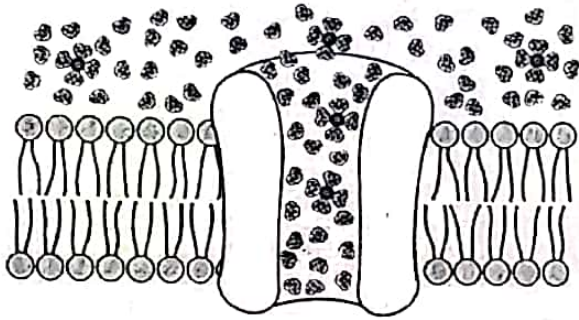
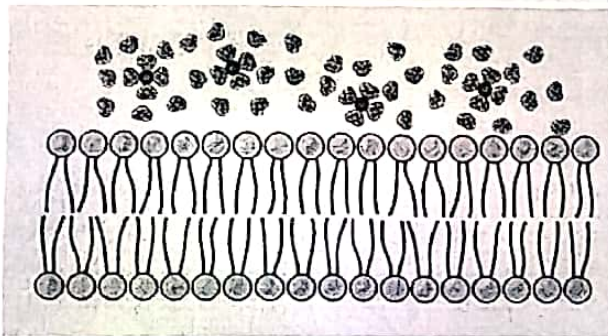


## Ion channel structure and gating function

**Ion Channels Provide a Polar Environment for Diffusion of Ions Across the Membrane**



**Ions Cannot Diffuse Across the Hydrophobic Barrier of the Lipid B**



- Mediate the generation, conduction and transmission of electrical signals in the nervous system
- Control the release of neurotransmitters and hormones
- Initiate muscle contraction
- Transfer small molecules between cells (gap junctions)
- Mediate fluid transport in secretory cells
- Control motility of growing and migrating cells
- Provide selective permeability properties important for various

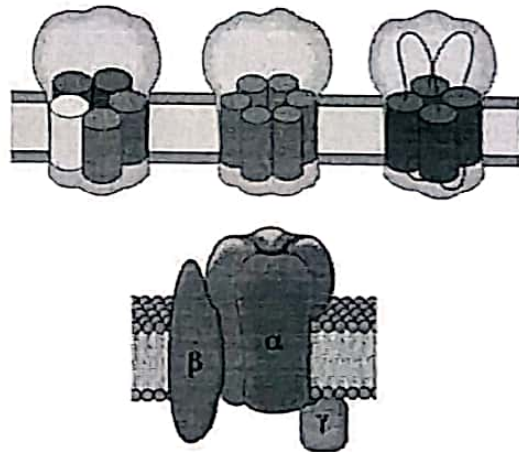
### Conduction

❖ Ion channels conduct up to  $10^8$  Ions/sec

❖ Ion Channels Act As Catalysts

- Speed up fluxes
- Do not impart energy
- Driving force is provided by electrochemical potential

**Channels are Made Up of Subunits**



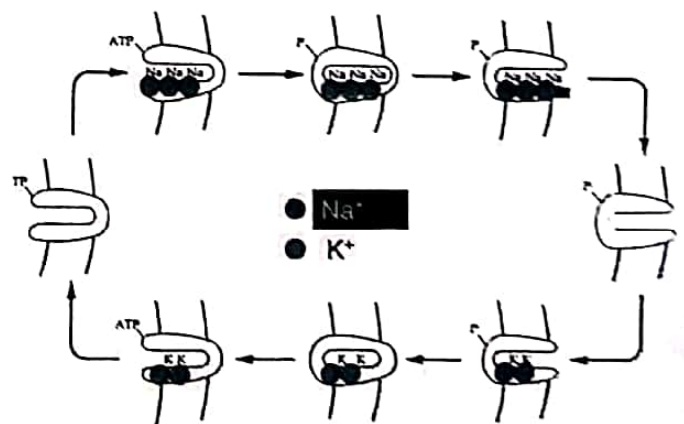
### Conduction

❖ Ion channels conduct up to  $10^8$  Ions/sec

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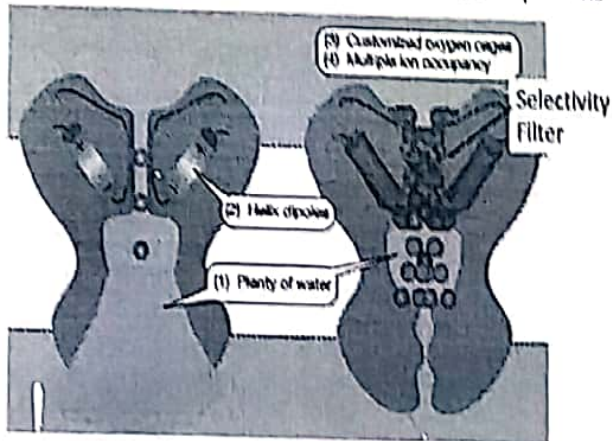
**Unlike Channels, Ion Pumps Do Not Provide a Continuous Pathway Through the Membrane**



