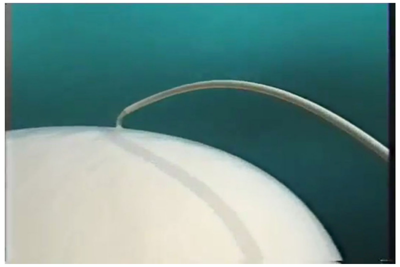
Molecular mechanisms of biological motion.

Zsolt Mártonfalvi

Biological motion

Molecular motion



Bacterial flagellum

Cellular motion

Keratocyte moving on surface

Body motion

Motorproteins

Mechanoenzymes that convert chemical energy to mechanical work.

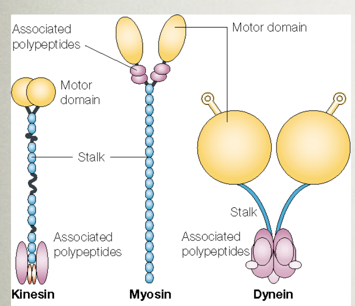
a) Specifically bind to cytoskeletal filaments or bioploymers (f.e. DNA)

b) Displace along the filament and generate force

c) Use ATP as source of chemical energy.

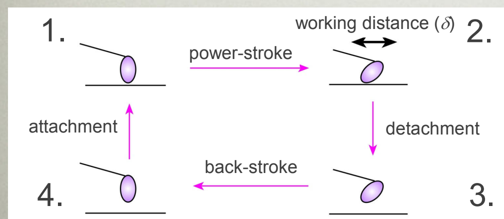
Common features of motorproteins

Structural homology



Globular head on the N-terminus: this is the motor domain (ATPase), that bind to specific filaments.

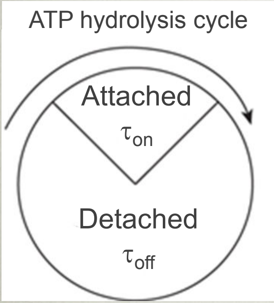
Functional binding site on C-terminus.



Duty cycle:

1. Attachment
2. Power stroke (*pull*)
3. Detachment
4. Back-stroke (*recovery*)

Duty cycle of motor proteins



Duty ratio (r):

$$r = \frac{\tau_{on}}{\tau_{on} + \tau_{off}} = \frac{\delta \cdot k}{v}$$

δ = working distance (nm)
k = ATPase rate (s^{-1})
v = sliding velocity (nm/s)

Processive motor: r~1
F.e. kinesin, DNA-, RNA-polimerase.
Stays attached in most of the cycle time.
Able to work as a single motor.

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

Force generated by a single motor protein: **~ pN**

Types of motor proteins

1. Actin based:
Miosyns: Move along aktin filaments towards plus end.

2. Microtubule based
a. Dyneins: Ciliary (flagellar) and cytoplasmic dyneins. Move towards the minus end along the microtubule.
b. Kinesins: Move towards the plus end along the microtubule.
c. Dynamins: *Vesicle formation (pinchase)*

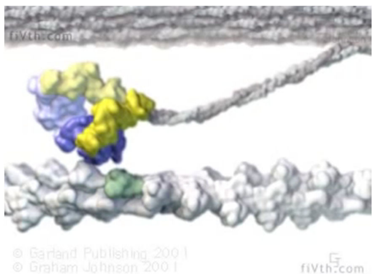
3. DNA based motors
DNA and RNA polymerases, virus capsid packaging motor, condensins
Produce force and displacement along the DNA strand

4. Rotary motors
F1Fo-ATP synthase
Bacterial flagellar motor

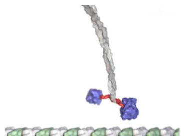
5. Mechanoenzyme complexes
Ribosome

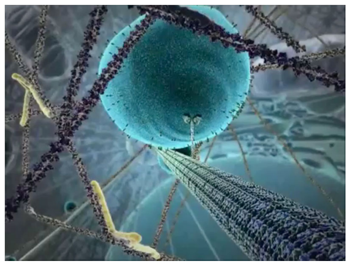
Cytoskeleton based motors

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



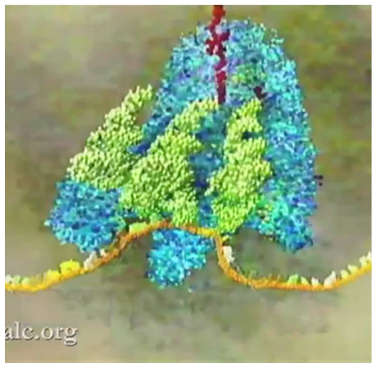
Processive motor
Kinesin
Moves along the microtubules.



