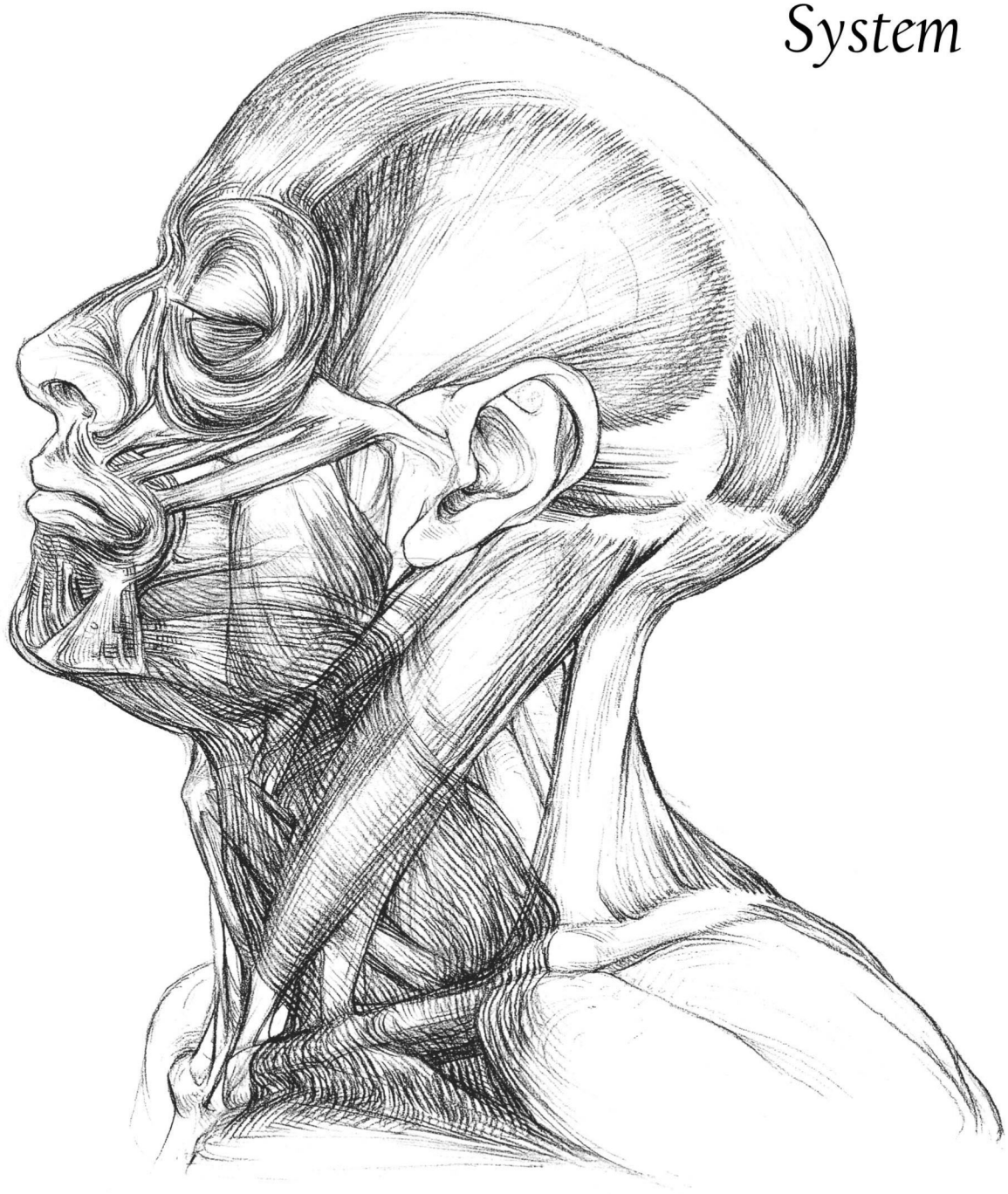
Medical Committee
The University of Jordan

The Skin and MUSCULOSKELETAL System



PHYSIOLOGY

SLIDES ☐
SHEET ■
LECTURE # 2

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DONE BY: **Doa'a Dahboor**

BY MOHAMED F. ABU ALIA

Physiology of MSS – 2nd lecture skeletal muscle contraction

- Notes :

* There is no need to refer to the slides since I put all the figures here in this sheet.
* References : Section one's record , Guyton (twelfth edition) & Wikipedia .
Good luck !

** At the beginning of the lecture a student asked the doctor about recording action potential (monophasic and biphasic APs) :

- Monophasic AP :

One electrode is placed inside the cell (at the inner side of the cellular membrane) and another electrode is placed outside the cell (at the outer side of the cellular membrane) to measure the potential difference between inside and outside .

-Biphasic AP :

The two electrodes are placed outside the cell at two different points . In the case of resting ; we get no potential difference (zero) between these two points .
If we give a stimulus so that one of the two points (I mean the points where we placed the electrodes at) undergoes depolarization while the other point is still in resting state ; we will get a potential difference between the two points . Here , a wave that represents depolarization is created (this is the FIRST wave) .
Now , after depolarization , repolarization starts (i.e. there's another potential difference in the negative (reverse) direction) , so we get another wave that represents repolarization (this is the SECOND wave) and definitely it'll be in the reverse direction of the first wave which represents depolarization . Because we have recorded TWO waves (depolarization and repolarization) we call this way of recording APs biphasic .
Once all the membrane becomes depolarized , we return back to zero .

Now, let us start discussing our topic for this lecture ;skeletal muscle contraction .

