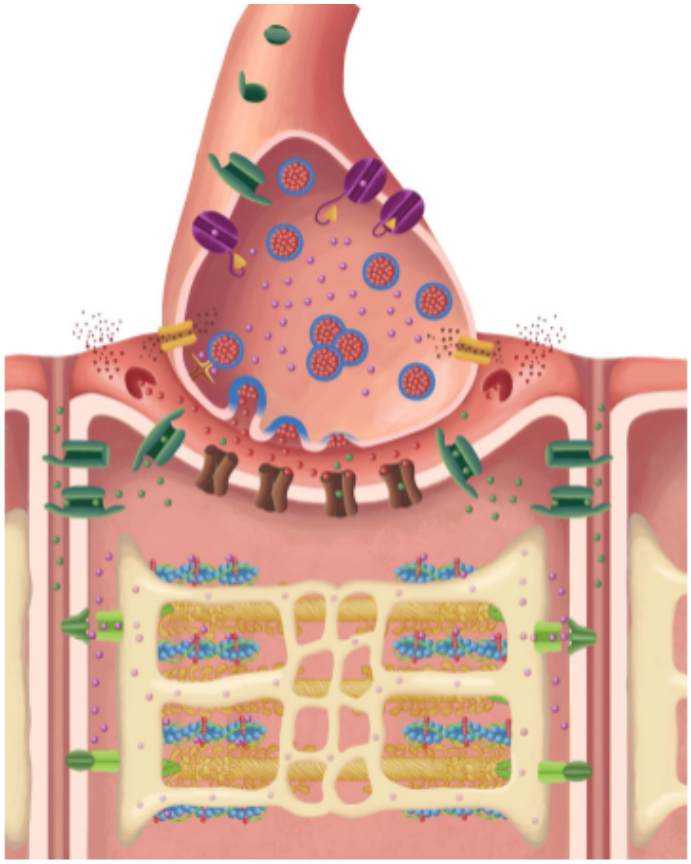
7.3.1

Neuromuscular Junction, Excitation-Contraction Coupling, and Sliding Filament Theory

An important part of understanding the full story of muscle contraction is understanding how a nerve communicates an electrical signal to a muscle fiber. To help with this, you should complete the following steps before reading further.

Step 01

Download a page sized image of the neuromuscular junction.



Neuromuscular Junction. Image drawn by BYU-Idaho student Spring 2013

Step 02

Complete an image labeling tutorial and label your own blank image.

Step 03

With your newly labeled image in hand, finish the rest of the reading on this page.

In order for these muscle fibers to contract, there needs to be an *electrical event* (an *action potential*) that is followed by a *mechanical event* (the contraction of the muscle fiber). Because you have already learned about the resting membrane potential and the action potential, we'll move past that and talk about the **sliding filament model of muscle contraction.**

Recall that we have already mentioned the fact that the thick and thin myofilaments slide over each other, like the parts of an extension ladder. The proteins themselves don't shorten. The muscle contraction and shortening occur as the myofilaments grip each other, slide past each other, and shorten the sarcomeres. Thus, this is known as the *sliding filament model of muscle* contraction. Let's also remember that in order for action potentials to both start and propagate (travel), it is necessary for various *ion* channels to open and close at just the right time. Some of these ion channels open in response to the binding of a *ligand*—an atom or molecule that binds to a receptor and stimulates a specific response. These types of ion channels are known as *ligand-gated ion channels.* Other ion channels open in response to a change in *voltage (*electricity) and are known as *voltage-gated ion channels*, and others respond because they are mechanically linked to another channel and are knows as *mechanically-gated ion channels.* Now, we'll discuss the sequence of events that occur when an action potential reaches the end of the motor neuron.

