Structure of skeletal muscle

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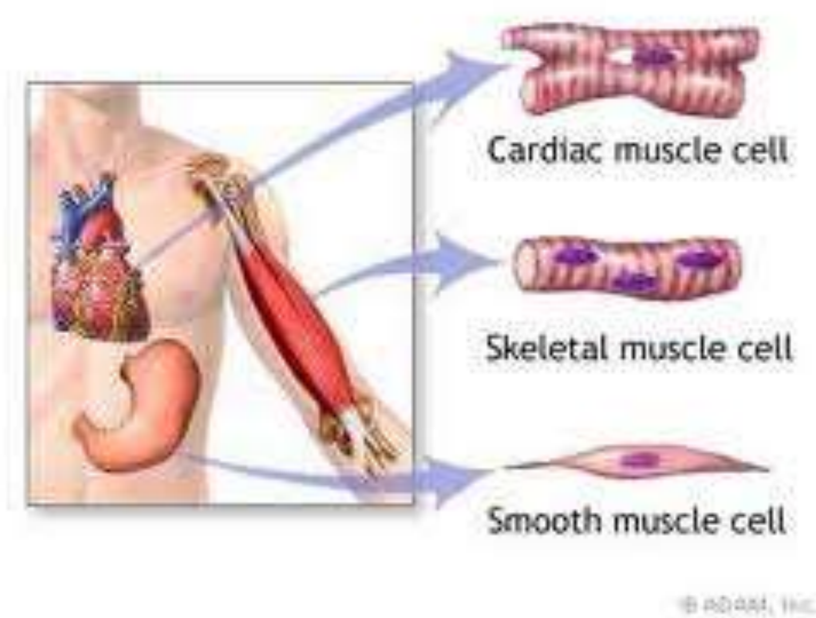
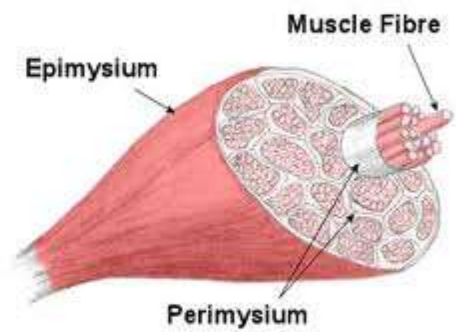
Types of muscles

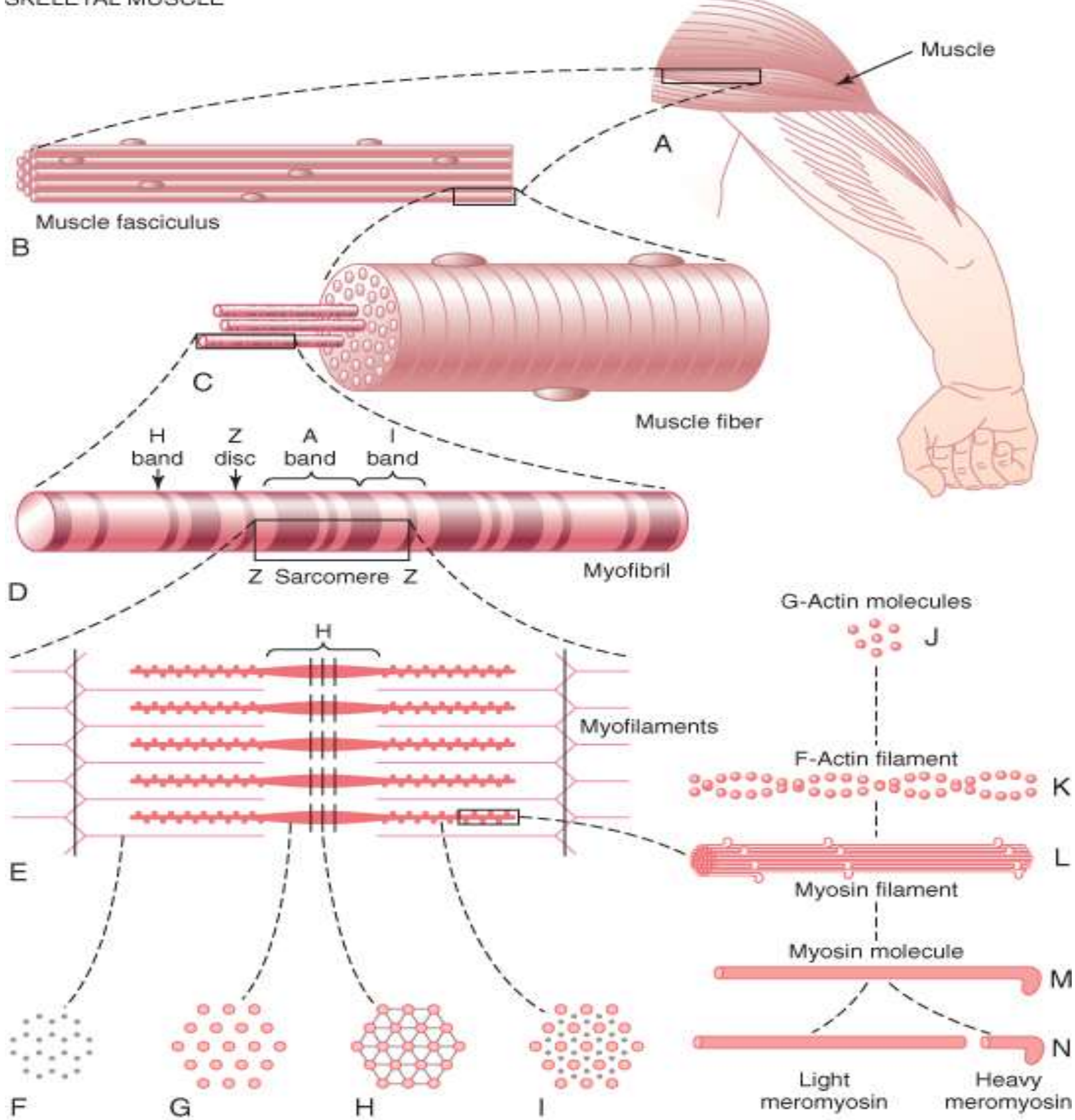
Muscle	Control	Stucture
Skeletal	Voluntary	Striated
Cardiac	Involuntary	Striated
Smooth	Involuntary	Non-striated

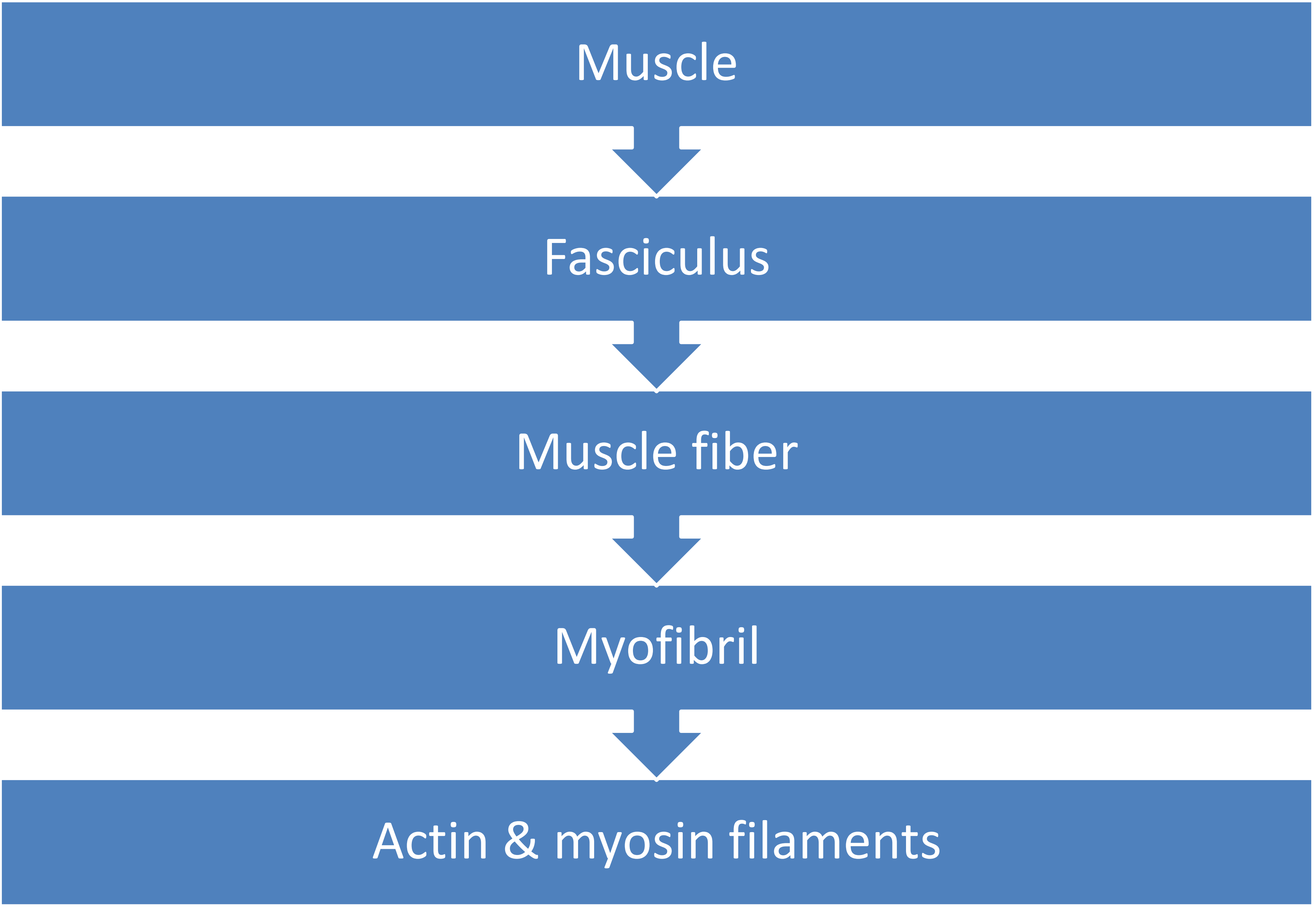


Structure of skeletal muscle

- Cross section shows multiple fascicles /bundles of muscle fibers
- **Epimysium** : covering of muscle.
- **Perimysium** : covering of fasciculus
- **Endomysium** : covering of muscle fiber