## Ion Channels are Selectively Permeable

Cation Permeable	Anion Permeable
Na <sup>+</sup>	Cl <sup>-</sup>
K <sup>+</sup>	
Ca <sup>++</sup>	

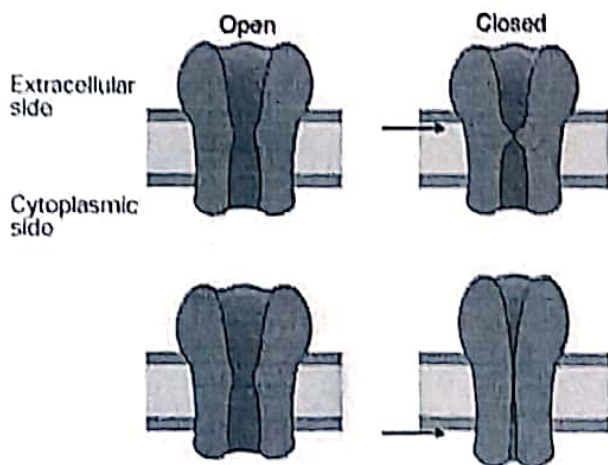
Structure of K<sup>+</sup> channel has multiple functional adaptations



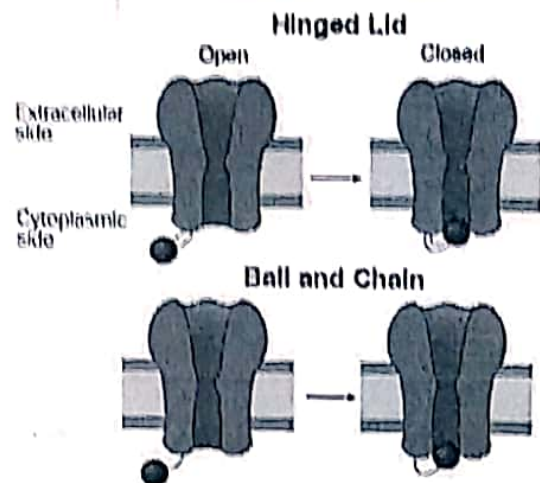
There are two major types of gating actions

1. Conformational Changes Along the Channel Walls
2. Involve Plugging the Channel

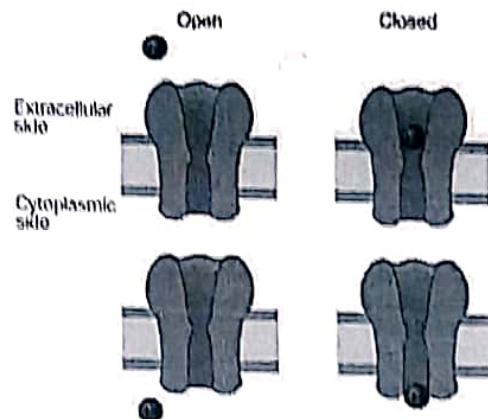
Gating Can Involve Conformational Changes Along the Channel Walls



