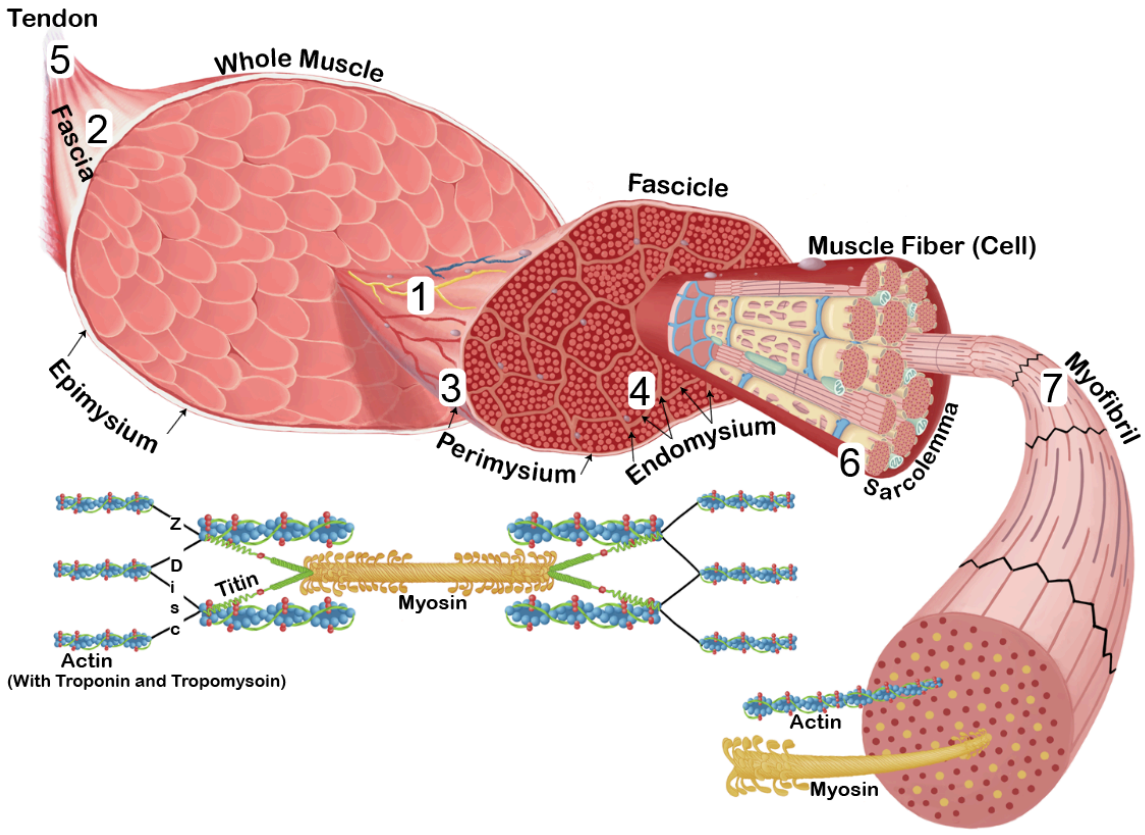
2.1

Structural Organization of Skeletal Muscle

Skeletal muscle is also known as **voluntary muscle** because we can consciously, or voluntarily, control it in response to input by nerve cells. However, and somewhat ironically, most of the daily control of skeletal muscle is reflexive, or unconsciously controlled! More on that regulation later. Skeletal muscle is also referred to as **striated** ("striped") because when you take a thin slice of it and look at it with a microscope it looks like tiger skin. This "tiger skin" appearance is caused by numerous proteins that are arranged in very symmetrical ways and are necessary for the contractile properties of skeletal muscle. Looking at the thin slice of muscle will also reveal lots of nuclei pressed up against the cell membrane. This is because skeletal muscle fibers are made by combining many cells together making one single strand. These strands (fibers) can be quite long, some extending over a meter in length. The entire muscle is made of lots of individual fibers bound tightly together. All the skeletal muscles together make up over 40% of our body weight! This section will go into more detail about the individual proteins that make up the skeletal muscle fibers.



