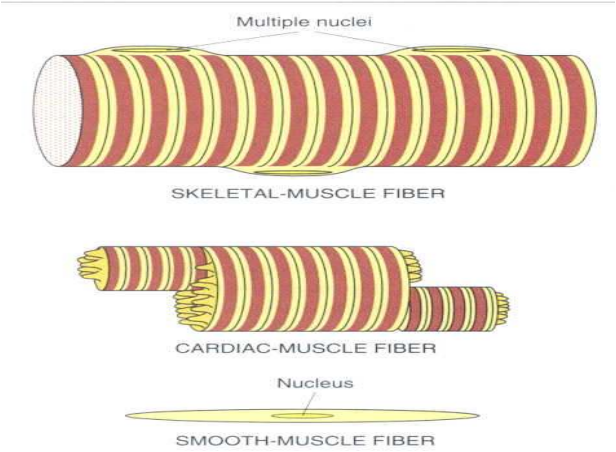
Chapter 5

Muscle Physiology

Muscles constitute roughly 50% of the total body mass. Their job is to contract causing either movement (shortening - isotonic contraction) or force generation without shortening (maintenance of tone or posture - isometric contraction). Three main types of muscle exist:



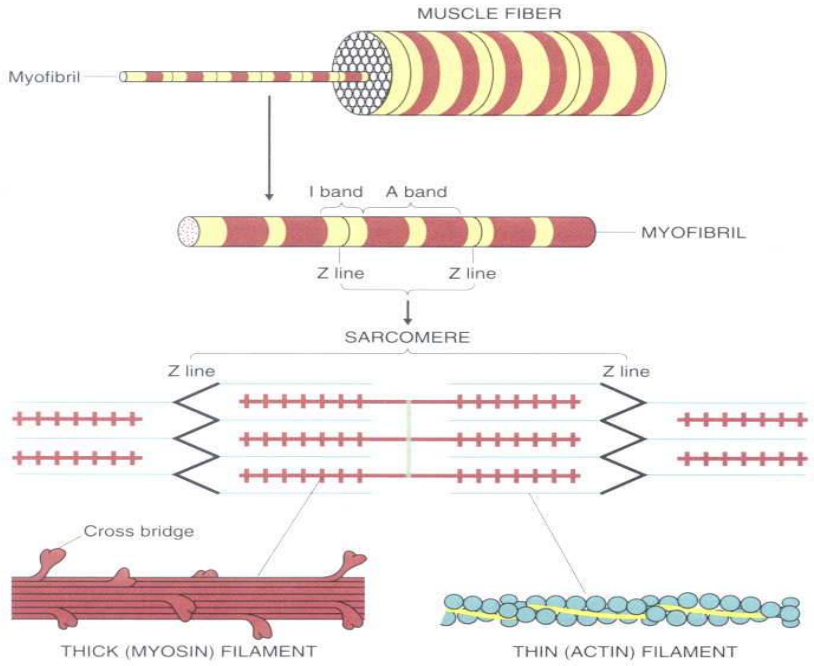
Skeletal - fibres 10 - 80 μm in diameter; up to several cm in length. Multinucleate (syncitial) with the nuclei normally lying beneath the sarcolemma. Characteristic pattern of cross-striations (light or I bands alternating with dark or A bands). Running down the middle of each light band is a dark line, the Z-line. The segment of the fibre in between successive Z-lines is termed a **sarcomere**. Activated by somatic nerves.

Cardiac - fibres 10 - 20 μm in diameter; about 50 - 100 μm in length (1/4 the diameter of skeletal fibres). They are also cross-striated. The fibres are uninucleate, branched structures. Individual fibres are joined together by special junctions - the intercalated discs. These have characteristics tight junctions holding the cells firmly together to form a strong, meshwork basket, and gap junctions, allowing electrical continuity between all the joined cells. The cells function as a syncitium although they are anatomically uninuclear. Spontaneous periodic discharges are modulated by hormones and the autonomic nervous system.

Smooth - fibres 2 - 5 μm in diameter; about 20 - 500 μm in length (1/4 the diameter of cardiac fibres). Arranged in sheets around hollow organs of the body for the most part. May show sustained activity using little ATP. May display spontaneous basal rhythmicity. Modulated by endocrine and paracrine secretions and by the ANS.

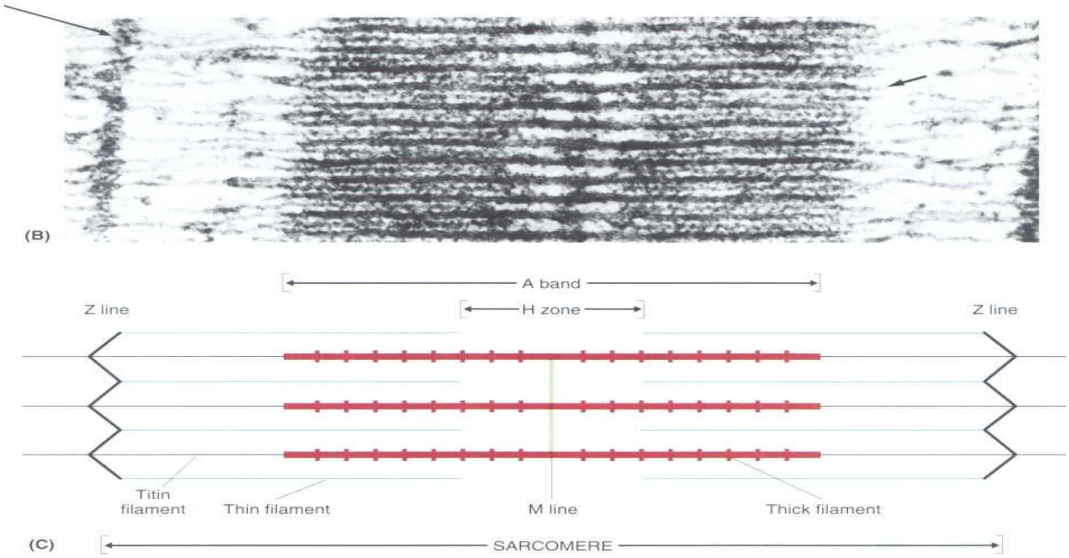
Skeletal muscle is attached to the bony skeleton across joints.

Its fibres are large, multinucleate, cylindrical cells, 10-80 μm in diameter, often running the length of the muscle. They have a characteristic, cross-striated appearance, and hence are termed striated muscle. They contract and relax rapidly, only in response to neural activation.



The banding pattern along the fibre divides it into repeating units called **sarcomeres** which lie between thin dark lines (the Z-lines - or better, the Z-discs) found in the middle of the light region (the I-band or isotropic band). In this isotropic region of the fibre, there are aligned thin filaments made of the protein **actin**, attached to the protein (**alpha actinin**) of the Z-disc.

In the darker A-band (anisotropic band) toward the middle of the sarcomere, are the thick, myosin containing filaments. The these are held in place partly by a meshwork of protein filaments in the middle region, which forms the slightly darker M-line (grey). The region of overlap between the actin and myosin filaments is very dark. The lighter central region around the M-line has only myosin and is called the H-zone.



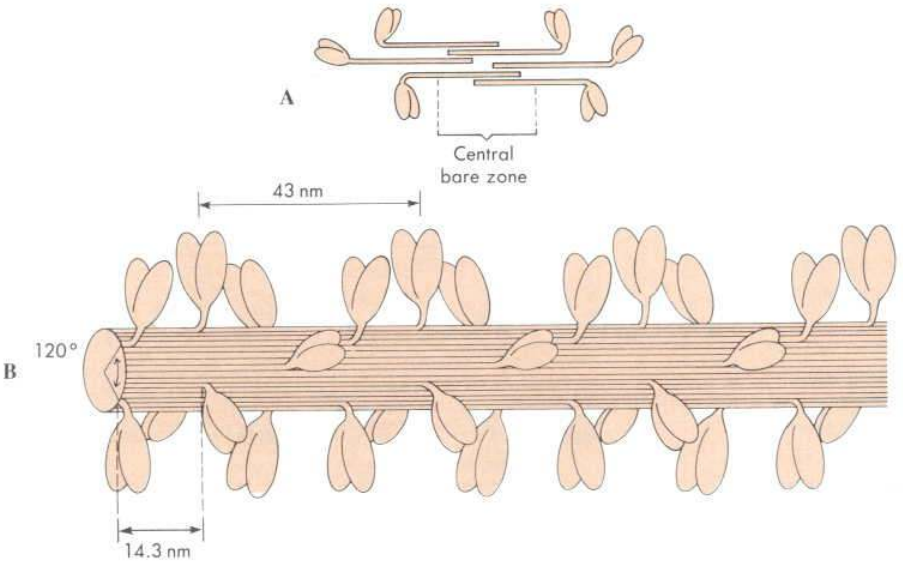
The thick filaments are also held in place by the longitudinal S-filaments of the protein **titin.**

The thin actin filament is a dimeric polymer of G-actin sub-units arranged like two strings of beads twisted together.