Gating Can Involve Plugging the Channel

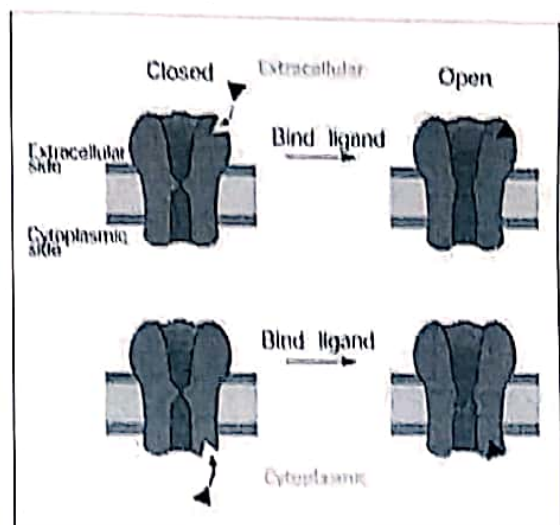


Gating Can Result from Plugging by Cytoplasmic or Extracellular Gating Particles



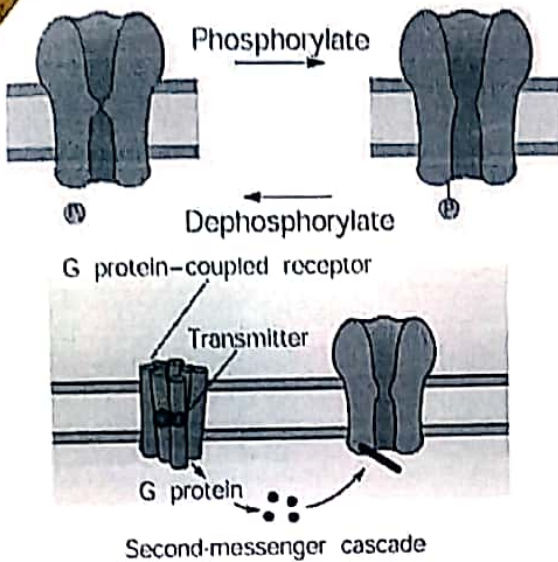
There are Five Types of Gating Controls

a) Ligand Binding

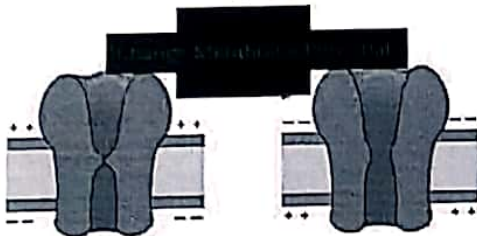




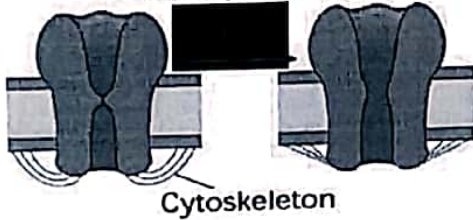
## Phosphorylation



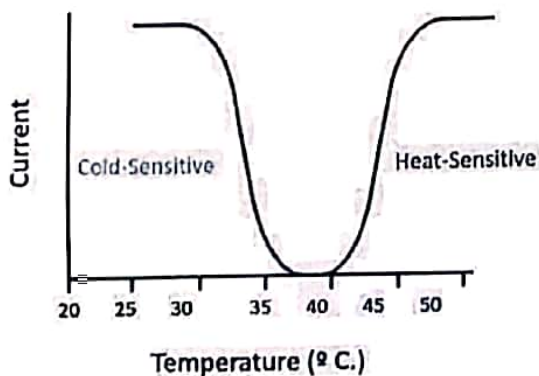
## C Voltage-gated



## D Stretch or pressure-gated

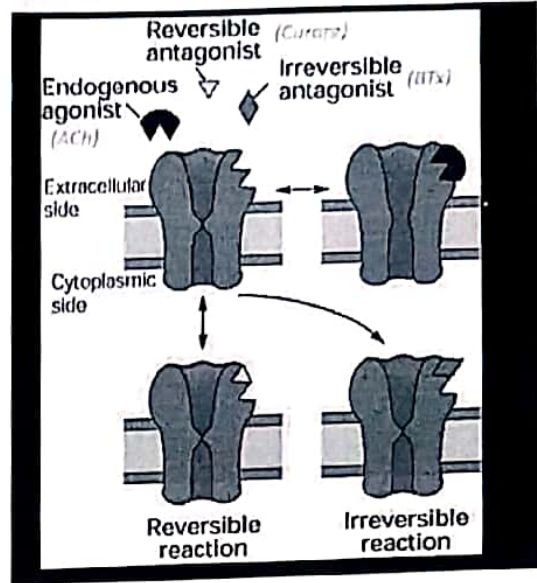


## e) Temperature Gated

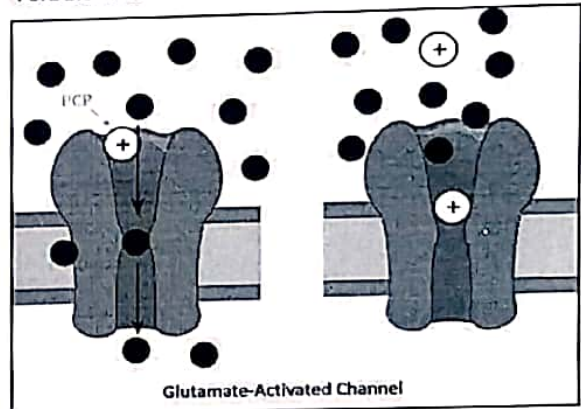


## Modifiers of Channel Gating

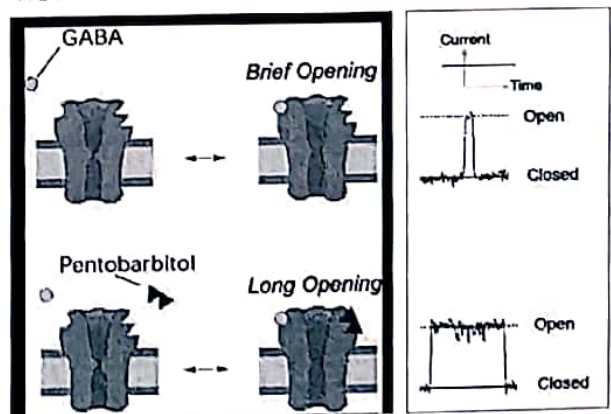
### Binding of Exogenous Ligands Can Block Gating



### Ion Permeation Can be Prevented by Pore Blockers



### Exogenous Modulators Can Modify the Action of Endogenous Regulators



## Ion channels have three basic functional properties

- Conduct
- Select
- Gate

- ❖ Evolutionary relationships between ion channels
- ❖ Various factors contribute to ion channel diversity

### Ion Channel Gene Superfamilies

#### I) Channels Activated by Neurotransmitter-Binding (pentameric channel structure):

- Acetylcholine