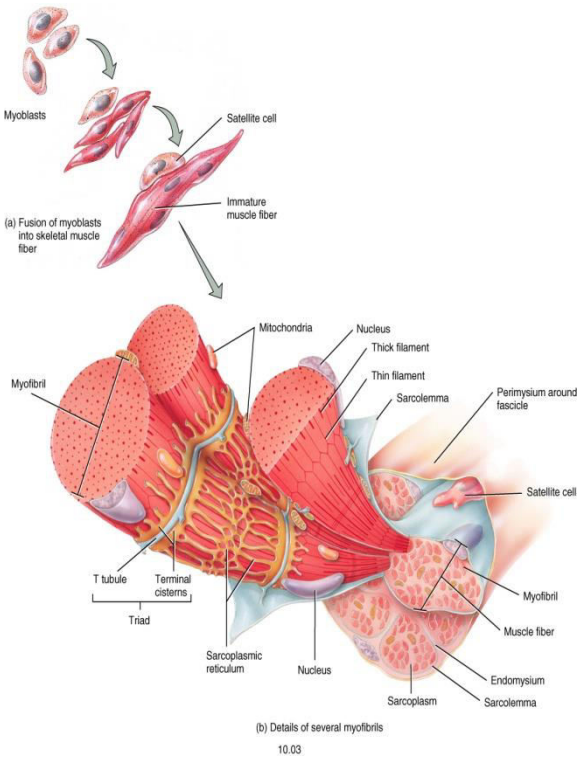
Physiologic anatomy of skeletal muscle :

A muscle cell is also called a muscle fiber (sometimes we refer to it as muscle myofiber; remember that the prefix myo- means muscle) .

Each muscle fiber contains cylindrical structures which are known as muscle myofibrils . Myofibrils are responsible for the striated appearance of the skeletal muscles because their structure is represented by a certain organization of contractile proteins (thick and thin filaments ; myosin and actin respectively) that give this striated appearance .

** Remember : There are two types of muscles ; striated (skeletal and cardiac muscles) and unstriated (smooth muscles).

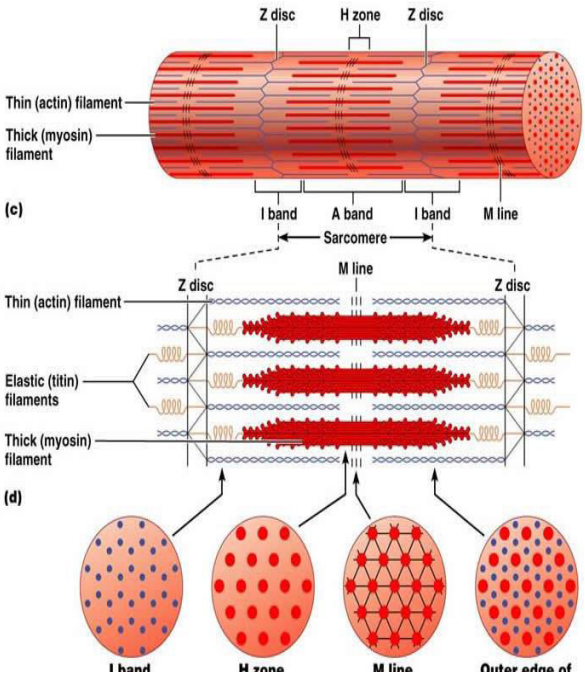
** Our book mentions that each fiber is usually innervated by only one nerve ending .



Histologically , thick filaments appear as dark regions ; whereas thin filaments appear as lighter regions .

The idea of skeletal muscle contraction is that these two types of filaments interact in a specific way that results in contraction (this will be clarified later inshAllah).

** Notice from the second figure that thick and thin filaments overlap in some regions .



Let us return again to dark and light regions (bands) :

- Light regions are composed of thin filaments only (actin only) and they are called I bands .
- Dark regions contain myosin filaments as well as the ends of actin filaments where they overlap the myosin and we call them A bands .

** The following piece of information was not mentioned by the doctor :
The basis of naming the previously mentioned bands is the behavior of polarized light as it passes through these bands ; I stands for isotropic and A stands for anisotropic .

- A deeper look ; exact organization of myofibrils :

We have certain organization of contractile proteins (the thick and the thin filaments) which fits the function they do :

* In the middle of the I band there is a structure that *holds thin filaments* (actin) which is the **Z disk** (this term is used to refer to the structure in three dimensional view) or the Z line (this term is used to refer to the structure in two dimensional view) .
* The portion of the myofibril that lies between two Z disks (the distance between two Z discs) is called the **sarcomere** . *The sarcomere is the functional unit of the muscle* .
* There is a region within the A band which represents the zone of thick filaments that is NOT superimposed by the thin filaments , this region is called the **H band.** (In other words , there is NO overlap between thin and thick filaments in the H zone) .
* Inside the H zone there is a thin **M line** . The M line runs through the exact center of the sarcomere and the doctor says that it aids *in holding thick filaments* (myosin) in their positions .
*** Titin** (Not mentioned by the doctor) : A filamentous protein that acts as a framework that holds the myosin and actin filaments in place so that the contractile machinery of the sarcomere will work . In other words , this protein maintains the side-by-side relationship between the myosin and actin filaments .

