Neuroscience of Human Movement
Department of Multidisciplinary
Indian Institute of Technology, Madras

Lecture – 14
Skeletal Muscles – Part 1

So, welcome to this class on Neuroscience of Human Movement, in today's class we will be talking about Skeletal Muscles. So, this is part 1 of our series on skeletal muscles ok.

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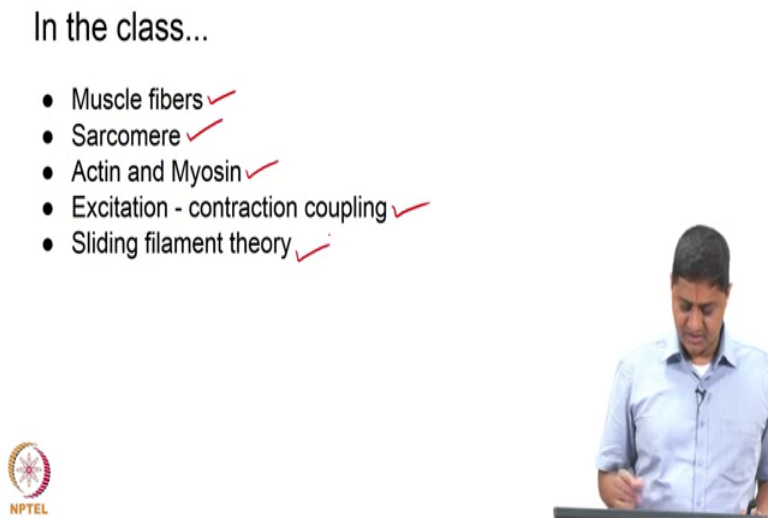

In this class we will be talking about muscle fibers, we will introduce the notion of Sarcomere, which is the smallest functional unit in a muscle and in discussion of the function of sarcomere we will also introduce Actin and Myosin and how they interact to produce force in a muscle, we will discuss Excitation - contraction coupling and we will discuss Sliding filament theory.

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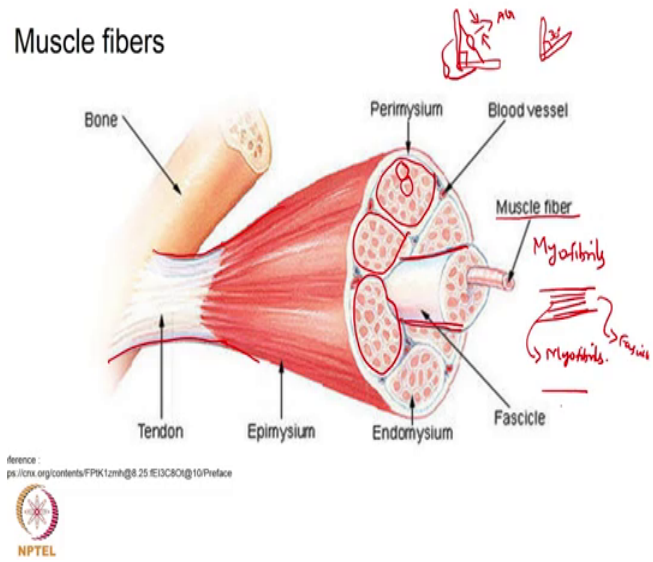

Let us remember what our grand goal is, our grand goal is to understand human movements so, movements are produced when one bone moves relative to the another. Let us consider a situation let us say that is one bone, I am going to call that as one bone and having another bone, let us say for example, these two bones are connected by a muscle an agonist and say another muscle an antagonist right.

Suppose this muscle which is the agonist contracts moves in that direction, then what will happen is that this configuration can be expected to change say for example, could that in other words what was earlier 90 degrees could become an acute angle say could be 60 degrees or could be below 45 degrees say 30 degrees any such number.

So, when these two bones move relative to each other it appears as movements right. So, all the moments that are visible to the eyes happen in this form. So, basically the skeleton or bones move relative to each other and relative to the ground right and these bone moments themselves are caused by contraction of muscles.