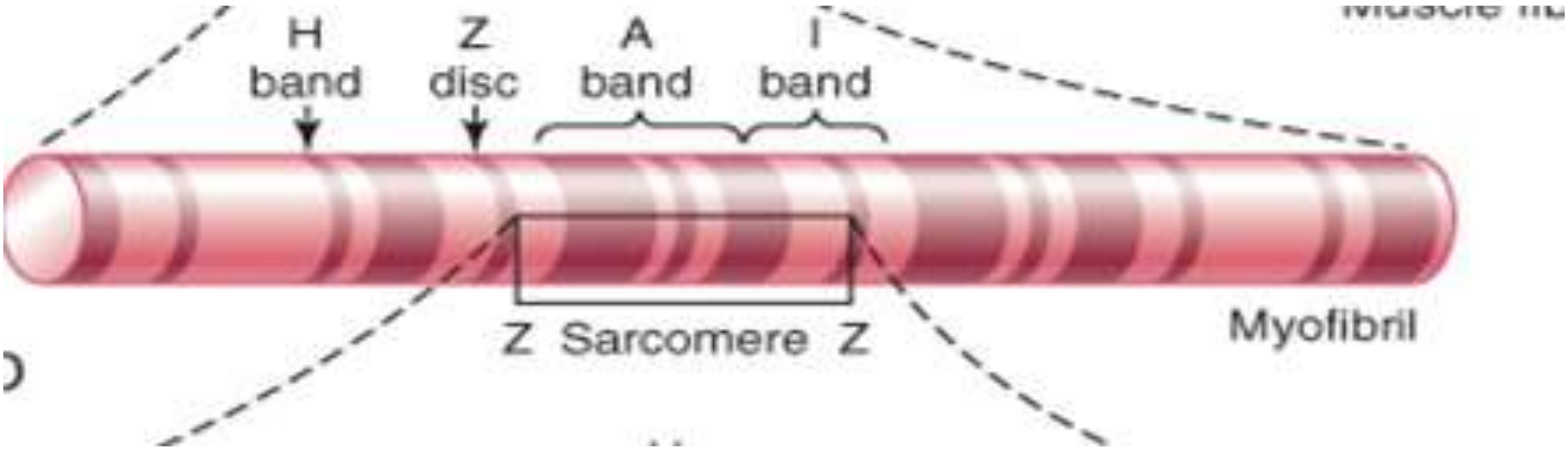

Muscle
A
Muscle fasciculus
B
C
Muscle fiber
H band
Z disc
A band
I band
D
Myofibril
Z Sarcomere Z
G-Actin molecules
J
H
Myofilaments
F-Actin filament
K
L
E
Myosin filament
Myosin molecule
M
N
Light meromyosin
Heavy meromyosin
F
G
H
I


Muscle
Fasciculus
Muscle fiber
Myofibril
Actin & myosin filaments

Muscle fiber

- Each muscle fiber is single cell, cylindrical and multinucleated.
- Each fiber extends the whole length of muscle.
- Many myofibrils are suspended side by side.
- **Diameter:** 10-80 um
- **Sarcolemma:** cell membrane of muscle cell.
- **Sarcoplasm:** cytoplasm of muscle cell.
- Multiple mitochondria in sarcoplasm-provide ATP.
- **Sarcoplasmic Reticulum-** rich in Ca^{++}

Myofibril



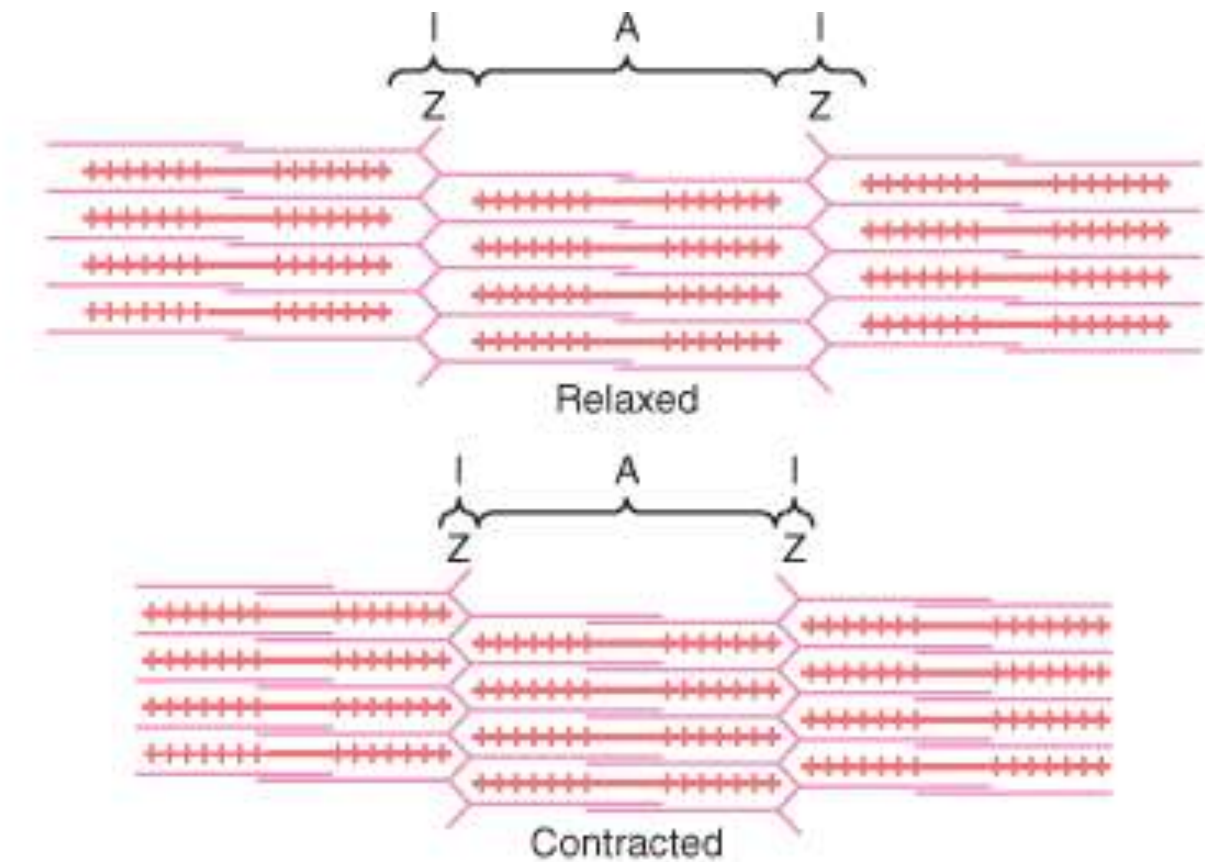
Myofibril

- Contains 1500 myosin filaments & 3000 actin filaments.
- Actin & myosin filaments partially interdigitate to form alternate light & dark bands.
- Light (**I**)bands – only actin filaments - isotropic to polarized light
- The dark (**A**) bands - contain myosin filaments - anisotropic to polarized light
- **Z** line is present in the middle of I band to which actin filaments are attached.

Sarcomere

- The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a *sarcomere.*
- It is the functional unit of muscle.
- Consists of one A band surrounded by half I band on each side.
- In the middle of A band – faint H zone – M line.
- When the muscle fiber is contracted the length of the sarcomere is about 2 um.

Sarcomere



Sarcomere

- In the relaxed state, the ends of the actin filaments extending from two successive Z discs barely begin to overlap one another.
- Conversely, in the contracted state, these actin filaments have been pulled inward. Also, the Z discs come close to each other.
- Thus, muscle contraction occurs by a **sliding filament mechanism.**

