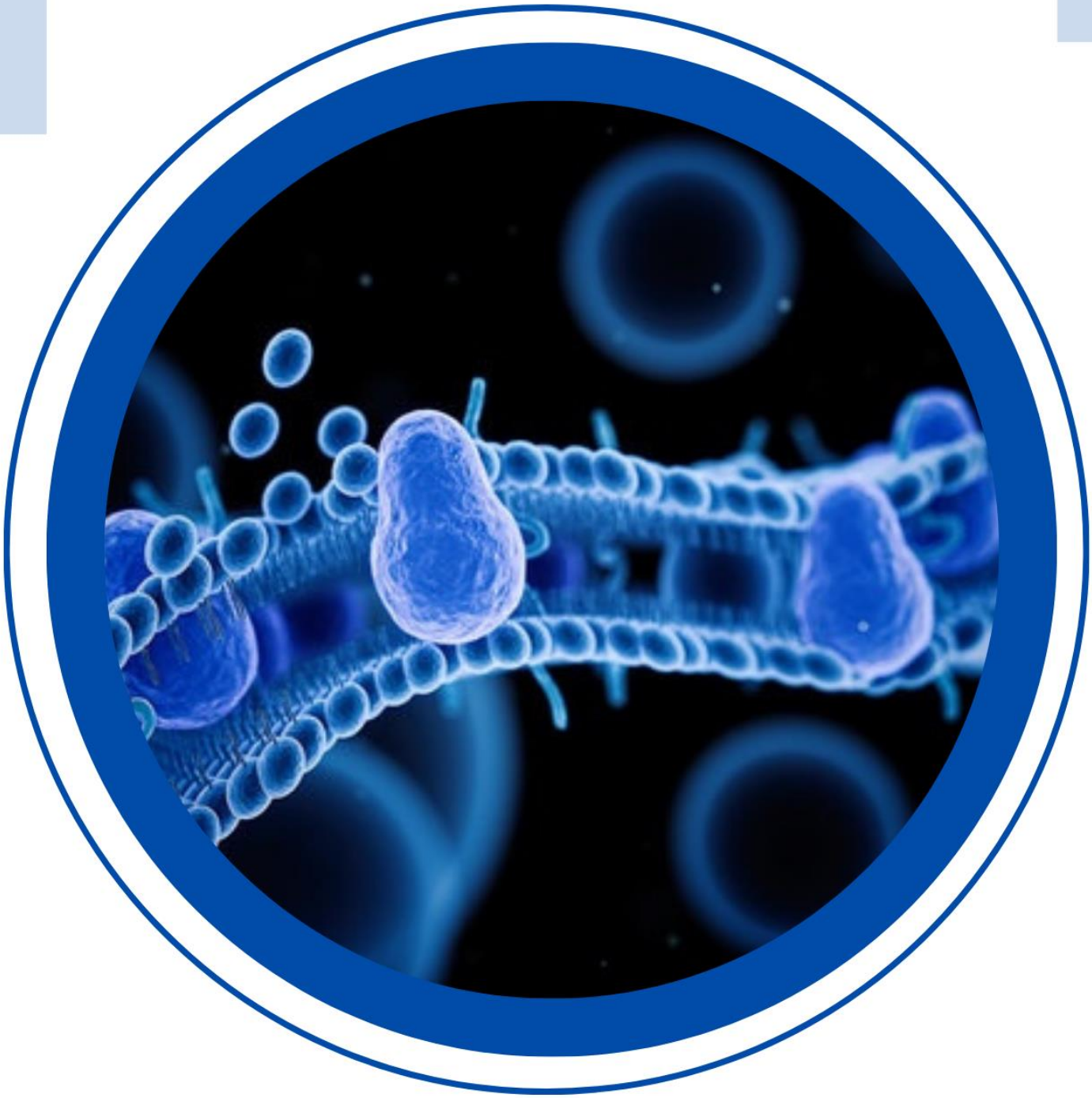
MSS

PHYSIOLOGY

#2&3



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This sheet includes the first 7 pages of the second handout.
My notes will be in this color.

There are three types of muscles and these are: skeletal, cardiac and smooth muscles, and are classified:

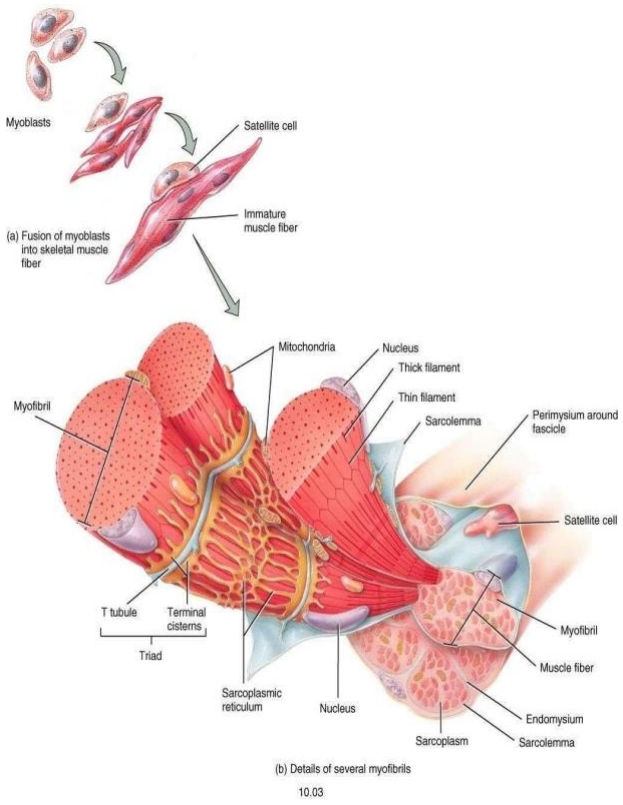
(according to their appearance under the microscope) **striated** muscles (that includes skeletal muscle,cardiac muscle) and **unstriated** smooth muscle cells.
(according to their innervation): **voluntary** (have somatic innervation), an example: skeletal muscle, and **involuntary** (have autonomic innervation), example: cardiac and smooth muscle.

These cells are found where mechanical activity is needed. Movements of the whole body or parts of it need contraction of skeletal muscles. Pumping of blood in vessels need contraction of cardiac muscle. Emptying the content of hollow organs requires contraction of smooth muscle in that particular organ.

