Skeletal Muscle

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- There are voice record buttons on slides where you can listen the explanations.

- For all the muscle lectures, please refer to «Vander's Human Physiology 15th ed. Chapter 9» and «lecture slides»

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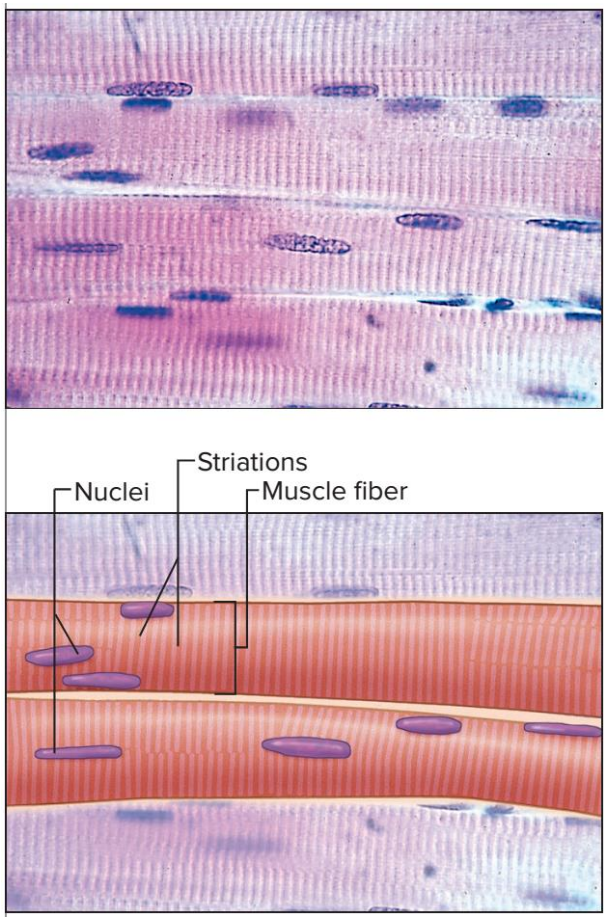
Skeletal Muscle

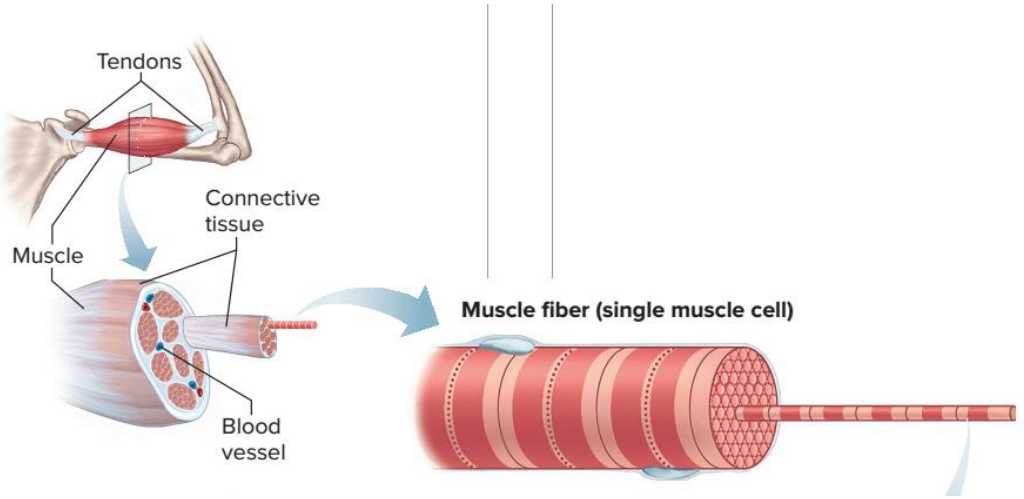
- Muscle fiber
  - Fusion of undifferentiated myoblasts into a single multinucleated cell during development
    - Each nucleus participates in regulation of gene expression and protein synthesis within its local domain
  - Differentiation completed around birth
    - Increase in size from infancy to adulthood

- Satellite cells
  - Undifferentiated stem cells
  - Between the plasma membrane and surrounding basement membrane
  - Differentiation to myoblast



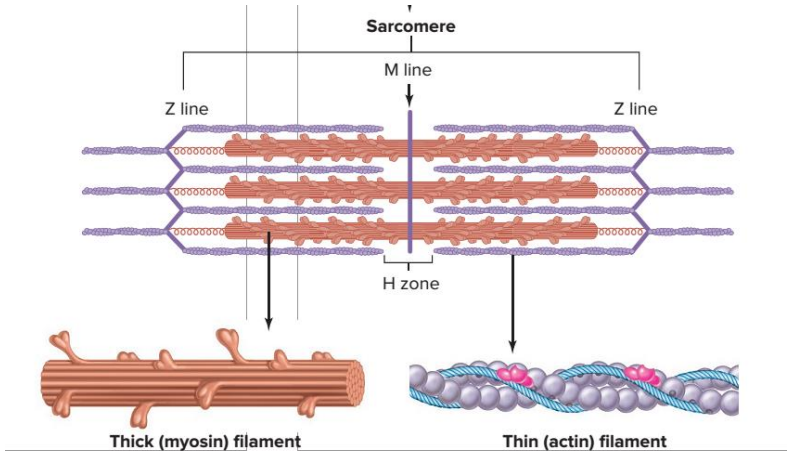
Skeletal Muscle

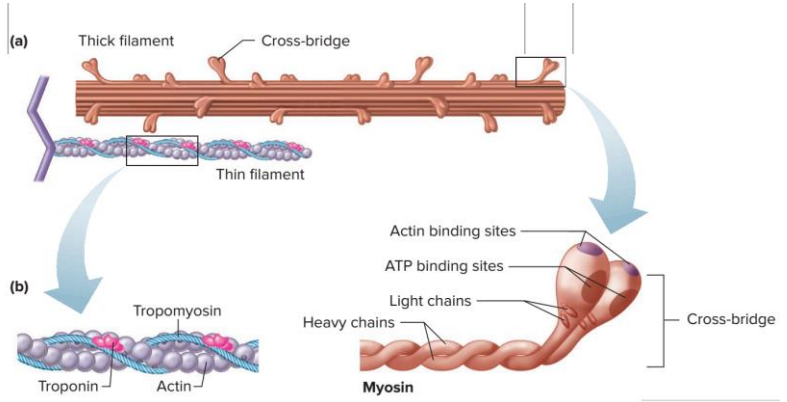
- Muscle
  - a number of skeletal muscle fibers bound together by connective tissue
- Tendon
  - Bundles of connective tissue consisting of collagen fibers



Thick filament

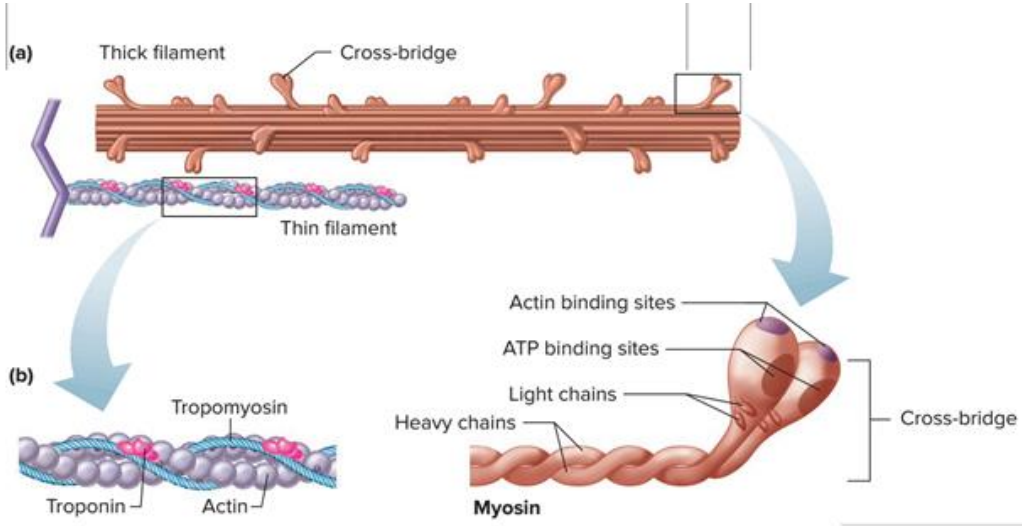
- Myosin
- Two globular heads and a long tail
- Cross-bridge: contact with thin filament and exert force during contraction
- Actin binding site: attachment to actin
- ATP binding site : myosin-ATPase





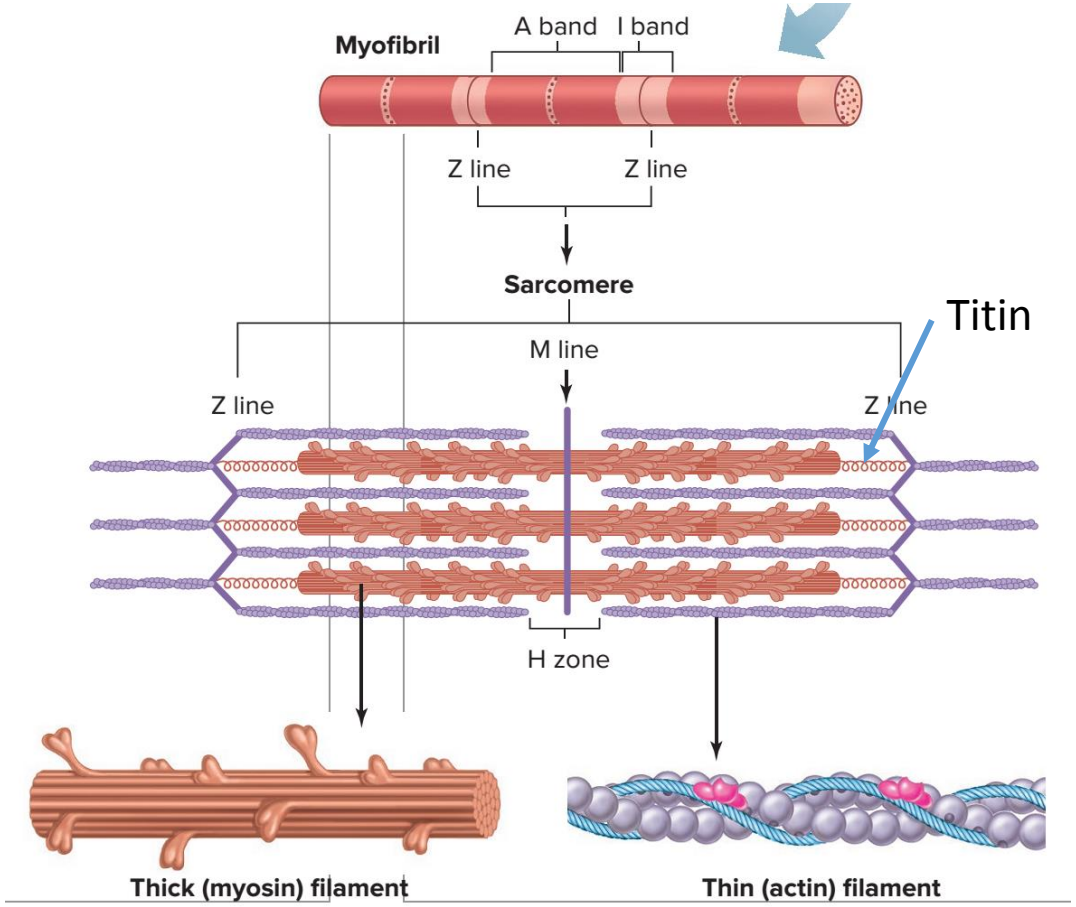
Thin filaments

- Actin, nebulin, troponin, tropomyosin
  - Actin: two interwined, helical chains. Core of the thin filament. Binding site for myosin
  - Nebulin: thin filament assembly
  - Troponin & Tropomyosin: regulation of contraction



