

YO! Physiologer dudes

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Many of my friends have found these notes useful in their study for Physiology 1A.

But before you take a look at them and start cramming as if your life depends on it, take a moment to meet the God that created a universe that is so complex and worthy of study, yet knows you and I personally:

Psalm 139:13-14 - "For you created my inmost being; you knit me together in my mother's womb. I praise you because I am fearfully and wonderfully made; your works are wonderful, I know that full well."

Check it out sonnnnnn!: <http://www.matthiasmedia.com.au/2wtl/>



1 Lecture 1 and 2

1.1 Draw a sarcomere naming all the proteins and show the position of the *I* and *A* bands

- Skeletal muscle consists of **fascicles**; bundles of elongated, cells called **muscle fibres**, each of which contain many elongated sarcoplasmic contractile threads called **myofibrils**.
- Myofibrils are composed of **sarcomeres**, the smallest functional unit of contraction in skeletal muscle.
- Each sarcomere is delineated at each end by **thick, dark, Z disks**. Within each sarcomere exists **dark A bands** corresponding to the position of the **thick filaments (myosin)**, and the **light I bands** corresponding to the position of the **thin filaments (actin)** which span the Z disks.
- The central **M line** is the attachment site for myosin.
- The **H zone** is the area spanned by the **M line**.

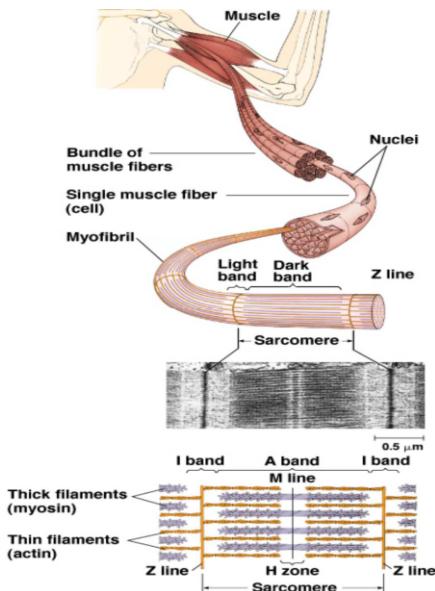


Figure 1: Exploded view of a bundle of muscle

1.2 Name and draw the location of the connective tissue sheaths found in skeletal muscle and explain the role they play in contraction in conjunction with tendons, Z disks, and the molecule titin.

If the fragile lipid bilayer was the only thing enclosing the molecular motors, the muscle would disintegrate upon contraction. The reason this doesn't occur is due to three connective tissue sheaths associated with the muscle as seen in Figure 2.

- The **epimysium** surrounds the entire muscle.
- Each fascicle is surrounded by the **perimysium**.
- Each muscle fibre is surrounded by a basement membrane called the **endomysium**. The connection between the endomysium and the contractile proteins it houses is vital; when genetic mutations alter this connection, major muscular dystrophies result.
- The sarcomere is delineated by two *Z* disks composed of α -actinin. At these sites, force is transmitted along the muscle through to the tendons which move the skeleton. Extending from the *Z* lines are actin and **nebulin** molecules (but not far enough to reach the *M* line). In mutations in which nebulin is absent, the actin filaments may be only 1/3 to 1/2 the length of a normal actin filament, leading to severe muscle weakness.

Nebulin holds the actin in an orientation in which the myosin heads can effectively interact with it, acting as a scaffold for the regulation of its length, as well as structurally supporting it through the stress/strain of contraction. Myosin is pictured; its smooth central head is held by the *M* line, and the cross bridge heads interact with binding sites on the actin, collectively forming the molecular motor powering contraction.

- **Titin** also extends from the *Z* discs albeit all the way to the *M* line. It:
 - Closely associates with myosin, maintaining its central position.
 - Generates passive tension via elastic extension when the sarcomere is stretched during elastic extension.

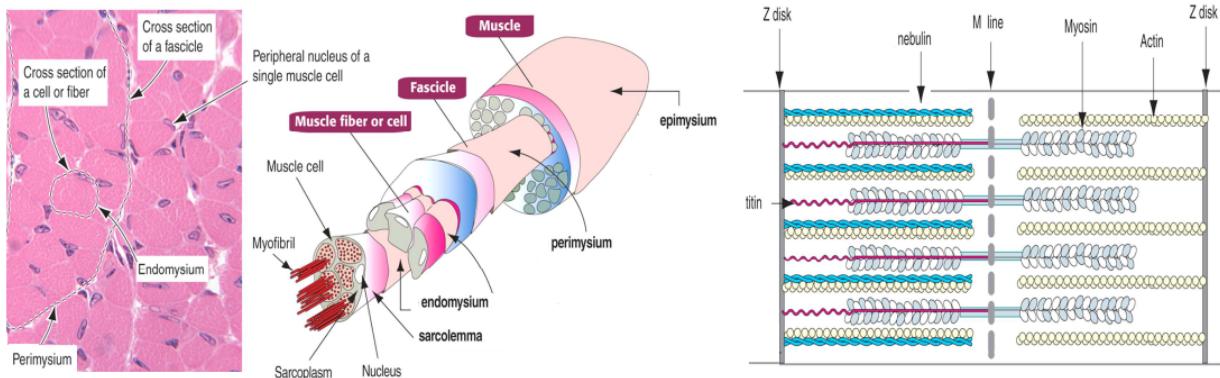


Figure 2: Connective tissue sheaths and proteins of the sarcomere

1.3 Describe the sliding filament hypothesis of skeletal muscle contraction and provide one piece of experimental evidence in support of it.

The sliding filament hypothesis states:

1. Muscle contracts via the relative sliding of thick (myosin) and thin (actin) filaments.
2. This sliding is caused by cross-bridges projecting from the myosin filaments interacting with specific sites on actin filaments.
3. The cross bridges move only 10 nM.
4. However, this happens cyclically again and again, splitting a molecule of ATP per cycle. Since a single muscle fibre consists of trillions of myosin heads, we can produce large contractions.