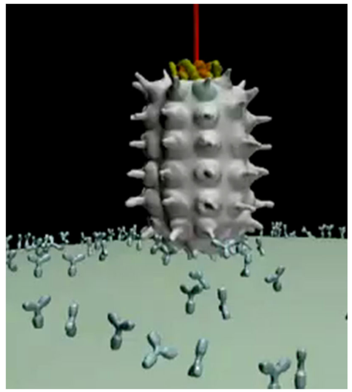


Nucleic acid based motors

Ribosome
Mechanoenzyme complex



Virus portal motor
DNA „packaging"

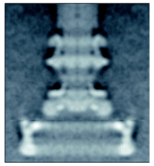


Rotatory motors

driving force: proton gradient

Flagellar motor

Bacterial motion

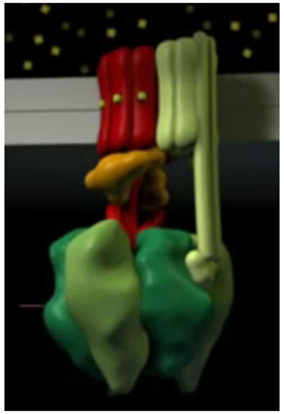


Bacterial Flagellar Motor

「ERATO 難波プロトニックナノマシンプロジェクト終了報告ビデオ」より

F_1F_o ATP synthase

Reversible mechanical cycle

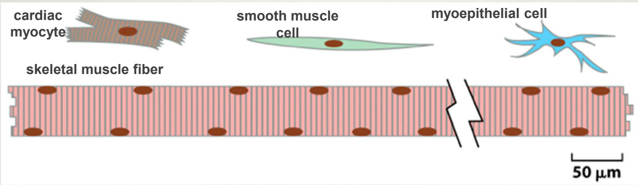


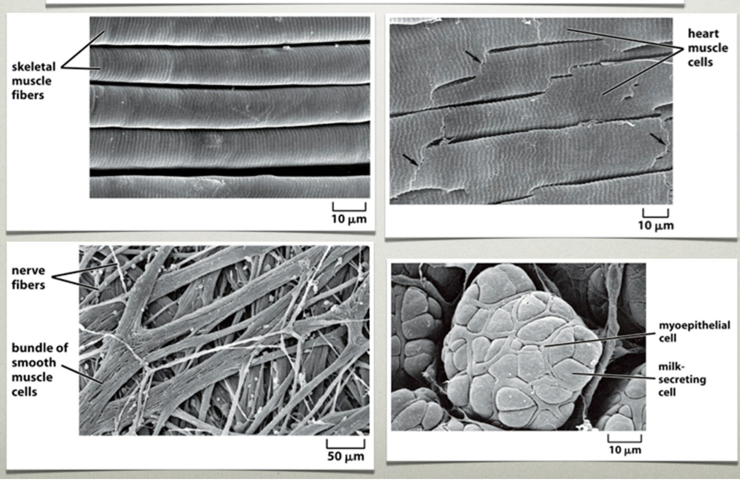
Muscle biophysics

Tissue and / or cell specialized for the generation of force and movement.