How do muscles contact that is the question, but before we go into muscle contraction let us and try and understand the structure of muscles, I am going to keep this relatively brief because this is a course on neuroscience part of this not muscle mechanics, there may be other courses that we will talk about mechanics of muscle function, structure and function of muscles.

So, I am going to keep it relatively brief. So, a muscle attaches to a bone via what are called as Tendons, Tendons are basically composed of elastic material such as collagen and elastin proteins such as collagen and elastin. These continue on to become muscle or these attach to the muscles, the muscles themselves are composed of several bundles of fascicles it turns out that so, say for example, that is one bundle, that is another bundle, that is another bundle and so on.

So, each of these bundles themselves contains several smaller sized bundles such as those ok, these are called as a primary bundle, secondary bundle, tertiary bundle and so on and so forth, within this you know let us take a zoomed out version of a single fascicle right a fascicle is basically composed of several muscle fibers.

So, this muscle fiber itself is composed of several Myofibrils, several myofibrils are arranged in parallel to constitute one fascicle these are myofibrils. But what is found within each myofibril, one myofibril is composed of so, alternating dark and light bands are visible in the myofibrils as you can see in the next slide.

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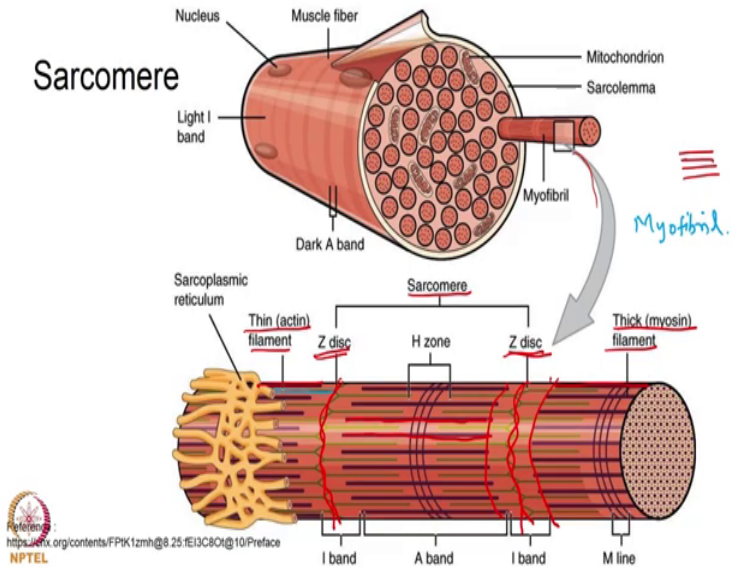

So, you see that is a myofibril and when you zoom in to the myofibril what you are seeing is, there are dark bands and then there are light bands characteristic, typical of skeletal muscles. So, skeletal muscles are also called as striated muscles as in striated as in having stripes right. So, these stripes are basically composed of alternating dark and

light bands, the dark bands are formed due to the visible thin and thick filaments together.

So, there are 2 kinds of filaments within this so, one myofibril is composed of several dark band. So, then one dark band is here, the band is there and then there are some light bands that are here, these are the light bands and another light band is here, another light band is there, another light band is there etcetera.

This alternating dark and light bands constitute sarcomere basically these alternating bands of dark and light color together when they are connected in series they constitute myofibril. Let us remember several myofibrils in parallel constitute a muscle fiber and several muscle fibers in parallel constitute a fascicle and several fascicles constitute bundles of muscle fibers that.

So, let us remember several myofibrils in parallel constitute muscle fiber and several muscle fibers in parallel constitute fascicle and so on and so forth ok. Now what do this thick and thin bands signify that is the question, it turns out that the thick band is basically composed of 2 kinds of filaments, basically the thick filament or myosin and the thin filament Actin.

So, when you see the area where both the thick filament and thin filament are present appears as a darker band and the area where only the thin filament is present say that zone right. That is the zone where only thin filament is present that zone is going to appear as a lighter band. So, that zone for example, is going to appear as a darker band because both thick and thin filaments are visible here.