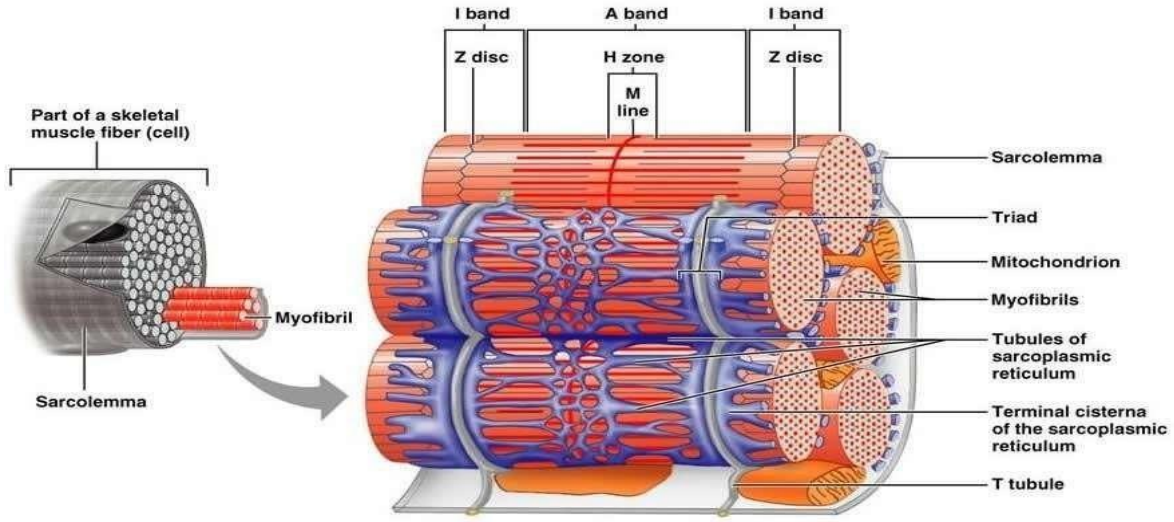
STRUCTURE OF SKELETAL MUSCLE:

Skeletal and cardiac muscle cells are called **muscle fiber** that are lying parallel to each other and bundled together by a connective tissue, the most dominant structure in muscle fibers is the presence of cylindrical like structures called **myofibrils.** Each myofibril consists of regular arrangement of cytoskeletal contractile elements known as thick and thin filaments. Which give the striated appearance (alternating light and dark regions, I and A bands) in skeletal muscle.
-Dark regions correspond to bands containing <u>thick filaments</u> (A bands).

-Light regions correspond to bands containing <u>thin filaments only</u> (I bands).



IMPORTANT STRUCTURES IN THE MYOFIBRIL:



-A band is located in the center of the sarcomere and contain the thick filaments (which gives this band its dark appearance) overlapped with some thin filaments at both ends.

-H zone is a part of the A band that is not overlapped by thin filaments, it contains only thick filaments.

-M line is a network structure that holds thick filaments in all directions in the middle of the A band .

-I band is a region of thin filaments only hence it appears light.

-Z disc is a dense vertical structure (flattened disc-like structure that hold thin filaments in all directions in the middle of I band).
(In 2D its called line in 3D its called disc)

-T tubules (transverse tubules) are found at the junction between A and I band.

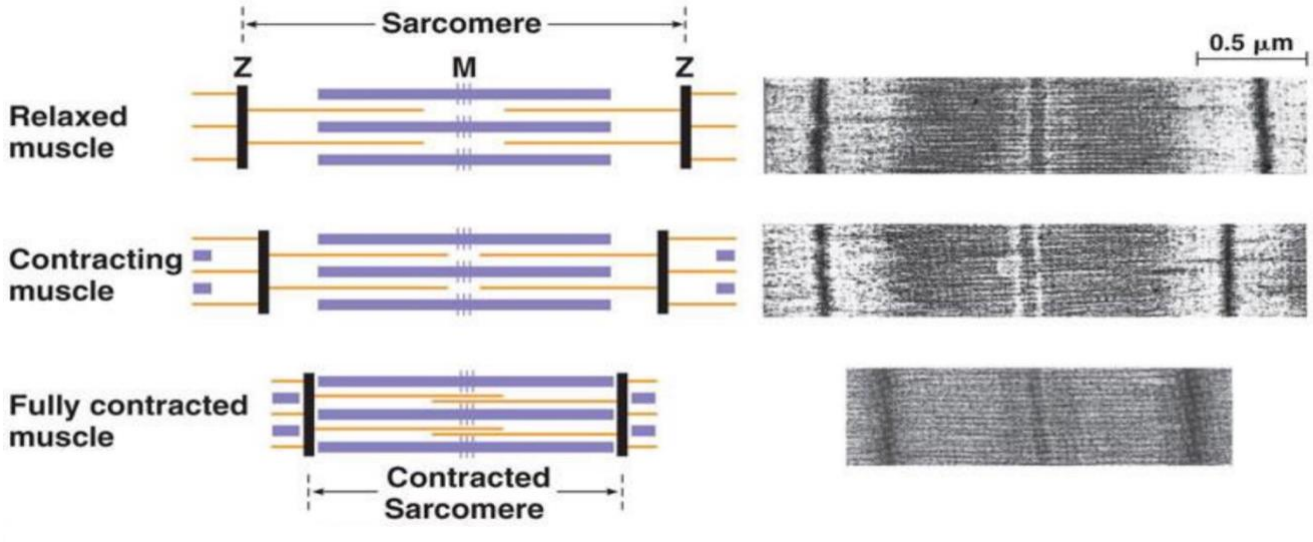
-Sarcomere is the area between two Z discs, and it represents the functional unit in the myofibril that is shortened or elongated upon stimulation.

-Sarcoplasmic reticulum represents the endoplasmic reticulum in a muscle cell that stores calcium ions.

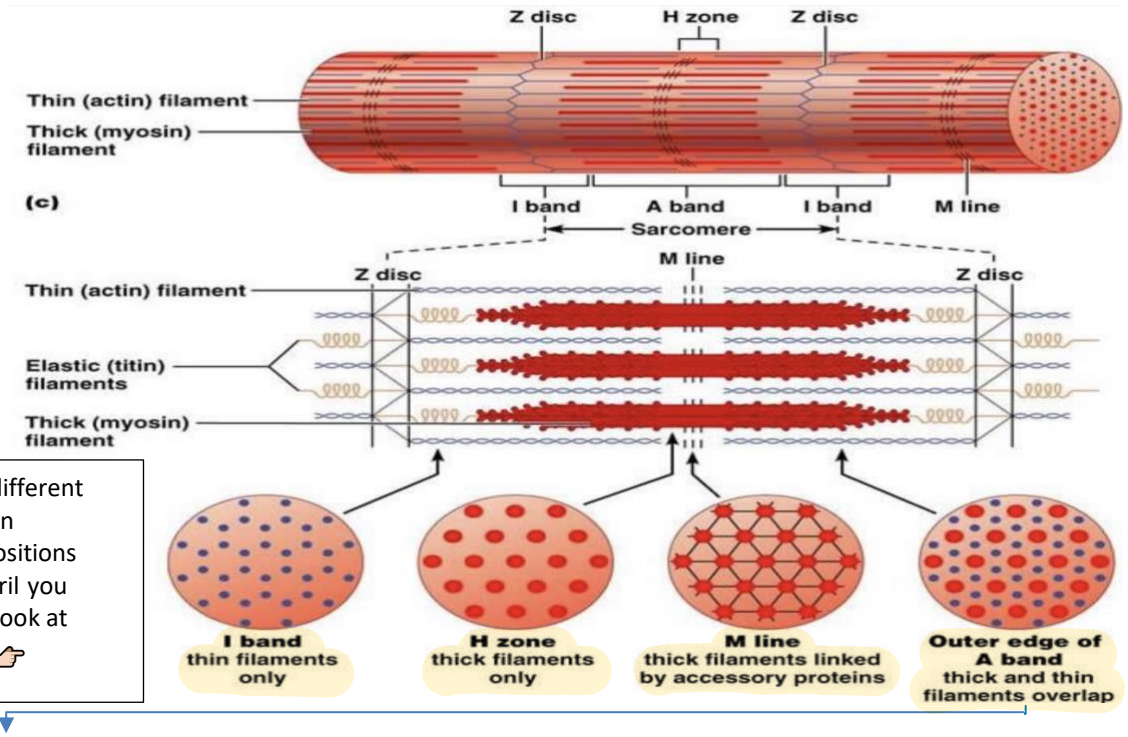
-Sarcolemma is the cell membrane of muscle cells.

