Muscles
Structure & Function
Muscle Overview

- Use molecular **myosin** to capture and convert energy trapped in ATP into the mechanical energy of movement.

- Myosin is a large protein that interacts with **actin**, another protein, to produce force.
Muscle Overview

- Muscle is a tissue that consists of specialized contractile cells.

- Two categories of muscles:
  - **Striated muscles**: make up skeletal (attached to bone) and cardiac (heart) muscle
  - **Smooth (unstriated) muscles**: found in hollow or tubular organs such as the intestines, uterus, and blood vessels.
Cellular Movements

- **Microfilaments**: type of cytoskeletal fiber used in movement.

- Composed of long strings of the protein **actin**
Actin Structure

G-actin → Nucleation → Elongation → F-actin

(-) (+)
Actin Structure

- Can spontaneously assemble

- Growth is 6x faster from the positive end.

- Total length held constant if:
  - Growth from (+)end = shrinkage from (-)end
Actin Treadmilling v. Actin Growth

Elongation

(-)

(+)

F-actin

Capping protein

Actin treadmilling

Actin growth
Actin & Myosin

- Microfilaments are used in combination with myosin.

- Different arrangements enable cells to transport vesicles and organelles, change shape, and move from place to place.
Myosin Structure

• Head: Provides energy for movement.

• Tail: Allows the binding of cargo (vesicles, organelles, plasma membranes)

• Neck: Regulates the activity of the head
Myosin Structure

Myosin I
- Head Neck
- Tail
- Calmodulin light chains

Myosin V
- Head Neck
- Tail

Myosin II
- Head Neck
- Tail
- Regulatory light chain
- Essential light chain
- 130 nm
Sliding Filament Theory

- **Myosin =** motor protein,
  - ATPase: converts energy from ATP into mechanical energy.

- Integration of chemical events at myosin enzymatic head and structural changes throughout that result in movement.
Sliding Filament Theory

- **Cross-bridge**: myosin forms a bond with actin.

- **Power Stroke**: myosin bends, pulling actin toward its tail.
Sliding Filament Theory

- Cross-bridge cycle:
  - formation of the cross-bridge
  - power stroke
  - return to resting position

- Breakdown of ATP provides energy for mechanical changes.
• **Rigor**: no ATP is available, myosin remains firmly attached to actin.
Cellular Movement

- Within the cell, actino-myosin movement depends on which of the elements (actin or myosin) is immobilized.

- Actin immobile $\rightarrow$ Myosin walks along
  - Ex. myosin carrying vesicle through cell

- Myosin immobile $\rightarrow$ Actin filament moves
  - Ex. change in cell conformation
Cellular Movement

- **Unitary Displacement**
  - Distance myosin steps during each cross-bridge cycle.
  - Period = 36nm

- Prevents complication of spiral trajectory when carrying a large vesicle or organelle.
Cellular Movement
Cellular Movement

- **Duty Cycle**
  - Proportion of time in each cross-bridge myosin is attached to actin.
  - Non-muscle myosin: duty cycle is about 0.5

- Vesicles & organelles avoid falling off the microfilament by:
  - Using dimers of myosin
  - Using multiple myosin dimers
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<td>Circulatory physiology: Vascular smooth muscle controls the diameter of blood vessels. Digestion: Visceral smooth muscle forces food down the intestinal lumen.</td>
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Muscles
Muscles

- Muscles provide the contractile force needed in many multicellular tissues and physiological systems:
  - Locomotion
  - Cardiac function/heart
  - Digestion
  - Posture
Muscles

- Myocytes = Muscle cells
  Confer *contractile properties* of the muscle
Muscles

- Main Components:
  - Thick Filament = Myosin polymer
  - Thin Filament = Actin polymer
(a) Thick filament

(b) Thin filament

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Thick v. Thin

- **Thick Filaments:**
  - Two bouquets of myosin end-to-end
  - 150 myosins in each bouquet
  - 300 myosin heads at each end

- **Thin Filaments**
  - Capped at minus and plus ends.
  - In some muscle associated with proteins troponin and tropomyosin
Muscles

Striated Muscle:
- Skeletal
- Cardiac

Smooth Muscle:
- Blood Vessels

Differ in the way thick and thin filaments are organized
Structure of Striated Muscle

- Thick and thin filaments are arranged into sarcomeres.

- Each thick filament is surrounded by an array of thin filaments.