So, essentially these thick filaments are myosin and thin filaments are Actin and it turns out that boundary between one band one group of thick and thin filaments and another group. So, here is a thick filament and here is a think filament and the boundary between this is called as a Z disk and on the left you have one more Z disk. The distance or all the physiological unit between one Z disk and another Z disk is called as a sarcomere, this is the smallest functional unit of a muscle.

Now, what happens at the neuromuscular junction?

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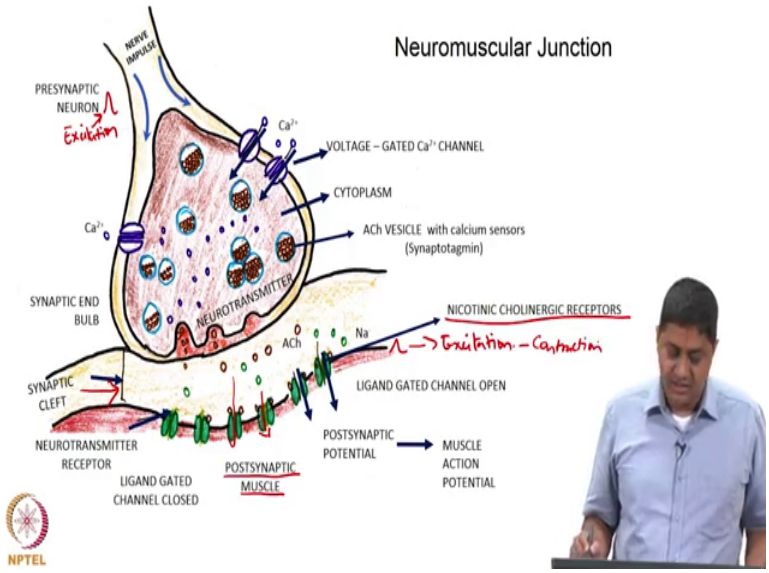

So, we will review this very briefly and continue our discussion back to the muscle fiber force production case right. So, action potential arriving at the synaptic end bulb of the presynaptic neuron opens voltage gated calcium channels at let us in a lot of calcium that causes vesicles to fuse to the membrane and exocytose acetylcholine. And whenever acetylcholine is released into the synaptic cleft here it attaches to the nicotinic cholinergic receptors and which open and a lot of sodium enters inside the postsynaptic cell which is the muscle cell is it not and an action potential is produced on the muscle side right. Because of a large amount of sodium that is entering inside which by itself is constitute acetylcholine binding to the nicotinic cholinergic receptors.

So, action potential is concerned the muscle cell right, now what happens at the muscle cell that causes the force to be produced that is the question, but before that what happens to the excitation. So, basically you have excitation coming in this is excitation this action potential is basically excitation and that excitation after the chemical synapse appears as excitation here. However, we are interested in what happens at the muscle level, how is force produced, force is produced due to contraction, we are interested in understanding the relationship between excitation and contraction or more specifically Excitation - Contraction coupling.

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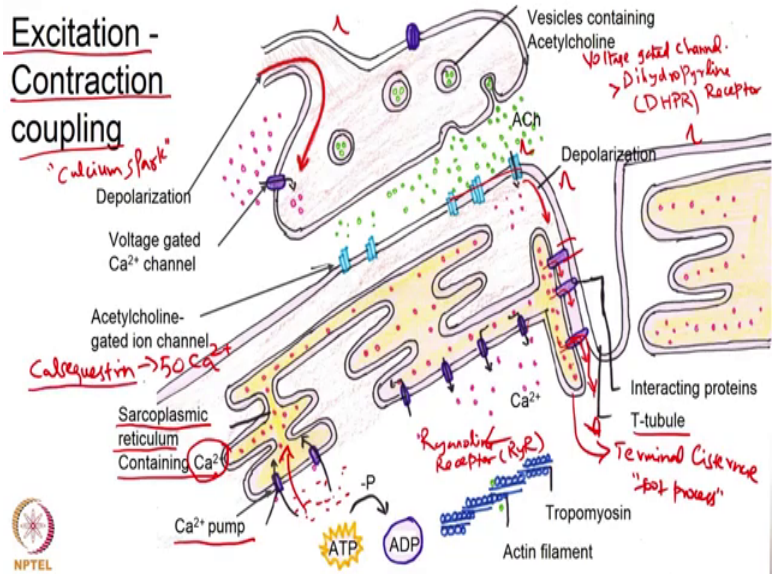

