# Skeletal Muscle

Mimi Jakoi, PhD
Jennifer Carbrey, PhD

The underlined headings correspond to the two skeletal muscle videos.

## 1. Introduction and contraction

### Muscle Types

There are three types of muscle in the human body: skeletal, cardiac, and smooth. Each muscle cell is called a fiber. The three fiber types differ in structure and function within the body.

**A Skeletal muscle fiber** is a large (10-100 μm diameter), multinucleated syncytium. Those fibers attached to bone, mediate voluntary movement of the skeleton, and/or maintain body position and posture. Others such as the extra-ocular muscle of the eye and the tongue are not attached to the skeleton but provide precise voluntary movements. Skeletal muscle contraction is controlled by the somatic nervous system.

**Cardiac muscle fibers** are small (10-15 μm in diameter) cells with one (or two) nuclei that are connected to each other by gap junctions. These cells form a functional coordinated unit found in the walls of the heart and at the base of the large veins that empty into the heart. Cardiac muscle is regulated by the autonomic (parasympathetic and sympathetic) nervous system.

**Smooth muscle cells** are small (2-15 μm in diameter) cells found as bundles or sheets in the walls of blood vessels, the GI tract, and uterus. Where smooth muscle cells are connected by gap junctions, the bundle or sheet acts as a single coordinated unit. Smooth muscle is regulated by the autonomic nervous system.

All three types of muscle contain the contractile proteins, **myosin** and **actin**, contract to generate force, and share 3 common principles:

1. **Sliding filament mechanism** in which myosin filaments bind to and pull actin filaments as a basis for shortening.
2. Regulation of contractile proteins by calcium ions.
3. Changes in membrane potential lead to a rise in intracellular calcium resulting in contraction (**E-C coupling**).

### Skeletal Muscle Structure

During early development of skeletal muscle, undifferentiated myoblasts fuse to form a single multinucleated cylinder or fiber. Differentiation is completed by birth after which the muscle fibers increase in size but not number. Adult muscle fibers can vary in length from a few millimeters to almost a meter.

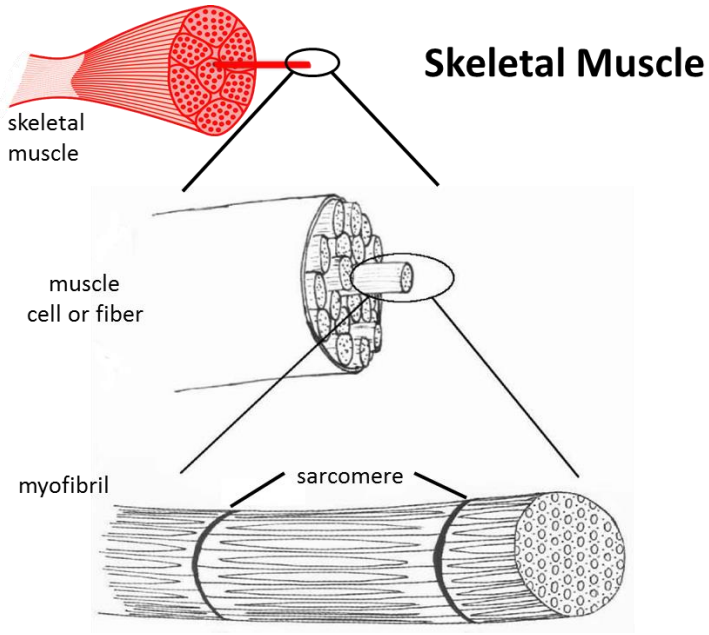


**Figure 1**. Organization of skeletal muscle. Top image by image by OCAL (modified), http://www.clker.com/profile-1068.html, public domain , middle and bottom image by Rama (modified), http://commons.wikimedia.org/wiki/File:Skeletal_muscle.jpg, Creative Commons Attribution-Share Alike 3.0 Unported license

