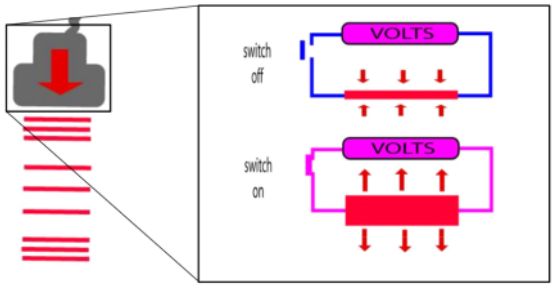


no moving parts

Diagnostic Ultrasound Imaging

→ Piezo Electric Crystal

- By switching the voltage applied the piezo element can contract or expand

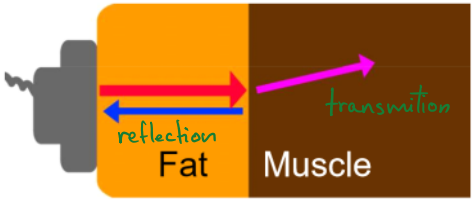


- It is also sensitive to mechanical perturbation

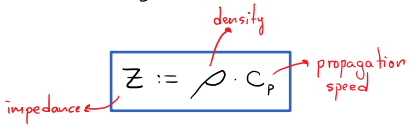
⇒ Can also be used to read vibrations (of the reflected waves)

→ Acoustic Impedance

- Ultrasound waves can either be **reflected**, **transmitted** or **absorbed**
- Every substance (fat, muscle etc) has a unique property called acoustic impedance
- Acoustic impedance determines the proportion of waves reflected or transmitted

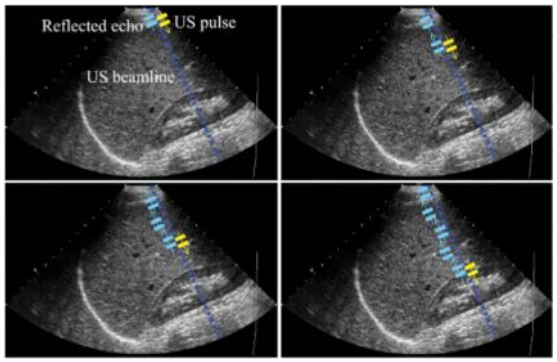


- It is determined by the propagation speed and density



- Ultrasound waves cross from one tissue to the next, each with a different acoustic impedance and each reflecting different proportions of the wave back
- Multiple reflected waves return to the probe and the machine uses this information to display an image representing the different tissues

→ Propagating wave ⇝ Reflected waves



→ Reflection and Transmission Factor

- Assuming the wave is propagating from material with acoustic impedance Z_1 to a material with acoustic impedance Z_2

$$RF = \frac{Z_2 - Z_1}{Z_2 + Z_1}$$

TF = 1 + RF

$$TF = \frac{2Z_2}{Z_2 + Z_1}$$

- 3 interesting cases

i) A free boundary (i.e. bone to air)

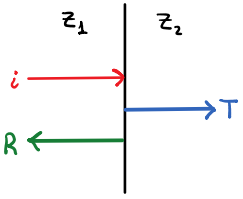
$Z_2 \approx 0 \Rightarrow RF = -1,\ TF = 0$

ii) A matched boundary (i.e. bone to bone)

$Z_1 = Z_2 \Rightarrow RF = 0,\ TF = 1$

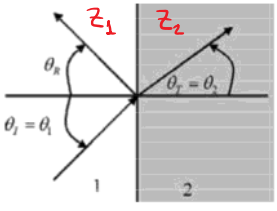
iii) A rigid boundary (i.e. air to bone)

$Z_2 \to \infty \Rightarrow RF = 1,\ TF = 2$



→ Snell's Law

- Acoustic impedance for oblique waves



Snell's Law

$$\frac{\sin(\theta_1)}{\sin(\theta_2)} = \frac{C_1}{C_2}$$

$$Z_{1,\theta_1} = \frac{Z_1}{\cos(\theta_1)}$$

$$Z_{2,\theta_2} = \frac{Z_2}{\cos(\theta_2)}$$

$$RF = \frac{Z_{2,\theta_2} - Z_{1,\theta_1}}{Z_{2,\theta_2} + Z_{1,\theta_1}}$$

$$TF = \frac{Z_{2,\theta_2}}{Z_{1,\theta_1} + Z_{2,\theta_2}}$$

→ Absorption

- Part of the ultrasound waves are absorbed
- It is measured in dB

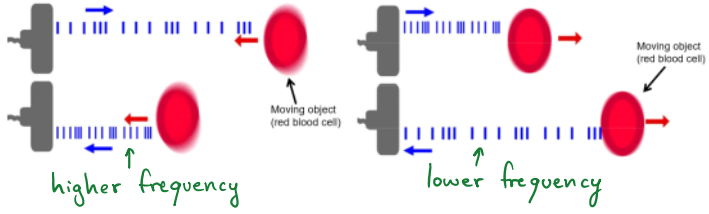
$$\text{Absorption} = \alpha f^{\gamma} z$$

α = absorption coefficient — dB · MHz^{-1} cm^{-1}
f = frequency — MHz
γ = exponent of power law — (normally 1)
z = depth of penetration — cm

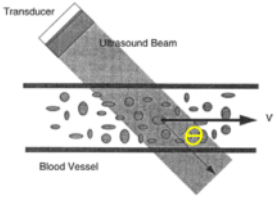
Material	A (dB/MHz/cm)
Air	160
Blood	0.2
Bone, cortical	6.9
Brain	0.6
Fat	0.48
Liver	0.5
Marrow	0.5
Muscle	1.09
Tendon	4.7
Soft tissue (average)	0.54
Water	0.0022

→ Doppler Effect

- The wave that bounces off an object moving towards the probe will have a higher frequency (and moving away from the probe will have a lower frequency)



- This effect can be used to calculate **speed** and **direction** of a moving object (like blood flow)



$$f_D = f_0\left[2\left(\frac{v}{c_0}\right)\cos\theta\right]$$

c_0: sound speed of intervening medium