Skeletal Muscle Organization. Image drawn by BYU-Idaho student Nate Shoemaker Spring 2016

Image drawn by BYU-Idaho student Hannah Crowder Spring 2013

Even though muscle fibers are comprised of many cells fused together, the resultant structure becomes one unit called the muscle cell, which we refer to as the **muscle fiber**. These muscle fibers are bound together into bundles, or **fascicles**, and are supplied with a rich network of blood vessels and nerves (see figure above number **1**). The fascicles are then bundled together to form the intact muscle. Muscle fibers are the same diameter as hair follicles (100-120um). As you look down at your bicep, visualize small strands of hair follicles extending from your shoulder to the radius bone in your forearm. Clearly, one hair follicle would be too fragile to move your arm, but hundreds of millions are very adequate! Let's dissect a skeletal muscle, beginning with the entire muscle and continuing internally down to the submicroscopic level of a single muscle cell. Please use the numbered figure above as reference as you read through this section. In an intact skeletal muscle, a rich network of nerves and blood vessels nourish and control each muscle cell (**1**). These muscle fibers are individually wrapped (endomysium; **4**) and then bound together (perimysium; **3**) by several different layers of fibrous connective tissue.

The **epimysium** (*epi* means “outside,” and *mysium* means “muscle”) is a layer of dense fibrous connective tissue that surrounds the entire muscle

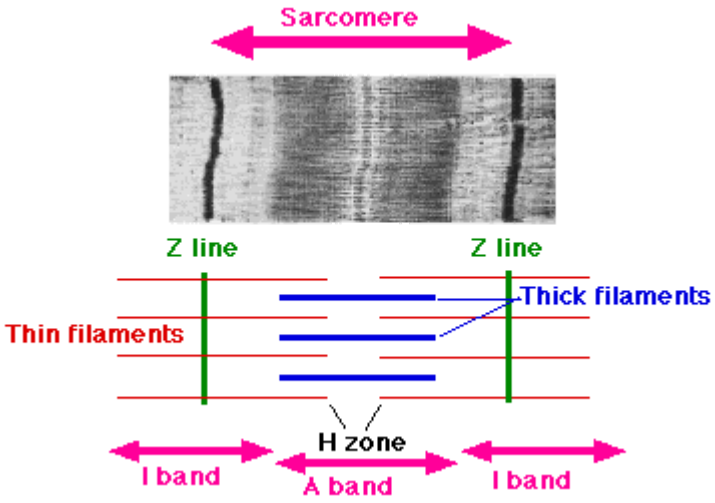
(labeled above). This layer is also often referred to as the **fascia** (**2**). Each skeletal muscle is formed from several bundled fascicles of skeletal muscle fibers, and each fascicle is surrounded by **perimysium** (*peri* means “around”; **3**). Each single muscle cell is wrapped individually with a fine layer of loose (areolar) connective tissue called **endomysium** (*endo* means “inside”; **4**). These connective tissue layers are continuous with each other, and they all extend beyond the ends of the muscle fibers themselves, forming the **tendons** that anchor muscles to bone (**5**), moving the bones when the muscles contract.

Deep to the endomysium, each skeletal muscle cell is surrounded by a cell membrane known as the **sarcolemma** (you will see the prefixes *sarc-* and *myo-* quite a bit in this discussion, so you should understand that these are prefixes that refer to "muscle"; **6**). Most of the space in the cytoplasm, or **sarcoplasm** is taken up by cylindrical (rod-like) **myofibril** protein structures (**7**). Each muscle fiber contains hundreds or even thousands of myofibrils that extend from one end of each muscle fiber to the other. These myofibrils take up about 80% of the intracellular space and are so densely packed inside these cells that mitochondria and other organelles get sandwiched between them while the nuclei get pushed to the outside and are located on the periphery, right under the sarcolemma.

