Molecular mechanisms of biological motion

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Various levels of biological motion

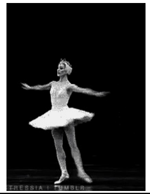
Molecular motion

Axoplasm

Cellular motion

crawling keratinocyte

Body motion



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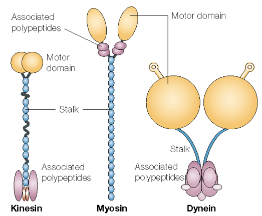
Motor proteins

Mechanoenzymes capable of converting chemical energy into mechanical work.

1. Specifically attach to a cytoskeletal filament or other biopolymer (DNA).
2. They generate force when moving along the filament.
3. They utilize energy from nucleotide cleavage for force generation.

3

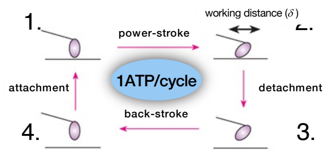
Common characteristics of motor proteins



I. Structural homology

The globular head at the N-terminus is the ***motor domain*** (ATPase) and provides a specific binding-site for the respective cytoskeletal filament.

The C-terminus binds to the surface that is being moved



II. Cyclic operation

1. Attachment
2. Power-stroke (pull)
3. Detachment (dissociation)
4. Back-stroke (relaxation)

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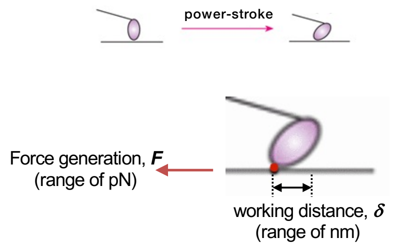
Force generation of motor proteins



Work done by a single motor protein, ***W***

$$W = F \cdot \delta$$

range of 10^{-20} J *(zeptojoule =* 10^{-21}*J)*

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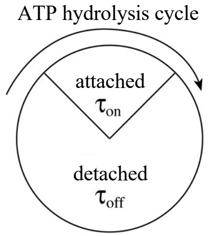
Duty cycle of motor proteins



Duty ratio (r):

$$r = \frac{\tau_{on}}{\tau_{on} + \tau_{off}} = \frac{\tau_{on}}{\tau_{total}}$$

Processive motor protein: r~1
F.e. kinesin, DNA-, RNA-polymerase.
They remain attached in most of the cycle time. They function individually.

Non-processive motor protein: r~0
F.e. conventional myosin (skeletal muscle myosin II.) They remain detached in most of the cycle time. They function in ensembles.

δ = working distance
v_{stroke} = stroke velocity
k_{ATPase} = ATPase rate

$$v_{stroke} = \frac{\delta}{\tau_{on}}$$

$$\tau_{on} = \frac{\delta}{v_{stroke}}$$

$$\tau_{total} = \frac{1}{k_{ATPase}}$$

$$r = \frac{\delta \cdot k_{ATPase}}{v_{stroke}}$$

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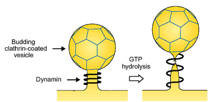
Types of motor proteins

1. Actin based
- ***Myosins:*** They move towards the plus end along the actin filament.
(lamellipodium formation, muscle contraction)

2. Microtubule based
- ***Dyneins:*** Ciliary (flagellar) and cytoplasmic dyneins. They move towards the minus end along the microtubule. *(axonal retrograde transport)*
- ***Kinesins:*** They move towards the plus end along the microtubule. *(axonal anterograde transport)*
- ***Dynamins:*** Microtubule activated GTPase function. *(pinchase)*



3. DNA based mechanoenzymes
- They exert force and move along the DNS double helix. *(DNA- and RNA-polymerases, viral capsid portal motor)*

4. Rotary motors
- They are transmembrane mechanoenzymes that utilize the proton gradient across the membrane. *F1Fo-ATP synthase, bacterial flagellar motor*

5. Mechanoenzyme complexes
- *Ribosome*

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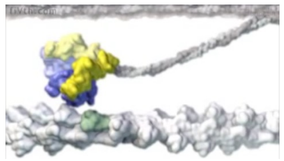
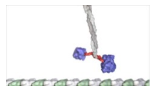
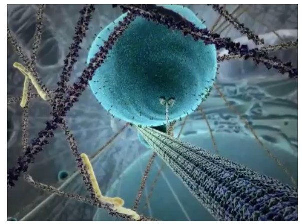
Citoskeleton based motors

