MSS

physiology

LEC no. 2

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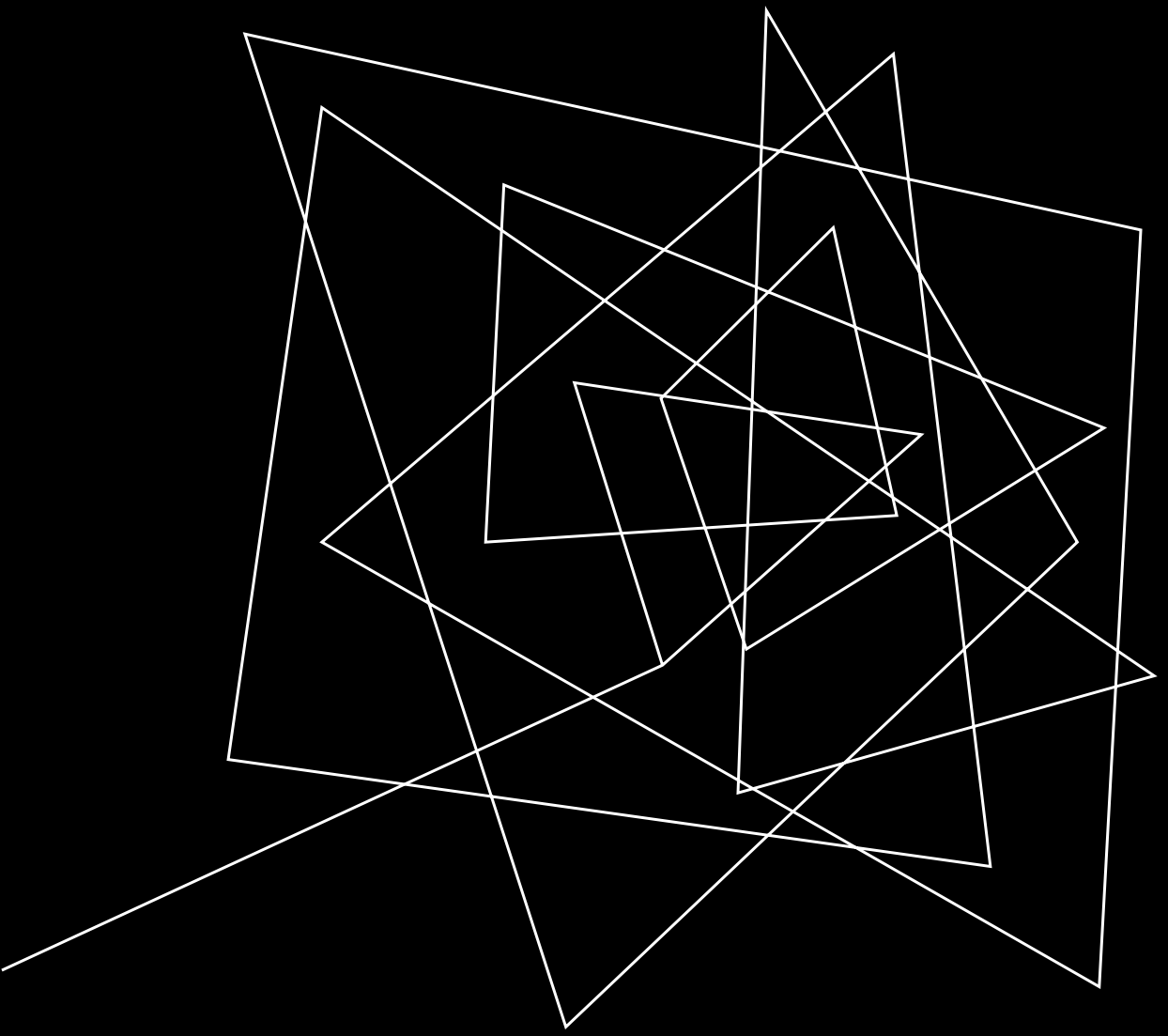


SKELETAL MUSCLE

structure

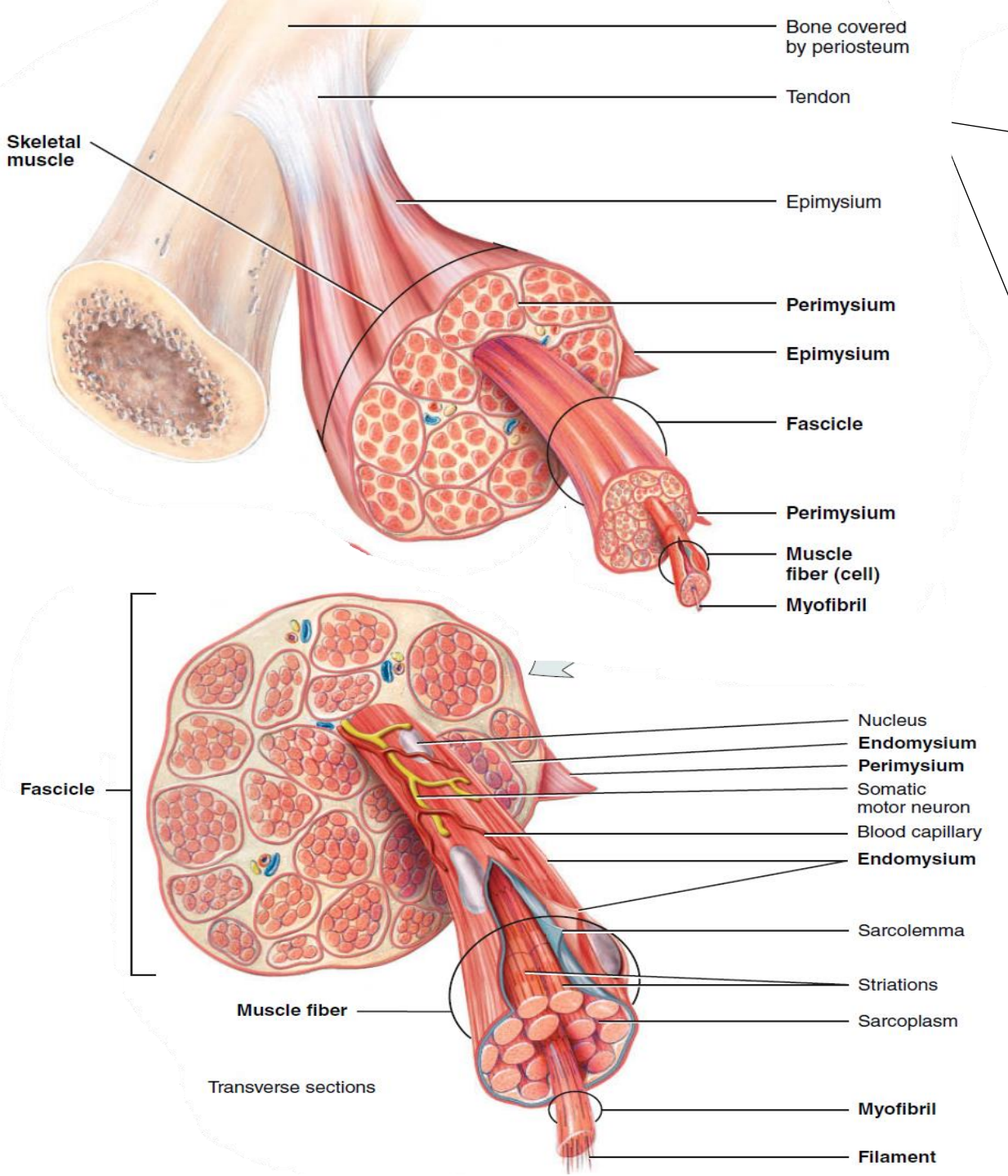
SKELETAL MUSCLE
structure

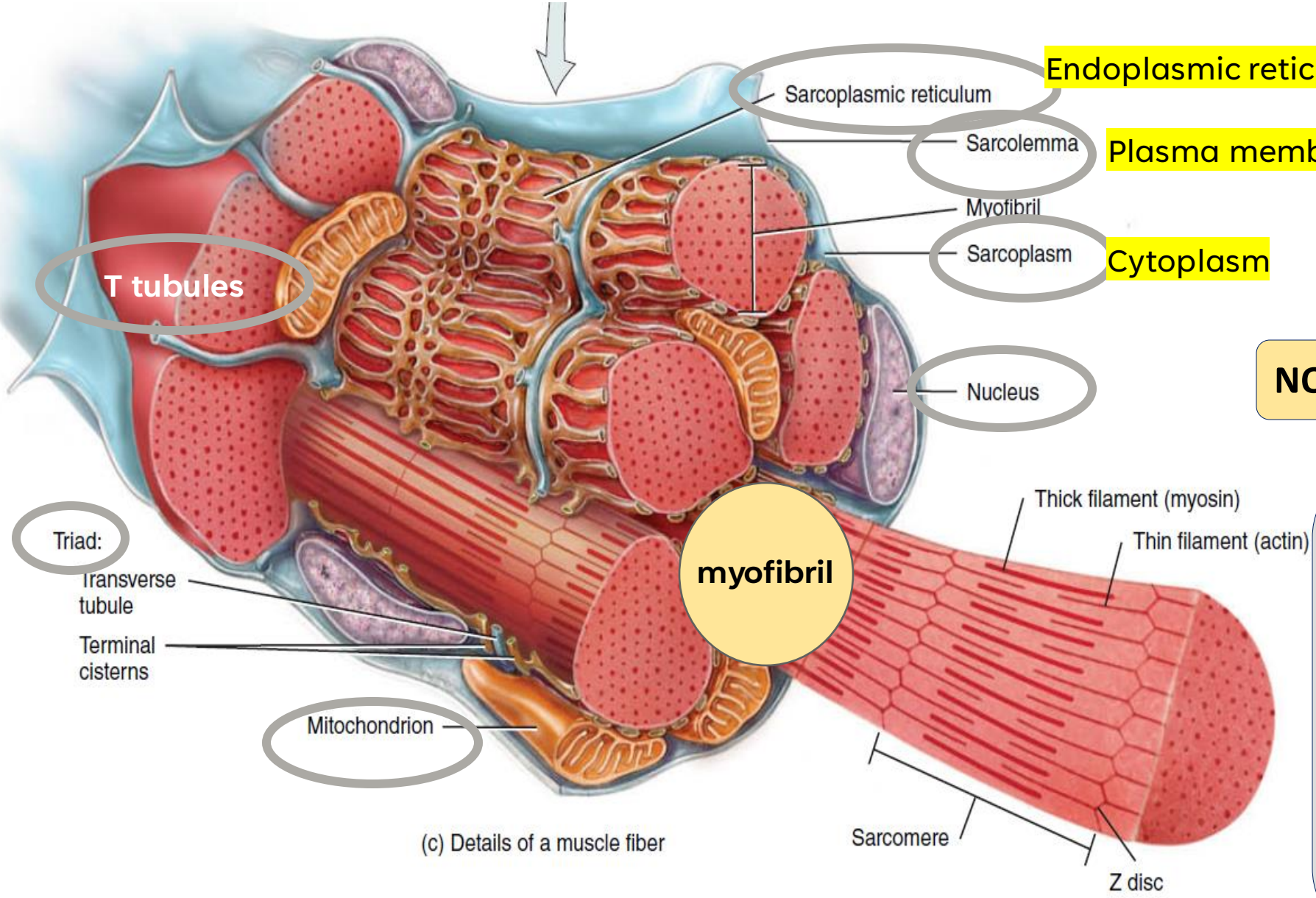
Pay attention to the notes in yellow boxes and with black font, they are from the doctor's PowerPoint notes, hence they are very important.

- To Understand Skeletal muscle physiology, we need first to make some revision on skeletal muscle structure.
- Our body contains 3 types of muscles: - Skeletal
  - Cardiac
  - Smooth
- Also, they can be classified into striated vs non-striated and voluntary vs involuntary.
- Skeletal muscles are striated and voluntary muscles, that are innervated by somatic motor neurons.
- Look at the picture in the next slide and come back!!
- The skeletal muscles of the body are composed of number of Fascicles. The number of fascicles depends on the size of the muscle. example, the muscle of the eye & the muscle of quadriceps, we can't make a comparison between them .
- The fascicles contain a number of many muscle fibers (muscle cell).
- Summary: Skeletal Muscle > Fascicle > Muscle Fibers > Myofibrils.
- Muscle fiber= myocyte= muscle cell

NOTES: Skeletal muscle tissue consists of long, cylindrical, striated fibers (striations are alternating light and dark bands within fibers that are visible under a light microscope).

- Skeletal muscle fibers vary greatly in length, from a few centimeters in short muscles to 30–40 cm (about 12–16 in.) in the longest muscles.
- A muscle fiber is a roughly cylindrical, multinucleated cell with nuclei at the periphery. Since during early embryonic development, they were different cells that fuse together to form a muscle fiber.
- Skeletal muscle is considered voluntary because it can be made to contract or relax by conscious control.
- **Location**: Usually attached to bones by tendons.
- **Function**: Motion, posture, heat production, protection.





NOTES: Sarco = Flesh

Sarco —> related to skeletal muscles for example:
Sarcolemma: cell membrane of skeletal muscles
Sarcoplasm: cytoplasm of skeletal muscles

Notes for the previous slide:

- The sarcolemma consists of a true cell membrane, called the plasma membrane, and an outer coat made up of a thin layer of polysaccharide material that contains numerous thin collagen fibrils. The sarcolemma makes invaginations or finger-like projections toward sarcoplasm (cytoplasm) called Transverse tubules (T tubules). At each end of the muscle fiber, this surface layer of the sarcolemma fuses with a tendon fiber. The tendon fibers, in turn, collect into bundles to form the muscle tendons that then connect the muscles to the bones.