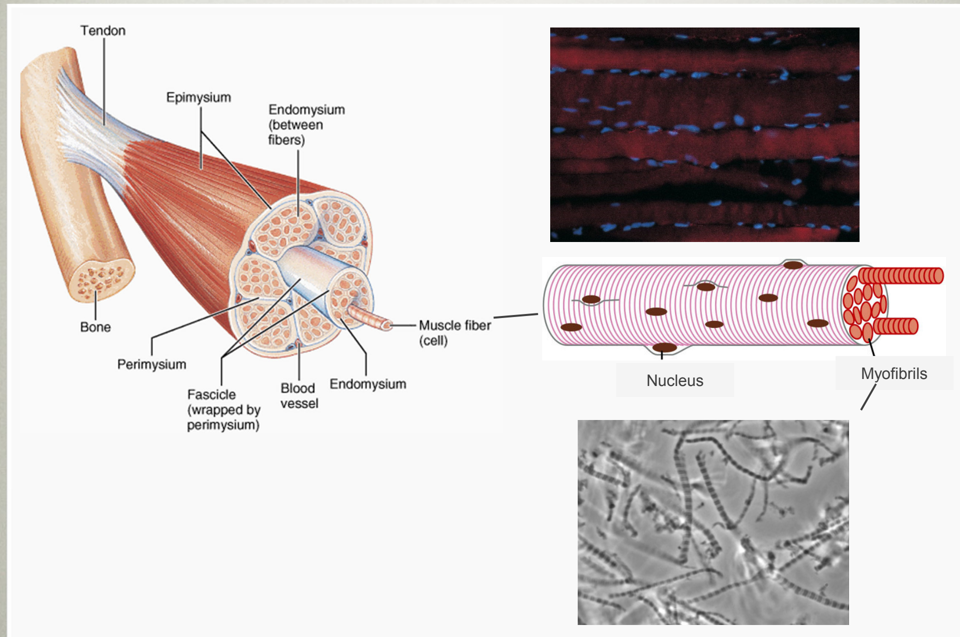
It can only pull, not push (...).

Types of muscle

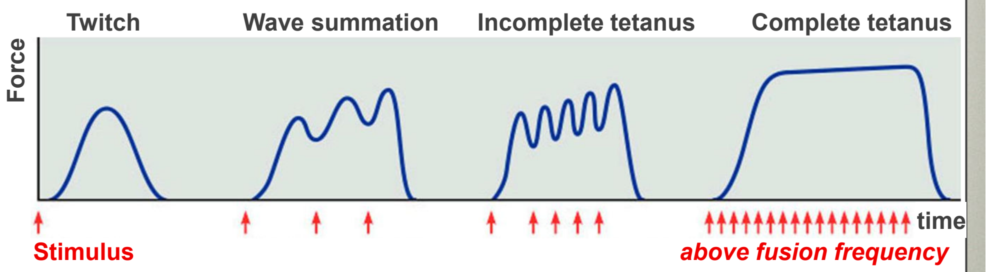




Skeletal muscle



Basic phenomena of muscle function I.



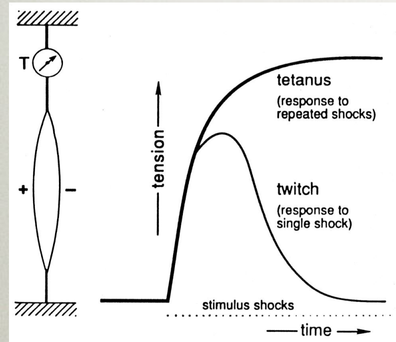
A single stimulus results in a single contractile response – a muscle **twitch** (contracts and relaxes).

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

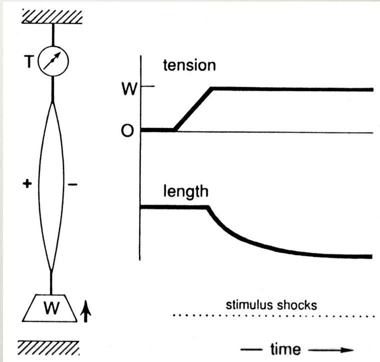
A sustained contraction that lacks even partial relaxation is known as **tetanus.**

