Chapter 8

Muscle Physiology

V edit. Pg. 257-297

VI edit. Pg. 253-297
Classification of Muscle Tissue

- Striated muscle
  - Skeletal muscle
  - Cardiac muscle
- Unstriated muscle
  - Smooth muscle
  - Voluntary muscle
  - Involuntary muscle
Organization of Skeletal Muscles

Skeletal muscles consist of many muscle cells called muscle fibers.

Each muscle fiber contains a large number of myofibrils, or specialized contractile elements consisting of alternating light and dark bands.
Structure of a Skeletal Muscle Fiber

A. Multiple nuclei
B. Large number of mitochondria
C. Cell membrane (**sarcolemma**) and transverse tubules (**T-tubules**)
D. Cytoplasm (**sarcoplasm**)  
E. Sarcoplasmic reticulum  
F. Myofibrils: bundle of overlapping actin and myosin filaments
Structure of Skeletal Muscle Fibers

- Sarcolemma
- Sarcoplasm
- Myofibrils
- Lateral sacs
- Segments of sarcoplasmic reticulum
- Transverse (T) tubule
- I band
- A band
Striations of Muscle Tissue

(a)
Sarcomere

Functional unit of skeletal muscle fiber

Consist of overlapping thin (actin) and thick (myosin) filaments, which produce striation

Components of a sarcomere:
Two main bands: **I-band** (light band consisting mainly of actin) and **A-band** (dark band consisting mainly of myosin)

Two lines: **Z line** in the I-band binding actin filaments and the **M-line** in the A-band binding myosin filaments
Striations of Muscle Tissue
Geometrical Arrangement of Actin and Myosin
Structure of the Thin Filaments

- Actin molecules
  - Binding site for attachment with myosin cross bridge
- Actin helix
- Tropomyosin
- Troponin
- Thin filament

Calcium-binding protein
Structure of Myosin

(a) Myosin molecule

(b) Thick filament
Role of Calcium Ions in Muscle Contraction

Muscle fiber relaxed; no cross-bridge binding because the cross-bridge binding site on actin is physically covered by the troponin-tropomyosin complex.

Muscle fiber excited; released Ca^{2+} binds with troponin, pulling troponin-tropomyosin complex aside to expose cross-bridge binding site; cross-bridge binding occurs.

Binding of actin and myosin cross bridge triggers power stroke that pulls thin filament inward during contraction.
Function of Myosin: Cross Bridge Activity

Actin molecules in thin myofilament

Myosin cross bridge

Z line

BINDING Myosin cross bridge binds to actin molecule.

POWER STROKE Cross bridge bends, pulling thin myofilament inward.

DETACHMENT Cross bridge detaches at end of power stroke and returns to original conformation.

BINDING Cross bridge binds to more distal actin molecule; cycle repeated.
Contraction occurs as the result of actin filaments sliding on top of myosin filaments. Thin filaments slide toward the CENTER of the sarcomere.

Actin and myosin filaments DO NOT change length during the contraction process. Only the length of the sarcomere changes during a contraction.
Sarcomere Contraction
Excitation-Contraction Coupling: Link Between Nerve Action Potential And Muscle Contraction
Generation of Muscle Contraction

- Action potential arrives at nerve terminal
- Ca entry into nerve terminal
- Release of acetylcholine into synaptic cleft
- Binding of Ach to nicotinic Ach receptors at the motor end plate
- Generation of action potential in muscle fiber

http://www.blackwellpublishing.com/matthews/myosin.html
http://harveyproject.science.wayne.edu/development/muscle/juncti~1.htm
Signaling within Skeletal Muscle Cells

- Sarcolemma
- Sarcoplasm
- T-tubule
- Terminal cisternae (calcium reservoir)
- Triad: place where T-tubules meet the terminal cisternae
How is the signal from the T-tubules transmitted to the terminal cisternae?