Attached to the actin chain of the thin filament, are the proteins **troponin** (Tn) and **tropomyosin**.

A **tropomyosin** molecule runs along each actin chain, bound to the actin. Each tropomyosin sub-unit covers about 7 G-actin sub-units.

The **troponin** molecule has three sub-units: **TnT** that binds to tropomyosin near the ends of the tropomyosin sub-units; **TnI** that binds to the actin; and **TnC** that binds to the TnI and TnT sub-

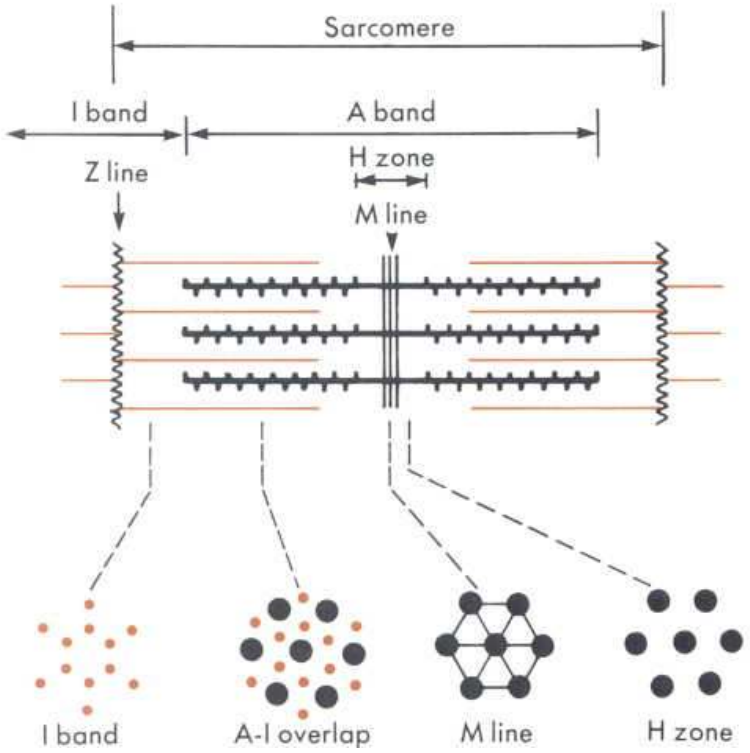


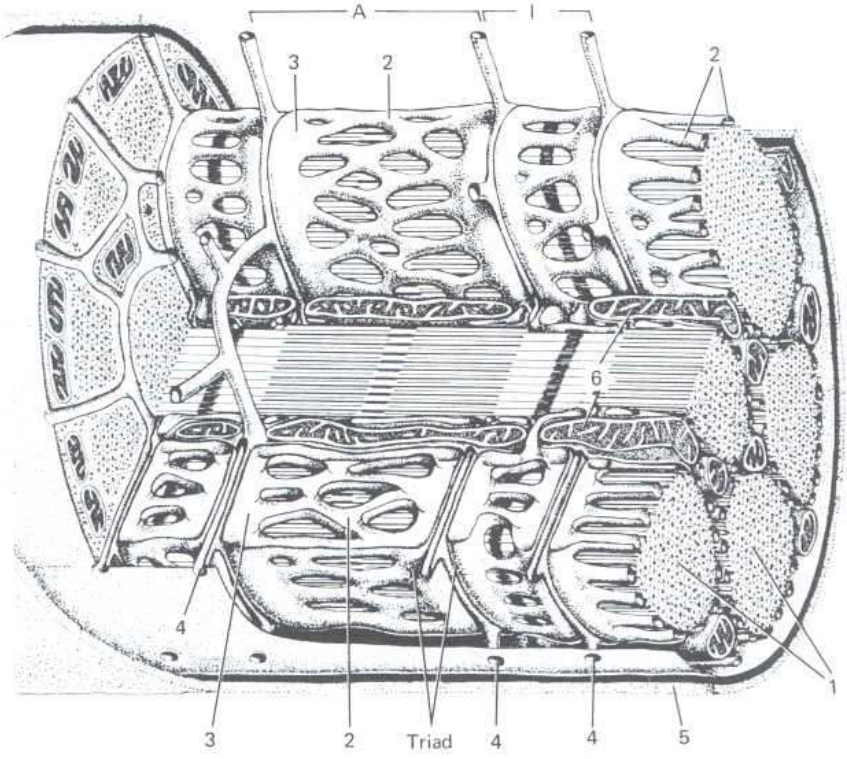
units, and which also has a strong affinity for Ca^{2+} at four binding sites. The thick filaments, at either end, have sticking off at regular intervals, the fibrillar necks and globular, **ATPase** heads of the myosin subunits - the polymerized tails of which make the backbone of the filament.

The heads at the opposite ends of the thick filament stick off in opposite directions leaving a bare middle region (pseudo H-zone) on the filament.

Each successive myosin head is staggered so that six rows of heads stick off in six directions (60^o intervals) around the filament.

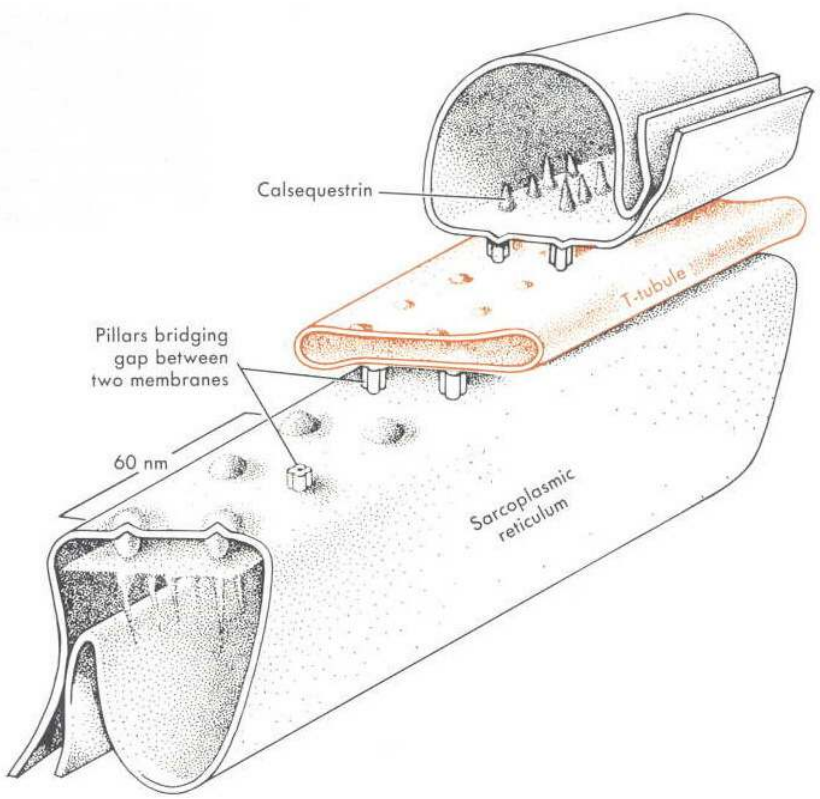
Each myosin filament is surrounded by six actin filaments and each actin filament by three myosins.