Sarcomere

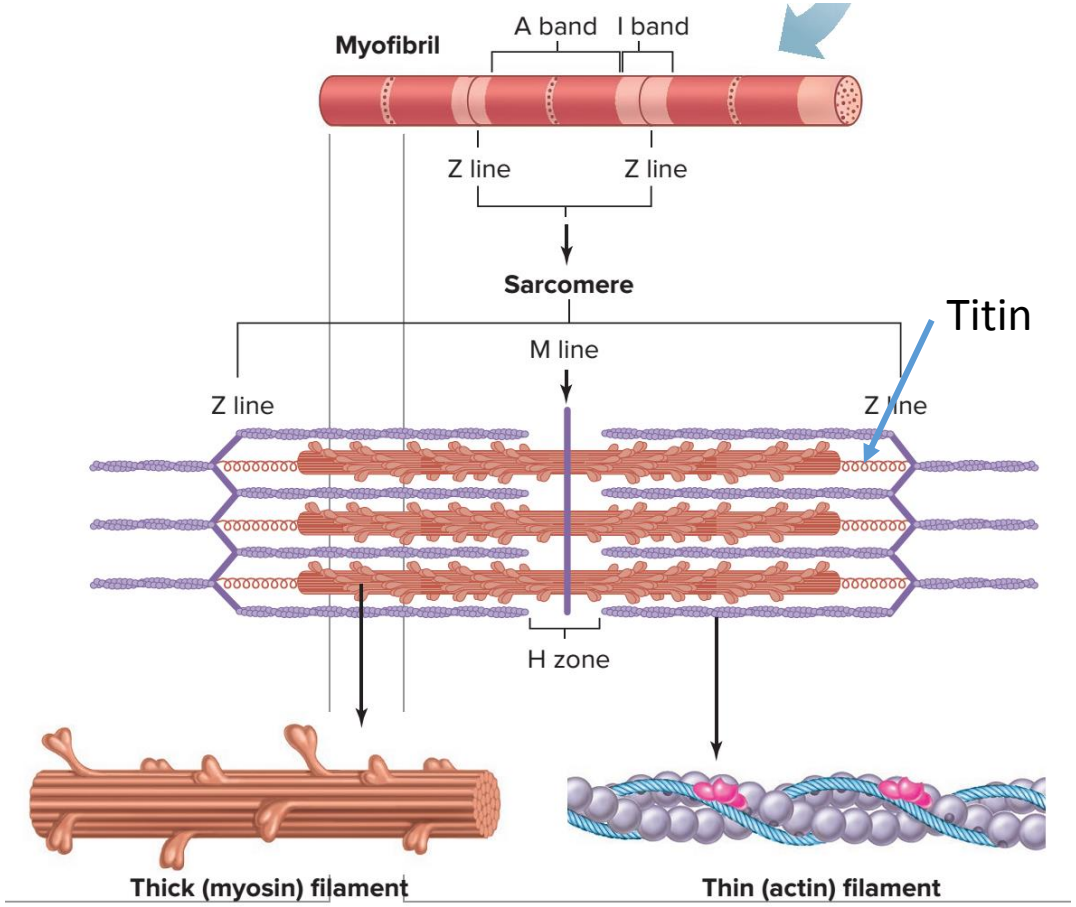
- One unit of repeating pattern of thick and thin filaments
  - *A band*: thick filaments
  - *Z line*: network of interconnecting proteins
  - *I band*: thin filaments only
  - *H zone*: space between opposing ends of the thin filaments
  - *M line*: proteins that link the central region of thick filaments



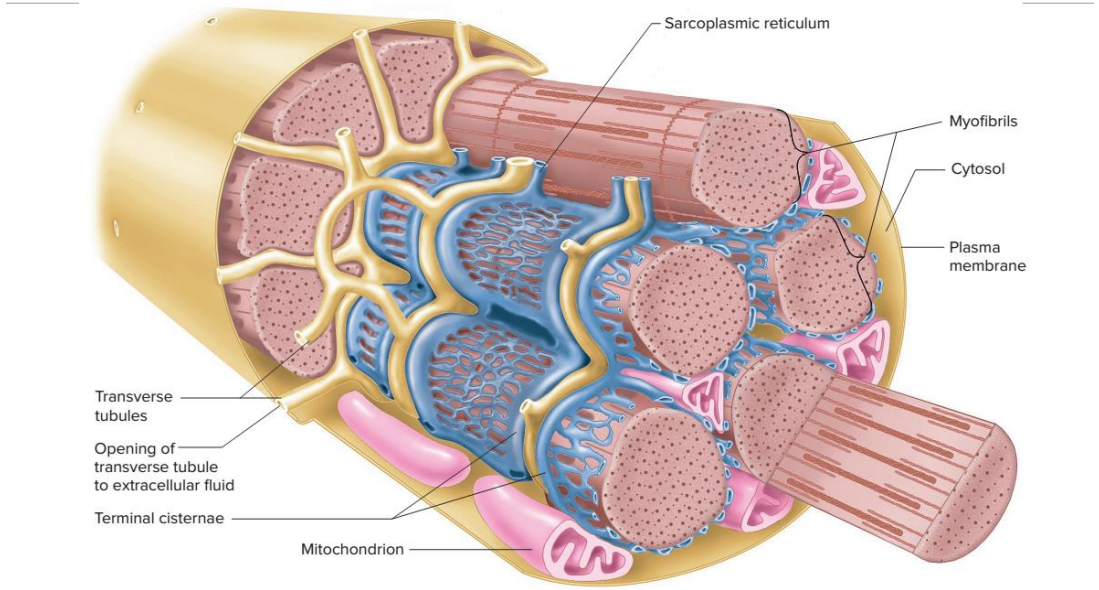
Sarcomere

- Titin:
  - Elastic protein
  - Extend from Z line to the M line and are linked to both the M-line proteins and the thick filaments.

- M-Line and titin
  - Maintain alignment of thick filaments

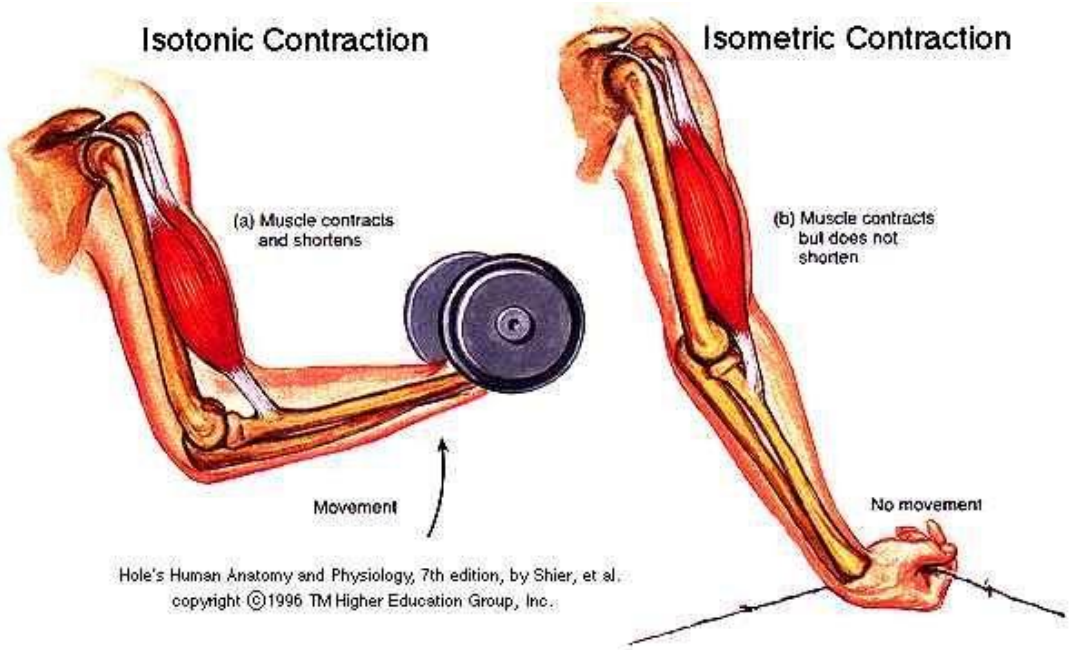


- Sarcoplasmic retikulum
- Terminal cisternae (lateral sacs)
  - Calsequestrin :Ca^{2+} binding element
  - Storage of large quantitiy of Ca^{2+}
- Transverse tubules (T-tubules)
  - Associated with terminal cisternae
  - Continous with the plasma membrane
  - Action potential propogation to interior of the muscle
  - Continous with extracellular fluid



Contraction

- Activation of the force-generating sites within muscle fiber (the cross-bridges)



