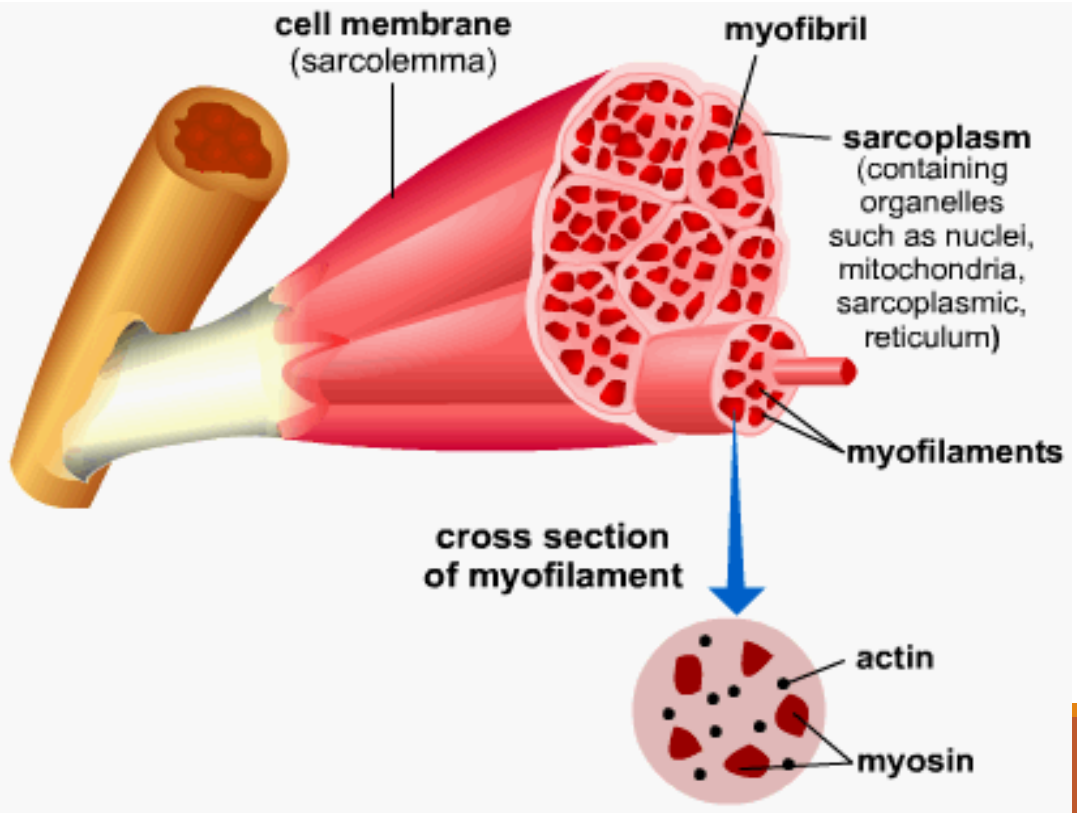
BIOCHEMISTRY OF MUSCULAR TISSUE



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Overview of the lecture:

1. Structure and composition of muscle tissue. Muscle proteins, their functions.
2. Biochemical mechanisms of muscle contraction and relaxation. Role of ions in regulation of muscle contraction.
3. Muscle energy metabolism. Sources of ATP for muscle contraction, role of creatine phosphate, creatine kinase.

I.

Structure and composition of muscle tissue. Muscle proteins, their functions.

MUSCULAR SYSTEM Is an organ system consisting of skeletal, smooth and cardiac muscles.

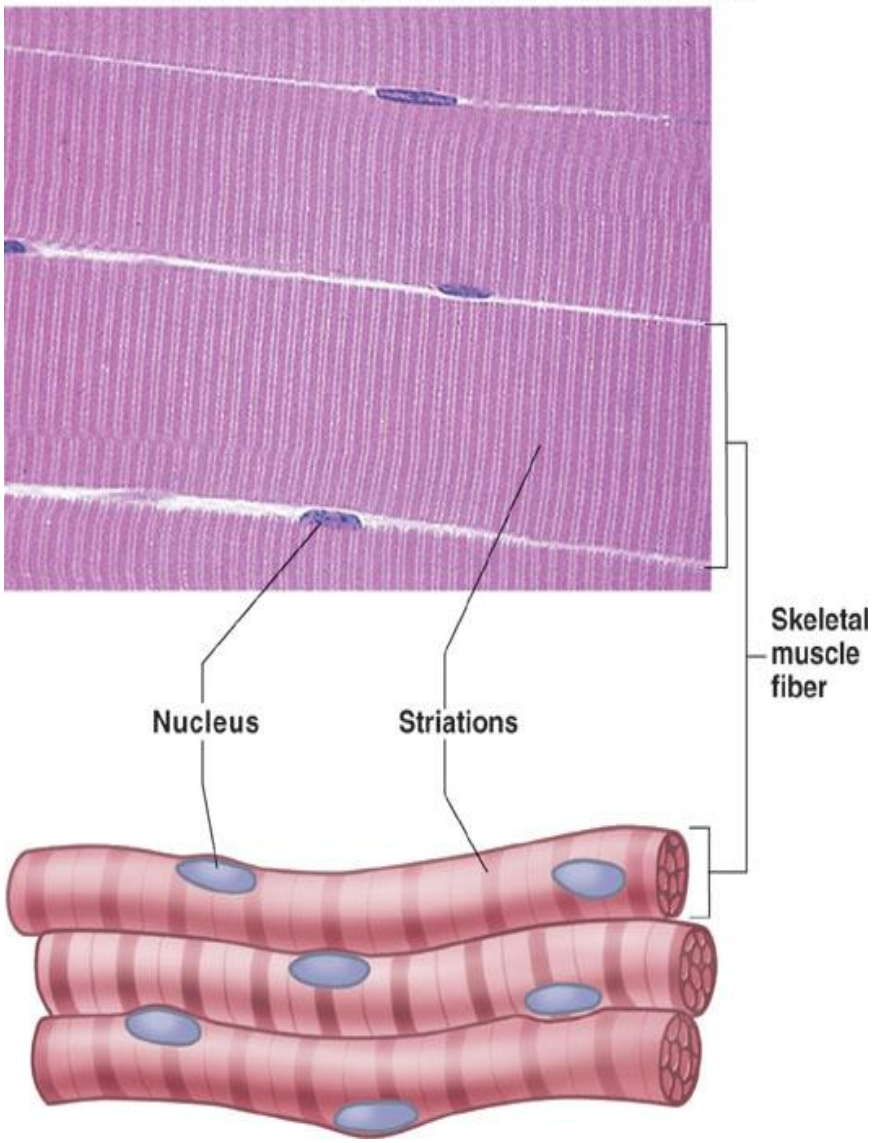
Smooth Muscle

- are non-striated muscle.
- Smooth muscle cells control involuntary movements such as the peristalsis contractions in the oesophagus and stomach.
- cells have a spindle shape with the single central nucleus

Cardic muscle

- involuntary, striated muscle that is found in the walls and histological foundation of the heart, specifically the myocardium
- depend on aerobic metabolism for energy needs because contain many mitochondria and very little glycogen

Skeletal muscle



It is a form of striated muscle tissue which is under the 'voluntary' control of the somatic nervous system.

Are composed of tubular cells called MYOCYTES, known as MUSCLE FIBERS.

