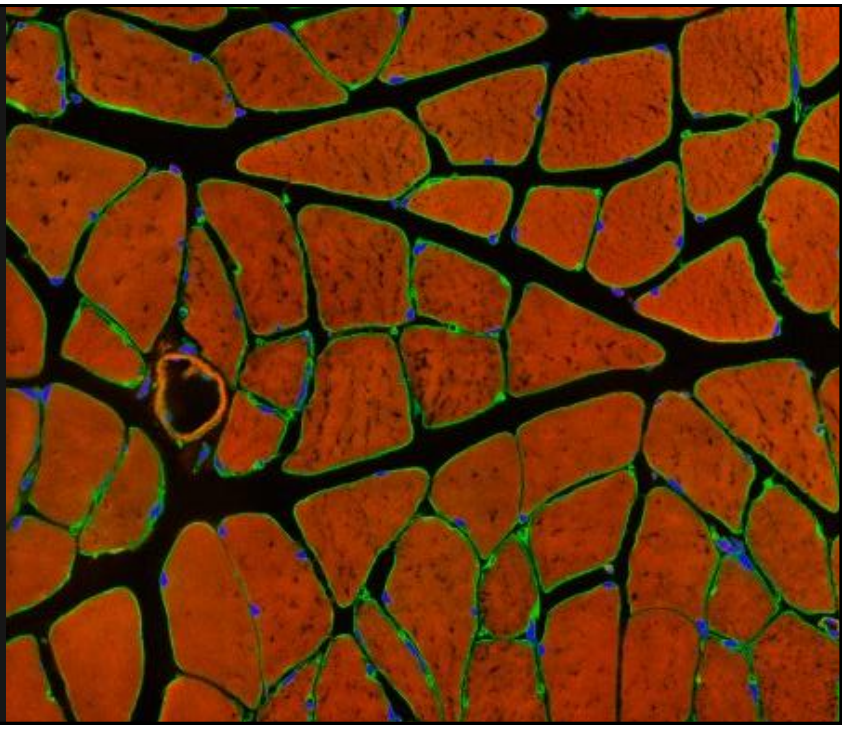
Muscle Physiology



Muscle Physiology

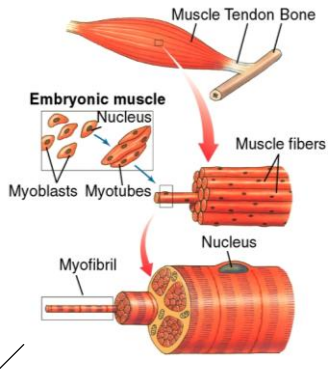
Skeletal Muscle Anatomy:

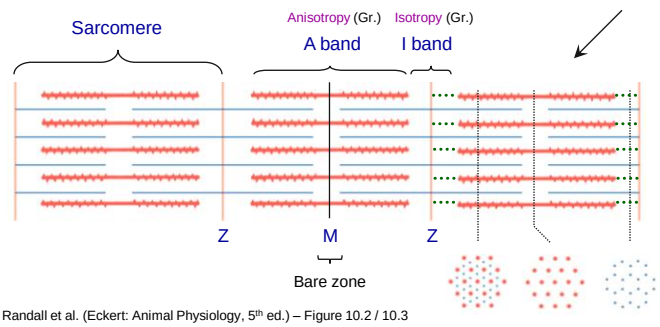
Muscle fibers (= individual muscle cells):

- Multi-nucleated (mitosis sans cytokinesis)
- Sarcolemma (= plasma membrane + collagen fibers)
- Sarcoplasm (= cytoplasm; ↑ mitochondria)

- Myofibrils (contractile elements):
  - Actin filaments (thin)
  - Myosin filaments (thick)

Dystrophin:
Anchors myofibril arrays to cell membrane



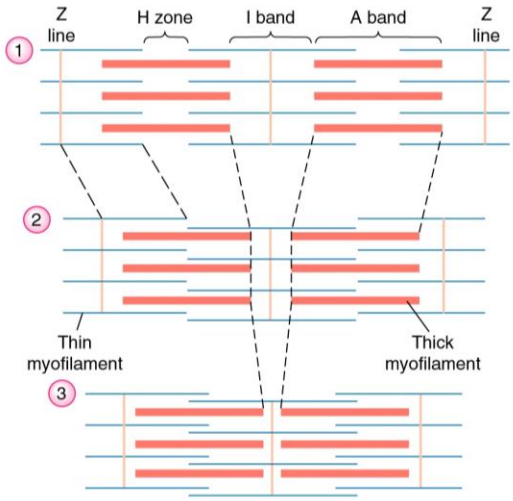


Titin:
Filamentous structural protein (“springy”)

Muscular dystrophy

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.2 / 10.3

Sliding Filament Theory (Huxley and Huxley – 1954):



Contraction results from sliding action of inter-digitating actin and myosin filaments

Evidence?

Myosin head interacts with actin (cross-bridging)

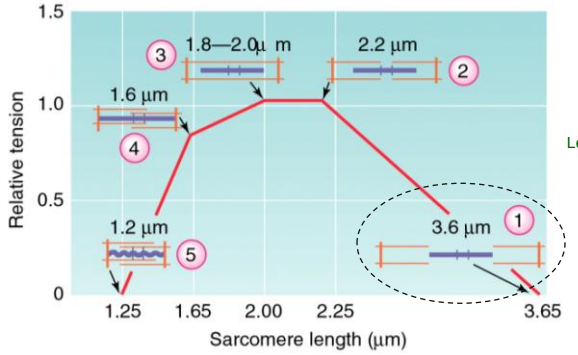
Each cross-bridge generates force independent of other cross-bridges

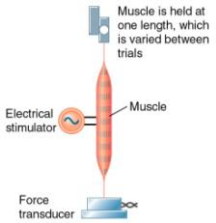
Thus

Total tension developed by sarcomere proportional to number of cross-bridges
(proportional to filament overlap)

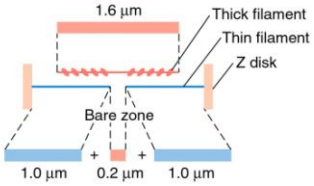
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8

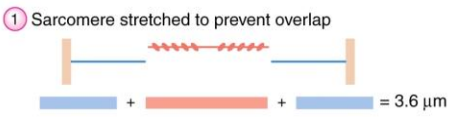
Sliding Filament Theory (Huxley and Huxley – 1954):





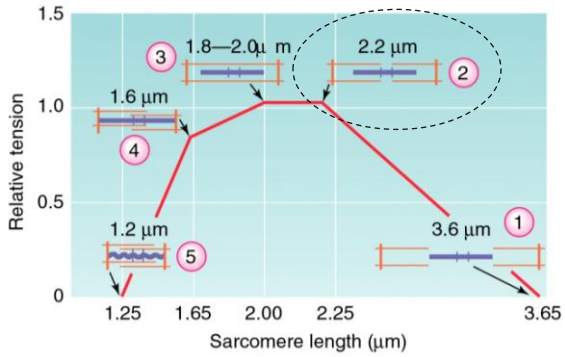
Length-tension relationship

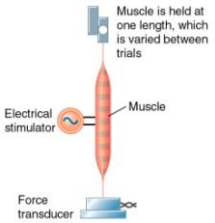




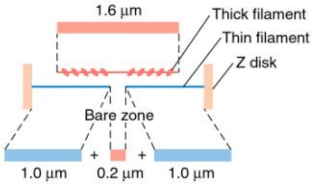
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9

Sliding Filament Theory (Huxley and Huxley – 1954):

