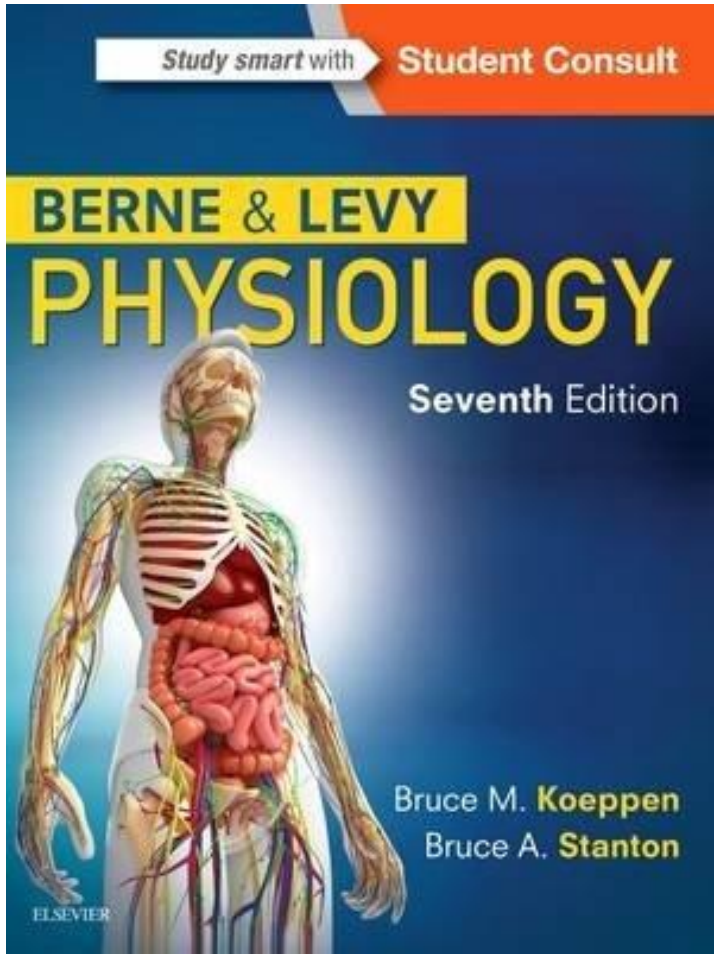
Muscle Physiology



- **Skeletal Muscle Chapter 12**
- **Cardiac Muscle Chapter 13**
- **Smooth Muscle Chapter 14**

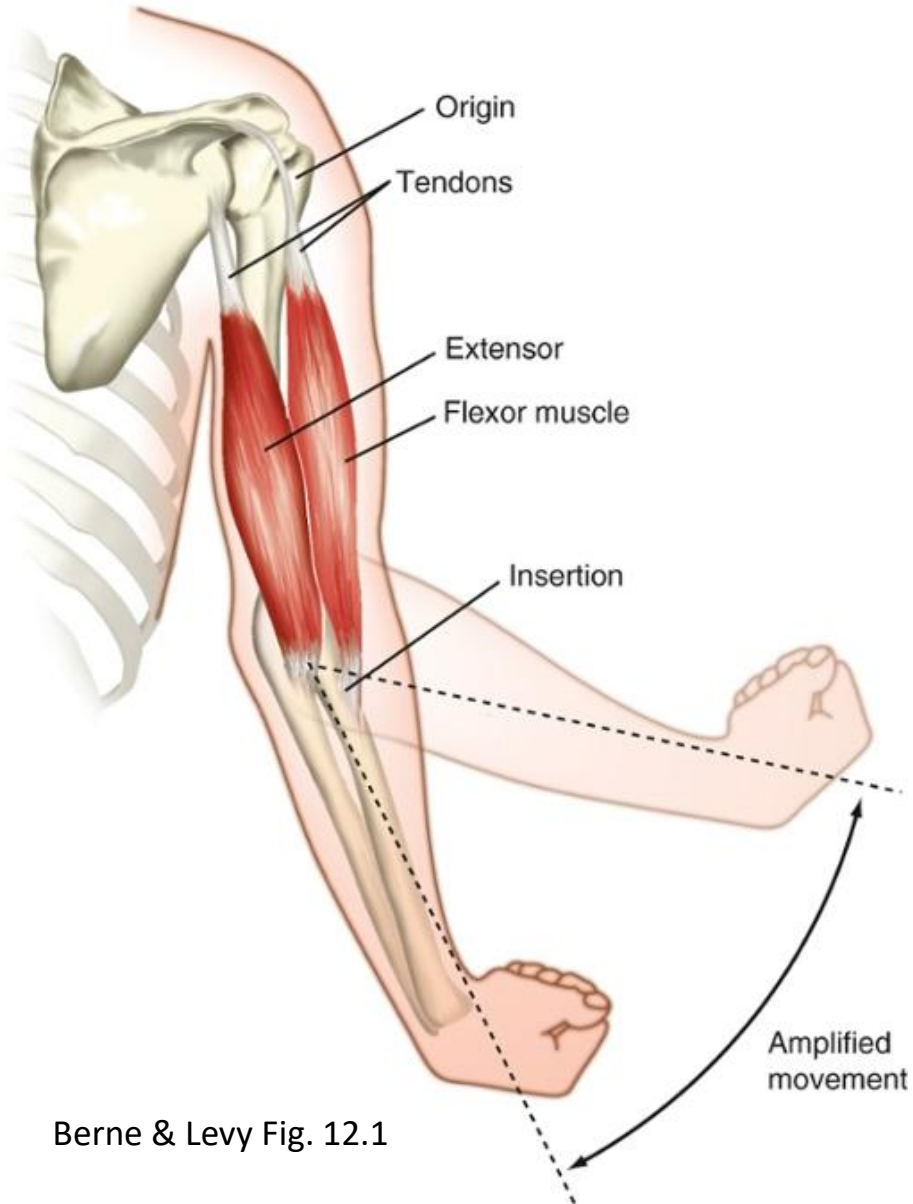
Skeletal Muscle

Muscle cells are highly specialized for the conversion of chemical energy to mechanical energy.

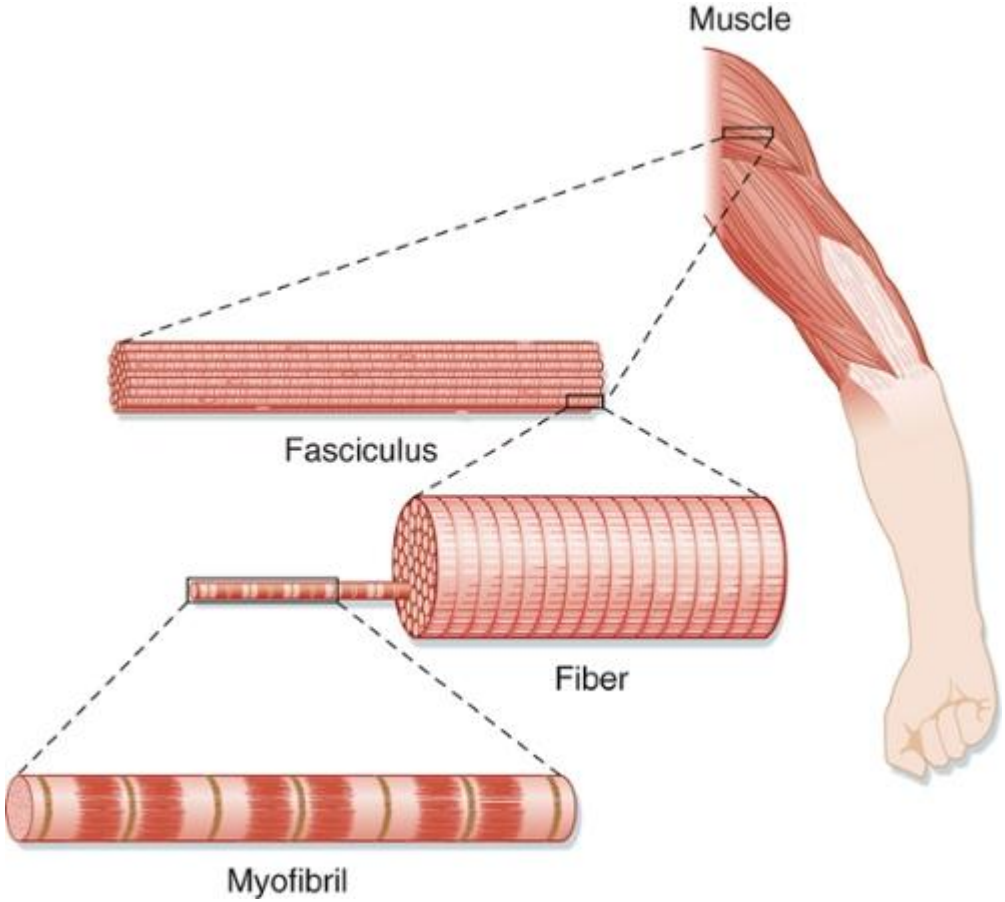
The three basic types of muscle are **skeletal muscle, cardiac muscle,** and **smooth muscle.**

Skeletal muscles act on the skeleton and are under voluntary control.

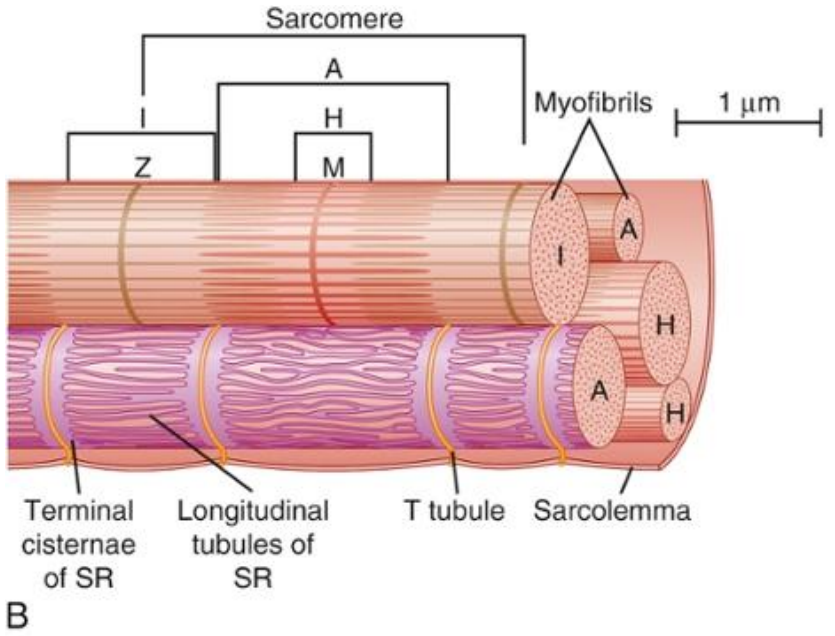
When viewed under the microscope, skeletal muscle exhibits transverse striations (at intervals of 2 to 3 µm) that result from the highly organized arrangement of actin and myosin molecules within the skeletal muscle cells. Thus, skeletal muscle is classified as a **striated muscle.**