-Sarcoplasm is the cytosol inside a muscle fiber.

Cardiac muscles differ in structure from skeletal muscles they have: less representation of sarcoplasmic reticulum.T tubules are found near or at the Z disc (not at the junction between the A and I band as in the skeletal muscle).



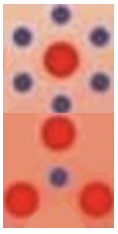
During contraction thin filaments slide over thick filaments to the center and increase its overlapping causing shortening of the sarcomere and the distance between the two Z discs will be less in addition to shortening in the I band and H zone, but its <u>A band remains consistent</u> because it represents the length of thick filaments.



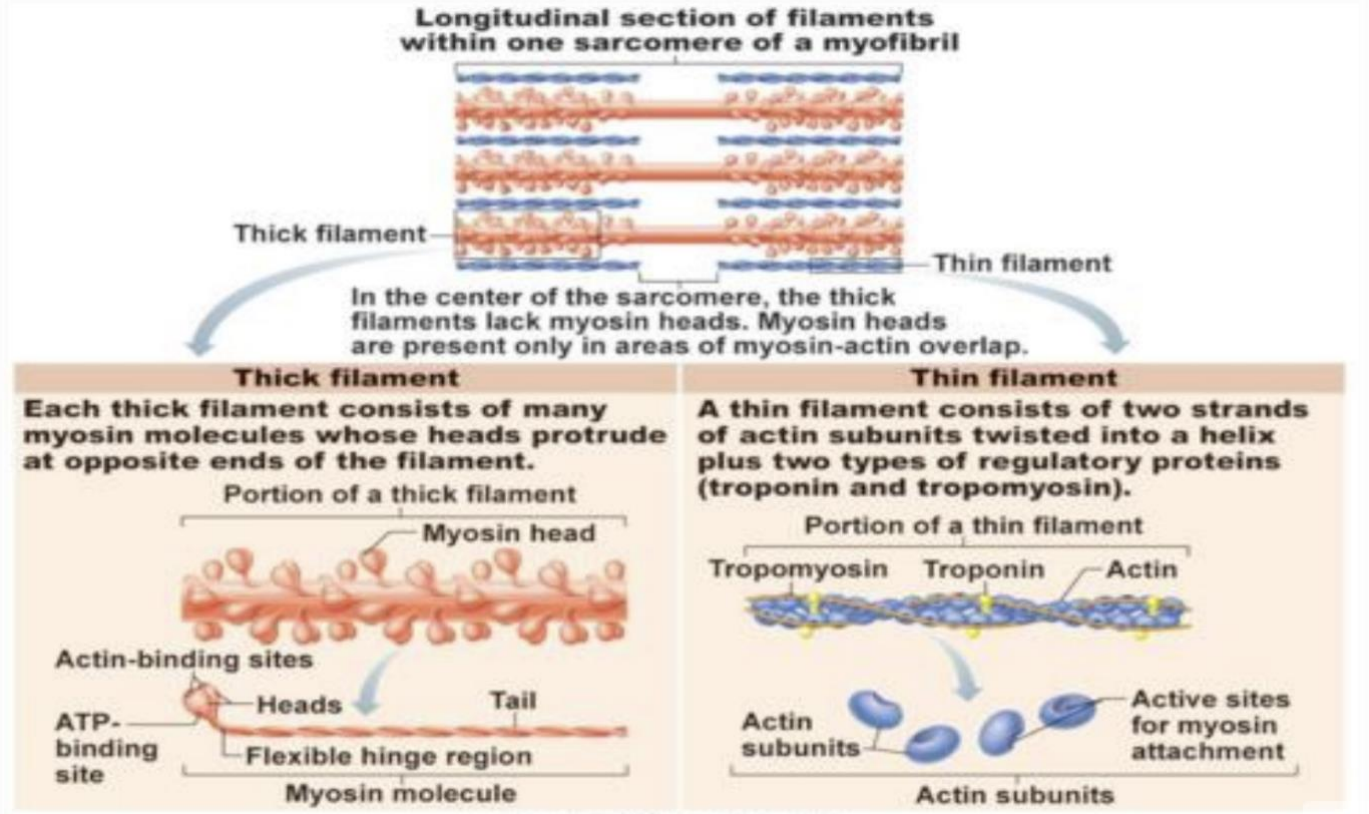
There are different structures in different positions in a myofibril you can take a look at them here👉

In the cross sectional arrangement in the area where is an overlap between thin and thick filaments shows:
6 thin filaments around one thick filament,

and 3 thick filaments around one thin filament.



The ratio of thick to thin filaments is **2:1**.



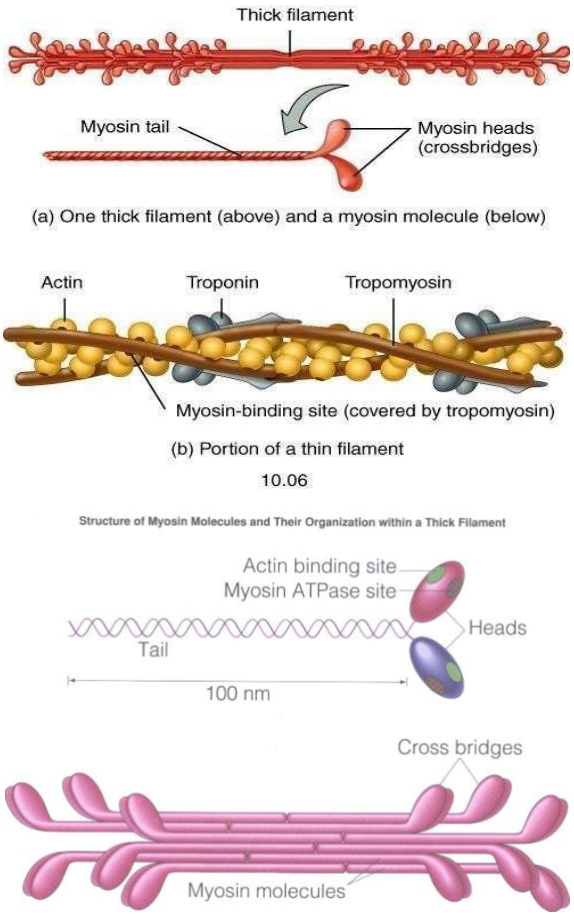
▪THICK FILAMENT:

(1.6 um length) is composed of several hundreds of **myosin** molecules that are held together in a specific arrangement.

A myosin molecule is composed of 2 identical subunits. Each myosin has two globular heads that projects out to one end and a tail that is intertwined with the tail of the other molecule forming the backbone.