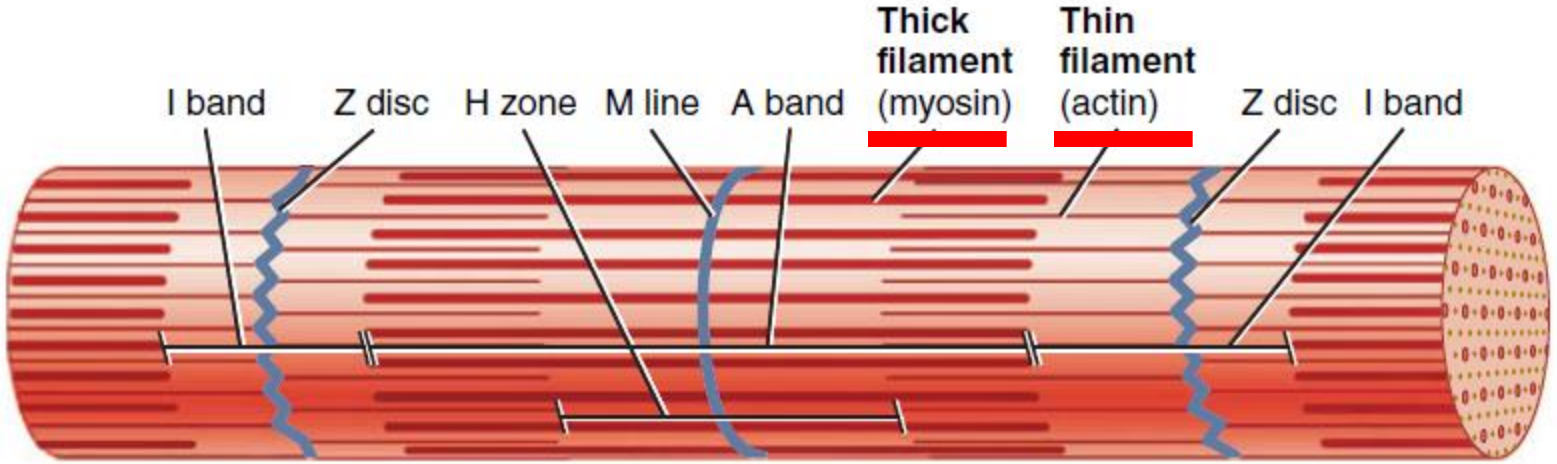
- The spaces between the myofibrils are filled with intracellular fluid called sarcoplasm, containing large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes.

- There is tremendous numbers of mitochondria that lie parallel to the myofibrils. These mitochondria supply the contracting myofibrils with large amounts of energy in the form of adenosine triphosphate (ATP) formed by the mitochondria.

- Sarcoplasmic reticulum has a special organization that is extremely important in regulating calcium storage, release, reuptake and therefore muscle contraction. The ends of the sarcoplasmic reticulum are called terminal cisternae. The function of the terminal cisternae is to store and release calcium ions(Ca^{+2})
- Triad= 2 terminal cisterns (sides) + 1 Transverse tubule.
- Each muscle **fiber** contains several **hundred to several thousand** myofibrils.

Go to the next slide for explanation

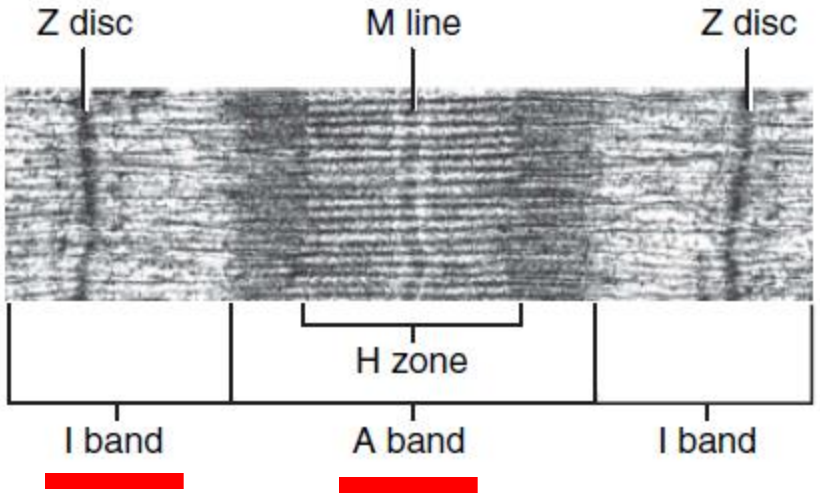
myofibril

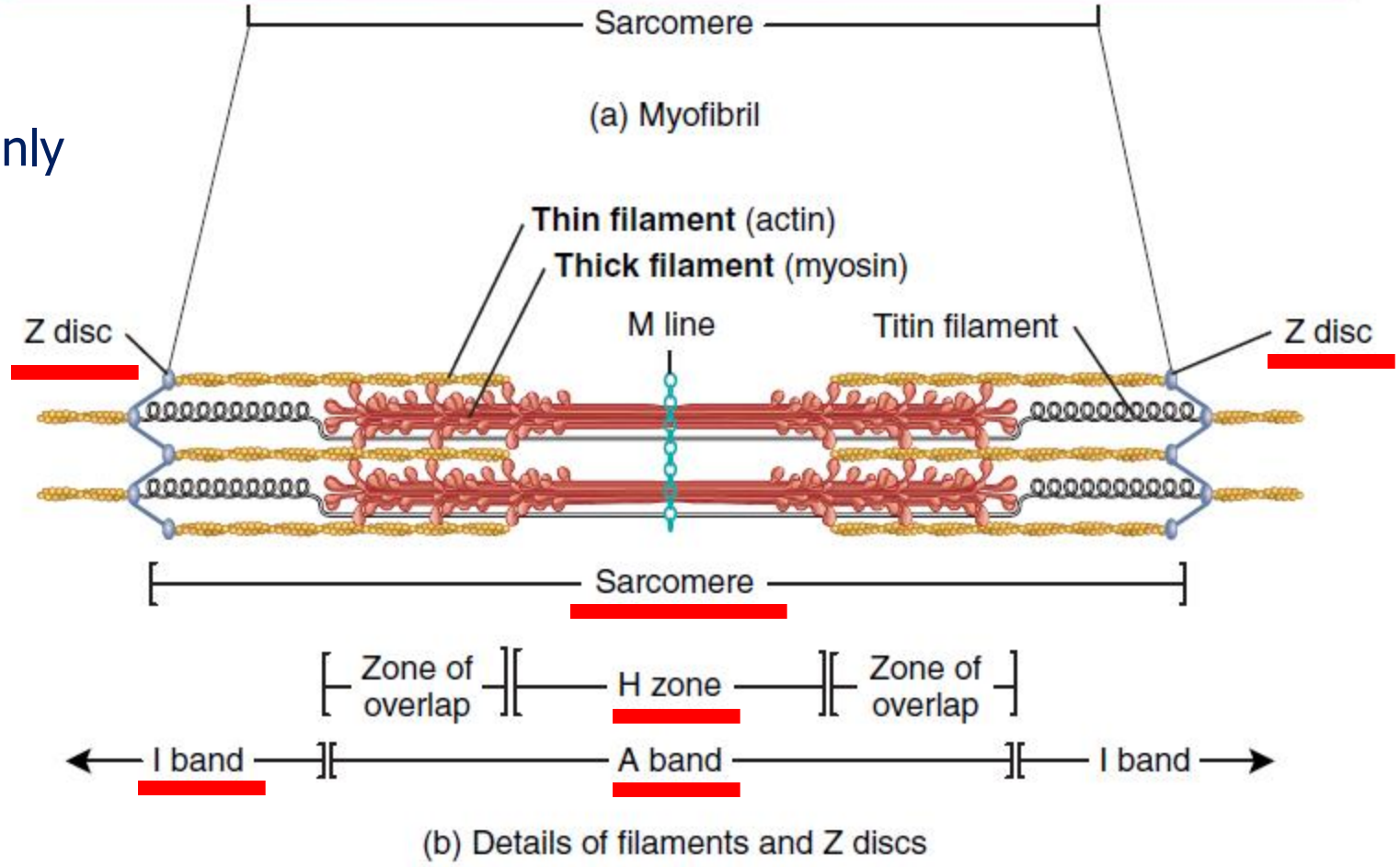


I–band = thin filaments (actin) only

H-zone = Thick filaments (myosin) only

A–band = both Thick + thin





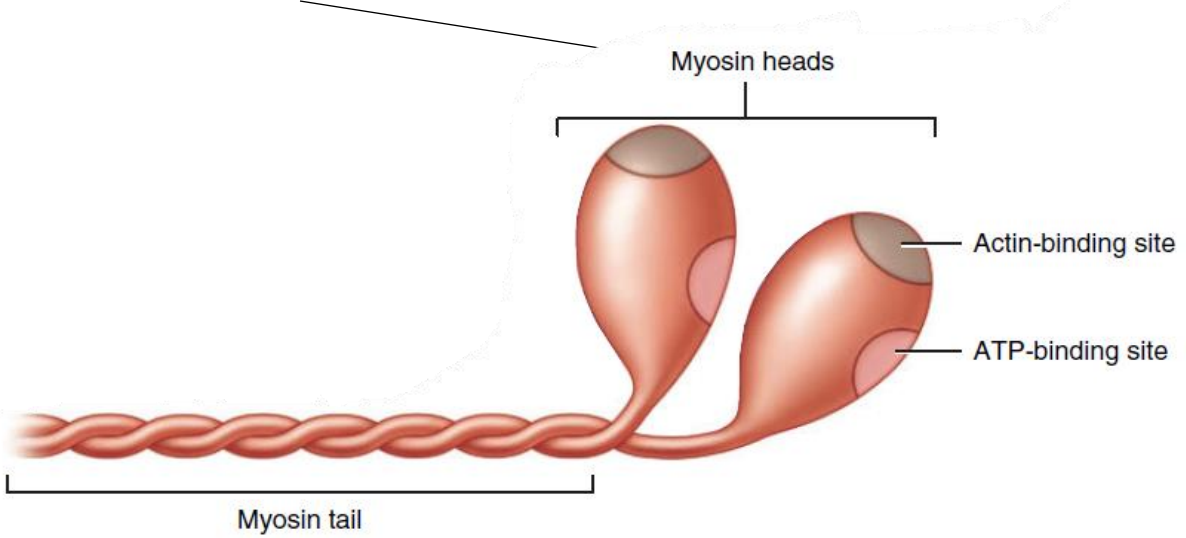
The numbers 3,000 and 1,500 are not for memorization. They are only to imagine the situation.

- **NOTES:**
- Each muscle **fiber** contains several **hundred to several thousand** myofibrils.
- Each **myofibril** is composed of about **1500 adjacent myosin filaments (**thick filaments**) and 3000 actin filaments (**thin filaments**)**, which are large polymerized protein molecules that are responsible for the muscle contraction.
- The reason why skeletal muscle is striated is because under the electron microscope, some regions appear more darker than other, which gives striated appearance.
- The different regions are:
- 1- The **light bands** contain only actin filaments and are called **I bands** because they are **isotropic (متماثل) to polarized light. –** google- when polarized light is passed through the muscle fiber, light rays are refracted at the same angle, looks lighter.
- **2- The dark bands** contain myosin filaments, as well as the ends of the actin filaments, where they overlap the myosin, and are called **A bands** because they are **anisotropic (متباين)** to polarized light. –google- exhibits different patterns under polarized light, looks darker. The A band is further divided into:
    a) H band= thick filaments only.
    b) Zone of overlap= both filaments.
- There are certain structures that gives vertical orientations making a zig zag called Z-disc. Plus, there is also M-line (middle line).
- Sarcomere is the structure between 2 Z-discs. Sarcomere, which is the functional unit of skeletal muscle. A functional unit of any organ is the smallest component that can perform all functions of that organ; in case of skeletal muscles, its function is to contract so it gets shorter.

