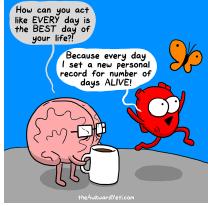


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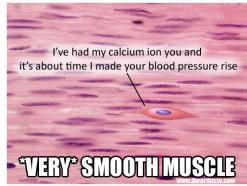
Muscle 3: Wrap up of Skeletal Muscle + Cardiac & Smooth Muscle



Please log in to ECHO360/ Lecture Recordings+ via moodle to participate in active learning activities

Dr. Chelsea Goulton

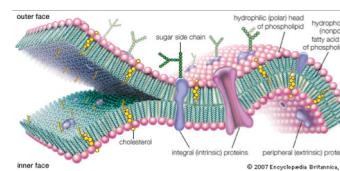
21-March-2018



Consider this...

We have these strings of molecular motors, moving around and generating force, bundled up inside the sarcolemma

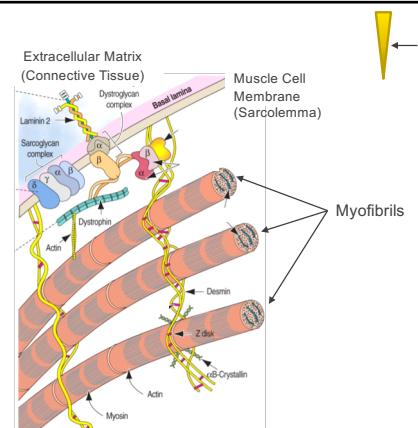
- The sarcolemma is a lipid bilayer, how does all this movement not just bust it apart?



Structural Proteins

One essential role is in protecting the muscle cell from being damaged during contraction

- Proteins involved in stabilizing the sarcolemma
 - Dystrophin & the Dystrophin Associated Complex
 - Responsible for a class of genetic disorders – Muscular Dystrophies





But the sarcolemma is still fragile...

Even in healthy cells muscle damage can occur after strenuous activity

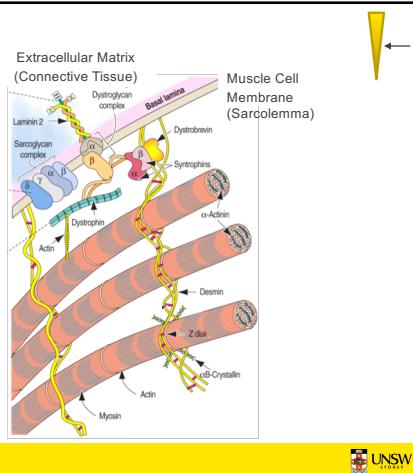
- Delayed Onset Muscle Soreness (DOMS)
 - Generally felt a few hours after exercise and can last up to a few days
- Partly due to small tears in the muscle tissue
 - Levels of creatine kinase and myoglobin are elevated in the blood
 - Suggests sarcolemma damage is involved
 - Leads to activation of pain receptors
- But what doesn't kill you makes you stronger!
 - Muscle damage in small amounts leads to hypertrophy.