1. An action potential arrives at the axon terminal of a somatic motor neuron. The axon terminal of the motor neuron connects to the muscle fiber via the neuromuscular junction (a synapse).
2. The arrival of the action potential stimulates *voltage-gated Ca2+ channels* in the axon's membrane to open, and Ca2+ enters the axon terminal from the extracellular space. *Note: these channels are on the neuron, not the muscle, be careful not to mistake these channels for the *voltage-gated Ca2+ channels* or DHP found in the T-tubule of muscle cells.
3. The *axon terminal* contains *synaptic vesicles* filled with the neurotransmitter *acetylcholine (ACh)*. The increased Ca2+ levels is the signal that stimulates exocytosis of these synaptic vesicles and the release of ACh into the synaptic cleft.
4. The ACh diffuses across the synaptic cleft, binding to and activated ligand-gated ion channels (nicotinic type I) on the sarcolemma of the post synaptic tissue (the muscle fiber). This specialized region of the sarcolemma is known as the **motor end plate**, and this is the location of the ACh receptors (nicotinic type 1).
5. ACh binding causes the channel to open, hence the name *ligand-gated*. These ion channels are permeable to both Na+ and K+. However, more Na+ diffuses into the cell than K+ diffuses out of the cell. This may seem odd since both would be moving down their concentration gradients. The difference has to do with the charge on the membrane. Since the inside of the cell is negative, which will attract Na+, Na+ will be moving down **both** its concentration and its electrical gradients. Potassium, on the other hand, would move down its concentration gradient but ***against*** its electrical gradient (the negative charge inside the cell will attract the K+). The Na+ entering the cell *depolarizes* the sarcolemma, which then will cause the closely associated voltage-gated Na+ channels to open, initiating an action potential that spreads out from the neuromuscular junction. The action potential not only travels across the sarcolemma but also down the T-tubules. Remember, T-tubules are just invaginations (inward protrusions) of the sarcolemma and are filled with extracellular fluid that is high in sodium (Na+) and low in potassium (K+). Also, please notice that the ACh receptors are *ligand-gated,* but movement of Na+ through them causes the closely associated v*oltage-gated* Na+ channels to open, resulting in *generation* and *propagation* of an action potential.
    a. While the action potential spreads, let's take a break and describe how the stimulation of the ACh receptors is terminated. For the muscle to relax, ACh must be removed from the synaptic cleft. This is done when ACh is cleaved (split) by an enzyme that resides in the cleft called *acetylcholinesterase.* This enzyme splits ACh into its two components, *acetate (acetyl)* and *choline*, rendering it nonfunctional. The acetate portion of acetylcholine diffuses out of the synaptic cleft. The *choline*, which is an essential nutrient in the Vitamin B group (B4), is taken up by the axon terminal, where it is recycled to make more acetylcholine. Although our bodies can make choline, we cannot produce enough for our needs and must get it in our diet and recycle what we have.
6. The action potential does its thing (if you have forgotten the basics of action potentials, review module 5).
7. As the action potential spreads along the sarcolemma and the T-tubules, the resultant change in potential causes other voltage-gated channels in the T-tubule to respond. These channels are called dihydropyridine channels (DHP) or L-type Ca2+ channels and are mechanically linked to ryanodine receptor channels (RyR), which are calcium channels located in the sarcoplasmic reticulum membrane. These two protein channels span the distance between the T-tubule and the terminal cisternae of the sarcoplasmic reticulum. In response to the change in membrane potential, the DHP channel causes the RyR to open and allows Ca2+ ions to flow through it (RyR) from the sarcoplasmic reticulum into the sarcoplasm. These calcium ions bind to troponin, causing it to move the tropomyosin molecules off of the active sites on each G-actin molecule.
8. Uncovering the active sites allows the myosin heads to bind to the actin binding sites, forming **cross bridges**. In the resting state, the myosin head is "cocked" and ready to go. It also has ADP and phosphate (Pi) attached to it. The binding to actin releases energy, some of which is released as heat, and the remaining is capture in the phosphate bond which breaks the bond, releasing Pi and causing the myosin head to bend. This bending or **power stroke** forcefully pulls the actin past the myosin. During the power stroke, the ADP is also released from the myosin. Recall that in the arrangement of the thick filaments, half of the myosin molecules are pointing one way,