- GABA
- Glycine
- Serotonin

#### II) Channels Activated by ATP or Purine Nucleotide-Binding (quaternary or trimeric channel structure)

#### III) Channels With Quaternary Structure Related to Voltage-Gated, Cation-Permeant Channels:

##### A) Voltage-gated:

- $K^+$  permeant
- $Na^+$  permeant
- $Ca^{++}$  permeant
- Cation non-specific-permeant

##### B) Cyclic Nucleotide-Gated (Cation non-specific-permeant)

##### C) TRP Family (Cation Non-specific): Gated by:

- Osmolarity
- pH
- mechanical force (hearing, etc.)
- ligand binding
- temperature

##### D) Channels Activated by Glutamate-Binding

- quaternary channel structure
- cation non-specific permeability

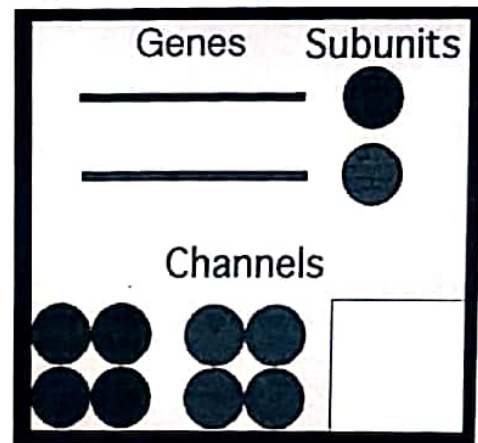
#### IV) "CLC" Family of $Cl^-$ -Permeant Channels (dimeric structure):

##### Gated by:

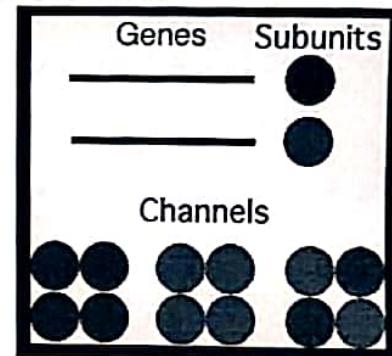
- Voltage
- Cell Swelling
- pH

#### V) Gap Junction Channels (non-specific permeability; hexameric structure)

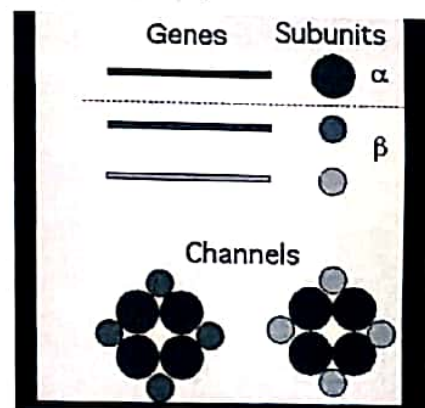
### Different Genes Encode Different Pore-Forming Subunits