Each myofibril is comprised of several varieties of protein molecules that form the **myofilaments**, and it is these myofilaments (actin, myosin, titin) that give muscles their contractile properties. The myofilaments are arranged in structures called **sarcomeres** (*sarc- means “*muscle,” and *mere* means “part”). The striations seen microscopically within skeletal muscle fibers are formed by the regular, organized arrangement of myofilaments—much like what we would see if we painted stripes on chopsticks and bundled them together with plastic wrap, with the plastic wrap representing the sarcolemma (see histological micrograph below).

Repeating structures like sarcomeres make anatomists like Bro. Anderson giddy with excitement because they can start putting names on things! The arrangement of the sarcomere is repeating and predictable and under a microscope shows alternating dark and light areas. The dark areas are called **A bands**, which is easy to remember because "A" is the second letter in "dark." The light areas are called **I bands** and are also easy to remember because "i" is the second letter in "light." ("A" actually stands for *anisotropic*, and "I" stands for *isotropic*. Both of these terms refer to the light absorbing character of each band. However, we'll stick to A and I bands.) The image

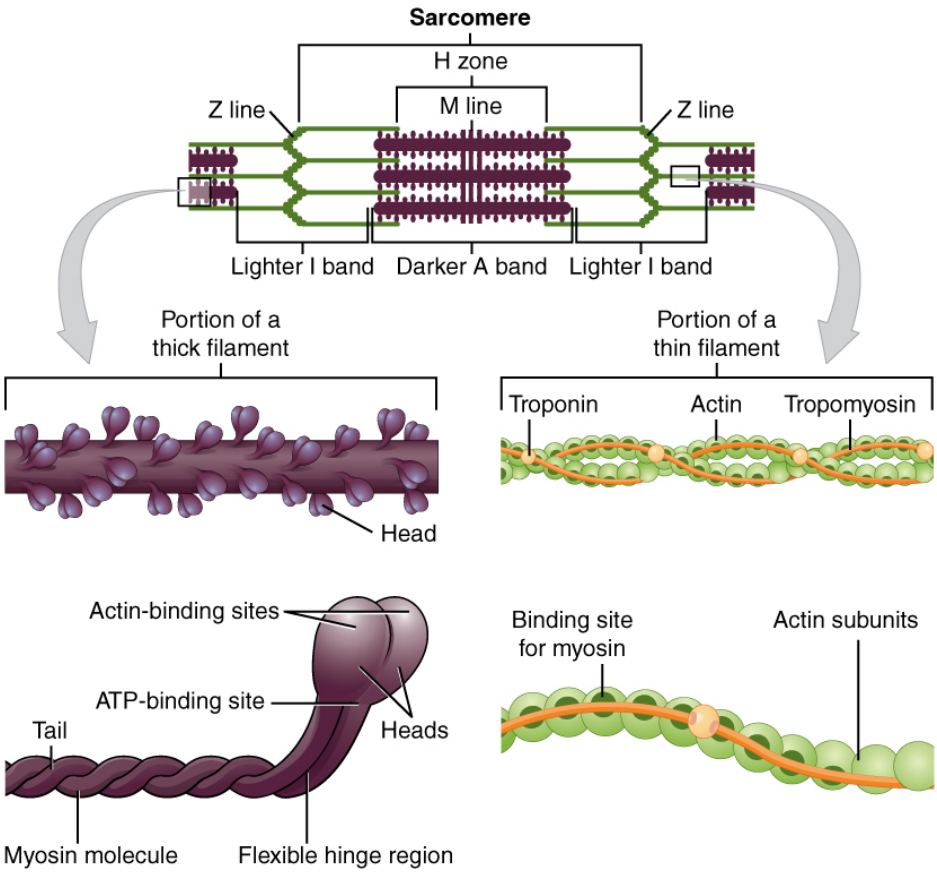
below shows a micrograph of a sarcomere, along with a drawing representing the different parts of the sarcomere.



