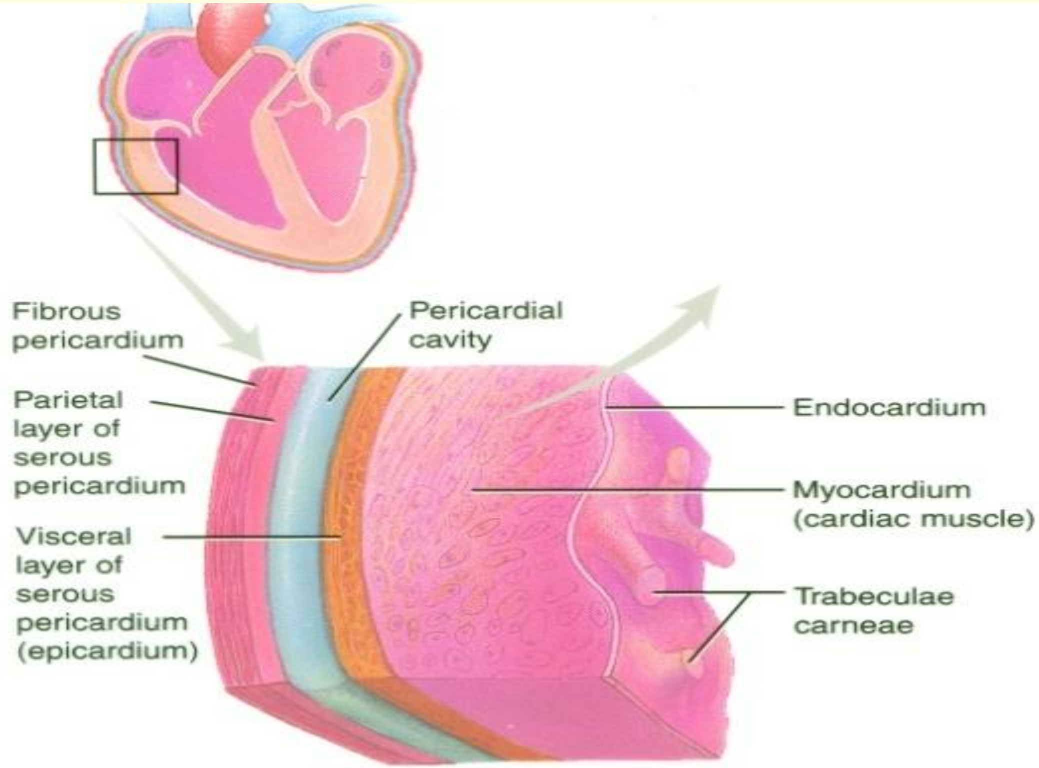
Cardiac Muscle Physiology

Faisal Mohammed, MD, PhD
Yanal A. Shafagoj, MD, PhD

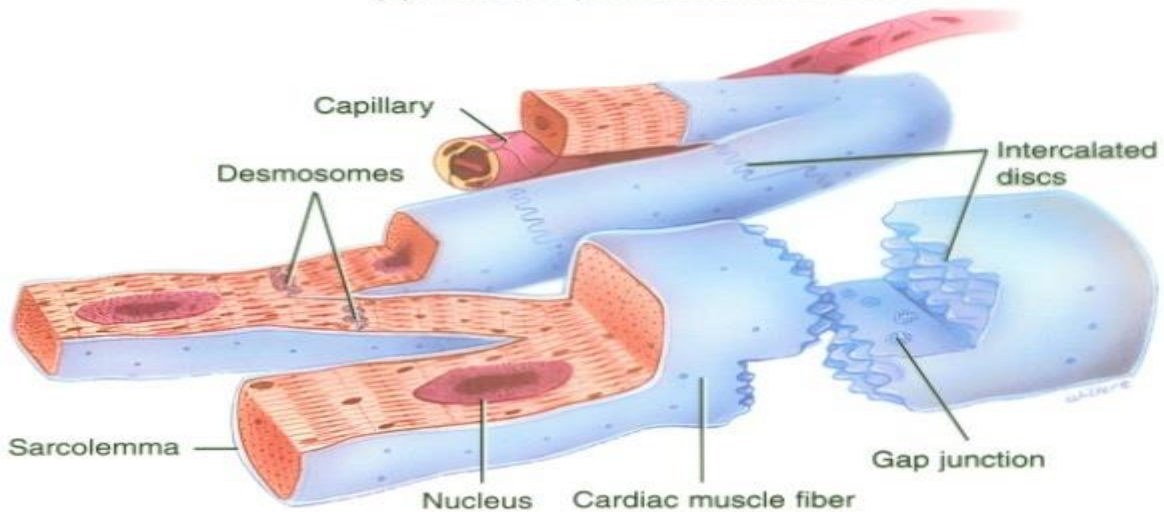
Objectives:

By The end of this lecture students should be able to:

- Distinguish the cardiac muscle cell microstructure
- Describe cardiac muscle action potential
- Point out the functional importance of the action potential
- Follow the cardiac muscle mechanism of contraction
- Delineate cardiac muscle energy sources
- Outline the intracellular calcium homeostasis
- Explain the relationship between muscle length and tension of cardiac muscle (Frank-Starling law of the heart)



(a) Portion of pericardium and heart wall



(b) Cardiac muscle fibers

Endocardium→myocardium→ Epicardium →Pericardium

The myocardium: The innermost fibers are called endocardial fibers and outermost fibers are called epicardial cells.

The pericardium:

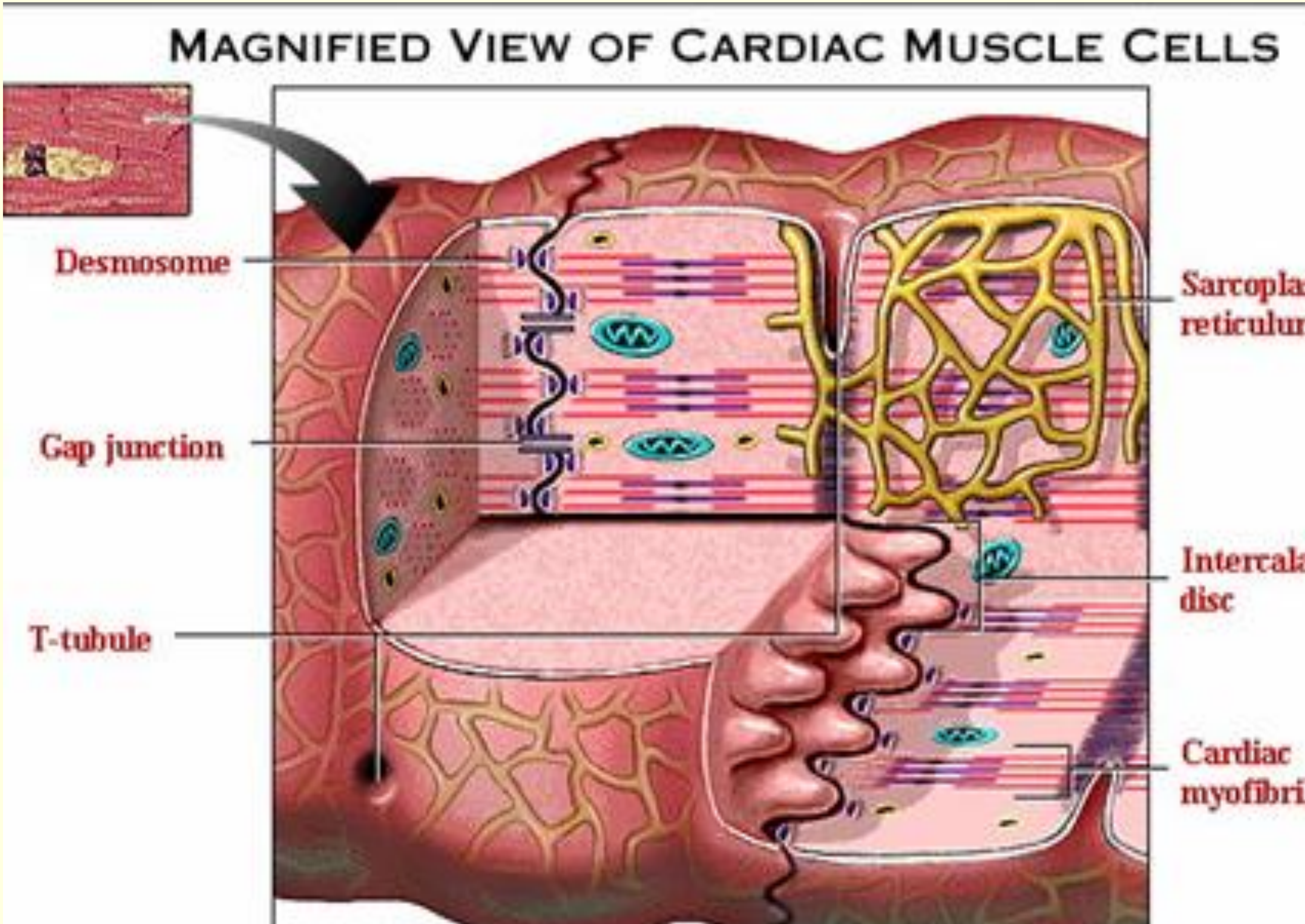
1. The outer layer is tough fibrous layer connect the heart to the great vessels and sternum, and the diaphragm. This layer prevents overstretchability of the heart.

2. The inner layer has two Layers

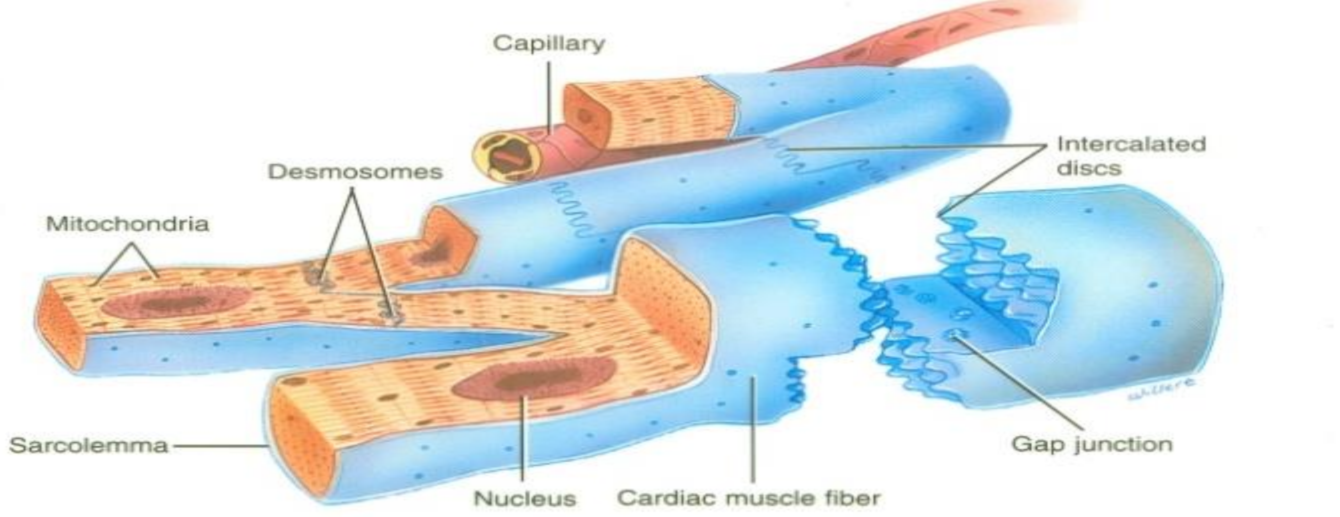
A. The visceral layer also known as **epicardium** which folds on itself to form:

B. the parietal layer.

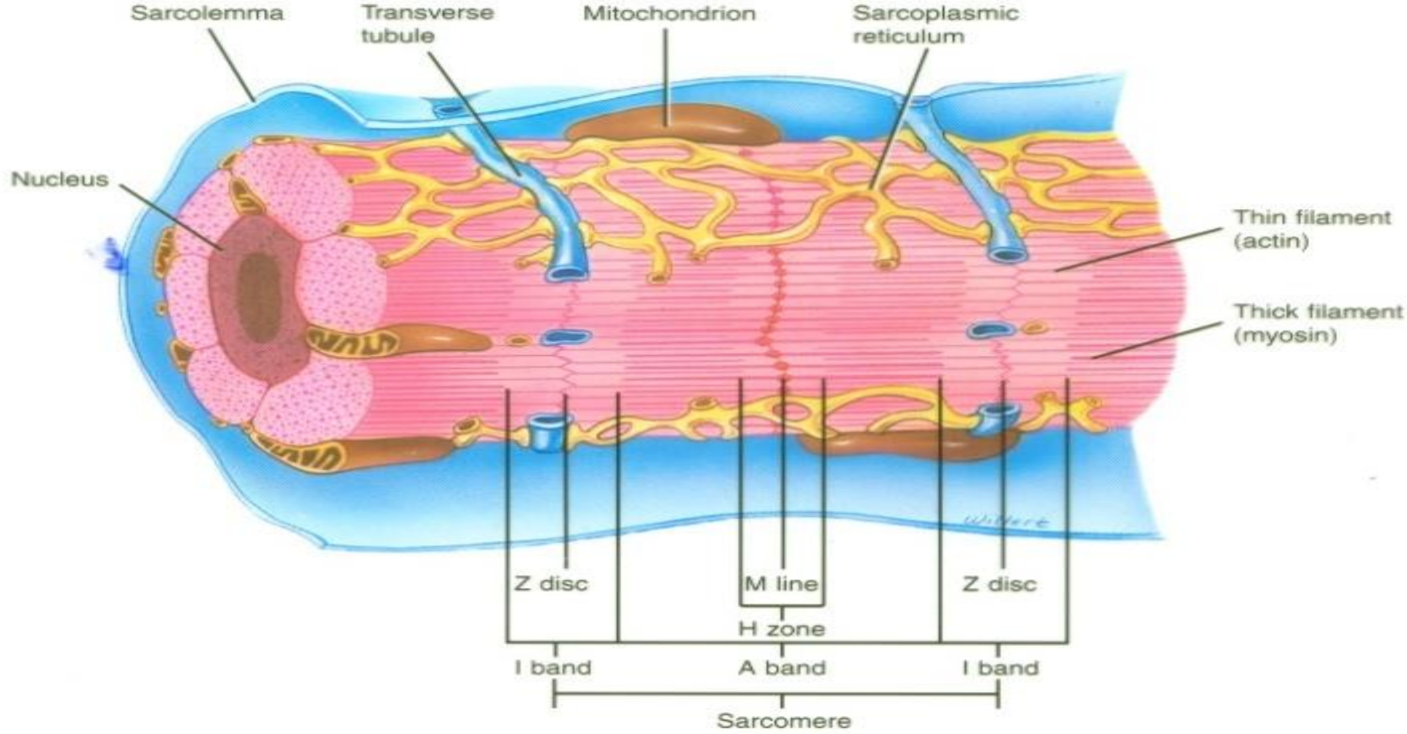
Between these two layers is the 30-50 ml of serous fluid



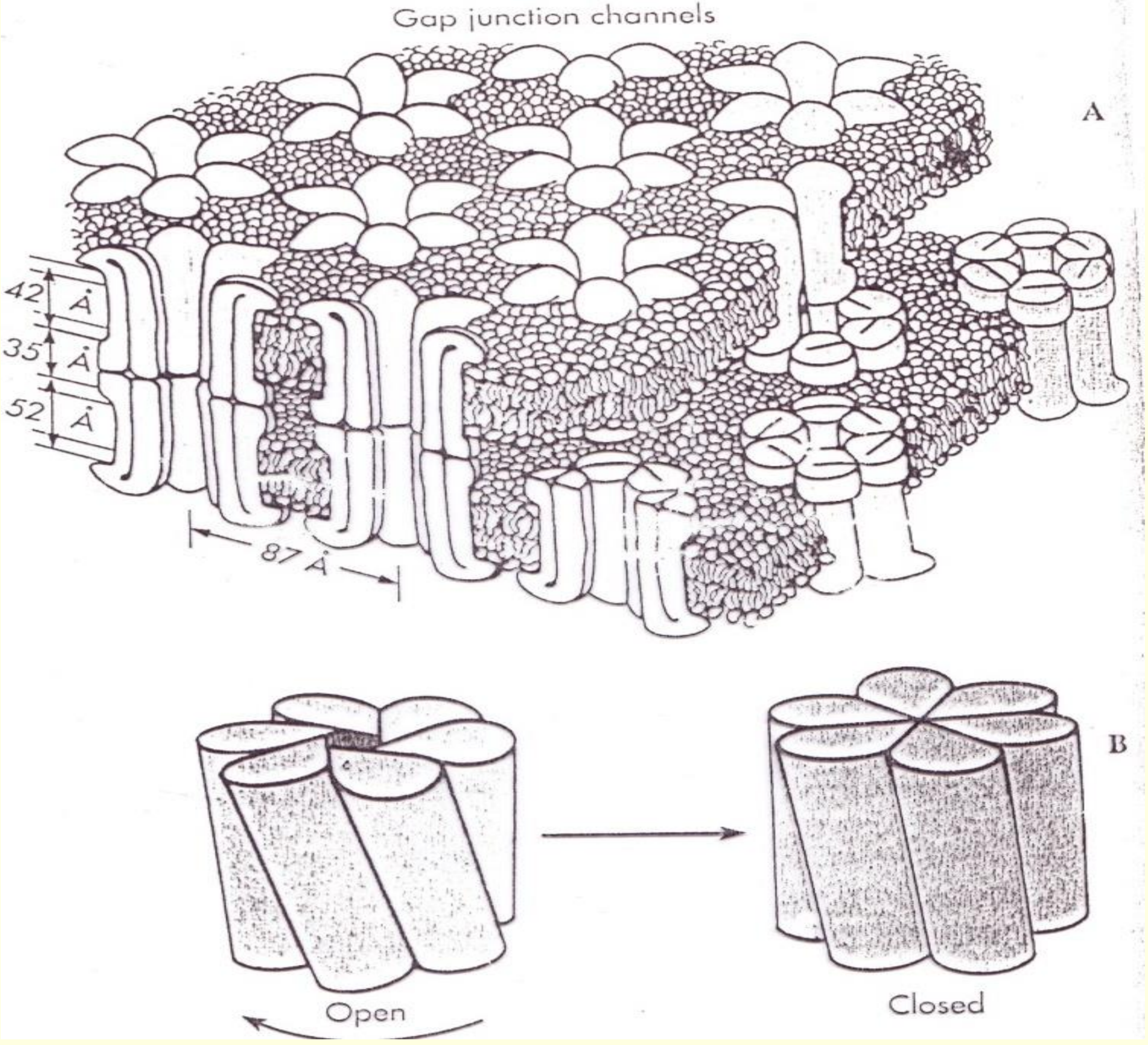
MAGNIFIED VIEW OF CARDIAC MUSCLE CELLS
Desmosome
Gap junction
T-tubule
Sarcoplas
reticulum
Intercala
disc
Cardiac
myofibril



