Physiology of the Heart

Conduction System

Cardiac Cellular Electrophysiology

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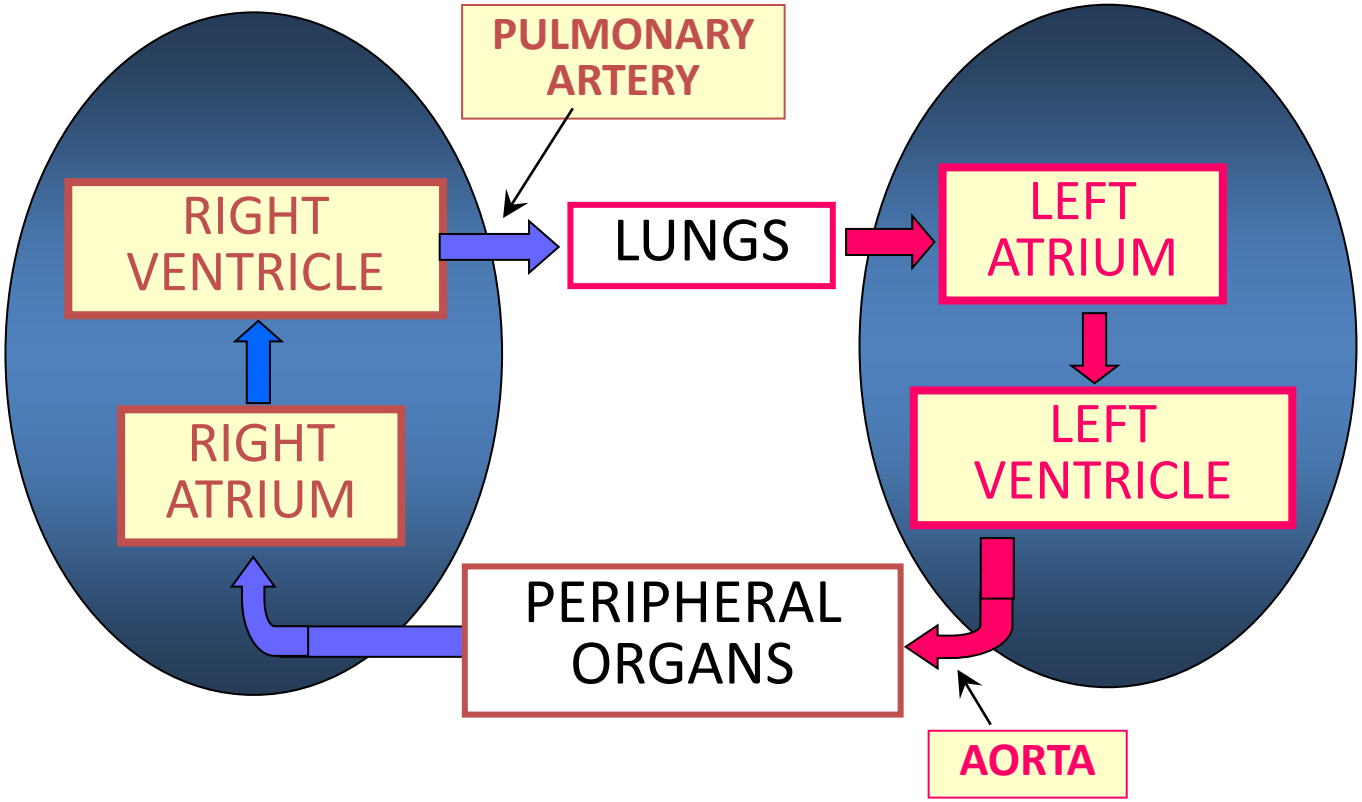
ORGANIZATION OF CARDIOVASCULAR SYSTEM

Roles of the Cardiovascular System

- **primary role** - distribution of dissolved gases and other nutrients
- **several secondary roles, for example:**
  - fast chemical signalling to the cells (circulating hormones)
  - thermoregulation (delivery of heat from the core to the surface of the body)
  - immune reaction
- **roles of the heart:**
  - primary role - pumping of blood
  - endocrinne function (natriuretic peptides)

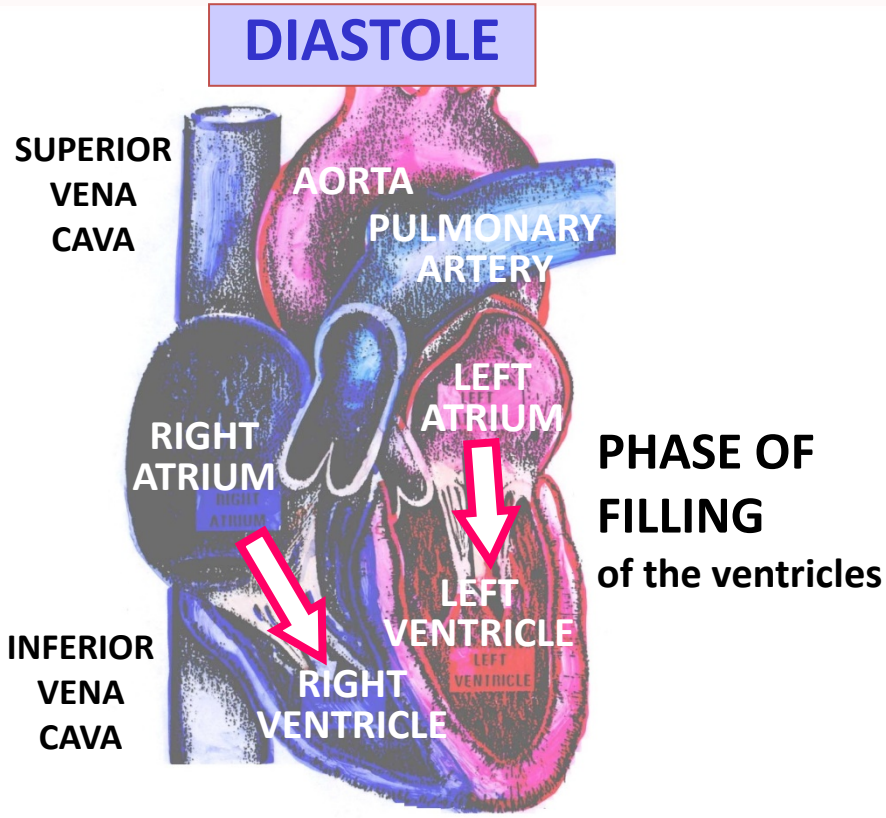
ORGANIZATION OF CARDIOVASCULAR SYSTEM

TWO PUMPS INTERCONNECTED IN SERIES

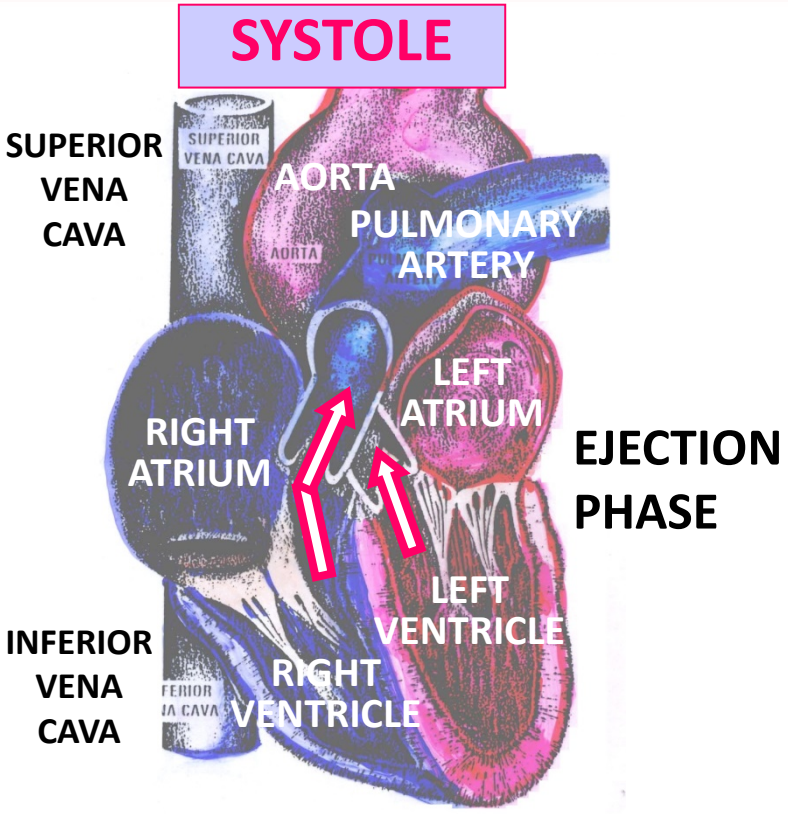


ORGANIZATION OF CARDIOVASCULAR SYSTEM

Two Main Phases of the Cardiac Cycle



PHASE OF FILLING
of the ventricles



EJECTION PHASE

ONE WAY VALVES	DIASTOLE	SYSTOLE
ATRIOVENTRICULAR (mitral and tricuspid)	open	closed
SEMILUNAR (aortal and pulmonary)	closed	open

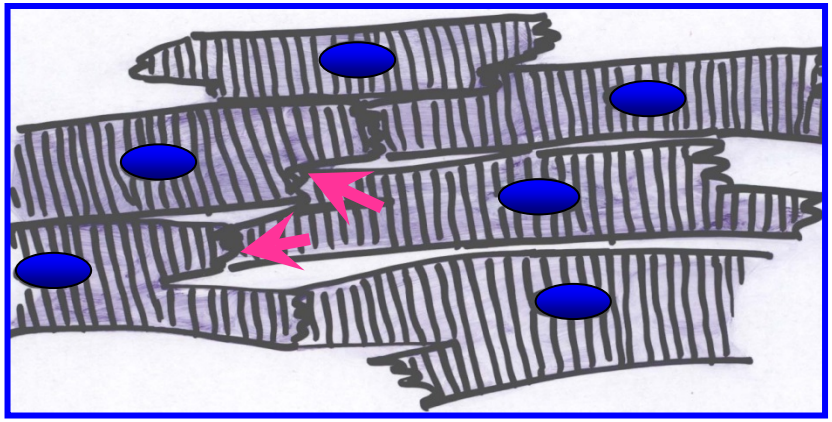
ORGANIZATION OF CARDIOVASCULAR SYSTEM

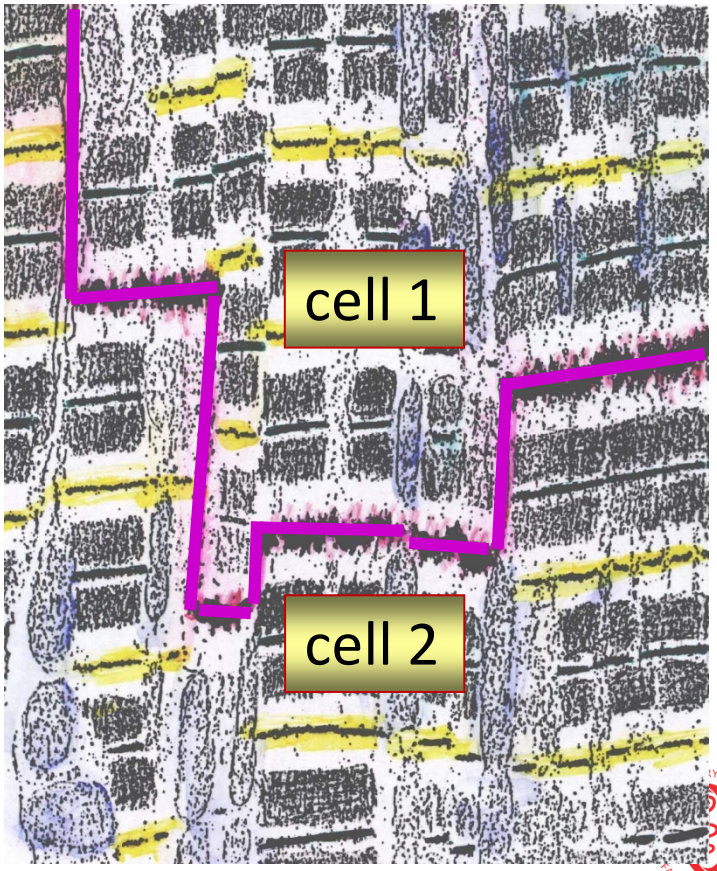
Two Major Types of Cardiac Cells

- **cardiomyocytes of the working myocardium** - specialized for contraction (atrial and ventricular myocytes)