How is Excitation and Contraction coupled that is the question ok, Depolarization or the wave of depolarization that starts in the muscle cell travels along the membrane of the muscle cell as it would in any other excitable cell. Basically how does that travels, basically there are voltage gated sodium channels that regenerate action potential at each point in space. And so, here is one a voltage gated sodium channel there is one action potential there here is another voltage gated sodium channel there is another action potential there etcetera right.

In the muscle cell there are some special spaces called T- tubules that have the structure that resemble the English alphabet T right. So, if you see here this is going to come down and go up like that so, that resembles approximately at T. So, these T- tubules have some special significance for our purpose. So, what happens is depolarization arrives here right and close to the T- tubules you have what are called as Terminal Cisternae of the Sarcoplasmic reticulum. It turns out that sarcoplasmic reticulum contains a large amount of calcium; sarcoplasmic reticulum stores a relatively large amount of calcium right.

So and how does it store so much calcium it turns out that the details are too much for this class, but I will at least mention this it turns out that there is this special protein called Calsequestrin, which is capable of attracting up to 50 calcium irons. So, because of the special nature of Calsequestrin sarcoplasmic reticulum stores a very large amount of calcium and it is Terminal Cisternae are close to the T -tubule ok. This is the terminal

cisternae and this terminal cisternae are close to the t tubule and it is in the T-tubule the depolarization is happening not in the terminal cisternae depolarization in action potential is travelling in the t tubule and on the sarcolemma is it not.

Basically on the muscle cell membrane the terminal cisternae itself is not depolarized ok, it turns out that there is a protein here a channel a very special channel here ok. This channel is a voltage gated channel it is called as I am going to write, it is name there it is called as Dihydro Pyridine Receptor or DHPR ok, action potential arrives they open, but they also open the channels that guard the calcium in the sarcoplasmic reticulum.

So, here in the sarcoplasmic reticulum you have some channels these are channels that guard these are the channels that keep the calcium inside the sarcoplasmic reticulum locked right. So, these channels are called as Ryanodine Receptors or RYR ok. So, this ryanodine receptors interact with the DHPR receptors, it turns out that whenever the DHPR receptor opens it undergoes a conformational change and through what are called as food processes, basically the food process of the DHPR receptor opens the ryanodine receptor.

So, this is like pulling the other channel open. So, ryanodine receptors channel is opened by the voltage gated DHP receptor. So, whenever an action potential arrives at the t tubule the DHP receptor opens and it causes through it is food processes opening of the ryanodine receptor. Note that the ryanodine receptor itself is not on the T- tubule, but on the terminal cisternae of the sarcoplasmic reticulum ok.

So, but these 2 are in very close proximity in the T - tubule here these 2 are in very close proximity that whenever the DHP receptor opens that the ryanodine receptor also opens and this causes a great efflux of calcium, a lot of calcium enters outside. Outside means what; from the sarcoplasmic reticulum to the cytoplasm are the sarcoplasm of the muscle right.

So, outside does not mean extracellular fluid, basically from the sarcoplasmic reticulum the calcium enters the cytoplasm of the muscle cell or the sarcoplasm right. So, that is what happens. So, a lot of calcium goes out, why does it go, whenever action potential reaches the T- tubule excuse me whenever action potential reaches a T- tubule the DHP receptor opens and thus opens the ryanodine receptor.

