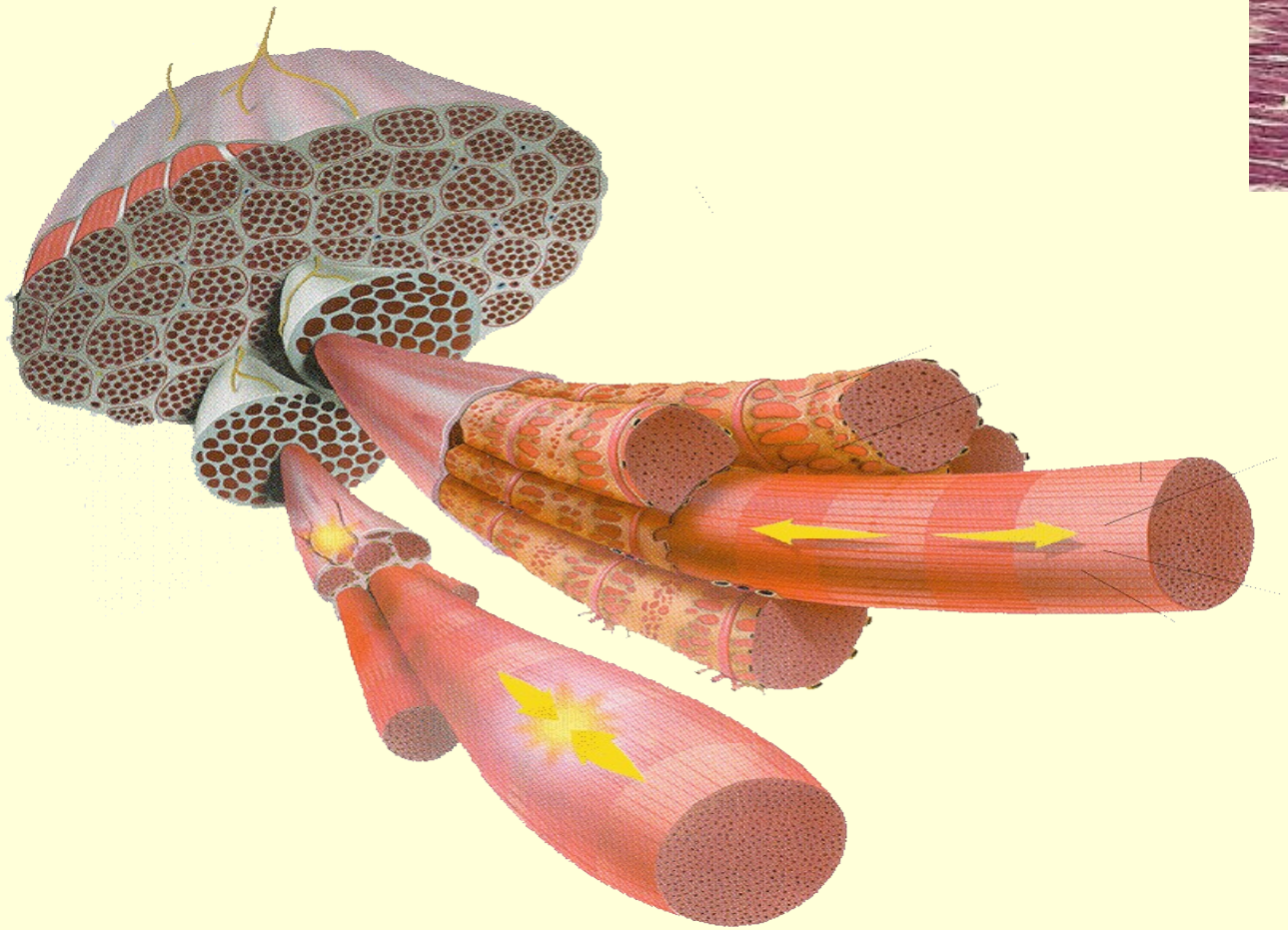
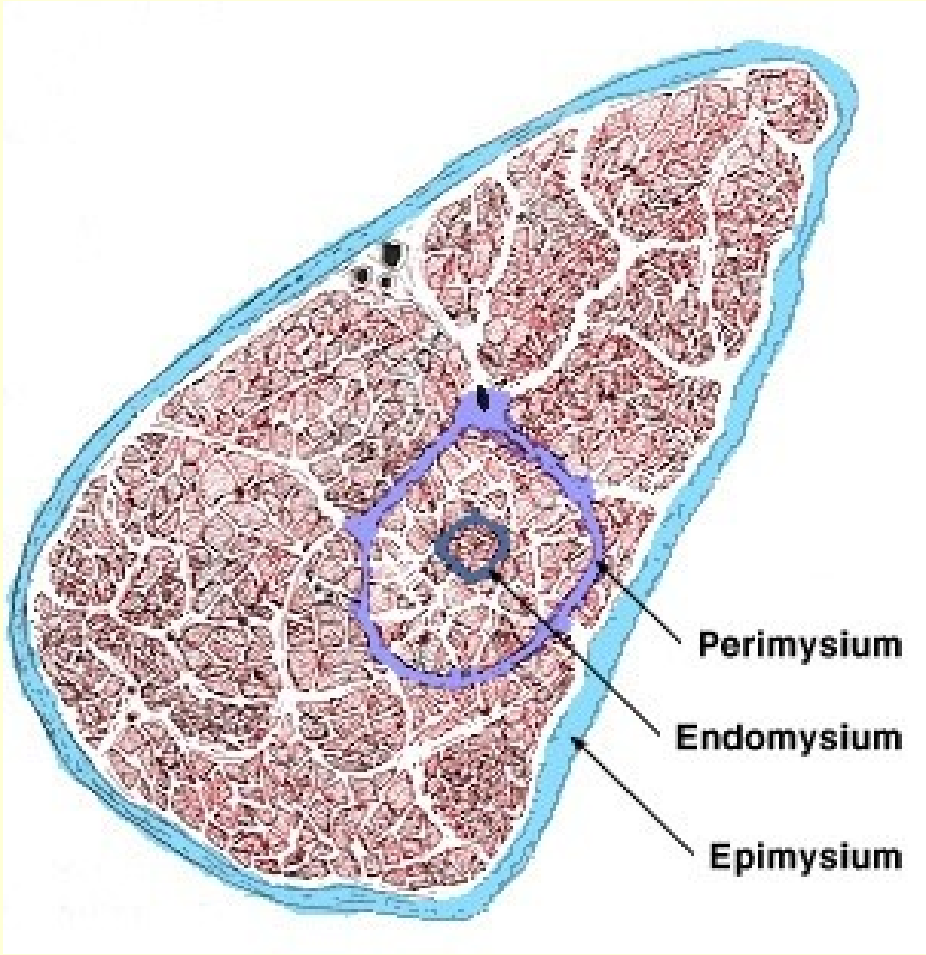
SKELETAL MUSCLES



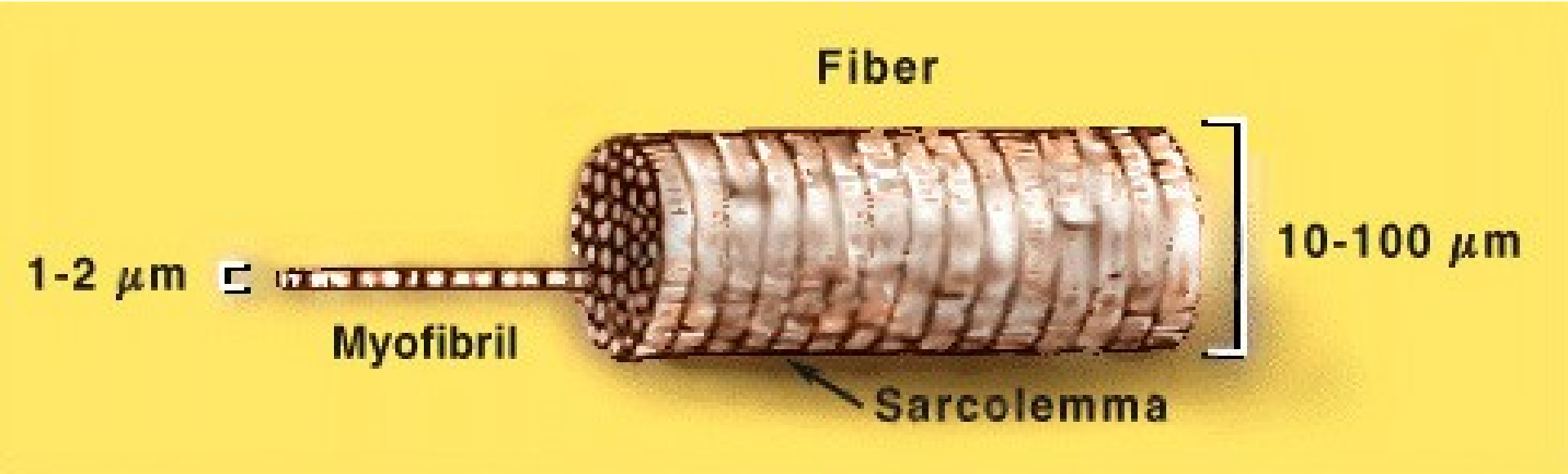
WHOLE MUSCLE

- Skeletal muscles in the body are made up of individual muscle cells, which are referred to as muscle fibers.
- Individual fibers are surrounded by a layer of connective tissue called the ***endomysium***.
- Groups of neighboring fibers are bundled into fascicles by a connective tissue sheath called the ***perimysium***.
- The fascicles make up the whole muscle itself, which is covered by the connective tissue layer called the ***epimysium***.

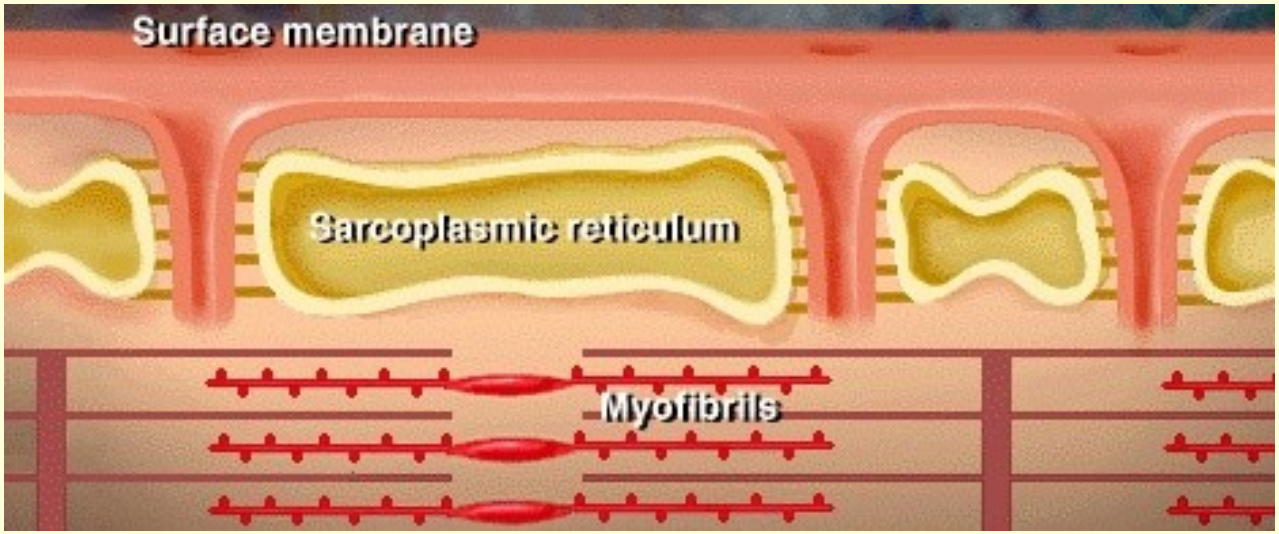


SINGLE SKELETAL MUSCLE FIBERS

- Each skeletal muscle fiber is about 10 to 100 micrometers in diameter and has tendons at either end that attach to bone or connective tissue sheaths.
- The surface membrane of the fiber is called the *sarcolemma*; this, like nerve cells, contains electrically excitable channels that permit action potentials to be generated in response to adequate stimuli.

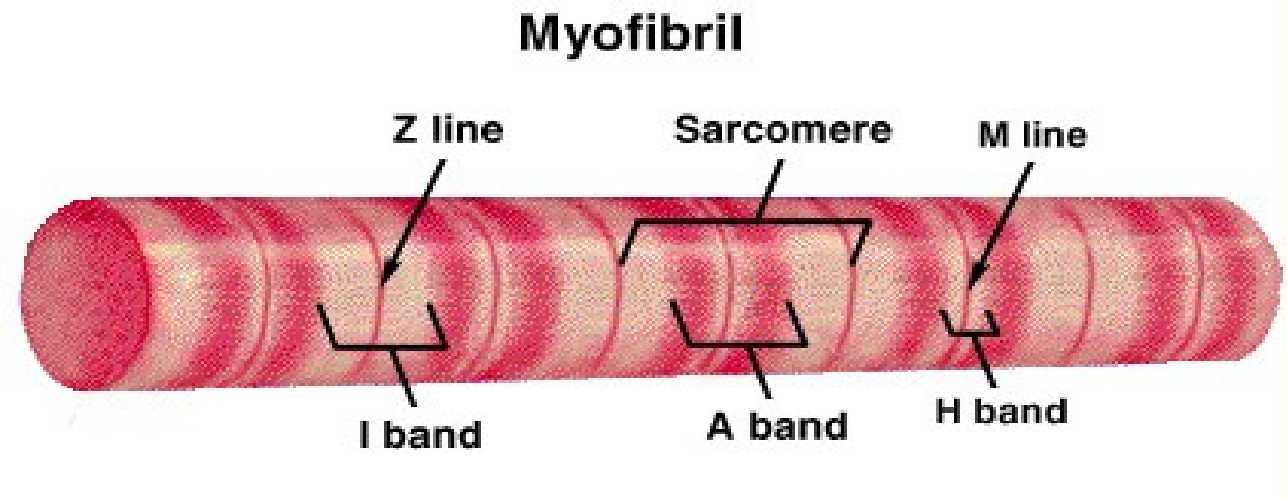


SINGLE SKELETAL MUSCLE FIBERS



- **Within each fiber are small regions 1 to 2 micrometers in diameter called myofibrils.**
- **Myofibrils are surrounded by sarcoplasmic reticulum, an intracellular structure analogous to the endoplasmic reticulum (found in many types of cells).**

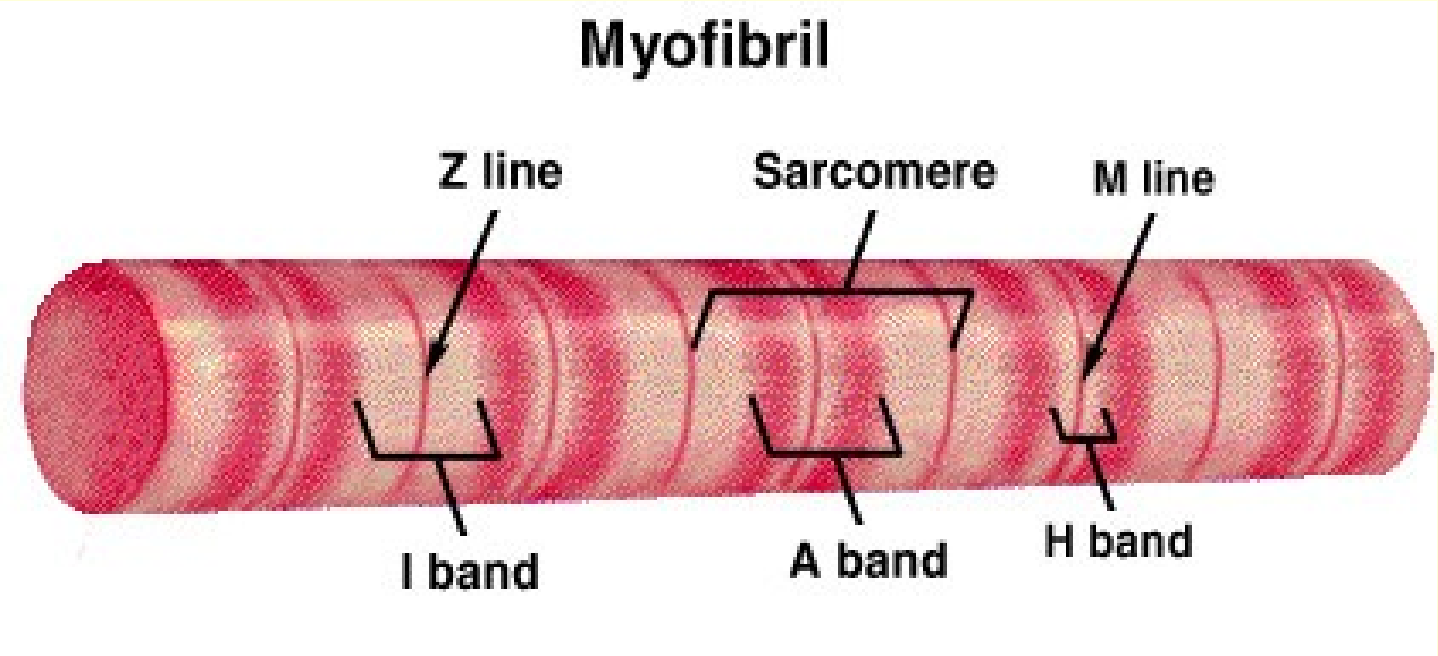
THE SARCOMERE: NOMENCLATURE



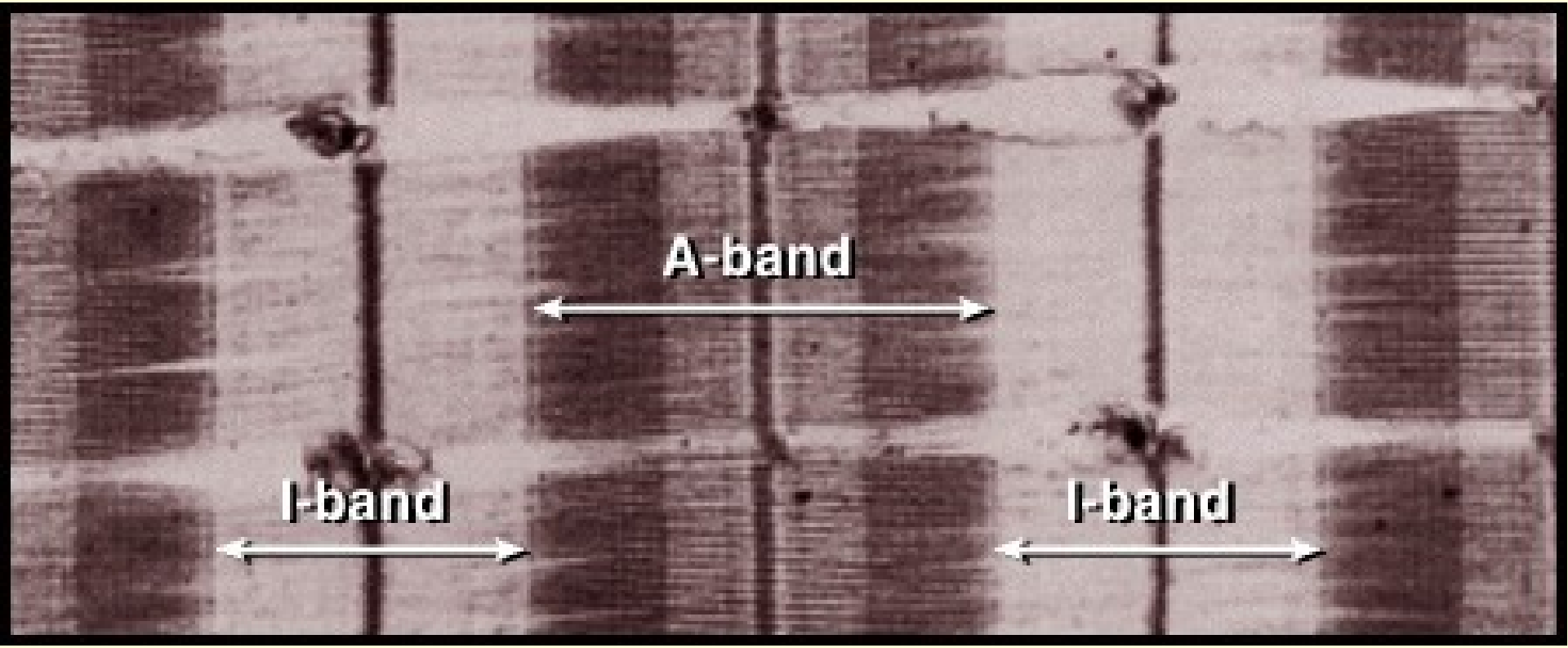
- **The light microscope reveals that skeletal muscle fibers show regular stripes. Striations are also observed in cardiac muscle. Thus skeletal and cardiac muscle cells are termed *striated* muscle cells.**
- **The sarcomere is the major repeating striated unit, and is the fundamental contractile unit in both skeletal and cardiac muscle.**

THE SARCOMERE: NOMENCLATURE

- A sarcomere is defined as the structure from one Z-line to the next Z-line. In the center of each sarcomere is a region about 1.6 micrometers long called the A-band .
- The center of the A-band is termed the H-band, with an M-line in the middle. On either side of the A-band is an I-band. In the center of each I-band is a Z-line.