(a) Cardiac muscle fibers



(b) Diagram based on an electron micrograph

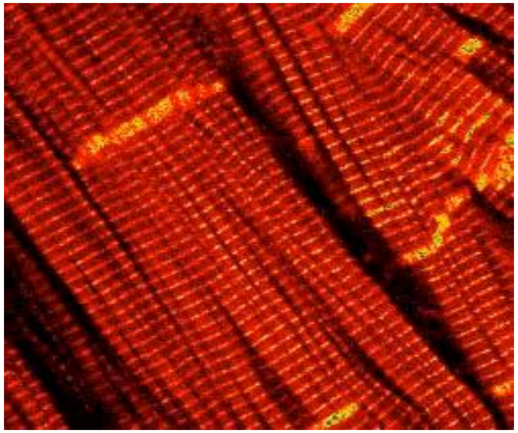

Gap junction channels
A
42 Å
35 Å
52 Å
87 Å
B
Open
Closed

Cardiac Muscle Tissue and the Cardiac Conduction System

- Histology
  - Shorter and less circular than skeletal muscle fibers
  - Branching gives “stair-step” appearance (Y-shape)
  - Usually, one centrally located nucleus
  - Ends of fibers connected by intercalated discs (longitudinally)
  - Discs contain desmosomes (hold fibers together) and gap junctions (allow action potential conduction from one fiber to the next) → **syncytium (cells together)**
  - Mitochondria are larger and more numerous than skeletal muscle (red fibers)
  - Same arrangement of actin and myosin

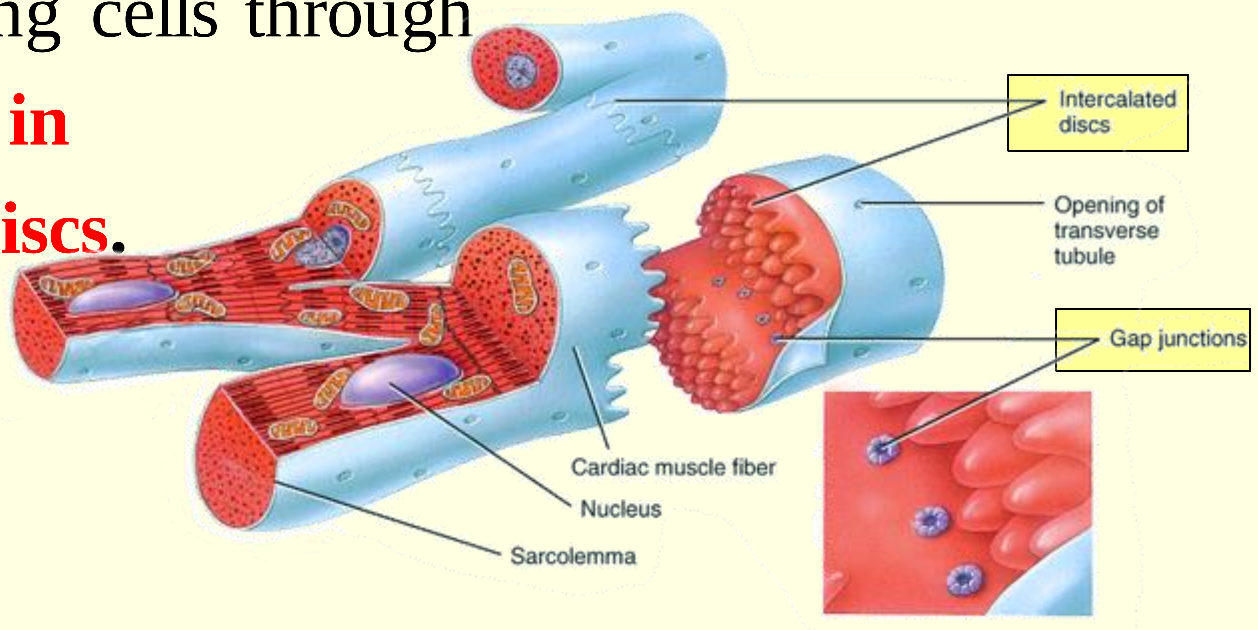
Cardiac Myocyte

- 50-100 μm long
- 10-20 μm in diameter
- single central nucleus
- the cell is branched, attached to adjacent cells in an end-to-end fashion (intercalated disc)
  - desmosomes (connexons)
  - gap junction



Cardiac Muscle Tissue

- Cardiac muscle, like skeletal muscle, is striated. Unlike skeletal muscle, its fibers are shorter, they branch, and they have only one (usually centrally located) nucleus.
- Cardiac muscle cells connect to and communicate with neighboring cells through **gap junctions in intercalated discs**.



Cardiac and Skeletal Muscles
Differences

Skeletal muscle

- Neurogenic
  (motor neuron-end plate-acetylcholine)
- Insulated from each other
- Short action potential

Cardiac Muscle

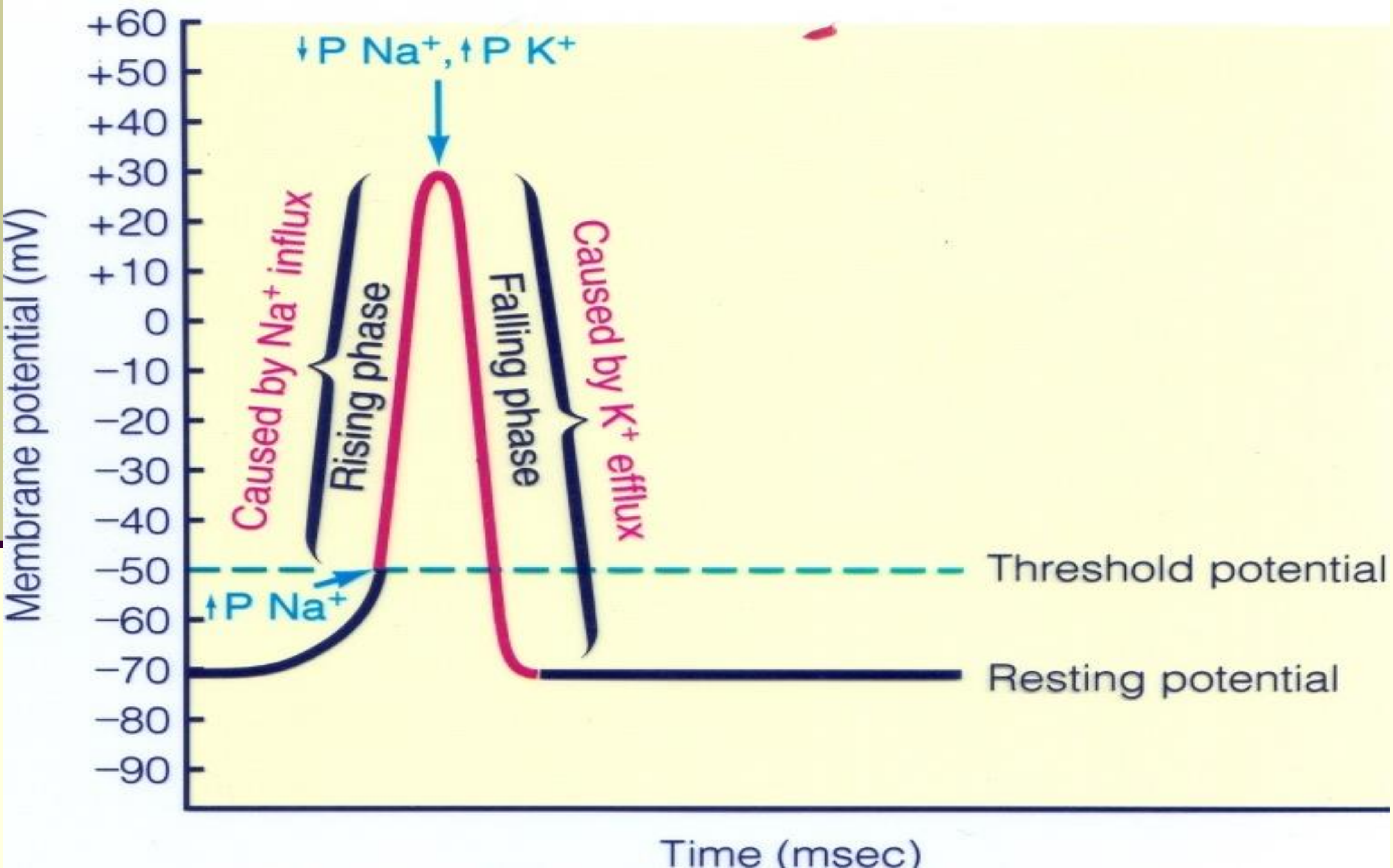
- Myogenic
  (action potential originates within the muscle)
- Gap-junctions
- Action potential is longer

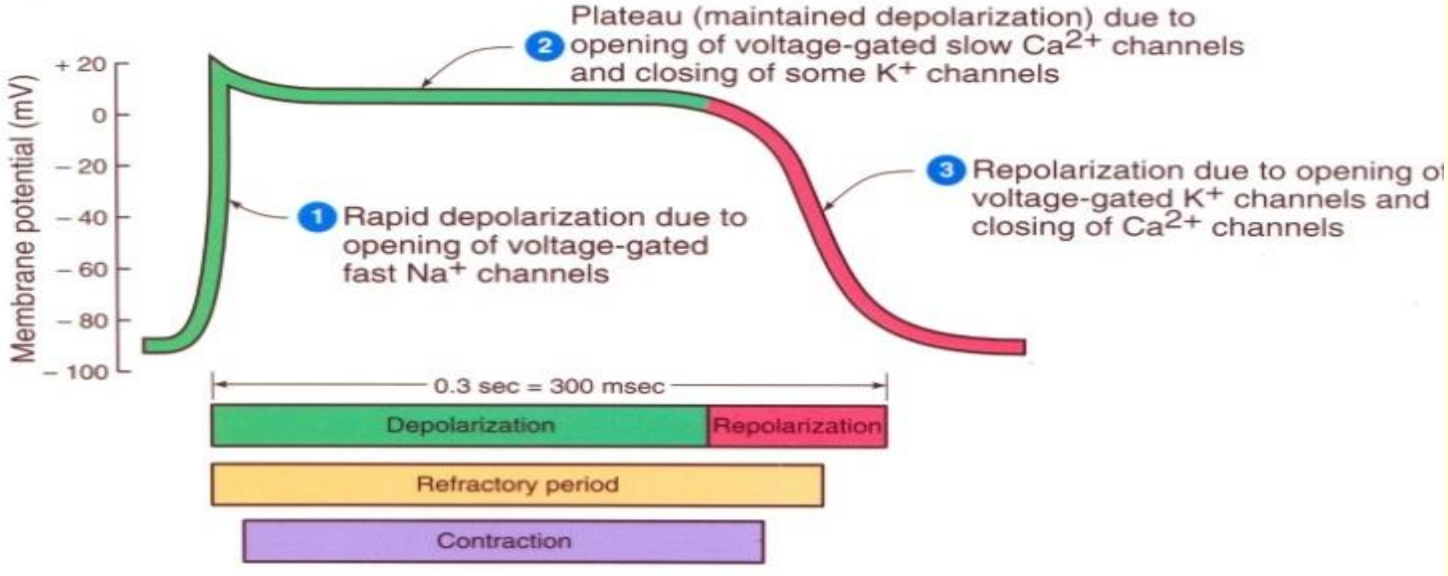
Cardiac Muscle Vs Skeletal Muscle

- Syncytium structure
- Gap Junction (electrical coupling) low resistance area (R=1/400)
- Poorly developed Sarcoplasmic reticulum (SR)
- Transverse (T)Tubule on Z-line (i.e.One T-tubule per sarcomere) Shorter and broader.
- Rich in mitochondria
- Low in nuclei

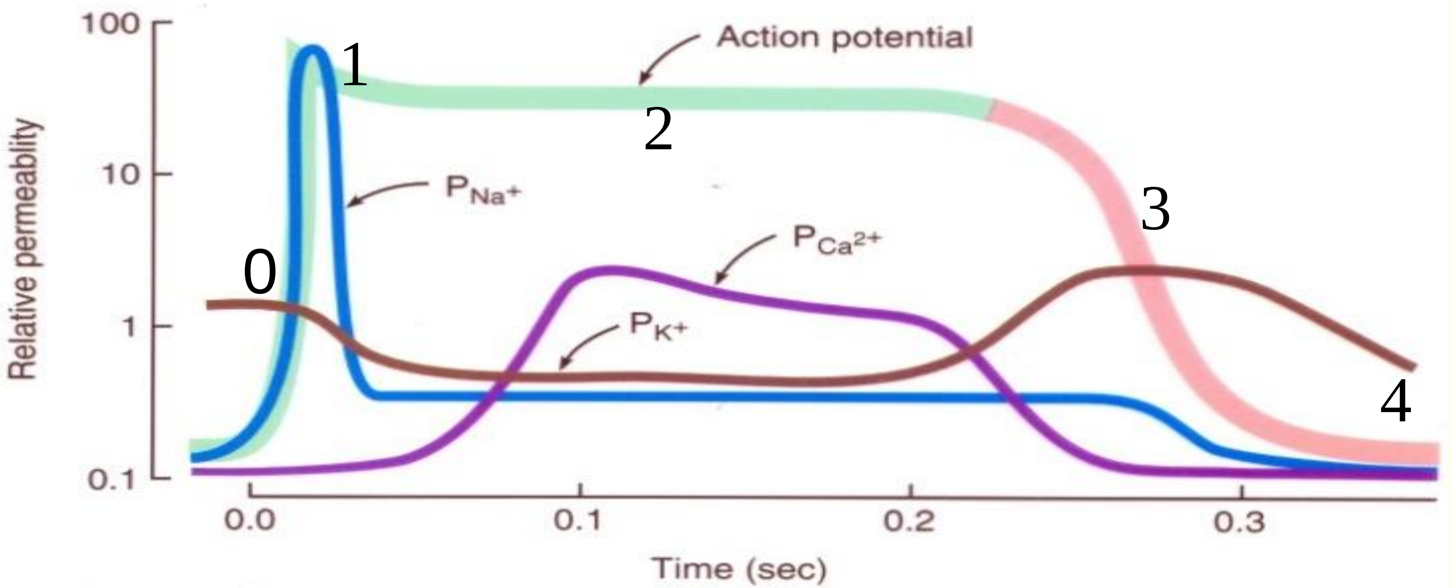
T-Tubules are shorter and broader. They have 5 times more diameter. This results in a 25 fold increase in volume. It makes sense to have more ECF volume with more Ca^{++} in it. Located at the Z-line (one TT for each sarcomere). In skeletal muscle, at both ends of the myosin: the border of A-I bands (two TT for each sarcomere). If removed in skeletal muscle (detubulation with osmotic shock it uncouples excitation from contraction). In cardiac, their importance in excitation-contraction coupling is questionable. Contain Ca^{++} binding sites. In frog and birds, their ventricles contain no TT. In mammals, atria contain no TT.

Permeability Changes and Ionic Fluxes During an Action Potential (skeletal Muscle)





(a) Action potential, refractory period, and contraction



(b) Membrane permeability (P) changes

Action Potentials and Contraction

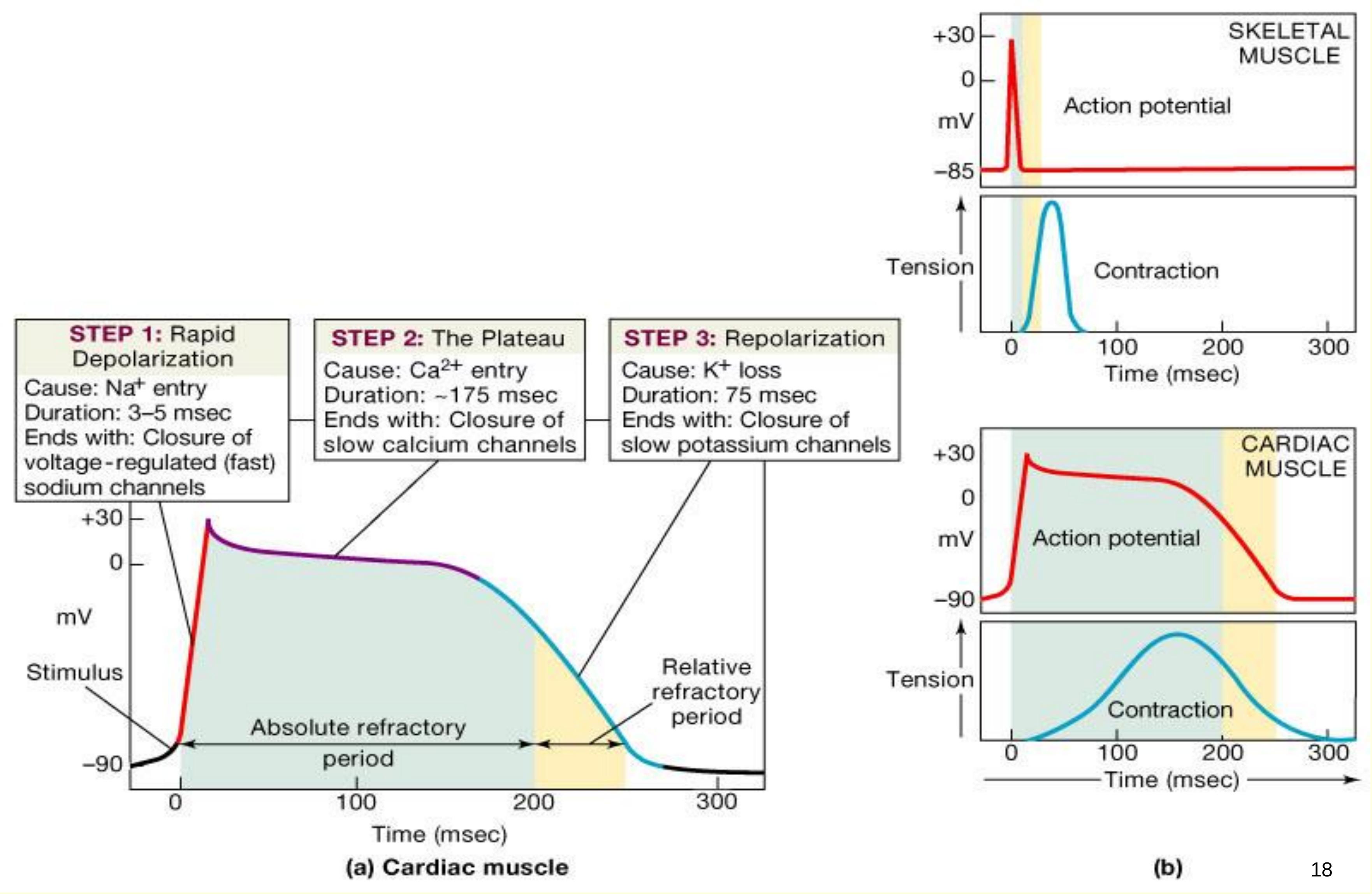
1. Depolarization – contractile fibers (ventricular) have stable resting membrane potential. They cannot reach threshold by themselves (not autorhythmic)
   - Voltage-gated fast Na^+ channels open →Na^+ flows in
   - Then deactivate and Na^+ inflow decreases
2. Plateau – period of maintained depolarization
   - Due in part to opening of voltage-gated slow Ca^{2+} channels – Ca^{2+} moves from interstitial fluid into cytosol
   - Ultimately triggers contraction
   - Depolarization sustained due to voltage-gated K^+ channels balancing Ca^{2+} inflow with K^+ outflow