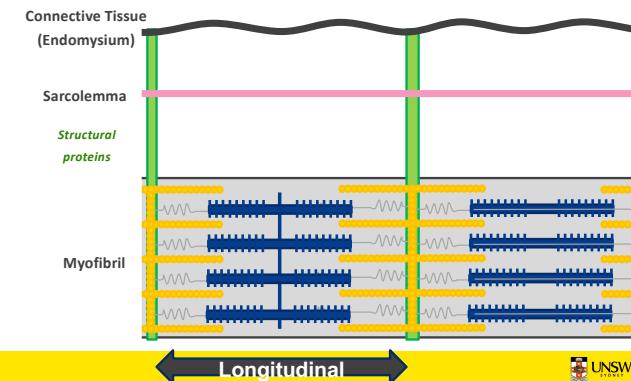
Structural Proteins

Another role is in transmitting force outside the cell to the connective tissues

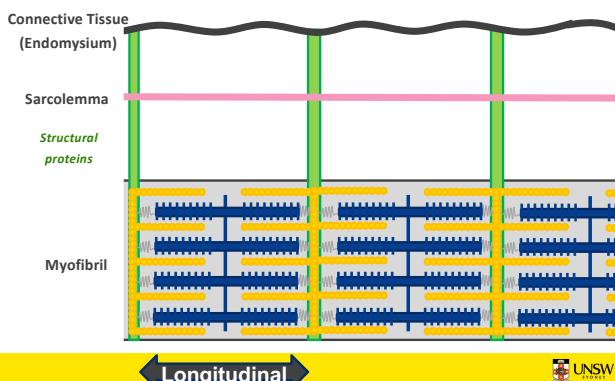
- Don't need to know specific proteins involved
- Z-lines of myofibrils are aligned by these structural proteins
- These attach to the sarcolemma and also interact with the surrounding connective tissue
- In this way, force is transmitted laterally as well as longitudinally