Sarcomere filaments and their striated appearance

Skeletal Muscle Sarcomere: Thick and Thin Filaments, Z Line, H Zone, I & A Bands. File:Sarcomere.gif; Author: Sameerb; Site: https://commons.wikimedia.org/wiki/File:Sarcomere.gif; License: Public Domain, No restrictions

Notice that in the middle of each I band is a darker line called the **Z line** or **Z disc.** The Z lines are the divisions between the adjacent sarcomeres. Sarcomeres are connected, end to end, along the entire length of the myofibril. Also, in the middle of each A band is a lighter **H zone** (H for *helle*, which means "bright"), and each H zone has a darker **M line** (M for "middle") running right down the middle of the A band.



Sarcomere filaments

Sarcomere: Detailed Illustration of Thick and Thin Filaments: Title: 1003_Thick_and_Thin_Filaments.jpg; Author: OpenStax College; Site: http://cnx.org/contents/6df8aab3-1741-4016-b5a9-ac51b52fade0@3/Skeletal-Muscle;License: licensed under a Creative Commons Attribution 4.0 License.

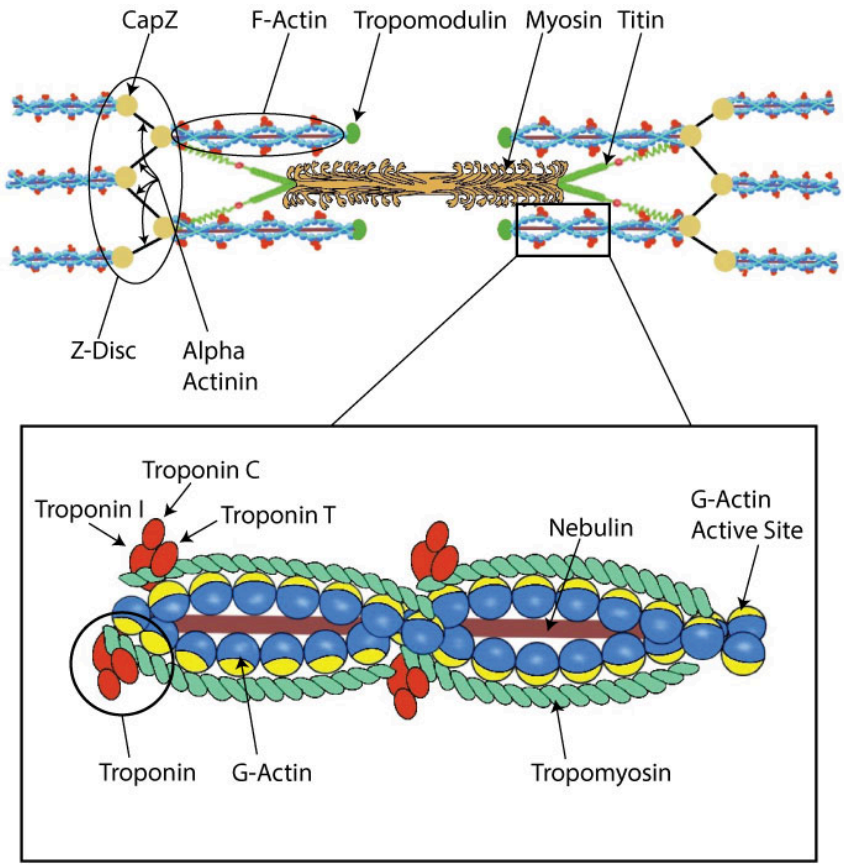


Image by JS F23

Z-disc proteins make up the Z-line that create perpendicular borders that form the repeating sarcomeres. **CapZ** and **alpha-actinin** anchor the protein **nebulin** to the Z line and extend out to the center where the length is capped off by the protein **tropomodulin**. Between molecules of nebulin is the elastic protein called **titin**. Titin is thought to play a major role in resetting the sarcomere after each contraction. Thus, each sarcomere consists of nebulin and titin proteins that set the stage for the organization of the contractile and regulatory proteins.