Sarcomeres → myofibrils → Muscle fibers → Whole muscle

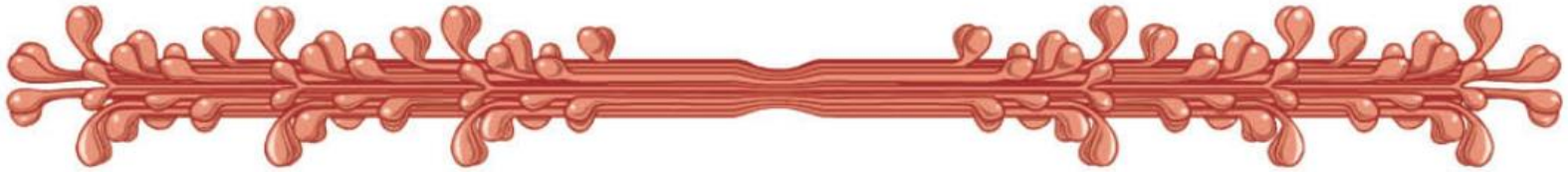
Contract Contract Contract Contracts

NOW, we classify the proteins of the skeletal muscles into structural proteins, contractile proteins & Regulatory proteins.
Contractile proteins are
1. Myosin 2. Actin



Contractile Proteins

Myosin



(a) Thick filament (below) and myosin molecule (above)

NOTES:

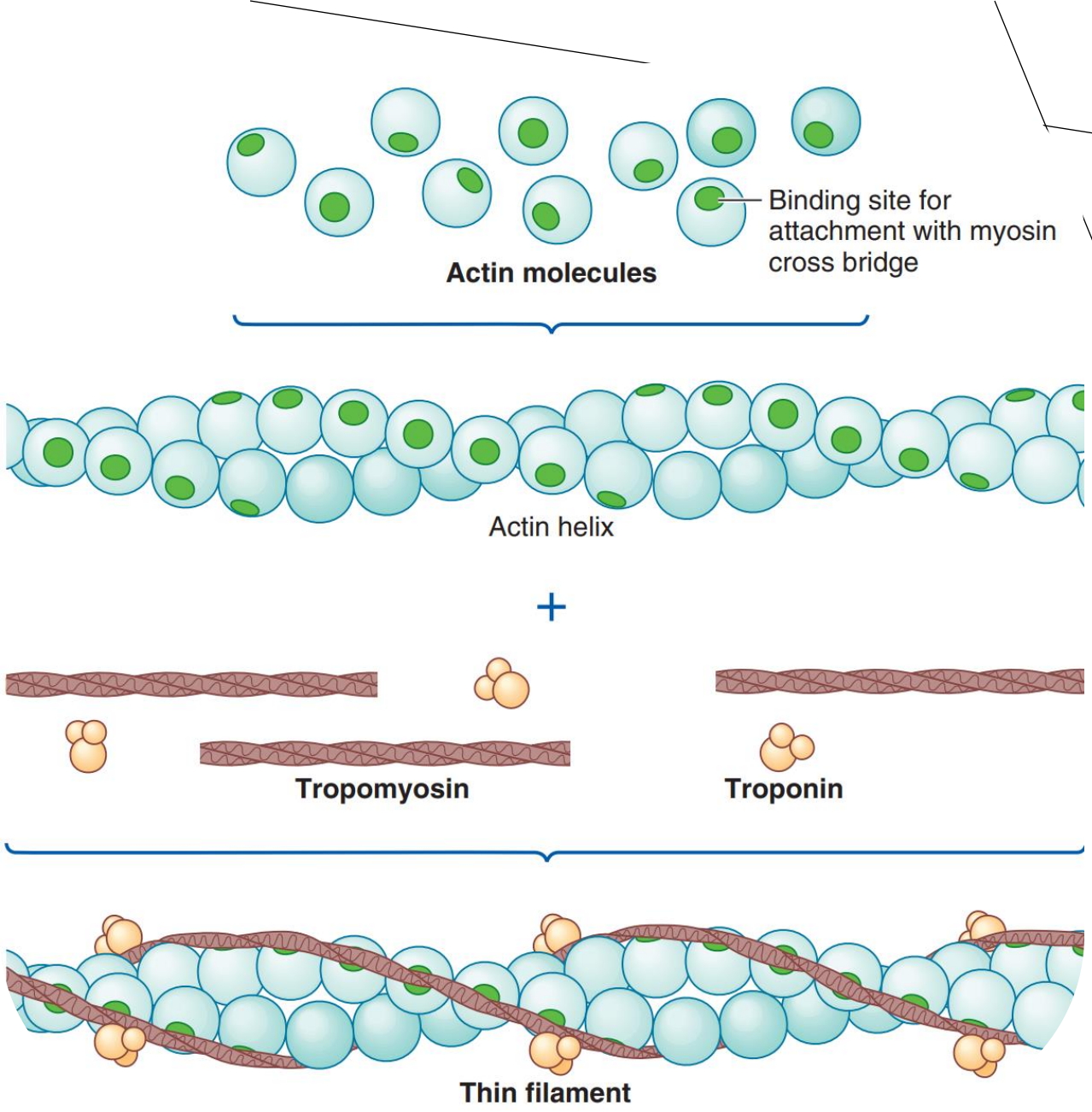
- Each **thick filament** has **several hundred myosin molecules** packed together in a specific arrangement.
- A myosin molecule is a protein consisting of two identical subunits (head and tail).
- Each myosin head has 2 binding sites; one for actin-binding & other for ATP-binding.
- ATP- binding site has enzymatic activity (ATPase).So, when ATP binds, it will be hydrolyzed into ADP & phosphate group.
- The two myosin heads of each myosin molecule act independently, with only one head attaching to actin at a given time. هون بحكيلك لما بصير انقباض بس رأس واحد للميوسن بربط بالأكتن

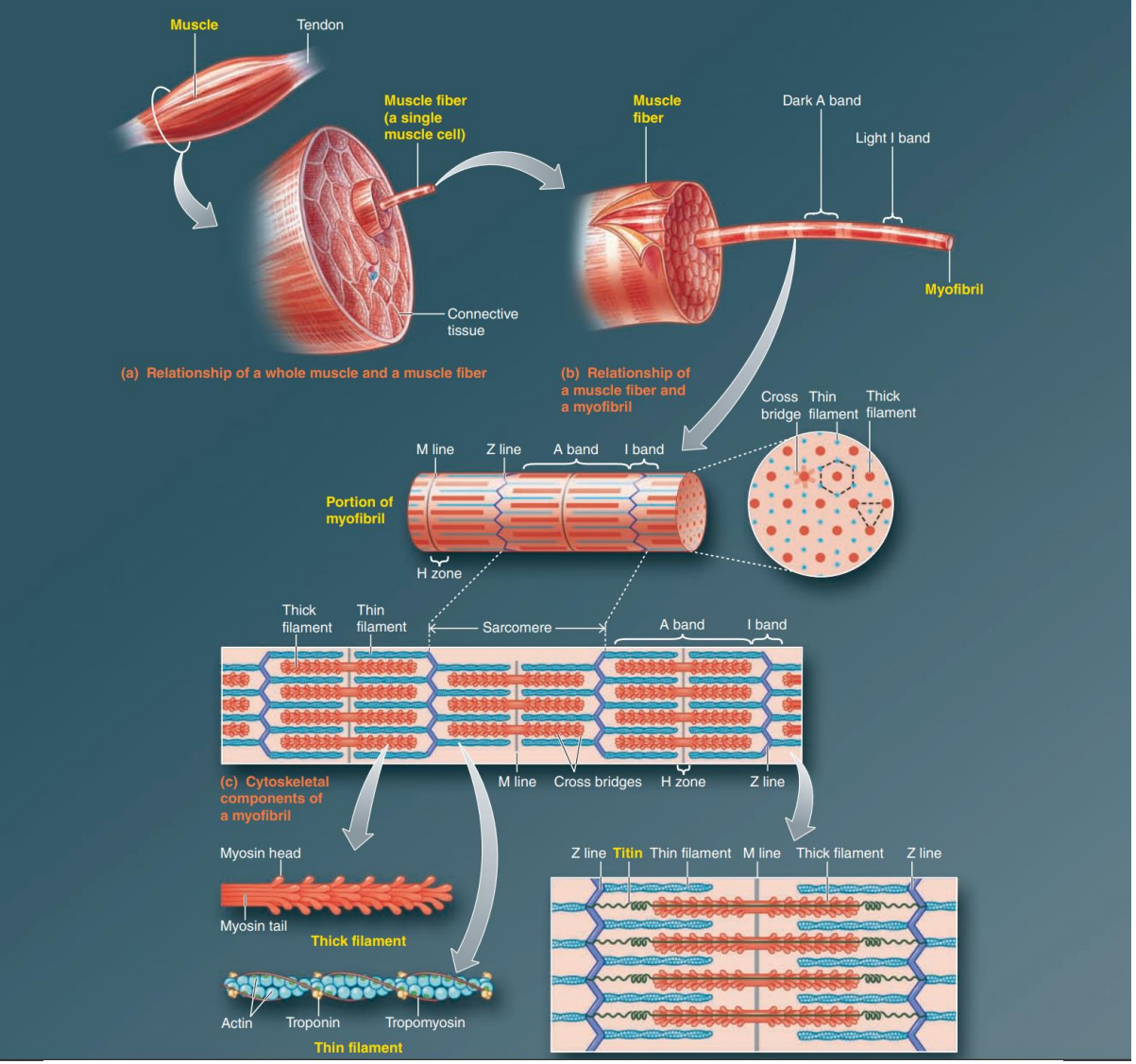
Contractile Proteins

Actins

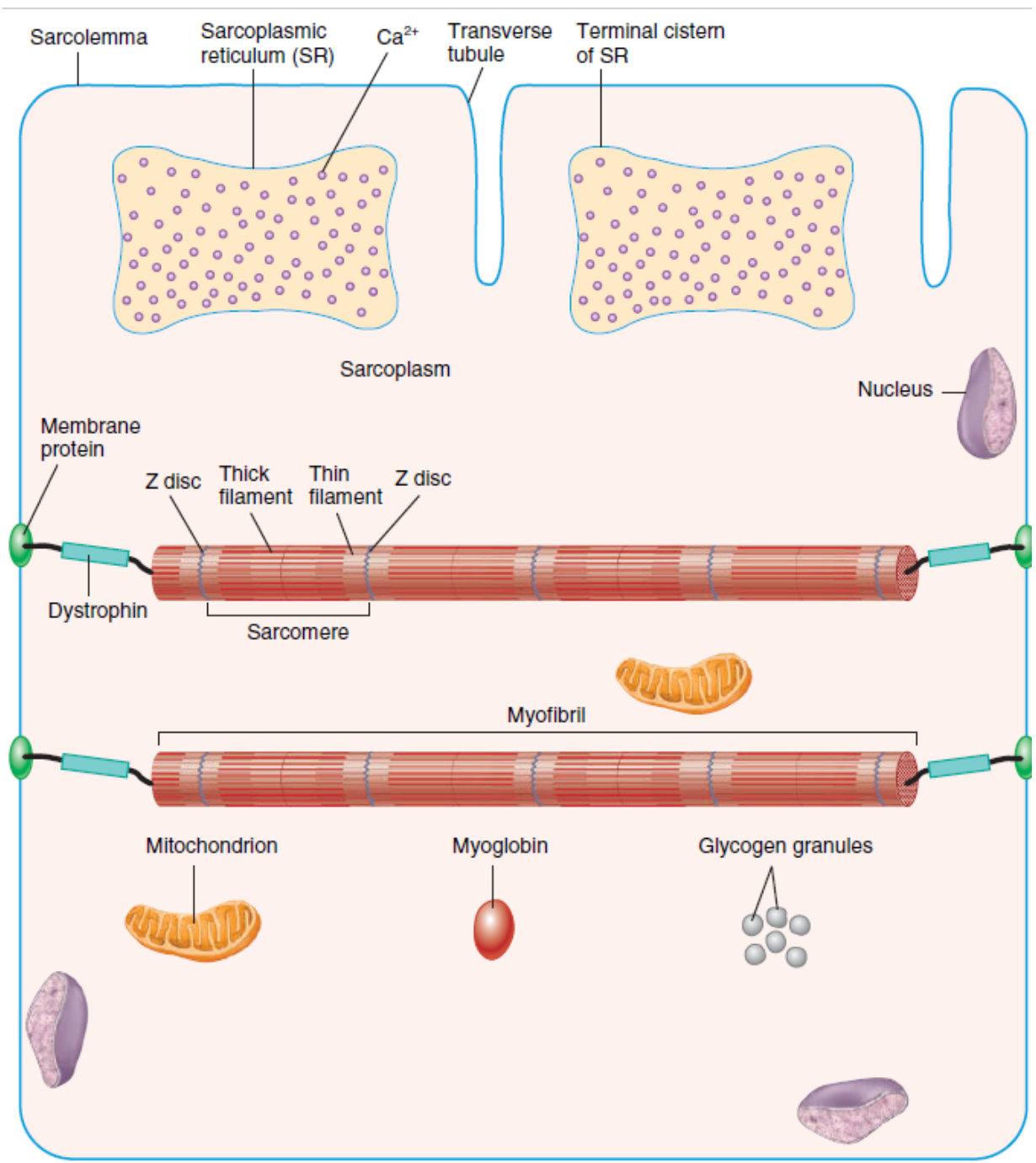
NOTES:

- Thin filaments consist of three proteins: actin (mainly), tropomyosin, and troponin.
- Actin molecules are globular proteins that form filamentous structures. The polymerization of actin is dynamic.
- Actin has a binding site for myosin cross bridges.
- Tropomyosin & troponin are regulatory proteins. In relaxed muscle, Tropomyosin blocks myosin binding site & Troponin when bound to calcium ions(Ca^{+2}), it will uncover the binding sites.

