Skeletal Muscle – Structure & Function.
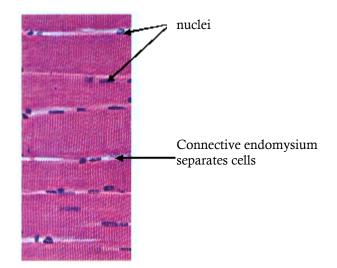
Learning Objectives.

At the end of this course, you should be able to :
1. **describe the structure of skeletal muscle**
2. **understand the function of a motor unit**
3. **give a basic description of the mechanism of muscle contraction**
4. **discuss the main sources of energy for skeletal muscle**
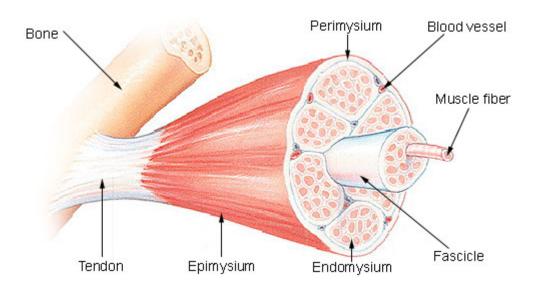5. **know the difference between isometric and isotonic muscle contraction.**

Structure.

Skeletal muscle, as the name suggests, is usually associated with the skeletal system. It is also called striated muscle because of the presence of alternating dark and light bands along the length of its fibres, or voluntary muscle because it is subject to voluntary control (although involuntary, reflex contractions and spontaneous, automatic movements also occur).

nuclei

Connective endomysium separates cells

Mature skeletal muscle cells are long and slender; they range from 10 to 60 micrometers in diameter and may extend from one end of a muscle to the other, in some cases reaching a length of as great as 30cm. Since their length is much greater
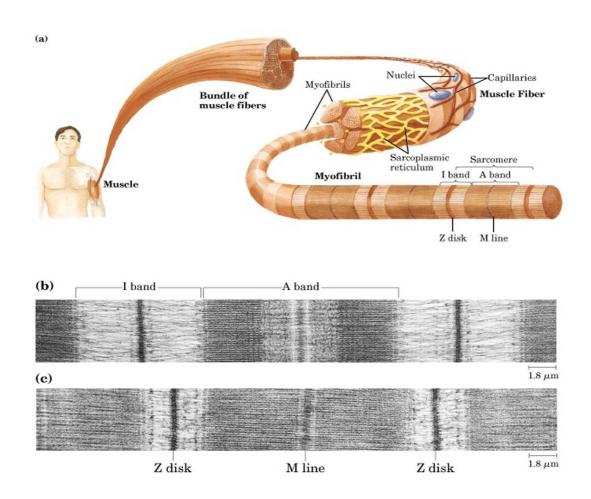
than their width, these cells are called fibres. Each muscle fibre is multinucleated and is surrounded by an electrically polarized membrane - the sarcolemma . The nuclei are usually located just under the sarcolemma.

The entire muscle consists of a number of bundles of muscle fibres known as fasciculi. Surrounding each fibre and filling in the space between fibres within a fasciculus is a delicate connective tissue called the endomysium. Each fasciculus is bounded by a stronger connective tissue sheath, the perimysium, which in turn is continuous with a tough connective tissue, the epimysium, enveloping the whole muscle. The superficial fascia (subcutaneous adipose tissue) forms a covering over the entire muscle trunk, and various arrangements of connective tissue, some having specific names, others generally referred to as deep fascia, surround or penetrate between individual muscles or groups of muscles.

When viewed under the microscope, the skeletal muscle fibre is seen to have regular striations. These striations are due to transverse alternating dark and light bands on the myofibrils, which are parallel, threadlike structures in the sarcoplasm (muscle cytoplasm) of a muscle fibre. Myofibrils, the smallest elements of the muscle fibre visible under the light microscope, are the contractile units of the fibre. With the electron microscope the striations on the myofibrils can be seen to arise from the
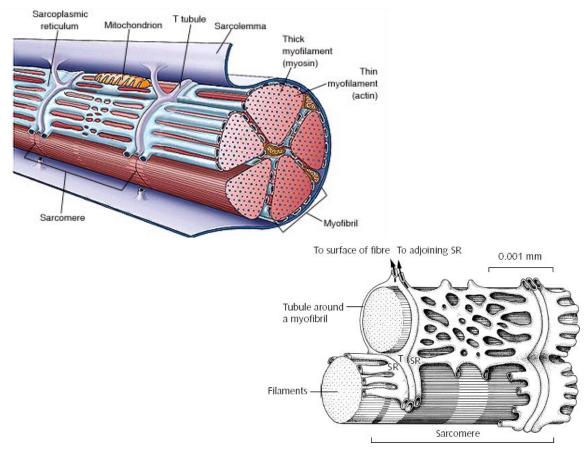
arrangement of its subunits into thick and thin filaments. The thick filaments are composed largely of the protein myosin, the thin filaments of three proteins - actin (the principal one), tropomyosin, and troponin. The dark, or A band of the myofibril corresponds to the thick filaments, overlapped on either end with thin filaments; the light, or I band, corresponds to the region where there are only thin filaments.