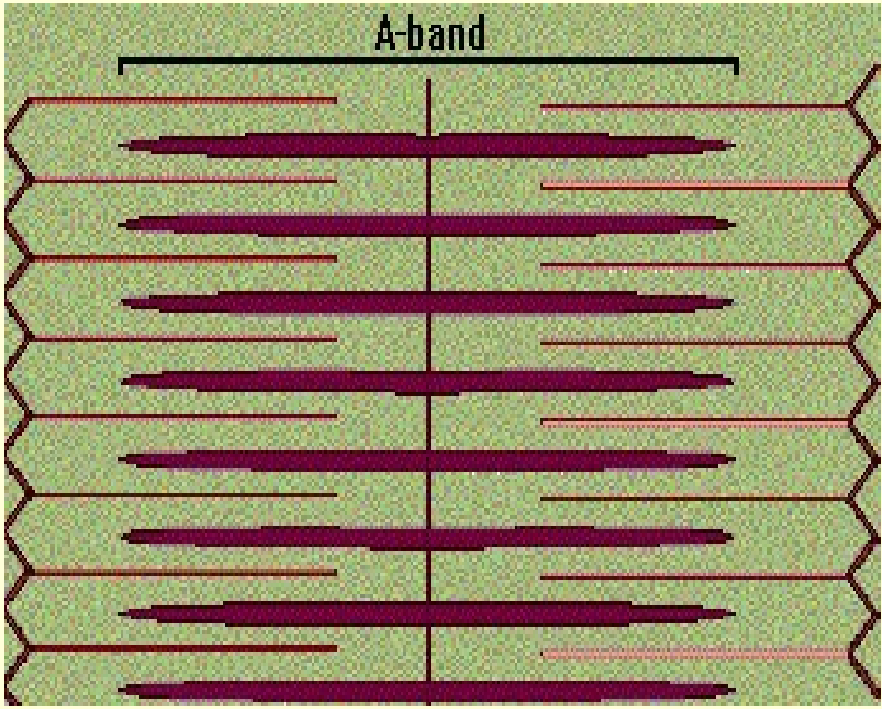


ELECTRON MICROSCOPY



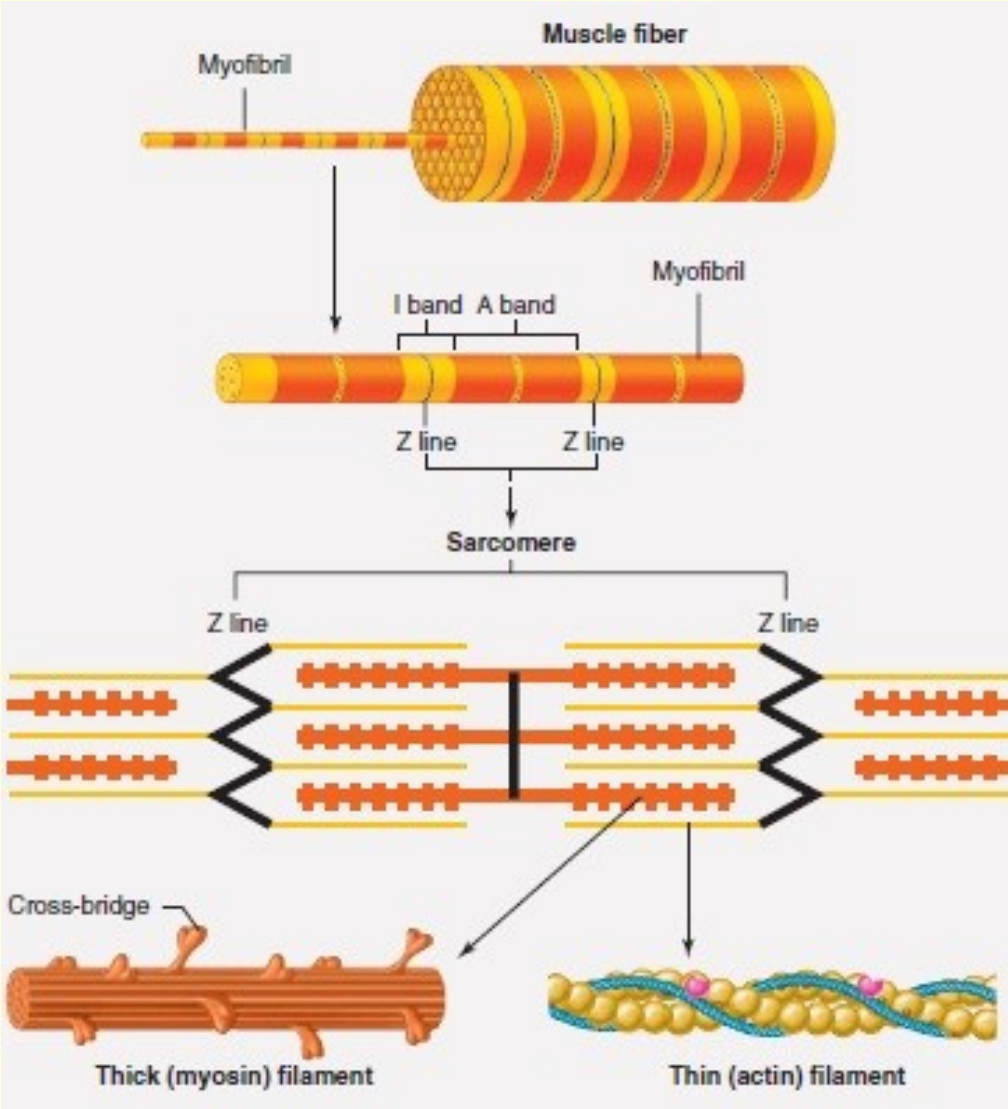
EFFECT OF LENGTH CHANGES

- When the length of a muscle fiber is varied, the sarcomere length varies as well. Over the range of lengths that the fiber experiences physiologically, the A-band length remains constant, while the I-band varies.
- As the muscle length is changed, the thick and thin filaments slide easily past one another but do not themselves change in length. It is this sliding filament mechanism that forms the functional basis for the contractile process.



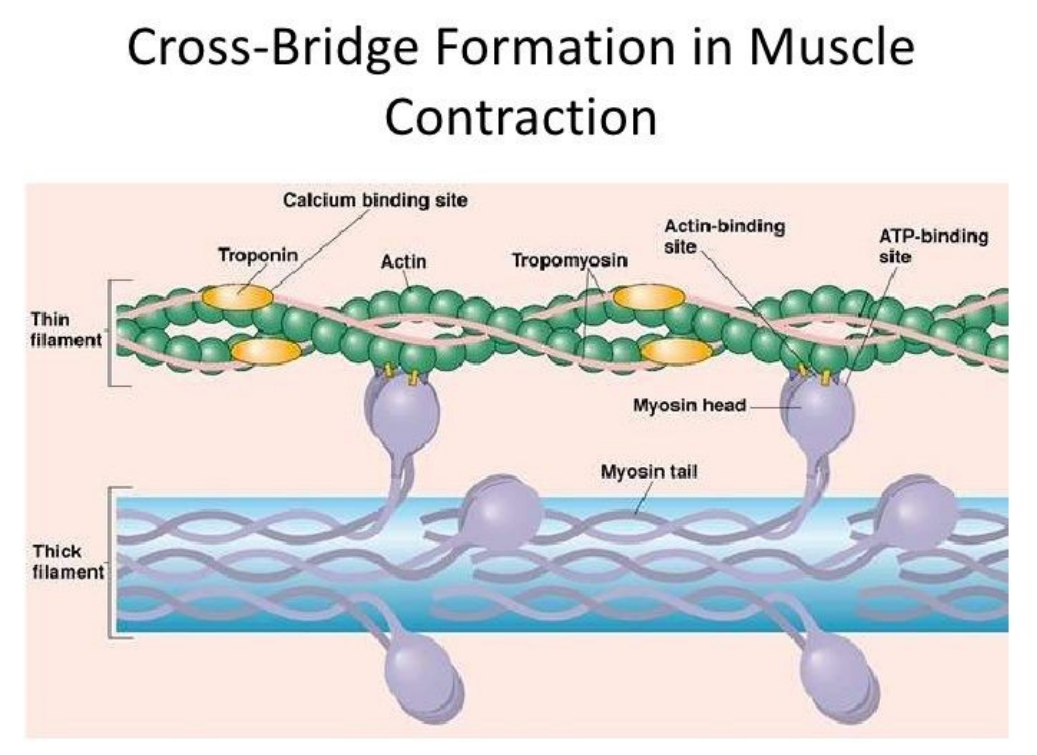
THICK FILAMENTS

- The thick filaments of striated muscles are made up mainly of the protein myosin. There are short projections from the thick filament that bridge the gap between the thick and thin filaments.

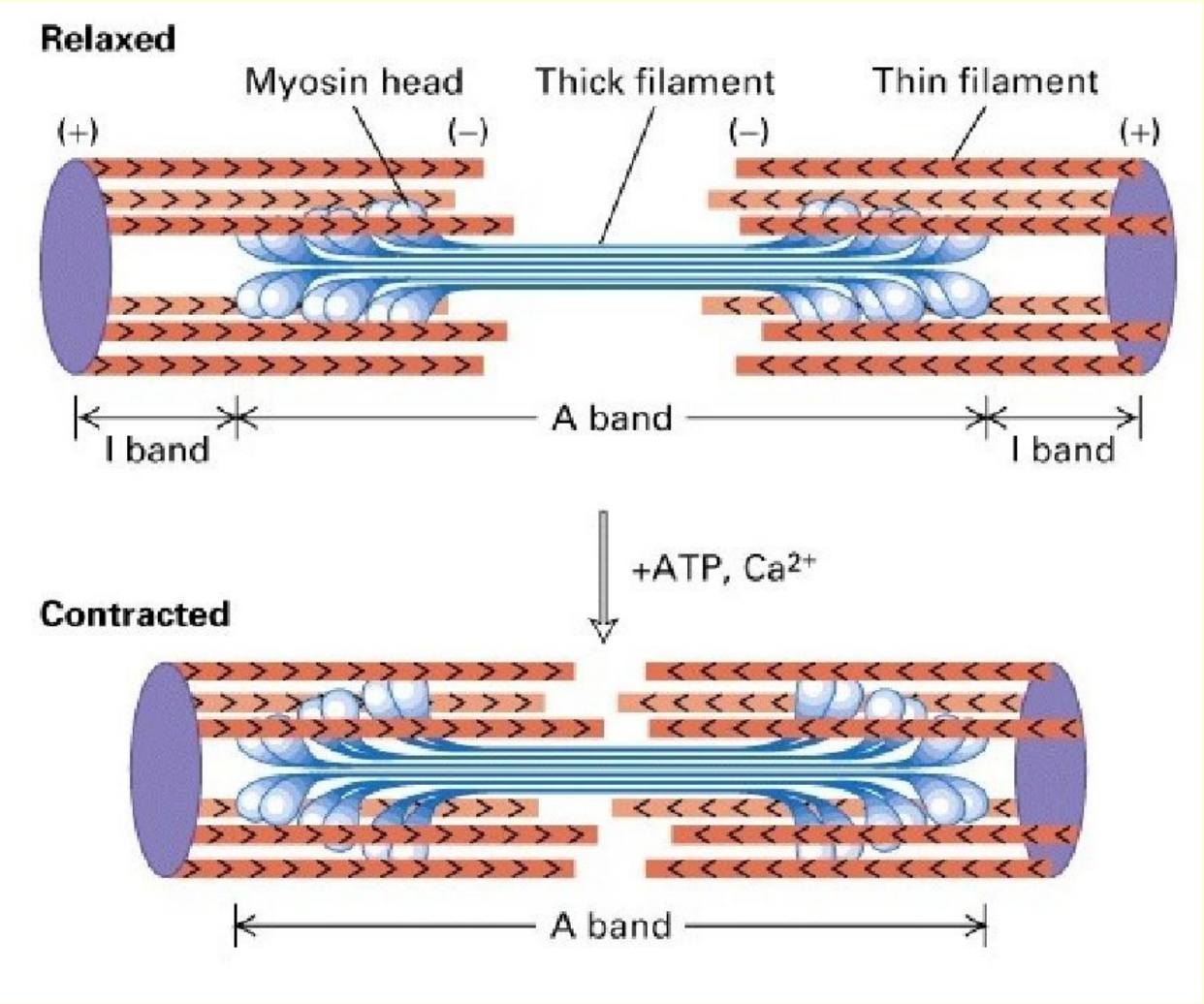


THICK FILAMENTS

- These structures, which originate on the thick filaments, are called crossbridges and are part of the myosin molecules that form the thick filament.
- It is generally accepted the crossbridges bind actin monomers on the thin filaments and give rise to contractile force.



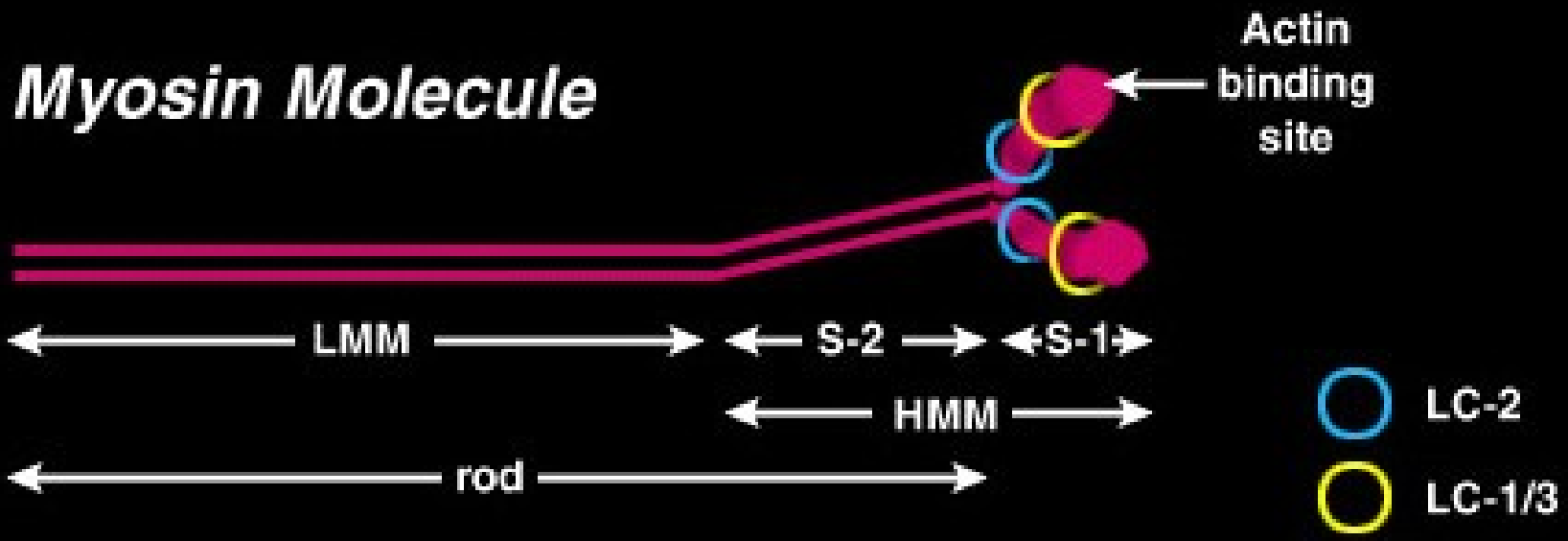
CROSSBRIDGES



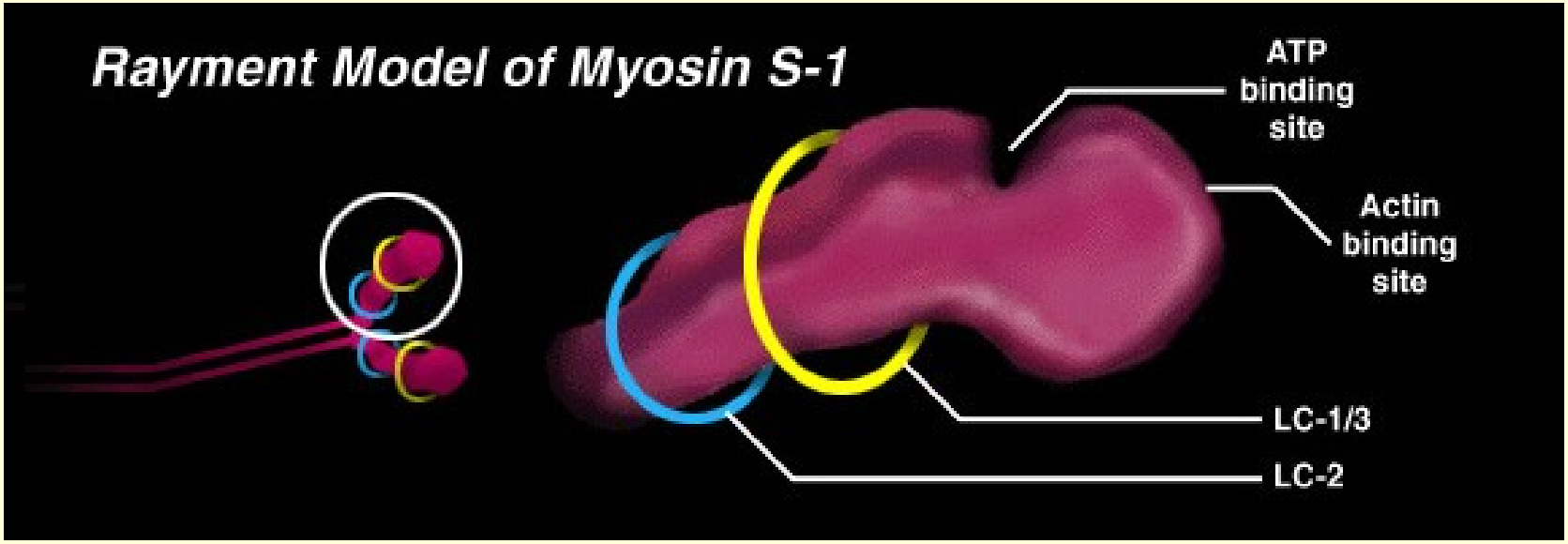
- This is a disposition of the crossbridges on the surface of the thick filament.
- Each crossbridge is the N-terminus region of a myosin molecule.

CROSSBRIDGES

- Myosin is a long, oligomeric protein consisting of two heavy chains and four light chains.
- Using proteolytic enzymes, the heavy chains can be cleaved into a long, rod-like region, termed light meromyosin (LMM), and a globular region with a short tail termed heavy meromyosin (HMM).
- Further cleavage of HMM cuts the tail (S-2) from the globular end region (S-1).



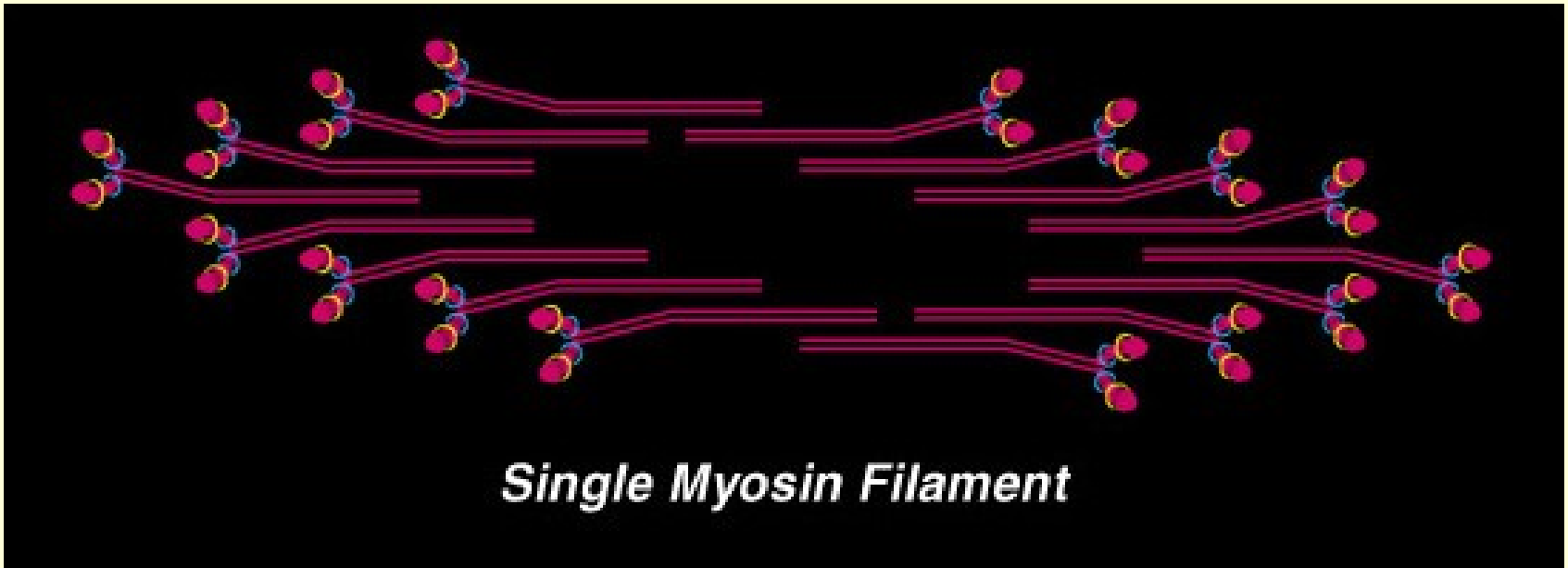
CROSSBRIDGES



- The S-1 portion contains the actin-binding domain, and a distinct adenosine triphosphate (ATP)-binding domain that binds and hydrolyzes ATP, the energy source for contraction.