- This is repeated in parallel throughout the muscle cell.
**Sarcomere**

- **Z-disk**: forms the end of each sarcomere
  - Thin filaments extend from

- **A-band**: thick filament occurs
  - dark region

- **I-band**: spans portions of thin filaments without overlap of thick filaments.
  - Light region
  - spans a z-disk

- **M-line**: central region of sarcomere
  - Between 2 minus ends of thin filament
Sarcomere

I-band

A-band

I-band

CapZ

Z disk

Titin

Tropomodulin

Nebulin

Z-disk

Thin filament

Thick filament

Sarcomere

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Sarcomere

- Specific proteins maintain the structural relationship:
  - Nebulin – Runs along the thin filament
  - Titin – Holds the thick filament in position and connects to the z-disk.
    - Compressable.
Sarcomere Relaxed v. Contracted
Sarcomere Contraction

- Sliding Filament Theory

- Thick filament movement = sum of many individual crossbridge events.

- Muscle myosin II has duty cycle of .05

http://www.youtube.com/watch?v=U2TSaz8-yNQ&feature=related
This process underlies all sarcomere contractions!
Sarcomere Contraction

- Degree of overlap between thick and thin filaments influences contractile properties.

- Degree of overlap is reflected in the sarcomere length =
  - distance between z-disks.
Sarcomere Contraction

- Most vertebrate striated muscle shows a resting sarcomere length of 2.0 µm.

- 2.0 µm = optimal overlap = maximal force generated
The diagram illustrates the relationship between tension and the overlap of thick and thin filaments during muscle contraction. The tension increases as the overlap decreases, reaching a peak at an optimal overlap. After this, tension decreases as the overlap continues to decrease. The diagram shows the following key points:

1. **1.25 μm** - Increasing overlap with decreasing length.
2. **1.65 μm** - Optimal overlap of thick and thin filaments.
3. **2.0–2.25 μm** - Maximum tension.
4. **3.65 μm** - Decreasing overlap with increasing length.

The illustrations below the graph correspond to each point, showing the configuration of the filaments at various lengths.
Myofibrils

- Single continuous stretch of interconnected sarcomeres.
- Stretches the length of the muscle cell.
Skeletal v. Cardiac Muscle Cells

- Skeletal muscle
- Myofiber
- Cardiomyocyte
- Heart
- Myofibrils
- Nuclei
- Myofibril
- Sarcomere (2 μm)
- 20 μm
- 1–2 μm

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Skeletal v. Cardiac Muscle Cells

- **Myofiber:**
  - Run the length of the muscle so vary in length
  - Typically much longer than cardiomyocyte
  - Multinucleated

- **Cardiomyocyte:**
  - Myofibrils typically 100 sarcomeres long
  - 1 nucleus
Skeletal Muscle Cell

- Myofiber length is variable depending on the muscle:
  - Stapedius = smallest muscle in humans, 1.3 mm long
  - Sartorius = longest muscle in humans, 60 cm long
Contraction & Relaxation

- **Sarcolemma** = muscle plasma membrane thin and elastic, envelops fiber, and conducts electrical signals

- Muscle activity is initiated by excitation → depolarization of the sarcolemma
Contraction & Relaxation

- Excitation-contraction (EC) coupling: transition of excitatory signal at sarcolemma into stimulation of muscle contraction

- Excitatory signal results in elevated $[\text{Ca}^{2+}]$ within the myocyte.
Contraction & Relaxation

- $\uparrow[Ca^{2+}]$ activates actino-myosin machinery to induce contraction.

- Relaxation ensues when $[Ca^{2+}]$ falls to resting levels.
Ca\(^{2+}\) Sensitivity

- Troponon & Tropomyosin are thin filament proteins that together make up a troponin-tropomyosin complex.
Ca$^{2+}$ Sensitivity

- When [Ca$^{2+}$] is low, the troponin tropomyosin complex blocks actin binding sites for myosin.

- Prevents cross-bridge formation
Ca$^{2+}$ Sensitivity

- $\uparrow[\text{Ca}^{2+}]$ and troponin-tropomyosin complex rolls out of the way, allowing myosin to bind to actin.

- Initiating cross-bridge cycle.
Troponin Tropomyosin Complex

- **3 components of troponin:**
  - TnC
  - Tnl
  - TnT

- **Tropomyosin:**
  - Double stranded protein
  - Blocks myosin binding sites
Troponin Tropomyosin Complex

- **TnC** has 4 $\text{Ca}^{2+}$ binding sites:
  - 2 C-terminal sites
  - 2 N-terminal sites
Troponin tropomyosin complex acts as a single unit, shifting in response to $\text{Ca}^{2+}$.
Ca$^{2+}$ Sensitivity

- Binding of Ca$^{2+}$ causes structural changes:
  - TnC – TnI interaction strengthened
  - TnI – actin interaction weakened
  - Troponin slides into groove in actin

- Strong TnT – tropomyosin interaction ensures that troponin and tropomyosin move as a complex.
(a) Cross-section

(b) Longitudinal view
- Bridging cycle can continue as long as the complex remains locked in permissive position and there is sufficient ATP

![Diagram of myosin and actin cycle with steps labeled:](http://www.youtube.com/watch?v=gJ309LfHQ3M)
Ca^{2+} Sensitivity

- Strength of contraction depends on [Ca^{2+}]. \( \rightarrow \) dictates how many complexes are affected

- Duration depends on how long [Ca^{2+}] remains elevated.
Ca\(^{2+}\) Sensitivity

- $\downarrow [\text{Ca}^{2+}]$ back to resting levels and structural changes are reversed.