(a)

Muscle

Bundle of muscle fibers

Myofibrils

Nuclei

Capillaries

Muscle Fiber

Myofibril

Sarcoplasmic reticulum

Sarcomere

I band   A band

Z disk   M line

(b)

I band

A band

1.8 μm

(c)

Z disk

M line

Z disk

1.8 μm

Two additional markings are of importance - the Z line, a narrow band in the central region of the I band representing a structure to which the thin filaments are attached on either side, and the H zone, a lighter region, located in the central portion of each A band, into which the thin filaments do not penetrate. The area between two adjacent Z lines, called a sarcomere, represents the repeating unit of a myofibril, each about 2.5 micrometers long in resting muscle. The shortening of a sarcomere during muscular contraction will be discussed further when contraction is described.

Sarcotubular Systems.

Electron micrographs show myofibrils to be surrounded by structures made up of membranes in the form of vesicles and tubules. These structures form two systems. One consists of what are called T (for transverse) tubules, which are actually invaginations of the membrane of the muscle fibre. The other, the principal system, called the sarcoplasmic reticulum, consists of tubules running parallel to the myofibrils. Each T tubule runs between a pair of sacs formed by fusion of the sarcoplasmic reticulum. These three transverse structures make up what is known as a triad. The triad is important functionally because, although there is no open continuity between the sarcoplasmic reticulum and the T tubules at the triad, the close association of the two systems at this site enables the T tubules to function as a conduit for transmission of the electrical impulse, the normal muscle stimulus, to the sarcoplasmic reticulum. The arrival of the electrical impulse activates the release from the sarcoplasmic reticulum of calcium, the triggering agent for muscle contraction.
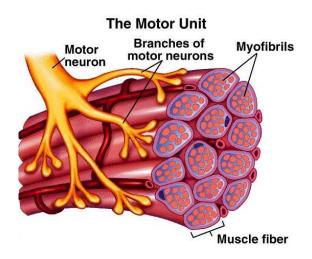
KEY LEARNING POINTS.

1. Skeletal muscle cells are long and thin, known as fibres, and are surrounded by the sarcolemma.

2. Striations are apparent due to the myofibrils, which are the contractile units of the fibre.

3. The myofibrils are made up of thick and thin filaments, containing the proteins myosin, actin, tropomyosin, and troponin.

4. The relative arrangement of these filaments is important for muscle contraction.

5. The sarcoplasmic reticulum and the T-tubules surround the myofibrils, and their role is to conduct electrical impulses so as to initiate muscle contraction.

Muscle Contraction

The Motor Unit.

As a result of terminal branching, a single nerve fibre innervates on average about 150 muscle fibres. All of these fibres and the single nerve fibre innervating them are called a motor unit because muscle fibres of the unit are always excited simultaneously and contract in unison. It is important to note that terminal divisions of a motor neuron are distributed throughout the muscle belly. Stimulation of a single motor unit, therefore, causes weak action in a broad area of muscle rather than a strong contraction at one specific point.
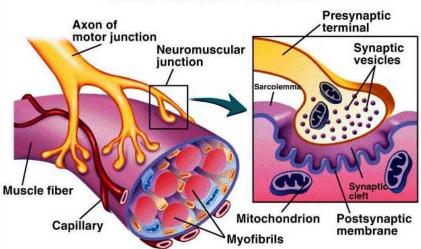

Muscles controlling fine movements are characterized by the presence of a few muscle fibres in each motor unit, i.e. the ratio of nerve fibres to muscle fibres is high. For instance, each motor unit present in the ocular muscle contains less than 10 muscle fibres. On the other hand, gross movements, e.g. major limb muscles, may be governed by motor units containing 1000 or more muscle fibres.