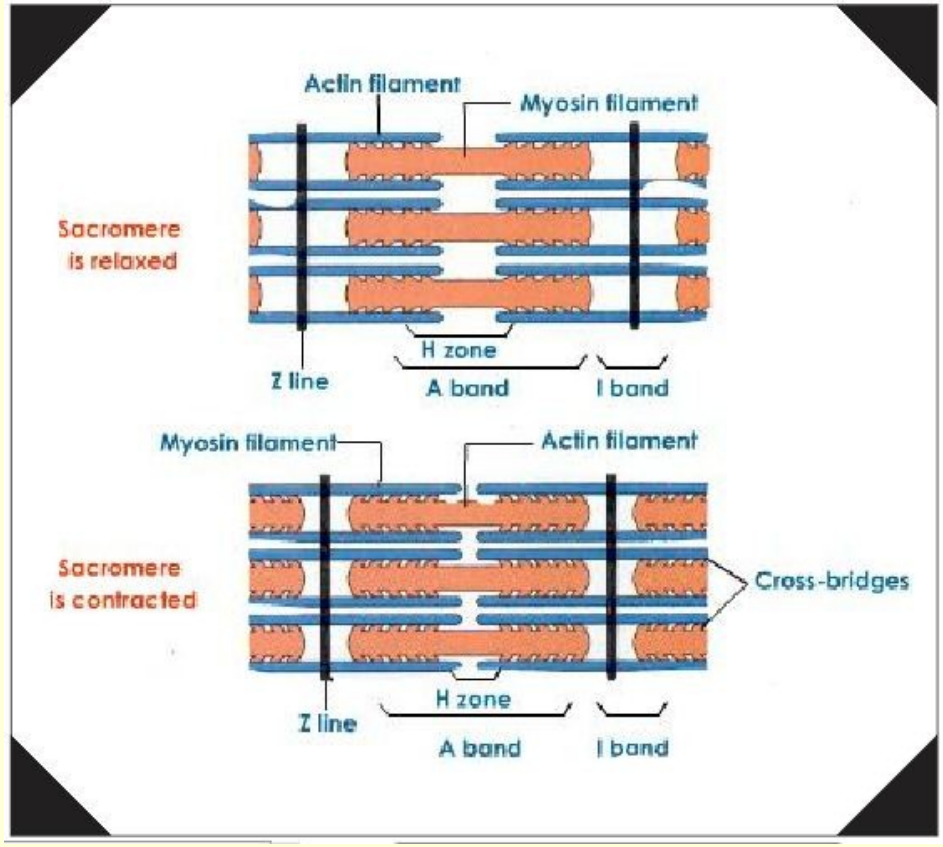
THICK FILAMENTS: ASSEMBLY

- The thick filament is formed by side-to-side aggregation of myosin molecules in the LMM region by electrostatic interactions.
- Cross-bridges are helically arranged around the thick filament. They are found at uniform spacing along all but the central region of the thick filament.
- The zone in the middle of the thick filament devoid of cross-bridges is due to the reversal of the orientation of myosin assembly in the center of the filament.
- The reversal of the orientation of myosin gives a polarity to the thick filament, which is essential to the contractile process.

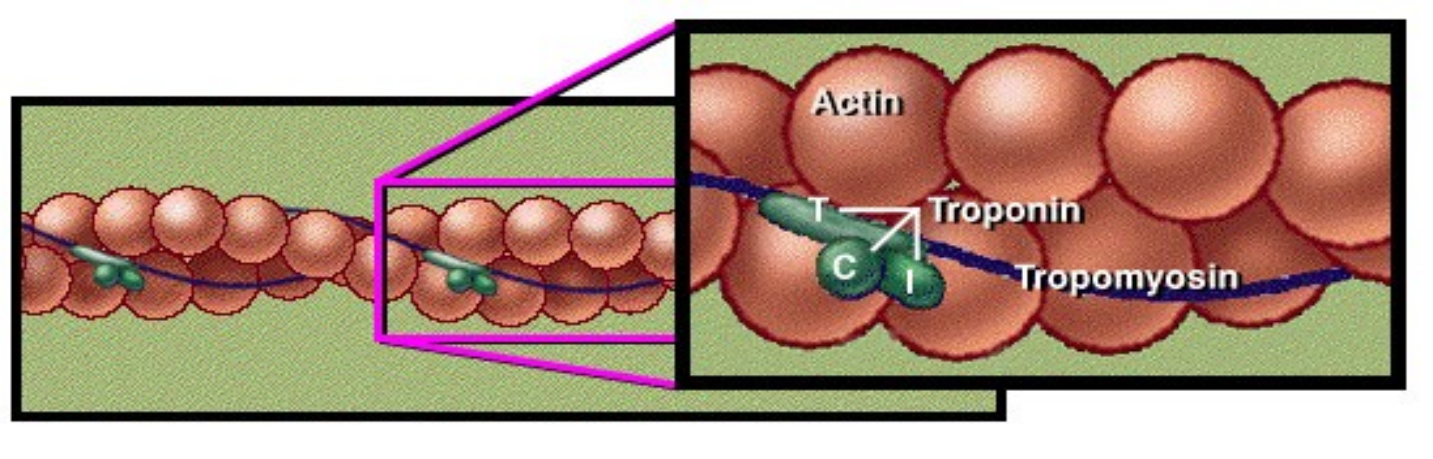


CONTRACTILE PROTEINS: THIN FILAMENTS

- The thin filaments are composed primarily of actin, which is a globular protein. Each actin molecule contains a myosin-binding domain.
- Actin molecules are arranged in two helically twined strands to form the backbone of the thin filament.



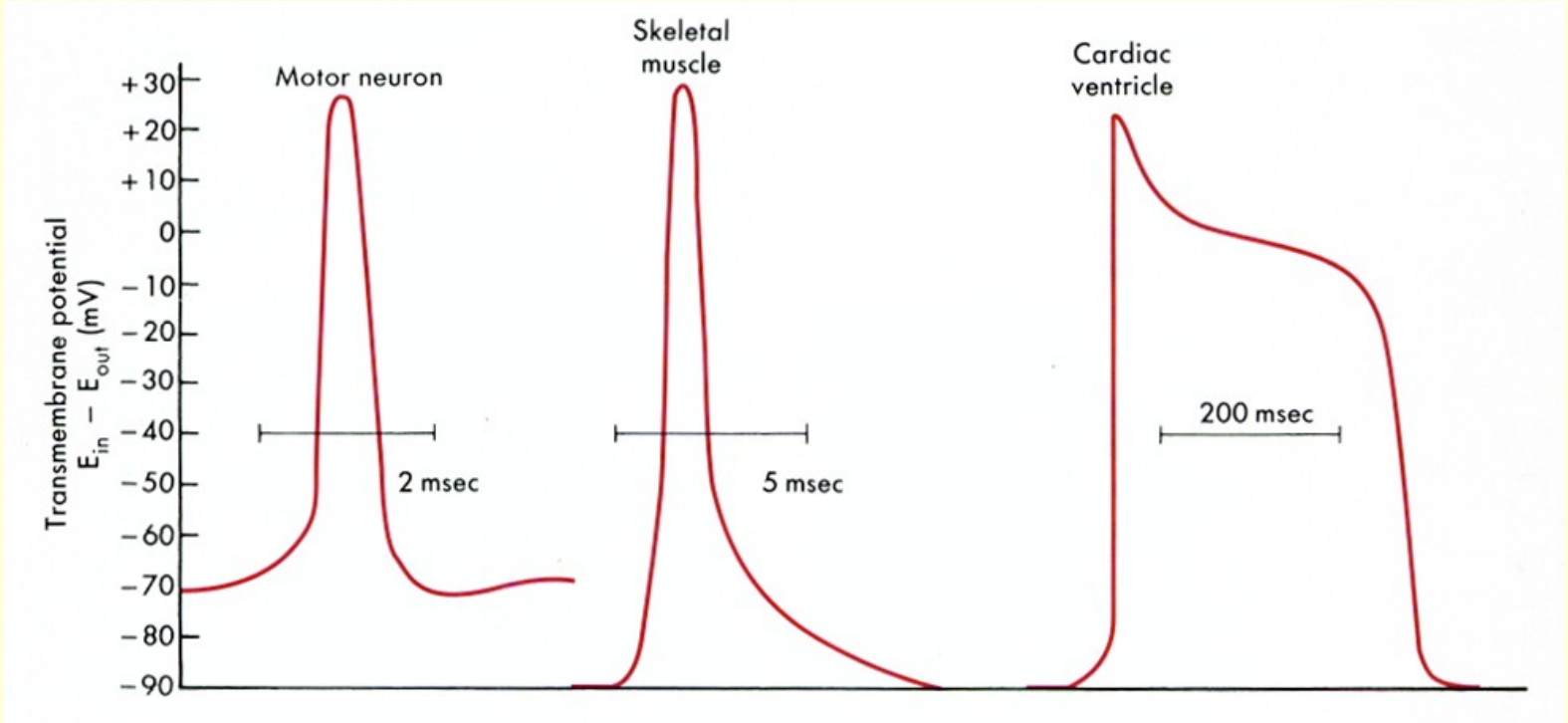
CONTRACTILE PROTEINS: THIN FILAMENTS



- Running in the groove of the actin strands are long tropomyosin molecules. Troponin molecules are in close association with actin and tropomyosin.
- Troponin consists of three subunits, called troponin T (TnT), troponin I (TnI), and troponin C (TnC).
- TnT anchors the troponin molecule to tropomyosin. TnI inhibits the interaction of actin and myosin. TnC binds calcium and provides calcium sensitivity for the contractile process. The thin filament consists of actin, tropomyosin, and troponin in the ratio 7:1:1.

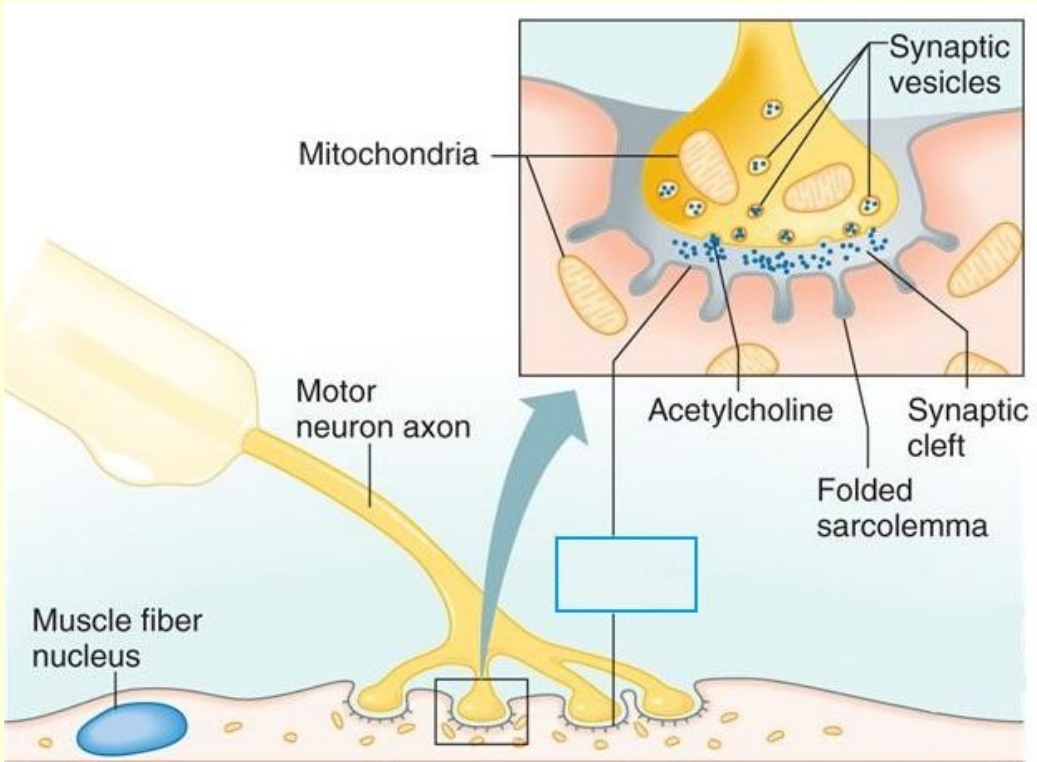
ACTION POTENTIAL

- The action potential across the skeletal muscle membrane (the sarcolemma) is normally initiated by stimulation of the motor nerve associated with the muscle fiber.
- The action potential in skeletal muscle is somewhat longer than the action potential of a nerve and does not show a phase of after hyperpolarization.



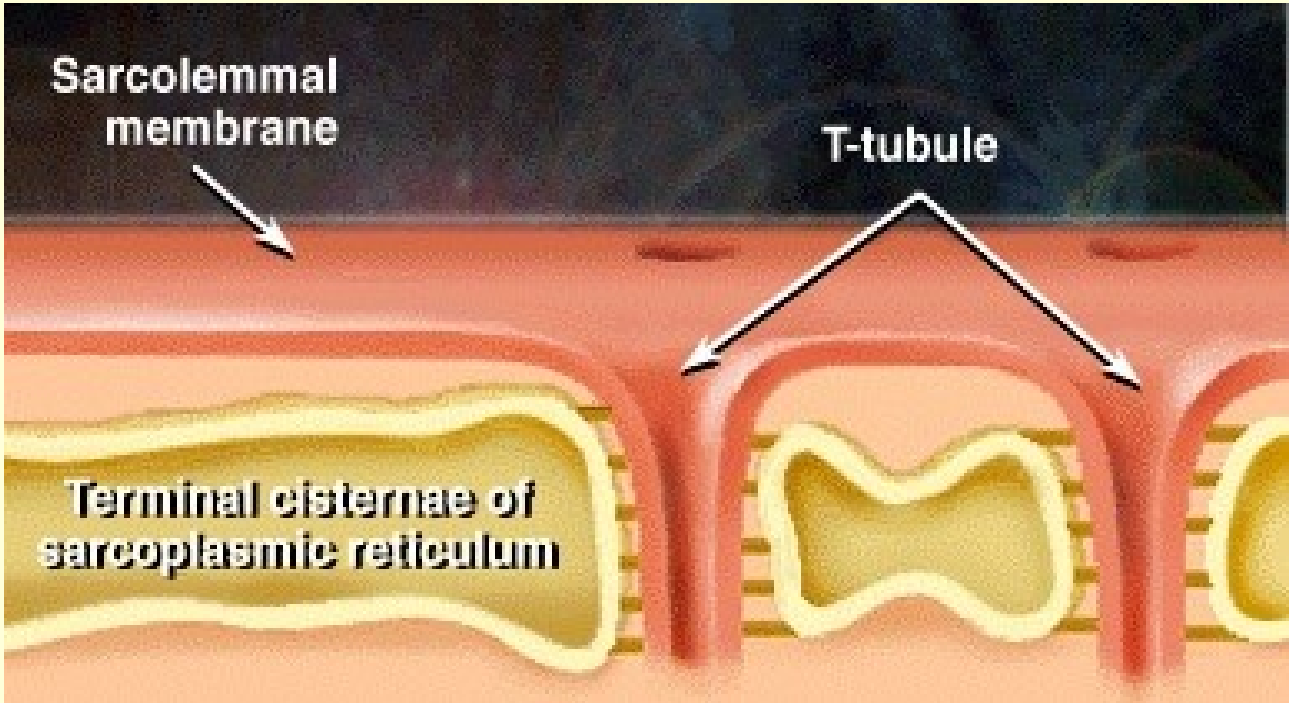
ACTION POTENTIAL

- **The motor end-plate is found in the middle of the muscle fiber in vertebrate skeletal muscles. Thus the action potential sweeps out from the center towards the ends of the fiber. Because the propagation velocity of a muscle action potential is high (3 to 5 m/sec), even a long muscle fiber depolarizes very quickly.**
- **For example, in a 10 cm muscle fiber, the action potential will reach the ends of the muscle only 17 to 25 ms after its initiation at the motor end-plate.**



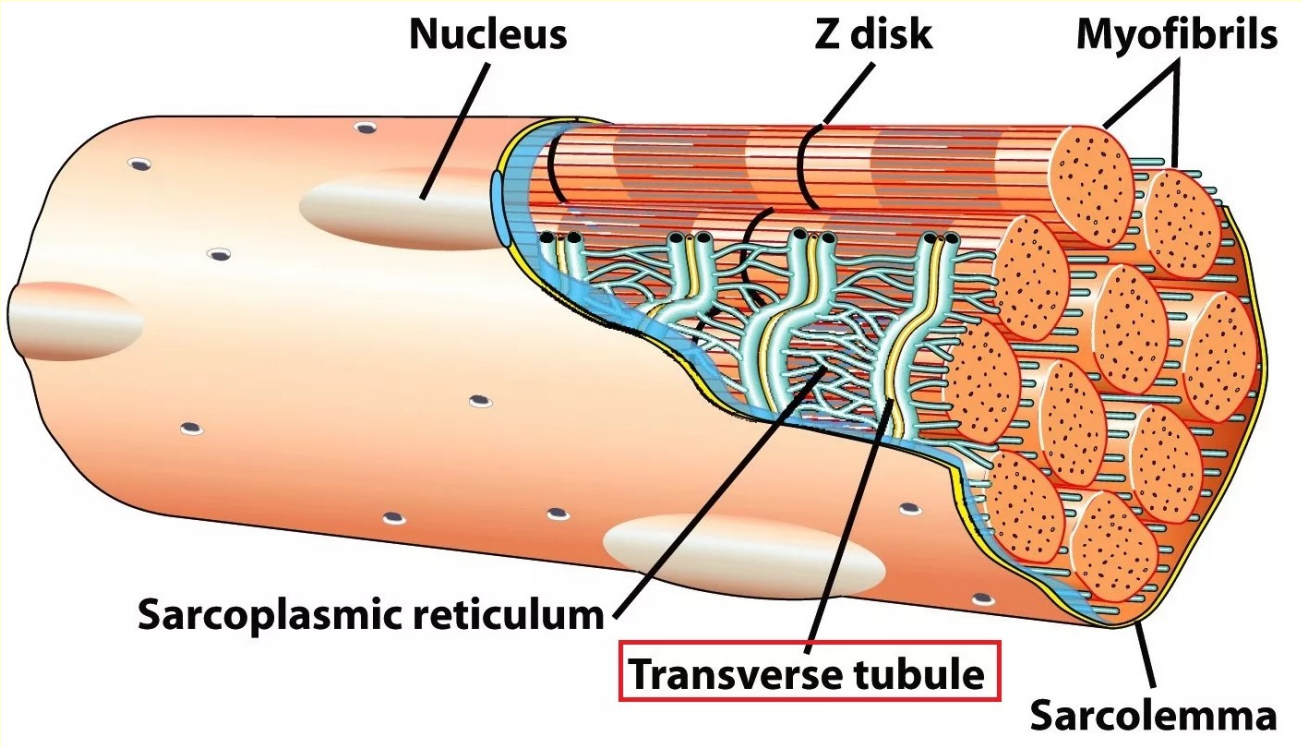
TRANSVERSE TUBULES

- Skeletal muscle cells are rather large (10 to 100 micrometers in diameter). The contractile apparatus of the entire cell is activated very quickly after the surface membrane is stimulated.
- This process is too rapid to be due to simple diffusion of an activator substance from the membrane to the center of the cell.



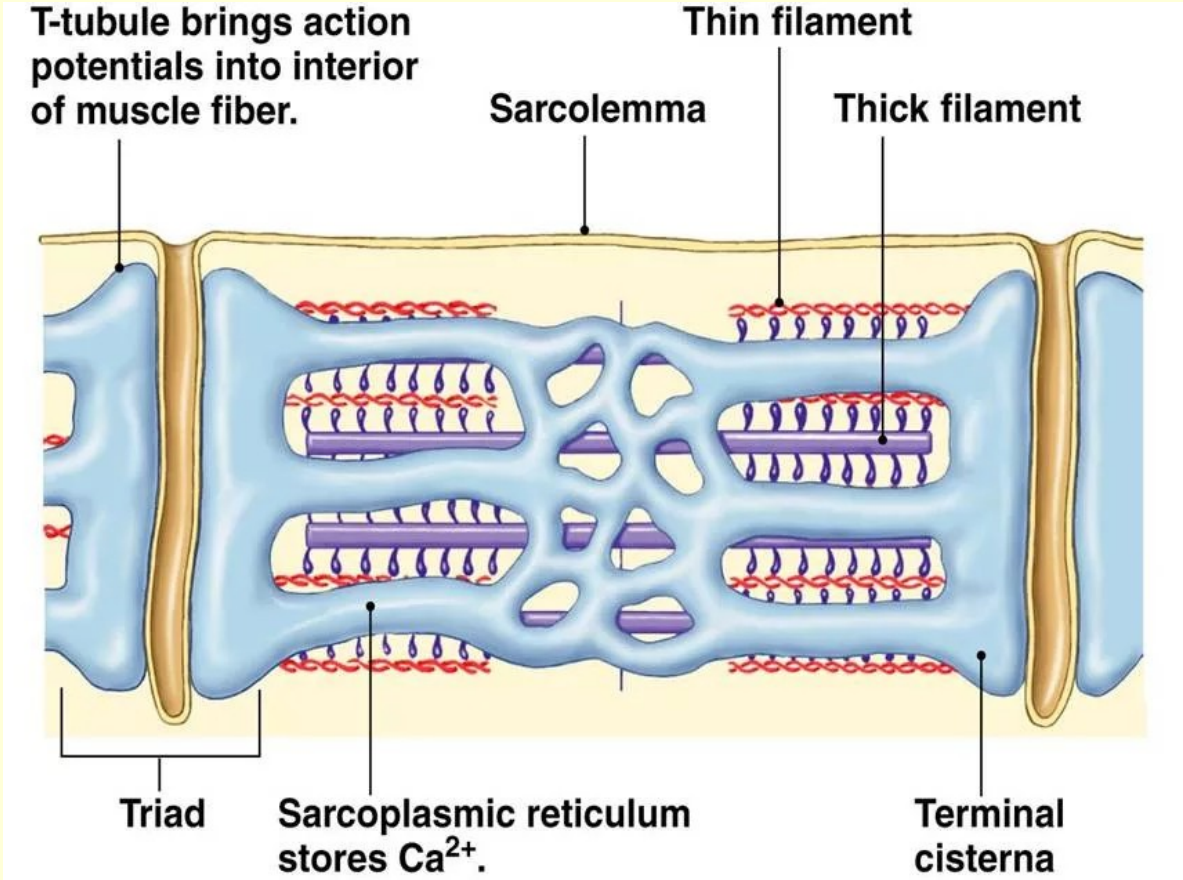
TRANSVERSE TUBULES

- To accomplish such rapid cellular activation, skeletal muscle cells have a network of small tubules penetrating from the surface to the center of the fiber.
- Most tubules are oriented radially inward, transverse to the long axis of the fiber. Thus they are called transverse tubules, or T-tubules, for short.