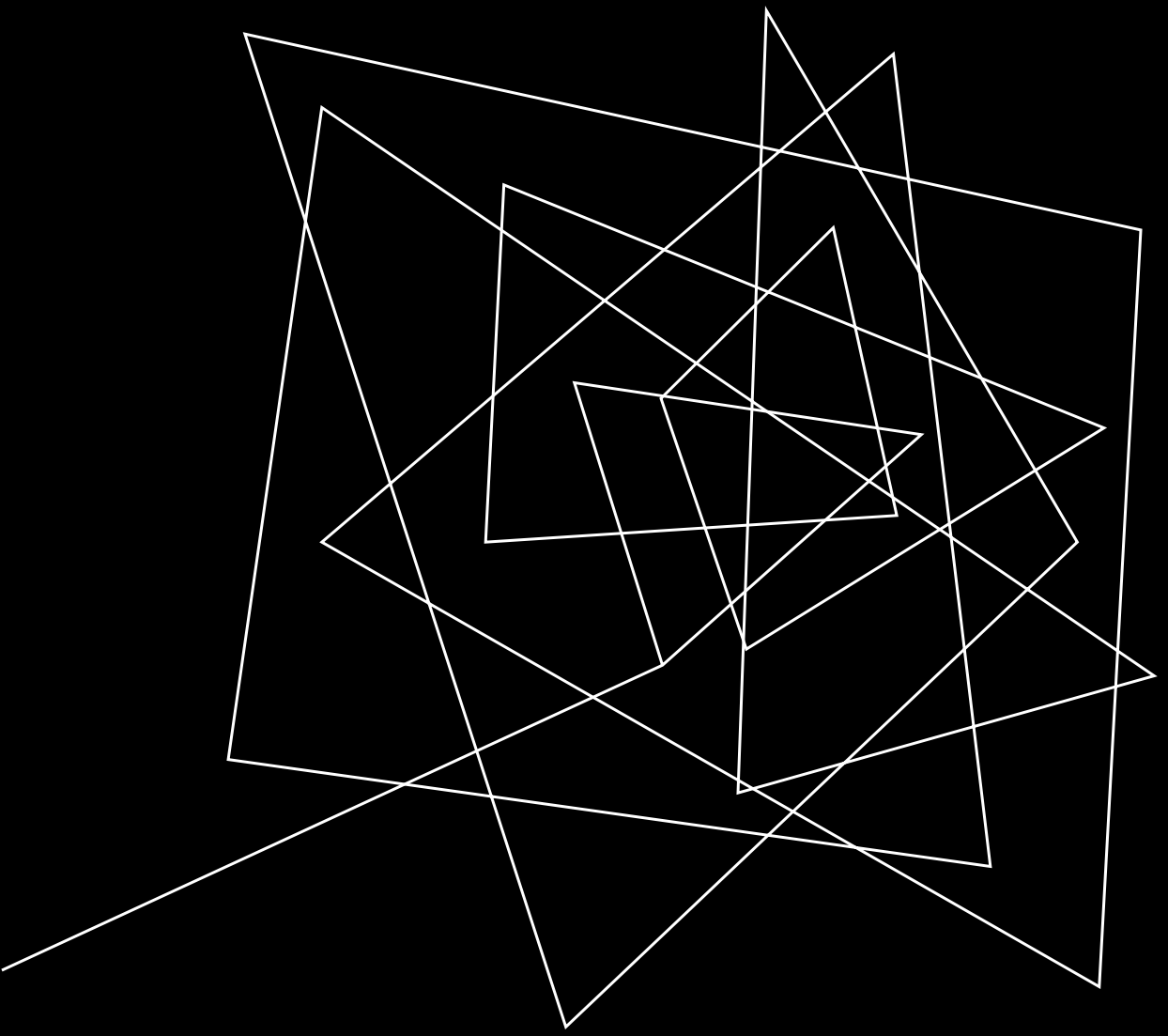




Whole muscle (an organ) → muscle fiber (a cell) → myofibril (a specialized intracellular structure) → thick and thin filament (cytoskeletal elements) → myosin and actin (protein molecules)



(d) Simplistic representation of the components of a muscle fiber



SKELETAL MUSCLE

Molecular Basis of Skeletal Muscle Contraction

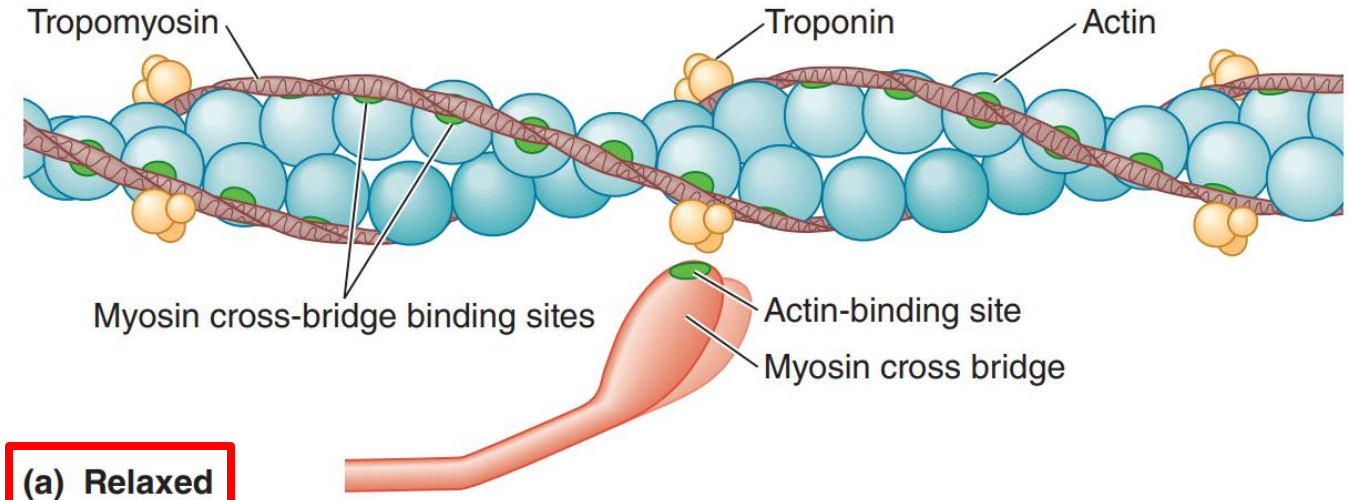
sliding filaments

Cross-bridging

NOTES:

- Cross-bridge interaction between actin in the myosin binding site and myosin in the actin binding site brings about muscle contraction by means of the sliding filament mechanism.

Relaxed muscle	Contracted muscle
❖ Tropomyosin covers the myosin binding sites of actin. ❖ Calcium ions(Ca^{+2}) are not released from Terminal cisternae.	❖ Calcium ions(Ca^{+2}) are released. ❖ Actin is bound to myosin (cross-bridging) ❖ Myosin binding sites are not covered. ❖ Calcium ions(Ca^{+2}) are bound to Troponin.

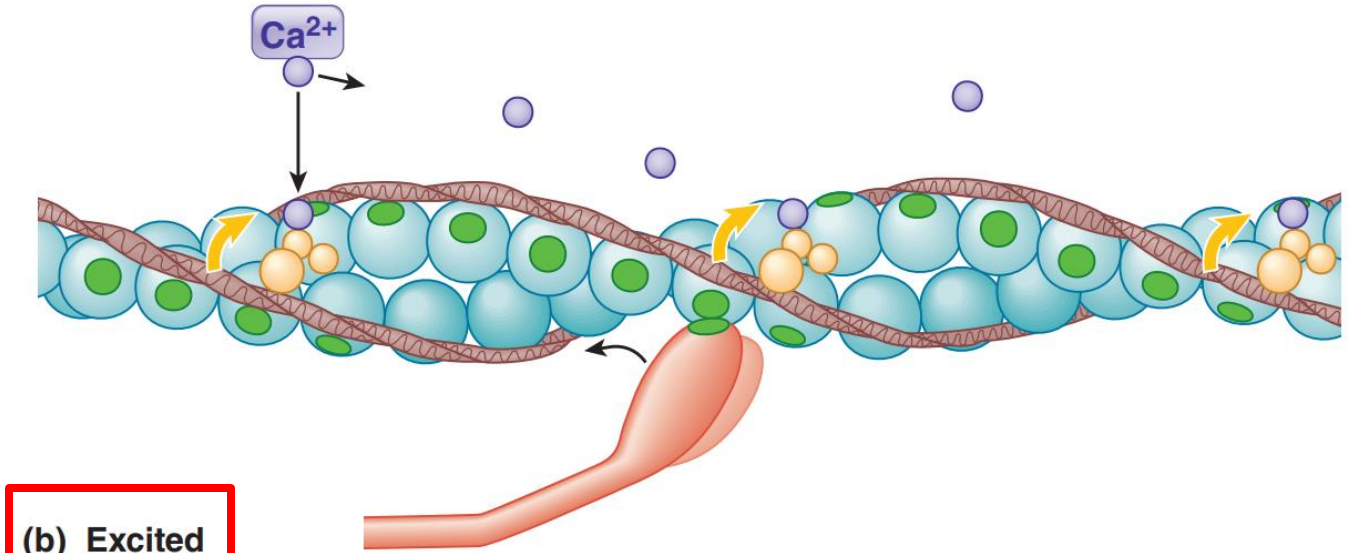


(a) Relaxed

1 No excitation.

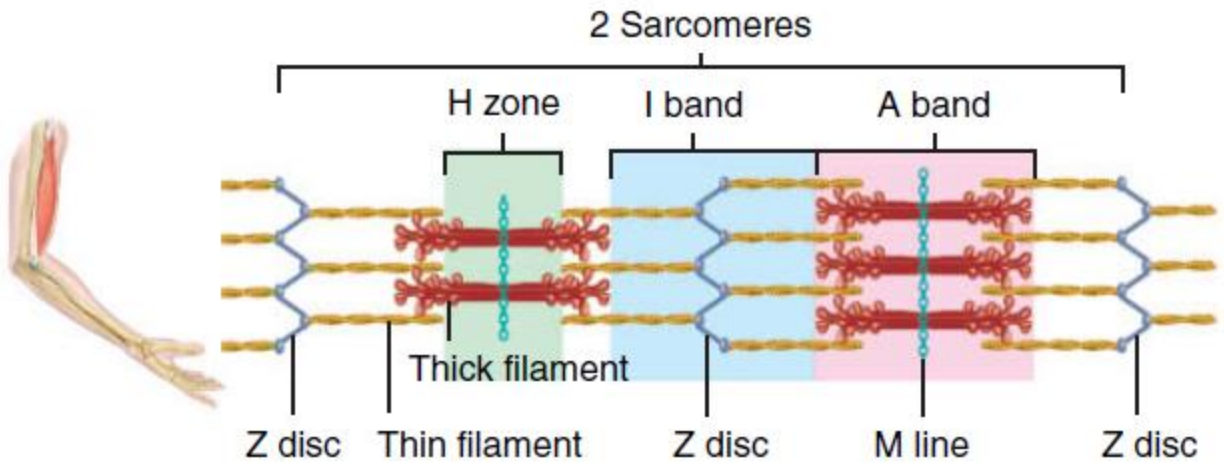
2 No cross-bridge binding because cross-bridge binding site on actin is physically covered by troponin–tropomyosin complex.