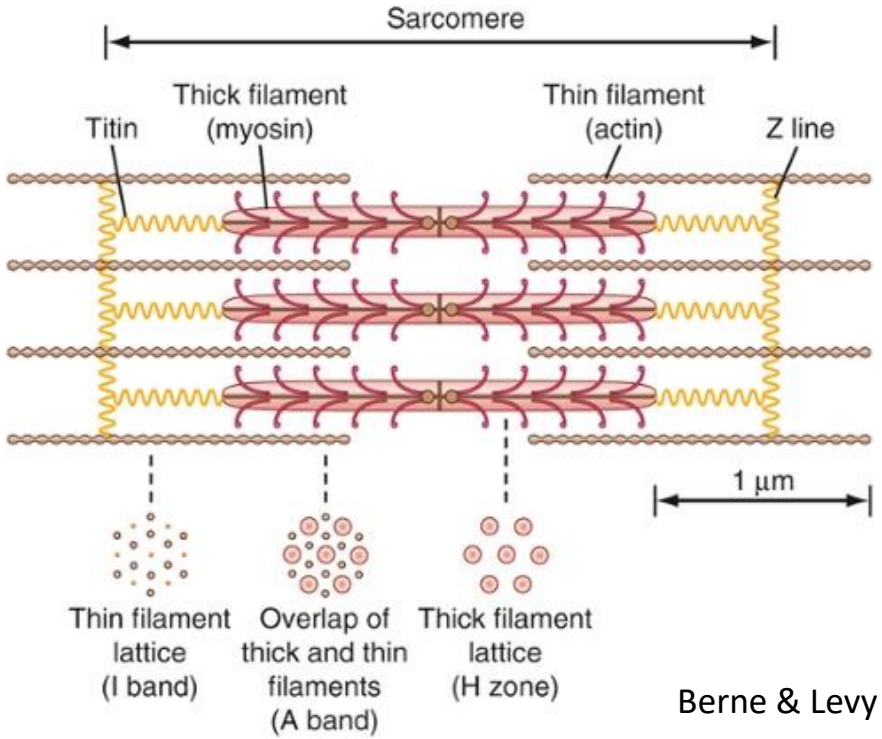


Berne & Levy Fig. 12.1

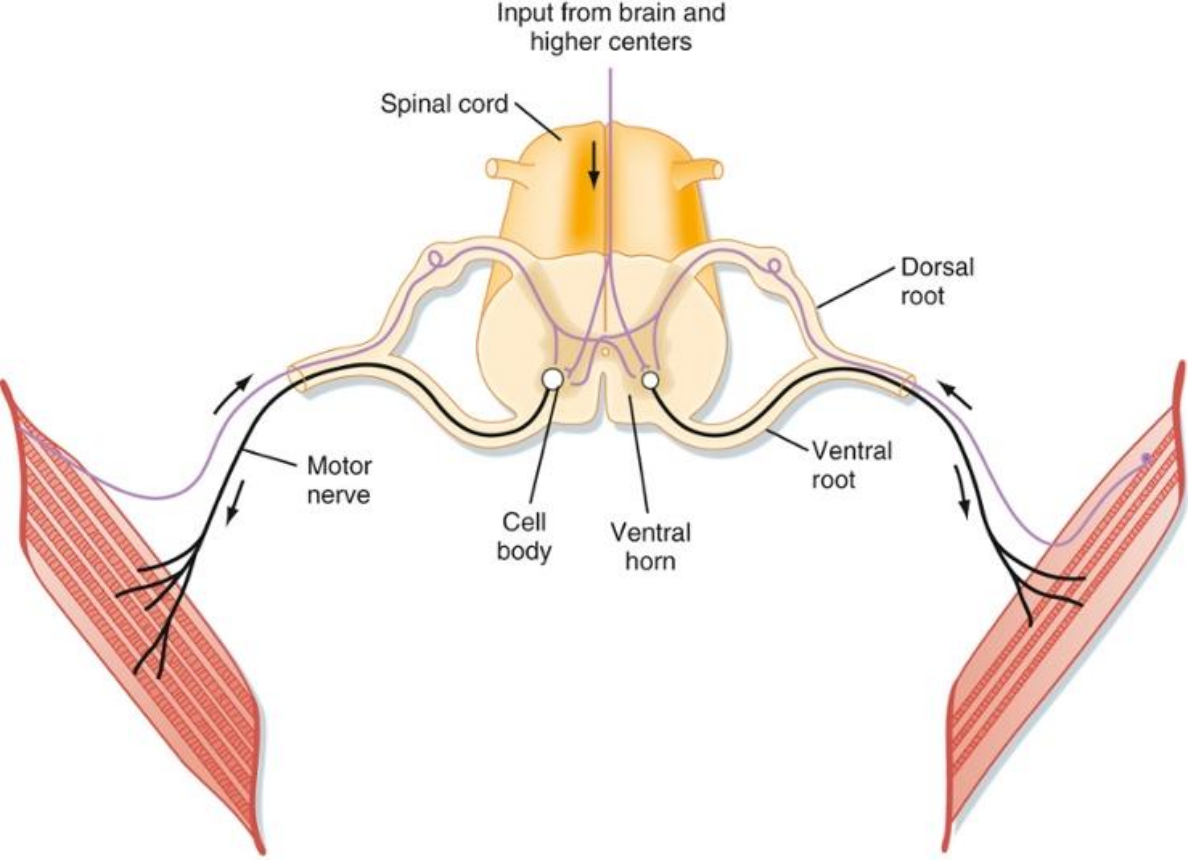


Berne & Levy Fig. 12.2





Berne & Levy Fig. 12.3



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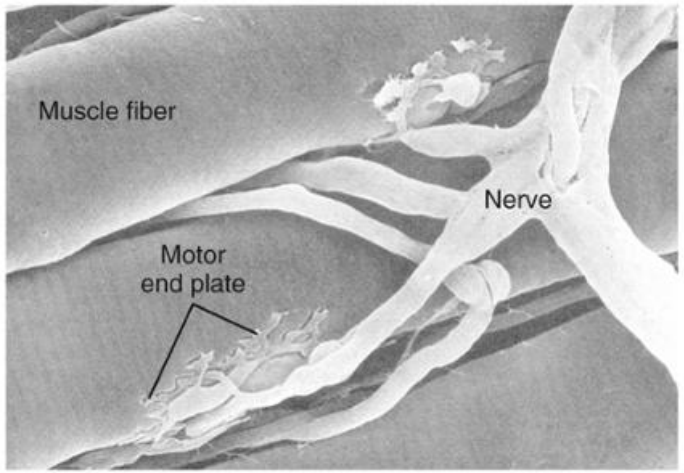


B

Berne & Levy Fig. 12.7

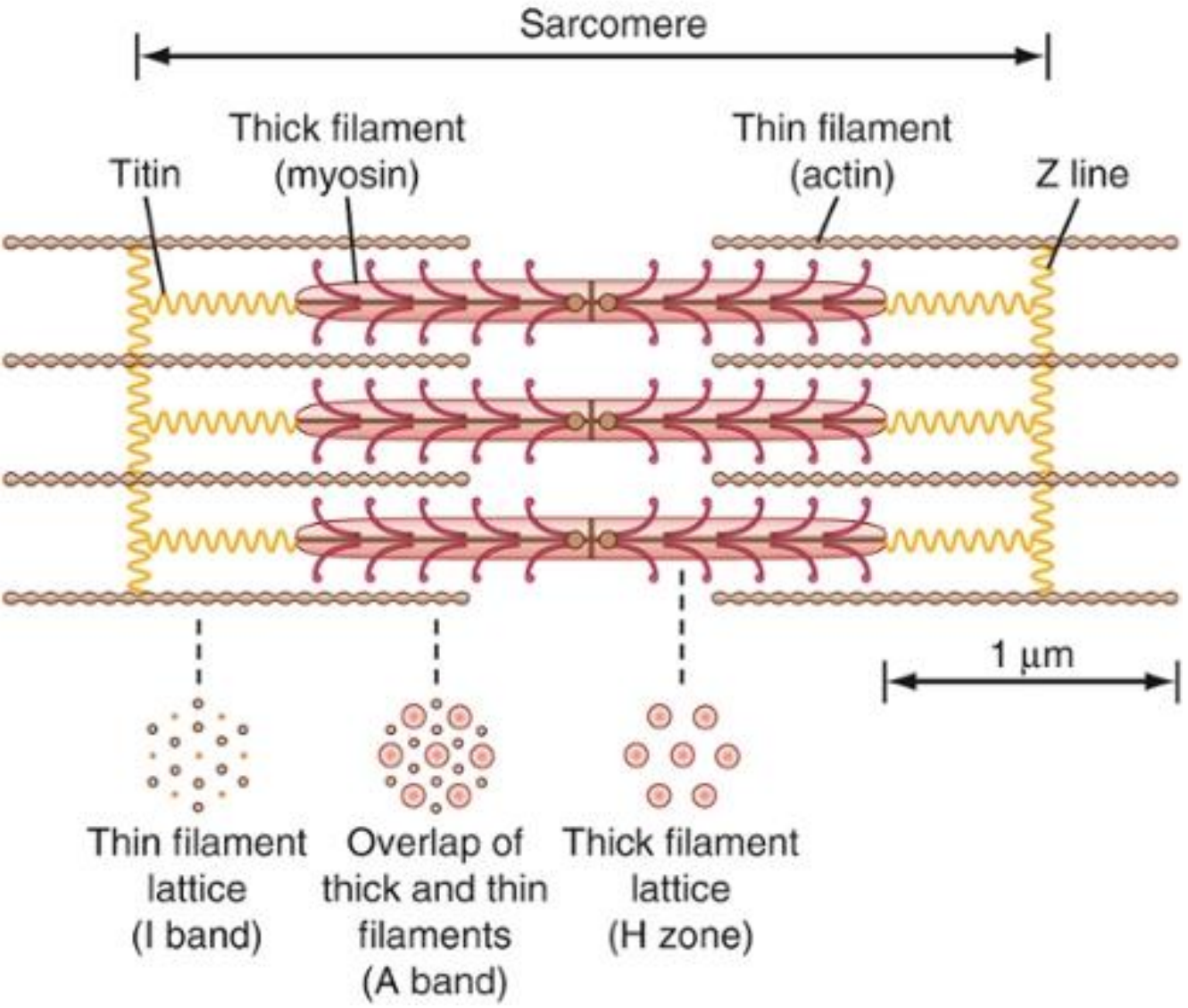
Each skeletal muscle fiber is innervated by an α **motor neuron.**

A **motor unit** consists of the motor nerve and all the muscle fibers innervated by the nerve. The motor unit is the functional contractile unit

Activation of varying numbers of motor units within a muscle is one way in which the tension developed by a muscle can be controlled