Most are attached by tendons to bones

Cells are multinucleate

Striated – have visible banding

Skeletal muscle fiber or myocyte

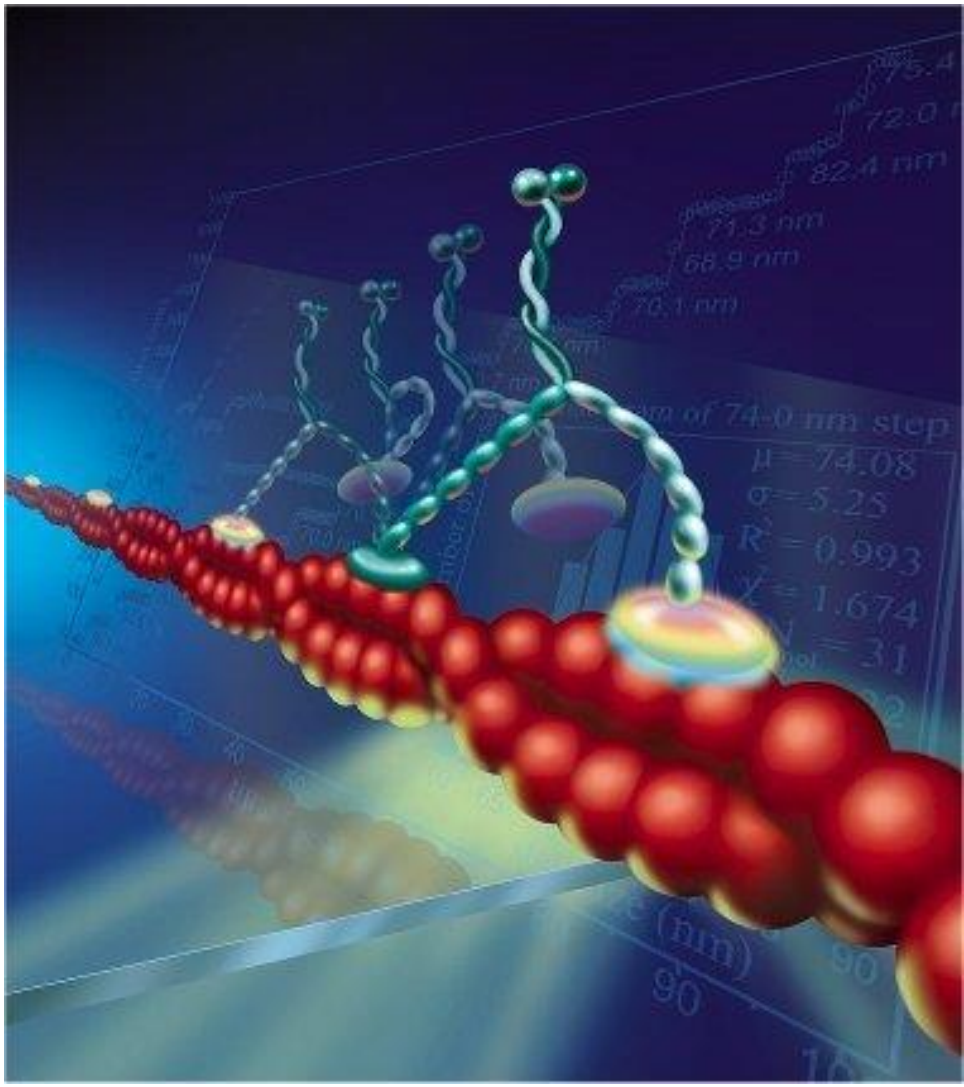
- is composed of a SARCOPLASM (cytoplasm) filled with MYOFIBRILS, composed of myofilaments.
- Each fiber contains many MITOCHONDRIA, which produce most of the ATP needed for muscle contraction under aerobic conditions.
- plasma membrane around the fiber (cell) = the SARCOLEMMA, which also extends *into* the cell to form transverse tubules (T-TUBULES)
- T-TUBULES are in contact with specialized endoplasmic reticulum in muscle cells called SARCOPLASMIC RETICULUM (SR), which contains high concentrations of Ca2+.

3 types of muscle proteins

1) proteins of sarcoplasm

2) proteins of stroma

3) proteins of myofibrils



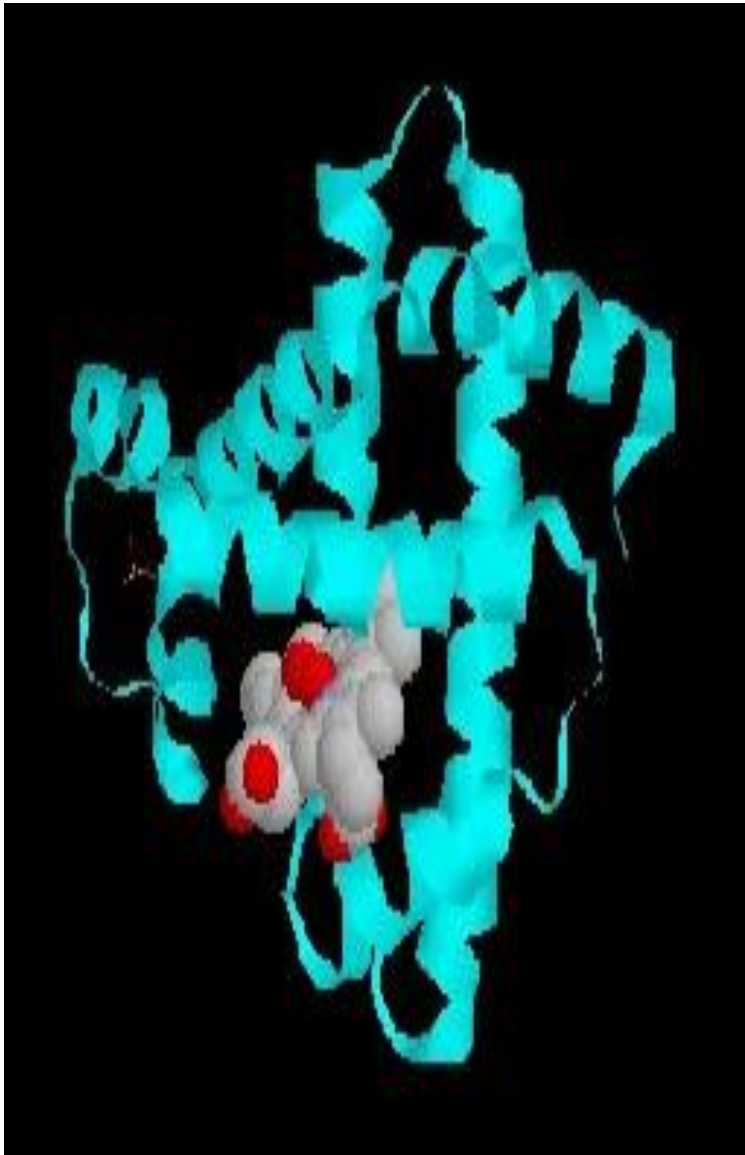
1.Proteins of Sarcoplasm

- **Myogen fraction**

(enzymes of glycolysis etc.)

- **Albumins**
- **Globulins**
- **Myoglobin**

***(chromoprotein, provides the red color to muscles, responsible for oxygen storage*)**

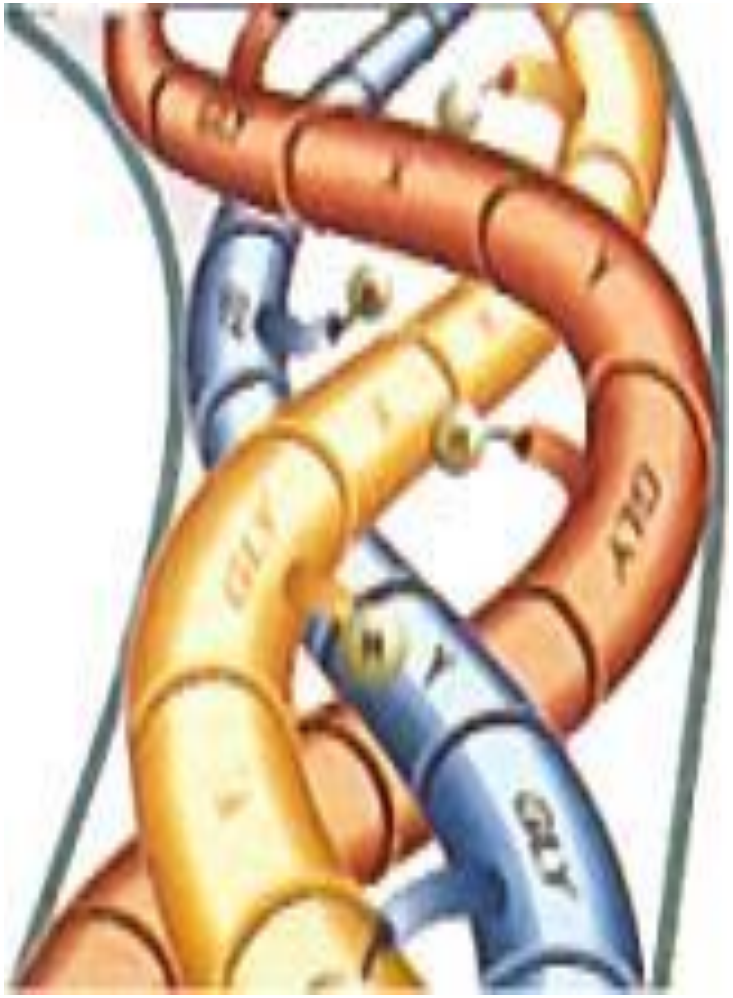


2. Proteins of Stroma

- **Collagen**
- **Keratin**
- **Elastin**
- **Myostromin**

➢ **are constituents of connective tissue of vessel walls, nerves, and sarcolemma.**

➢ **Form supportive framework of muscles.**



Extractive compounds of muscles (soluble in the water and salt solutions)