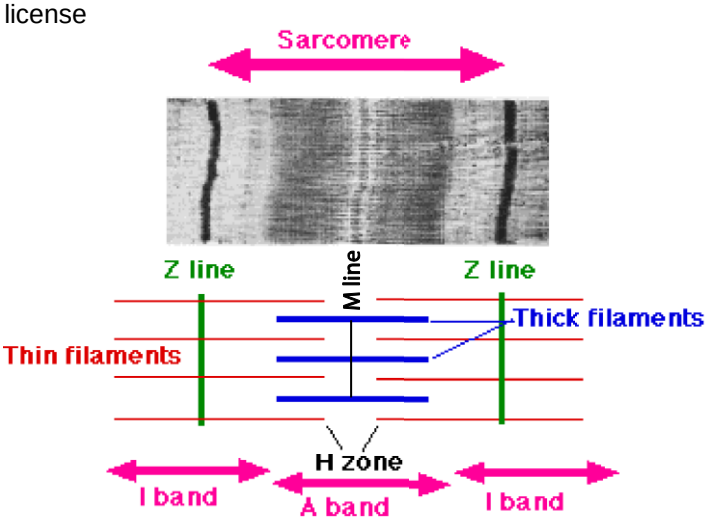


**Figure 2**. Sarcomere structure. Image by Sameerb (modified), http://commons.wikimedia.org/wiki/File:Sarcomere.gif, public domain

In the body, connective tissue surrounds each muscle fiber, each bundle of muscle fibers (called a **fascicle**), and several fascicles to form a muscle. The connective tissue wrapping is essential to force transduction. At the end of the muscle, the connective tissue continues as a tendon which usually attaches the muscle to bone.

Skeletal muscle often overlaps a joint in the limb thereby allowing for lever action. In this arrangement a small degree of muscle cell shortening produces a large movement of the limb. The limb muscles are arranged in pairs such that muscles on opposite sides of the limb act in opposition. For example, **flexors** contract to close the angle at the joint and **extensors** contract to open the angle at the joint.

Each muscle fiber (single cell) is filled with longitudinally arranged **myofibrils** whose number determines the force generating capacity of the muscle fiber (Fig. 1). Each myofibril extends the length of the muscle fiber. **Myofibrils** are composed of **myofilaments** which are polymers of the contractile proteins, actin and myosin (Fig. 1). **Actin is called the thin filament; myosin the thick filament.**

Thick and thin filaments are organized into a series of repeating functional units called **sarcomeres** which give the striated appearance in the phase contrast microscope of skeletal (and cardiac) muscle. The striations are made of dark and light bands (Fig. 2), which are called A and I bands, respectively. Places where there is only actin are the I bands and anywhere there is myosin are the A bands.

Thin filaments are anchored to a dense line called the Z line which bisects the I bands. The sarcomere extends from one Z line to the next Z line (Fig. 2).

Thick filaments comprise the A band. These are polarized filaments in which the myosin tail region is anchored to the M line in the center of the sarcomere and the globular region (myosin head) extends away from the M line towards the Z lines. There are no myosin heads and no overlap with actin in the area immediately adjacent to the M line. This is called the H zone (Fig. 2).

The space between the thick and thin filaments contains the myosin heads. They are called cross bridges because they extend from the parallel axis of the thick filaments towards the thin filaments. During muscle contraction, these cross bridges make contact with the thin filaments (actin) and exert force on them.

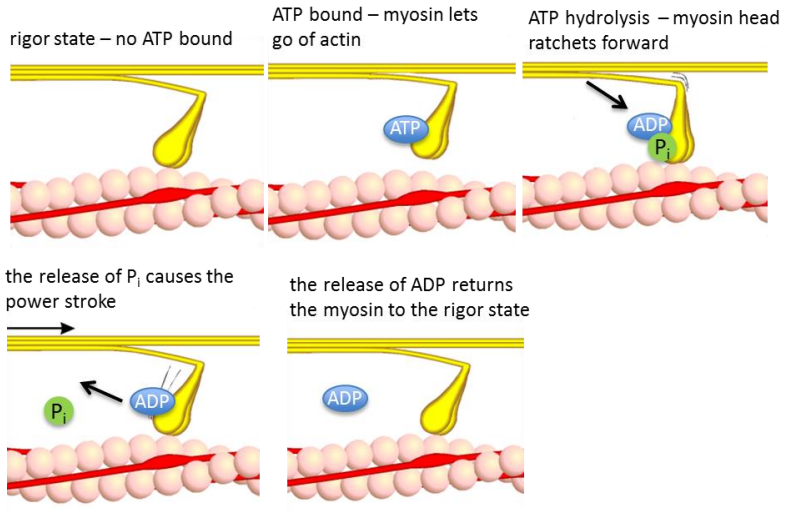


**Figure 3**. Cross bridge cycling. Image by Moralapostel (modified), http://commons.wikimedia.org/wiki/File:Querbr%C3%BCckenzyklus_1.png, Creative Commons Attribution-Share Alike 3.0 Unported license

## Molecular Mechanisms of Contraction

**Contraction** is the activation of the force generating sites (cross bridges = myosin heads) within the muscle fibers and does not necessarily mean shortening. (For example, the muscle will contract as you hold a tray of glasses but does not shorten.) The force generated is called tension.

