Molecular mechanisms of biological motion

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Various levels of biological motion

Molecular motion

Bacterial flagellum

Cellular motion

crawling keratinocyte

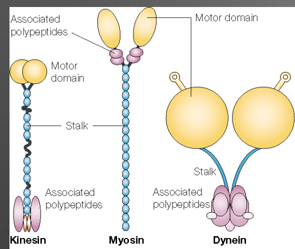
Body motion

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.

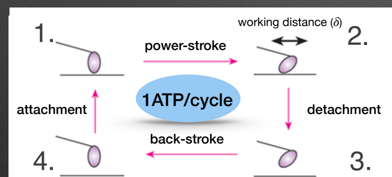
Common characteristics of motor proteins



I. Structural homology

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

The C-terminus contains functional binding sites.



II. Cyclic operation

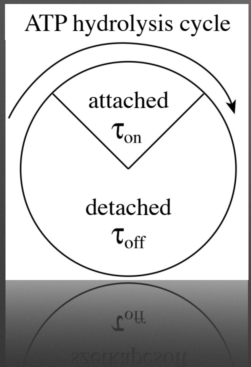
1. Attachment
2. Power-stroke (pull)
3. Detachment (dissociation)
4. Back-stroke (relaxation)

Work done by a single motor protein can be calculated from: $W = F \cdot \delta$

pulling force (F): in the range of pN
working distance (δ): in the range of nm

W: in the range of zJ (zeptojoule = 10^{-21} J)

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.

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

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

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

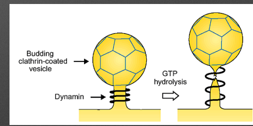
$$r = \frac{\delta k_{ATPase}}{v_{stroke}}$$

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

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)*



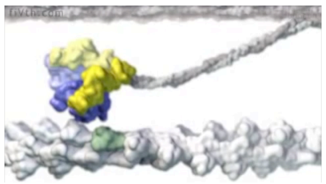
3. DNA based mechanoenzymes
- They exert force and move along the DNS double helix. *(DNA- and RNA-polymerases, viral capsid portal motor)*

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

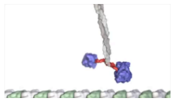
5. Mechanoenzyme complexes
- *Ribosome*

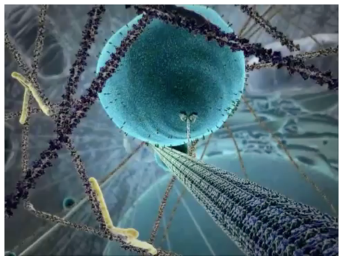
Citoskeleton based motors

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



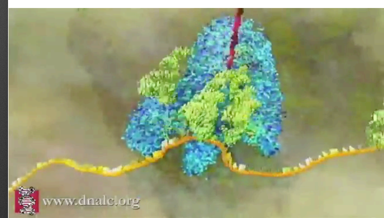
Processive motor
Kinesin
Moves along the microtubule



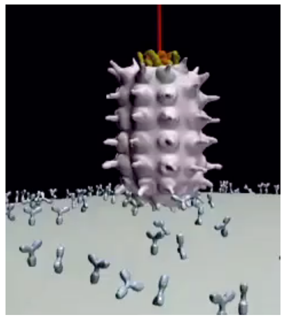


Nucleic acid based motors

Ribosome
mechanoenzyme complex



Virus portal motor
DNS „packaging“

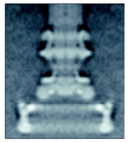


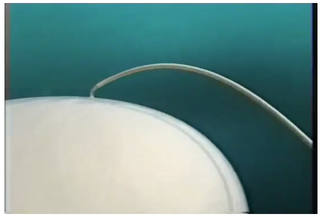
Rotating motors

driving force: proton gradient

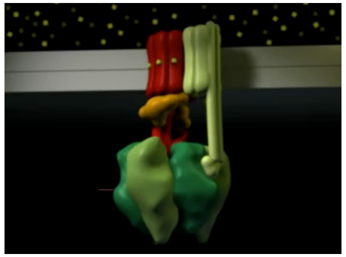
Flagellar motor

bacterial movement

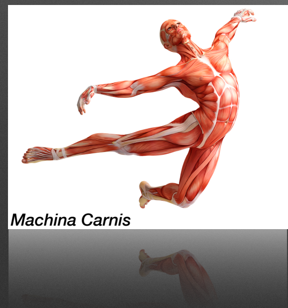




F_1F_o ATP synthase



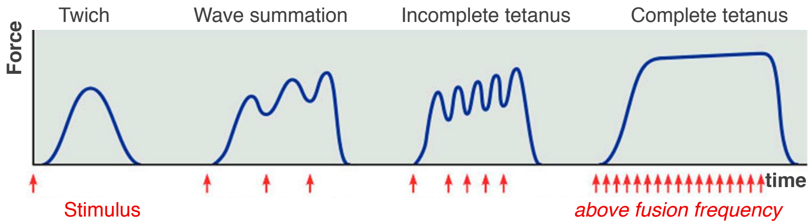
Muscle biophysics



Cell and tissue specialized for movement.