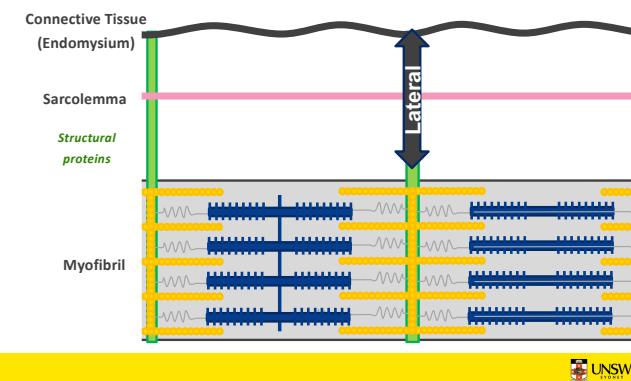
Relaxed

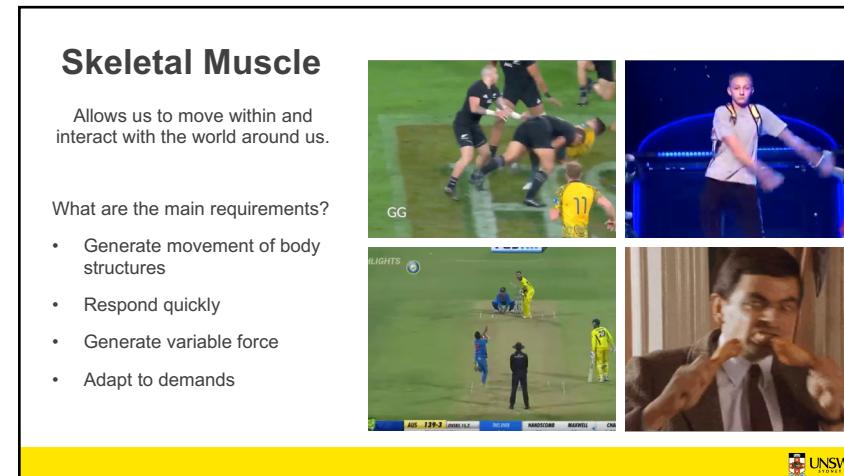
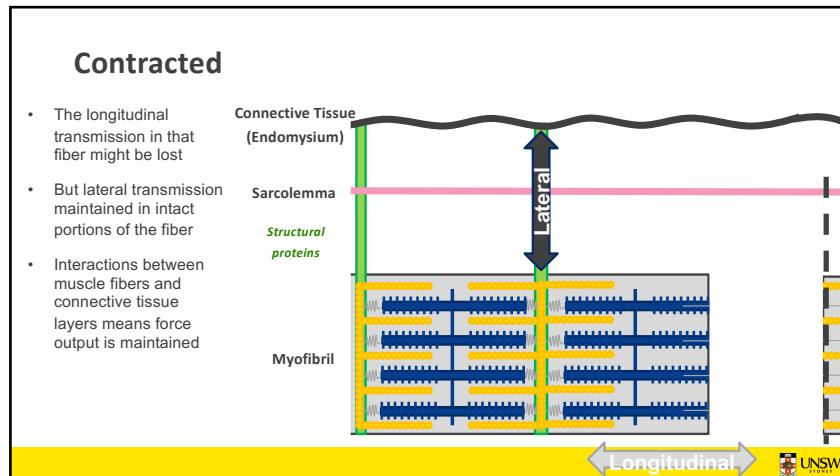
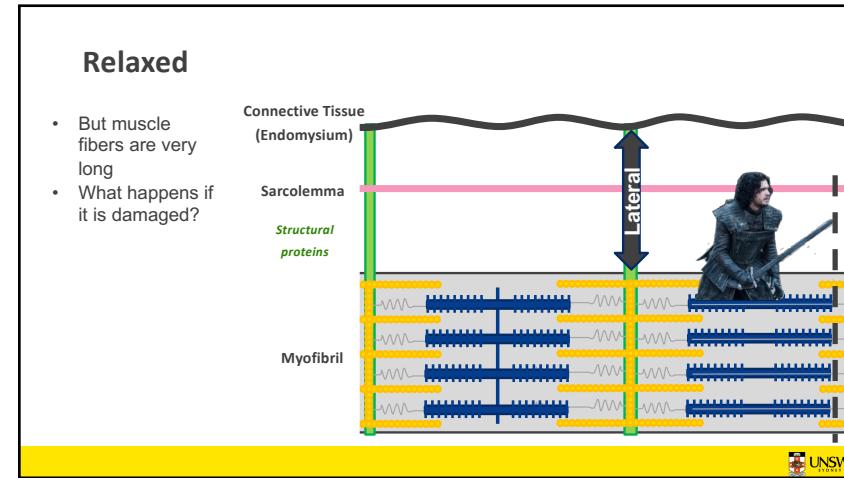
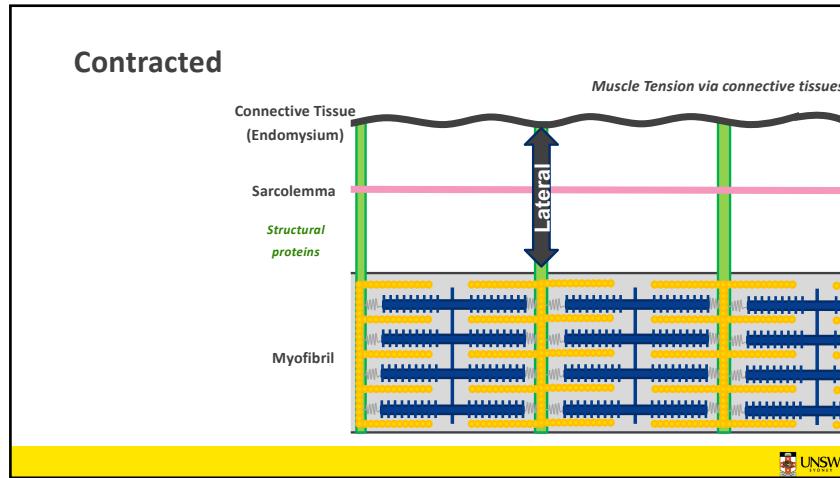


Contracted

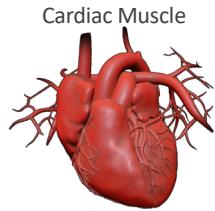
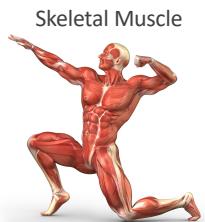


Relaxed





The Big Picture



Overall learning objectives:

- To describe the three types of muscle in the body in terms of structure and mechanisms of contraction
 - To compare and contrast between the different muscle types

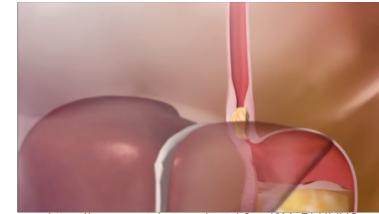


What is smooth muscle?

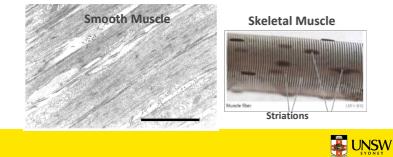
Smooth muscle is found in internal organs and structures that are **not** under voluntary control.