**Relaxation** is the cessation of force generating activity and a decline in tension.

**Sliding filament mechanism of contraction** states that the skeletal muscle fiber shortens when the overlapping thick filaments and thin filaments slide past one another, causing the Z lines of each sarcomere to move towards the M line (Fig. 2). There is no change in the length of either the thick or thin filaments. Which band - A, I or H also shortens?

Movement of the thin filaments toward the M line is powered by the myosin ATPase located in the myosin head (cross bridge). During shortening, the myosin cross bridges attach to the thin filament (actin), undergo a conformational change (power stroke) which pulls the actin filament toward the M line similar to the rowing action of oars moving through water (Fig. 3).

Energy (ATP) is needed to break a cross bridge, i.e., release the myosin head from its contact with actin. In the absence of ATP, cross bridges remain attached to actin in a state called **rigor** (Fig. 3).

**Regulation of contraction** involves Ca++. In skeletal muscle, regulation of contraction occurs on the thin filament by a complex of two proteins, **tropomyosin** and **troponin**. Tropomyosin lies along actin, blocking the myosin binding site. Troponin is anchored to tropomyosin and the binding of Ca++ to troponin causes tropomyosin to shift thereby exposing the myosin binding site on actin. Contraction will continue in the presence of Ca++ and ATP. Relaxation occurs when Ca++ is removed.

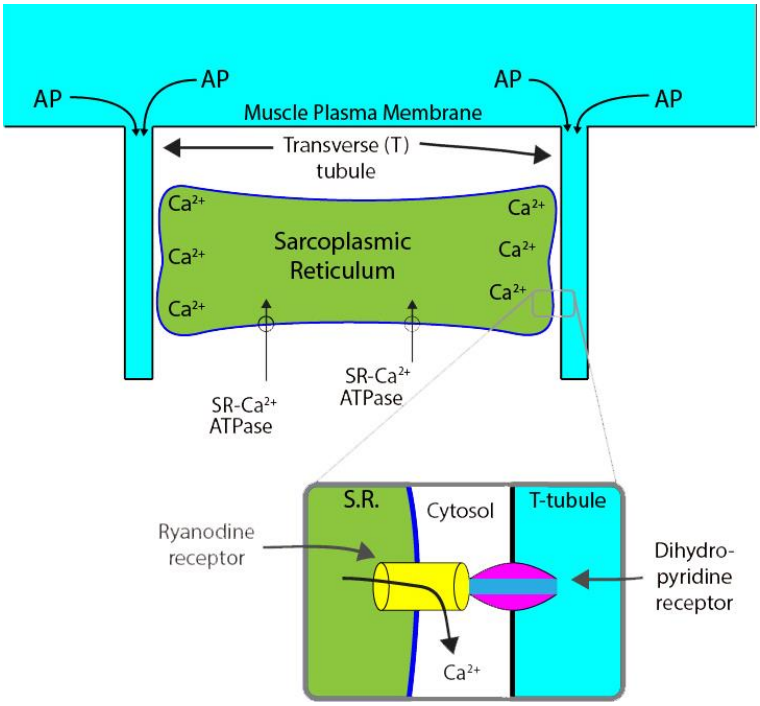


**Figure 4**. Excitation-Contraction Coupling. Image by Rick Melges, Duke University

In skeletal muscle, Ca++ is stored within the cell in a membrane bound compartment called the **sarcoplasmic reticulum** (SR). The SR wraps around myofibrils. Ca++ is released from the SR into the cytoplasm in response to an electrical signal (action potential). The action potential opens a voltage gated channel in the T tubule (invagination of the plasma membrane) which is adjacent to the SR (Fig. 4). This voltage gated channel is called the dihydropyridine receptor. Activation of the dihydropyridine receptor in turn opens a Ca++ channel (ryanodine receptor) on the SR and Ca++ enters the cytoplasm (Fig. 4). Ca++ is taken back up into the SR from the cytoplasm by the SR CaATPase.