Sarcomere
I band
A band
H zone
Z line
M line
I band
A-I overlap
M line
H zone


A
I
3
2
2
6
4
1
3
2
Triad
4
4
5

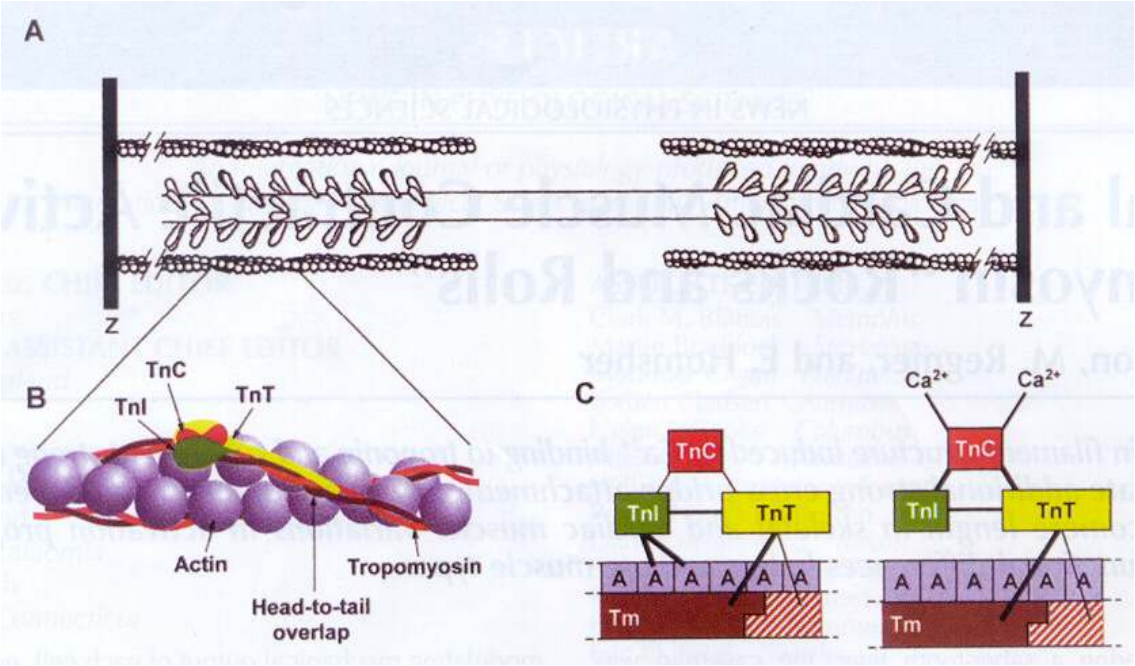
The cylindrical bundles of myofilaments (**myofibrils**) are separated from one another by a sac-like membrane system, the **sarcoplasmic reticulum -** SR (derived from the endoplasmic reticulum), which runs through each sarcomere. The sacs form a system of longitudinally running tubules (2) which meet and fuse at the level of the ends of the A-bands, to form a horizontally running **terminal cistern** (3). Also at the level of the ends of the A-band, the sarcolemma has a ring of fingerlike invaginations (transverse or **T-tubules**) which run around the myofibrils and fuse to form a system of tube-like girdles around each myofibril. The terminal cisterns from the SR on either side, closely abut, but do not fuse with, the membrane of the T-tubules. The membrane of the T-tubules (4) is continuous with the sarcolemma, and the lumen contains extracellular fluid. Like the sarcolemma, the T-tubular membrane can carry a propagated action potential.

Terminal cisternae and T-tubule loaded with ferritin by soaking the muscle fibre in a ferritin containing solution before fixing. The T-tubule is here seen aligned with the Z-line because this is a picture of frog (amphibian) muscle and not mammalian muscle which has the T-tubules at the A-I junction.



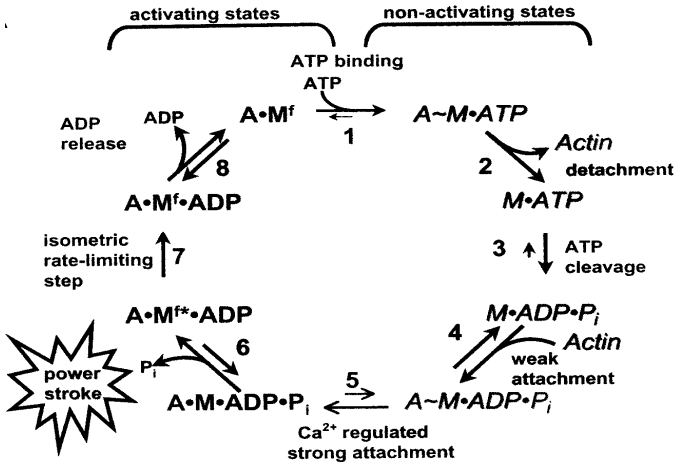
The outer membrane of the SR and the sarcoplasm contain a soluble, calcium binding protein **calbindin** or **parvalbumin**. The SR membrane also has an integral **Ca^{2+}-Mg^{2+}-ATPase-pump** with a higher affinity for Ca^{2+} than parvalbumin. Ca^{2+} ion in the cytosol are slowly bound by the parvalbumin, and transferred to the pump which actively transports the Ca^{2+} into the lumen of the SR, where it is loosely and reversibly bound to **calsequestrin**. (Calsequestrin is to Ca^{2+} as haemoglobin is to oxygen.) This system, along with the mitochondria which also pick up Ca^{2+}, helps to keep the Ca^{2+} concentration of the sarcoplasm (cytosol) of a resting muscle fibre at a very low level ($<10^{-7}$ M).

The T-tubules also have special Ca^{2+} channels termed 'dihydropyridine receptors'. These undergo configurational change when an action potential spreads along the sarcolemma and down the T-tubule. By an unknown mechanism, this change induces opening of other Ca^{2+} channels ('ryanodine receptors') in the membrane of the SR cisternae. The transient opening of these channels causes Ca^{2+} to be dumped from the cisternae into the cytosol, raising the concentration from $<10^{-7}$ M to $>10^{-4}$ M.



The myosin heads have attached, ADP and P_i, products of the breakdown of ATP [step 3 in cycle at bottom], which remain bound to the heads, preventing further ATPase activity in the resting state (**end product inhibition**). The myosin heads can combine with weakly reactive sites on the actin (thin) filaments (pale blue below) [see step 4 of cycle at bottom]. Adjacent, strongly reactive sites (red) are blocked by the tropomyosin molecule (black), which is pulled and held in position over the active sites by the troponin molecules (which bind to both tropomyosin and actin) (See B below).

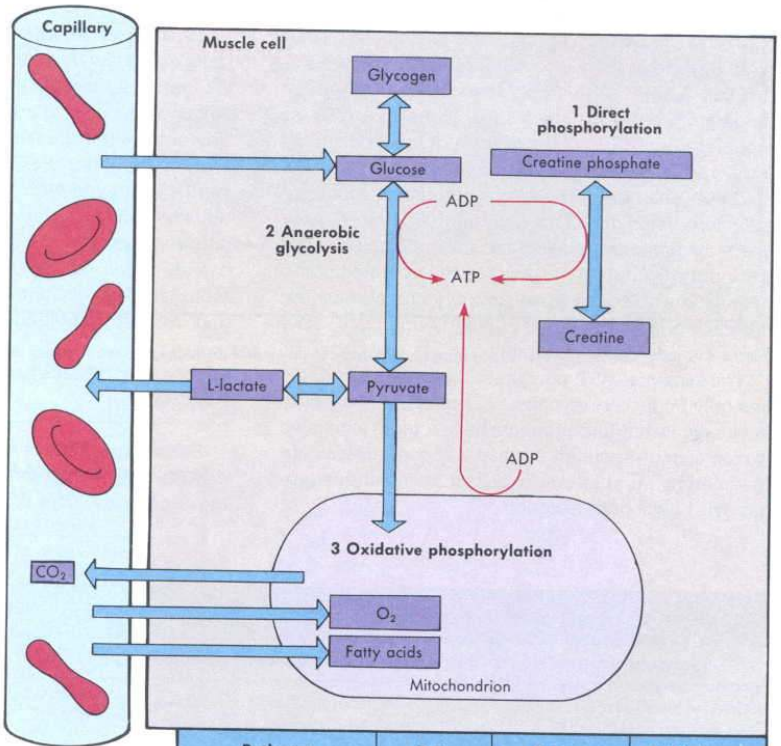
With the rise in sarcoplasmic concentration, Ca^{2+} combines with troponin causing it to release the tropomyosin from its blocking position over the active sites on the actin chain (C at left). The myosin heads are now free to combine with the strongly reactive sites on the actin filaments. Binding of any myosin heads synergistically enhance exposure of the strong binding sites (D at left). [See step 5 of cycle].



The combination of the myosin head with the strongly reactive sites on the actin, reduces the affinity of the myosin heads for the P_i molecules, which dissociate from the myosin heads, causing the heads to rotate on their necks, pulling the attached actin filaments inward by a small amount (1% of the total possible shortening distance). [See step 6 of cycle]

Next, at a rate inversely proportional to the force on the muscle, the ADP dissociates from the active site [steps 7 & 8 of cycle], permitting the myosin head to bind to any available ATP. Binding of ATP to the actin-myosin head complex, causes the release of the myosin head from the actin binding site, and its return to its original angle [steps 1 & 2 of cycle]. The actin is however, held in position by other myosin heads since all do not release at once. The released ATP-myosin head complex, now can't recombine with another actin site, until the ATP has been cleaved to form ADP and P_i [step 3]. One factor that governs the speed of shortening, therefore, will be the rate at which the myosin head can break down ATP (*i.e.* its ATPase potency). Clearly, it will take about 100 pulls of many heads in parallel, with an ATP being used up on each cycle of each head, for a sarcomere to shorten fully. This cycling will continue as long as the Ca^{2+} concentration remains high in the sarcoplasm, and ATP is available. As soon as the Ca^{2+} levels fall sufficiently, Ca^{2+} will dissociate from the troponin, and the tropomyosin/troponin complex will return to the blocking position. Relaxation will then occur as the myosin heads with ADP and P_i attached are unable to access the active sites on the actin.