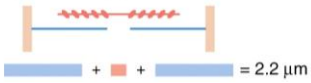




Length-tension relationship



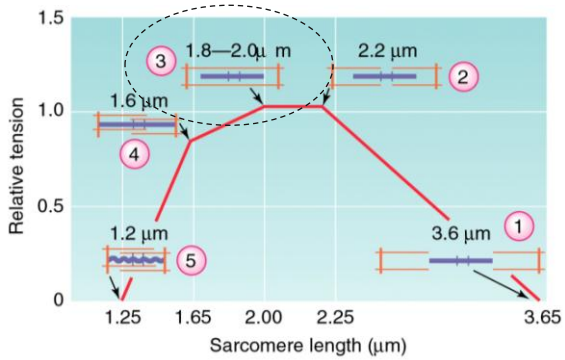
② Maximum overlap; shortening possible

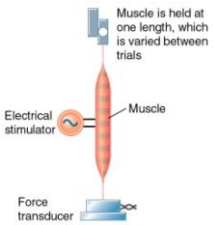


Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9

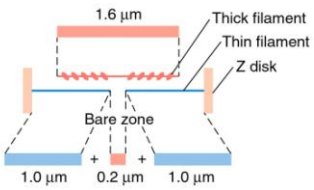
Muscle Physiology

Sliding Filament Theory (Huxley and Huxley – 1954):

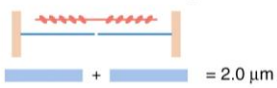




Length-tension relationship

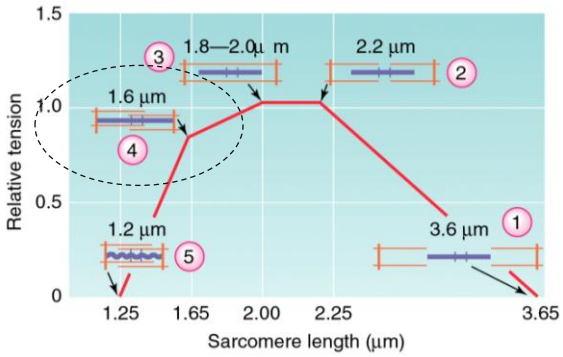


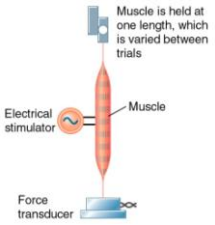
③ Overlap still maximum, but further shortening hindered



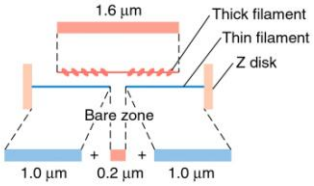
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9

Sliding Filament Theory (Huxley and Huxley – 1954):

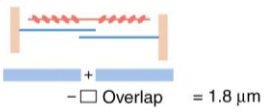




Length-tension relationship



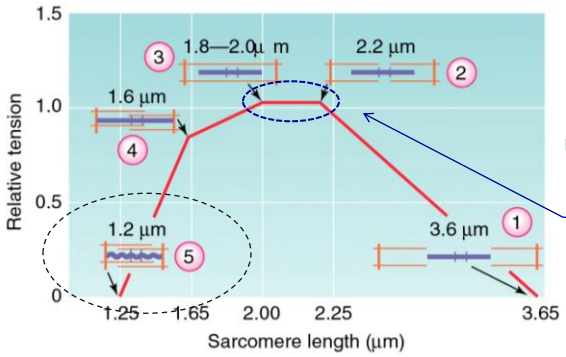
4 Cross-bridge binding hindered

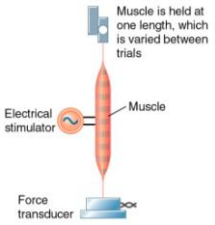


Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9

Muscle Physiology

Sliding Filament Theory (Huxley and Huxley – 1954):

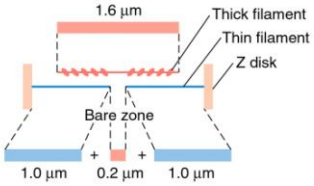




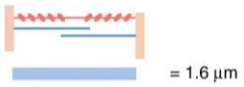
Length-tension relationship

Normal resting length of skeletal muscle

Maximum Contraction Strength: ~ 50 lbs. / inch^2

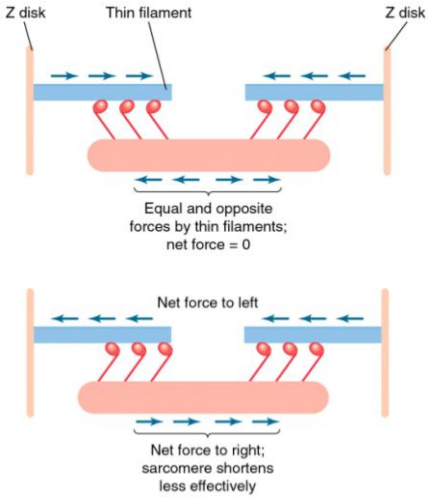


5 Shortening blocked



Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9

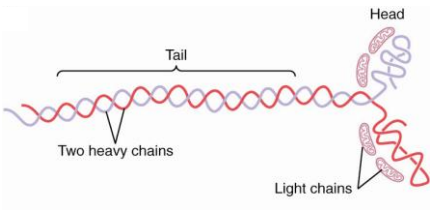
The geometry of myofilaments in a sarcomere strongly affects the contractile properties of the muscle



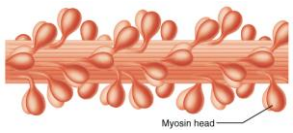
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Spotlight 10.1

Myofilament Anatomy:

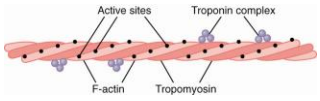
1) Myosin:
   - Two heavy chains (tail)
   - Four light chains (head)
     - Actin-binding sites
     - ATPase activity

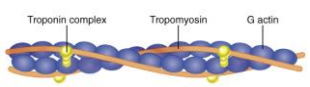


   - Myosin filament composed of 200+ individual myosin molecules (~1.6 μm in length)



2) Actin:
   - Two double-stranded helixes of G-actin polymers woven to form F-actin (~ 1 μm in length)
     - ADP attached to G-actin (active site)
   - Tropomyosin: Spiral around F-actin; cover active sites
   - Troponin: Attaches tropomyosin to F-actin



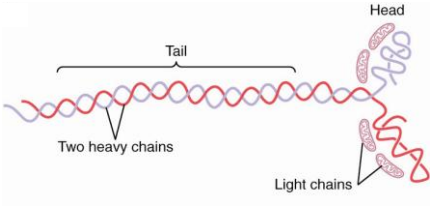


Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 6.5

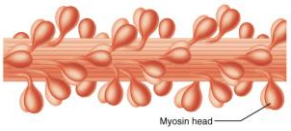
Myofilament Anatomy:

1) Myosin:

- Two heavy chains (tail)
- Four light chains (head)
  - Actin-binding sites
  - ATPase activity



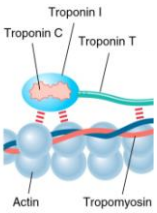
- Myosin filament composed of 200+ individual myosin molecules (~1.6 μm in length)



2) Actin:

Troponin (sub-units):

1) Troponin C: Binds calcium (up to 4 Ca^{++})
2) Troponin T: Binds tropomyosin
3) Troponin I: Binds actin (covers active site on actin)

