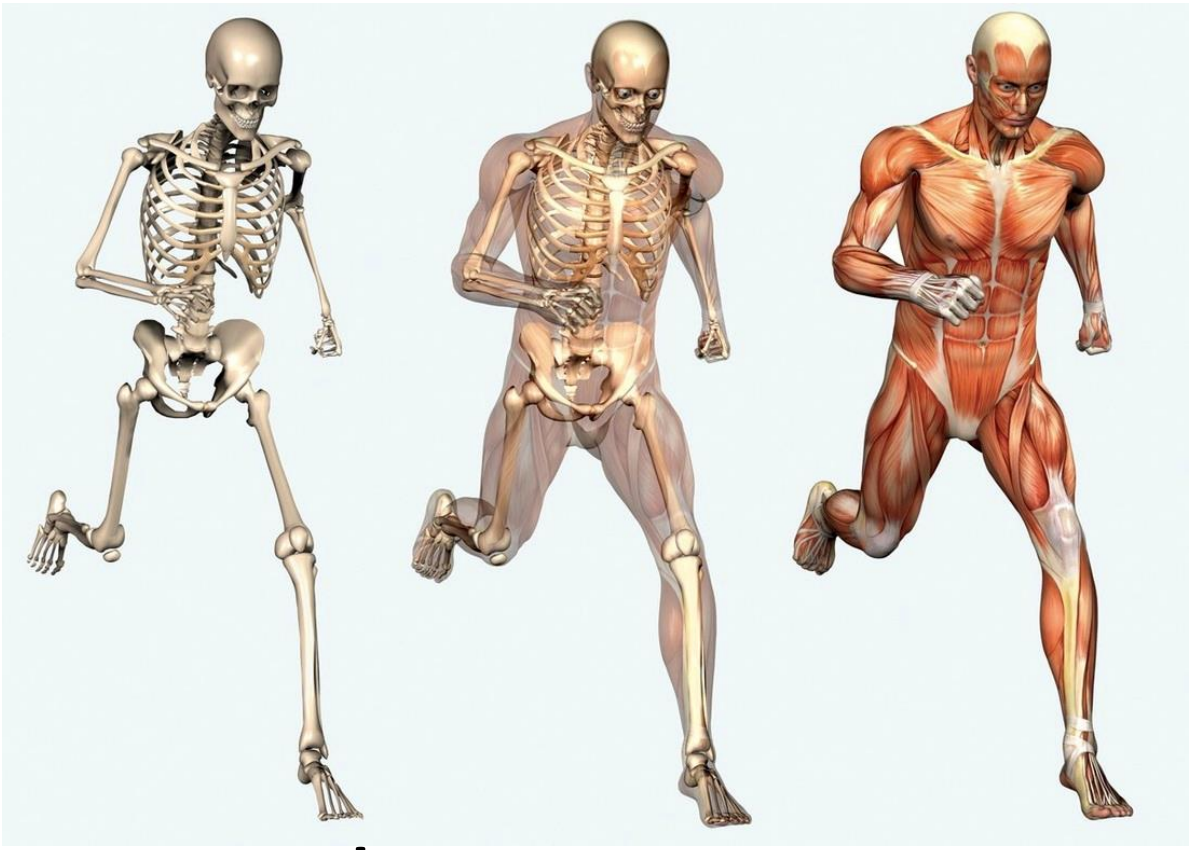
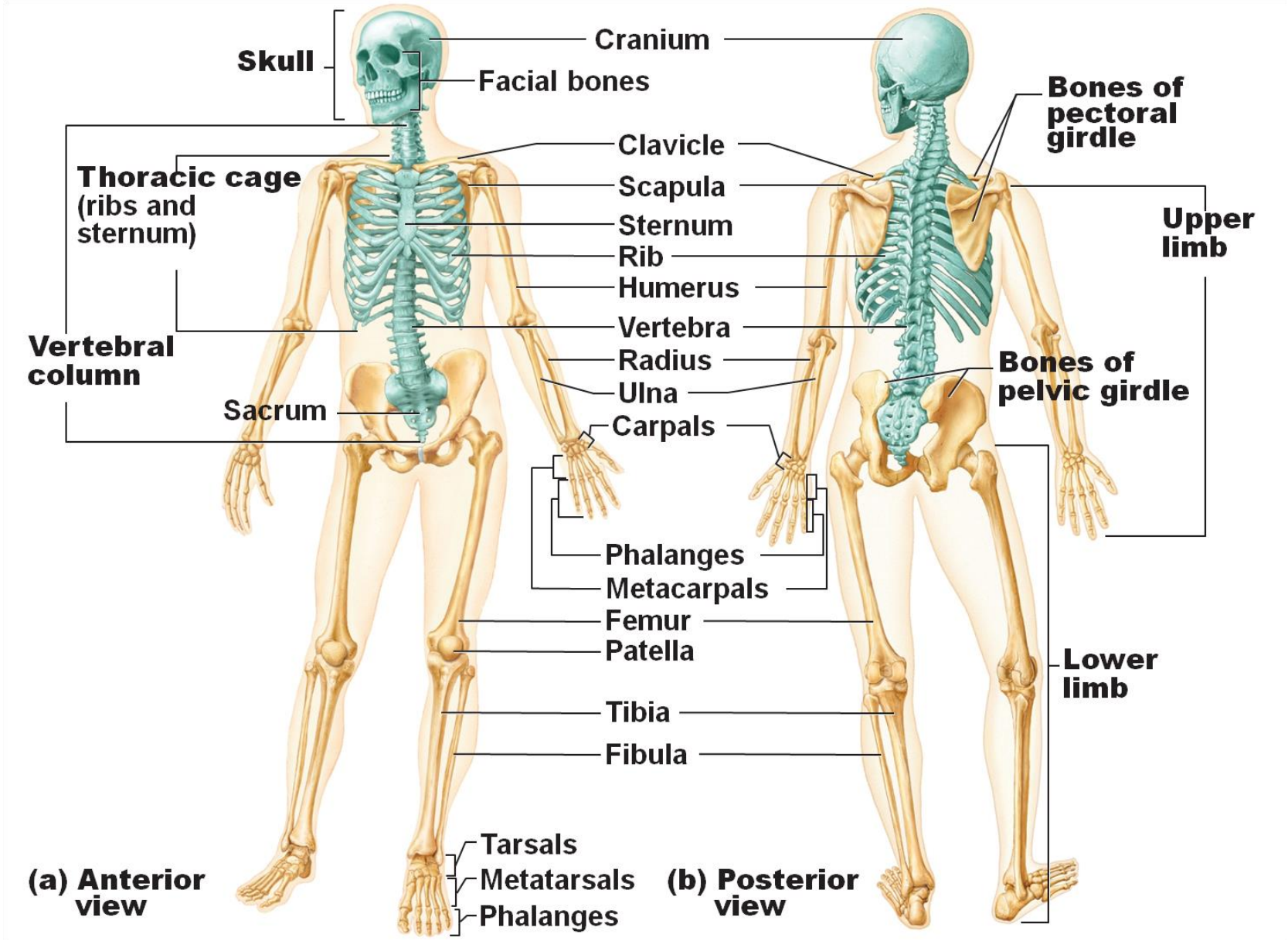


Chapter 6-7:

- Contraction of Skeletal Muscle
- Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling

major bones in your body



- In clinical practice, directional terms are used to describe the **relative positions of various parts of the body.**

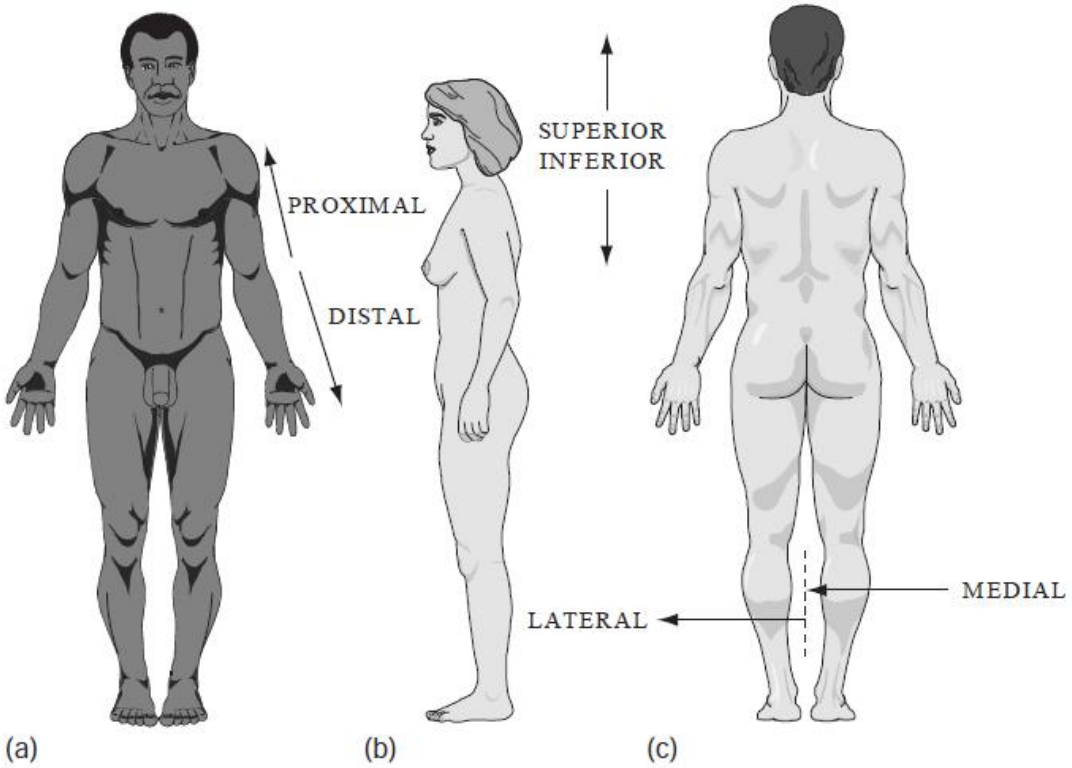


FIGURE 3.1 (a) Anterior view of male body in anatomical position. (b) Lateral view of female body. (c) Posterior view of male body in anatomical position. Relative directions (proximal and distal, superior and inferior, and medial and lateral) are also shown.

- Proximal parts are nearer to the trunk of the body or to the attached end of a limb than are distal parts (Figure 3.1a).
- Parts of the body that are located closer to the head than other parts when the body is in anatomical position are said to be superior (Figure 3.1b), whereas those located closer to the feet than other parts are termed inferior.
- Medial implies that a part is toward the midline of the body, whereas lateral means away from the midline (Figure 3.1c).

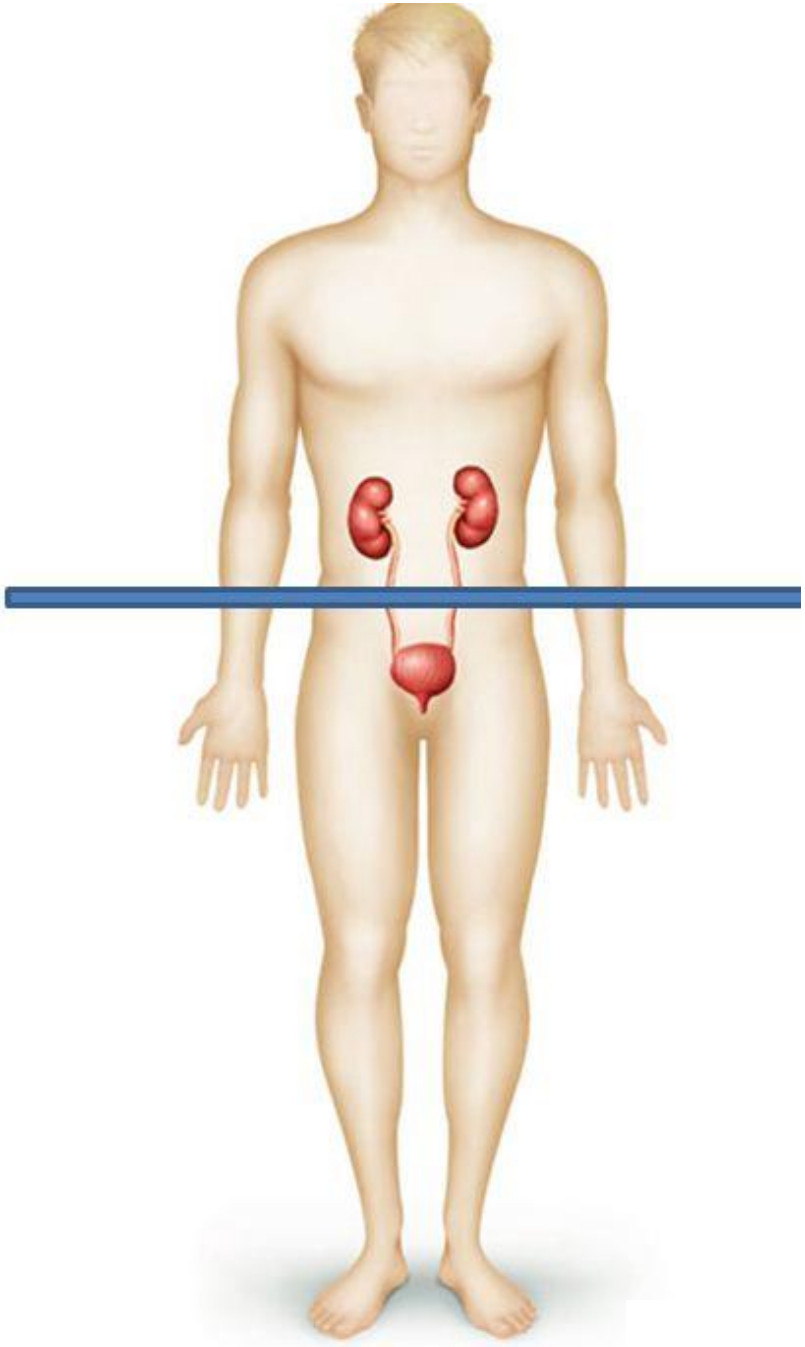
Superior vs. Inferior

Superior: Top. Or part that is above another part; closer to the head

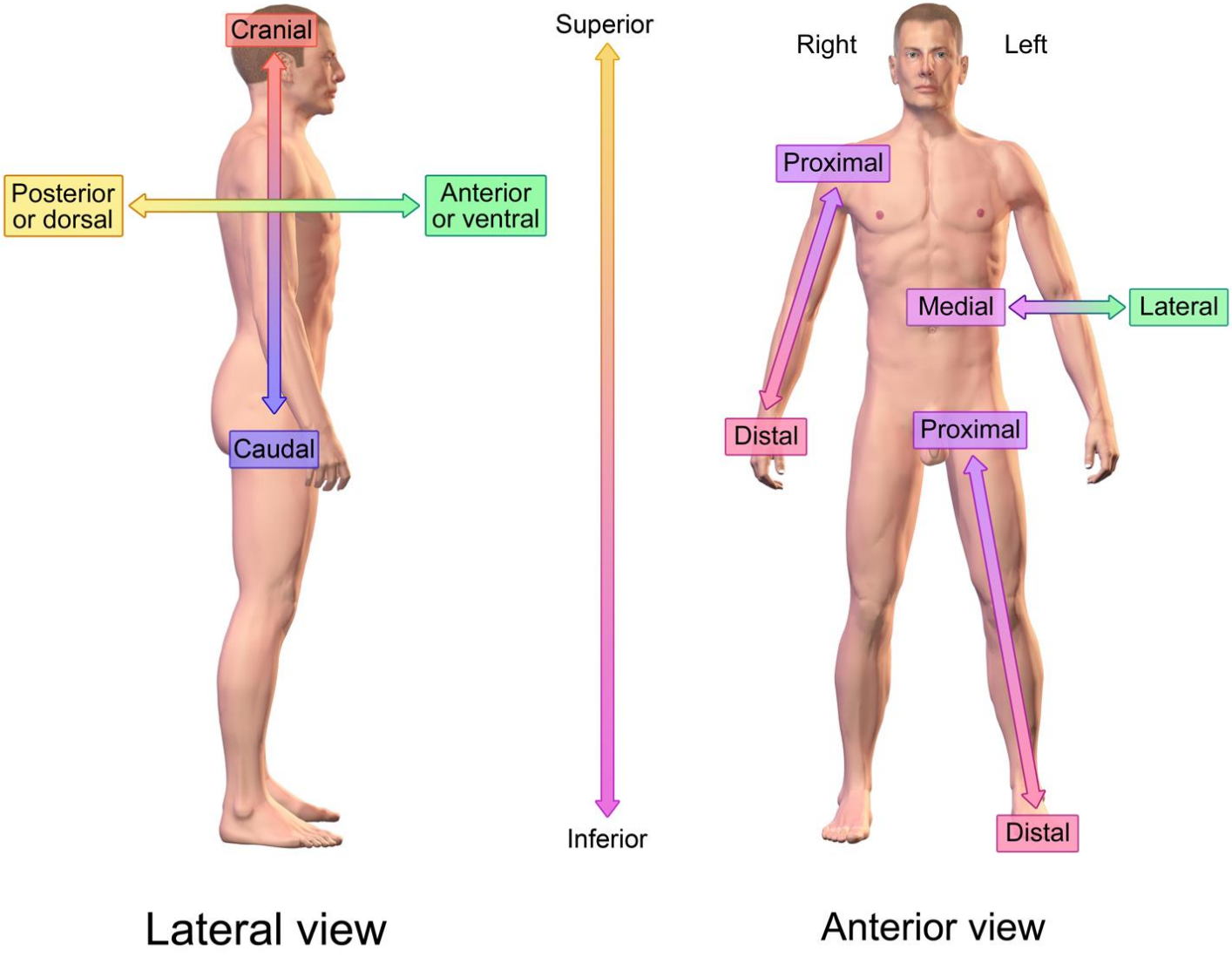
Ex: The Kidneys are superior to the bladder