Note that ATP is required to cleave the avidly formed bond between actin and myosin. In the absence of ATP the cross linking becomes fixed, and the muscle becomes rigid and inextensible. This condition is seen shortly after death when the muscles' energy supply is used up, and is known as **rigor mortis.**



of the three pathways
Adenosine monophos-

Pathway	Rate	Extent	ATP/glucose
1 Direct phosphorylation	Extremely fast	Very limited	0
2 Glycolysis	Very fast	Limited	2-3
3 Oxidative phosphorylation	Slow	Unlimited	36

ENERGY SUPPLY

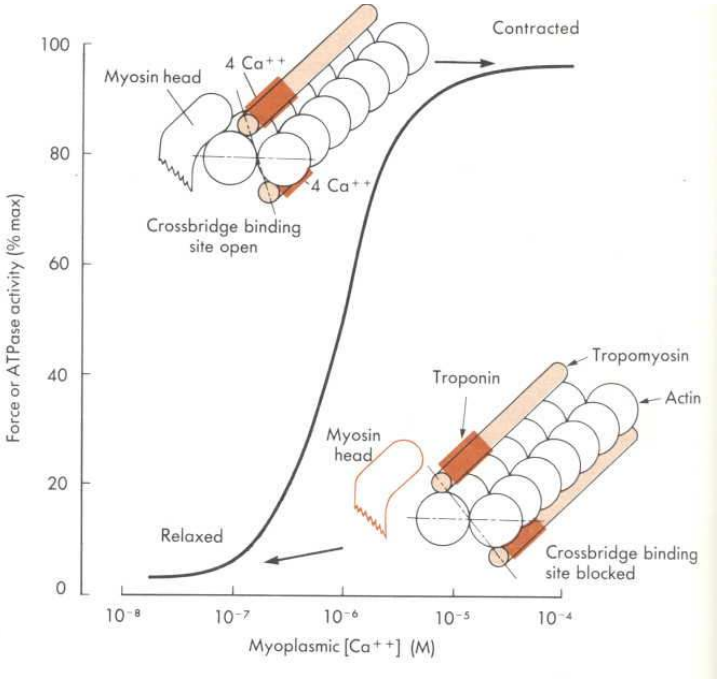
Clearly ATP is used up in large quantities during muscle contraction. Its levels must not be allowed to fall significantly since this will affect detachment of the myosin heads, and contraction will be impaired. (Rigor complexes will be formed). As it is used, ATP is rapidly regenerated from another high energy compound **creatine phosphate (CrP)**, in a reaction catalysed by the enzyme **creatine phospho-kinase (CPK).** CrP serves as an ATP buffer, but can sustain

the ATP levels in an active muscle only for a few seconds. Depleted CrP is later regenerated as the ATP stores build up during rest periods: ADP + CrP º ATP + Cr.

ATP for rapid, powerful contractions can be obtained by anaerobic glycolysis, using glucose from the blood (to produce 2 ATP molecules per glucose molecule) or stored glycogen (to produce 3 ATP molecules per glucose molecule). Pyruvate and NADH + H^+ are produced by this process of glycolysis. All the enzymes for this process are present in the cytosol (sarcoplasm / myoplasm), and the rate of diffusion of oxygen from the blood into the muscle is not a limiting factor. ATP produced in this way therefore, although limited in quantity, is rapidly and readily available to the contractile mechanism. If oxygen supplies are inadequate, the pyruvate interacts with the NADH and H^+ to form lactic acid, which builds up in the cell and causes fatigue.

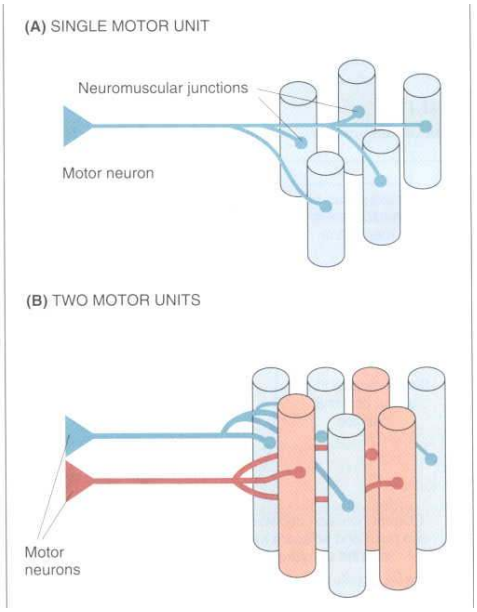
In the presence of adequate supplies of O_2 much more ATP can be obtained by oxidative phosphorylation, albeit more slowly and less readily available. This involves a progressive breakdown of pyruvate or Free Fatty Acids (FFAs) to CO_2 and water. Through oxidative phosphorylation 36 molecules of ATP can be obtained per glucose molecule. Over 140 molecules of ATP can be obtained per FFA molecule. Oxidative burning of fats therefore is clearly a much more efficient way of producing ATP. All the enzymes for this process are located in the mitochondria, and the process is heavily dependent upon the availability of oxygen.

Resting muscles and muscles working at low intensity preferentially burn FFAs. Muscles working at high intensity preferably burn glycogen. Exercise sustained for more than about 30 min also begins to mobilise FFAs as a preferred energy source as the glycogen stores diminish.



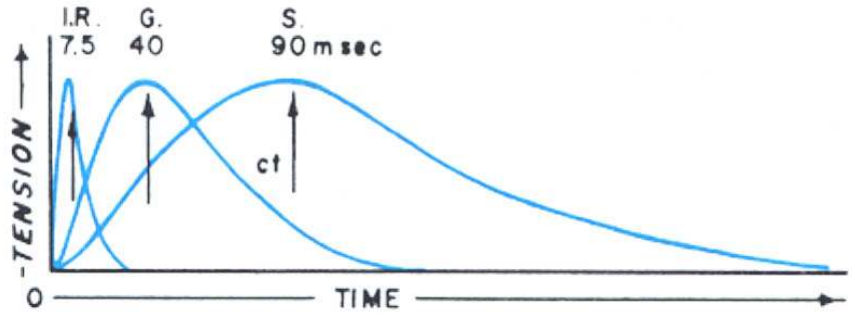
The arrival of an action potential in the T-tubule activates the voltage sensitive dihydropyridine receptors (Ca^{2+} channels) in the membrane. These in turn, induce transient opening of the ryanodine sensitive Ca^{2+} channels in the SR causing Ca^{2+} to be dumped from the terminal cisternae into the cytosol, and raising the concentration from $<10^{-7}$ M to $>10^{-4}$ M. The Ca^{2+} combines with TnC and causes exposure of the strong binding sites on the actin filament, initiating contraction. As the action potential passes, the ryanodine channels close. The released Ca^{2+} is soon bound to the calbindin (parvalbumin) in the cytosol, which has a higher affinity for Ca^{2+} than does TnC, but which combines with Ca^{2+} more slowly since the Mg^{2+} to which it is bound, must first be displaced. The Ca^{2+} is then transferred to the Ca^{2+}-Mg^{2+}-ATPase in the SR and pumped back into the lumen of the cisternae. Calcium ion concentration then, rises and falls as a brief pulse in response to the arrival of an AP in the muscle fibre.

This single pulse of Ca^{2+} released by a single action potential causes a brief contraction then relaxation, known as a **twitch.** The duration of this twitch varies in different muscle types, and in different types of skeletal muscle fibres.



A **motor unit** is a motor neuron plus all the muscle fibres which it innervates. When an AP travels down the axon it reaches all the fibres in the motor unit, and all will normally be activated. The neuron and all its fibres thus act as a unit. Failure at the mammalian nerve-muscle junction is rare.

The fibres belonging to a motor unit are not normally clumped together, but are interspersed among those from other motor units. The nature of the motor neuron and its firing pattern influences the characteristics of the muscle fibres in the motor unit.