Examples include:

- The GI tract for mixing and moving digested food
 - Blood vessels for regulating blood flow to organs
 - Uterus for contractions during childbirth



<https://www.youtube.com/watch?v=J6MaPhULIYQ>



Features of Smooth Muscle

- Tend to be long and slender ("spindle shaped")
 - Ranging from 5-10µM in diameter and 30-200µM in length
 - Have a single, centrally located nucleus
 - No T-tubules and sarcoplasmic reticulum forms a loose network throughout the sarcoplasm
 - Do have invaginations called caveolae and SR does tend to cluster around them
 - Very basic analogue of the T-tubule system
 - No myofibrils or sarcomeres
 - Hence, the muscle does not appear striated
 - But contraction still involves the thick & thin filaments interacting through the cross-bridge cycle

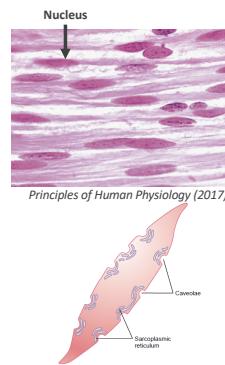


Figure 8-6
Sarcoplasmic tubules in a large smooth muscle fiber showing their relation to invaginations in the cell membrane called canaliculi.



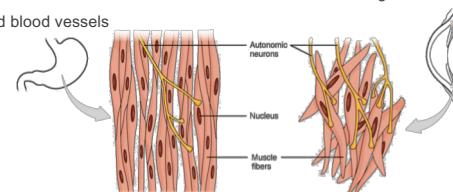
Multi-Unit vs. Single Unit Smooth Muscle

Single Unit Smooth Muscle

- Also referred to as visceral smooth muscle
 - Usually arranged in bundles or sheets with hundreds of cells contracting simultaneously
 - Adhere at multiple points and contain many gap junctions
 - e.g. GI tract and blood vessels

Multi-unit smooth muscle

- Each cell can contract independently and is innervated by a single neuron
 - Similar to skeletal muscle
 - E.g. iris muscle of the eye, piloerector muscles for "hair raising" effect



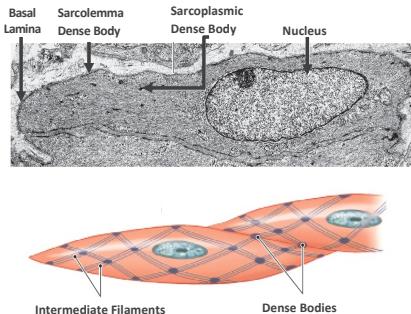
Features of Smooth Muscle

Surrounded by the basal lamina

- Layer of connective tissue which assists with force transmission between cells
- Similar role to endomycium in skeletal muscle

Dense bodies are scattered throughout the cytoplasm and plasma membrane

- Connected by a network of **intermediate filaments** which are made of the protein **desmin**
- Attachment point for actin filaments (equivalent of z-line in striated muscle)
- Transmit force to the exterior of the cell

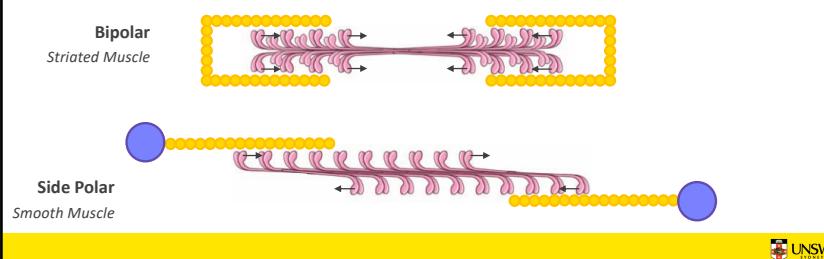


Fundamentals of Anatomy & Physiology (2017)



Sliding filaments in Smooth Muscle

- Side polar** arrangement of myosin heads allows them to pull in opposite directions on different sides of the filament
- This pulls the dense bodies towards each other