1.3.1 Evidence (Figure 3)

A direct prediction due of the fact that myosin heads interact with specific binding sites on actin, is that there **should be an optimal length at which the muscle produces maximum force**, i.e. **when all binding sites are occupied**.

- Define l as the sarcomere length. When $l = 1.05\mu m$, the sacromere is too compressed and the actin molecules obscure 100% of their binding sites and cannot produce force.
- At $l = 1.65\mu m$, the actin molecules obscure 20% of their binding sites and thus, only 80% of the maximum force is produced.
- At the optimal $l = 2.25\mu m$, none of the binding sites are obscured and all the binding sites are occupied by the myosin heads resulting in the maximum force.
- If the muscle is stretched to $l = 3.65\mu m$, the myosin heads cannot reach any binding sites and cannot produce force.

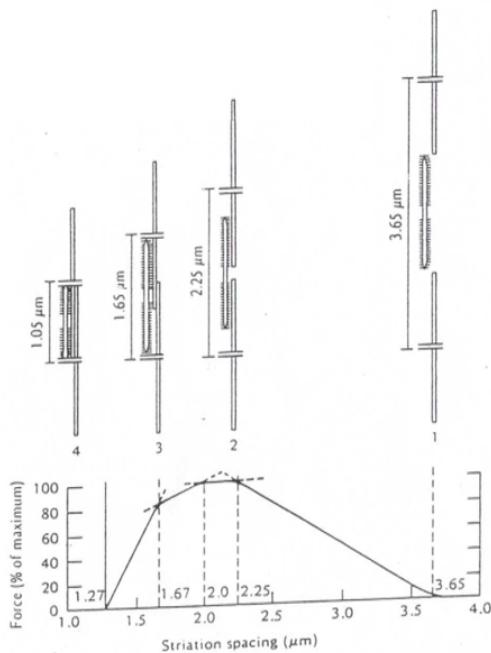


Figure 3: Sacromere length vs force profile

- 1.4 Show the position of dystrophin, dystroglycan associated proteins and laminin in relation to the sarcomere proteins and sarcolemma. Explain what happens when these proteins are absent or mutated.

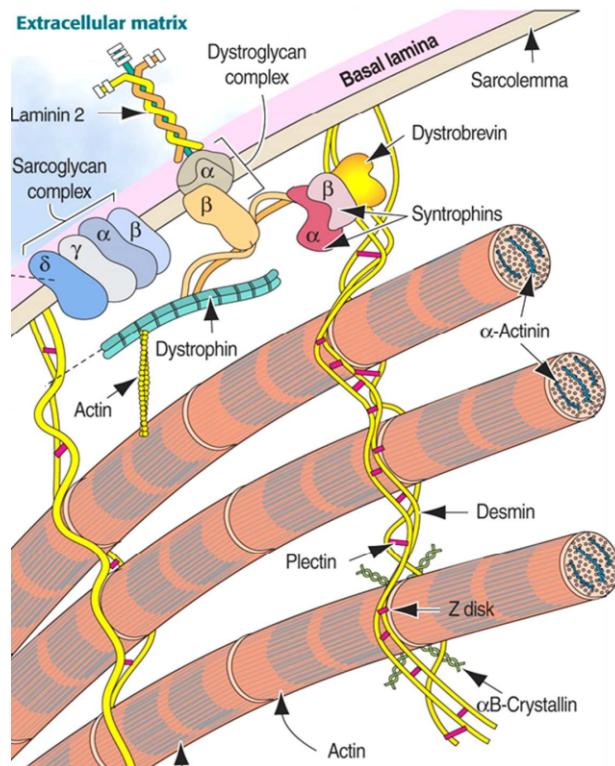


Figure 4: Different sacromere proteins

1.4.1 Brief description of some sarcomeric proteins/structures

Myofibrillar proteins of vertebrate skeletal muscle			
Protein	Molecular weight ($\times 10^3$)	Content wt %	Localization (band)
Contractile			
Myosin	520	43	A
Actin	42	22	I
Regulatory			
Tropomodulin	70	5	I
Tropomyosin	33 \times 2	5	I
M-Protein	165	2	M line
C-Protein	135	2	A
α -Actinin	95 \times 2	2	Z line
Cytoskeletal			
Titin	2800	10	A-I
Nebulin	750	5	I

Figure 5: Sarcomeric proteins occurring >1%

- Figure 5 lists the proteins occurring >1%
- The proteins occurring in < 1% are also important because **their absence results in muscle disease**.
- Surrounding the endomysia are **basal lamina** connective sheaths surrounding individual muscle fibres. These produce force which can be transferred longitudinally, but can also be **transmitted laterally** in the event a muscle section is damaged and no longer contractile.
- The yellow-ladder protein **desmin** holds the myofibrils in a specific orientation.
- **Plectin** links desmin filaments.
- **$\alpha\beta$ -Crystallines** are heat shock proteins which stabilise the muscle, allowing the proteins to reach higher temperatures before denaturing. Because proteins denature at approximately $40^\circ C$, $\alpha\beta$ -crystallines are vital because their absence/mutation would mean that even normal exercise would cause breakdown.
- Other protein groups exist which all serve as a protein scaffolding supporting the fragile lipid bilayer through the stress/strain of contraction. We now **specifically discuss dystrophin and dystroglycan associated proteins**.

