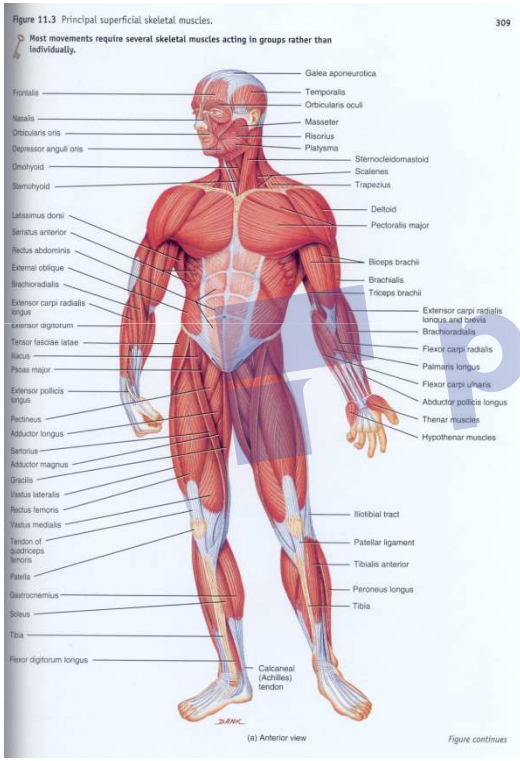
Physiology of Skeletal Muscle Contraction



Outline

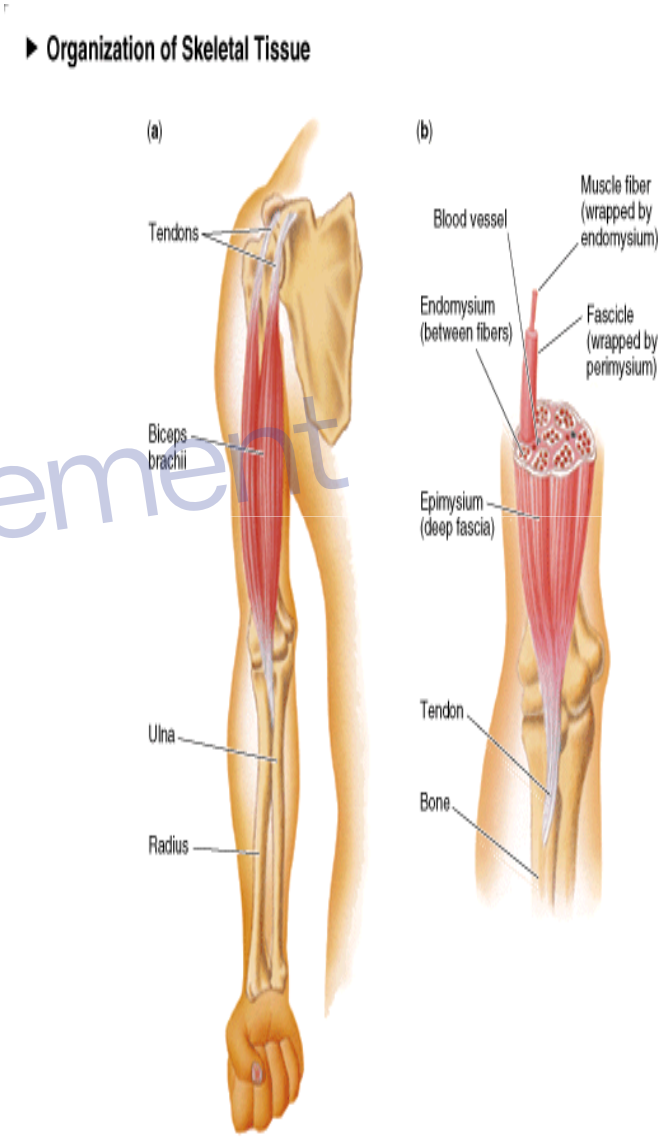
- **Objectives**
- **Background Knowledge**
- Characteristics of skeletal muscle
- Structure Of The Skeletal Muscle
  - *Microstructure*
  - *The Sarcomere*
  - Structure Of Thin Filaments (Actin Filament)
  - Accessory proteins
  - Structure Of Thick Filament (Myosin Filament)
- Skeletal Muscle Contractions
  - Mechanism Of Muscle Contraction
  - Sliding filament theory
  - Walk-along theory
- Role Of Ca++ On Regulation of Muscle Contraction
- Roles Of ATP In Skeletal Muscle Contraction
- **Summary**
- **Quick Assessment**

Objectives

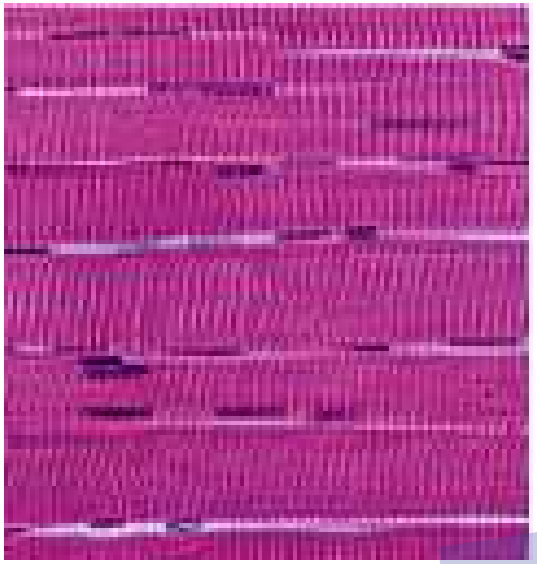
- To know the Organization of Skeletal Muscle
- To know the Characteristics of skeletal muscle
- To know the Structure Of The Skeletal Muscle
- To know the mechanism of Skeletal Muscle Contractions
- To know the role of Ca++ on Regulation of Muscle Contraction
- To know the roles of ATP In Skeletal Muscle Contraction

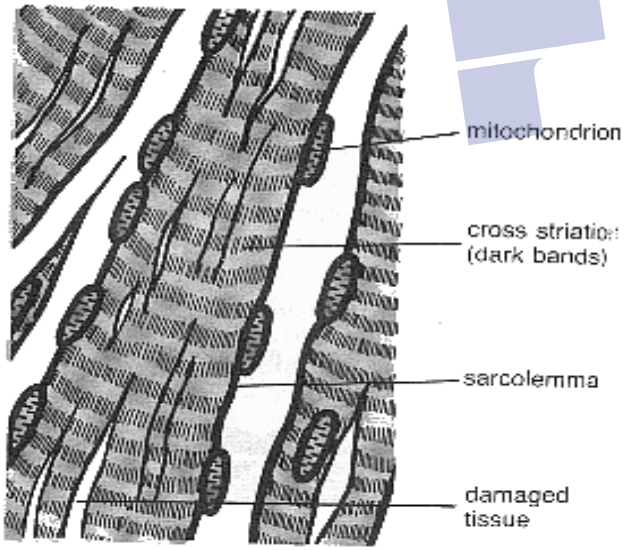
Background Knowledge

- Muscle is contractile tissue and is derived from the mesodermal layer of embryonic germ cells.
- Muscle fibres are large, multi-nucleated cells that are 10-100 mm in diameter and up to 30 cm long. The fibers are tapered or bifurcated at the ends.
- Human body contains over 400 skeletal muscles
  - 40-50% of total body weight.
- Functions of skeletal muscle
  - Force production for locomotion and breathing
  - Force production for postural support
  - Heat production during cold stress



Characteristics of Skeletal Muscle



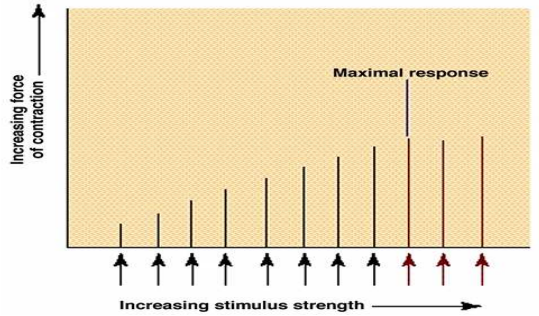


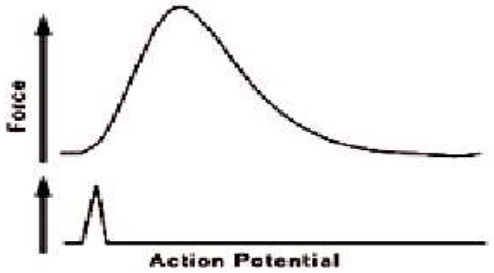
Striated appearance of skeletal muscle

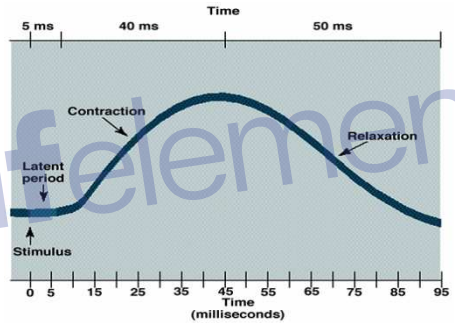
- striated
- Multinucleated (syncytium)
- under the control of the voluntary (somatic) nervous system
- contains myofibrils composed of sarcomeres (gives it the striated appearance)
- contains T tubules
- no gap junctions
- well developed sarcoplasmic reticulum
- fast contracting
- every fiber is controlled by a nerve
- rich network of capillaries

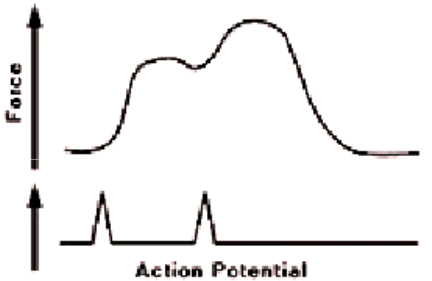
Characteristics of Skeletal Muscle

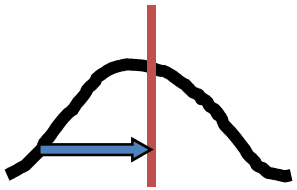
- Excitability-
- Contractibility-
- Extensibility-
- Elasticity-
- All-or-None response
- Summation
- Tetanus
- Refractory Period
- Muscle Fatigue
- Rigor Mortis