Excitation of Skeletal Muscle.

Muscle fibres possess the property of being excitable. Any force affecting this excitability is called a stimulus, which, in muscle tissue, is usually conveyed by nerve fibres. The stimulus is an electrical impulse transmitted from a nerve fibre branch to a

muscle fibre at a junctional region called the neuromuscular junction. At the junction a gap, the synaptic cleft, exists between a nerve branch terminal and a recess on the surface of the muscle fibre. A nerve impulse reaching the neuromuscular junction causes the release of acetylcholine, a neurotransmitter stored in synaptic vesicles within the nerve terminal. Acetylcholine crosses the gap and acts on the membrane of the muscle fibre, causing it to generate its own impulse, which travels along the muscle fibre in both directions at a rate of about 5 meters per second and is conducted to the sarcoplasmic reticulum via the T system.
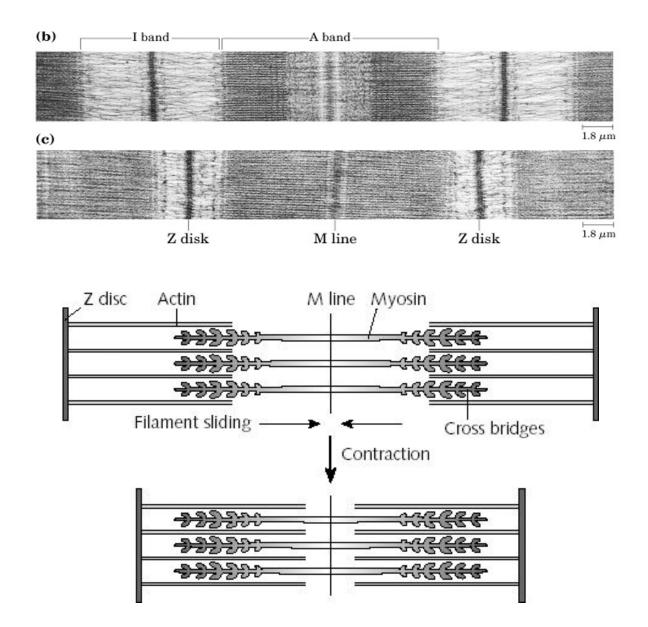

Mechanism of Contraction.

The generally accepted conception of how muscle contacts is known as the 'sliding filament model'. According to this model, the contraction is brought about by the sliding of the thin filaments at each end of a sarcomere toward each other between the stationary thick filaments. This draws the Z lines closer together, shortening the sarcomere. In sections of muscle, prepared at sequential stages of contraction, it can be seen that, as a sarcomere shortens, the I band of each myofibril (the region containing only thin filaments bisected by a Z line) narrows as the thin filaments move toward the centre of the sarcomere, while the A band (representing the length of the thick filaments) is unaltered. The H zone of the A band, the lighter, central

region not penetrated by thin filaments in relaxed muscle, disappears as thin filaments come to completely overlap the thick filaments in the contracted state. When contraction is marked, a dense zone appears in the centre of the A band as a result of overlap of thin filaments from opposite ends of a sarcomere. In cross section this overlap is identified as a doubling (over the relaxed condition) of the ratio of thin to thick filaments.

(b)

I band —— A band

1.8 μm

(c)