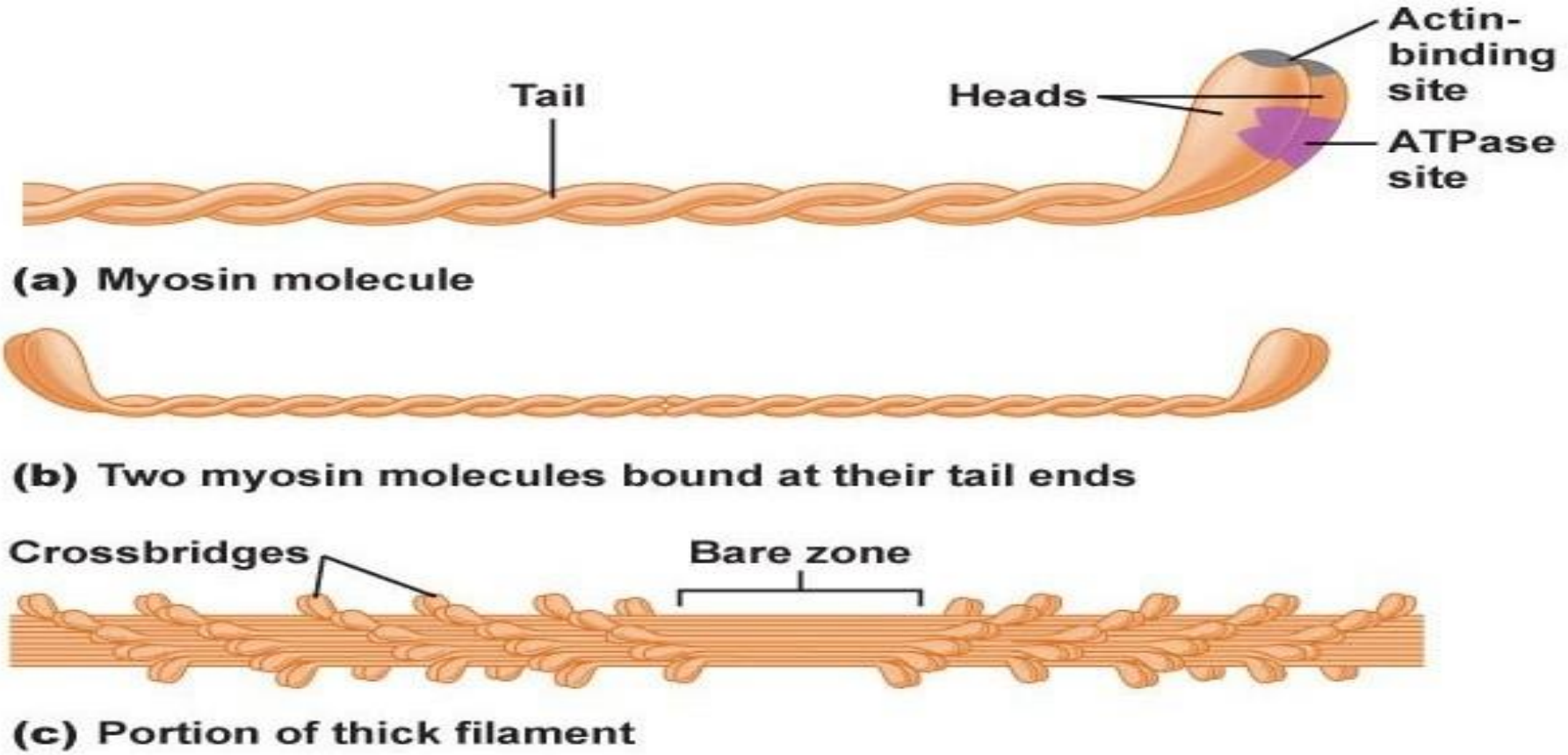
- Adenine nucleotides (ATP, ADP, AMP)
- Glycogen – alternate source of energy
- Creatine, creatine phosphate, creatinine
- Amino acids
- Carnosine, anserine
- Inorganic salts

3. Proteins of Myofibrils

1. Contractile proteins
   - Actin- thin filament
   - Myosin- thick filament
2. Regulatory proteins
   - Tropomyosin
   - Troponin
3. Attachment proteins
   - Titin, nebulin, alpha actinin, dystrophin

Several myosin molecules form myosin thick filament

- Each myosin molecule is composed of two parts (dimer). Each part consisting of A TAIL twisted around the other and A HEAD.
- The THICK MYOSIN FILAMENTS (or BANDS) are not single myosin proteins but are made of multiple myosin molecules.

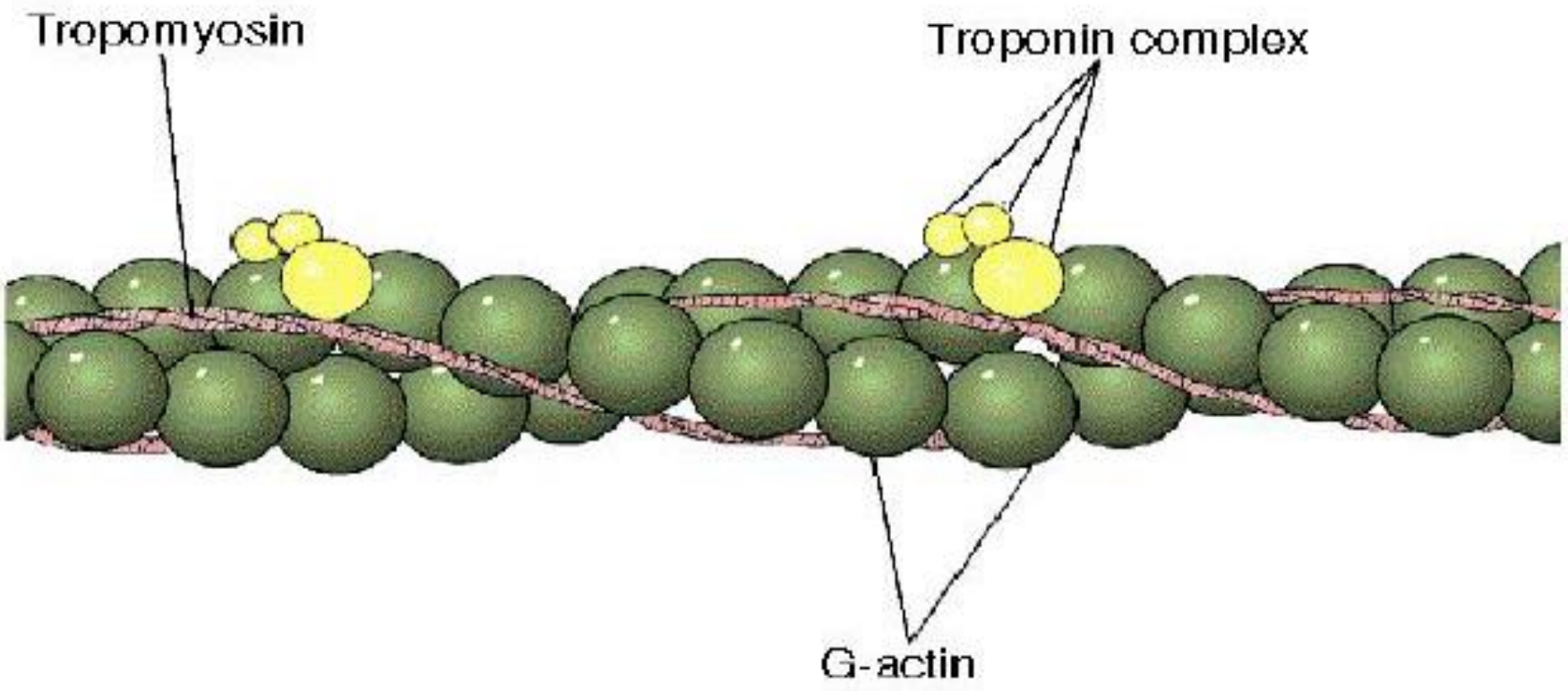


… the myosin heads

- Can bind to active sites on the actin molecules to form cross-bridges. (ACTIN BINDING SITE)
- They have ATPase activity: activity that breaks down ATP, releasing energy. Part of the energy is used to bend the hinge region of the myosin molecule during contraction

Actin structure (thin filament)

- **Two forms of actin: Globular G-actin and fibrillar F-actin.**
- **Globular actin molecules noncovalently connected to form F-actin. Two F-actin chains screwed into a spiral.**



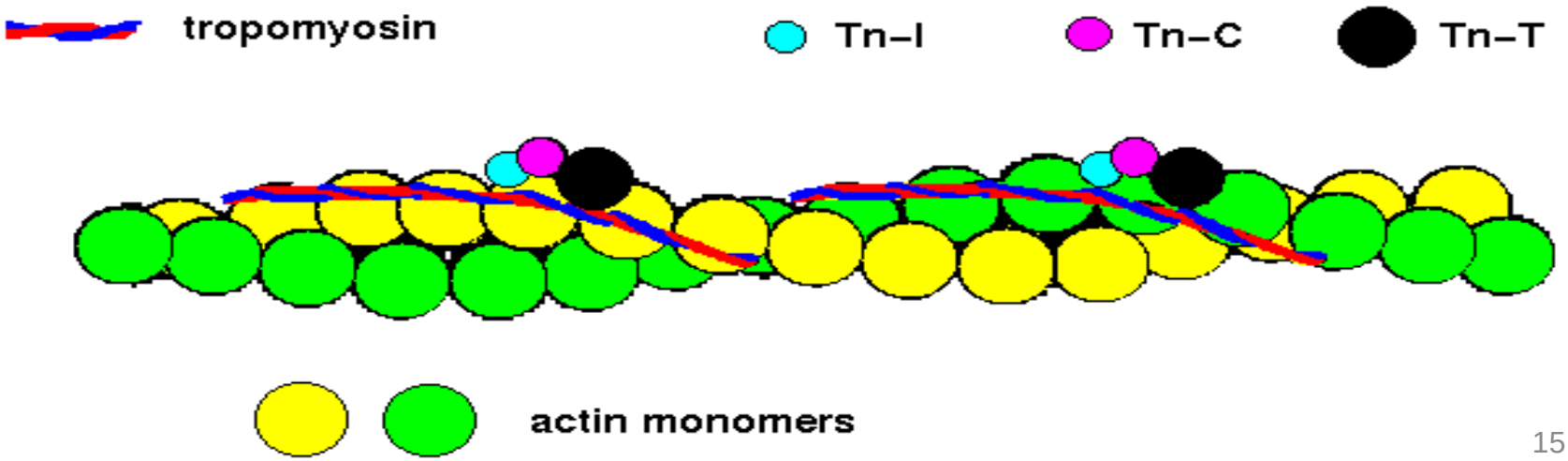
Regulatory proteins play a role in muscle contraction