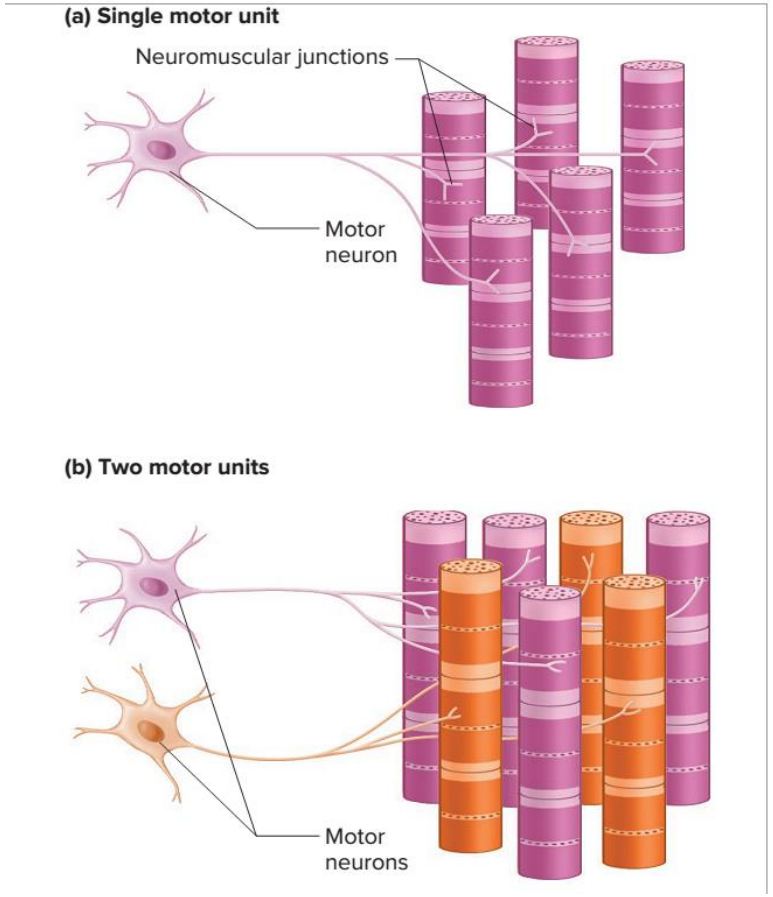
Neuromuscular junction

- Alpha motor neurons
  - Cell bodies in brainstem and spinal cord
  - Myelinated, largest diameter axons
  - High velocity action potential propagation (minimal delay)

Fiber Type	Function	Diameter (microns)	Mystification	Conduction Velocity (m/s)
Type A				
Alpha (α)	Proprioception, motor	12-20	Heavy	70-120
Beta (β)	Touch, pressure	5-12	Heavy	30-70
Gamma (γ)	Muscle spindles	3-6	Heavy	15-30
Delta (δ)	Pain, temperature	2-5	Heavy	12-30
Type B	Preganglionic autonomic	<3	Light	3-15
Type C				
Dorsal root	Pain	0.4-12	None	0.5-2.3
Sympathetic	Postganglionic	0.3-1.3	None	0.7-2.3

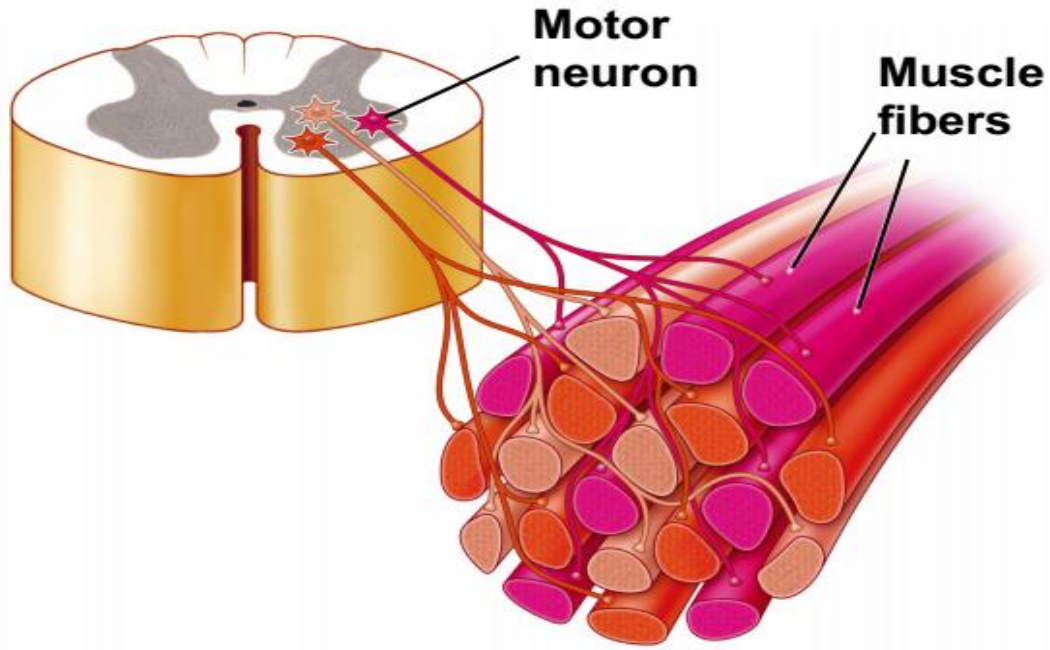
Motor Unit

- A motor neuron and innervated muscle fibers
  - Located in one muscle
  - Distributed throughout the muscle
  - All fibers stimulated at once
- The number of fibers innervated by a single motor neuron varies (from a few to thousand)
  - The fewer the number of fibers per neuron
    - the finer the movement



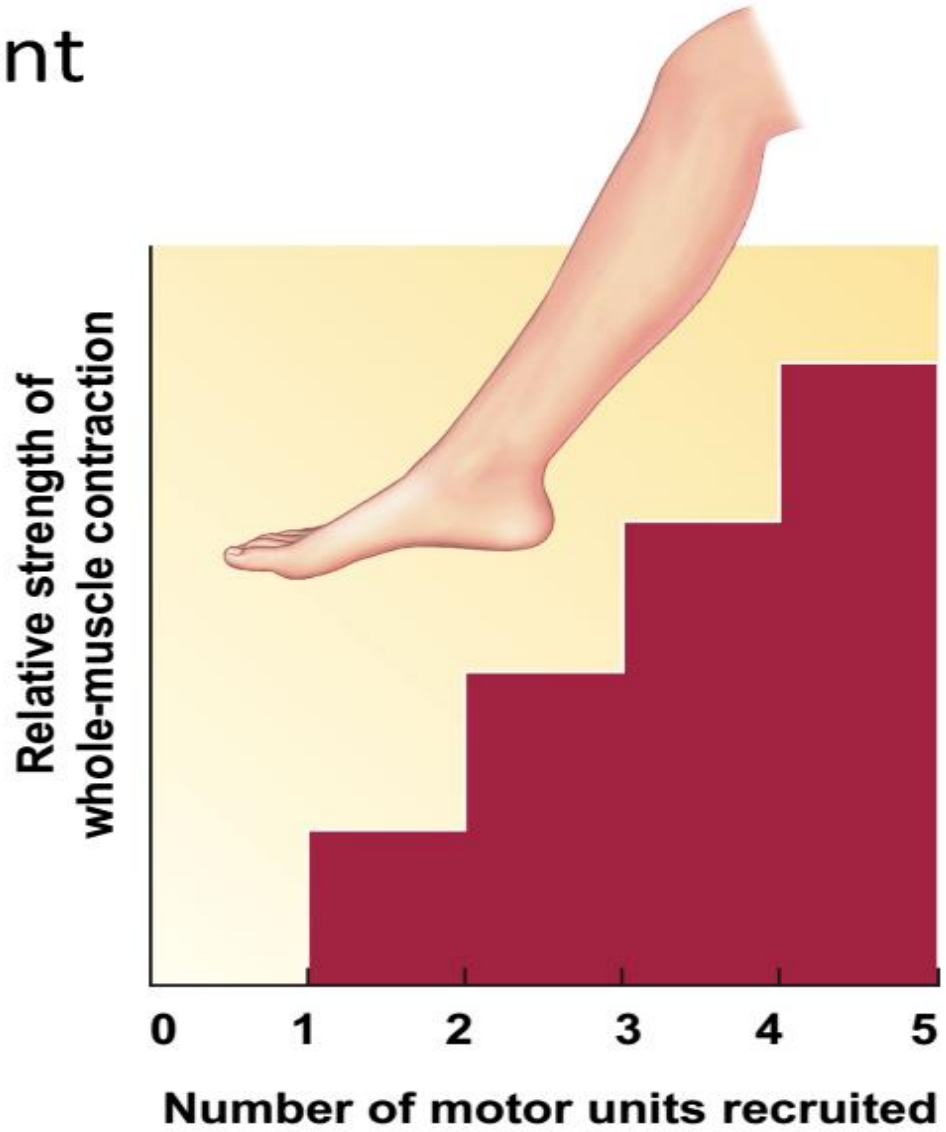
Motor Units

- All muscle fibers within a whole muscle are not active during every contraction
- A small subset of muscle fibers will be activated based on need
- The smallest subset is a **motor unit**: one motor neuron and all the muscle fibers it innervates