T-tubule
(voltage-gated calcium channels)

Terminal cisternae
(calcium-release channels or ryanodine channels)
Role of Calcium Ions in Muscle Contraction

(a) Cross-sectional view

- Thin filament
- Tropomyosin
- Actin
- Cross-bridge binding sites
- Troponin
- Myosin cross bridge

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(b) Longitudinal view

- Binding of actin and myosin cross bridge triggers power stroke that pulls thin filament inward during contraction

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Structure of the Thin Filaments

- Actin molecules
- Binding site for attachment with myosin cross bridge
- Actin helix
- Calcium-binding protein

- Tropomyosin
- Troponin

Thin filament
Structure of Myosin

(a) Myosin molecule

(b) Thick filament
Steps of Muscle Contraction

1. Acetylcholine released by axon of motor neuron crosses cleft and binds to receptors/channels on motor end plate.
2. Action potential generated in response to binding of acetylcholine and subsequent end plate potential is propagated across surface membrane and down T tubules of muscle cell.
3. Action potential triggers Ca\textsuperscript{2+} release from sarcoplasmic reticulum.
4. Calcium ions released from lateral sacs bind to troponin on actin filaments; tropomyosin physically moved aside to uncover cross-bridge binding sites on actin.
5. Ca\textsuperscript{2+} actively taken up by sarcoplasmic reticulum when there is no longer local action potential.
6. With Ca\textsuperscript{2+} no longer bound to troponin, tropomyosin slips back to its blocking position over binding sites on actin; contraction ends; actin slides back to original resting position.
7. Myosin cross bridges attach to actin and begin pulling actin filaments toward center of sarcomere; powered by energy provided by ATP.

http://entochem.tamu.edu/MuscleStrucContract.swf/index.html
Generation of Muscle Contraction

Depolarization travels through T-tubules to the triad

Release of Ca\textsuperscript{2+} ions from the terminal cisternae into sarcoplasm

Binding of Ca ions to troponin

Exposure of myosin-binding site in actin molecule

Link between actin and myosin filaments: cross bridge

http://www.blackwellpublishing.com/matthews/myosin.html
Cross Bridge Activity

Actin molecules in thin myofilament

Myosin cross bridge

Z line

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Excitation-Contraction Coupling

**Rest:** troponin-tropomyosin complex blocks myosin-binding site in actin molecule

**Contraction:** $\text{Ca}^{2+}$ ions released from the sarcolemma binds to troponin

Conformational change in tropomyosin molecule

“Extended” or “cocked” myosin head (by ATP\ ADP) binds to actin forming a cross-bridge

http://www.blackwellscience.com/matthews/myosin.html
Excitation-Contraction Coupling

**Power stroke**: Myosin heads swivel toward center pulling actin filaments

- ADP gets detached from myosin head
- ATP binds to myosin head and detaches it from actin
- Hydrolysis of ATP reorients myosin head into “extended” or “cocked” position

(Repeat cycle)
ATP and Rigor Mortis

1. Energized
2a. Binding
2b. Resting
3. Bending (power stroke)
4a. Detachment
4b. Rigor complex

Fresh ATP available
No ATP (after death)

Ca²⁺ present (excitation)
No Ca²⁺
Steps of Muscle Contraction

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Termination of Contraction

Ach is decomposed by acetylcholinesterase

Ca^{2+} ions are pumped back into the sarcoplasmic reticulum by Ca-ATPase molecules
Energy Supply for Muscle Contraction

Blood
- Blood glucose
- Liver glycogen
- Muscle glycogen

During contraction:
- Glycolysis
- Oxidative phosphorylation
- Protein (Amino acids)
- Lactic acid

During rest:
- Oxygen (O₂)
- Pyruvic acid
- Fatty acids
- Creatine phosphate

Muscle fiber
- ATP
- Myosin ATPase
- Ca²⁺ pump of sarcoplasmic reticulum

Contraction:
- ATP

Relaxation:
- ATP
- Creatine kinase

Fat stores
- CO₂, H₂O

Immediate source
- ATP

Main source when O₂ present
- ATP

Main source when O₂ not present
- Lactic acid

During contraction:
- Creatine
- ATP
Adaptations in Muscle Cells for Energy Production