### Different Pore-Forming Subunits Combine in Various Combinations

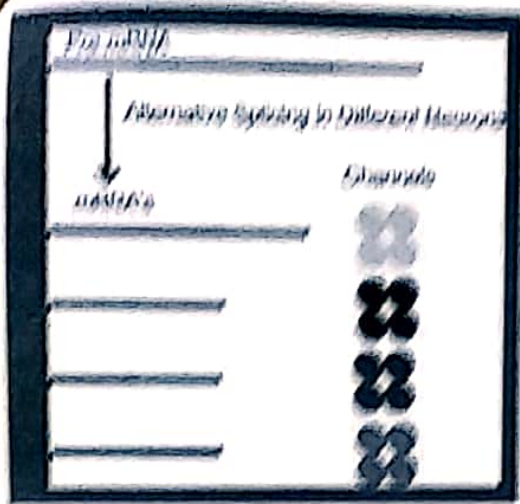


### The Same Pore-Forming Subunits Can Combine with Different Accessory Subunits

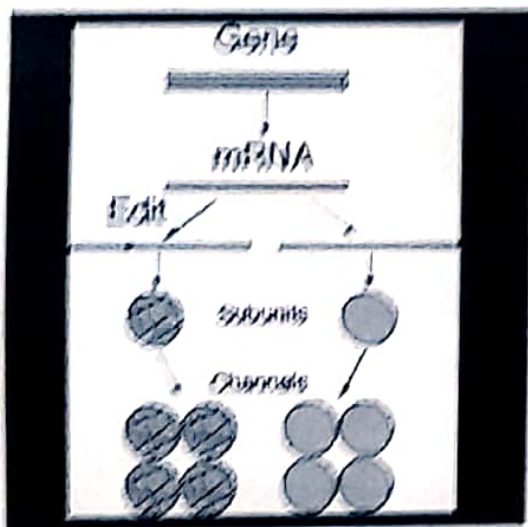




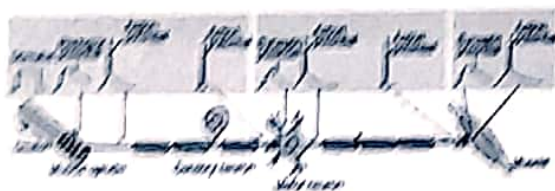
# Alternative Splicing of pre-mRNA



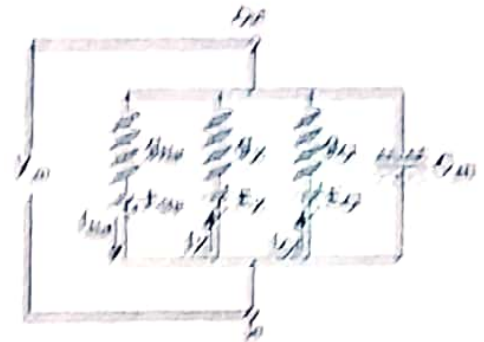
## Post-Transcriptional Editing of pre-mRNA



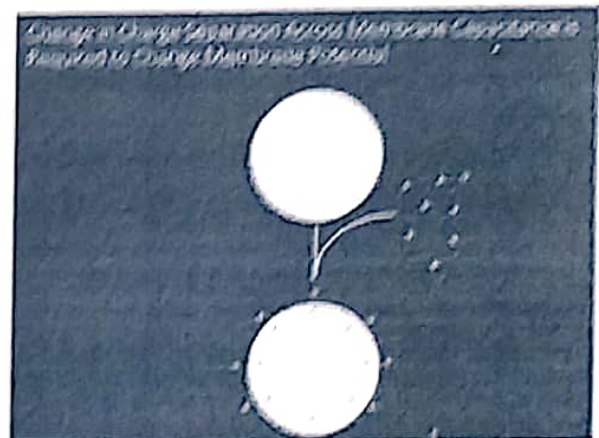
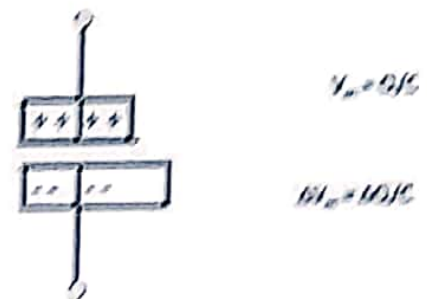
Chemical Potentials, Gravitational Potentials and Electric Potentials All Can Be Described by the Generalized Model of the Membrane



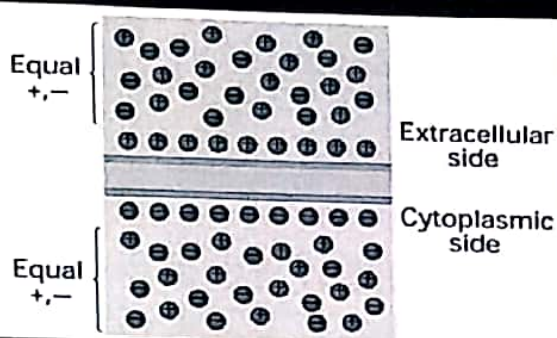
# Equivalent Circuit Model of the Membrane