** The following figures clarify what has been said above , take a look !

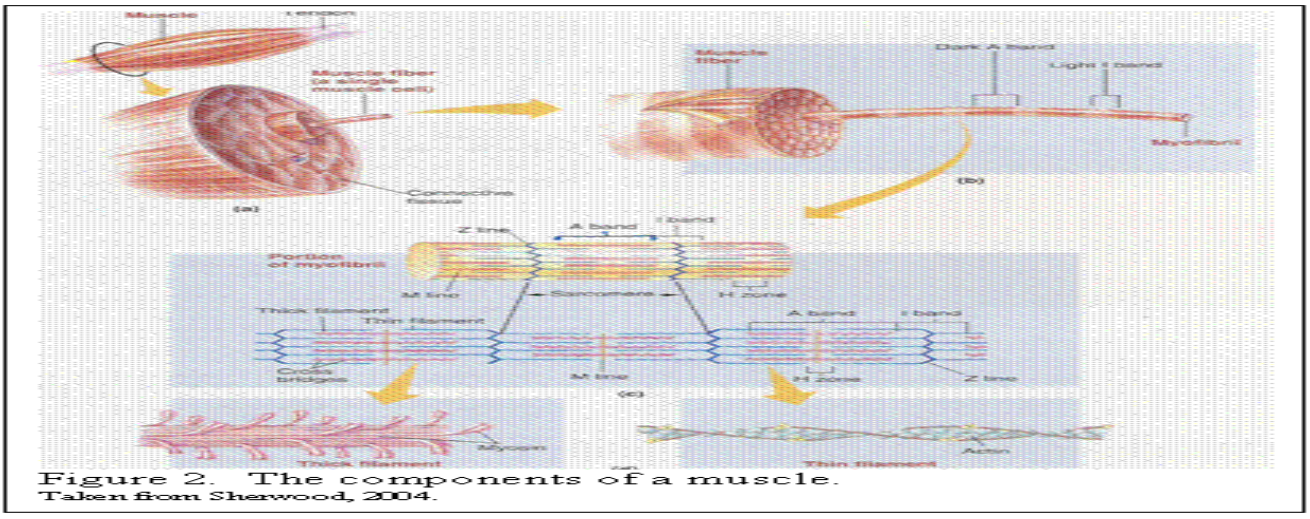
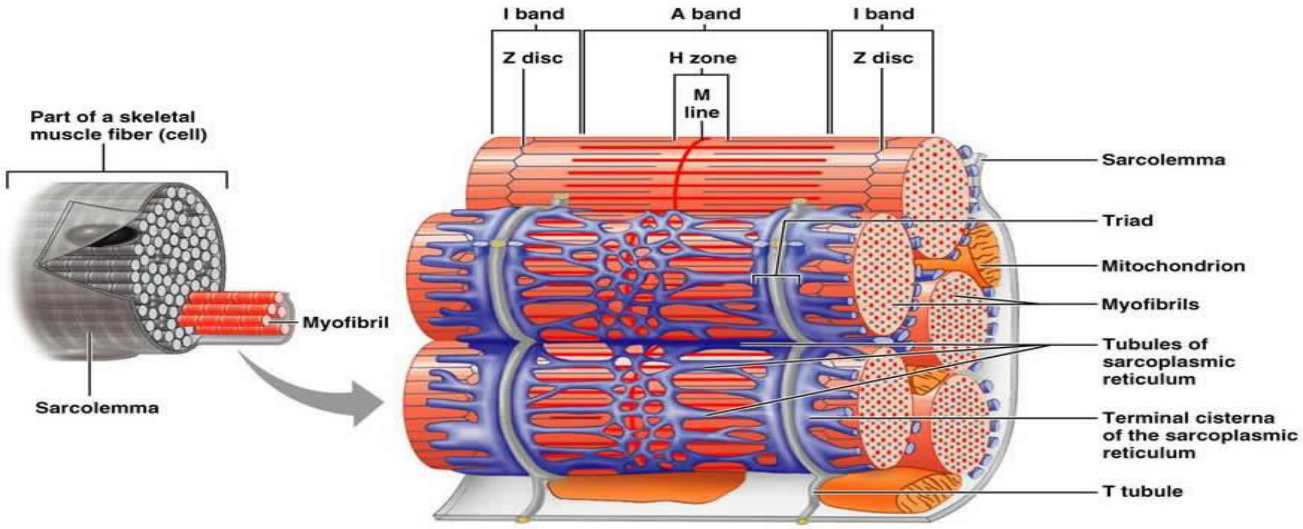
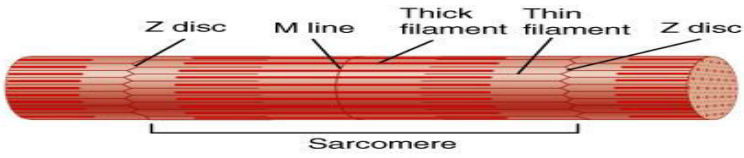
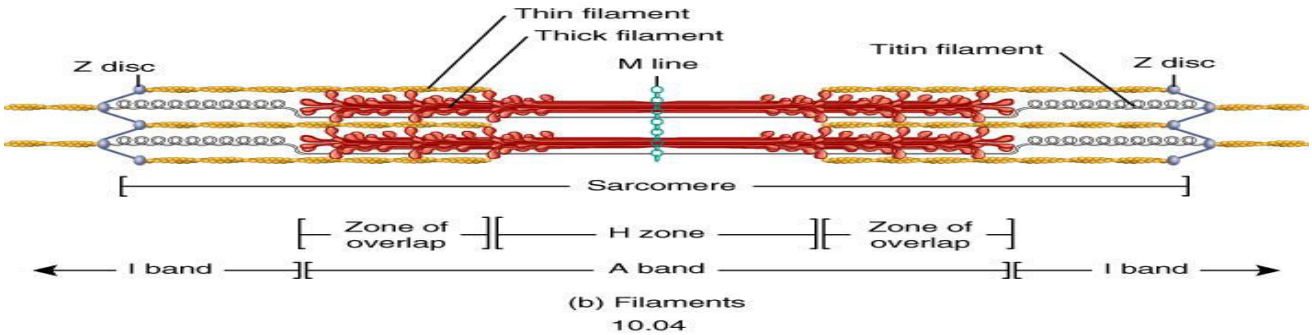


Figure 2. The components of a muscle.
Taken from Sherwood, 2004.





(a) Myofibril



(b) Filaments
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* Some organelles are named differently in muscle fibers :

-The endoplasmic reticulum of the muscle cell is called the **sarcoplasmic reticulum.** It has an important role in muscle contraction (discussed later) .

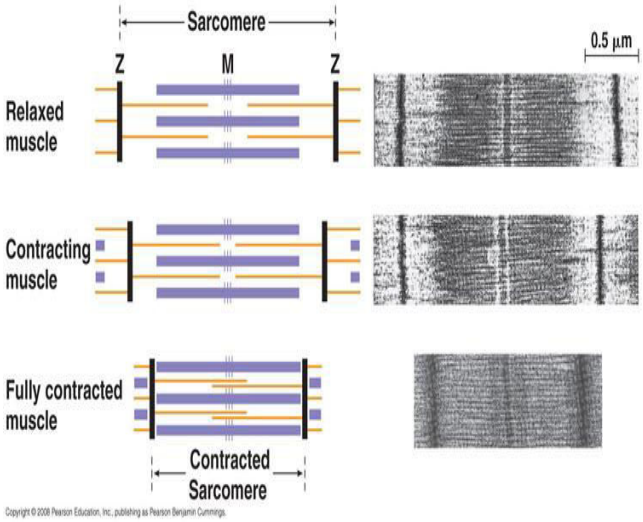
- The thin plasma membrane that encloses the skeletal muscle fiber is called the **sarcolemma** (resembles the plasma membrane in other cells) .