1) Creatine phosphate (CP)
   CP + ADP $\rightarrow$ Creatine + ATP
   (Creatine kinase)

2) Myoglobin
Muscle Energy Production

AT REST
(WHEN SUPPLY OF OXIGEN IS SUFFICIENT)

GLYCOLYSIS
CITRIC ACID CYCLE
ELECTRON TRANSPORT CHAIN

Excess energy is stored in creatine phosphate molecules
Muscle Energy Production

BEGINNING OF CONTRACTION
(WHEN SUPPLY OF OXIGEN START TO DECREASE)

GLYCOLYSIS
CITRIC ACID CYCLE
ELECTRON TRANSPORT CHAIN
(use oxygen stored in myoglobin)

ATP is also formed by energy transfer from creatine phosphate molecules
SUBSTAINED CONTRACTION
(WHEN SUPPLY OF OXIGEN IS DEPLETED)

GLYCOLYSIS
(leading to accumulation of lactic acid and acidosis of blood..NOT GOOD)
Conversion of Lactic Acid into Glucose: Oxygen Debt

- Muscle Fiber: Glucose → ATP → Lactic Acid
- Blood: Lactic Acid → Glucose
- Liver: Glucose → ATP → Lactic Acid
Skeletal Muscles Generate Graded Contractions
Motor Unit: consist of all muscle fibers innervated by one motor neuron
Single twitch: contraction of a single muscle fiber generated by one action potential

Total muscle contraction (force) is regulated by:

1) The number/nature of muscle fibers activated in a muscle
2) Force generated by each muscle fiber
Muscle Contraction
Summation and Tetanus

http://harveyproject.science.wayne.edu/development/muscle/twitch~1.htm
Length-Tension Relationship
There is an optimal muscle fiber length at which maximal force can be generated.
## Classification of Muscle Fibers

<table>
<thead>
<tr>
<th></th>
<th>Type I Slow twitch</th>
<th>Type IIa Fast twitch</th>
<th>Type IIb Fast twitch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Fatigue resistant</td>
<td>Fatigueable</td>
<td>Fatigue resistant</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Red fibers - a lot of myoglobin</td>
<td>White fibers - less myoglobin</td>
<td></td>
</tr>
<tr>
<td>Blood supply</td>
<td>Good blood supply, many mitochondria</td>
<td>Reduced blood supply, lower number of mitochondria</td>
<td></td>
</tr>
<tr>
<td>Energy source</td>
<td>Main source of energy: aerobic respiration</td>
<td>Main source of energy: glycolysis</td>
<td></td>
</tr>
<tr>
<td>Contraction</td>
<td>LONG CONTRACTION</td>
<td>SHORT CONTRACTION</td>
<td></td>
</tr>
</tbody>
</table>

http://harveyproject.science.wayne.edu/development/muscle/fibtyp.html
Recruitment Order of Motor Units

Spinal cord

- Motor unit 1
- Motor unit 2
- Motor unit 3

http://entochem.tamu.edu/VertInvertContractswf/index.html
The size of the motor units determines the strength of contractions in skeletal muscles.
Muscle Fatigue
Inability of a muscle to sustain a contraction

1) Muscle

2) Neuromuscular Junction

3) Motor neurons
1) Failure of the action potential to invade nerve terminal-Na⁺ channel inactivation

2) Vesicle depletion

3) Neurotransmitter desensitization

4) Accumulation of K⁺ ions on the extracellular space

5) Acidosis of muscle environment-lactic acid accumulation

6) Depletion of energy supplies-ATP, oxygen

6) Fast-slow twitch muscle fiber ratio
Motor Unit and Muscle Fatigue

Spinal cord

- = Motor unit 1
- = Motor unit 2
- = Motor unit 3

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The output of motor units is influenced by multiple neural inputs