1.4.2 Dystrophin and dystroglycan associated proteins

- Dystrophin connects the **dystroglycan complex across the sarcolemma into a cruciform shaped protein called laminin-2** which plugs into the basement membrane.
- In the absence of dystrophin, the sarcolemma is disrupted allowing Ca^{2+} entry which causes muscle fiber necrosis.
- Laminin-2 helps you plug into your connective tissue in order to stop it sliding relative to other tissues. Many skin diseases/congenital muscle dystrophies thus result due to a loss of laminin.
- Dystrophin reinforces/stabilises the sarcolemma during contraction, maintaining a link between the cytoskeleton and the ECM. Dystrophin deficiency causes **Duchenne's muscular dystrophy**, an X linked recessive condition in which the muscle fibres are continuously ripped apart because the membrane cannot sustain the normal stresses/strains of contraction. They are regenerated until regenerative capacity is lost and skeletal muscle is replaced by connective tissue resulting in heart/respiratory failure.
- **Note:** If a cross section of a muscle fibre is observed, you will notice that it is polynucleated and that in healthy skeletal muscle cells, nuclei should be on the periphery of the cross section. These nuclei control their own small portion of protein production of that cell. A central nucleus usually indicates muscle damage/disease.

1.5 Draw and describe the cross bridge cycle and the role it plays in muscle movement. Explain how the cross bridge cycle is initiated and terminated indicating the role of calcium in this.

- Before the cross bridge cycle can actually occur, the following must happen (see Figure 6).
 - An action potential triggers the release of Ca^{2+} from the SR, into the sarcoplasm. In a resting state, tropomyosin blocks myosin binding sites on the actin molecules, preventing cross-bridge formation, and thus prevent muscle contraction without nervous input. The protein complex troponin binds to and regulates tropomyosin, helping to position it on the actin molecule.
 - The Ca^{2+} binds to troponin, causing conformational changes in the protein complex that pulls tropomyosin out of the grooves, exposing the myosin binding sites and allowing the formation of a cross-bridge.
 - **Note:** that once muscle is switched on, and Ca^{2+} is loaded, it's all or nothing. If you produce 50% of the maximum force from a big muscle, than that 50% of maximum force is actually 100% of the force from 50% of your fibres.

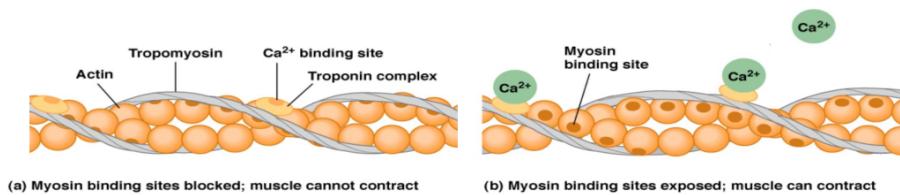


Figure 6: Ca^{2+} triggering the exposure of binding sites

The **cross bridge cycle** consists of 4 main steps.

1. As ATP binds to myosin, it causes the detachment of the myosin head from the actin filament.
2. The free myosin head moves from its low energy position, to its high energy position to attach to actin, during which the ATP is hydrolysed to ADP and P.
3. The free myosin heads along with ADP and P, rebind to the actin filament.
4. The cross-bridge generates force, and actin displaces ADP and P from the cross bridge. The actin-myosin cross bridge is now ready for the ATP binding of step 1.

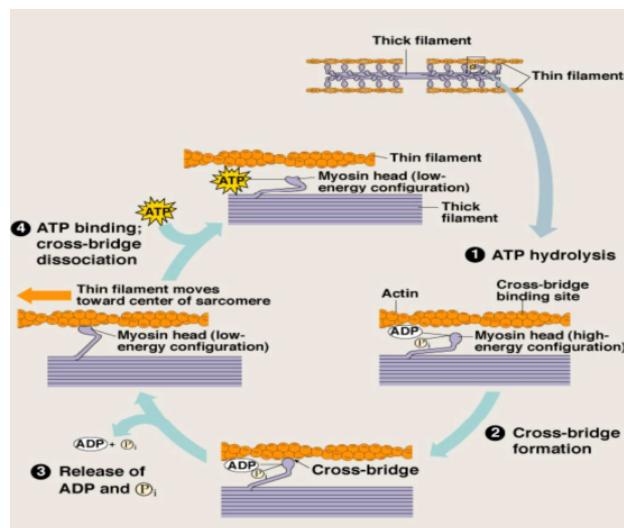


Figure 7: The cross bridge cycle

1.6 Draw and describe the function of the T-tubular system in relation to the internal calcium store the sarcoplasmic reticulum and explain how the process of excitation contraction coupling is thought to occur in skeletal muscle.

- To cause a contraction of the myofibrils in the deeper parts of the muscle cell, you must somehow carry the action potential deep within the fibre. This is accomplished using the **T-tubules** which are collectively known as the **T-tubular system**.
- The T-tubules invaginate the surface membrane of the muscle fibre and run deep into the muscle, contacting the myofibrils at the junction between the *A* and *I* band.
- In cardiac tissue Ca^{2+} diffuses from the plasma into the muscle cell. However in skeletal muscle, this would take too long and so, in fast fibres, each myofibril in addition to the T-tubules, is also enveloped in a **sarcoplasmic reticulum**; an internal calcium store, whilst in slow fibres, groups of myofibrils share an SR (elaborated on later).
- The term **triads** is often used to refer to the T-tubular system and the SR because if you look at them, you have the T-tubule system in the middle and two bulbous SR ends on either side.

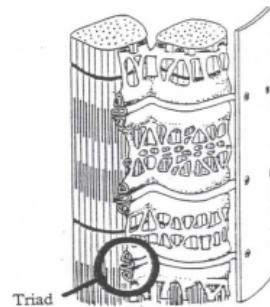


Figure 8: SR and T-Tubular system

The method in which an AP from the CNS is transformed into a Ca^{2+} signal, is via **excitation contraction coupling**:

1. An action potential travels along the surface membrane before diving into the T-tubules.
2. Voltage gated Na^+ channels open and Na^+ influx occurs, depolarising the cell from about -80 mV to +60 mV.
3. This causes a voltage induced conformational change in the DHP channel, pulling the plunger from the ryanodine channel.
4. The SR has a very high Ca^{2+} concentration compared to the myoplasm, so an explosion of Ca^{2+} into the myoplasm occurs, facilitating the cross bridge cycle.