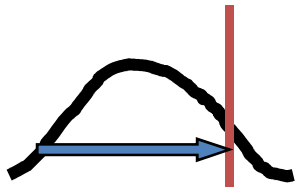




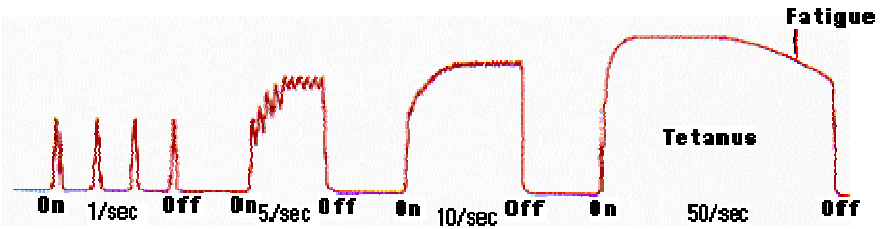




Skeletal Muscle

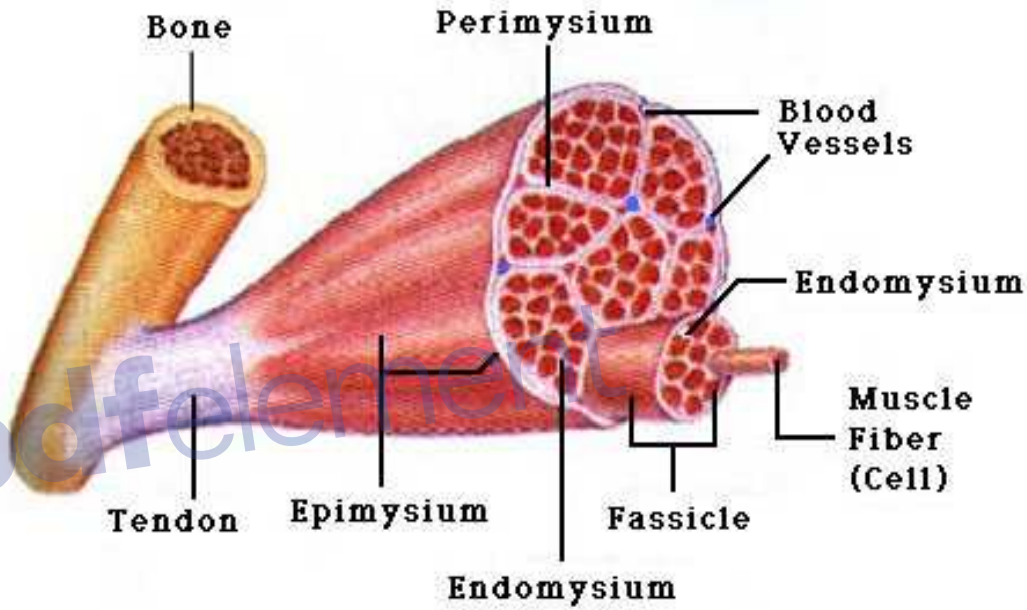


Cardiac Muscle



Structure Of The Skeletal Muscle

- Epimysium
  - Surrounds entire muscle
- Perimysium
  - Surrounds bundles of muscle fibers
- Endomysium
  - Surrounds individual muscle fibers



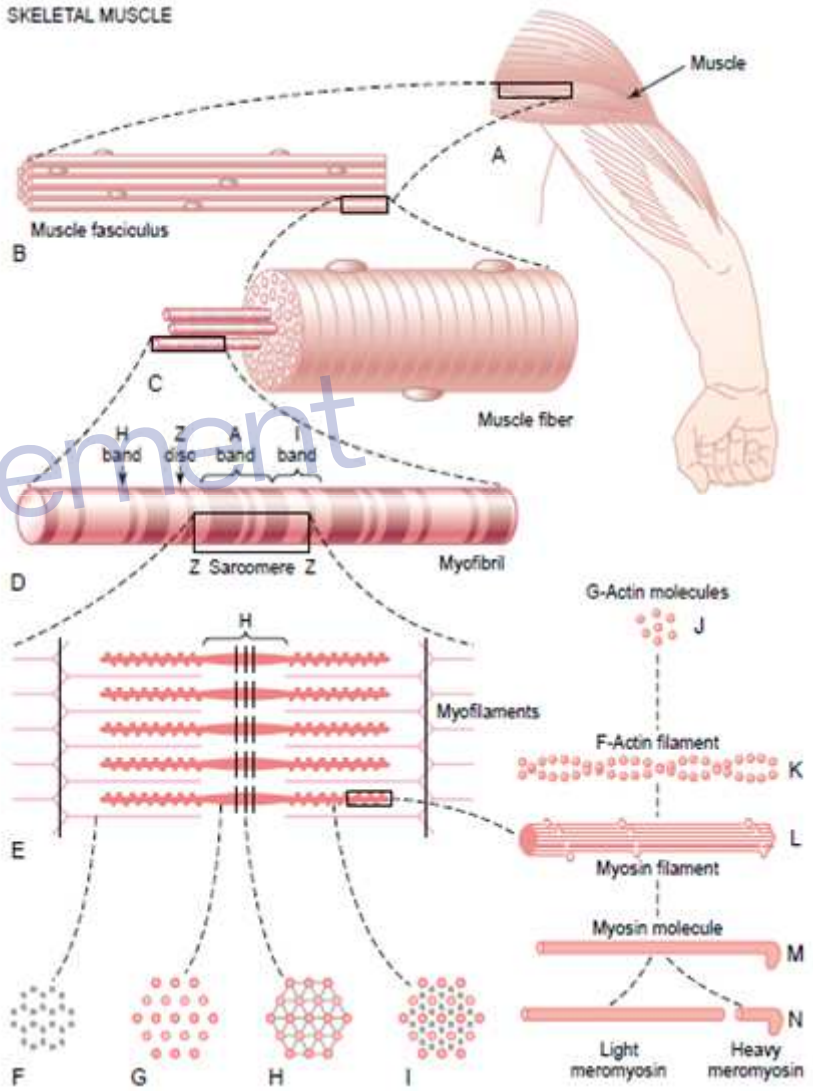
Structure of skeletal muscle

Muscle cell membrane - Sarcolemma
The cytoplasm of muscle cells - sarcoplasm

Structure of Skeletal Muscle: *Microstructure*

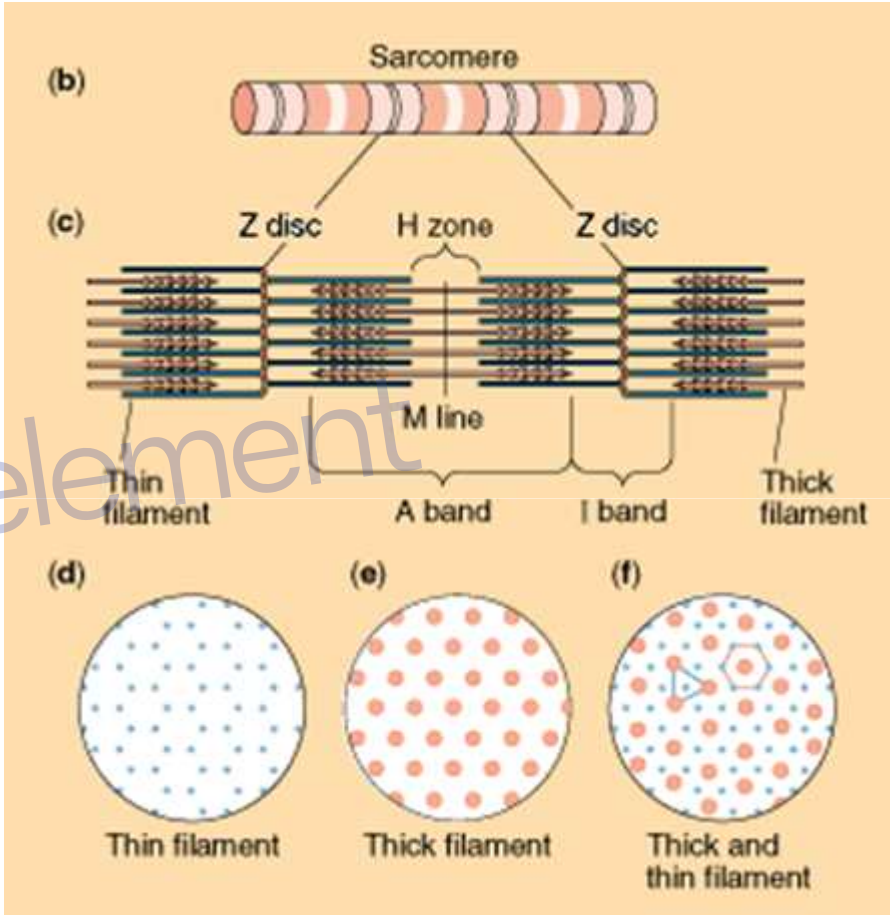
- Myofibrils are composed of myofilaments of the contractile proteins actin and myosin.

- Myofibrils
  - Threadlike strands within muscle fibers
  - Actin (thin filament)
    - Troponin
    - Tropomyosin
  - Myosin (thick filament)



Structure of Skeletal Muscle: *The Sarcomere*

- Further divisions of myofibrils
  - Z-line-The actin filaments are attached (Zwischenscheibe, means between discs in German). The portion of myofibril in between the 'Z' lines is called sacromere.
  - A-band (dark band, A-band: anisotropic).
  - I-band (light bands ,I-bands: isotropic)
  - H band (Henson band),
  - M line-darker area in the centre of the H band
- Within the sarcoplasm
  - Sarcoplasmic reticulum
    - Storage sites for calcium



T tubules (Transverse tubules)
Terminal cisternae

The Structure Of Thin Filaments (Actin Filament)

- Thin filaments- 7 nm wide and 1.0 mm long.
- composed primarily of 3 types of proteins
  - (i) actin, (ii) tropomyosin and (iii) troponin.
  - The ratio of these proteins in the skeletal muscle is 7:1:1.