Non-processive motor
Skeletal myosin II.
Moves along the actin filament



Processive motor
Kinesin
Moves along the microtubule





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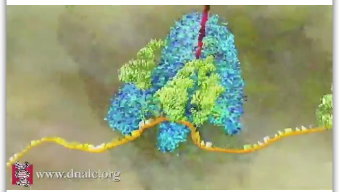
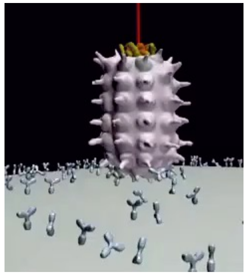
Nucleic acid based motors

Ribosome
mechanoenzyme complex



Virus portal motor
DNS „packaging“



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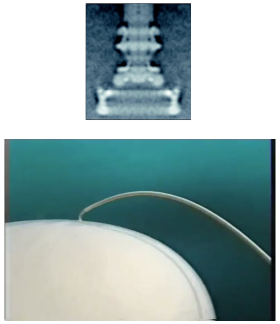
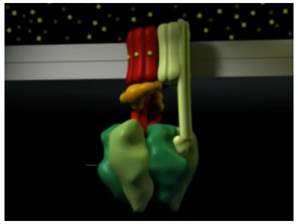
Rotating motors

driving force: proton gradient

Flagellar motor
bacterial movement



F_1F_o ATP synthase



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Muscle biophysics

(mechanobiology of actin filaments and the myosin motor protein)

Machina Carnis

Cell and tissue specialized for movement.

It can only pull, not push!

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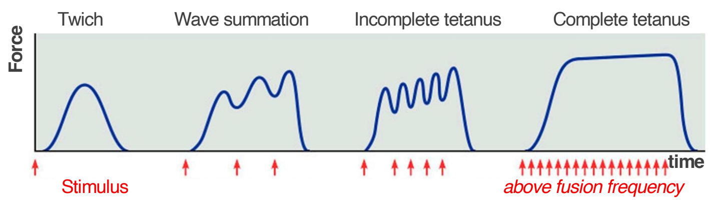
Basic phenomena of muscle function I.



A single stimulus results in a single contractile response – a muscle **twitch** (contracts and relaxes).

More frequent stimuli increases contractile force – **wave summation** - muscle is already partially contracted when next stimulus arrives and contractions are summed.

A sustained contraction that lacks even partial relaxation is known as **tetanus**.

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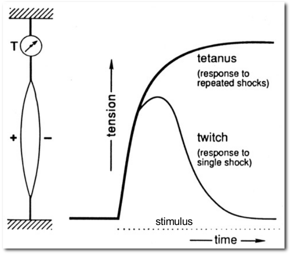
Basic phenomena of muscle function II.

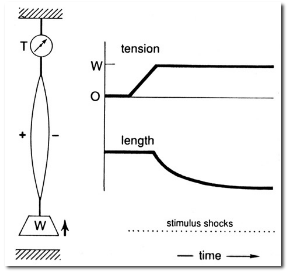
1. Isometric contraction

The muscle does not or cannot shorten, but the tension on the muscle increases.



2. Isotonic contraction

Tension remains unchanged while the muscle's length changes.



Auxotonic contraction (simultaneous shortening and force generation)

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Basic phenomena of muscle function IV.

1. Work and Power

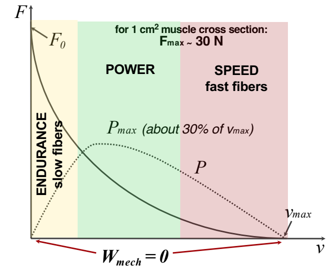
$$W = F \cdot s$$

$$P = \frac{W}{t} = \frac{F \cdot s}{t} = F \cdot v$$

If the shortening velocity is zero, the force is maximal: maximal isometric force (F_0)

If v = maximum, than $F = 0$

2. Force - velocity diagram



Hill equation:

$$(F + a)(v + b) = (F_0 + a)b$$

F: force, v: shortening velocity
a and b: constants,
F_0: maximal isometric force

$$v_{\max} = \frac{bF_0}{a}$$

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Energetics of muscle contraction