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. Work and Power

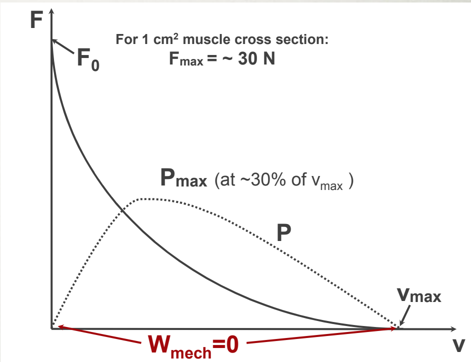
$$W = F \cdot s$$

If v=0, than F= maximum
Maximal isometric force (**F_0**)

If v=maximum, than F=0

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

2. Force-velocity diagram



Hill equation:

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

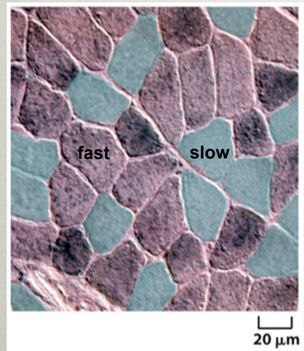
F: force, v: shortening velocity
a and b: constants,
F_0: maximal isometric force

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

Energetics of muscle I.

Source of energy:

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



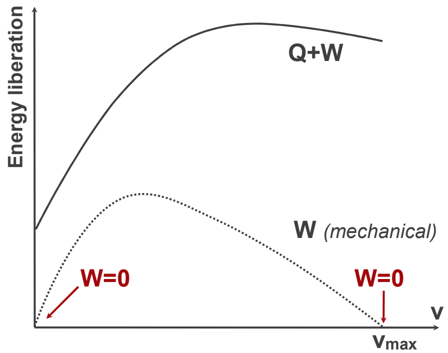
Type I fibers
* rich in mitochondria
* ATP generation by respiratory mechanisms
* slow fatigue
* rich in myoglobin: "red muscle"
* innervated by thin, slow nerves
* slow fiber
* dominates in postural muscles

Type II fibers
* few mitochondria
* rich in glycogen
* ATP generation by glycolysis
* rapid fatigue due to lactate
* devoid of myoglobin: "white muscle"
* innervated by large, fast neurons
* fast fiber
* present in fast muscles

Energetics of muscle II.

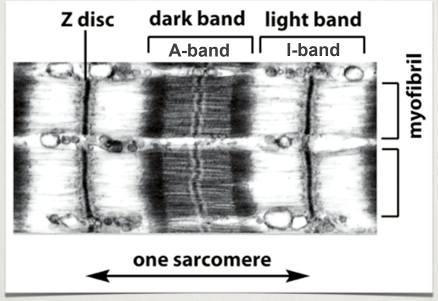
The majority of chemical energy used by the muscle is dissipated as heat

Fenn effect: The liberation of heat increases in a stimulated muscle when it is allowed to do mechanical work. Liberation of heat increases with increasing speed of contraction.



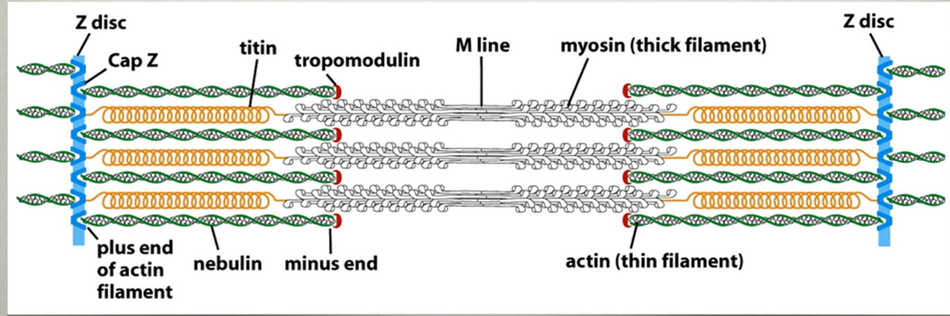
The sarcomere

sarcos: meat (Gr)
mera: unit
the smallest structural and functional unit of striated muscle.



A-band: Anisotropic-band
Thick filaments (myosin II.)