- The MW of actin filament- 42,000 D.
- The actin filament is a double helix- made up of F-actin.
- F actin is a polymer of small protein called G-actin.
- G-actin subunit has 1 ADP/ATP binding site.
- G-actin molecule has active site for binding with myosin head.

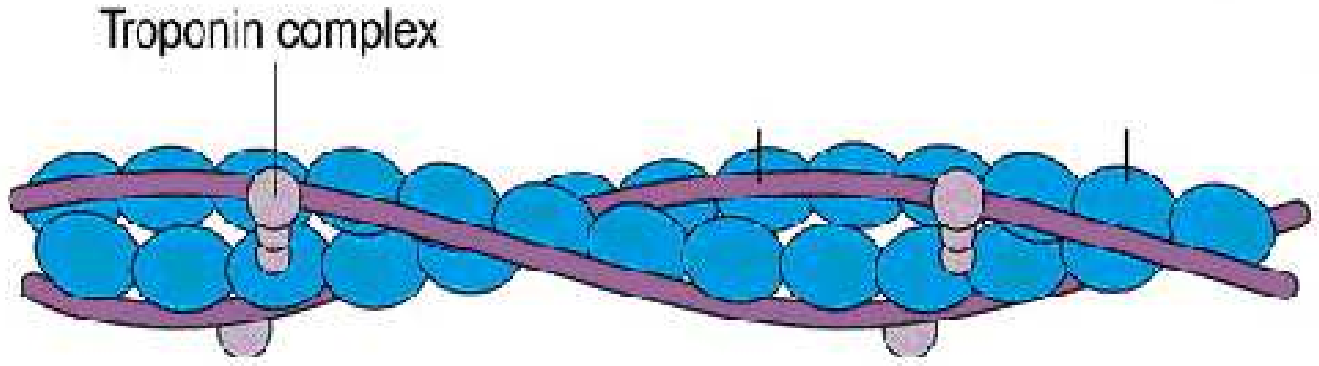
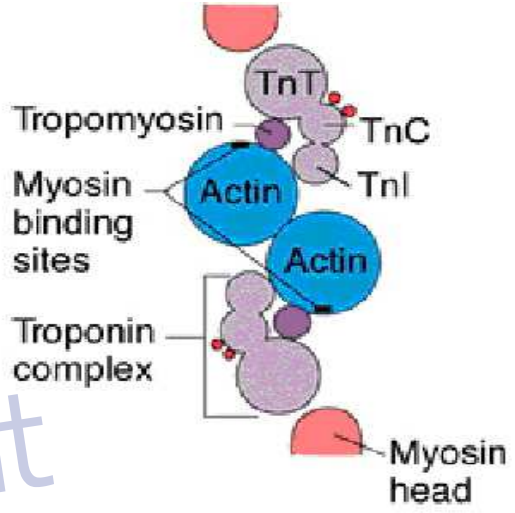


Figure: Molecular structure of thin filament

The Structure Of Thin Filaments (Actin Filament)

- **Accessory proteins-** tropomyosin and troponin.
  - Tropomyosin- MW 35,000 D.
  - elongated consists of 2 chains a, b helically-inter wound heterodimer, spans a length of 7 G-actin residues.
  - preventing interaction between actin and myosin



- Troponin consists of a complex of 3 sepetrate proteins:
- Troponin-T (Tn-T): Attached to tropomysin (molecular weight-30,000 D)
- Troponin-C (Tn-C): Attached to Ca++ ions (molecular weight-18,000 D)
- Troponin-I (Tn-I): Attached to F actin (molecular weight-22,000 D)

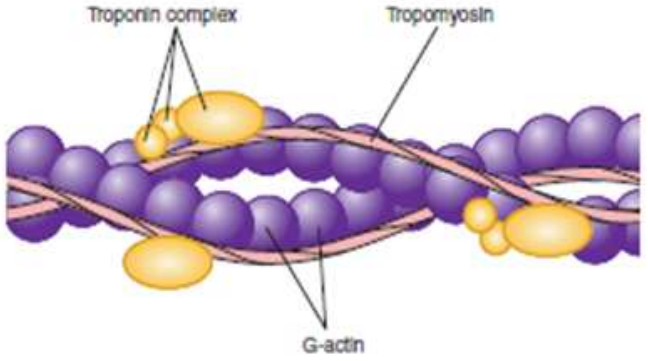


Figure: Showing the proteins of actin filaments

The Structure Of Thick Filament (Myosin Filament)

• Thick myofilaments –myosin, 10-14 nm wide and 1.6 mm long. Each filament -200 myosin molecules. MW- 4, 80, 000 D.

• Each myosin molecule is made up of 6 subunits, 2 very large, heavy chains (HC: MW- 2, 00,000 D), and 4 smaller, light chains (LC: MW-20, 000 D).

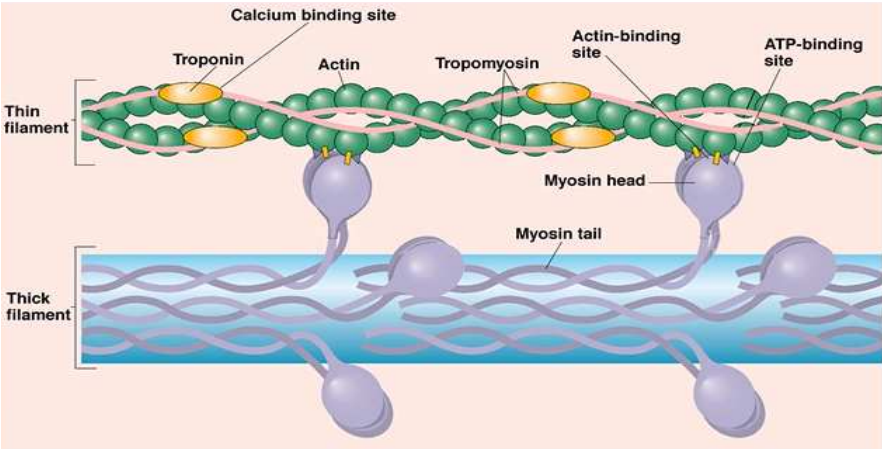
• Tail portion-2 HC- twisted forming a double helix.

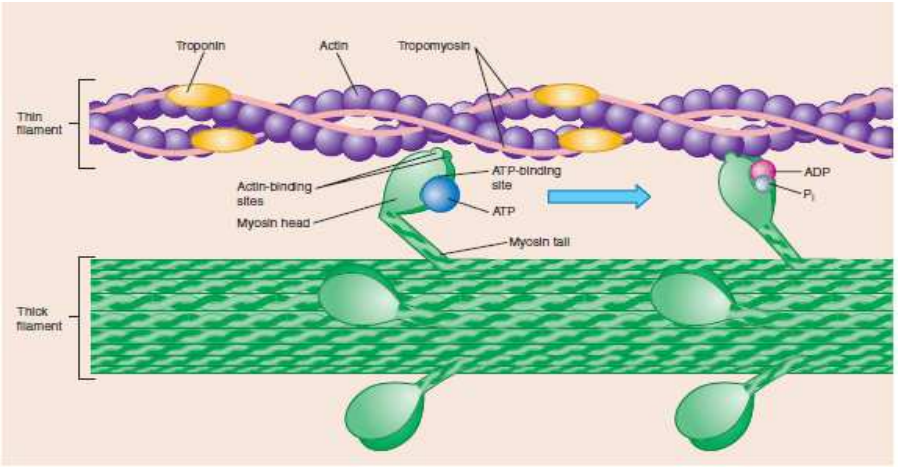
• Globular head (cross-bridges)- 4LC -turns to one side. Binds Ca++ ions with high affinity serve in the regulation of myosin's ATPase activity.

•It has ATP-binding sites

•It has Actin-binding sites

•It has a "hinge"- this allows the head to swivel back and forth, causes muscle contraction.

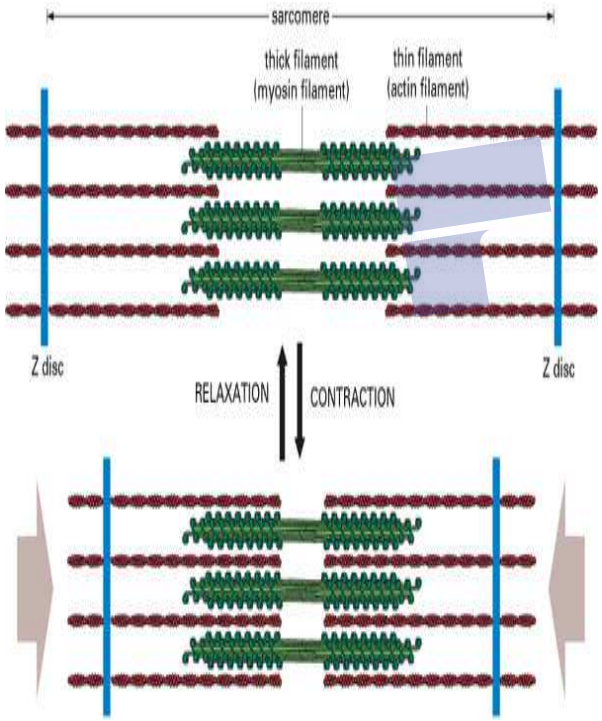




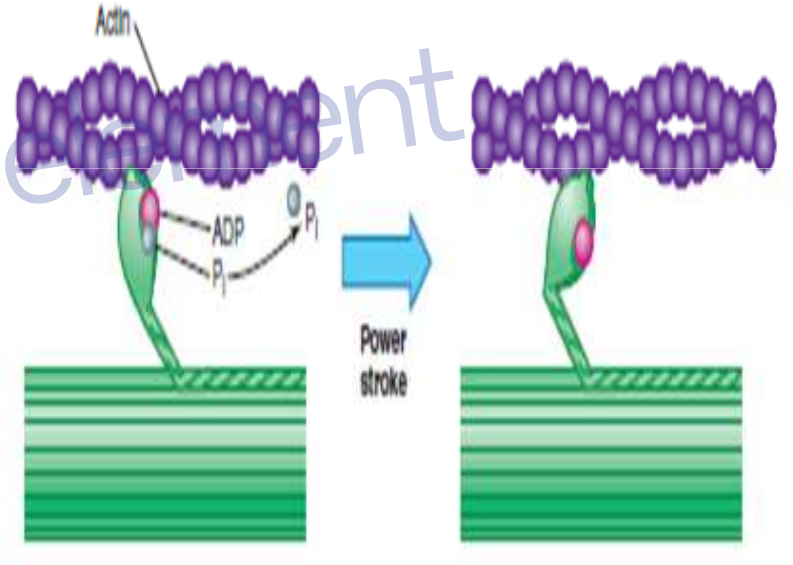
Skeletal Muscle Contractions

The process by which the muscle contraction occurs is supported by two theories.