3 Muscle fiber is relaxed.

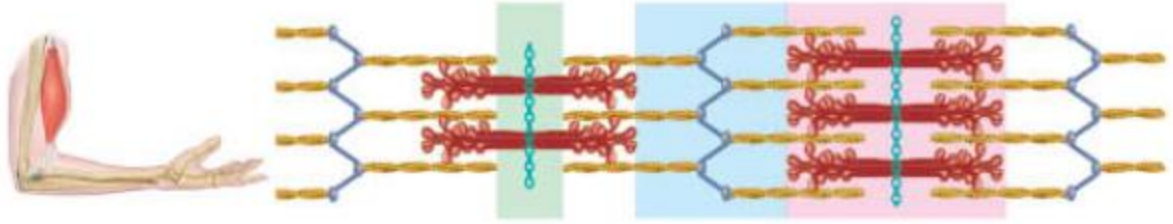


(b) Excited

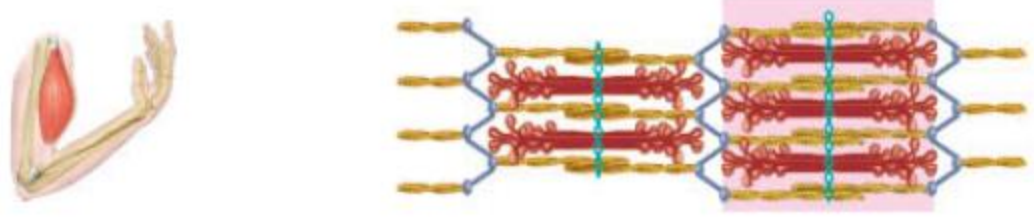
The Sliding Filament Mechanism



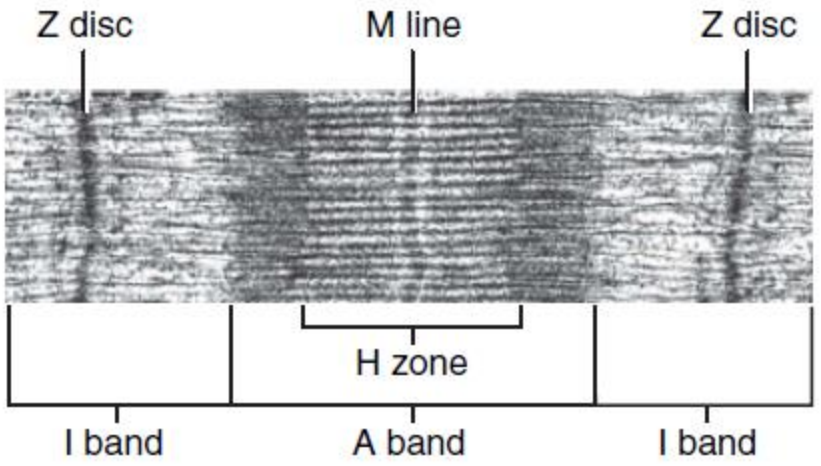
(a) Relaxed muscle

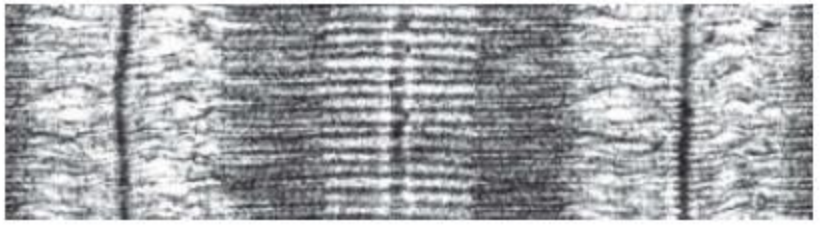


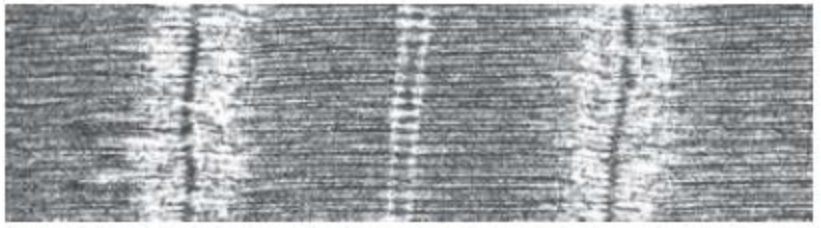
(b) Partially contracted muscle



(c) Maximally contracted muscle







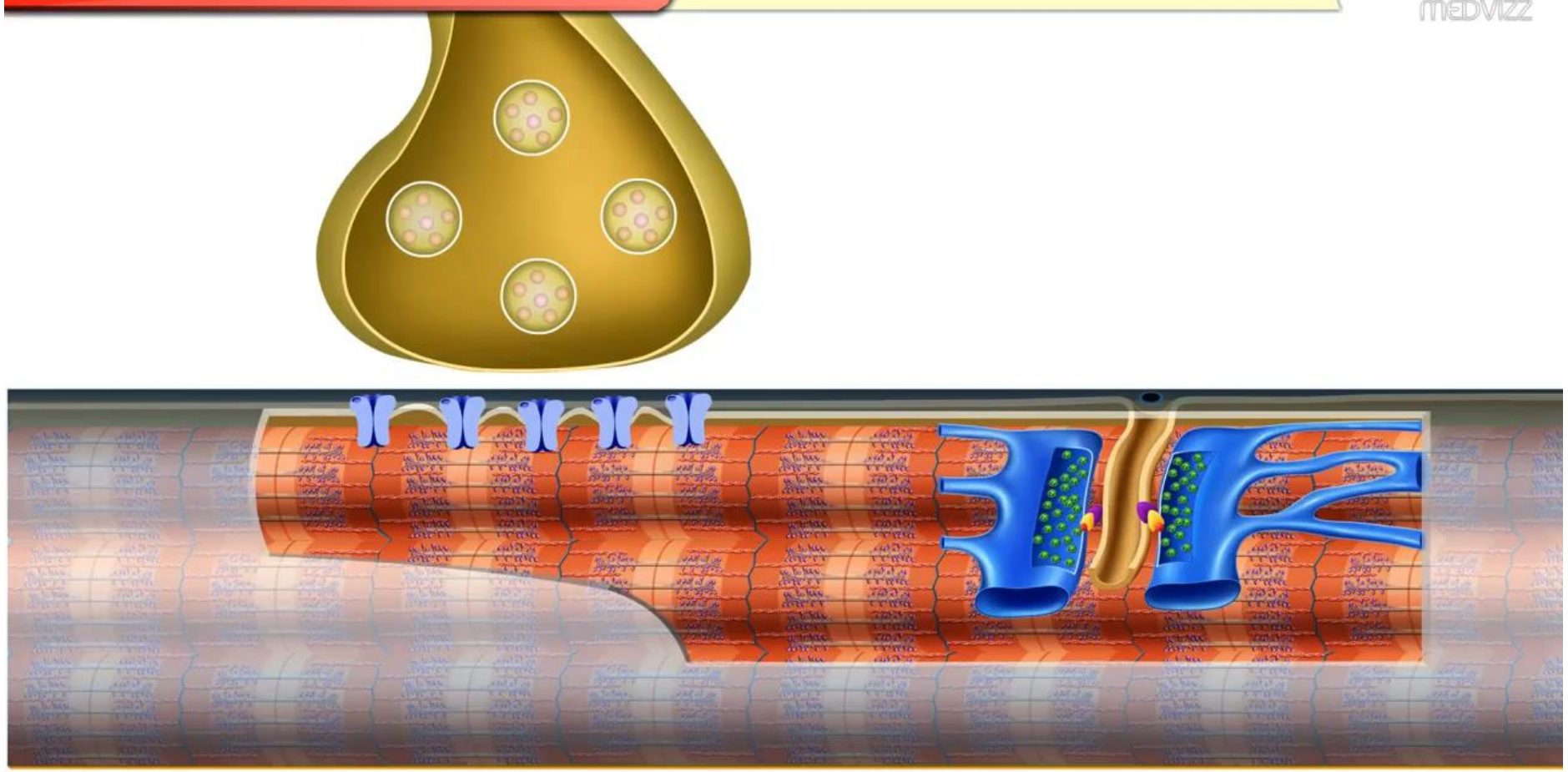
Courtesy Hiroyouki Sasaki, Yale E.Goldman and Clara Franzini-Armstrong

Notes:

- Initiation of Muscle contraction starts with an action potential that propagates through the sarcolemma (plasma membrane) until it reaches T tubules which leads to the release of calcium from Terminal cisternae of sarcoplasmic reticulum to sarcoplasm (cytoplasm).
- Calcium will bind to Troponin and cause a conformational change, pulling Tropomyosin and exposing myosin binding sites of the actin.
- Muscle contraction occurs because myosin heads attach to and "walk" along the thin filaments at both ends of a sarcomere, progressively pulling the thin filaments toward the M line.
- As a result, the thin filaments slide inward and meet at the center of a sarcomere. They may even move so far inward that their ends overlap.
- As the thin filaments slide inward, **the I band and H zone narrow and eventually disappear altogether when the muscle is maximally contracted.**
- Since the thin filaments on each side of the sarcomere are attached to Z discs, when the thin filaments slide inward, **the Z discs come closer together**, and the **sarcomere shortens**.
- **Shortening of the sarcomeres causes shortening of the whole muscle fiber, which in turn leads to shortening of the entire muscle**.
- **Note** that neither the thick nor the thin filaments decrease in length to shorten the sarcomere. Instead, contraction is accomplished by the thin filaments from the opposite sides of each sarcomere sliding closer together between the thick filaments.

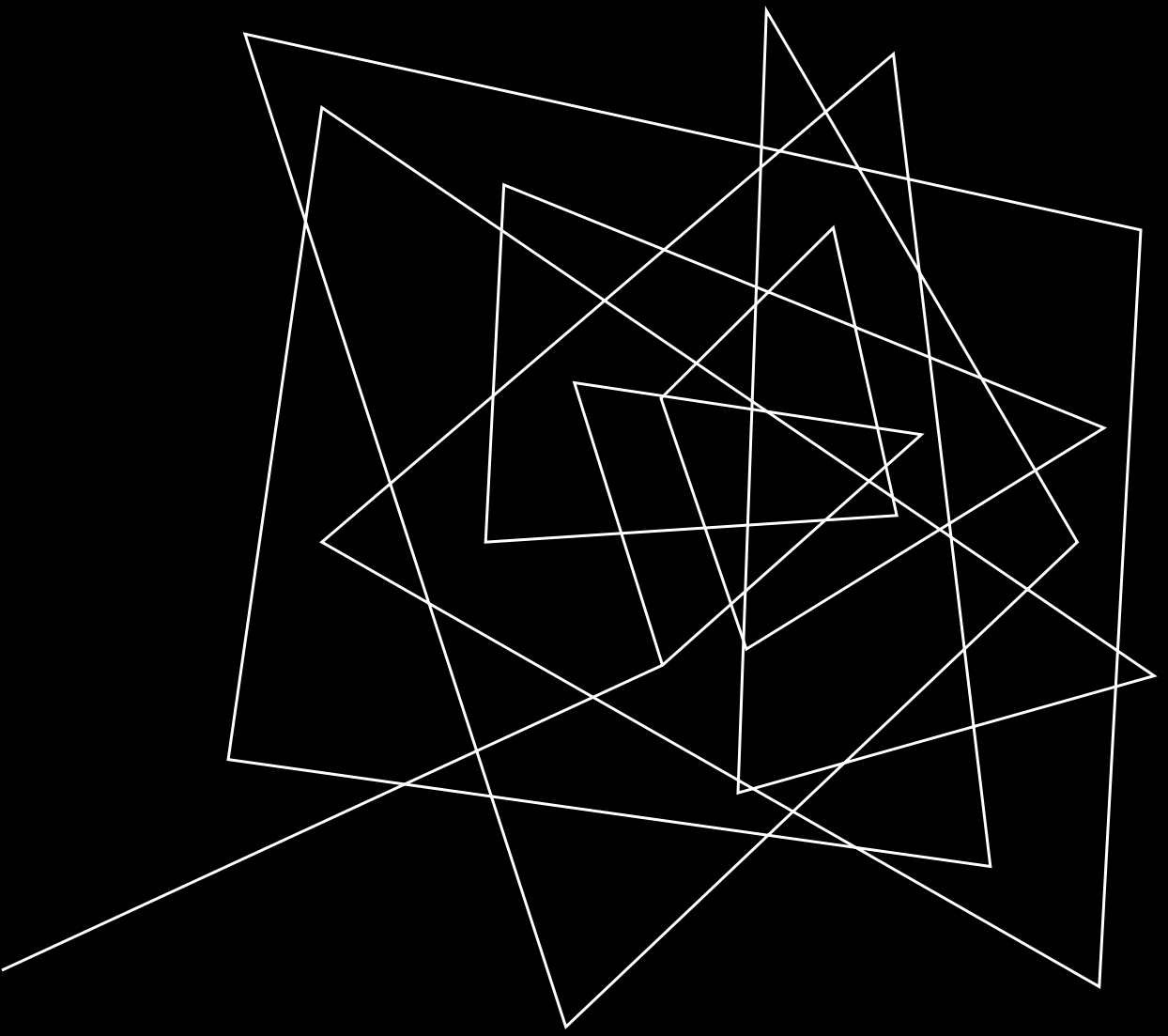
Skeletal Muscle Contraction

Excitation Contraction Coupling



NOTES: The video - [muscle contraction animation]

Note: The sliding mechanism sounds pretty obvious. However, it was thought previously that the contraction was caused by filaments folding on top of each other. The sliding mechanism was only discovered after they looked at images of contracted vs relaxed muscle in an electron microscope (look at the pictures in the next slide to compare). The evidence supporting the sliding mechanism when seen by electron microscope is that when the sarcomere contracts, the **length of the A band (which represents the length of the thick filaments) stays the same. Thus, the length of the filaments does not change, rather they slide over each other, and the area of overlap increases. If the folding mechanism was true, then it would look like the filaments got shorter under the microscope.



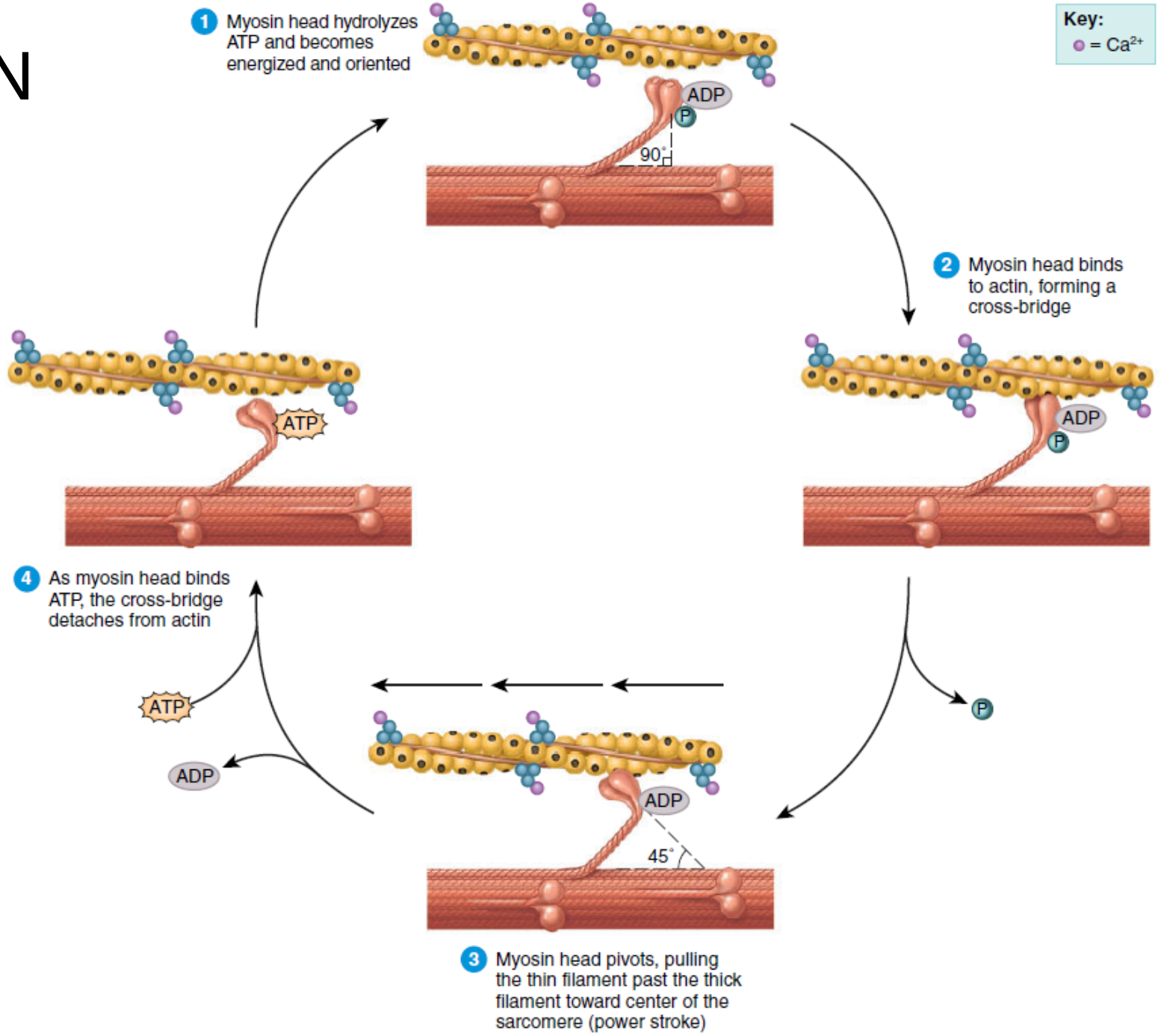
SKELETAL MUSCLE

Contraction _ contraction cycle

THE CONTRACTION CYCLE

It is divided into 4 steps as seen here:

