Isolated cardiac myocyte in culture
undergoing periodic contractions
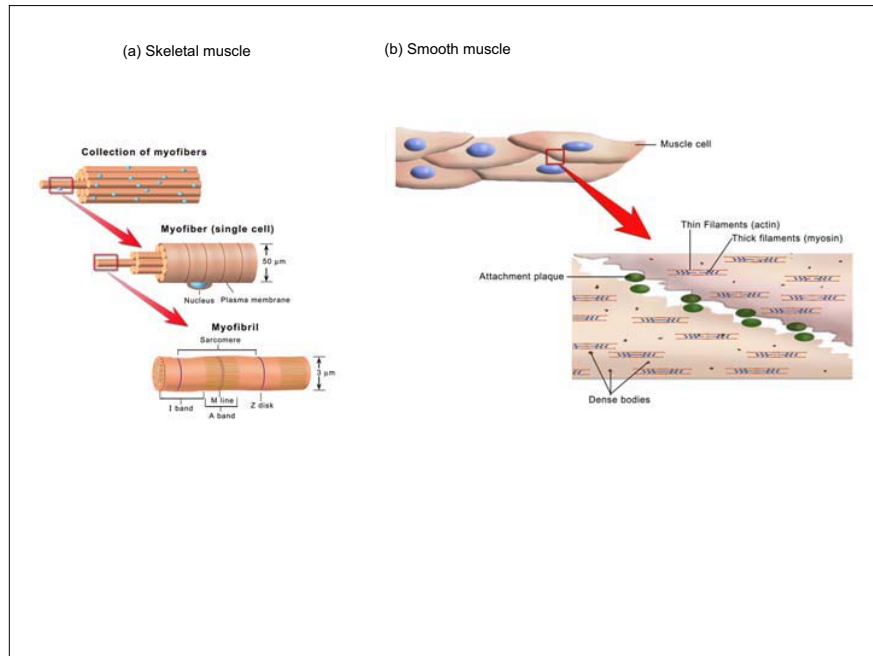
Frame: 00009930   Magnet: -X OFF I
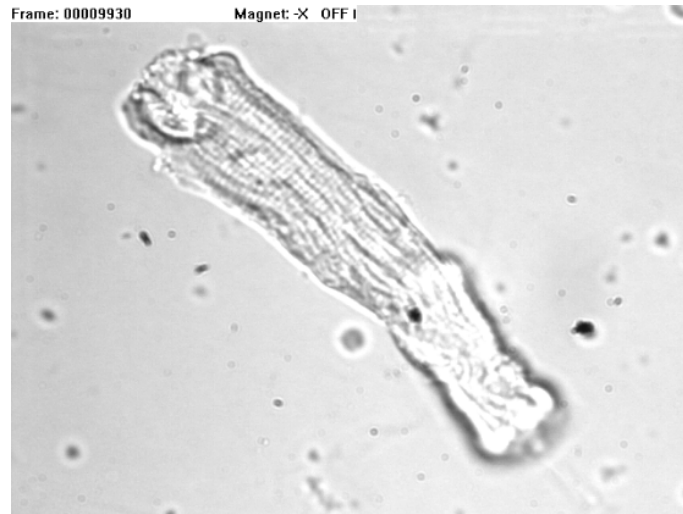
Structure of muscle

Image removed due to
copyright considerations.

Skeletal (striated) and smooth muscle

(a) Skeletal muscle

(b) Smooth muscle

Collection of myofibers

Myofiber (single cell)
50 µm
Nucleus Plasma membrane

Myofibril
Sarcomere

I band   M line   Z disk
A band

Muscle cell

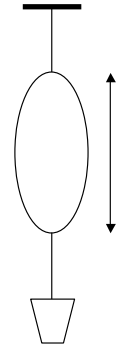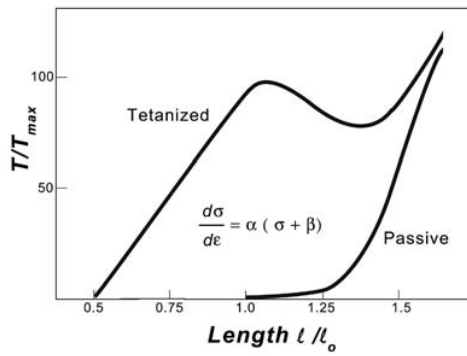Thin Filaments (actin)
Thick filaments (myosin)