## The Lipid Bilayer Acts Like a Capacitor

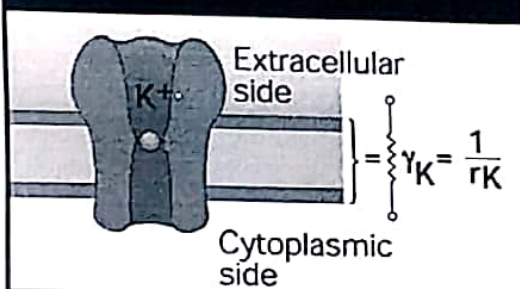


## The Bulk Solution Remains Electroneutral

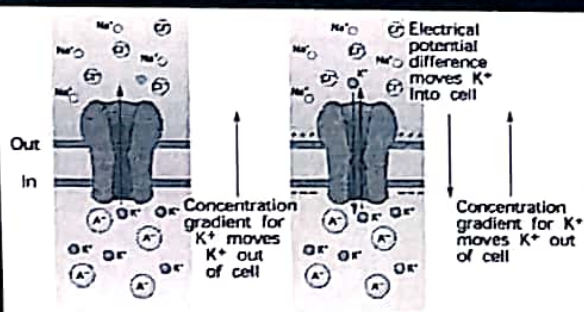


PHS, Fig 7-1

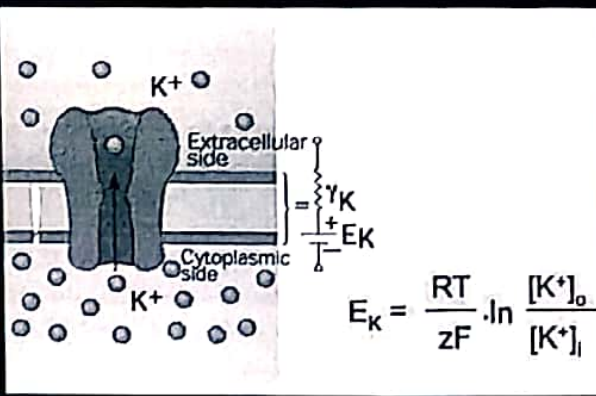
## Each K<sup>+</sup> Channel Acts as a Conductor



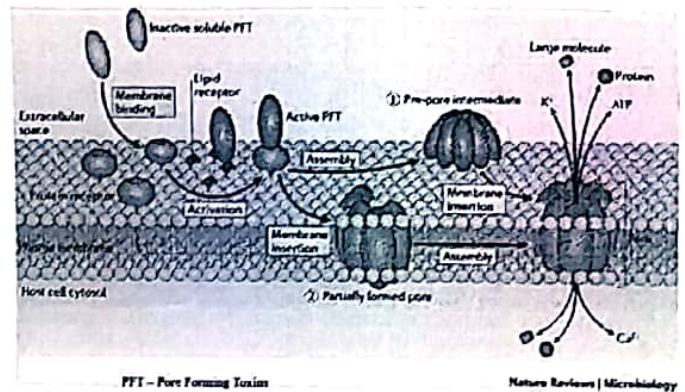
## Ion Channel Selectivity and Ionic Concentration Gradient Result in an Electromotive Force



## An Ion Channel Acts Both as a Conductor and as a Battery



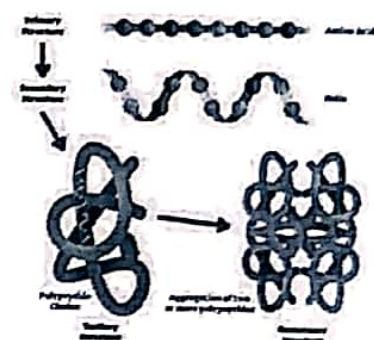
## PORE FORMATION



## Protein Structure

Protein structure is the three-dimensional arrangement of atoms in an amino acid chain molecule.

Proteins are polymers - specifically polypeptides - formed from sequences of amino acids, the monomers of the polymer.