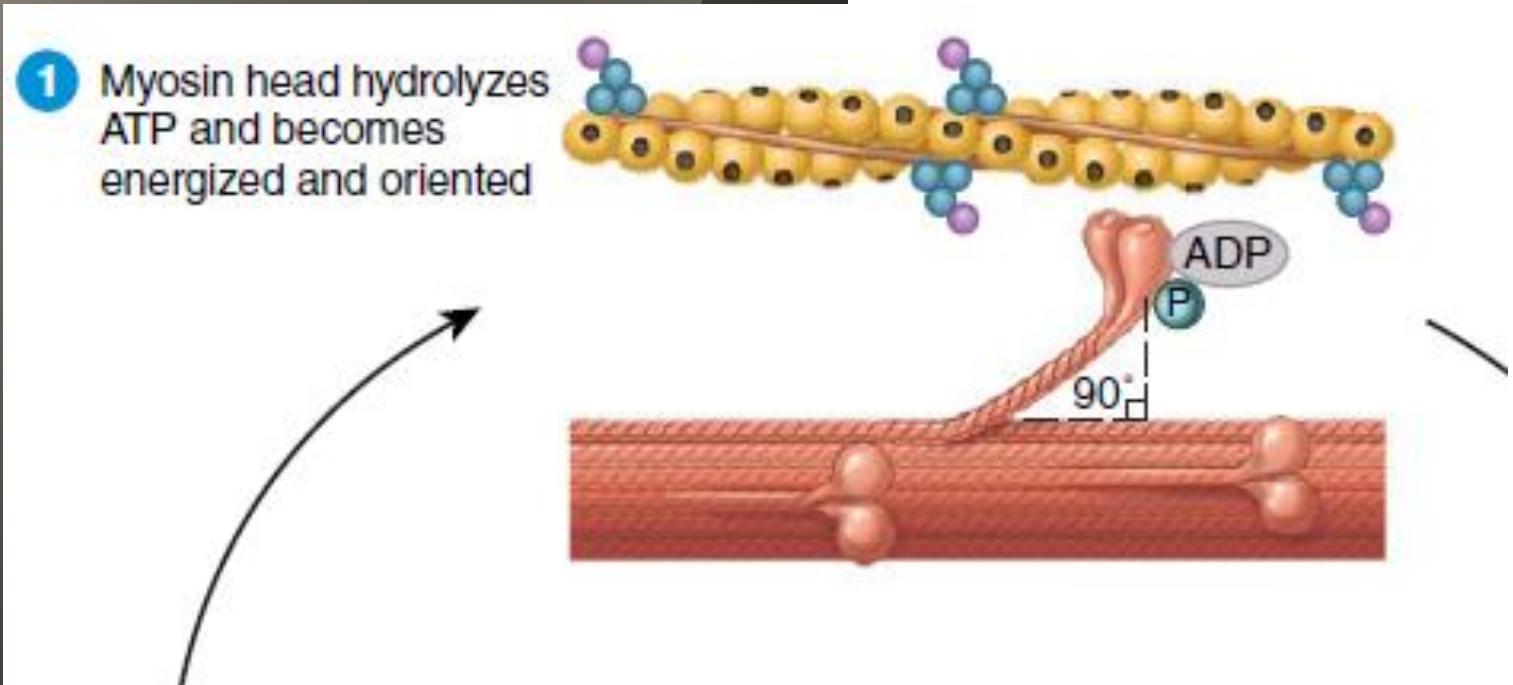
At the onset of contraction, the sarcoplasmic reticulum releases calcium ions (Ca2+) into the sarcoplasm. There, they bind to troponin. Troponin then moves tropomyosin away from the myosin-binding sites on actin. Once the binding sites are "free," the **contraction cycle**—the repeating sequence of events that causes the filaments to slide—begins.



STEP 1: ATP HYDROLYSIS.

This is still the relaxed state.

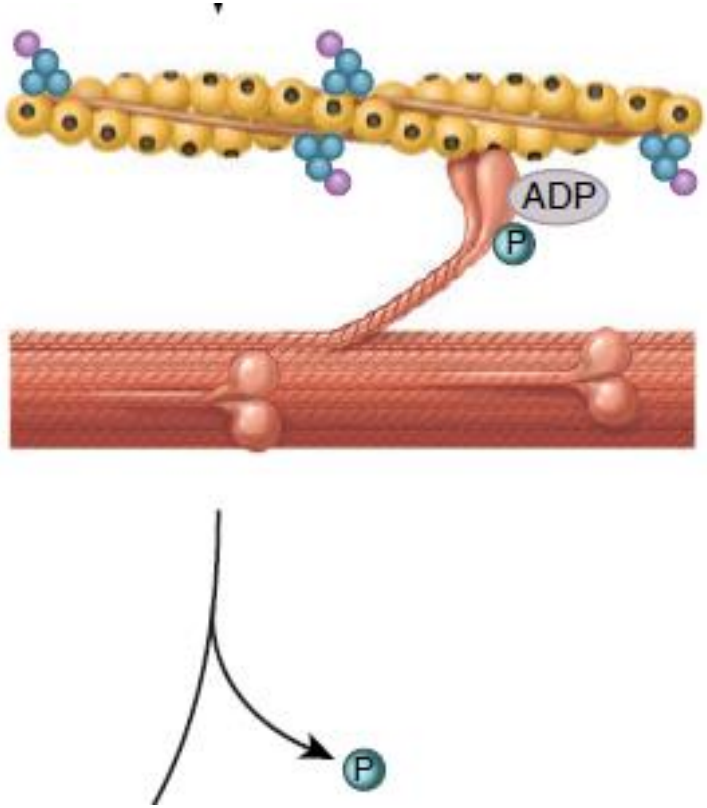
- The energy generated from ATP hydrolysis reaction is stored in the myosin head.
- The energized myosin head is perpendicular (at a 90° angle) relative to the thick and thin filaments and has the proper orientation to bind to an actin molecule.
- Notice that ADP and a phosphate group are still attached to the myosin head.



STEP 2: ATTACHMENT OF MYOSIN TO ACTIN

- Notice here that the myosin head is still at a 90^0 angle and the ADP is still attached to the myosin, but the phosphate is released.

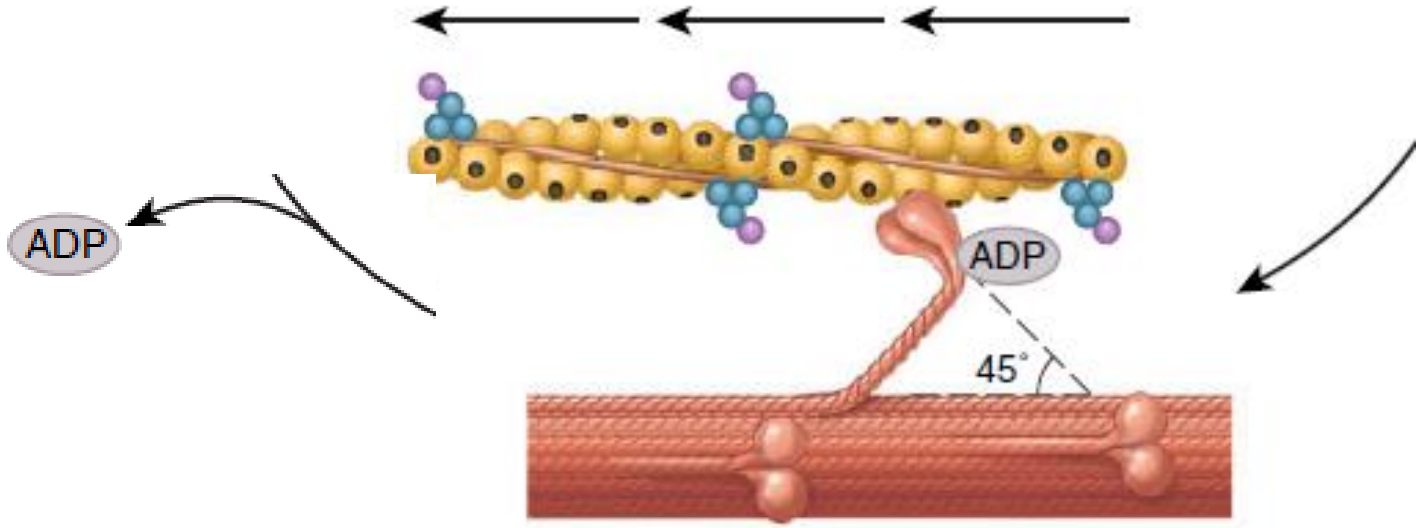
- The energized myosin head attaches to the myosin-binding site on actin and releases the phosphate group.
- When a myosin head attaches to actin during the contraction cycle, the myosin head is referred to as a **cross-bridge**.



STEP 3: POWER STROKE

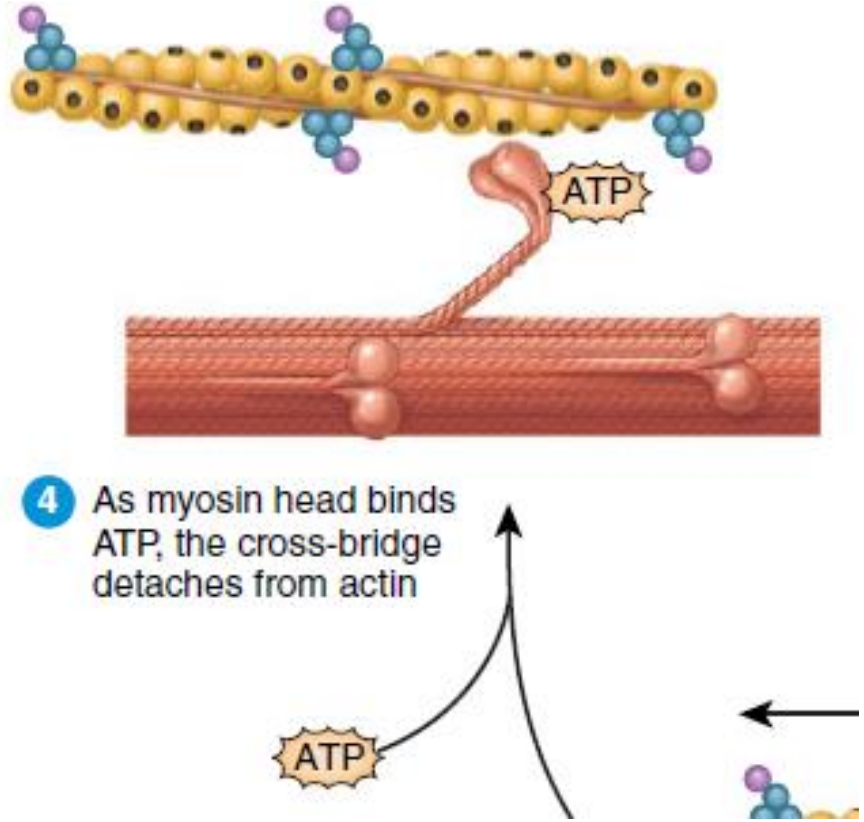
How is the energy from ATP stored? Hydrolysis of ATP is like when someone wants to fire a gun and they "cock" the gun first (or in other words remove the safety) to prepare to shoot . So, the myosin heads store the energy and are ready to bind to the actin filament but the energy is used only in the power stroke step (firing the gun). What exposes the actin? When calcium binds to troponin.

- After a cross-bridge forms, the myosin head pivots, changing its position from a **<u>90° angle to a 45° angle.</u>**
- As the myosin head changes to its new position, it pulls the thin filament past the thick filament toward the center of the sarcomere (M line), generating tension (force).
- This event is known as the **power stroke**.
- Once the power stroke occurs, ADP is released from the myosin head.