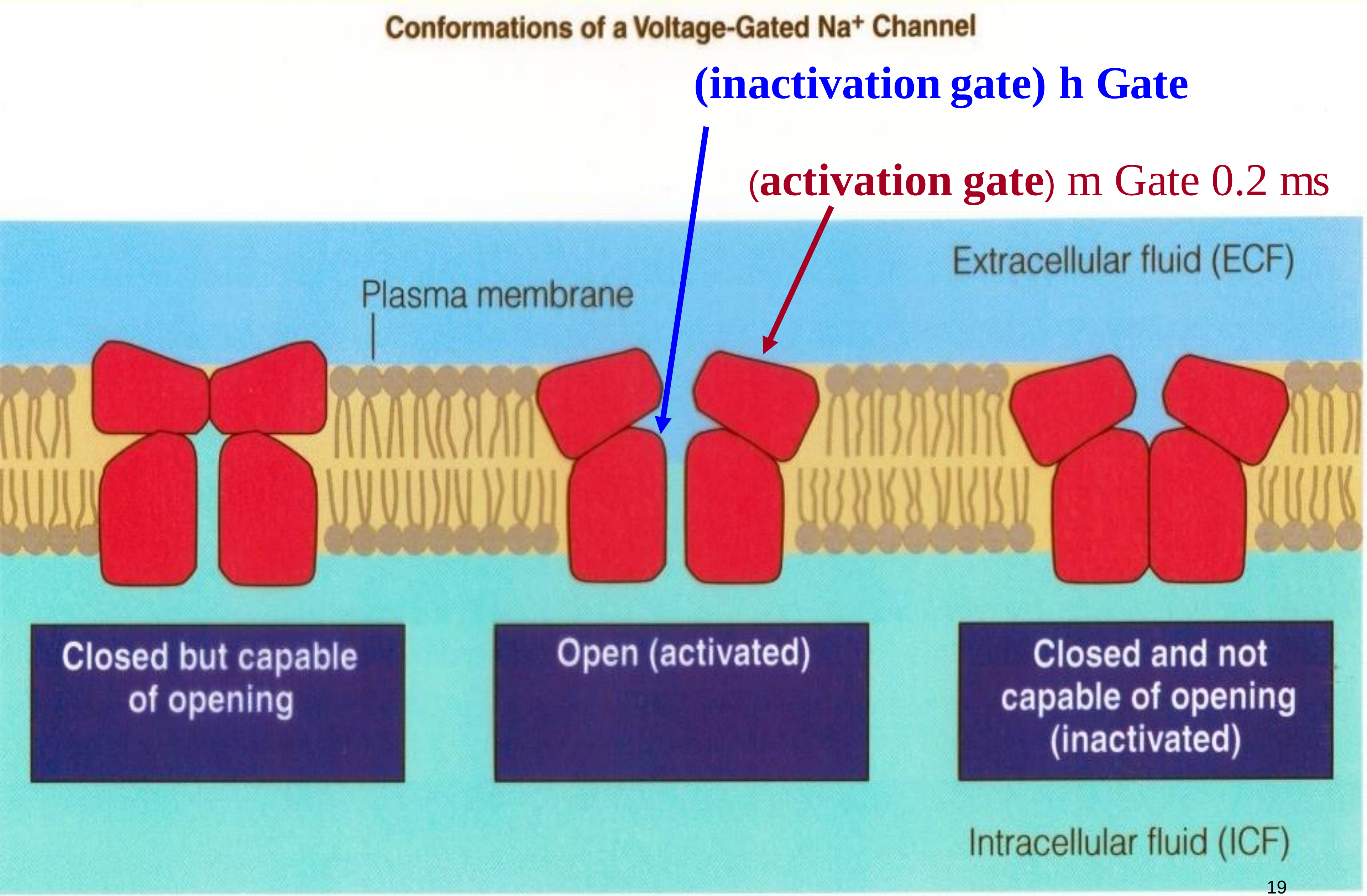
Action Potentials and Contraction

3. Repolarization – recovery of resting membrane potential
   - Resembles that in other excitable cells
   - Additional voltage-gated K^+ channels open
   - Outflow K^+ of restores negative resting membrane potential
   - Calcium channels closing

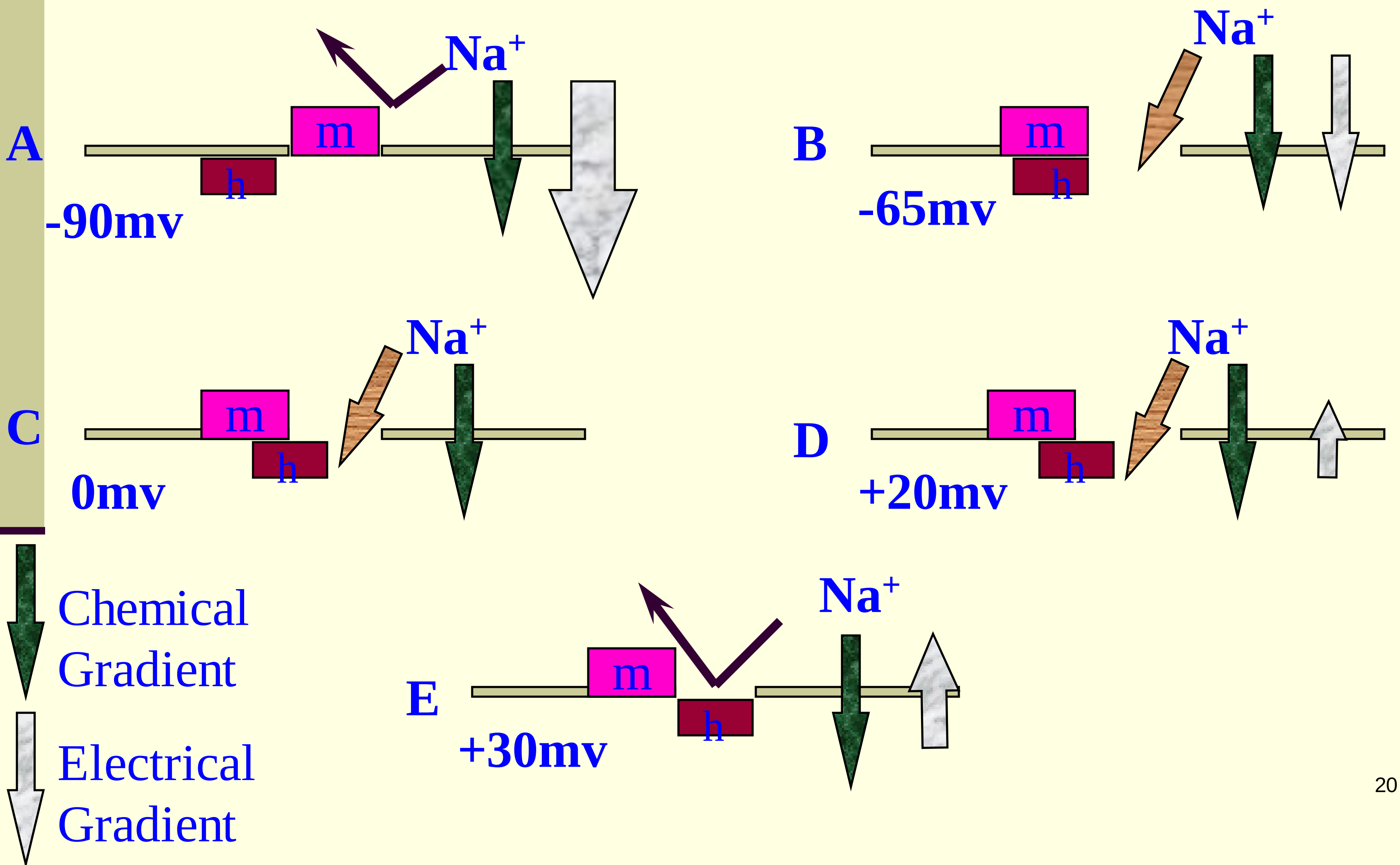
- Refractory period – time interval during which second contraction cannot be triggered
  - Lasts longer than contraction itself
  - Tetanus (maintained contraction) cannot occur in ventricles

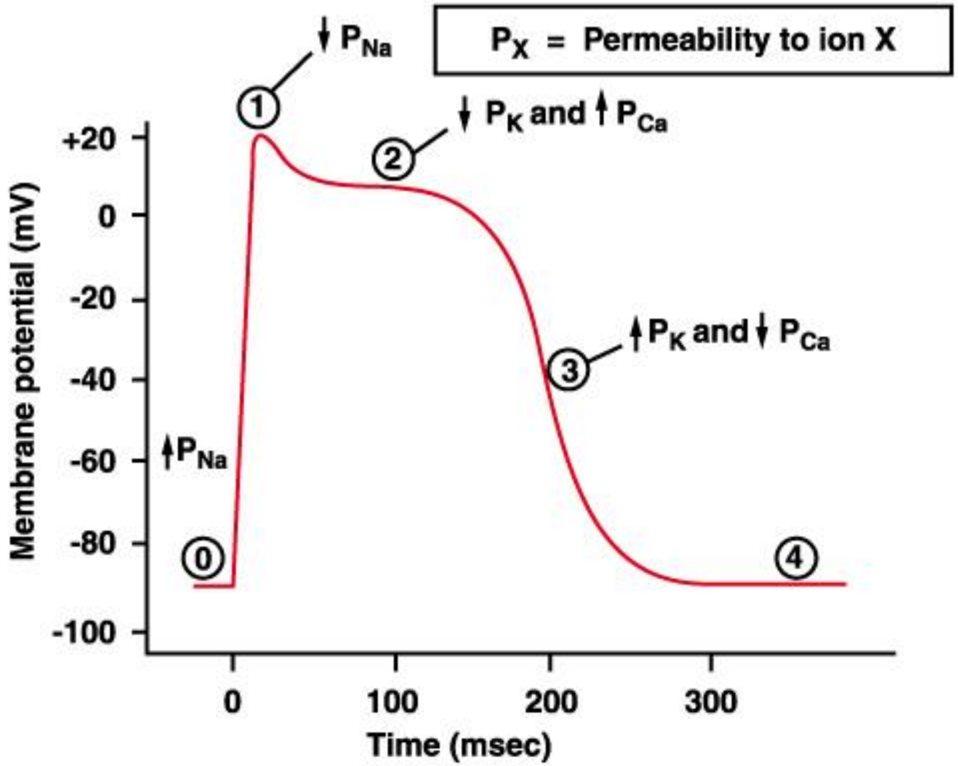
The Action Potential in Skeletal and Cardiac Muscle



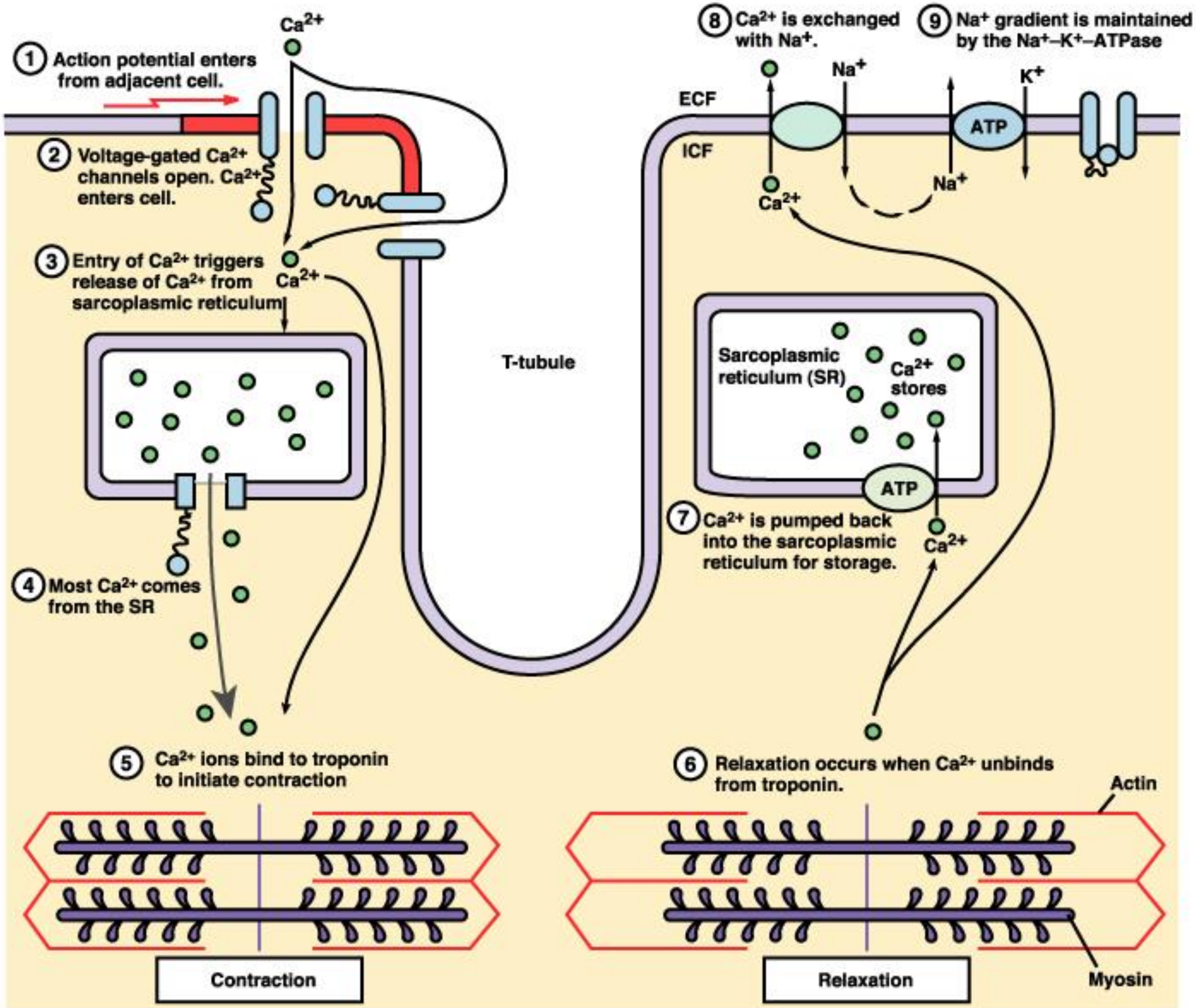

Conformations of a Voltage-Gated Na+ Channel
(inactivation gate) h Gate
(activation gate) m Gate 0.2 ms
Extracellular fluid (ECF)
Plasma membrane
Closed but capable of opening
Open (activated)
Closed and not capable of opening (inactivated)
Intracellular fluid (ICF)

PHASE 0 OF THE FAST FIBER ACTION POTENTIAL

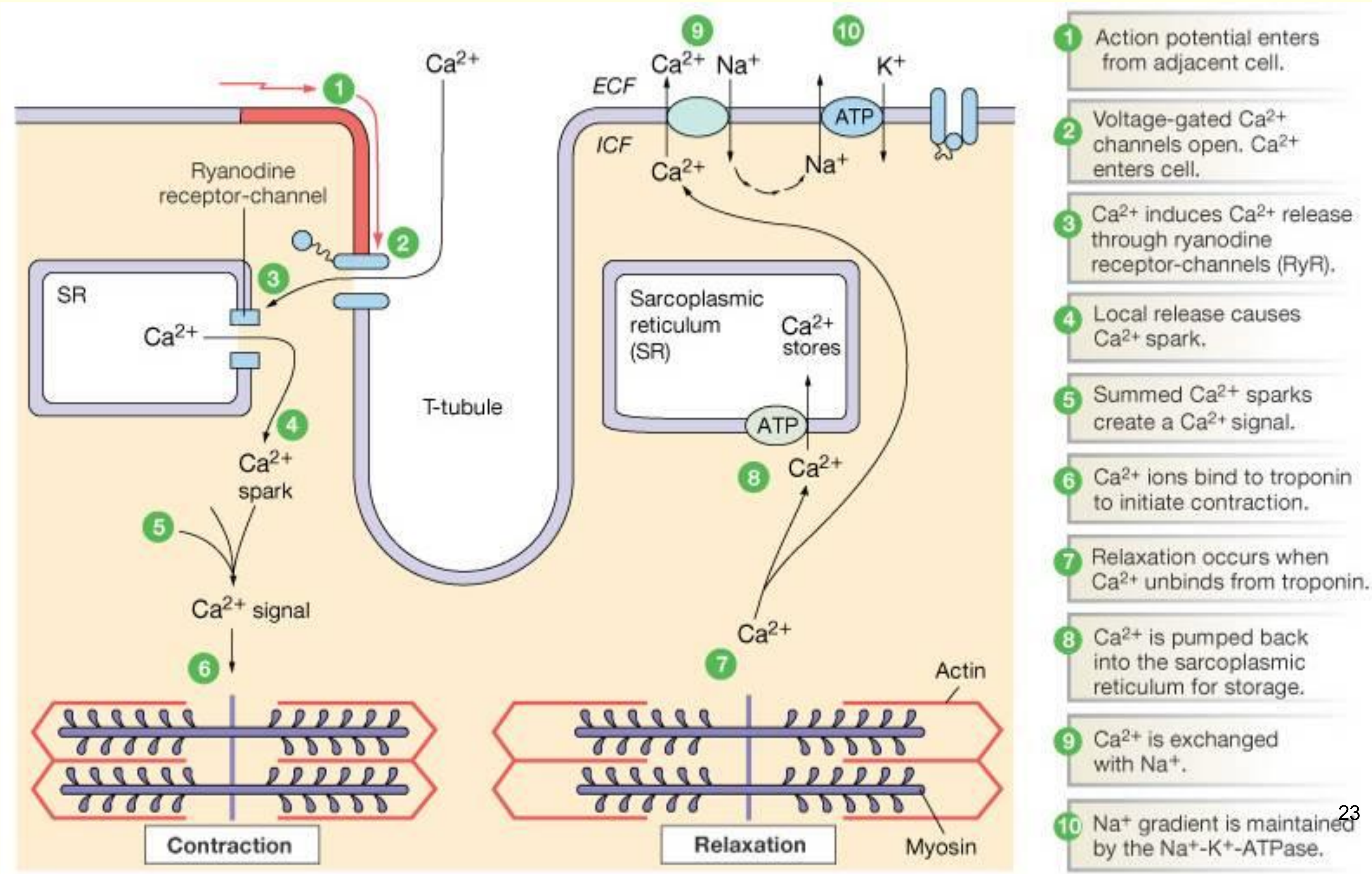




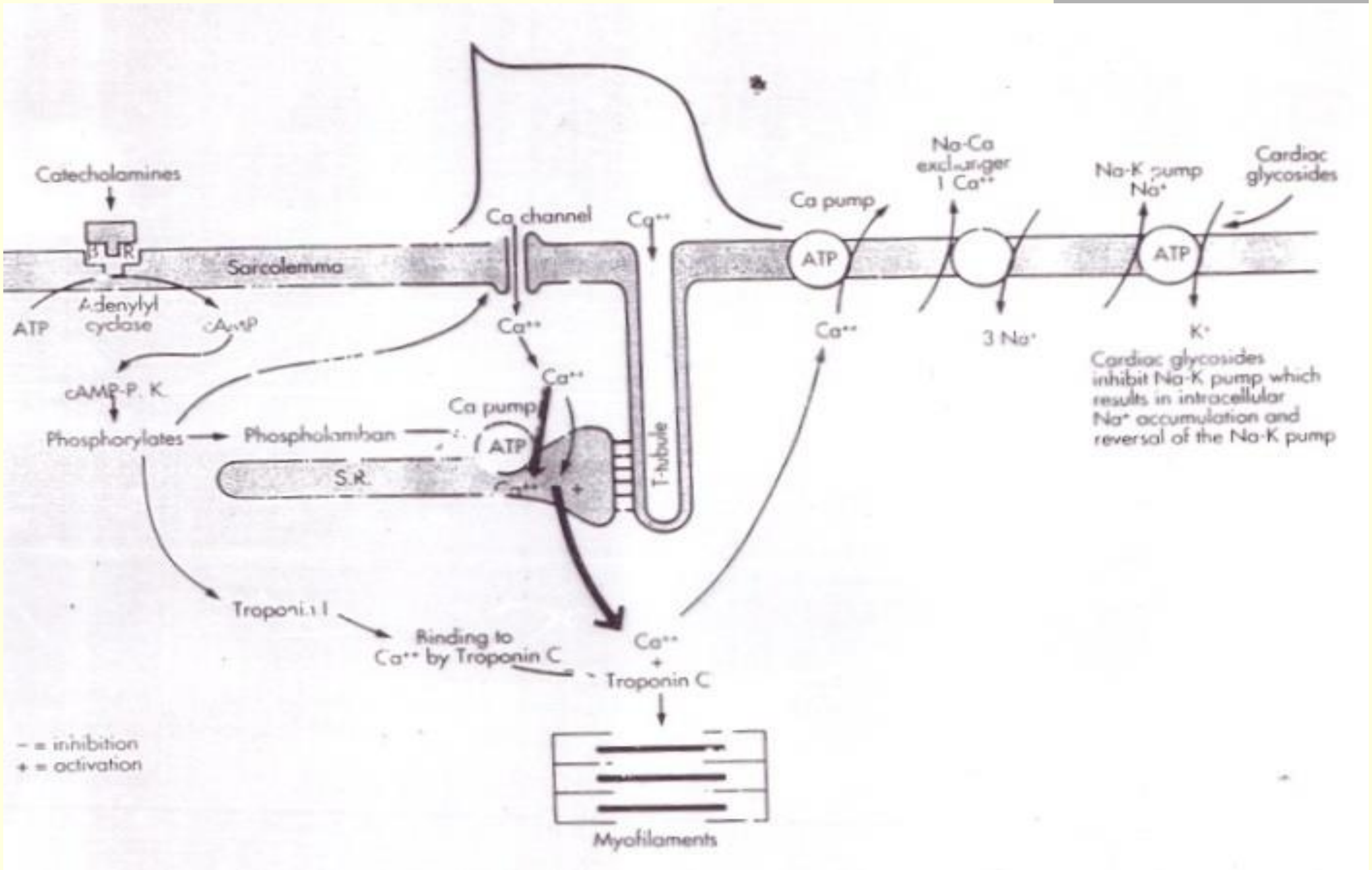
Phase	Membrane channels
⓪	Na^+ channels open
①	Na^+ channels close
②	Ca^{2+} channels open; fast K^+ channels close
③	Ca^{2+} channels close; slow K^+ channels open
④	Resting potential