Each myosin head has 2 binding sites. One can interact with thin filaments **(actin binding site)** and the other is **myosin ATP-ase site.**

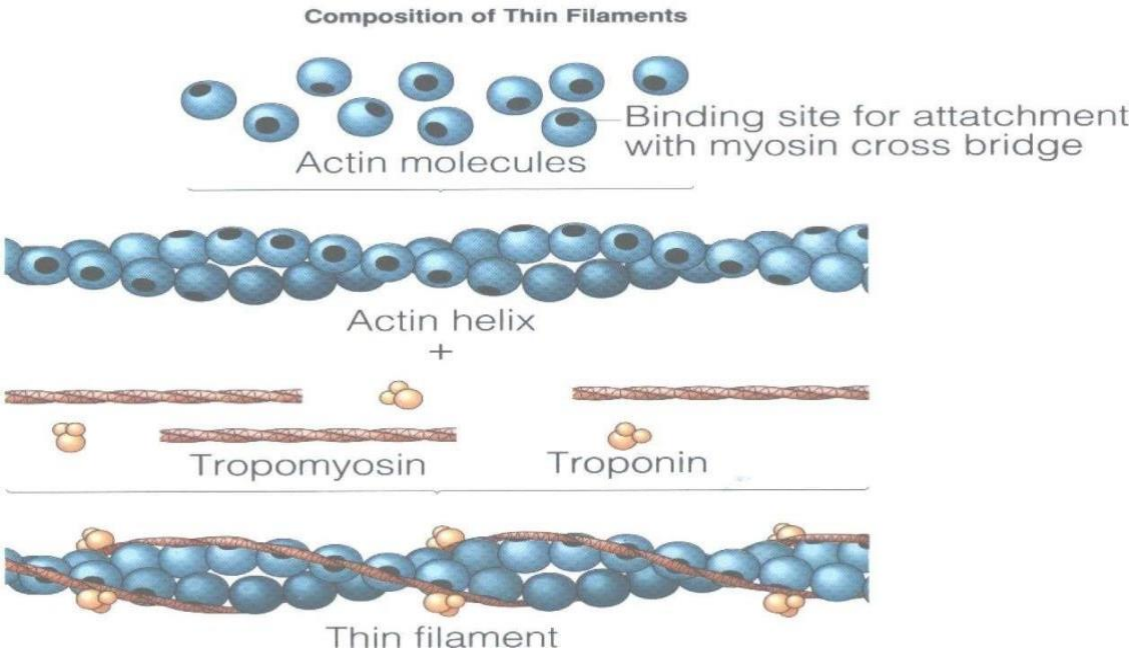
<u>The heads and the portions of the helical tail that are protruding from thick filaments at both ends</u> are known as **cross bridges.**



▪ THIN FILAMENT:

(1.0 um length) is composed of three proteins **actin**, **tropomyosin** and **troponin**.

F-Actin helix forms the backbone of a double stranded structure of the thin filaments. Each strand is formed of polymerized G-actin.



-**myosin binding site** can interact with myosin head, it is believed that this site is an ADP molecule bound to G-actin. The bases are inserted to Z disc, the ends lie in the space between thick filaments.

Note that actin has myosin binding site that is covered by tropomyosin and myosin has actin binding site and myosin ATPase site.

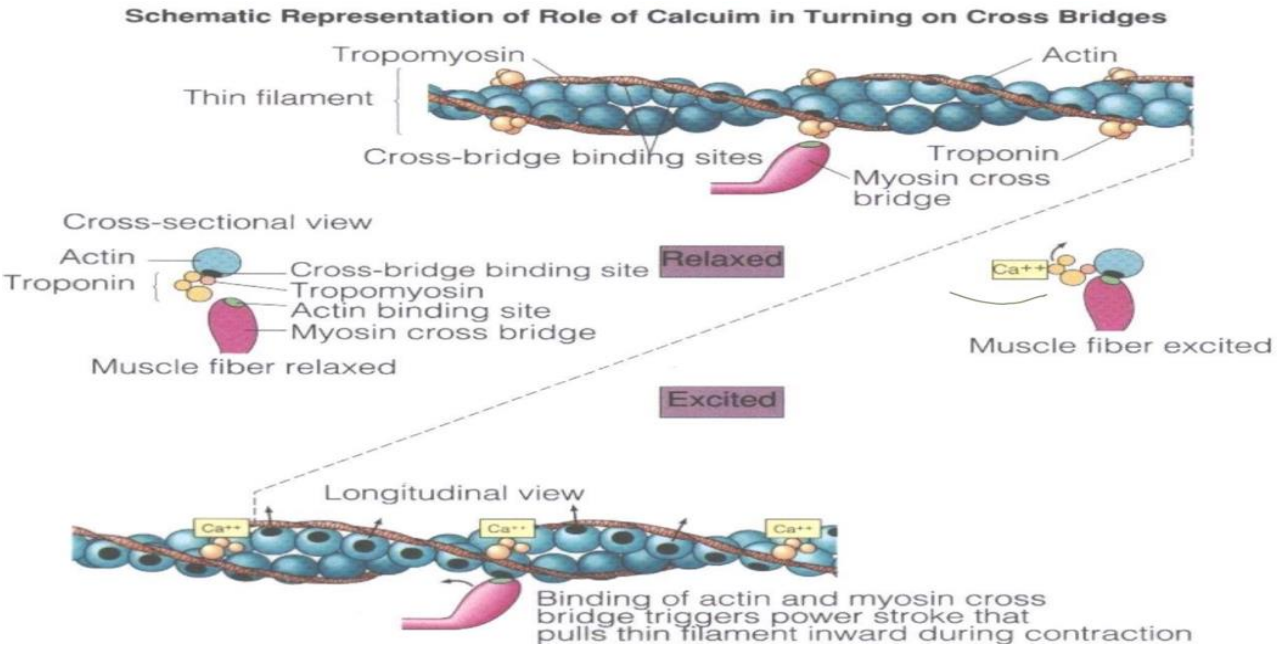
▪ **Actin** is a globular structure that forms the backbone of thin filaments.

▪ **Tropomyosin** is protein molecules that wrap around the F-actin helix. In resting state **Tropomyosin** covers the active site (myosin binding site) on actin and prevents interaction of actin with myosin head.

▪ **Troponin** is a complex structure of 3 subunits, which plays a role in controlling muscle contraction.

- **Troponin T** has affinity for **Tropomyosin**.
- **Troponin C** has affinity for **Ca++**.
- **Troponin I** has affinity for **actin**, and linkes the previous two togather.

In relaxed muscles, when troponin-tropomyosin complex is added the binding is inhibited. Because troponin-tropomyosin complex inhibits or physically covers the binding site on actin and prevents the interaction between myosin heads and actin.



DURING CONTRACTION:

the myosin binding sites on actin is the place where myosin heads bind to the actin. In the absence of troponin-tropomyosin complex, due to high Ca++ concentration inside the sarcoplasm (cytosol) and the binding of Ca++ to troponin C (up to 4 Ca++ bind to one molecule of troponin C), that produces conformational changes resulting in the displacement of tropomyosin away from the active sites on thin filaments. Then myosin can bind strongly to actin in the presence of ATP and Mg++.

-The role of Mg++: it's needed for the ATPase activity (splitting ATP to ADP and pi which remain bound to myosin before the head links to actin).
Low Mg++ conc. causes muscle spasm (contractures), which is also the result of **low Ca++** too, why?
Because generally we have more inhibition than excitation in our body and to get the release of excitatory or inhibitory neurotransmitters we need Ca++, once we have lower Ca++ conc. the inhibition becomes less, causing generating more action potentials in muscles because of loss of inhibition, resulting in muscle spasm (any small stimulus causes exaggerated response), that's why muscle spasm is one of the signs of hypocalcemia,and hypercalcemia causes muscle relaxation.

Also because Mg++ is needed for the contractile process to proceed its low conc.,It may result in some muscle relaxation! ,but it causes muscle spasm mainly.