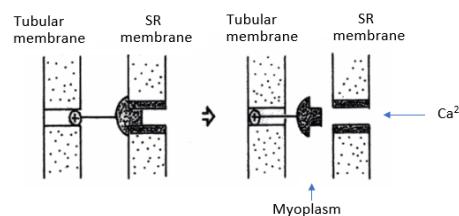


Figure 9: Excitation contraction coupling DHP-RYR plunger mechanism

- Note: the above is very different to secondary neurotransmitters at a neurojunction where the chemical transmission opens a channel. It is a **direct mechanical coupling**, so it is very quick, efficient, safe and as soon as the action potential has disappeared, the protein foot lodges back in closing the channel, albeit you have more control with chemical messengers.

1.7 Using both lists and diagrams catalogue the steps involved in skeletal muscle contraction and relaxation.

1. AP in the surface membrane (see 6.2 in Excitable Cells)
2. Action potential conducted down T-tubules
3. Cell depolarisation causes voltage induced DHP conformational change, pulling plunger from Ryanodine channel
4. Explosive SR Ca^{2+} influx into myoplasm
5. Myoplasmic Ca^{2+} increases
6. Ca^{2+} binds to TnC causing conformational change that dislodges Tm, exposing binding sites on actin
7. Cross bridge cycle, sarcomere shortens
8. Pumping of Ca^{2+} back into SR
9. Ca^{2+} unbinds from TnC, Tm inhibition resumes.
10. Cross bridge detachment, relaxation

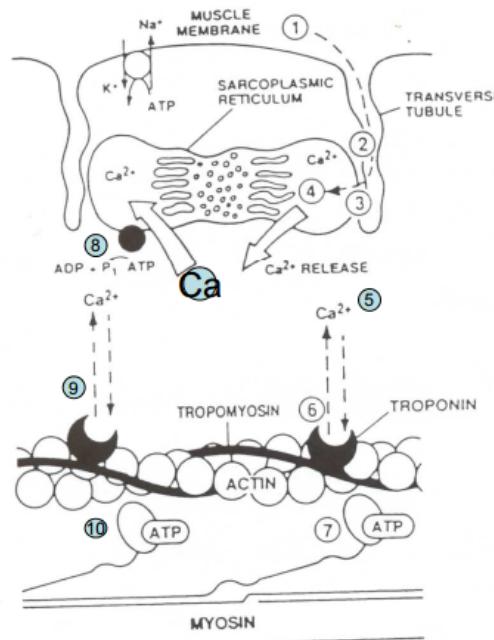


Figure 10: Contraction and relaxation

1.8 Explain isometric and isotonic contractions.

- **Isotonic contractions** generate force by changing the length of the muscle. Figure 11(left) displays a muscle shortening to lift a mass.
- **Isometric contractions** generate tension, but do not shorten in general (the muscle will still shorten 5-10% but this is because of the elastic elements of the muscle). Figure 11(right) displays a muscle exerting tension, but with a negligible change in length. The period of **pre-stretching** constitutes an isometric contraction (explained below).

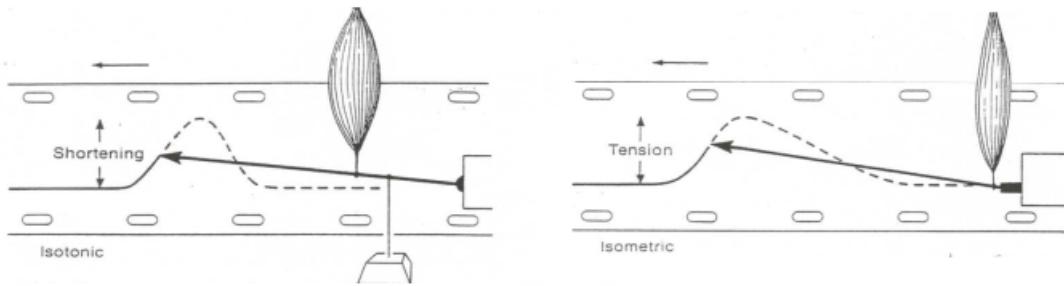


Figure 11: Isotonic (left), Isometric (right)

1.9 Explain what is happening during the active component in skeletal muscle contraction.

- We can model a muscle as an **actin-myosin motor** in parallel with an **elastic element**.
- The elastic element is collectively serially composed of the three protective connective sheaths, the tendons, the Z lines (α -actinin) and titin.
- Following an explosive Ca^{2+} influx and the beginning of the cross bridge cycle, observe steps *B* to *C* and notice that the position of the mass has not changed.

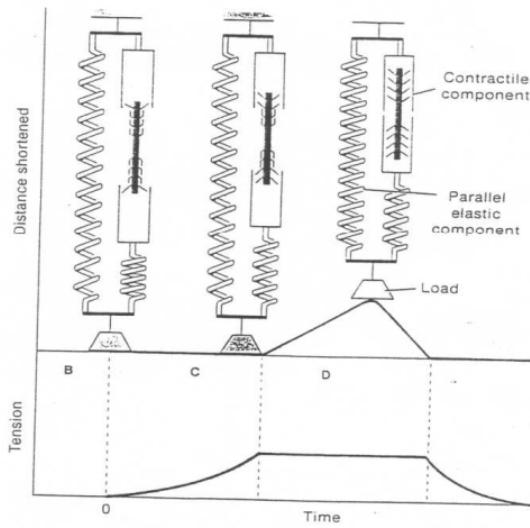


Figure 12: Pre-stretching and isotonic contraction

- **Why is this?** Imagine a mass connected to a rubber band. Before the mass can be lifted, you need to "pull the slack" from the rubber band to take up its elastic modulus before the you can actually lift the weight.