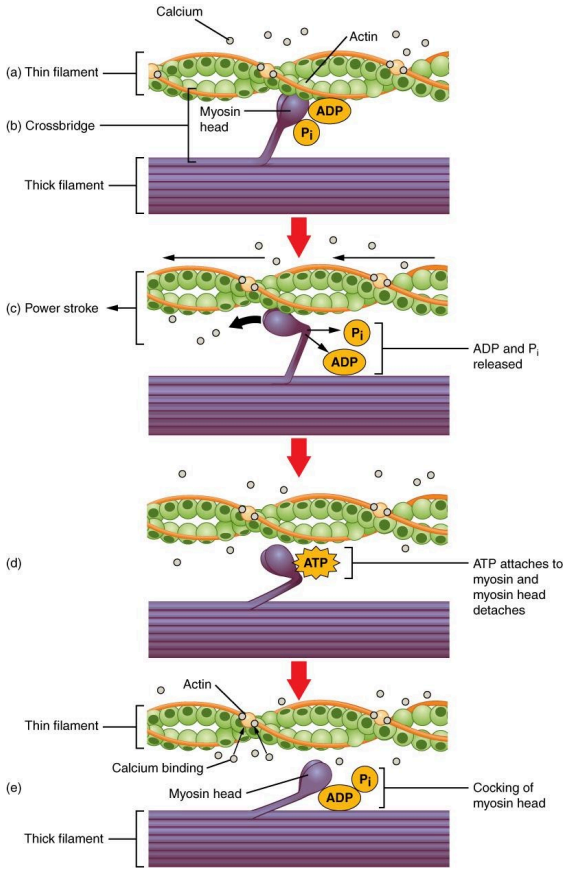
and half are pointing the other. Since the myosin heads on the opposite ends of the thick filaments all pull towards the middle, the overall effect is to cause the sarcomere to shorten. As all of the sarcomeres in the muscle fiber shorten, the entire muscle shortens or contracts.

9. In order for significant shortening of a skeletal muscle fiber to occur, the myosin heads must detach from the G-actin active sites and then re-attach to a different active site further along the neighboring actin molecule. This is rather similar to the fact that in order to climb a ladder, we must pull ourselves up a rung and then let go and move our hands and feet to higher rungs. In order for this release to occur, each myosin head must bind an ATP molecule. The binding of ATP to the myosin head allows it to release from the actin. The ATPase then hydrolyzes the ATP into ADP and a phosphate group, which causes the head to "re–cock" (the **recovery stroke),** preparing it for the next power stroke. Hence, binding ATP allows the head to release, and hydrolysis of ATP re–energizes the head for the next power stroke. During a single muscle cell contraction, each myosin molecule undergoes the entire cross-bridge cycle many times—a process known as **cross-bridge cycling**. As long as Ca2+ is present and the active sites are exposed, the process will continue.

One other important concept: Using the analogy above, when we climb a ladder, we don't take both hands off of the rungs at the same time. Likewise, when muscles contract, the myosin heads are cycling asynchronously, meaning that they don't all bind actin at the same time, and they don't all release at the same time. At any given time, the 300 or so myosin heads in one thick filament will be at different stages of the cross-bridge cycle.

The movement of myosin heads occurs in two phases:

1. The *power stroke* occurs when the myosin heads bend and ratchet the actin molecules past the myosin.
2. The *recovery stroke* involves the myosin heads detaching from actin and being cocked back into the high energy position to prepare for the next power stroke.