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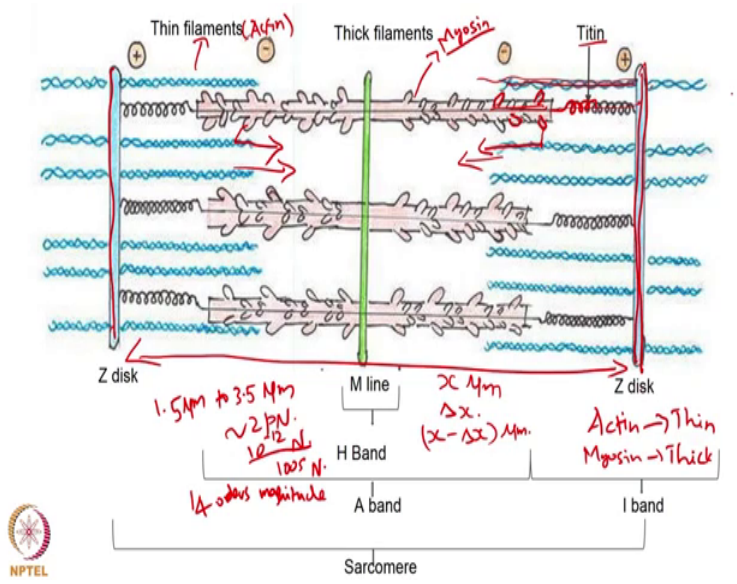

Thus causing an efflux or outflux of calcium from the sarcoplasmic reticulum into the sarcoplasm of the muscle right. Note how is the sarcoplasmic reticulum storing so much calcium right that is another question that is another process, it is an active process called as calcium pump or calcium ATPS, which takes calcium that is present in the sarcoplasm and packs it inside the sarcoplasmic reticulum ok.

So, the calcium pump through an active process takes calcium and stores it in the sarcoplasmic reticulum, this is how you have the original storage of calcium in the sarcoplasmic reticulum ok. Now let us go back to the situation when calcium is released through the ryanodine receptor right lot of calcium goes out crucial role for calcium in muscle function which we will see in the next few slides.

So, what we have seen so, far an action potential arriving at the presynaptic terminal causes a release of acetylcholine which then binds to the nicotinic cholinergic receptor leading to an influx of a sodium, when so much sodium enters that it could cause the threshold of the voltage gated sodium channels. It will cause an action potential and this action potential travels along the sarcolemma of the muscle and then when it reaches the T- tubule there are specialized channels called as a dihydropyridine receptor channels, which open which are depolarization sensitive which are voltage gated and when they open basically they also open neighboring nearby ryanodine receptors.

So, these ryanodine receptors causes an outflux a great outflux of calcium leading to a situation called as calcium spark the amount of calcium that is released is. So, great that this is called as calcium spark and we also saw how calcium is stored, because of the special nature of protein called calsequestrin which can bind up to a large number of calcium ions right.

Now what does this calcium itself do to force production that is the question right we have not yet gone there we will go there now. Let us go back to the situation of the Thick and Thin filaments, here are the thick filaments ok, what does the thick filament? What is the name? The name of the thick filament is Myosin, the thin filaments called as Actin, how do you remember which is which actin is thin, then the other one is thick and Myosin is thick.

So, actin rhymes with thin that is how you remember which is which. So, and the thick filament itself has what are called as heads several heads in the previous picture it seemed as if the thick filament is hanging in air actually this is not true right. The thick filament is attached to the Z disk via contractile proteins very strong contractile protein called Titin, one of the strongest or most elastic protein known to (Refer Time: 22:05) right. So, Titin attaches myosin to the Z disk so, that is the Z disk, this is the other Z disk and Titin basically attaches the thick filament myosin to the Z disk and thin filament hangs in from the Z disk right.

Now, what is the thin filament composed of we need to see that.