- In the same way, the sliding filaments must "pull the slack" from the elastic elements before an isotonic contraction can actually occur.
- Thus, during the active component of skeletal muscle contraction, ($B \rightarrow C$), the parallel elastic elements are being pre-stretched, and once the myosin-actin motor has "pulled the slack", the muscle can now do external work to lift the weight.

1.10 Explain the two mechanisms which control force output from skeletal muscle.

- The two methods of regulation of force output from muscles is:

1. Recruiting more motor units

- Referring back to Moorhouse's lectures, once a stimulus crosses the threshold, the full action potential is generated. If a greater stimulus is applied, the size of the action potential will not change. **Why then does an increasing the stimulus amplitude to an extent, increase the muscle contraction?**
- This is because a nerve is made up of thousands of nerve cells of varying diameters and thresholds; **not just one**.
- By the **size principle**, the first motor units to be recruited have the smallest values for axonal conduction velocity and contractile force, and are the slowest to contract and fatigue.
- At lower stimulus amplitudes, only the smaller motor nerves are recruited and fire action potentials. As we increase the stimulus amplitude, we reach a point where the stimulus is sufficient to recruit all of the 100% of the muscle fibres.

2. Changing the stimulus frequency

- Another paradox arises whereby, **if all the muscle fibres are recruited and contracting, why does increasing the frequency increase force output?**
- When a single stimulus is sent to the muscle causing it to contract, this is called a **twitch**. If the muscle is allowed to fully relax and another stimulus is sent, it produces an identical contraction.
- In the laboratory we observed that if a second stimulus arrived before the muscle could relax from the first stimuli, then you get a **summation of contractions** and the force generated increases as seen in Figure 13.

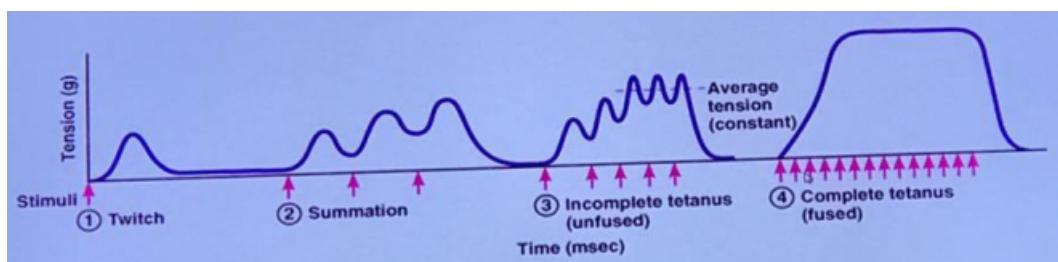


Figure 13: Summation

- If we further increase the frequency of the stimuli, the summation continues, until it reaches a point where there is no time at all for the muscle to relax in between stimuli and we reach a **complete (fused) tetanus** which is 4 times larger than a single twitch.
- **In summary**, the reason for this relates to the biomechanical structure of the muscle addressed in 1.9: **there is simply insufficient time during a single twitch to develop full force because you're spending time pre-stretching the elastic elements**.
- This can be confirmed in an experiment whereby if you prestretch the muscle, the twitch is the same height as the tetanus.

1.11 Explain the concept of fibre types and described what types of fibres are found in mammalian skeletal muscle. Describe how fibre types influence contraction. How are fibre types identified, both functionally and using histochemistry?

There are two main fibre types and different ways to identify them:

1.11.1 Organisation of SR

- In fast fibres, each myofibril is enveloped by its own SR allowing Ca^{2+} to explosively increase in concentration next to the contractile proteins, as opposed to the slow diffusion of Ca^{2+} to the fibres. This facilitates **rapid contraction** and **relaxation**. To relax the muscle, Ca^{2+} ATPases pump Ca^{2+} back into the SR against its concentration gradient.
- In slow postural fibres, groups of myofibrils share an SR because they **do not need to contract or relax rapidly**, and are thus **less energetically costly**.
- Slow pumping of Ca^{2+} back into the SR due to Ca^{2+} leaks constitutes the metabolic rate which generates bodily heat.

1.11.2 α -actinin 3

- The Z lines of fast fibres have the special protein α -actinin 3.

1.11.3 Fusion frequency/colour/fatigue/size

- Whilst most muscles in the body are 50-50 fast-slow fibres, the **extensor digitorum longus (fast)** and the **soleus (slow)** are exceptions.
- EDL is very white compared to the soleus which is relatively red. This is because the O_2 binding proteins myoglobin are found in a higher density within slow aerobic muscles.
- The soleus reaches maximum contraction at a lower frequency than the EDL. Energetically this makes sense because you fire your nervous system at lower rates to make the postural muscles contract and stay contracted. This is because slow muscle contracts/relaxes more slowly than fast. As you get mechanical summations, by the time the repeated signal comes along, there's not enough time for relaxation to occur, and because the relaxation is slower, the summation occurs more quickly.
- Fast fibres generally fatigue faster and larger in diameter than slow ones.

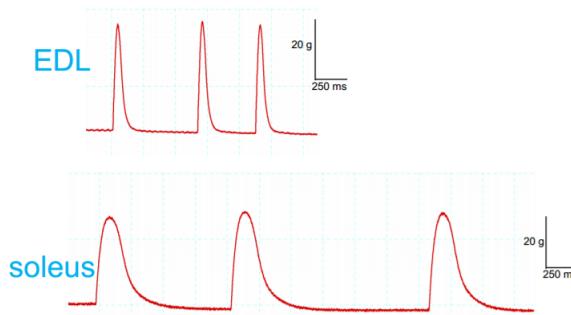


Figure 14: Soleus (slow) has a lower fusion frequency compared to EDL

1.11.4 Histochemical stains

- (a) Fast type-II fibres have high myosin ATPase activity at pH 9.4, whilst slow type-I fibres have low myosin ATPase activity at pH 9.4. Staining for myosin ATPase, pH 9.4 stains the fast fibres black.
- (b) Slow muscle is aerobic and its metabolic pathway uses O_2 and ATP produced from the Krebs cycle within the mitochondria. Thus, it has a higher density of mitochondria and a higher activity of NADH tetrazolium reductase which can be stained for.
- (c) The glycolytic enzyme activity (phosphorylase) is much higher in fast fibres and can also be stained for.