STEP 4: DETACHMENT OF MYOSIN FROM ACTIN

- At the end of the power stroke, the cross-bridge remains firmly attached to actin until it binds another molecule of ATP.
- As ATP binds to the ATP binding site on the myosin head, the myosin head detaches from actin



Note: The contraction cycle repeats as the myosin ATPase hydrolyzes the newly bound molecule of ATP, and **continues as long as ATP is available and the Ca2+ level near the thin filament is sufficiently high.**

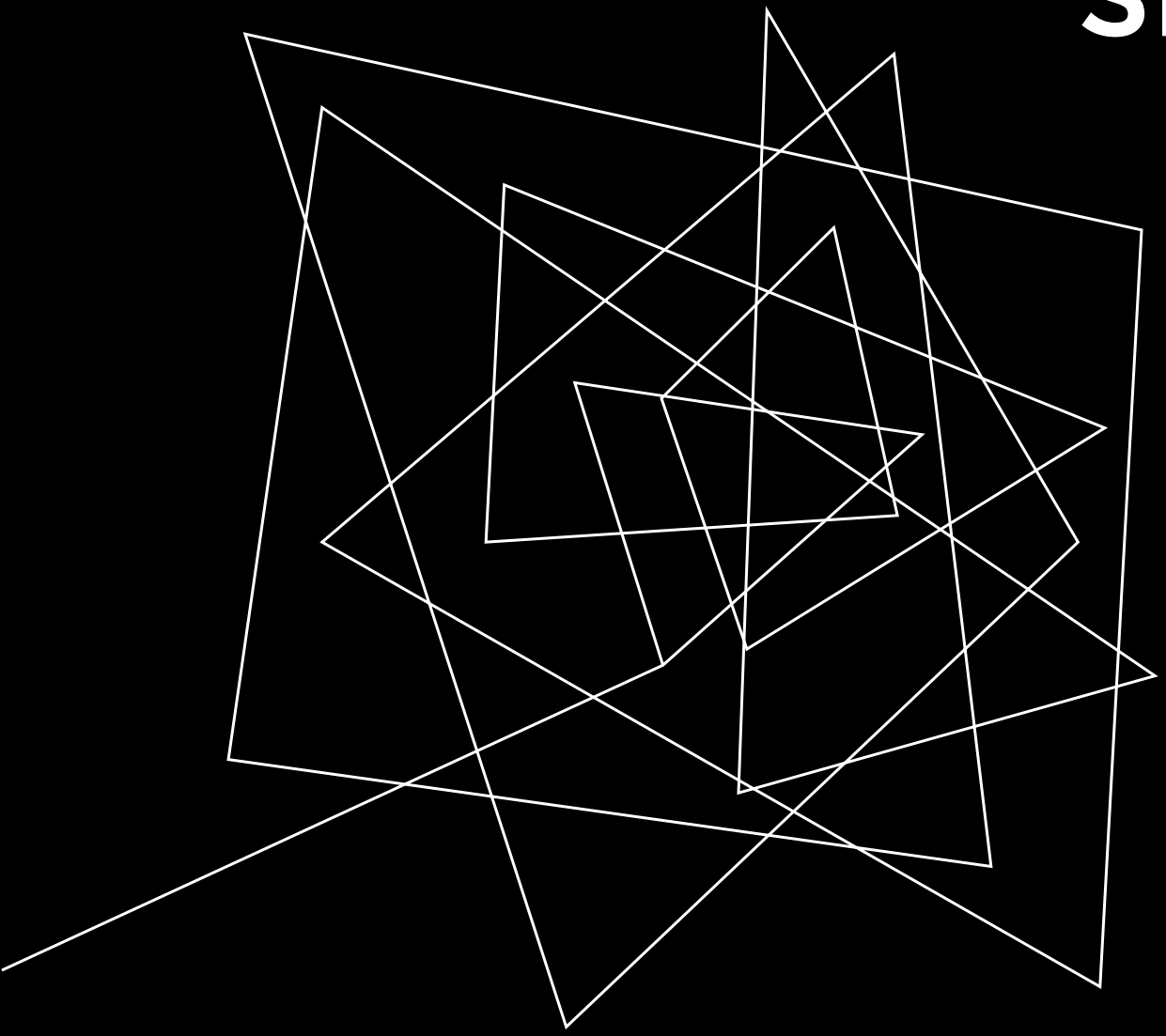
- In this step the ATP is ready to be hydrolyzed again and the cycle keeps repeating as long as there is enough Ca2+ to keep the tropomyosin detached from the myosin binding site on the actin.
- Note: One cycle is not enough of course to cause contraction, it is the collection of numerous cycles across many sarcomeres.

Rigor Mortis (Rigidity of death)

- A condition in which muscles are in a state of rigidity. يعني صلابة العضلات بعد الموت
- Begins 3–4 hours after death and lasts about 24 hours.
- Explanation : after death, cellular membranes become leaky. Calcium ions leak out of the sarcoplasmic reticulum into the sarcoplasm and allow myosin heads to bind to actin.
- ATP synthesis ceases shortly after breathing stops, however, so the cross-bridges cannot detach from actin. **(remember from the cycle that ATP is what causes the cross bridges to detach, so no ATP = no detachment = rigor mortis).**
- It disappears as proteolytic enzymes from lysosomes digest the cross-bridges **(so just as calcium was leaked, proteolytic enzymes also leak from the breakdown of membranes)**

SKELETAL MUSCLE

Excitation–contraction coupling

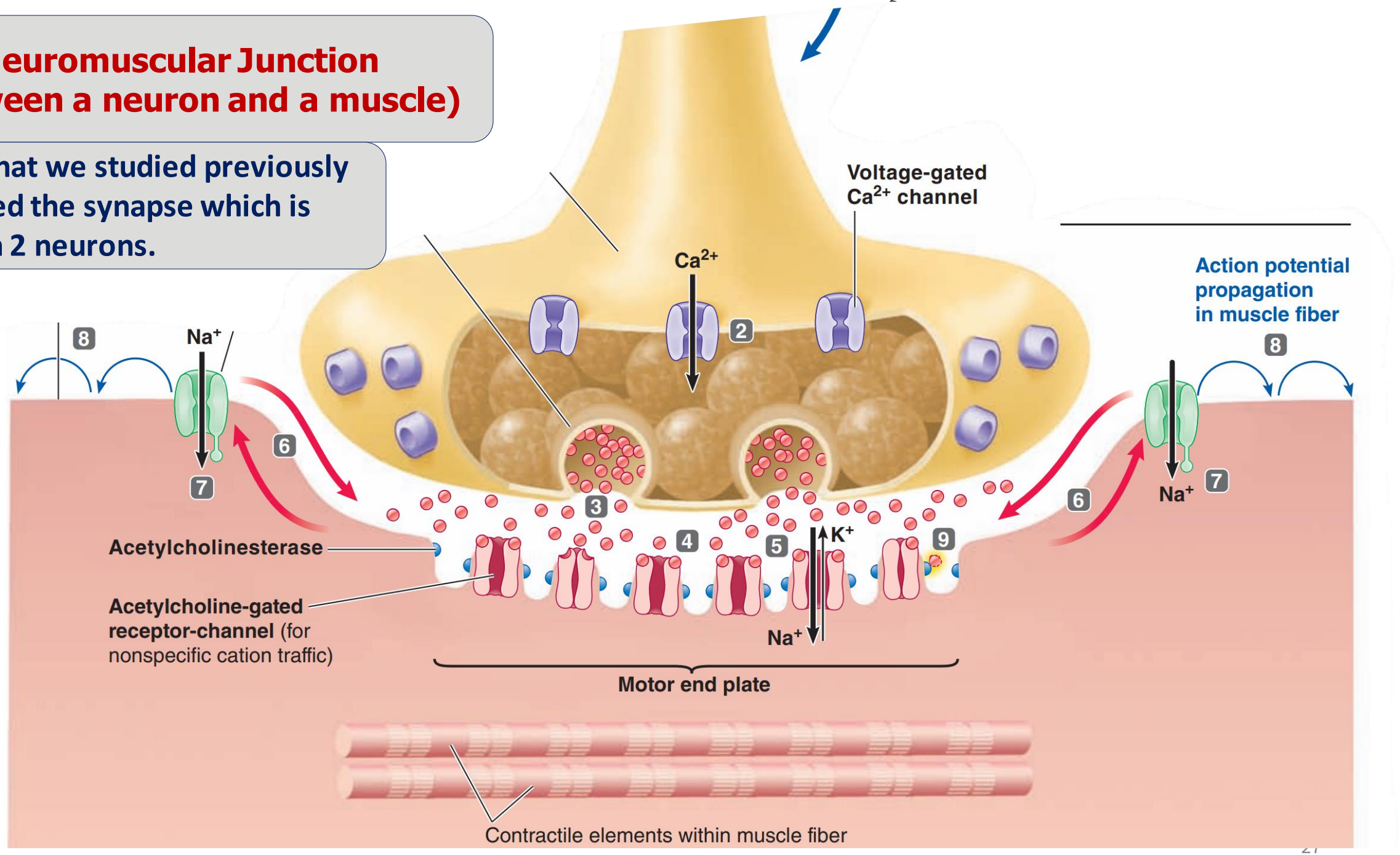


- **Note:** How does muscle excitation switch on this cross-bridge cycling? The term excitation–contraction coupling refers to the series of events linking muscle excitation (the presence of an action potential in a muscle fiber) to muscle contraction (cross-bridge activity that causes the thin filaments to slide closer together to produce sarcomere shortening).

Excitation-contraction coupling is the switch from electrical energy to mechanical energy, which causes movement.

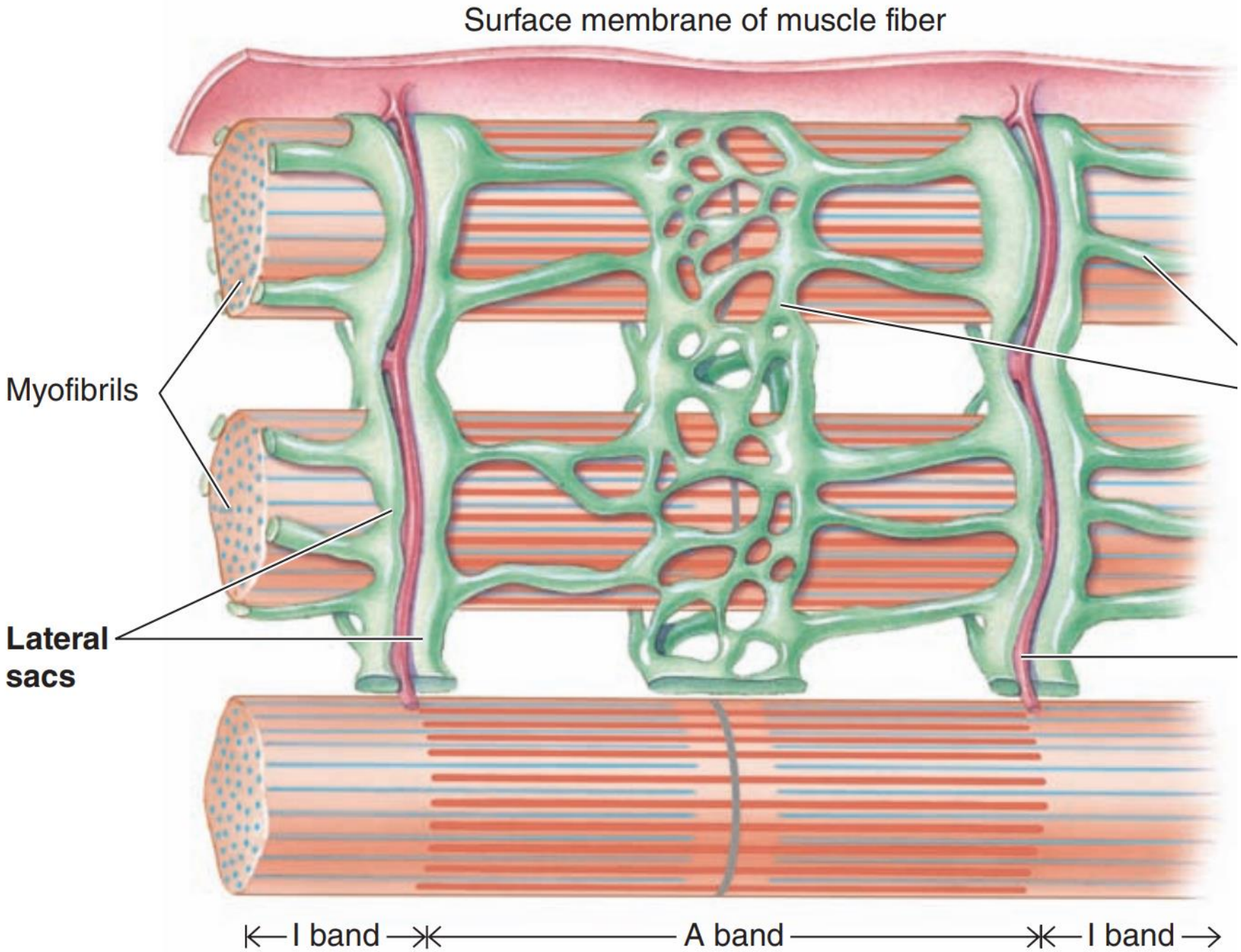
Neuromuscular Junction (between a neuron and a muscle)

While what we studied previously was called the synapse which is between 2 neurons.