Attachment plaque

Dense bodies

Temporal patterns of muscle contraction

- Single twitch
- Periodic sequence of excitations
- Fused tetanus (F_{max})

Tetanus

Tension, T
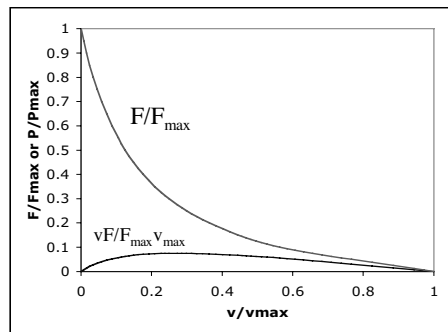
Unfused tetanus

Twitch

0   1   2

Time (sec)

l
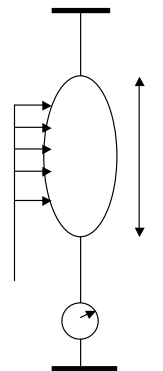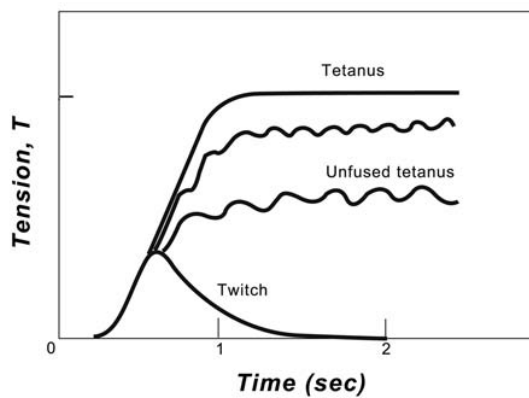
Tension-length curves for a muscle fiber (relaxed and maximally stimulated)

$$\frac{d\sigma}{d\varepsilon} = \alpha\,(\sigma + \beta)$$

Hill's equation

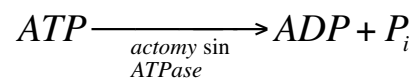Empirically determined force-velocity relationship obtained from macroscopic measurements

$$\frac{v}{v_{max}} = \frac{1 - (F/F_{max})}{1 + C(F/F_{max})} \qquad \frac{vF}{v_{max}F_{max}} = \frac{1 - (F/F_{max})}{(F_{max}/F) + C}$$

Source of energy for muscle☐

Hydrolysis of adenosine triphosphate (ATP) creating adenosine diphosphate (ADP):
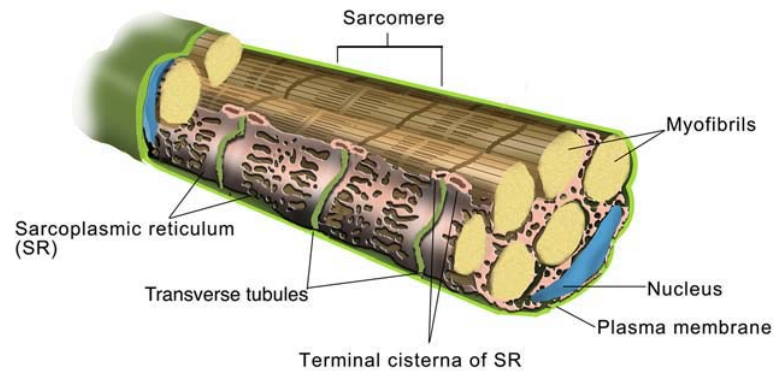
$$ATP \xrightarrow[\substack{actomy\,\sin \\ ATPase}]{} ADP + P_i$$

