Muscle Physiology

Skeletal Muscle Anatomy:

**Muscle fibers** (= individual muscle cells):
- Multi-nucleated (mitosis sans cytokinesis)
- Sarcolemma (= plasma membrane + collagen fibers)
- Sarcoplasm (= cytoplasm; ↑ mitochondria)

- **Myofibrils** (contractile elements):
  - Actin filaments (thin)
  - Myosin filaments (thick)

Dystrophin: Anchors myofibril arrays to cell membrane

Titin: Filamentous structural protein ("springy")

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.2 / 10.3
Sliding Filament Theory *(Huxley and Huxley – 1954)*:

Contraction results from sliding action of inter-digitating actin and myosin filaments

**Evidence?**

Myosin head interacts with actin (cross-bridging)

Each cross-bridge generates force independent of other cross-bridges

Thus

Total tension developed by sarcomere proportional to number of cross-bridges (proportional to filament overlap)

Randall et al. *(Eckert: Animal Physiology, 5th ed.)* – Figure 10.8
Muscle Physiology

Sliding Filament Theory (Huxley and Huxley – 1954):

Length-tension relationship

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.8 / 10.9
Sliding Filament Theory (Huxley and Huxley – 1954):

**Length-tension relationship**

**Normal resting length of skeletal muscle**

Maximum Contraction Strength:
~ 50 lbs./inch^2
The geometry of myofilaments in a sarcomere strongly affects the contractile properties of the muscle.

Myofilament Anatomy:

1) **Myosin**:
   - Two heavy chains (tail)
   - Four light chains (head)
     - Actin-binding sites
     - ATPase activity
   - Myosin filament composed of 200+ individual myosin molecules (~1.6 μm in length)

2) **Actin**:
   - Two double-stranded helices of G-actin polymers woven to form F-actin (~1 μm in length)
     - ADP attached to G-actin (active site)
   - **Tropomyosin**: Spiral around F-actin; cover active sites
   - **Troponin**: Attaches tropomyosin to F-actin
Myofilament Anatomy:

1) Myosin:
   - Two heavy chains (tail)
   - Four light chains (head)
     - Actin-binding sites
     - ATPase activity
   - Myosin filament composed of 200+ individual myosin molecules (~1.6 µm in length)

2) Actin:

   Troponin (sub-units):
   1) Troponin C: Binds calcium (up to 4 Ca^{2+})
   2) Troponin T: Binds tropomyosin
   3) Troponin I: Binds actin (covers active site on actin)

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 6.5

Walk-Along Theory:

Ca^{2+} enters sarcoplasm; tropomyosin shifts
Muscle Physiology

Walk-Along Theory:

Ca\(^{2+}\) enters sarcoplasm; tropomyosin shifts

Myosin head attaches to actin (active site)
Walk-Along Theory:

Ca\(^{2+}\) enters sarcoplasm; tropomyosin shifts

Myosin head attaches to actin (active site)

Release of phosphate associated with conformational change

POWER STROKE
Walk-Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts

Myosin head attaches to actin (active site)

POWER STROKE

Myosin head releases (ATP bound)
Walk-Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts

→

Myosin head attaches to actin (active site)

Myosin head "cocked"

Hydrolysis
(ATP → ADP + P)

Myosin head releases (ATP bound)

POWER STROKE
Muscle Physiology

Walking Along Theory:

Ca^{++} enters sarcoplasm; tropomyosin shifts

\[ \text{Myosin head attaches to actin (active site)} \]

Myosin head "cocked"

\[ \text{Hydrolysis} \quad (\text{ATP} \rightarrow \text{ADP} + \text{P}_i) \]

Myosin head releases (ATP bound)

\[ \text{ATP} \]

\[ \text{POWER STROKE} \]
**Muscle Physiology**

**Walk-Along Theory:**

Ca\(^{2+}\) enters sarcoplasm; tropomyosin shifts

Myosin head attaches to actin (active site)

Myosin head "cocked"

Hydrolysis

Myosin head releases

(ATP bound)

Process will continue until:

1) Full overlap of actin and myosin
2) Load on muscle becomes too great

**Rigor Mortis:**

State of contracture following death (~ 12 – 24 hours)
Excitation – Contraction Coupling:
Neuromuscular Junction:

**STEP 1:**
Secretion of acetylcholine by nerve terminals

A) Small vesicles formed in stoma of neuron; shuttled to axon terminal
B) Acetylcholine (ACh) synthesized in terminal; transported into vesicles (~ 10,000 Ach / vesicle)
C) Action potential travels down axon; activates voltage-gated Ca++ channels at terminal
D) Ca++ influx triggers vesicles to fuse with membrane (~ 125 vesicles / AP); ACh released
E) ACh binds with ACh-gated ion channels at mouth of subneural clefts (muscle fiber)
**Excitation – Contraction Coupling:**