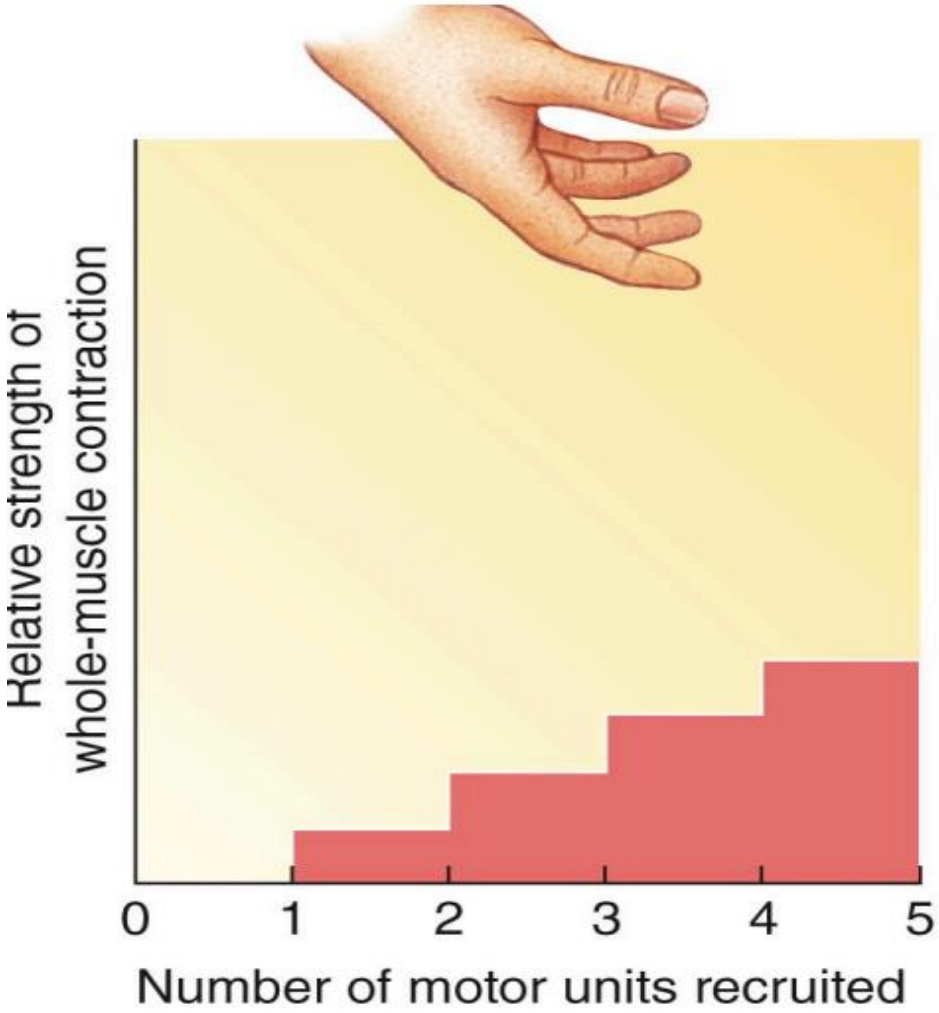


Motor Unit Recruitment

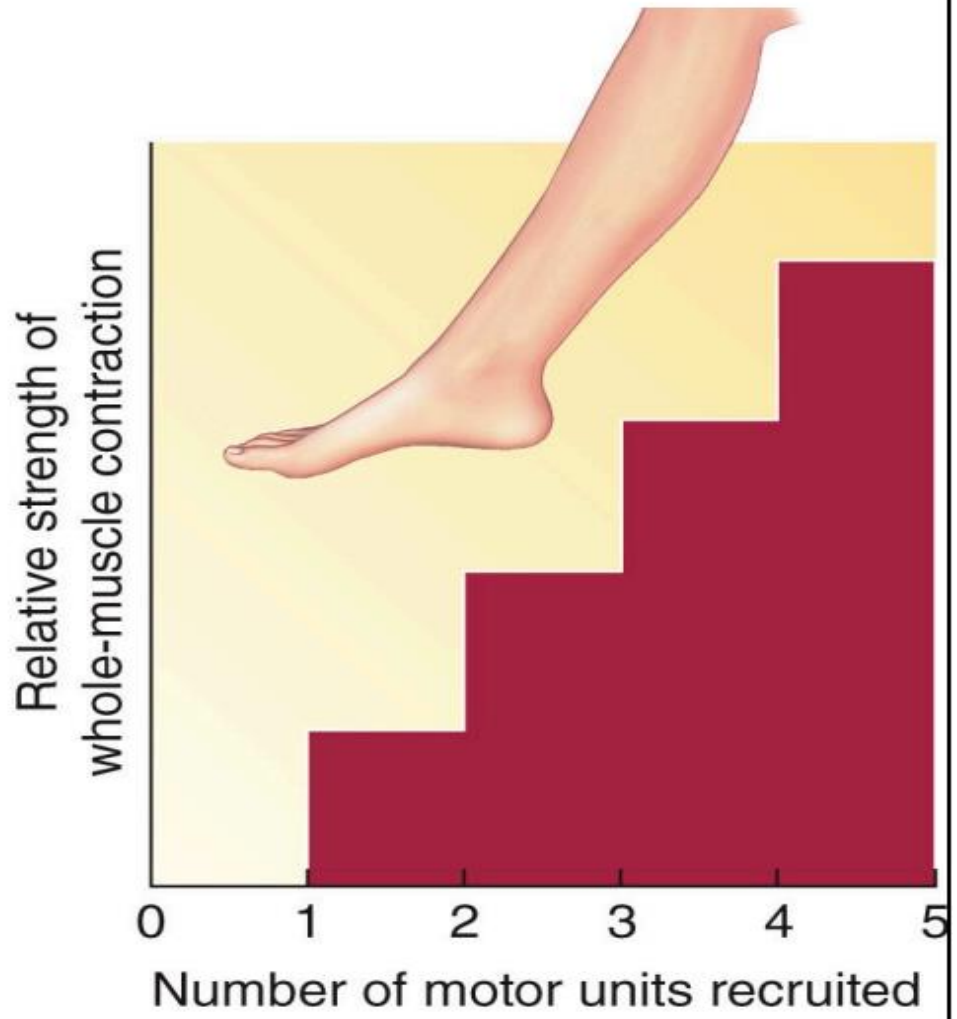
- **Baseline muscle tone**: some muscle fibers are always active to maintain muscles, even when no movement is taking place
- **Motor Unit Recruitment**: activation of more motor units to increase tension in the muscle as the load increases, i.e. more force needed