Inferior: Bottom. Or part that is below another part; toward the feet

Ex: The bladder is inferior to the kidneys

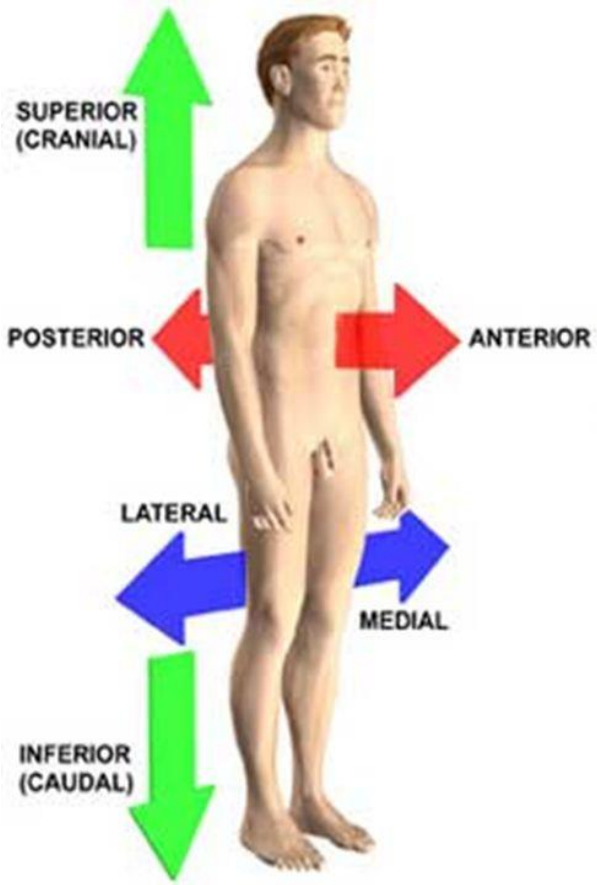


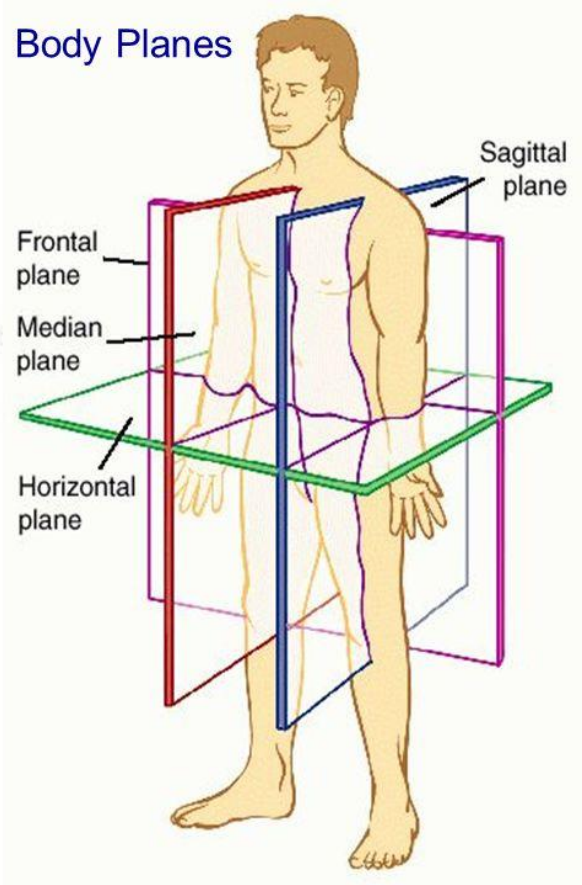
Urinary system



- Parts of the body that lie in the direction of the head are said to be in the cranial direction, whereas those parts that lie in the direction of the feet are said to be in the caudal direction

- **Anatomical locations can also be described in terms of planes.**

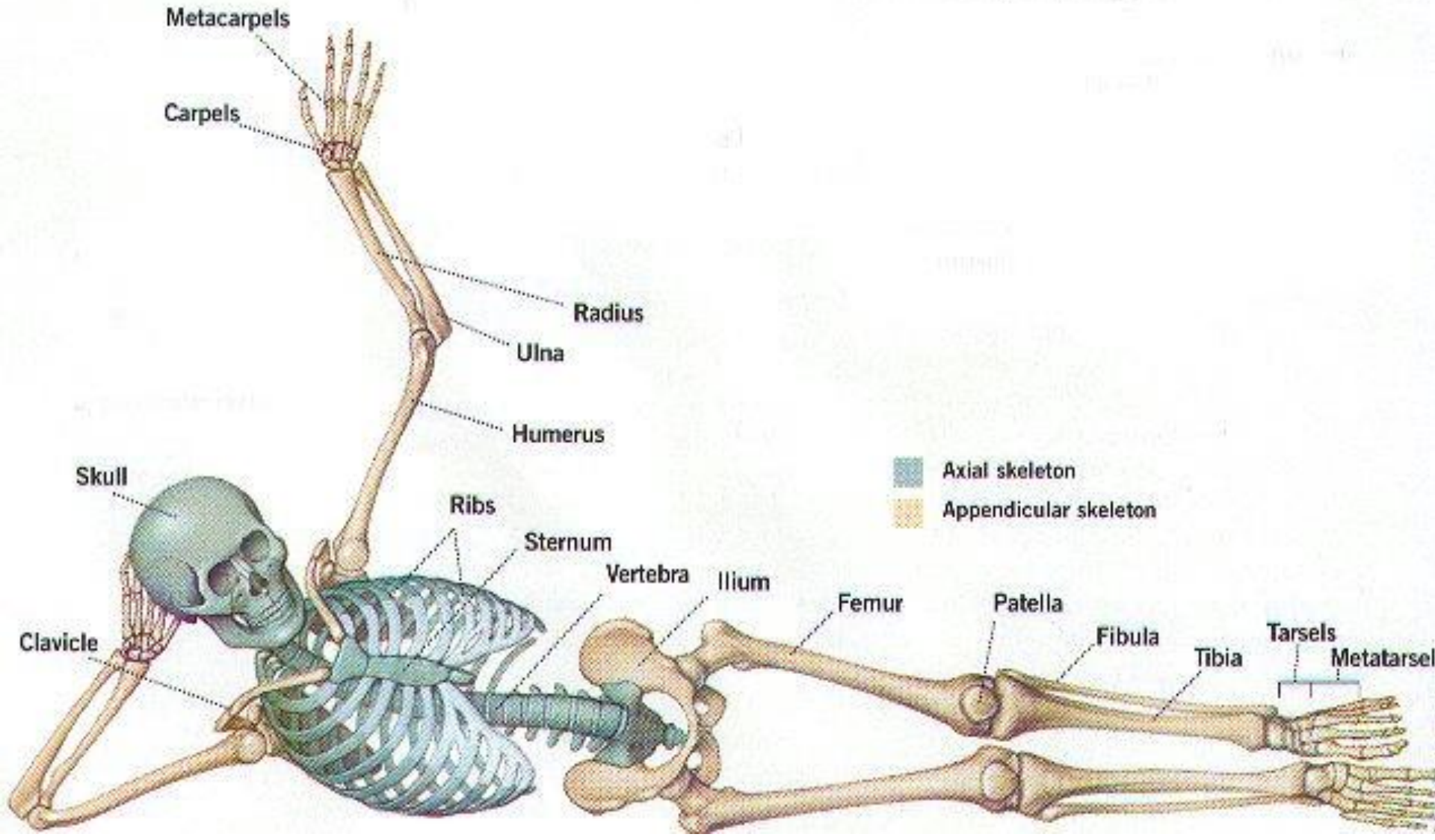




- The plane that divides the body into two symmetric halves along its midline is called the midsaggital plane
- Planes that are parallel to the midsaggital plane but do not divide the body into symmetric halves are called sagittal planes.
- The frontal plane is perpendicular to the midsaggital plane and divides the body into asymmetric anterior and posterior portions.
- Planes that cut across the body and are perpendicular to the midsaggital and frontal planes are called transverse planes.

- Human bodies are divided into two main regions: **axial and appendicular.**

- The axial part consists of the head, neck, thorax (chest), abdomen, and pelvis
- The appendicular part consists of the upper and lower extremities.



"Walk-Along" Theory

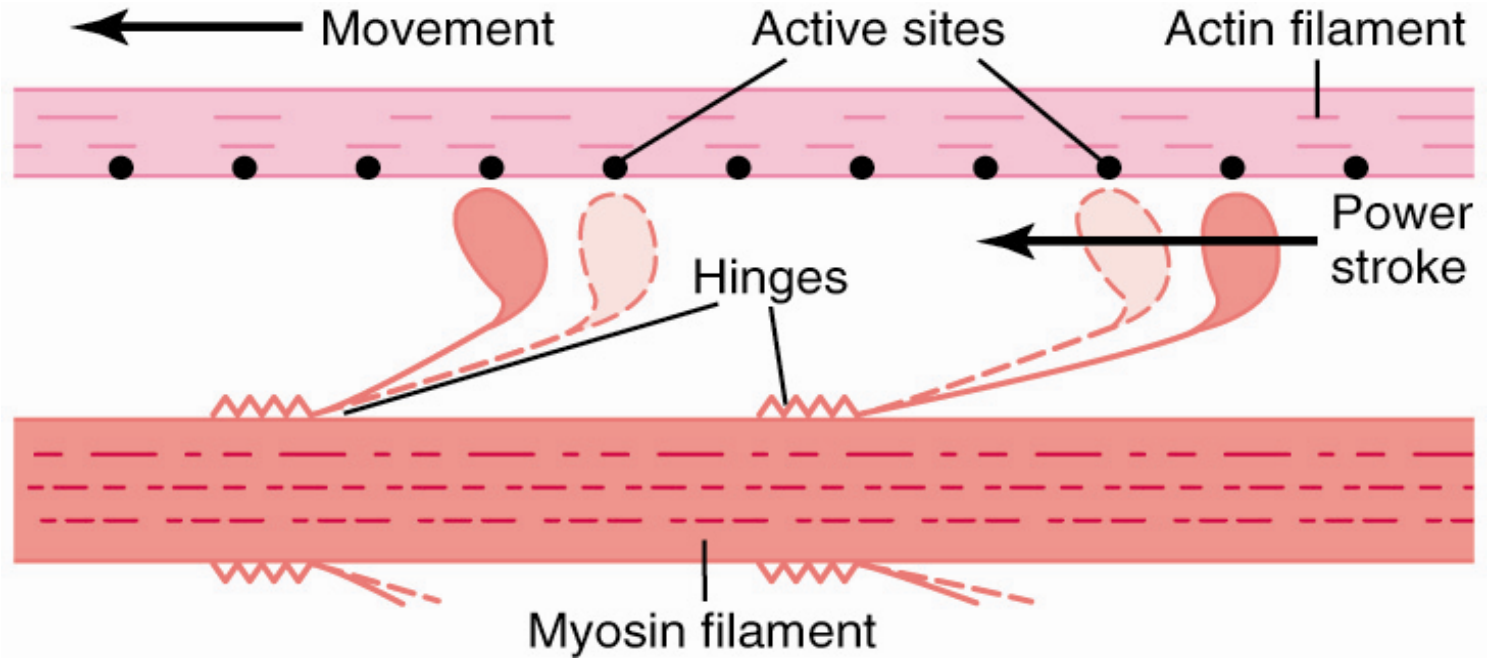


Figure 6-7; "Walk-along" mechanism for contraction of the muscle

Physiologic Anatomy of Skeletal Muscle

Gross organization:

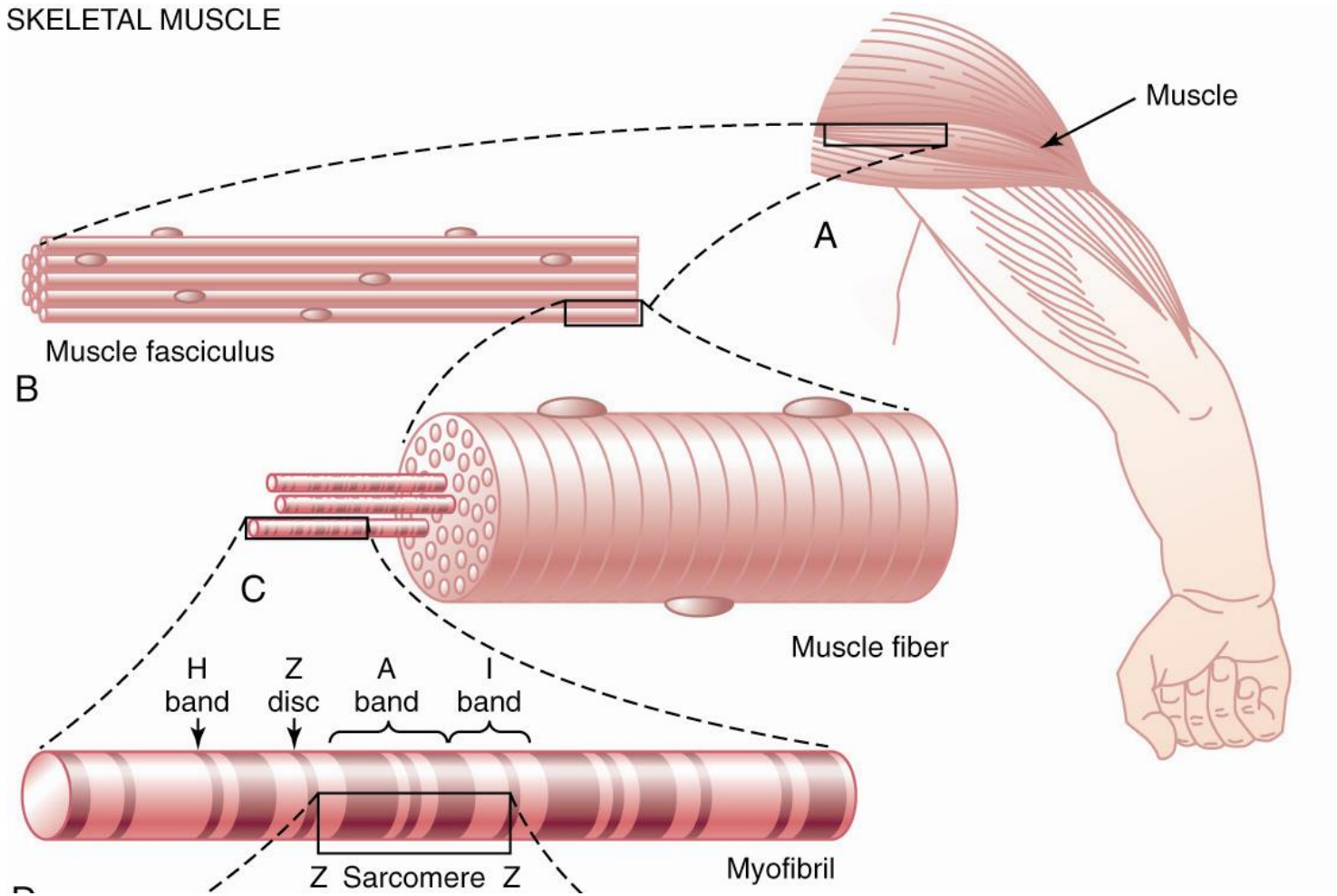


Figure 6-1; Organization of skeletal muscle, from the gross to the molecular level.