After binding of myosin heads to the active site on actin, myosin bends between the head and the arm of cross bridges, which pulling the thin filament toward the center of the sarcomere. Bending (tilting) of myosin head is known as **power stroke**.

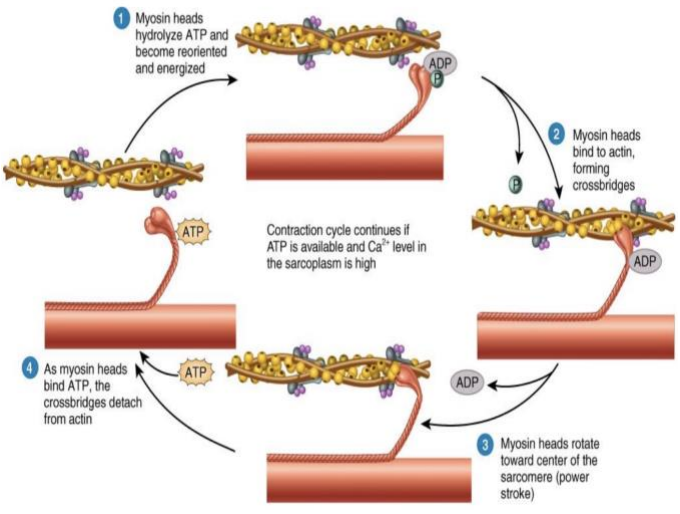
Then the head detach from the actin(by the ATPaes that dephosphorylates the phosphorylated head, lowering its affinity between the binding sites producing energy, ADP and pi).

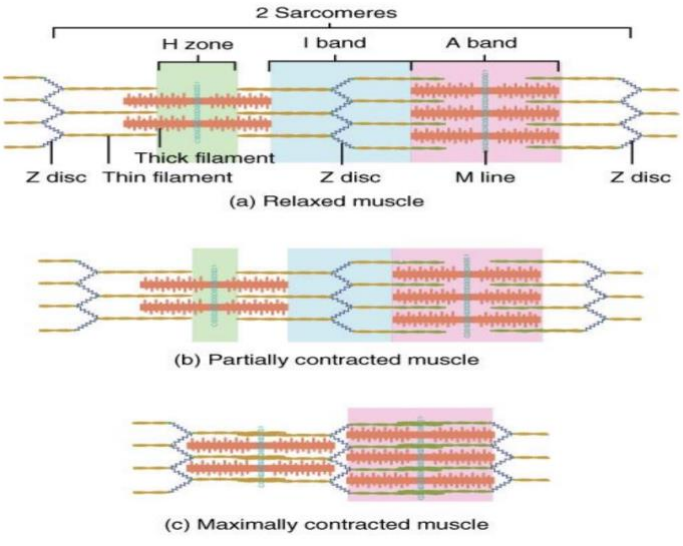
Then it binds to another active site (only if we have Ca++ if we don't it remains in the inactive form) on actin (by consuming the micro-energetic molecules produced by the previous step and rephosphorylating, that the generated energy from splitting is stored within the cross bridge, (reenergising) the head increasing its affinity to binding), and the cycle is repeated many times.

The result of this mechanism is more overlap will be obtained between thick and thin filaments by pulling thin filaments inside. This theory is known as "**sliding theory**" or "**walk-along**" theory.

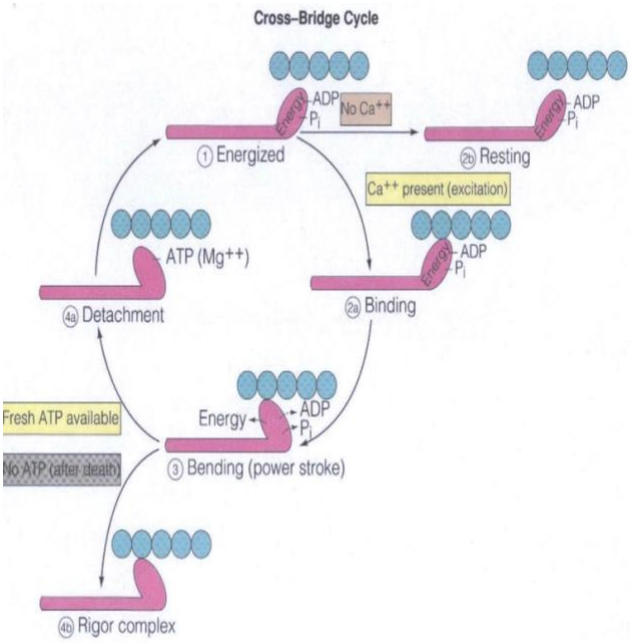
According to this theory, after many cycles of (binding, power stroke, detachment, then binding again) that are taking place between cross bridges and actin, a shortening of the sarcomere will be induced in the muscle by sliding thin filaments toward the sarcomere center.

A short video summarises most of what has been mentioned above:
https://www.youtube.com/watch?v=GneonFlcZG8





ATP is necessary for the detachment of cross bridges from actin.
Not enough ATP will cause muscle to stiff (stay contracted) **because of the inability cross bridges to detach from actin. This phenomenon is called rigor mortis (a stiffness of skeletal muscle after 3-4 hours of death,** which helps detecting the time of death).
Note that contractures of dead muscles, don't happen immediately after death because it needs some time to consume all available ATP.



https://www.youtube.com/watch?v=6YvdLWgT5mg

SOURCES OF ENERGY FOR MUSCLE CONTRACTION:

the amount of **ATP in the muscle** is used first but it isn't enough for the high activity of it it may cover some **seconds**.
Then we need to replenish that consumed ATP and our second source is another macro-energetic molecule stored in the muscle which is **Creatine Phosphate** (by getting an enzyme known as creatine kinase. that transfers the phosphate from the creatine phosphate to the ADP), The amount of creatine phosphate in muscle is 5 times that of ATP, but it only lasts for a couple of **minutes.**
If a muscle continues to contract for more than a few minutes, our third choice is **Glycolysis** which can generate small amounts of ATP and producing lactic acid in a **fast** process that can accumulate and cause fatigue. It's the breakdown of glycogen to glucose which can be broken down by glycolysis into two pyruvic acid molecules to yield 2 ATP molecules. Pyruvic acid can undergo further degradation by oxidative phosphorylation, also it is operating anaerobically (there is no need for O2).
We can also produce the most ATP (36) from various sources by **Oxidative Phosphorylation** at the level of mitochondria, it's a **slow** process that needs constant supply of O2.