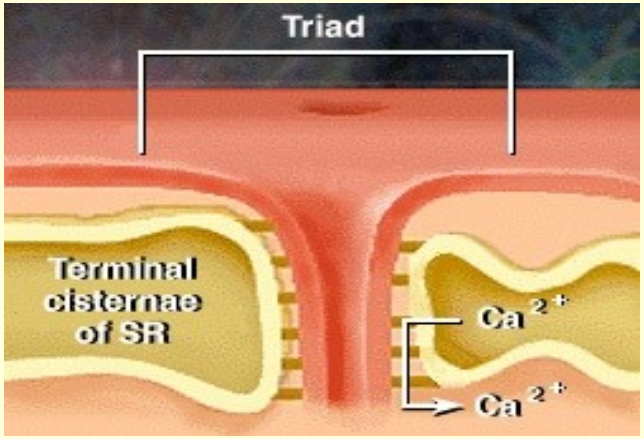


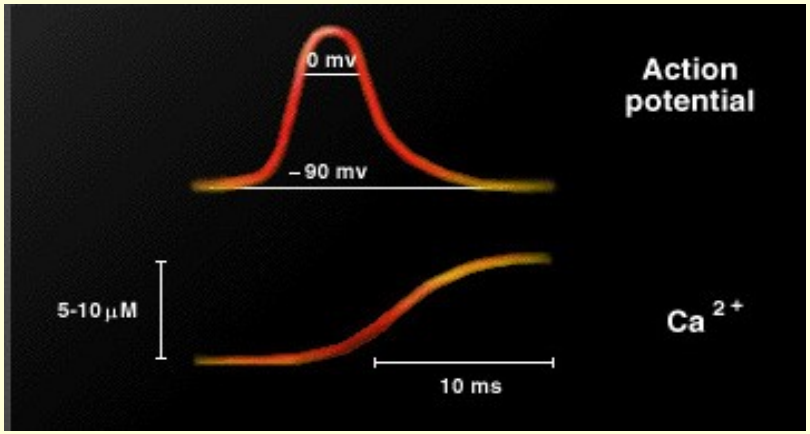
TRANSVERSE TUBULES

- T-tubules are open to the surface and their membrane is continuous with that of the sarcolemmal membrane.
- Thus the action potential sweeping along the surface of the sarcolemmal membrane also causes an action potential in each T-tubule as it passes by.
- This allows the depolarization to reach the center of the cell very rapidly.



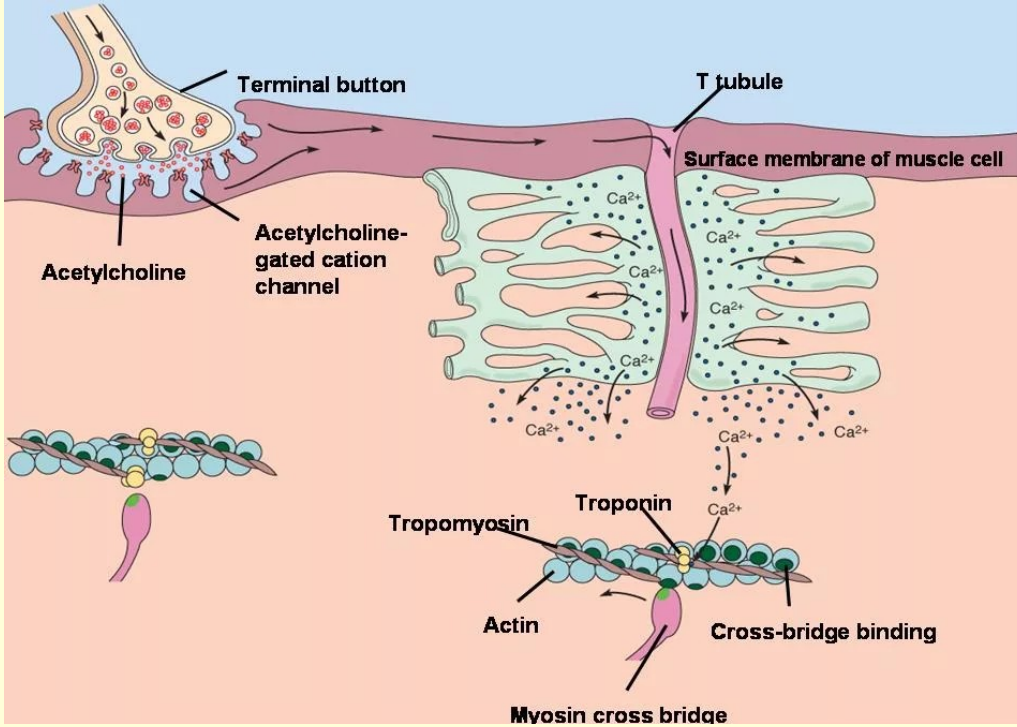
CALCIUM RELEASE FROM THE SPR





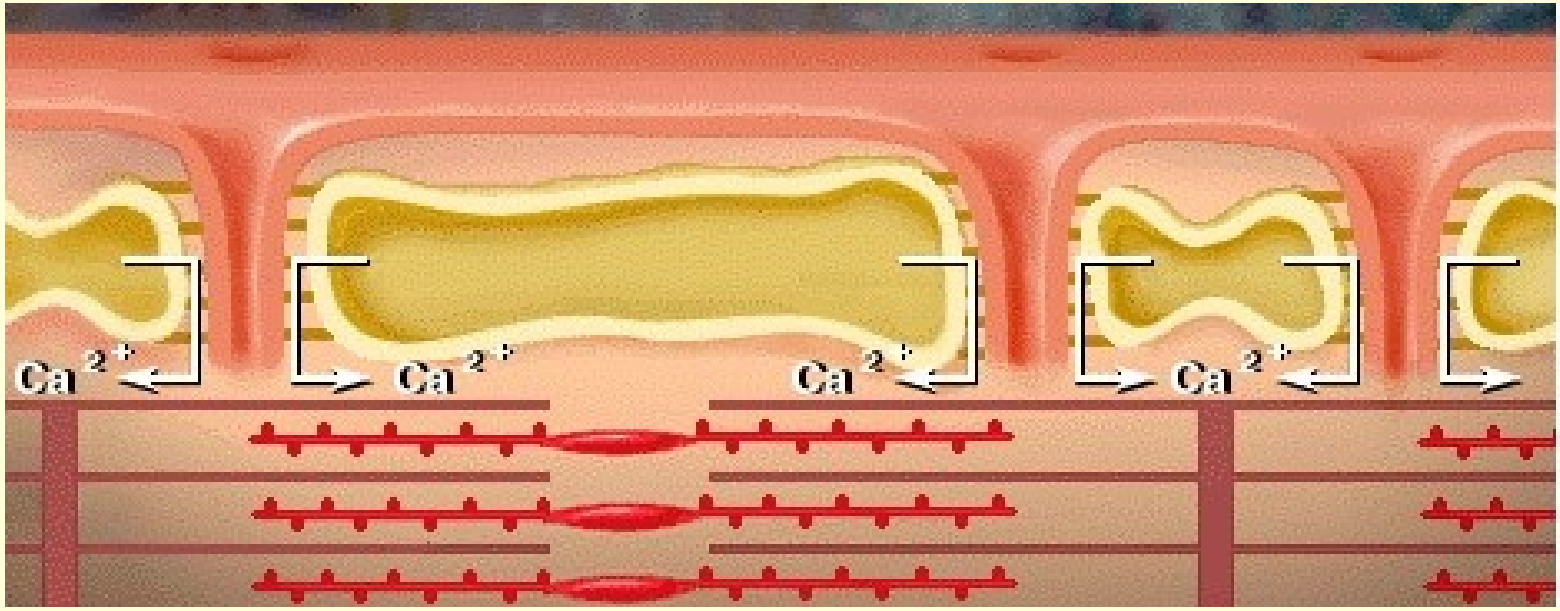
- Following depolarization of the T-tubule, the voltage sensors in the T-tubule membrane cause the calcium-release channels in the membrane of the SR to open.
- Calcium is high in concentration inside the sarcoplasmic reticulum but low in the cytosol surrounding the sarcoplasmic reticulum.
- Therefore, opening of the sarcoplasmic reticulum channels allows calcium to flow passively down its concentration gradient into the cytosol.

CALCIUM RELEASE FROM THE SPR



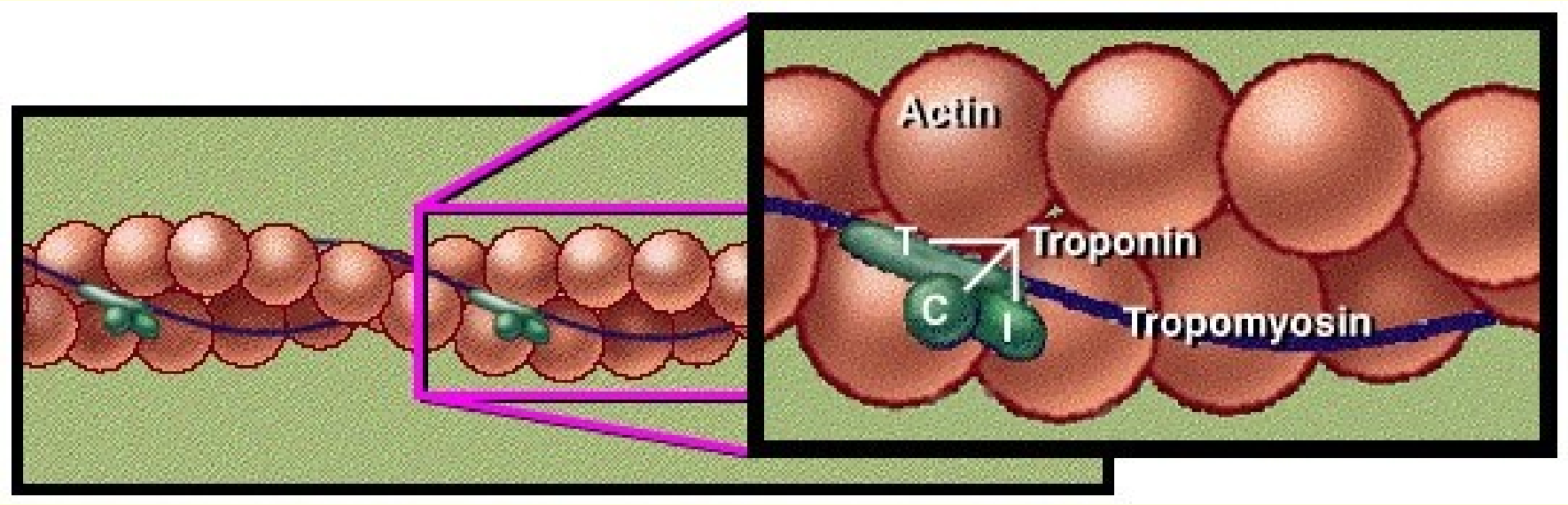
- Because the calcium-release channels are found only in the junction between the T-tubule and the terminal cisternae of the sarcoplasmic reticulum, all the calcium is thought to be released from this small region of the triad.
- Sufficient calcium is released from the sarcoplasmic reticulum to raise the concentration calcium in the cytosol. Because of the large quantity of sarcoplasmic reticulum within the cell, the rise of free calcium is rapid.

CALCIUM RELEASE FROM THE SPR



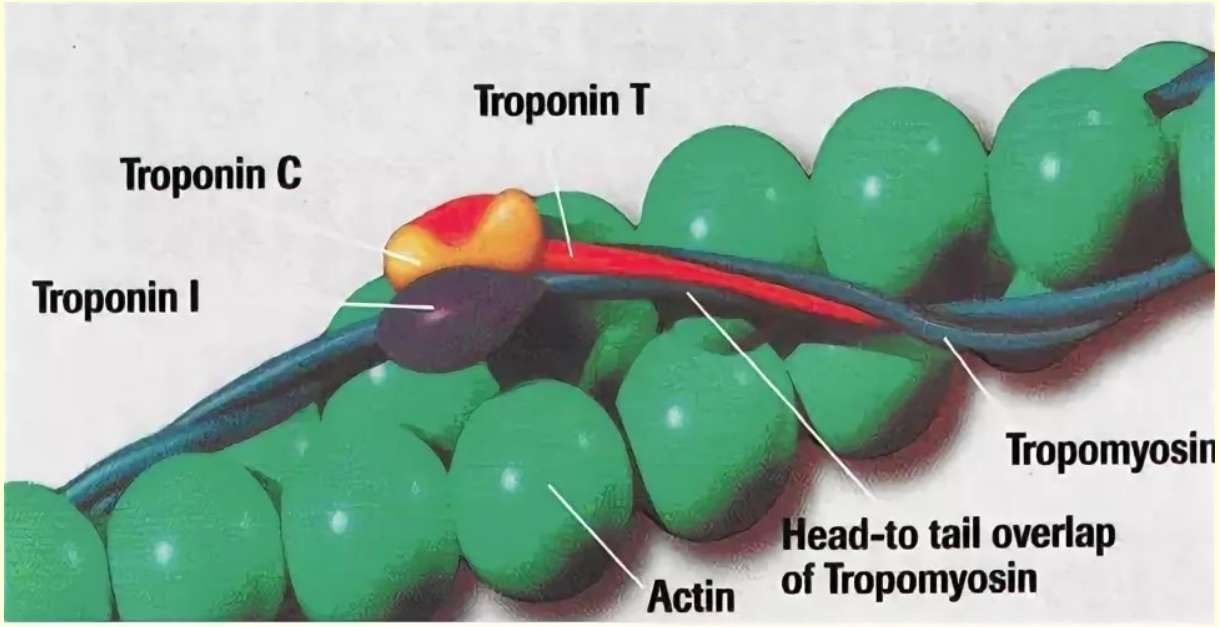
- Each sarcomere has two regions of calcium release separated by only about 1.5 mm.
- This ensures that calcium is quickly and uniformly distributed throughout the entire sarcomere.

CALCIUM ACTIVATION OF CONTRACTION



Calcium released from the SR diffuses rapidly throughout the sarcomere and binds to troponin C (TnC), the calcium-binding subunit of the troponin molecule. This protein is found on the thin filaments.

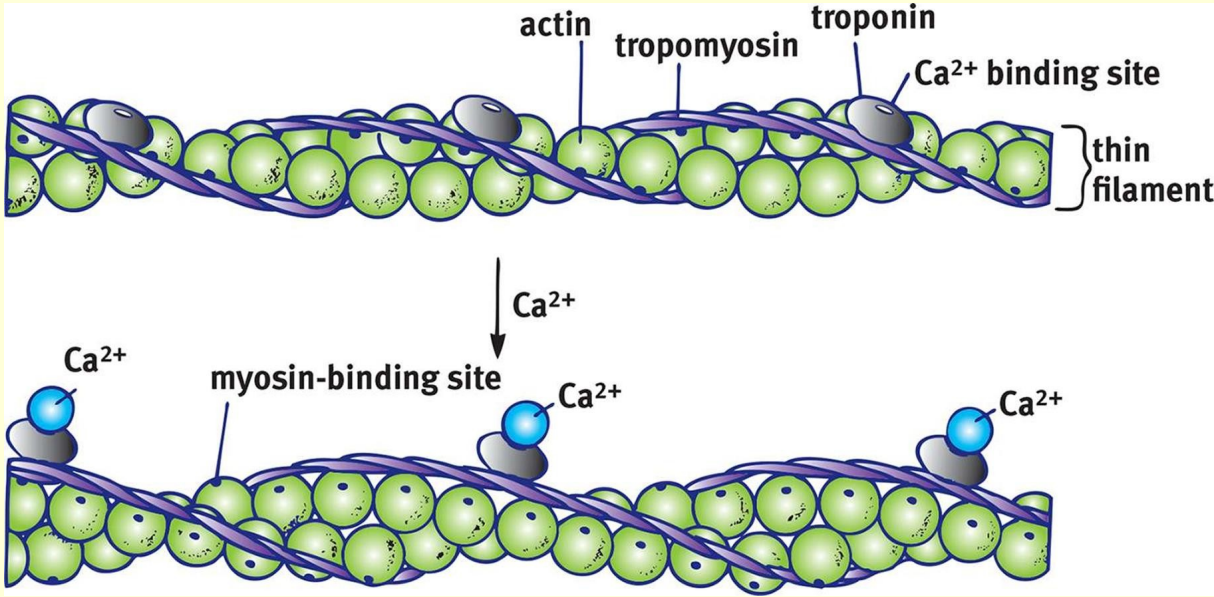
CALCIUM ACTIVATION OF CONTRACTION



- In resting muscle, free calcium concentration is low and the troponin subunits, tropomyosin, and the actin backbone of the thin filament are arranged as shown in the diagram.
- When calcium binds to TnC, these proteins rearrange, and tropomyosin shifts into the groove formed by the actin strands.

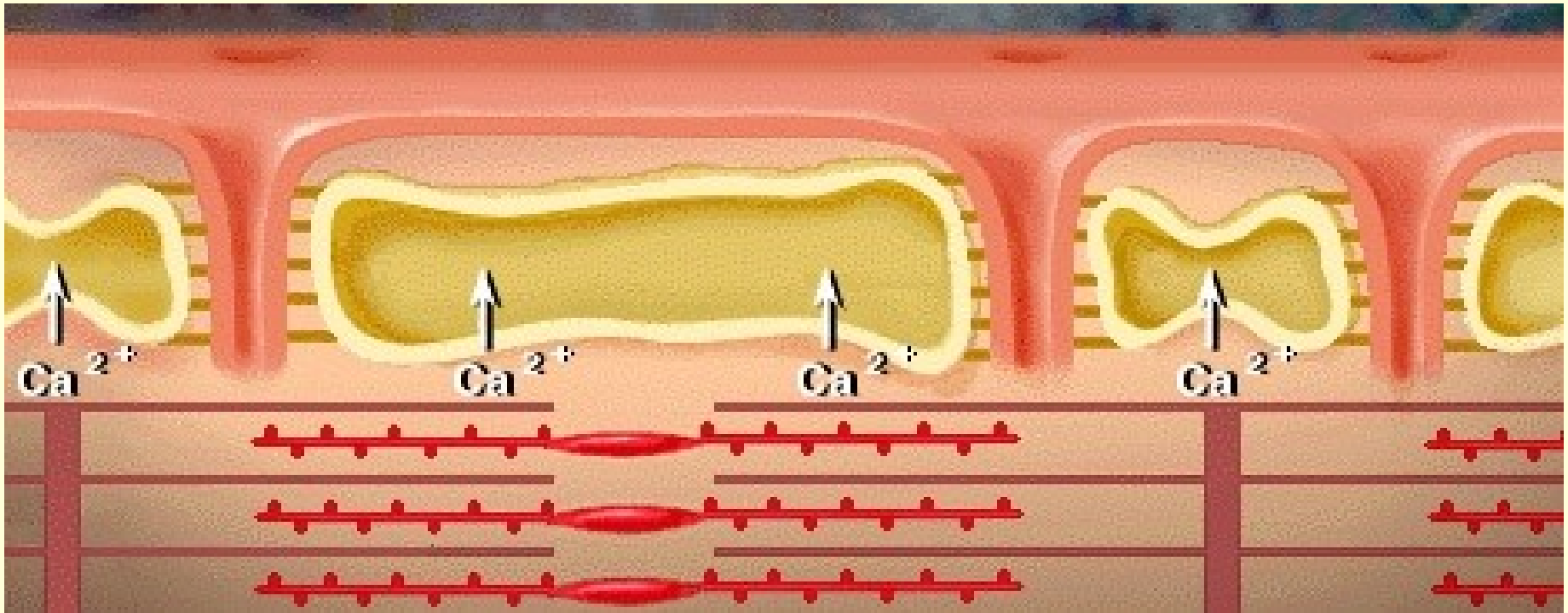
CALCIUM ACTIVATION OF CONTRACTION

- In the calcium-free configuration, tropomyosin lies in the region of actin that binds myosin. In the presence of calcium, tropomyosin shifts away from this region. This observation has lead to the hypothesis that contraction is regulated by a steric blocking mechanism.
- In this model, tropomyosin serves as a simple switch. Because tropomyosin is a long molecule, stretching along seven actin monomers, such a switch could effectively control the access of crossbridges to the actin molecules.