**ACh-gated Ion Channel:**

- 5 sub-units (2 alpha, 1 beta, 1 gamma, 1 delta); form tubular channel
  - Activation = 2 ACh molecules (bind to alpha units)
  - Primarily Na⁺ channel:
    - (-) charge restricts anions
    - (-) RMP of muscle fiber favors Na⁺ influx vs. K⁺ efflux

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**Safety Factor:**

Each AP arriving at neuromuscular junction causes – 3x end plate potential necessary to stimulate muscle fiber

MEPP\textsubscript{ACh} = 0.4 mV

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**Muscle Physiology**

**Acetylcholinesterase (AChE):**

- Deactivates ACh (synaptic cleft)
- Opening of ACh-gated ion channels produces end plate potential (EPP)
- Strong EPP triggers voltage-gated sodium channels (AP generation)

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**Neurophysiology**

**Pathophysiology:**

Various drugs / toxins / diseases exist that are capable of enhancing or blocking neuromuscular junction activity

**Drugs / Toxins - Inhibitors:**

- **Botulism** (bacterial toxin - ↓ ACh release)
- **Curare** (plant toxin – blocks ACh receptors)

**Drugs / Toxins - Stimulants:**

- **Nicotine** (plant derivative – mimics ACh)
- **Sarin Gas** (synthetic – deactivates AChE)

**Myasthenia Gravis**

("grave muscle weakness")

- Autoimmune; destruction of ACh-gated Na⁺ receptors
  - Result = Paralysis (Weak EPPs)
  - Treatment = Anti-AChE drugs

Rare Condition: 1 / 20,000

Can be fatal (diaphragm paralysis)
Excitation – Contraction Coupling:
Role of Calcium:

- Interacts with troponin in thin filament:

  When Ca\(^{++}\) binds:
  1) Troponin \(T / I / C\) bonds strengthen
  2) Troponin \(I / actin\) bond weakens
  (uncovers active sites)

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.15

Excitation – Contraction Coupling:

For a muscle contraction to occur, there must be a link between electrical excitation and increased intracellular Ca\(^{++}\) levels...

**Problem 1:**
Rate of diffusion from Ca\(^{++}\) to interior of cell (~25 – 50 \(\mu\)m) several orders of magnitude too slow to explain observed latent period

**Solution:**
Sarcoplasmic Reticulum

- Specialized ER; stores Ca\(^{++}\)
- SR membrane contains Ca\(^{++}\) pumps
  - Maintain < [10\(^{-7}\) M Ca\(^{++}\)]
- Calsequestrin: Binds Ca\(^{++}\) in SR
  - Reduces [gradient]

The only source of regulatory Ca\(^{++}\) in skeletal muscle is from the SR

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.12 / 10.15
Problem 2:
A potential difference across the plasma membrane of a muscle fiber affects an intracellular region a fraction of a µm deep (Myofibrils 50 – 100 µm thick)

Solution:
Transverse Tubules
Cytoplasmic extensions continuous with plasma membrane (~ 0.1 µm diameter); provide link between plasma membrane and myofibrils deep inside muscle fiber

Muscle Physiology

Excitation – Contraction Coupling:
For a muscle contraction to occur, there must be a link between electrical excitation and increased intracellular Ca²⁺ levels...

How does Ca²⁺ escape the SR?

Ryandine Receptors:
- Located in SR; Ca²⁺ channels

Dihydropyridine Receptors:
- Located in T-tubule; voltage-gated Ca²⁺ channels

Calcium-induced Calcium Release
(Positive feedback mechanism)

• Only ½ of the ryanodine receptors linked with dihyropyridine receptors

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 7.5

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 10.25
Muscle Energetics:

Major processes requiring energy:

1) Cross-bridging
2) Ca\(^{2+}\) and Na\(^{+}\) / K\(^{+}\) pumps

ATP usage: ~ 600 trillion / second

\[
\text{[ATP] in stimulated muscles} = \text{[ATP] in unstimulated muscles - ???}
\]

<table>
<thead>
<tr>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 m</td>
</tr>
<tr>
<td>400 m</td>
</tr>
<tr>
<td>5000 m</td>
</tr>
<tr>
<td>4x</td>
</tr>
<tr>
<td>2x</td>
</tr>
<tr>
<td>1x</td>
</tr>
</tbody>
</table>

(100 m)
I. Phosphocreatine → Creatine + PO\(_4\)\(^{-}\)
- Creatine phosphokinase
- ~ 5 – 8 seconds of fuel...