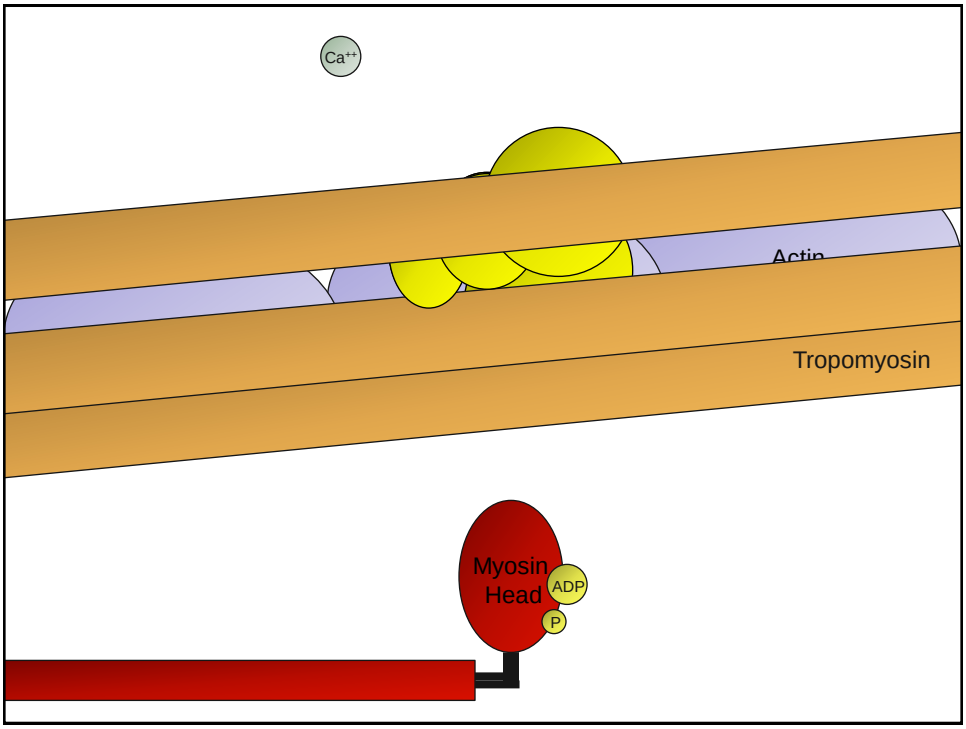


Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 6.5

Muscle Physiology

Walk-Along Theory:

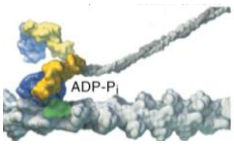
Ca^{++} enters sarcoplasm;
tropomyosin shifts



Muscle Physiology

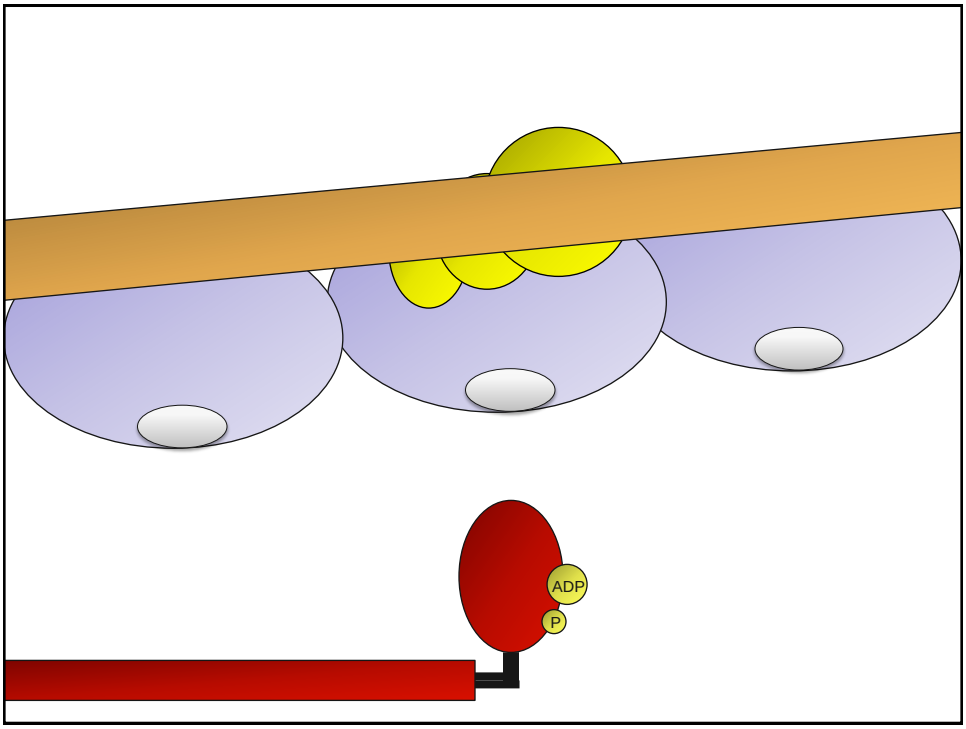
Walk-Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts



↓

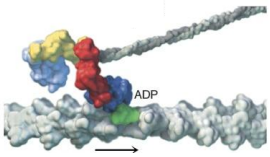
Myosin head attaches to actin (active site)



Muscle Physiology

Walk-Along Theory:

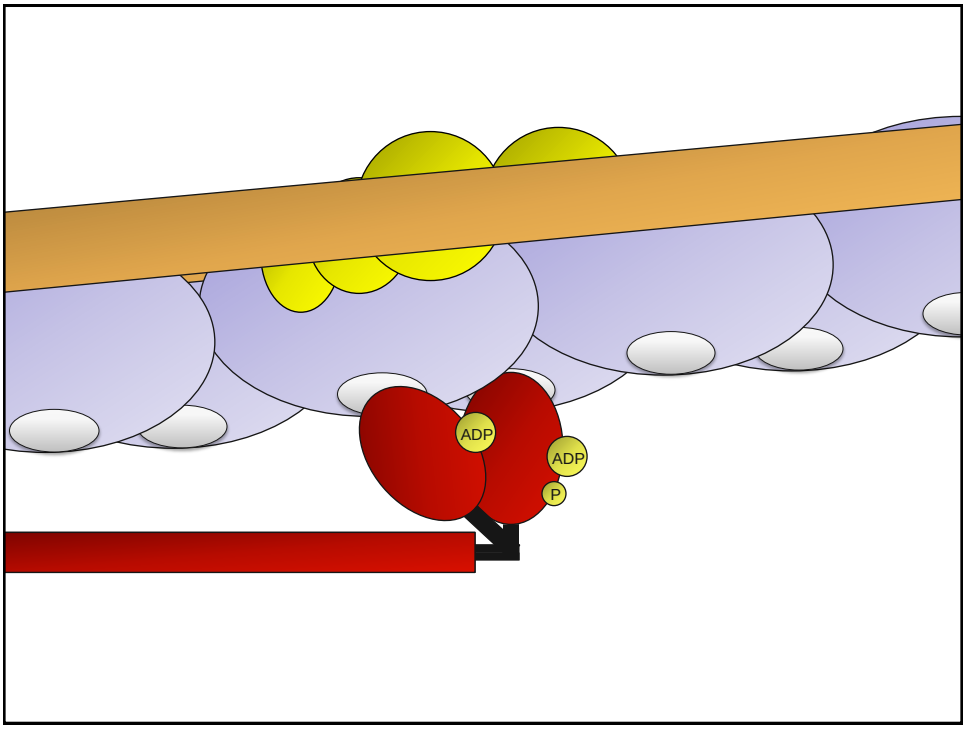
Ca^{++} enters sarcoplasm; tropomyosin shifts



Release of phosphate associated with conformational change

Myosin head attaches to actin (active site)

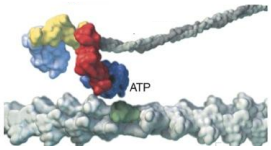
POWER STROKE



Muscle Physiology

Walk-Along Theory:

Ca^{++} enters sarcoplasm;
tropomyosin shifts

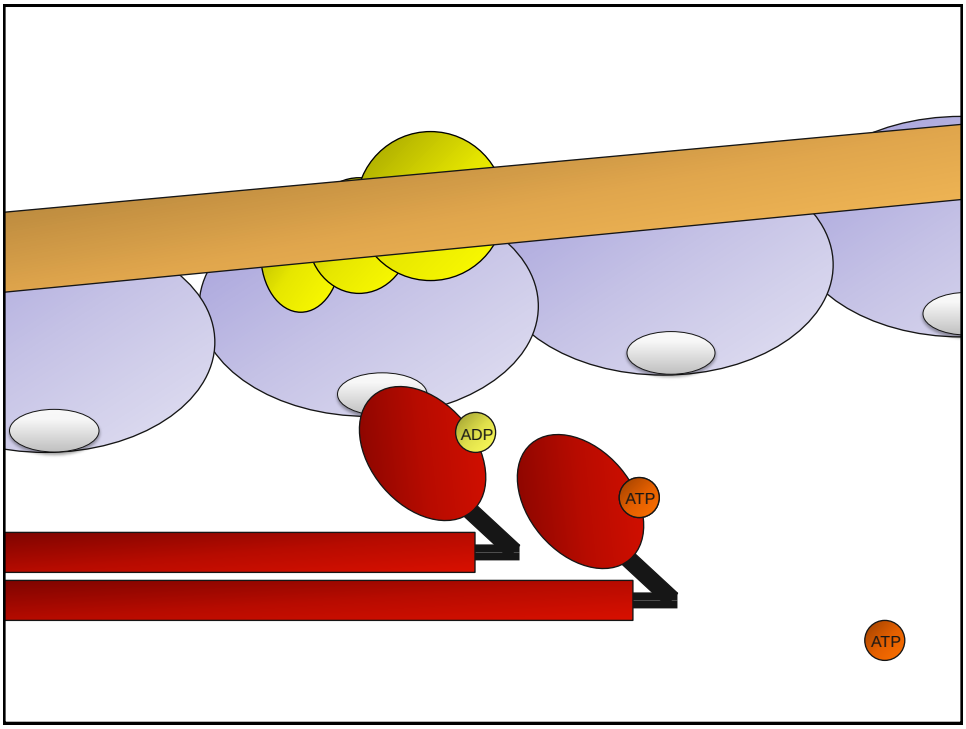


Myosin head attaches
to actin (active site)

POWER STROKE

ATP

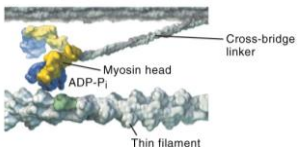
Myosin head releases
(ATP bound)



Muscle Physiology

Walk-Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts



Myosin head attaches to actin (active site)

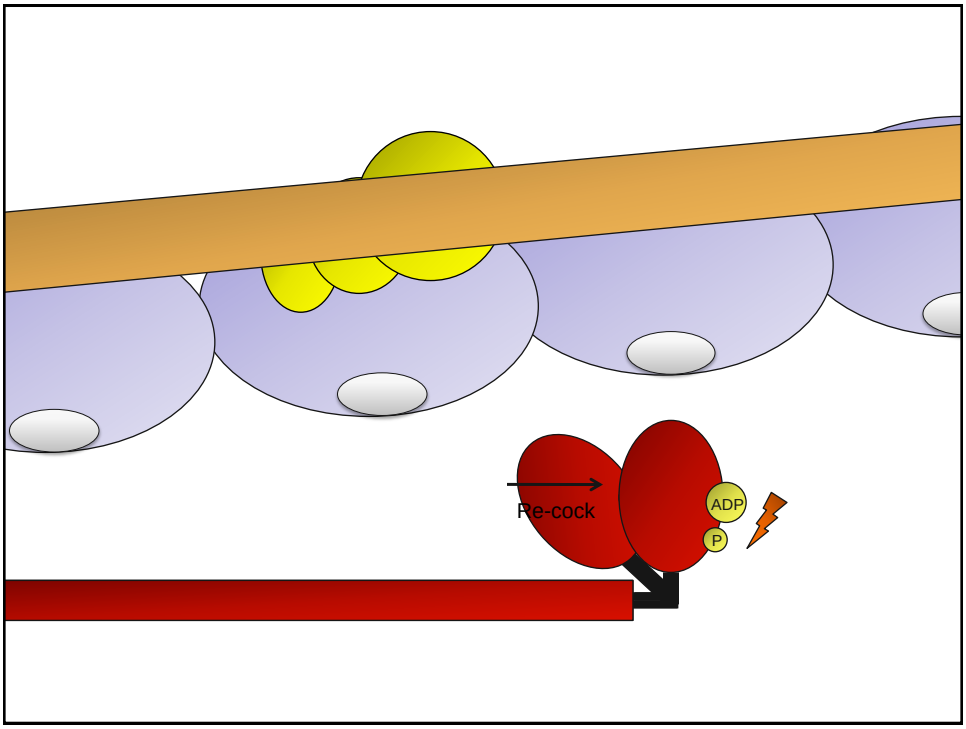
POWER STROKE

ATP

Myosin head releases (ATP bound)

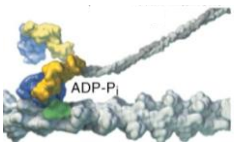
Hydrolysis ($ATP \rightarrow ADP + P_i$)

Myosin head "cocked"



Muscle Physiology

Walk-Along Theory:



Ca^{++} enters sarcoplasm; tropomyosin shifts

Myosin head attaches to actin (active site)

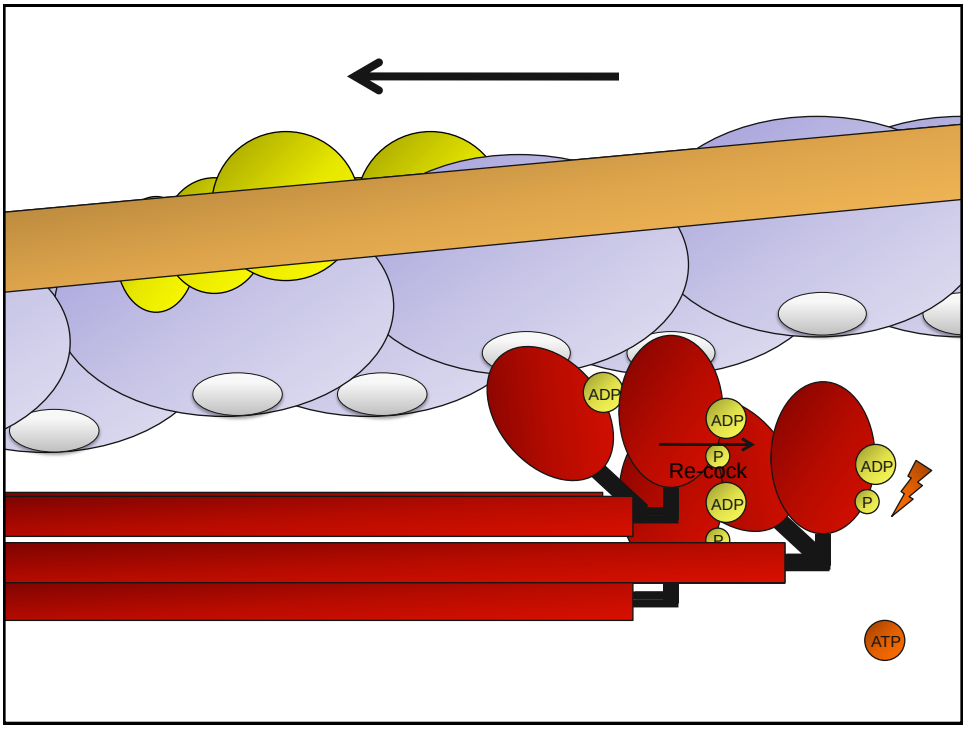
POWER STROKE

ATP

Myosin head releases (ATP bound)