- **TROPOMYOSIN:**
  - homodimer of long a-helical polypeptides (coiled coil)
  - binds to F-actin and prevents myosin binding
- **TROPONIN COMPLEX** (composed of 3 subunits):

  TnI (*I*nhibits myosin-actin interaction),

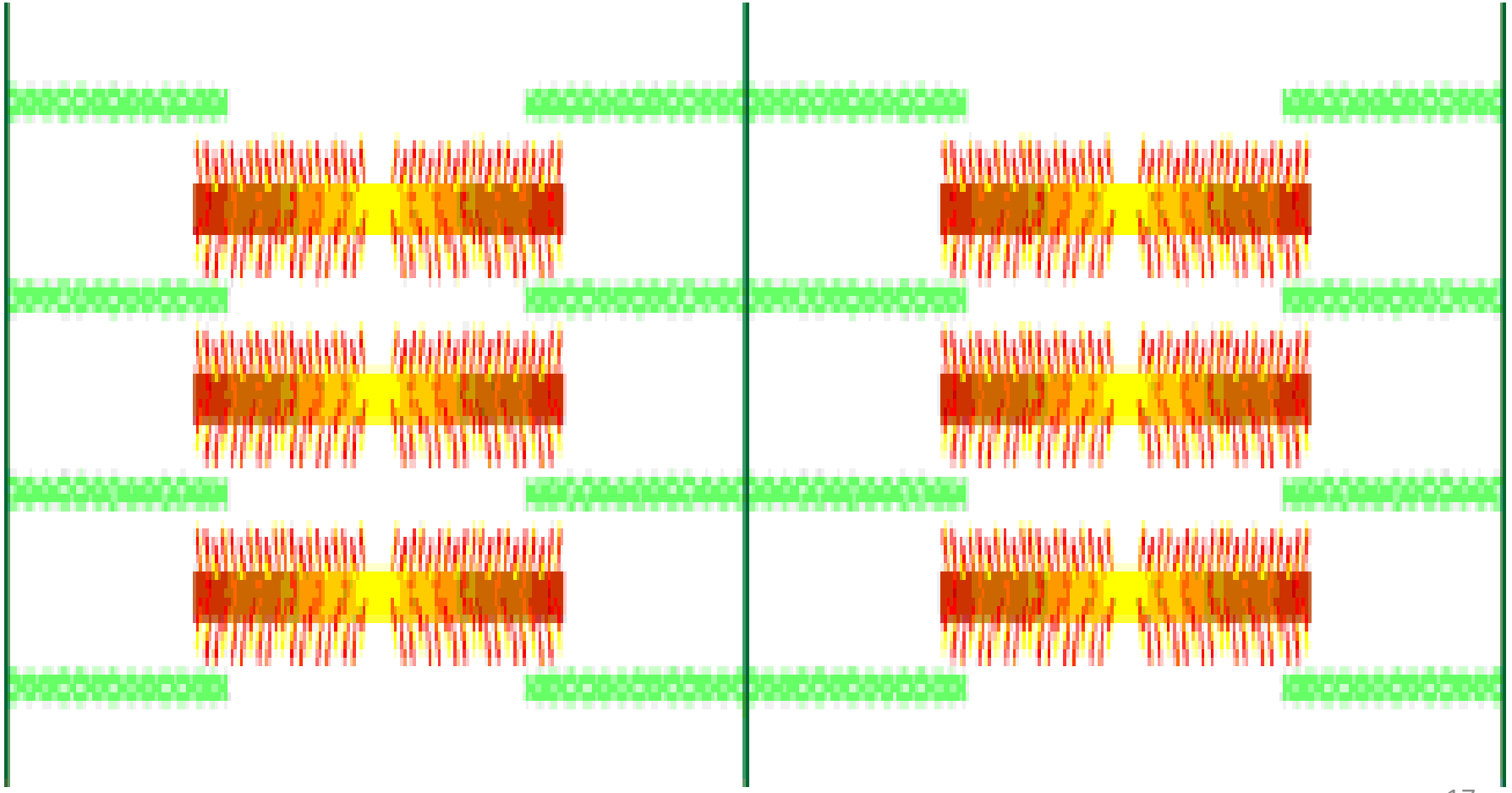
  TnT (binds *T*ropomyosin),

  TnC (binds Ca+)



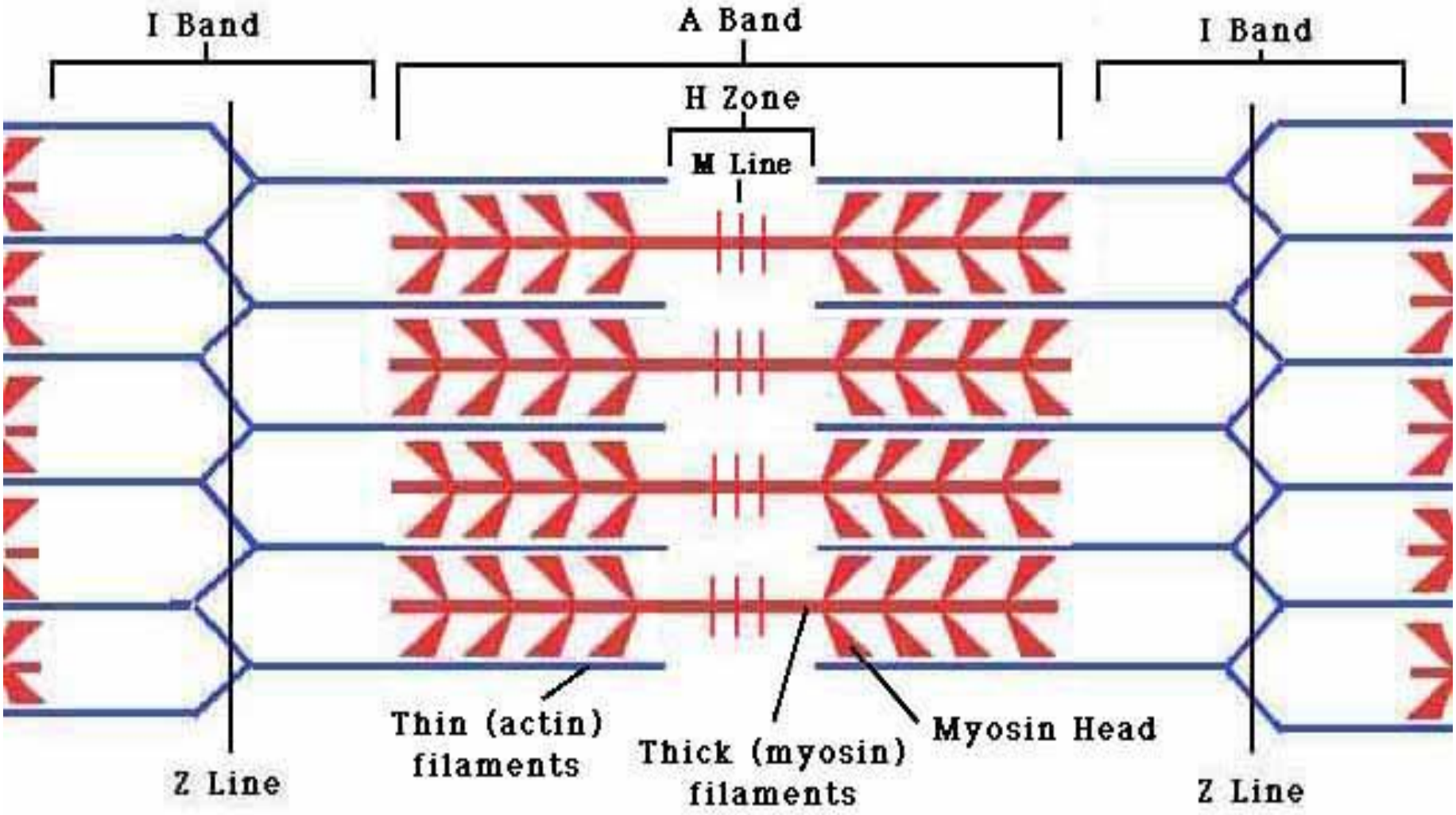
II.
Biochemical mechanisms of muscle contraction and relaxation. Role of ions in regulation of muscle contraction.

The Sliding Filament Cross-Bridge Model explains the mechanism of the muscle contraction and relaxation using the model of Sarcomere.