- Troponin-topomyosin complex returns to inhibitory position.
Triggering Muscle Contraction

- Depolarization of Sarcolemma
- $\uparrow [\text{Ca}^{2+}]$
- Sufficient ATP available

$=\text{Contraction}$
Contraction & Force

- Muscle response to activation is described in terms of:
  - Degree of change in length
  - Rate of change in length
  - Amount of force generated

- Type of contraction may differ
Types of Contractions

- **Shortening contractions**
  - muscle shortens

- **Isometric contractions**
  - muscle remains the same length

- **Lengthening contractions**
  - muscle lengthens
EC Coupling in Striated Muscle

- Muscles are excited by action potentials
- Depolarization of sarcolemma is induced by opening Na\(^+\) channels
- Influx of Na\(^+\) causes rapid reduction in membrane potential (depolarization).
EC Coupling in Striated Muscle

- Voltage sensitive Ca\(^{2+}\) channels open allowing an influx of Ca\(^{2+}\) into the cell from the extracellular space.

- After a period, Na\(^{+}\) channels and Ca\(^{2+}\) channels begin to close and voltage gated K\(^{+}\) channels open causing repolarization.
EC Coupling in Striated Muscle

- Depolarization and repolarization lead to the movement of ions.

- Active transporters are needed in order to reestablish ion gradients:
  - Na\(^+\)/K\(^+\) ATPase
  - Ca\(^{2+}\) Transporters
Cardiac v. Skeletal Action Potentials

- Dramatic differences in the shape and duration of action potentials.

- Striated muscle cells cannot depolarize again until the repolarization phase is near complete.
  - effective refractory period.
(b) Cardiac muscle
Cardiomyocytes

- Longer repolarization because voltage gated Ca^{2+} channels stay open longer.

- Duration of action potential = approx ½ of the contraction cycle.

- Prolonged effective refractory period is critical to the proper functioning of the heart.
Triggering Muscle Depolarization

- **Myogenic muscle cells** = contract spontaneously
  - Pacemaker cells (vertebrate heart)
    Heart contracts without neuronal input

- **Neurogenic muscle cells** = stimulated by the action of neurons
  - Most vertebrate skeletal muscles. Receive signals from motor neurons
Neurogenic muscle cells

- Receive signals from motor neurons and are excited by neurotransmitters.

- Motor neuron axon termini are located in a region called the **motor end plate**.

- Motor end plate is rich in nicotinic acetylcholine receptors.
Neurogenic Muscle

Motor neuron

Neuromuscular junction

Myofibers

Sarcolemma

Axon terminal of motor neuron

Synaptic vesicle

Motor end plate of skeletal muscle cell
Muscle Contraction

- Two main strategies to ensure the entire sarcolemma is depolarized uniformly:

  - **Tonic Muscle:**
    - Multiple innervations

  - **Twitch Muscles:**
    - Invaginations of the sarcolemma; *T-tubules*
Tonic Muscle

- **Tonic muscles** = vertebrate striated muscle with multiple innervations.

- Neurotransmitter release occurs at many sites along the tonic muscle fiber.

- Fiber is induced to contract at many points along the fiber.
Tonic Muscle

- Contract slowly but maintain tension for long periods of time.

- Not All-or-None
  - depolarization depends on the number and frequency of action potentials from a motor neuron.
Twitch Muscles

- Neurogenic skeletal muscles innervated by one, or a few, motor neurons.

- Action potentials spread rapidly along the sarcolemma, causing uniform contraction along the length of the myofiber.
Twitch Muscles

- Myofibers facilitate the conductance of action potentials with transverse tubules or T-tubules.

- Action potentials follow T-tubules into the muscle fiber.
Muscle Structure

- Sarcolemma
- T-tubules
- Sarcoplasmic reticulum
- Myofibril
Muscle Structure

- **Sarcoplasm** = “Goo” contains lipids, myoglobin, enzymes.
  - High numbers of mitochondria dictate the athletic ability of an animal

- **T-Tubules** = (transverse tubules) sarcolemmal invaginations that facilitate action potential conductance.
Muscle Structure

- **Sarcoplasmic reticulum** = tubules, sacs, vesicles, channels. PLUMBING OF CELL.
  - Important for RAPID TRANSMISSION of electrical impulse, ions, and lactate for muscle cells.
  - Internal Ca$^{2+}$ stores in the SR
  - Ensures low intracellular [Ca$^{2+}$].
Regulation of Ca$^{2+}$

- Many different Ca$^{2+}$ channels in sarcolemma:
  - DHPR
  - Ca$^{2+}$ ATPases
  - NaCaX

- Muscle SR also has its own Ca$^{2+}$ channels:
  - RyR
  - SERCA (ATPase)
Regulation of $\text{Ca}^{2+}$
Regulation of Ca^{2+}

- In some cases (ex. fish hearts) enough Ca^{2+} enters though DHRP to initiate contraction.