Muscle twitch in mammalian skeletal muscle

In skeletal muscle the range of contraction times (time to peak) is from 7.5 ms for **fast** (extraocular muscle: IR- internal rectus); 40 ms for intermediate (G - gastrocnemius); to 90 ms for **slow** (S - soleus) muscle fibres. Most skeletal muscles have a mixture of different types of fibres: slow; fast oxidative glycolytic (rare); or fast glycolytic. However, all fibres in a given motor unit are of the same type - the type being determined to some extent, by the nature of the motoneurone. Small tonically active motoneurones prompt development of slow fibre types; large, phasic motoneurones favour fast glycolytic fibres.

In any given muscle different fibre types can be found interspersed among one another.

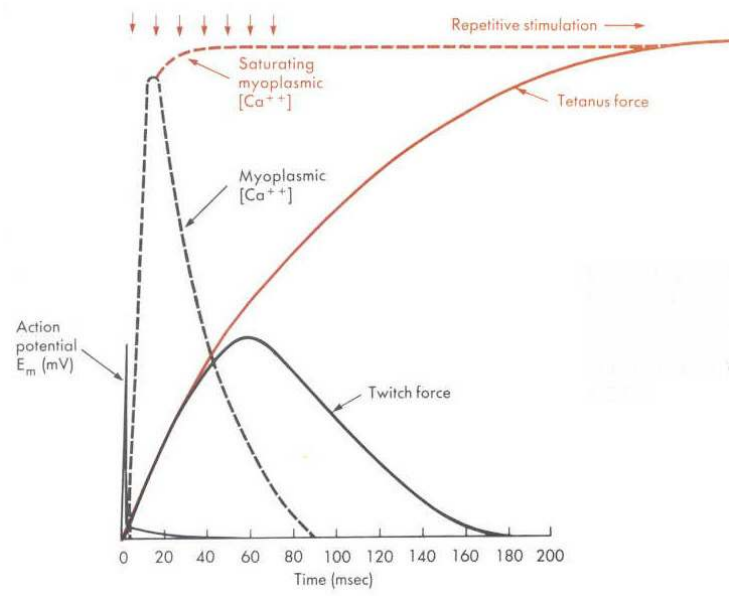
Successive cross-sections of the same muscle stained for different properties. (A) for slow myosin-ATPase; (B) for succinic dehydrogenase (oxidative phosphorylation) activity; and (C) for glycolytic capacity.

Fast fibres (Type II) express a relatively potent myosin-ATPase variant. These fibres are specialised to contract rapidly and powerfully. They need to obtain a rich and ready supply of ATP. ATP from glycolysis is produced in the cytosol right in the vicinity of the myofibrils. Fast fibres are therefore designed to preferentially use glycolysis.
Since glycogen provides 3 ATP per glucose molecule, and can be stored right in the cytoplasm, they also 'prefer' this source over glucose from the blood (which will provide only 2 ATP per molecule). They do not rely on ATP produced by oxidative phosphorylation (OP). Oxidative Phosphorylation produces ATP efficiently and in abundance for each molecule of glucose or FFA burnt, but the ATP is made in the mitochondria and the process is dependent upon inward diffusion of oxygen. All this is too slow for fast fibres, which abandon OP. They are therefore supplied by relatively few capillaries, have few mitochondria and store relatively little myoglobin (but lots of glycogen and glycolytic enzymes). They are therefore pale in colour (white meat). The fibres are quite large in diameter, since diffusion is not a problem - but they do need to generate powerful contractions. The SR is usually abundant (to supply large quantities or Ca^{2+}) and has a potent Ca^{2+}-ATPase to rapidly resequester the released Ca^{2+}. Sprinters have proportionately large numbers of fast fibres in their muscles.

Slow fibres express a relatively weak myosin-ATPase variant. Since they are not in so much of a hurry, they rely on the more efficient oxidative processes to produce ATP. The fibres are relatively thin, rich in mitochondria and myoglobin, richly supplied with capillaries, poor in glycogen, and have relatively sparse SR, with a relatively weak Ca^{2+}-ATPase. These fibres are dark in colour (red meat). Long distance runners have abundant slow fibres in their muscles.

Fast fibres sacrifice durability for power. They produce pyruvate + NADH + H^+ as end products which react to produce lactate and NAD^+ in order to preserve the redox balance of the cells. The lactate does not leave the fibre easily. The intracellular pH therefore falls, impairing functioning of the Ca^{2+}-ATPase in the SR and of the actomyosin ATPase. The fast fibres thus fatigue readily.

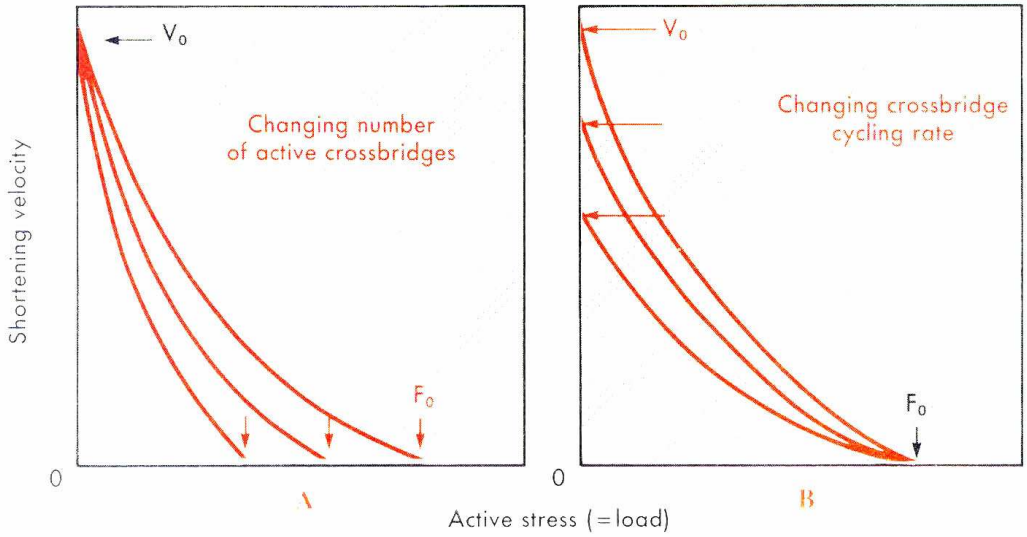
Fast & slow fibres do not readily interconvert, but training can increase capillary density, buffering capacity and ability to extract oxygen from the blood. An intermediate type of fibre (IIA) may convert more to fast type with strength training and more to slow type with endurance training.



In a typical skeletal muscle fibre, contraction is triggered by an all or nothing action potential lasting for c. 2 ms or so. This causes a more or less fixed pulse of Ca^{2+} in the sarcoplasm, peaking at c. 10 ms and lasting for c. 50 ms. This means that by the time the Ca^{2+} pulse peaks (point of closure of the ryanodine channels) a second AP can be triggered in the fibre, to cause re-opening of the SR Ca^{2+} channels. This will cause the Ca^{2+} concentration in the sarcoplasm to remain high for a longer time, and prolong the contraction. The mechanical twitch resulting from the successive APs therefore, can **summate.** During a single twitch, the force recorded at the tendon is not equal to the force exerted by the contractile elements, because sufficient time is not allowed for the pull to be transferred through the spring-like tendons (the **series elastic component**). With summation however, more time is allowed, so that the transmitted force increases. With repetitive stimulation at a low rate successive twitches summate with brief partial relaxations in between, giving an **unfused tetanus**. At a sufficiently high stimulus rate, no relaxations can be seen between successive stimuli, giving a **fused tetanus**. The **fusion frequency** is high for fast muscles and low for slow muscles. The

maximum force recorded is proportional to the stimulus frequency, up to a peak level. The peak force during a tetanus is usually about 4X that for a single twitch. This is the Tetanus/Twitch ratio.

Force exerted depends on the number of myosin heads pulling together at the same time. Since the maximum overlap of thick and thin filaments (and hence the maximum number of possible cross-bridges formed) will depend on the length at which the muscle is held (for *isometric contractions*), force developed should depend on muscle length. A plot of the tension developed in a muscle stretched to different lengths without stimulating, gives a **passive tension curve**, representing the elastic properties of the **parallel elastic component** (fascia, blood vessels etc). A plot of peak tetanic tension developed at different lengths (during stimulation) gives the **total tension curve**. Subtraction of these two curves, gives the **active tension curve**, which has a characteristic shape: low active tension develops at short lengths, because the thin filaments on either side of the M-line interfere with each other; low tensions develop at long sarcomere lengths when overlap is restricted; and maximal tension is developed at a length which allows maximum overlap, without interference. This relationship helps to verify the hypothesis that it is the linking of cross-bridges between the actin and myosin filaments which generates the contractile tension.