1) Inputs from afferent neurons
2) Inputs from cortical neurons in primary motor cortex
3) Inputs from brainstem
Cortical level
Subcortical level
Brain stem level
Spinal cord level
Periphery

Premotor and supplementary motor areas
Primary motor cortex
Brain stem nuclei (including reticular formation and vestibular nuclei)
Afferent neuron terminals
Motor neurons
Cerebellum

Peripheral receptors
Muscle fibers
Movement

Sensory consequences of movement
Other peripheral events, such as visual input

Pathways conveying afferent input
Corticospinal motor system
Multineuronal motor system
Muscle Activity is Controlled by Afferent Information: Skeletal Muscle Propioireceptors

1) Muscle Spindles
2) Golgi Tendon Organ
Golgi Tendon Organs: Detect Changes in Tension

http://www.physpharm.fmd.uwo.ca/undergrad/medswbl/L7SpindleMuscle/M7Muscle.swf
Muscle Spindles: Detect Changes in Length

- Capsule
- Intrafusal (spindle) muscle fibers
- Contractile end portions of intrafusal fiber
- Noncontractile central portion of intrafusal fiber

- Alpha motor neuron axon
- Gamma motor neuron axon
- Secondary (flower-spray) endings of afferent fibers
  - Sense change in length
- Extr fusal (“ordinary”) muscle fibers
  - Primary (annulospiral) endings of afferent fibers
  - Sense change in length and speed
Co-activation of gamma and alpha motoneurons

1. Afferent input from sensory endings of muscle spindle fiber
2. Alpha motor neuron output to regular skeletal muscle fiber
3. Gamma motor neuron output to contractile end portions of spindle fiber
4. Descending pathways coactivating alpha and gamma motor neurons
Relaxed muscle; spindle fiber sensitive to stretch of muscle

Contracted muscle in hypothetical situation of no spindle coactivation; slackened spindle fiber not sensitive to stretch of muscle

Contracted muscle in normal situation of spindle coactivation; contracted spindle fiber sensitive to stretch of muscle
Stretch Reflex and Spindle Fiber Function

1. Afferent input from sensory endings of muscle spindle fiber
2. Alpha motor neuron output to regular skeletal muscle fiber
3. Gamma motor neuron output to contractile end portions of spindle fiber
4. Descending pathways coactivating alpha and gamma motor neurons
Stretch Reflex: Knee-Jerk Reflex

http://www.brainviews.com/abFiles/AniPatellar.htm
Diseases of the Motor Unit

1) Diseases of nerve conduction (motor neuron diseases and peripheral neuropathies): multiple sclerosis, amyotrophic lateral sclerosis, nerve/spinal cord injury

2) Diseases of chemical transmission: myasthenia gravis, Lambert-Eaton syndrome

3) Diseases of the muscle: Duchenne muscular dystrophy, muscle atrophy
Diseases of the Motor Unit

Neurogenic disorders
- Cause weakness of distal limbs
- Cause fasciculations and fibrillations

Myopathic disorders
- Cause weakness of proximal muscles
- No fasciculations and fibrillations
Motor unit

Normal  Motor neuron disease  Muscle fiber disease

Fibrillations  Fasciculation
Amyotrophic Lateral Sclerosis (Lou Gehrig’s disease)

A. Disease of the corticospinal tract causing degeneration of upper level motoneurons (except motoneurons supplying ocular nerves and bladder sphincter).