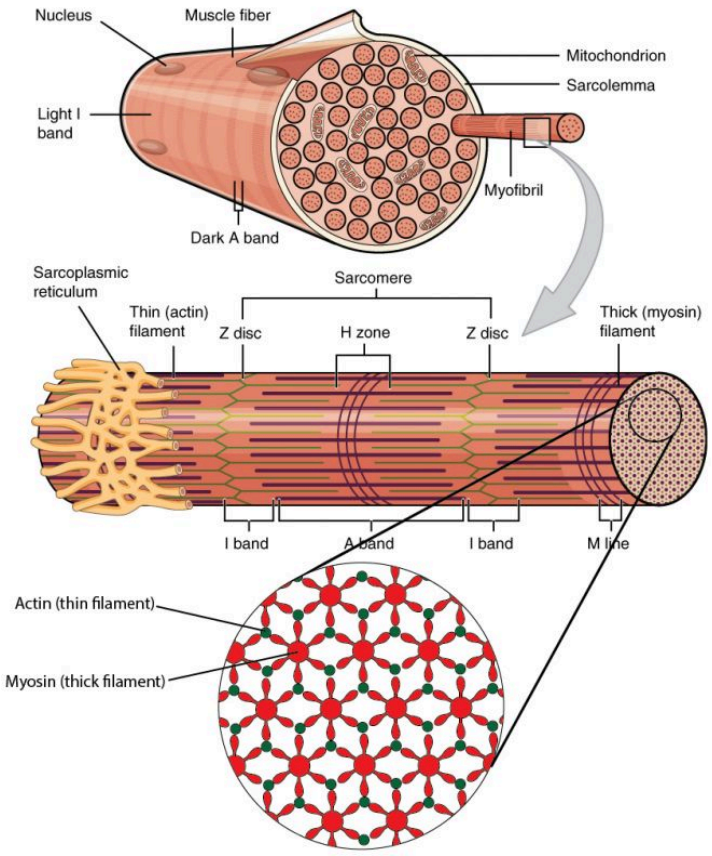
Each actin is composed of two strands of *fibrous actin (***F-actin**) and a series of **troponin** and **tropomyosin** molecules. Each F-actin (also known as the thin filament) is formed by two strings of *globular actin* (**G-actin)** wound together in a double helical structure, much like twisting two strands of pearls with each other. In this analogy, each G-actin is like an individual pearl and each F-actin is a strand of pearls. Each G-actin monomer has a binding site for ATP that it uses to polymerize to another G-actin monomer and nebulin. Following polymerization of G-acting monomers to form F-actin strands, the original ATP binding site is altered and becomes a binding site for the molecule myosin, called an **active site**. Dimers of the protein **tropomyosin** extend over the entire F-actin filament and cover the newly created myosin

binding sites. Each tropomyosin molecule is long enough to cover the active binding sites on seven G-actin molecules. These proteins run, end to end, along the entire length of the F-actin. Associated with each tropomyosin molecule is a third polypeptide complex known as **troponin**. Troponin complexes contain three globular polypeptides (*Troponin I*, *Troponin T*, and *Troponin C*) that have distinct functions. Troponin I binds to actin, troponin T binds to tropomyosin and helps position it on the F-actin strands, and troponin C binds calcium ions (new figure). Troponin C has four binding sites for calcium, two high-affinity binding sites and two low-affinity-binding sites (new figure). At low intracellular Ca2+ concentrations the high-affinity binding sites are occupied and help maintain the stability of the troponin complex. When intracellular calcium concentrations rise, then the low-affinity binding sites are occupied which causes a conformational change in the entire complex. This conformation change will result in troponin "pulling" the tropomyosin molecule away from the myosin binding sites of actin.

The final contractile myofilament (also called the thick filaments) is composed of about 300 myosin type II molecules bound together and surrounding the molecule titin (new figure). Each myosin type II protein is made up of six protein subunits, *two heavy chains* and *four light chains* (new figure). The heavy chains have a shape similar to a golf club, having a long shaft-like structure, to which is connected the globular myosin head. The shafts, or tails, wrap around each other and interact with the tails of other myosin molecules, forming the shaft of the thick filament. The globular heads project out at right angles to the shaft. Half of the myosin molecules have their heads oriented toward one end of the thick filament, and the other half are oriented in the opposite direction. It is the myosin heads that bind to the active sites on the actin. The connection between the head and the shaft of the myosin molecules function as a hinge and as such is referred to as the **hinge region.** The hinge region can bend and, as we shall see later, creates the power stroke when the muscle contracts. The center of the thick filament is composed only of the shaft portions of the heavy chains.