Muscle Size: Bigger Muscles have more fibers per motor neuron



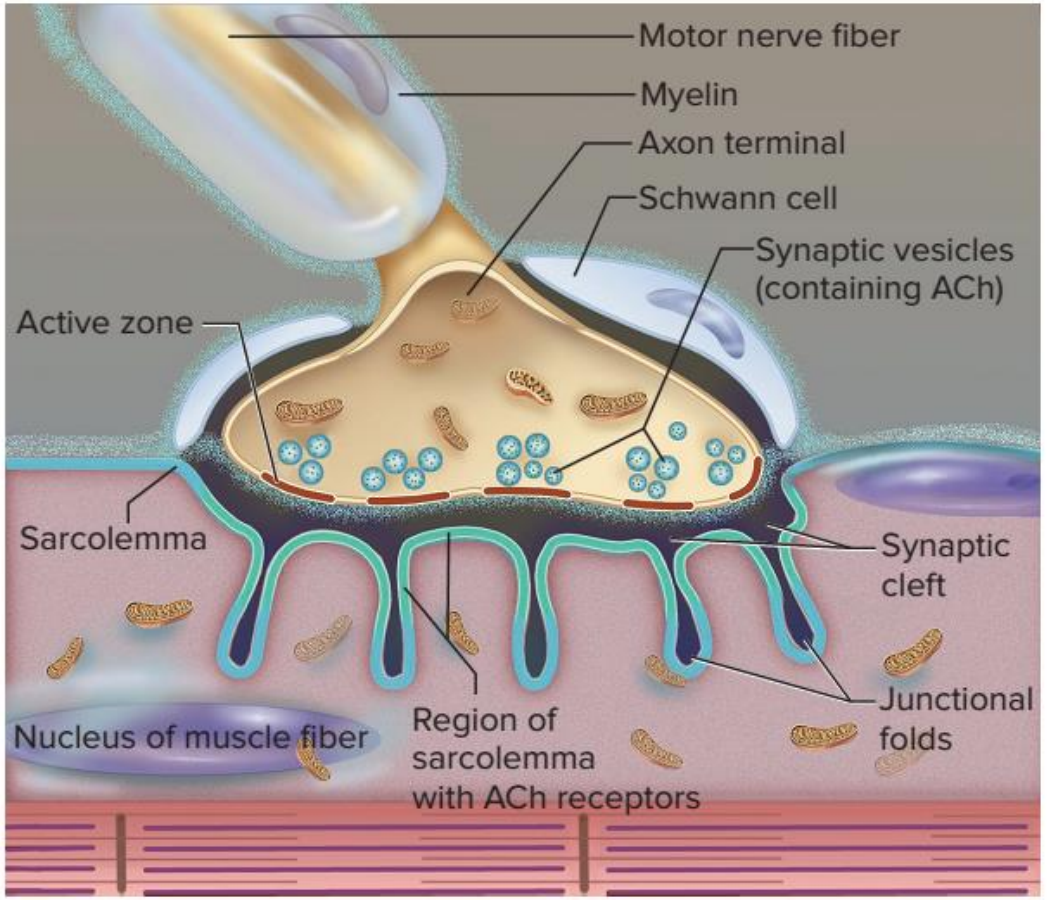
(a) Recruitment of small motor units



(b) Recruitment of large motor units

Neuromuscular junction

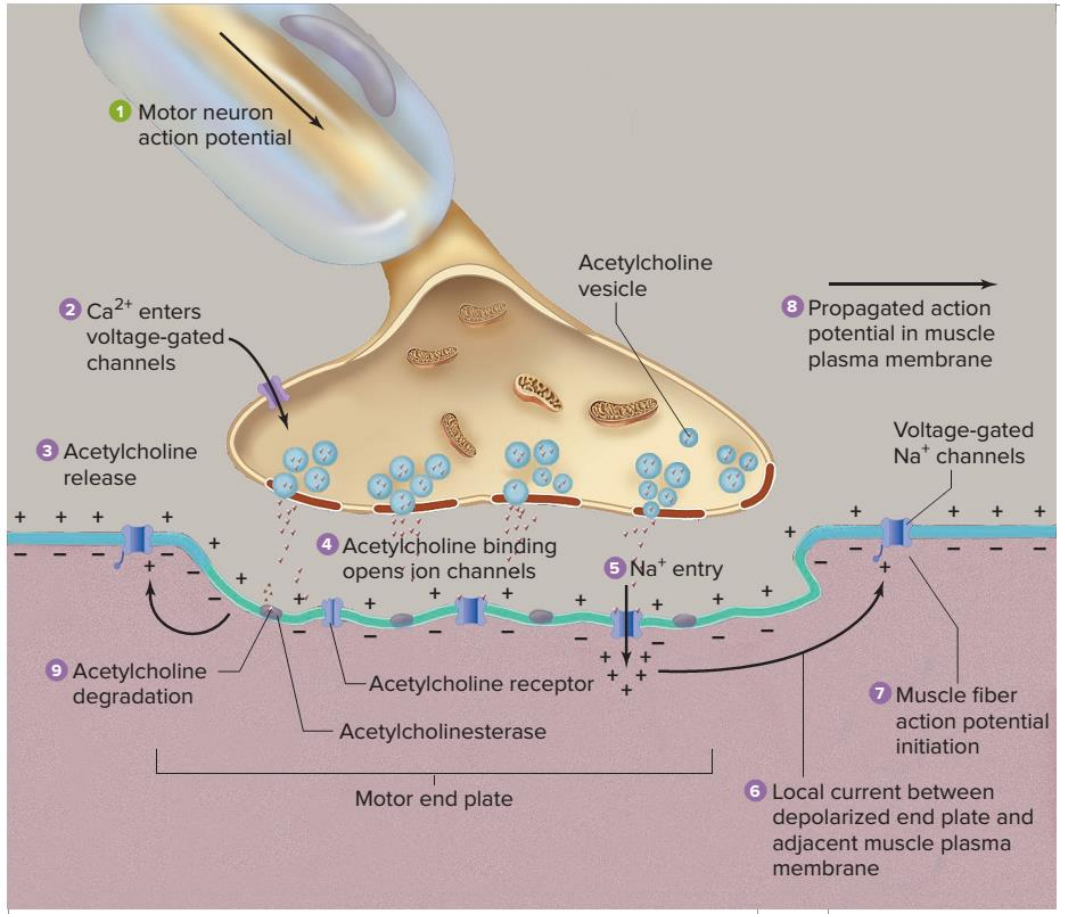
- Acetylcholine (ACh)
- Motor end plate



Neuromuscular junction

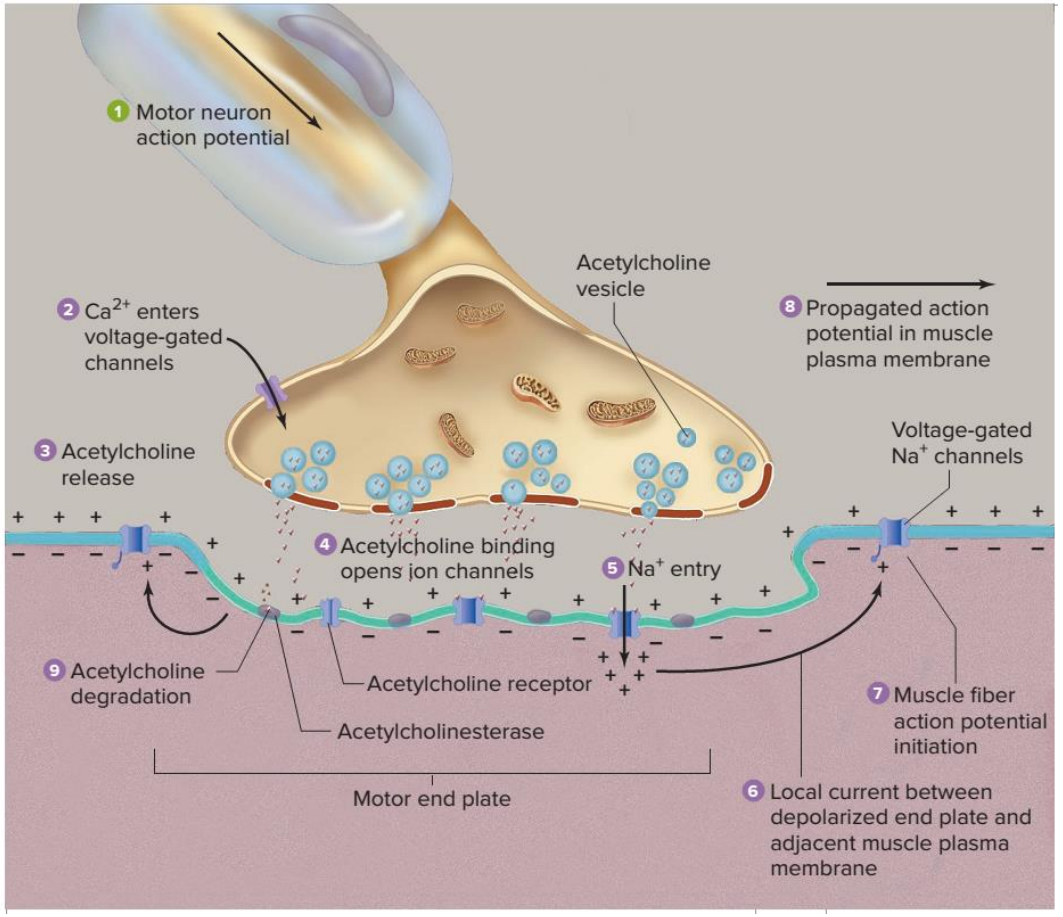
- Action potential
- Ca^{2+} entry
- Acetylcholine release

- Nicotinic Ach receptors open (Na and K Channel)
- Na^{+} entry
- *End-plate potential (EPP)*



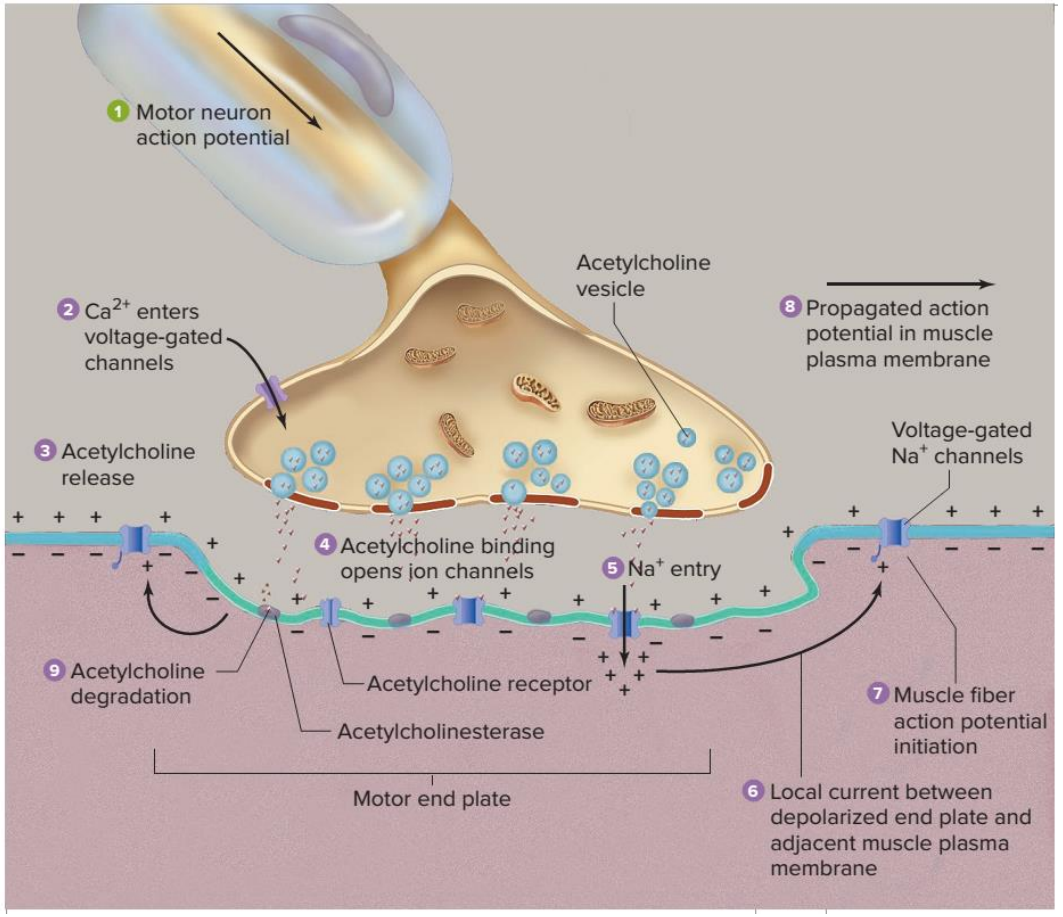
End plate potential

- Transmission is fast and reliable
  - An action potential in the motor axon always causes an action potential in the muscle cell it innervates
    - One of the largest synapses in the body
    - The postsynaptic membrane of the folds is packed with neurotransmitter receptor
  - Single action potential in the presynaptic terminal triggers the exocytosis of about 200 synaptic vesicles, causing an EPSP of 40 mV or more



End plate potential

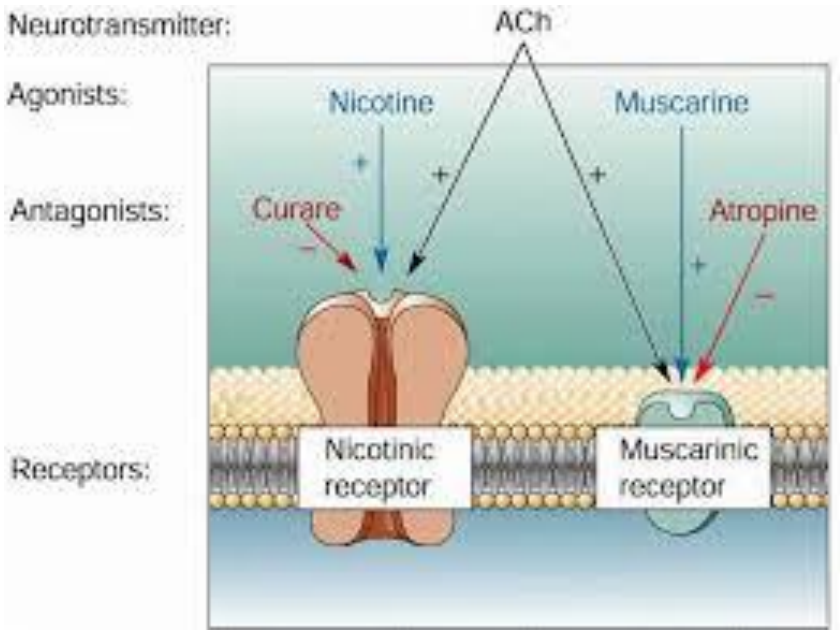
- Local currents
  - Similar to unmiyelinated axons
  - Propogation in both directions
- Muscle fiber action potential initiation
- Voltage gated Na^+ channels open



Curare

- Nondepolarizing and competitive inhibitor of ACh at neuromuscular junctions
- Resistant to destruction by acetylcholinesterase

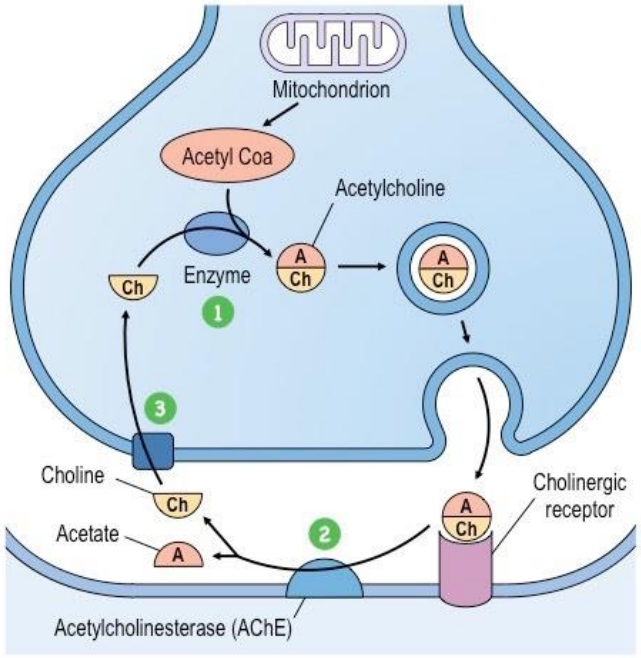
- Paralysis of voluntary muscle groups
- Death by asphyxiation