Cellular Organization

Muscle fibers

- single cells
- multinucleated
- surrounded by the sarcolemma

The sarcolemma is the cell membrane of the muscle fiber

Myofibrils

- contractile elements
- surrounded by the sarcoplasm

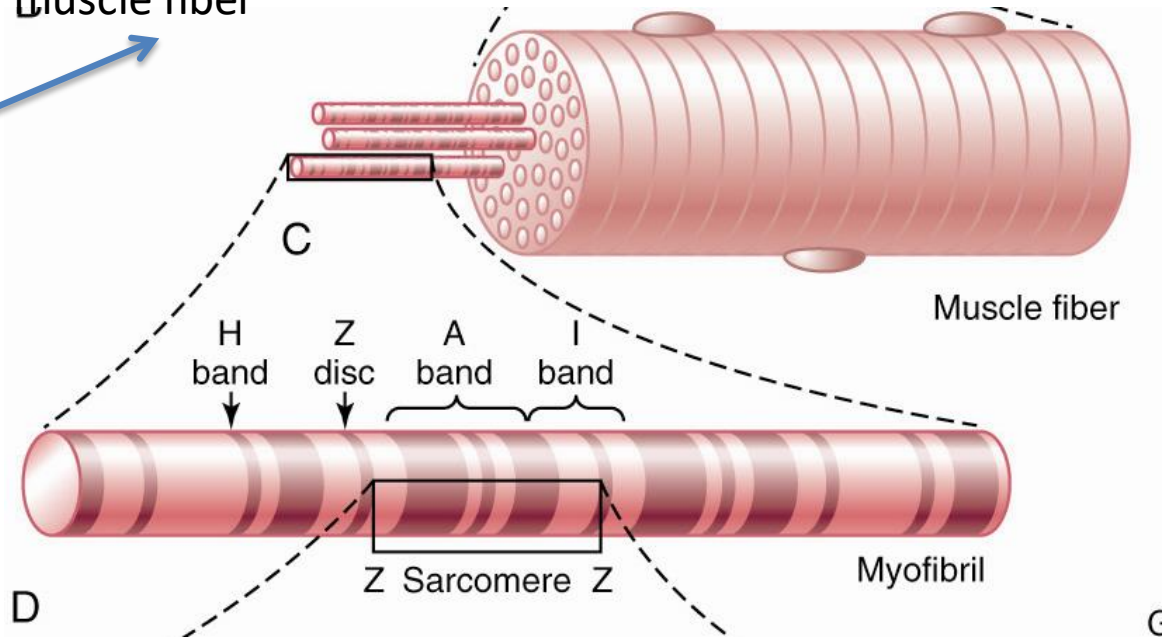


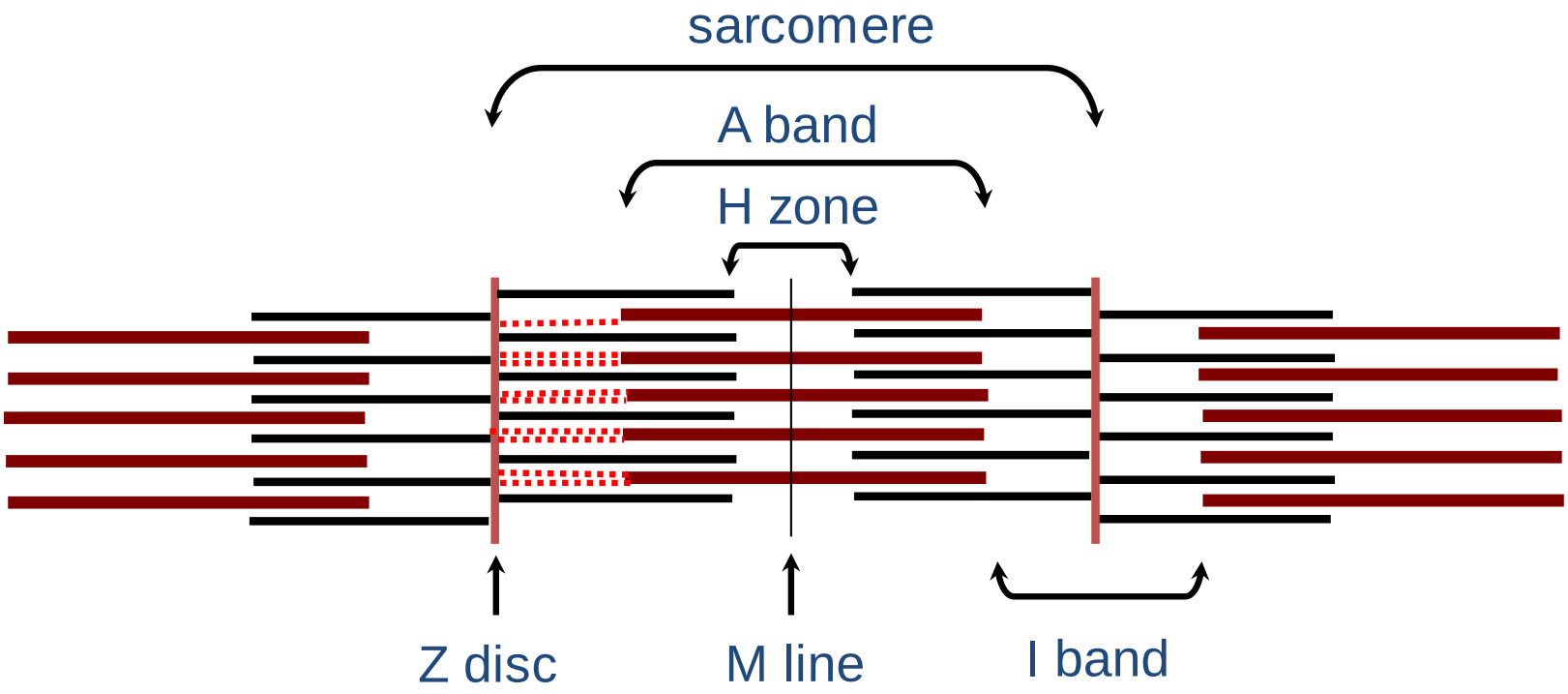
Figure 6-1; Organization of skeletal muscle, from the gross to the molecular level.

Cellular organelles - lie between myofibrils (mitochondria, sarcoplasmic reticulum etc.)

Sarcoplasm. The many myofibrils of each muscle fiber are suspended side by side in the muscle fiber. The spaces between the myofibrils are filled with intracellular fluid called sarcoplasm, containing large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes. Also present are tremendous numbers of mitochondria that lie parallel to the myofibrils. These supply the contracting myofibrils with large amounts of energy in the form of adenosine triphosphate (ATP) formed by the mitochondria.

The Sarcomere

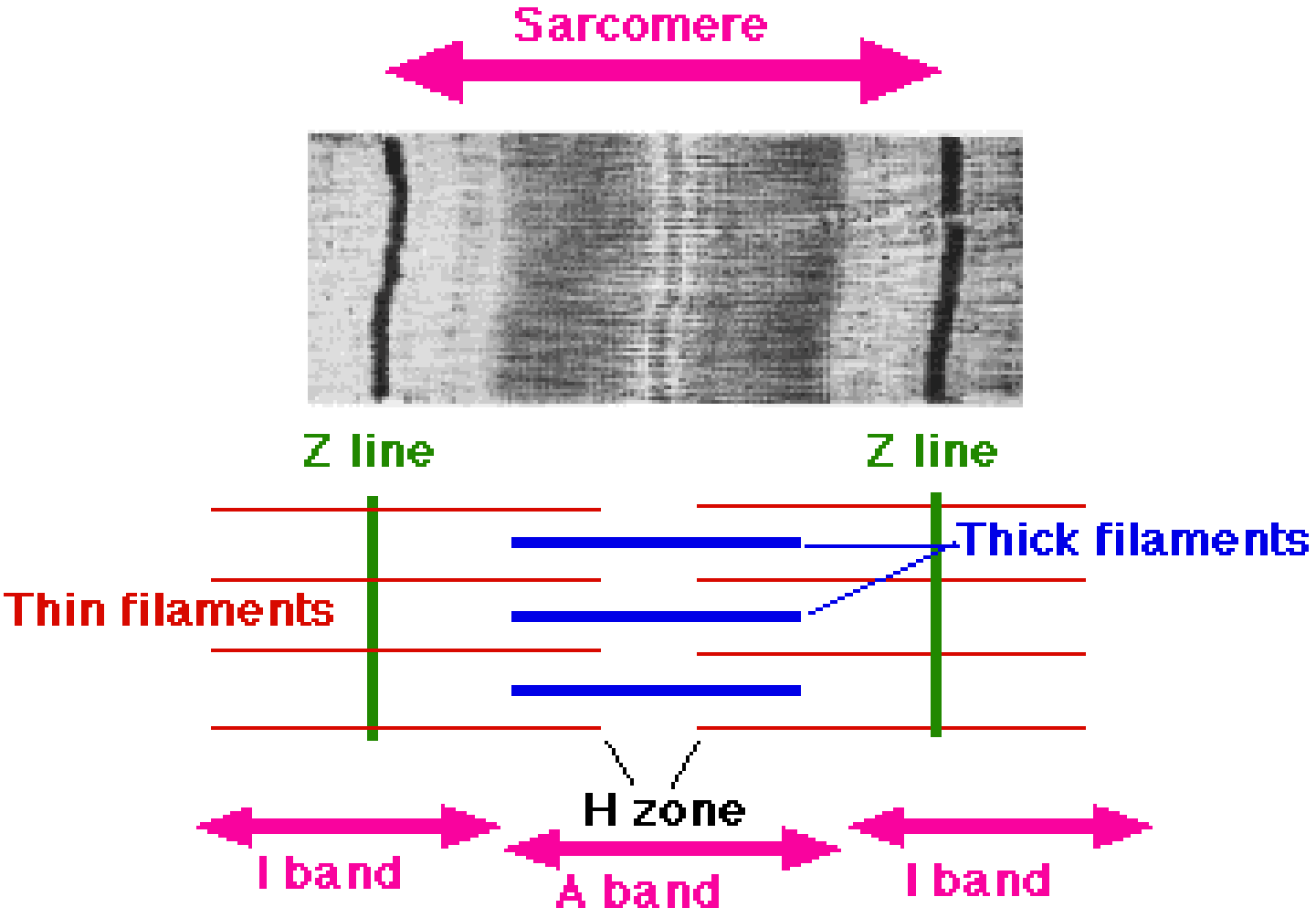
- The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a sarcomere.



thick filament (myosin)

thin filament (actin)

titin (filamentous structural protein, The side-by-side relationship between the myosin and actin filaments is maintained by titin.)


Sarcomere
Z line
Z line
Thick filaments
Thin filaments
H zone
I band
A band
I band

- **Molecular Characteristics of the Contractile Filaments**

➢ The Myosin Molecule:

- two **heavy chains** (MW 200,000)
- four **light chains** (MW 20,000)
- "head" region - site of **ATPase** activity

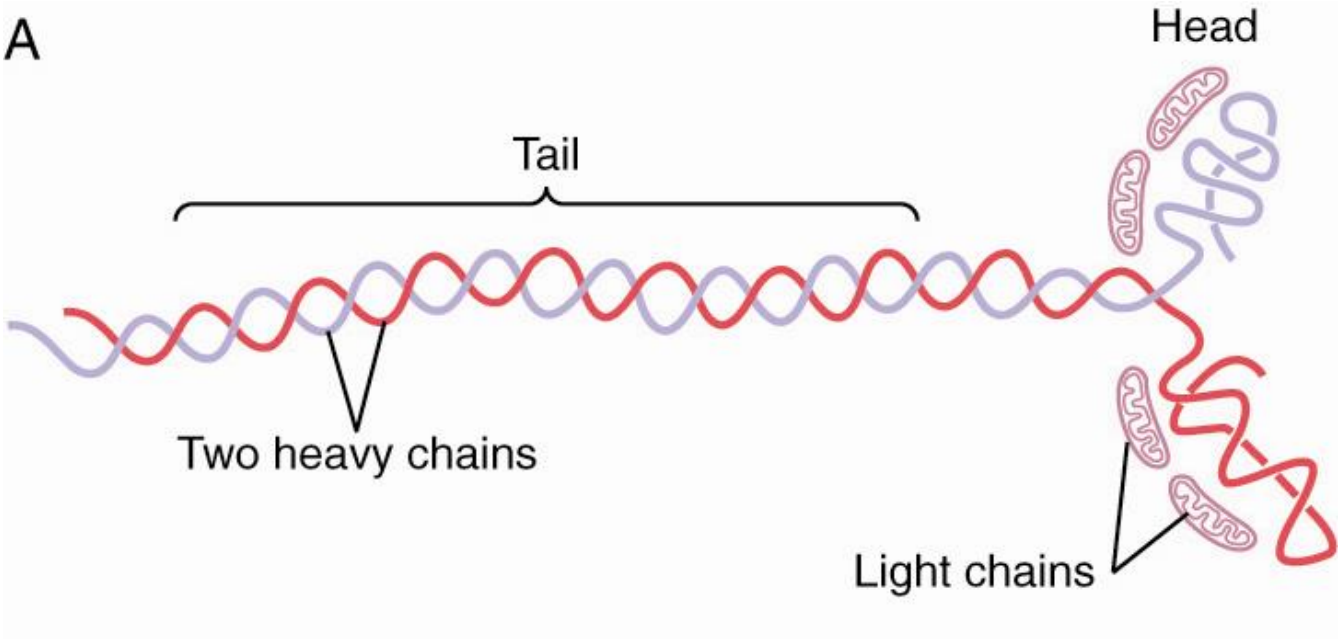


Figure 6-5: Myosin molecule

➢ The Actin Filament

- the I band filament
- tethered at one end at the Z disc
- 1 μm long

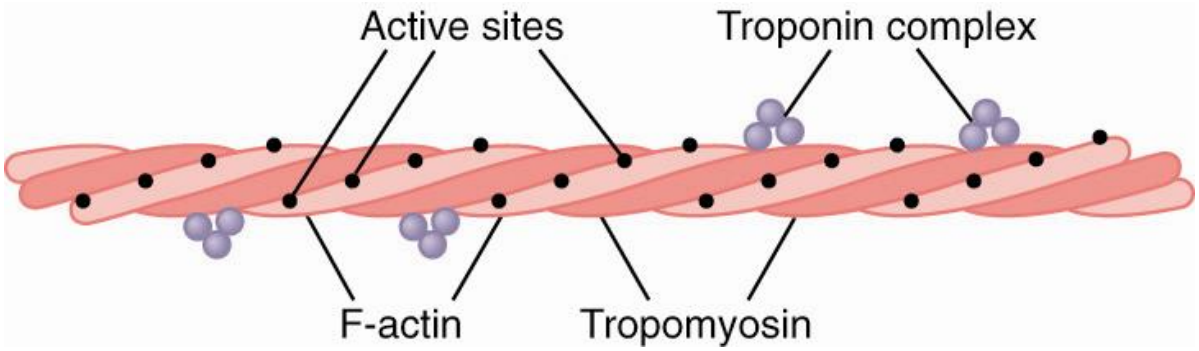


Figure 6-6; Actin filament, composed of two helical strands of F-actin molecules and two strands of tropomyosin molecules that fit in the grooves between the actin strands. Attached to one end of each tropomyosin molecule is a troponin complex that initiates contraction.