- The space between the myofibrils is filled with the **sarcoplasm** (similar to cytoplasm in other cells) , i.e. the sarcoplasm is found outside the myofibrils but inside the myofibers . In other words , too many myofibrils are found within the sarcoplasm of each individual muscle fiber (muscle cell) .

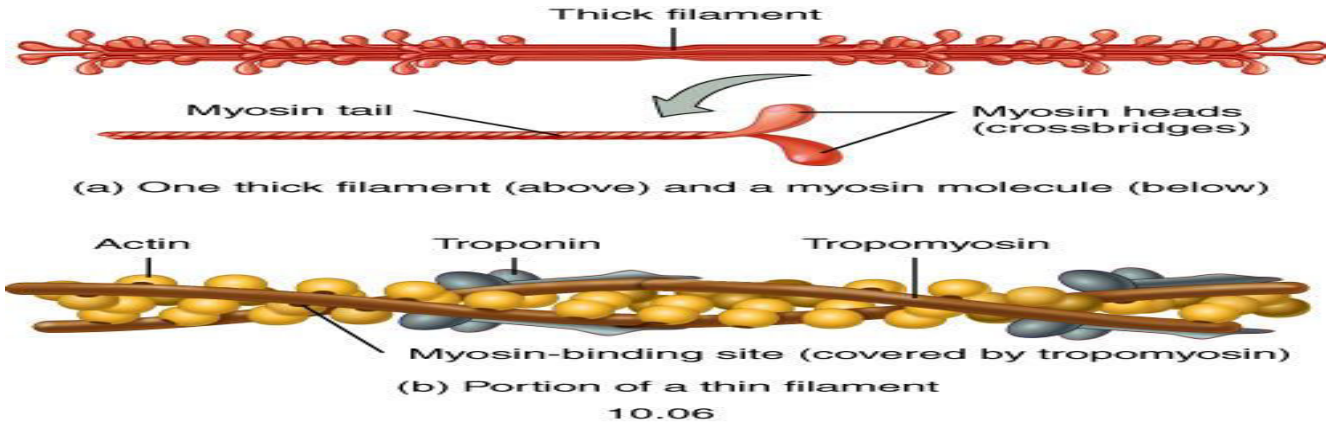
Look at the figure beside and notice the following :

When the muscle is relaxed , all the previous aspects of skeletal muscle anatomy (the A & I bands , H zone , M line & Z line) will be seen clearly in their previously mentioned organization after a good staining procedure .

When the muscle is contracted , thin filaments slide over thick filaments so that the length of the muscle becomes less (muscle shortens) .

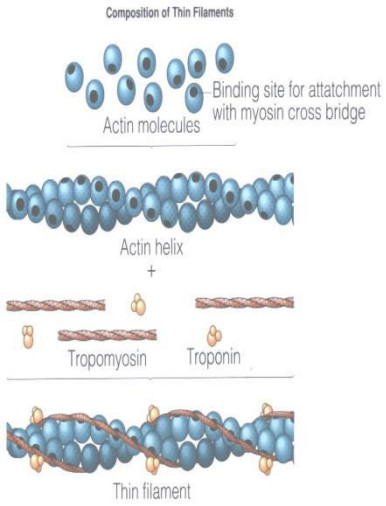


* In order to understand the sliding mechanism of contraction , we have to understand the structure of thick and thin filaments , so let's carry on !



- Structure of thin filaments (actin filaments) :

The backbone of the actin filament is a double stranded **actin protein molecule** (actin molecules are polymerized to form an alpha helix structure which is the backbone of the actin filament) .
Notice that actin molecules contain **binding sites** for attachment with myosin cross-bridge (attachment with myosin head) to achieve contraction .

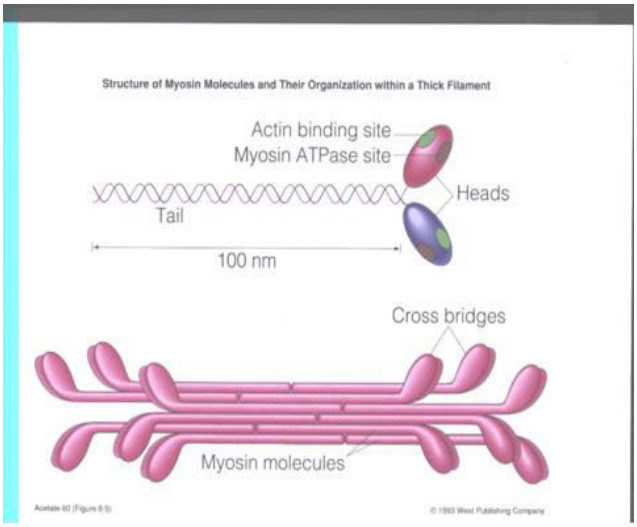


The binding (active) sites are covered (in state of muscle relaxation) by another regulatory protein which is **tropomyosin .**
* You may ask : How do these active sites bind myosin heads to cause muscle contraction though they're covered ?
This will be explained later in this sheet .