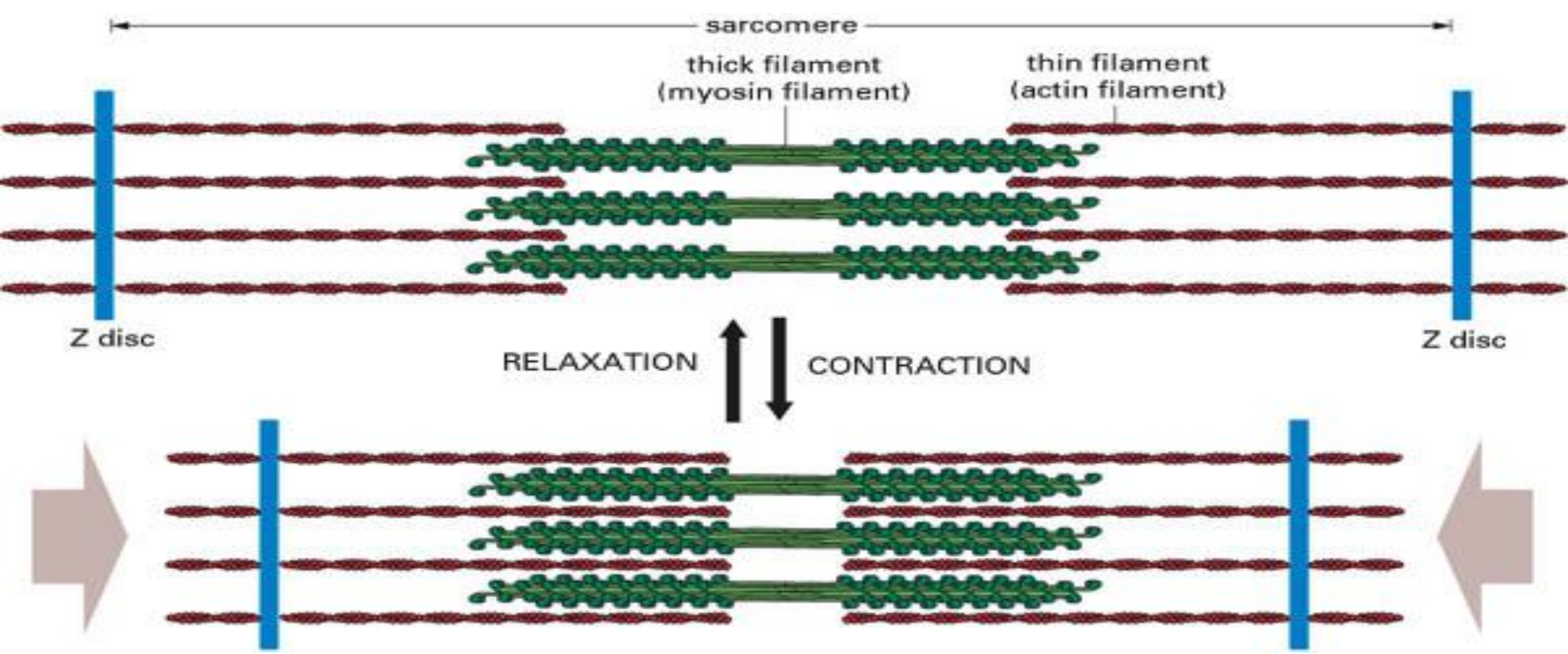


Sarcomere

- **Is the smallest contractile unit in the myofibril.**
- **Is the region between 2 neighbouring Z LINES**
- **is composed of long, fibrous proteins as filaments that slide past each other when a muscle contracts or relaxes.**
- **When the myofibril is examined by electron microscopy, alternating dark and light bands can be observed.**
  - **A BANDS, or DARK BANDS – anisotropic, birefringent in polarized light**
  - **I BANDS, or LIGHT BANDS – isotropic or not altered by polarized light**
  - **H ZONE is the central region of the A band, that appears less dense then the rest of the band.**
  - **The I band is bisected by a very dense and narrow Z LINE, made up of a protein titin.**

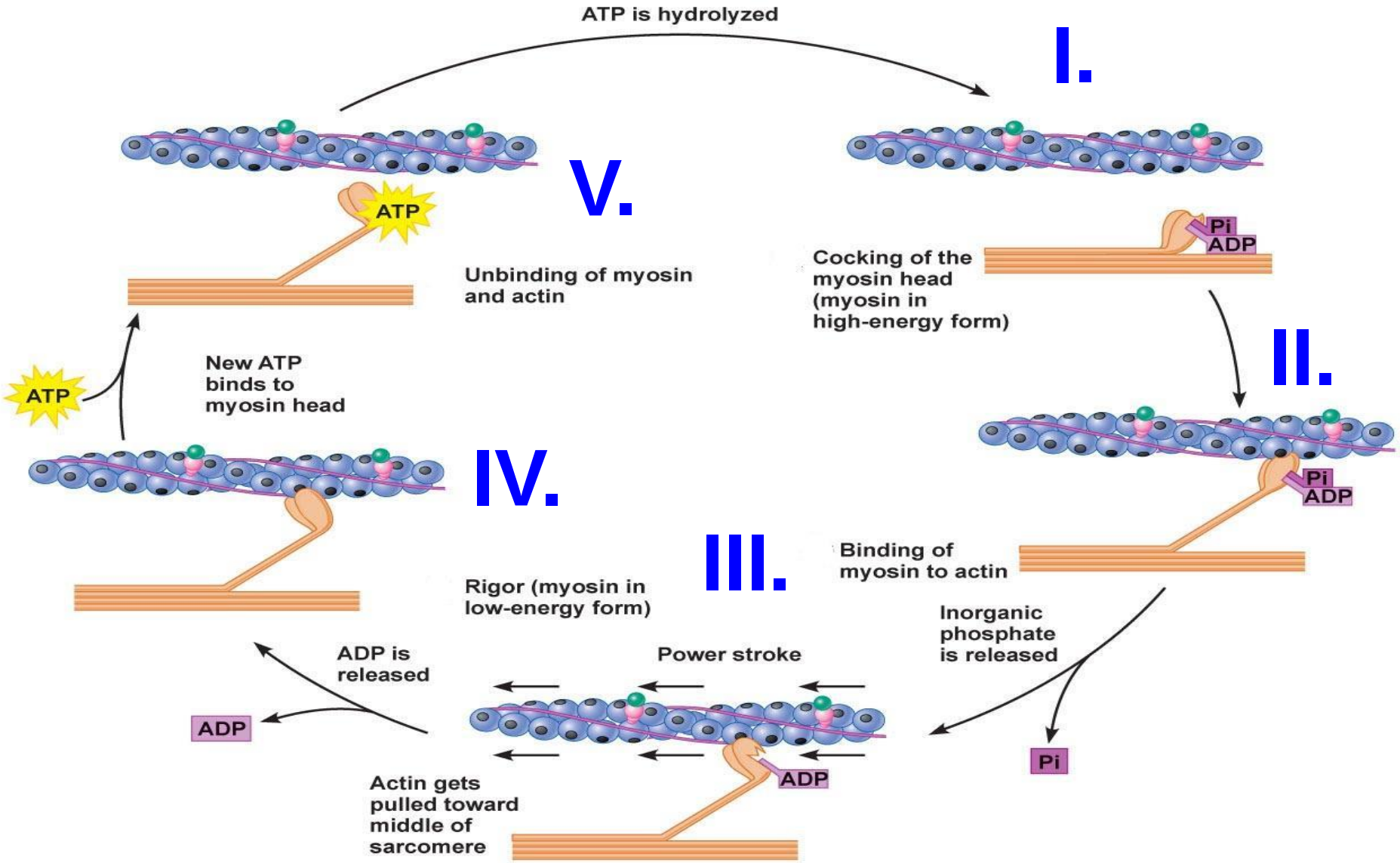


Thick filaments: primarily myosin; myosin S1 "heads" are crossbridges that bind to actin
Thin filaments: F-actin, tropomyosin, and the troponin complex.