F-actin

- double-stranded helix
- composed of polymerized G-actin
- ADP bound to each G-actin (active sites)
- myosin heads bind to active sites

tropomyosin

- covers active sites
- prevents interaction with myosin at rest

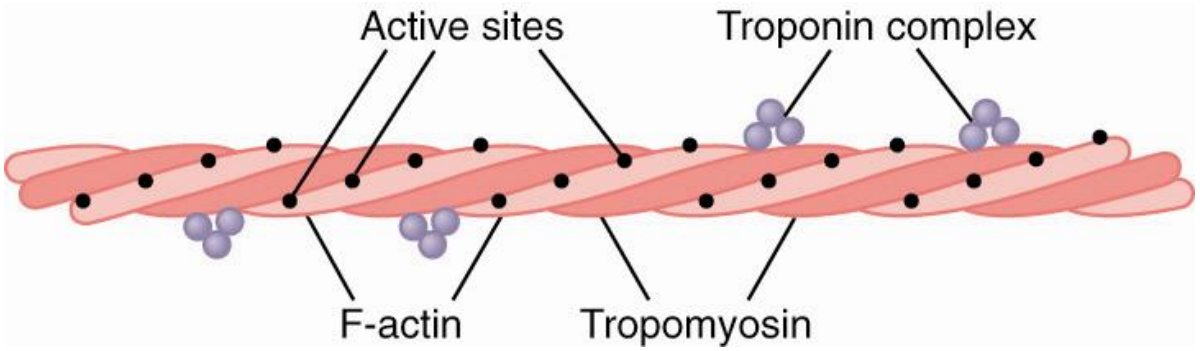
troponin

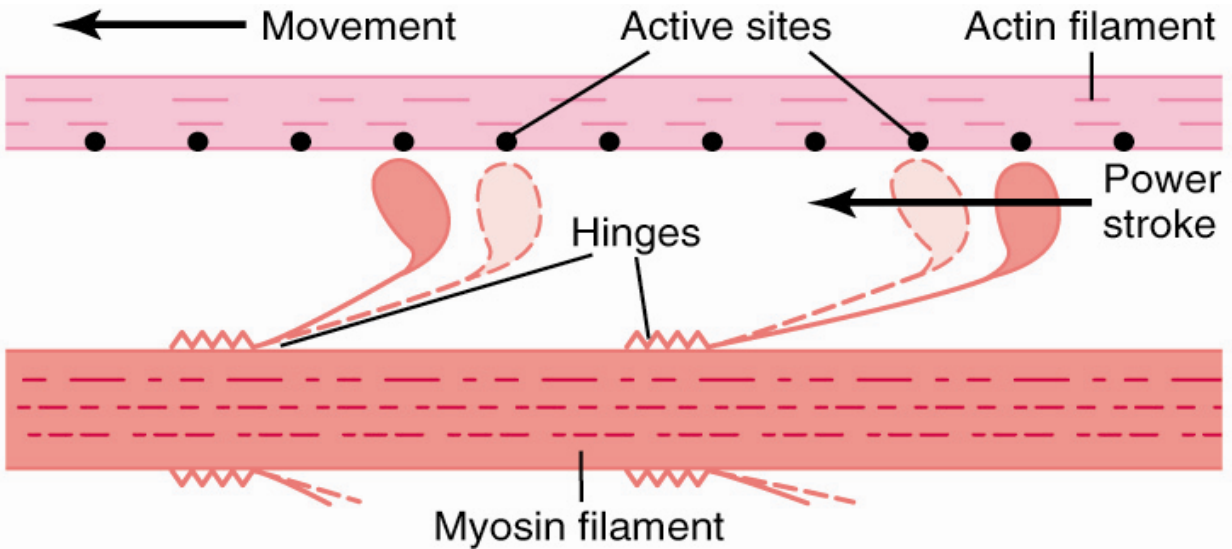
- **I** - binds actin
- **T** - binds tropomyosin
- **C - binds Ca^{2+}**

Mechanism of Muscle Contraction

Theory:

Binding of Ca^{2+} to **troponin** results in a conformational change in **tropomyosin** that "uncovers" the active sites on the actin molecule, allowing for myosin to bind.





"Sliding Filament" Mechanism

Contraction results from the sliding action of interdigitating actin and myosin filaments

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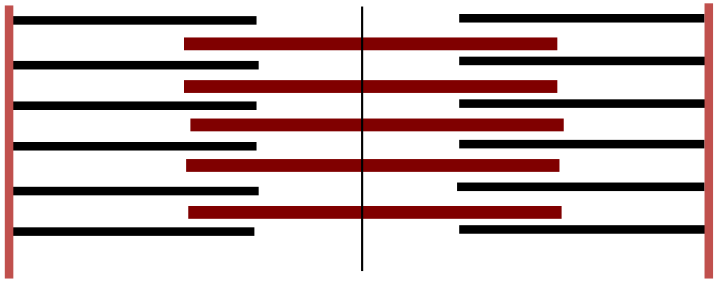

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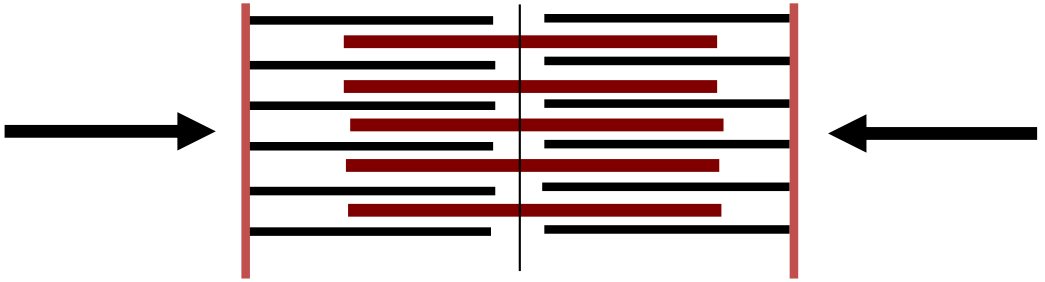


Neuromuscular Transmission

- The Neuromuscular Junction -

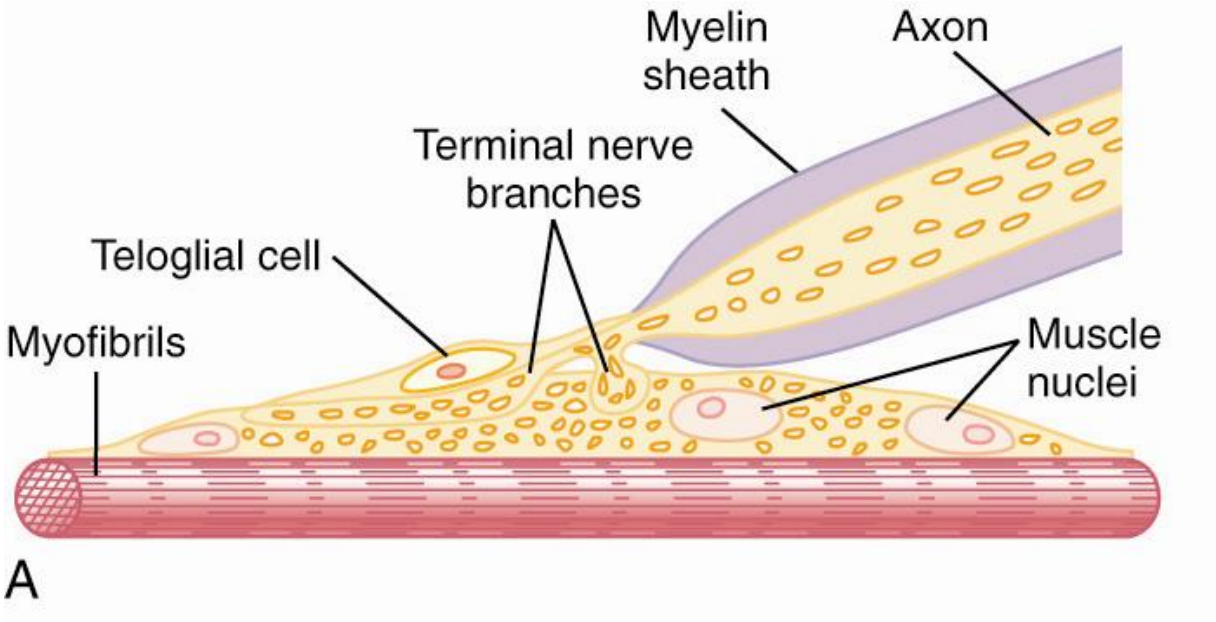
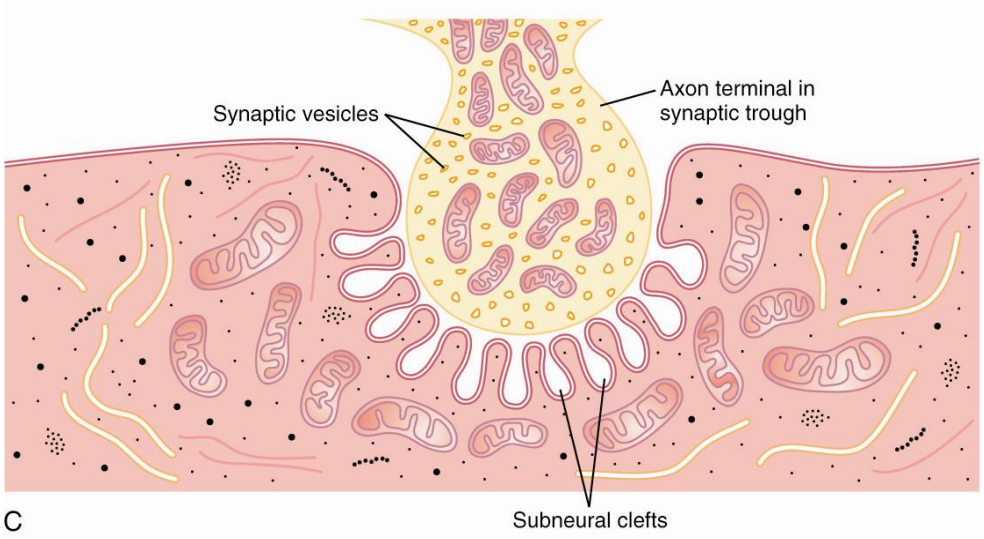


Figure 7-1; Longitudinal section through the end plate

- Specialized **synapse** between a **motoneuron** and a muscle fiber
- Occurs at a structure on the muscle fiber called the **motor end plate** *(usually only one per fiber)*

Neuromuscular Junction *(nmj)*

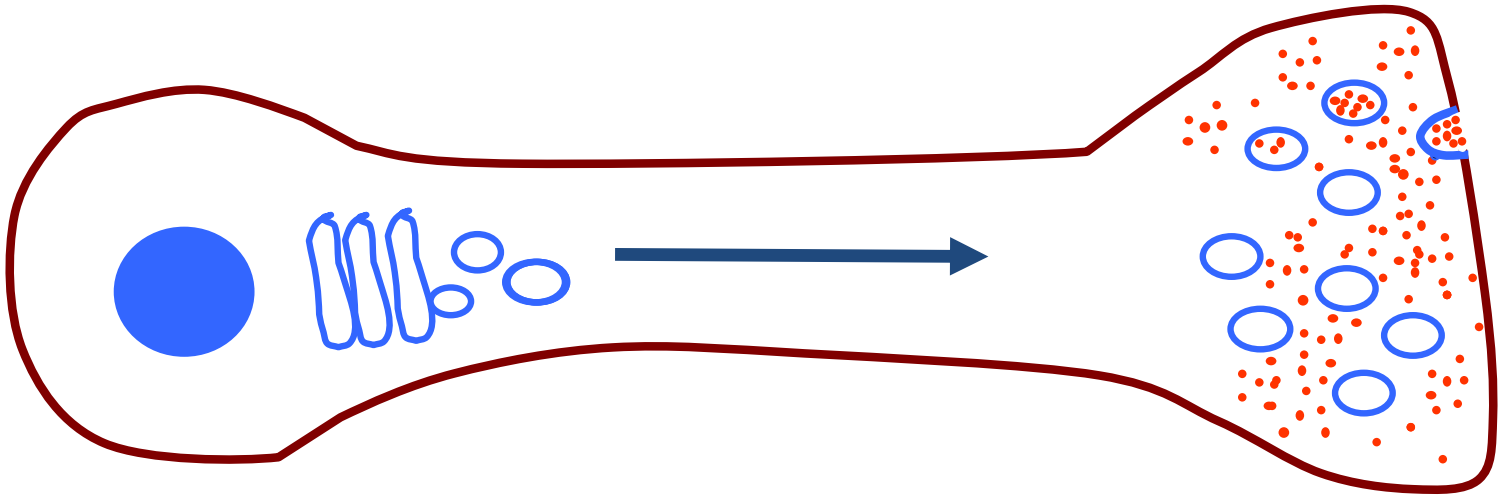
Synaptic trough: invagination in the motor endplate membrane



- **Synaptic cleft:**
  - 20-30 nm wide
  - contains large quantities of acetylcholinesterase (AChE)
- **Subneural clefts:**
  - increase the surface area of the post-synaptic membrane
  - Ach gated channels at tops
  - Voltage gated Na^+ channel in bottom half

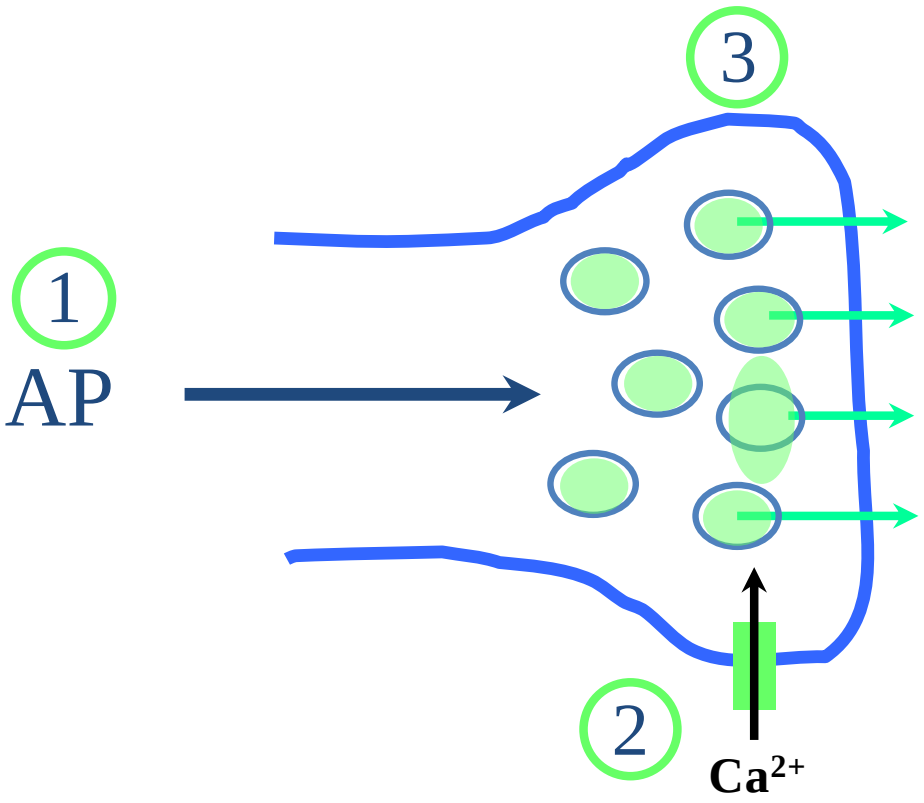
Figure 7-1: Electron micrographic appearance of the contact point between a single axon terminal and the muscle fiber membrane.

The Motoneuron – *vesicle formation*



- **Synaptic vesicles:** are formed from budding Golgi and are transported to the terminal by axoplasm "streaming" (~300,000 per terminal)
- **Acetylcholine** (ACh) is formed in the cytoplasm and is transported into the vesicles (~10,000 per)
- Ach filled vesicles occasionally fuse with the pre-synaptic membrane and release their contents. This causes **miniature end-plate potentials** in the post-synaptic membrane.

The Motoneuron - *ACh Release*



1. AP begins in the ventral horn of spinal cord.
2. Local depolarization opens voltage-gated Ca^{2+} channels.
3. An increase in cytosolic Ca^{2+} triggers the fusion of ~125 synaptic vesicles with the pre-synaptic membrane and release of ACh *(exocytosis)*.