Termination of signal

- ACh $\xrightarrow{\text{Acetylcholineesterase}}$ Acetate + Choline

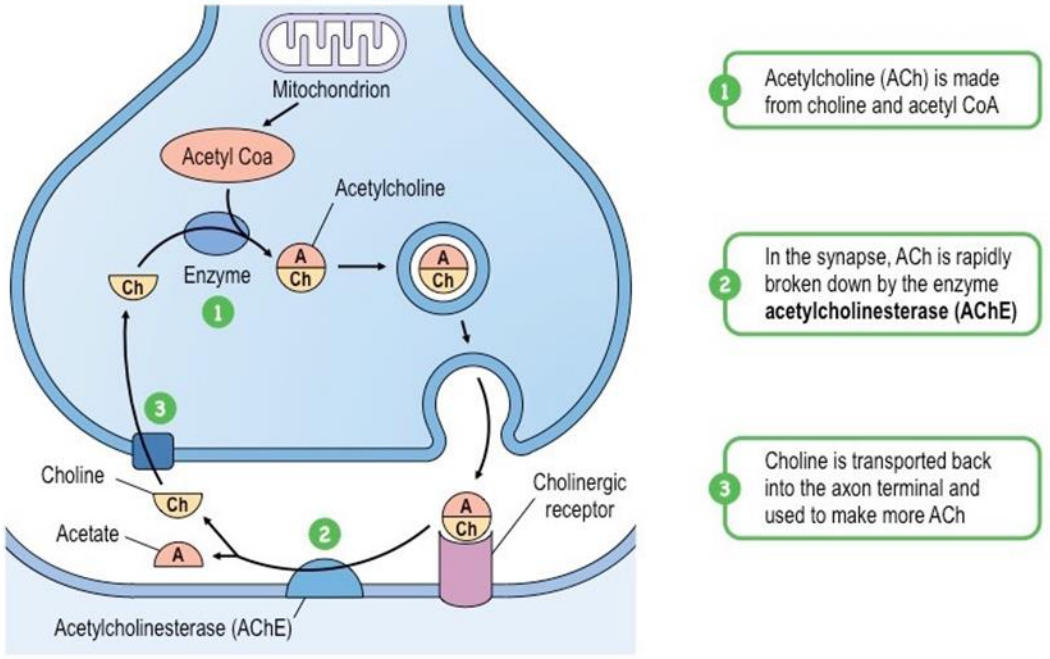
- Less ACh
- Less binding to receptor
- End of EPP



1. Acetylcholine (ACh) is made from choline and acetyl CoA
2. In the synapse, ACh is rapidly broken down by the enzyme **acetylcholinesterase (AChE)**
3. Choline is transported back into the axon terminal and used to make more ACh

Organophosphates

- Inhibits AChE
- Channels stay open
  - maintained depolarization of the end plate
- Can not produce action potentials
  - the voltage-gated Na+ channels in the membrane become inactivated, which requires repolarization to reverse
- Desensitization of ACh receptors
  - Current stops entering
  - Na+ channels rectivated
  - Loss of receptor responsiveness to ACh causes skeletal muscle paralysis and death from asphyxiation

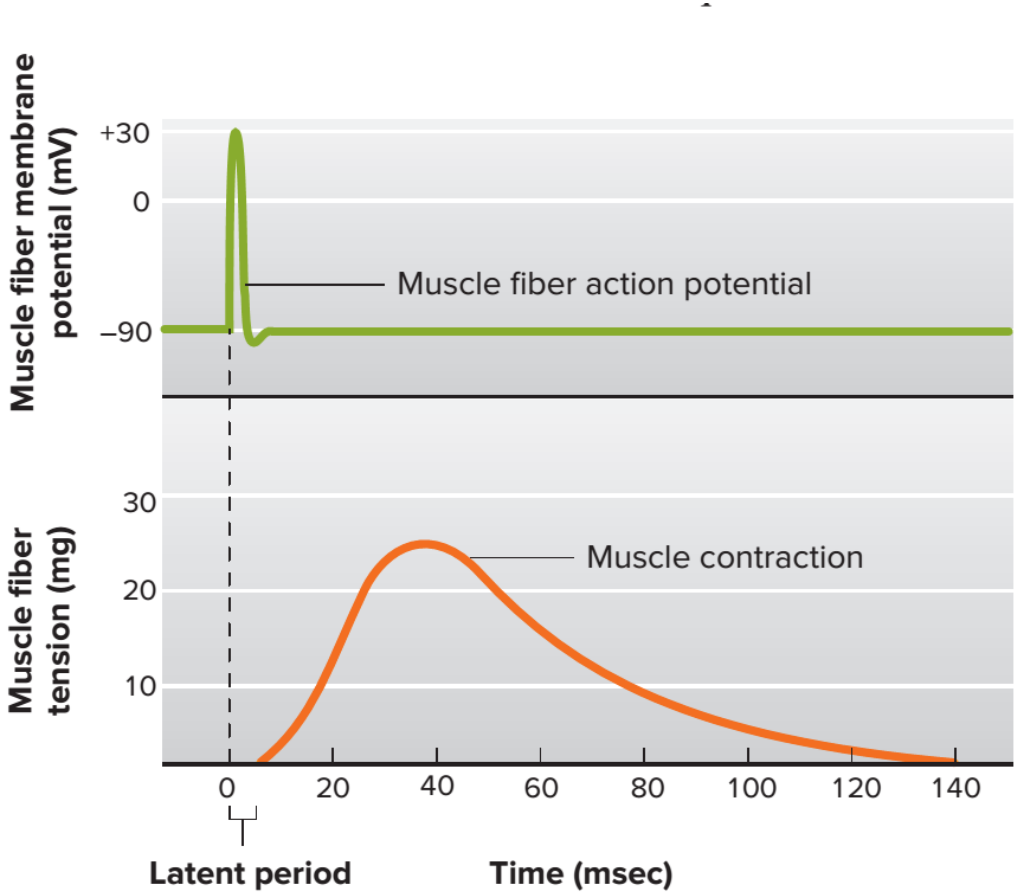


Excitation–Contraction Coupling

- Sequence of events by which an action potential in the plasma membrane activates the force-generating mechanisms

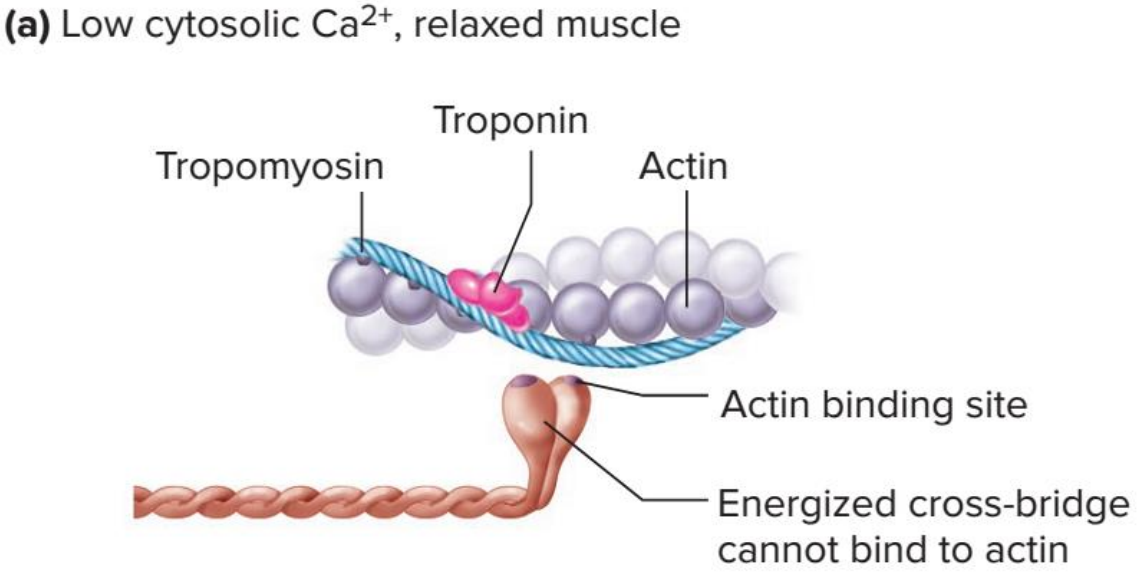
- Action potential – 1-2 msec
- Mechanical activity ≥ 100 msec

- Action potential → internal Ca^{2+} concentration



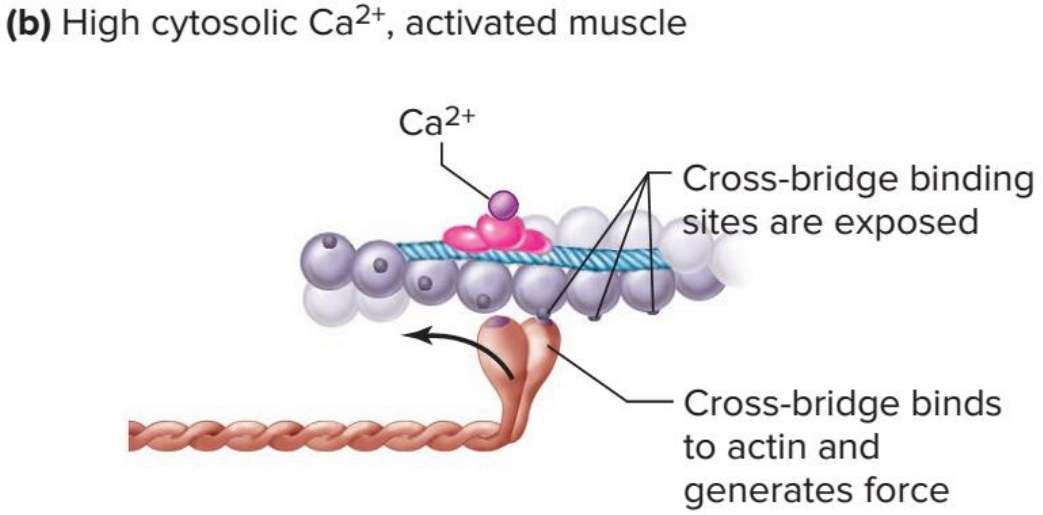
Ca^{2+} in Cross-Bridge Formation

- Tropomyosin
  - Equal to the length of seven actin monomers
  - Partially cover the myosin binding site on each actin monomer
- Troponin
  - Holds tropomyosin in blocking position
  - I: inhibitory, T: tropomyosin-binding, C: Ca^{2+} binding