FUNCTIONAL SYNCYTIUM

- mechanical connections
- electrical connections - **gap junctions**





ORGANIZATION OF CARDIOVASCULAR SYSTEM

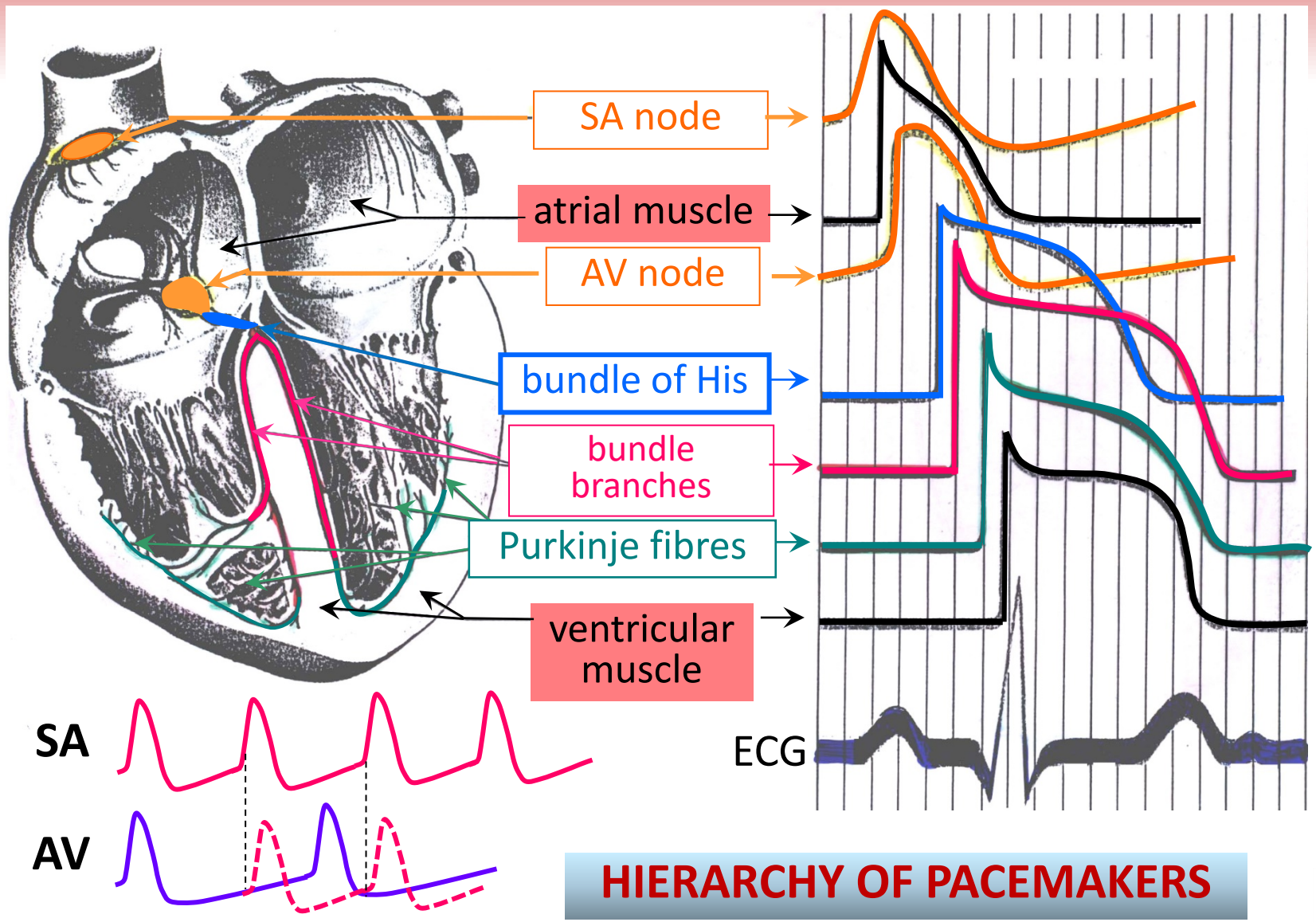
Two Major Types of Cardiac Cells

- **cardiomyocytes of the working myocardium** - specialized for contraction (atrial and ventricular myocytes)
- **cardiomyocytes of the cardiac conduction system** - specialized for:
  - automatic excitation (pacemaker activity)
  - conduction of excitation

The cardiac conduction system ensures:

1) generation of automatic electrical activity of the heart (pacemaker activity) that initiates its mechanical activity
2) optimal timing of the mechanical activity of the heart as a pump

CARDIAC CONDUCTION SYSTEM



HIERARCHY OF PACEMAKERS

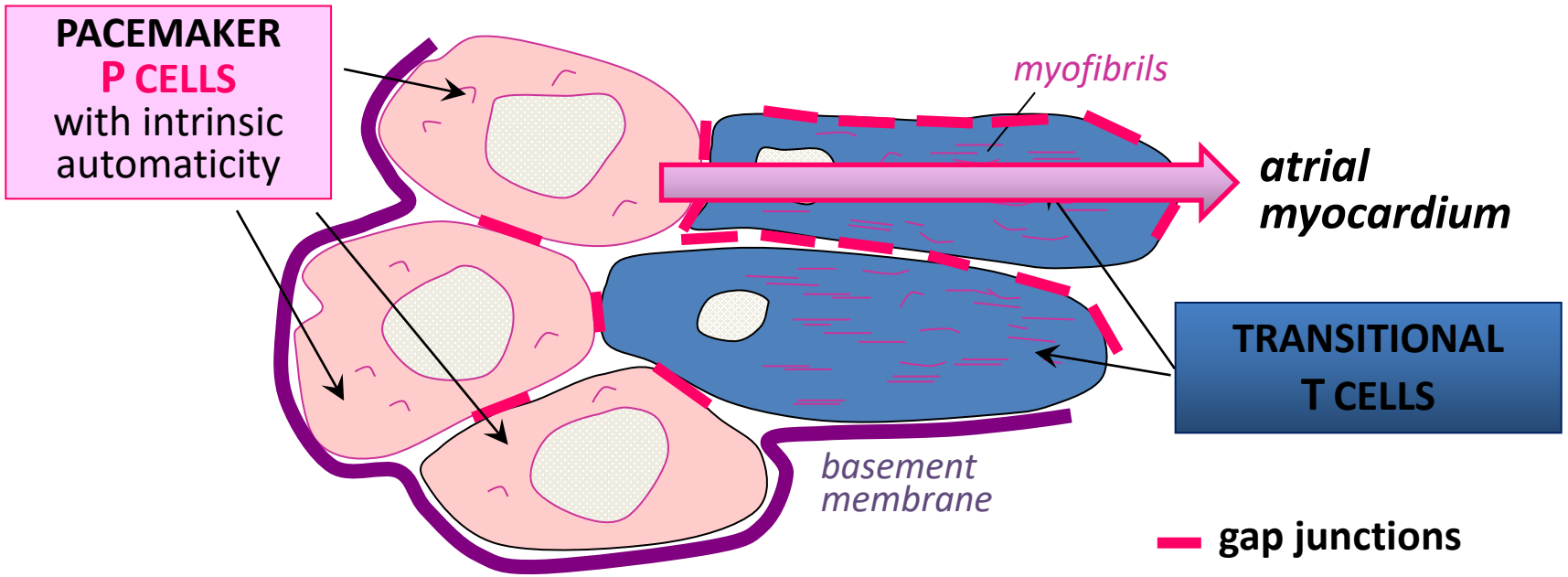
CARDIAC CONDUCTION SYSTEM

- **SINOATRIAL (SA) NODE**
  PRIMARY pacemaker (60-100 impulses/min)

CARDIAC CONDUCTION SYSTEM

SA node

TWO TYPES of the SA-nodal cells



SICK SINUS SYNDROME

- ***pacemaker P cells are impaired, activity is slowed or stopped***
- ***transmission of excitation* from *P cells to the atrial cells is reduced or interrupted***

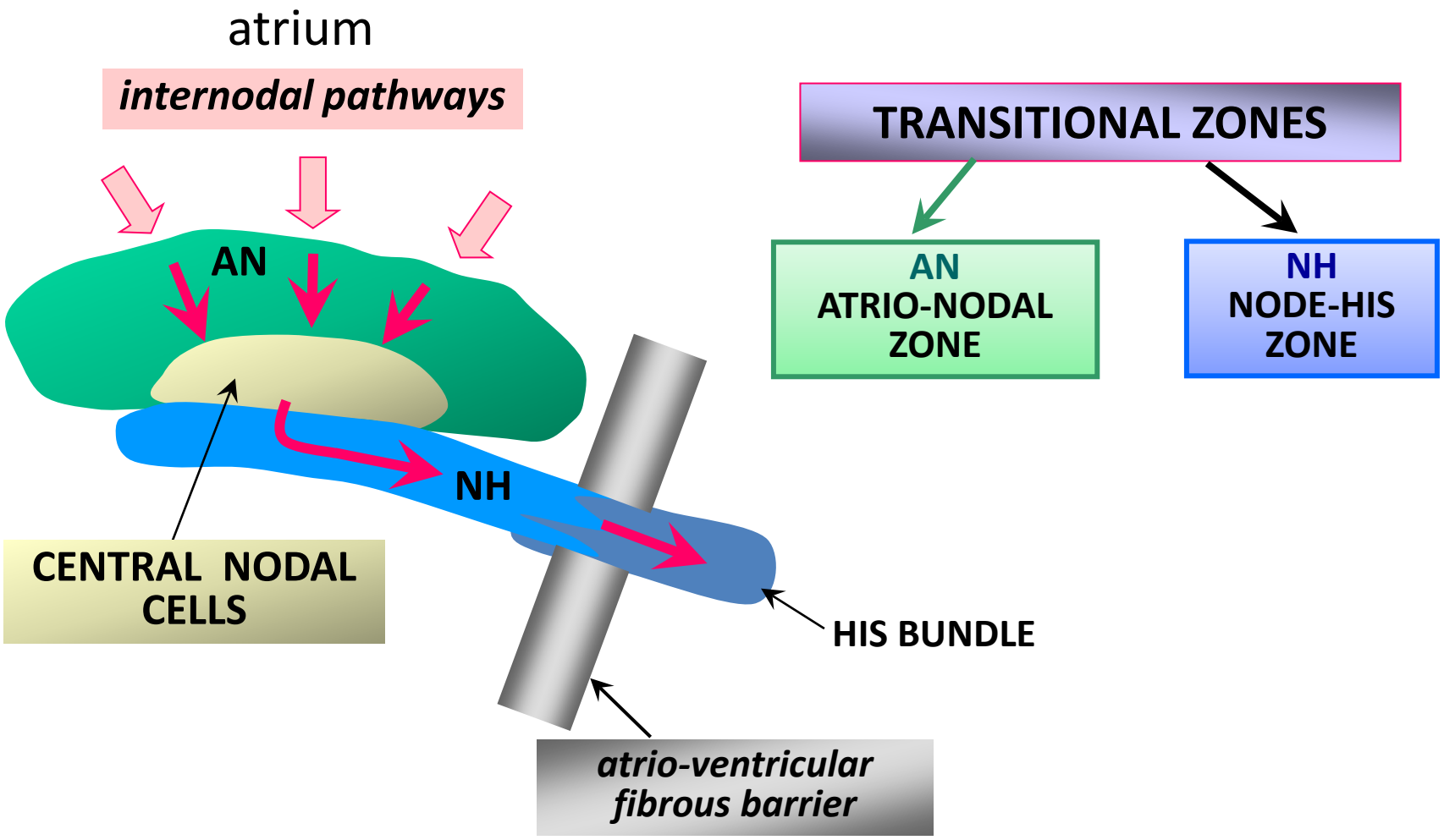
CARDIAC CONDUCTION SYSTEM

- **SINOATRIAL (SA) NODE**
  PRIMARY pacemaker (60-100 impulses/min)
- **INTERNODAL PREFERENTIAL PATHWAYS**
- **ATRIOVENTRICULAR (AV) NODE**
  SECONDARY pacemaker (40-55 impulses/min)

CARDIAC CONDUCTION SYSTEM

AV node

THREE TYPES of the AV-nodal cells



CARDIAC CONDUCTION SYSTEM

AV node

- **SUBSTITUTIVE (SECONDARY) PACEMAKER** (40-55 impulses/min; importance in the case of sick sinus syndrome)
- **SOLE PATHWAY** FOR PROPAGATION OF EXCITATION FROM ATRIA TO VENTRICLES (NH zone merges into the bundle of His)
- **DELAY** IN PROPAGATION OF EXCITATION, ~100 ms (important for adequate timing of atrial and ventricular contractions)
- **FILTER OF SUPRAVENTRICULAR TACHYARRHYTHMIAS** atrial excitations are transmitted to the ventricles only up to the limited frequency 180-200 excitations/min (the heart function as a pump is preserved)