The neuromuscular junction formed by the α motor neuron is called an **end plate**

Increasing tension by repetitive stimulation of the muscle is called *tetany*



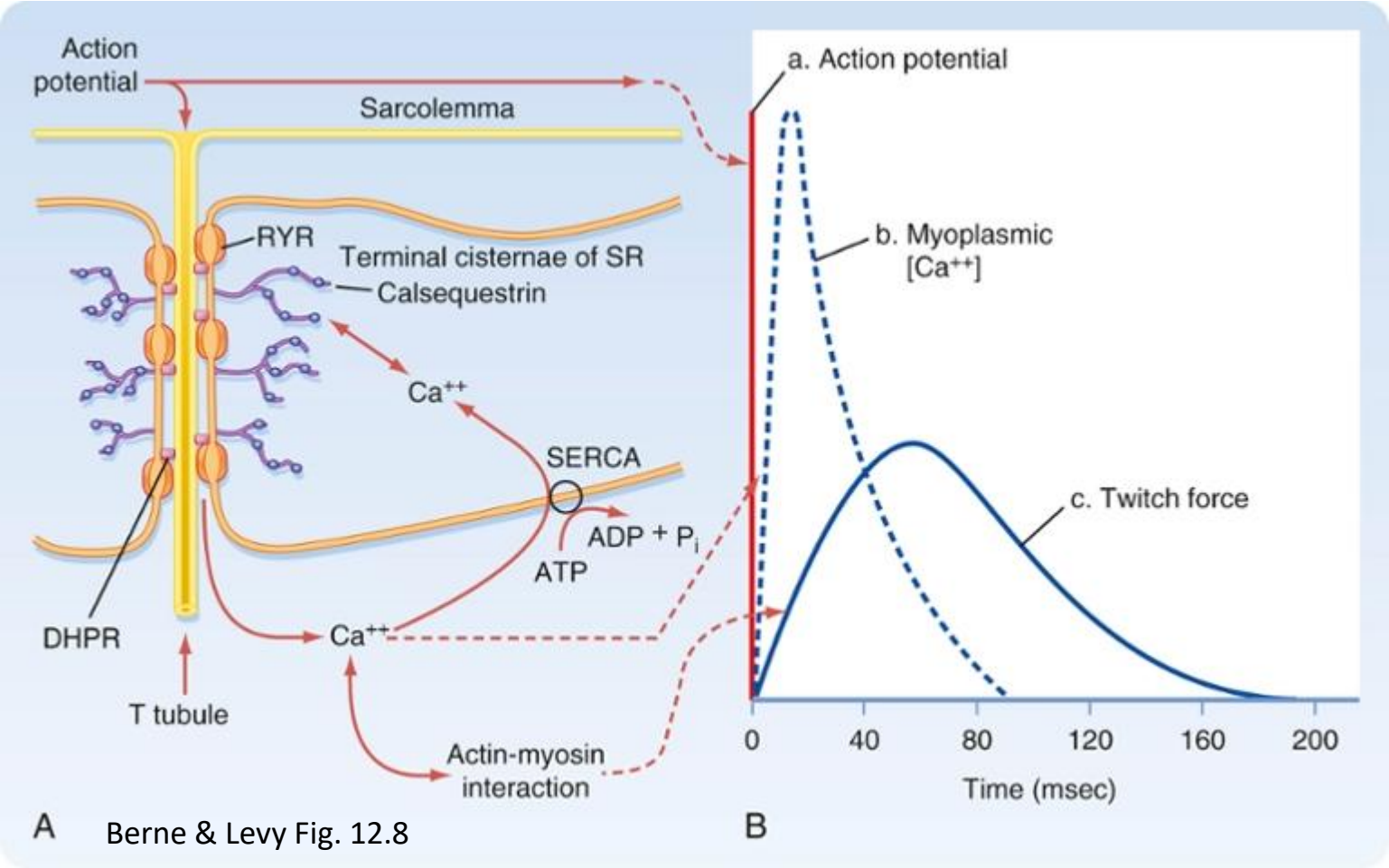
The thin filament is formed by aggregation of **actin** molecules

Dimers of the protein **tropomyosin** extend over the entire actin filament and cover myosin binding sites on the actin molecules. Each tropomyosin dimer extends across seven actin molecules

A **troponin complex** consisting of three subunits **(troponin T, troponin I,** and **troponin C)** is present on each tropomyosin dimer and influences the position of the tropomyosin molecule on the actin filament and hence the ability of tropomyosin to inhibit binding of myosin to the actin filament

The thick filament is formed by aggregation of **myosin** molecules. Myosin is a large protein (≈480 kDa) that consists of one pair of large heavy chains (≈200 kDa) and two pairs of light chains (≈20 kDa). the N-terminal portions of each heavy chain form a large globular head, that can bind to actin.

The two pairs of light chains are: i) The *essential light chains* are crucial for the ATPase activity of myosin. ii) The *regulatory light chains,* can be phosphorylated and influence the interaction of myosin with actin



Berne & Levy Fig. 12.8

Stimulation of a skeletal muscle fiber initiates an action potential in the muscle that travels down the T tubule and induces release of Ca++ from the RYR in the terminal cisternae of the sarcoplasmic reticulum (SR). The rise in intracellular [Ca++] causes a contraction.

As Ca++ is pumped back into the SR by sarcoplasmic endoplasmic reticulum Ca++-ATPase (SERCA), relaxation occurs. DHPR, dihydropyridine receptor; Pi, inorganic phosphate; RYR, ryanodine receptor.

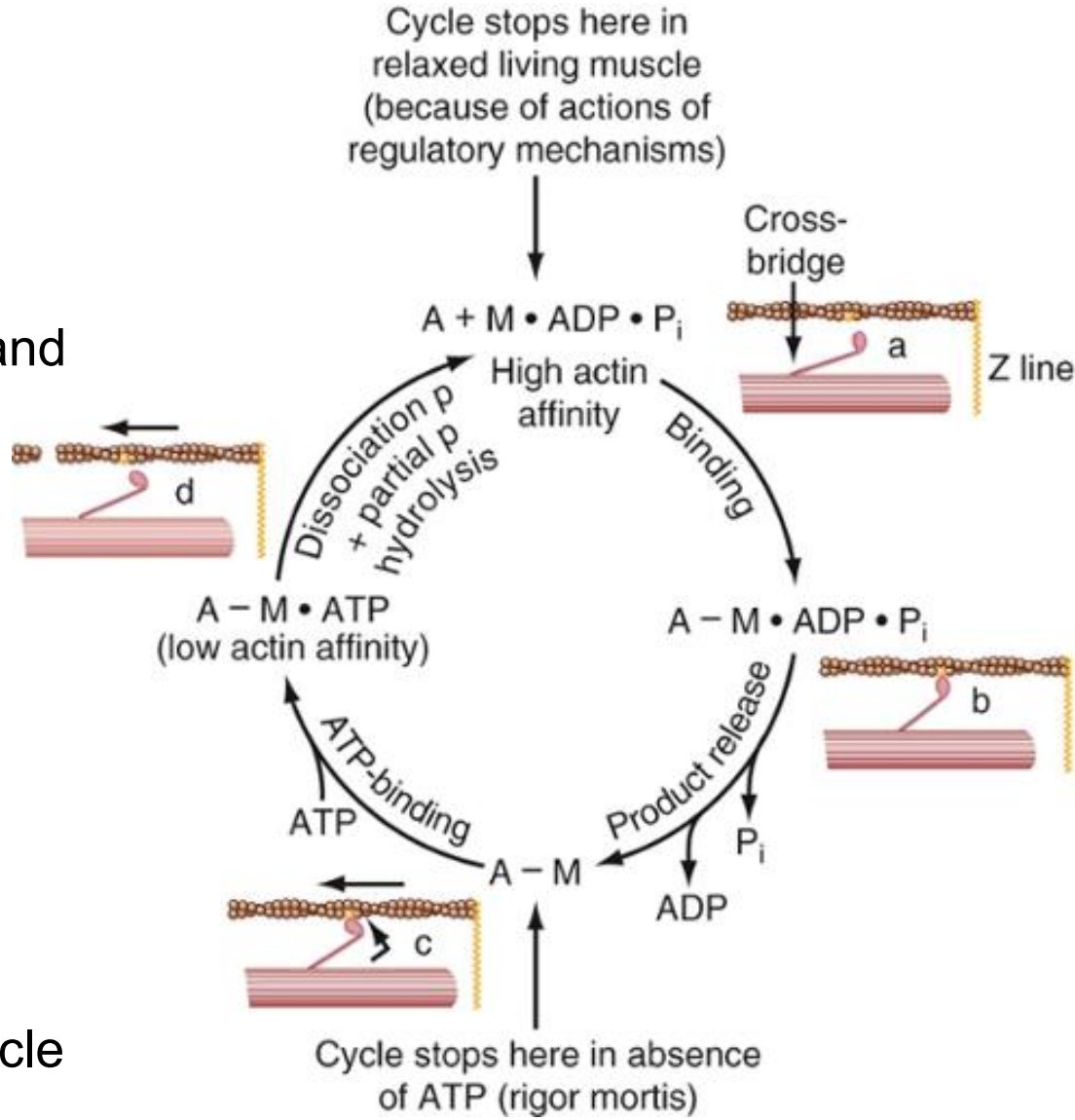
https://www.youtube.com/watch?v=_5AOv6Quays&ab_channel=PhysioFlip