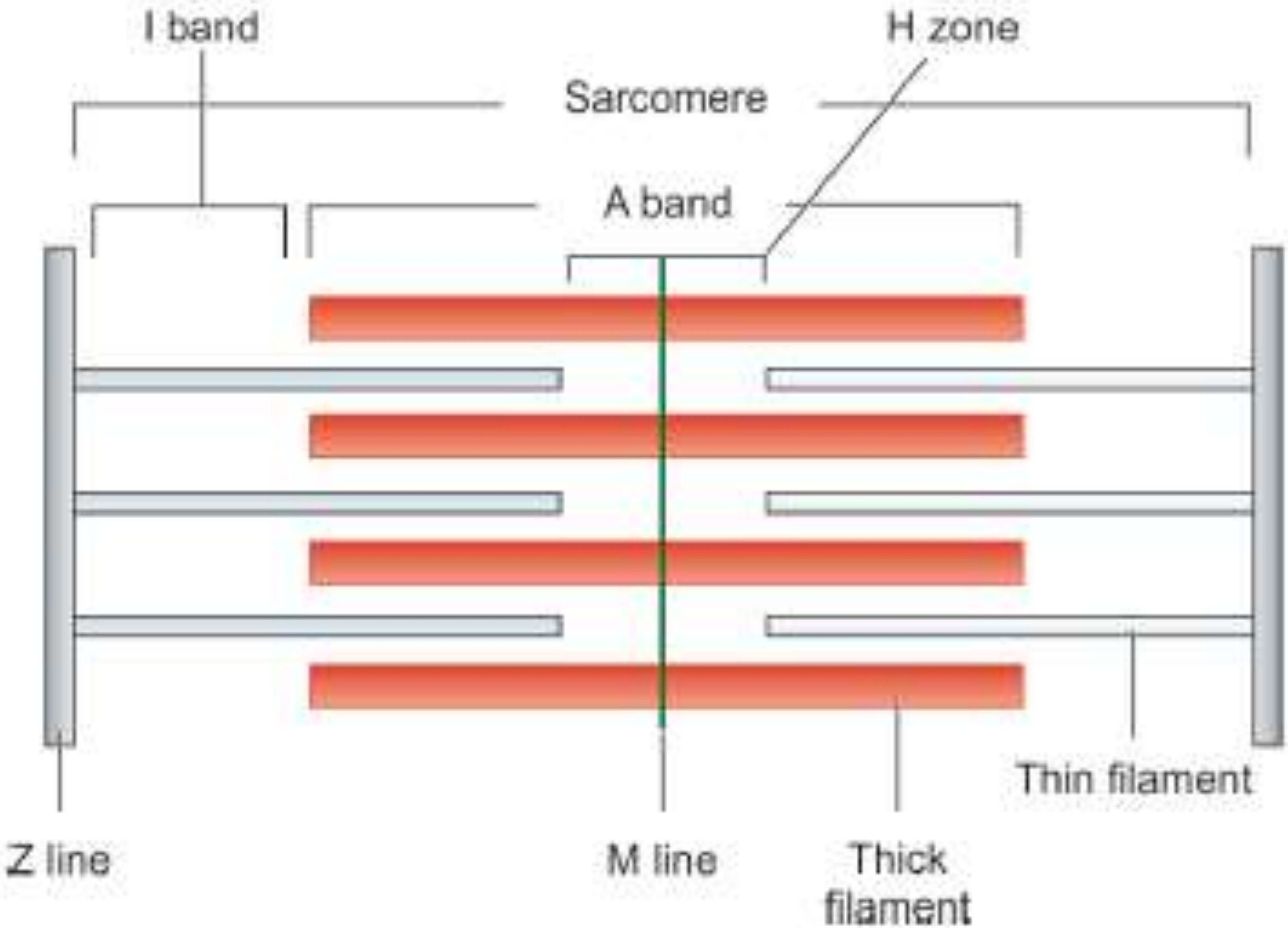


Fig. 30.10: Structure of sarcomere.

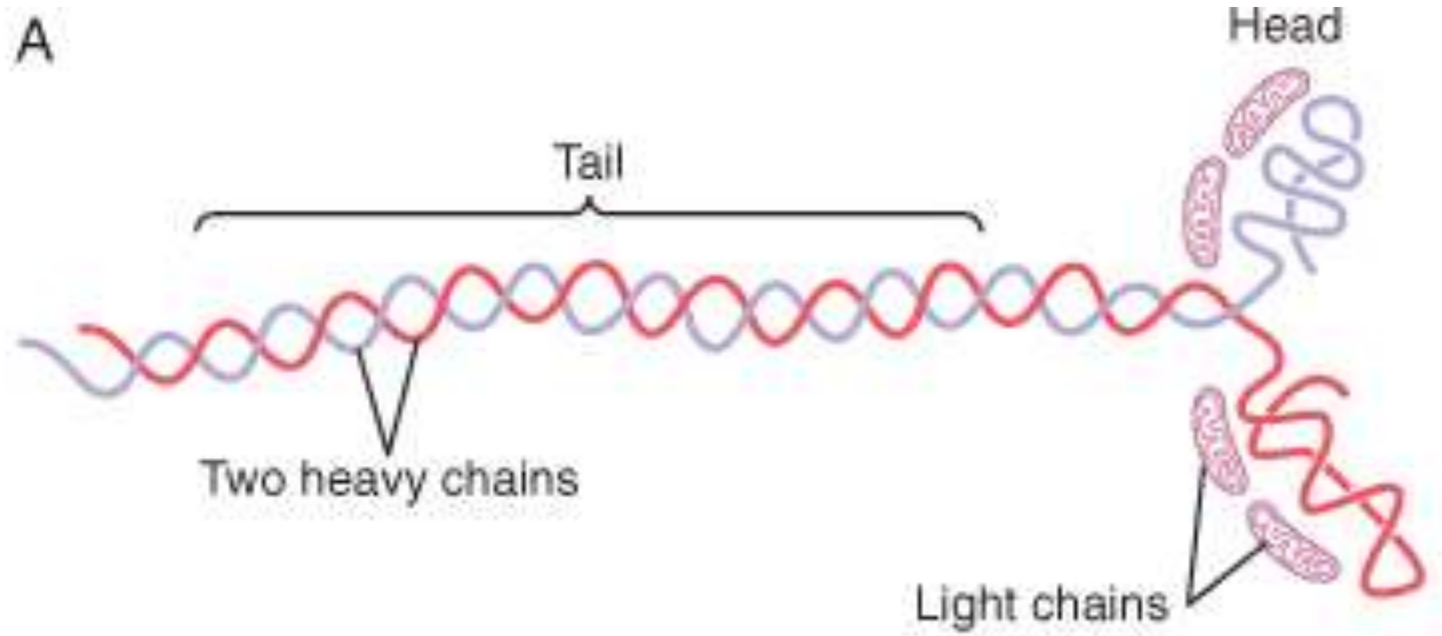
Muscle Proteins

- There are three types of proteins in skeletal muscle:
- 1. Contractile proteins: Myosin and actin
- 2. Regulatory proteins: Troponin and tropomyosin
- 3. Attachment proteins: Titin, nebulin, alpha actinin, desmin, myomesin, and dystrophin.

Myosin filament

- The myosin filament is composed of 200 myosin molecules.
- Molecular weight about 480,000.
- Six polypeptide chains—
  - 2 *heavy chains (*molecular weight 200,000 each)
  - 4 *light chains (molecular weight about 20,000 each)*
- Double helix forms a body/ tail, globular part forms bifid head on which light chains are present.

Myosin filament



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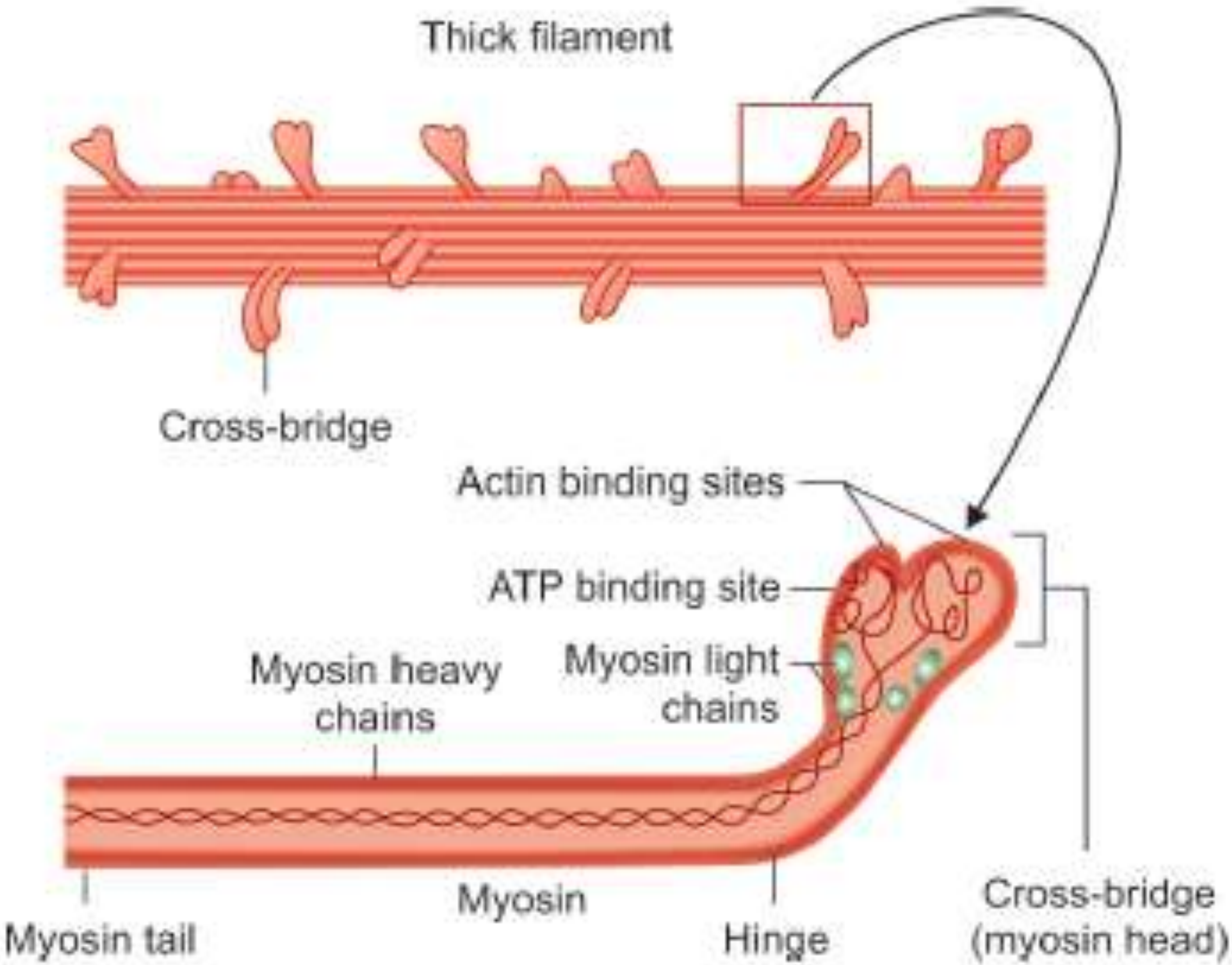
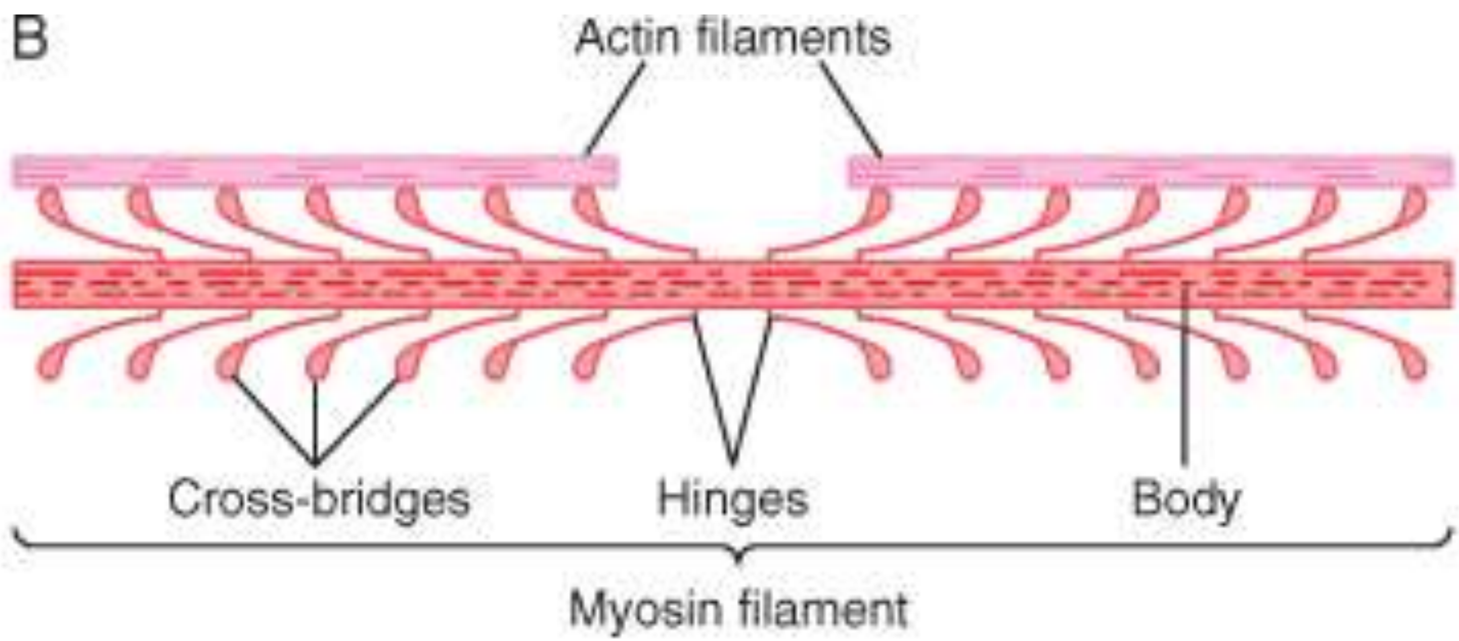
- Myosin molecules are arranged like a bunch of flowers to form myosin filament
- Tails are bunched together & heads project out laterally in pair.
- Each pair of heads is twisted from previous pair by 120 ^{o}.
- Head of myosin has ATPase action.
- The protruding arms and heads together are called *cross-bridges.*
- *Each cross-bridge is flexible at* 2 points called *hinges*
  - one where the arm leaves the body
  - the other where the head attaches to the arm