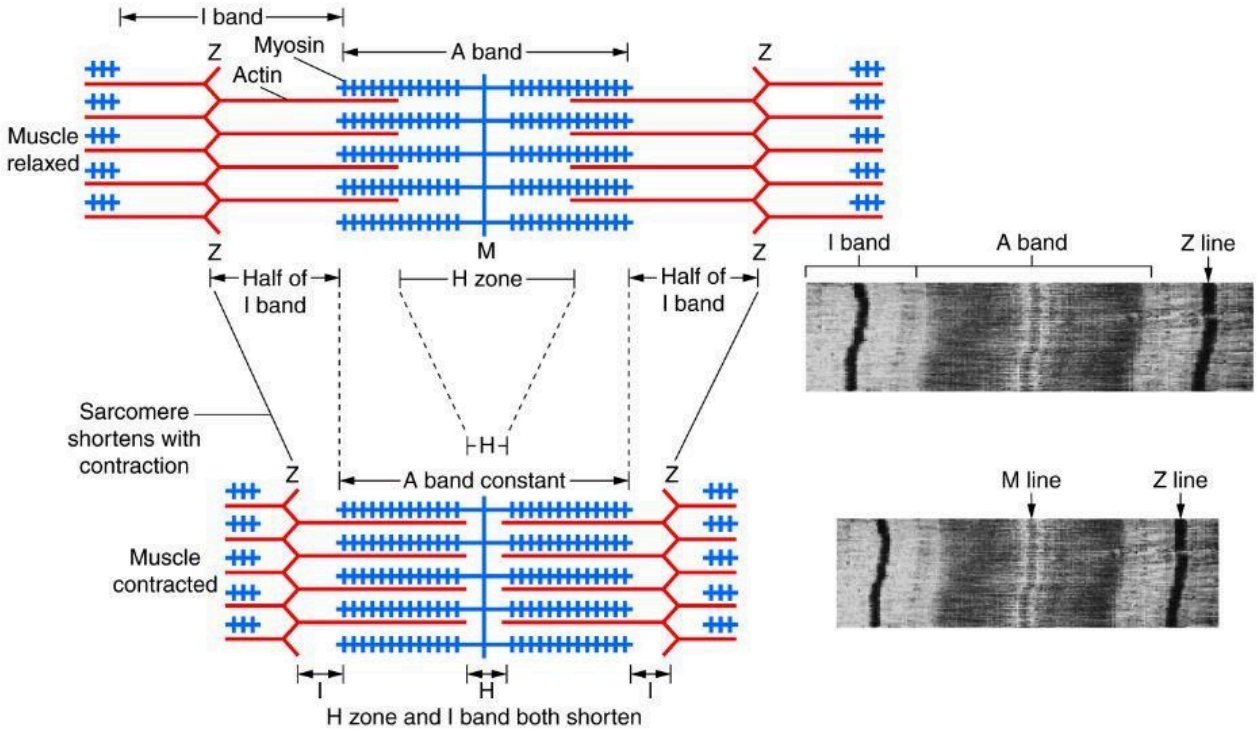


Skeletal Muscle Contraction. *Downloaded from Wikimedia Commons Dec 2013; Author: OpenStax College; Source:* https://books.byui.edu/-TZVB

(a) Calcium binds to Troponin and active site on actin exposed. (b) Myosin binds to Actin forming cross-bridge. (c) Phosphate released in a power stroke causing the myosin head to pivot and releasing ADP/Phosphate group released. (d) ATP attached to myosin head detaching cross bridge. (e) Myosin head hydrolyzed ATP to ADP and phosphate turning myosin back to ready position.

Relaxation begins when the release of acetylcholine ceases at the neuromuscular junction. The acetylcholine already in the synapse is broken down by acetylcholinesterase, ending action potential generation and propagation. This stops the release of Ca2+ from the sarcoplasmic reticulum (SR). Ca2+ ions diffuse away from troponin as the Ca2+ is actively transported back into the SR. This allows the troponin-tropomyosin complex to resume its resting position, blocking the active binding sites on the individual G-actin molecules. This prevents cross bridges from reforming and results in muscle relaxation. Even though each step begins the events of relaxation, the muscle will not fully relax until all calcium is pumped back into the SR.

To quickly review, the sliding filament model of muscle contraction explains the fact that when skeletal muscle fibers contract, the individual proteins (actin and myosin) don't shorten. Rather, they slide over each other. ATP is necessary for the detachment of myosin heads from actin. Notice also that when a sarcomere contracts, both the H zone and the light I band shrink in width, while the dark A band doesn't appear to narrow.



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