Cross-Bridge Cycle

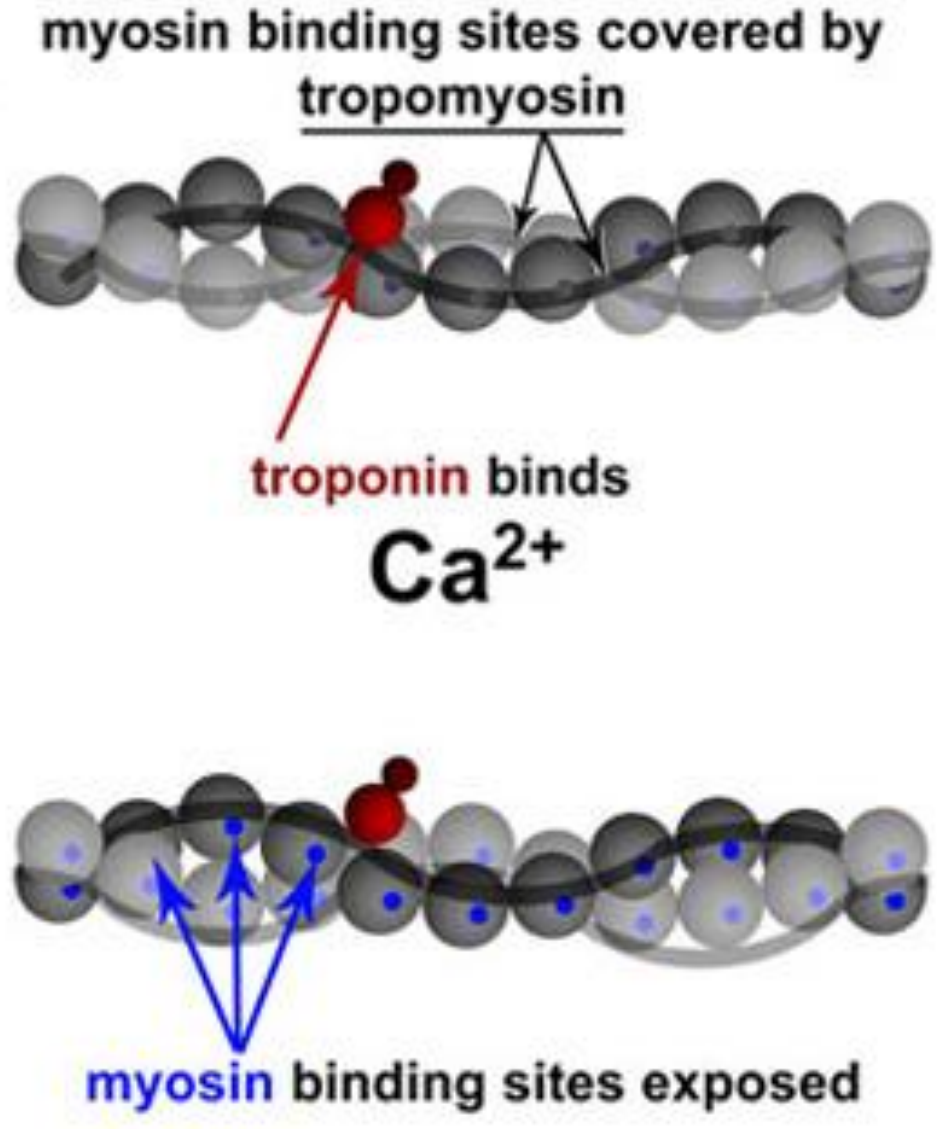
Contraction of skeletal muscle requires an increase in intracellular [Ca^{++}].
Ca^{++} released from the SR binds to troponin C. Once bound with Ca^{++}, troponin C facilitates movement of the associated tropomyosin molecule towards the cleft of the actin filament. This exposes myosin binding sites on the actin thin filament and allows a cross-bridge to form and thereby generate tension. Binding of myosin to the actin filaments appears to cause a further shift in tropomyosin.

Once myosin and actin are bound, ATP-dependent conformational changes in the myosin molecule result in movement of the actin filaments toward the center of the sarcomere. Such movement shortens the length of the sarcomere and thereby contracts the muscle fiber.
If the supply of ATP is exhausted, as occurs with death, the cycle stops in state *c* with the formation of permanent actin-myosin complexes (i.e., the rigor state). In this state, the muscle is rigid, and the condition is termed **rigor mortis.**

The cross-bridge cycling mechanism just described is called the **sliding filament theory**



Berne & Levy Fig. 12.13


myosin binding sites covered by
tropomyosin
troponin binds
Ca^{2+}
myosin binding sites exposed

Skeletal Muscle Type

Fast-twitch (I) and **slow-twitch (II)** muscle fibers.

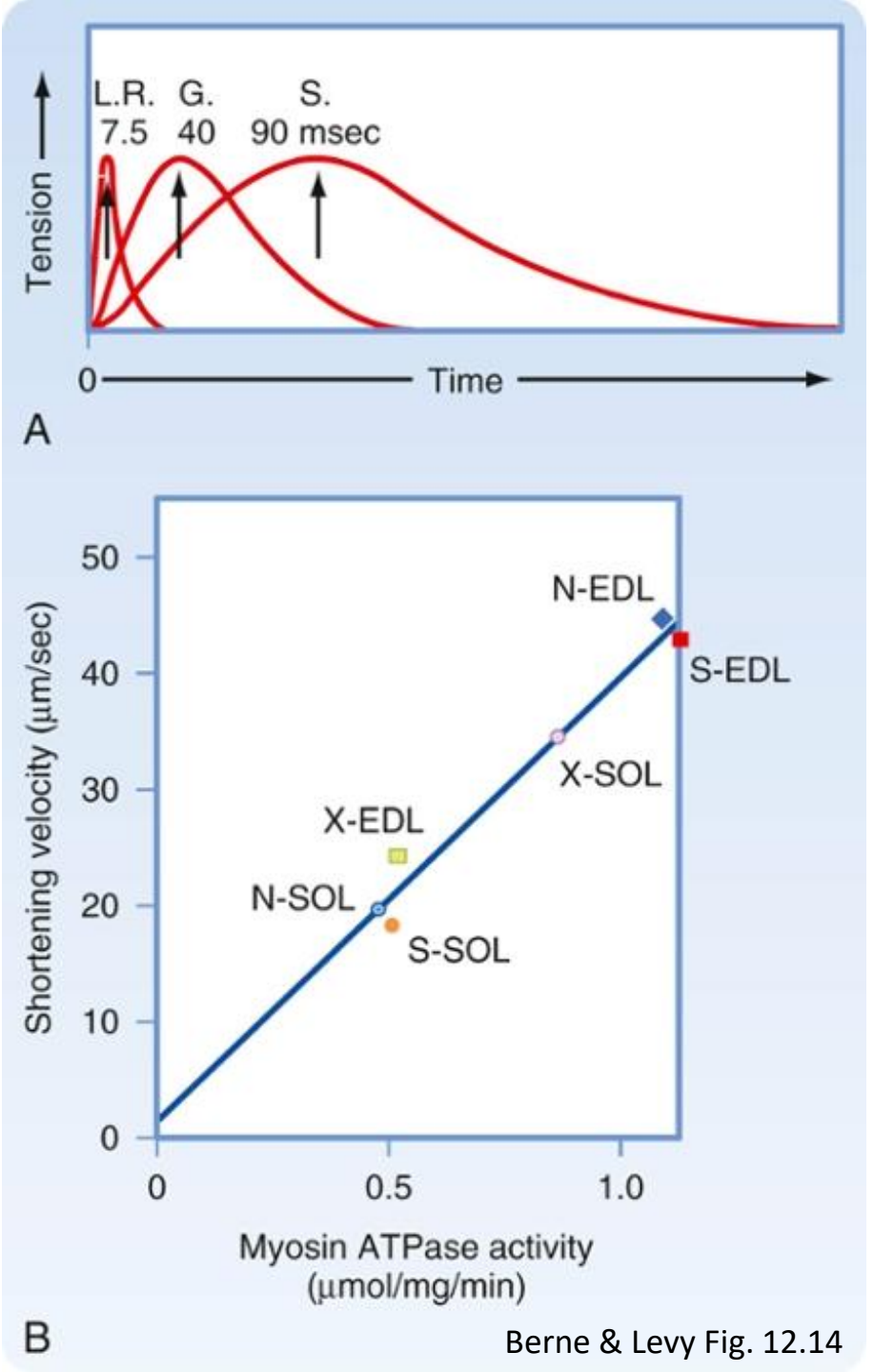
The difference in speed of contraction between fast-twitch and slow-twitch muscles is correlated with myosin ATPase activity.

Slow-twitch muscle fibers express type I myosin heavy chain, whereas fast-twitch skeletal muscle fibers could contain type IIa, type IIx, or type IIb myosin heavy chains.

Fast fibers are more susceptible to fatigue than slow fibers.

The low ATPase activity of myosin in slow motor units, coupled with their high oxidative capacity, facilitates the ability of these slow motor units to maintain posture at low energy cost and thus resist fatigue. The smaller diameter of slow muscle fibers, and the higher capillary density in slow muscle, also helps slow muscle resist fatigue.

The fast motor units typically contain more muscle fibers



Berne & Levy Fig. 12.14

Skeletal Muscle Type

The motor neuron in slow muscle is more easily excited than that in fast muscle, and so slow muscles are typically recruited first.

The neuromuscular junction of fast muscle differs from that in slow muscle

The SR is more highly developed in fast muscle than in slow muscle, with higher levels of RYR, SERCA, lumenal Ca, and a higher DHPR/RYR ratio

Slow fibers begin to develop tension at lower [Ca++] than fast fibers do. This difference in sensitivity to Ca++ is related in part to the fact that the troponin C isoform in slow fibers has only a single low-affinity Ca++-binding site, whereas the troponin C of fast fibers has two low-affinity binding sites.

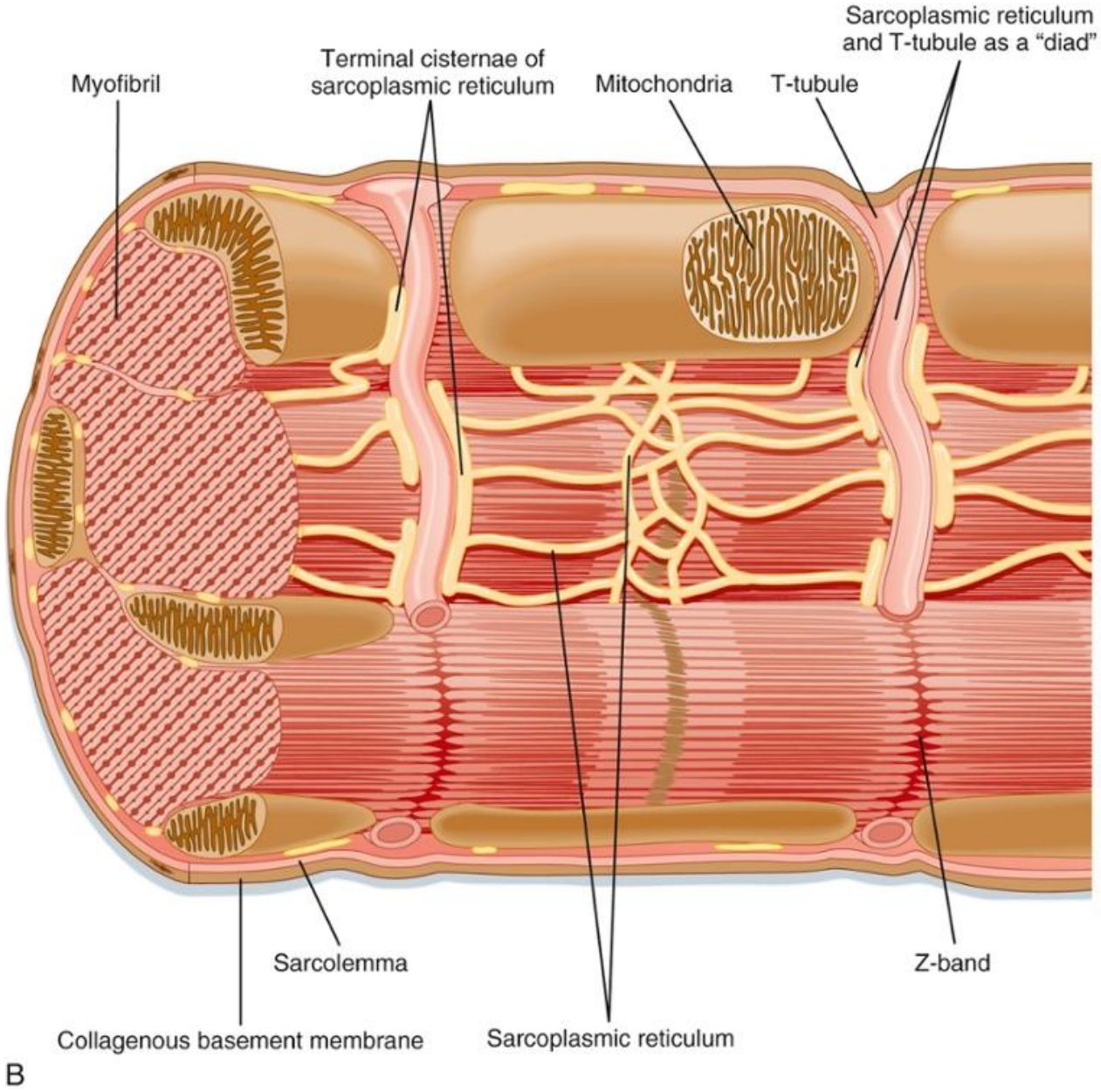
Cardiac Muscle

Cardiac muscle cells are much smaller than skeletal muscle cells (10 μm x 100 μm). Cardiac cells are connected to each other through **intercalated cells** (mechanical junctions and electrical connections) forming an electro-mechanical syncytium.