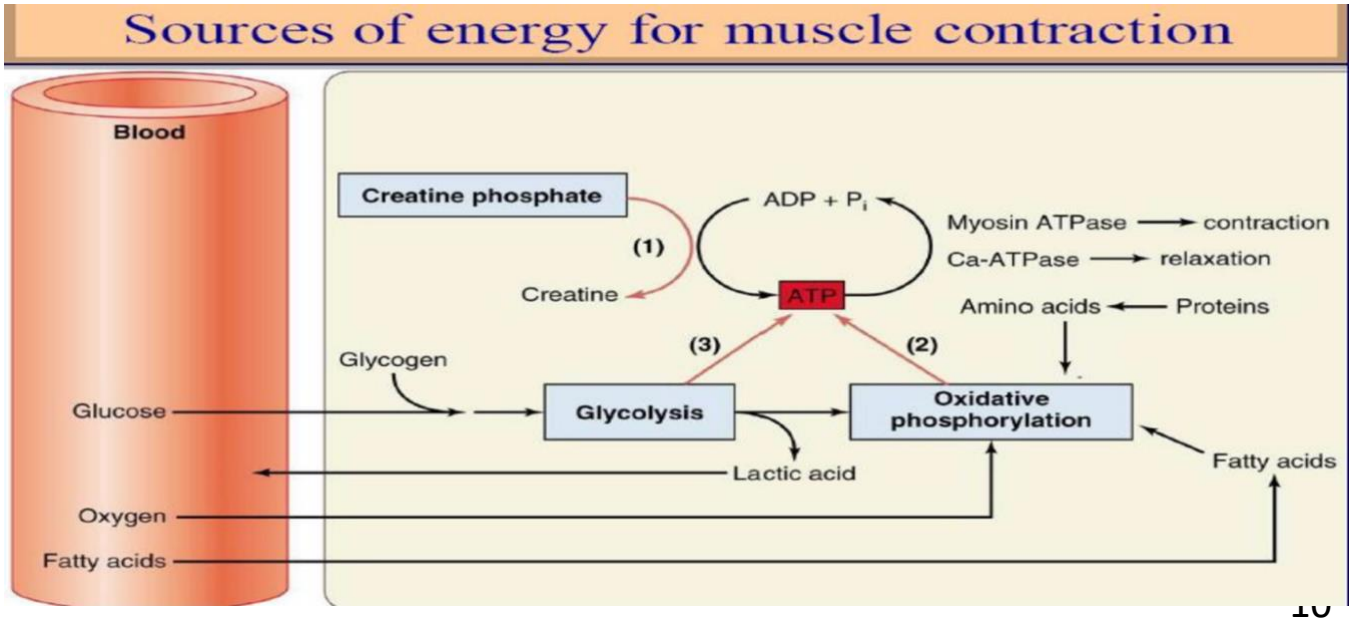
-fast muscles depend on glycolysis and slow muscles depend on oxidative phosphorylation.

SUMMARY:

We have mentioned that myosin head has an ATPase site. At this site ATP binds, where it splits into ADP and Pi. (This needs Mg++ to attach the ATP before ATP-ase can split ATP molecule). This breakdown of ATP occurs before the head links to actin. The resulted ADP and Pi remain bound to myosin and the generated energy from splitting is stored within the cross bridge.

During muscle activity, ATP is needed to provide energy for the power stroke. In addition to that, Ca++ is pumped into the sarcoplasmic reticulum by the activity of Ca++ pump. This pump needs ATP for its operation. Pumping of Na+ and K+ through sarcolemma maintains the ionic composition of cytosol and permits optimal activity of muscle cells. All these activities need a direct use of ATP.

During relaxation of the muscle, the head is energized. When the muscle fiber is excited, the increase in Ca++ concentration in the sarcoplasm, pulls tropomyosin-troponin complex out of their blocking position. This will enable myosin head to attach to actin. When attached, myosin head can use stored energy to bend. After this power stroke, the head releases ADP and Pi from their site. At this point, the detachment of myosin head will take place ONLY when another ATP molecule binds to myosin head. After detachment the new molecule is cleaved, the head returns to its position and energized by splitting ATP. The cycle continues as long as we have high Ca++ concentration inside the sarcoplasm (cytosol) to keep active sites on actin ready for interaction with myosin.



*A new topic:

MUSCLE MECHANICS:

Contraction doesn't always mean shortening.

We can get contraction without shortening, by stimulating the muscle, through adding Ca++ as an example and having interactions between thick and thin filaments while fixing the heads of the myofiber causing **increased tension without changing the length** this type of contraction is called **isometric contraction.** (which can be recorded by using electronic force transducer to measure tension).

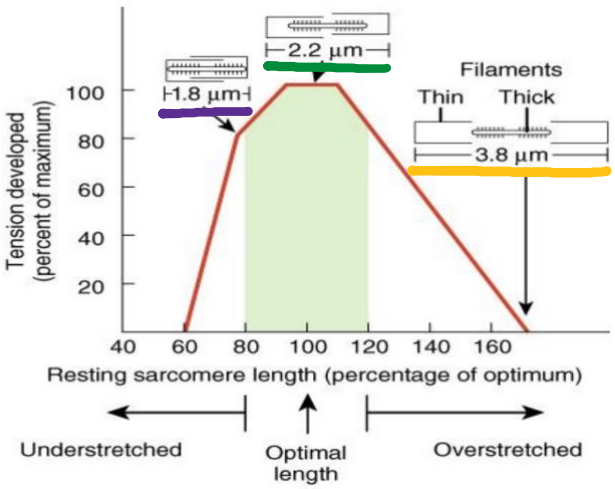
It happens when we take a muscle fiber and stretch it till there is no overlap left between thick and thin filaments and fix its heads, then stimulate it, the tension will increase and the length will stay constant. This is **isometric contraction**.

The second type of contraction is called **isotonic contraction**: meaning that the tone is not changing, happens when the **tension isn't changing and the length is decreased.**

What actually happens in the body is a combination between the two contractions.

TENSION AND SARCOMERE LENGTH RELATION:

Look closely at this picture, you can see that:



1- When sarcomere length is more than **3.6** -3.8 um (length of one thick filaments and 2 thin filaments), the **tension** that can develop is almost **zero.** (as you can see above the yellow line, the myosin heads don't touch actin so they can't be pulled towards the center, hence there will be no tension, which we can call isometric tension).

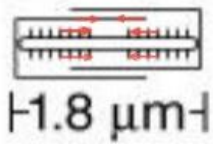
2- When the sarcomere length decreases (**2.0-2.2** um) (this known as optimal, resting length in normal conditions without stretching or contracting), the **maximum tension** can be developed. Because When the sarcomere length decreases, the tension increases as the overlap increases (one thin filament overlaps with one half of the thick filament on each side)

and cross bridges that can be recruited for muscle contraction increases. This increase reaches a maximum level after that more overlap will reduce developed tension, which happens in the next stage.

(above the green line, you can see that all myosin heads are able to bind to actin filaments and pull it to the center that's why we get the maximum tension).

3- Below that length (**2.0-1.6** um) (in contraction) an interaction between thin filaments and cross bridges from the other half of sarcomere may result in a **decrease in tension**. As we get more overlap but one thin filament starts overlapping with the second half of the thick filament.

(actin filaments are reaching the second half of this myosin filament which pulls actin in the opposite direction from the first half and as a result, the net tension will be less).



A short helpful video regarding this topic:
https://youtu.be/uVFqEi5j1v0

TENSION AND WHOLE MUSCLE LENGTH RELATION:

It happens when we take the whole muscle not just the myofibril as in the last example.

Any stretch starting from the resting length will increase the tension without contraction in that muscle as in the sky blue line which is called **passive tension**.

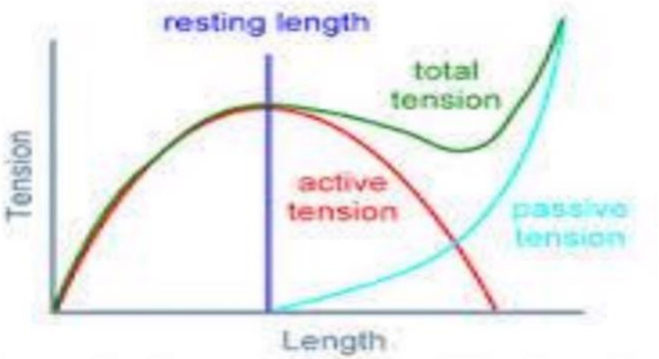
Active tension: is the tension that's recorded by stimulation .