I-band: Isotropic-band
Thin filaments (actin, tropomyosin, troponin)



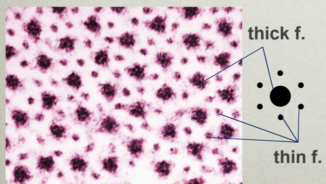
Mechanisms of muscle shortening

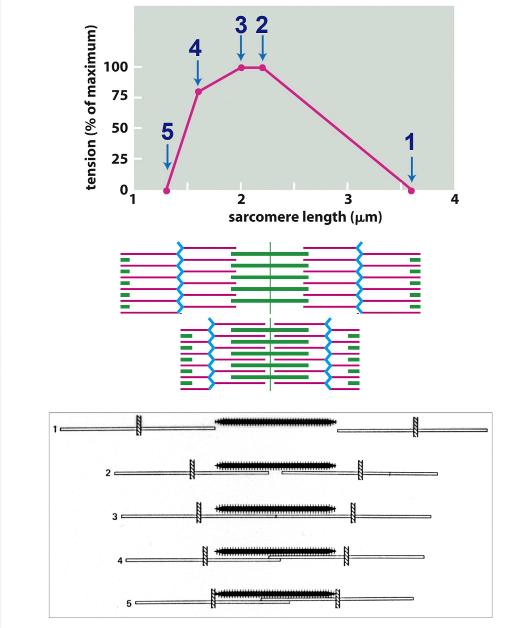
Phenomenological mechanism:

Sliding filament theory

Andrew F. Huxley, Jean Hanson, Hugh E. Huxley

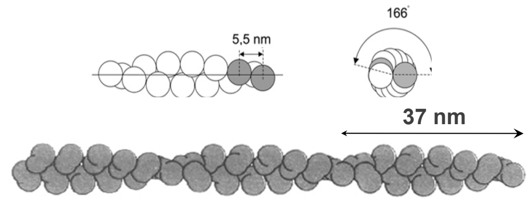
Sarcomere cross section

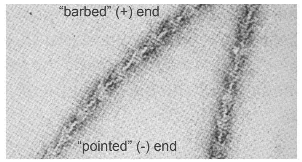




Molecular mechanisms of muscle contraction: Cyclic, ATP-dependent actin-myosin interaction

The actin filament





~7 nm thick, length *in vitro* exceeds 10 µm, *in vivo* 1-2 µm

Right-handed double helix.

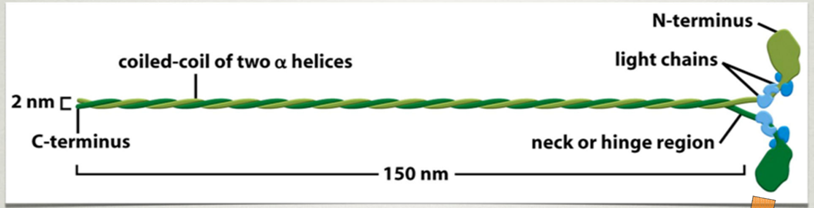
Semiflexible polymer chain (persistence length: ~10 µm)

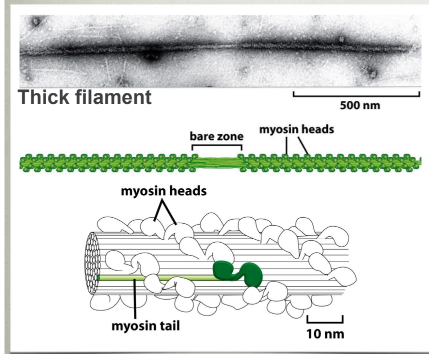
Structural polarity ("barbed", "pointed" ends)

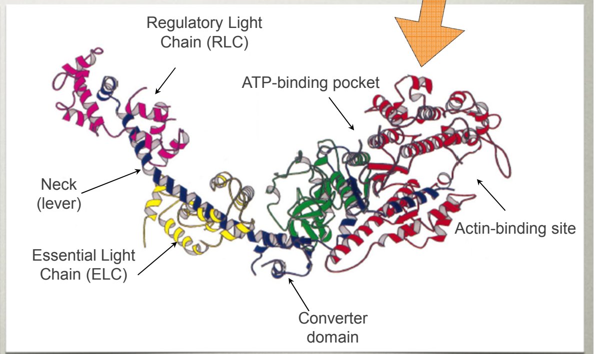
Tensile strength of actin: appr. 120 pN (N.B.: under isometric conditions up to 150 pN force may reach a filament.