Z disk   M line   Z disk   1.8 μm

Z disc   Actin   M line   Myosin

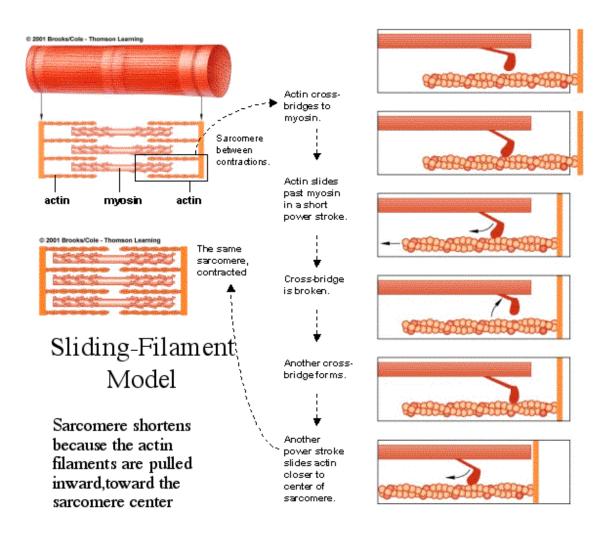Filament sliding   Cross bridges

Contraction

The movement of the thin filaments can be accounted for by cross-bridges extending from thick to thin filaments, which are utilized as mechanical pulling devices. Myosin molecules, from which thick filaments are constructed, have a globular head and linear tail. They can be readily split enzymatically (with trypsin) into two subunits. One, called heavy meromyosin, contains the globular head and a linear tail section; the other, called light meromyosin, is an all-linear tail segment. The head of heavy meromyosin, which can be enzymatically separated from the tail section, has the property of combining with actin and contains ATP-splitting enzymes. The linear light meromyosin subunits have a self-combining property. Thick filaments are assembled by tail-to-tail aggregation of myosin molecules so that in each half of the filaments the heads, which form the ends of the cross-bridges, face opposite directions . This built-in directionality explains how thin filaments at opposite ends of a sarcomere can be pulled inward toward the centre of the thick filaments.

The thin filament is an assembly of three proteins:

- actin, the principal one,
- tropomyosin,
- troponin.

Actin consists of two strands of spherical molecules coiled around one another. On the surface of each strand of actin is a filamentous tropomyosin. Troponin is a complex of three globular subunits positioned at regular intervals (about 400 angstroms apart) along the thin filament. The largest subunit of troponin, designated Tn-T, binds to tropomyosin. Another, Tn-I (the inhibitory subunit), reversibly binds to actin; when bound, the troponin complex, linked to tropomyosin and actin, seems to act as a latch, holding tropomyosin in a position that blocks the myosin binding site on actin. The latch is released when calcium binds the smallest subunit, Tn-C, causing the troponin complex to undergo a change in conformation which breaks the link between the Tn-I subunit and actin.

actin   myosin   actin

Sliding-Filament Model

Sarcomere shortens because the actin filaments are pulled inward, toward the sarcomere center

Sarcomere between contractions.

The same sarcomere, contracted

Actin cross-bridges to myosin.

↓

Actin slides past myosin in a short power stroke.

↓

Cross-bridge is broken.

↓

Another cross-bridge forms.

↓

Another power stroke slides actin closer to center of sarcomere.

The sequence of events leading to the contraction of muscle may be summarised as follows:

1. The electrical impulse travelling along the membrane of a muscle fibre reaches the sarcoplasmic reticulum via the T tubules.

2. This stimulates the release of calcium, which combines with the Tn-C subunits of troponin and induces a change in the conformation of the troponin molecules.

3. Tropomyosin moves away from the myosin binding sites on actin, and the myosin heads, charged with ATP, combine with actin (it has been suggested that the energized, force-generating state of the myosin heads is a complex of myosin with ADP and phosphate formed following the cleavage of ATP by myosin ATPase).

4. When actin and myosin interact, the energized myosin complex breaks down, providing the energy for the propulsive force (probably a swivelling of the myosin heads) for pulling the thin filaments toward the centre of the sarcomere.
5. Successive cycles, involving binding of ATP to myosin heads, detachment of myosin heads from actin, and reattachment in a new position on actin, followed by the power stroke that moves the thin filaments, result in the continued sliding of the thin filaments.
6. Contraction ends when calcium returns to the sarcoplasmic reticulum.

Rigor Complex.

The detachment of the myosin cross-bridges from actin after ATP is split can take place only after a new ATP binds to the myosin beads. The low energy complex between actin and myosin without bound ATP is called a rigor complex. Rigor complexes, unlike active actin-myosin complexes, can form in either the absence or presence of calcium. The depletion of ATP after death results in the formation of rigor complexes and accounts for the development of rigor mortis.

Energy Sources.

ATP is a direct source of energy for muscular contraction. ATP is synthesised during the aerobic breakdown of glucose and the fatty acid component of fat to carbon dioxide and water and, during glycolysis, the anaerobic breakdown of glucose (or glycogen) to lactic acid. ATP must be continuously resynthesised in muscle, since its reserves are very small. Muscle contains a small auxiliary source of high energy phosphate in the form of creatine phosphate. Creatine phosphate can be utilised during muscular contraction for the rapid re-synthesis of ATP by phosphate transfer to ADP. When muscle is at rest, the reverse reaction, phosphate transfer from ATP to creatine, rebuilds the reserves of creatine phosphate.