Hydrolysis ($ATP \rightarrow ADP + P_i$)

Myosin head "cocked"



Muscle Physiology

Walk-Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts

Rigor Mortis:
State of contracture following death (~ 12 – 24 hours)

Myosin head attaches to actin (active site)

POWER STROKE

ATP

Myosin head releases (ATP bound)

Hydrolysis
(ATP → ADP + P_i)

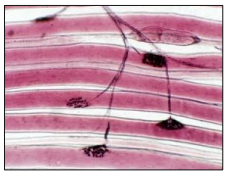
Myosin head "cocked"

Process will continue until:

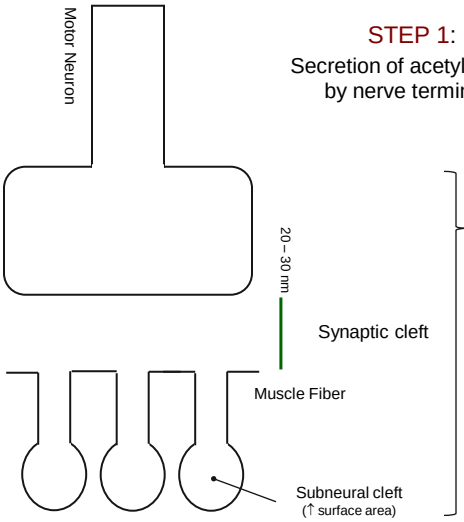
1) Full overlap of actin and myosin
2) Load on muscle becomes too great

Excitation – Contraction Coupling:

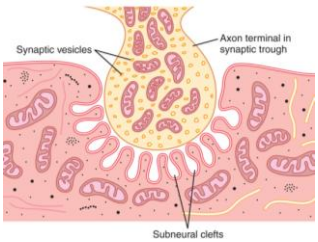
Neuromuscular Junction:



Neuron → Muscle fiber
1 connection / muscle fiber



STEP 1:
Secretion of acetylcholine
by nerve terminals



Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 7.1

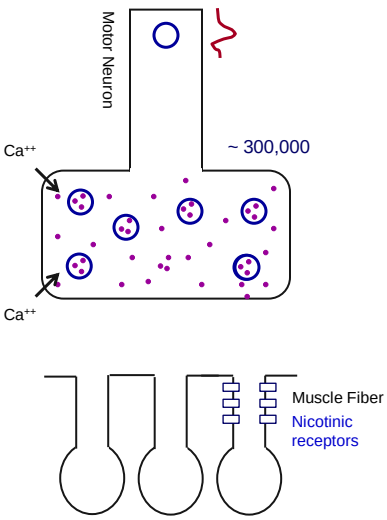
Muscle Physiology

Excitation – Contraction Coupling:

Neuromuscular Junction:

choline acetyltransferase

Choline + Acetyl CoA ⟶ Acetylcholine



A) Small vesicles formed in stoma of neuron; shuttled to axon terminal

B) Acetylcholine (ACh) synthesized in terminal; transported into vesicles (~ 10,000 Ach / vesicle)

C) Action potential travels down axon; activates voltage-gated Ca^{++} channels at terminal

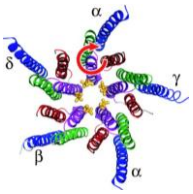
D) Ca^{++} influx triggers vesicles to fuse with membrane (~ 125 vesicles / AP); ACh released

E) ACh binds with ACh-gated ion channels at mouth of subneural clefts (muscle fiber)

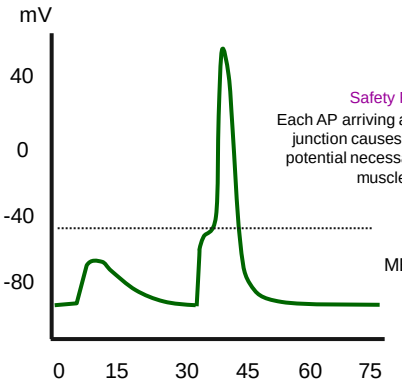
Acetylcholinesterase (AChE):
Deactivates ACh
(synaptic cleft)

Excitation – Contraction Coupling:

ACh-gated Ion Channel:



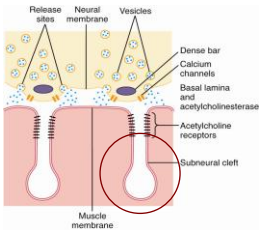
- 5 sub-units (2 *alpha*, 1 *beta*, 1 *gamma*, 1 *delta*); form tubular channel
  - Activation = 2 ACh molecules (bind to *alpha* units)
  - Primarily Na^+ channel:
    - (-) charge restricts anions
    - (-) RMP of muscle fiber favors Na^+ influx vs. K^+ efflux



Safety Factor:
Each AP arriving at neuromuscular junction causes ~ 3x end plate potential necessary to stimulate muscle fiber

$MEPP_{ACh}$ = 0.4 mV

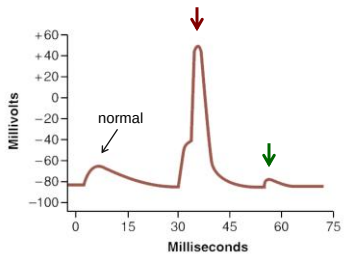
- Opening of Ach-gated ion channels produces end plate potential (EPP)
- Strong EPP triggers voltage-gated sodium channels (AP generation)



Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 7.2

Pathophysiology:

Various drugs / toxins / diseases exist that are capable of enhancing or blocking neuromuscular junction activity



Drugs / Toxins - Inhibitors:

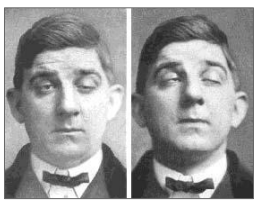
Botulism (bacterial toxin - ↓ ACh release)

Curare (plant toxin – blocks ACh receptors)

Drugs / Toxins - Stimulants:

Nicotine (plant derivative – mimics ACh)

Sarin Gas (synthetic – deactivates AChE)



Myasthenia Gravis
("grave muscle weakness")

Autoimmune; destruction of ACh-gated Na^+ receptors

Result = Paralysis (Weak EPPs)

Treatment = Anti-AChE drugs

Rare Condition:
1 / 20,000

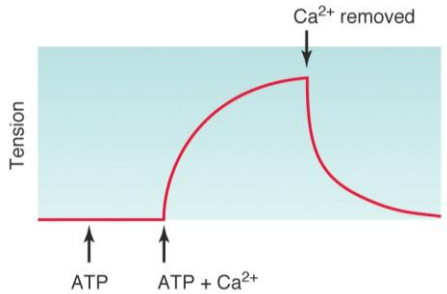
Can be fatal
(diaphragm paralysis)

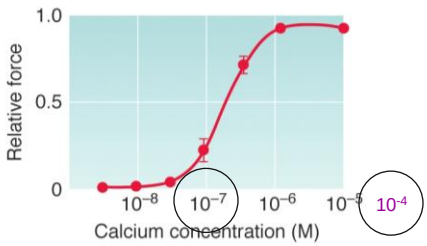
Excitation – Contraction Coupling:

Role of Calcium:

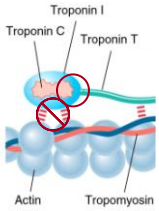
Sidney Ringer
(1836 – 1910)

Isolated Frog heart stopped beating if Ca^{++} omitted from bath





- Interacts with troponin in thin filament:



When Ca^{++} binds:

1) Troponin T / I / C bonds strengthen
2) Troponin I / actin bond weakens

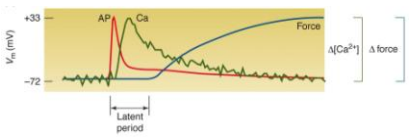
(uncovers active sites)

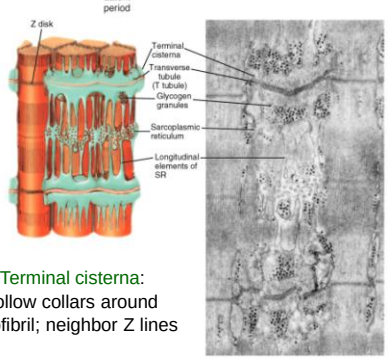
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.15

Excitation – Contraction Coupling:

AP triggers voltage-gated Ca^{++} channels in plasma membrane which flood cell with Ca^{++}…

For a muscle contraction to occur, there must be a link between electrical excitation and increased intracellular Ca^{++} levels…





Terminal cisterna:
Hollow collars around myofibril; neighbor Z lines

Problem 1:

Rate of diffusion from Ca^{++} to interior of cell (~ 25 – 50 μm) several orders of magnitude too slow to explain observed latent period

Solution:
Sarcoplasmic Reticulum

- Specialized ER; stores Ca^{++}
- SR membrane contains Ca^{++} pumps
  - Maintain < [10^{-7} M Ca^{++}]
- Calsequestrin: Binds Ca^{++} in SR
  - Reduces [gradient]

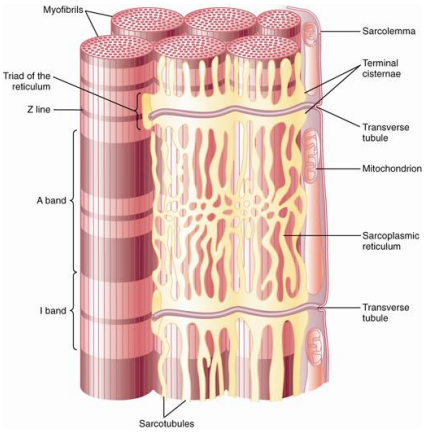
The only source of regulatory Ca^{++} in skeletal muscle is from the SR

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.12 / 10.15

Excitation – Contraction Coupling:

OK… intracellular Ca^{++} stores released by AP spreading along surface of muscle cell…

For a muscle contraction to occur, there must be a link between electrical excitation and increased intracellular Ca^{++} levels…



Problem 2:

A potential difference across the plasma membrane of a muscle fiber affects an intracellular region a fraction of a μm deep (Myofibrils 50 – 100 μm thick)

Solution:

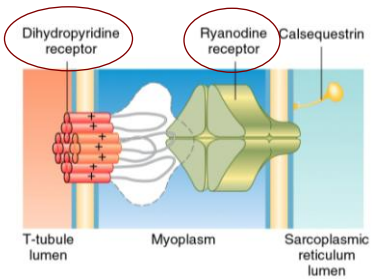
Transverse Tubules

Cytoplasmic extensions continuous with plasma membrane (~ 0.1 μm diameter); provide link between plasma membrane and myofibrils deep inside muscle fiber

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 7.5

Excitation – Contraction Coupling:

How does Ca^{++} escape the SR?

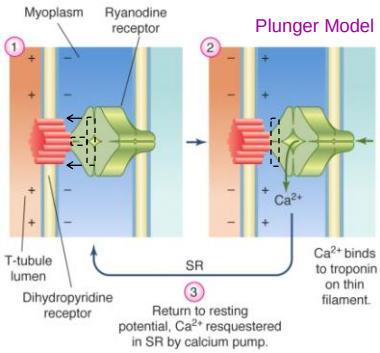


Ryanodine Receptors:

- Located in SR; Ca^{++} channels

Dihydropyridine Receptors:

- Located in T-tubule; voltage-gated Ca^{++} channels



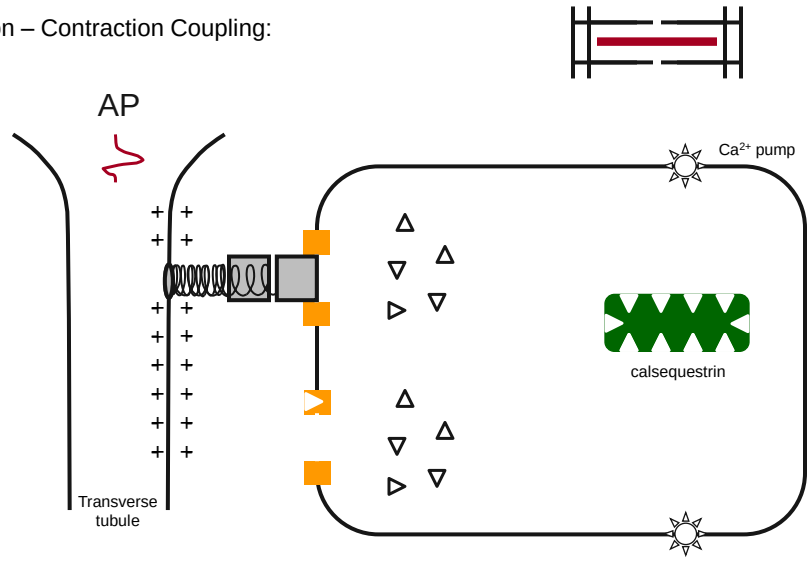
- Only ½ of the ryanodine receptors linked with dihyropyridine receptors

Calcium-induced Calcium Release
(Positive feedback mechanism)

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.25

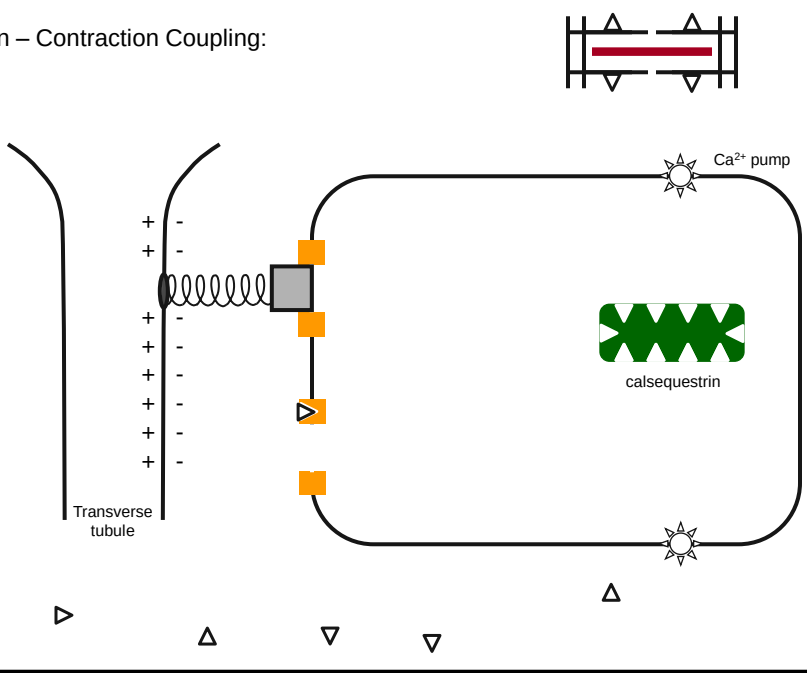
Muscle Physiology

Excitation – Contraction Coupling:



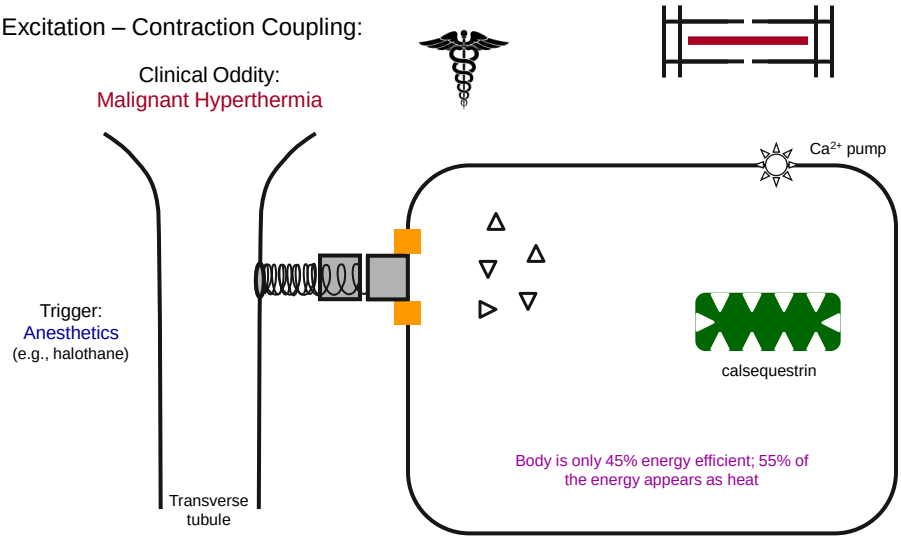
Muscle Physiology

Excitation – Contraction Coupling:



Excitation – Contraction Coupling:

Clinical Oddity:
Malignant Hyperthermia



Familial tendency… can be tested for by muscle biopsy

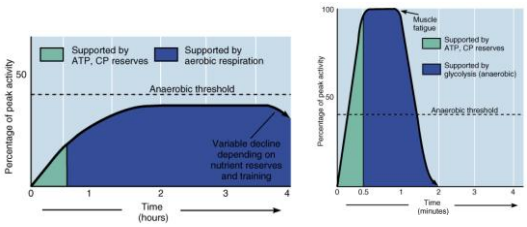
- Skeletal muscle rigidity
- Metabolic acidosis (hypermetabolism)
- Spontaneous combustion

Muscle Energetics:

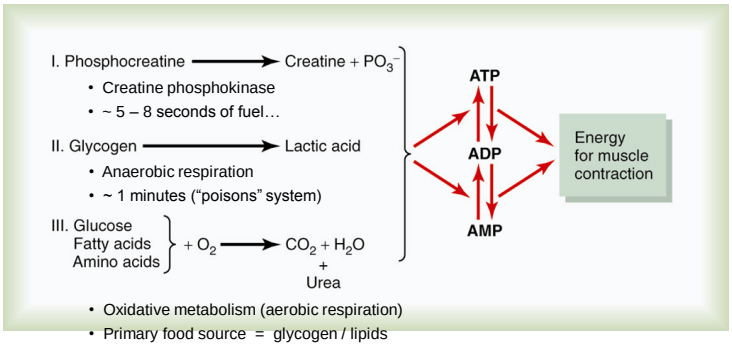
Major processes requiring energy:

1) Cross-bridging
2) Ca^{++} and Na^{+} / K^{+} pumps

ATP usage: ~ 600 trillion / second



[ATP] in stimulated muscles = [ATP] in unstimulated muscles - ???

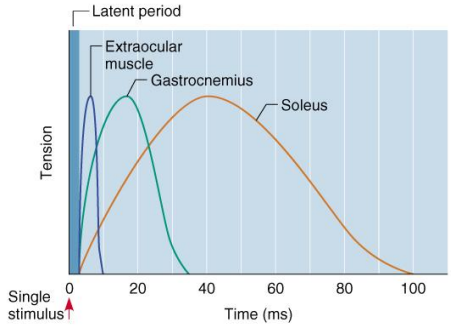


Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 84.1

Muscle Mechanics:

Muscle fibers can be divided into two primary types based on anatomical and physiological properties

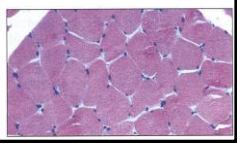
1) Cross-bridge detachment rate (fast detachment = fast contraction)
   - Chemical nature of myosin head (V_{max} of ATPase)
2) Density of Ca^{++} pumps (affects clearance of Ca^{++})
3) Mitochondria # / vasculature (affects oxidative ATP production capacities)



Marieb & Hoehn (Human Anatomy and Physiology, 9th ed.) – Figure 9.14

Fast Glycolytic Fibers:
- Rapid cross-bridge cycling
- Rapid Ca^{++} clearance
- Low endurance (anaerobic respiration)
  - (↑) glycolytic enzyme content
  - (↑) glycogen reserves

Large diameter (powerful)



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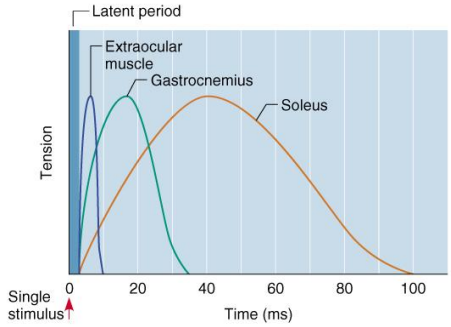
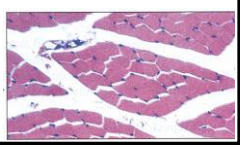


Marieb & Hoehn (Human Anatomy and Physiology, 9th ed.) – Figure 9.14

Slow Oxidative Fibers:
- Slow cross-bridge cycling
- Slow Ca^{++} clearance
- High endurance
  - (↑) mitochondria / capillaries
  - (↑) myoglobin content

Small diameter



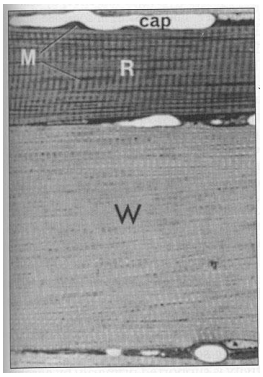
Muscle Mechanics:

- Genetically determined
- No evidence that training significantly alters proportions

Muscle fibers can be divided into two primary types based on anatomical and physiological properties

White Muscle: Muscle dominated by fast fibers (e.g. chicken breast)

Red Muscle: Muscle dominated by slow fibers (e.g. chicken leg)



	Fast Fibers	Slow Fibers
Marathon Runners	**18%**	**82%**
Swimmers	**26%**	**74%**
Avg. Human	**55%**	**45%**
Weight Lifters	**55%**	**45%**
Sprinters	**64%**	**37%**
Jumpers	**63%**	**37%**

Most human muscles contain both types of muscle fibers; proportions differ

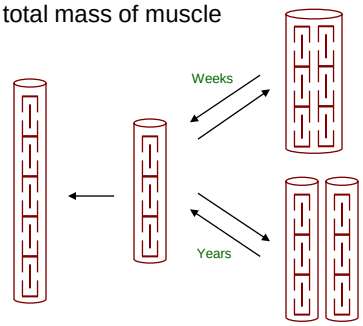
Muscle Remodeling:

Muscle Hypertrophy: Increase in total mass of muscle

a) Lengthening (normal growth)
- Sarcomeres added to existing myofilaments

b) Fiber Hypertrophy (most common)
- Increase in myofilament number
- Trigger = Near maximal force generation

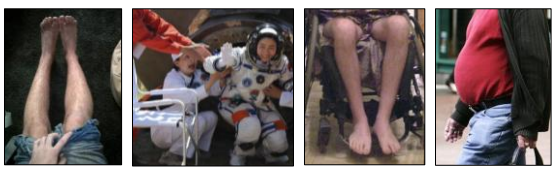
c) Hyperplasia (rare)
- Increase in muscle fiber number
- Trigger: Extreme muscle force generation