**Transverse tubule system** or T tubules are invaginations of the sarcolemma located between the SR terminals. The T tubule membrane contains the voltage gated Ca++ channels (dihydropyridine receptors) which open with depolarization of the membrane (Fig. 4).

**E-C coupling (excitation-contraction coupling)** Figure 4 refers to the electrical events which trigger a contraction. Each skeletal muscle is innervated by an alpha motor neuron. An action potential arriving at the neuromuscular junction releases the neurotransmitter acetylcholine from the presynaptic site. Acetylcholine transverses the synaptic cleft and binds to nicotinic receptors on the post synaptic muscle. These ligand (acetylcholine) gated Na+ channels open resulting in a graded potential (EPSP) sufficiently large to depolarize the sarcolemma to threshold. The voltage gated Na+

channels open and trigger an action potential. As this action potential moves along the muscle plasma membrane (sarcolemma), it sweeps down the T tubules, opens the dihydropyridine receptors and thereby triggers Ca++ release from the SR (Fig. 4). Contraction ensues. During contraction the SR CaATPase removes Ca++ from the cytoplasm (Fig. 4). This Ca ATPase will restore cytosolic Ca++ levels in less than 30 msec after the nerve impulses stop.

# 2. Tension and metabolism

## Muscle Tension

The mechanical response of a single muscle fiber to a single action potential is called a **twitch**.

Following an action potential there is brief period before **tension**, the force exerted on an object**,** develops. This is known as the **latent period**. The action potential of a single impulse lasts only 2 milliseconds. The associated contraction time (twitch) lasts for 10-100 milliseconds. This means that repeated stimulation of a skeletal muscle will cause summation of the contractions until there is no relaxation and fused tetanus is reached (Fig 5). Not all muscle fibers have the same contraction times. Some fast fibers contract in 10 milliseconds; slower fibers take 100 milliseconds or longer. The duration depends on the SR-ATPase activity.

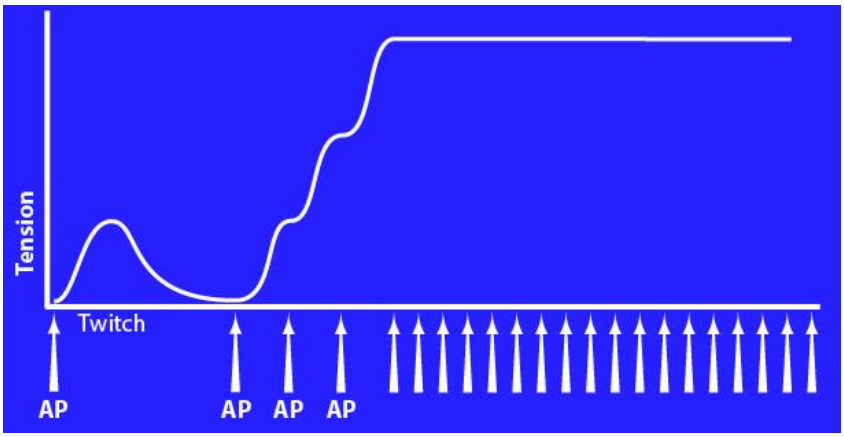


**Figure 5**. Muscle contraction in response to action potentials. Image by Rick Melges, Duke University

**Tension & Load.** The tension generated varies with load. In order for a muscle to shorten and thereby move a load, muscle tension must exceed the opposing load. Maximal velocity of shortening occurs with no opposing load. In **isotonic contractions**, the muscle shortens and moves the load. Higher loads lengthen the latent period, slow the velocity of shortening, shorten the duration of contraction, and shorten the distance moved. In **isometric contractions**, the muscle develops tension but does not shorten (or lengthen) because the opposing load equals or exceeds the force generation of the muscle.