Thick filament
Cross-bridge
Actin binding sites
ATP binding site
Myosin light chains
Myosin heavy chains
Myosin tail
Myosin
Hinge
Cross-bridge (myosin head)

Actin & Myosin: Contractile proteins of muscle



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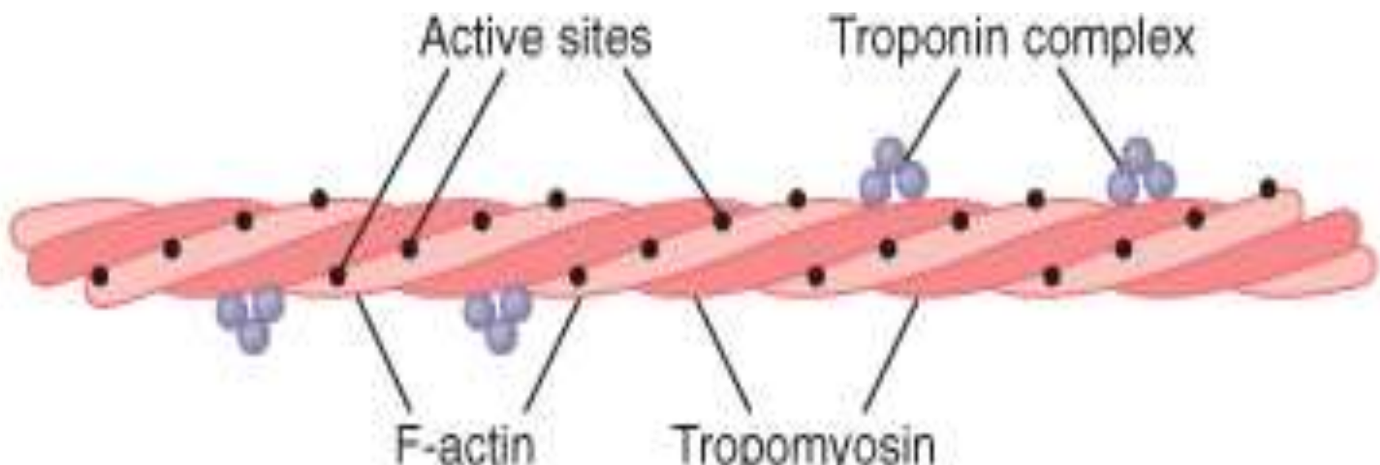
Actin filament

- The bases of the actin filaments are inserted into the Z discs; the other ends lie in the spaces between the myosin molecules.
- It is composed of three protein components: *actin, tropomyosin, and troponin.*



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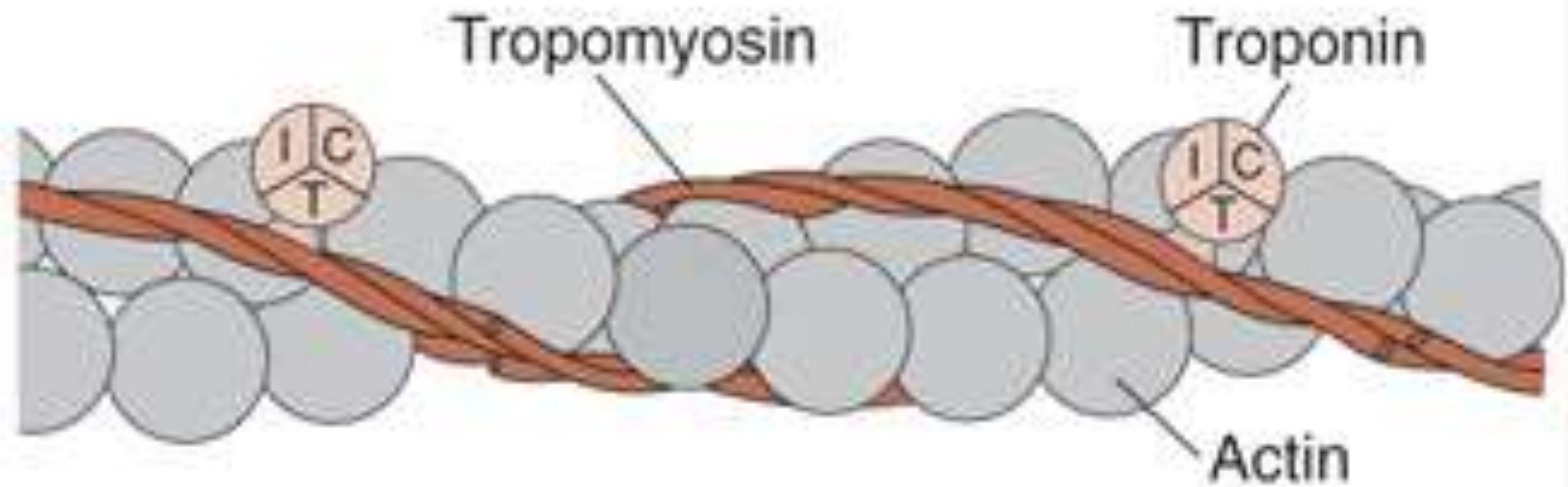
- The thin filaments are made up of actins. The actin filament (F-actin) is made up of globular molecules of G-actin.
- Actin filament is a double stranded *F-actin molecule.*

- G-actin is a globular protein with a diameter of 4–5 nm and MW 42,000.
- ADP is attached to each G- actin – ‘active site’.