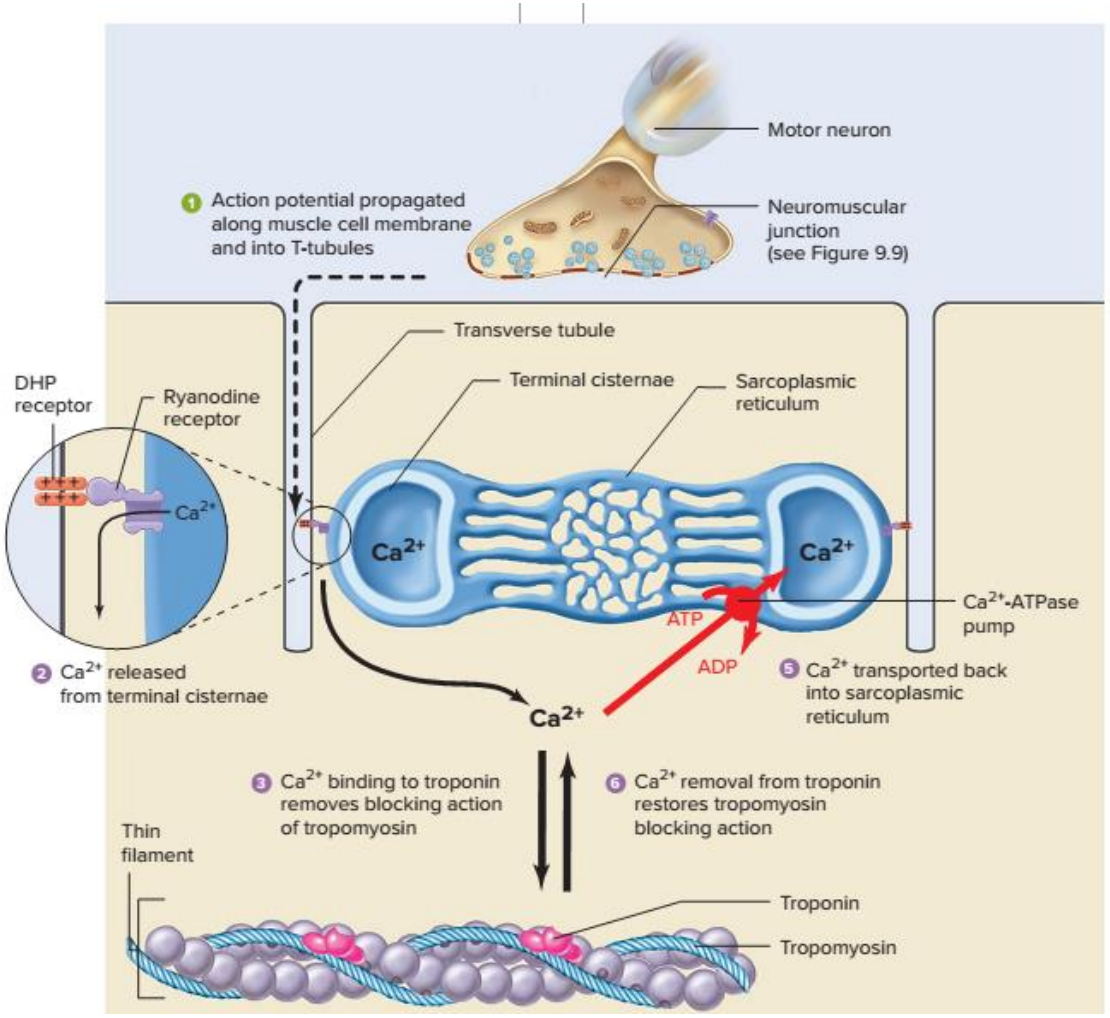
Ca^{2+} in Cross-Bridge Formation

- Ca^{2+} binding to troponin
- Change in tertiary structure
- Moving of tropomyosin from cross-bridge binding site
- Initiation of contraction



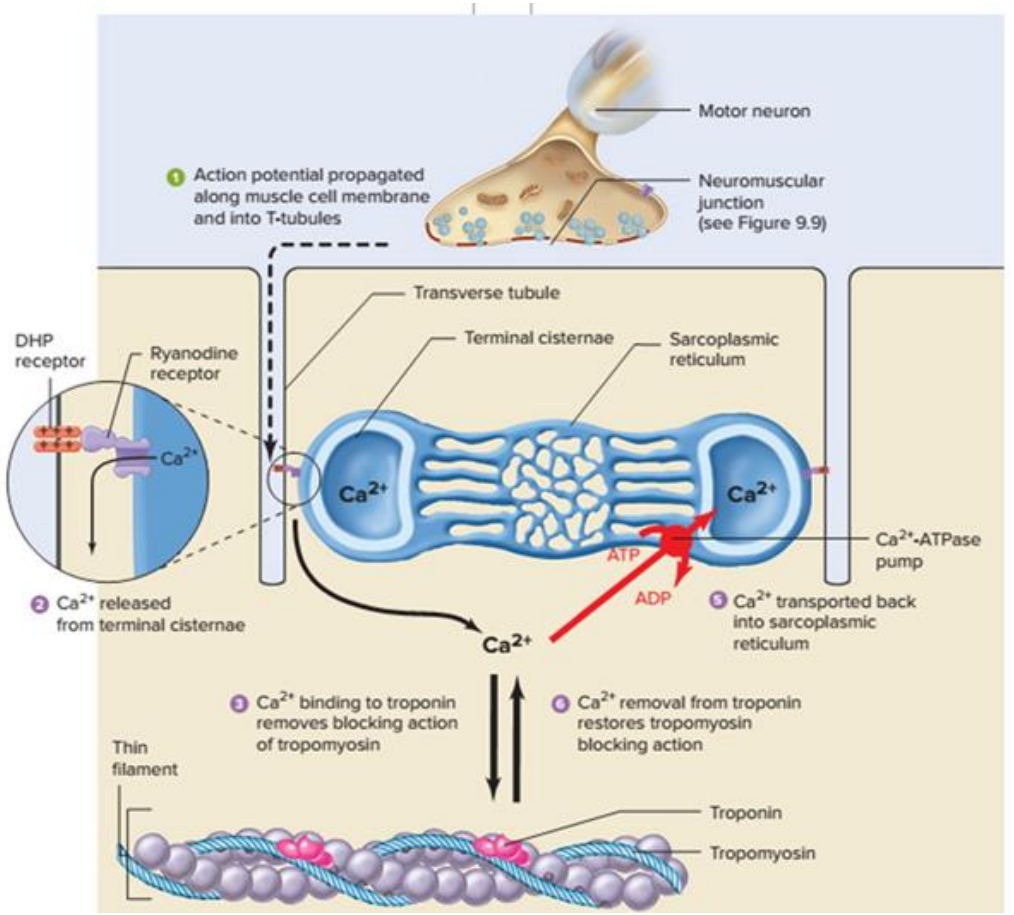
Mechanism of Cytosolic Increase in Ca^{2+}

- Ca^{2+} concentration in a resting muscle fiber cytosol 10^{-7} mol/L
- Source of internal Ca2+ is sarcoplasmic reticulum
- Junctional feet
  - Dihydropyridine (DHP) receptor
    - Voltage sensor
  - Ryanodine receptor
    - Ca^{2+} channel
- Ca^{2+} release to cytoplasm from terminal cisternae
  - Single AP is enough for all troponin-binding sites



Contraction Termination

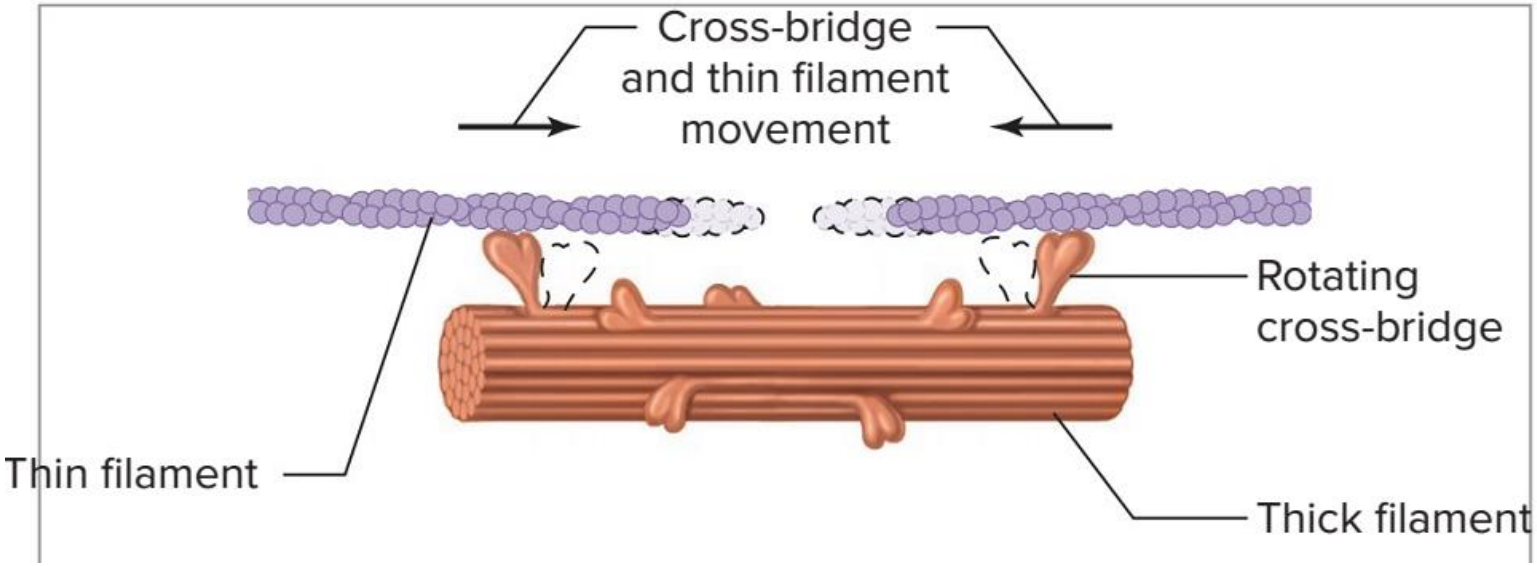
- Removal of Ca^{2+} cytosol back to sarcoplasmic reticulum
  - primary active-transport proteins—Ca^{2+}ATPases
  - Active transport takes longer time
    - Cytosolic concentrations remains elevated for a longer time



Sliding-Filament Mechanism

- During shortening of the sarcomeres, there is no change in the lengths of either the thick or thin filaments

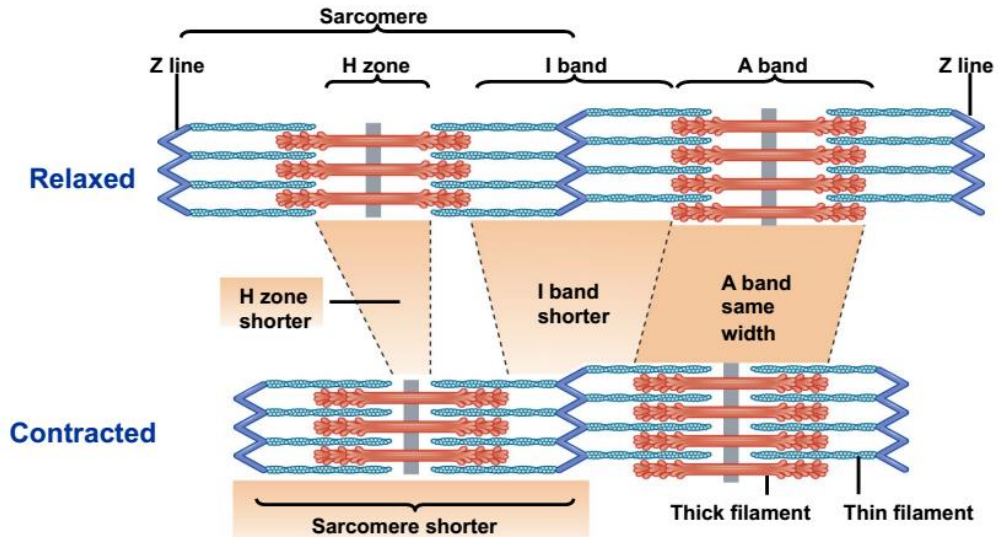
- Thick and thin filaments in each sarcomere move past each other by movements of cross-bridges