(400 m)
II. Glycogen → Lactic acid
- Anaerobic respiration
- ~ 1 minutes ("poisons" system)

(5000 m)
III. Glucose
- Oxidative metabolism (aerobic respiration)
- Primary food source = glycogen / lipids

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 84.1
Muscle Mechanics:

Muscle fibers can be divided into two primary types based on anatomical and physiological properties

1) Cross-bridge detachment rate (fast detachment = fast contraction)
   • Chemical nature of myosin head ($V_{\text{max}}$ of ATPase)
2) Density of Ca$^{++}$ pumps (affects clearance of Ca$^{++}$)
3) Mitochondria # / vasculature (affects oxidative ATP production capacities)

Fast Glycolytic Fibers:
• Rapid cross-bridge cycling
• Rapid Ca$^{++}$ clearance
• Low endurance (anaerobic respiration)
  • (↑) glycolytic enzyme content
  • (↑) glycogen reserves

Slow Oxidative Fibers:
• Slow cross-bridge cycling
• Slow Ca$^{++}$ clearance
• High endurance
  • (↑) mitochondria / capillaries
  • (↑) myoglobin content
**White Muscle:**
Muscle dominated by fast fibers (e.g. chicken breast)

**Red Muscle:**
Muscle dominated by slow fibers (e.g. chicken leg)

### Table: Muscle Fiber Proportions

<table>
<thead>
<tr>
<th>Activity</th>
<th>Fast Fibers</th>
<th>Slow Fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marathon Runners</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>Swimmers</td>
<td>26%</td>
<td>74%</td>
</tr>
<tr>
<td>Avg. Human</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Weight Lifters</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Sprinters</td>
<td>64%</td>
<td>37%</td>
</tr>
<tr>
<td>Jumpers</td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Most human muscles contain both types of muscle fibers; proportions differ.

**Muscle Hypertrophy:** Increase in total mass of muscle

- **Lengthening** (normal growth)
  - Sarcomeres added to existing myofilaments

- **Fiber Hypertrophy** (most common)
  - Increase in myofilament number
  - Trigger = Near maximal force generation

- **Hyperplasia** (rare)
  - Increase in muscle fiber number
  - Trigger: Extreme muscle force generation

**Muscle Atrophy:** Decrease in total mass of muscle

Loss of muscle performance (↓ contractile proteins = ↓ force / ↓ velocity)

**Causes:**
- Plaster cast
- Space flight (zero gravity)
- Denervation / neuropathy
- Sedentary lifestyle
Smooth Muscle:
- Form muscular walls of hollow organs
  - Produce mobility (e.g., gastrointestinal tract)
  - Maintain tension (e.g., blood vessels)
- Mono-nucleated cells (20 – 500 μm length / 1-5 μm width)

Types of Smooth Muscle:

- Discrete muscle fibers
- Nervous control (single innervation / fiber)
- Location: Iris, piloerector muscles

- Sheets / bundles of muscle fibers
- Electronically-coupled (gap junctions)
- Multiple controls (e.g., hormonal / spontaneous)
- Location: Walls of viscera

Properties of Smooth Muscle:

**Smooth Muscle – How Does it Differ from Skeletal Muscle?**

1) **Physical Organization:**

Contraction occurs via actin / myosin interaction (ATP)

**HOWEVER**

Smooth muscle appears non-striated

- Dense-bodies: Analogous to Z lines
  - Anchor actin filaments
  - Dispersed / attached to cell membrane

- Intermediate Filaments (structural backbone)

Smooth muscle can operate over large range of lengths (~ 75% shortening possible)
Properties of Smooth Muscle:

Smooth Muscle – How Does it Differ from Skeletal Muscle?

2) Neuromuscular Junction:
   
   Diffuse junctions present in smooth muscle

   Varicosities:
   Bulbous swellings along innervating neuron

3) Mechanical Operation:
   
   • Slow cycling of myosin cross-bridges (1/10 – 1/300 of skeletal)
     • ↓ ATPase activity (↓ = energy required: ~ 1% of skeletal muscle)
   
   • Slow onset of contraction / relaxation (0.2 – 30 sec.)
     • Slow cross-bridge action; Slow Ca\textsuperscript{2+} influx / efflux
   
   • Prolonged contraction periods (hours / days / weeks)
     • “Latch” mechanism (poorly understood…)

4) Ca\textsuperscript{2+} Source:
   
   • Primarily extracellular (poorly developed SR)
     • Latent period = 200 – 300 ms (50x longer than skeletal muscle)
     • Force of contraction dependent on [extracellular Ca\textsuperscript{2+}]
   
   • More extensive SR = More rapid contraction
     • Caveolae (T.T. analogs)
   
   • Ca\textsuperscript{2+} pumps (S.R. / plasma membrane) clear Ca\textsuperscript{2+} (slow-acting)

5) Activation Mechanism:
   
   • Regulation is myosin-based (not actin-based)
     • Troponin complex absent
   
   • Myosin must be phosphorylated before it can hydrolyze ATP (become activated)
     • Regulatory chain = Myosin light chain phosphorylated

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 8.6
Excitation – Contraction Coupling:

Events:
1) Voltage-gated Ca\(^{++}\) channels open
2) Ca\(^{++}\) binds with calmodulin
3) Ca\(^{++}\) - calmodulin complex activates myosin light chain kinase
4) When Ca\(^{++}\) levels fall; myosin phosphatase deactivates myosin

Additional Sources of Ca\(^{++}\):

Costanzo (Physiology, 4th ed.) – Figure 1.29