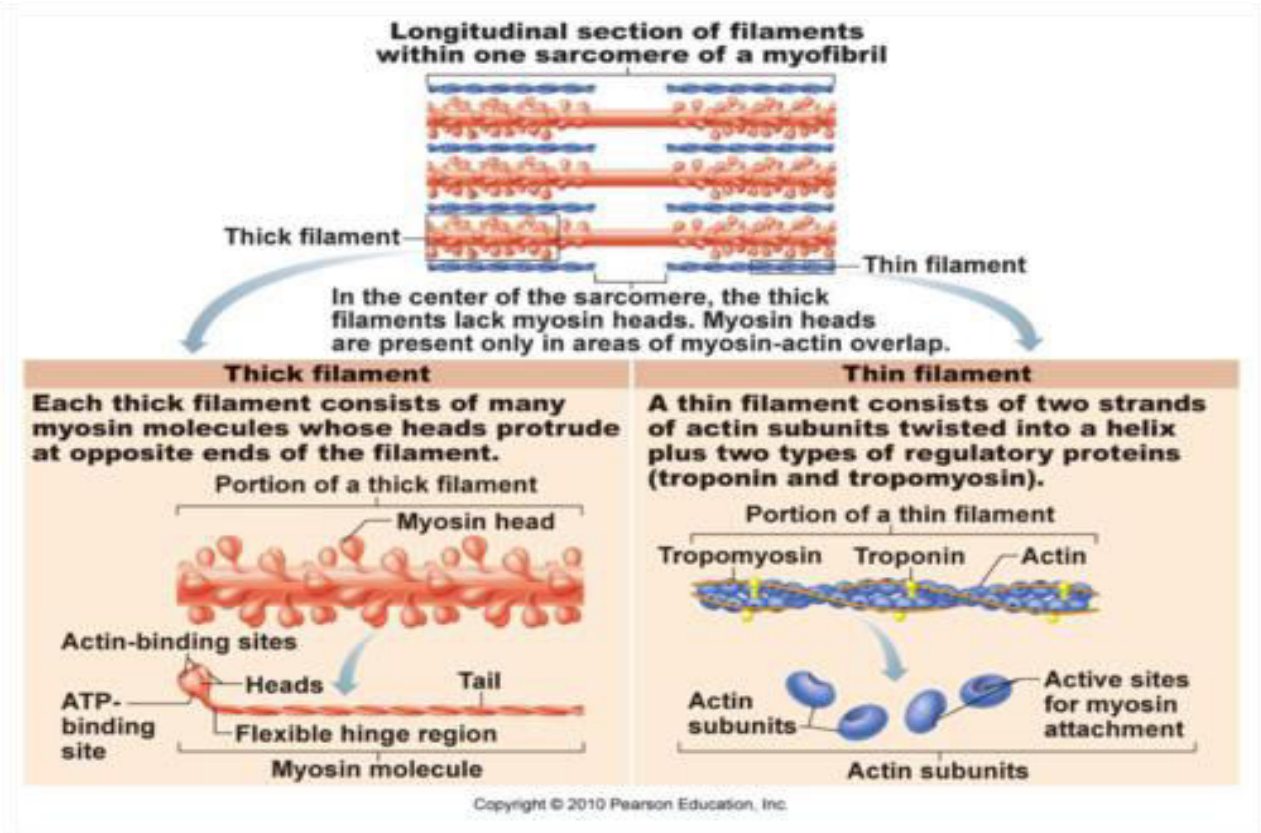
There is another regulatory protein that is linked to tropomyosin which is **troponin .**
Troponin is composed of three subunits :
** Troponin **T** : Has a strong affinity for ***t***ropomyosin , that's why it's named so .
** Troponin **C** : Has a strong affinity for ***c***alcium ions , that's why it is named so .
** Troponin **I** : Has a strong affinity for actin (Guyton says that) , and according to professor Khatatbeh the I stands for an ***i***ntermediate between the two other subunits (troponin C & T) that binds them together .

- Structure of thick filaments (myosin filaments) :

Myosin filaments are composed of multiple myosin molecules .
Two globular proteins form the two heads of a myosin molecule . The tail of the myosin molecule is an alpha helix structure and it is considered the backbone of the myosin molecule . In contrast , the heads protrude outside to form cross-bridges by linking to active sites on actin filaments as mentioned before .

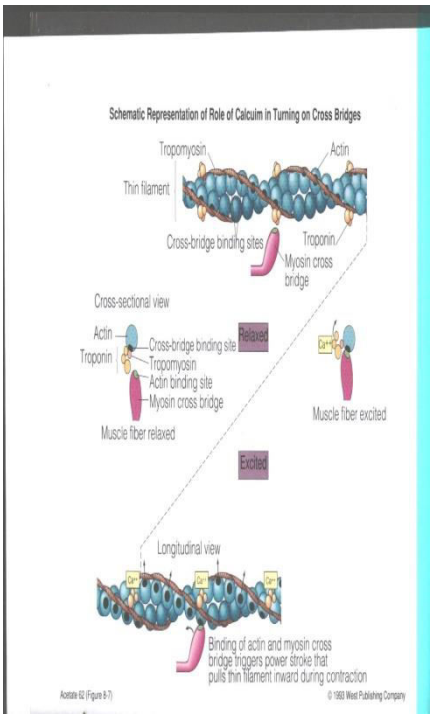


A myosin head contains two binding sites as illustrated in the figure ; one is for actin (formation of a cross-bridge) and the other is an ATPase site that's responsible for splitting ATP into ADP and P_i . Splitting ATP is necessary for contraction process (discussed later) .



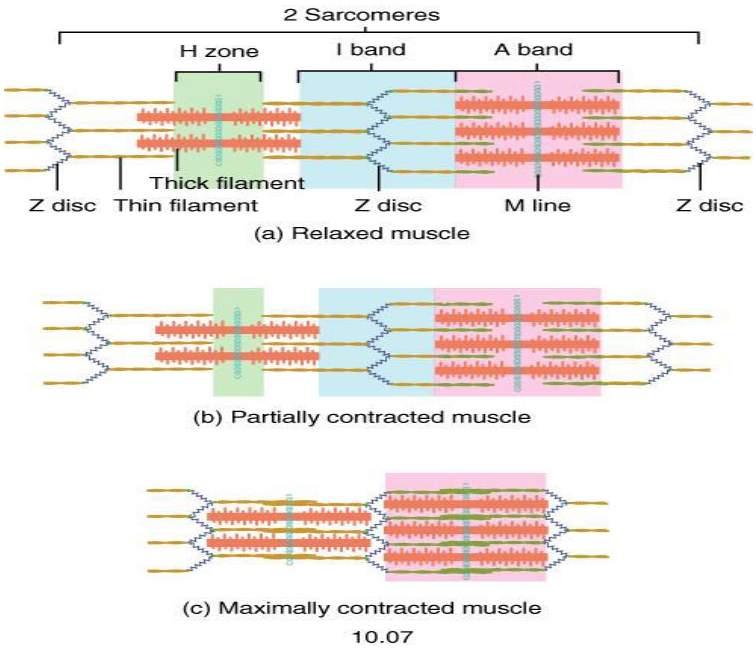
Mechanism of muscle contraction :

To get interaction between myosin heads and active sites of actin, an ion is needed which is calcium ion (Ca++) .
Troponin C has four sites for four calcium ions . Once calcium is released ☆ , these four sites are occupied by four calcium ions . This binding leads to a conformational change in troponin C that results in displacement of tropomyosin from the active sites of actin so that they become discovered (not covered). Now , interaction between myosin heads and active sites of actin (cross-bridges formation) can occur .