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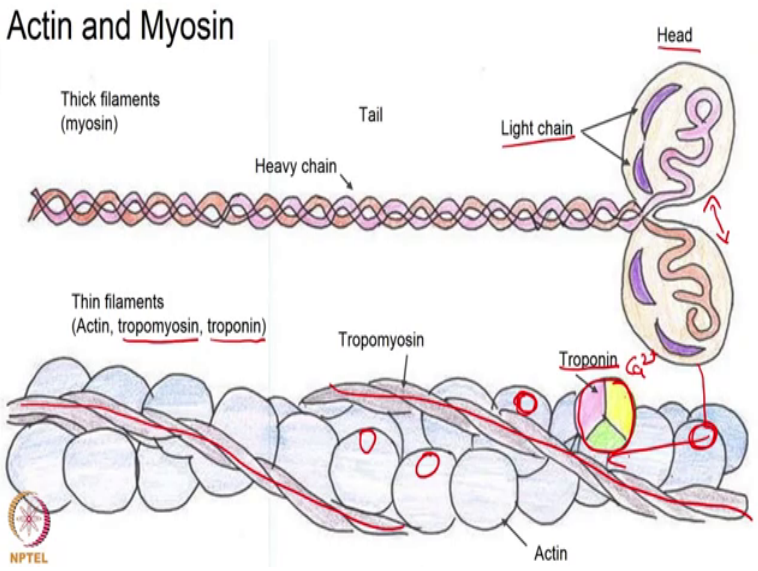

The thin filament itself is composed of not just actin, but there are other things actually which are essential for it is function. Actin is a crucial component of course, and it contains what are called as active sites or binding sites. These are the sites to which the thick filaments head can attach, these are the sites to which the thick filaments head can possibly attach, but it turns out the thin filament also contains other proteins such as Tropomyosin and Troponin. The tropomyosin is like a rope or a thread that is wound around the actin filament in such a way that in it is rest state it will essentially cover all the binding sites of the actin.

So, basically the tropomyosin in it is normal state will cover the binding sites of the actin filament and on the tropomyosin you have another protein called as Troponin. This troponin has a special property that is whenever calcium comes into the picture whenever troponin attaches to calcium it undergoes a conformational change. So, it change a shape in such a way that it slightly moves the tropomyosin, when tropomyosin is moved what happens is that the binding sites on the actin filament are exposed ok.

So, essentially the thin filament is composed of actin which contains the binding sites and tropomyosin which covers these binding sites and troponin which sits on top of the tropomyosin and will cause movement of tropomyosin whenever calcium is present. So, when calcium is present troponin will undergo a conformational change, but since troponin is attached to tropomyosin it will cause a movement of tropomyosin in such a

way that the binding sites will become exposed. When the binding sites become exposed only at that time the thick filaments head can attach to the binding sites. So, at even otherwise the binding site is present, but it is not visible it is covered by tropomyosin.

So, calcium acts as the key that opens the lock of binding sites and in other words basically tropomyosin is locking the binding sites whenever calcium comes in it attaches to troponin and opens the lock in such a way that the binding sites are exposed and free to host when the binding sites are exposed the binding sites are free to host the head of the thick filament.

Let us talk about the thick filament; the thick filament itself is composed of 2 heads actually multiple heads only 2 are shown here multiple heads in multiple molecules. So, basically there are 2 heads here and these heads can attach to the active sites or the binding sites on actin and then undergo, what is called as a power stroke in the presence of ATP at the expense of energy this can pull the thin filament in a particular direction ok.

So, this is what happens.

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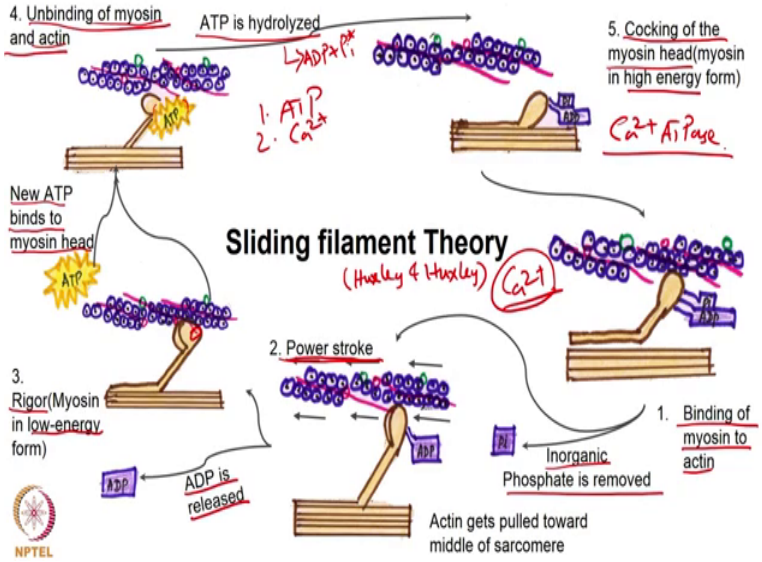