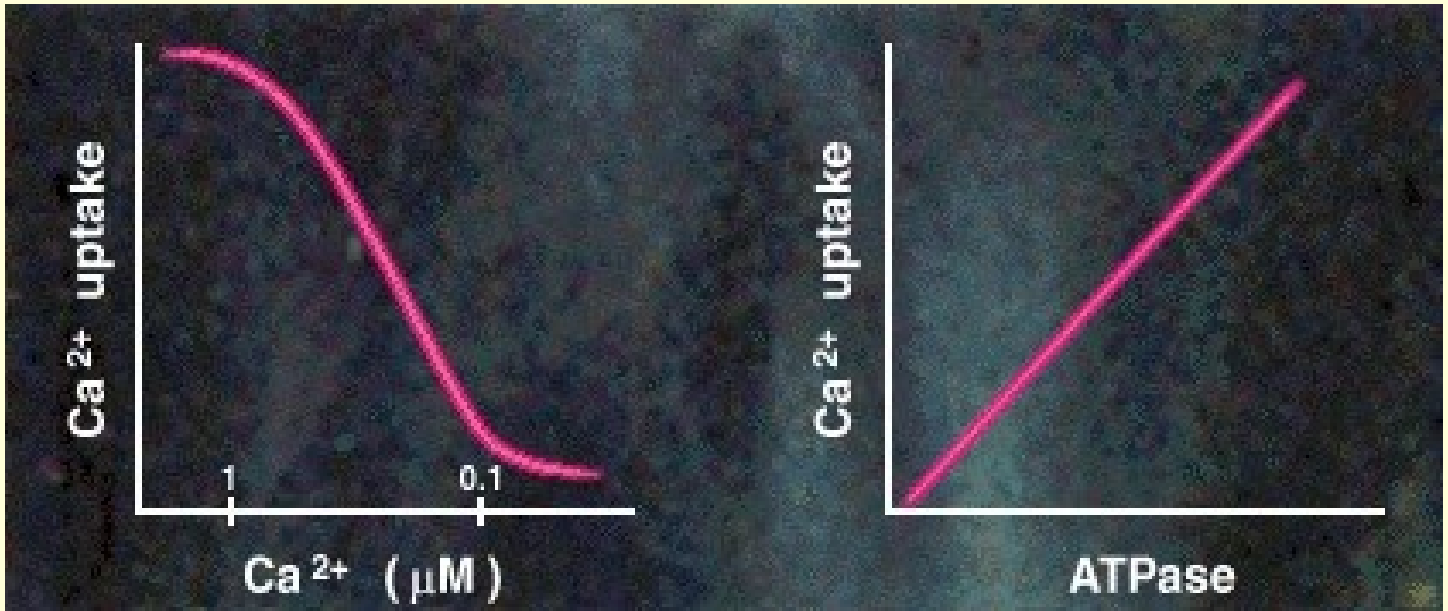
CALCIUM UPTAKE BY THE SPR

- The calcium released by the sarcoplasmic reticulum is rapidly taken up again by calcium pumps in the sarcoplasmic reticulum membrane.
- These pumps are found in great abundance on the nonjunctional regions of the sarcoplasmic reticulum.



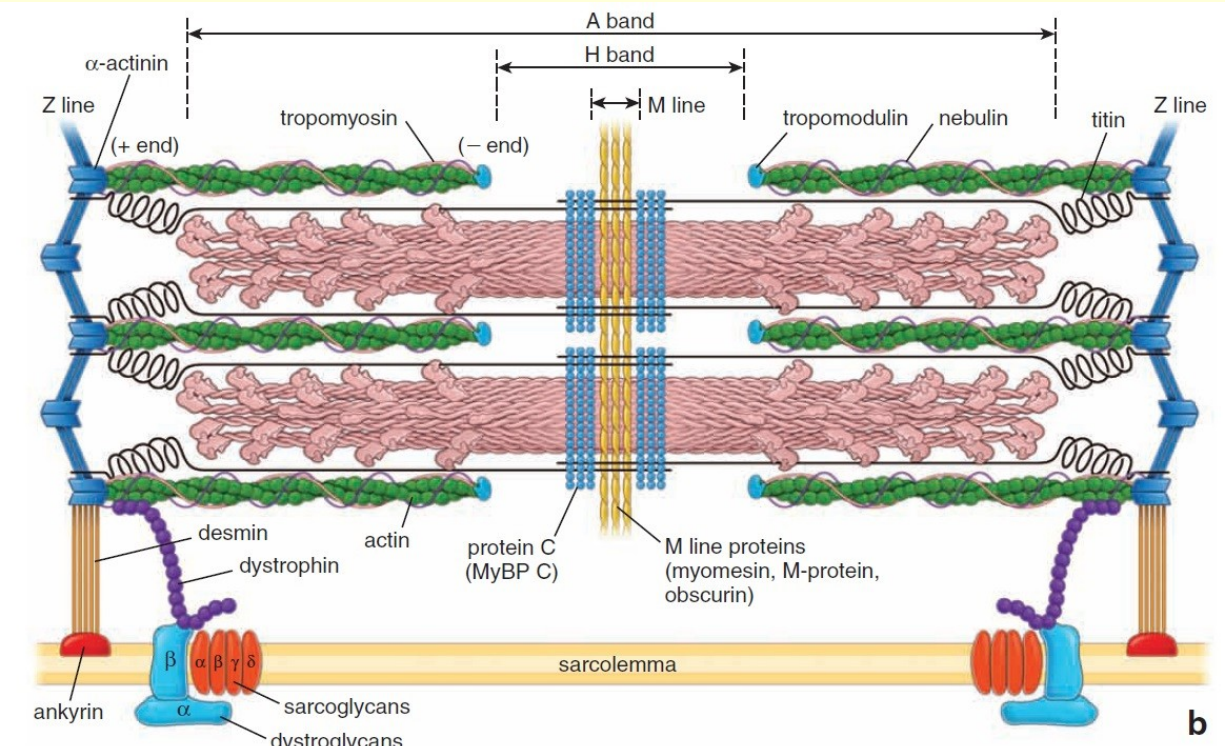
CALCIUM UPTAKE BY THE SPR

- The calcium uptake rate is regulated by the free calcium concentration, so that in resting muscle the uptake rate is low and in active muscle the uptake rate is high.
- Calcium uptake by the sarcoplasmic reticulum requires energy because calcium is being accumulated against its concentration gradient. The pumping rate is proportional to the adenosine triphosphate (ATP) hydrolysis rate.
- The sarcoplasmic reticulum uses ATP to power its calcium pump; this can represent about 25 % of the total energy used by an active muscle cell.

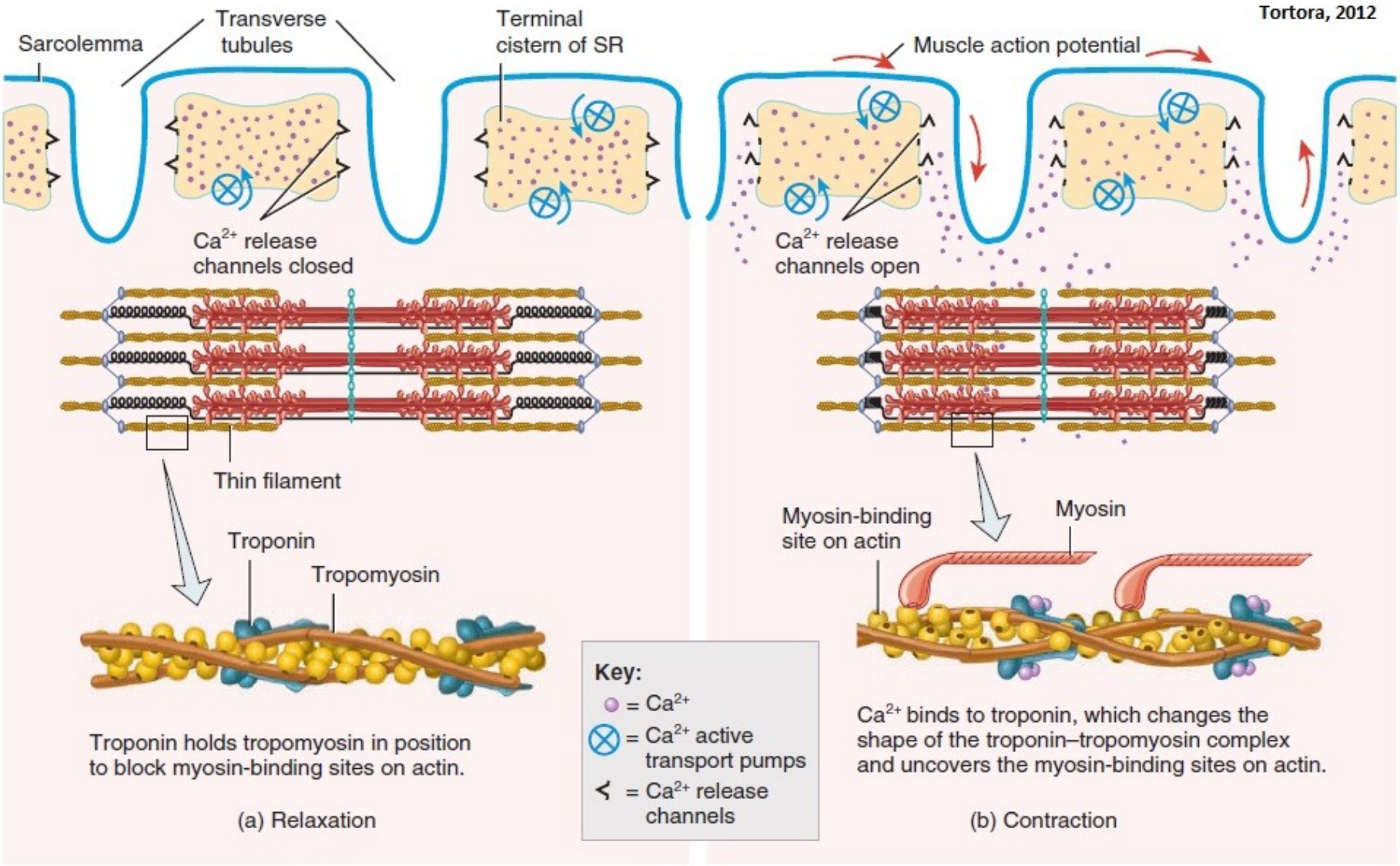


DEACTIVATION OF CONTRACTION

- As the calcium concentration in the cytosol decreases under the influence of the sarcoplasmic reticulum calcium pump, the calcium saturation of TnC decreases. This causes contractile force to decrease.
- The process of deactivation (relaxation) is just the reverse of the activation process. That is, the troponin subunits and tropomyosin rearrange, allowing tropomyosin to shift out of the groove formed by the actin monomers.
- In the steric blocking model, this movement would be the switch turning off cross-bridge binding to the thin filament.

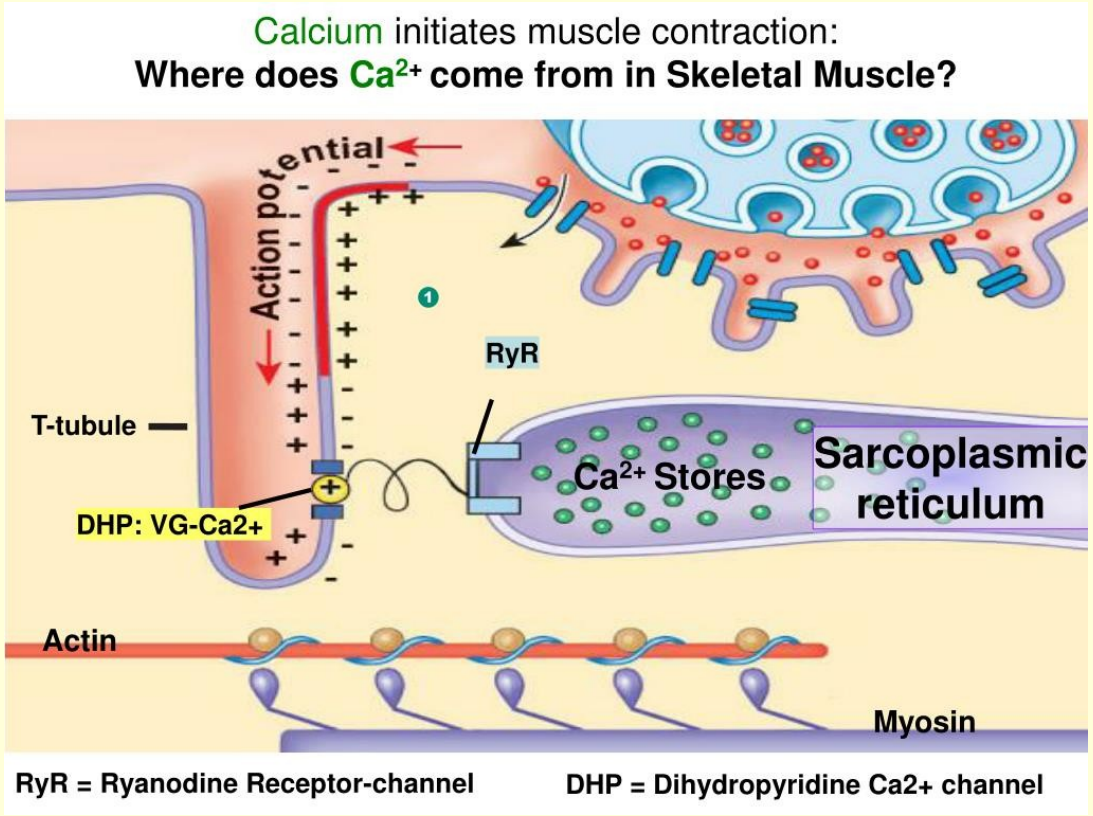


DEACTIVATION OF CONTRACTION



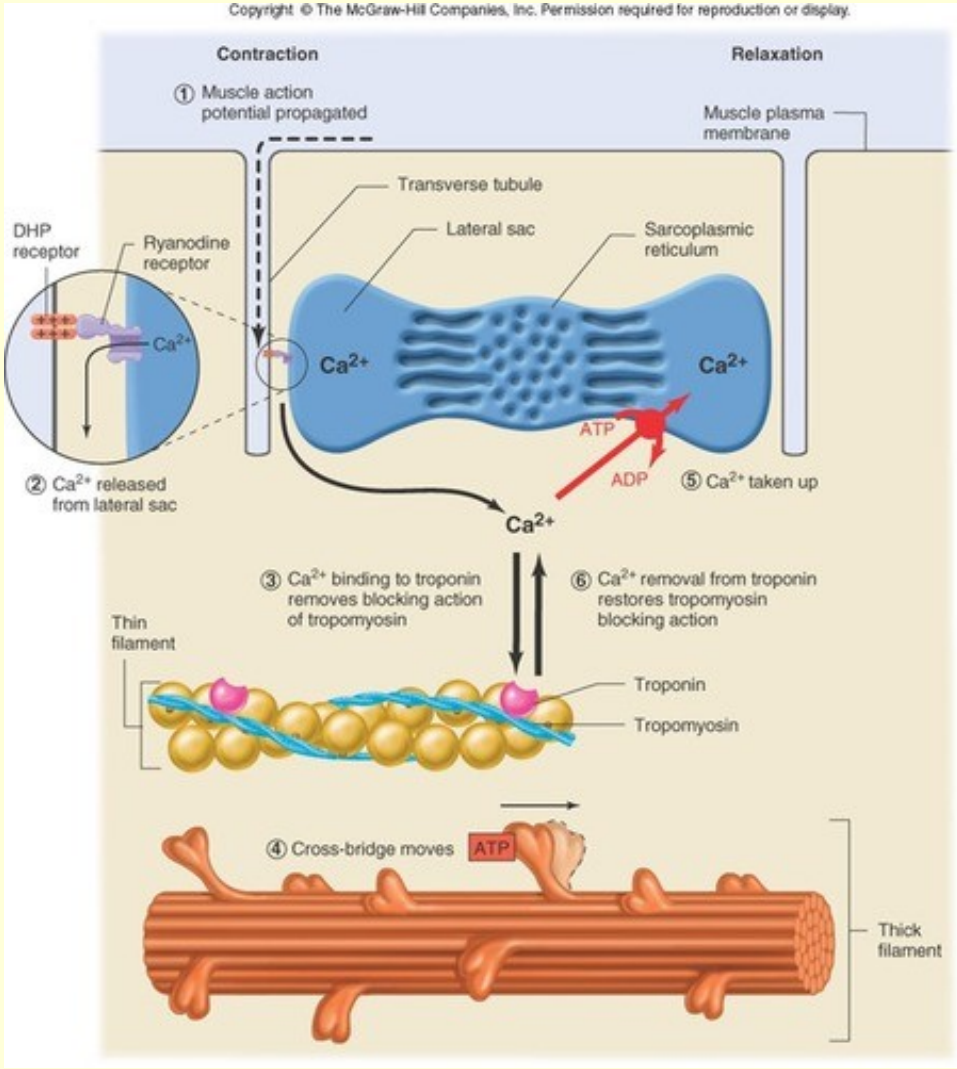
SOURCES OF CALCIUM FOR CONTRACTION OF SKELETAL MUSCLE

- **The calcium used in the excitation-contraction coupling process in skeletal muscle comes exclusively from the sarcoplasmic reticulum. This can be shown quantitatively because sufficient calcium is released to fully saturate all the troponin C present in the myofibrils.**



SOURCES OF CALCIUM FOR CONTRACTION OF SKELETAL MUSCLE

- **It can also be shown that extracellular calcium is not necessary, because skeletal muscle fibers can contract for up to 30 to 60 minutes in solutions that do not contain calcium. This contrasts with the heart or smooth muscle, which stop contracting immediately in calcium-free solutions.**

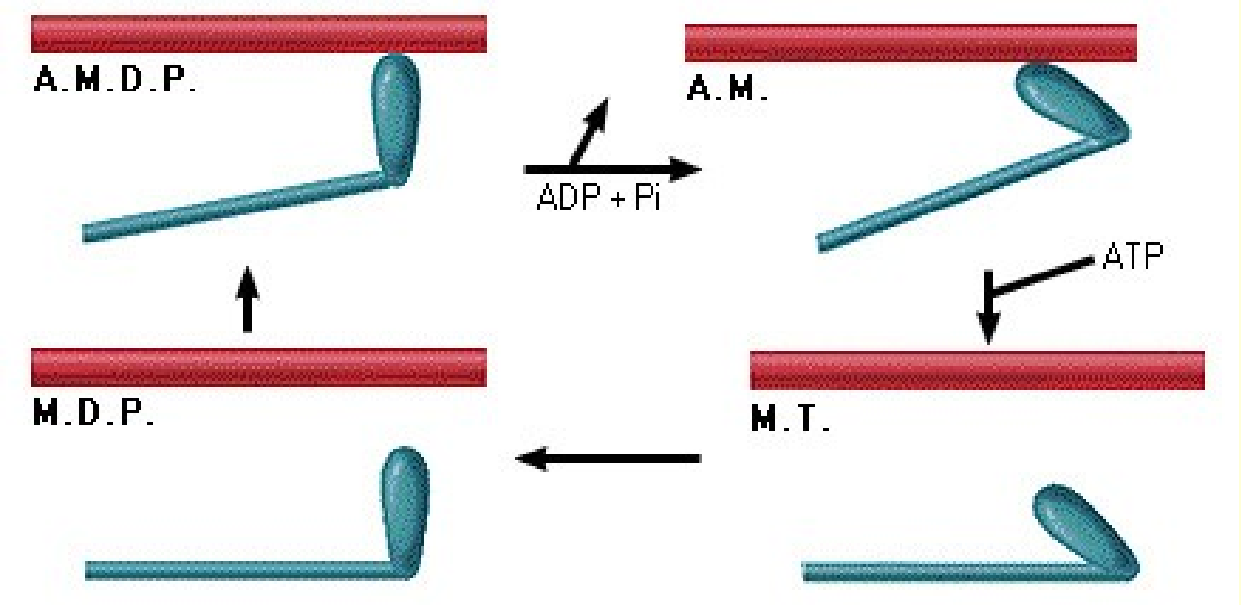


SOURCES OF CALCIUM FOR CONTRACTION OF SKELETAL MUSCLE

- In the long run, however, some calcium entry from extracellular sources is necessary. There appears to be a small net loss of calcium with each contraction. Thus a fiber contracting longer than about 60 minutes in calcium-free medium will begin to grow weaker as the internal calcium stores are depleted.

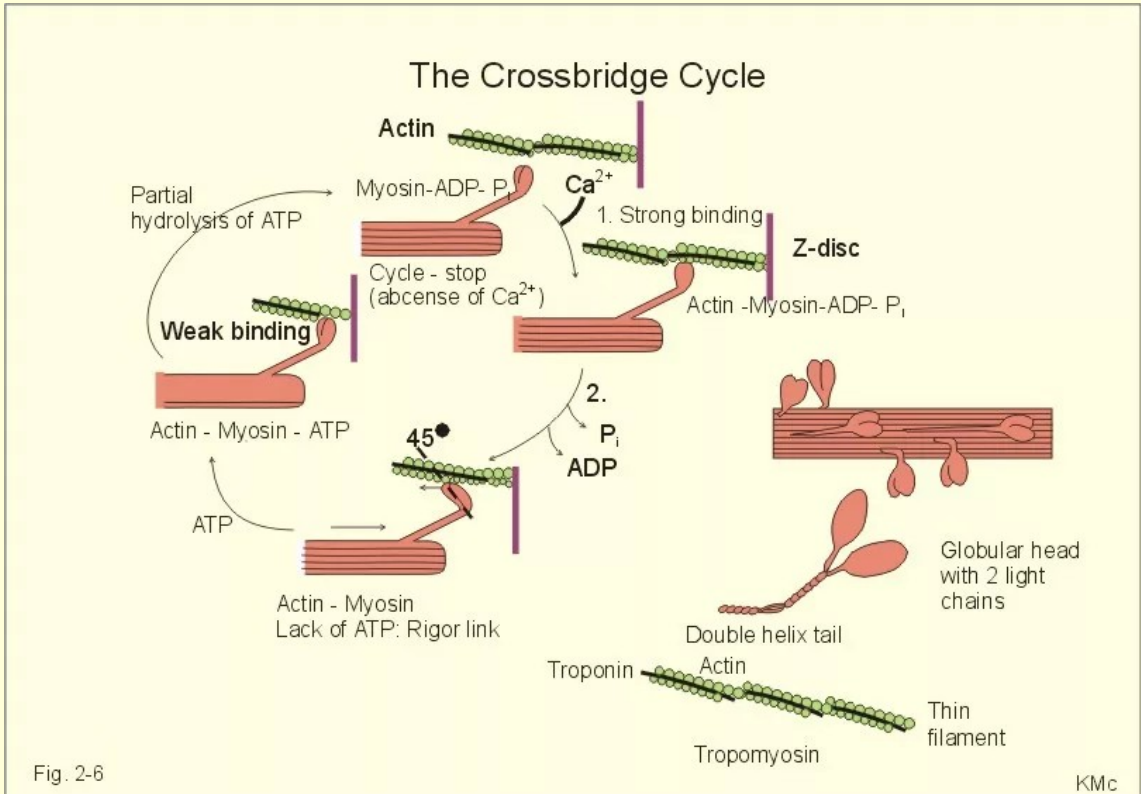
THE CROSSBRIDGE CYCLE

- When a skeletal muscle contracts and shortens, the myofilaments slide by one another without changing their length. It is thought that the sliding is caused by physical interaction between myosin molecules in the thick filament and actin molecules in the thin filament.
- Because a muscle can shorten a large proportion of its length (i.e., many centimeters), and the length of the crossbridge portion of a myosin molecule is 10 to 20 nanometers, the physical interaction between myosin and actin must be cyclic.