☆ I checked the slides and I found that release of calcium ions and NMJ (neuromuscular junction) will be discussed in the next lecture , so don't worry about that .

The figure beside illustrates that as the muscle contracts , the sarcomere shortens .
Notice that the length of the A band does NOT change during contraction while that of the I band becomes LESS and LESS as the muscle contracts till the I band disappears when the muscle maximally (fully) contracts .



The reason of that is the fact that thin filaments (represented by the I band) slide over thick filaments (represented by the A band) not the other way round , so the I band becomes shorter due to this sliding while the A band is not affected .

Another result of sliding is shortening of the H zone (the zone of NO overlap between the two types of filaments decreases because while thin filaments slide over thick filaments they move inward i.e. overlap increases between actin and myosin) .

- How contraction occurs ; a closer look !

Ca++ binds to troponin C

↓

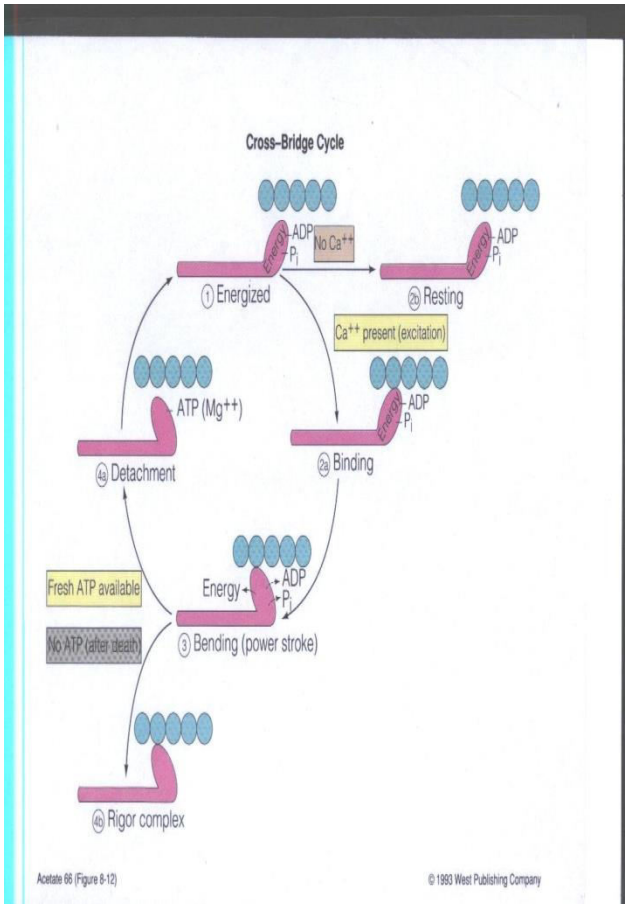
Tropomyosin is displaced

↓

Activation of actin filaments (binding sites are discovered)

↓

Myosin heads bind the active sites over actin .



Once myosin heads bind actin , a conformational change of the level of these heads occur (they bend automatically toward the center of the sarcomere after binding actin) . This bending (rotating) process is called the **power stroke .**

** Remember that a myosin's head contains two sites ; one is for actin binding and the other one is an ATPase .

** To understand the following , notice from the figure that at the beginning of the process and even before binding to actin , the myosin head has already splitted ATP into ADP and P by its ATPase activity (btw the products of splitting which are ADP and P_i are still bound to the myosin head) . When binding occurs and therefore when the power stroke occurs , the situation does NOT change . I mean that the myosin head is still having ADP and P bound to it .

After muscle contraction is complete , detachment between actin and myosin heads must occur . This requires the replacement of ADP that is bound to myosin heads by an ATP molecule . Once ATP replaces ADP , the affinity between actin and myosin decreases and detachment between them occurs .

Now the ATPase activity of myosin heads split the ATP molecules again into ADP and P_i and the fibers return back to their initial (relaxed) position which is called the energized position . *The presence of Mg++ is necessary for ATPase activation , therefore ; if there is no magnesium ions there will be no ATP splitting and muscle cannot get back to the energized state* . The heads return back to their position before binding to actin (before the power stroke that made them bend) . Now , myosin heads are ready to repeat the whole process again in the presence of Ca++ .
So it is a cycle !

* Result :

If someone suffers from hypomagnesemeia (low Mg++ levels in blood) , ATPase activity of myosin heads decreases and thus ATP splitting decreases . The result is that filaments do NOT easily return back to their energized position and it is hard for them to relax after contraction , so these people suffer from prolonged periods of muscle contraction (muscle spasm) .
* Note : Luckily , hypomagnesemia is rare .