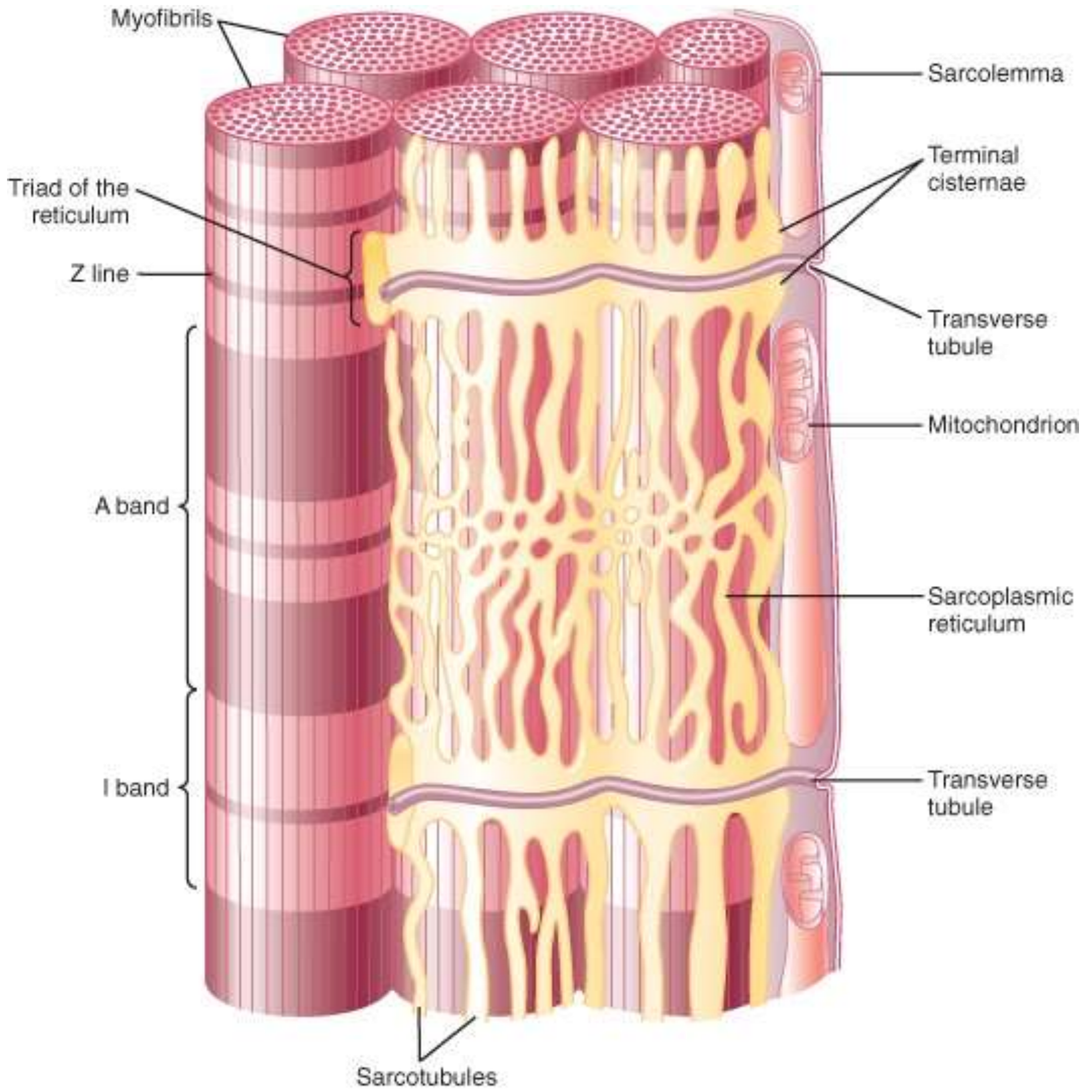
Actin molecule



- Tropomyosin is a filamentous protein which covers active sites of actin.
- There is a globular protein at regular intervals on tropomyosin called troponin.
- It has 3 parts – I, C & T.
- Troponin C – receptor site for Ca++ attachment.
- Troponin T – tightly bound to tropomyosin. Helps to cover active site of troponin.
- Troponin I – bound to actin. (It is called I, because it inhibits the binding of actin to myosin by blocking the myosin binding site on actin.)

Sarcotubular system

Sarcotubular system



- The process by which depolarization of the muscle fiber initiates contraction is called **excitation–contraction coupling.**

Sarcotubular System

Inside a muscle fiber, fibrils are surrounded by membranous structures known as sarcotubular system.

Structure

It consists of

1. Sarcoplasmic reticulum forming L-tubules and
2. T- (transverse) tubules.

T-tubules

The T-tubules, also called **sarcotubules,** are tubular extensions of the sarcolemma, about **0.03 µm in diameter**.

They run perpendicular to myofibrils, enter at A-I junction.

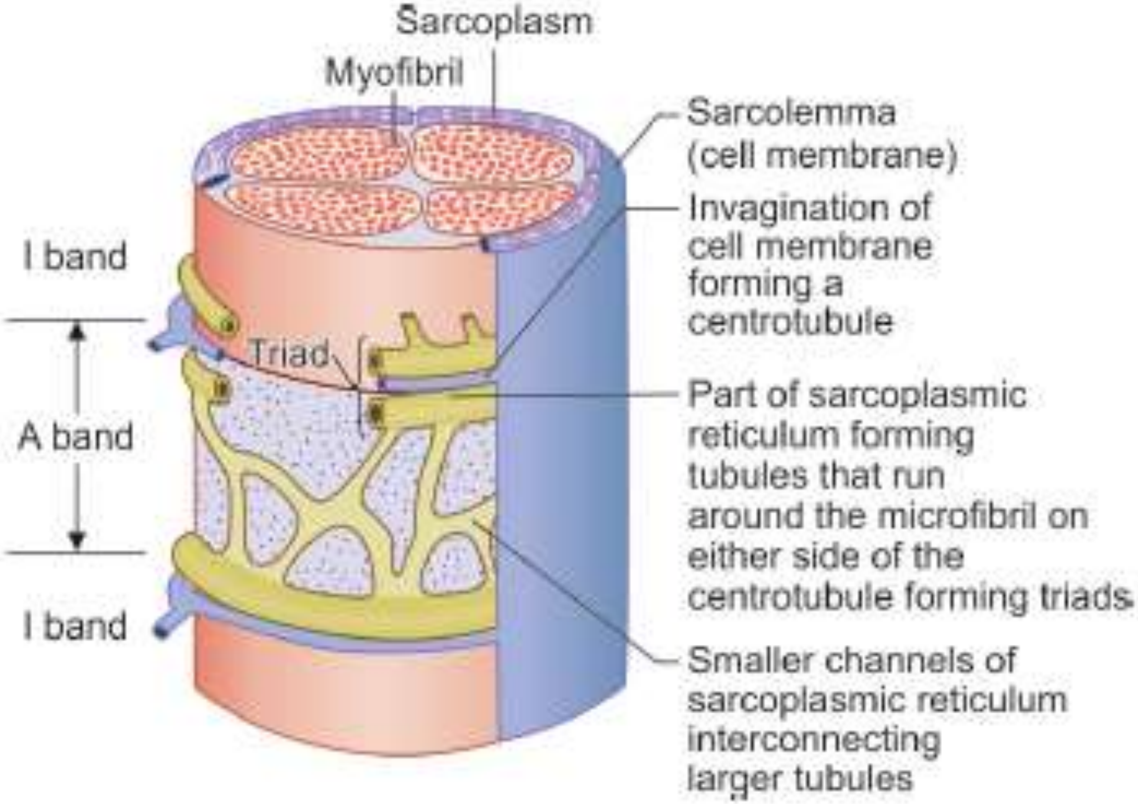


Fig. 30.14: Arrangement of sarcotubular system in the myofibril. Note the relationship of sarcoplasmic reticulum and T-tubules with I and A bands of sarcomere, in a myofibrils.

Sarcoplasmic Reticulum (L tubules)

The sarcoplasmic reticulum (SR) in skeletal muscle corresponds to the endoplasmic reticulum found in other cells.

1. It runs parallel to the myofilaments.
2. The slender tubules have a dilated portion at both ends known as lateral sacs or **terminal cisternae**.
3. The cisternae lie in close contact with the T-tubules at the A-I junction.
4. The combination of the T-tubule membrane and its two neighboring cisternae is called a **triad.**