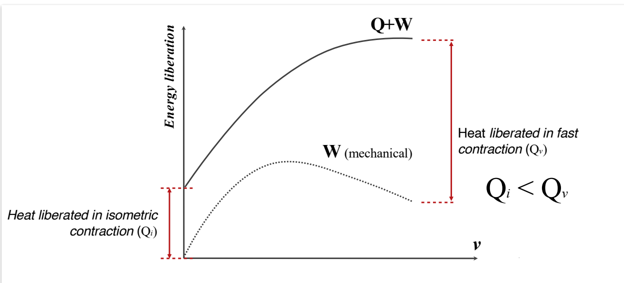
ATP hydrolysis, heat liberation

Source of energy:

$$Mg.ATP^{2-} + H_2O \rightleftharpoons Mg.ADP^{1-} + Pi^{2-} + H^{+}$$

Fenn effect: The liberation of heat increases when the muscle is doing work during shortening. The amount of heat liberated increases with increasing speed of contraction.

The majority of chemical energy used by the muscle is dissipated as heat



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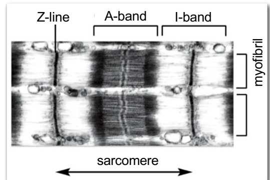
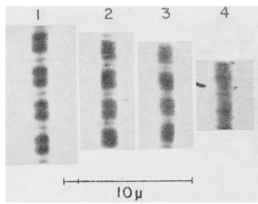
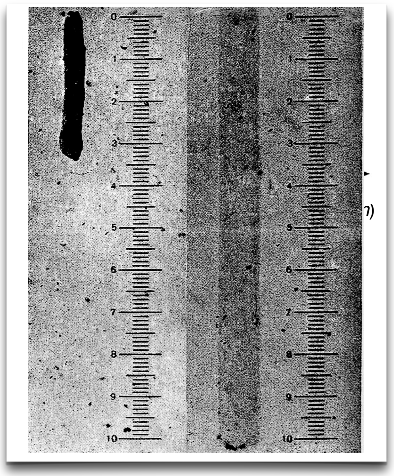
The mechanism of muscle shortening

Phenomenological mechanism: sliding filament model

Sarcomere







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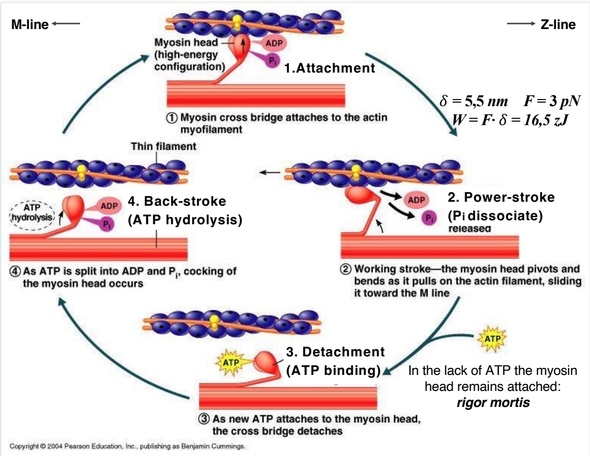
The myosin „cross-bridge“ cycle

Molecular bases of muscle contraction



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Medical Biophysics II.

Biomechanics

Biomolecular and tissue mechanics

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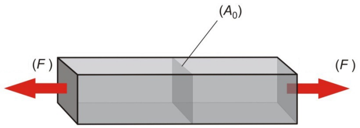
Physical bases of biomechnaics

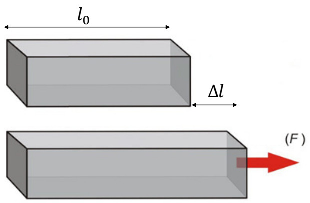
Stress

$$\sigma = \frac{F}{A_0} \qquad \left[\frac{N}{m^2} = Pa\right]$$



Strain (deformation)

$$\varepsilon = \frac{\Delta l}{l_0} \qquad \left[\frac{m}{m}\right]$$ *no dimension*



Strain is proportional to stress!