Ca2+
1 Action potential enters from adjacent cell.
2 Voltage-gated Ca2+ channels open. Ca2+ enters cell.
3 Entry of Ca2+ triggers release of Ca2+ from sarcoplasmic reticulum
Ca2+
4 Most Ca2+ comes from the SR
5 Ca2+ ions bind to troponin to initiate contraction
T-tubule
ECF
ICF
8 Ca2+ is exchanged with Na+.
9 Na+ gradient is maintained by the Na+–K+–ATPase
Na+
K+
ATP
Na+
Ca2+
Sarcoplasmic reticulum (SR)
Ca2+ stores
ATP
7 Ca2+ is pumped back into the sarcoplasmic reticulum for storage.
Ca2+
6 Relaxation occurs when Ca2+ unbinds from troponin.
Actin
Myosin
Contraction
Relaxation

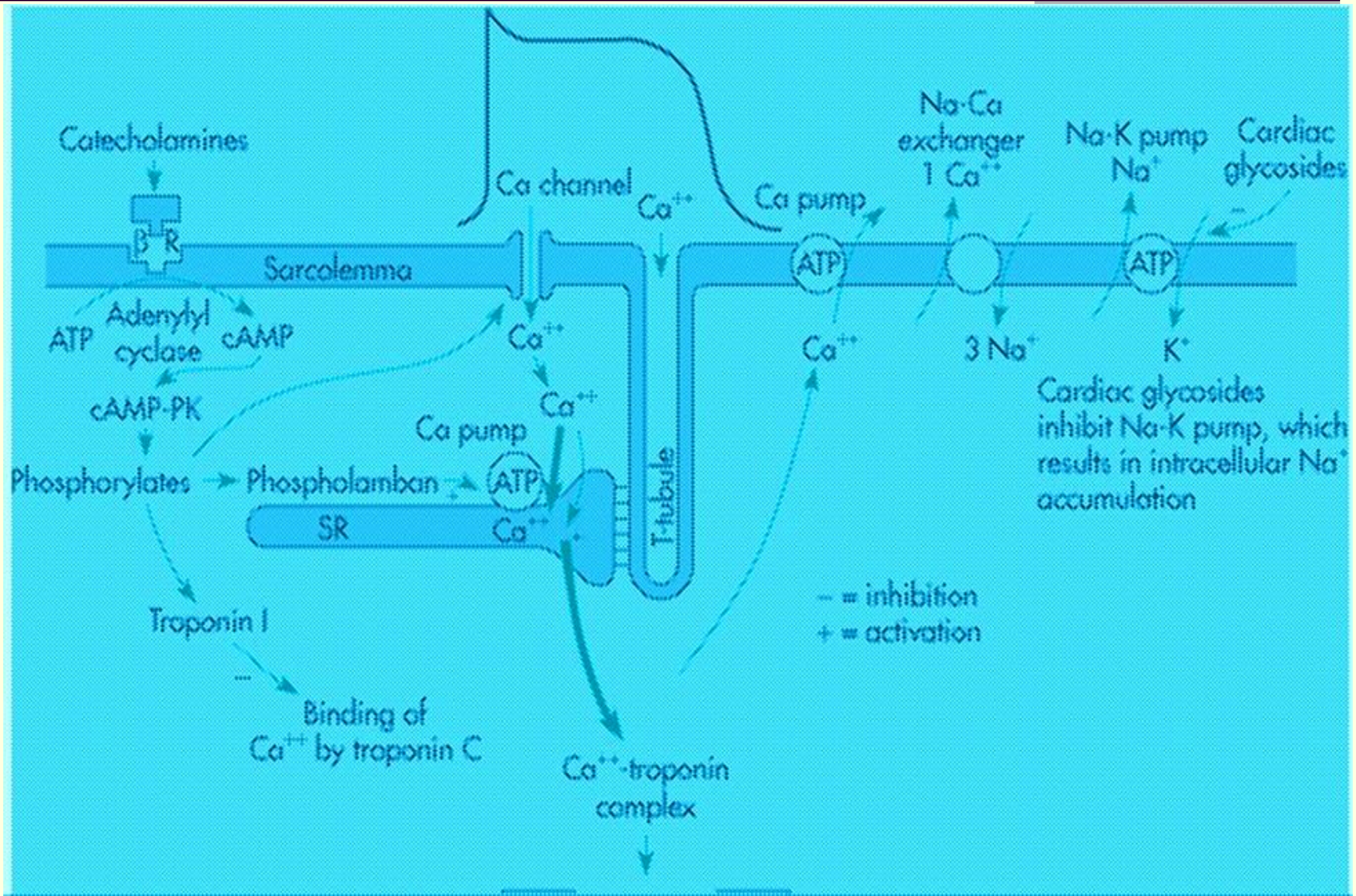
Mechanism of Cardiac Muscle Excitation, Contraction & Relaxation

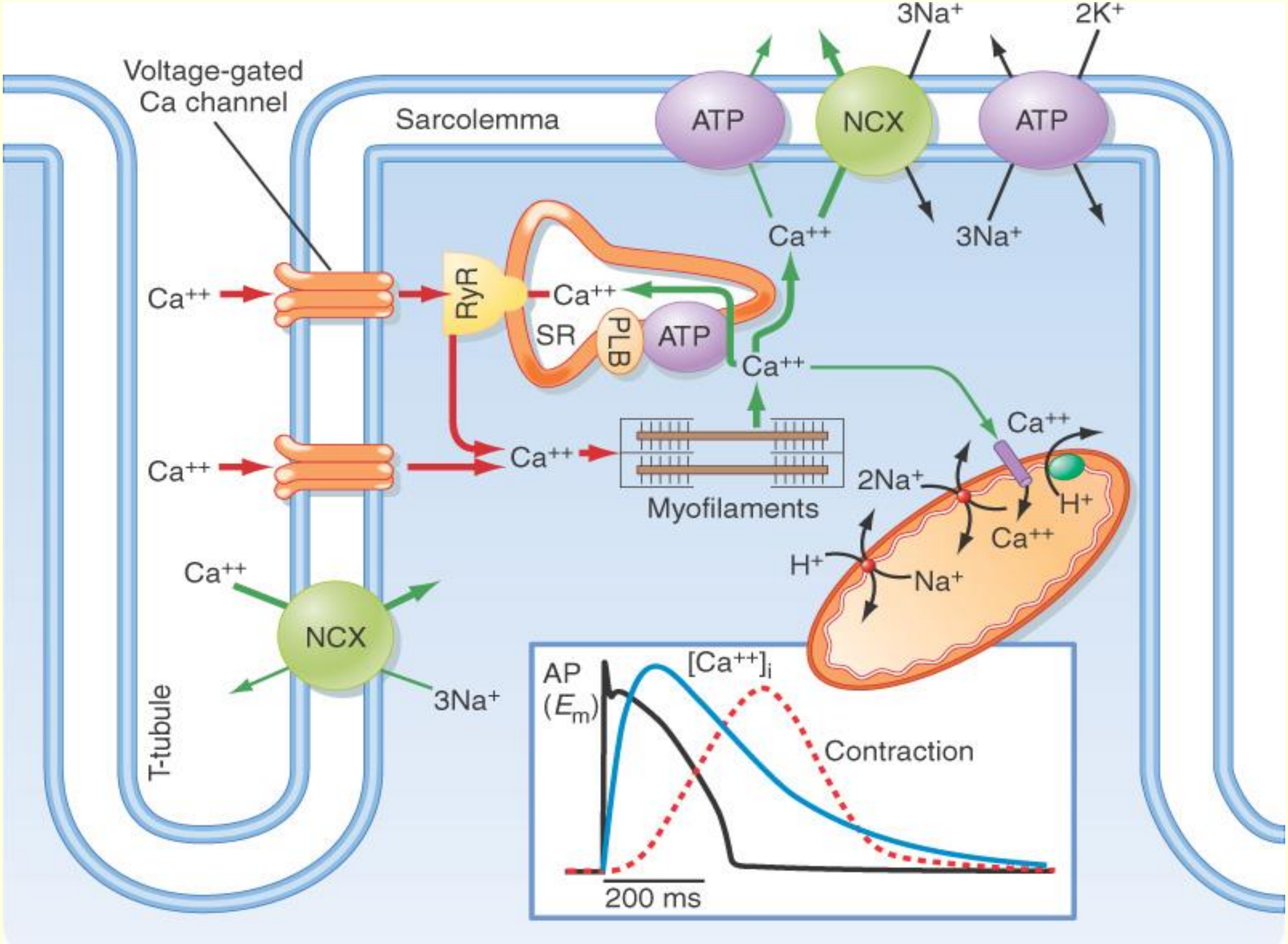


Intracellular Calcium Homeostasis…1



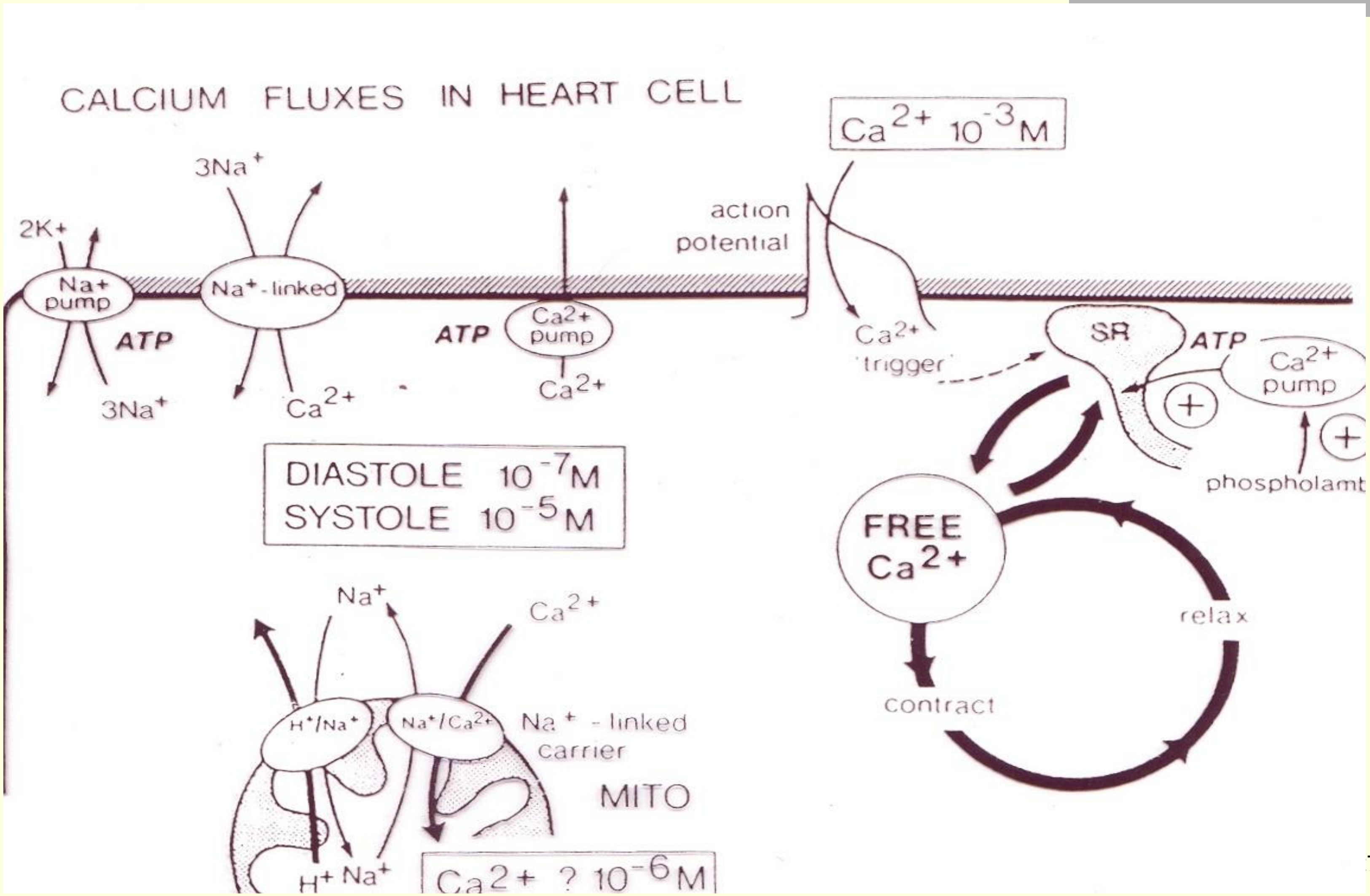
Intracellular Calcium Homeostasis…1



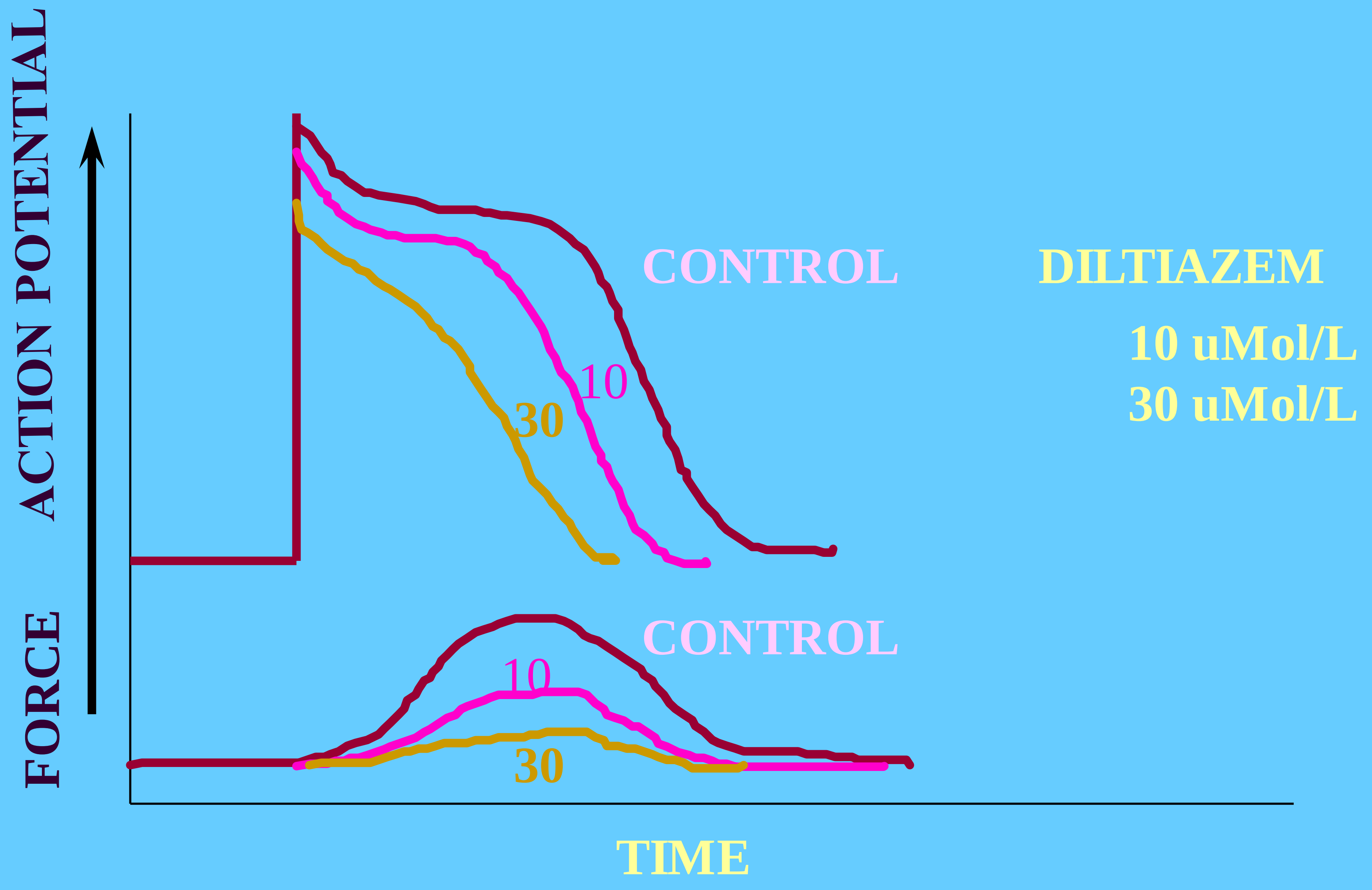


(Redrawn from Bers DM: Nature 415:198-205, 2002.)