- Sliding filament theory
- Walk-along theory



Skeletal muscle contraction by Sliding filament theory

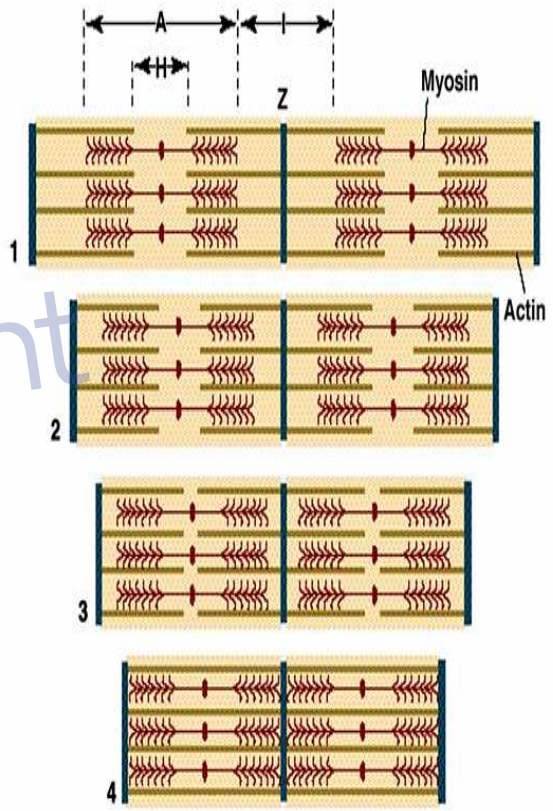


Walk-along theory:

The Power stroke of the cross bridge

Sliding filament theory

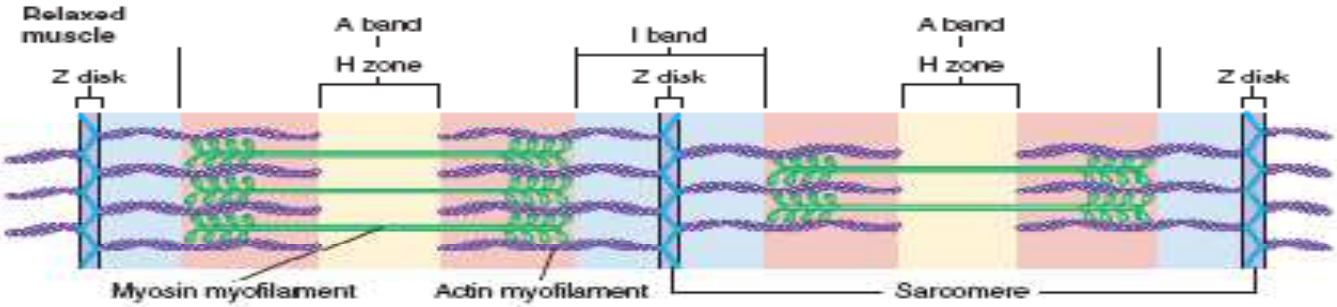
- During muscle contraction, the Z-lines come closer, the width of the I-bands decreases.
- The width of the H-zones decreases, but there is no change in the width of the A-band. Conversely, as a muscle is stretched, the width of the I-bands and H-zones increases, but there is still no change in the width of the A-band.
- The actin and myosin filaments themselves do not change length, but slide past each other.
- Each myosin molecule contains a globular subunit called the myosin head. The myosin heads have two binding sites for:
  (i) The actin molecules and (ii) ATP.
- Activation of the muscle fiber causes the myosin heads to bind to actin. ulls the thin filament a short distance (~10 nm) over the thick filament, causing muscle contraction occurs by a sliding filament mechanism.
- When the linkages break and reform farther along the thin filament, the process repeats.



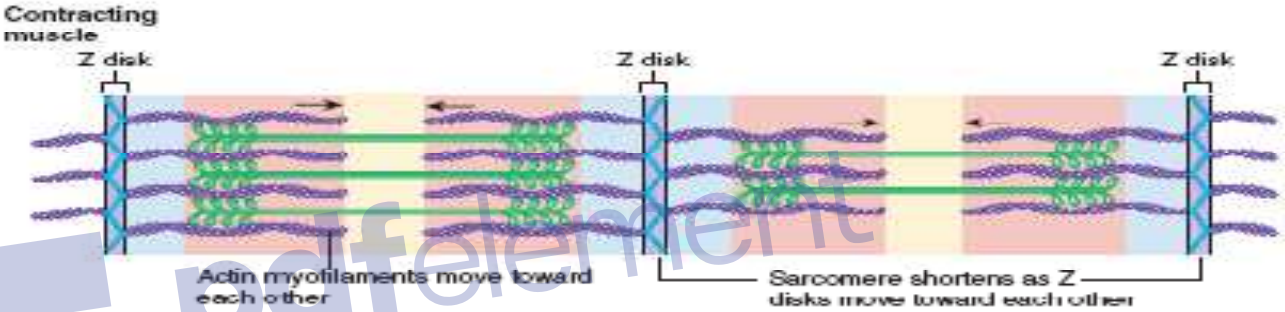
Skeletal muscle contraction by Sliding filament theory

Sliding filament theory

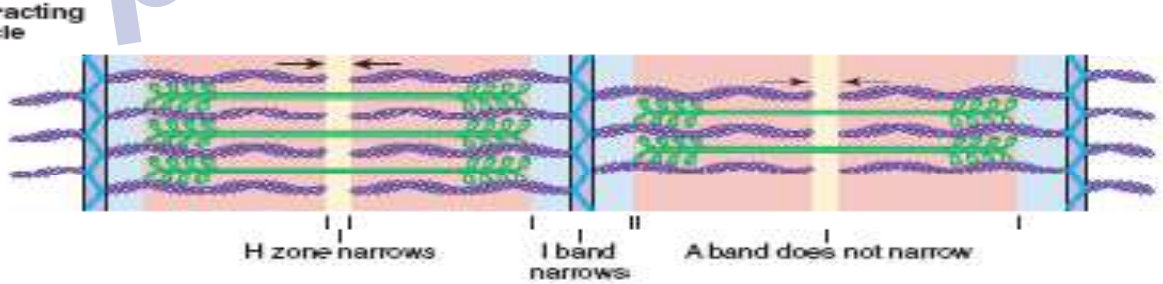
1. Actin and myosin myofilaments in a relaxed muscle (*right*) and a contracted muscle (*#4 below*) are the same length. Myofilaments do not change length during muscle contraction.



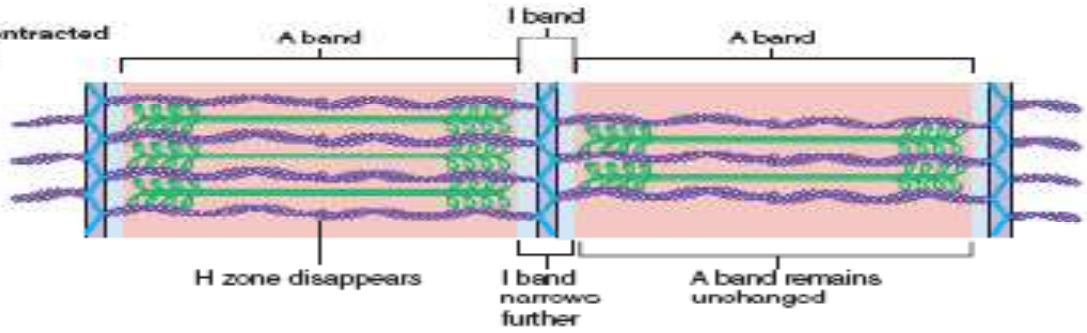
2. During contraction, actin myofilaments at each end of the sarcomere slide past the myosin myofilaments toward each other. As a result, the Z disks are brought closer together, and the sarcomere shortens.



3. As the actin myofilaments slide over the myosin myofilaments, the H zones (*yellow*) and the I bands (*blue*) narrow. The A bands, which are equal to the length of the myosin myofilaments, do not narrow, because the length of the myosin myofilaments does not change.