Structure of the sarcomere is similar to the skeletal muscle cell. The actin filament is anchored to the Z line by α-actinin. The thick filaments are tethered to the Z lines by **titin**.

There is abundance of connective tissue in the heart. This helps prevent muscle rupture (as in skeletal muscle), but it also prevents overstretching of the heart.

Within cardiac muscle cells, myofibrils are surrounded by the **sarcoplasmic reticulum** (**SR,** less developed than in skeletal muscles), Terminal regions of the SR abut the **T tubule** or lie just below the **sarcolemma**.



Berne & Levy Fig. 13.1

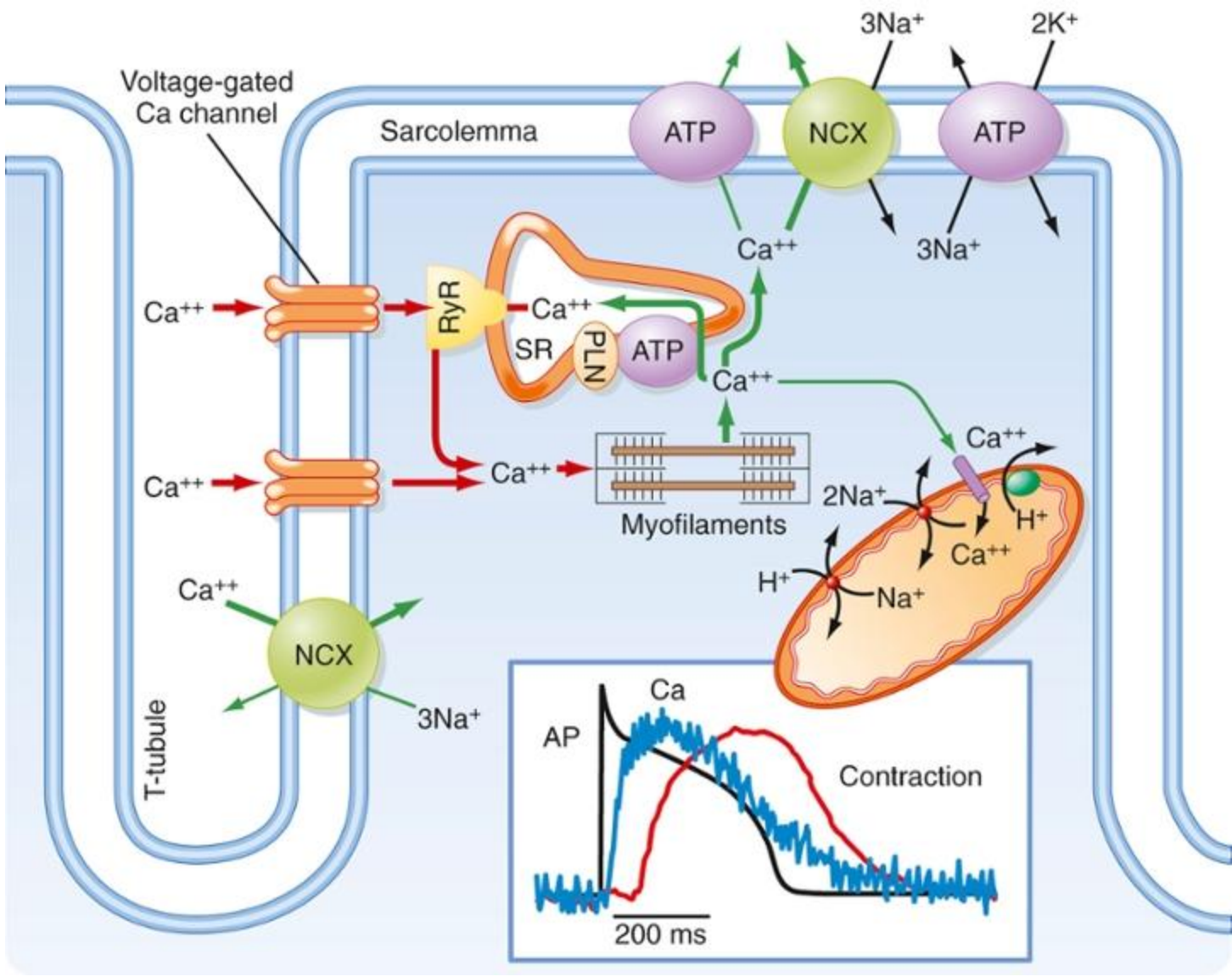
The heart requires extracellular Ca^{++} to contract.

Action potentials in cardiac muscle are prolonged, lasting 150 to 300 msec.

Slow inward Ca^{++} current through a **voltage-gated L-type calcium channel** in the sarcolemma. The amount of Ca^{++} coming into the cardiac muscle cell is relatively small and serves as a trigger for release of Ca^{++} from the SR.

The α_1 subunit of the L-type calcium channel is also called the **dihydropyridine receptor (DHPR)**.

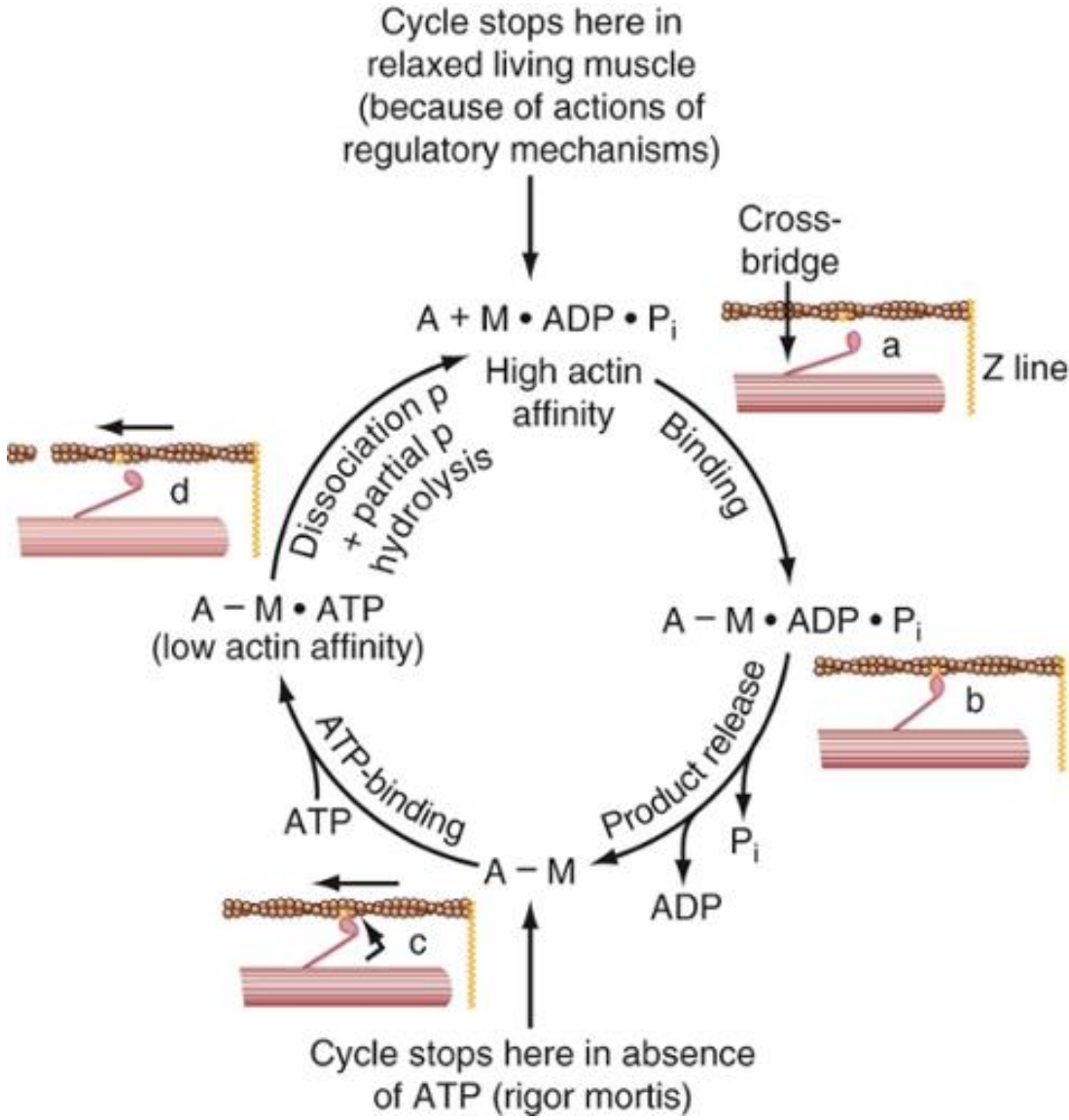
Excitation-contraction coupling in cardiac muscle is termed **electrochemical coupling** (involving Ca^{++}-induced release of Ca^{++}), whereas excitation-contraction coupling in skeletal muscle is termed **electromechanical coupling** (involving direct interactions between the DHPR in the T tubule and the RYR in the SR)



Berne & Levy Fig. 13.2

Cardiac muscle and skeletal muscle differ, however, in the level of intracellular [Ca^{++}] attained after an action potential and hence in the number of actin-myosin interactions.