Intracellular Calcium Homeostasis…2

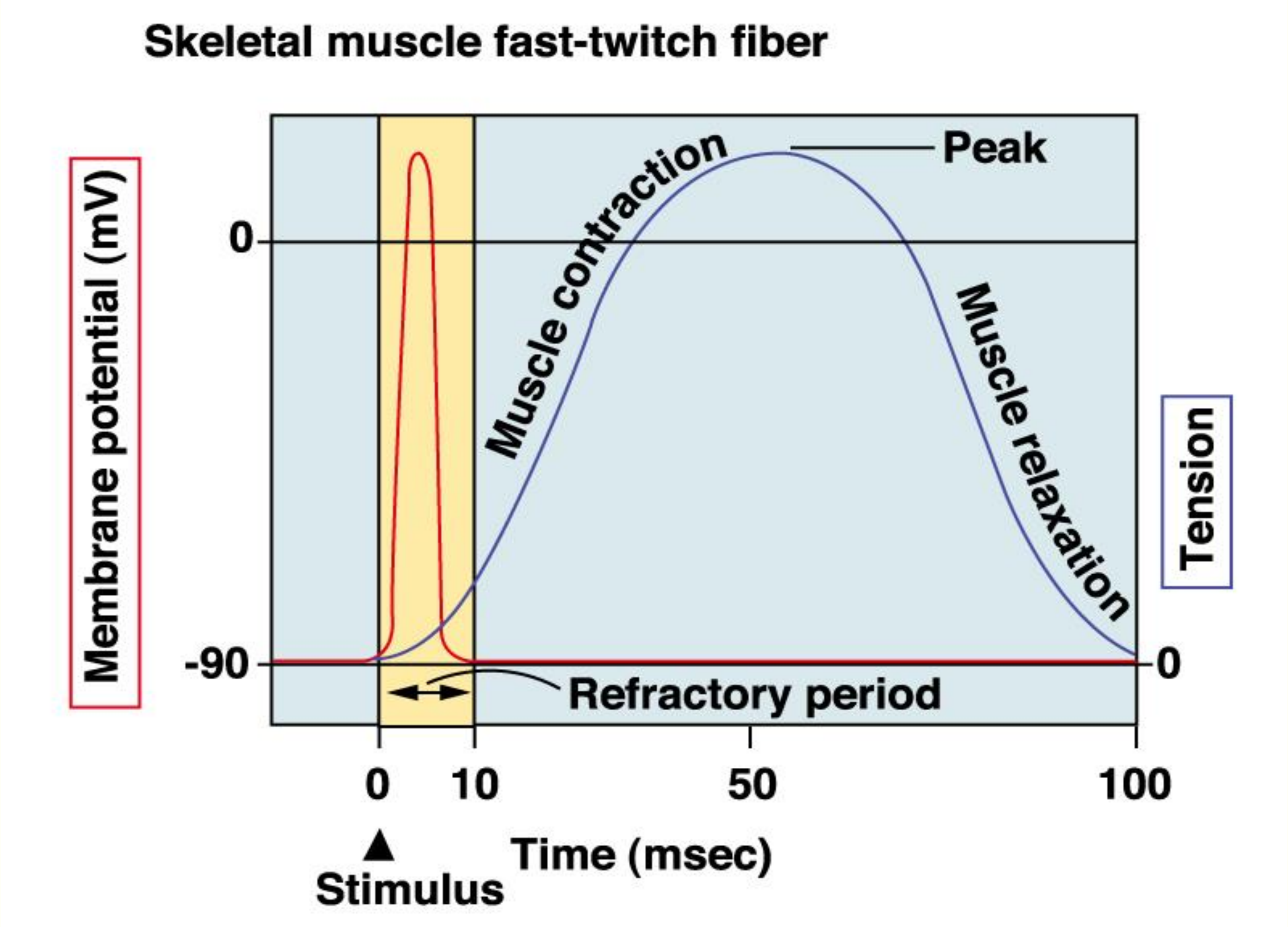


EFFECTS OF Ca++ CHANNEL BLOCKERS AND THE CARDIAC CELL ACTION POTENTIAL

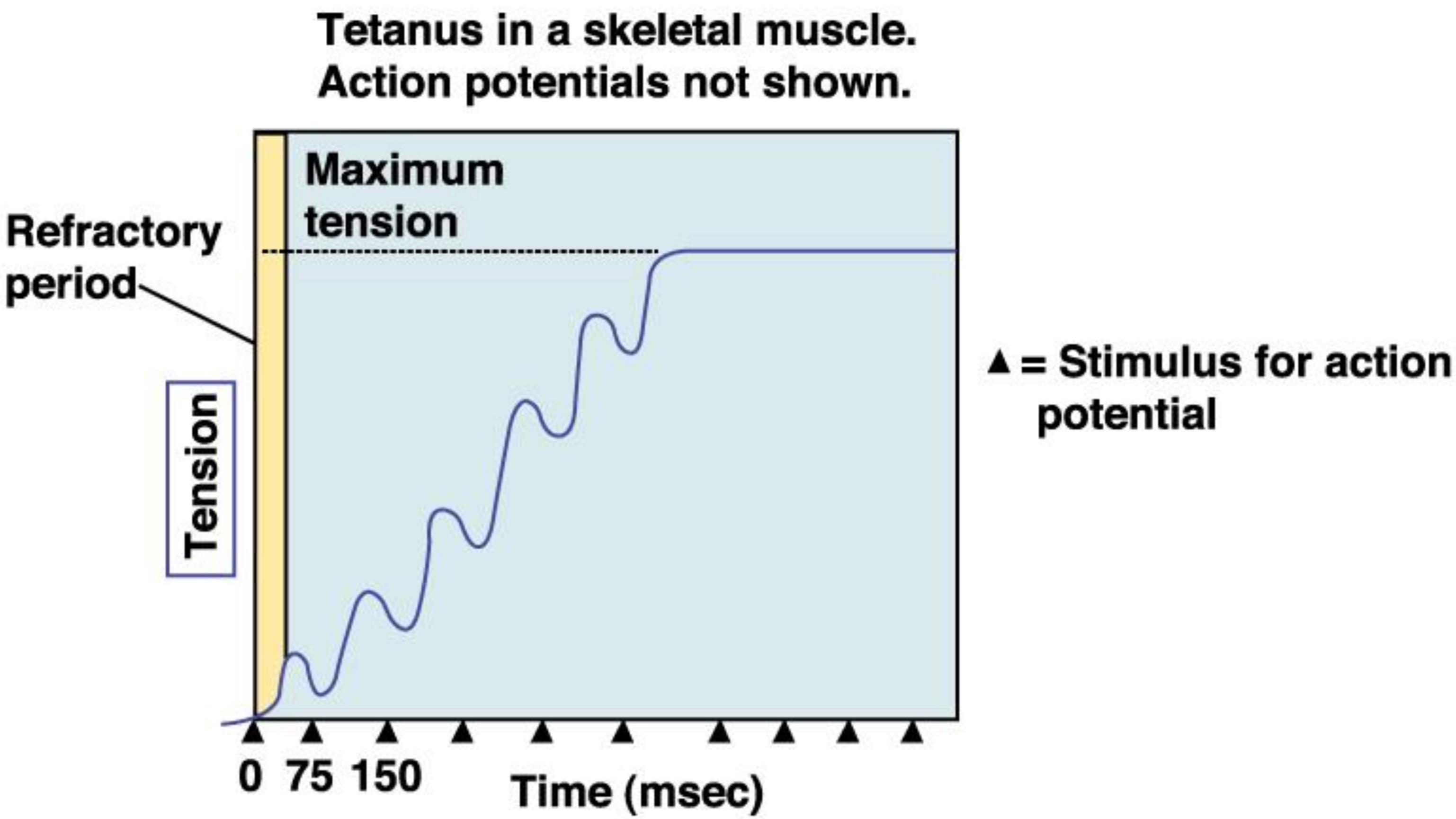


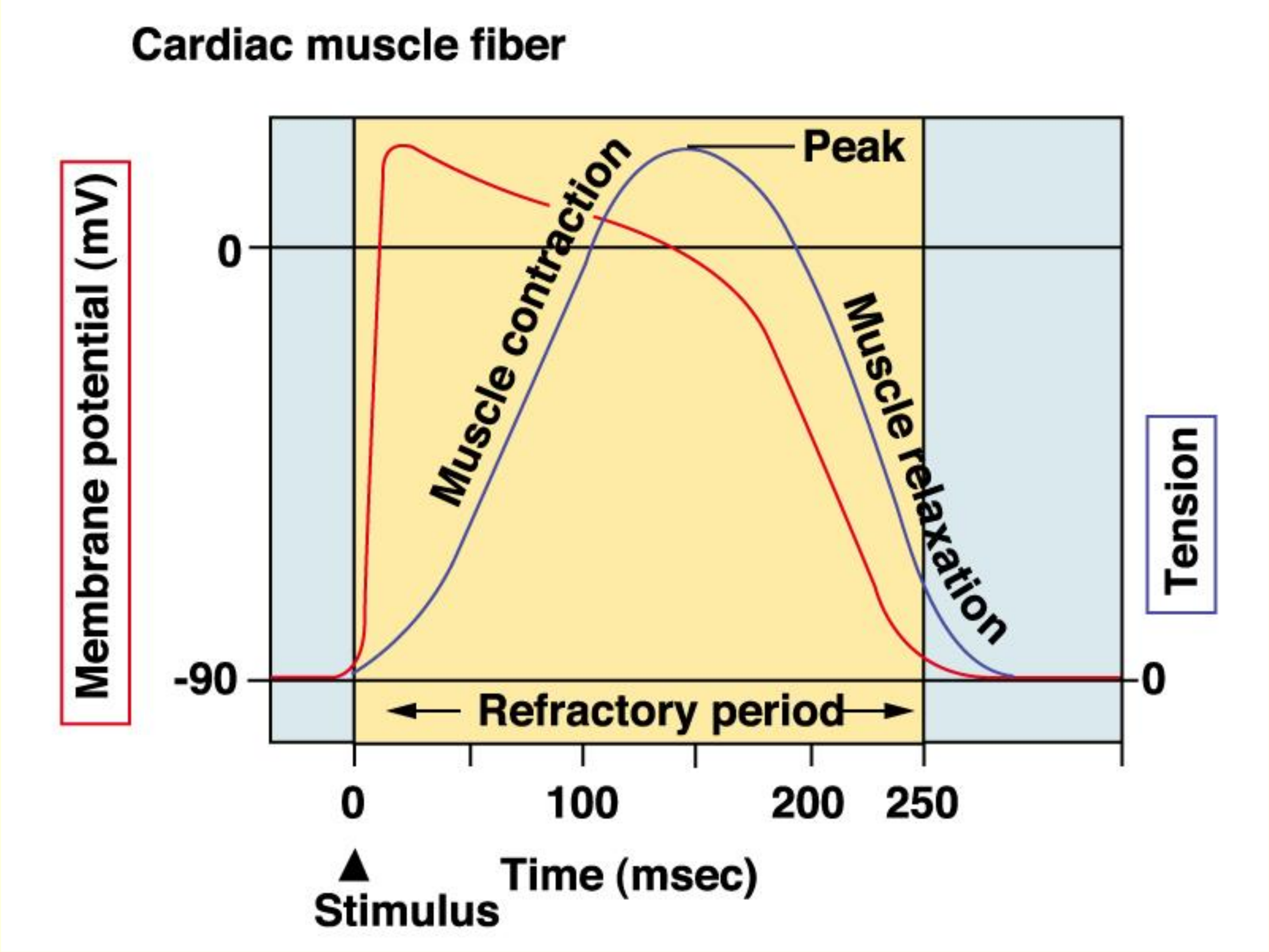
Cardiac Muscle action potential Vs. Skeletal Muscle

- Phase 0 –Depolarization phase (Na^+ influx)
- Phase 1 partial repolarization (Not in skeletal)
- Phase 2 Plateau (depolarization not in skeletal) slow calcium channels
- Phase 3 fast repolarization phase (K^+ efflux
- Phase 4 resting membrane potential

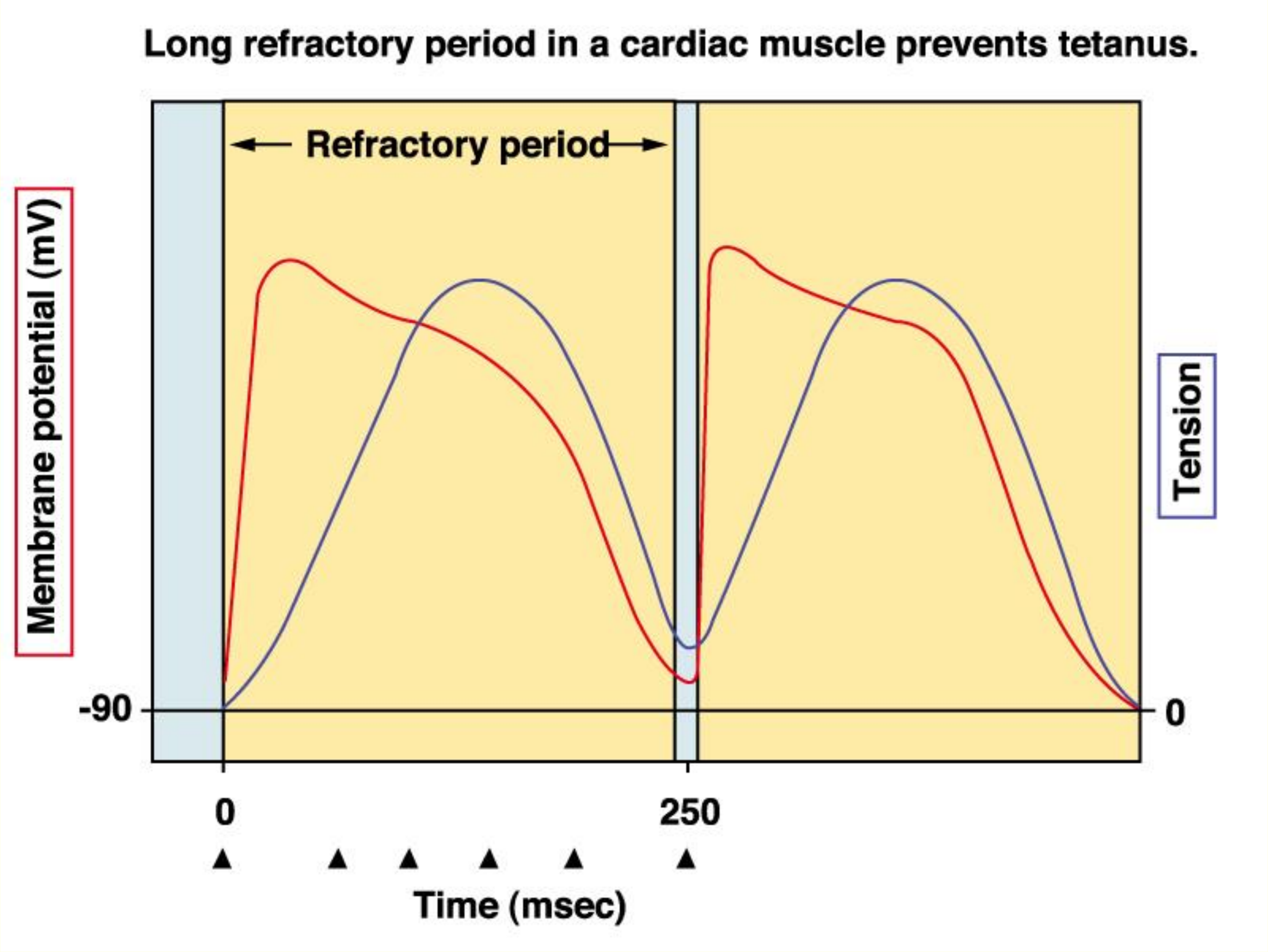


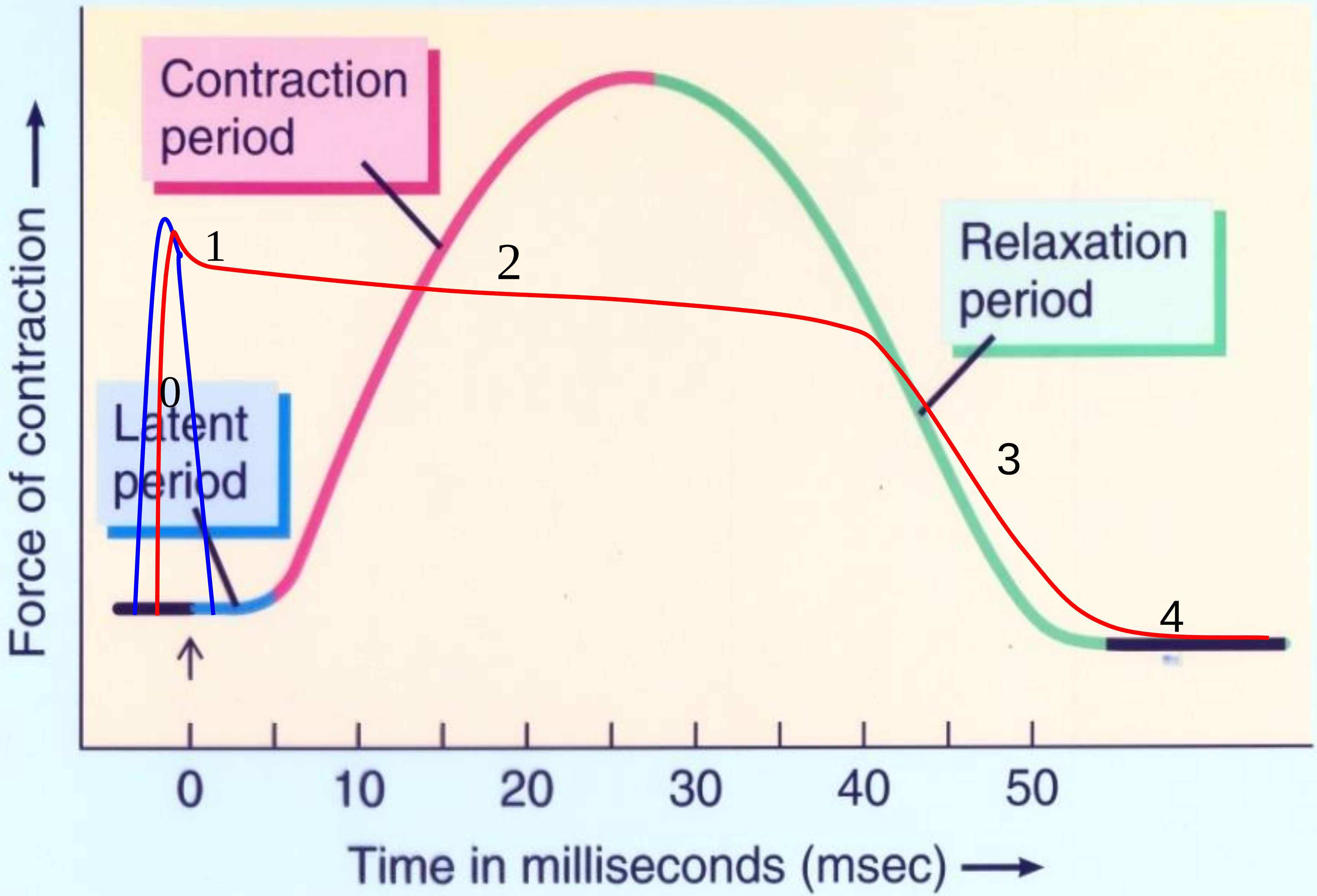
Skeletal muscle fast-twitch fiber
Peak
Muscle contraction
Muscle relaxation
Membrane potential (mV)
Tension
0
-90
0
Refractory period
0
10
50
100
Stimulus
Time (msec)