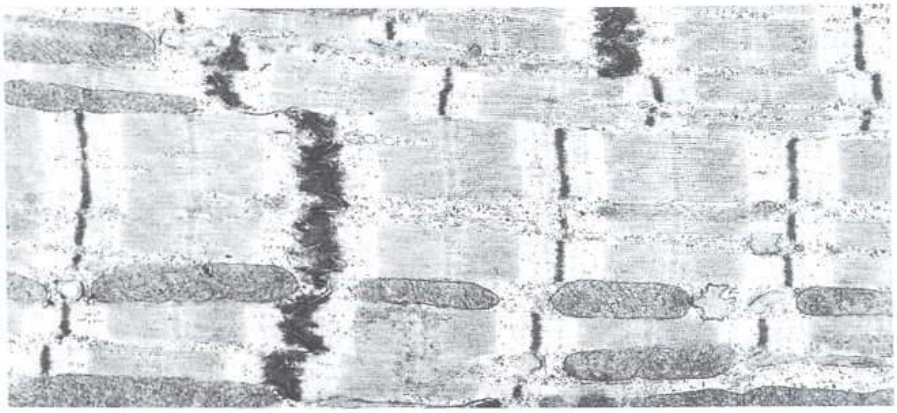


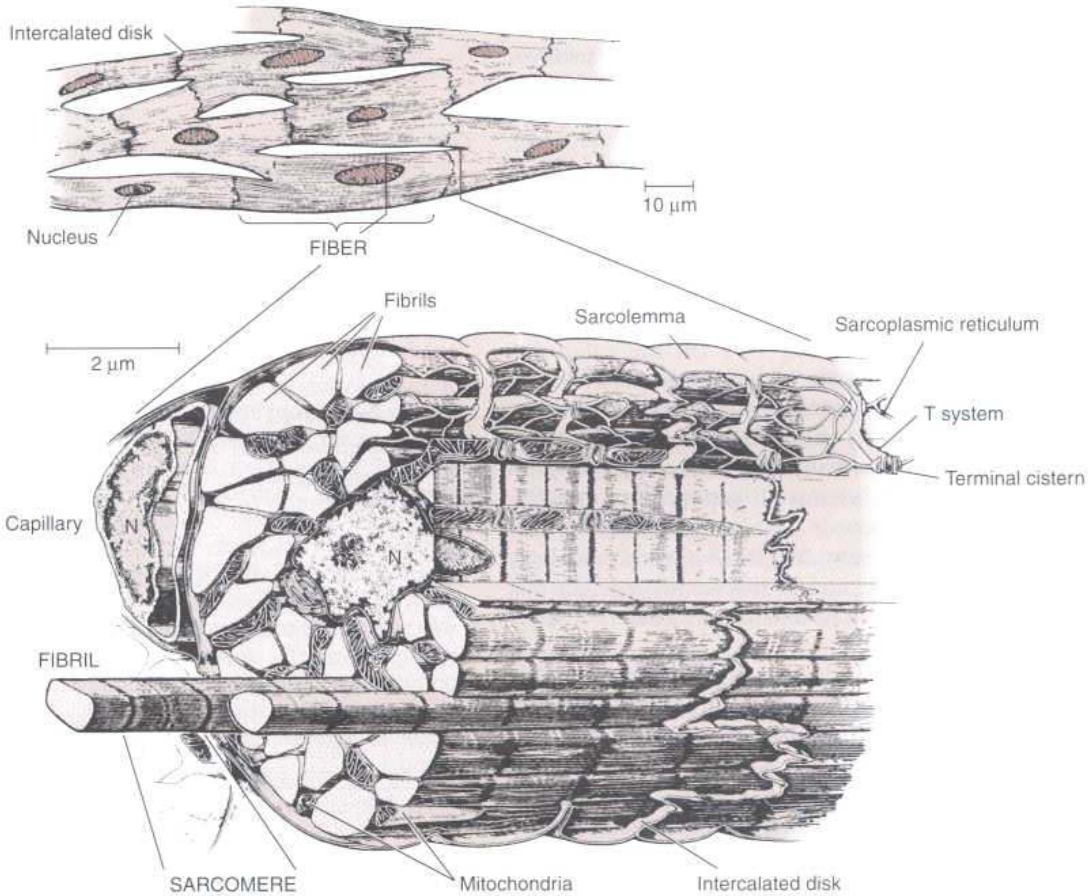
During *isotonic contraction* a muscle lifts a load, shortening at a certain initial velocity, that depends on the difference between the load (W) and the force of the contractile mechanism (F). When F = W no shortening occurs (velocity = 0) and contraction is isometric. By plotting velocity of shortening vs load, a curve is obtained, which, extrapolated to 0 load, gives the maximal possible velocity, V_{max}. V_{max} is related to the speed of cross-bridge cycling, and hence (see above) is usually proportional to the potency of the myosin ATPase. Setting a muscle at different lengths alters the force it can exert, but does not alter the ATPase potency. A muscle set at different initial lengths therefore will give different FORCE-VELOCITY curves, all of which extrapolate to the same V_{max}. Factors which alter cross-bridge cycling rate, and number of cross bridges active at any given length, may also enhance force generation, but will alter V_{max} as well. Such factors are **positive inotropic** agents, and are said to increase contractility - that is, inherent contractile strength, independent of length. A heart muscle for example, may increase its force of contraction simply as a result of being stretched to a longer length (heterometric regulation - constant V_{max}), or may increase in contractility ($8V_{max}$) under the influence of adrenaline. This may also occur in smooth muscle but is less true of skeletal.

Cardiac Muscle

Cardiac muscle is found only in the heart, where it forms a muscular bag the myocardium in the atria and in the ventricle. The cells are uninucleate cylinders, 10-20 µm diameter (c. ¼ skeletal). They are short (50-100 µm) but are often branched, and joined to each other end-to-end to form an interlacing meshwork. The junctions between cells (intercalated discs) are partly tight junctions for strong adherence, and partly low resistance gap junctions which allow free spread of small molecules and electrical currents (ions) between fibres. The fibres are cross-striated like skeletal muscle fibres. This muscle gives spontaneous, forcible contractions, repetitively throughout life.

For cardiac muscle time to peak contraction may be about 150 ms. Time to peak in skeletal muscle is 7.5 ms to about 90 ms and for smooth muscle, of the order of 500 ms. Cardiac muscle behaves like very slow skeletal muscle. It is rich in mitochondria and myoglobin and highly dependent on a good oxygen supply. The differential speeds of contraction are related to differences in (1) the potency of the myosin ATPase isozyme in the muscle, (2) in smooth muscle, the attachment time of the myosin heads - which may be quite prolonged at low Ca^{2+} levels (latch mechanism), and (3) the abundance of SR and the potency of the Ca^{2+}-Mg^{2+}-ATPase and/or (in cardiac and smooth muscle) the potency of Na^{+}-Ca^{2+} exchanger in the sarcolemma. Item (3) determines relaxation rate as well as contraction rate. Items (1) and (2) determine cycling time for the myosin heads, and thereby, speed of contraction.