$$\Delta G = \Delta G_0 - kT \ln\left(\frac{[ATP]}{[ADP][P_i]}\right)$$
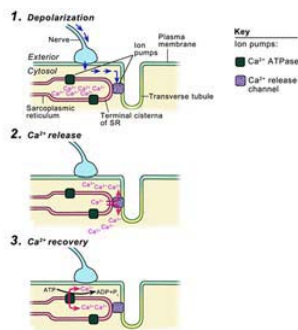
or approximately -25 kT (displacement ~ 5 nm)

Power/weight ~ same as an automobile engine

A rise in cytosolic Ca^{2+} triggers muscle contraction (part I)

Sarcomere

Myofibrils

Sarcoplasmic reticulum (SR)

Transverse tubules

Nucleus

Plasma membrane

Terminal cisterna of SR

A rise in cytosolic Ca^{2+} triggers muscle contraction (part II)

Step 1: An excitation signal travels along the efferent nervous pathways towards the muscle.

Step 2: The excitation signal de-polarizes the cell membrane. This allows spread of the action potential along the sarcoplasmic reticulum.

Step 3: The potential triggers the release of calcium into the sarcoplasmic matrix surrounding the filaments of the motor unit.

Step 4: This removes the hindrance (tropomyosin) for interactions between actin and myosin filaments through chemical, mechanical, and electrostatic actions.

Step 5: The stepping action of myosin along the adjacent actin filament causes the two to slide relative to each other, reducing the length of the sarcomere, producing contraction.

Step 6: Sequestration of calcium ions in the sarcoplasmic reticulum (ATP-dependent) switches the contraction activity off.
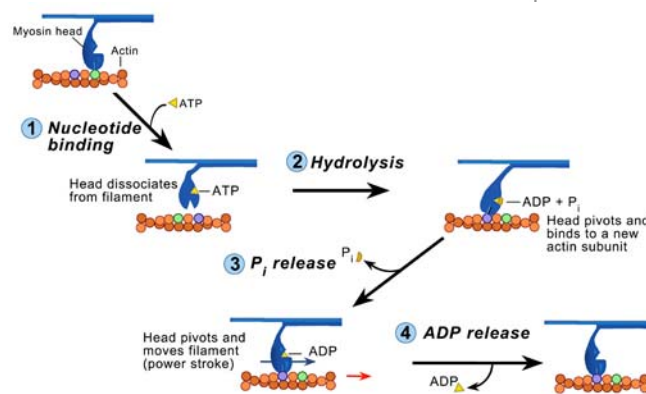
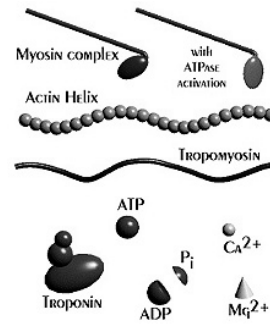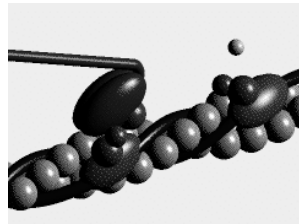# Skeletal muscle contains a regular array of actin and myosin
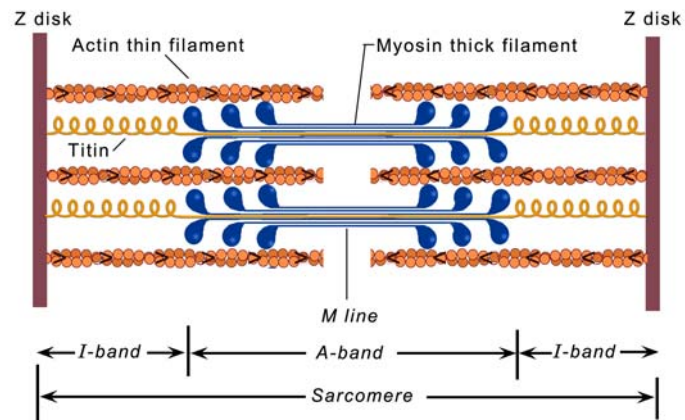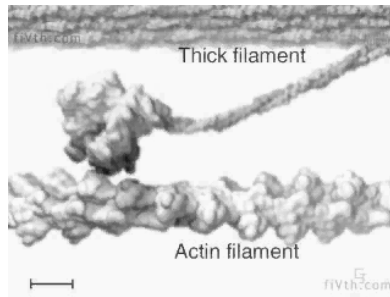
http://www.scripps.edu/milligan/research/movies/myosin_text.html