CARDIAC CONDUCTION SYSTEM

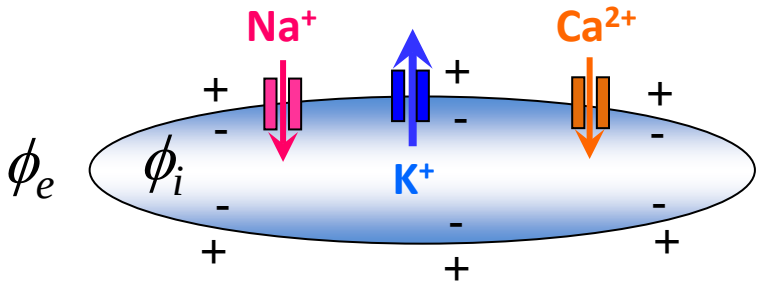
- **SINOATRIAL (SA) NODE**
  PRIMARY pacemaker (60-100 impulses/min) — **0.05 m/s**
- **INTERNODAL PREFERENTIAL PATHWAYS** — **1 m/s**
- **ATRIOVENTRICULAR (AV) NODE**
  SECONDARY pacemaker (40-55 impulses/min) — **0.05 m/s**
- **BUNDLE OF HIS** — **1 m/s**
- **BUNDLE BRANCHES** (LEFT AND RIGHT) — **1 m/s**
- **PURKINJE FIBRES**
  TERCIARY pacemaker (25-40 impulses/min) — **4 m/s**

Conduction velocity in atrial and ventricular muscle: 1 m/s

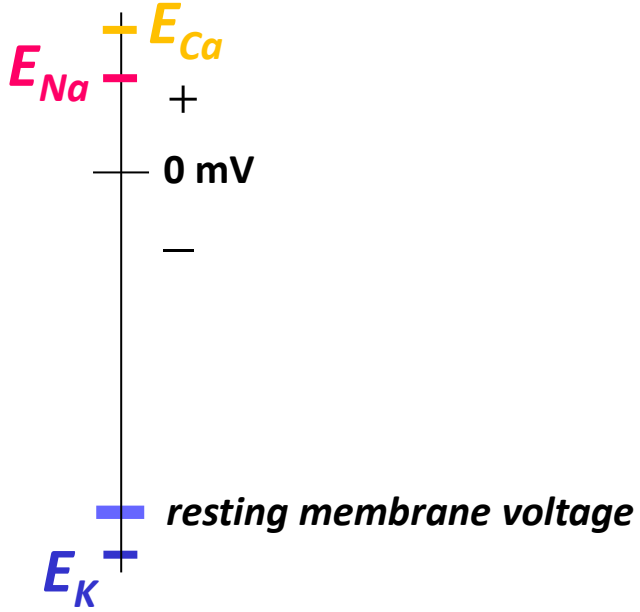
CARDIAC CELLULAR ELECTROPHYSIOLOGY

Ionic Channels

Movement of ions through the open channels
down their electrochemical (concentration + electrical) gradients

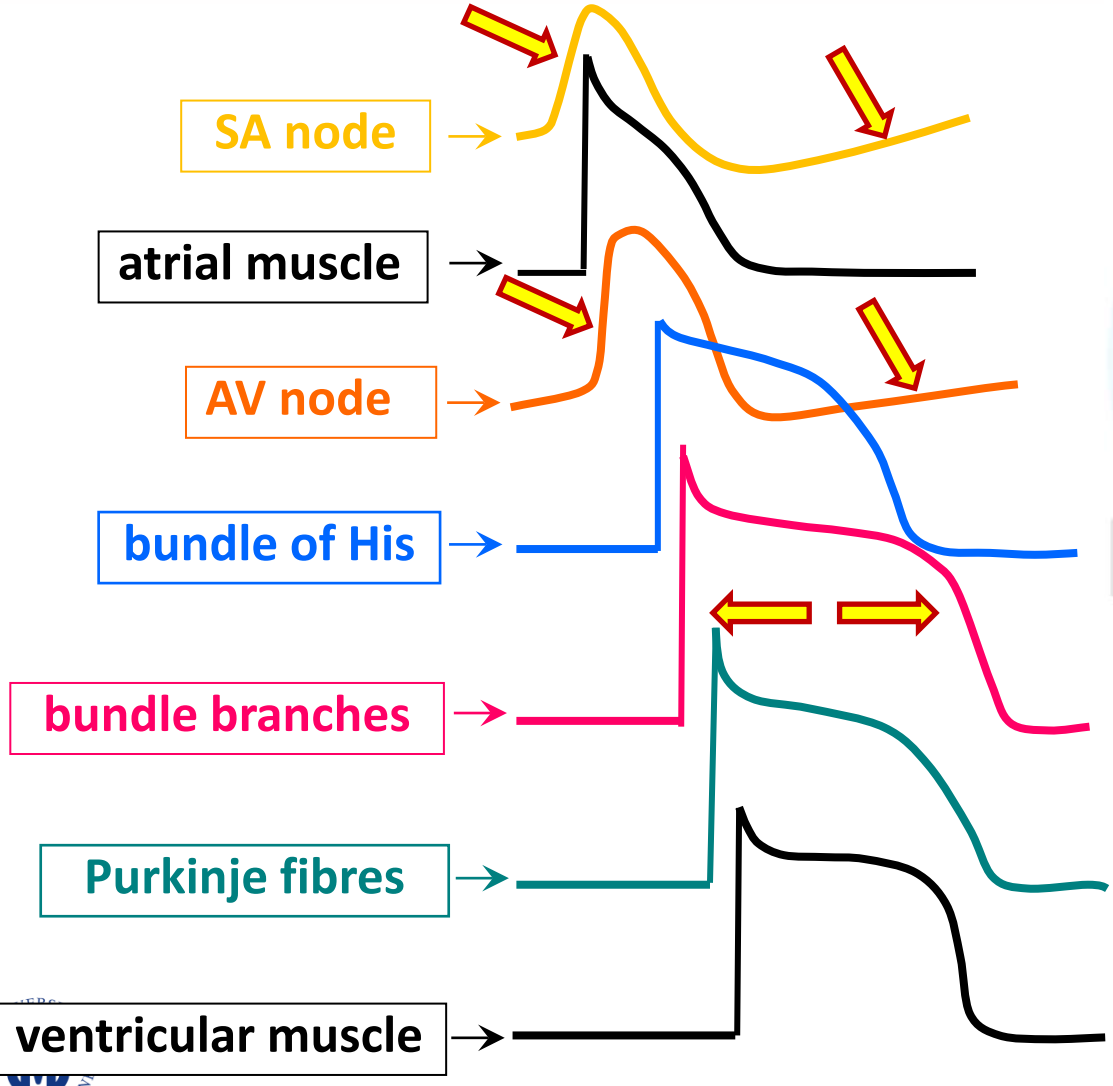


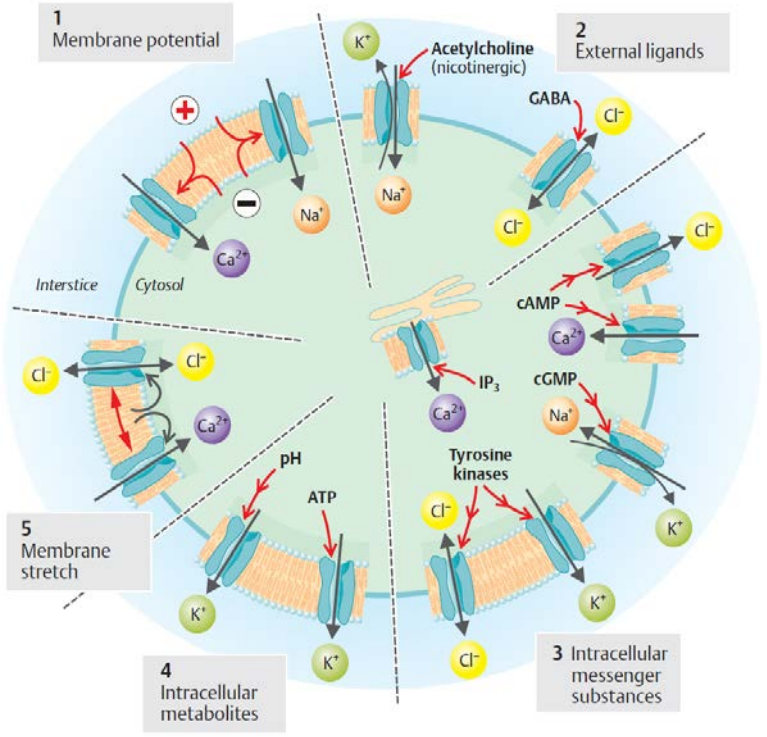
$$V_m = \phi_i - \phi_e$$



CARDIAC CELLULAR ELECTROPHYSIOLOGY

Ionic Currents Underlying Action Potential Configuration





Despopoulos, Color Atlas of Physiology © 2003

CARDIAC CELLULAR ELECTROPHYSIOLOGY

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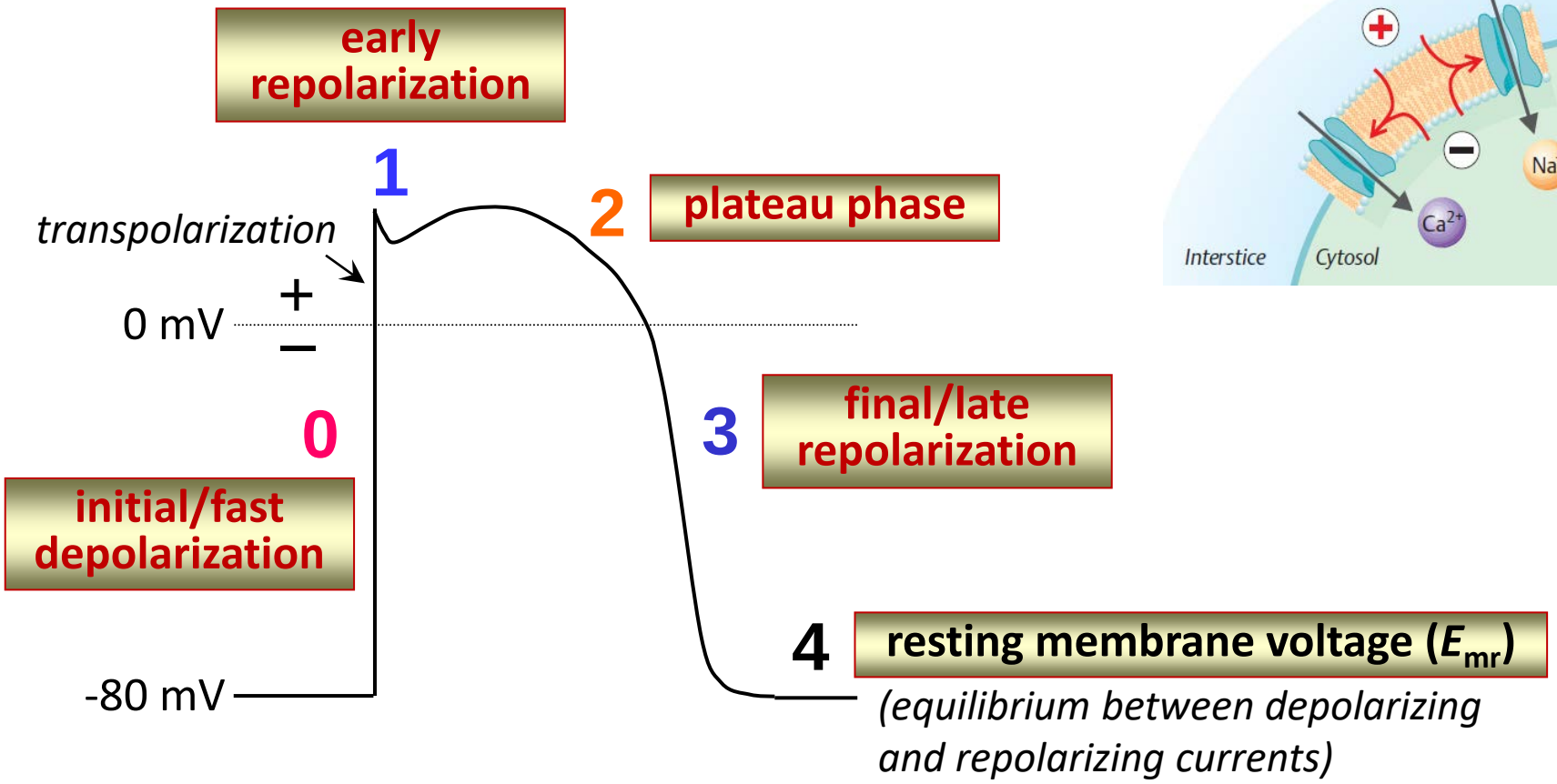
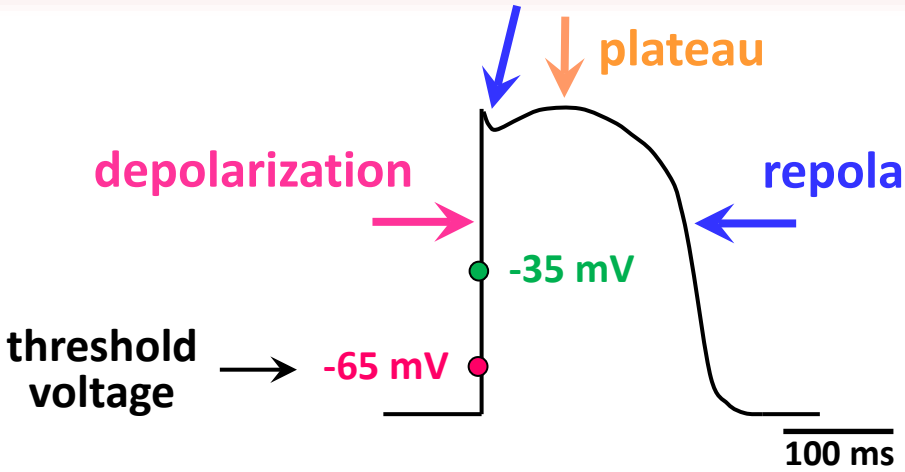
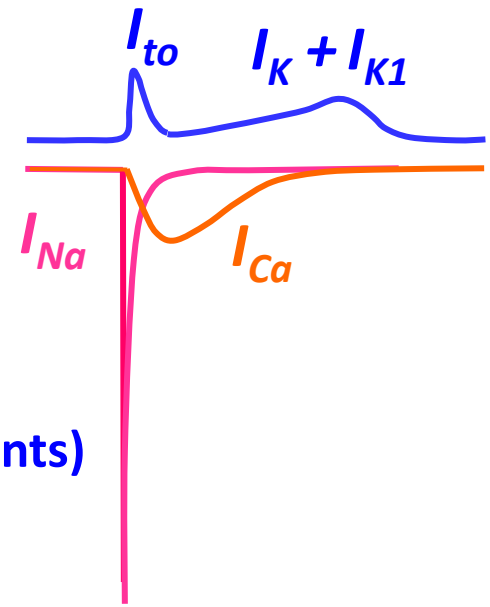