* Clinical application ; Rigor Mortis :

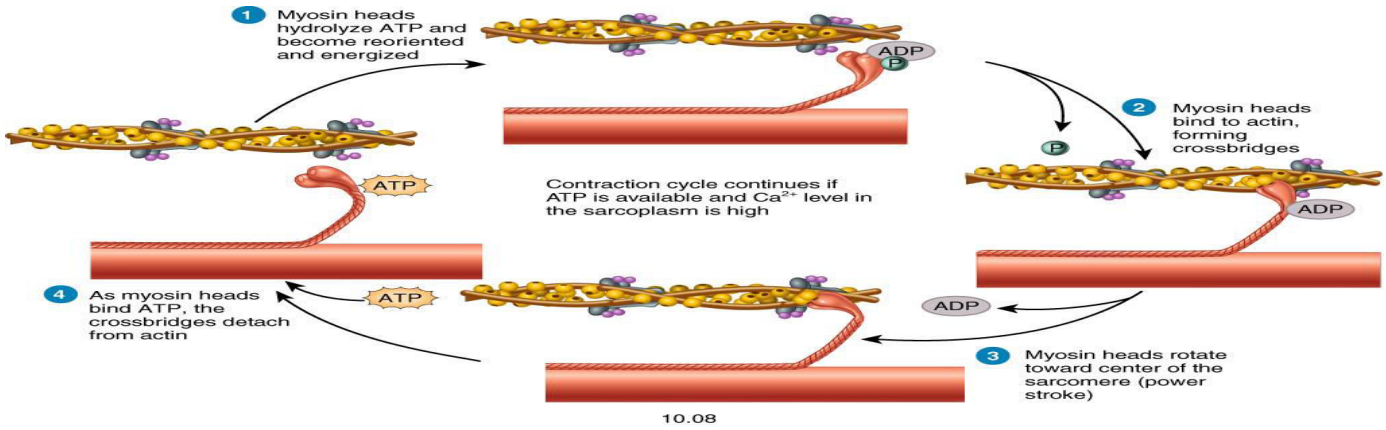
If there is NO ATP in the muscle , the myosin filament is stuck in the position it acquired after the power stroke (it's called Rigor complex in this case , refer to the previous figure) , i.e. the muscle is stuck in contraction !

The doctor says that this is seen in some dead bodies . You come to these bodies after few hours of death (three to five hours) and you notice that the muscles are stuck in contraction due to the absence of ATP that is needed to detach thick filaments from thin filaments to relax the muscle . This condition is called Rigor Mortis .

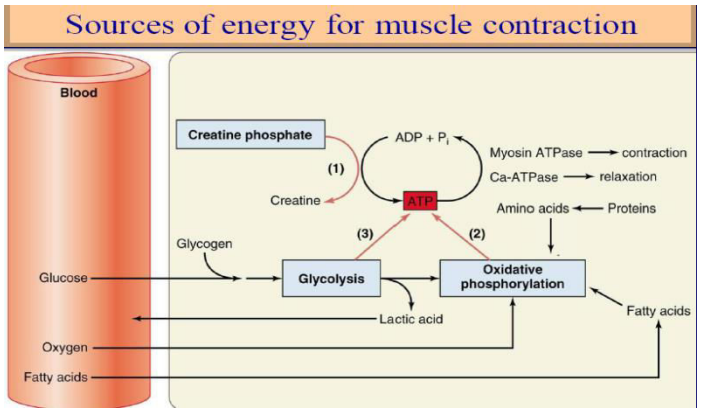
** Compare !

Both cases (Mg++ deficiency or hypomagnesemia and ATP deficiency that causes Rigor Mortis) result in difficulty in relaxation after contraction . The difference is that in case of Rigor filament the myosin is stuck linked to actin (i.e. detachment does NOT occur) , while in the case of Mg++ deficiency with enough amounts of ATP present , detachment that requires ATP is achieved normally but the filaments CANNOT get back to their energized position (conformation) because this process requires Mg++ .

** Now take a look at this figure and revise what we have discussed .



Sources of energy for muscle contraction :



ATP is needed for many processes in our body . For example , after an action potential , the distribution of ions is a bit disturbed . An active ion pump (i.e. needs ATP) is needed to re-establish the concentration of ions at the two sides of the sarcolemma .

Actually , we have studied the role of this pump in the previous lecture and the doctor says that he'll explain it further in the coming lectures .

Remember from the previous lecture that this pump pushes Na+ from inside the cell to outside and pushes K+ from outside to inside (this is how it re-distributes the ions back) . Here in the case of skeletal muscle contraction , in addition to the previous function of such pumps , these pumps also have to pump Ca++ back to the sarcoplasmic reticulum where they were released from . All these processes need ATP .

Also , we mentioned that ATP is needed for detachment of myosin heads from actin , so from where do our skeletal muscles get ATP and what is the needed amount of ATP by each type of muscles ?

Original ATP molecules that are already present in the muscle are enough for only few seconds , after that our muscles need another ATP supply from another source . Our skeletal muscles are in a continuous need for ATP !

Indeed , there's another macro-energetic molecule in our muscles that can replenish the consumption of ATP . This macro-energetic molecule is **creatine phosphate .** There's an enzyme that transfers the phosphate group of creatine phosphate (it becomes creatine after that) to ADP to get ATP . This is how creatine phosphate aids in increasing the amount of ATP in our muscles (by a transfer reaction) , but also creatine phosphate gives ATP that is enough only for few minutes , so we need another source of ATP .

ATP can be replenished after that (I mean after the consumption of original ATP in the muscle and after using the maximum amount of creatine phosphate that can be used to give ATP) by two processes :
Glycolysis and **oxidative phosphorylation .**

Glycolysis gives small amount of ATP . Most of the ATP that is needed by the muscle is generated by oxidative phosphorylation .

** Remember : OXPHOS occurs in the mitochondria .

OXPHOS process requires oxygen (aerobic process that yields aerobic energy) . On the other hand , glycolysis can occur with or without oxygen (if glycolysis occurs without oxygen it is called anaerobic glycolysis and the yielded energy is referred to as anaerobic energy) .

Q : Which process is faster in generating ATP ?

A : *Glycolysis* .

OXPHOS needs more time than glycolysis to occur and to generate ATP .

In our body , there are fast muscles as well as slow muscles . Logically , fast muscles need to get ATP quickly so they depend on the faster process of generating ATP which is glycolysis . In contrast , slow muscles function slowly so they need not to get ATP as quickly as the fast ones , they get their energy supply by the slower way in generating ATP which is OXPHOS .

Q : OXPHOS process requires oxygen ; how do our muscles store oxygen ?

A : By *myoglobin* (Myoglobin is an iron and oxygen binding protein found in the muscle tissue of vertebrates and it is related to hemoglobin which is an iron and oxygen binding protein in blood , to be more accurate in RBCs) . Myoglobin is red . Slow muscles depend more on OXPHOS that requires oxygen which is stored in myoglobin , so we conclude that slow muscles have more myoglobin than fast muscles and of course they'll appear more reddish (Usually we refer to slow muscles as red muscles and to fast muscles as white muscles) .Also , it makes sense that slow muscles have more vascularization (rich supply of oxygenated blood) than fast muscles because they need more oxygen to function .