$\sigma \backsim \varepsilon$

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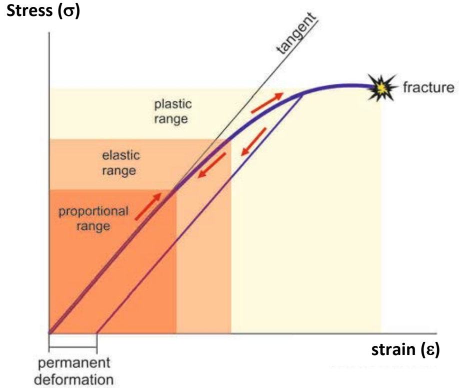
Stress-strain diagram



1. Elastic range
Range of reversible deformation. Unloaded length (l_0) recovers when released. Hysteresis may occour.

Proportional range
(part of elastic range)
Deformation is linearly proportional to the load.
No hysteresis.

2. Plastic range
After a critical stress value, object undergoes irreversible change of its structure. Unloaded length (l_0) does not recover. Permanent deformation of object.

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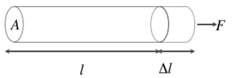
Hooke's law

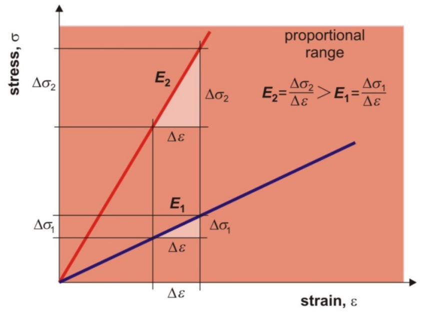


$\sigma = E \cdot \varepsilon$

$\frac{F}{A_0} = E \cdot \frac{\Delta l}{l_0}$ Hooke's law

$F = \frac{E \cdot A_0}{l_0} \cdot \Delta l$

$F = k \cdot \Delta l$



Young's modulus = 1. Stiffness

(material stiffness)

$E = \frac{\sigma}{\varepsilon} = \frac{F}{A_0} \cdot \frac{l_0}{\Delta l}$ $\quad E = \left[\frac{N}{m^2} = Pa\right]$

Spring constant

(body stiffness)

$k = \frac{F}{\Delta l}$ $\quad k = \left[\frac{N}{m}\right]$

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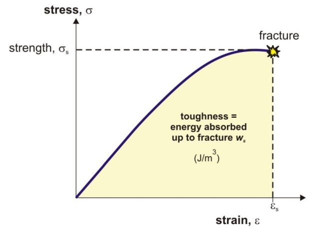
2. Strength

σ_s: the stress value belonging to fracture. Tensile-, compressive-, etc.

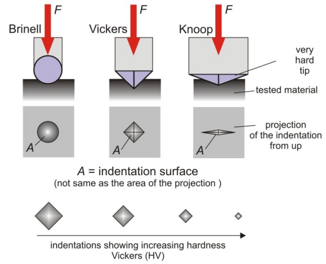


3. Toughness

w_s: the work done on unit volume up to fracture.

4. Hardness

property of the material that characterizes the resistance against plastic deformation during mechanical interaction with a harder material.



$H = \frac{F}{A} = [Pa]$

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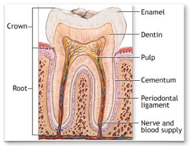
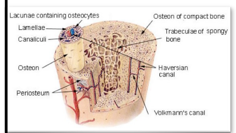
E: ~GPa — stiffness — **E: ~MPa**

Tooth



Bone

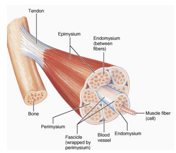


Composite of collagen (organic) and apatite (inorganic).

Organic component provides: toughness

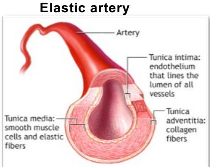
Inorganic component provides: strength

Muscle



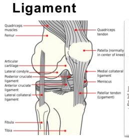
titin, desmin, collagen

Elastic artery

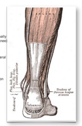


Collagen and elastin

Ligament



Tendon



Cartilage

Collagenn, proteoglycans (water)

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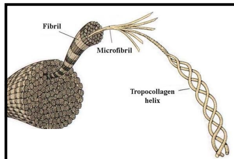
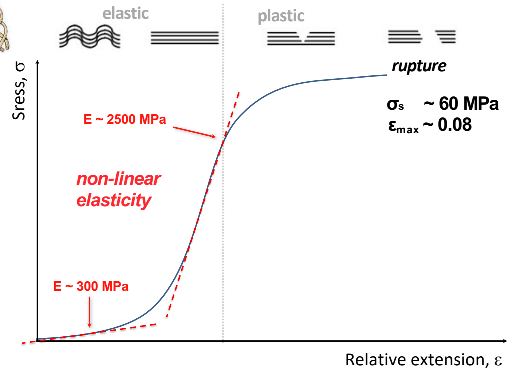
Collagen