It can only pull, not push!

Basic phenomena of muscle function I.



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

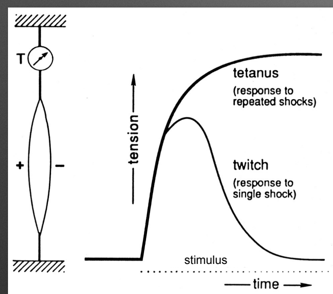
More frequent stimuli increases contractile force – **wave summation** - muscle is already partially contracted when next stimulus arrives and contractions are summed.

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

Basic phenomena of muscle function II.

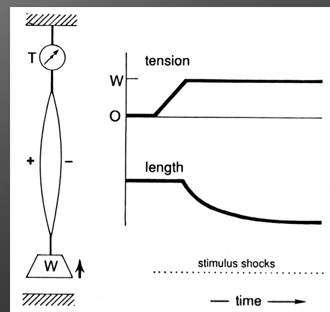
1. Isometric contraction

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



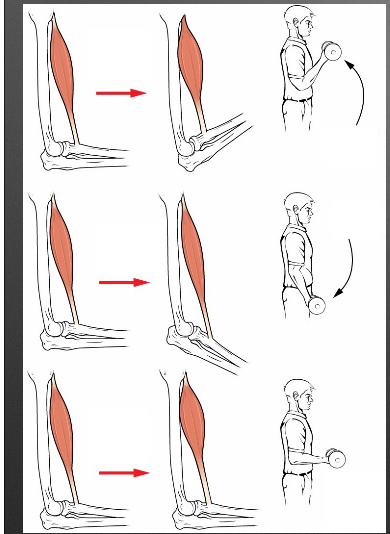
2. Isotonic contraction

Tension remains unchanged while the muscle's length changes.



Auxotonic contraction (simultaneous shortening and force generation)

Basic phenomena of muscle function III.



1.Concentric muscle action
The muscle shortens during force generation

2. Excentric muscle action
The muscle elongates during force generation

3. Isometric muscle action
The muscle length remains constant during force generation

Basic phenomena of muscle function IV.

1. Work and Power

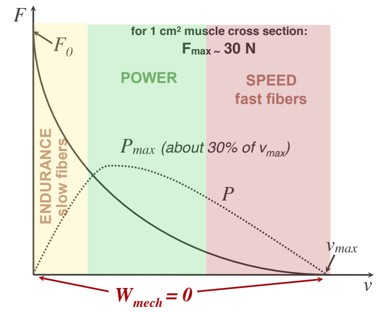
$$W = F \cdot s$$

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

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

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

Energetics of muscle contraction

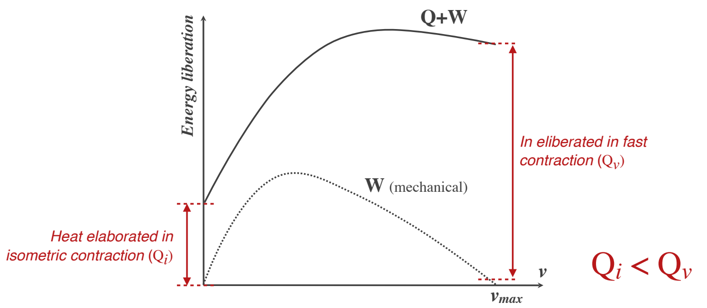
ATP hydrolysis, heat liberation

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 durig shortening. The amount of heat liberated increases with increasing speed of contraction.