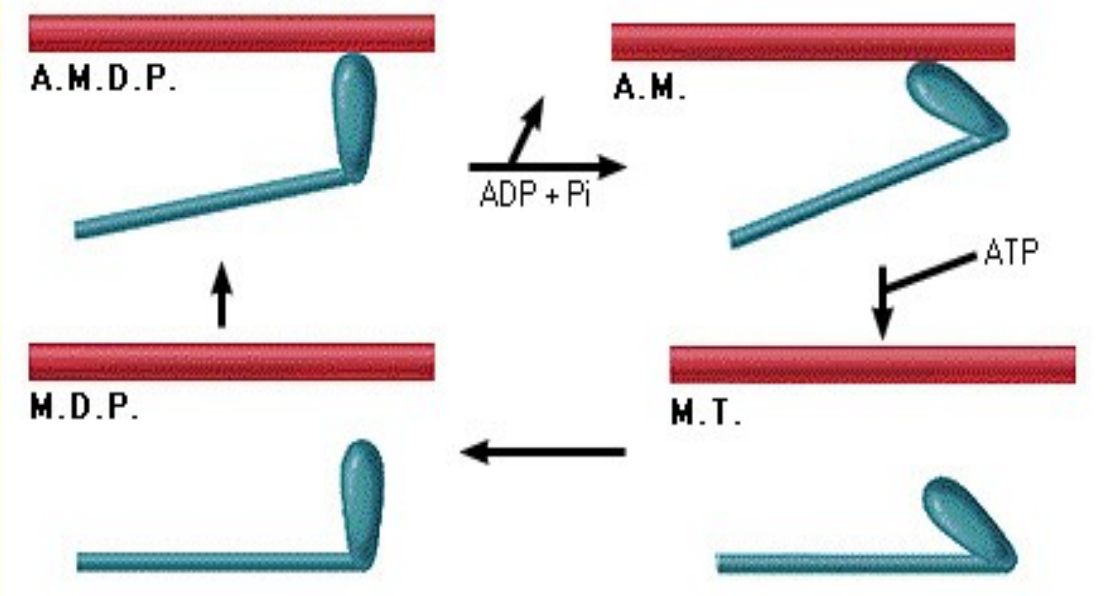
THE CROSSBRIDGE CYCLE

- When the muscle is stimulated, intracellular calcium rises and strong crossbridge interaction is permitted (i.e., the complex A.M.D.P is formed).
- Crossbridge attachment leads to the power stroke (transition to complex A.M), whereby the crossbridge exerts force on the thin filament.
- This force is caused by a conformational change in the crossbridge structure.



THE CROSSBRIDGE CYCLE

- The power stroke is associated with the sequential release of Pi and ADP from myosin. ATP then binds to the crossbridge, causing myosin to rapidly detach from actin.
- The cycle is completed by hydrolysis of the bound ATP to form a high-energy crossbridge, which is now available for further cycling.
- Each crossbridge is thought to cycle independently of the others, with an overall cycle rate of roughly five to ten per second in skeletal muscle at body temperature.

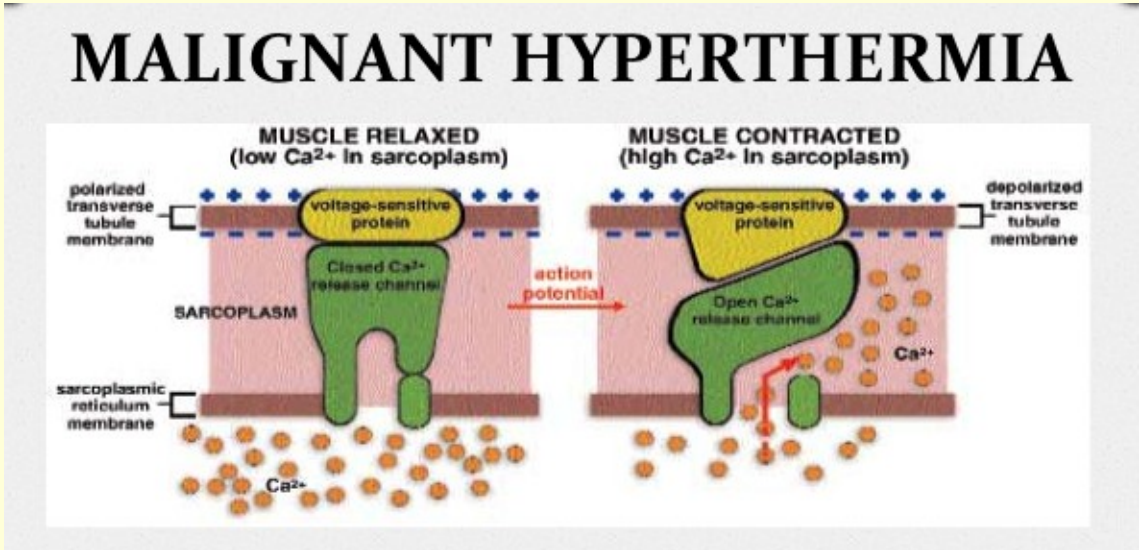


MUSCLE HEAT PRODUCTION: SHIVERING

- The amount of heat produced by ATP hydrolysis will be maximized if the muscle produces little or no mechanical work. This can be advantageous if an individual is chilled until widespread shivering is invoked.
- In this case the muscles undergo uncoordinated contractions that do not lead to large-scale limb movements and thus not much mechanical work. Here, most of the energy liberated by ATP hydrolysis is converted into heat, which helps counteract any drop in body temperature.

MUSCLE HEAT PRODUCTION: MALIGNANT HYPERTHERMIA

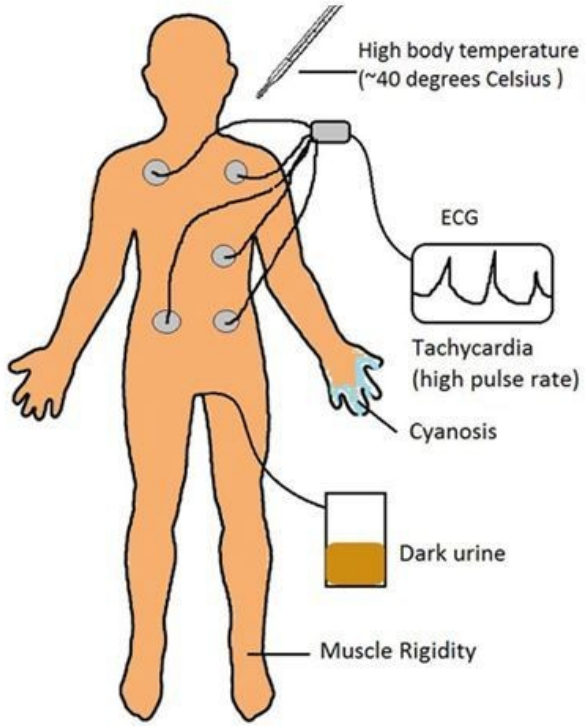
- The amount of heat liberated by skeletal muscle can be quite substantial. In fact, it can be life threatening, as in malignant hyperthermia.
- Some individuals are sensitive to certain agents used for general anesthesia. When exposed to these agents, their skeletal muscles are more or less fully activated and begin producing enormous quantities of heat.
- Unless controlled, a bout of malignant hyperthermia leads to a rapid rise in body temperature, which can result in death.



MUSCLE HEAT PRODUCTION: MALIGNANT HYPERTHERMIA

Late Clinical Signs of Malignant Hyperthermia

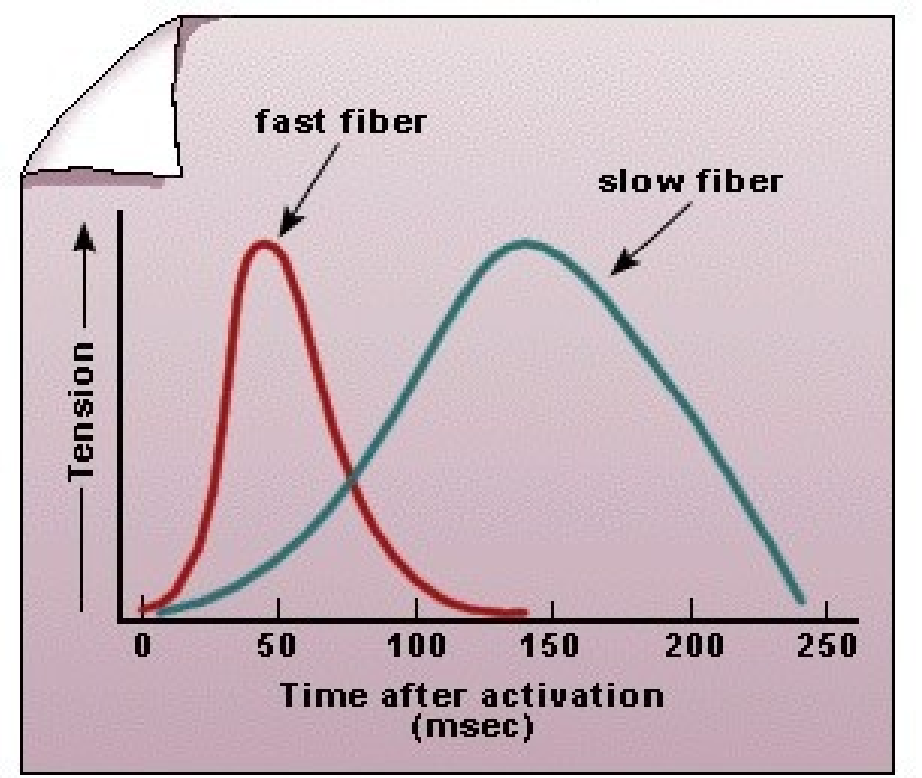
- Generalized skeletal muscle rigidity
  - Ability to generate ATP is nearly exhausted.
- Lactic acidosis
- Cyanosis
  - Low oxygen saturation
  - Skin appear to be purple or blue
- Dark urine
  - increased creatine kinase
- Temperature rise above 40°C
- Death



Hopkins, P. M. (2000) Malignant hyperthermia: advances in clinical management and diagnosis. Br. J. Anaesth. 85, 118–128.c

MUSCLE FIBER TYPES: SLOW TWITCH OXIDATIVE MUSCLE FIBERS

- In mammals, individual muscle fibers can be grouped into three basic fiber types: I, IIa, and IIb. In humans, whole muscles are made up of a mixture of muscle fibers of these fiber types.
- Type I fibers are also called slow oxidative (SO) fibers, which is more descriptive. These fibers are deemed "slow" because both the rate of rise and fall of twitch force and the maximal velocity of isotonic shortening are about half that of type II fibers, which are termed "fast" fibers.



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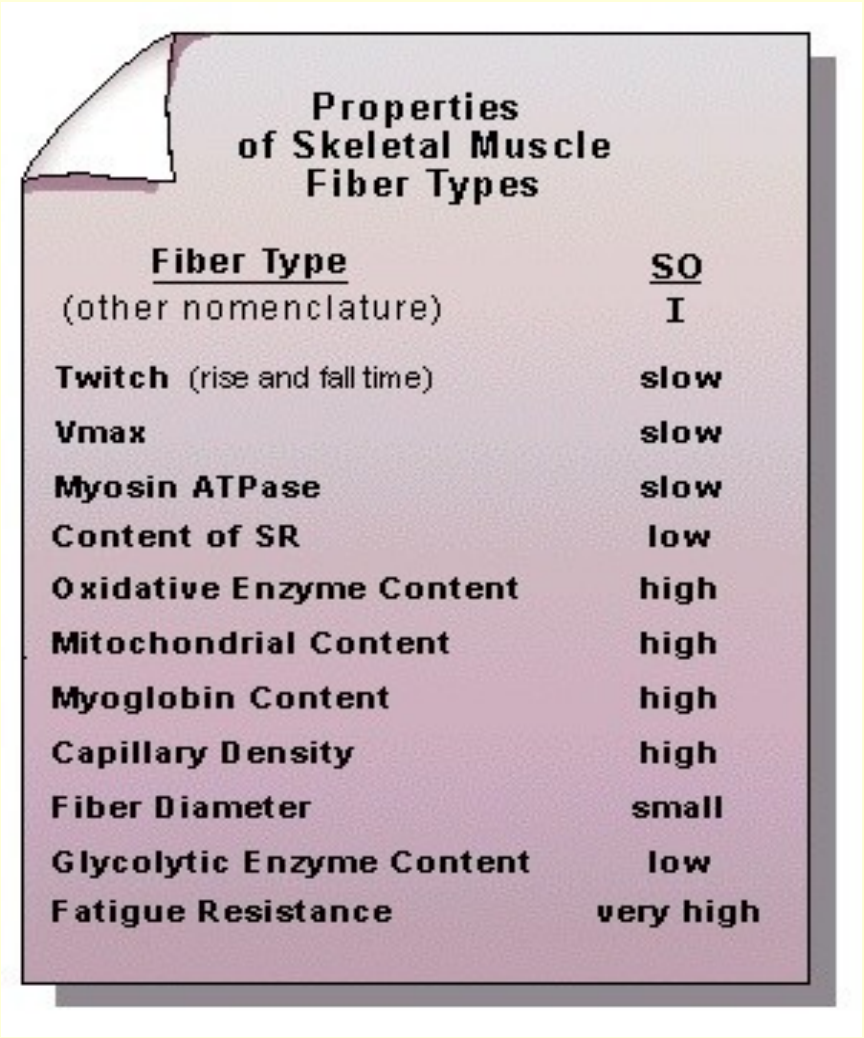
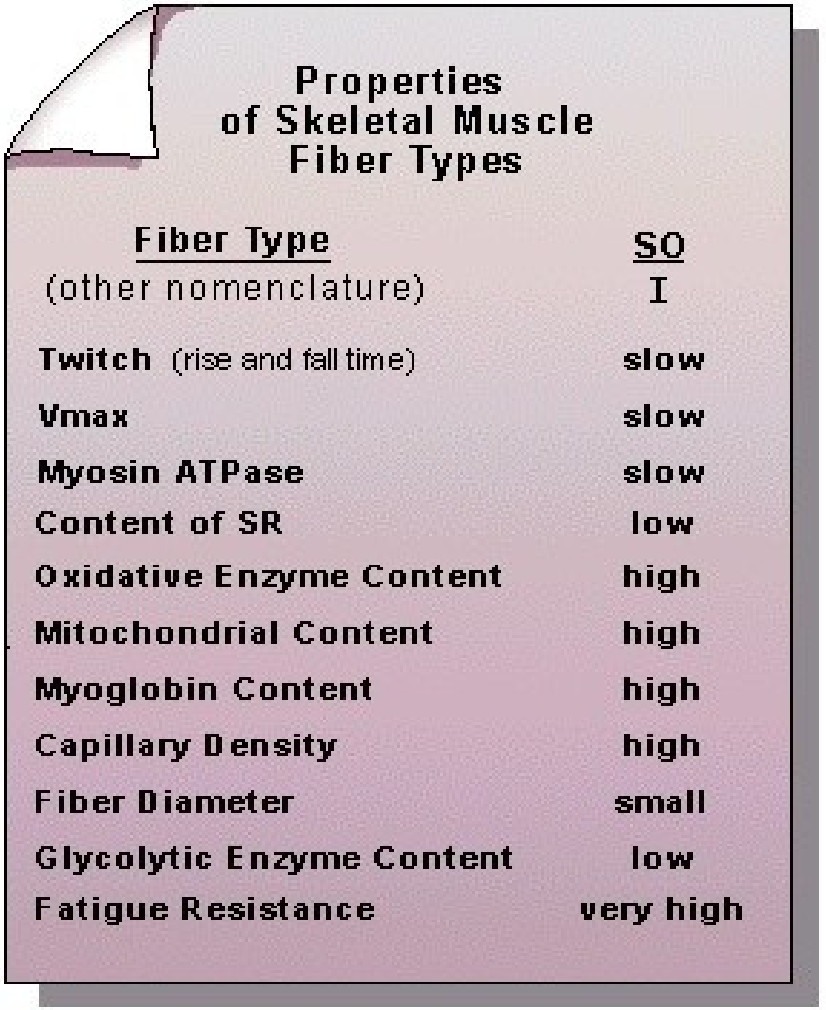


Properties of Skeletal Muscle Fiber Types

Fiber Type (other nomenclature)	SO I
Twitch (rise and fall time)	slow
Vmax	slow
Myosin ATPase	slow
Content of SR	low
Oxidative Enzyme Content	high
Mitochondrial Content	high
Myoglobin Content	high
Capillary Density	high
Fiber Diameter	small
Glycolytic Enzyme Content	low
Fatigue Resistance	very high

- **The myosin ATPase rate in SO fibers is lower than that of fast fibers, which is consistent with the slower force rise and slower isotonic shortening.**
- **The content of sarcoplasmic reticulum in slow fibers is also about half that of fast fibers, which is consistent with the slower rate of fall in twitch force.**

MUSCLE FIBER TYPES: SLOW TWITCH OXIDATIVE MUSCLE FIBERS



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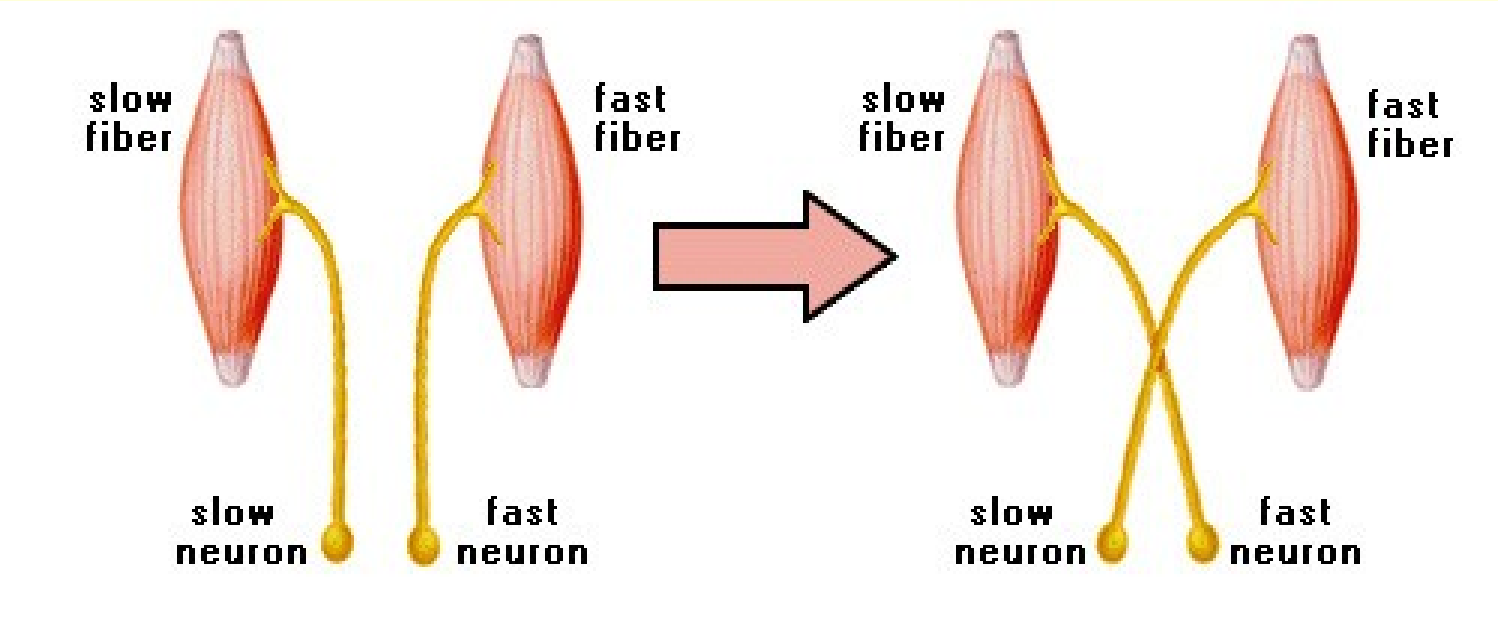
- SO fibers have a high oxidative capacity for ATP production. They have many mitochondria and contain high concentrations of myoglobin.
- Myoglobin, like hemoglobin, avidly binds oxygen and aids its diffusion into the muscle fibers. High myoglobin content makes the fibers red.
- The many capillaries around SO fibers facilitate diffusion of oxygen into and carbon dioxide out of the fiber. In cat muscle, the fiber diameter is less than that of fast type IIb fibers, which also speeds the diffusion of O_2 and CO_2. The content of glycolytic enzymes is low in SO fibers.
- The SO fibers are very resistant to fatigue. As a result, they predominate in postural muscles, which must be chronically active.