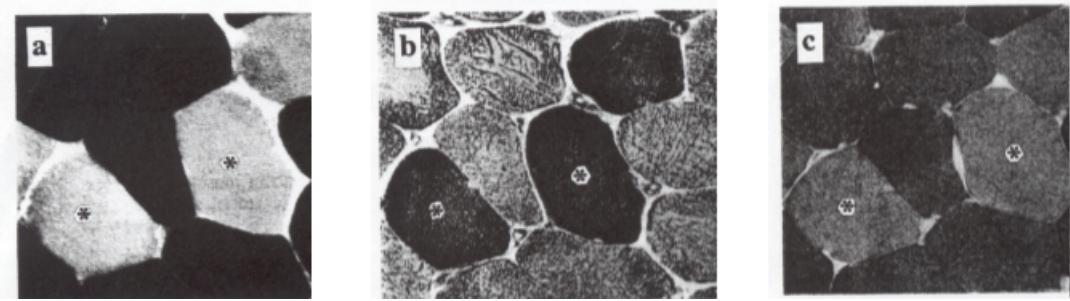


Figure 15: Different histochemical stains used to discern fast/slow fibres

1.12 Briefly explain the main cellular mechanisms responsible for producing the decay in force we experience during skeletal muscle fatigue

- During fatigue, there is a reduction in ATP and a build up of phosphate ions from its hydrolysis.
- These phosphate ions enter the SR, precipitating Ca^{2+} .
- This reduces the free ionic calcium available for release from the SR reducing the force output.

2 Lecture 3

2.1 Understand the mechanism of smooth muscle contraction and explain how it is regulated

2.1.1 Contraction

- The dense bodies (smooth muscle Z discs) are attached to the membrane via desmin and vimentin intermediate filaments.
- Actin filaments and associated myosin attach to the plasma membrane and within the cytoplasm to the dense bodies.
- Because the arrangements of contractile proteins are oriented in random directions all over the cell, when it is activated, there is a global contraction.

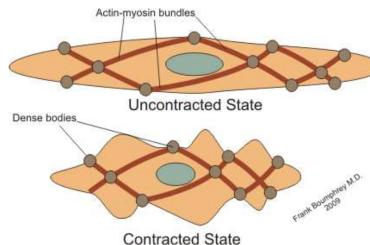


Figure 16: Global contraction of smooth muscle

2.1.2 Regulation (Contraction)

- Ca^{2+} diffuses into the cell from the ECF, triggering Ca^{2+} induced Ca^{2+} release from the SR.
- Ca^{2+} binds to/activates calmodulin (CaM)[the regulatory complex].
- This activates myosin light chain kinase (MLCK).
- MLCK phosphorylates light chains in myosin heads and converts inactive myosin to active myosin. This increases myosin ATPase activity (because it requires ATP).
- Cross bridge cycle occurs.
- Note that Ca^{2+} can directly enter the cell via mechanosensitive channels, or it can also have receptor mediated activation causing a second messenger to be released inside the cell (IP3) which stimulates SR Ca^{2+} .

2.1.3 Regulation(Relaxation)

- Ca^{2+} channels facilitating influx close. Mechanosensitive channels may no longer be stretched, the cell maybe repolarised closing voltage activated channels, or an agonist binding to a second messenger system has been removed.
- Ca^{2+} -ATPases (Ca , Mg ATPases and Na^{2+}/Ca^{2+} exchangers) pump Ca^{2+} back into the SR, but also across the membrane because the SR isn't very large.
- The myosin light chain is enzymatically dephosphorylated.