4. In a fully contracted muscle, the ends of the actin myofilaments overlap and the H zone disappears.



Skeletal Muscle Contractions

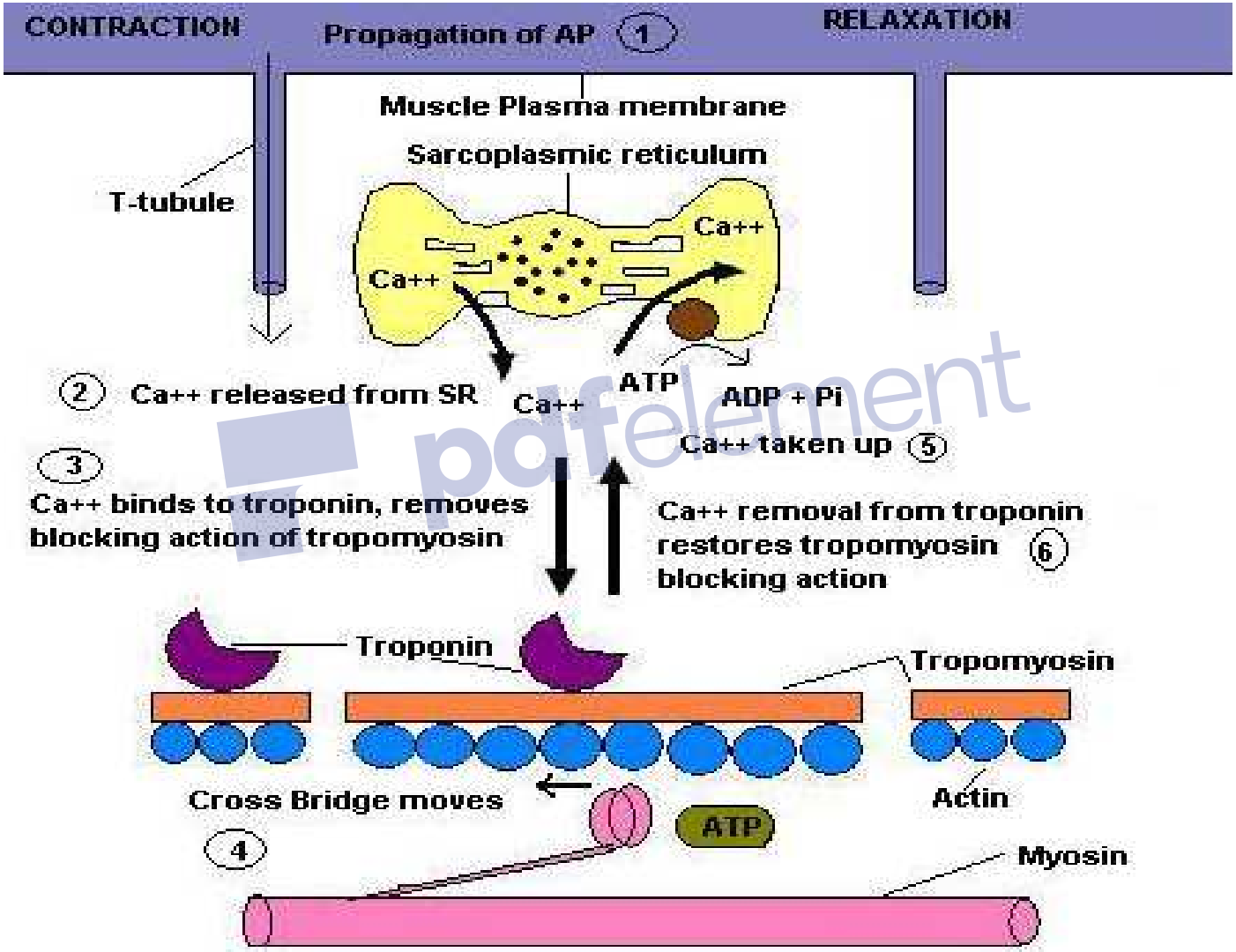
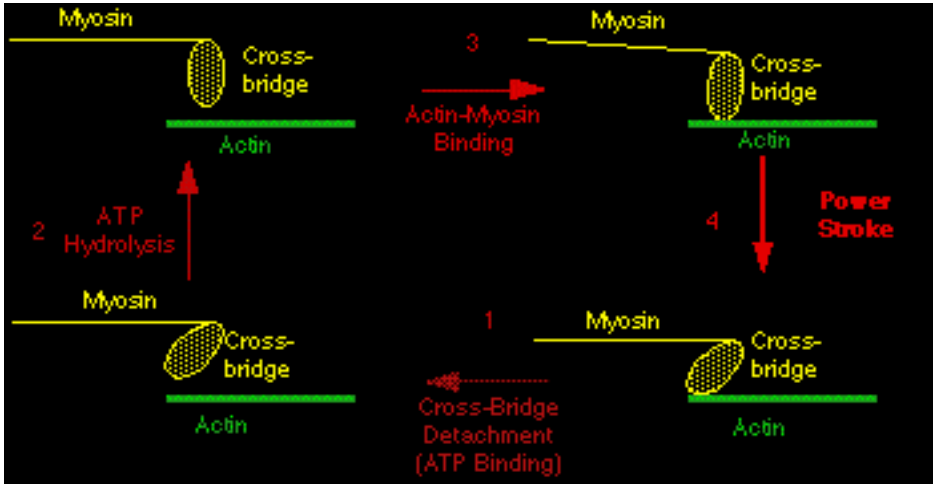


Figure: The steps of skeletal muscle contraction

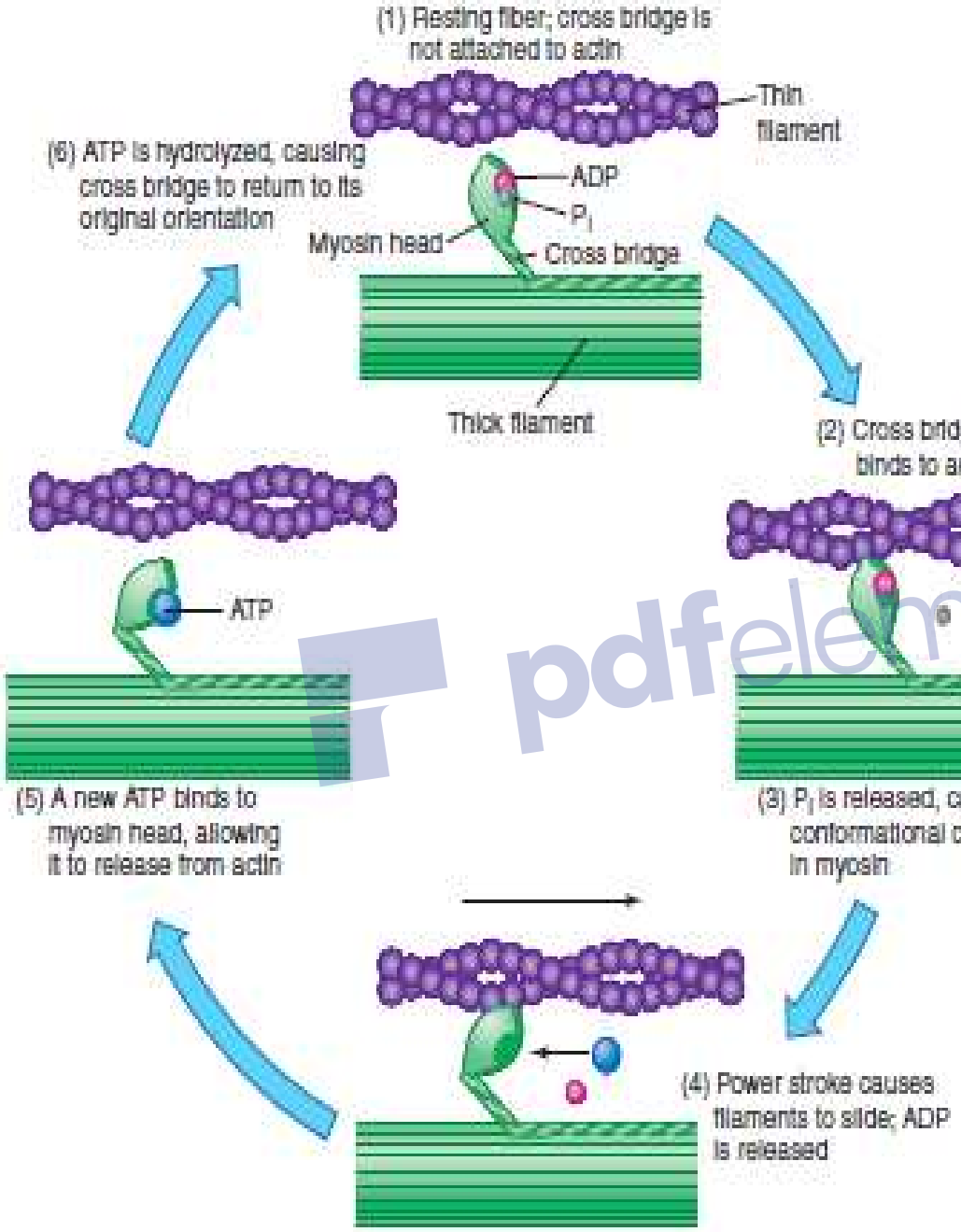
Walk-along theory

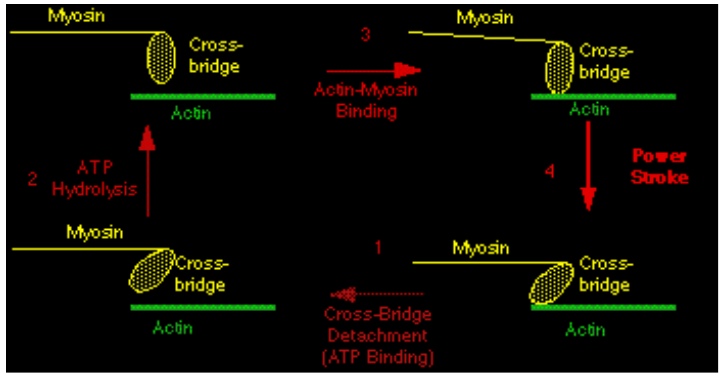
- Binding of Ca^{2+} to actin filament activates the myosin filaments. Myosin attracted to the active sites of the actin filament and the cross-bridge is formed this causes muscle contraction.
- This attachment simultaneously causes changes in the intramolecular forces between the head and arm of the cross-bridge.
- The new alignment of force causes the head to tilt toward the arm and to drag the actin filament along with its. This tilt of the head is called the *power stroke*.
- Immediately after tilting, the head automatically breaks away from the active site, and returns to its normal position, where it combines with a new active site farther down along the actin filament. This causes tilting of the head again to produce a new power stroke, and the actin filament moves one step forward.