Tetanus in a skeletal muscle.
Action potentials not shown.
Maximum
tension
Refractory
period
Tension
0 75 150
Time (msec)
▲ = Stimulus for action
potential

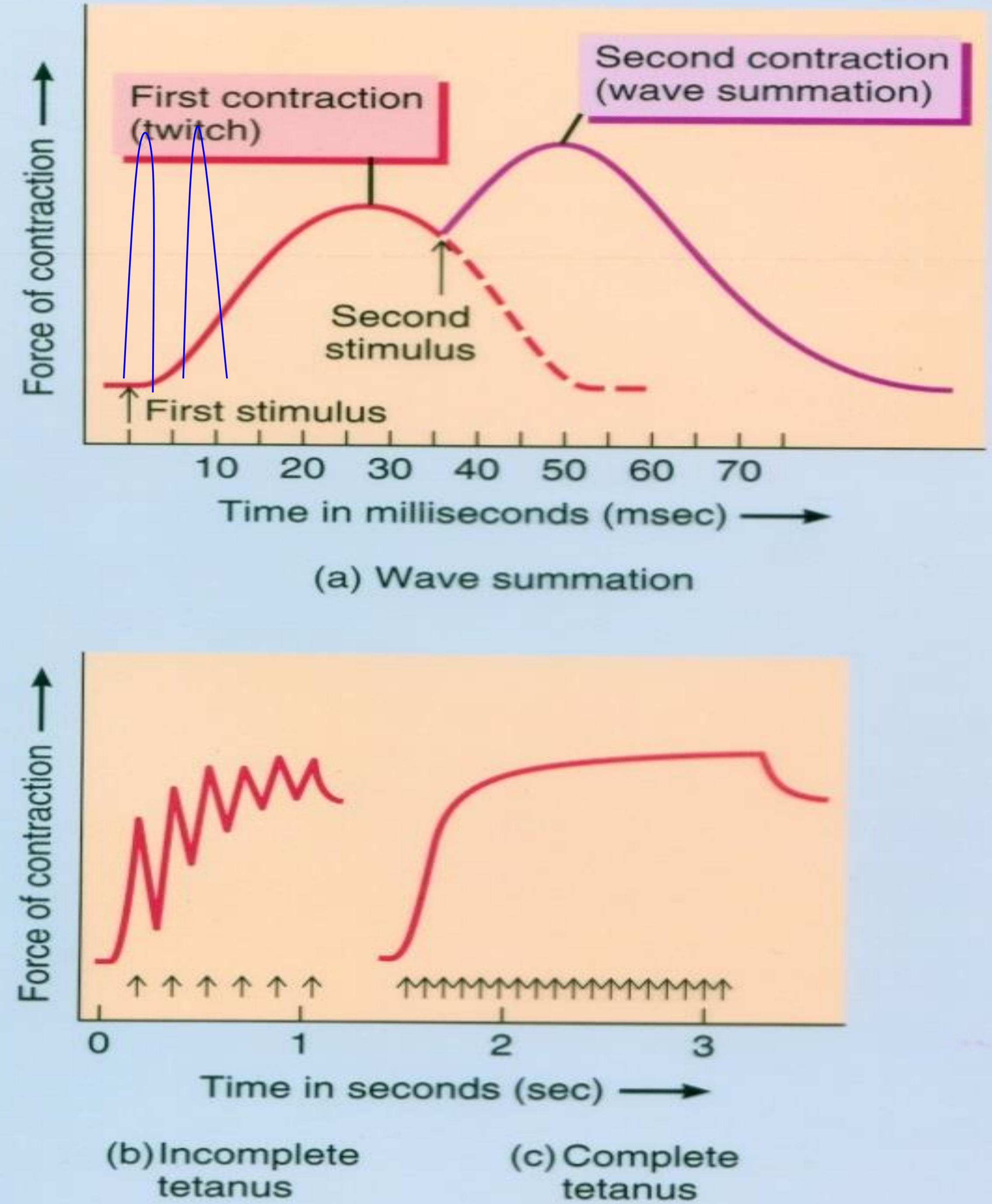


Cardiac muscle fiber
Membrane potential (mV)
0
-90
Peak
Muscle contraction
Muscle relaxation
Tension
0
Refractory period
0
100
200
250
Time (msec)
Stimulus

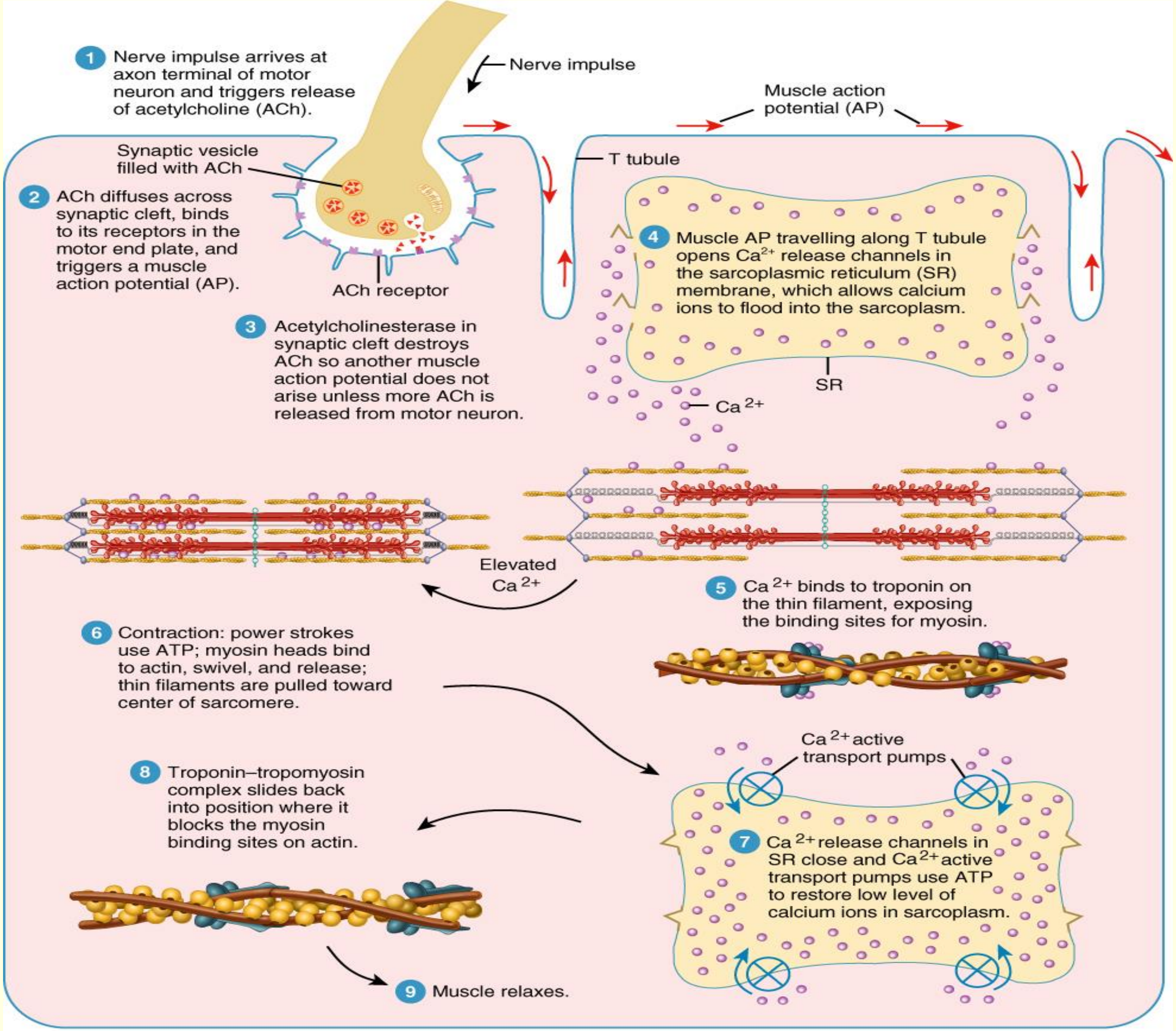

Long refractory period in a cardiac muscle prevents tetanus.
Refractory period
Membrane potential (mV)
Tension
-90
0
0
250
Time (msec)



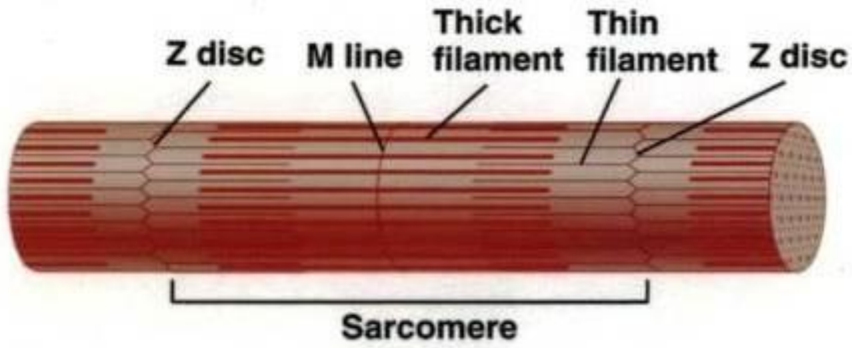
Contraction period
Relaxation period
Latent period
1
2
0
3
4
Force of contraction
0
10
20
30
40
50
Time in milliseconds (msec)



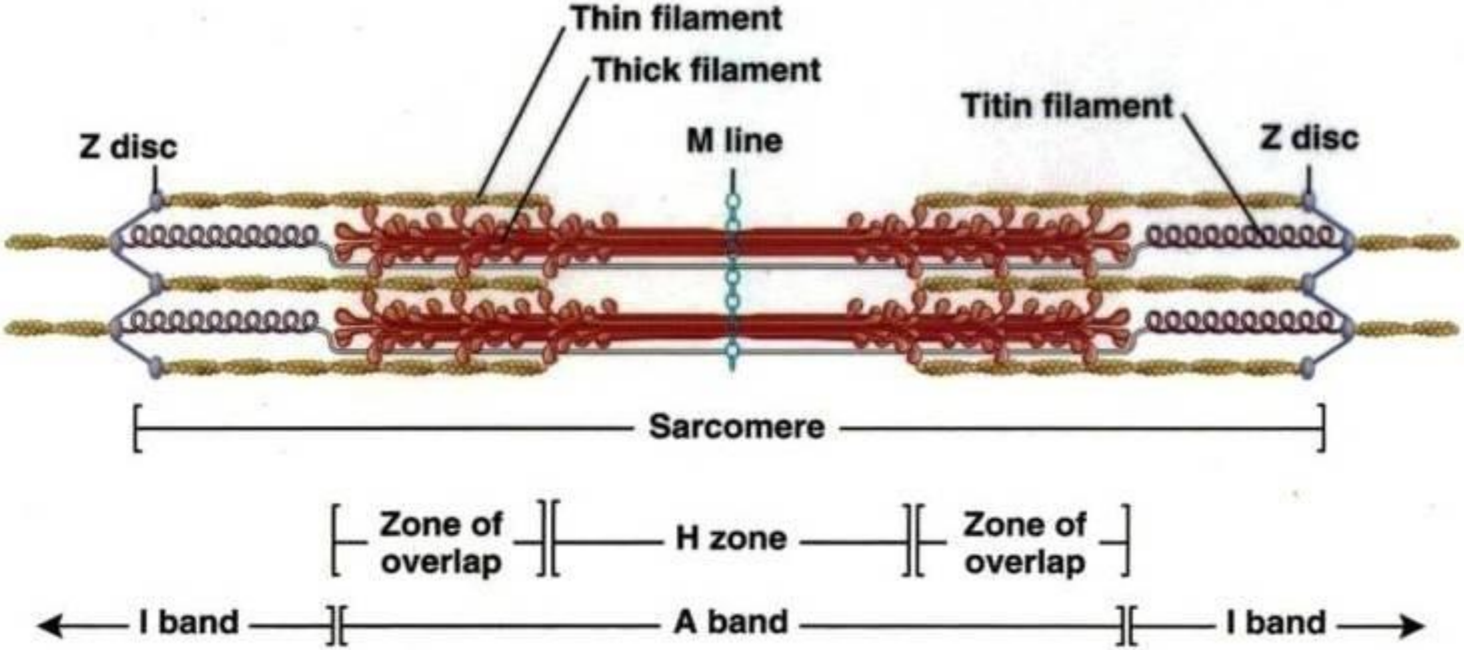
First contraction (twitch)
Second contraction (wave summation)
Second stimulus
First stimulus
Force of contraction
10 20 30 40 50 60 70
Time in milliseconds (msec)
(a) Wave summation
Force of contraction
0 1 2 3
Time in seconds (sec)
(b) Incomplete tetanus
(c) Complete tetanus


1 Nerve impulse arrives at axon terminal of motor neuron and triggers release of acetylcholine (ACh).
Nerve impulse
Muscle action potential (AP)
Synaptic vesicle filled with ACh
T tubule
2 ACh diffuses across synaptic cleft, binds to its receptors in the motor end plate, and triggers a muscle action potential (AP).
ACh receptor
4 Muscle AP travelling along T tubule opens Ca^{2+} release channels in the sarcoplasmic reticulum (SR) membrane, which allows calcium ions to flood into the sarcoplasm.
3 Acetylcholinesterase in synaptic cleft destroys ACh so another muscle action potential does not arise unless more ACh is released from motor neuron.
SR
Ca^{2+}
Elevated Ca^{2+}
5 Ca^{2+} binds to troponin on the thin filament, exposing the binding sites for myosin.
6 Contraction: power strokes use ATP; myosin heads bind to actin, swivel, and release; thin filaments are pulled toward center of sarcomere.
Ca^{2+} active transport pumps
8 Troponin–tropomyosin complex slides back into position where it blocks the myosin binding sites on actin.
7 Ca^{2+} release channels in SR close and Ca^{2+} active transport pumps use ATP to restore low level of calcium ions in sarcoplasm.
9 Muscle relaxes.