In cardiac muscle, the rise in intracellular [Ca^{++}] can be regulated, which affords the heart an important means of modulating the force of contraction without recruiting more muscle cells or undergoing tetany. Recall that in the heart, all the muscle cells are activated during a contraction, and so recruiting more muscle cells is not an option.

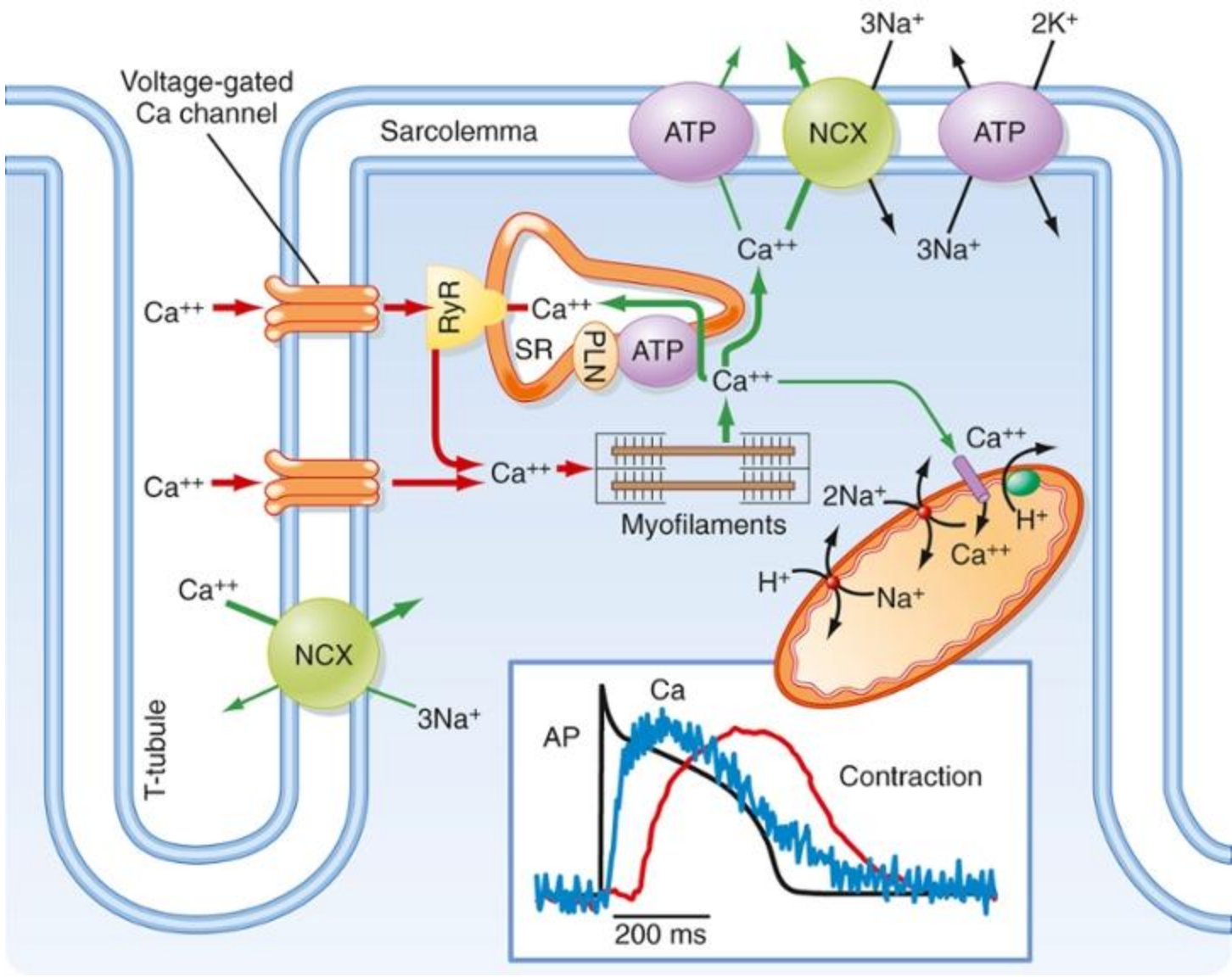


Berne & Levy Fig. 12.13

Relaxation of cardiac muscle cells

SERCA plays a key role in the decrease in cytosolic [Ca^{++}] in cardiac muscle, but some trigger Ca^{++} must enter the cardiac muscle cell through the sarcolemmal calcium channels during each action potential. Ca^{++} must therefore exit the cell. **Sarcolemmal $3Na^{+}$-Ca^{++} antiporter** and **Ca^{++} pump**.

The resting intracellular [Ca^{++}] is approximately 50 to 100 nmol/L; half-maximal force of contraction requires approximately 600 nmol/L of free Ca^{++}. However, because of Ca^{++}-binding proteins, the total myoplasmic concentration must increase by 70 µmol/L. Up to 30% of the rise in intracellular [Ca^{++}] may be attributable to influx of Ca^{++} through voltage-gated calcium channels in the sarcolemma

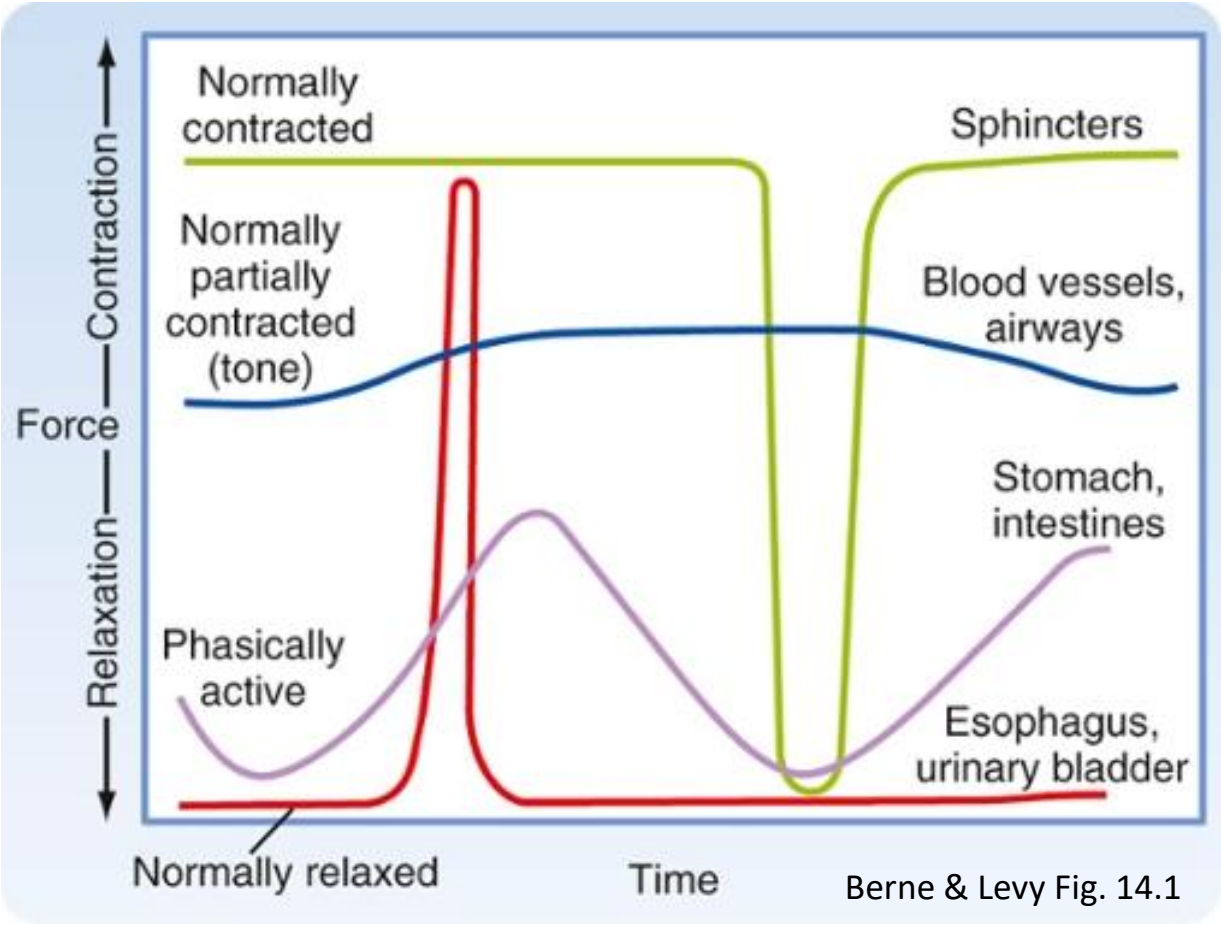


Berne & Levy Fig. 13.2

Smooth Muscle

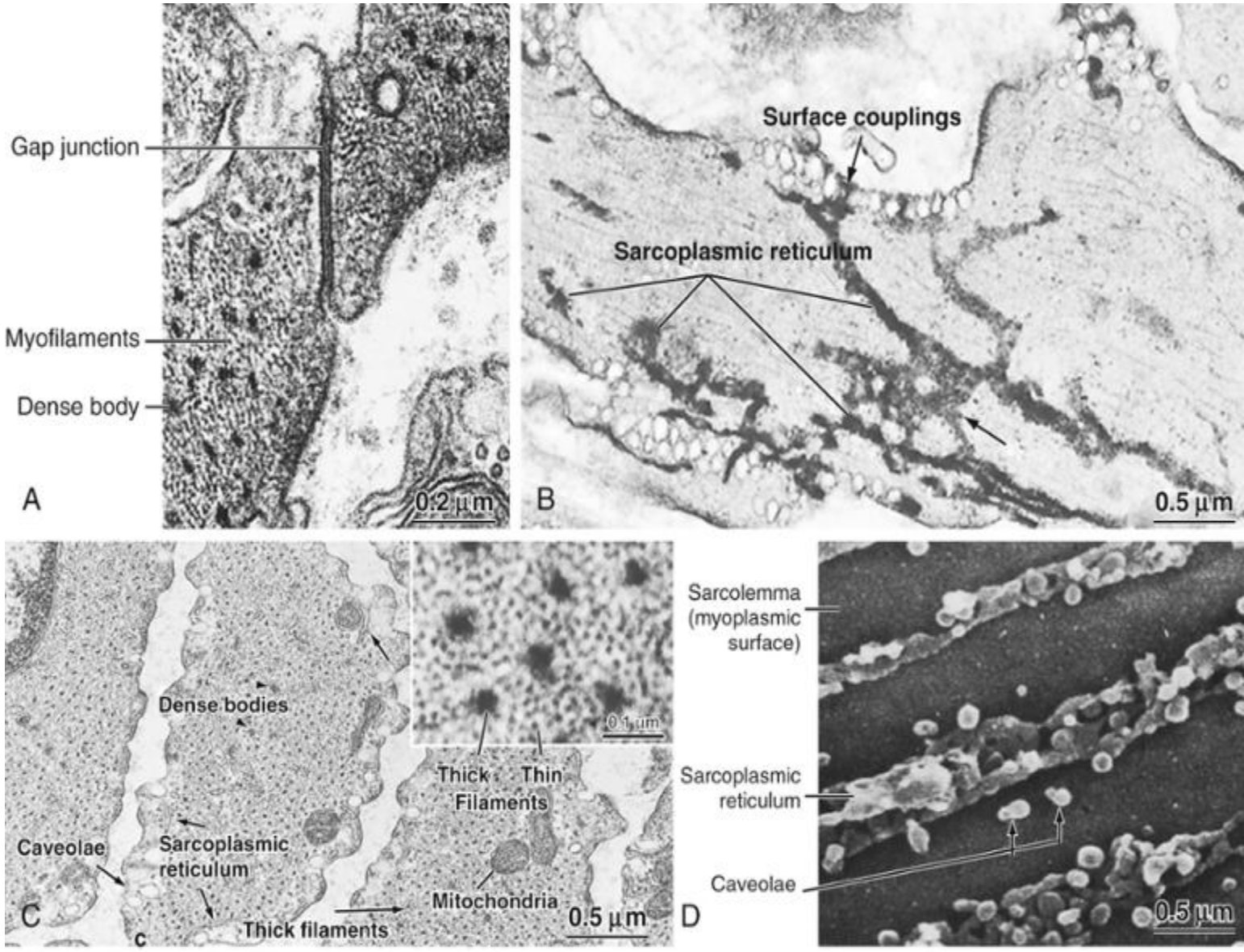
Smooth muscle has been subdivided into two groups: **single unit** and **multiunit.**
In single-unit smooth muscle the smooth muscle cells are electrically coupled. Multiunit smooth muscle cells are not electrically coupled.