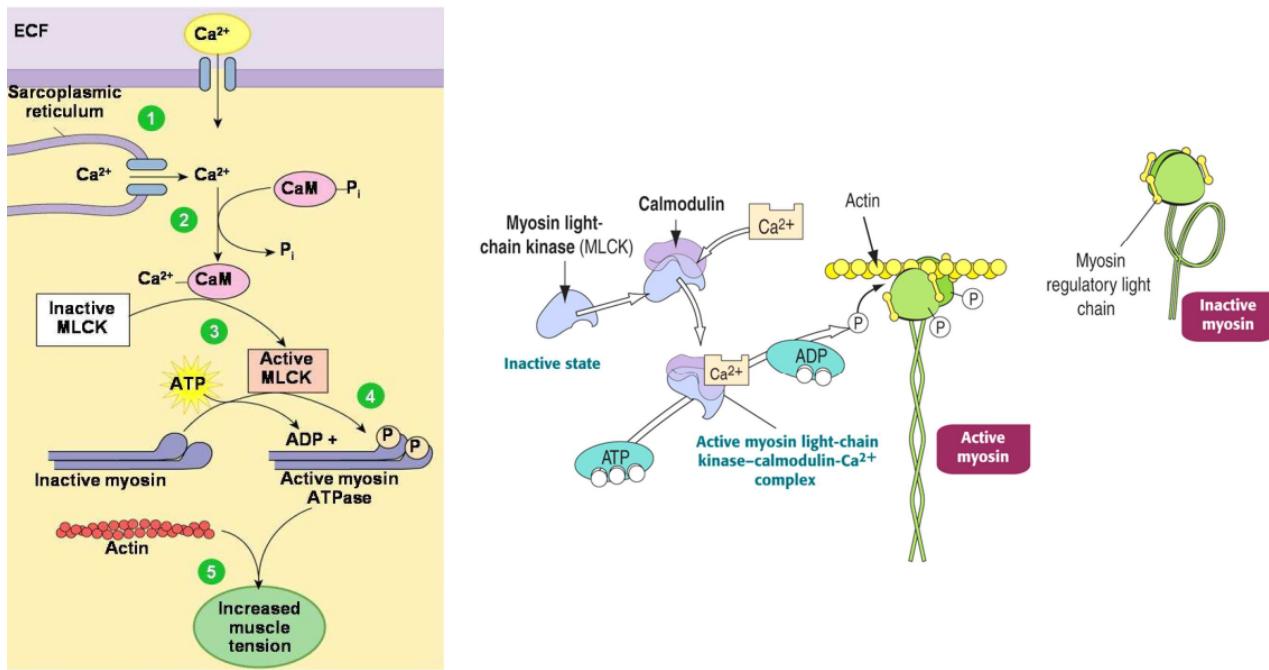


Figure 17: Regulation of smooth muscle

2.2 Explain the formation and function of caveoli

Caveolae are permanent structures; depressions in the plasma membrane at the end of the cell.

2.2.1 Functions

1. **Increase surface area**, allowing the inelastic membrane to stretch and contract without being destroyed.
2. Detach to form **pinocytotic vesicles** initiating **endocytosis**.
3. **Enclose poisons** to protect the cell.
4. **Concentrate signalling molecules** including Src-like tyrosine kinases, G-proteins and nitric oxide (*NO*). *NO* is concentrated inside caveoli using nitric oxide synthases (*NOS*). When stimulated by high muscle load, *NO* is released, diffusing across the membrane into the blood vessels. This causes dilation increasing *O₂* to the muscle and allowing it to produce the extra *ATP* it requires at the time.

2.2.2 Formation

1. Caveolin binds to **cholesterol** on a **lipid raft** (cholesterol/sphingolipid rich region). This cholesterol is important in stabilising and controlling membrane fluidity. Without caveoli however, it is inelastic. The lipid region is responsible for exo/endocytosis and signal transduction.
2. Caveolin pulls the cholesterol, causing an invagination.
3. If this process continues, a pinocytotic vesicle pinches off from the membrane.

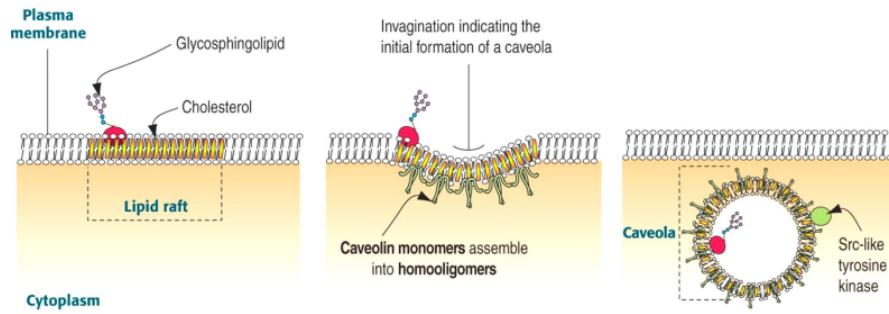


Figure 18: Formation of caveoli and pinocytotic vesicle

2.3 Describe the positions and roles played by smooth muscle in the body

- Contracts or relaxes in blood vessels to regulate blood flow.
- Myogenically stimulated to contract in the walls of the GI tract to produce a peristaltic action.
- Push bile from the gall bladder into the bile duct.
- Regulate airflow by contracting/dilating the bronchi/bronchioles.
- Smooth muscle in the ureters push urine from kidneys to bladder.
- Triggered by hormones during childbirth to contract, pushing the child out.

2.4 Draw and describe a smooth muscle cell

- Note, each smooth muscle cell is surrounded by a **basal lamina** which helps to transmit force in all directions not just longitudinally.
- Descriptions are provided throughout these notes.

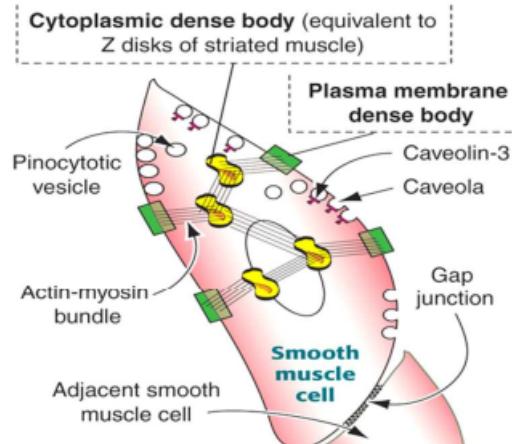


Figure 19: Smooth muscle cell

2.5 Draw the structure of a cardiac myocyte and explain how it differs in form and function from a skeletal myocyte

2.5.1 Cardiac myocytes vs skeletal myocytes

1. Contract constantly without fatiguing.
2. Much shorter ($85\text{--}250\ \mu\text{m}$) compared to skeletal myocytes (up to 14 cm).
3. 2 nuclei vs thousands in skeletal myocytes.
4. Branched fibres with intercalated discs so that the cardiomyocytes contract as a unit to effectively eject blood instead of long cylinders.
5. T tubules found at Z discs instead of AI junction and are larger.
6. T tubule interacts with one SR cisterna instead of two, forming a diad instead of a triad.
7. SR less dense/spindly/extensive and plays more of an additional role than in skeletal muscle. A lot of Ca^{2+} required to trigger contraction, because we don't need to do it quickly, originates externally. Uses Ca^{2+} induced Ca^{2+} release from cardiac SR to provide Ca^{2+} boost.
8. Much longer action potential due to Ca^{2+} induced plateau.
9. Mitochondria more abundant because it is a very aerobic tissue, and contains numerous cristae (infolds).