ACh Release - *details*

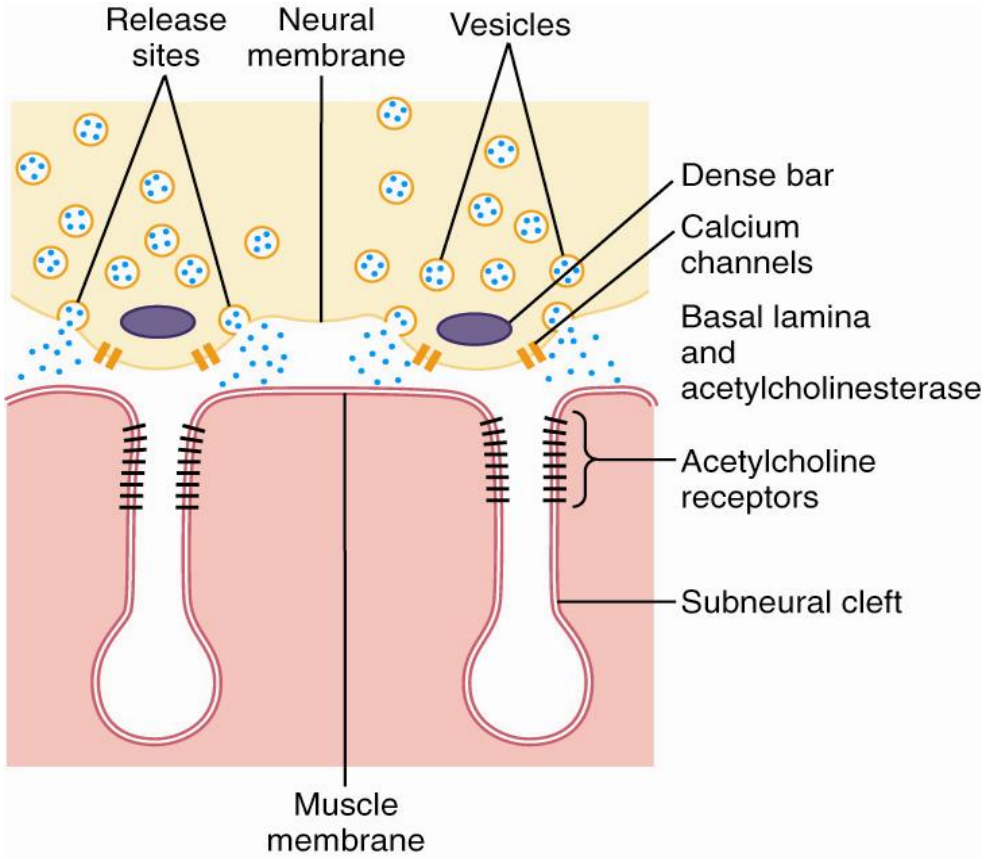


Figure 7-2; Guyton & Hall

- Ca^{2+} channels are localized around linear structures on the pre-synaptic membrane called **dense bars.**

- Vesicles fuse with the membrane in the region of the dense bars.

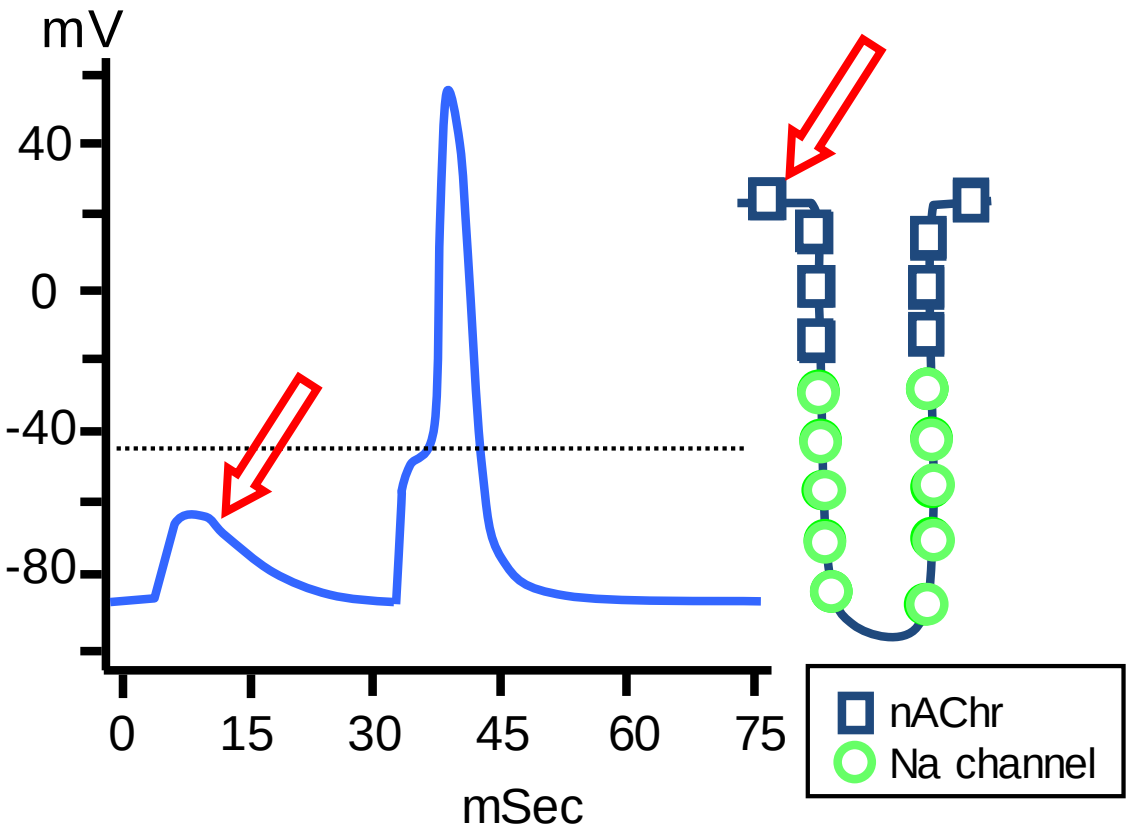
- Ach receptors located at top of subneural cleft.

- Voltage gated Na^{+} channels in bottom half of subneural cleft.

End Plate Potential and Action Potential

- at the motor endplate -

• ACh released into the neuromuscular junction binds to, and opens, nicotinic ACh receptor channels on the muscle fiber membranes (Na^+, K^+, Ca^{2+}).



• Opening of nACh receptor channels produces an **end plate potential,** which will normally initiate an AP if the local spread of current is sufficient to open voltage sodium channels.

• *What terminates the process?* ***acetylcholinesterase***

Drug Effects on End Plate Potential

- Inhibitors -

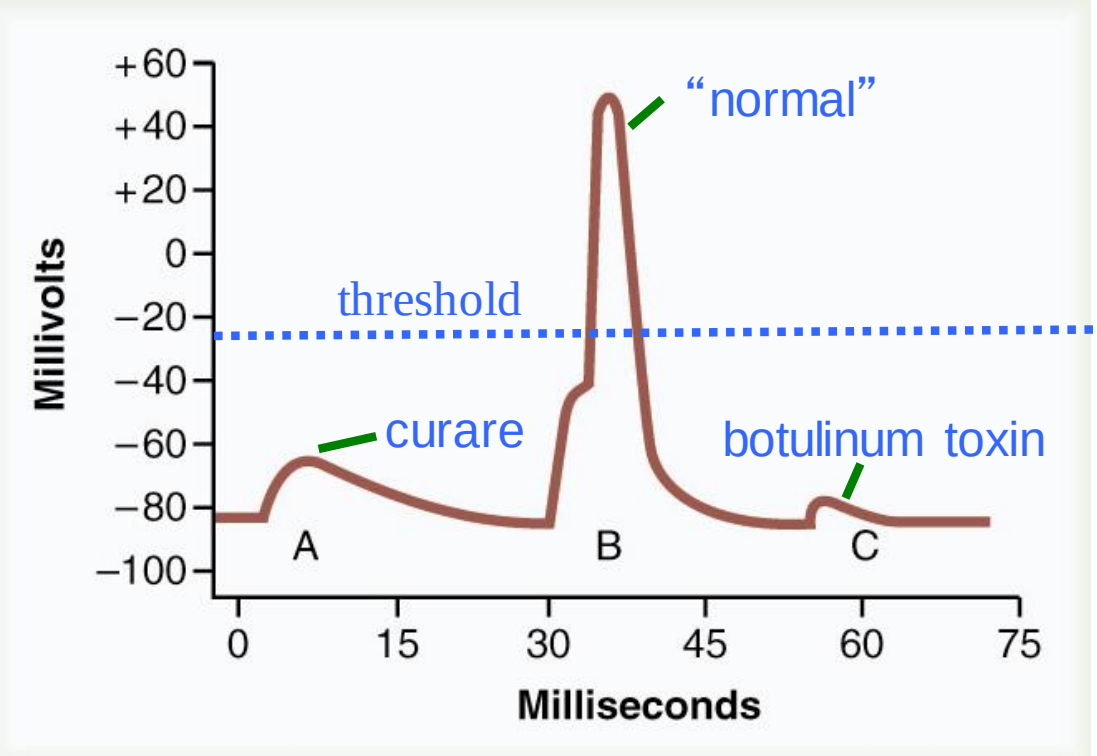


Figure 7-4; Guyton & Hall

Curariform drugs (D-turbocurarine)

- block nicotinic ACh channels by competing for ACh binding site
- reduces amplitude of end plate potential therefore, no AP

Botulinum toxin

- decreases the release of Ach from nerve terminals
- insufficient stimulus to initiate an AP

Drug Effects on End Plate Potential

- Stimulants -

ACh-like drugs *(methacholine, carbachol, nicotine)*

- bind and activate nicotinic ACh receptors
- not destroyed by AChE – prolonged effect

Anti-AChE *(neostigmine, physostigmine, diisopropyl fluorophosphate or "nerve gas")*

- block the degradation of ACh
- prolong its effect

Excitation-Contraction Coupling

Transverse tubule / SR System

T-tubules:

- Invaginations of the **sarcolemma** filled with extracellular fluid
- Penetrate the muscle fiber, branch and form networks
- Transmit AP's deep into the muscle fiber

Sarcoplasmic Reticulum:

- terminal cisternae and longitudinal tubules
- **terminal cisternae** form junctional "feet" adjacent to the T-tubule membrane
- intracellular storage compartment for **Ca^{2+}**

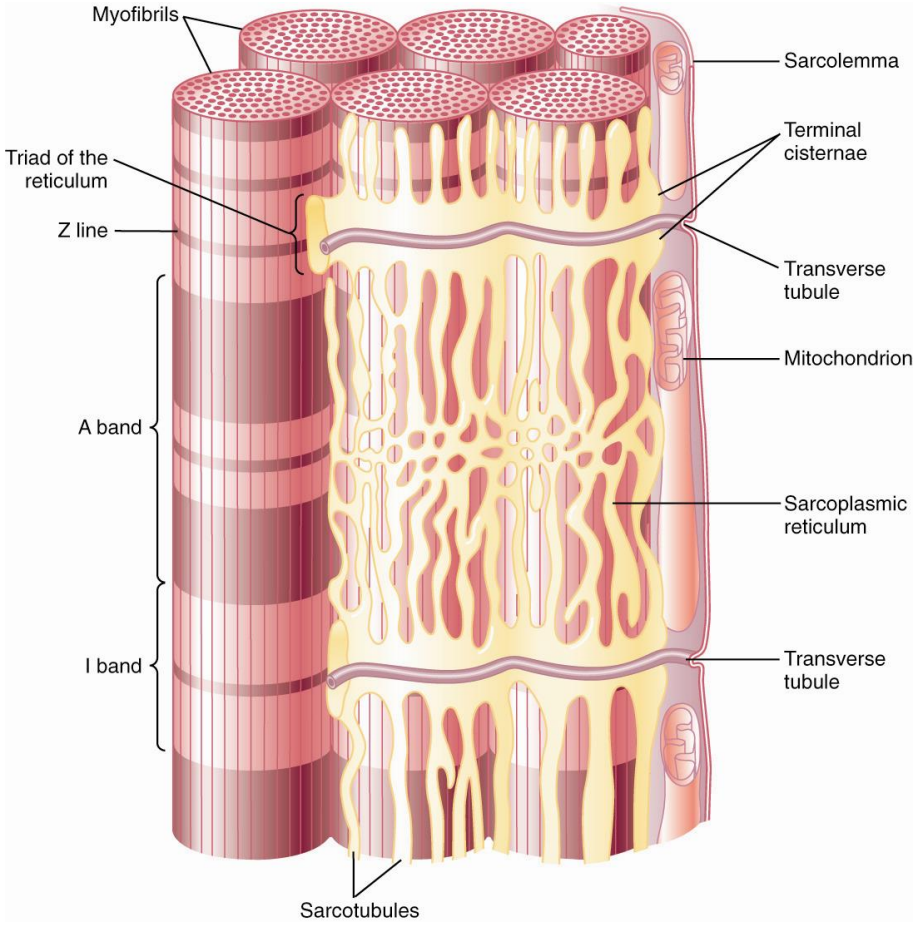


Figure 7-5; Guyton & Hall Transverse (T) tubule–sarcoplasmic reticulum system. Note that the T tubules communicate with the outside of the cell membrane, and deep in the muscle fiber, each T tubule lies adjacent to the ends of longitudinal sarcoplasmic reticulum tubules that surround all sides of the actual myofibrils that contract. This illustration was drawn from frog muscle, which has one T tubule per sarcomere, located at the Z line. A similar arrangement is found in mammalian heart muscle, but mammalian skeletal muscle has two T tubules per sarcomere, located at the A-I band junctions.

Arrangement of T-tubules to Myofibrils

- Skeletal muscle vs cardiac muscle -

Vertebrate skeletal muscle:

- Two T-tubule networks per sarcomere
- Located near the ends of the myosin filaments (zone of overlap)