1400 amino acids/chain
3 chains (triple helix)
Glicine (1/3)
Proline (1/10)
Hidroxiproline

Posttranslational modification is required for mechanical stability: Prolin-hidroxilase and vitamin-C



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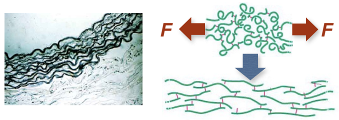
Biomechanics of elastic arteries

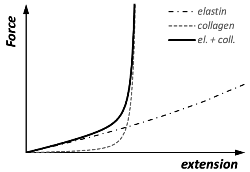
Elastin – elastic protein network

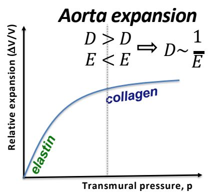


Collagen and elastin have different functions

Collagen: protection against overstretch

Elastin: provides distensibility





Distensibility

The change in vessel volume under pressure

$$D = \frac{\Delta V / V_0}{\Delta p} = \frac{\Delta V}{\Delta p \cdot V_0}$$

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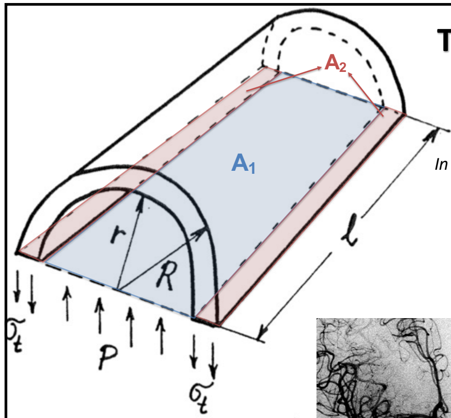
Tangential stress of blood vessel wall



In case of equilibrium, the forces acting on the two surfaces are equal

$$F_{A_1} = F_{A_2}$$

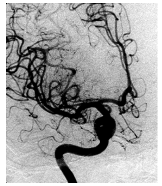
$$p \cdot A_1 = \sigma_t \cdot A_2$$

$$p \cdot 2r \cdot l = \sigma_t \cdot 2(R - r) \cdot l$$

$$\sigma_t = \frac{r}{R-r} \cdot p$$

Laplace-Frank equation

p: transmural pressure
σ_t: tangential stress
r: inner radius of blood vessel
R: outer radius of blood vessel
R-r: wall thickness



Significance: High blood pressure, aneurism

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Bone

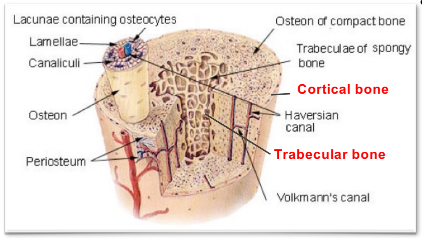
Due to the different structure of bone tissue along the cross section of long bones, the **Young's modulus distribution is anisotropic**. Denser cortical bone has greater Young's modulus vs. the trabecular bone.

Young's-modulus: 5-20 GPa

Decalcified bone (acid treatment): flexible

Removal of organic compounds (heating): brittle

Composite of collagen and hydroxylapatite
collagen: elasticity, toughness
apatite: strength, stiffness, hardness



Bone is a composite material composed of an organic polymer (collagen) and an inorganic mineral (hydroxilpatite) which combines the mechanical properties of each.

Stiff, hard and strong but tough and slightly elastic.

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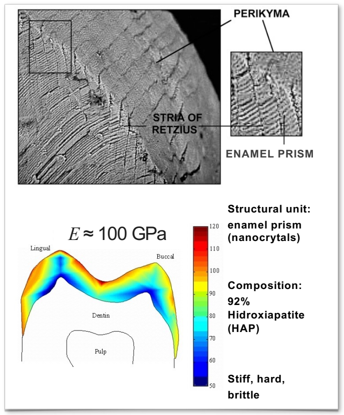
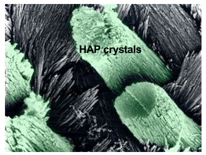
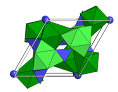
Enamel





Stiffest and hardest material in human body, but brittle!