This means essentially what is going on is, that the thick filament let us go through one more time what is the situation, the situation is this is the thin filament and this is the thick filament right. The thick filament attaches to the thin filament and pulls the thin

filament in that direction whereas, here the myosin head attaches to the actin here and pulls in that direction, what will now happen? Now that is pull in opposite directions here and since Z disk itself cannot be in equilibrium essentially the distance between the Z disks is reduced actually right.

Let us suppose earlier this was some x microns now it is reduced by some delta x. So, now, the new length after the attachment of the thick filament to thin filament and the power stroke will be a smaller length x minus delta x micrometers. So, important to note is that the fibers themselves are between 10 and 60 microns in diameter and between 1 and 500 millimeters in length ok. Now what about each sarcomere, each sarcomere is between 1.5 microns to 3.5 microns in length all right so, approximately.

So, essentially when the thick filament attaches to the thin filament and pulls on them the distance between to Z disk become smaller, this essentially is what appears, as movement we would think we are talking about a little small scales how much force would this be producing actually the amount of force that this is producing is of the order of port 2 Pico Newtons so, 10 power minus 12 Newtons right.

Now let us compare this situation with what could happen in big muscle in a large muscle, in a large muscle forces of the order of several 100s of Newtons can be produced so; that means, we are talking about 14 orders of magnitude 10 power minus 12 to 10 power 2 at least. So, we are talking about 14 to 15 orders of magnitude in fourth space right.

But then how is this 10 power minus 12 Newton converted into 100s of Newtons well, what happens is that several of these sarcomeres attached in series constitute one myofibril several of these myofibrils arranged in parallel constitute one muscle fiber several muscle fibers arranged in parallel constitute a fascicle etcetera right and there are bundles of these that when put together, we can achieve the scale that we need ok.

So, something to remember, but let us go back to the situation of the thin and thick filament interacting, we said that the thin filament basically is composed of actin tropomyosin and troponin actin has the binding sites and tropomyosin covers the binding sites and troponin when it interacts with calcium exposes the binding sites and the myosin it is heads can interact with the binding sites whenever ATP is present.

So, essentially we are saying that the thick filament and thin filament are sliding over each other leading to a hypothesis that it is the sliding of these 2 filaments over each other that causes production of force. This was proposed by Huxley and Huxley this is the sliding filament theory due to Huxley and Huxley and colleagues ok.

Now since this is the sliding filament theory are the cross bridge cycle we could start explaining this anywhere we will start at say here ok, whenever ATP binds to myosin head ATP binds to myosin head basically myosin and actin are unbound basically they are disconnected when ATP binds to the myosin head right then ATP is hydrolyzed into ADP plus phosphate right.

So, ATP is hydrolyzed into ADP plus pi now this takes myosin to a high energy form this situation is also called as the cocking of myosin head it is ready for the next action next cycle of action ok. Now then when calcium comes into the picture now here approximately here calcium comes into the picture, when calcium comes into the picture the binding sites on the actin are exposed then myosin binds to actin. Essentially what happens is, initially in the high energy form small region of the binding site is exposed to that region the head of the myosin is attached, but it is not completely exposed because of that reason it is in a weak state ok.

So, there is a weak attachment of myosin to the actin in the high energy state, once when calcium comes into the picture once when calcium comes in troponin attaches to the calcium and moves the tropomyosin completely exposing the actin binding site, because of this reason the head can comfortably attach to the actin binding site or both heads can attach and then basically the inorganic phosphate is removed energy is released right energy is released leading to what is called as power stroke.

When the inorganic phosphate is removed the myosin head pulls the actin or the thin filament toward the middle of the sarcomere essentially reducing the distance between 2 z disks and producing a force that is serially transmitted actually that force is transmitted both serially and laterally ok, but lateral force transmission is a relatively technical topic deep topic that we will not discuss as part of this course it also produces a force for our purposes that is serially transmitted ok.