## Importance of Proteins

- > Muscle structure depends on protein-protein interactions
- > Transport across membranes involves protein-solute interactions
- > Nerve activity requires transmitter substance-protein interactions
- > Immune protection requires antibody-antigen interactions

## Types of Protein structure

- Primary Structure
- Secondary Structure
- Tertiary Structure
- Quaternary Structure

## Primary Structure

Polypeptide chains → Amino Acids

Largest polypeptide chain approx has 5000AA but most have less than 2000AA

Amino Acid Basic Structure  $H_2N-CH-COOH$

Arrangement of the 20 amino acids in the polypeptide is the amino acid sequence which composes the primary structure of the protein





**Nonpolar,  
hydrophobic**

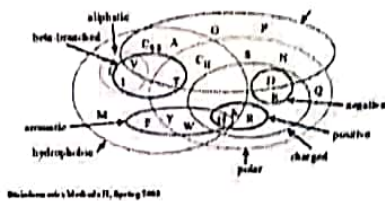
[illegible]

**Polar, uncharged**

**Polar, charged**

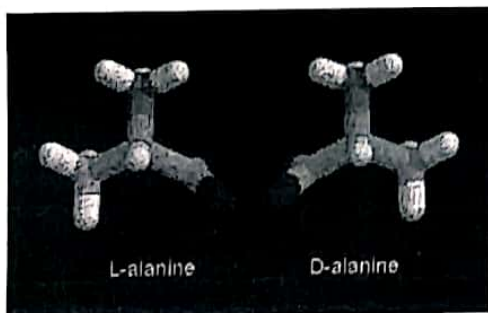
<http://www.people.virginia.edu/~rjh9u/aminacid.html>

## Amino Acid Classification



A Venn diagram showing the relationship of the 20 naturally occurring amino acids to a selection of physico-chemical properties thought to be important in the determination of protein structure.

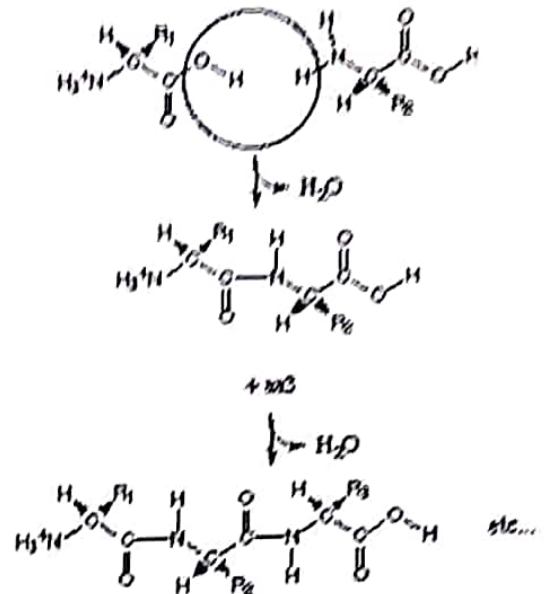
### Stereochemistry (Configuration of amino acids in proteins)



## Bond Formation

### Linking two amino acids together

### Definitions (N-terminal, C-terminal, polypeptide backbone, amino acid residue, side chains)



<http://web.mit.edu/esgblo/www/lm/proteins/peptidebond.html>

## Primary Structure

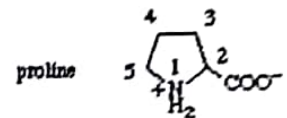
### What is a native protein?

### Protein conformation & problem of protein folding

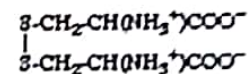
- Hydrophobic, hydrophilic
- Charge
- Chaperones

## Special Purpose Amino Acids

**Proline**



### Cysteine



## Protein Secondary Structure

## Introduction

### Peptide bond geometry

### Ramachandran plot

## Structures

## Peptide Bond



<http://www.mhhe.com/biochem/4e/figure01/figure01-10a.html>

## Peptide Bond

### Resonance

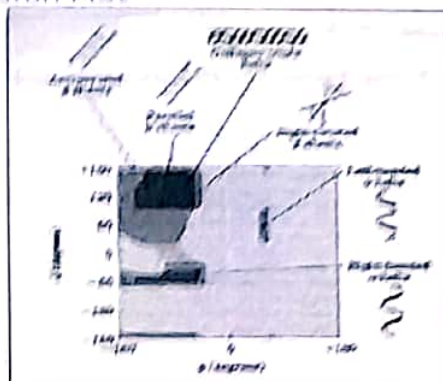
C-N bond length of this peptide is 139 pm, shorter than that found in pure C-N single