Cardiac muscle *(and lower animals):*

- Single T-tubule network per sarcomere
- Located at the level of the Z disc

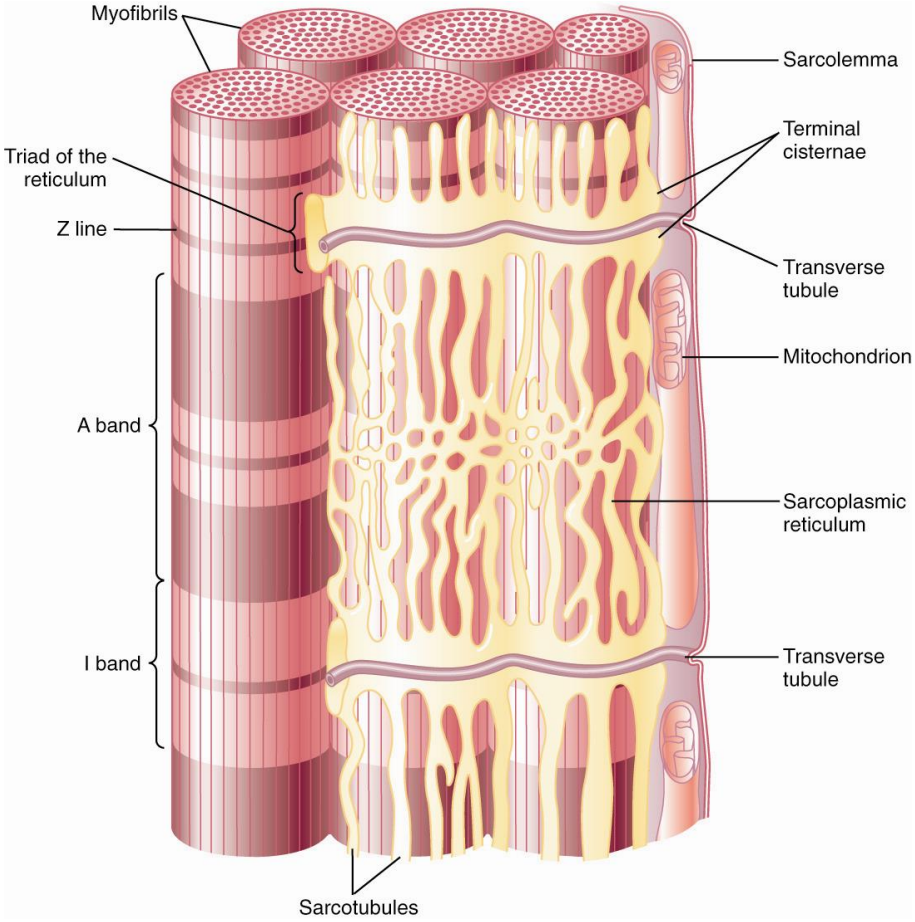
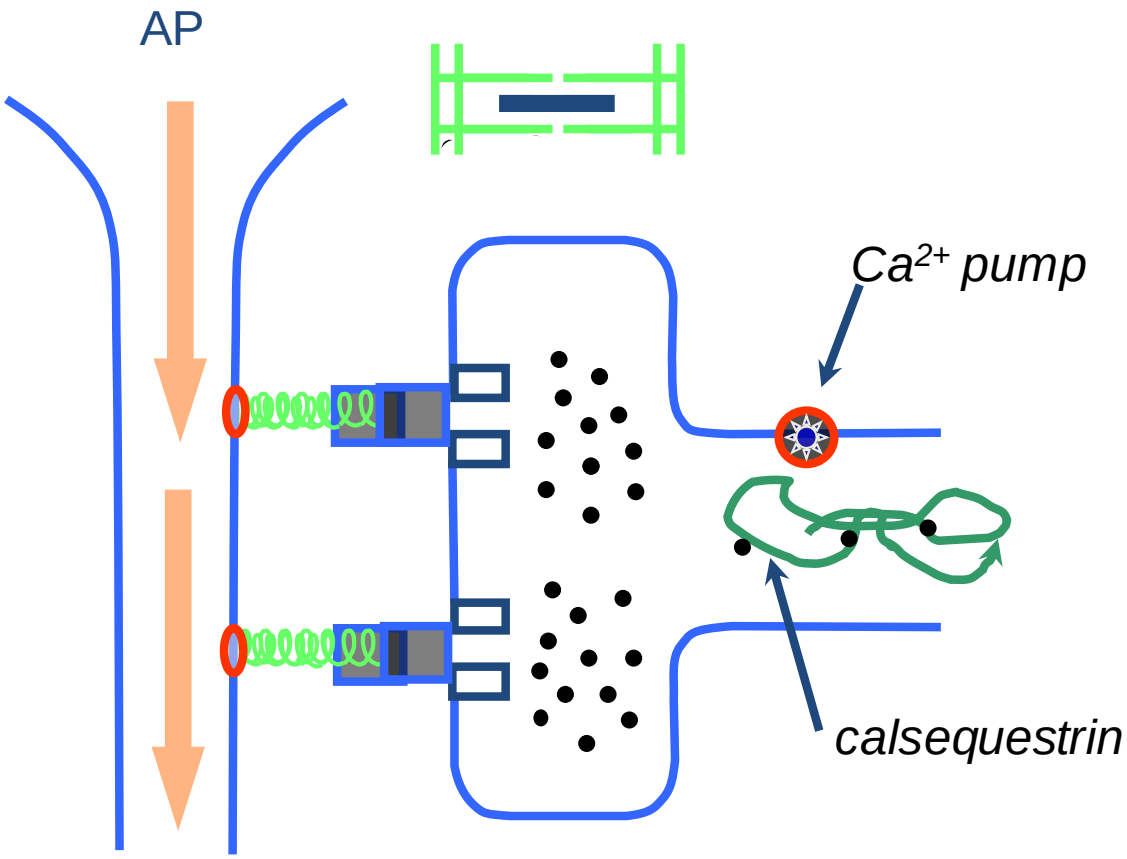


Figure 7-5; Guyton & Hall

EC Coupling – *how it works (skeletal muscle)*

Sequence of Events:

1. AP moves along T-tubule
2. The voltage change is sensed by the DHP receptor.
3. Is communicated to the ryanodine receptor which opens. *(VACR)*
4. Contraction occurs.
5. Calcium is pumped back into SR. Calcium binds to calsequestrin to facilitate storage.
6. Contraction is terminated.

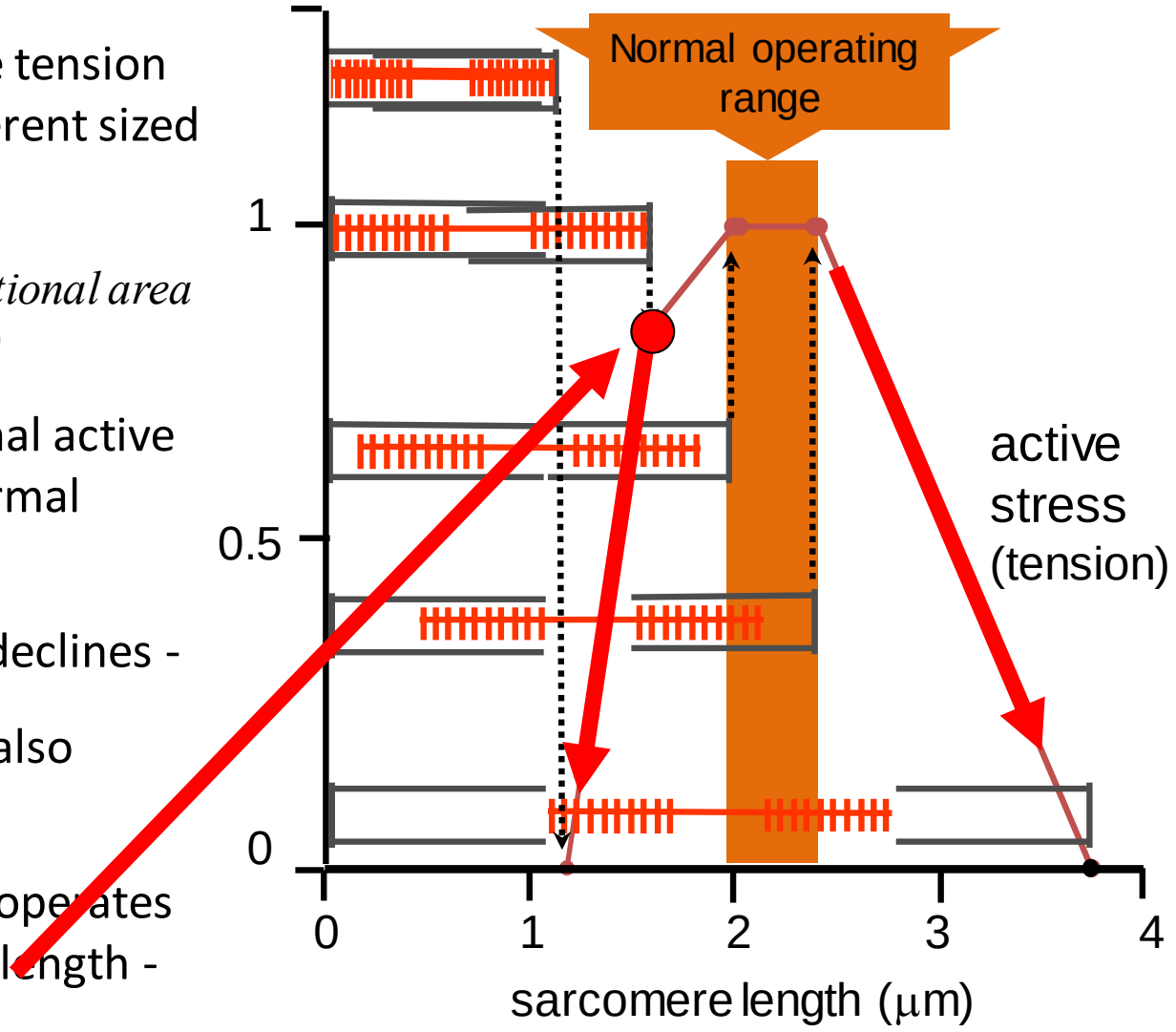


Watch video # 2!!

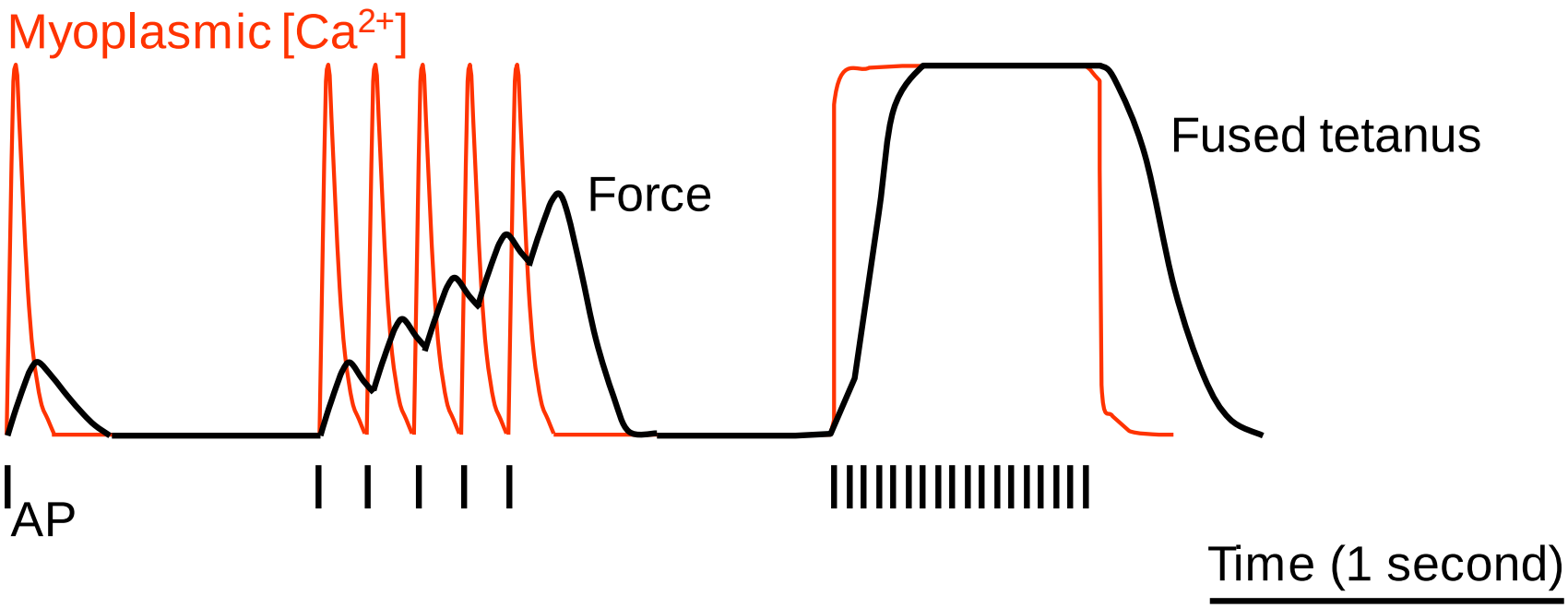
Muscle Mechanics

Tension as a Function of Sarcomere Length

- Stress is used to compare tension (force) generated by different sized muscles
  - *stress = force/cross-sectional area of muscle; units kg/cm²)*
- In skeletal muscle, maximal active stress is developed at normal resting length ~ 2 μm
- At longer lengths, stress declines -
- At shorter lengths stress also declines -
- Cardiac muscle normally operates at lengths below optimal length -



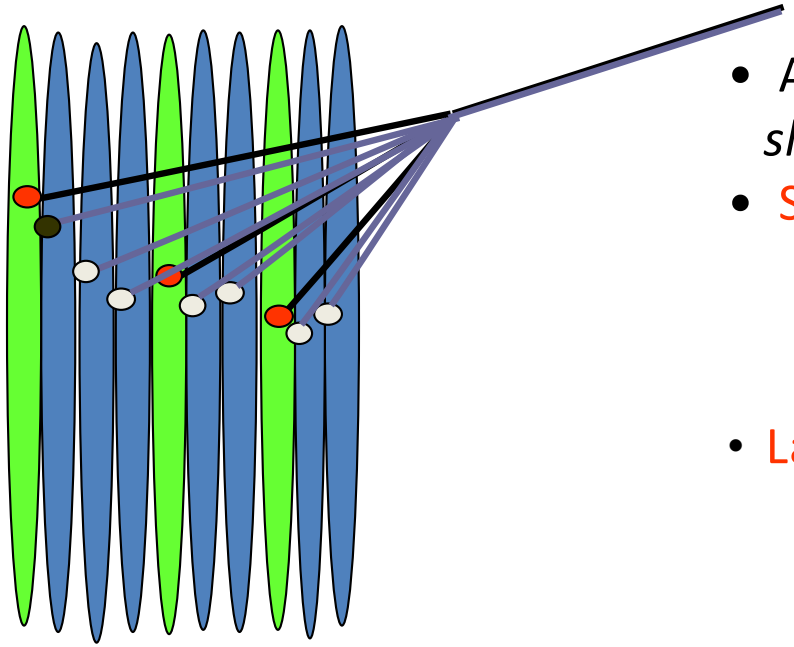
Frequency Summation of Twitches and Tetanus



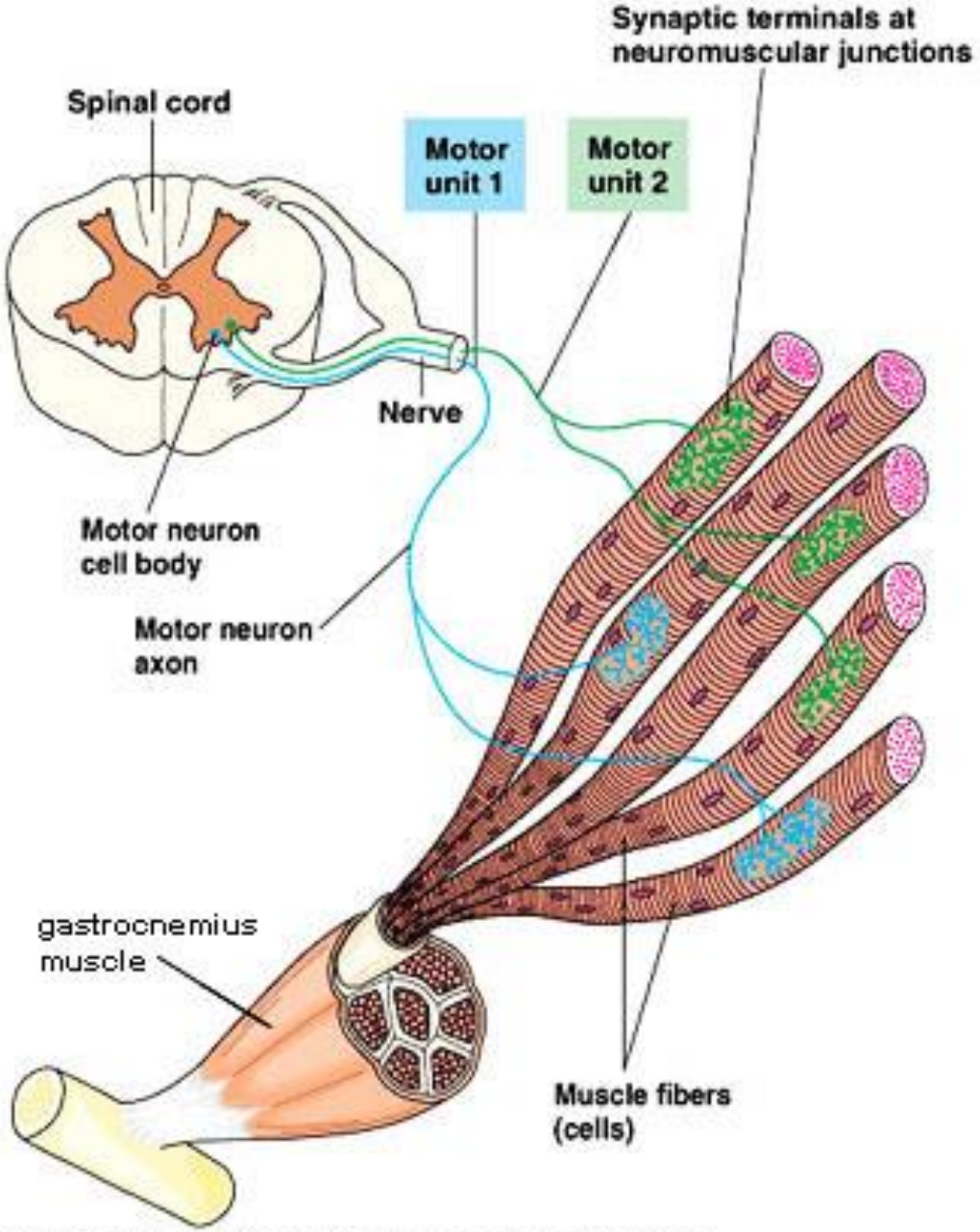
- Myoplasmic Ca^{2+} falls (initiating relaxation) before development of maximal contractile force
- If the muscle is stimulated before complete relaxation has occurred the new twitch will sum with the previous one etc.
- If action potential frequency is sufficiently high, the individual contractions are not resolved and a 'fused tetanus' contraction is recorded.