- Delivery through the DHPR is either too slow or too minor to achieve contraction threshold for most striated muscles.
Muscle Structure

- **Terminal cisternae** = enlargements of the sarcoplasmic reticulum.
  
  - Increases the capacity for $\text{Ca}^{2+}$ storage and localize it to discrete regions within muscle.
  
  - Well developed in muscles that contract quickly, such as fast-twitch skeletal muscles.
(a) Skeletal myofiber

(b) Cardiomyocyte

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Regulation of Ca$^{2+}$

- DHRPs cluster near terminal cisternae

- Cardiac Muscles:
  - Ca$^{2+}$ induced Ca$^{2+}$ release

- Skeletal Muscles:
  - Depolarization induced Ca$^{2+}$ release
Ca\textsuperscript{2+} Induced Ca\textsuperscript{2+} Release

- Depolarization opens DHRP and Ca\textsuperscript{2+} enters cell.
- Local [Ca\textsuperscript{2+}] increases and triggers opening of cardiac muscle RyR.
- SR stores are released into cytoplasm.
1. Depolarization of the plasma membrane (sarcolemma) opens DHPR, allowing $\text{Ca}^{2+}$ to enter the cell.

2. Elevated $[\text{Ca}^{2+}]$ triggers the opening of RyR, allowing $\text{Ca}^{2+}$ to escape the SR. The elevated cytoplasmic $[\text{Ca}^{2+}]$ triggers actino-myosin ATPase.
Depolarization Induced Ca$^{2+}$ Release

- Depolarization opens DHPR and Ca$^{2+}$ enters cell.

- Voltage-dependent changes in DHRP structure trigger RyR to open.

- Two channels physically interact to couple sarcolemmal depolarization and Ca$^{2+}$ release from the SR.
1. Excitation. Depolarization of the plasma membrane opens DHPR. While Ca\(^{2+}\) enters the cell, it is the changes in DHPR structure that trigger the opening of RyR.

2. Calcium release. RyR opening allows Ca\(^{2+}\) to escape the SR. The elevated cytoplasmic [Ca\(^{2+}\)] triggers actino-myosin ATPase.
Regulation of Ca\(^{2+}\)

- Once membrane repolarizes: Ca\(^{2+}\) transporters pump Ca\(^{2+}\) out of cytoplasm:
  - Back across sarcolemma
  - Into SR

- Both sarcolemma & SR possess ATPases

- Sarcolemma also posesses NaCaX
Cardiac Muscle

Skeletal Muscle

3. After repolarization, ion pumps begin returning Ca^{2+} to resting locations, outside the cell and in the SR.

3. Relaxation. After repolarization, ion pumps begin returning Ca^{2+} to resting locations, outside the cell and in the SR.
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<th>Skeletal</th>
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<td>Single cells (cardiomyocytes) about 10 to 20 μm in diameter and 100 μm in length.</td>
<td>Multiple cells fused into large myofibers that are 10 to 100 μm in diameter and 1 to 100 mm in length.</td>
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<td>Myogenic and involuntary.</td>
<td>Neurogenic and usually voluntary.</td>
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<td>$\text{Ca}^{2+}$-induced $\text{Ca}^{2+}$ release.</td>
<td>Depolarization-induced $\text{Ca}^{2+}$ release.</td>
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<td><strong>Sarcoplasmic reticulum</strong></td>
<td>Well-developed terminal cisternae in birds and mammals. Poorly developed SR in lower vertebrates.</td>
<td>Amount of terminal cisternae depends on fiber type.</td>
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Smooth Muscle

- Layers of smooth muscle induce slow regular contractions:
  - Blood vessels
  - Airways
  - Digestion (intestines, bowel, etc)

- Lack sarcomeres!
Smooth Muscle

- Collection of individual cells that are organized into a functional network.

- Gap junctions between cells allow them to communicate.
  - Allow them to communicate
  - Functional group acts as a unit.
Smooth Muscle

- *Scattered clusters* of thick and thin filaments throughout the cytoplasm.

- Aggregations of filaments interconnect to form a network within the cytoplasm.

- Attach to the plasma membrane at specific regions - **adhesion plaques**: 
Smooth Muscle

- 3D arrangement allows smooth muscle to contract in all dimensions.