Smooth muscle exhibiting rhythmic or intermittent activity is termed **phasic smooth muscle** and includes smooth muscles in the walls of the GI and urogenital tracts. Smooth muscle that is continuously active, on the other hand, is termed **tonic smooth muscle.** Vascular smooth muscle, respiratory smooth muscle, and some sphincters are continuously active. The continuous partial activation of tonic smooth muscle is not associated with action potentials, although it is proportional to membrane potential. Tonic smooth muscle would thus correspond to the multiunit smooth muscle



Berne & Levy Fig. 14.1

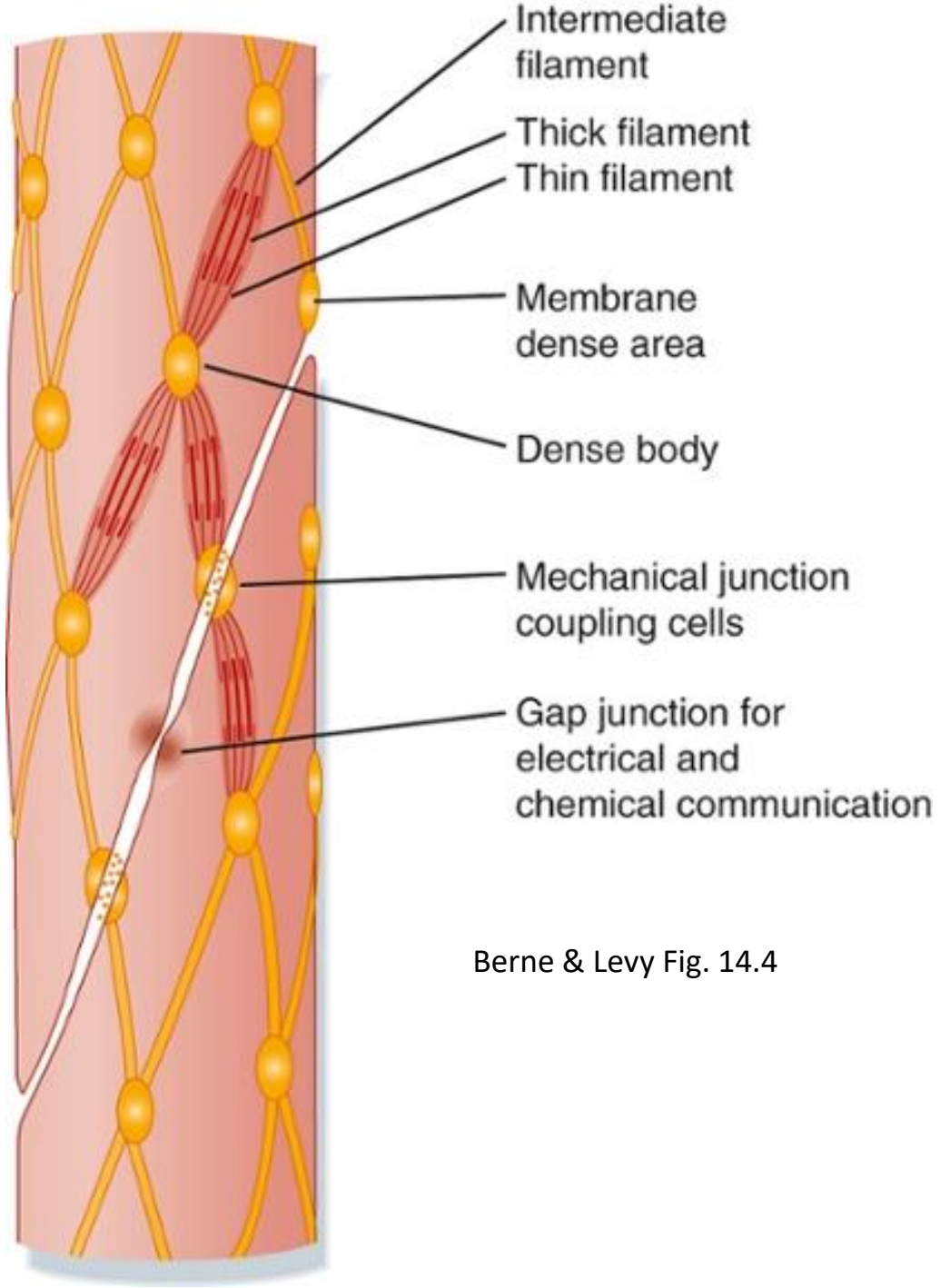
Smooth muscle cells lack T tubules.
The sarcolemma has longitudinal rows of tiny sac-like inpocketings called *caveolae.*
"Ca^{++} sparks" and a variety of Ca^{++}-handling proteins have been observed in the vicinity of caveolae.
Smooth muscle also has an intracellular membrane network of SR that serves as an intracellular reservoir for Ca^{++}. Calcium can be released from the SR into the myoplasm when stimulatory neurotransmitters, hormones, or drugs bind to receptors on the sarcolemma.
Ryanodine receptor (RYR) and the **inositol 1,4,5-trisphosphate (InsP3)**-gated Ca^{++} channel.
Intracellular [Ca^{++}] is lowered through the action of an **SR Ca^{++}-ATPase (SERCA)** and extrusion of Ca^{++} from the cell via a $3Na^{+}$-$1Ca^{++}$ antiporter and a sarcolemmal Ca^{++}-ATPase.



Berne & Levy Fig. 14.3

The contractile filaments in smooth muscle are not in uniform transverse alignment (no striations). The thick and thin filaments are organized in contractile units that are analogous to sarcomeres.
The thin filaments of smooth muscle have an actin and tropomyosin composition and structure similar to that in skeletal muscle (about twice).
The myosin content of smooth muscle is only a fourth that of striated muscle. These groups of thick filaments with interdigitating thin filaments are connected to **dense bodies.**
The contractile apparatus of adjacent cells is mechanically coupled by the links between membrane-dense areas.

The cytoskeleton in smooth muscle cells serves as an attachment point for the thin filaments and permits transmission of force to the ends of the cell. Z lines are lacking.
Intermediate filaments with diameters between those of thin filaments are prominent in smooth muscle. These filaments link the dense bodies and areas into a cytoskeletal network.
The intermediate filaments consist of protein polymers of **desmin** or **vimentin.**

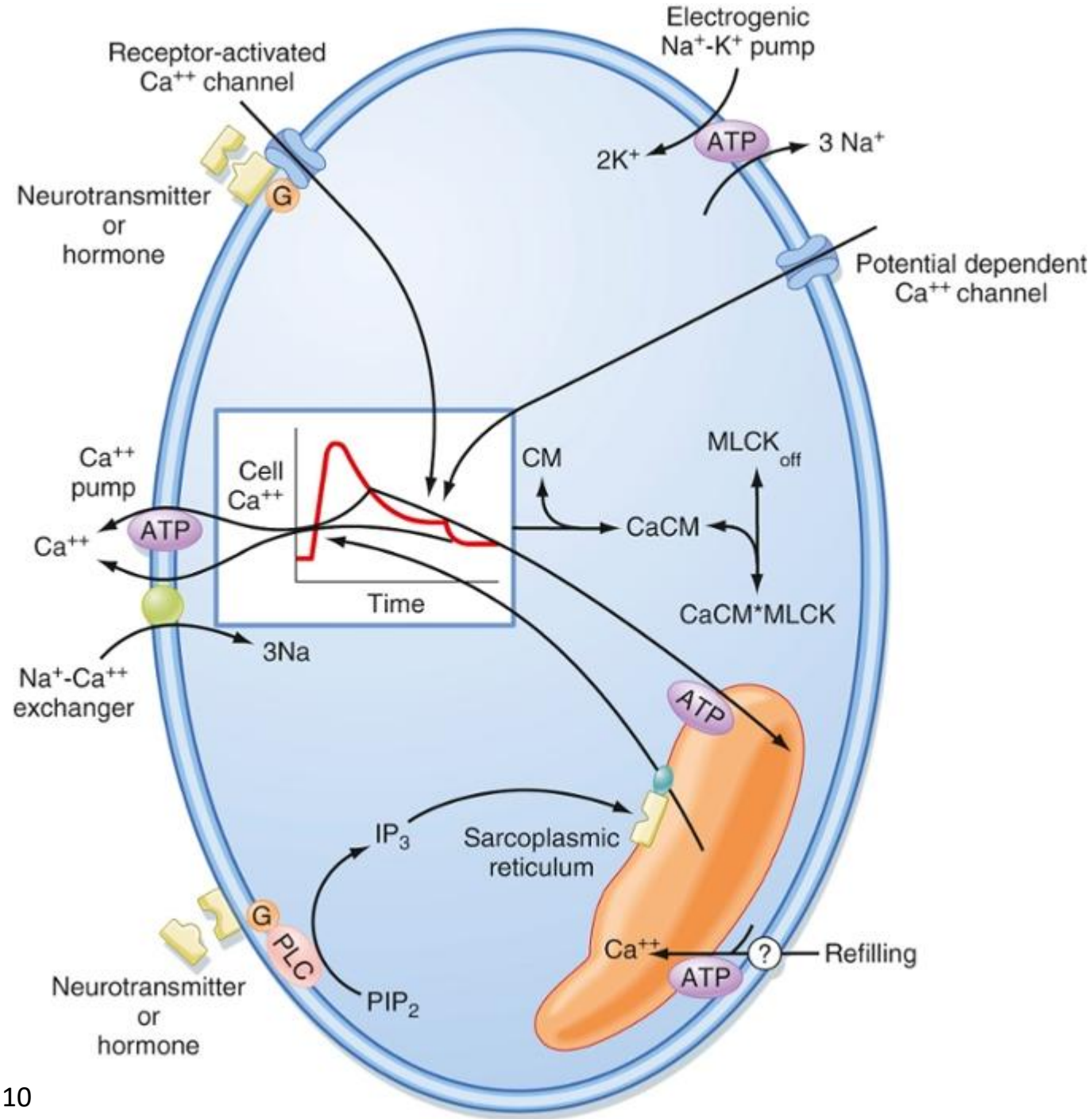


Berne & Levy Fig. 14.4

Control of Smooth Muscle Activity

Like skeletal or cardiac muscle, contraction of smooth muscle is dependent on Ca^{++}. Action potentials induce but are not necessary for contraction. Contraction of smooth muscle in response to an agent that does not produce a change in membrane potential is termed **pharmacomechanical coupling** (InsP3).