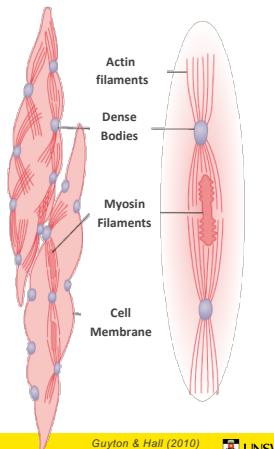
Contractile Proteins in Smooth Muscle

Thin filament (actin)

- Does not** contain the calcium sensing troponin complex
- This means binding sites for the myosin heads are always available

Thick filament (myosin)

- Interspersed among actin filaments
- This is why it lacks the regular cross-sectional structure of striated muscle
- Myosin heads must be phosphorylated before cross bridges can form

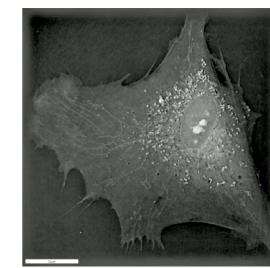
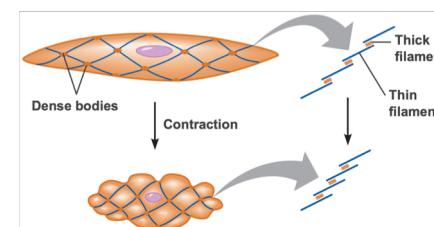


Guyton & Hall (2010)



Smooth Muscle Contraction

During a contraction, the sliding filaments pull the dense bodies towards each other



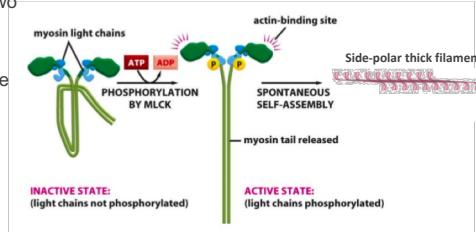
Cultured pulmonary smooth muscle cell contracting
Gaffield et al (2017)
<https://www.youtube.com/watch?v=DieKymj2Fxk>



More on the Thick Filament (Myosin)

Regulation of contraction is targeted to the thick filament in smooth muscle

- The myosin head is made up of two **light chains** & two **heavy chains**
- The light chain must be phosphorylated to activate ATPase activity and expose the actin binding site
- This is done by **Myosin Light Chain Kinase (MLCK)** regulates smooth muscle activation

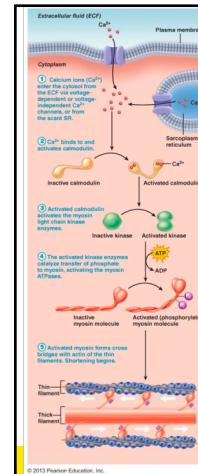


So is calcium involved in triggering smooth muscle contractions?



Excitation-Contraction Coupling in Smooth Muscle

- Intracellular Ca^{2+} concentration increases
 - Ca^{2+} channels in the sarcolemma
 - Ca^{2+} induces calcium release from the sarcoplasmic reticulum (SR)
- Ca^{2+} binds to **calmodulin**
 - Triggers a conformational change
- Ca^{2+} -Calmodulin complex activates the enzyme **myosin light chain kinase (MLCK)**
- MLCK phosphorylates the myosin heads
 - Unfolds the myosin molecule
 - Increases myosin ATPase activity
 - Exposes actin binding site
- The cross-bridge cycle is initiated



E-C Coupling in Smooth Muscle Continued

Contractions are much more **slow and sustained** than than skeletal muscle

- Takes longer for Ca^{2+} levels to peak
 - Relying more on extracellular Ca^{2+} influx
 - Less sarcoplasmic reticulum Ca^{2+} release
 - Less driving force for Ca^{2+} influx
- Takes longer for relaxation to occur
 - Requires more than just Ca^{2+} re-uptake
 - Phosphorylation must be removed by phosphatase enzymes
- Myosin ATPase activity is slower
 - 10-100 times slower so cross-bridge cycling takes longer
 - Also means that less energy is needed to maintain a contraction

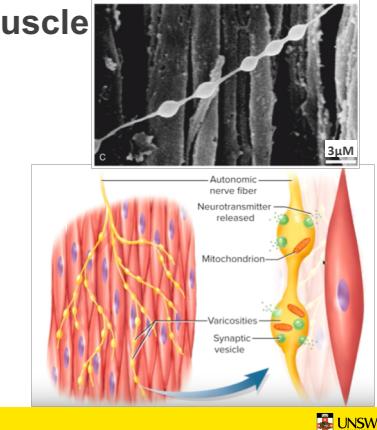
But it's okay, because smooth muscle wasn't build for speed!