$Ca_{10}(PO_4)_6(OH)_2$
$Ca_{10}(PO_4)_6F_2$



Hexagonal ion crystal
20-60 nm x 6 nm - dentin, bone
500-1000 nm x 30 nm - enamel

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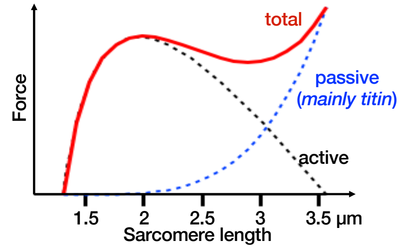
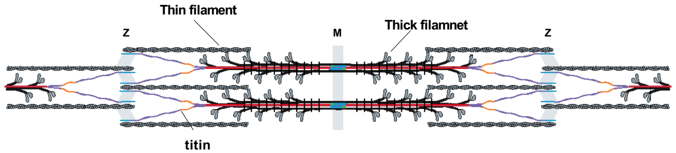
Titin: the elastic filament of the sarcomere





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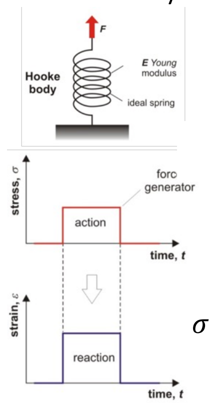
Viscoelasticity

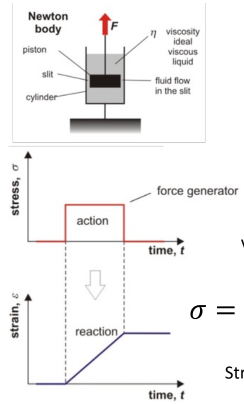
(mechanical model)

Elastic body



$$\sigma = E\varepsilon$$

Viscous body



viscosity

$$\sigma = \eta\,\frac{\Delta\varepsilon}{\Delta t}$$

Strain rate

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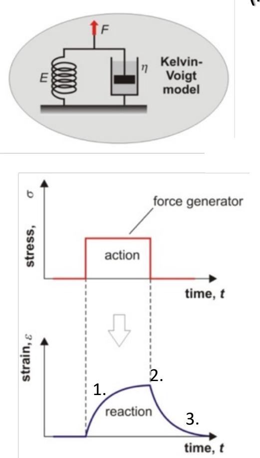
Viscoelasticity

(mechanical model)



Viscoelasticity means the co-appearance of viscous and elastic behavior.

model: parallel connection of spring and dashpot (Kelvin-Voight model)

Spring: ideal elastic (Hooke) body
Dashpot: ideal viscous (Newton) body

1. Upon stretch, the extension of the spring is slowed down by the dashpot.
2. Extension stops when the elastic spring force equals the external force.
3. When the external force is quenched, the contraction of the spring is slowed down by the dashpot.

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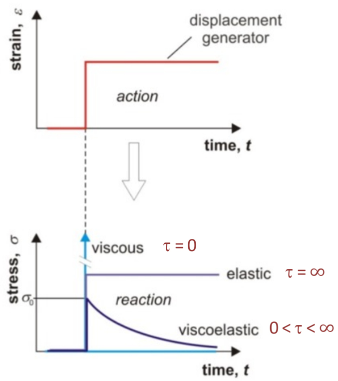
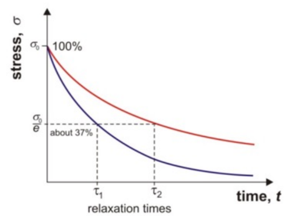
Stress-relaxation in viscoelastic system

Decrease in stress while strain remains constant





$$\sigma = \sigma_0 \cdot e^{-\frac{t}{\tau}}$$

Stretching

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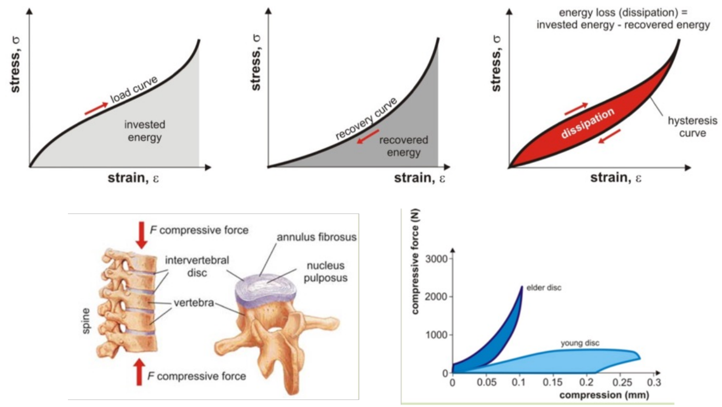
Energy dissipation in viscoelastic system
(hysteresis)