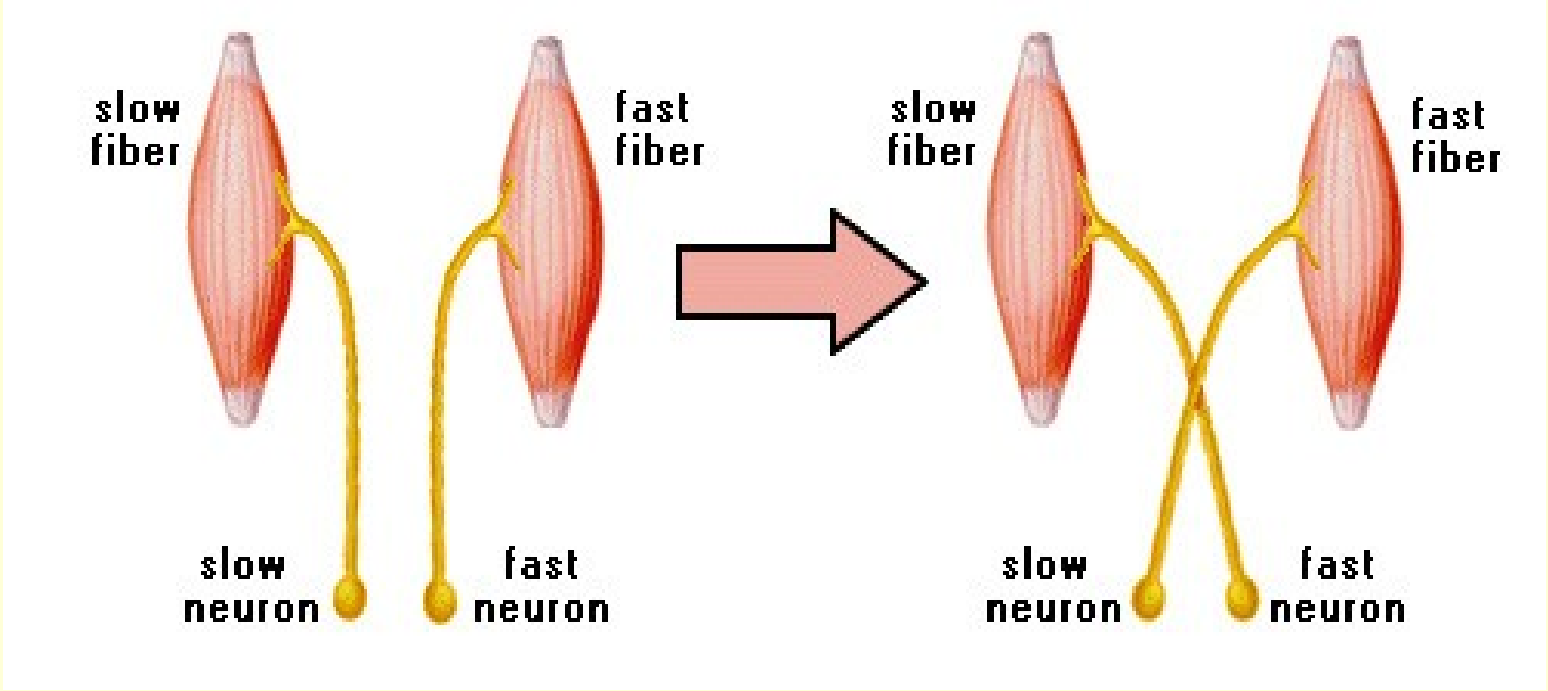
MUSCLE FIBER INNERVATION

- The motor neuron serving a muscle fiber has a dominant influence over the contractile and metabolic parameters we use to describe the different fiber types.
- Nerves innervating slow muscles and fast muscles can be interchanged and will reinnervate the opposite muscle fiber types.



MUSCLE FIBER INNERVATION

- This causes the fast muscle fibers to slow and the slow muscle fibers to speed up. In addition, cross-innervated fast muscles begin to express slow myosin, mitochondria proliferate, and the content of glycolytic enzymes decreases.
- Likewise, slow fibers reinnervated by fast nerves begin to express fast muscle myosin, mitochondrial content decreases, and the concentration of glycolytic enzymes increases.



MUSCLE FIBER FATIGABILITY

- **Because slow muscle fibers are very resistant to fatigue, a higher proportion of slow fibers would be useful to an athlete who specializes in endurance events, such as marathons.**

MUSCLE FIBER FATIGABILITY

- Likewise, because fast muscle fibers are stronger and faster, a higher proportion of fast fibers would be advantageous to athletes specializing in brief, high-intensity events, such as power weight lifting or sprints.

MUSCLE FIBER FATIGABILITY

MUSCLE FIBER FATIGABILITY

- Muscle biopsies from elite athletes indicate that those trained for endurance events have a higher proportion of slow muscle fibers in the requisite muscles, whereas those trained for brief, high-intensity events have a higher proportion of fast muscle fibers.
- There are, however, few data to suggest that these differences arise from training. Rather, they are more likely to be due to heredity.

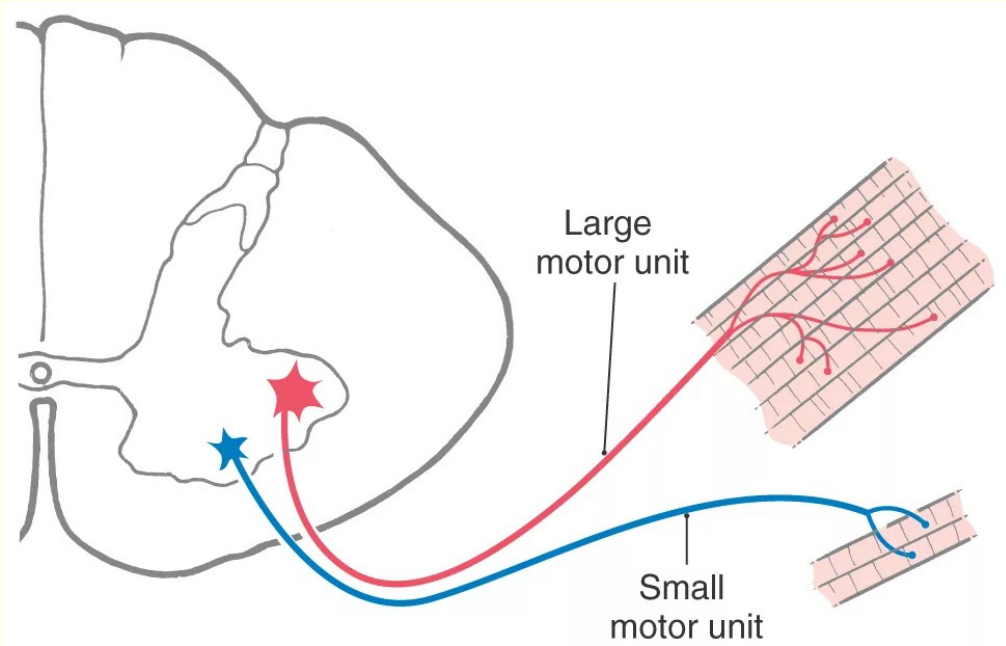
LONG, Slow, WEAK

VS

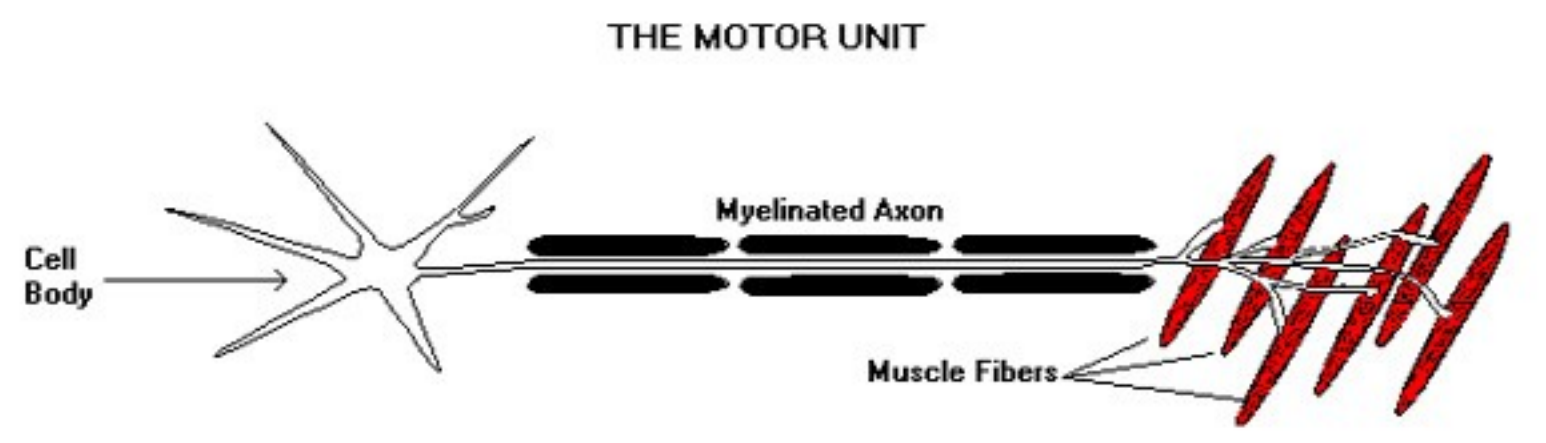
SHORT, Fast, STRONG!

THE MOTOR UNIT

- A motor unit consists of a motor nerve (neuron) and all the skeletal muscle fibers it innervates.
- In humans, a single motor neuron innervates a number of muscle cells, but each muscle fiber is innervated by only one motor neuron.
- The motor unit is the smallest functional unit that the central nervous system can command for controlling muscular contraction.

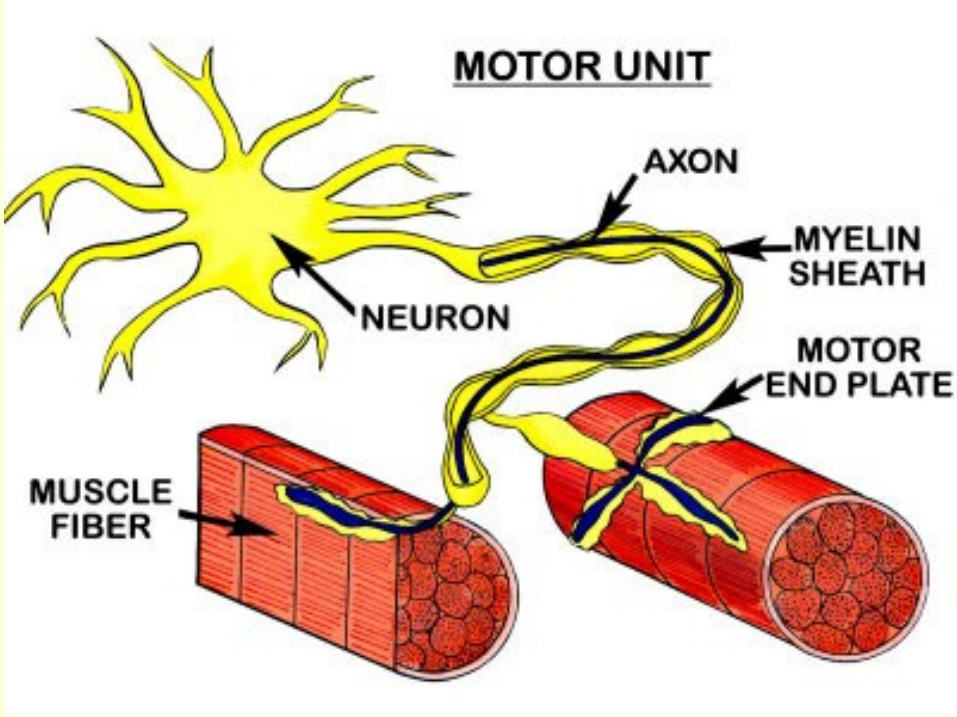


THE MOTOR UNIT



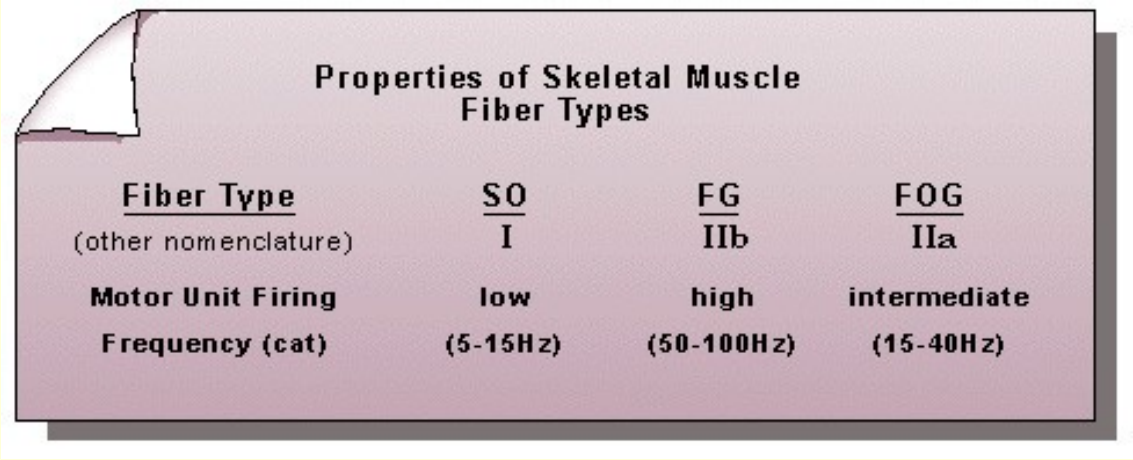
- The number of muscle fibers in motor units is variable. A small number of muscle fibers per motor unit provides fine motor control, for example, in ocular muscles. A large number of muscle fibers per motor unit provides only gross control, for example, in muscles of the back. Any whole muscle is composed of many motor units. Individual muscle fibers in any motor unit are diffusely distributed within the whole muscle.

THE MOTOR UNIT



- All the muscle fibers in a motor unit are of the same fiber type. This is consistent with the concept that properties of the motor nerve (i.e., firing pattern) determine the muscle fiber type.
- Muscle cells within a motor unit contract simultaneously upon stimulation of the motor neuron. Because both nerve fibers and muscle fibers are electrically insulated from their neighbors, muscle fibers within any motor unit fire independently of other motor units.

THE MOTOR UNIT

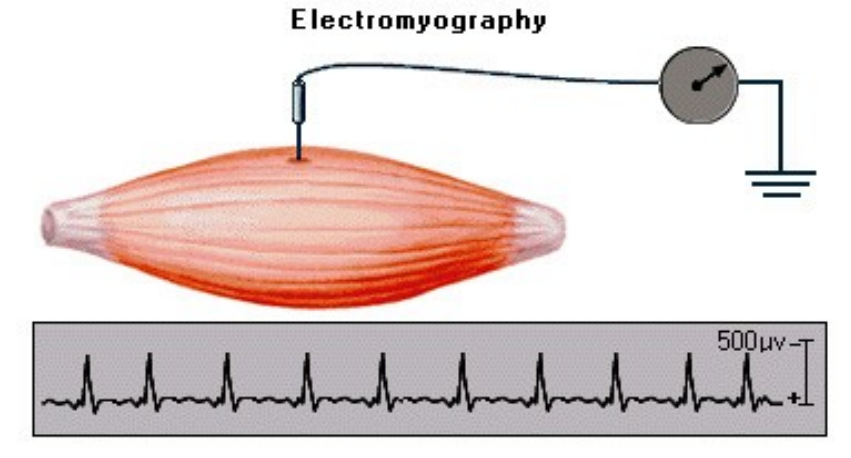


Properties of Skeletal Muscle Fiber Types

Fiber Type (other nomenclature)	SO I	FG IIb	FOG IIa
Motor Unit Firing Frequency (cat)	low (5-15Hz)	high (50-100Hz)	intermediate (15-40Hz)

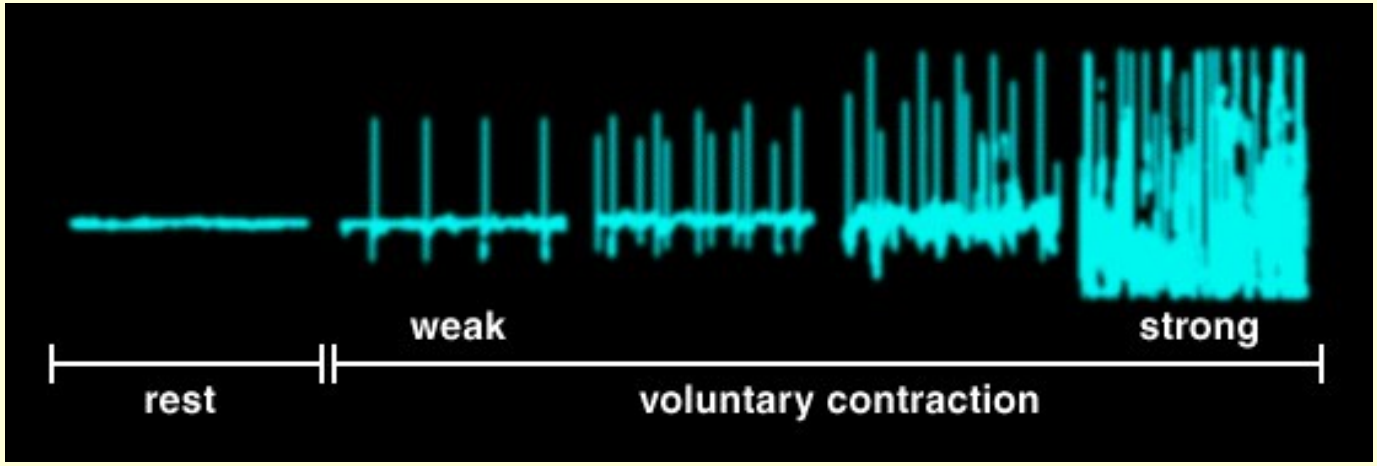
- **Force development of the whole muscle is proportional to the number and rate of firing of its motor units. Since the tension developed by any motor unit can be graded from the twitch up to a fully fused tetanus, the force generated by a whole muscle can be graded over a very large range. Asynchronous activity of motor units within a whole muscle helps maintain constancy of force development.**
- **In development of whole muscle force, slow motor units are recruited first and fire at low, steady frequencies. At higher force, FOG motor units are recruited, and the highest force levels require the recruitment of FG motor units firing intermittantly at high frequencies.**

ELECTROMYOGRAPHY



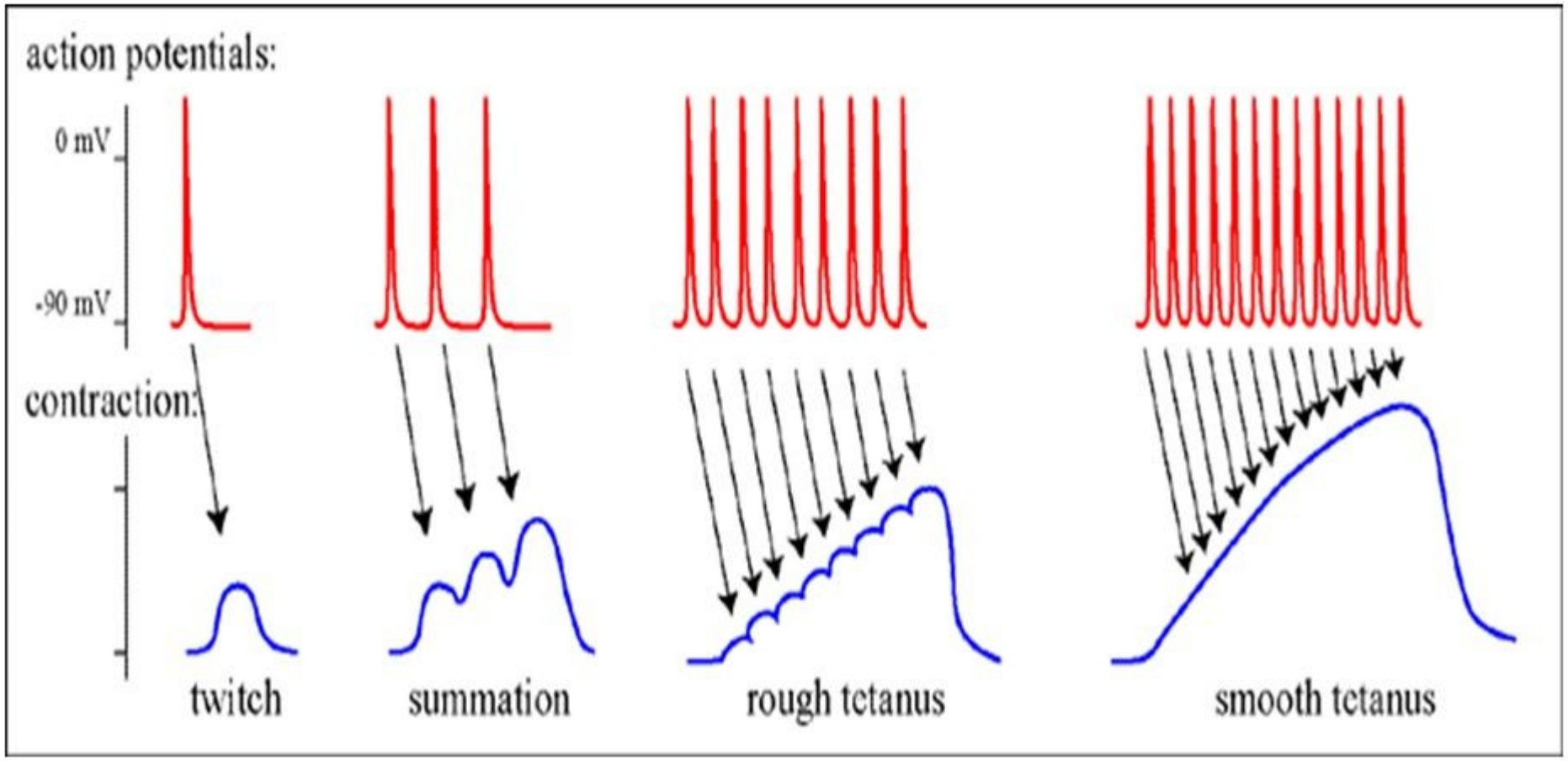
- Electromyography is a technique for recording the electrical activity of muscle cells. A fine needle is placed into the whole muscle to make an extracellular recording of the muscle action potentials. This record is called an electromyogram (EMG).
- An EMG is associated with the firing of fibers in a single motor unit. The deflections are due to the summated action potentials of muscle fibers within a few millimeters of the electrode.
- Note that even though the muscle action potential is monophasic, the EMG record of the action potentials is multiphasic, as expected from an extracellular electrode.