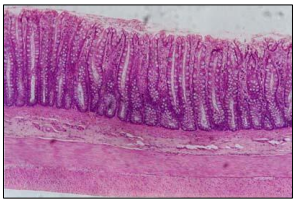


Muscle Atrophy: Decrease in total mass of muscle

Loss of muscle performance (↓ contractile proteins = ↓ force / ↓ velocity)

Causes: Plaster cast
Space flight (zero gravity)
Denervation / neuropathy
Sedentary lifestyle





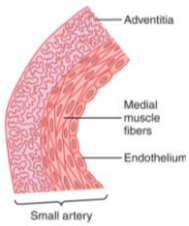
Smooth Muscle:

- Form muscular walls of hollow organs
  - Produce mobility (e.g., gastrointestinal tract)
  - Maintain tension (e.g., blood vessels)
- Mono-nucleated cells (20 – 500 μm length / 1-5 μm width)

Types of Smooth Muscle:

Multi-unit smooth muscle

- Discrete muscle fibers
- Nervous control (single innervation / fiber)
- Location: Iris, piloerector muscles



Unitary smooth muscle

- Sheets / bundles of muscle fibers
- Electronically-coupled (gap junctions)
- Multiple controls (e.g., hormonal / spontaneous)
- Location: Walls of viscera

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 8.1

Mechanical Junction

Properties of Smooth Muscle:

Smooth Muscle – How Does it Differ from Skeletal Muscle?

1) Physical Organization:

Contraction occurs via actin / myosin interaction (ATP)

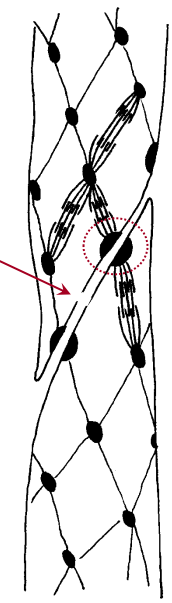
HOWEVER

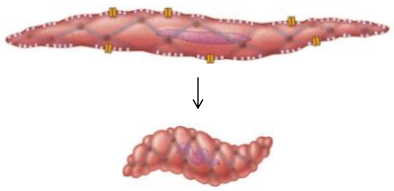
Smooth muscle appears non-striated

Dense-bodies: Analogous to Z lines

- Anchor actin filaments
- Dispersed / attached to cell membrane

Intermediate Filaments
(structural backbone)





Smooth muscle can operate over large range of lengths
(~ 75% shortening possible)

Marieb & Hoehn (Human Anatomy and Physiology, 9th ed.) – Figure 9.27

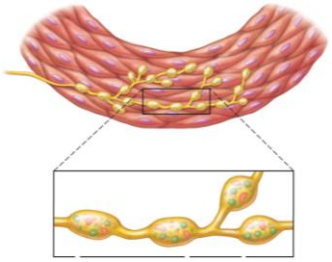
Properties of Smooth Muscle:

Smooth Muscle – How Does it Differ from Skeletal Muscle?

2) Neuromuscular Junction:

Diffuse junctions present in smooth muscle

Varicosities:
Bulbous swellings along innervating neuron



3) Mechanical Operation:

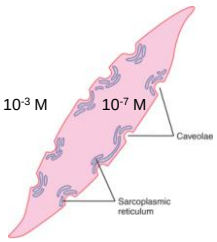
- Slow cycling of myosin cross-bridges (1/10 – 1/300 of skeletal)
  - ↓ ATPase activity (↓ = energy required: ~ 1% of skeletal muscle)
- Slow onset of contraction / relaxation (0.2 – 30 sec.)
  - Slow cross-bridge action; Slow Ca^{++} influx / efflux
- Prolonged contraction periods (hours / days / weeks)
  - "Latch" mechanism (poorly understood…)

Properties of Smooth Muscle:

Smooth Muscle – How Does it Differ from Skeletal Muscle?

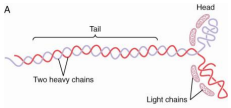
4) Ca^{++} Source:

- Primarily extracellular (poorly developed SR)
  - Latent period = 200 – 300 ms (50x longer than skeletal muscle)
  - Force of contraction dependent on [extracellular Ca^{++}]
- More extensive SR = More rapid contraction
  - Caveolae (T.T. analogs)
- Ca^{++} pumps (S.R. / plasma membrane) clear Ca^{++} (slow-acting)



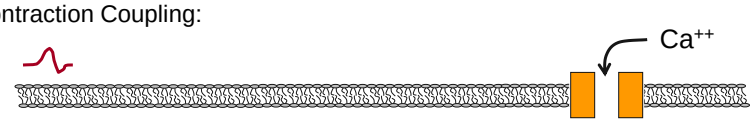
5) Activation Mechanism:

- Regulation is myosin-based (not actin-based)
  - Troponin complex absent
- Myosin must be phosphorylated before it can hydrolyze ATP (become activated)
  - Regulatory chain = Myosin light chain phosphorylated



Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 8.6

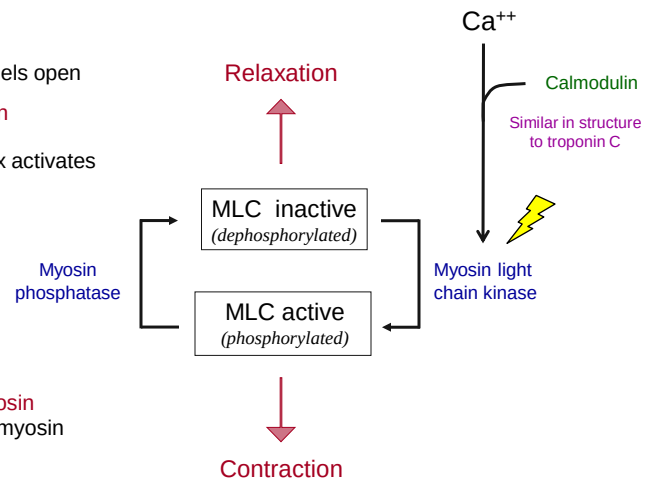
Excitation – Contraction Coupling:



Events:

1) Voltage-gated Ca^{++} channels open
2) Ca^{++} binds with calmodulin
3) Ca^{++} - calmodulin complex activates myosin light chain kinase

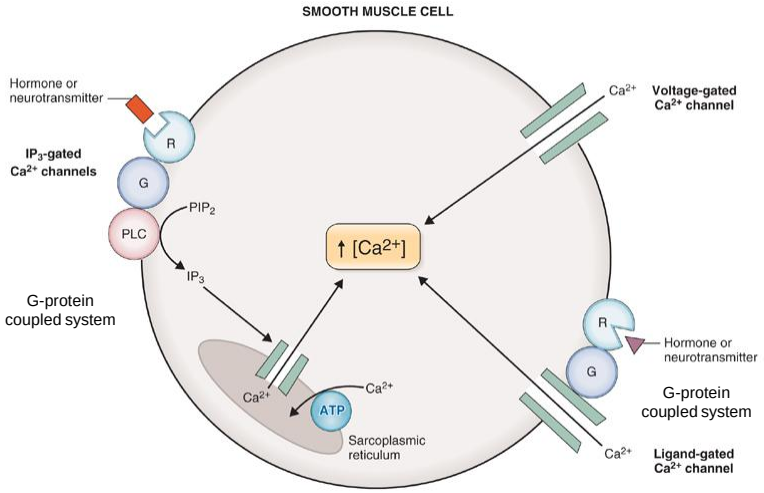
Amount of active myosin phosphatase can greatly affect the time required for relaxation



4) When Ca^{++} levels fall; myosin phosphatase deactivates myosin

Excitation – Contraction Coupling:

Additional Sources of Ca^{++}:



Costanzo (Physiology, 4th ed.) – Figure 1.29