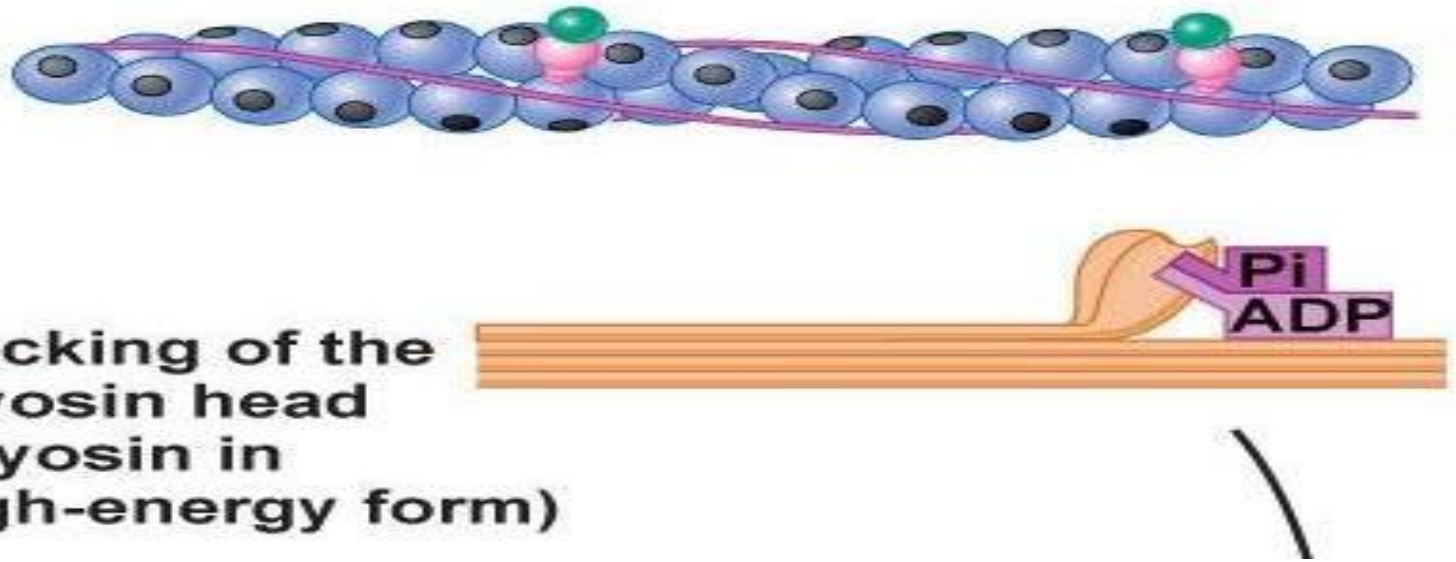
- **Muscle contraction is carried out due to the sliding of thick and thin filaments past one another, that is followed by the shortening of the H zones and I bands.**
- **Chemical energy – ATP hydrolysis**
- **Contraction is regulated by Ca^{2+} concentration**

- The sequence of events in crossbridge formation includes 5 stages:



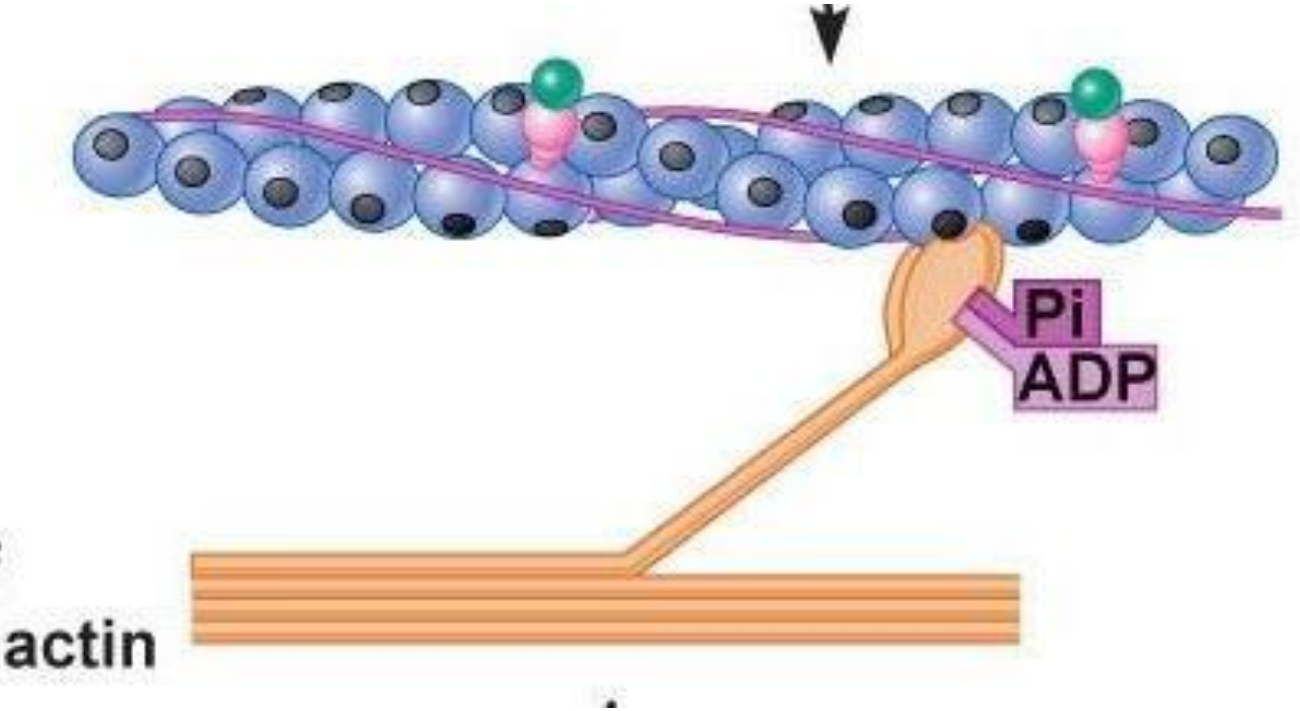
I Stage – Relaxation phase:

- **The head of myosin hydrolyzes ATP to ADP and Pi, but these products remain bound.**
- **The resultant ADP-Pi-MYOSIN COMPLEX has been energized and is in a so-called high-energy conformation.**



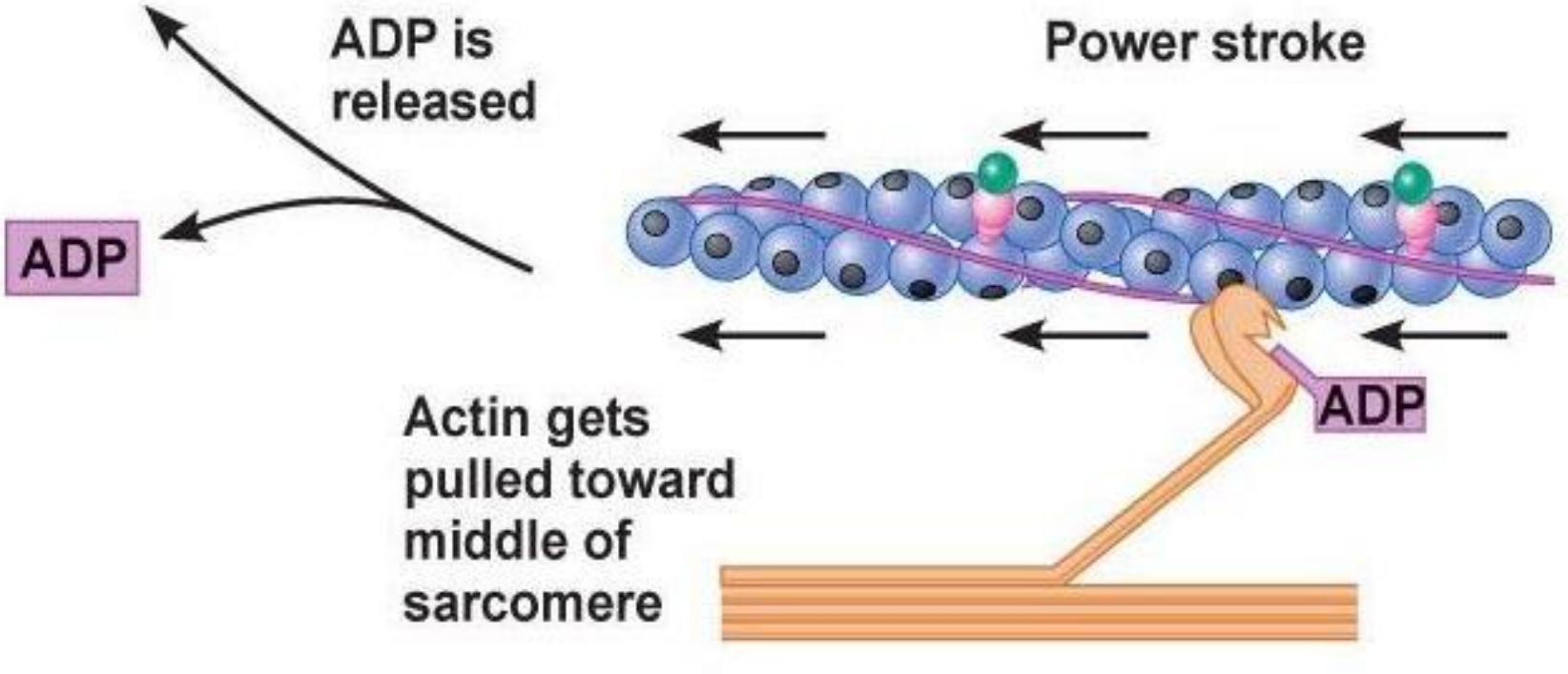
Stage II - stimulation of muscle contraction :

- **Binding of Actin and formation of the ACTIN-MYOSIN-ADP-PI COMPLEX and stimulation of muscle contraction. The events involve binding of Ca2+ to troponin C, changing of the tropomyosin position. Actin becomes accessible and the S-1 head of myosin finds it.**