- Thus the heads of the cross-bridge bend back and forth an step by step walk along the actin filament this pulls the ends of the actin filaments toward the centre of the myosin filament.

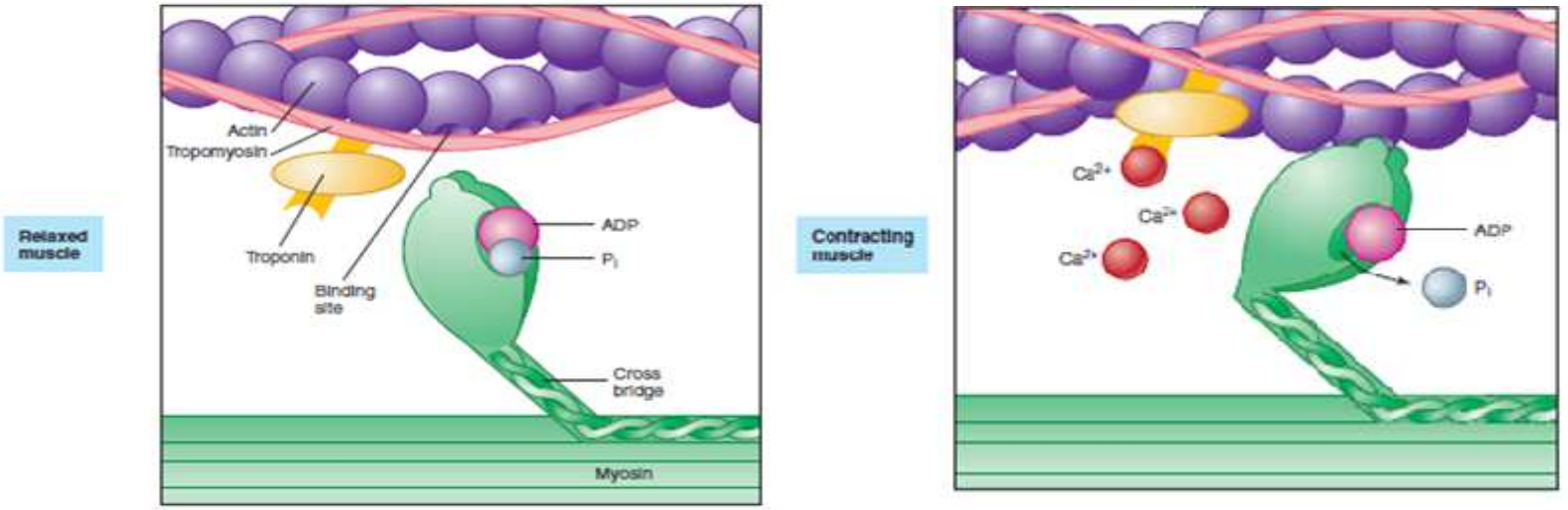
Walk-along theory





Role of Ca++ on Regulation of Muscle Contraction

- Ca^{2+} are need to release the inhibition of ATP hydrolysis by myosin in the presence of regulated actin.
- In the absence of Ca^{2+}(concentration <0.1 mm) Tropomyosin blocks the attachment of myosin to actin.
- In the presence of Ca^{2+}, when Ca^{2+} binds to the Tn-C, there is a conformational change in the troponin complex. The Tn-I dissociates from the actin and the tropomysin.
- The tropomyosin now no longer blocks the interaction of myosin with actin, and muscle contraction occurs.
- Troponin-tropomyosin in the absence of Ca^{2+} prevents only the strongly attached state of myosin but not the weakly attached state.



Roles of ATP in Skeletal Muscle Contraction

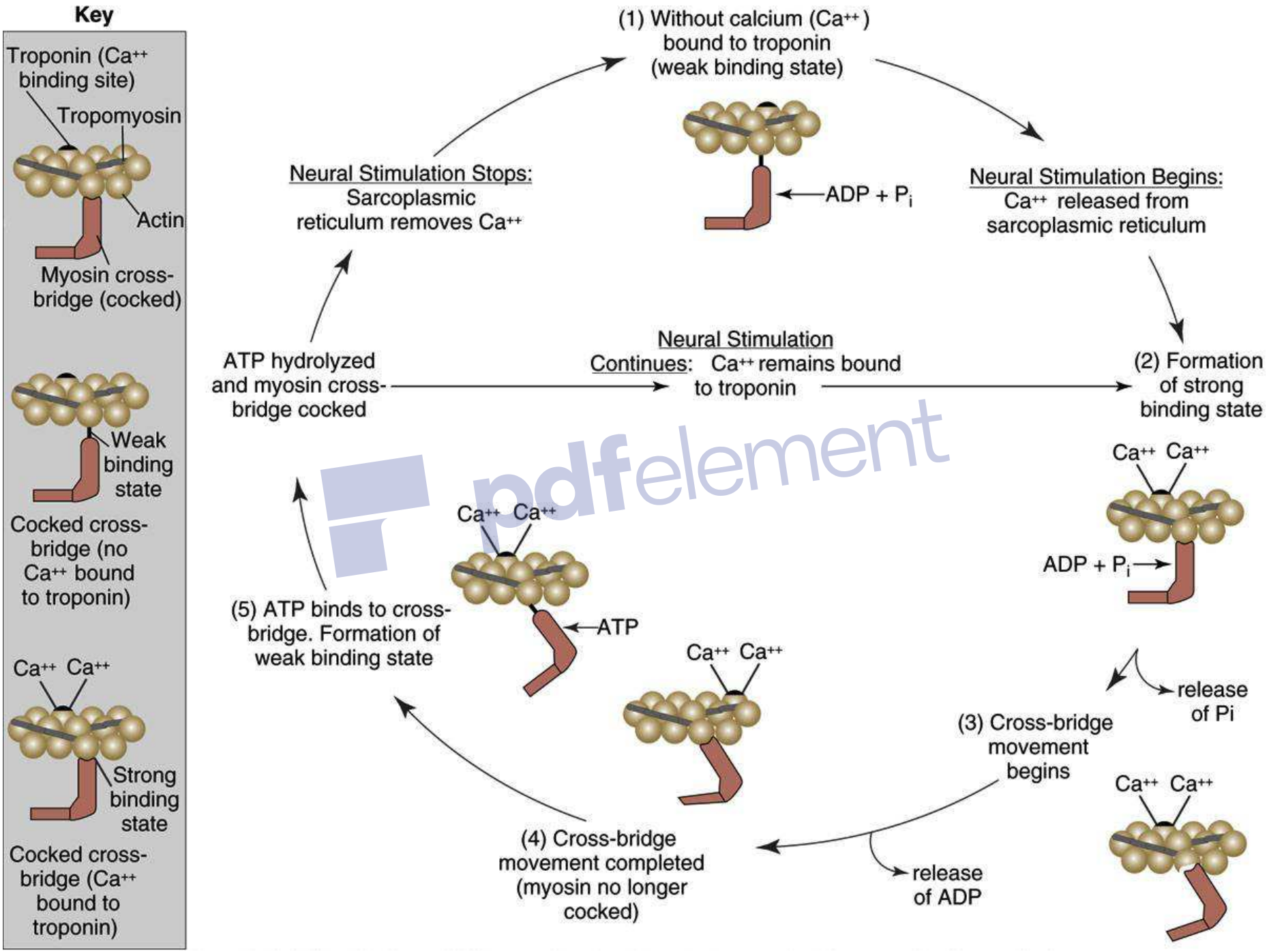
- Large amounts of ATP are cleaved to form ADP during the contraction process; the greater the amount of work performed by the muscle, the greater the amount of ATP that is cleaved (*Fenn effect).*

- First, as in all cells, ATP provides the energy to power the sodium/potassium pump, which keeps intracellular potassium and sodium out of equilibrium with the extracellular medium. Na+, K+ ions are pumped through the muscle fibre membrane to maintain an appropriate ionic environment for the propagation of action potential.