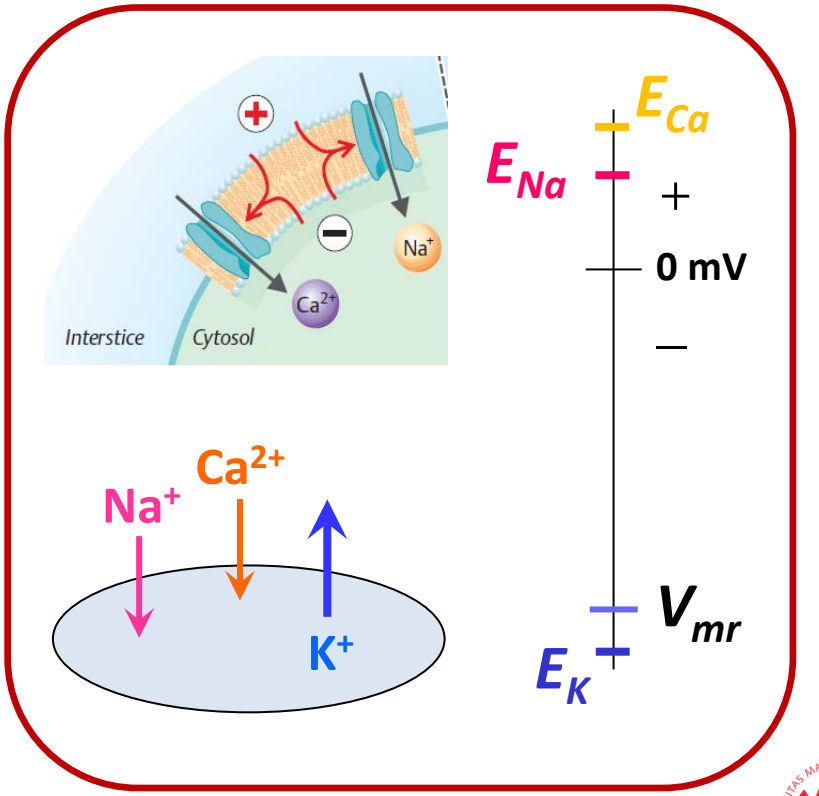
CARDIAC CELLULAR ELECTROPHYSIOLOGY

Ionic Currents Underlying Action Potential Configuration





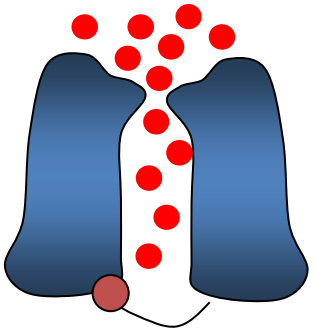
many subtypes of potassium channels (currents)



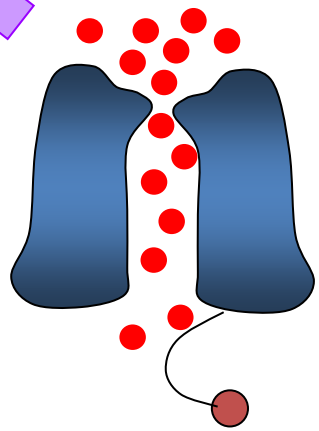
CARDIAC CELLULAR ELECTROPHYSIOLOGY

Ionic Currents Underlying Action Potential Configuration

INACTIVATED STATE
(closed)

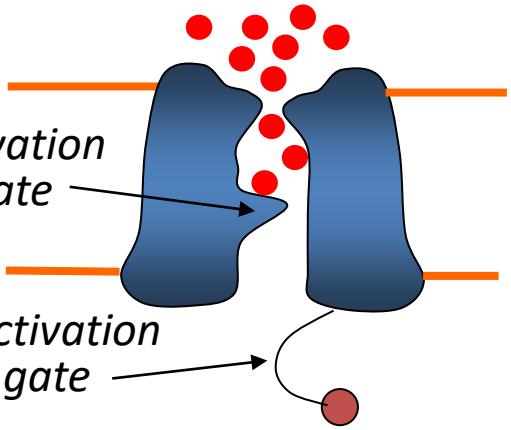


INACTIVATION
(at maintained membrane depolarization)



OPEN STATE

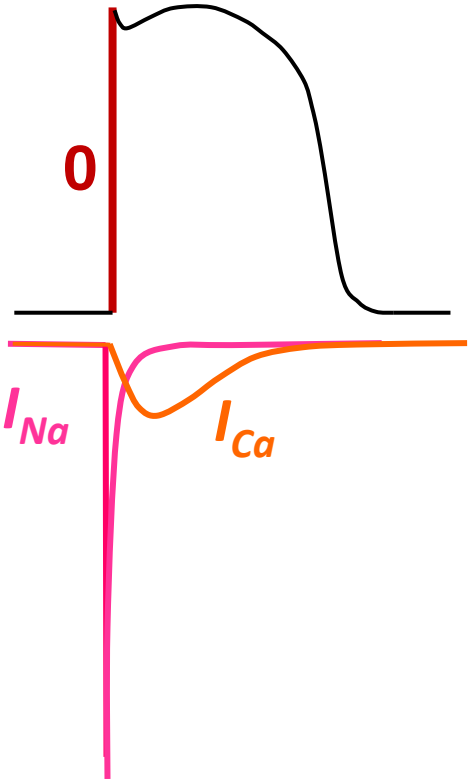
ACTIVATION
(depolarization over threshold voltage)



RESTING STATE
(closed)

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Mechanism of the initial fast depolarization (phase 0)



regenerative (self restoring) process

produced by POSITIVE FEEDBACK between MEMBRANE VOLTAGE and CONDUCTANCE of MEMBRANE CHANNELS (g_{Na}, g_{Ca})

working myocardium - I_{Na}

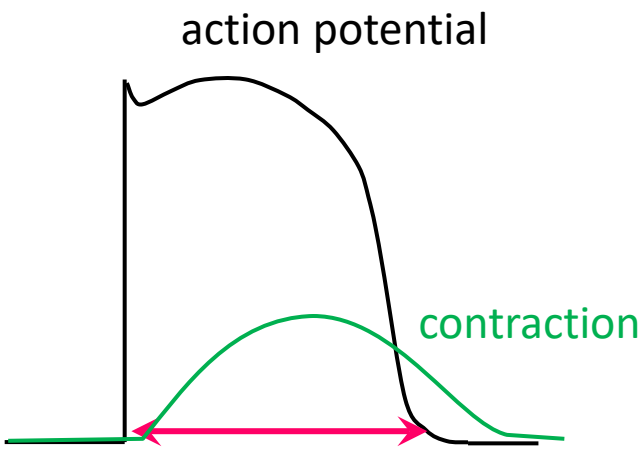
depolarizing currents

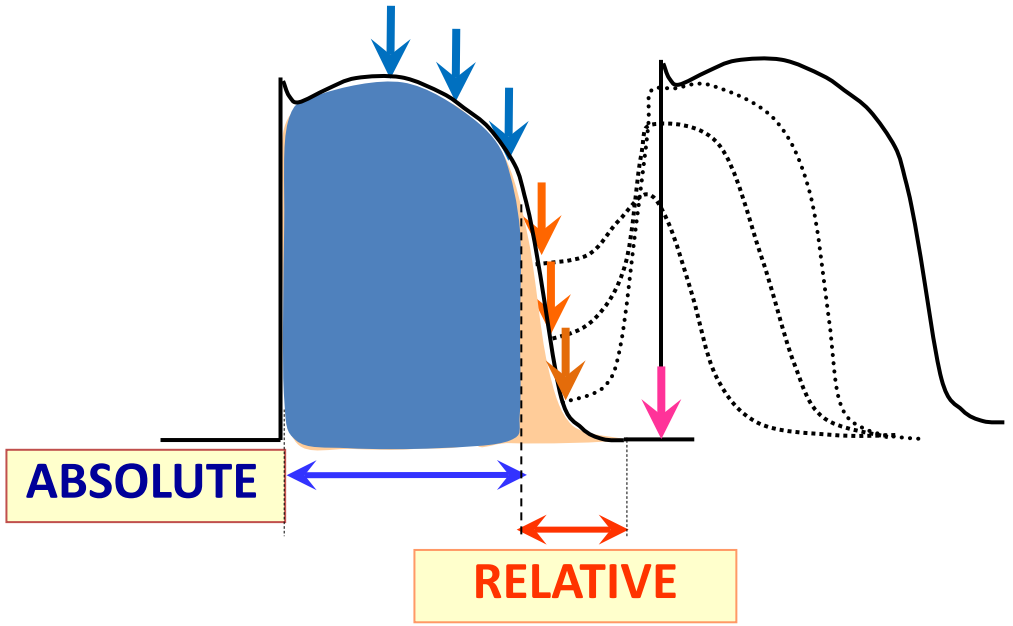
↑ depolarization ⇒ ↑conductance of Na^+ (Ca^{2+}) channels ⇒ ↑ I_{Na} (I_{Ca})

(directly proportionate to the fraction of Na^+ (Ca^{2+}) channels in the open state)

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Refractory Period – Suppression of Excitability