Conformational changes in the myosin head couple ATP hydrolysis to movement

http://www.sci.sdsu.edu/movies/actin_myosin.html

Image removed due to
copyright considerations.

Rhodamine phalloidin labeled actin moves on a myosin coated cover slip (black)
observed with epifluorescence microscopy. This motility assay uses the antibody
capture technique.

D. A. Winkelmann, L. Bourdieu, A. Ott, F. Kinose, A. Libchaber: "Flexibility of
Myosin Attachment to Surfaces Influences F-Actin Motion" Biophys J. 68, 1995,
2444-2453.

The sliding filament model
A. Huxley & Niedergerke, H. Huxley & Hanson,
*Nature*, 1954

A quantitative model
A. Huxley 1957
See also textbooks by T. McMahon or J. Howard

While in the bound state, the myosin head behaves as though loaded by linear springs with spring constant, κ, and that it passes through the necessary biochemical processes including binding of ATP, ATP hydrolysis, and release of ADP.

Only the case of constant (time-invariant) relative sliding velocity and force generation is considered.

The muscle is assumed to be maximally activated throughout.

Attachment and detachment is assumed to obey simple kinetics.

Effects of other elastic components in the muscle are ignored.

Myosin head

Myosin filament

Actin binding site

Actin filament

x

k_+

k_-

x
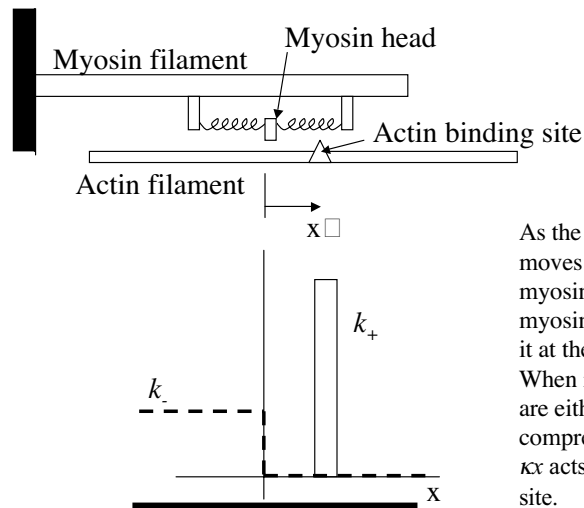
As the actin filament moves past the (fixed) myosin filament, the myosin head can bind to it at the red triangle. When it does, the springs are either stretched or compressed and a force κx acts at the binding site.

Equations governing the probability $n(x,t)$ that a cross-bridge is attached
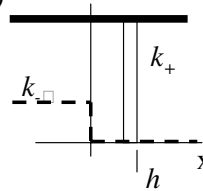
$$\frac{dn(x,t)}{dt} = \frac{\partial n(x,t)}{\partial t} - v\frac{\partial n(x,t)}{\partial x} = \left[1 - n(x,t)\right]k_+(x) - n(x,t)k_-(x)$$

Formation of new bonds

Detachment of existing bonds

At steady state $[n = n(x)]$

$$-v\frac{dn(x)}{dx} = \left[1 - n(x)\right]k_+(x) - n(x)k_-(x)$$

k_+ = attachment rate; k_- = detachment rate; n = probability of attachment

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The sliding filament model

$x > h$:

In this region the actin binding site is approaching the free myosin head, unoccupied.
Since both k_+ and k_- are zero, no binding occurs:
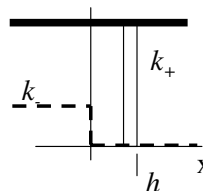
$$n(x) = n(h) = 0$$

$h-x_0 < x < h$:

If binding is to occur, it has to do so (according to this simple model) within this narrow
region where the binding rate constant is large, described by the equation:

$$-v\frac{dn}{dx} = (1-n)k_+^0$$

$$n(h - x_0) = 1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)$$

0 < x < h-x₀

Both the attachment and detachment rate constants are zero, so the myosin head can neither bind to nor detach from an actin filament, and the probability of attachment remains constant:
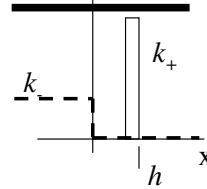
n(x) = n(h-x₀) = constant

x < 0

As the complex moves into the region *x < 0*, the force of interaction sustained at the actin-myosin bond changes sign and its probability of attachment begins to fall, as described by the equation:

$$-v\frac{dn}{dx} = -k_-^0 n$$

$$n(x) = n(0)\exp\left(\frac{k_-^0 x}{v}\right) = \left[1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right]\exp\left(\frac{k_-^0 x}{v}\right)$$

Work done by a single cross-bridge that attaches at *x=a* and detaches at *x=b*:

$$W = \int_{-b}^{a} \kappa x\, dx = \frac{\kappa}{2}\left(a^2 - b^2\right) \qquad \sigma/A = \int_{-\infty}^{\infty}\left[n(x)\rho_s As/2\right]\kappa x\, dx$$
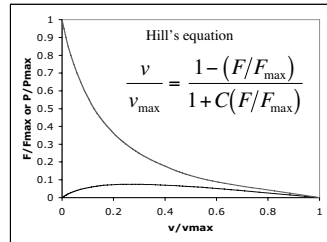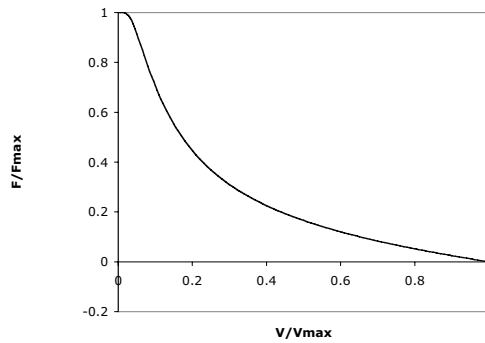
$$\sigma = \frac{\rho_s As\kappa}{2lA}\int_{-\infty}^{\infty} n(x)x\, dx = \frac{\rho_s As\kappa}{2lA}\left[\int_{-\infty}^{0} n(0)x\exp\left(\frac{k_-^0 x}{v}\right)dx + \int_{0}^{h} n(0)x\, dx\right]$$

$$\sigma = \frac{\rho_s s\kappa h^2}{4l}\left[1 - 2\left(\frac{v}{hk_-^0}\right)^2\right]\left[1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right]$$

$$\frac{\sigma}{\sigma_{max}} = \left[1 - \left(\frac{v}{v_{max}}\right)^2\right]\left[1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right] \qquad \sigma_{max} = \frac{\rho_s s\kappa h^2}{4l}$$

$$v_{max} = \frac{hk_-^0}{\sqrt{2}}$$

Predicted force-velocity curve from cross-bridge model

Hill's equation

$$\frac{v}{v_{max}} = \frac{1 - (F/F_{max})}{1 + C(F/F_{max})}$$

$$\frac{F}{F_{max}} = \left[1 - \left(\frac{v}{v_{max}}\right)^2\right]\left[1 - \exp\left(-\frac{k_+^0 x_0}{v}\right)\right]$$