Number of actin filaments in muscle: 2 x 10^{11}/cm^2-muscle cross section.

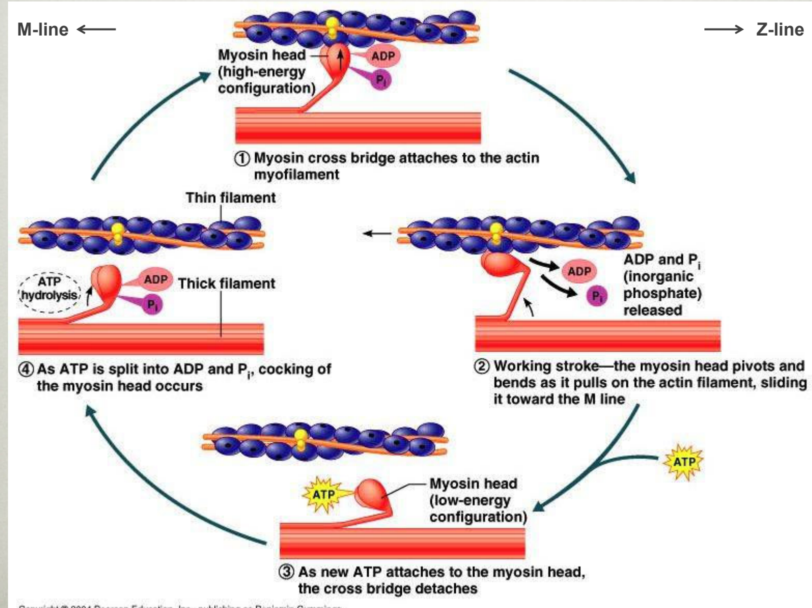
Myosin II



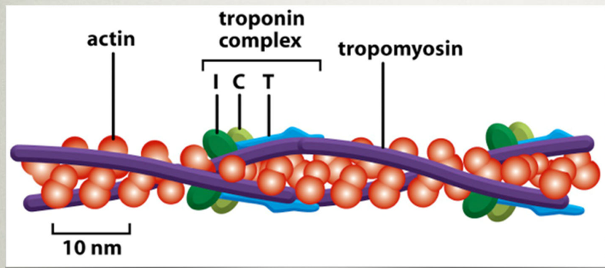


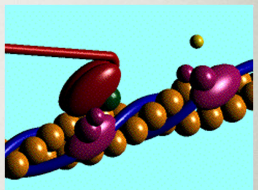


The myosin “cross-bridge” cycle



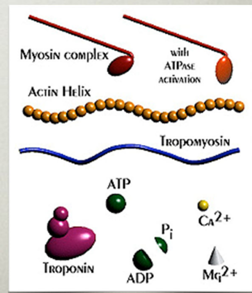
Contraction regulation in striated muscle



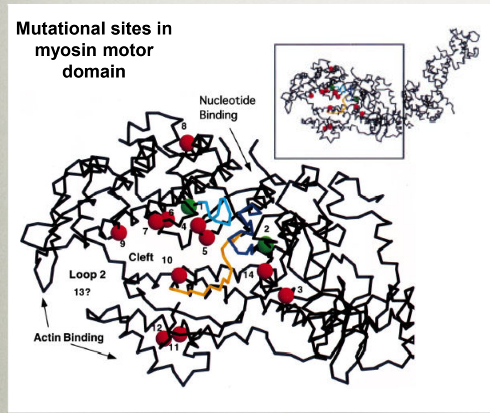


Tropomyosin: blocks myosin-binding site on actin

Troponin complex: 3 subunits, (C, T, I)
Troponin C binds free Ca^{2+}, which causes the conformational change of tropomyosin, thus myosin-binding sites expose.



Myosin mutation - pathology



Arg403Gln mutation: hypertrophic cardiomyopathy

Excitation-contraction coupling