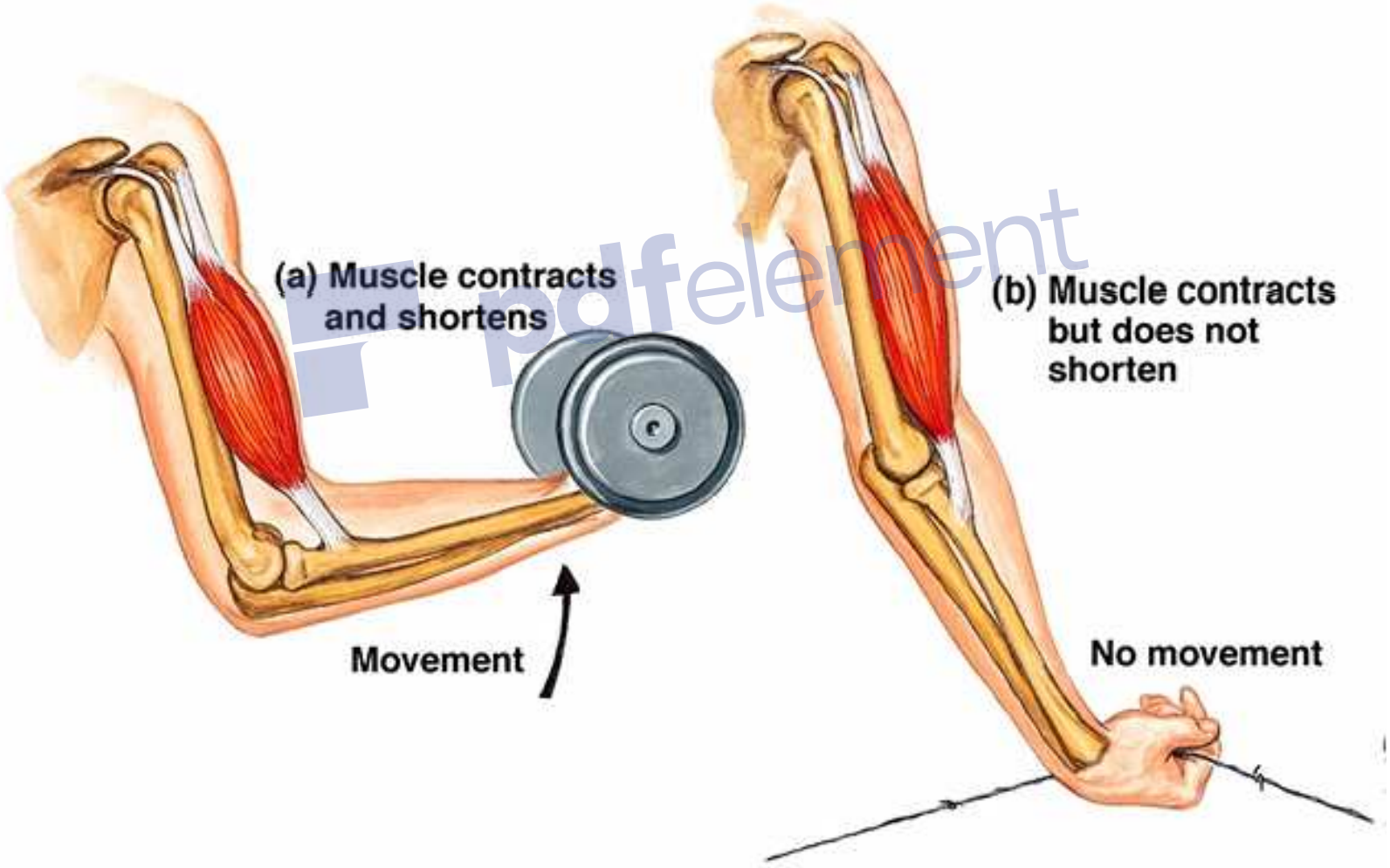
- Second, ATP provides the energy for the cross-bridge cycle, which underlies the contraction of the muscle cell. Most of the ATP is used to activate the walk along mechanism of muscle contraction.

- Third, ATP is the energy source that powers the calcium pump of the sarcoplasmic reticulum. Ca^{2+} are pumped back into the sarcoplasmic reticulum after the contraction ends.

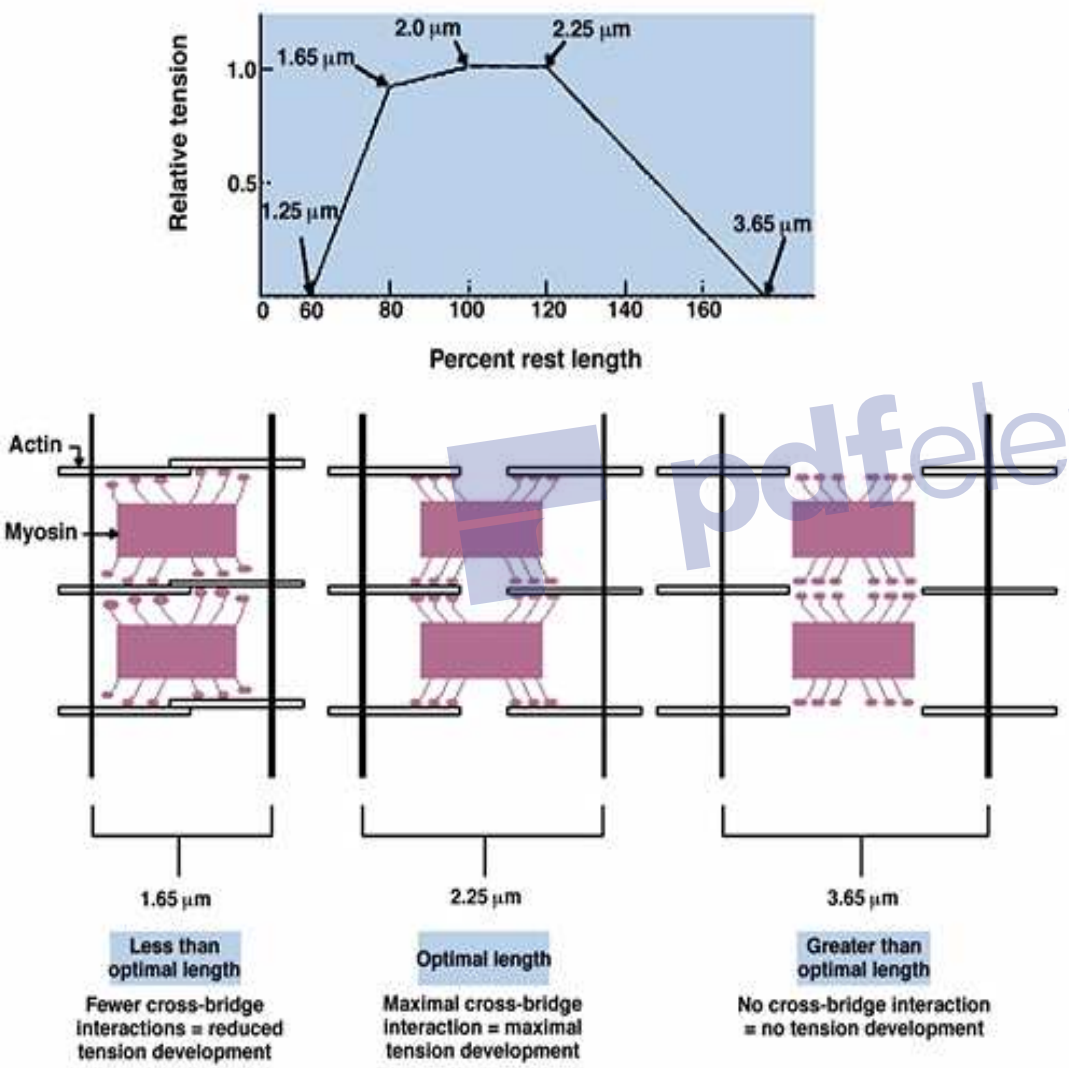
- Fourth, ATP binding is required to detach the cross-bridge after the power stroke. Note that ATP provides the energy for both contraction (at the myosin head) and relaxation (via SERCA) sarcoplasmic or endoplasmic reticulum Ca^{2+}ATPase (SERCA) pump.



Isotonic and Isometric Contractions

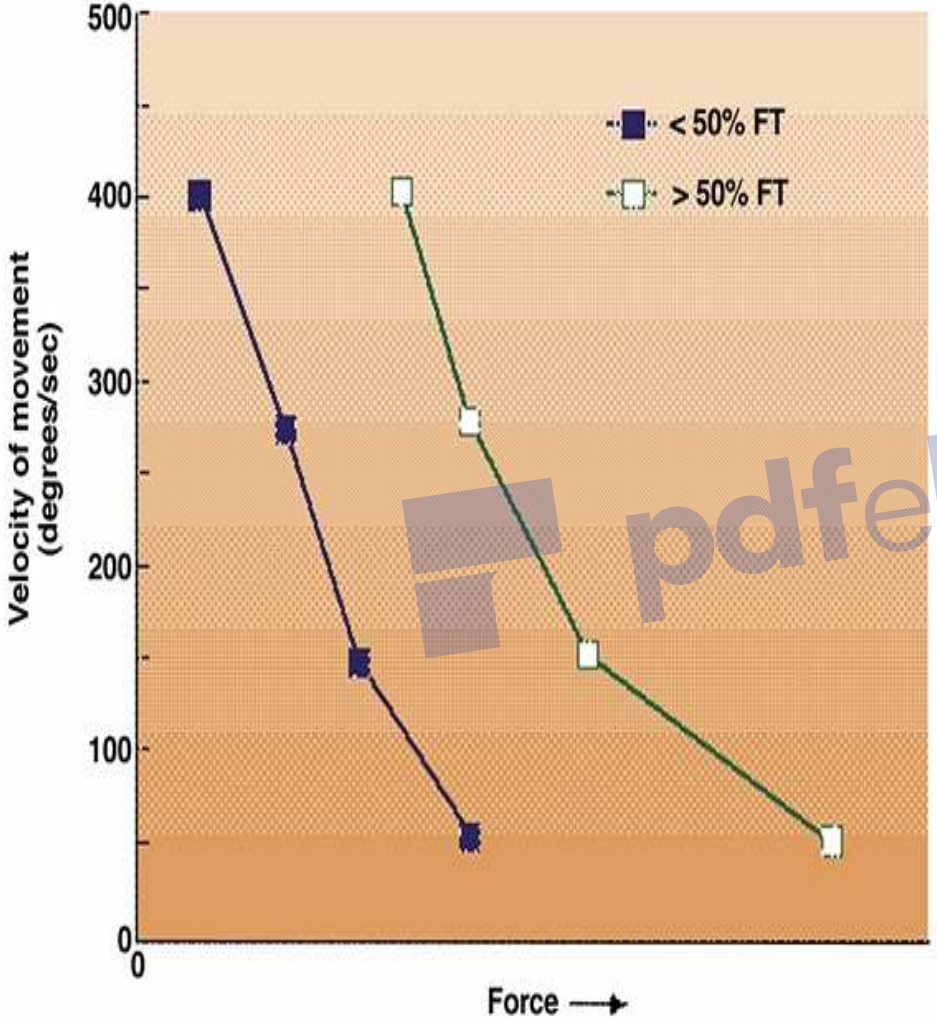


Length-Tension Relationship in Skeletal Muscle



- When the sarcomere is stretched beyond its resting length, number of active sites within reach of myosin heads is decreased reducing tension development.
- When the sarcomere is shortened beyond its resting length, actin strands begin to overlap which covers up available active sites which reduces tension development.
- There is a passive stretch on the connective tissue at longer sarcomere lengths that resists further lengthening; this results in an added force to the tension development at longer sarcomere lengths.