Total tension: is the summation of active and passive tension.

Total tension – passive tension =active tension.

Similar to what happens in the myofibril, the highest recorded tension is at the resting state. More stretch result in decreased total tension.

We have seen that maximum tension develops at a sarcomere length of (**2.0 –2.2** um). This corresponds with the resting length of the muscle. At its normal length, **the muscle also responded with the maximum active tension** (tension induced by stimulation).



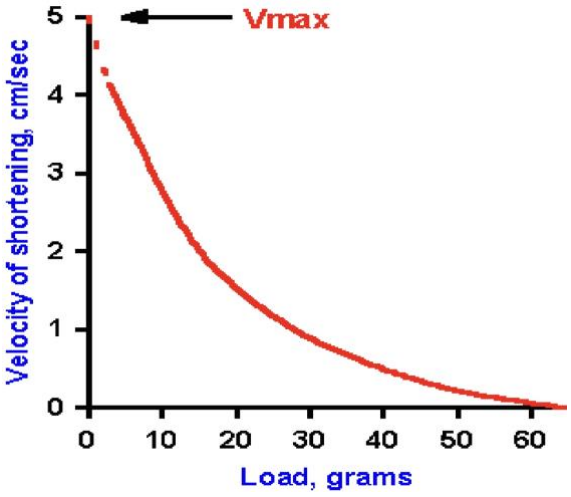
Length-Tension Curve of a Muscle

By stretching the muscle (increasing its length), before stimulation we **increase the inactive (passive) tension** (due to elastic property) in the muscle.
When the muscle stimulated at this new length will develop less active tension. That corresponds to the increase in sarcomere length beyond 2.2um.
From this we can conclude that more overlap between thin and thick filaments located in the same half of sarcomere will induce more tension. This tension is reduced by decreasing the overlap in the same side, or increase in the interaction of thin filaments with cross bridges from the other side of thick filaments (increasing overlap with the other side).

VELOCITY OF CONTRACTION AND LOAD:

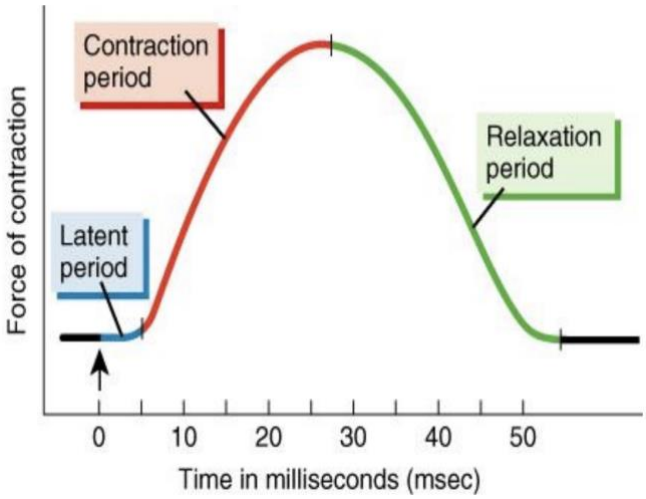
Skeletal muscle contracts with maximum velocity when it is not loaded. By loading the muscle, the velocity of contraction decreases as the load increases.

- If we have **no load** we will have the **maximum velocity** (highest speed) of shortening.
-**By loading** the **velocity decreases** because we need some tension to overcome that load.
-If we loaded a muscle **over its maximal capacity** we get no shortening the velocity will be **zero**.



MUSCLE TWITCHES AND CHARACTERISTICS :

After stimulation ,the muscle will be shortening, and can be recorded like this curve (in blue color). The **maximum shortening** is reached **at the tip of contraction period.**
Higher speed 👉 higher curve.
After it, you will get **relaxation** and the muscle will go back to original state. In this curve you can record 3 periods:



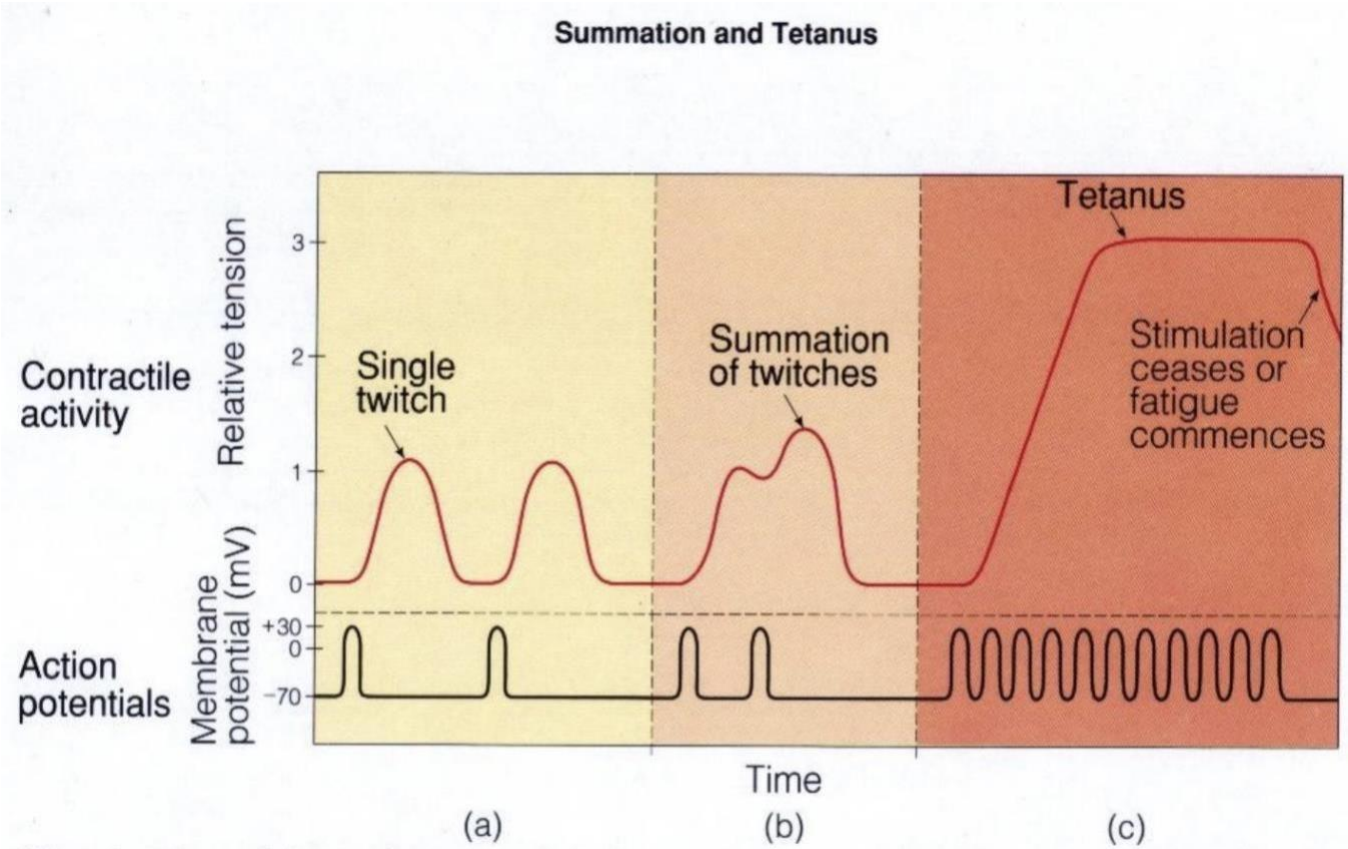
1. **Latent period**
2. **Contraction period**
3. **Relaxation period**