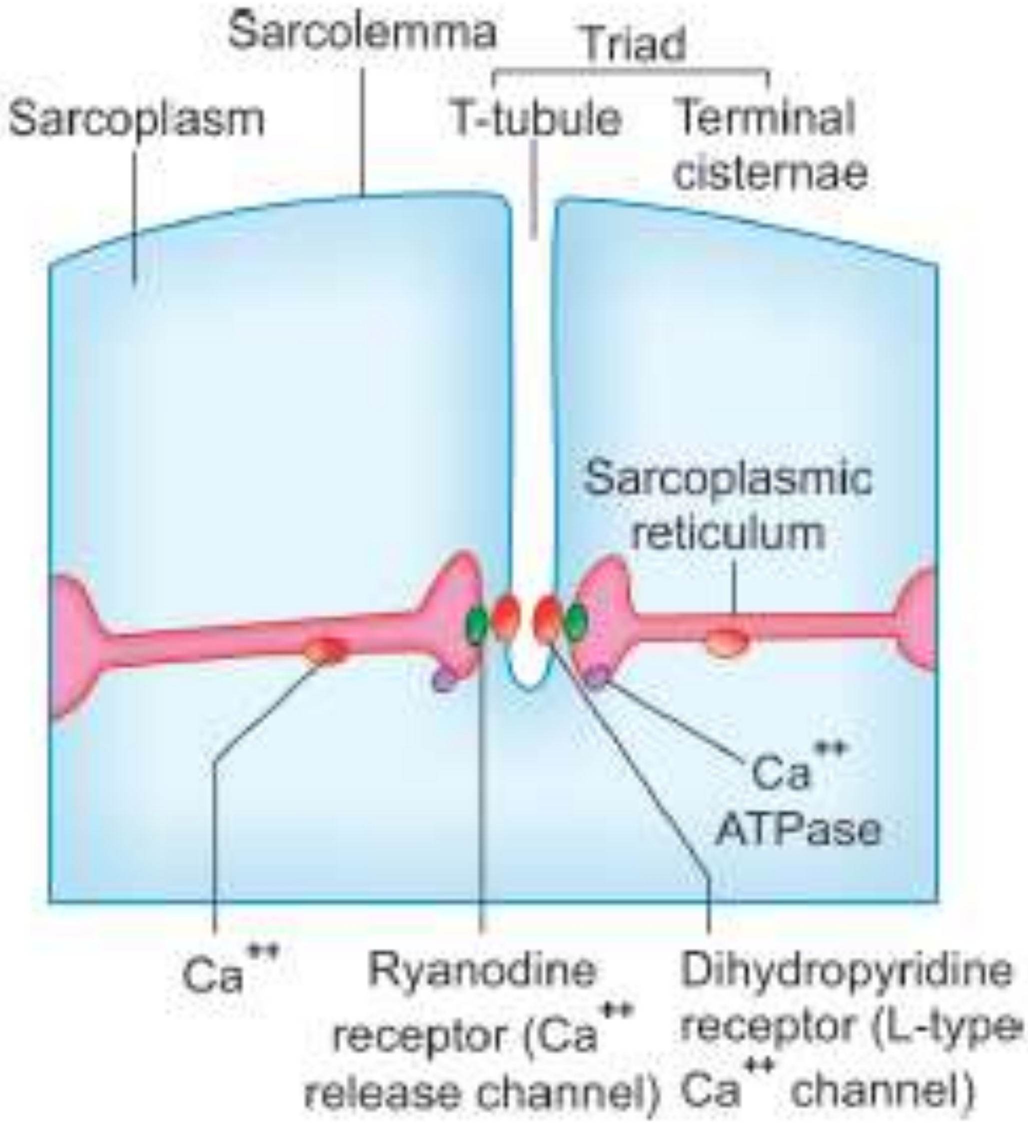
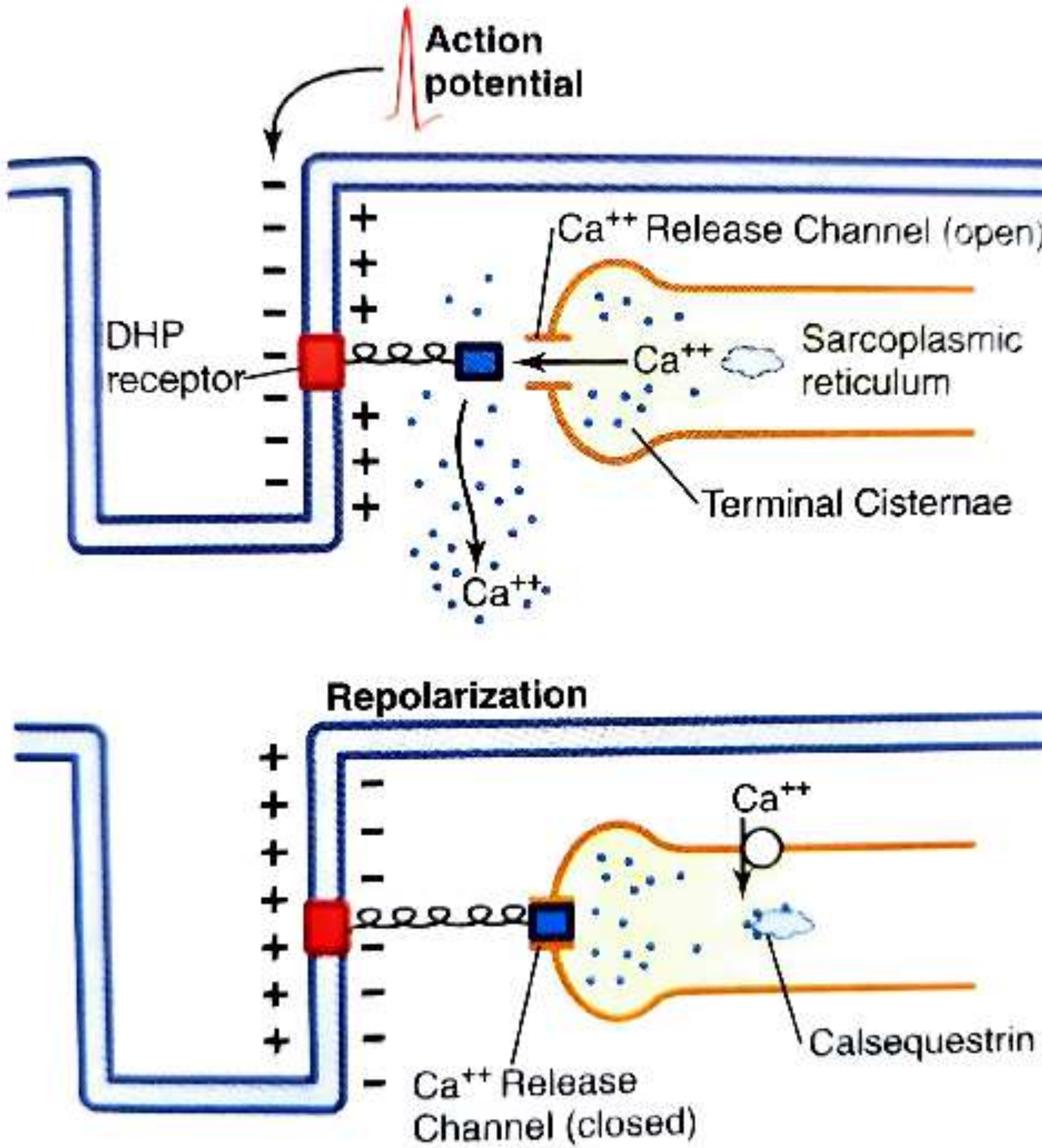


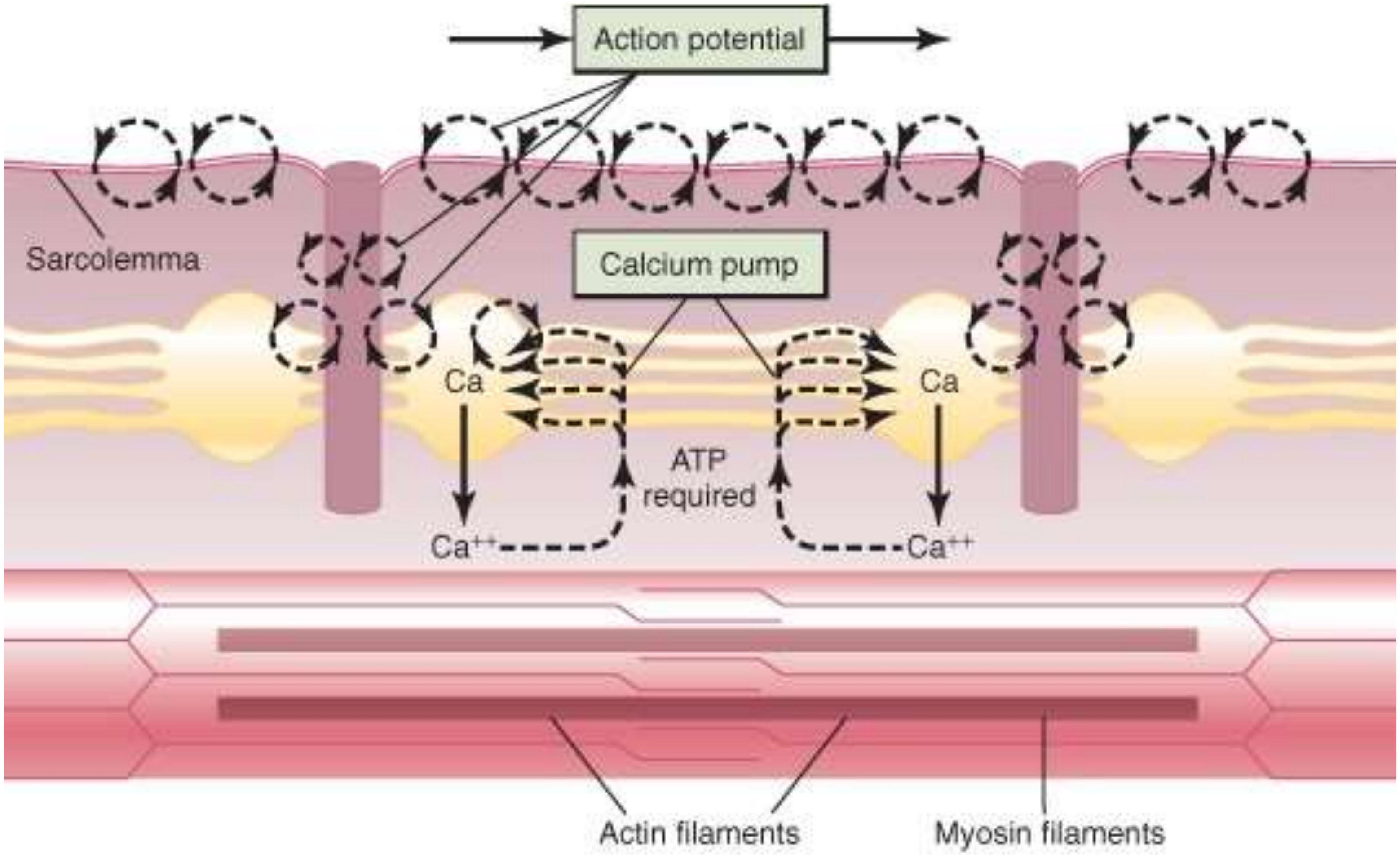
Fig. 30.15: Structure of sarcotubular system.

Channels at triad

- 1. The T-tubule contains a modified ***voltage-sensitive calcium channel*** known as the **dihydropyridine (DHP) receptor.** Primarily, the receptor acts as a ***voltage sensor*** *rather than a calcium channel*.
- 2. Terminal cisternae membrane that faces the T-tubules contains proteins known as the **ryanodine receptors**. They mainly act **as *calcium release channels***.
- 3. There is also **calcium ATPases** present on the membrane of SR that pumps calcium back into the SR.


Action
potential
DHP
receptor
Ca++ Release Channel (open)
Ca++
Sarcoplasmic
reticulum
Terminal Cisternae
Ca++
Repolarization
Ca++
Calsequestrin
Ca++ Release
Channel (closed)

T tubules & L tubules



Functions of sarcotubular system

1. It transfers action potential from the surface of the muscle fiber to the interior, closer to the myofibrils.
2. It raises cytoplasmic calcium concentration by calcium release from SR.
3. It ensures muscle relaxation by calcium reuptake by SR
4. The cisternae of SR act as storage sites for calcium.