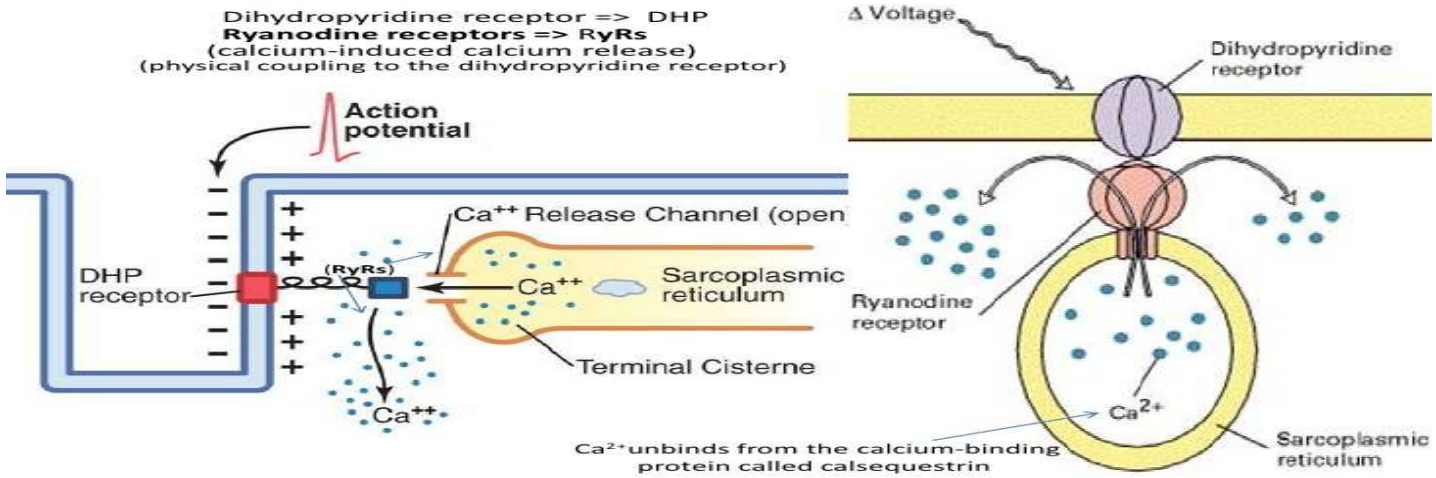
Force-Velocity Relationship



- The velocity of shortening in an isotonic contraction depends on the load in a characteristic way.
- The maximal velocity of shortening differs in different muscle types. In general, the maximal velocity of shortening is proportional to the maximal rate at which myosin hydrolyzes ATP.
- Power output by the muscle reaches an optimum when the load is about one third of the maximum isometric force. there is an optimal load (~40% of max) which allows for the greatest power development-any load less than or greater than this decreases power output.
- If the load placed on the muscle is greater than the maximal force the muscle can generate, the muscle will not shorten when stimulated.

Role of Ryanodine receptors in Muscle Contraction

- **Ryanodine receptors** (**RyRs**) form a class of intracellular Ca^{2+} channels in various forms of excitable animal tissue like muscles and neurons. There are three major iso-forms of the ryanodine receptor (RyR1, RyR2, RyR3).
- The RYR2 ryanodine receptor iso-form is the major cellular mediator of **calcium-induced calcium release (CICR)** in animal cells.
- In skeletal muscle, activation of **RyRs** occurs via **dihydropyridine receptors (DHPR)** (voltage-gated Ca^{2+} channels in the T tubule membrane), whereas, in cardiac muscle, the primary mechanism of activation is calcium-induced calcium release (CICR), which causes calcium outflow from the SR.
- Ca^{2+} is reduced in the muscle cell by the sarcoplasmic or endoplasmic reticulum Ca^{2+}ATPase (SERCA) pump. The pump uses ATP to remove Ca^{2+} from the cytosol back into the terminal cisterns, and stored until released next AP.

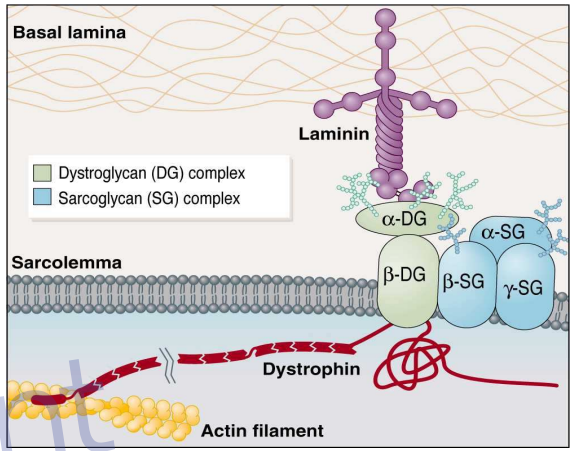


Role of Ryanodine receptors in Muscle Contraction

- **Ryanodine receptors** (**RyRs**) form a class of intracellular Ca^{2+} channels in various forms of excitable animal tissue like muscles and neurons. There are three major iso-forms of the ryanodine receptor (RyR1, RyR2, RyR3).
- The RYR2 ryanodine receptor iso-form is the major cellular mediator of **calcium-induced calcium release (CICR)** in animal cells.
- **RyRs** mediate the release of Ca^{2+} from the sarcoplasmic reticulum (SR) and endoplasmic reticulum (ER), an essential step in muscle contraction.
- In skeletal muscle, activation of **RyRs** occurs via **dihydropyridine receptors (DHPR)** (voltage-gated Ca^{2+} channels in the T tubule membrane), whereas, in cardiac muscle, the primary mechanism of activation is calcium-induced calcium release (CICR), which causes calcium outflow from the SR.
- Ca^{2+} is reduced in the muscle cell by the sarcoplasmic or endoplasmic reticulum Ca^{2+}ATPase (SERCA) pump. The pump uses ATP to remove Ca^{2+} from the cytosol back into the terminal cisterns, and stored until released next AP.
- Once the [Ca^{2+}] outside the reticulum has been lowered, chemical interaction between myosin and actin ceases and the muscle relaxes.
- If transport of Ca^{2+} into the reticulum is inhibited, relaxation does not occur even though there are no more action potentials; the resulting sustained contraction is called a **contracture.**

Dystrophin–Glycoprotein Complex

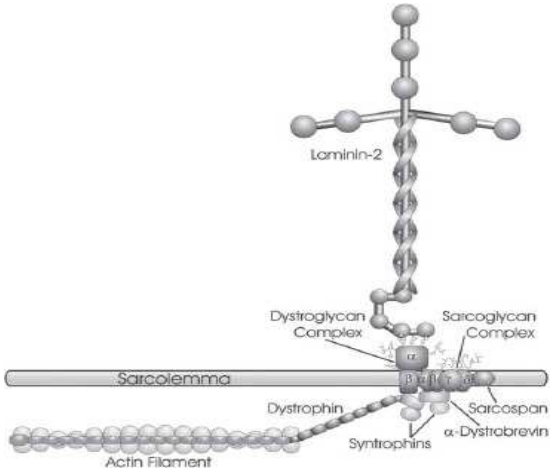
Dystrophin–Glycoprotein Complex -The large **dystrophin** protein (MW 427,000 D) forms a rod that connects the thin actin filaments to the transmembrane protein β **-dystroglycan** in the sarcolemma by smaller proteins in the cytoplasm, **syntrophins.**



β-dystroglycan is connected to **merosin** in the extracellular matrix by α**-dystroglycan**.

The dystroglycans are in turn associated with a complex of four trans-membrane glycoproteins: α –, β –, γ –, and δ **-sarcoglycan.**

This **dystrophin–glycoprotein complex** adds strength to the muscle by providing a scaffolding for the fibrils and connecting them to the extracellular environment. Disruption of the tightly choreographed structure can lead to several different pathologies, or muscular dystrophies .
There are muscle disorders associated with loss, abnormalities, or both of the sarcoglycans and merosin.



Summary

- Human body contains over 400 skeletal muscles, skeletal muscle helps in (a) Force production for locomotion and breathing, (b) Force production for postural support, (c) Heat production during cold stress.
- Skeletal muscles has the properties like – Excitability, Contractibility, Extensibility-
- Elasticity, All-or-None response, Summation, Tetanus, Refractory Period, Muscle Fatigue, Rigor Mortis.
- Myofibrils are composed of myofilaments of the contractile proteins actin and myosin. Accessory proteins- tropomyosin and troponin.
- The portion of myofibril in between the 'Z' lines is called sacromere.
- The process by which the muscle contraction occurs is supported by two theories (a) Sliding filament theory, (b) Walk-along theory.
- During muscle contraction sacromere shorten, actin and myosin slide past each other.
- When Ca^{2+} binds to the Tn-C, there is a conformational change in the troponin complex. The Tn-I dissociates from the actin and the tropomysin, and muscle contraction occurs.
- Large amounts of ATP are cleaved to form ADP during the contraction and relaxation process- 4 stages where ATP is required.

Quick Assessment

1. What are the functions of skeletal muscle?
2. What are the characteristics of skeletal muscle?
3. State the structure of sacromere.
4. State how myofibrils are composed?
5. What are the accessory proteins in skeletal muscle?
6. Enumerate the process by which the muscle contraction occurs.
7. State the Sliding filament theory of the muscle contraction.
8. Explain the Walk-along theory of the muscle contraction.
9. Enumerate the role of Ca^{2+} ions in muscle contraction.
10. What are the steps in muscle contraction where ATP is required?

THANK YOU