Once a nerve of the nerve-muscle preparation is electrically stimulated, the muscle will respond by a contraction then followed by relaxation. The whole recordings from the beginning of stimulation until the end of muscle relaxation is known as s**imple muscle twitch**.
The simple muscle twitch can take less time in muscles composed of fast fibers such as ocular muscle, or longer time in muscles composed of slow fibers such a muscles of the soles.
These muscles not only differ in their speed of contraction
but also in their color and composition. Fast fibers are large fibers, have extensive sarcoplasmic reticulum, contain large amount of glycolytic enzymes, and fewer mitochondria. These fibers also have less extensive blood supply. Slow fibers are smaller, have more extensive blood supply, and contain more mitochondria. These fibers also contain larger amount of myoglobin (iron containing molecule similar to hemoglobin that can combine with O2), which stores O2 until needed by fibers for oxidative phosphorylation. The presence of large amounts of myoglobin gives the slow fibers a reddish appearance. For this reason, slow muscles are known as red muscles while the muscles containing fast fibers are white muscle.

Slow muscles	Fast muscles
Depend on oxidative phosphorylation	**Depend on glycolysis**
Useful in marathons	Useful In short races, light and moderate exercise (walking, jogging, or swimming).
Have more mitochondria	Have less mitochondria
Have more myoglobin	Have less myoglobin
Red	White

Skeletal muscles are innervated by motor neurons that originate from the central nervous system (CNS). Each neuron innervates a certain number of muscle fibers. Muscle fibers that are innervated by single nerve fiber are called **motor unit**. The number of muscle fibers in motor unit depends on the function of the muscle. Muscle that controls fine movements such as laryngeal muscles have only two or three muscle fibers in a motor unit.
Movements that do not need fine control of muscle contraction may contain up to 100 muscle fibers in one unit.

SUMMATION OF SIMPLE MUSCLE TWITCHES:



The duration of the action potentials is not drawn to scale but is exaggerated.

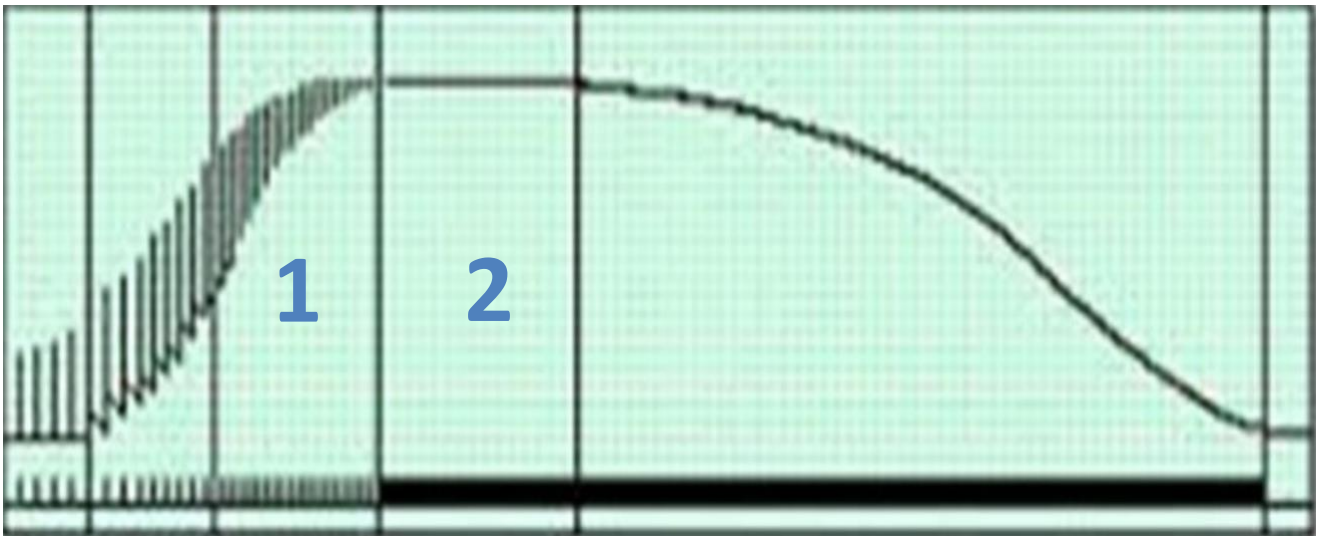
(a) down is the stimulation twitch then after latent period another twitch.
(b) if you have two stimuli, one come after the other and you are starting the relaxation period, the second one lately can cause another twitch, this is called **summation of twitches or frequency summation,** because we get the two waves summation for contractile.
(c) if we have higher frequency of stimuli, you are still in the contraction period and another stimuli are coming, by high frequency of stimuli you get a point where you have contrition without any relaxation ,this is called **tetanization.**

Two types of summation are known in the muscle:

1. **Frequency summation** (wave summation) and tetanization: When a muscle is stimulated by more than one stimulus, this will result in successive and complete simple twitches if the time between 2 successive stimuli is more than the duration of

simple muscle twitch.
Increasing the frequency of stimulation (shortening the time between stimuli), permits excitation by another stimulus while the muscle is in simple muscle twitch.
This may result in summing of the successive contractions. (As in the second phase the picture above).
When frequency of stimulation is more increased and the muscle responds by contraction without any relaxation, we can say that the muscle is in **tetanization**. (As in the third phase in the picture above).

2. **Motor unit summation** (multiple fibers summation): If only few nerve fibers in a nerve that innervates a muscle are stimulated, this will induce shortening in the muscle that corresponds to contraction of motor units that are innervated by stimulated nerve fibers.
When the number of nerve fibers stimulated increases, this will recruit more motor units in contraction.The increase in contraction will result in an increase in the amplitude of simple muscle twitch. In human body this summation is important for gradation of forces during contraction.



This is a real recording, many stimuli are coming, if you have increased the frequency of stimuli, and the time between the two stimuli is shorter than the contraction period, you will get contraction without any relaxation, **tetanus**.

1. Incomplete tetanization.
2. Complete tetanization.

What happen if you continuing with high frequency of stimulation?

This will not last forever, after a period of time the length of the muscle started to be reduce until reach the original baseline of recording, so even though you increase the frequency very high, you will not get any contraction in this muscle which is called **muscle fatigue**.

PAST PAPERS:

1. All of the following are features of slow fibers except:

A. Slow fiber is smaller than fast fiber.

B. Contain numerous numbers of mitochondria.

C. Have an extensive sarcoplasmic reticulum than fast fibers.

D. Posses high number of myoglobin, an iron-containing protein.

2.Which of the following pairs of events are NOT related to each other in skeletal muscle contractile mechanisms:

A. Replacement of ADP with an ATP.

B. Rigor mortis: decreased ATP in the sarcoplasm.

C. T tubules: transmission of action potentials.

D. Fatigue: increased Ach concentration in cleft.

E. Tetanization: frequency summation.

C

D

V2

Pages 16 & 17 were added.