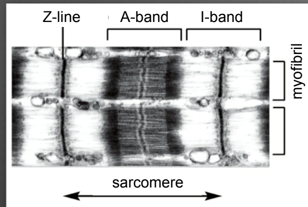
The majority of chemical energy used by the muscle is dissipated as heat

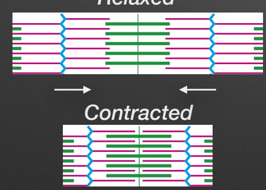


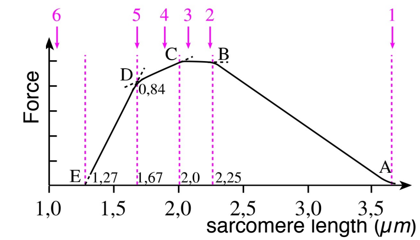
The mechanism of muscle shortening

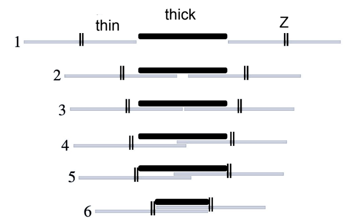
Phenomenological mechanism: sliding filament model

Sarcomere



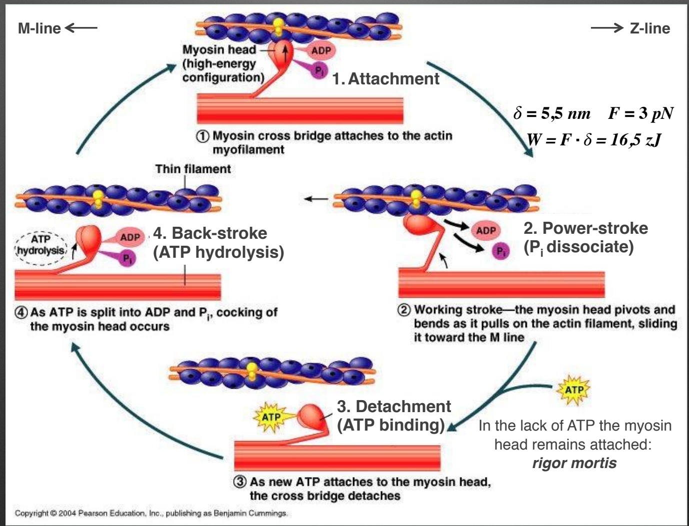






The myosin „cross-bridge“ cycle

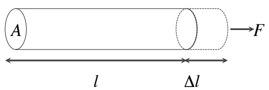
Molecular bases of muscle contraction



Biomechanics of bimolecules and tissues

Basics of tissue mechanics

Hooke's law



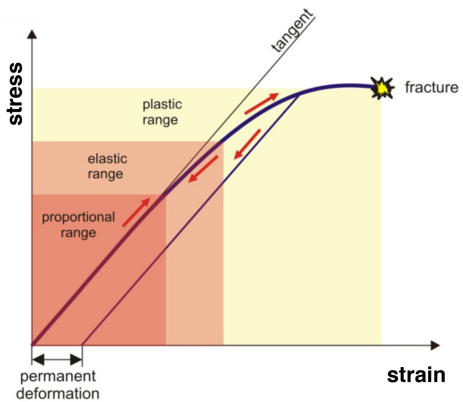
$$\frac{F}{A} = E\,\frac{\Delta l}{l}$$

$$\sigma = E\varepsilon$$

F = force
A = cross sectional area
l = rest length
Δl = extension

F/A = σ = stress (N/m² = Pa)
Dl/l = ε = strain (dimensionless)
E= σ / ε Young's modulus (Pa)
(elastic modulus - the name is misleading! it describes stiffness)

Stress-strain diagram



Flashback: What did you learn about ultrasound propagation…. ?

How much is the speed of sound in different tissues?

Acoustic properties of various tissues are determined by their mechanical properties.

	E (GPa)	κ (GPa^{-1})	c_{sound} (m/s)
Bone	18	0.05	3600
Muscle	7x10^{-5}	0.38	1568

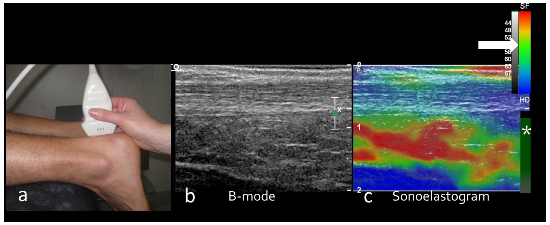
$$c_{sound} = \frac{1}{\sqrt{\rho \cdot \kappa}}$$

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

compressibility (κ), strain ($-\Delta V/V$), stress (Δp)

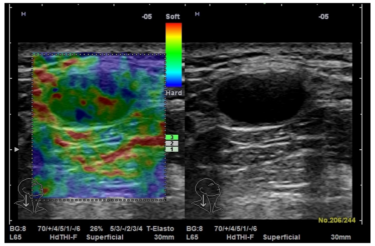
Smaller compressibility, faster speed of sound