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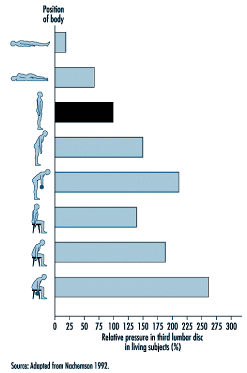
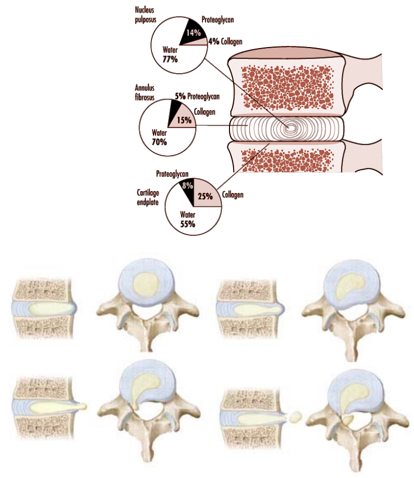
Example: Consequence of mechanical stress on intervertebral discs
(*discus hernia*)

Stress on the L3 disc at various positions





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Flashback: What did you learn about US propagation....?

In wich types of tissue does sound propagate faster?
The acoustic properties of each tissue are charahcterized by theeir stiffness

	E (GPa)	κ (GPa⁻¹)	c_{sound} (m/s)
Cortical bone	18	0.05	3600
Muscle	7x10⁻⁵	0.38	1568

$$c_{sound} = \frac{1}{\sqrt{\rho \cdot \kappa}}$$

$$\kappa = \frac{-\Delta V/V}{\Delta p}$$

Volumetric strain

stress

compressibility

Greater Young-modulus, faster propagation speed

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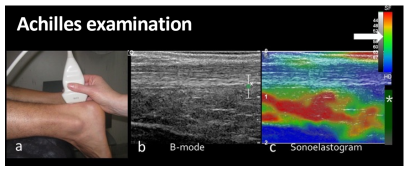
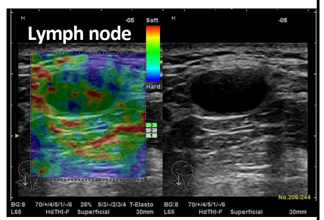
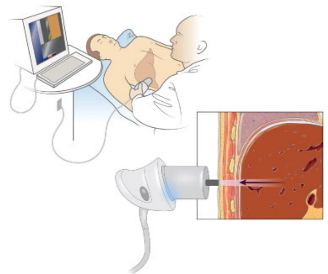
Diagnostic application: sonoelastography







Transient elastography (measurement of liver stiffness based on pulse-echo principle)

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Calculations (required for the final exam!)

To stretch a relaxed biceps muscle 3 cm requires a force of 25 N. To do the same stretch of a contracted muscle at its maximal tension requires a force of 500 N. Find the Young's modulus for both relaxed and tense muscle tissue. Assume the biceps is a uniform cylinder of length 20 cm and diameter 6 cm. (59 kPa, 1.18 MPa)

Collagen fiber is stressed with 12 N force. The cross-sectional area of the fiber is 3 mm2, its Young's modulus is 500 MPa. Give the percentage of relative extension. (0.8 %)

The length of an elastic thread used in orthodontics is 6 cm, its cross-sectional area is 1 mm2, its Young's modulus is 5 MPa. We extend the thread with 40 %. How large is the retracting force and what is the amount of elastic energy stored in the thread?(2 N, 24 mJ)

Bone has an average Young's modulus of 18 GPa. Under compression, it can withstand a stress of about 2.7×10^8 Pa before breaking. Assume that a femur (thigh-bone) is 46 cm long, and calculate the amount of compression this bone can withstand before breaking. (6.9 mm)

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