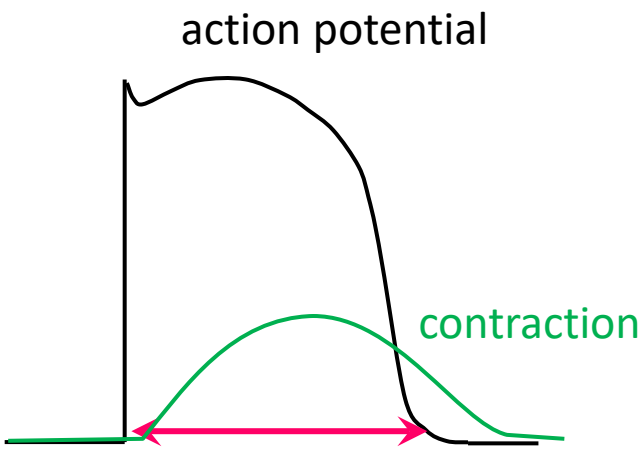


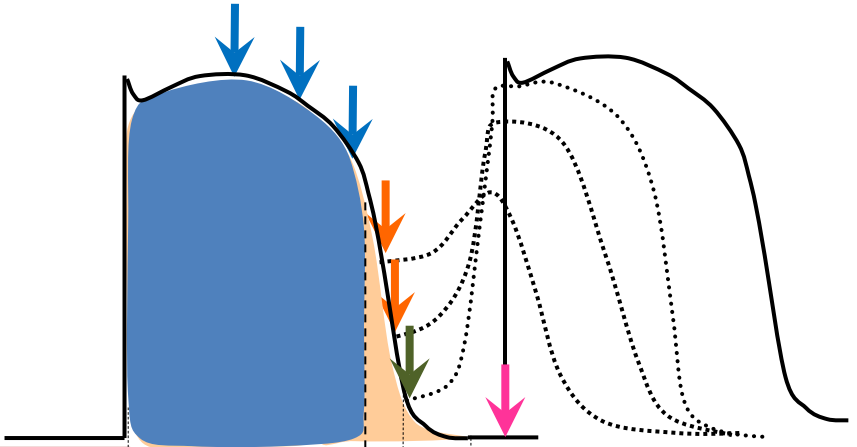
protection of the heart against:

- retrograde propagation of excitation (reentry)
- tetanic contraction at higher heart rate

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Refractory Period – Suppression of Excitability





ABSOLUTE

RELATIVE

CLINICAL ASPECTS

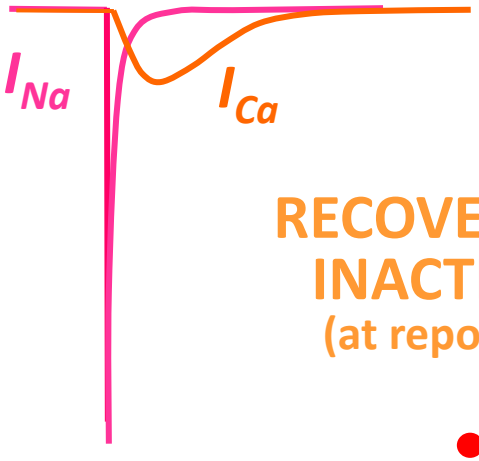
EFFECTIVE REFRACTORY PERIOD
(ARP + period of responses that do not propagate)

VULNERABLE PERIOD
(propagated responses)

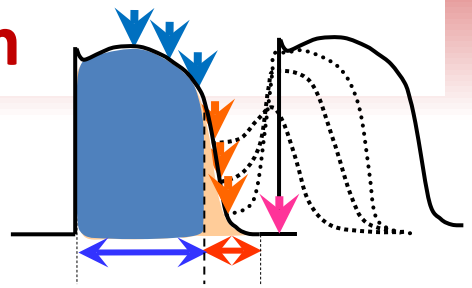
increased susceptibility to ventricular fibrillation !!!

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Refractory Period - Mechanism

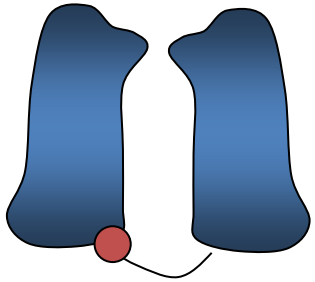


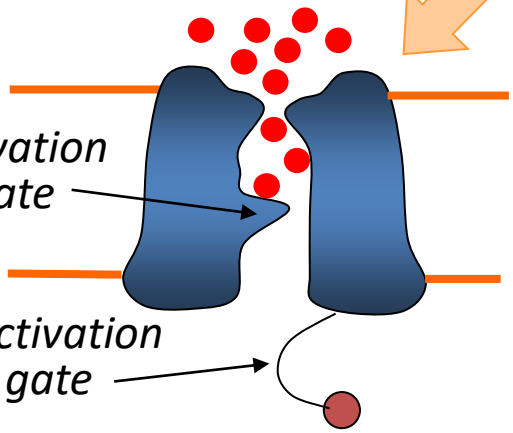
INACTIVATED STATE
(closed)



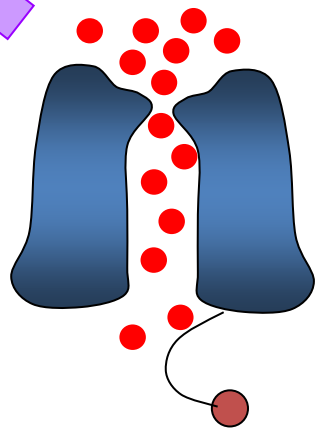
INACTIVATION
(at maintained membrane depolarization)

RECOVERY FROM INACTIVATION
(at repolarization)





ACTIVATION
(depolarization over threshold voltage)

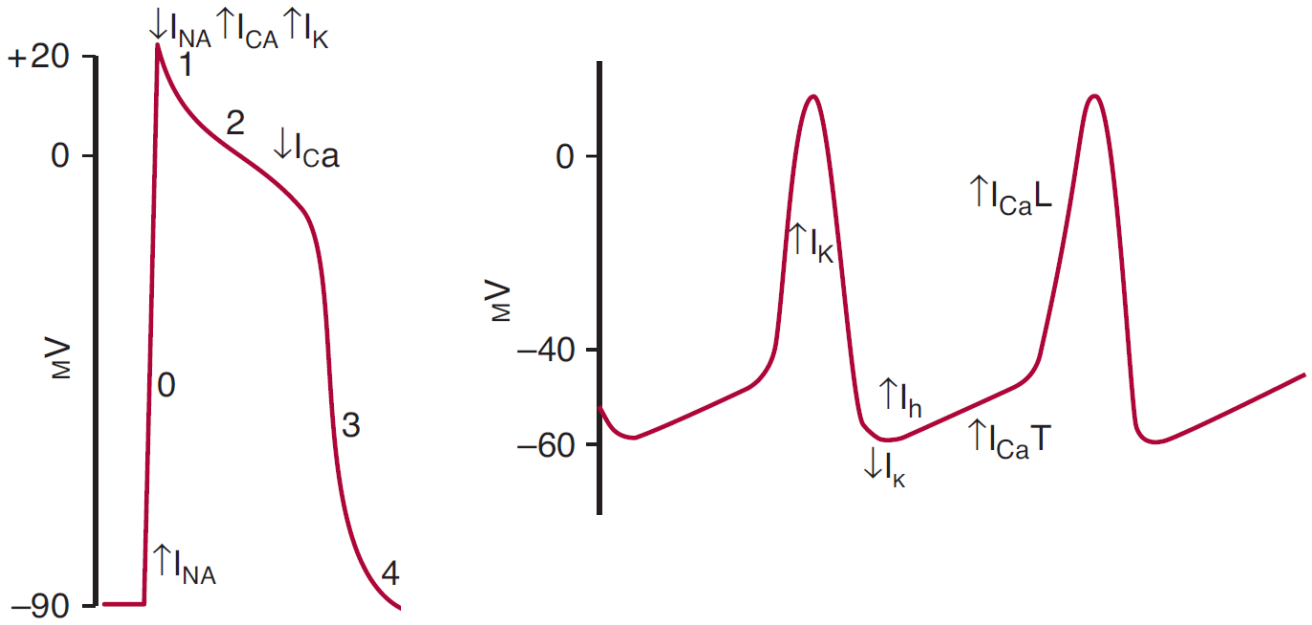


RESTING STATE
(closed)

OPEN STATE

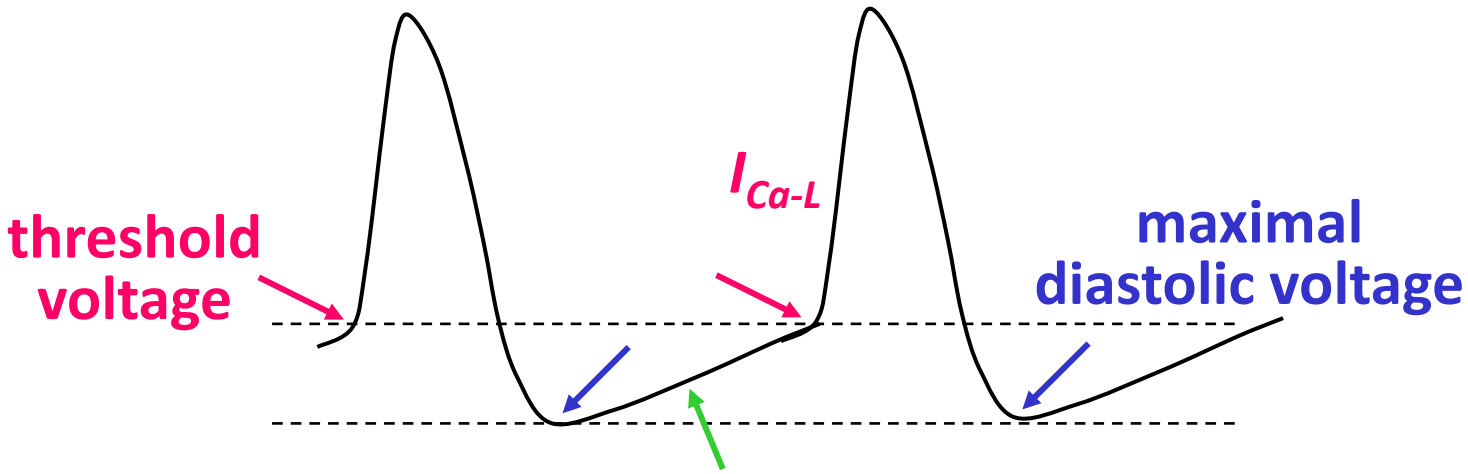
CARDIAC CELLULAR ELECTROPHYSIOLOGY

Pacemaker Activity - Mechanism



CARDIAC CELLULAR ELECTROPHYSIOLOGY

Pacemaker Activity - Mechanism

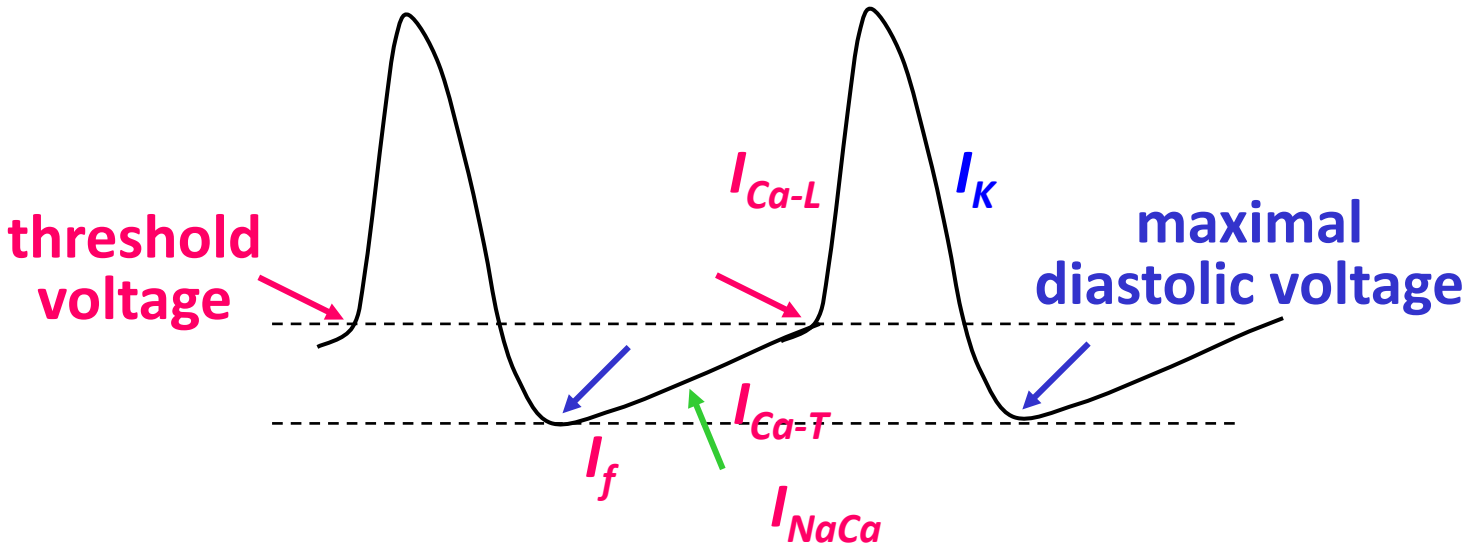


FACTORS DETERMINING THE HEART RATE:

1) maximal diastolic voltage
2) steepness of diastolic depolarization
3) threshold voltage for activation of $I_{Ca\text{-}L}$