2.5.2 Diagram

- Observe the intercalated discs; junctional complexes with step-like transverse portions perpendicular to the cell's long axis, and longitudinal portions running parallel to the myofibrils.
- The transverse component is represented by the Z disc, consisting of:
 1. **Desmosomes** mechanically linking cells
 2. **Fasciae adherentes** containing α -actinin/viniculin and provide an insertion site for the thin filaments of the last sarcomere of each cardiocyte.
- **Gap junctions** restricted to the long portion of the discs enable **ionic cellular communication leading to synchronous muscle contraction**.
- The terminal fibres of the heart's conducting system are the **Purkinje fibres** (larger, paler stained, less myofibrils (not contractile), pacemaking). Its purpose is to conduct signals from the AV node to the bottom of the heart.
- The sarcomeres are similar to skeletal muscle.
- Sarcolemma is the cardiocyte's membrane.

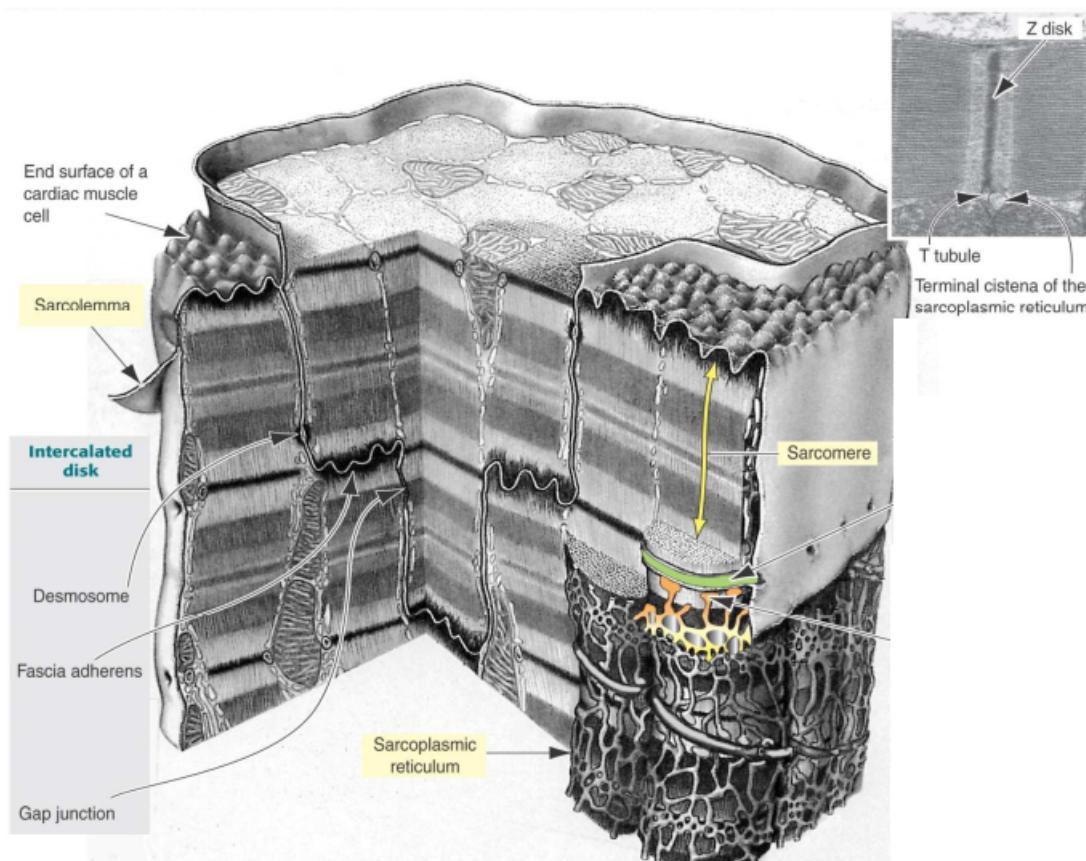


Figure 20: Cardiac myocyte

2.6 Compare and contrast smooth muscle with striated muscle

2.6.1 Smooth muscle vs striated

- Spindle shaped vs branched or cylindrical fibres.
- Mononucleated instead of multinucleated.
- Dense bodies instead of *Z* lines (both of which have α -actinin. Not organised in sarcomeres. Randomly organised to facilitate global contractions).
- Caveolae serve as primitive *T*-tubule systems that transmit electrical excitation into the cell.
- Cardiac and smooth muscle are both shorter than skeletal muscle fibres.
- Produces slow contractions which are less powerful than those of striated muscle; the Ca^{2+} must diffuse from the outside rather than the SR (no need for fast contractions).
- Ca^{2+} dependent phosphorylation and MLCKs are the control factor for contraction vs troponin which binds Ca^{2+} in skeletal muscle.
- Similar to cardiac muscle in which the tight junctions induce contraction as a unit.
- Some Ca^{2+} is pumped into the SR, but most is pumped across the membrane during relaxation.

2.7 Explain what happens to cardiac myocytes after a heart attack (myocardial infarction)

Background

- **Myocardial infarction** is predominately caused by **cardiac ventricular hypertrophy**.
- When a cardiomyocyte gets too large, it cannot act as a unit to effectively eject blood from the ventricles, contracting within itself without closing the chamber for ejection. It also forces O_2 to diffuse further to power the mitochondria, leading to progressively weaker contractions ending in heart failure.
- Ultimately myocardial infarction is the consequence of a loss of myocardial blood supply due to an obstructed atherosclerotic coronary artery.

After a heart attack

- If the ischaemic time is < 20 minutes, the resultant reperfusion injury is below the viability threshold, salvaging cells that otherwise progress to irreversible injury.
- An ischaemic time > 20 minutes results in irreversible injury.
 - Within the first 24 hours of ischaemia, there is mononucleocytic infiltration, inflammation and necrosis. Cardiocytes display eosinophilic cytoplasm lacking regular intracellular striations.
 - Within 3 days, neutrophils surround necrotic cardiocytes.
 - Within 3 weeks, capillaries, fibroblasts, macrophages and lymphocytes surround area.
 - Within 3 months, the infarcted region is replaced by scar tissue.