Motor Unit:

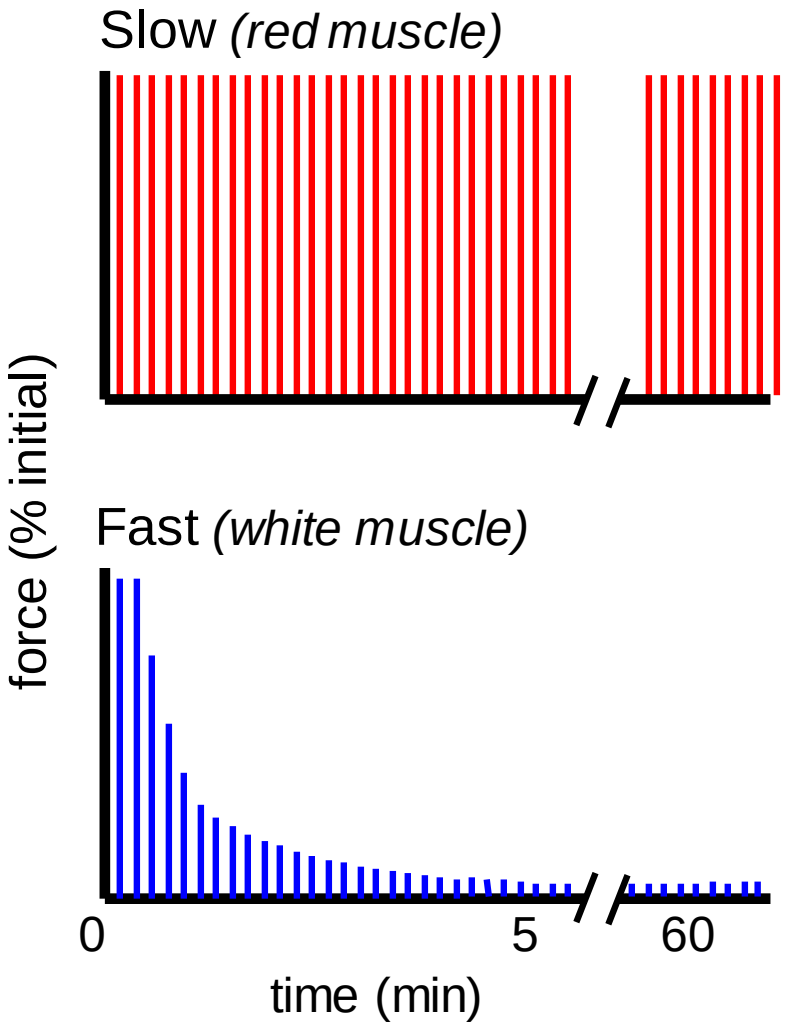
All the muscle fibers innervated by a single nerve fiber are called a motor unit.



- All fibers are same type *(fast or slow)* in a given motor unit
- Small motor units *(eg, larnxy, extraocular)*
  - as few as 10 fibers/unit
  - precise control
  - rapid reacting
- Large motor units *(eg, quadriceps muscles)*
  - as many as 1000 fibers/unit
  - coarse control
  - slower reacting



Types of Skeletal Muscle



- fast and slow fibers show different resistance to fatigue
- slow fibers
  - oxidative
    - small diameter
    - high myoglobin content
    - high capillary density
    - many mitochondria
    - low glycolytic enzyme content
- fast fibers
  - glycolytic

Types of Skeletal Muscle

- speed of twitch contraction -

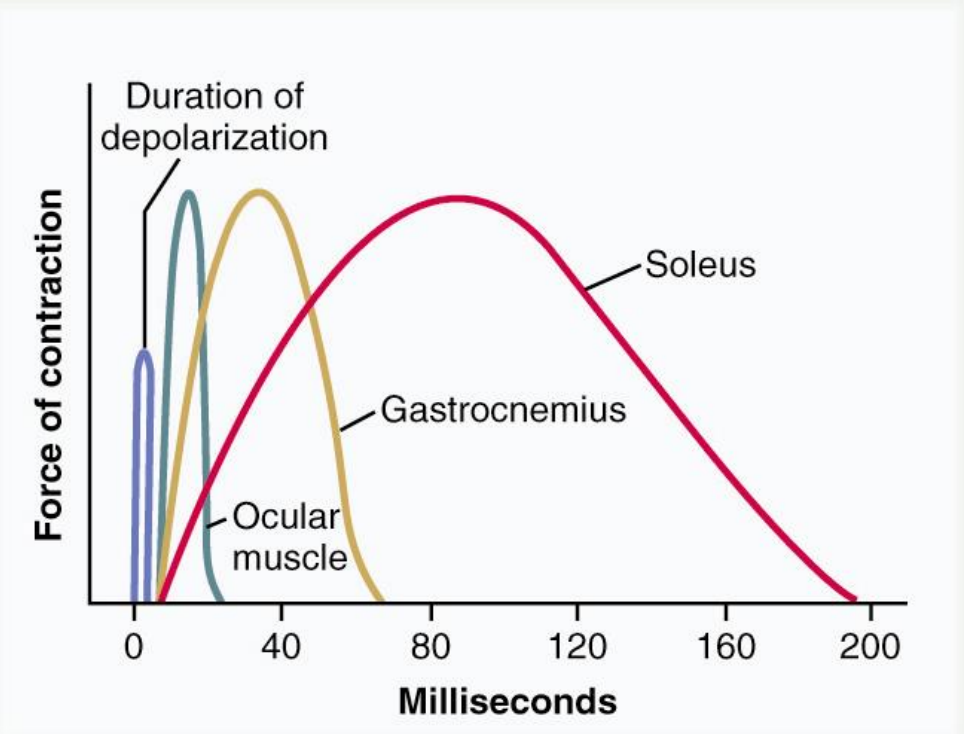
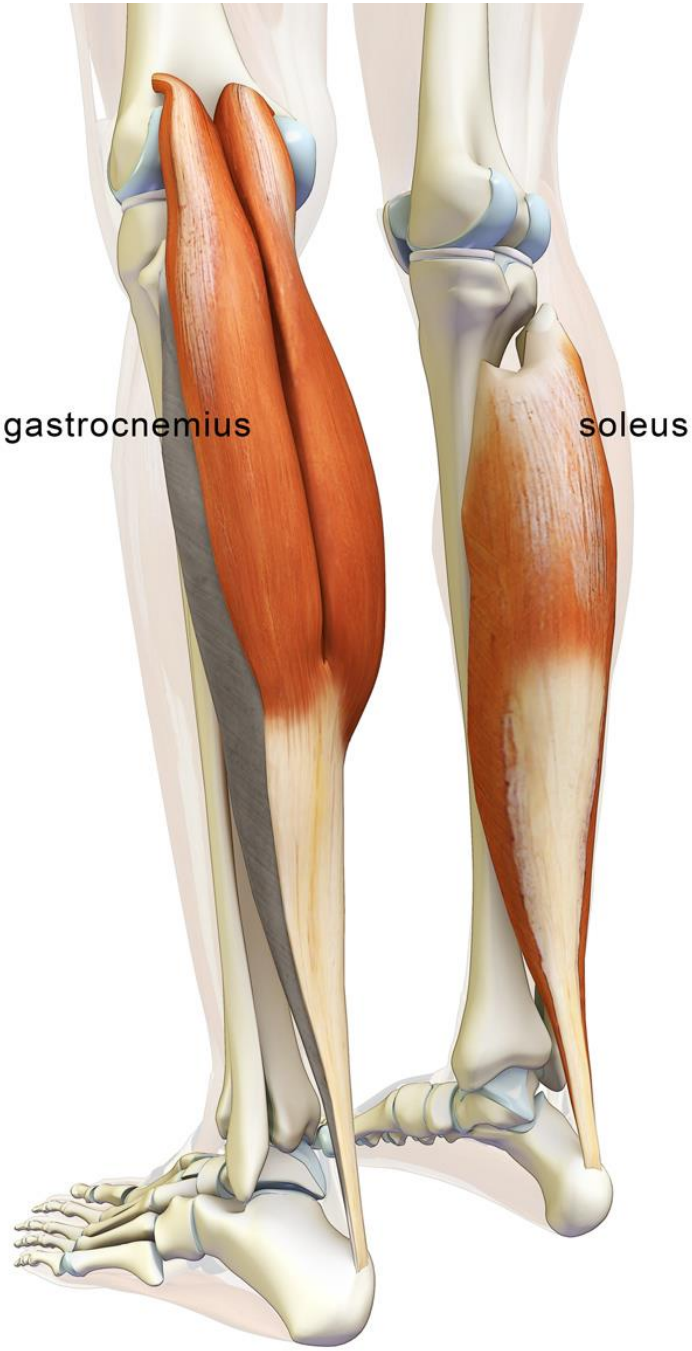


Figure 6-12; Duration of isometric contractions for different types of mammalian skeletal muscles, showing a latent period between the action potential (depolarization) and muscle contraction.

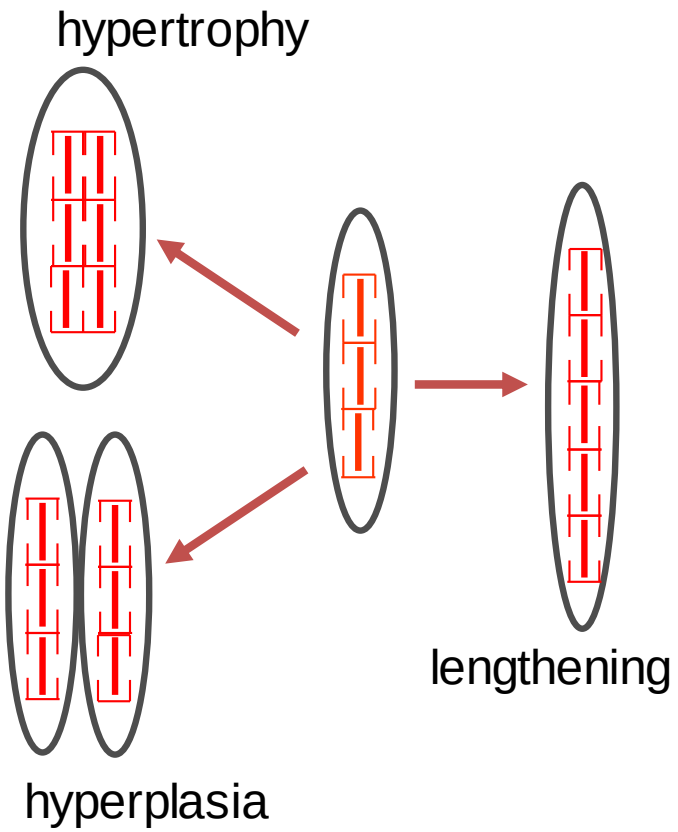
- Speed of contraction determined by V_{max} of myosin ATPase.
  - High V_{max} *(fast, white)*
    - rapid cross bridge cycling
    - *rapid rate of shortening (fast fiber)*
  - Low V_{max} *(slow, red)*
    - slow cross bridge cycling
    - slow rate of shortening (slow fiber)
- Most muscles contain both types of fiber but proportions differ
- All fibers in a particular motor unit will be of the same type i.e., fast or slow.

- Ocular movements must be extremely rapid to maintain fixation of the eyes on specific objects to provide accuracy of vision. The gasrocnemius muscle must contract moderately rapidly to provide sufficient velocity of limb movement for running and jumping, and the soleus muscle is concerned principally with slow contraction for continual, long-term support of the body against gravity.


gastrocnemius
soleus

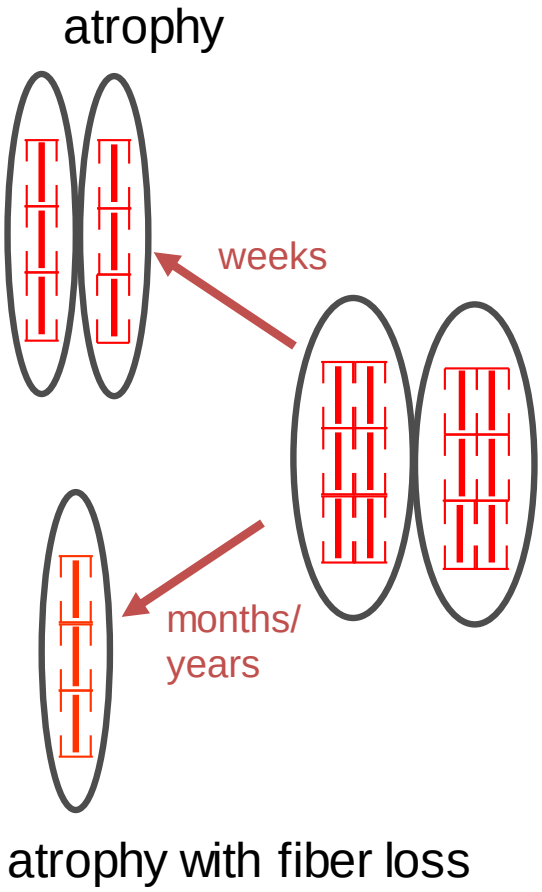
Muscle Remodeling - *growth*

- When the total mass of a muscle increases, this is called *muscle hypertrophy.* When it decreases, the process is called *muscle atrophy.*



- Hypertrophy *(common, weeks)*
  - Caused by near maximal force development *(eg. weight lifting)*
  - Increase in actin and myosin
  - Myofibrils split
- Hyperplasia *(rare)*
  - Formation of new muscle fibers
  - Can be caused by endurance training
- Hypertrophy and hyperplasia
  - Increased force generation
  - No change in shortening capacity or velocity of contraction
- Lengthening *(normal)*
  - Occurs with normal growth
  - No change in force development
  - Increased shortening capacity
  - Increased contraction velocity

Muscle Remodeling - *atrophy*



- Causes of atrophy
  - Denervation/neuropathy
  - Sedentary life style
  - Plaster cast
  - Space flight (zero gravity)
- Muscle performance
  - Decreased max force of contraction
  - Decreased velocity of contraction
- Atrophy with fiber loss
  - Disuse for 1-2 years
  - Very difficult to replace lost fibers

Chapter 8:

Contraction and Excitation of Smooth Muscle

Types of Smooth Muscle

- Mononucleate cells with no striations *(smooth in polarized light)*.
- Form muscular walls of hollow organs - gut, airways, blood vessels & urogenital system
- 2 sorts of organization
  - **Unitary:** sheets of electrically coupled cells which act in unison *(**a 'syncytium'** e.g. gut and bladder)*
  - **Multiunit:** tissue made of discrete bundles of cells (no coupling) which are densely innervated and contract only in response to its innervation *(e.g. iris)*