Phosphorylation of a myosin light chain is required for the interaction of myosin with actin, and although Ca^{++}-dependent phosphorylation plays a key role in this process, the level of myosin phosphorylation (and hence the degree of contraction) is dependent on the relative activities of both **myosin light-chain kinase** (**MLCK**) and **myosin phosphatase** (**MP**).

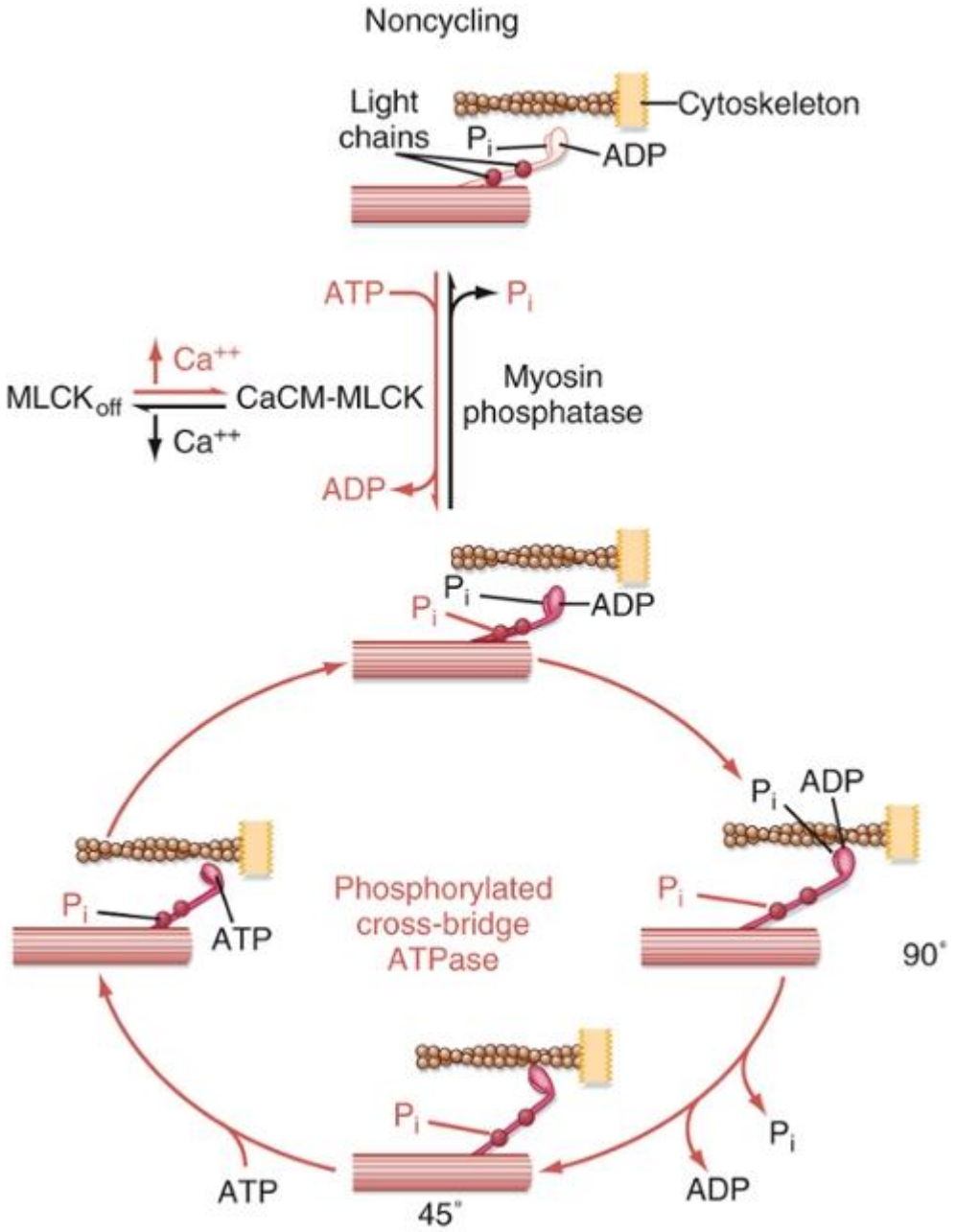


Berne & Levy Fig. 14.10

A rise in intracellular [Ca^{++}] in smooth muscle results in the binding of 4 Ca^{++} ions to the protein calmodulin, and then the Ca^{++}-calmodulin complex activates MLCK, which phosphorylates the regulatory light chain of myosin.
Contraction of smooth muscle is thus said to be *thick-filament regulated*

The cross-bridge cycle in smooth muscle is similar to that in striated muscle in that after attachment to the actin filament, the cross-bridge undergoes a ratchet action.
The cross-bridge cycle continues as long as the myosin light chain remains phosphorylated.
The kinetics of cross-bridge cycling is much slower for smooth muscle.

With the decrease in [Ca^{++}], MLCK becomes inactive, and the myosins are dephosphorylated by MP.
Although intracellular Ca^{++} is required for smooth muscle contraction, the sensitivity of contraction to Ca^{++} is variable (**Ca^{++} sensitization** or **desensitization**).

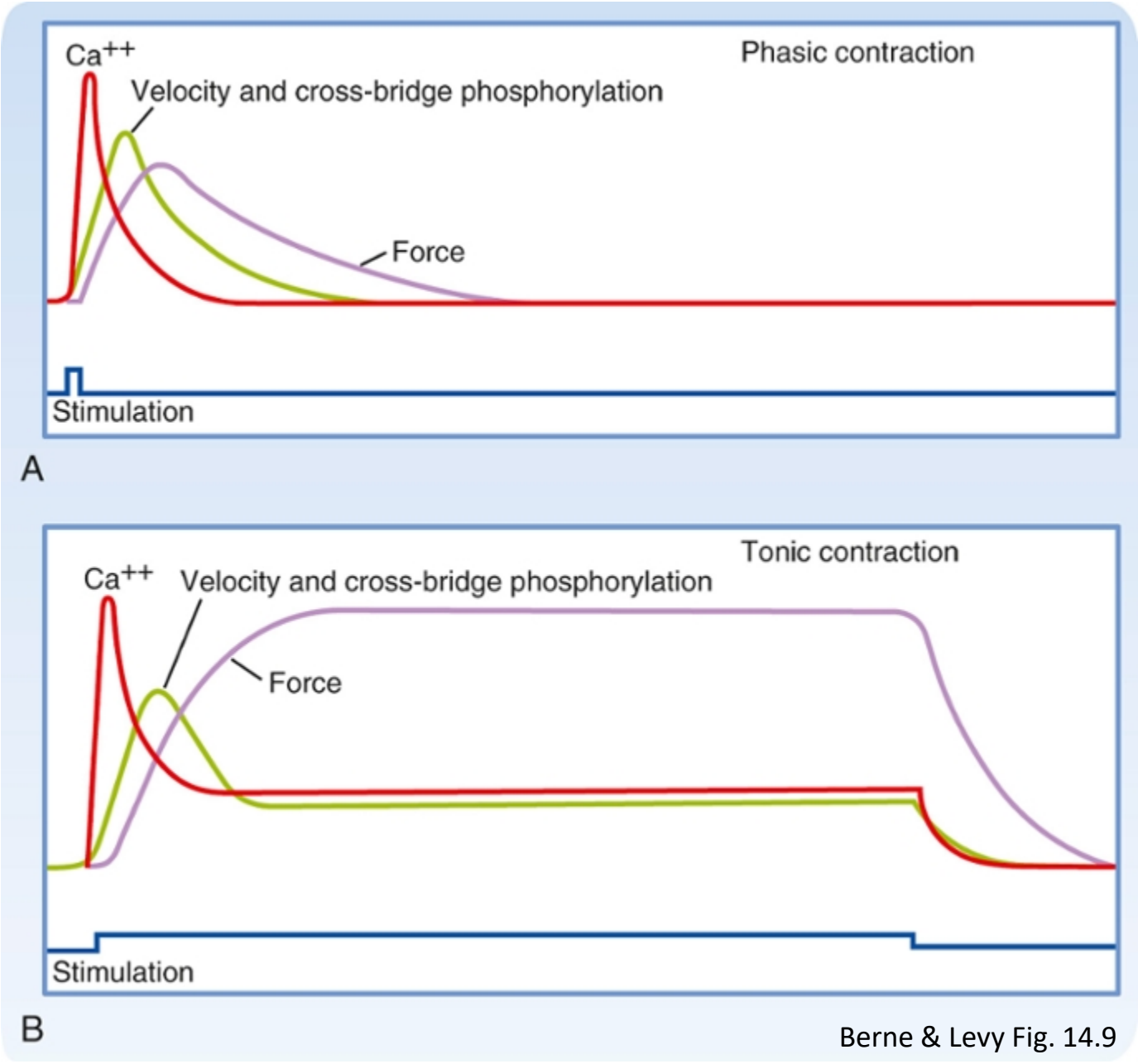


Berne & Levy Fig. 14.7

Phasic versus Tonic Contraction

During a phasic contraction, myoplasmic [Ca^{++}], cross-bridge phosphorylation, and force reach a peak and then return to baseline. In contrast, during a tonic contraction, myoplasmic [Ca^{++}] and cross-bridge phosphorylation decline after an initial spike but do not return to baseline levels. The term ***latch state*** refers to this condition of tonic contraction during which force is maintained at low energy expenditure.

The mechanism contributing to the ability of smooth muscle to maintain force at a low intracellular [Ca^{++}] during tonic contraction is thought to involve dephosphorylation of the myosin regulatory light chain while the myosin cross-bridge is attached to the actin filament, resulting in slowing of the rate of dissociation of the myosin from the actin, allowing the myosin to spend more time in an attached, force-generating conformation.



Berne & Levy Fig. 14.9