Diagnostic usage: sonoelastography

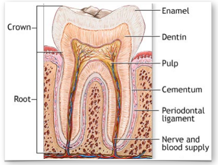


Achilles examination

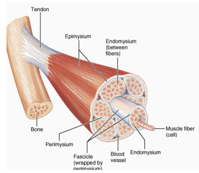
Lymph node examination



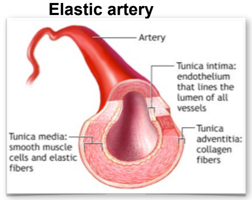
Tooth



Skeletal muscle



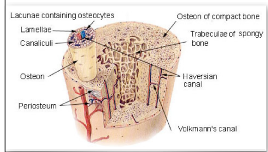
Elastic artery



collagen, elastin

Passive mechanics: titin, desmin
Active mechanics : actin, myosin

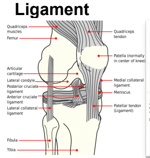
Bone



Main components:
collagen (organic),
apatite (inorganic)

Organic compound gives toughness
Inorganic compound gives stiffness

Ligament

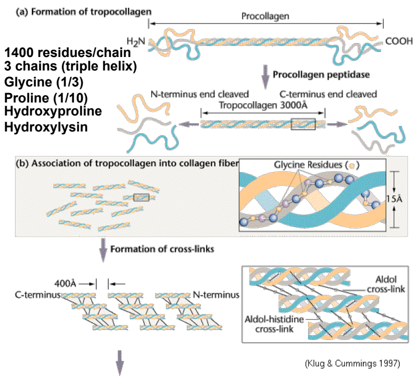


Tendon

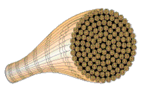
Cartilage

Collagen, proteoglycans (water)

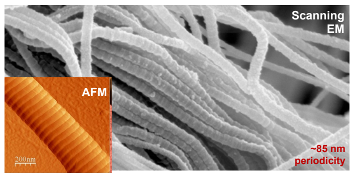
Collagen

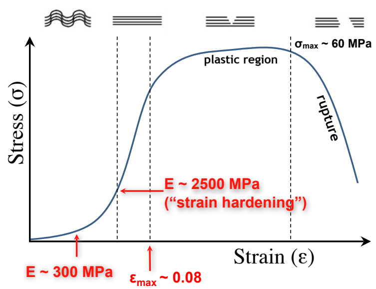


1400 residues/chain
3 chains (triple helix)
Glycine (1/3)
Proline (1/10)
Hydroxyproline
Hydroxylysin



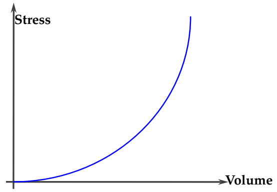
Post translational modification is necessary for tropocollagen polymerization
Hydroxylation of lysin and praline residues requires vitamin-C as cofactor!





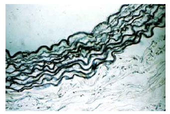
Elastic arteries

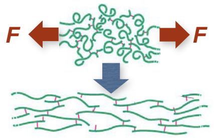
Non-liear elasticity
Strain is not linearly proportional to stress.

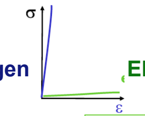


Determinants of vascular elasticity:
Elastin
Collagen
Smooth muscle

Implications of vascular easticity:
Storage of potential (elastic) energy
Dampening of pressure pulses
Constant flow rate







Collagen | **Elastin**

E = 300 MPa .... 2 500 MPa
$\sigma_{sz} \approx 60$ MPa $\varepsilon_{sz} \approx 0{,}08$

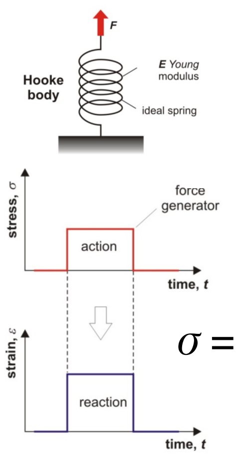
E = 0,1 MPa .... 0,4 MPa
$\sigma_{sz} \approx 0{,}6$ MPa $\varepsilon_{sz} \approx 3$

strength | **elasticity**

Viscoelasticity

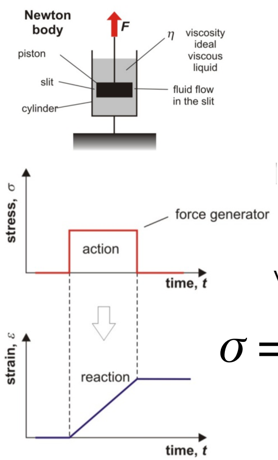
(mechanical model)