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Pacemaker Activity - Mechanism

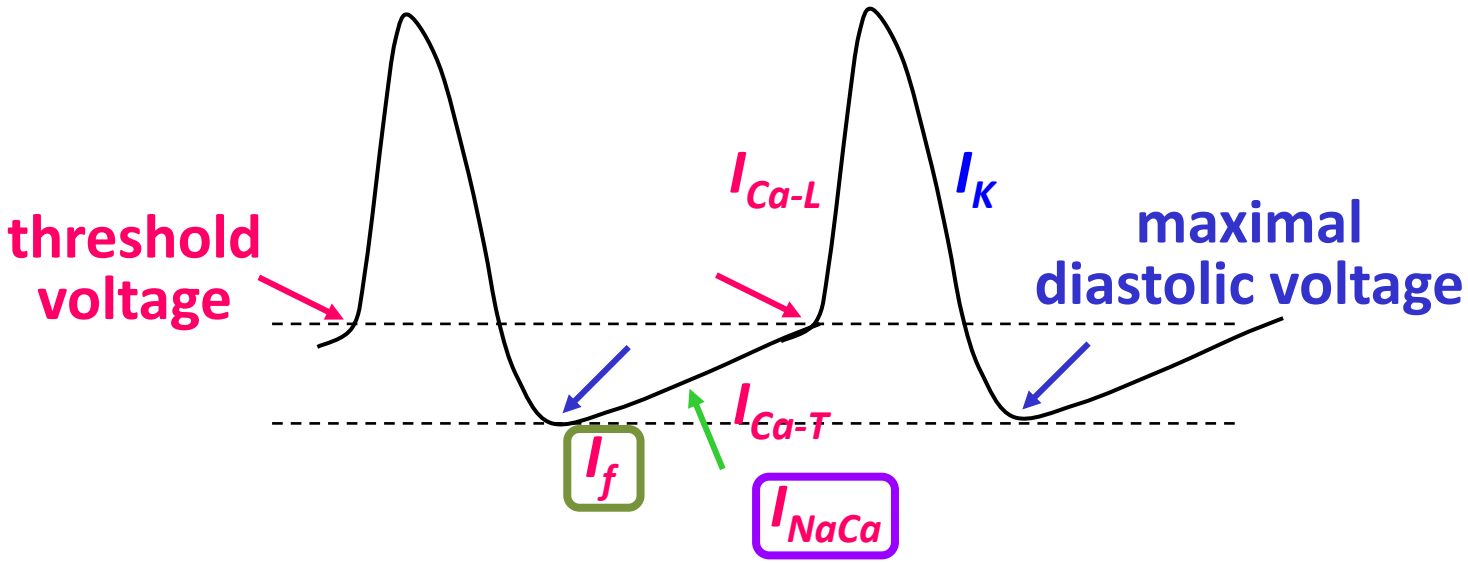


COMPLEX PROCESS resulting from an INTERPLAY between

- **REPOLARIZING CURRENTS, namely I_K (including $I_{K,Ach}$)**
- **DEPOLARIZING CURRENTS, namely I_f, I_{Ca-T}, and I_{NaCa}**

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Pacemaker Activity - Mechanism



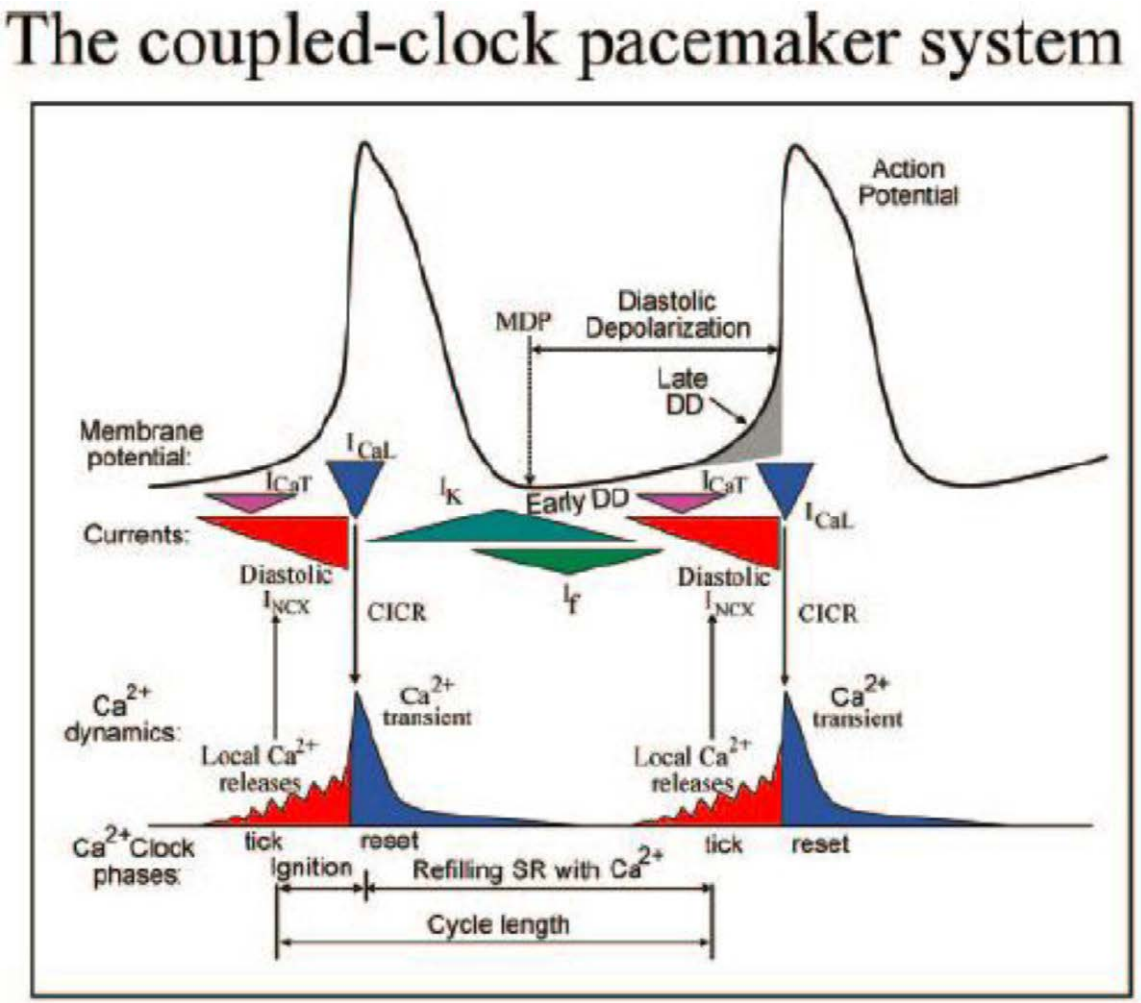
COMPLEX PROCESS resulting from an INTERPLAY between

- **REPOLARIZING CURRENTS, namely I_K (including $I_{K,Ach}$)**
- **DEPOLARIZING CURRENTS, namely I_f, I_{Ca-T}, and I_{NaCa}**

voltage clock & calcium clock

CARDIAC CELLULAR ELECTROPHYSIOLOGY

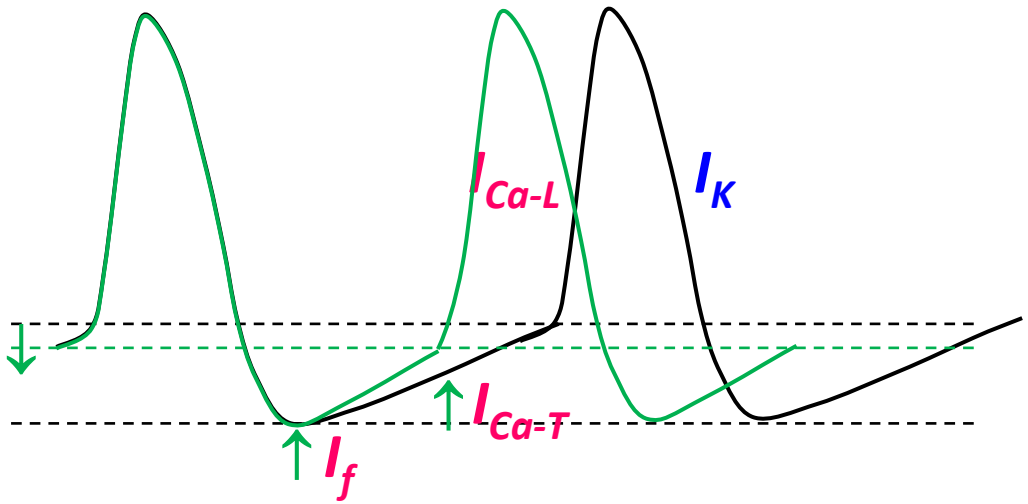
Pacemaker Activity - Mechanism



Lakatta et al., Circ Res 2010; 106: 659-673

CARDIAC CELLULAR ELECTROPHYSIOLOGY

Pacemaker Activity - Mechanism

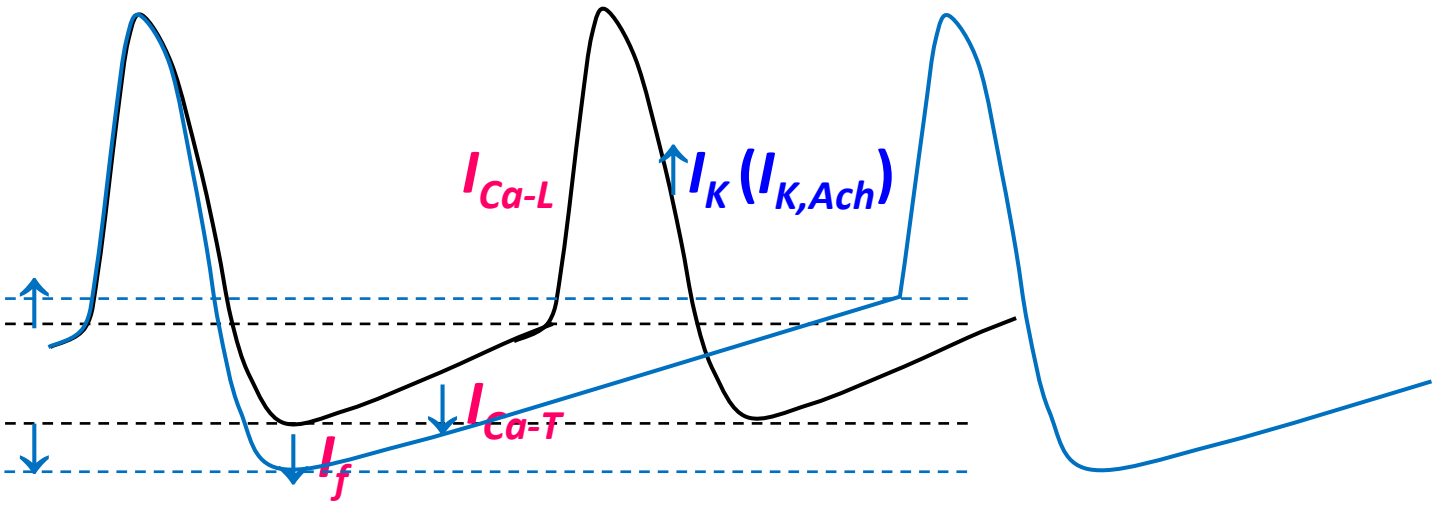


SYMPATHETIC STIMULATION

- ↑ cAMP ⟶ ↑ I_f and I_{Ca-T} ⟶ ↑ rate of diastolic depolarization
  ⟶ ↓ threshold voltage for activation of I_{Ca-L}
  (↑ excitability)