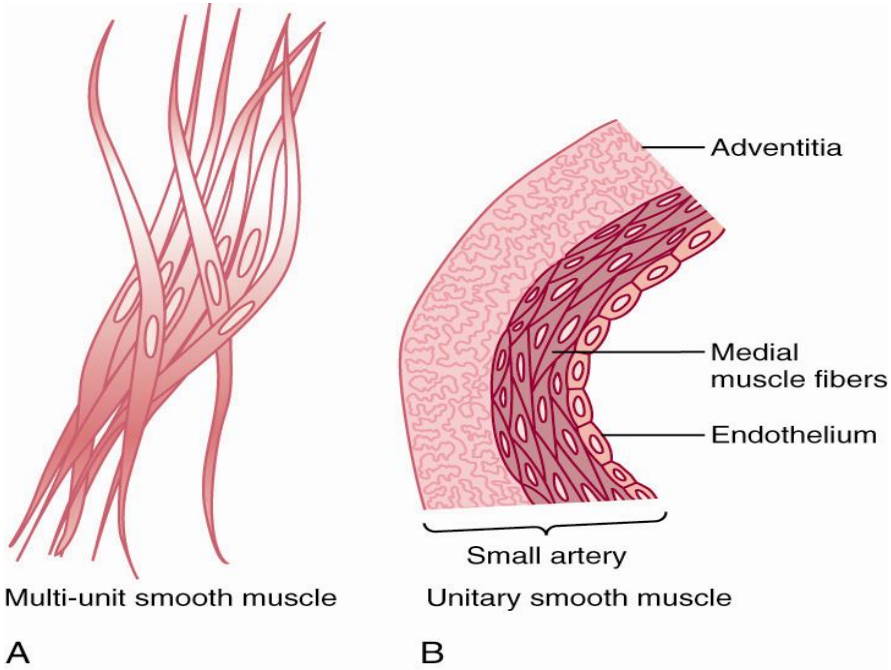
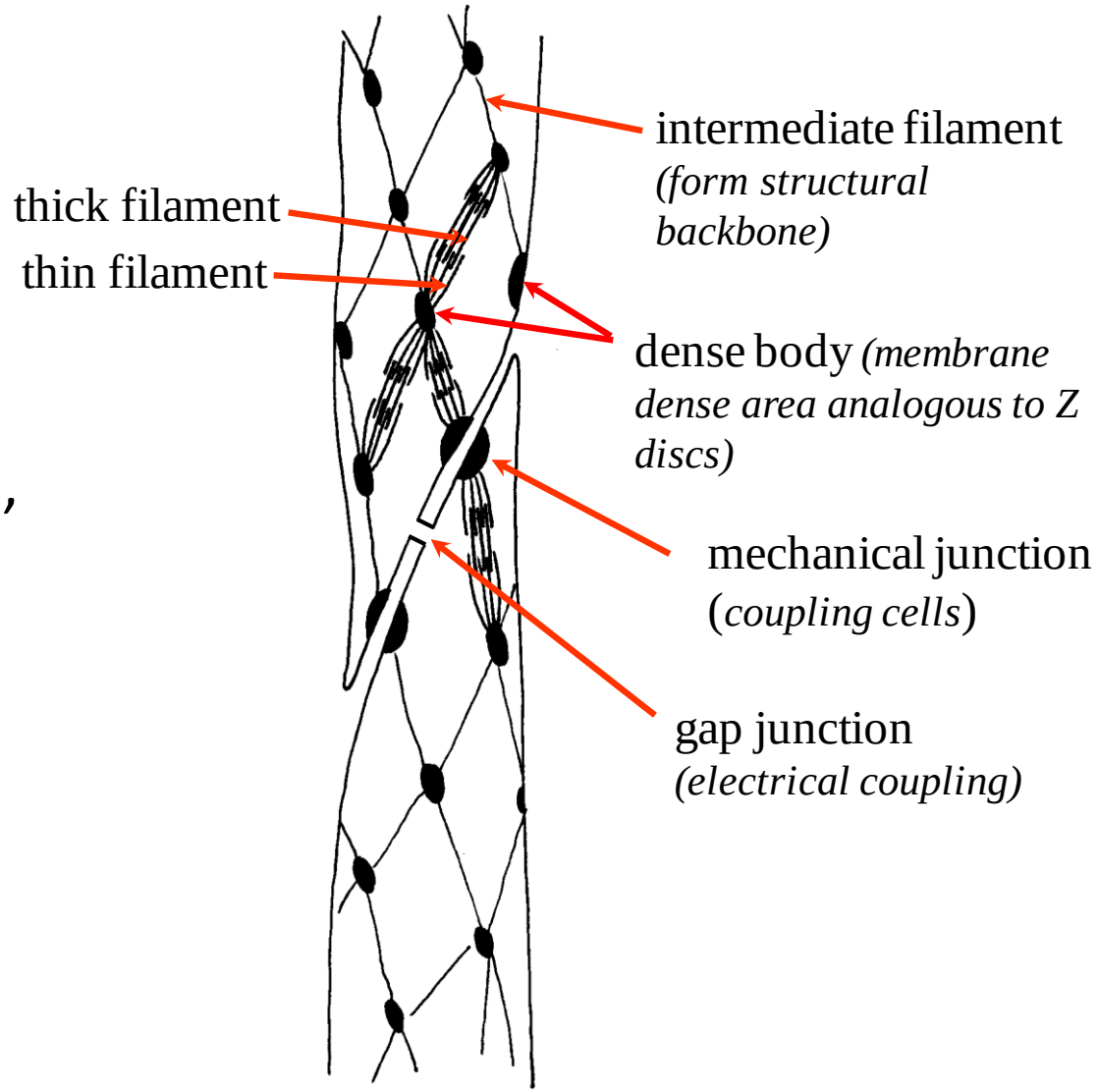


Figure 8-1; Multi-unit (A) and unitary (B) smooth muscle.

Special features of smooth muscle

Smooth muscle:

- Can operate over large range of lengths
- Is very energy efficient
- Can maintain force for long periods (hours, days, weeks) via latch state
- Can be myogenic (spontaneously active)
- Has Ca^{2+} action potentials. Ca entering through channels is a very important source of calcium
- Poorly developed SR



Neuromuscular Junction

Important points

- Autonomic nerve fibers branch and form "diffuse junctions" with underlying smooth muscle fibers.
- **Varicosities** in the terminal axons contain neurotransmitter.
- Excitation is transmitted by Ca action potential or simple diffusion of Ca into fiber.

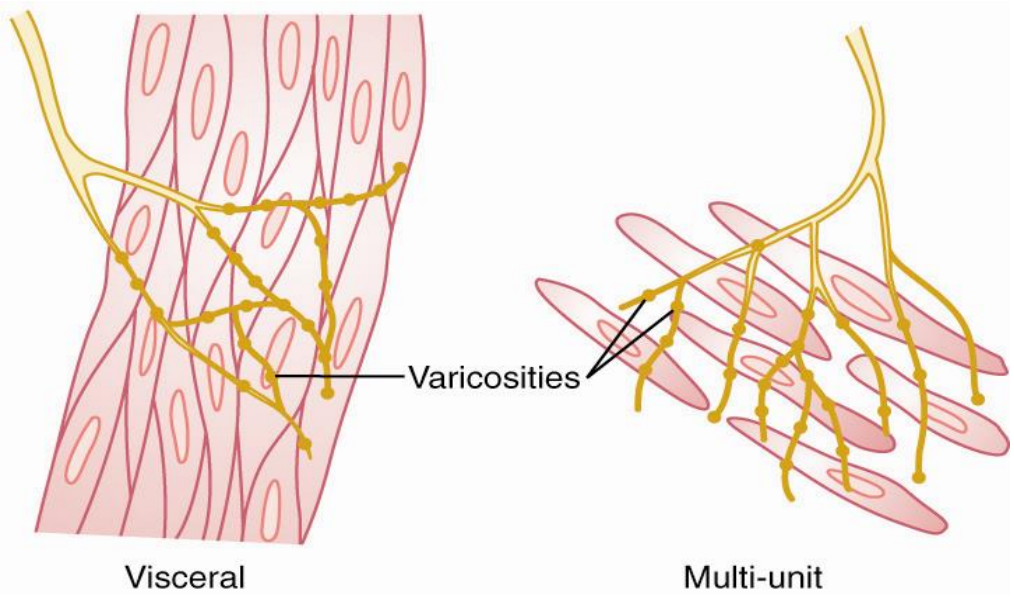
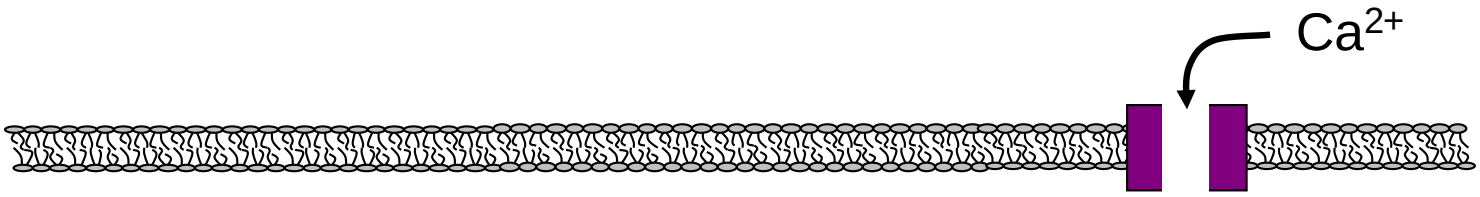


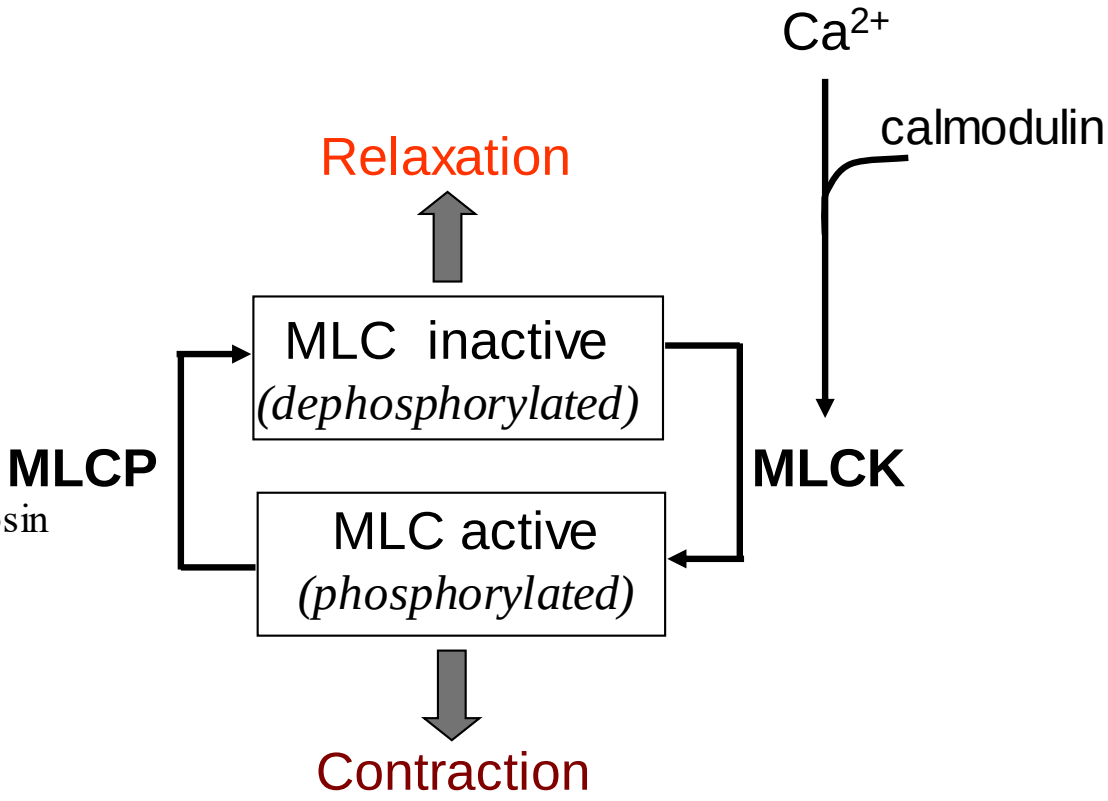
Figure 8-3; Guyton & Hall

Contraction-Relaxation – *myosin based regulation*



Important points:

1. Initiated by calcium
2. Calcium binds to calmodulin (instead of troponin as in skm)
3. Ca-calmodulin-MLCK complex leads to phosphorylation of MLC (requires 1 ATP)
4. MLC is part of myosin head
5. Phosphorylated myosin head binds to actin and power stroke occurs automatically
6. A second ATP is required to release myosin head from actin
7. Cross-bridge cycling requires both MLCK and MLCP



MLCK, myosin light chain kinase
MLCP, myosin light chain phosphatase

Muscle Metabolic Systems

- Phosphocreatine (also called creatine phosphate) has a high-energy phosphate bond and after decomposion to creatine and phosphate ion, large amounts of energy is released.
- The stored glycogen in muscle can be split into glucose and the glucose then used for energy.
- glucose, fatty acids, and amino acids from the foodstuffs—after some inter- mediate processing—combine with oxygen to release tremendous amounts of energy that are used to convert AMP and ADP into ATP

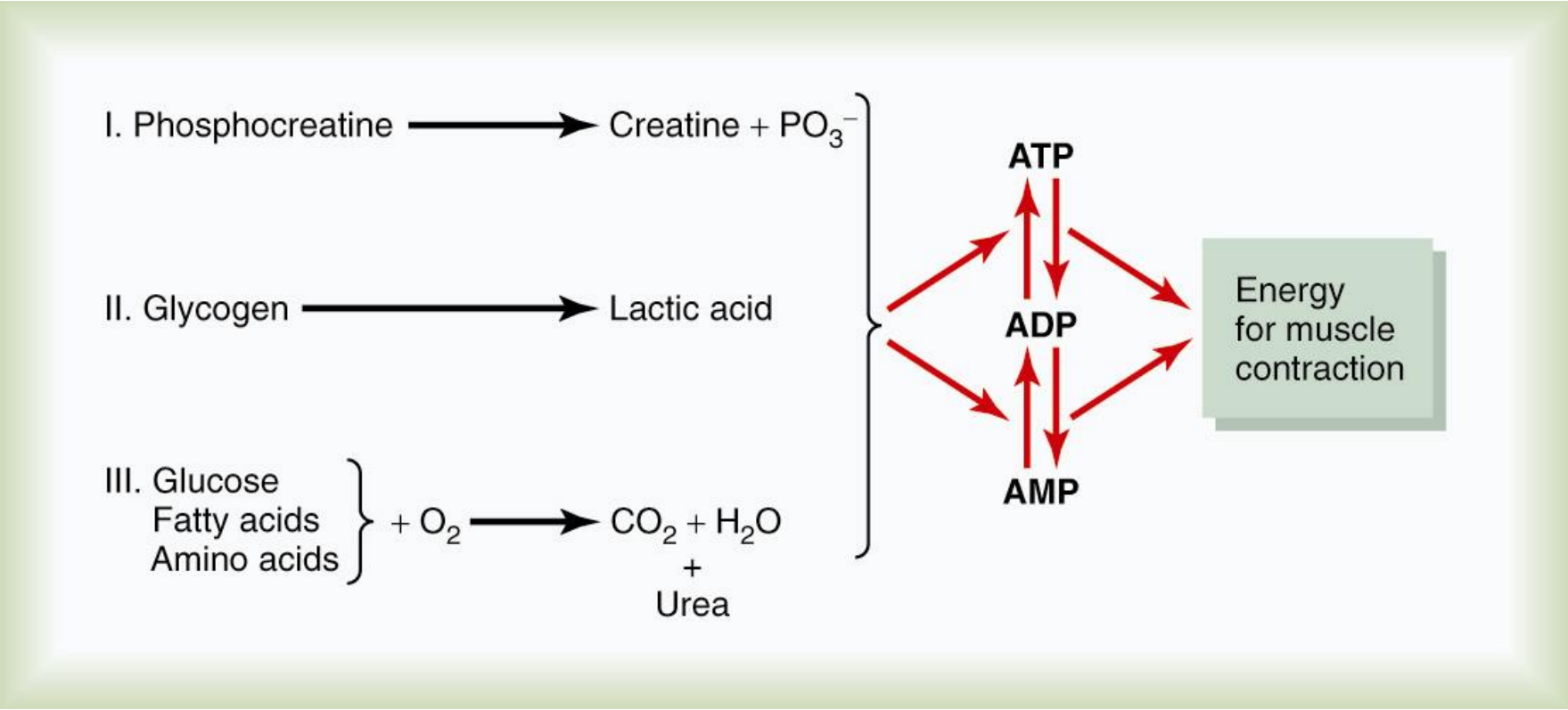


Figure 84-1; Important metabolic systems that supply energy for muscle contraction.

Muscle Metabolic Systems

- phosphate
  - enough stored for 8-10 sec max work
  - can supply 4x ATP/min as aerobic
- glycolysis
  - anaerobic
  - strongly inhibited by low pH
  - forms lactic acid
  - can supply 2.5x ATP/min as aerobic

- Muscle Metabolic Systems

- aerobic can last indefinitely
- metabolic recovery