Additionally, each myosin head has an ATPase that binds to and hydrolyzes ATP during muscle contraction. It is the ATP that provides the energy for muscle contraction. Each of the myosin heads is associated with two myosin light chains, an alkali light chain and a regulatory light chain (new figure), that play a role in regulating the actions of the myosin heads. The three-dimensional arrangement of the myosin heads is very important. Imagine that you were looking at a thick filament from the end, and there is a myosin head sticking straight up. As you moved around the circumference of the thick filament, you would see myosin heads every 30 degrees. This allows

each thick filament to interact with six thin filaments. Likewise, each thin filament can interact with three thick filaments. This arrangement requires that there be two thin filaments for every thick filament in the myofibril (see image below).



Muscle Fiber Organization

Muscle Fiber Detailed Diagram. Adapted from the following image: Title: 1022_Muscle_Fibers_(small).jpg; Author: OpenStax College; Site: http://cnx.org/contents/6df8aab3-1741-4016-b5a9-ac51b52fade0@3/Skeletal-Muscle License: licensed under a Creative Commons Attribution 4.0 License;

During muscle contraction, the myosin heads link the thick and thin myofilaments together, forming **cross bridges** that cause the thick and thin myofilaments to slide over each other, resulting in a shortening of each sarcomere, each skeletal muscle fiber, and the muscle as a whole—much like the two parts of an extension ladder that slide over each other (need a new figure). To summarize, in order for the shortening of the muscle to occur, the myosin heads have three important properties: 1.) The heads can bind to active sites on G-actin molecules, forming *cross bridges.* 2.) The heads are attached to the rod-like portions of the heavy myosin molecules by a *hinge region* as already discussed. 3.) The heads have *ATPase* enzymes that can break down ATP, using the resulting energy to bend the hinge region and allow detachment of the myosin heads from actin (need a new figure, or incorporate into previous figure).

There are several other important structural proteins, but we will only discuss one more: **dystrophin**. Dystrophin is a protein located between the sarcolemma and the outermost myofilaments (need a new figure). It links actin to an integral membrane protein, which, in turn, links the muscle cell to the endomysium of the entire muscle fiber. Genetic mutation of the gene coding for dystrophin is one of the root causes of a class of muscle diseases known collectively as *muscular dystrophy (MD)*. The most common form of MD is Duchene muscular dystrophy (DMD), which is inherited in a "sex-linked" fashion and affects boys. Most DMD patients become wheelchair bound early in life, usually by age 12 or so. Difficulty breathing usually becomes problematic by age 20 and sadly is often the cause of their premature death.