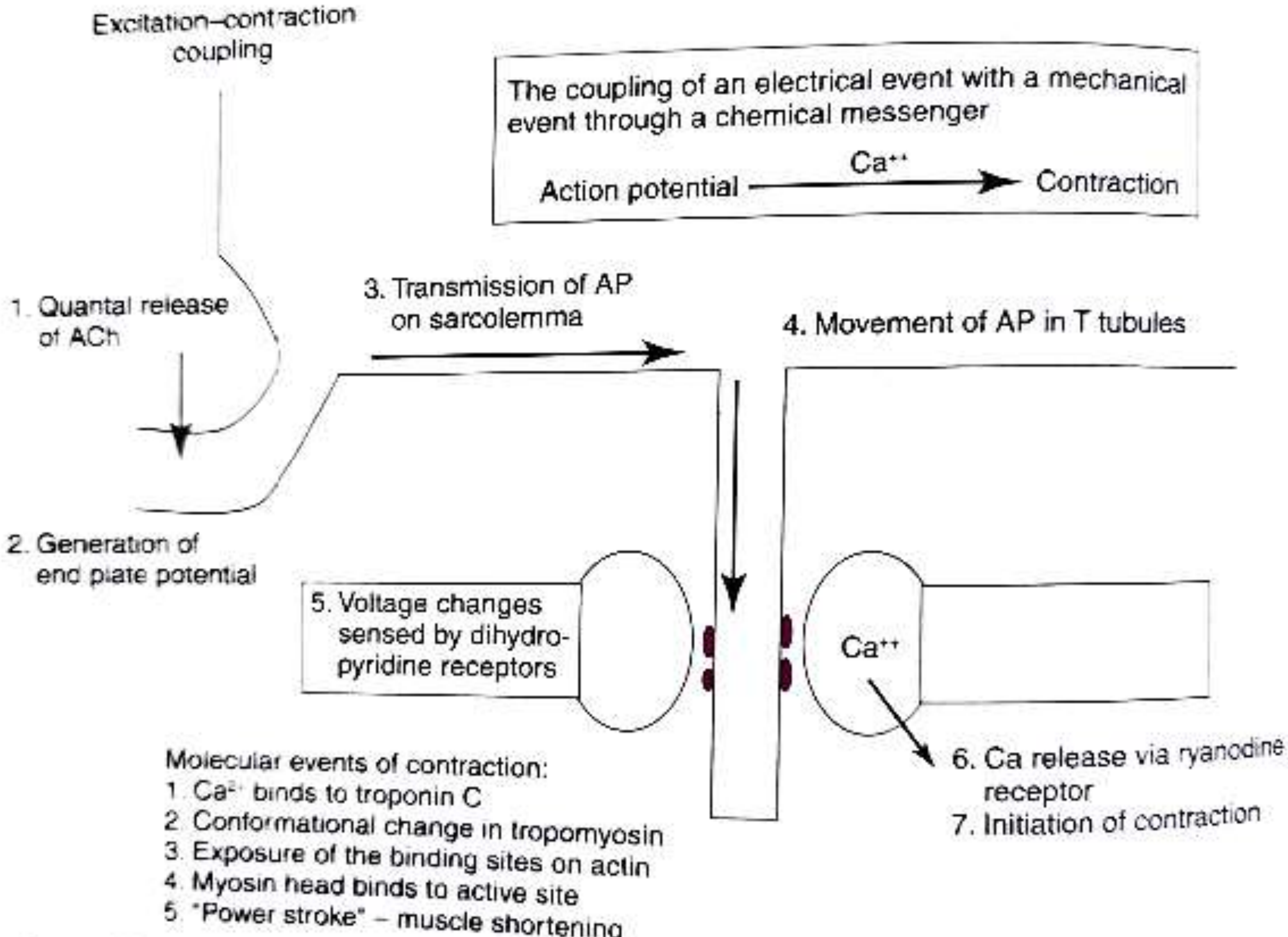


Figure 13-4 Summary of the entire process of excitation–contraction coupling. AP, action potential

The action potential is transmitted to all the fibrils in the fiber via the T system

↓

Depolarization of the T tubule membrane activates the sarcoplasmic reticulum via **dihydropyridine receptors (DHPR)**

↓

the DHPR that serves as the voltage sensor unlocks release of Ca^{2+} from the nearby sarcoplasmic reticulum via physical interaction with the RyR

↓

It triggers the release of Ca^{2+} from the terminal cisterns, the lateral sacs of the sarcoplasmic reticulum next to the T system

↓

The released Ca^{2+} is quickly amplified through calcium-induced calcium release.

↓

Ca^{2+} Initiates the process of contraction

↓

When excitation is over, Ca^{2+} is actively pumped back to sarcoplasmic reticulum

It triggers the release of Ca^{2+} from the terminal cisterns, the lateral sacs of the sarcoplasmic reticulum next to the T system

↓

The released Ca^{2+} is quickly amplified through calcium-induced calcium release.

↓

Ca^{2+} Initiates the process of contraction

↓

When excitation is over, Ca^{2+} is actively pumped back to sarcoplasmic reticulum

↓

by the s arcoplasmic or e ndoplasmic r eticulum C a^{2+}A TPase (SERCA) pump

↓

This initiates relaxation

Role of STS in Muscle Contraction and Relaxation

Mechanism of Calcium Release

Following depolarization at the motor end plate, action potentials propagate along the sarcolemma and down the T-tubule membrane.

1. Depolarization of the triad region of the T-tubules induces *conformational changes* in each of the four DHP receptor proteins, which leads to a ***conformational change in the ryanodine receptor*** resulting in **opening of the ryanodine receptor channel**.
2. Calcium is thus released from the terminal cisternae of the SR into the cytoplasm, **activating cross-bridge cycling**.
3. The entire process, starting from depolarization of the T-tubule membrane to the initiation of the cross-bridge cycling is termed *excitation-contraction coupling*.

4. Further, conformational change in DHP receptor allows calcium entry from the ECF into the cytoplasm through the DHP receptor channel and this ***increase in calcium level*** inside the cell can as well ***activate the ryanodine receptors*** resulting in calcium release. This mechanism is known as **calcium induced calcium release** (CICR). However, this pathway has a much lesser role in contraction of skeletal muscle.
5. Calcium-induced calcium release plays an important role in cardiac muscle contraction.
6. Increase in Ca2+ concentration near the sarcoplasmic reticulum is known as ***calcium spark****.*

Mechanism of Calcium Uptake (Muscle relaxation)

- The membrane of the SR contains a **protein** called ***Sarcoplasmic Endoplasmic Reticulum Calcium ATPase*** (SERCA). This is so named as it is present in all cells in connection with the endoplasmic reticulum.

1. The protein is a **Ca2+ ATPase** that pumps free calcium ions from the sarcoplasm to the SR, from where the calcium ions are moved to their storage sites in the terminal cisternae.
2. The pump relocates two molecules of Ca2+ into the SR for each molecule of ATP hydrolyzed. It becomes active as soon as the Ca2+ concentration in cytoplasm becomes high.
3. In the terminal cisternae, a Ca2+-binding protein, called **calsequestrin**, favors storage of calcium at high concentration.
4. With decrease in cytoplasmic calcium concentration, contractile activity ceases and relaxation process begins (Flowchart 30.1).

MECHANISM OF CONTRACTION

The term contraction means attachment of myosin heads to actin and activation of the cross-bridge cycles so that force is generated with shortening of muscle fibers.

However, in isometric contraction, e.g. holding an object at a constant position, there is activation of the cross-bridge cycles without apparent shortening.

Sliding Filament Theory: In 1957, **A.F. Huxley** proposed

"Sliding Filament Theory" of muscle contraction.

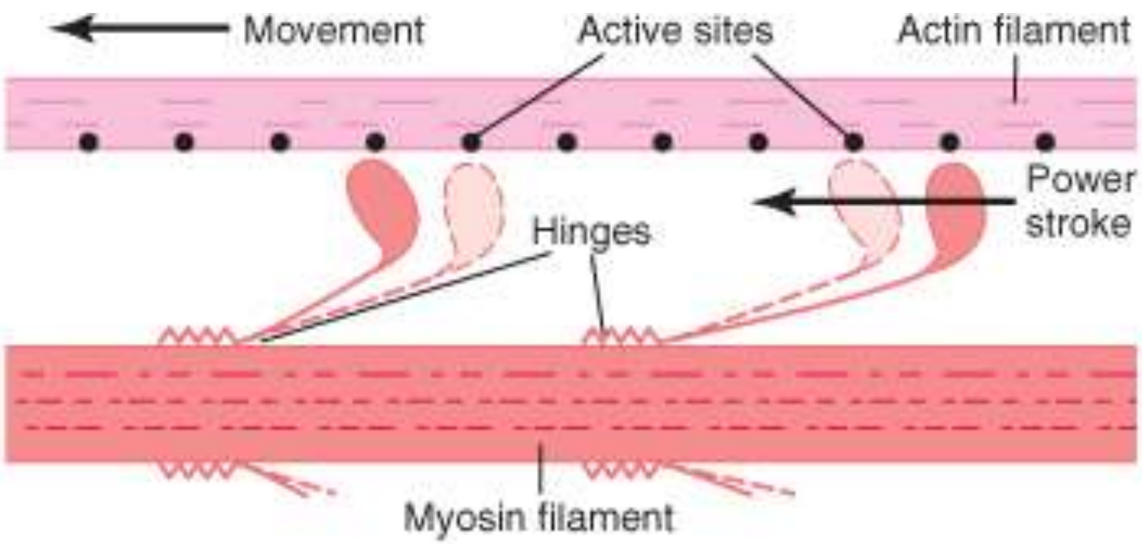
- Shortening of a muscle fiber occurs due to **sliding of thin filaments over thick filaments** toward the center of the sarcomere (described below in "molecular mechanisms of muscle contraction").
- It was observed that the **length of A band does not change** during contraction, but **the H zone and I band decrease in width** and the Z lines move closer together.

Molecular Basis of Muscle Contraction

The **sliding motion of the filaments** occurs as a result of a ***cyclic interaction between the myosin cross bridges and the actin filaments***, in the presence of calcium and ATP.

1. This is known as the **cross-bridge theory** or the **ratchet theory** as the strokes are similar to the action of a ratchet.
2. The force generation and shortening are produced at the cross-bridge sites where the chemical energy stored in the muscle is converted into mechanical energy.

Sliding filament theory



Sliding filament theory/ Rachet theory/ walk along theory

AP spreads along muscle

↓

Ca ++ released by sarcotubular system attaches to troponin C

↓

Tropomyosin moves, active sites on actin exposed

↓

Myosin head attaches to active site

↓

Power stroke

↓

ATP binding & cross bridge detatchment

↓

Recovery stroke

↓

Cycle repeats again & again

↓

Sliding between Actin myosin occurs: Muscle contracts

Role of Troponin, Tropomyosin and Calcium

Calcium ions: chemical link in the excitation-contraction coupling.