Elastic body



$$\sigma = E\varepsilon$$

Viscous body



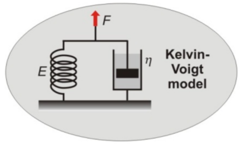
viscosity

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

strain rate

Viscoelasticity

(mechanical model)

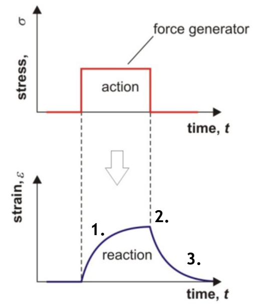


Viscoelasticity means to co-appearance of viscous and elastic behavior. A

model: parallel connection of spring and dashpot

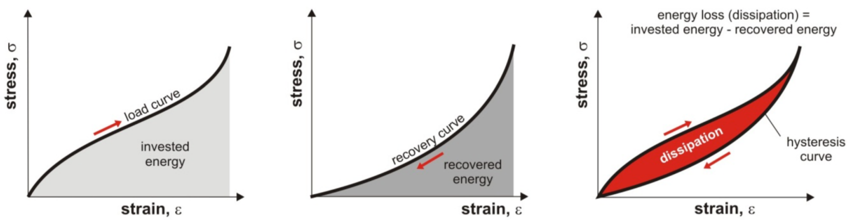
(Kelvin-Voigt model)

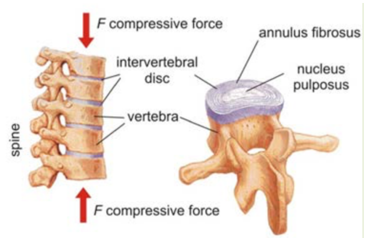
Spring: ideal elastic (Hooke) body
Dashpot: ideal viscous (Newton) body

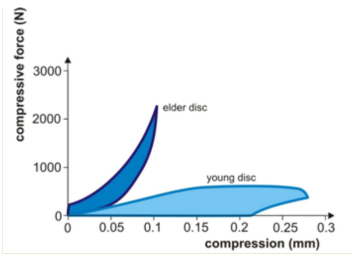


1. Upon stretch, the extension of the spring is slowed down by the dashpot.
2. Extension stops when the elastic spring force equals the external force.
3. When the external force is quenched, the contraction of the spring is slowed down by the dashpot.

Energy dissipation in viscoelastic system

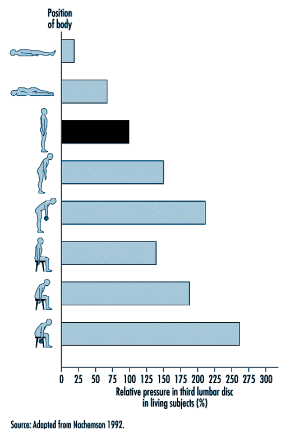


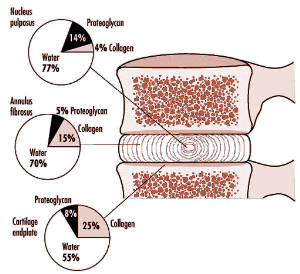


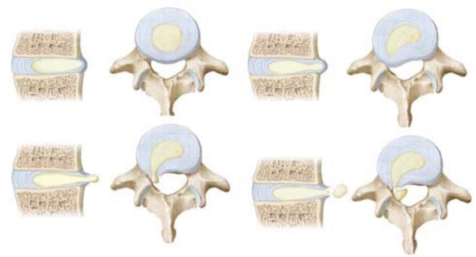


Example I: Consequence of mechanical stress on intervertebral discs (*discus hernia*)

Stress acting on L3 disc at various positions

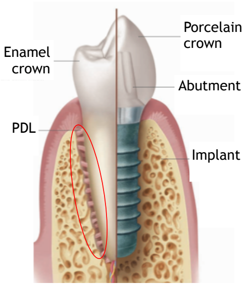


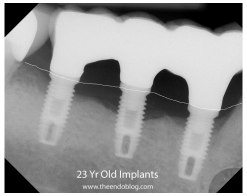




Example II: Implants vs natural tooth

PDL makes the difference!





Absence of PDL results in:
- **loss of masticatory force perception**
- **loss of viscoelastic dampening**
- **loss of force sensory mechanism**
- **no implant movement**

Implant is in direct contact with bone tissue

⇩

Increased compressive stress during mastication

⇩

Bone loss (0.2 mm /year)
Loss of gingival height

Implants ⇔ Root canal treatment

Calculations

- **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 mm^2, 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 mm^2, 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 2.7x10^8 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)**