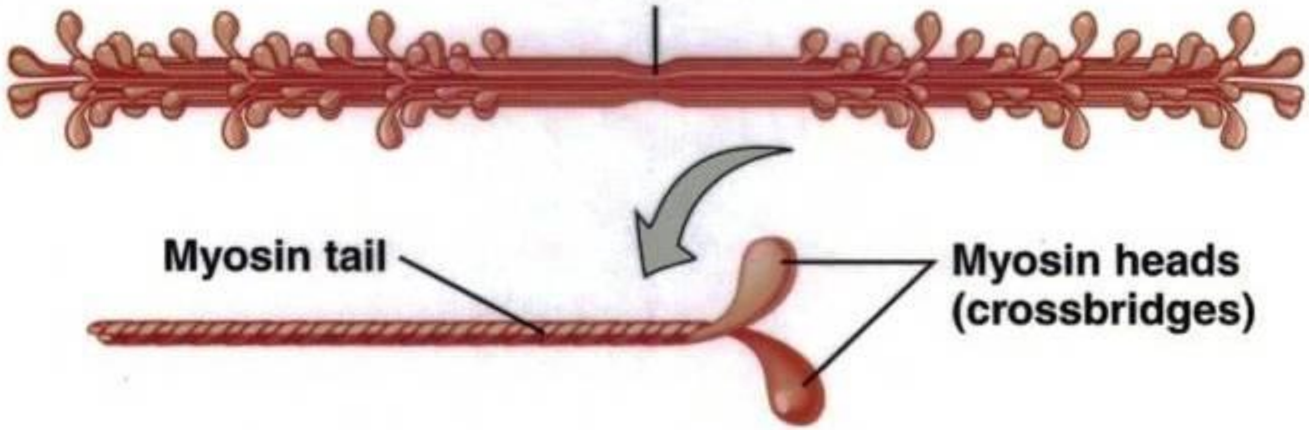
10.12



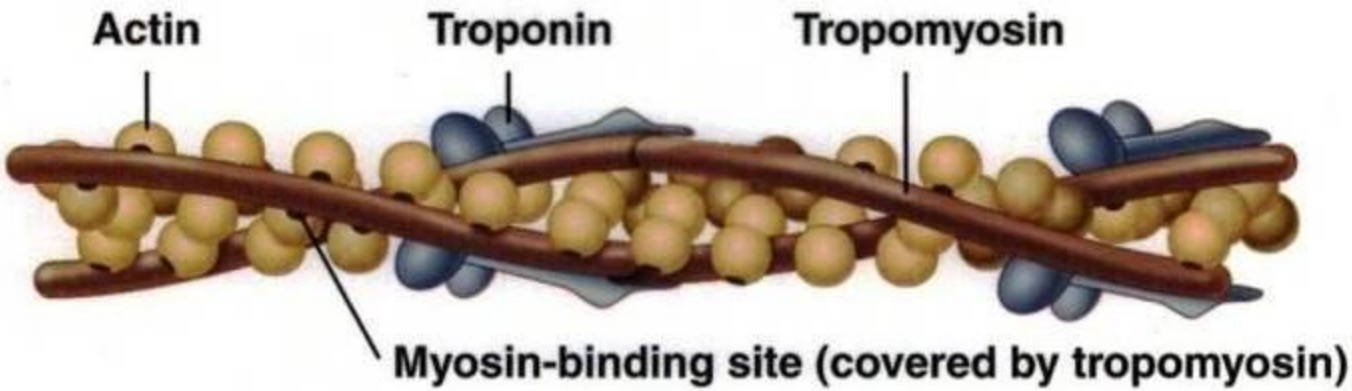
(a) Myofibril



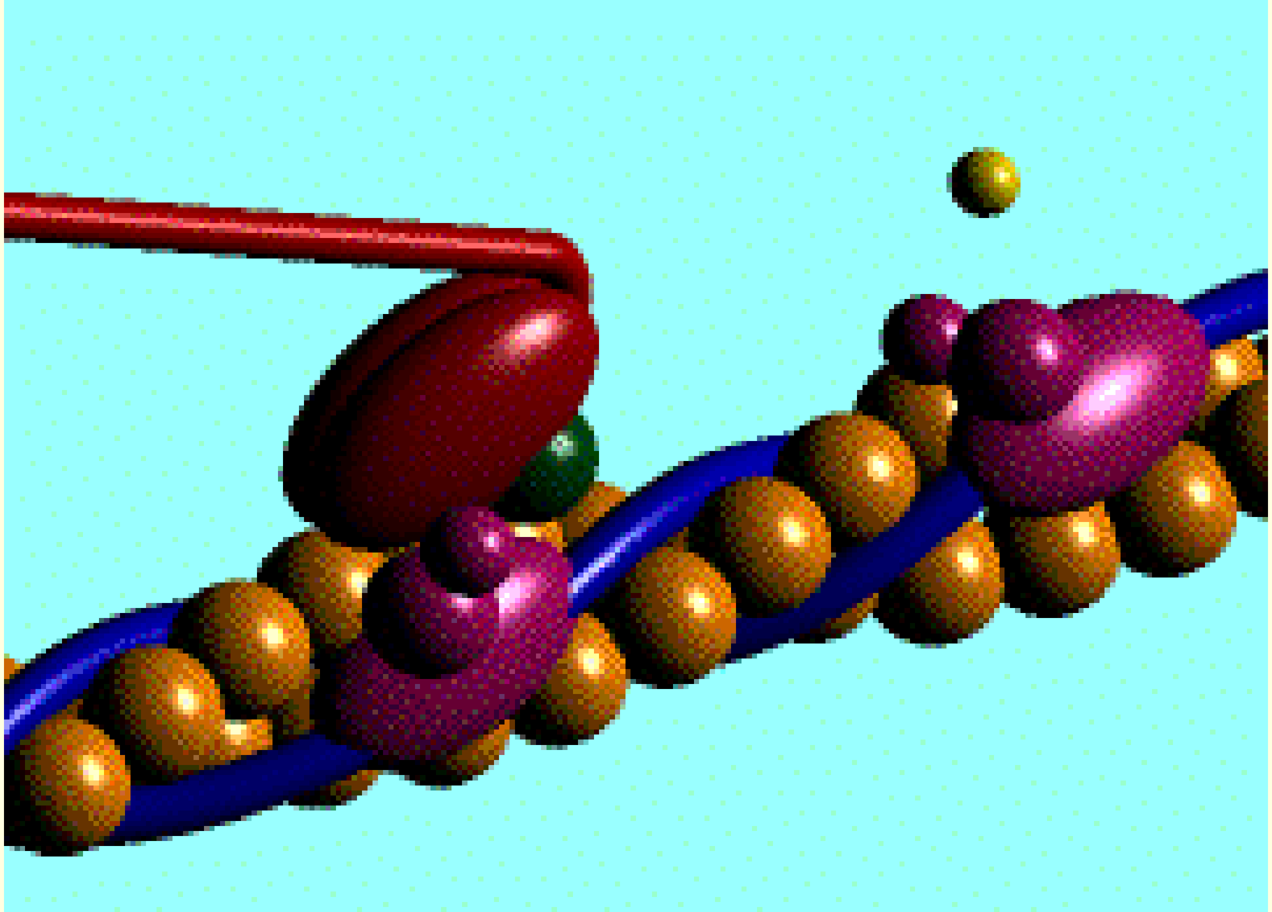
(b) Filaments

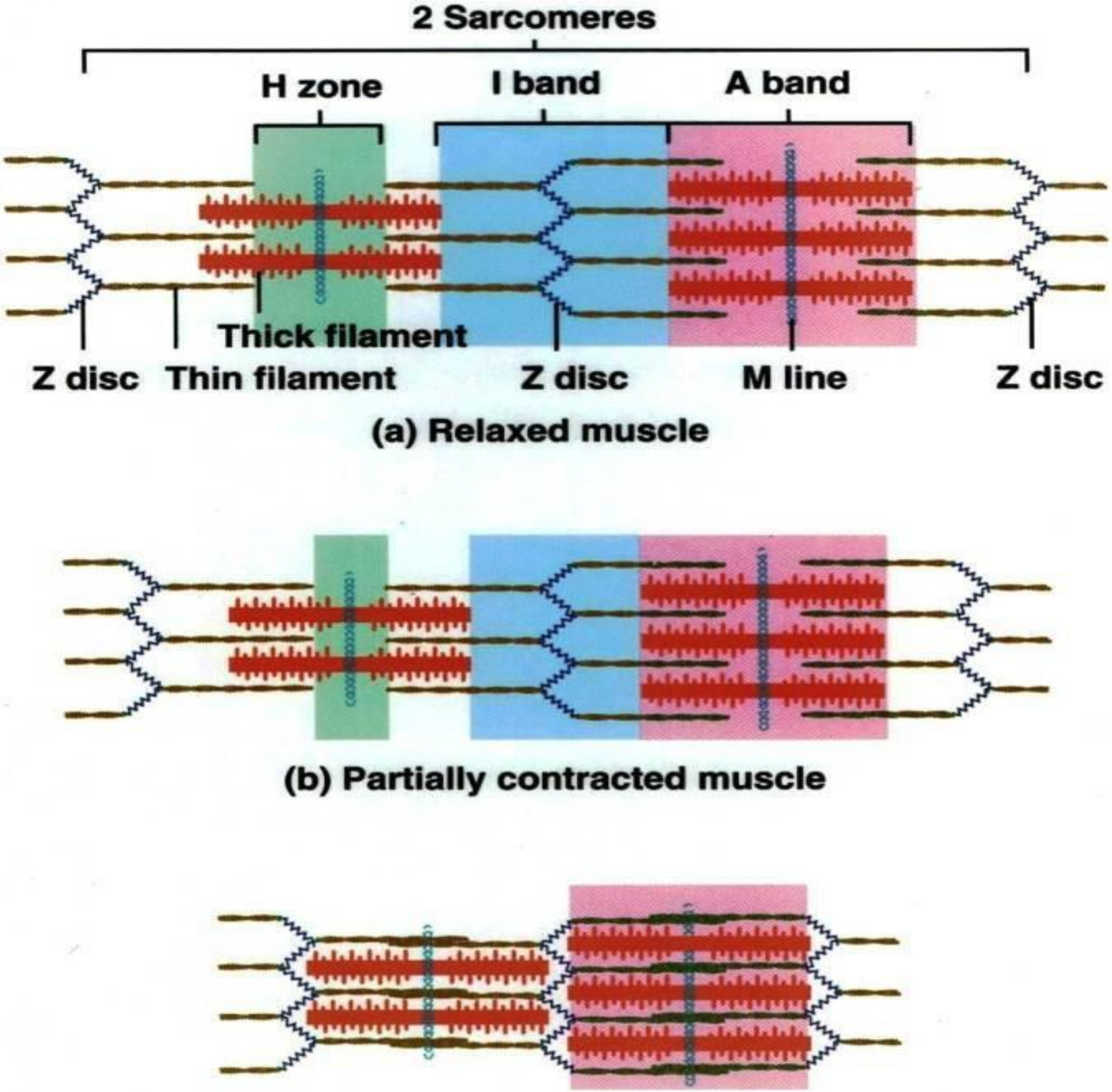


(a) One thick filament (above) and a myosin molecule (below)



(b) Portion of a thin filament

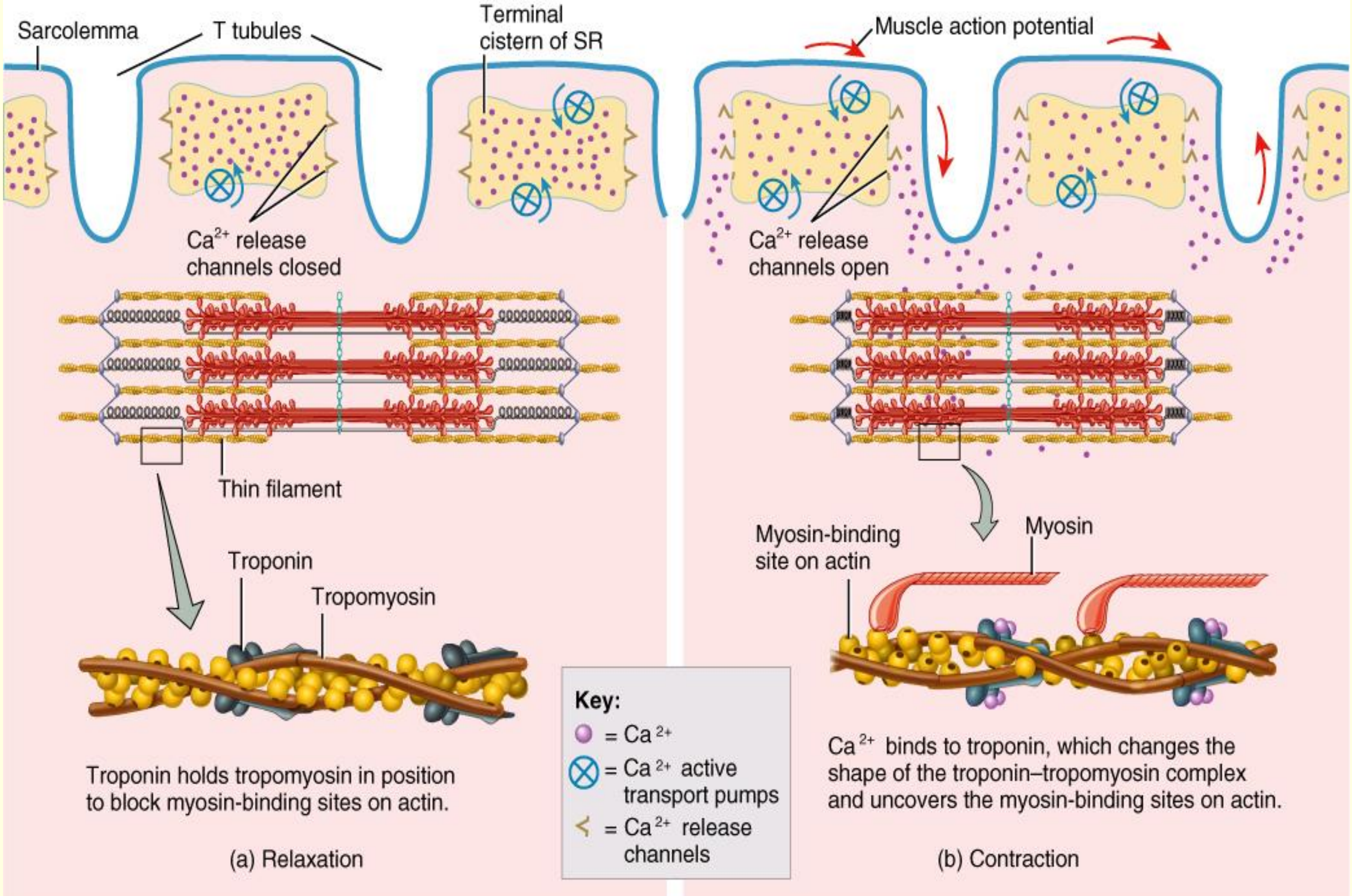




(a) Relaxed muscle

(b) Partially contracted muscle

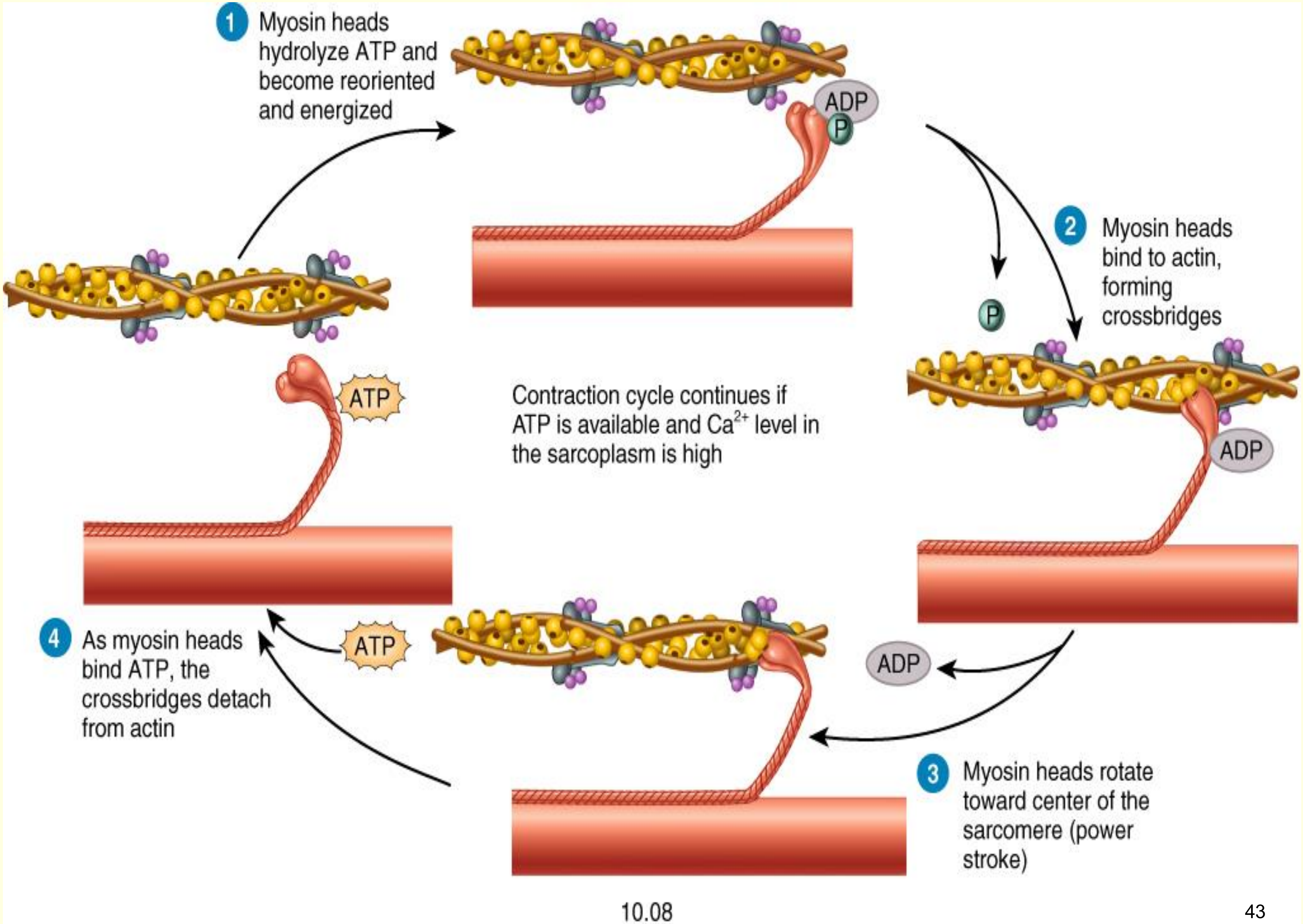
(c) Maximally contracted muscle

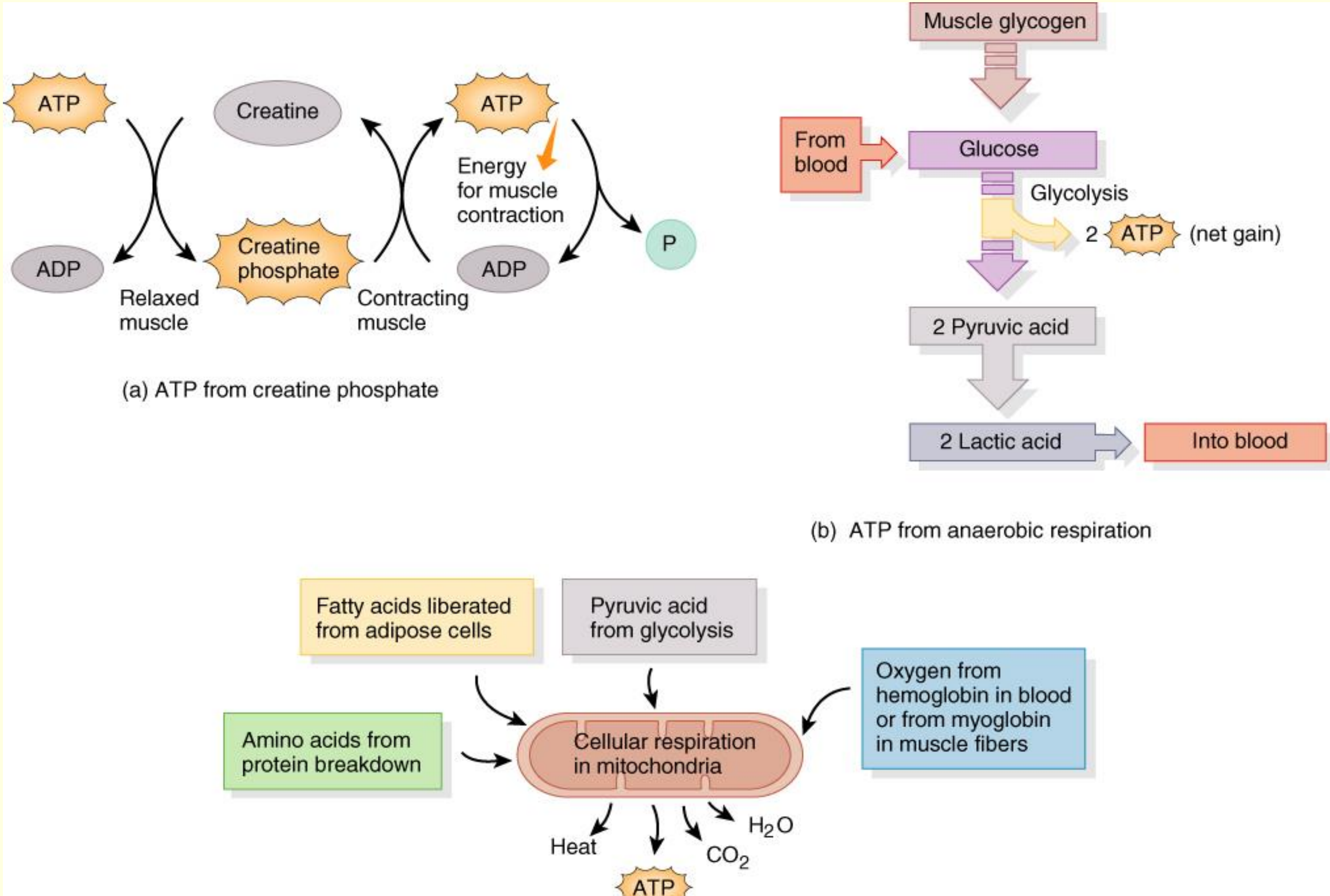

Sarcolemma
T tubules
Terminal cistern of SR
Muscle action potential
Ca2+ release channels closed
Ca2+ release channels open
Thin filament
Troponin
Tropomyosin
Myosin-binding site on actin
Myosin
Troponin holds tropomyosin in position to block myosin-binding sites on actin.
(a) Relaxation
Key:
= Ca 2+
= Ca 2+ active transport pumps
= Ca 2+ release channels
Ca 2+ binds to troponin, which changes the shape of the troponin–tropomyosin complex and uncovers the myosin-binding sites on actin.
(b) Contraction

10.09

Cardiac Muscle contraction Vs. Skeletal Muscle

- Sliding filament hypothesis
- No tetany (Long refractory period because of plateau)
- Fatty acids main source of energy unlike skeletal muscle (Anaerobic and Aerobic)
- Attachment and detachment cycle and ATP dependence is the same


1 Myosin heads hydrolyze ATP and become reoriented and energized
ADP
P
2 Myosin heads bind to actin, forming crossbridges
P
ADP
Contraction cycle continues if ATP is available and Ca2+ level in the sarcoplasm is high
ATP
ADP
3 Myosin heads rotate toward center of the sarcomere (power stroke)
ATP
4 As myosin heads bind ATP, the crossbridges detach from actin
10.08