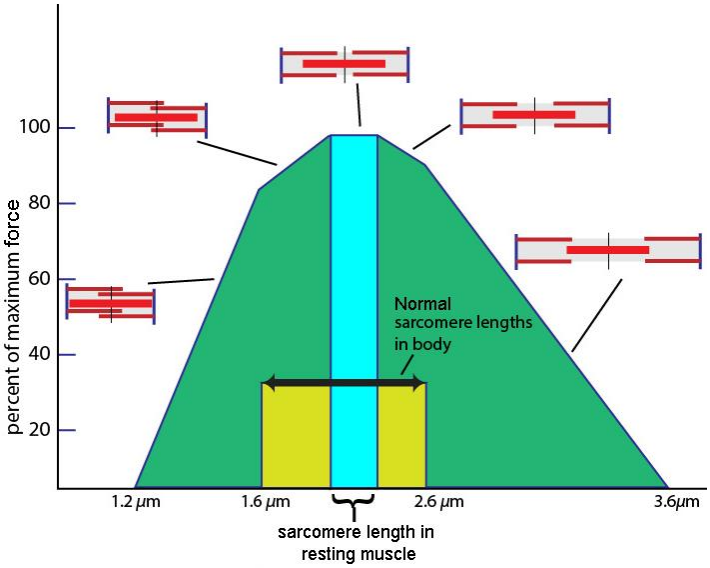


**Figure 6**. Variation in active tension with muscle fiber length. Image by Rick Melges, Duke University

**Length-Tension Relationship.** The maximal amount of force (tension) a muscle can generate is determined by the degree of overlap of the thick and thin filaments (Fig. 6). The basal state and slightly stretched state provide optimal force generation (Fig. 6). Because the muscle is anchored to bone within the body, conditions of excess stretch or non-overlap and excess contraction are avoided. However, with injury, irreversible damage to the actin and myosin filaments can occur.

## Skeletal Muscle Metabolism

Muscle fibers depend on ATP to produce force. There are three pathways a muscle fiber uses to make ATP. **Creatine phosphate** converts ADP to ATP in a single, fast reaction. As a result, 4 moles of ATP are produced per minute from creatine phosphate. However, the stores of creatine phosphate are limited so they are used up in the first 10 seconds of intense exercise. Creatine phosphate is the primary source of ATP during a short, high intensity activity such as the 100 meter dash. **Anaerobic metabolism** burns glucose as well as the large stores of muscle glycogen (a glucose polymer) to produce lactic acid and ATP in the absence of oxygen. Since only glycolysis is used, 2.5 moles of ATP can be produced per minute. Anaerobic metabolism is used during the first 1.5 minutes of high intensity activity and is the primary source of ATP for the 400 meter dash. **Aerobic metabolism** uses glycogen, blood glucose, or fatty acids to produce ATP, $CO_2$, and water in the presence of oxygen. Only 1 mole of ATP is made per minute but the available fuel sources are limited only in extreme circumstances. Aerobic metabolism is the primary source of ATP during endurance activities such as a marathon.

With repeated stimulation, the tension generated by a muscle fiber decreases. This is called **fatigue**. This is not due to a lack of ATP and is not well understood. Several factors have been implicated including:

a. Buildup of extracellular K+ which leads to a persistent depolarization of the cell.
b. Buildup of metabolites which affect the activity of proteins such as the SR-CaATPase.
c. Buildup of ADP and $P_i$ in the cytoplasm, which inhibits cross bridge detachment and slows cross bridge cycling.
d. Decrease in fuel stores, glycogen, fatty acids and glucose.

## Skeletal Muscle Fiber Types

Skeletal muscle fibers are classified into one of three types distinguished by the speed of their myosin ATPase and preferred metabolism:

1. fast, glycolytic fibers fatigue quickly
2. fast, oxidative, glycolytic fibers resist fatigue
3. slow, oxidative fibers resist fatigue

Fast fibers undergo cross-bridge cycling about 4 times faster than slow fibers. Oxidative fibers contain lots of mitochondria for aerobic metabolism during tasks that require endurance. Glycolytic fibers use only small amounts of oxygen and are larger in diameter than oxidative fibers. As a result of their larger diameter, each glycolytic fiber can produce more tension than an oxidative fiber. Most skeletal muscles include all three fiber types. However, each motor unit contains only a single type of muscle fiber. Motor units containing slow, oxidative fibers contain fewer fibers than motor units containing fast fibers.

**Recruitment** is the process of activating different types of muscle fibers within a fascicle in response to need. Recruitment starts with slow, oxidative fibers that do not provide a lot of force but can provide fine muscle control. If more tension is needed, fast-oxidative-glycolytic fibers can be recruited. Finally, fast, glycolytic fibers that fatigue rapidly increase tension the most dramatically are recruited.