Innervation of Smooth Muscle

Nervous control of smooth muscles is via autonomic neurons

- There is no neuromuscular junction
 - No specialized motor end plate
 - Neurotransmitter is still released
- Autonomic nerves have **varicosities**
 - Swellings where neurotransmitter is released
 - Many of these along axon length
- Sympathetic or parasympathetic system may cause contraction or relaxation
 - Depends on the receptor expressed and its effect on Ca^{2+}



Innervation of Smooth Muscle

Nervous control of smooth muscles is via autonomic neurons

- Single unit/Visceral Smooth Muscle
 - Gap junctions mean that excitation is spread throughout the muscle
 - Every myocyte does not need to be innervated
- Multi-unit smooth muscle
 - Still innervated by varicosities
 - Each cell is technically independent
 - But groups of myocytes innervated by the same neuron can act much more like a motor unit in skeletal muscle

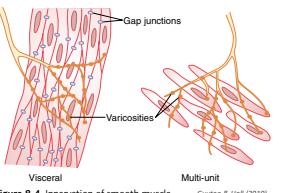
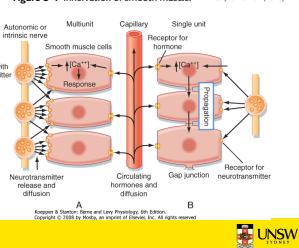


Figure 8-4 Innervation of smooth muscle. Guyton & Hall (2010)



Kennedy & Ganong and Ganong Physiology, 14e, Copyright © 2010 by Pearson Education, Inc. All rights reserved.



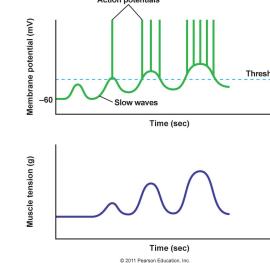
Properties of Smooth Muscle Contractions

Both multi-unit and single unit smooth muscle tend to have a normal background level of resting tension or **tone**

- Resting level of Ca^{2+} high enough to maintain a low level of cross-bridge cycling

When stimulation occurs, it tends to cause a **graded** change in the level of force produced

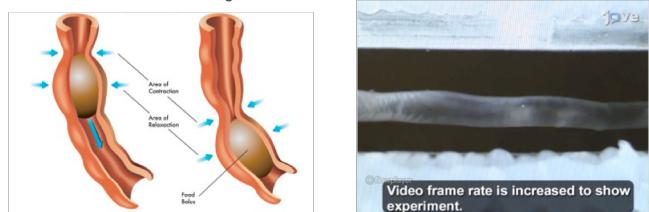
- This is different to the distinct twitch-like contractions seen in skeletal muscle
- Stimulation can be excitatory or inhibitory, causing a depolarization or hyperpolarization of the membrane
- An action potential is not necessary to cause a contraction



Properties of Smooth Muscle Contractions

Smooth muscle contraction or relaxation doesn't need to be directly stimulated by neural activity - Also activated by stretch or hormones

- E.g. Peristalsis
 - Series of wave like contractions which move food through the gut
 - Stretch activates mechano-gated Ca^{2+} channels in the membrane



Swaminathan et al (2016)

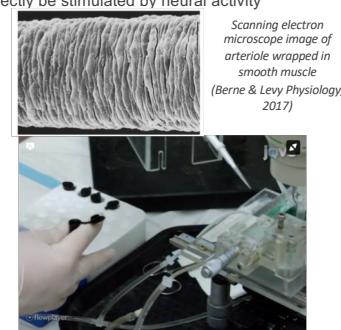


Properties of Smooth Muscle Contractions

Smooth muscle contraction or relaxation doesn't need to be directly stimulated by neural activity