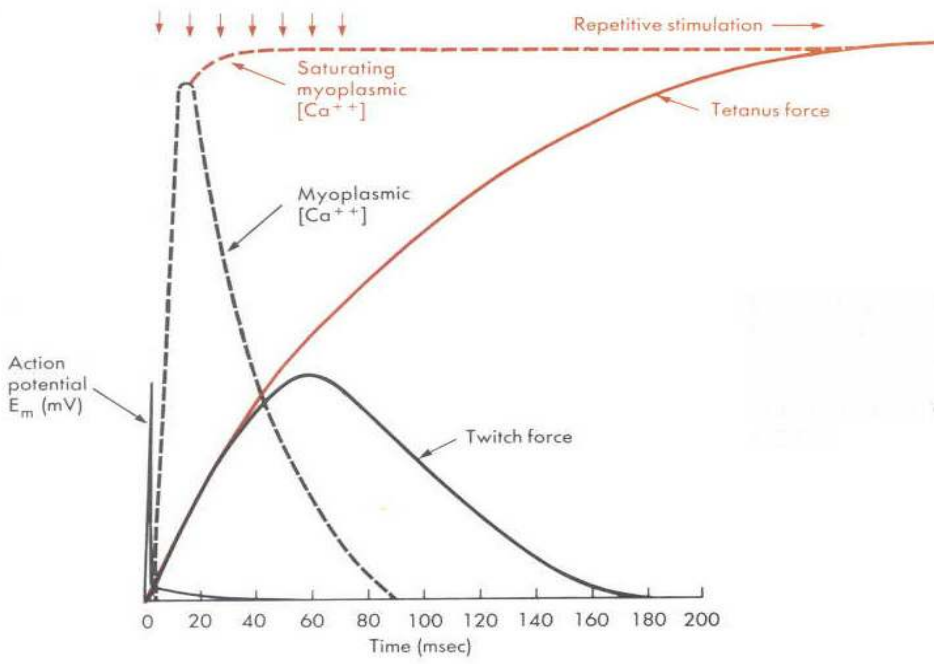




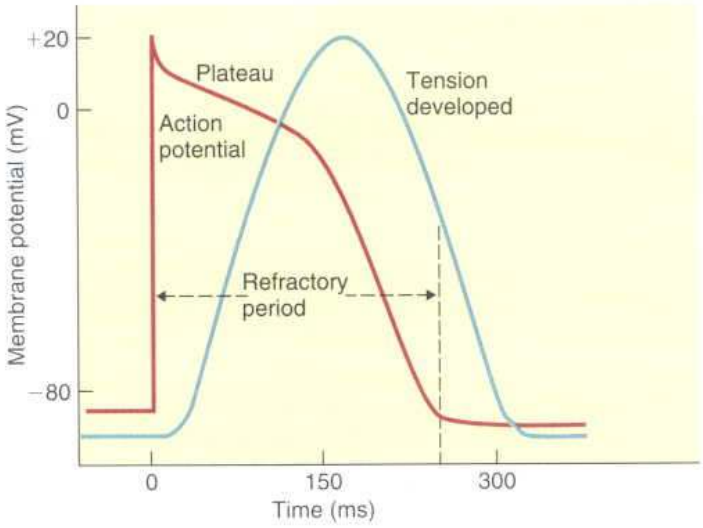
In cardiac muscle, the mechanism of contraction is essentially the same as in skeletal, but the excitation-contraction coupling mechanism differs slightly. T-tubules invaginate at the level of the Z-lines. The SR is relatively poorly

developed (cisternae are small or absent - in most EM sections 'diads' and not 'triads' are seen), and provides insufficient Ca^{2+} to fully activate the contractile apparatus. Unlike those in skeletal muscle the ryanodine channels in cardiac muscle are activated by Ca^{2+} in the cytosol (**calcium activated calcium release**) and Ca^{2+} entry through the dihydropyridine channels is an important trigger of Ca^{2+} release. Significant amounts of Ca^{2+} enter the fibre from the ECF during the AP, which consequently has a long plateau phase caused by slowly inactivating Ca^{2+} channels in the sarcolemma, prolonging AP (c. 200 ms). Ca^{2+} is also released from sub-sarcolemmal binding sites during the AP. Because the AP lasts almost as long as the twitch, heart muscle cannot be tetanized.

After contraction, Ca^{2+} is pumped back into the SR by a Ca^{2+}-Mg^{2+}-ATPase pump (relatively weak), and back to the extra-cellular fluid by a Na^{+}-dependent Ca^{2+} pump in the sarcolemma (these two pumps compete with each other). The calcium ion in the SR is the more readily available, and the greater the amount of Ca^{2+} in the SR is the more fully activated will the contractile apparatus be, on each contraction. Poisoning the Na^{+}/K^{+} pump with *digitalis,* and reducing the extra/intra-cellular Na^{+} gradient, can therefore actually enhance contraction of the heart muscle. Because the extracellular Ca^{2+} is necessary however, cardiac **contractility** (see below) is significantly affected by extracellular Ca^{2+} levels (not so in skeletal muscle).



In skeletal muscle the action potential (AP) duration is about 2 ms and is over long before the peak of the twitch. The twitch, being a very transient rise and fall of force, is over too quickly to allow full transmission to the tendon (the series elastic component of the muscle is not fully extended by the twitch). Repetitive stimulation can therefore lead to summation of twitches, more complete extension of the series elastic component and a rise in the force recorded at the tendon (tetanus).

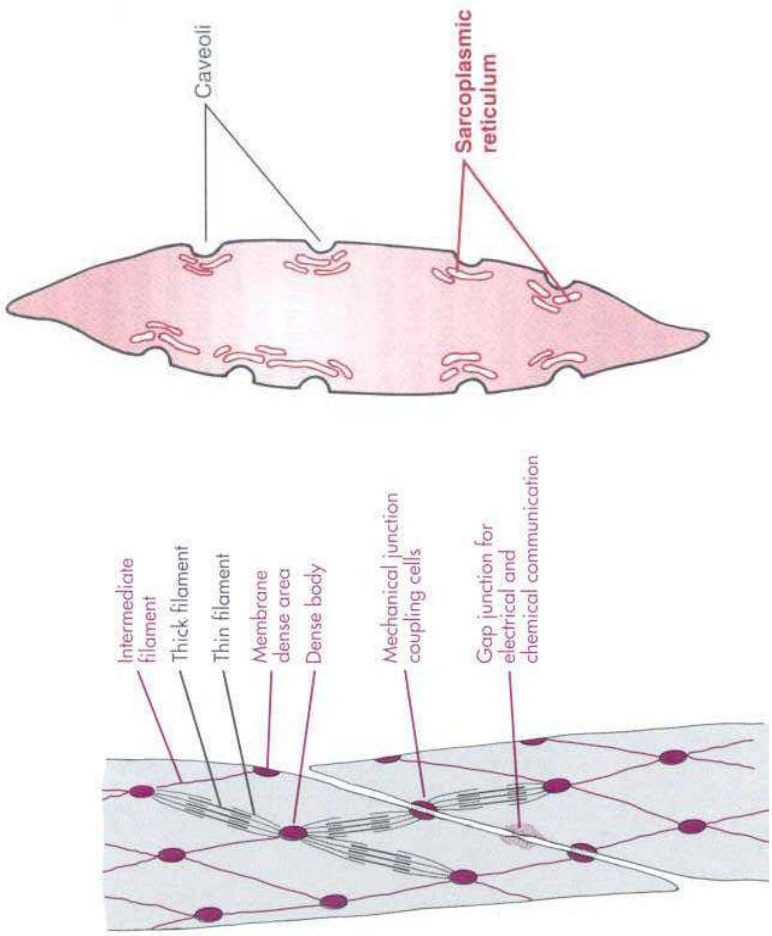


In the cardiac action potential, sodium channel opening is followed by inactivation. Sodium inactivation is accompanied by opening of slowly inactivating Ca^{2+} channels at the same time as a few fast K^+ channels open. The balance between the outward flow of K^+ and the inward flow of Ca^{2+} causes a plateau of variable length (*c.* 150 ms). The delayed opening of additional Ca^{2+}-activated K^+ channels (activated by build-up of Ca^{2+} in the sarcoplasm) as the Ca^{2+} channels close, terminates the plateau and leads to repolarisation. The muscle twitch is of almost the same duration as the action potential, and since the refractory period extends beyond the end of the AP, the muscle cannot readily be tetanised. This is important since tetany of the heart muscle would not allow effective pumping.

The AP spreads along the T-tubules and (unlike in skeletal muscle) Ca^{2+} entry through the dihydropyridine sensitive channels stimulates opening of the ryanodine sensitive channels in the relatively sparse SR, dumping Ca^{2+} into the cytosol. The Ca^{2+} released from the SR is insufficient to fully activate the contractile mechanism, and is augmented by Ca^{2+} entry via channels in the general sarcolemma, and release from sub-sarcolemmal binding sites, triggered by the AP. On termination of the AP, Ca^{2+} is pumped back into the SR by a Ca^{2+}-Mg^{2+}-ATPase enzyme and to the extracellular fluid by a Na^+/Ca^{2+} antiport in the sarcolemma.