ELECTROMYOGRAPHY



- An EMG from a resting muscle is silent. As the patient exerts greater voluntary effort, both the frequency and amplitude of the EMG deflections (spikes) increase. This reflects the increase in the number and rate of firing of active motor units.
- The EMG recordings are usually amplified and played through a speaker, since many features of the EMG can be easily discriminated by ear.
- In this example, a patient is asked to completely relax the muscle into which the EMG electrode is inserted. He then contracts the muscle voluntarily with increasing strength. When he reaches a maximal effort, he suddenly relaxes this muscle.

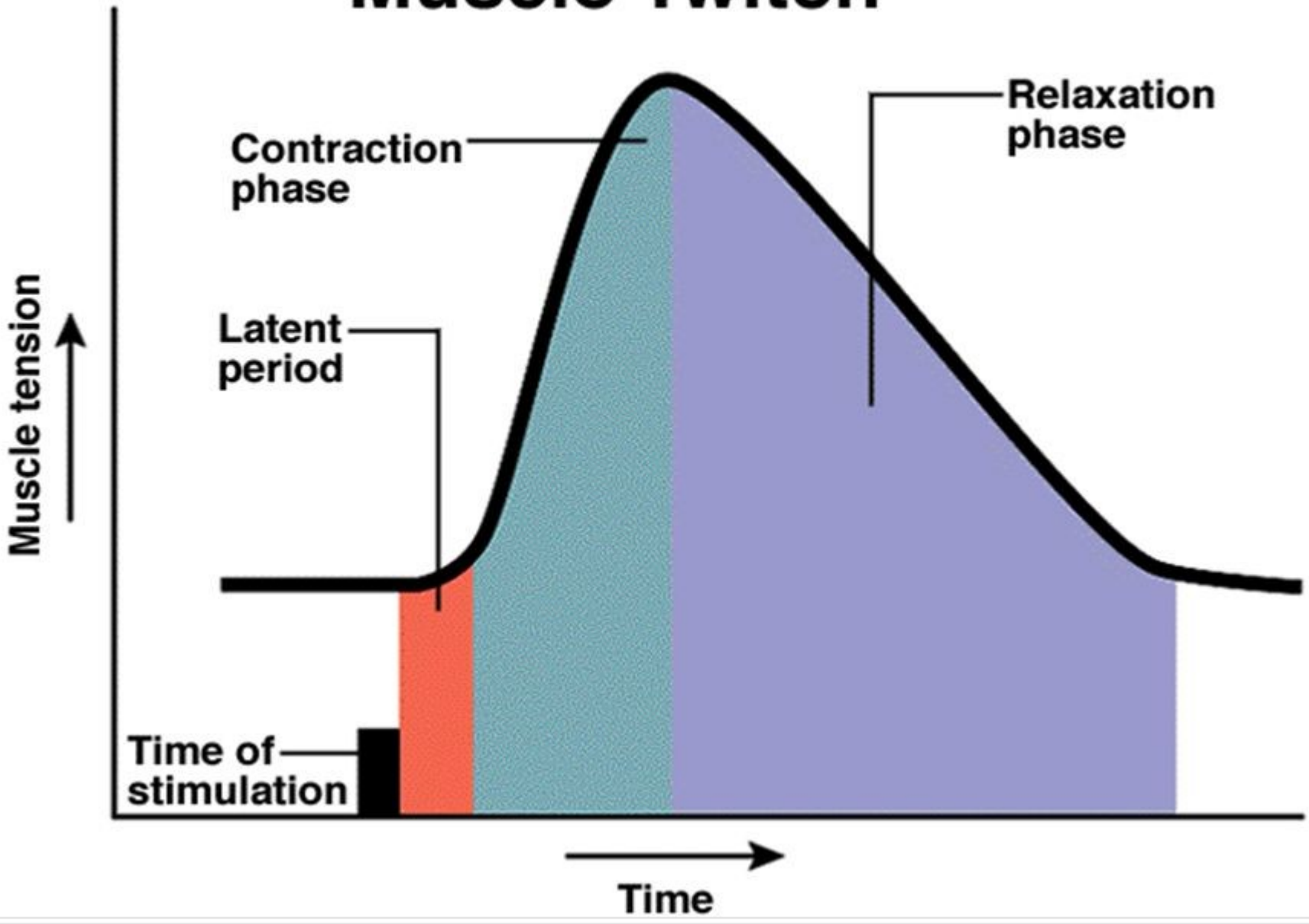
Contraction Types



All or None Law – A muscle fiber will fully contract if it reaches threshold.

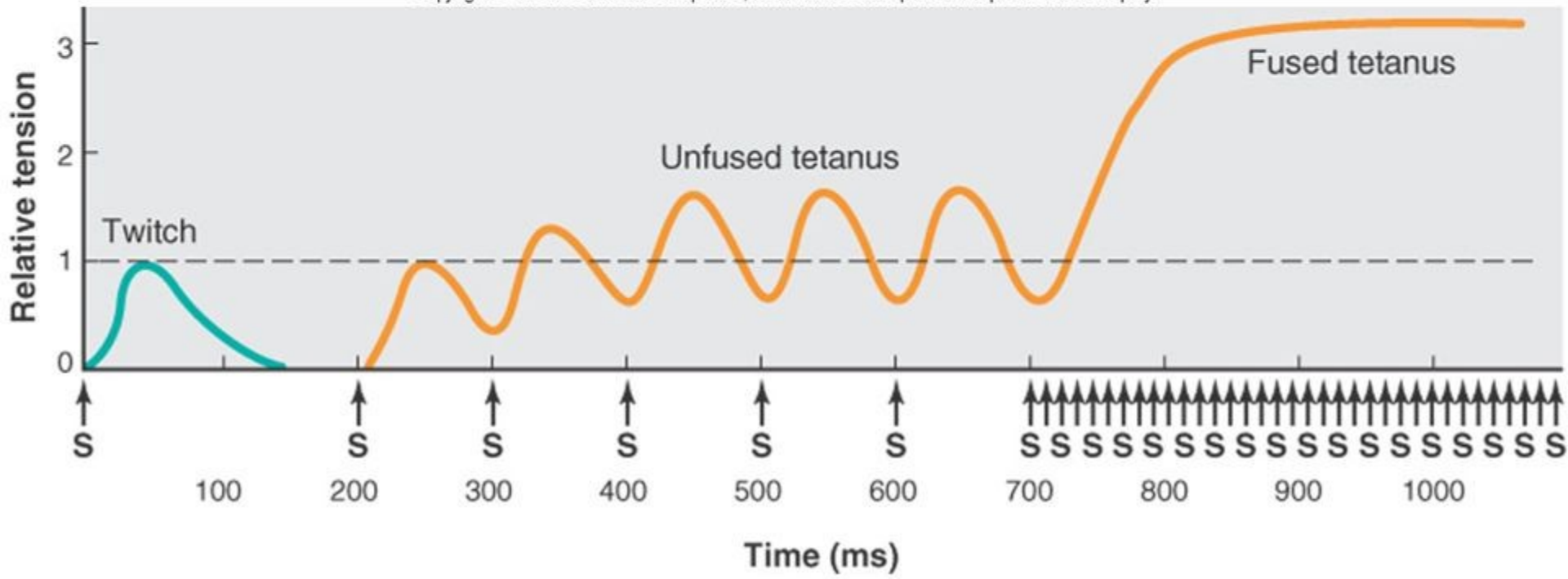
TONIC CONTRACTION – Keeps your tone. Right now you are recruiting enough fibers to maintain your posture over gravity.

Muscle Twitch

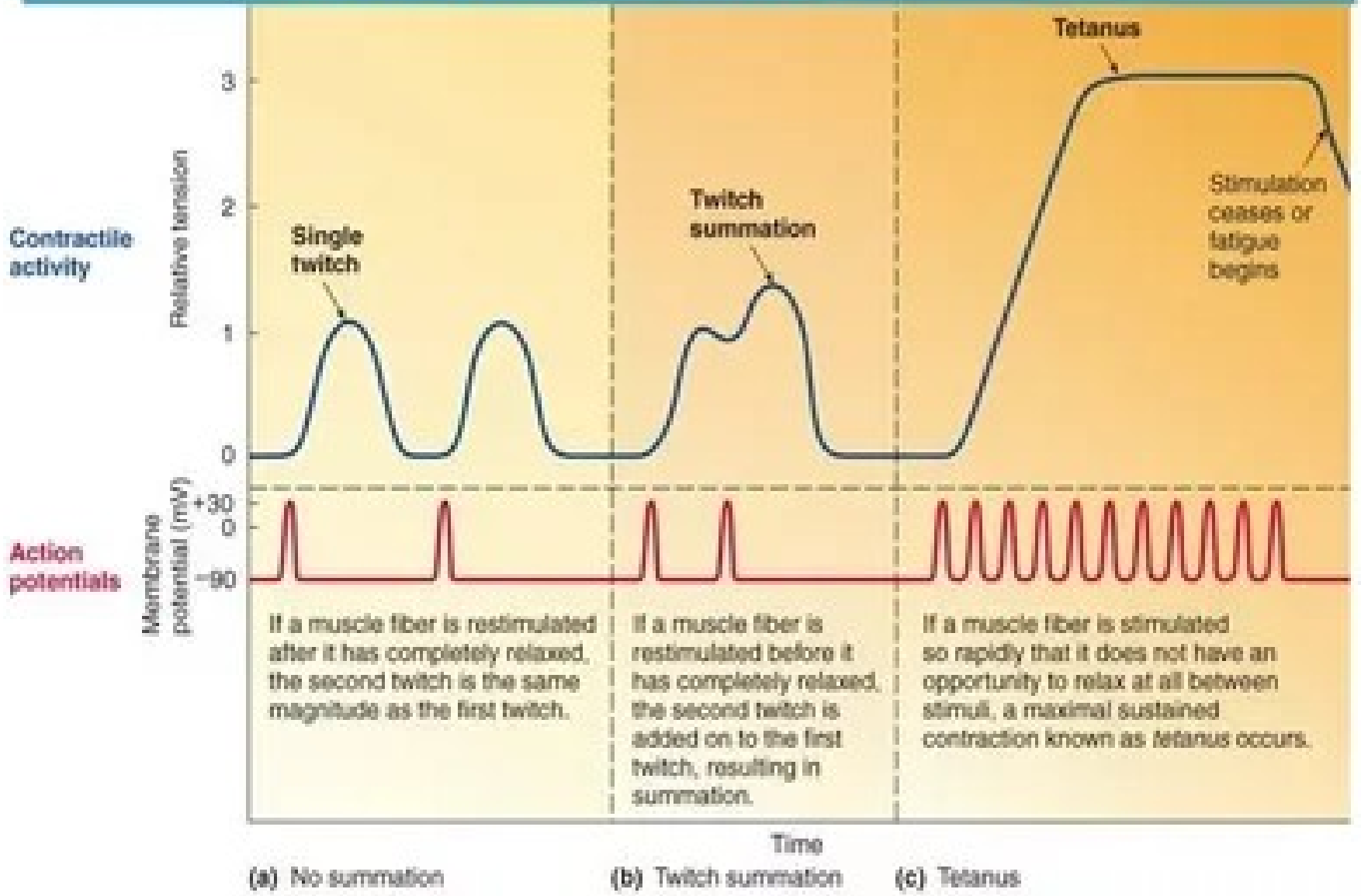


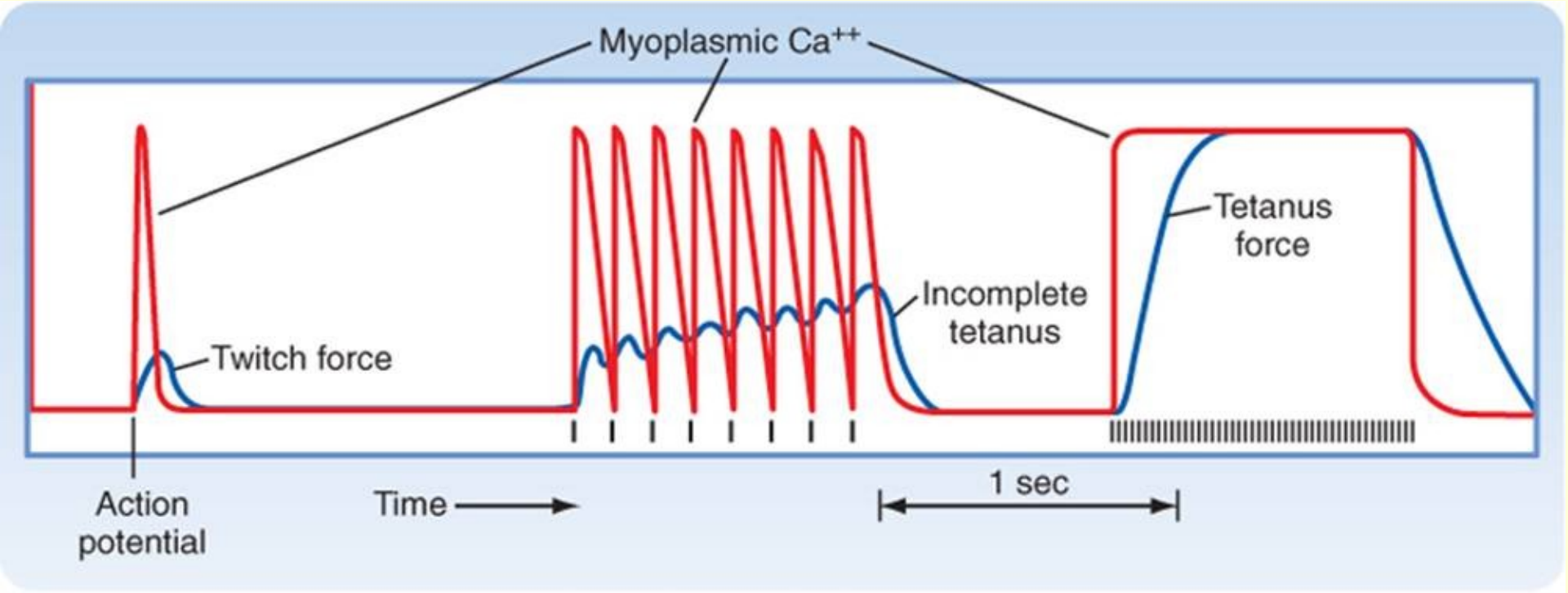
Striding Requires Contraction and Relaxation

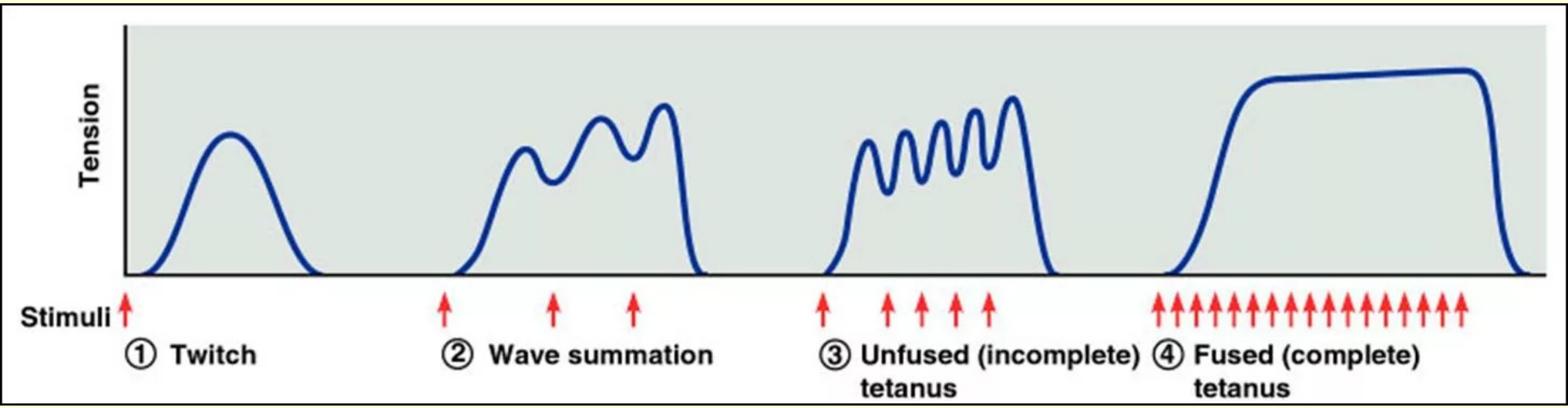
For Sustained SPEEDS the Muscle Groups Must Contract as well as Relax – Otherwise No Continued Movement

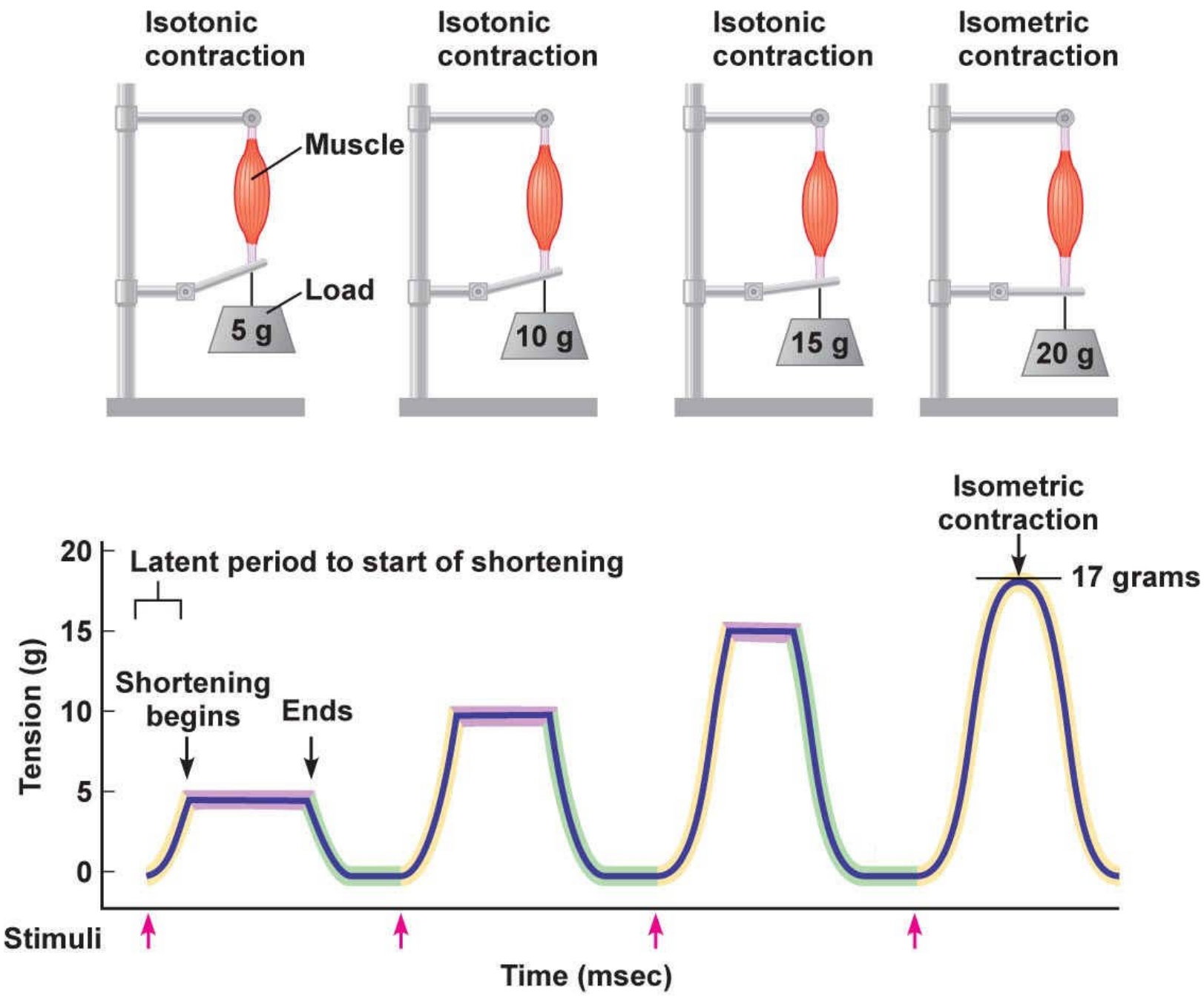


Summation and Tetanus









A comparison of the properties of skeletal, cardiac, and visceral muscle

Property	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Striations?	Yes	Yes	No
Relative Speed of Contraction	Fast	Intermediate	Slow
Voluntary Control?	Yes	No	No
Membrane Refractory Period	Short	Long	
Nuclei per Cell	Many	Single	Single
Control of Contraction	Nerves	Beats spontaneously but modulated by nerves	Nerves Hormones Stretch
Cells Connected by Intercalated Discs or Gap Junctions?	No	Yes	Yes

I thank all of you for your patience!