(a) ATP from creatine phosphate

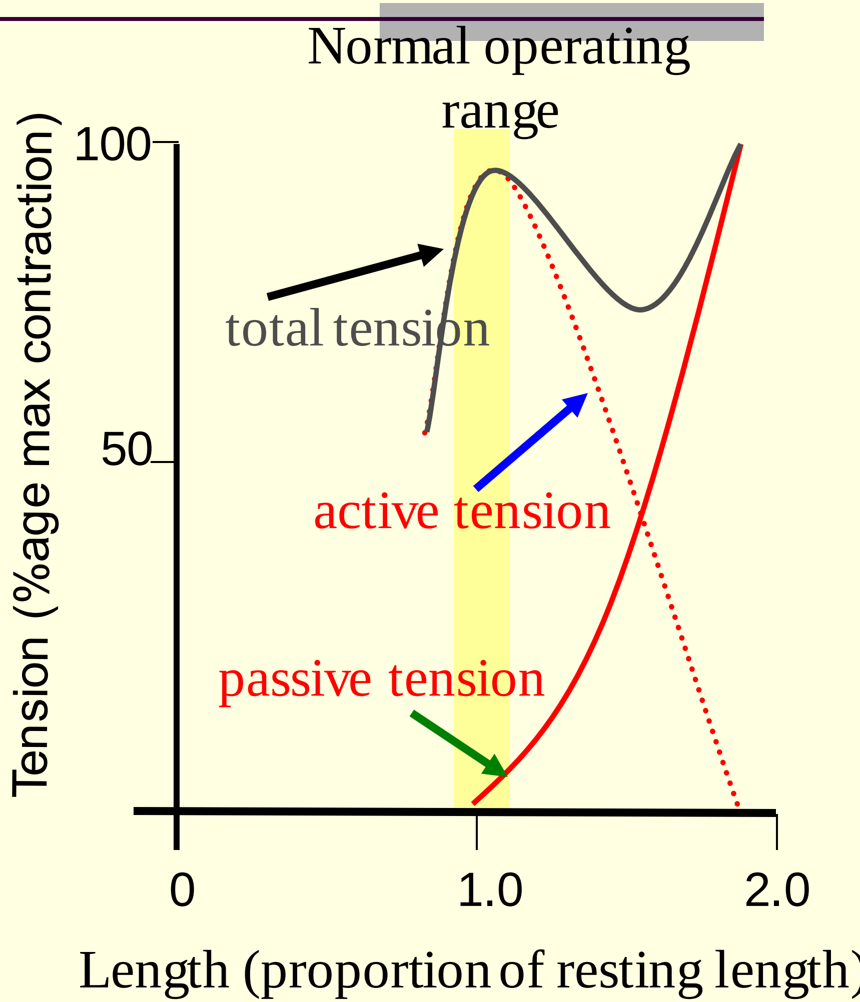
(b) ATP from anaerobic respiration

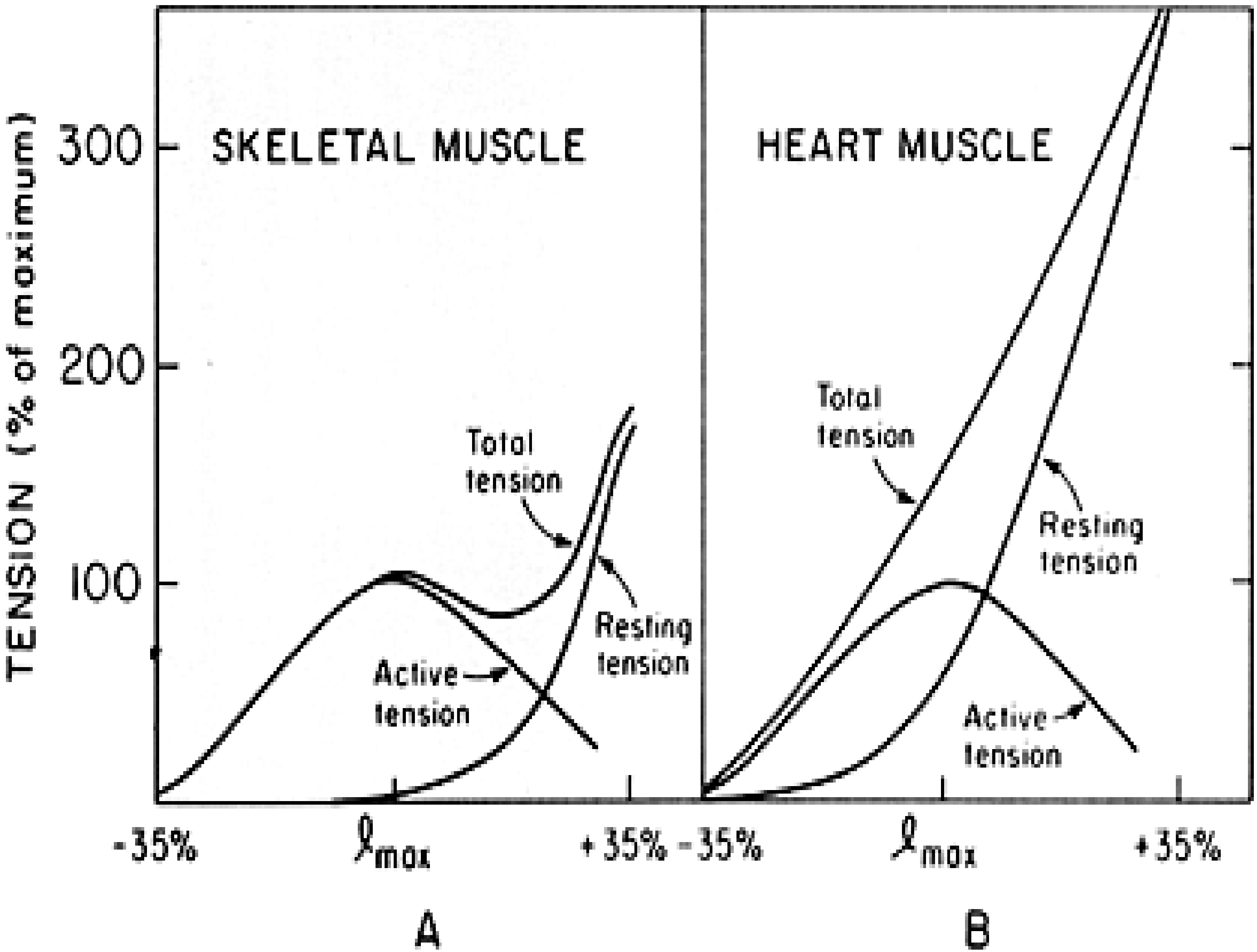
(c) ATP from aerobic cellular respiration

10.13

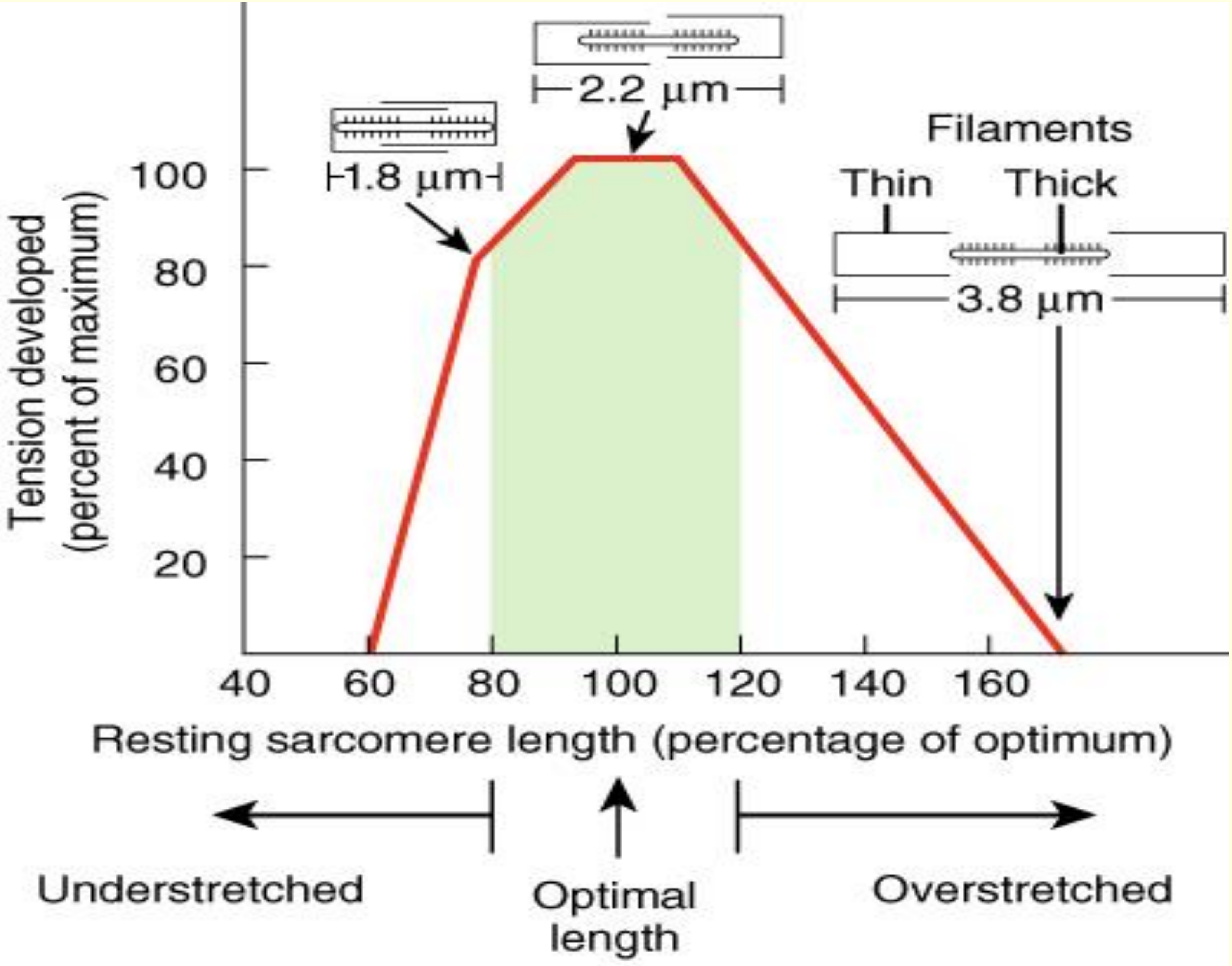
Length-Tension Relation for Skeletal Muscle

- Active tension cannot be measured directly
- What can be measured?
  - (1) passive tension - *tension required to extend a resting muscle*
  - (2) total tension - *active tension and passive combined*
- Active is calculated from 1 & 2
- (AT = TT – PT)
- Note that active tension falls away linearly with increasing length





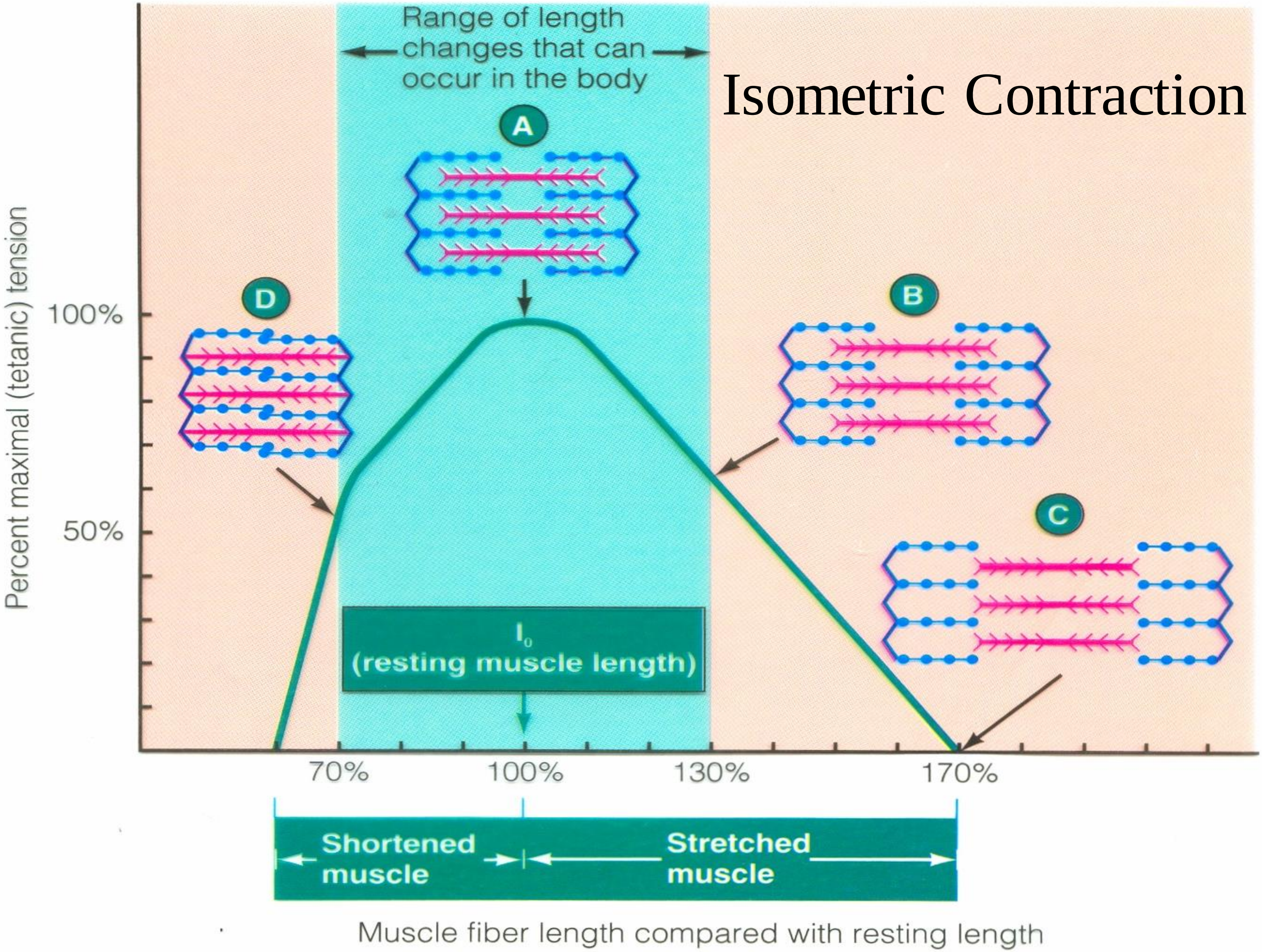
TENSION (% of maximum)
300
200
100
SKELETAL MUSCLE
HEART MUSCLE
Total tension
Resting tension
Active tension
Total tension
Resting tension
Active tension
-35%
l_{max}
+35%
-35%
l_{max}
+35%
A
B

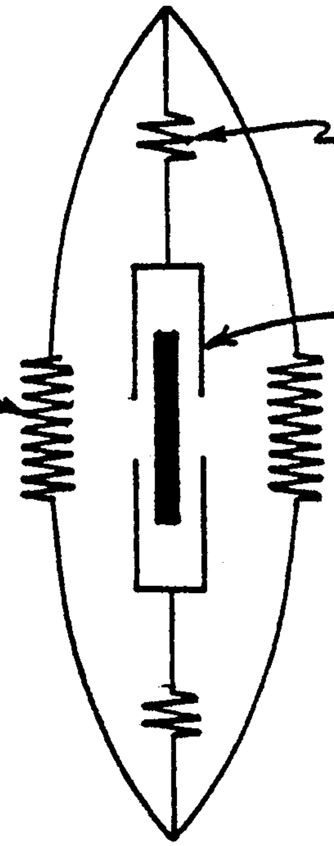


2.2 µm
1.8 µm
Filaments
Thin
Thick
3.8 µm
Tension developed
(percent of maximum)
100
80
60
40
20
40
60
80
100
120
140
160
Resting sarcomere length (percentage of optimum)
Understretched
Optimal
length
Overstretched

10.10

Isometric Contraction

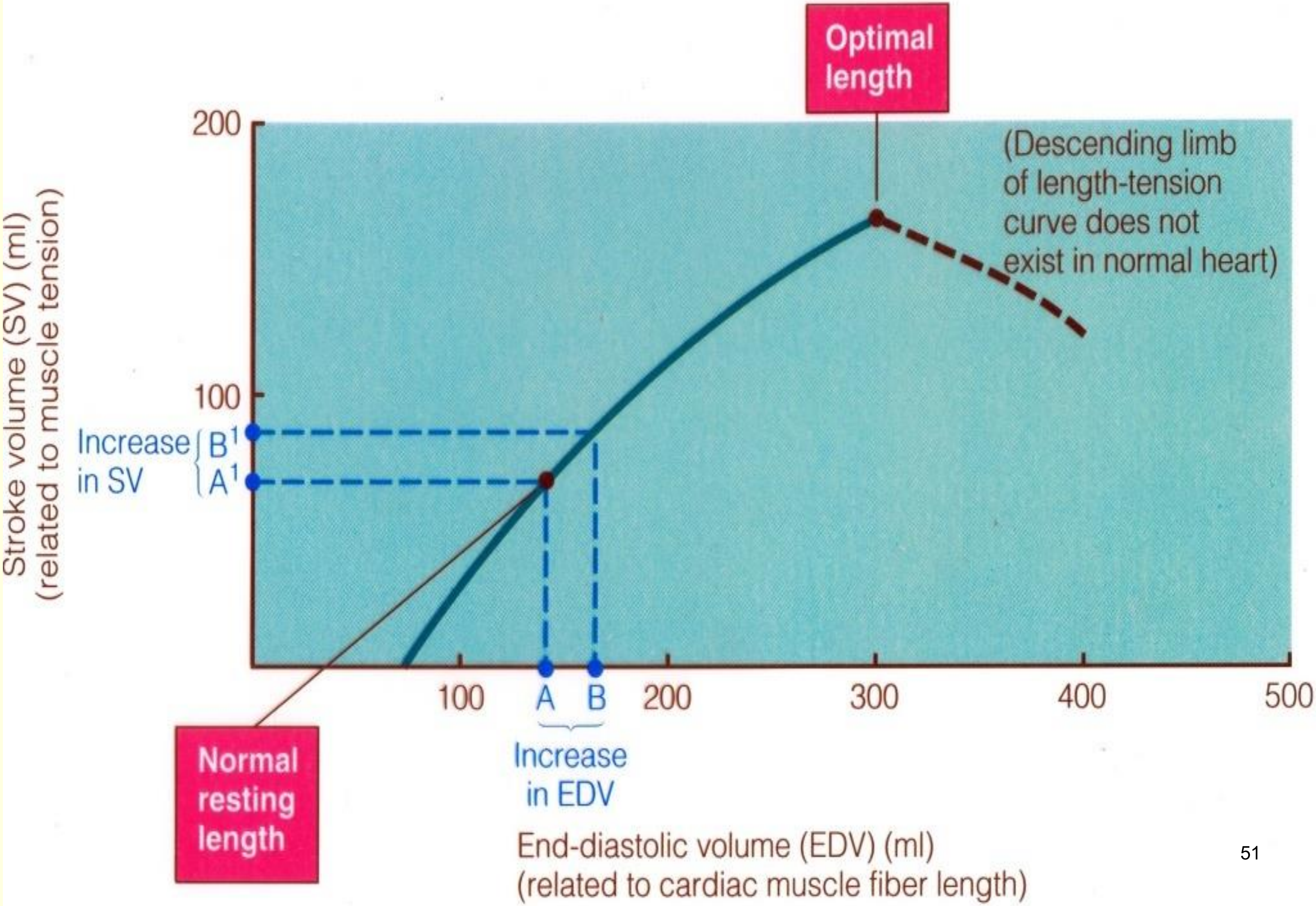



SERIES ELASTIC ELEMENTS
CONTRACTILE COMPONENT
(ACTIVE TENSION)
PARALLEL ELASTIC ELEMENTS
(PASSIVE TENSION)
TOTAL TENSION

Cardiac Muscle length-tension relationship

- Cardiac muscle works at much less than its maximum length in contrast to skeletal
- Total, Active and Passive length-tension relationship differ
- Frank-Starling law of the heart

Intrinsic Control of Stroke Volume (Frank-Starling Curve)



Thank You