CARDIAC CELLULAR ELECTROPHYSIOLOGY

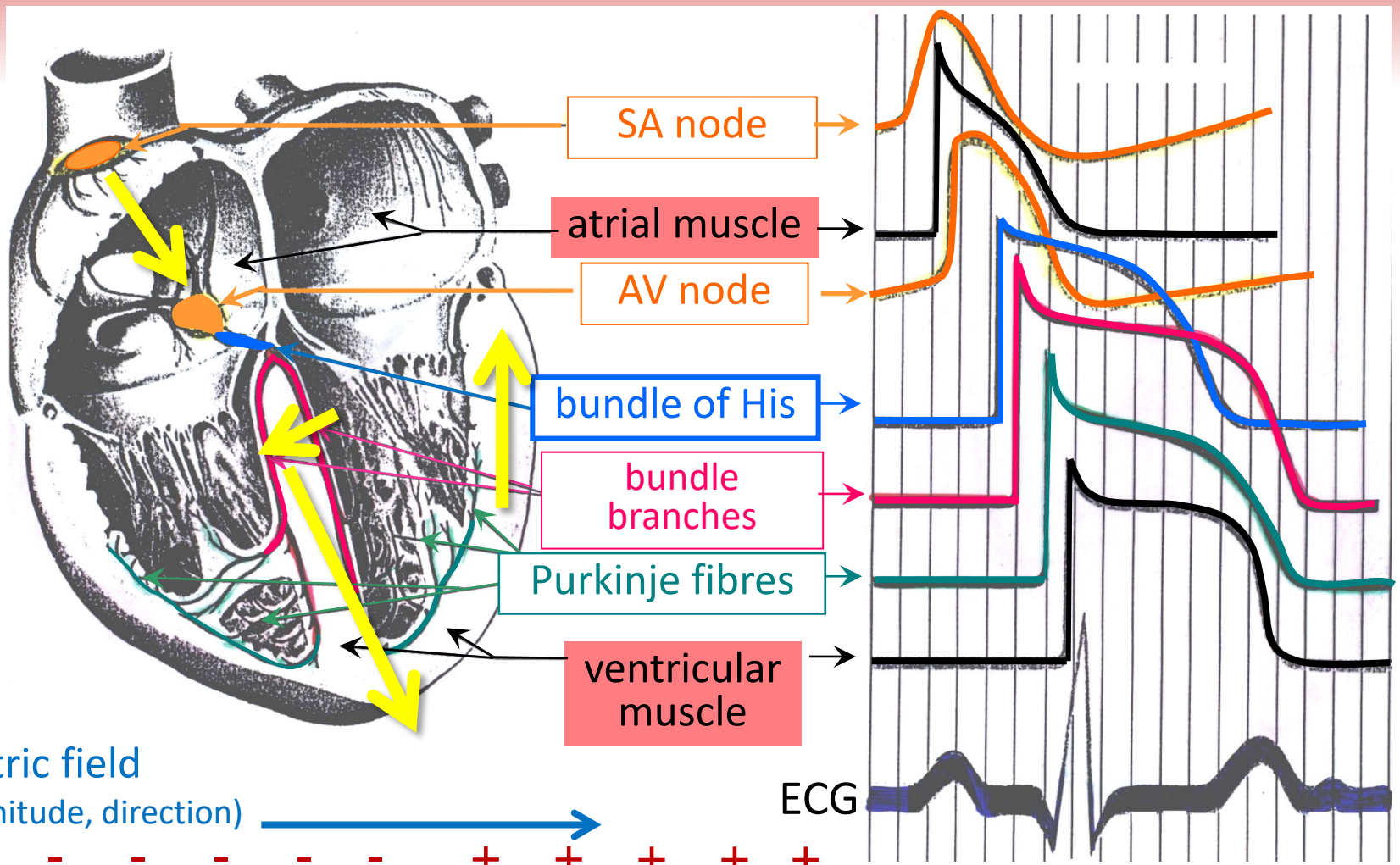
Pacemaker Activity - Mechanism



PARASYMPATHETIC STIMULATION

- ↓ cAMP ⟶ ↓ I_f and $I_{Ca\text{-}T}$ ⟶ ↓ rate of diastolic depolarization
  ⟶ ↑ threshold voltage for activation of $I_{Ca\text{-}L}$
  (↓ excitability)
- activation of $I_{K,Ach}$ ⟶ ↓ maximal diastolic voltage

SPREADING OF EXCITATION IN THE HEART

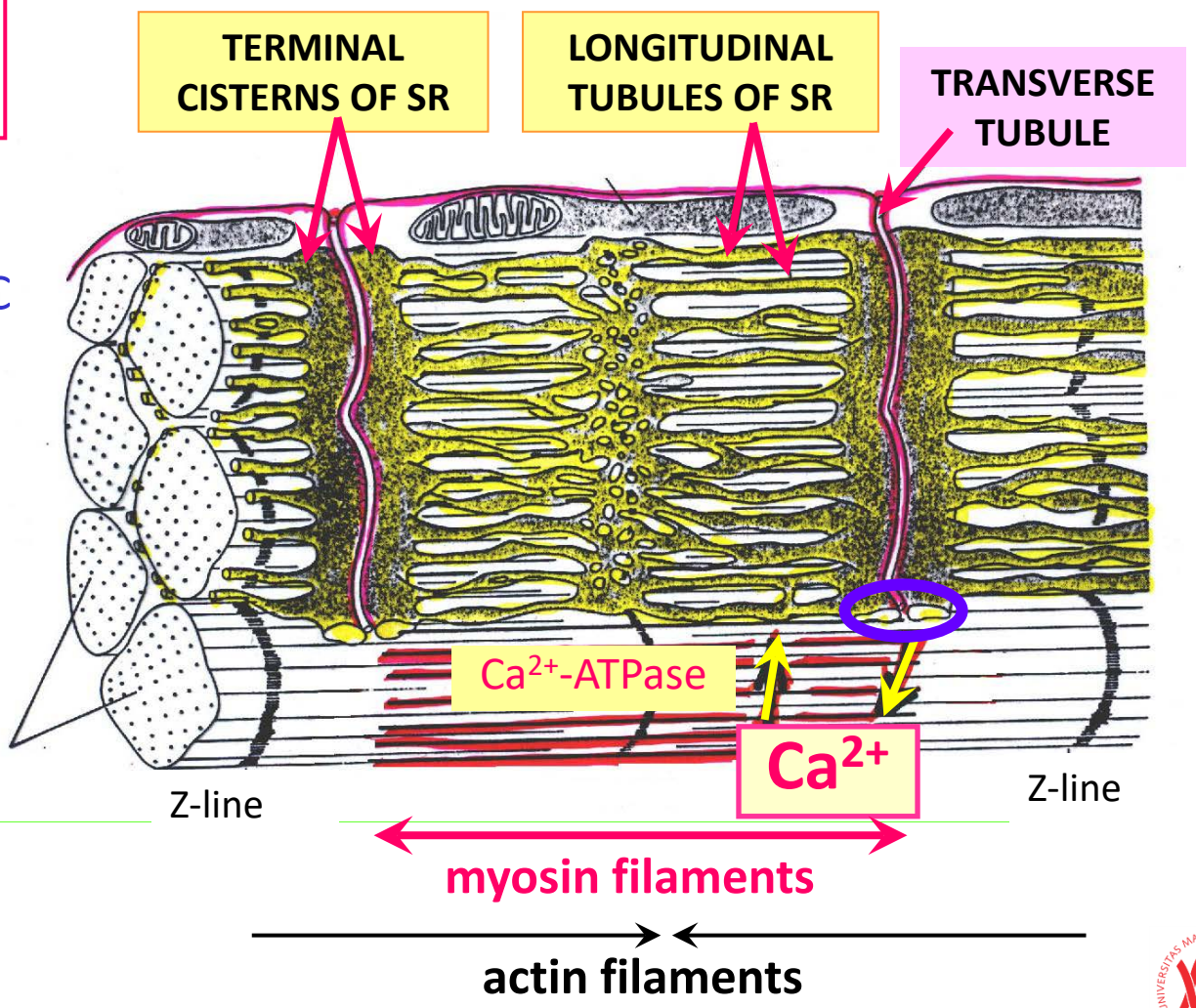


ELECTROMECHANICAL COUPLING

Excitation-Contraction Coupling

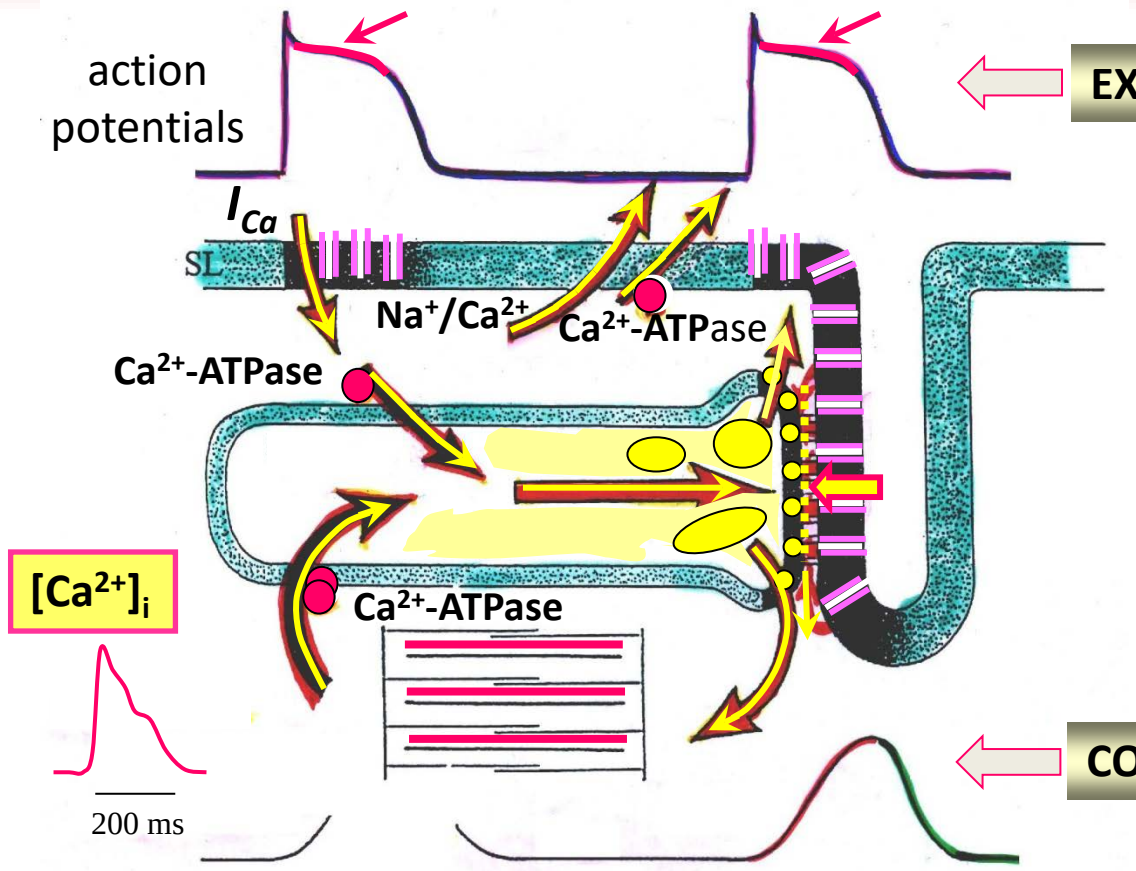
SARCOTUBULAR SYSTEM

SIMILAR ARRANGEMENT IN SKELETAL AND CARDIAC MUSCLE CELLS



ELECTROMECHANICAL COUPLING

Excitation-Contraction Coupling in Cardiomyocytes



voltage-dependent Ca^{2+} channels in the cell membrane (both the surface membrane and membrane of t-tubules)

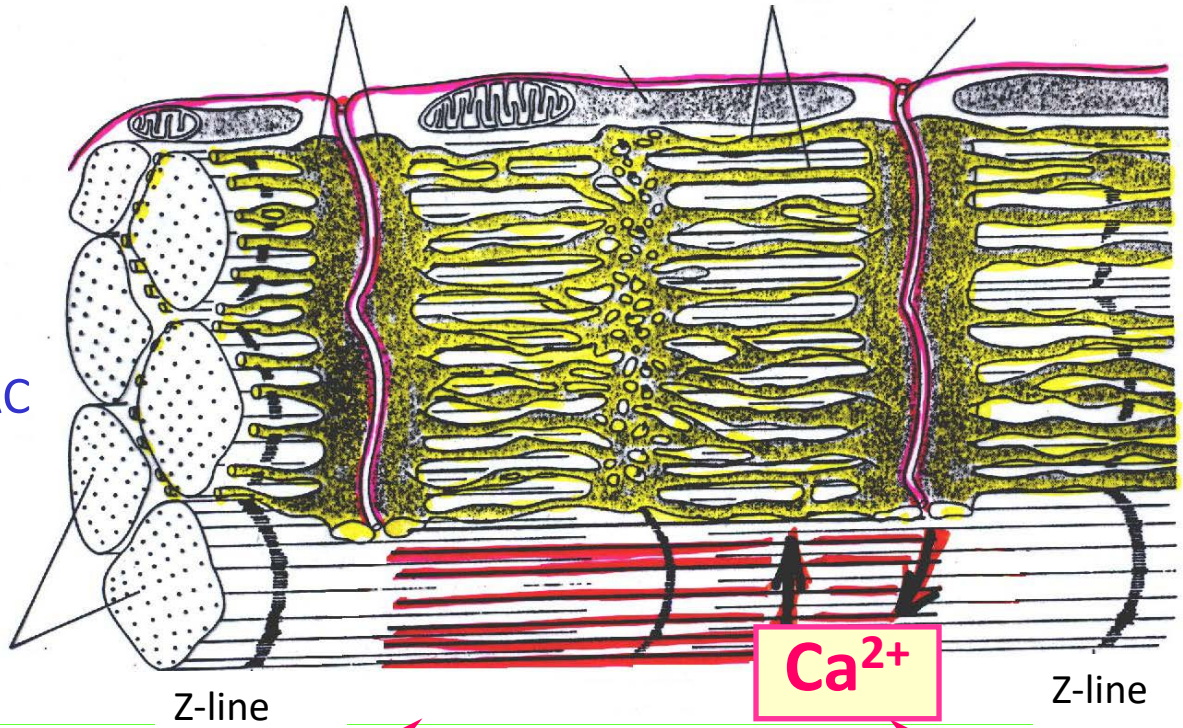
Ca^{2+}-RELEASE channels in SR (Ca^{2+}-sensitive)