- **In resting skeletal muscle**, cytoplasmic calcium ion concentration is low, which is about 10^{-7} M.

  Myosin-binding site is covered by troponin & tropomyosin. filament.

  Thus, the troponin-tropomyosin complex behaves as a ***relaxing protein*** that prevents undesirable contraction

Troponin-Tropomyosin Interaction

During excitation, **calcium concentration rises to 10^{-4} M** in the sarcoplasm, which accounts for about ***1,000-fold rise*** of the ion.

1. Calcium **binds to troponin C** and induces a conformational change in the troponin molecule.
2. This results in ***shifting of troponin I from the actin filament***, allowing tropomyosin to move deeper into the actin groove, **unmasking the myosin-binding sites**.
   - Moreover, the conformational change alters the position of troponin T that drags tropomyosin away from the myosin-binding sites.
3. The exposure of the binding sites allows **myosin heads to interact** with actin and engage in **cross-bridge cycling**.

The Cross-bridge Cycle

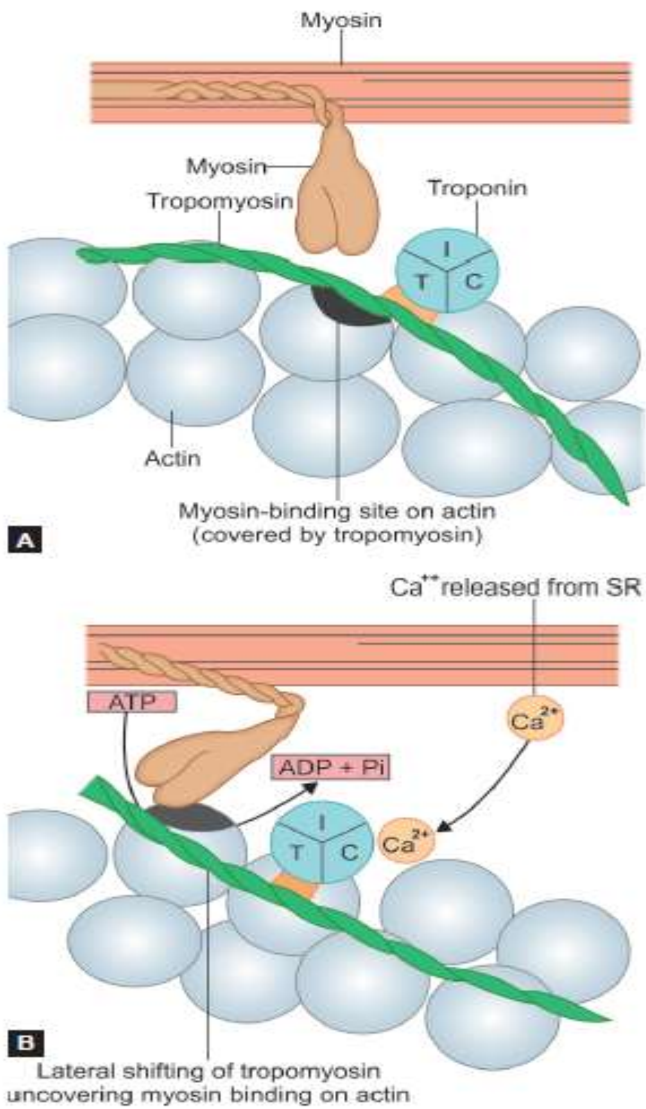
The sequence of events that occur during the interaction between the myosin cross-bridges and the actin molecules is termed as a cross-bridge cycle.

1. During each cycle, **cross bridge** (myosin head) ***attaches to thin filament*** causing displacement of thick filament over thin filament followed by **detachment of myosin head in a repetitive fashion**.
2. **ATP is required** during the cycle, for the movement of the cross bridge as well as for its detachment.

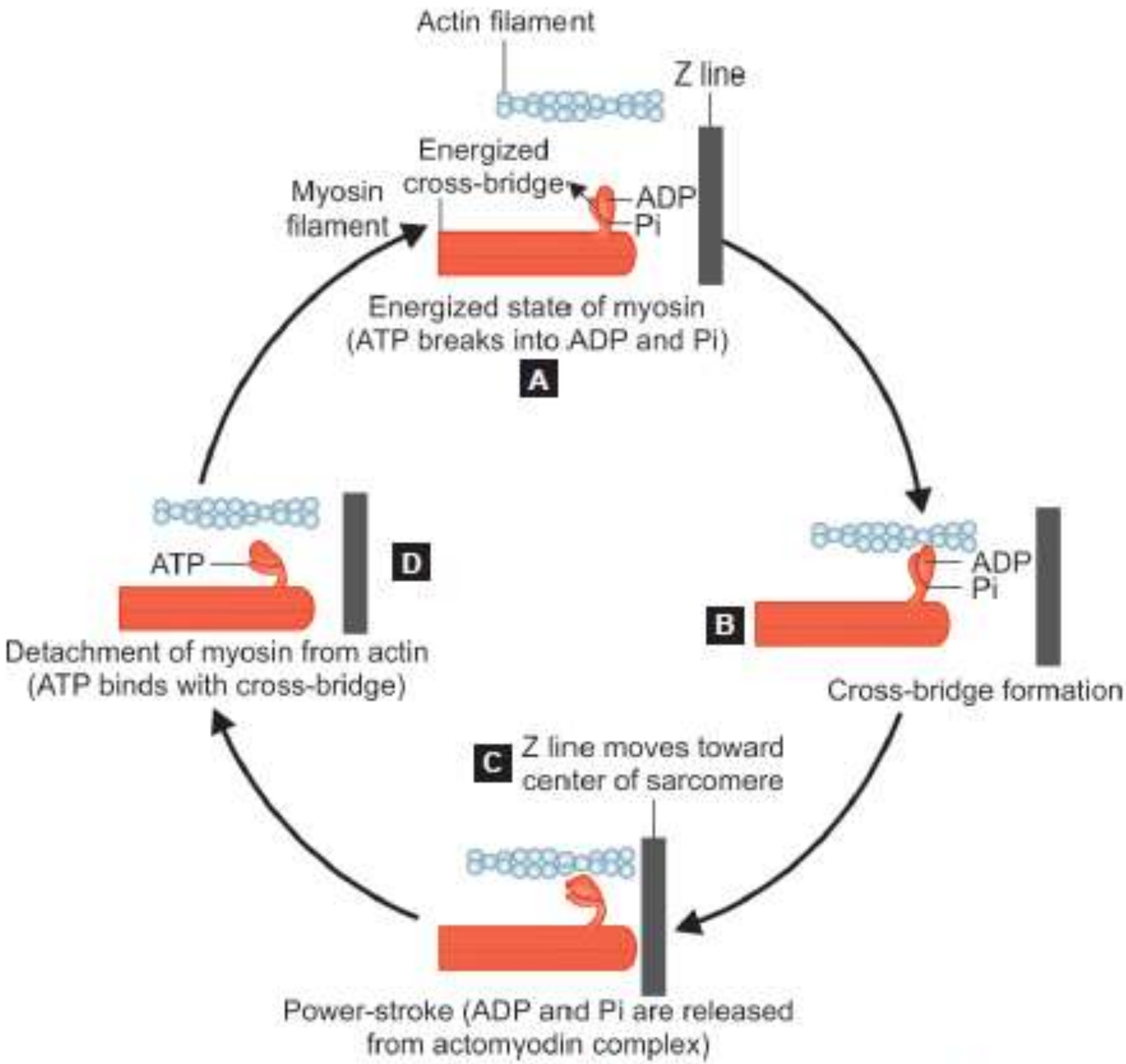
Events in the Resting Muscle

When the muscle is at rest, the cytoplasmic ATP gets attached to its specific binding site in the head of the myosin molecule and the globular head is not attached to actin.

1. The intrinsic ATPase activity of the myosin head **breaks down ATP to ADP and Pi** (Fig. 31.2A).
2. This results in ***rotation of the myosin head*** around the hinge.
3. This resting conformation is known as the energized state or the "cocked position of the myosin head" in which energy is stored in the form of Pi, similar to the potential energy stored in a coiled spring.
4. When most of the cross-bridges in a muscle are in this energized state, keeps the muscle prepared for future contraction.



Figs. 31.1A and B: Role of troponin-tropomyosin interaction in muscle contraction. Binding of calcium with troponin C induces conformational change in the troponin molecule, which shifts troponin I from the actin filament, and simultaneously troponin T that drags tropomyosin away from the myosin-binding site on actin. Exposure of this binding site allows myosin heads to interact with actin and engage in cross-bridge cycling. Note, ATP is converted to ADP during this interaction.



s-bridge cycle. (A) Resting state (cross-bridge is energized by breaking down of ATP to ADP and Pi that provi

FOUR-STEP PROCESS: The process of cross-bridge cycle occurs **in four main steps**

1. ATP hydrolysis in the myosin head leading to energized state of the myosin.
2. Cross-bridge formation in the presence of increased calcium.
3. Release of Pi and ADP from myosin head producing power stroke.
4. Binding of ATP to myosin head causing detachment of myosin from actin.

- Note, **during muscle contraction**, Z lines move toward M line that decreases sarcomeric length (muscle shortening), and **during muscle relaxation**, Z lines remain wide apart.
- In this process of contraction and relaxation, ***A band remains constant*** and **changes occur in I band and H zone**.

Steps in relaxation

Ca++ pumped back to L tubules

↓

Ca++ from troponin C released

↓

Troponin- tropomyosin binding becomes tight

↓

All active sites over G actin covered

↓

Actin myosin detatchment

↓

Relaxation

Applied aspect: Rigor mortis

- Continuous state of contracture in skeletal muscle after death.
- Cause: Loss of ATP – required for separation of cross bridges during relaxation process.
- Begins 3-6 hours after death, Completes in 12 hours

- Disappears after 40-60 hrs due to autolysis of proteins.
- Body remains in same position for long time.
- Medicolegal importance: Time since death, and cause of death