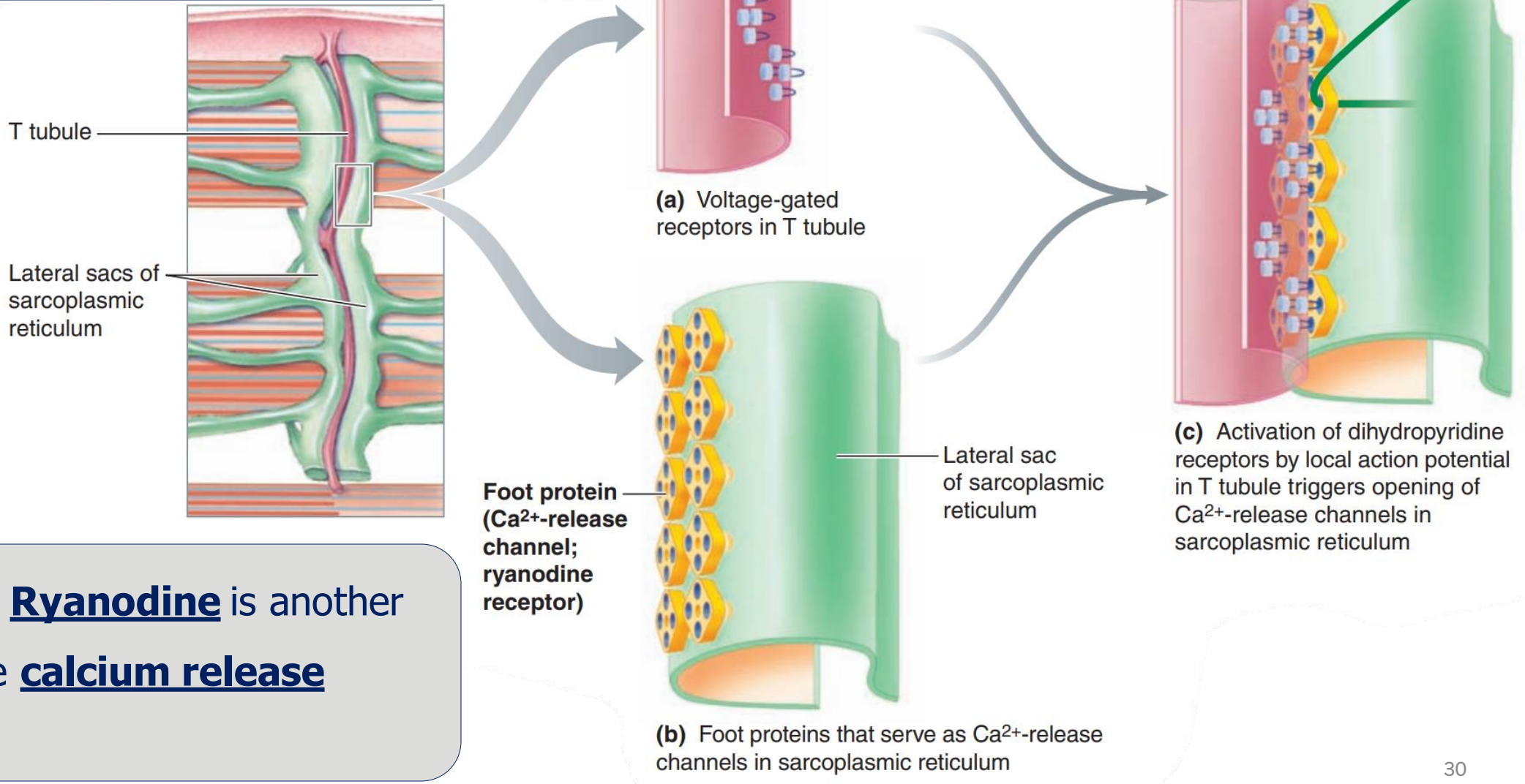


Excitation contraction coupling steps:

1. Action Potential reaches the nerve ending.
2. Causes opening of **voltage-gated calcium channels** at the nerve ending, thus an increase in calcium levels intracellularly.
3. This induces exocytosis of the neurotransmitter (Acetylcholine in the case of the neuromuscular junctions).
4. Acetylcholine is released and binds to its receptor on the muscle.
5. This opens the sodium-potassium channel which lets **Na^+ in** and lets K^+ out (but mainly we just refer to this process as influx of Na+ because its effect is more prominent). **This is not yet a true action potential.**
6. The depolarization wave travels until it reaches…
7. **Voltage-gated sodium channels, which starts the true action potential.**
8. The action potential is propagated to the whole muscle fiber and through the T-tubules which are adjacent to the terminal cisternae which store Ca2+(remember the triad).
9. The acetylcholine in the neuromuscular cleft is broken down by acetylcholinesterase or endocytosed back into the neuron. If the neuron is not stimulated, then it will not release acetylcholine. Eventually, there won't be enough acetylcholine in the cleft to cause an action potential in the muscle.

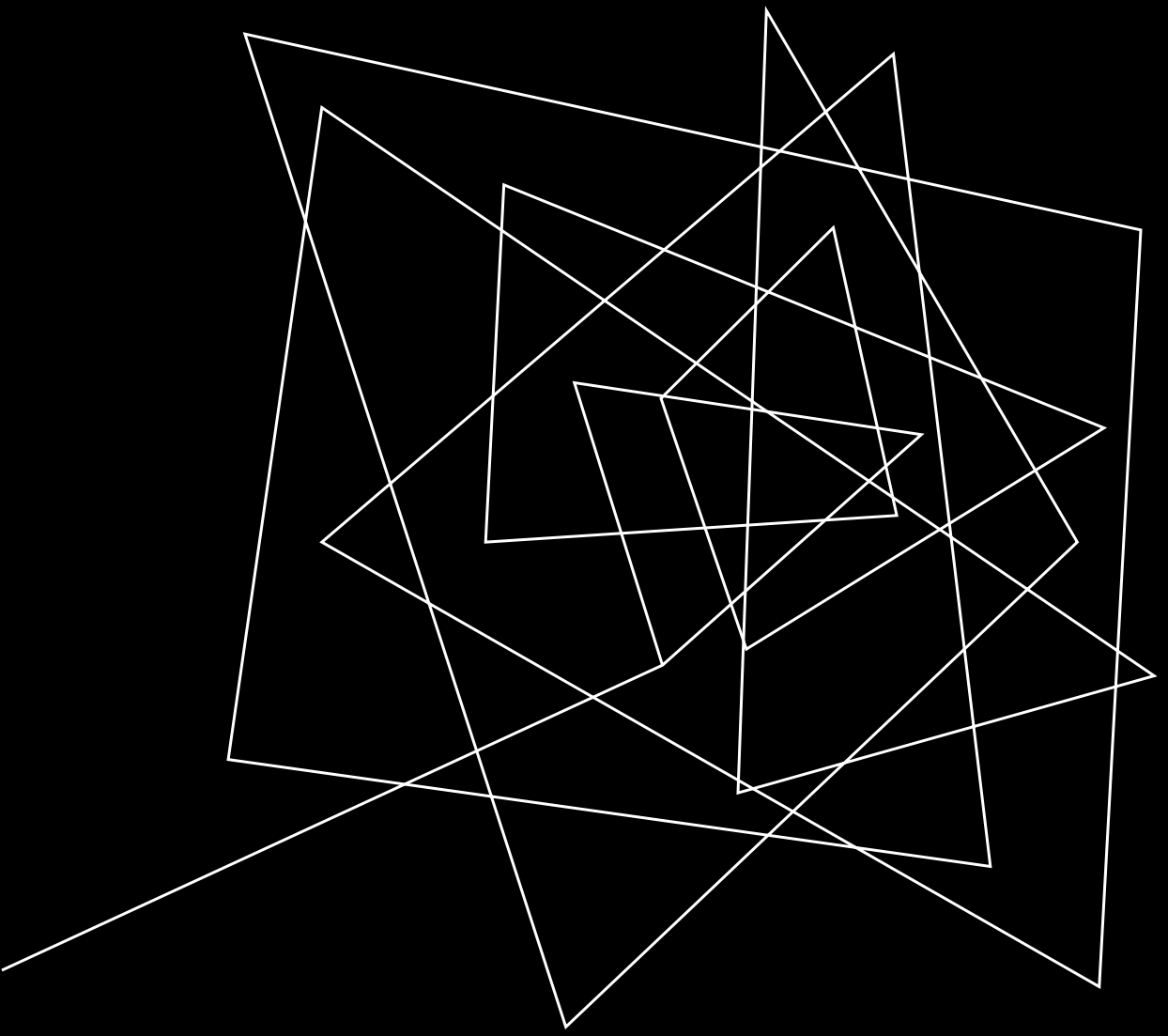

Surface membrane of muscle fiber
Myofibrils
Lateral sacs
I band
A band
I band

Explanation: **Dihydropyridine** is just another name for the **voltage-gated receptors in the T-tubules**.



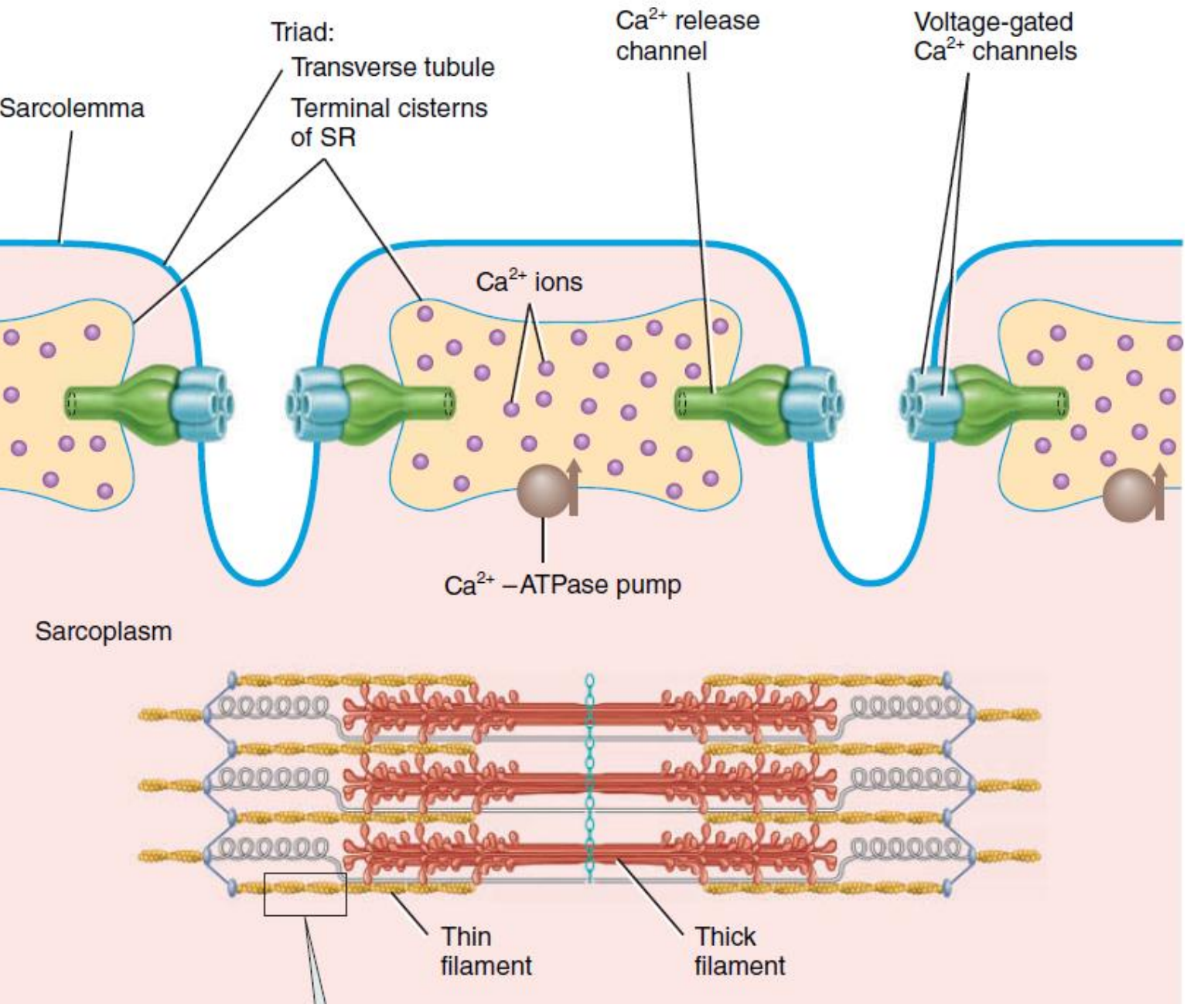
Explanation: **Ryanodine** is another name for the **calcium release channels**

Note: T-tubule membrane proteins known as dihydropyridine receptors serve as voltage sensors. Local depolarization of the T tubules activates the dihydropyridine receptors, which in turn trigger the opening of directly abutting foot proteins (Ca-release channels or ryanodine receptors) in the adjacent lateral sacs. When these Ca^{2+} release channels are opened in the presence of a local action potential in the adjacent T tubule, Ca^{2+} is released into the cytosol from the terminal cisternae.



SKELETAL MUSCLE

Relaxation



Explanation: The action potential traveling through the T-tubules opens voltage-gated calcium channels, which act as a plug for the Ca^{2+} release channels. The calcium in the terminal cisternae is released into the sarcoplasm and binds to troponin. As long as there is calcium a contraction cycle can occur.

Note: The terminal cisternal membrane of the sarcoplasmic reticulum also contains **Ca^{2+}-ATPase pumps** that use ATP to constantly transport Ca^{2+} from the sarcoplasm into the SR. As long as muscle action potentials continue to propagate along the T tubules, the Ca2+ release channels remain open and Ca^{2+} flows into the sarcoplasm faster than it is transported back into the SR by the Ca^{2+}-ATPase pumps. After the last action potential has propagated throughout the T tubules, the Ca^{2+} release channels close. As the Ca^{2+} -ATPase pumps move Ca^{2+} back into the SR, the Ca^{2+} level in the sarcoplasm rapidly decreases.

So how does the contraction cycle stop? The Ca^{2+}-ATPase pump is constantly pumping calcium back into the sarcoplasmic reticulum. In addition to the acetylcholinesterase which breaks down acetylcholine, so there will be no action potential to cause the release of calcium from the cisternae, and the already existing Ca2+ will return back to the sarcoplasmic reticulum and the sarcoplasm will run out of calcium to bind with troponin.

So where do we use ATP in all these processes?
1- in the detachment of myosin heads
2- in the pumping of Ca2+ back into the sarcoplasmic reticulum to stop the contraction cycle (because it's an active process that needs ATP)