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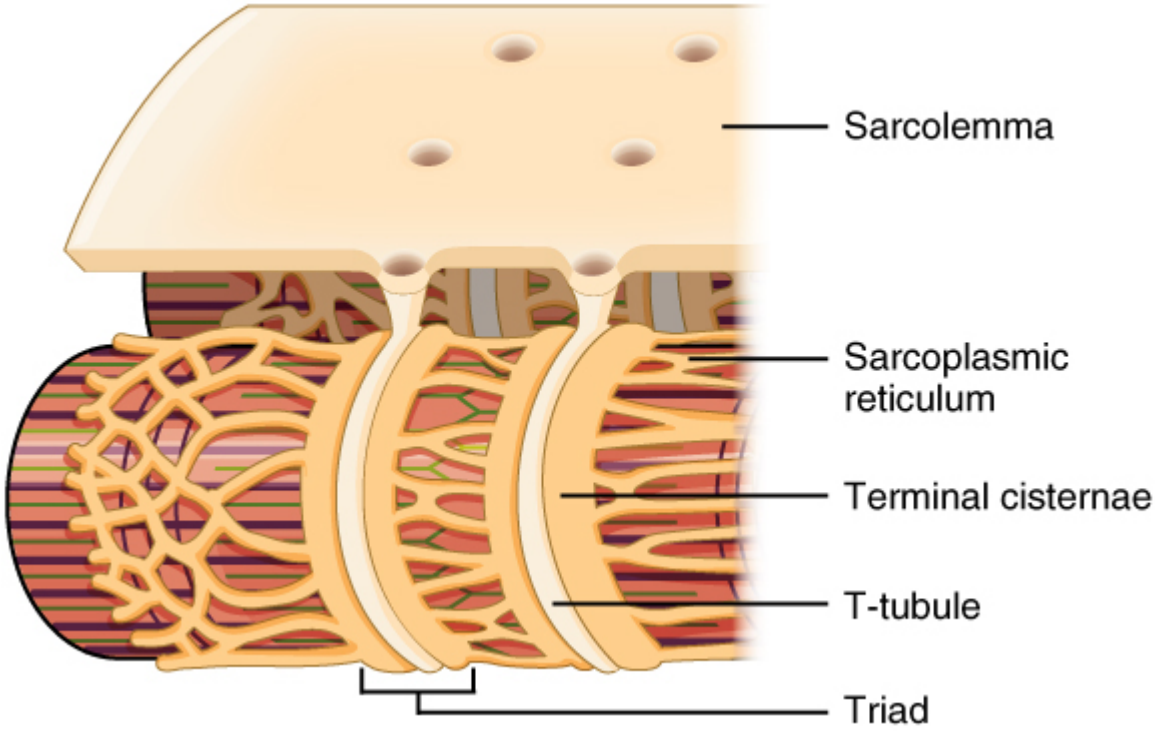
Sarcoplasmic Reticulum and T Tubules



T-tubules and sarcoplasmic reticulum

There are two sets of tubules within skeletal muscles fibers that carry out critical functions during muscle contractions: the sarcoplasmic reticulum and the T-tubules.

T-tubules (transverse tubules) are invaginations, or indentations, of the sarcolemma (1). They are formed much like a young picky-eater poking holes in his mashed potatoes. T-tubules communicate with the extracellular

space and are filled with extracellular fluid. They are located on the sarcomere at the point where the A band and I band overlap. The T-tubules are flanked on either side by dilated regions of the cell's endoplasmic reticulum—the sarcoplasmic reticulum (2).

Sarcoplasmic reticulum (SR) is an elaborate network of smooth endoplasmic reticulum that surrounds and encases each myofibril, much like a loosely knitted sweater that covers your arms (3). It stores calcium which can then be released into the sarcoplasm when an action potential is conducted along the sarcolemma of the T-tubule. Most of the sarcoplasmic reticulum runs parallel to the myofibrils, but there are right-angle enlargements of the SR at the A band/I band junctions that flank the T-tubules. These enlargements are known as **terminal cisternae** ("end sacs") (see the image above; 4). One T-tubule along the two terminal cisternae that parallel it form the **triad (5)**. The triad is critical in skeletal muscle function. At each triad, the T-tubule membrane contains large numbers of voltage-dependent proteins called **dihydropyridine (DHP)** channels or L-type calcium channels (6). Although these are called channels, they do not allow calcium to move through them; rather, they are physically linked to calcium release channels on the terminal cisternae known as **ryanodine** receptor channels **(RyR) (7)**. When the membrane is depolarized by an action potential, the DHP channel detects a depolarization and causes the RyR channels to open, resulting in the release of calcium from the terminal cisternae of the SR (more on this in the next unit). To ensure a large concentration gradient for calcium is present at the terminal citsterna, each ryanodine channel as an addition protein linked to it called **calsequestrin (8)**. This protein binds up calcium ions so that they don’t diffuse throughout the long network of tubes of the sarcoplasmic reticulum. The binding is very low affinity, but enough to keep calcium ions near the channel. This arrangement ensures that once the ryanodine channel is triggered to open, there will be a substantial calcium gradient to exit through the channel and into the sarcoplasm.

Neuromuscular Junction, Excitation-Contraction Coupling

Muscle Contractures and Cramps