Sarcomere Shortening

- Z lines move toward the center
- I band reduce
- H band reduce
- A band stable

- One end of the muscle is stable, the other end shortens toward it

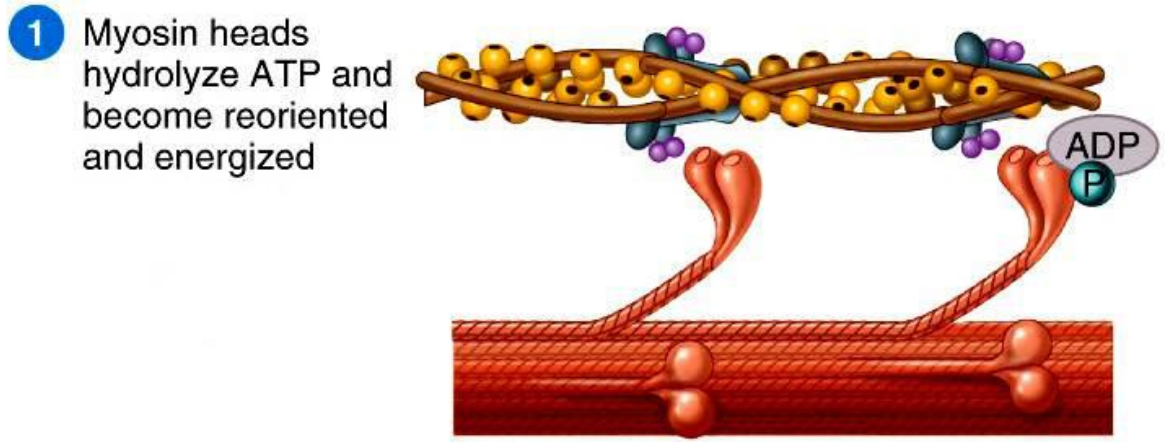


Cross-bridge cycle

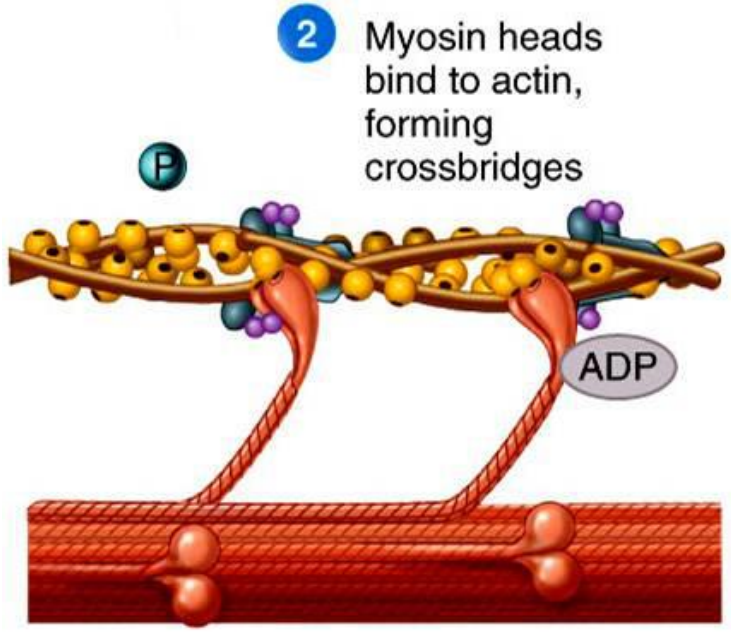
- The sequence of events that occurs between the time a cross-bridge binds to a thin filament, moves, and then is set to repeat the process

1. Attachment of the cross-bridge to a thin filament
2. Movement of the cross-bridge, producing tension in the thin filament
3. Detachment of the cross-bridge from the thin filament
4. Energizing the cross-bridge so it can again attach to a thin filament

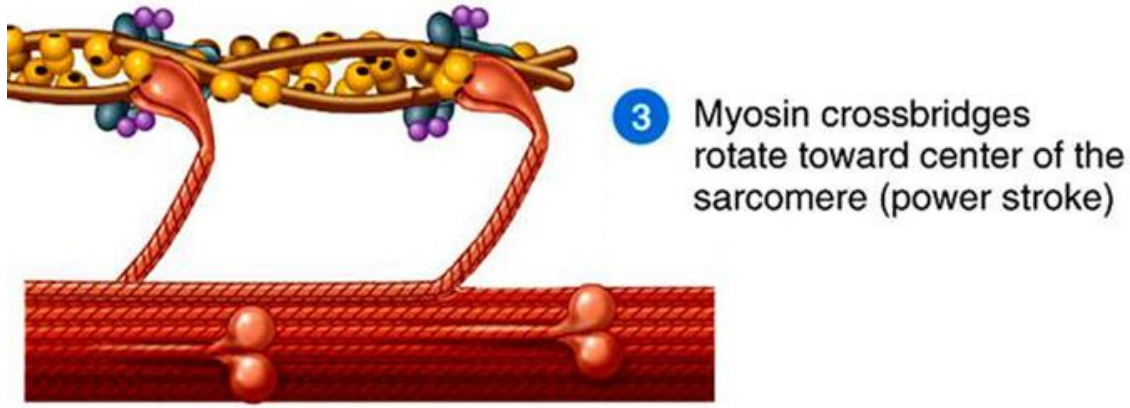
- **Step 1: ATP hydrolysis**



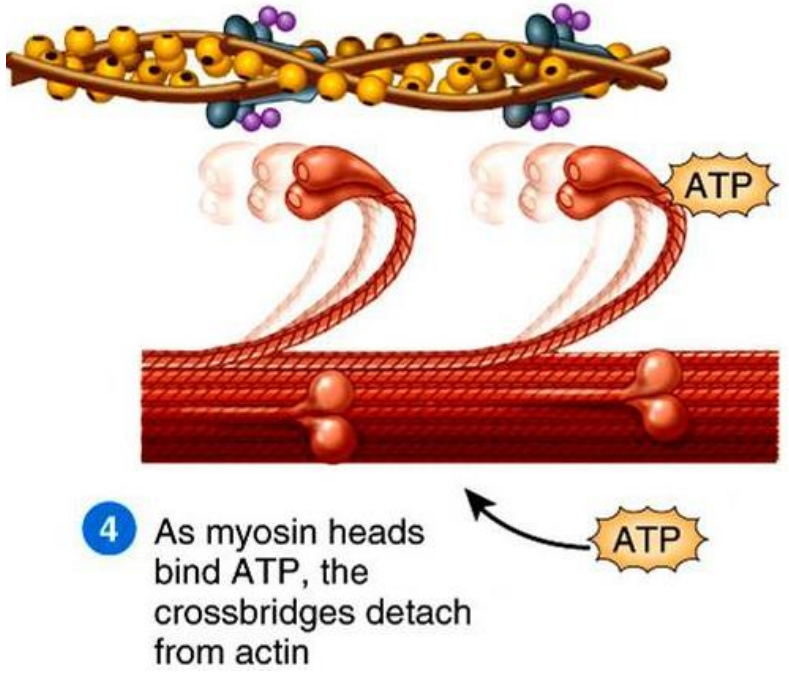
- **Step 2: Attachment**



- **Step 3: Power Stroke**



- **Step 4: Detachment**



Cross-Bridge Cycle

A single power stroke pulls the thin filament inward only a small percentage of the total shortening distance.

Repeated cycles of cross-bridge binding and bending complete the shortening.

Each cross-bridge has its own cycle (not all the cross-bridges active at the same time)

Functions of ATP in Skeletal Muscle Contraction

Hydrolysis of ATP by the Na^+/K^+-ATPase in the plasma membrane maintains Na^+ and K^+ gradients, which allows the membrane to produce and propagate action potentials (review Figure 6.13).
Hydrolysis of ATP by the Ca^{2+}-ATPase in the sarcoplasmic reticulum provides the energy for the active transport of calcium ions into the reticulum, lowering cytosolic Ca^{2+} to prerelease concentrations, ending the contraction, and allowing the muscle fiber to relax.
Hydrolysis of ATP by myosin-ATPase energizes the cross-bridges, providing the energy for force generation.
Binding of ATP to myosin dissociates cross-bridges bound to actin, allowing the bridges to repeat their cycle of activity.

TABLE 9.2 Sequence of Events Between a Motor Neuron Action Potential and Skeletal Muscle Fiber Contraction

1. Action potential is initiated and propagates to motor neuron axon terminals.
2. Ca^{2+} enters axon terminals through voltage-gated Ca^{2+} channels.
3. Ca^{2+} entry triggers release of ACh from axon terminals.
4. ACh diffuses from axon terminals to motor end plate in muscle fiber.
5. ACh binds to nicotinic receptors on motor end plate, increasing their permeability to Na^+ and K^+.
6. More Na^+ moves into the fiber at the motor end plate than K^+ moves out, depolarizing the membrane and producing the end-plate potential (EPP).
7. Local currents depolarize the adjacent muscle cell plasma membrane to its threshold potential, generating an action potential that propagates over the muscle fiber surface and into the fiber along the T-tubules.
8. Action potential in T-tubules induces DHP receptors to pull open ryanodine receptor channels, allowing release of Ca^{2+} from terminal cisternae of sarcoplasmic reticulum.
9. Ca^{2+} binds to troponin on the thin filaments, causing tropomyosin to move away from its blocking position, thereby uncovering cross-bridge binding sites on actin.
10. Energized myosin cross-bridges on the thick filaments bind to actin:

$$A + M \cdot ADP \cdot P_i \rightarrow A \cdot M \cdot ADP \cdot P_i$$

11. Cross-bridge binding triggers release of ATP hydrolysis products from myosin, producing an angular movement of each cross-bridge:

$$A \cdot M \cdot ADP \cdot P_i \rightarrow A \cdot M + ADP + P_i$$

12. ATP binds to myosin, breaking linkage between actin and myosin and thereby allowing cross-bridges to dissociate from actin:

$$A \cdot M + ATP \rightarrow A + M \cdot ATP$$

13. ATP bound to myosin is split, energizing the myosin cross-bridge:

$$A + M \cdot ATP \rightarrow A + M \cdot ADP \cdot P_i$$

14. Cross-bridges repeat steps 10 to 13, producing movement (sliding) of thin filaments past thick filaments. Cycles of cross-bridge movement continue as long as Ca^{2+} remains bound to troponin.
15. Cytosolic Ca^{2+} concentration decreases as Ca^{2+}-ATPase actively transports Ca^{2+} into sarcoplasmic reticulum.
16. Removal of Ca^{2+} from troponin restores blocking action of tropomyosin, the cross-bridge cycle ceases, and the muscle fiber relaxes.