Peptide bond planar

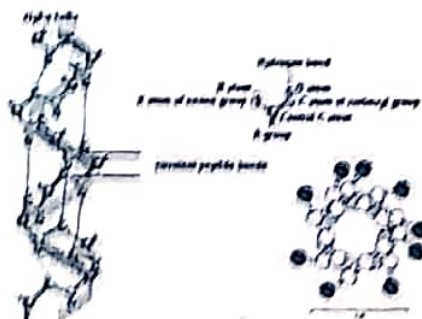
$\omega$ , angle around peptide bond,

IP for cis, 180° for trans

## Ramachandran Plot



## Alpha Helix



## Alpha Helix

Left-handed

Right-handed



## Alpha Structure Features

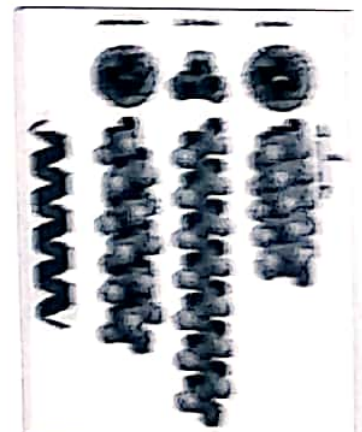
2.5 residues per turn

5.4 residues per 100° rotation

Carboxyl group of residue 1 hydrogen bonds to amino group of residue 4

## Helix Structures

TS & Hbond 180°  
Alpha 572-45 1.1-4 25 25  
Beta 572-45 1.1-2 25 25  
Gamma 572-45 1.1-5 25 25

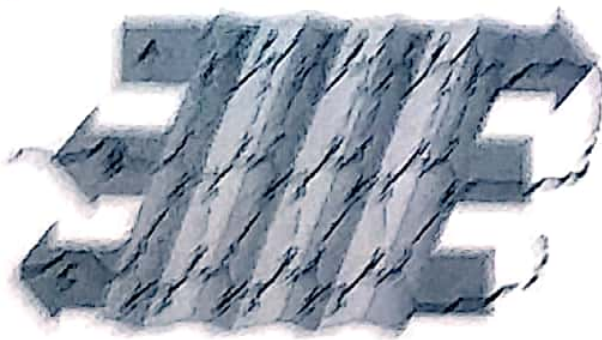


## More Helix Structures

Type	φ	ψ	comments
Collagen	-51	153	Fibrous proteins Three left-handed helices (Gly, X) <sub>n</sub> , X = Pro / Lys
Type II helices-75	150		left-handed helices formed by polyglycine



## Beta Sheet



### Beta Sheet Features

Hydrogen bonds are the main force of stability.  
 Hydrophobic interactions between the side chains of the polypeptide chains also contribute to the stability.  
 Hydrophobic interactions are the main force of stability in the interior of the protein.

### More Beta Structures

Beta sheet structure (left) and beta barrel structure (right).

Left: beta sheet



Beta sheet structure (left) and beta barrel structure (right).

Right: beta barrel



Right: beta barrel

### Tertiary Protein Structure

Refers to the three-dimensional structure of a protein molecule, which is determined by the sequence of amino acids in the primary structure.

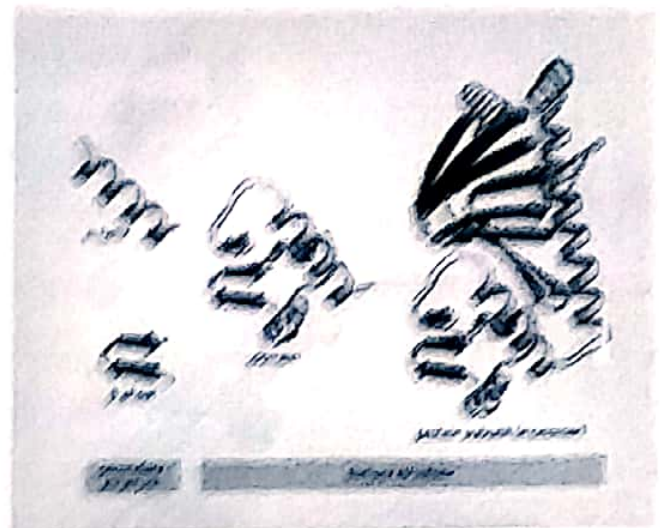
Stabilized by:

Hydrophobic interactions, which determine tertiary structure.

Hydrophobic interactions are the main force of stability in the interior of the protein.

Hydrophobic interactions are the main force of stability in the interior of the protein.

Hydrophobic interactions are the main force of stability in the interior of the protein.



## Quaternary Structure

Not all proteins have a quaternary structure.

A composite of multiple polypeptide chains is called an oligomer or multimeric.

Hemoglobin is an example of a tetramer.

Globular vs. Fibrous