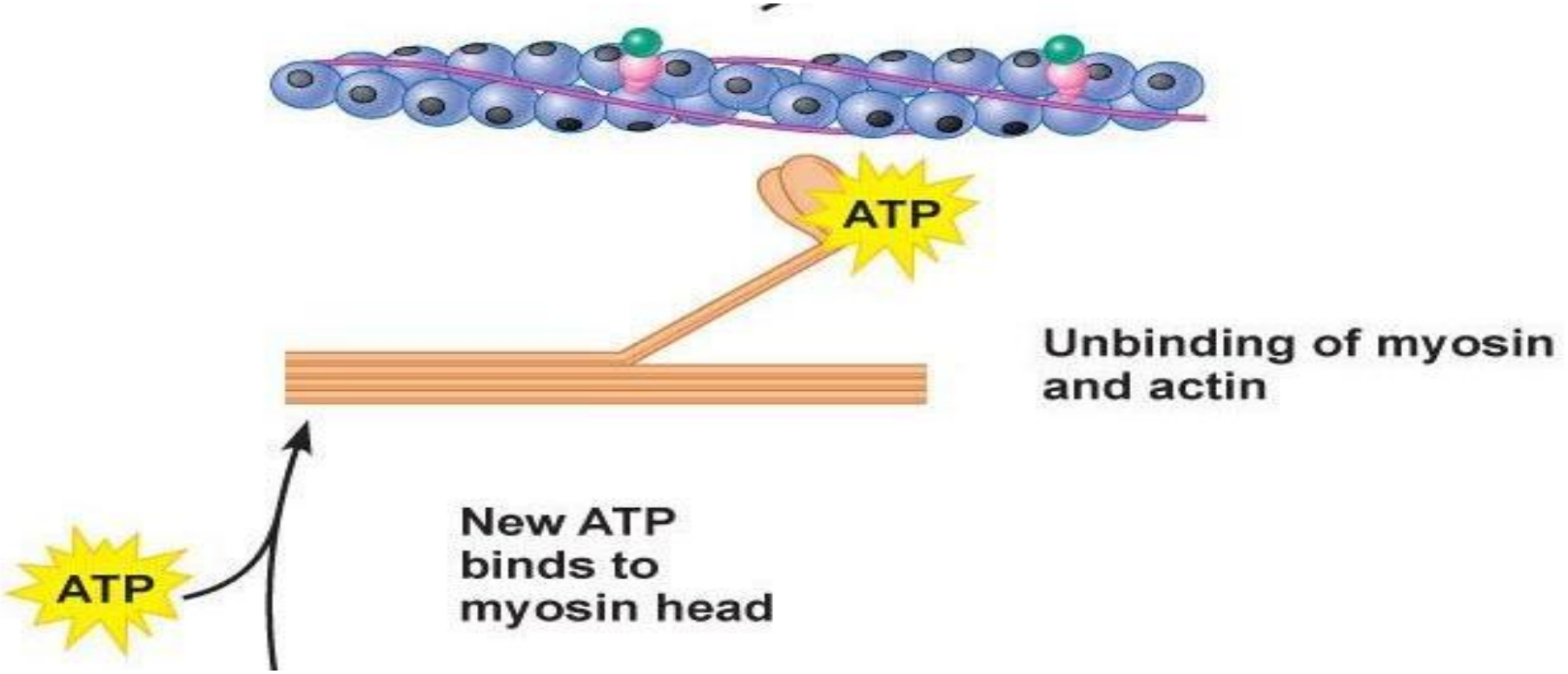
Stage III- POWER STROKE.

- **Release of Pi from the complex initiates the power stroke. This is followed by release of ADP and is accompanied by a large conformational change in the head of myosin in relation to its tail, pulling actin about 10 nm toward the center of the sarcomere. The myosin is now in a so-called low-energy state, indicated as Actin-myosin.**



Stages IV and V:

- **IV. Binding of the ATP molecule to the S-1 head of myosin and formation of An ACTIN-MYOSIN-ATP COMPLEX.**
- **V. Myosin-ATP has a low affinity for actin, and actin is thus released.**



The role of [Ca2+] in the muscle contraction

I. Muscle contraction is initiated by nerve impulse delivered to muscle, that produces an electrochemical signal (Action Potential)

II. Action potential spreads over the Sarcolemmal membrane and *into the fiber* along the t-tubule network.

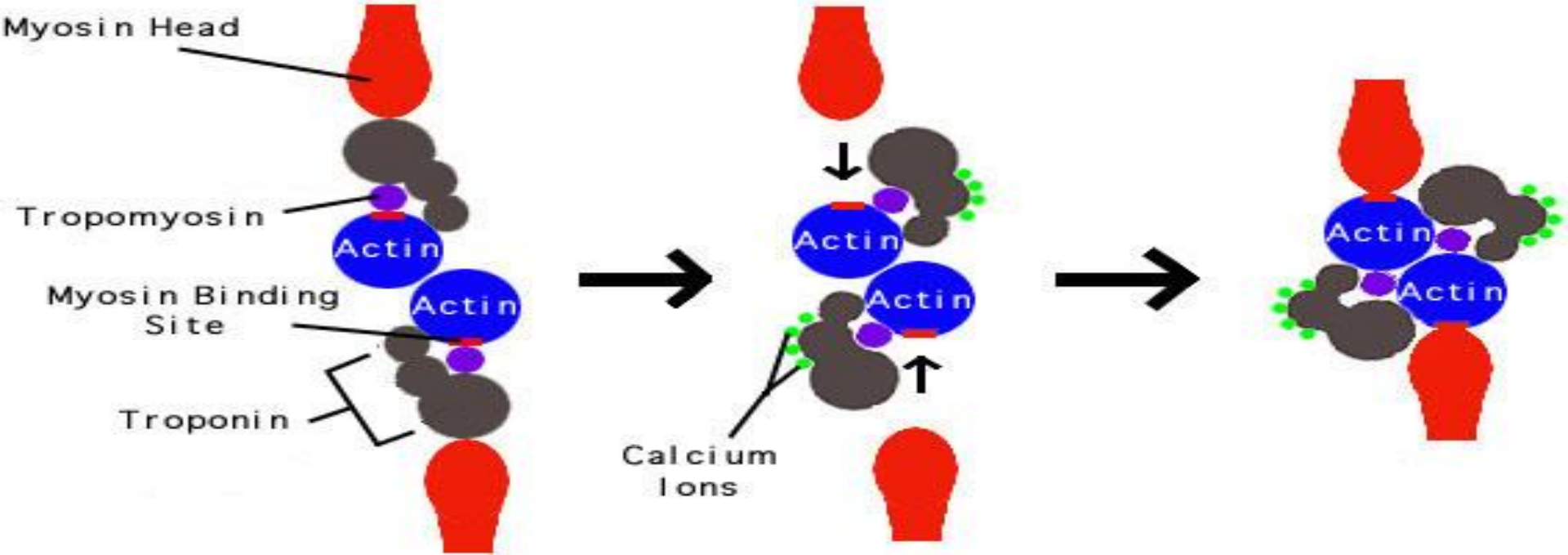
III. After that the signal passes from sarcolemma (t-tubules) through special junctions to the Sarcoplasmic Reticulum (SR).

IV. Opening of Ca2+ channels (proteins) in the membrane of SR permits Ca2+ to flow from the high concentration region inside the SR to the low concentration region, the cytosol.

V. In cytosol Ca2+ ions bind to the troponin complex, specifically Troponin C, TNC that then changes conformation.

VI. After that the position of tropomyosin is changed and the S1 head of myosin can bind to actin. Muscle contraction occurs.

VII. When the nerve impulse ceases, the Ca2+ are *pumped* back from cytosol into SR via a *Ca2+ pump* driven by ATP hydrolysis- Relaxation Phase.



3.

Muscle energy metabolism. Sources of ATP for muscle contraction, role of creatine phosphate, creatine kinase

The most active metabolic pathways in muscles

- High intensity of energy metabolism
- The main pathways that produce energy are:
  - Glycolysis (both aerobic and anaerobic)
  - Breakdown of Glycogen
  - β-oxidation of fatty acids
  - Utilization of ketone bodies.
- Role of Myoglobin in storing of O_2 molecules
- Metabolic processes are different in the slow (red) and fast (white) twitch fibers

RED (SLOW) FIBERS

- Small fiber diameter
- Increased concentration of capillaries
- Higher myoglobin *content*
- Many mitochondria
- ATP requirements are provided mainly from fatty acids and aerobic glycolysis,
- Maintain relatively sustained contractions
- Used for prolonged aerobic exercise
- The number of the RF increases in athletes training for marathons