Muscle also has its own glycogen stores. Calculations based largely upon measurements of oxygen consumption and lactic acid production in human subjects suggest that during moderate exercise the energy is initially supplied by stored ATP and ATP resynthesized from creatine phosphate. Within a few seconds, the oxidation of fatty acids and glucose, taken up from the blood stream, provides an additional source of ATP. Oxygen consumption rises rapidly as increased amounts of fatty acids and glucose are oxidized. If any anaerobic breakdown of glycogen occurs under these conditions, it is too small to be detected. When the exercise is strenuous, a point is reached when the oxygen supply is insufficient to meet the energy needs of active muscle. When this occurs (estimated as an energy expenditure of approximately 220 calories per minute per kilogram of body weight), glycolysis provides a sizable portion of the energy needs.

Far less ATP is produced by the anaerobic process than by the aerobic process. The lactic acid produced during glycolysis is released from the muscles into the blood stream to be subsequently taken up by the liver (where it is converted to glucose and glycogen). A reasonably accurate measure of the extent of glycolysis can be obtained by determining the concentration of lactic acid in a blood sample drawn two to three minutes after a strenuous exercise trial lasting up to a few minutes. Exercising to a state of exhaustion is associated with a steep and continuous rise in blood lactic acid. Reducing the effort or introducing rest intervals is reflected in a levelling off of blood lactic acid concentrations.

Oyxgen Debt.
The depletion of energy stores during exercise represents a debt that is paid after exercise during a period when oxygen consumption returns gradually to normal. The oxygen debt is defined as the amount of oxygen consumed above the resting level during the post-exercise period. If the exercise was moderate, the oxygen consumption returns to normal within a few minutes and the debt is small. Oxidation of fatty acids and glucose during this brief period replenishes the approximately half-depleted stores of ATP and creatine phosphate. Strenuous

exercise results in a large oxygen debt, and the return to resting oxygen consumption is slow (requiring an hour or more). The large debt is incurred because a portion of the glycogen stores as well as possibly all of the stores of ATP and creatine phosphate must be replaced. Furthermore, glycolysis continues during the recovery period in order to contribute to the replenishment of ATP and creatine phosphate. Since the glycogen used during this period must also be replaced, this adds to the debt.

All-Or-None Law.

The weakest stimulus that will initiate contraction of the fibres of a motor unit (or of an individual, isolated fibre) is known as the threshold, liminal, or minimal stimulus. To be effective the stimulus must also be applied for a minimum duration. A stimulus strong enough to elicit a response will produce maximal contraction. The contraction is either all or none. Increasing the strength of the stimulus will not increase the response. If the stimulus is of lesser intensity, it is called sub-threshold, sub-liminal, or sub-minimal. The combination of two sub-minimal stimuli, when applied in rapid succession, may be equivalent to the minimal stimulus, causing contraction of the cell. This is known as summation of stimuli.

Contraction of Isolated Skeletal Muscle.

Contraction of a muscle can be recorded in the laboratory by attachment of a tendon to a moving lever. In common practice, the gastrocnemius muscle of the frog is used in such preparations. A single, brief contraction is called a muscle twitch. Analysis of such a contraction of skeletal muscle shows a brief period after stimulation before contraction occurs. This latent period is followed by a period of contraction and, finally, by a period of relaxation. The response depends on ;

- the strength of a stimulus,
- the speed of application of a stimulus,
- the number of stimulations,
- the initial length of the muscle,
- the temperature.

If a muscle is subjected to successive stimuli of increasing strength, nerve fibres with higher thresholds will respond and activate the fibres of their respective motor units and the force of the muscle twitch will increase progressively as increasing numbers of motor units are recruited.

It is also possible to increase the magnitude of the response by stimulating a muscle while a twitch is still in progress. This summation of twitches is believed to result in part from the release by the initial contraction of elastic elements (attributed, among other things, to connective tissue components of muscle and its tendinous attachments) which resist the shortening. A volley of stimuli at low frequency will produce a succession of rising peaks of contraction, a response known as clonus or incomplete tetanus. Stimulation at a high frequency will cause the fusion of summated twitches, resulting in a sustained contraction called tetanus.

It is apparent that the distinct muscle twitch is a laboratory phenomenon, as in normal function smooth contractions are maintained by tetanisation or, if the stimulation frequency is too low for tetanisation, asynchronous excitation of motor units by nerve impulses.