ELECTROMECHANICAL COUPLING

Molecular Mechanism of Contraction

FORMATION OF CROSS BRIDGES BETWEEN ACTIN AND MYOSIN FILAMENTS

MECHANISM IDENTICAL
IN SKELETAL AND CARDIAC
MUSCLE CELLS

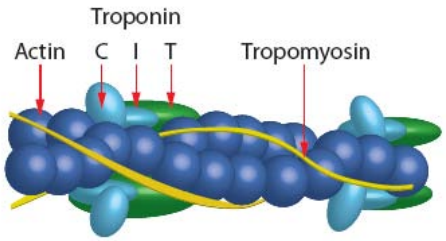


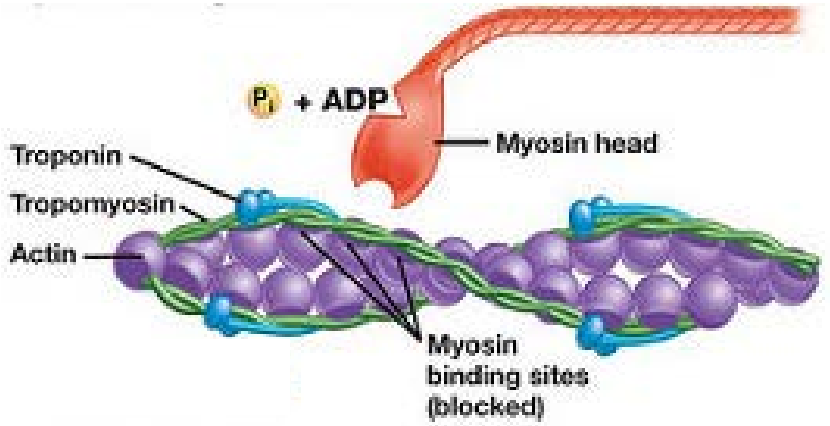
ELECTROMECHANICAL COUPLING

Molecular Mechanism of Contraction

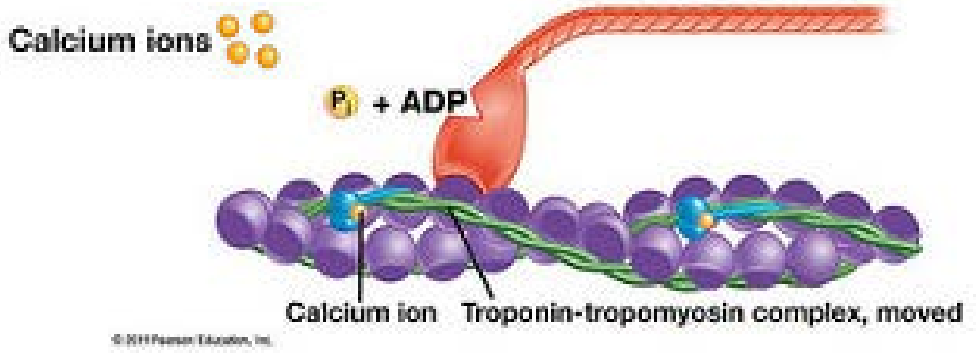
TROPONIN-TROPOMYOSIN COMPLEX

RESTING MUSCLE





CONTRACTING MUSCLE

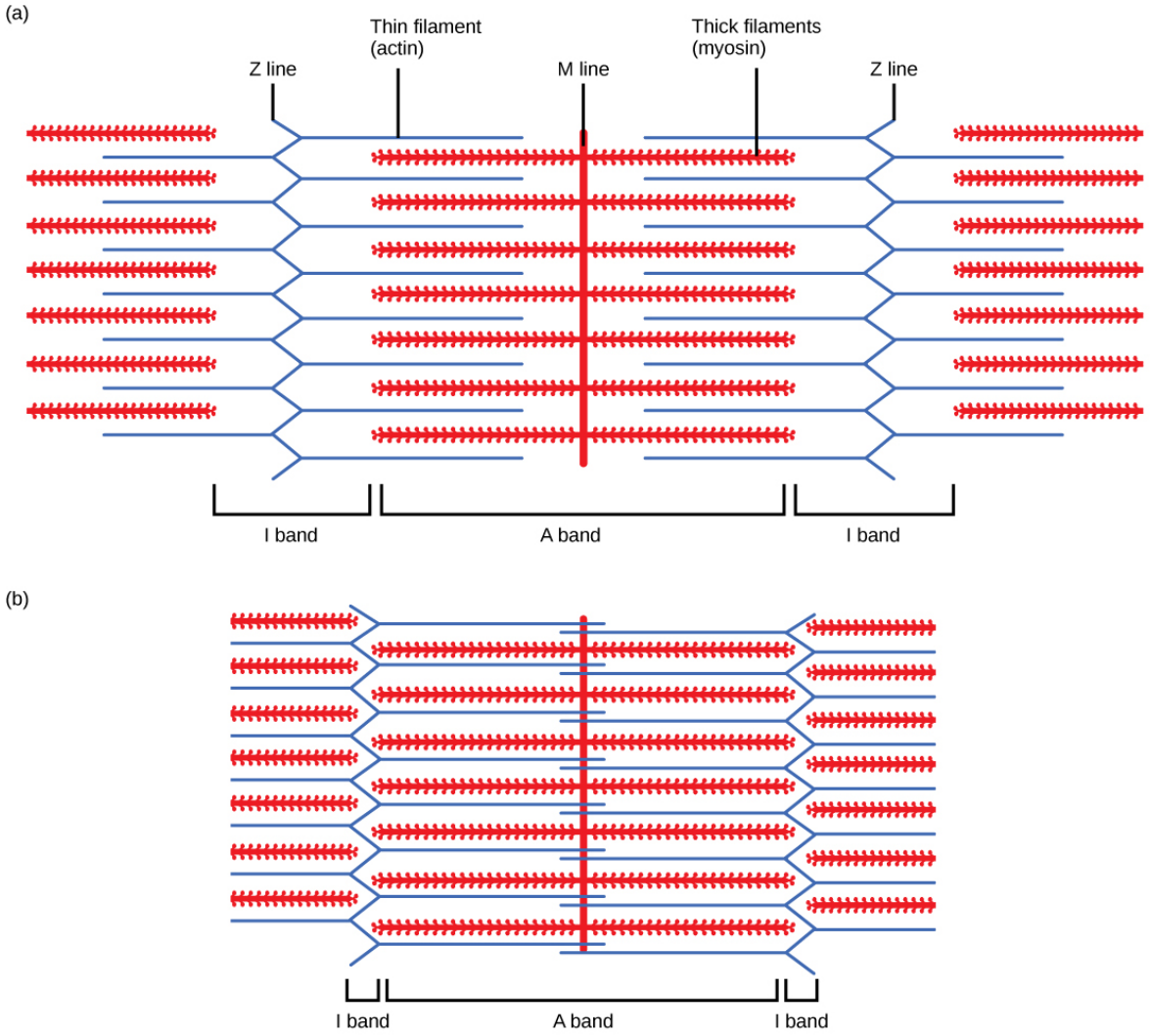


ELECTROMECHANICAL COUPLING

Molecular Mechanism of Contraction

ELECTROMECHANICAL COUPLING

Molecular Mechanism of Contraction



ELECTROMECHANICAL COUPLING

Contractility

= ability of cardiac muscle cell to contract at constant initial (resting) length of the sarcomere

Contractility is regulated by INOTROPIC FACTORS

that cause changes in excitation-contraction coupling (positive or negative) ⇒ ↓↑contractility

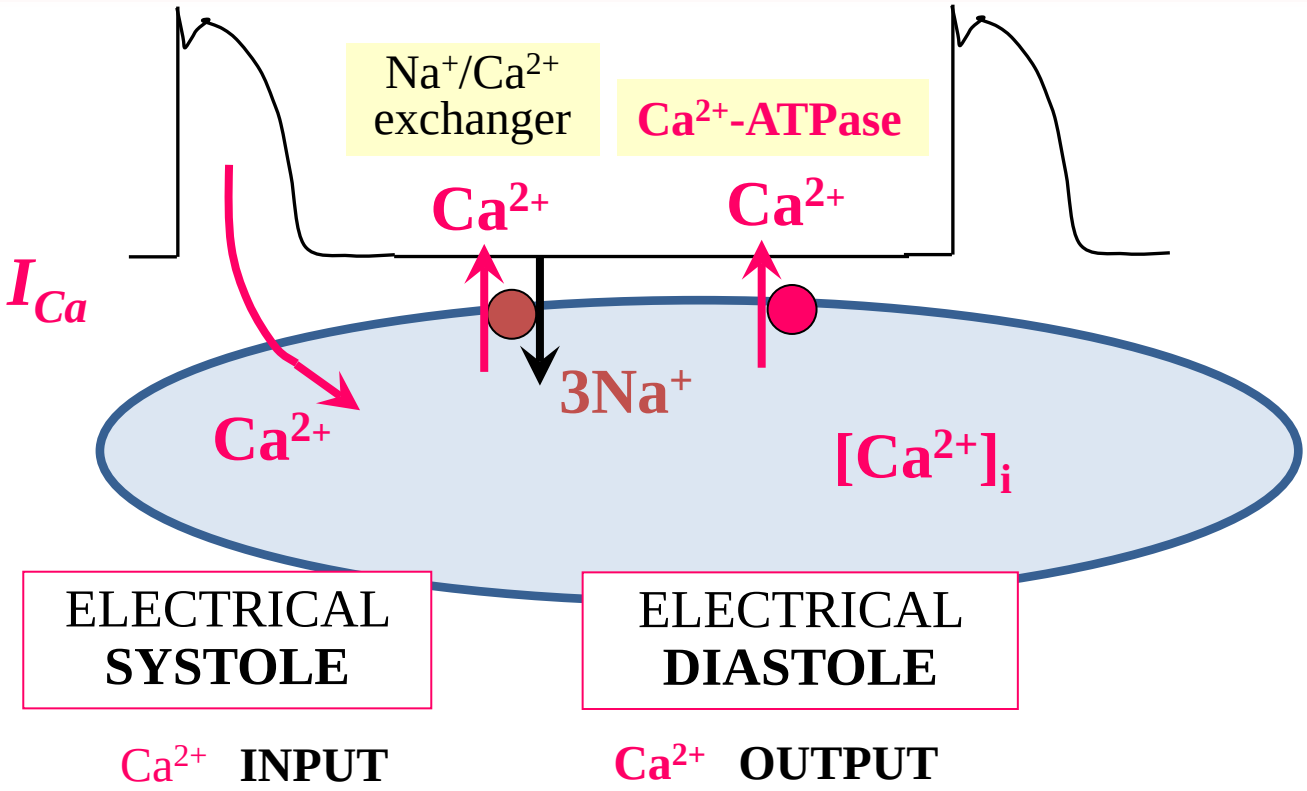
↓↑ $[Ca^{2+}]_i$

- **LIGAND-RECEPTOR INTRACELLULAR PATHWAYS** at:
  - ↑↓ **activity of AUTONOMIC NERVE SUPPLY** to the heart (**sympathetic / parasympathetic**)
  - ↑↓ **level of specific HORMONES** in the blood

- **FREQUENCY EFFECT**
  ↑ **mechanical response to an increased frequency of stimulation**

ELECTROMECHANICAL COUPLING

Mechanism of Frequency Effect



↑ frequency ⇒ shortening of electrical diastole ⇒ Ca^{2+} input > Ca^{2+} output ⇒

↑ $[Ca^{2+}]_i$ ⇒ ↑ contractility