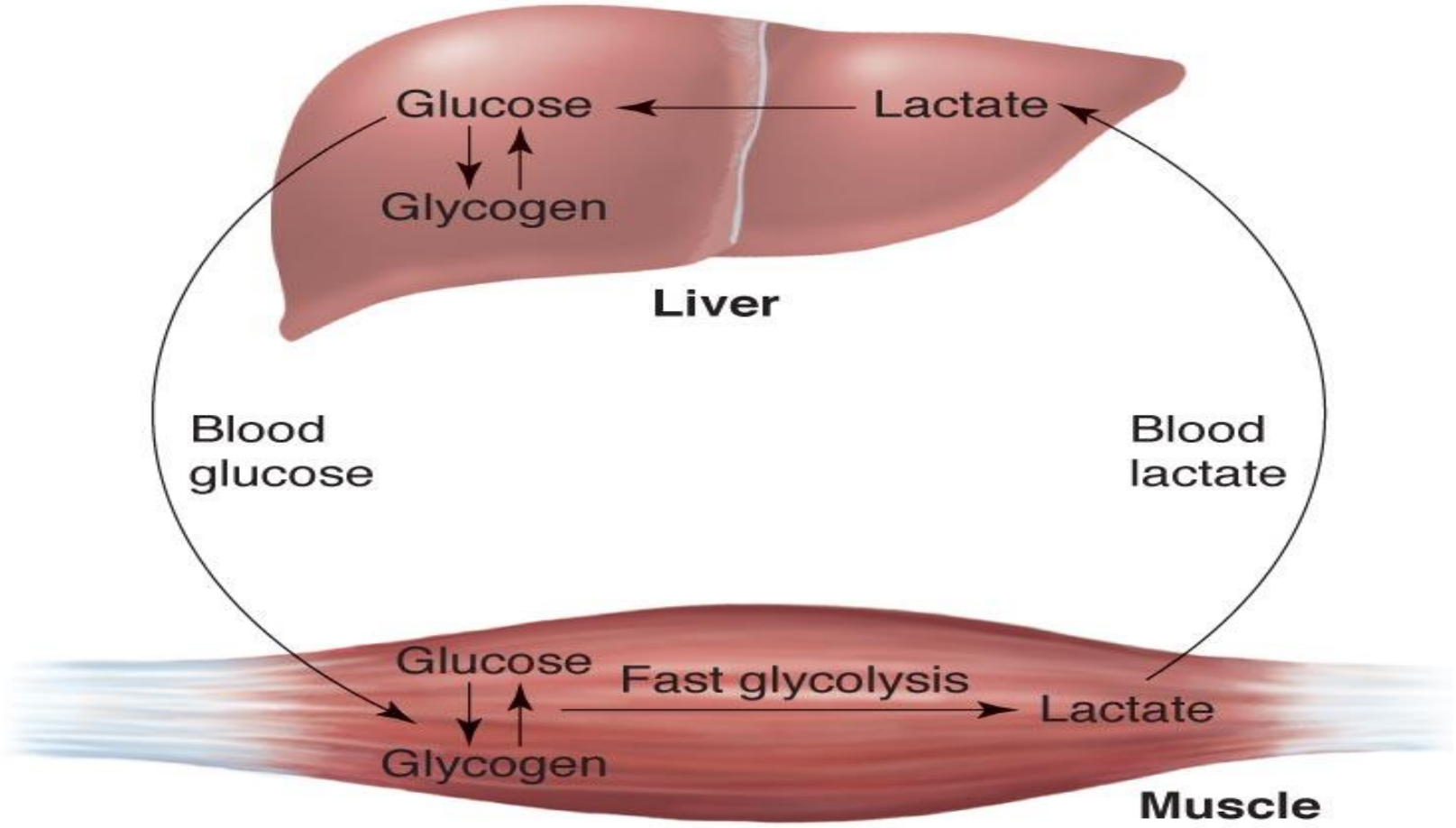
WHITE (FAST) FIBERS

- Larger fiber diameter
- Lower concentration of capillaries
- Low myoglobin content
- Low mitochondria content
- Limited aerobic metabolism
- ATP requirements are provided from anaerobic glycolysis,
- Fast speed of contraction.
- Used for sprinting and resistance tasks
- The number of the WF increases in sprinters

Sources of ATP for muscle contraction

1. **Breakdown of Glycogen to Glucose-6-phosphate and Glycolysis leading to formation of Lactate (Anaerobic conditions; 2 ATP molecules).**
2. **Breakdown of Glycogen to Glucose-6-phosphate and Glycolysis Leading to Oxidative Phosphorylation of ADP in mitochondria (Aerobic conditions; 38 ATP molecules).**
3. **From the glucose molecules regenerated in the Cori's cycle (anaerobic or aerobic Glycolysis)**
4. **From creatine phosphate**
5. **AMP kinase reaction**

In skeletal muscles the Cori's Cycle is used to regenerate glucose from lactate produced during intensive muscle contraction



ATP and Creatine Phosphate

- **In resting muscles excess of ATP molecules is used to produce Creatine Phosphate (Phosphocreatine).**

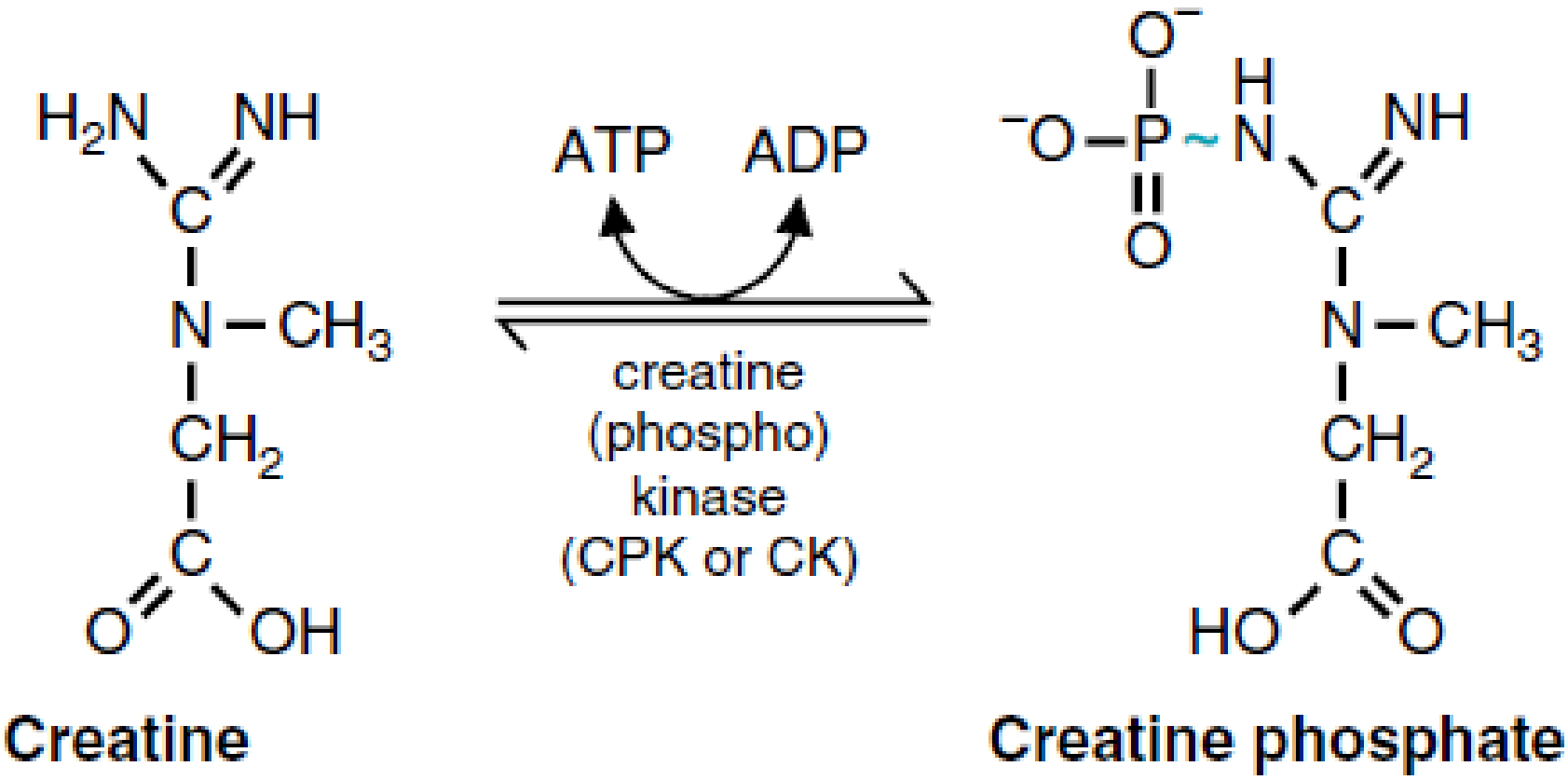
  creatine +ATP → creatine~P + ADP

- **Under conditions of muscle activity Creatine Phosphate acts as energy source that can be rapidly converted to ATP when the limited cellular reserves of ATP are depleted.**

  creatine~P + ADP → creatine +ATP

Both reactions are catalyzed by CREATINE KINASE

Creatine phosphokinase reaction (Creatine kinase; CK)



Creatine phosphokinase Isoenzymes

1. CK-BB – 2 subunits of brain type
2. CK-MM – 2 subunits of muscle type
3. CK-MB - 1 M-subunit and 1 B-subunit.

Skeletal muscle expresses CK-MM (98%) and low levels of CK-MB (1%).

The myocardium (heart muscle), in contrast, expresses CK-MM at 70% and CK-MB at 25–30%.

CK-BB is predominantly expressed in brain and smooth muscle, including vascular and uterine tissue.

AMP-kinase reaction

- ADP + ADP → ATP + AMP

- takes place during low energy situations such as extreme exercise or conditions of hypoxia
- creation of AMP resulting from this reaction stimulates various intracellular enzymes geared towards increasing energy supply (eg. Aerobic glycolysis)

Thank you for attention!