B. Cause unknown

C. Lateral sclerosis refers to the hardness of the spinal cord at autopsy
Babinski reflex

Normal plantar response

Extensor plantar response (Babinski sign)

Down

Up

Fanning of toes
Multiple Sclerosis
Demyelinating disease
Disease of the Neuromuscular Junction: Myasthenia Gravis

1) Inability to control muscles

2) Autoimmune disease targeting the neuromuscular junction acetylcholine receptors
Myasthenia gravis

MG affects cranial muscles

MG can be induced in rats by injection of purified ACh receptors
Main symptoms of MG

A. Produce muscle weakness specially cranial muscles

B. Does not produce any electromyographic sign of denervation, loss of tendon reflex, or muscle atrophy

C. Can be treated by inhibitors of cholinesterase

D. In some patients, removal of thymus also reduce symptoms of the disease
Myasthenia Gravis

Reduction of NMJ foldings

Reduction in the number of acetylcholine receptors
Myasthenia gravis
Cholinesterase inhibitors improve signs in MG patients
Lambert-Eaton Syndrome

1) Autoimmune disease due to presence of antibodies against voltage-gated \( \text{Ca}^{2+} \) channels in presynaptic terminals

2) Found in persons with lung cancers

3) Symptoms are improved by successive stimulations
Diseases of Skeletal Muscles

A. Produce muscle weakness without any electromyography sign of denervation

B. Generate motor unit potentials that are smaller and short in duration

C. Can be detected by measurements of serum enzyme activities: in particular creatine kinase and lactate dehydrogenase
Muscle Atrophy

Control

Muscular Dystrophy

Polyneural Innervation

Duchenne Muscular Dystrophy
Classification of Muscle Tissue

- Striated muscle
  - Skeletal muscle
  - Voluntary muscle
- Unstriated muscle
  - Cardiac muscle
  - Involuntary muscle
  - Smooth muscle
# Common Features of Muscle Tissue

<table>
<thead>
<tr>
<th>Skeletal</th>
<th>Cardiac</th>
<th>Smooth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle contraction requires calcium ions and interaction between actin and myosin filaments</td>
<td>ATP is the energy source for cross-bridge cycling</td>
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</tr>
</tbody>
</table>

![Diagram of muscle contraction and ATP use](Image)
# Muscle Tissues

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<tbody>
<tr>
<td>Attach to bones</td>
<td></td>
<td>Found in the heart</td>
<td></td>
</tr>
<tr>
<td>Involved in <strong>voluntary</strong> contractions</td>
<td></td>
<td><strong>Automatic</strong> contractions</td>
<td></td>
</tr>
<tr>
<td>Consist of long, narrow cells or muscle fibers with a T-tubule system and sarcoplasmic reticulum</td>
<td></td>
<td>Long fibers interconnected via gap junctions (intercalated disks) with a T-tubule system and sarcoplasmic reticulum</td>
<td></td>
</tr>
<tr>
<td><strong>Multinuclear, striated</strong> muscle cells</td>
<td></td>
<td>Single-nucleus, striated cells</td>
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<td>Contractile protein arranged into sarcomere</td>
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<tr>
<td>Require <strong>intracellular calcium</strong> for contraction</td>
<td></td>
<td>Require <strong>extracellular calcium</strong> as well as <strong>intracellular calcium</strong></td>
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Cardiac Muscle

Cardiac Muscle Tissue

- Nucleus
- Intercalated disk
- Striations
- Nucleus
- Intercalated disk

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Pacemaker Activity of Cardiac Muscle

Pacemaker potential is a slow depolarization of the membrane potential that can reach threshold.
Contraction in Cardiac Muscle

1) Require Ca\(^{2+}\) entry via voltage-gated, dihydropyrimine-sensitive Ca\(^{2+}\) channels

2) Ca\(^{2+}\) binding to troponin

3) Actin-myosin crossbridge
Cross Bridge Activity

Actin molecules in thin myofilament

BINDING Myosin cross bridge binds to actin molecule.

Myosin cross bridge

POWER STROKE Cross bridge bends, pulling thin myofilament inward.

Z line

DETACHMENT Cross bridge detaches at end of power stroke and returns to original conformation.

BINDING Cross bridge binds to more distal actin molecule; cycle repeated.