E.g. Smooth muscle around blood vessels

- Fight or flight response
- Hormones in the bloodstream which will cause smooth muscle contraction or relaxation to direct blood flow to areas where nutrients are in high demand
- You will get to see this for yourself under the microscope in the **Microcirculation Practical**



Butcher et al (2012)



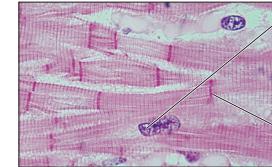
Cardiac Muscle

- Another involuntary muscle (thankfully!)
- Has an important job to do and must be able to keep doing it for a long time
- While the structure as a whole is complicated, the basis of contraction of individual muscle cells is the same
 - Not going into the conduction system of the heart and how it functions
 - Just focus on the similarities and differences of cardiac myocytes to skeletal and smooth muscle cells



Features of Cardiac Muscle

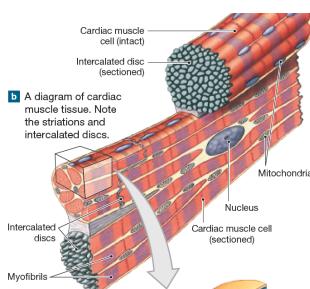
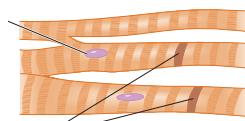
- Cardiac muscle cells are only found in the heart – surprise!
- Like skeletal muscle, cardiac muscle has an organized arrangement of thick and thin filaments
 - Also referred to as striated muscle
 - Same organized myofibrils & sarcomere structure
 - Contractions are regulated by the troponin/tropomyosin system
- Their major similarity to the smooth muscle is that the cells are connected by gap junctions
 - Electrical excitation is passed between cells



However there are a number of features which are unique...

Unique Features of Cardiac Myocytes

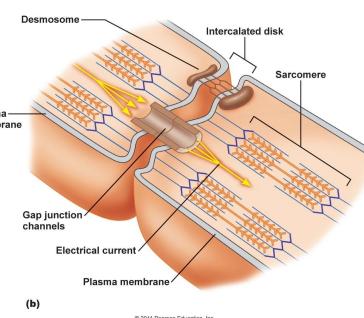
- Each cell contains one or two nuclei and is usually branched
- Lots more mitochondria than skeletal or smooth muscle
 - Up to 30% of heart volume is made up of mitochondria
 - Only aerobic respiration as it can't afford to get fatigued
- Each cell contacts others at a specialized site called an intercalated disc



Unique Features of Cardiac Myocytes

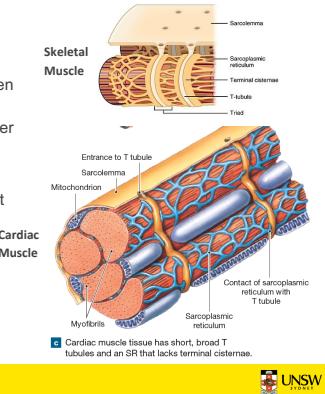
Each cell contacts others at a specialized site called an **intercalated disc**

- Desmosomes** are contact points which stabilize the positions of adjacent cells to maintain 3D structure
- Efficient transmission of force as myofibrils of cells are anchored to the plasma membrane
- Contains **gap junctions** to allow the transmission of ions
 - Important for the rhythmic contractions to occur



Unique Features of Cardiac Myocytes

- T-tubules are fewer, shorter and not as broad
 - Found around the z-lines of the sarcomere
 - In skeletal muscle, T-tubules are at the borders between A band and I band
 - Form a **dyad** with the sarcoplasmic reticulum, rather than a triad
- Sarcoplasmic reticulum is not as extensive
 - Although it is positioned close to the T-tubules, it does not form direct connection like skeletal muscle
 - Stores fewer Ca^{2+} ions



Triggering Contractions in Cardiac Myocytes

Cardiac myocytes are physically, chemically and electrically coupled

- They act like a single enormous cell or a **syncytium**.
- This makes them similar to visceral smooth muscle
- Makes sense as function is to pump blood rhythmically through different chambers



Normally electrical coupling is a good thing, but...