** The ratio of fast muscles : slow muscles differs from a person to another . Many factors control this ratio , one of these factors is the activities the person does . For example , sporty people who participate in fast races (races for one hundred meters for instance) tend to have more fast muscles (high "fast : slow" muscles ratio) . On the other hand , people who participate in marathons (and similar long lasting sport activities) have more slow muscles (lower "fast : slow" muscles ratio) , so it is hard for people who usually participate in fast races to participate in marathons because their muscular building in the aspect of fast to slow muscles ratio does NOT fit long lasting sports that require more slow muscles to function as long as possible . Fast races participants has more fast muscles than slow muscles , more fast muscles are needed to function as quick as possible in such types of sports .

What really happens that people who used to participate in fast races have more divisions of fast muscular fibers in their bodies to get more of them in order to be used while doing fast sports . Remember that fast muscles depend mostly on glycolysis . Lactic acid is a product of glycolysis (to be more specific it is a product of anaerobic glycolysis) , so after glycolysis occurs many times while using these muscles , lactic acid accumulates and generates pain , so these people will not be able to participate in marathons , i.e. they cannot run for long distances , they are able to participate in fast races (running quickly over short distances) .

The doctor added that while a person is doing a fast sport , his body motivates division of fast fibers (increase in number , hyperplasia) . This division is not long lasting , it is limited ! So if the person who usually does fast sports tries to do a slow fibers requiring sport like marathon , after a certain period of time there'll be no more divisions of the muscular fibers , they'll increase in size rather than in number (hypertrophy) , this causes pain , so the person will not be able to carry on doing this long lasting sport for a long period of time.

So sporty people differ in their muscular composition (fast : slow muscles ratio) and due to that they differ in their abilities to do different kinds of sports .

A student asked the doctor about the kinds of sports that can be done by people who have high amount of fast muscle fibers and he said that they can do any type

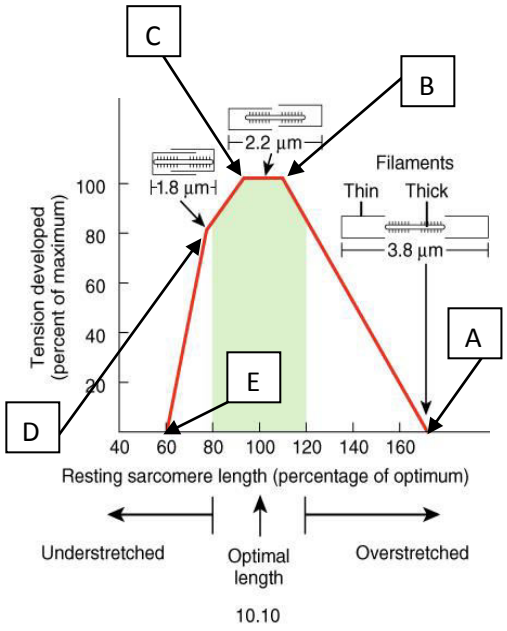
of fast sports that need fast movement for a short period of time , for ex. races for fifty to one hundred meters and basketball .

The doctor added that some muscles in our body like eyelid and lips muscles are also considered fast in their activity because these muscles do not stay contracted for long periods , they contract and relax continuously and quickly . The muscles that contract for prolonged periods in our body are composed mainly of slow fibers .

The doctor again insures that people have different distribution (ratio) of slow and fast muscular fibers according to the functional activities they usually do .

The amount of actin & myosin filament overlap determines tension developed by the contracting muscle :

* In the diagram shown here , we are going to discuss muscular activity recorded at the level of one sarcomere .



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* The horizontal line represents the length of the sarcomere (as percentage of optimum) and the vertical line represents tension (as percentage of maximum) . Notice that the length is optimum (one hundred percent of optimum) at resting state . We will start studying the figure from point A to point E (right to left) as this trace represents changes that occur from the beginning of contraction where tension is zero (point A) till the end of contraction represented by point (E) where tension becomes again 0.

Look at point A , this point states a condition where there is muscle stimulation by Ca++ binding to troponin C and therefore there is stretch of filaments but still there is NO overlap between thick and thin filaments (The actin filament has pulled all the way out to the end of the myosin filament with no actin – myosin overlap) . Here , there is no muscle contraction yet and there is no tension (tension is zero) .

** Rule : No overlap between filaments = No tension , as overlap increases and length decreases , tension increases .

Then as the sarcomere shortens and overlap between thick and thin filaments increases , tension increases (refer to the figure to notice this) . Tension continues to increase with decreasing the length till reaching (point B) where the tension is at its maximum value .

Now , look at the straight line in the figure starting from point B till reaching point C, you can conclude that here the muscle shortens but tension stays the same . Tension is at its maximal value and it cannot increase further . This line represents a type of contraction that is called **isotonic contraction .**

** Iso- means the same , not changing , -tonic refers to tension .

The doctor says that contraction does NOT necessarily mean shortening . If stretching occurs but the myosin heads are fixed in the active sites of actin , shortening will not occur even with Ca++ stimulation . There is contraction but there is no shortening in the muscle length . This contraction is referred to as **isometric contraction** (metric means length) , so there is NO change in the length of the sarcomere . How can we record this type of muscle contraction though length does not change ? Even though length does not change in this case , tension increases , so this type of contraction is recorded by measuring tension using special electrodes for this procedure .

So far we have discussed two types of contraction ; isometric and isotonic .

As the sarcomere length falls from point C down to point D the strength of contraction decreases rapidly .As contraction proceeds to still shorter sarcomere lengths , the ends of the myosin filaments are crumpled and the strength of contraction approaches zero (point E),(relaxation is about to occur at this point) .

** I have spent a day and a half writing this sheet using a sound amplifier so forgive me if there is any mistake , it was surely unintentional .

** That's it !

Doa'a S. Dahboor . ☺