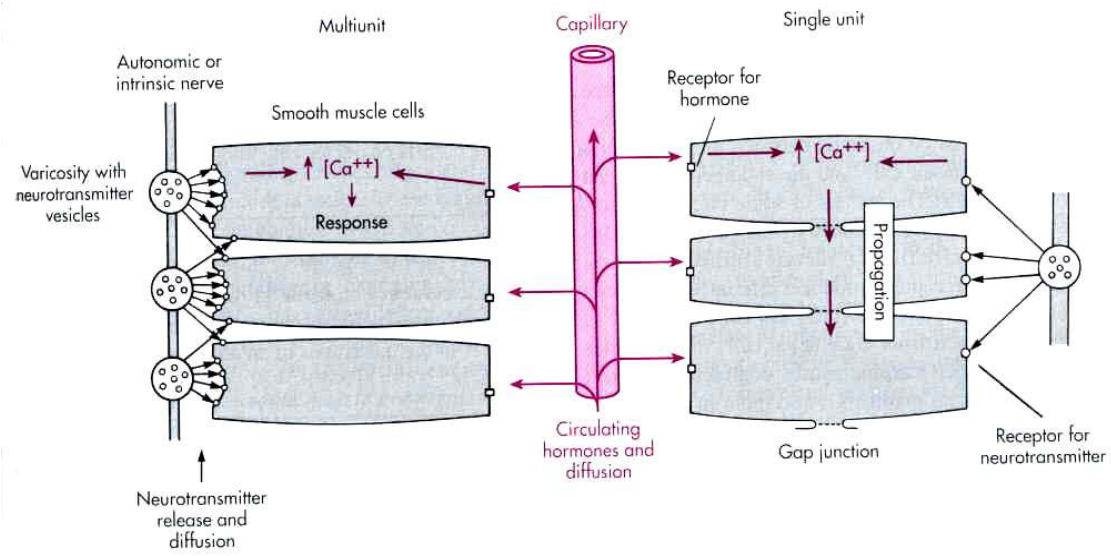
Smooth Muscle

In the small smooth muscle fibers the SR is very sparse indeed. There is no T-tubular system, but in-pocketings of the sarcolemma form caveolae (not caveoli) which are associated with the SR elements. Smooth muscle action potentials show a wide range of properties, some being less Ca^{2+} dependent (normal APs) and others being more so - very much like the cardiac AP with a plateau corresponding to a period of Ca^{2+} entry. The AP in many smooth muscles is not altered by removal of extracellular Na^+ but is abolished by removal of Ca^{2+}. Because of the small fibre size and large surface/volume ratio, quite significant quantities of Ca^{2+} can enter from the extracellular fluid (ECF) to supplement that released from the SR. Like cardiac muscle (but unlike skeletal), smooth muscle contraction is weakened by hypocalcaemia.

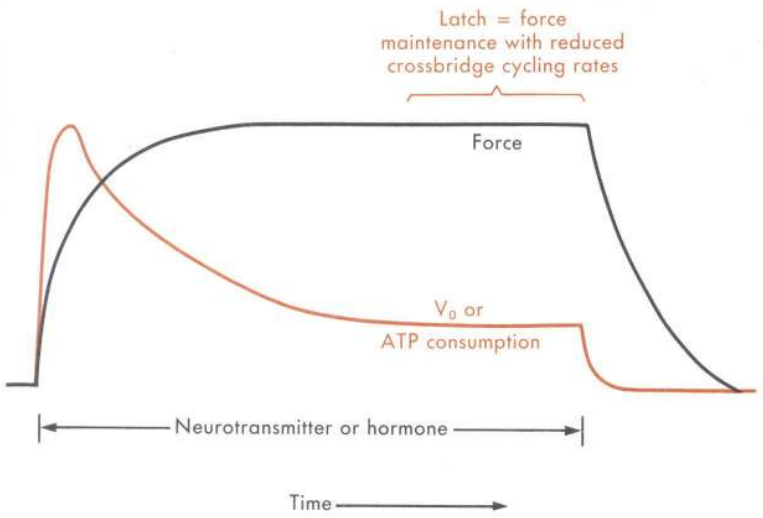


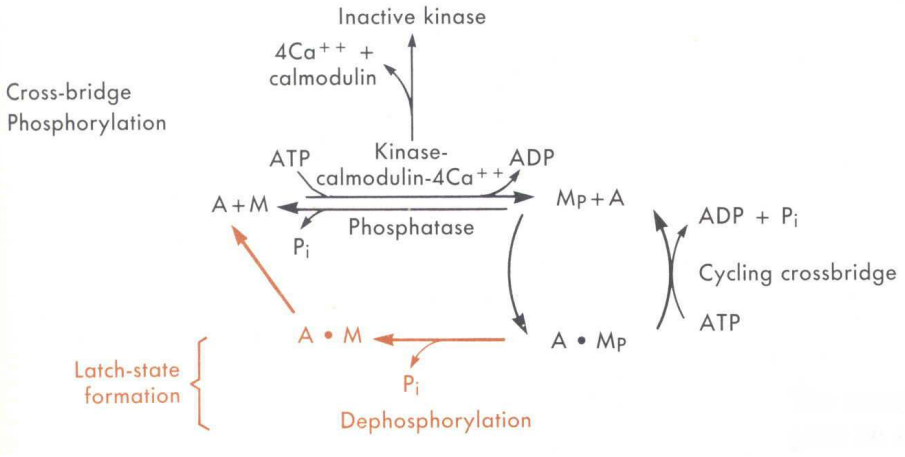
As in cardiac muscles, smooth muscle fibres may be joined by gap junctions to provide electrical continuity between fibres and tight junctions for adherence between cells. These are not, however, consolidated into intercalated disks.

There are no cross-striations, because the filaments and Z-line material are organised in a less orderly arrangement. Alpha actinin forms dense bodies attached to the cell membrane or to an intracellular scaffolding of intermediate (desmin) filaments. As in striated muscle, the thin (actin) filaments are attached to the alpha actinin (dense bodies) and interdigitate between the thick (myosin) filaments. This arrangement allows for considerable shortening of the smooth muscle fibres. These muscles contract for long periods to maintain tone (sphincters) or to cause movement (e.g. peristalsis) with minimal expenditure of energy. (A few sphincters, as noted before, are composed of striated muscle.)



There are two types of smooth muscle. In the first (right, bottom), fibres are inter-connected with each other via gap junctions, allowing the spread of electrical excitation through the sheet of cells. The cells may show spontaneous rhythmic contractions and relaxations in step with periodic membrane depolarisation and repolarisation (a basic electrical rhythm - BER). Sympathetic and/or parasympathetic axons course through the tissue, at intervals forming swellings or varicosities in which synaptic vesicles accumulate. Synaptic gaps are large. This is known as unitary or visceral smooth muscle (gut, uterus) since all the fibres in a layer act as a single unit. In the second type (left, bottom), gap junctions are rare, synaptic gaps are narrow and fibres may act more or less independently of each other. No BER is shown. This type of muscle is known as multiunit smooth muscle (e.g. ciliary muscle, iris, arrector pili; walls of large blood vessles).

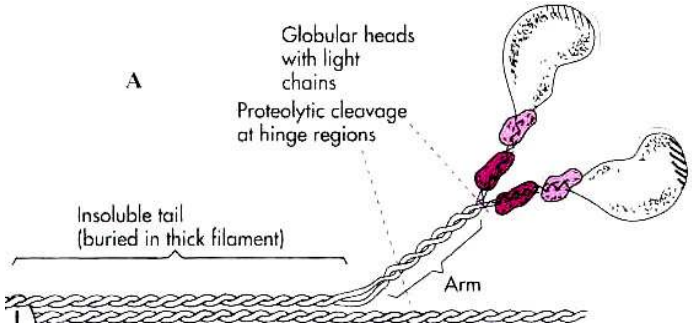




EXCITATION CONTRACTION COUPLING IN SMOOTH MUSCLE

The Excitation-Contraction coupling process in smooth muscle differs from that in striated muscles. In smooth muscle thin (actin) filaments are arranged in bundles attached to dense plaques (α-actinin) either on the sarcolemma (unipolar) or bound to the desmin cytoskeleton (bipolar). Thick (myosin) filaments (bipolar) interdigitate among the thin filaments, but there is no regular alignment, hence the absence of striations.

Tropomyosin is present on thr actin filaments, but troponin is absent. Depolarisation, or the opening of chemically (hormonally) gated Ca^{2+} channels in the membrane causes Ca^{2+} entry. The Ca^{2+} combines with a protein **calmodulin** which is very similar to the calcium binding subunit of troponin (TnC). The $(Ca^{2+})_4$-calmodulin complex activates **myosin light chain kinase** which phosphorylates a small protein **myosin light chain** which is bound to the myosin head near the neck, and which prevents it from swiveling normally, thus hindering combination with the actin. The phosphorylation activates the myosin head, initiating contraction.



At very low Ca^{2+} levels, a phosphodiesterase (always present) dephosphorylates the Myosin Light Chain (dephosphorylation outweighs phosphorylation), inactivates the myosin, and so stops contraction. At intermediate Ca^{2+} levels (orange portion of the cross-bridge cycle), dephosphorylation of some of the myosin heads while they are still attached to actin, may prolong attachment time, slow down cycling, and allow prolonged maintenance of tone at a given length, without the use of large amounts of ATP (latch mechanism).

In skeletal, cardiac and smooth muscle therefore the trigger for contraction is Ca^{2+} ion. In skeletal and cardiac muscles it operates by combination with troponin bound to the actin filament. In smooth muscle it operates by combination with calmodulin in the cytosol, and thus activating the light chain attached to the myosin head.