Commotio cordis - ("agitation of the heart")

- Disruption of heart rhythm that occurs as a result of a blow to the area directly over the heart (the precordial region),
- Must occur at a critical time during the cycle of a heart beat
- Causes cardiac arrest, so is often fatal

Cardiac cells contain mechano-gated calcium channels

- This is part of a stretch reflex in the heart
- Activation of these channels causes an out of sync depolarization



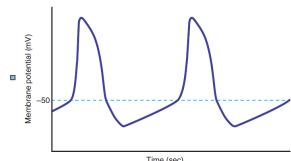
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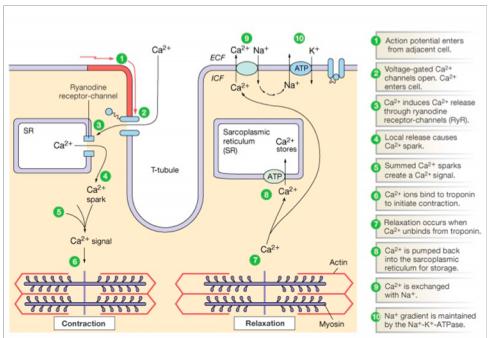
Cardiac myocytes do not need neuronal input to contract, as they have an internal rhythm

- The heart contains specialized cells (**pacemaker cells**) that determine the rate of contraction
- You will also be able to demonstrate this to yourself in the Microcirculation Practical
- Nervous system can then modulate this rate (autonomic innervation)

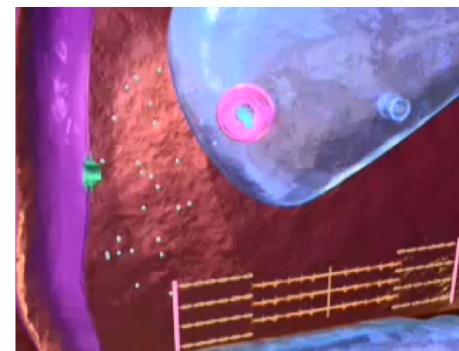


Excitation Contraction Coupling

- An action potential depolarizes the cardiac cell membrane
- This activates **voltage sensitive calcium channels (VSCC)** causing a Ca^{2+} influx from the extracellular space
- This triggers further Ca^{2+} release from the sarcoplasmic reticulum
- Remaining steps for contraction and relaxation are the same as skeletal muscle

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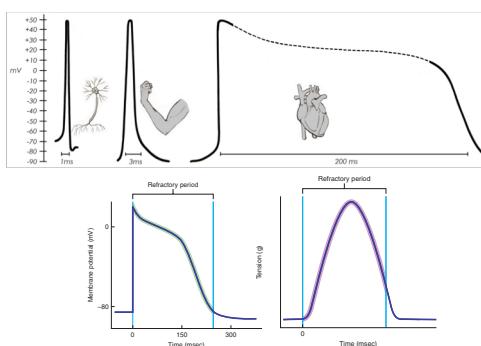
Excitation Contraction Coupling

Full video: <http://www.dailymotion.com/video/xhb0j0>UNSW
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Cardiac Action Potentials & Contraction

Cardiac action potentials are long and broad due to the much slower Ca^{2+} influx

- Much larger refractory period, almost as long as the entire contraction
- This means summation can not occur, even if stimulated at a high frequency
 - No tetanic contractions, which is a good thing!

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A Comparison of Muscle Types

	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Voluntary?	Yes	No	No
Number of nuclei?	Hundreds	2	1
Cell shape?			
Neuromuscular Junction?			
Fast or Slow Contraction?			
Source of Ca^{2+} ?			
...			

The final tutorial is designed to get you thinking about these comparisons

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Learning Objectives:

Smooth Muscle & Cardiac Muscle (Lecture 3)

1. Describe the structure and organisation of myocytes in smooth & cardiac muscle.
2. Explain how muscle contraction is initiated for smooth & cardiac muscle.
3. Describe the process of excitation-contraction coupling in smooth & cardiac muscle.
4. Compare and contrast properties of the three muscle types in terms of structure and function.