A curious phenomenon observed at beginning of a series of complete muscle twitches is known as treppe (the German word for staircase). The magnitude of the first few twitches increases in a stepwise manner. Although this response is still not well understood, it has been suggested that a progressive build-up of calcium in the sarcoplasm by the successive stimuli could account for it. The calcium build-up would increase the propulsive energy by increasing the number of myosin-actin linkages.

The following phenomena are also observed if the stimulations are continued at a constant rate: After treppe the magnitude of the contractions levels off. As the stimulations are continued, the contractions weaken. This state of fatigue, brought about by depletion of nutrients and oxygen and the accumulation of waste products

(especially lactic acid), eventually leads to a complete absence of response. As the state of fatigue sets in, the muscle fails to relax completely after each contraction. This condition is known as contracture. The term contracture is also used clinically to describe a partially contracted state of muscle.

An important factor governing the force with which a muscle contracts is its initial length. Maximum force is obtained when a muscle is stretched to its approximate resting length in its normal attachments in the body. At this length there is a maximum overlap between thin filaments and the myosin heads. The optimum temperature at which muscles perform their best work is 37°C in man. As the temperature rises above this level, excitability is lost, the muscle finally entering a state of heat rigor, or permanent shortening. This accounts for the pugilistic positioning of limbs in bodies subjected to burning.

Comparison of Isometric and Isotonic Contraction.
The tension developed during contraction is utilised to perform work in moving a load some distance. This occurs normally when walking, climbing, lifting objects, or turning the head. If a muscle does not shorten as it contracts, the tension may be utilised for such actions as holding an object in a fixed position or maintaining posture against the force of gravity. The contraction is called isotonic when the muscle shortens against a constant load and isometric when it does not shorten.

Contraction Times of Muscles and Motor Units.
Muscles differ considerably in the speed of their contractions. For example, the contraction times of the lateral rectus, gastrocnemius and soleus of the cat are, respectively, 7.5, 40, and 90 milliseconds. These contraction times correlate with normal functions: rapid eye movements (lateral rectus), moderately rapid movements in walking and running (gastrocnemius), and prolonged supportive action (soleus).

Traditionally, certain muscles have been described on the basis of appearance and speed of contraction as either;

1. red, slow-contracting, and having a preponderance of small-diameter reddish fibres, or
2. white, fast-contracting, and having a preponderance of large-diameter, pale fibres.

Most muscles fall somewhere between the two extremes, and the proportions of the two basic fibre types vary considerably from one muscle to another. It has also been observed that the motor units of a muscle can be distinguished on the basis of contraction times and other characteristics. Fibres of fast-contracting units, which also fatigue rapidly, are of large diameter, have few capillaries and mitochondria, and contain an abundance of glycogen. Their apparent dependence upon anaerobic glycolysis could explain their rapid fatigue. Large-diameter fibres also have an extensive sarcoplasmic reticulum. Since this would allow rapid release and uptake of large amounts of calcium ions, it is consistent with their faster contraction.

Fibres of slow-contracting, fatigue-resistant units have small diameters, a rich capillary supply, many mitochondria and little glycogen. This profile suggests a high capacity for aerobic energy pathways. Small-diameter fibres also contain large amounts of the oxygen-carrying heam protein myoglobin. This characteristic and the presence of cytochromes (also heam proteins) in the abundant mitochondria, as well as the vascularity of these fibres, account for the description of small fibres as red, as distinguished from the large, white fibres.

The fibres of a third group of motor units, described as fast-contracting and fatigue-resistant, are of variable diameter and liberally supplied with capillaries. Their glycogen and mitochondrial content suggests utilization of both aerobic and anaerobic pathways.

KEY LEARNING POINTS.

1. A motor unit consists of a single nerve fibre and a number of muscle fibres. The lower the number of muscle fibres involved, the finer the movement will be.

2. A nerve impulse crosses the neuromuscular junction via the action of acetylcholine acting as a neurotransmitter.

3. The sliding filament theory suggests that the thin filaments slide between the thick filaments, drawing the outer edges of the sarcomere closer.

4. Myosin in the thick filaments forms cross-bridges, which act as 'latches', attaching to the actin of the thin filaments.

5. As the actin slides across the myosin, the cross bridges are broken, and the latch re-attaches at a point further along the actin, closer to the Z disc.

6. Energy for contraction comes from the utilization of ATP or creatinine phosphate.

7. Isotonic contraction is where muscle shortens in length.

8. Isometric contraction is where there is no shortening of muscle length.