(a)

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Smooth Muscle

Smooth muscle cells are small, spindle-shaped, unstriated cells found in the walls of hollow organs.
Contractile proteins in smooth muscle cells are not organized into sarcomeres. Actin filaments are anchored to dense bodies (or Z line-like structures).
Actin-myosin filaments do no form myofibrils and are oriented slightly diagonally from side to side.

During a contraction the distance between neighboring dense bodies shorten.
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<td>Long fibers with gap junctions (intercalated disks)</td>
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<td>Single-nucleus, striated cells</td>
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<tr>
<td>Contractile protein arranged into sarcomere</td>
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<tr>
<td>Extracellular and intracellular calcium</td>
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<tr>
<td><strong>Smooth</strong></td>
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<tr>
<td>Found in wall of hollow organs</td>
</tr>
<tr>
<td>Automatic contractions (regulated by ANS)</td>
</tr>
<tr>
<td>Spindle-shaped cells</td>
</tr>
<tr>
<td>Single nucleus, non-striated cells</td>
</tr>
<tr>
<td>No sarcomere structure-actin binds to dense bodies</td>
</tr>
<tr>
<td>Extracellular calcium (some intracellular calcium)</td>
</tr>
</tbody>
</table>
Thin Filaments in Smooth Muscle

Actin filaments do not contain troponin and tropomyosin does not block actin cross-bridge binding sites.
Thick Filaments in Smooth Muscle

Myosin heads have an actin-binding side, a myosin ATPase site and a light chain binding side. The light chain contains a myosin kinase site.
Smooth Muscle Contraction

Smooth muscle contraction requires phosphorylation of the myosin light chain by a calcium-dependent mechanism.
Smooth muscle

Muscle excitation

Rise in cytosolic Ca^{2+} (mostly from extracellular fluid)

Series of biochemical events

Phosphorylation of myosin in thick filament

Binding of actin and myosin at cross bridges

Contraction

Skeletal muscle

Muscle excitation

Rise in cytosolic Ca^{2+} (entirely from intracellular sarcoplasmic reticulum)

Physical repositioning of troponin and tropomyosin

Uncovering of cross bridge binding sites on actin in thin filament

Binding of actin and myosin at cross bridges

Contraction
## Termination of Contraction in Skeletal and Smooth Muscles

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<th>Smooth Muscles</th>
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<tr>
<td>Ca(^{2+}) ions are pumped back into the sarcoplasmic reticulum by Ca-ATPase molecules</td>
<td>Ca(^{2+}) ions are pumped out of the cell or back into the sarcoplasmic reticulum by Ca-ATPase molecules</td>
</tr>
<tr>
<td>Acetylcholine is decomposed by acetylcholinesterase</td>
<td></td>
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</table>
Activation of Smooth Muscle
Smooth muscle cells can become activated as single or multiunits.
Multiunit smooth muscles require nerve stimulation for contraction.
Example: ciliary muscle, iris, large blood vessels, base of hair follicles.
Single unit smooth muscles do not require nerve stimulation for contraction.
Example: smooth muscles in walls of hollow visceral organs.
Single unit smooth muscles are myogenic (self excitable)

Action potential generated in a pacemaker cells spreads to surrounding non-pacemaker cells through gap junctions
Like Cardiac Muscle, Single Unit Smooth Muscle Have Pacemaker Activity

Pacemaker potential is a slow depolarization of the membrane potential that can reach threshold.
Single unit smooth muscles do not require nerve stimulation

Action potential generated in a pacemaker cells spreads to surrounding non-pacemaker cells through gap junctions

From Takaki, J Smooth Muscle Res, 2003
There is no gradation of single unit smooth muscle contraction
The presence of gap junctions in single unit smooth muscles results in an all or none contractions of the whole muscle
Automonic innervation can regulate the activity in single unit smooth muscles.

Smooth muscle fibers are stimulated by multiple synaptic sites (varicosities).
T-L Relationship in Smooth Muscle

Differently from skeletal muscles, smooth muscles can generate significant amounts of force even when stretched 2.5 times its resting length.