So, this situation where the thick filament is pulling the thin filament in the presence of calcium is called as power stroke right, essentially it is pulling the thin filament and

reduces the distance between the Z disk and produces a relatively small amount of force right. After the power stroke what happens, ADP is released ADP is released then myosin goes to a low energy state because there is no more ATP then myosin is attached to actin in a relatively low energy state this is called as rigor right.

What happens with death right, after death there is a situation called as rigor mortis that sets in which leads to a situation when actin and myosin are attached, but they are not able to move right because there is no more ATP because there is no oxygen right because there is death right this leads to situation where there is a considerable rigidity right. So, this is called as a rigor mortis those who are interested can read about it, but that is unrelated to part of this course anyway.

So, rigor is the situation when myosin is attached to actin in low energy form, now when ATP attaches to myosin. So, when ATP attaches to myosin then myosin unbinds or disconnect itself from actin and then ATP is hydrolyzed into ADP and phosphate and then it cocks it the head and goes to a high energy firm and then the cycle repeats crucial to this function are 2 things one obviously, ATP or energy, 2 calcium, if neither of this or if even one of this is not present then this will not happen.

So, this is the crucial role of calcium in the sliding filament theory or this is the crucial role of calcium in the production of force by the muscle. So, what we have seen is how calcium is coming into the picture, basically calcium is coming into the picture via the terminal cisternae are basically released through the ryanodine receptor located at the terminal cisternae close to the T- tubules in the sarcoplasmic reticulum.

But once the calcium is released basically you have the remaining things, which are basically the, which are the thick and thin filaments and their interaction that is enabled that is enhanced by calcium right. But then once there is no more action potential in the neuron or the motor neuron or there is no more action potential in the muscle what happens is that all the calcium is taken back and stored into the sarcoplasmic reticulum through an active process called as calcium atpase.

So, there is an active process energy is expended to take calcium and put it back into the sarcoplasmic reticulum. So, it is used only when needed ok. So, calcium when it is released it causes the muscle to contract and produce force this is the theory behind the force production by a sarcomere.

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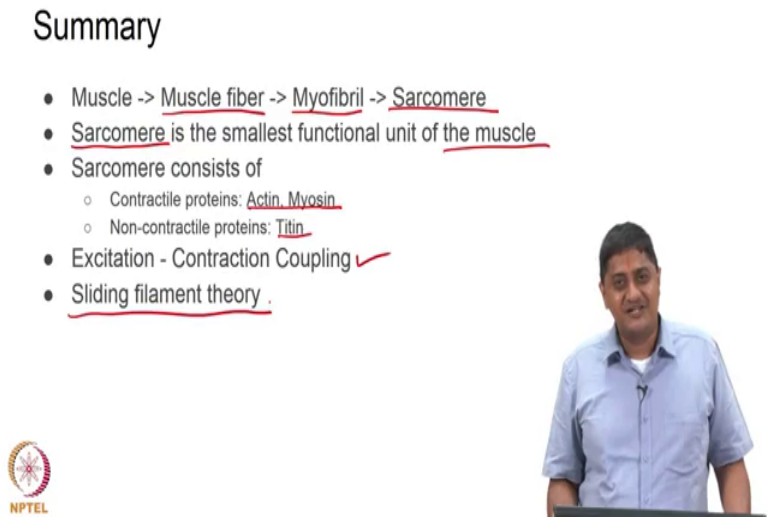

So, what we have seen so far is, muscles are basically composed of muscle fiber which are composed of myofibrils, which are composed of sarcomere and the smallest functional unit of the muscle is basically the sarcomere it consists of actin and myosin and non contractile proteins such a Titin that hold the thick filament in place. And we also saw in today's class excitation contraction coupling how excitation that is coming in causes contraction, how is this cause due to the crucial role of calcium right and we also discussed in relatively good detail the sliding filament theory with this we come to the end of this lecture.

Thank you very much for your attention.