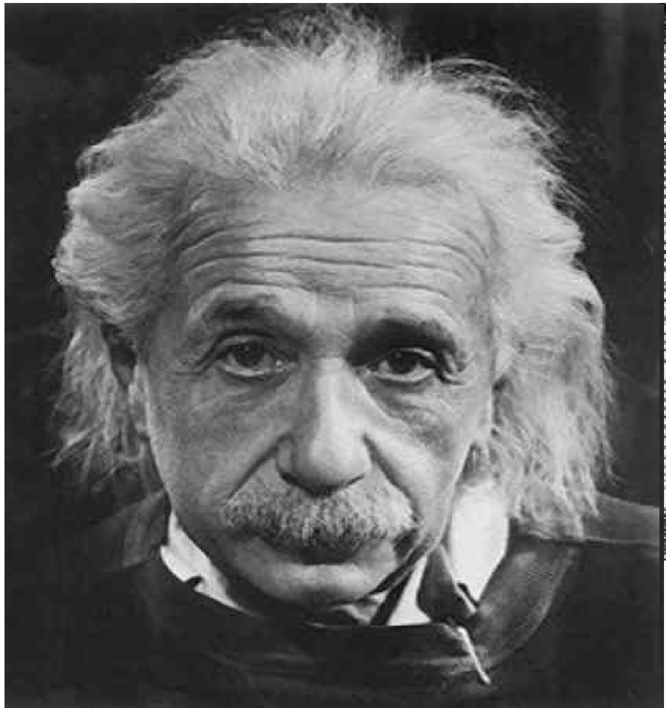
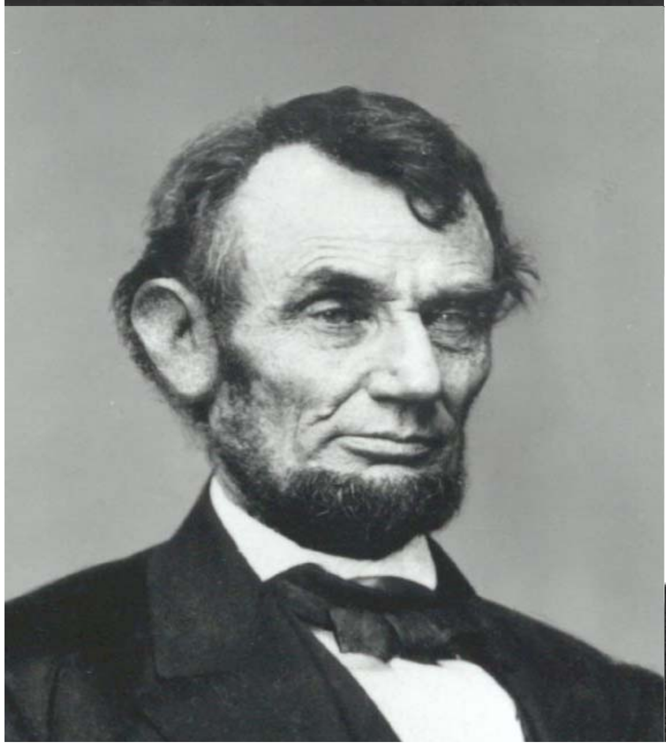
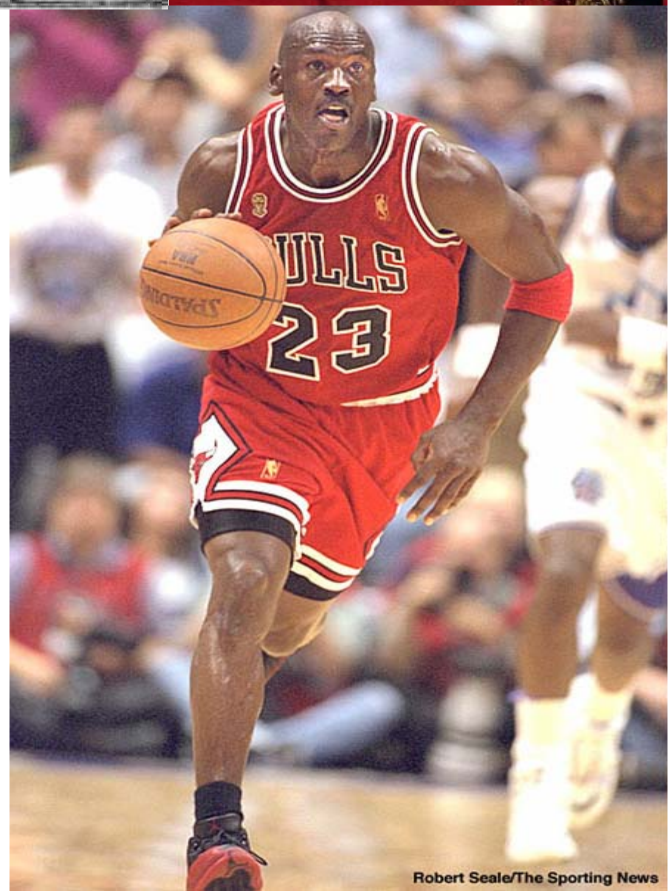
Introduction to Neuroscience:

From Neuron to Synapse

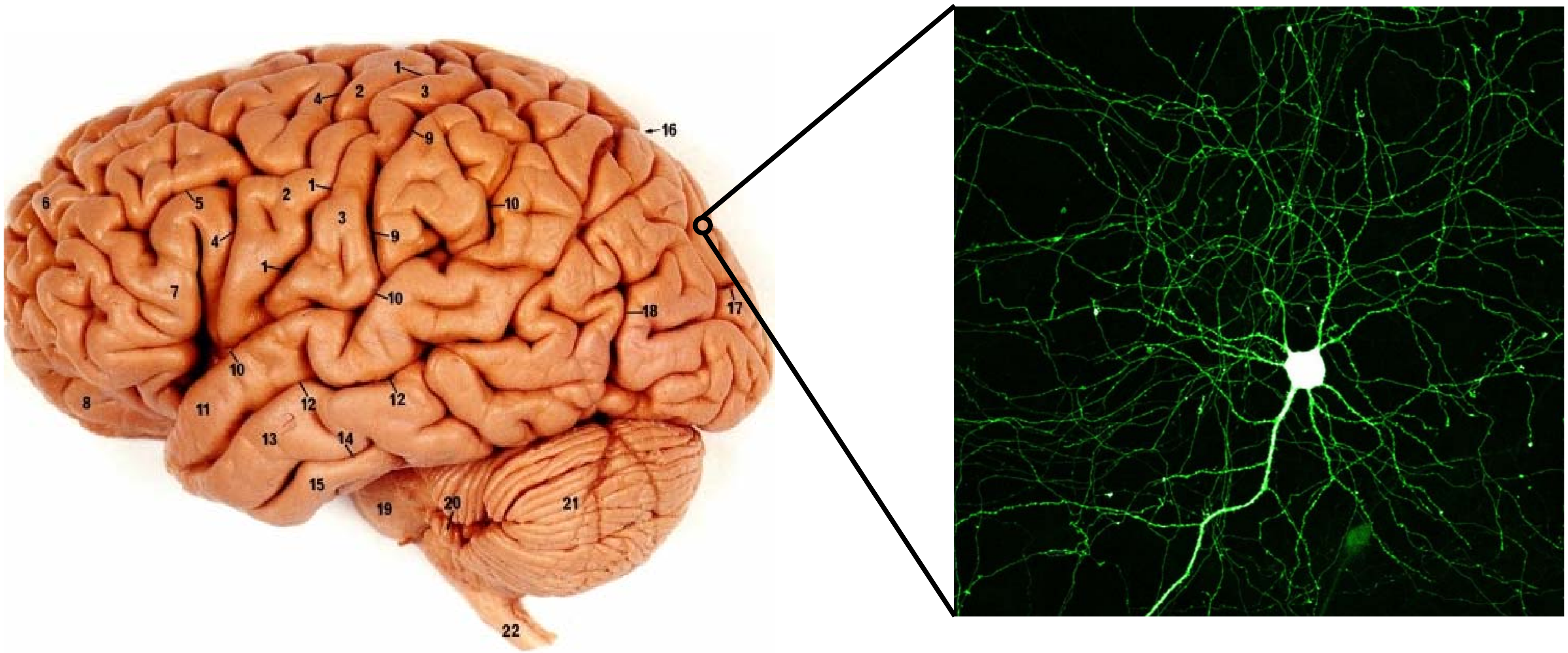






Robert Seale/The Sporting News

The brain underlies all human achievement – and it is the hub of all our sensations, memories, feelings, behaviors...



The current course will focus on the function of the basic element of the brain – the neuron – and on interactions among neurons

Outline of today's lecture

- **The current course in the context of other Neuroscience courses @ Weizmann**
- **Course Syllabus & Procedural Introduction to the course**
- **A primer on neurons**

Neuroscience Courses at the Weizmann Institute

Levels of Analysis of the Nervous System	Four Fundamental Courses in Neuroscience (will be given in precise 2-year alternation, one course/semester)
Molecular → Cellular →	**Introduction to Neuroscience: Molecular Neuroscience – Concepts and Methods** (yr 2010-2011)
Cellular → Synaptic →	**Introduction to Neuroscience: From Neuron to Synapse** (yr 2009-2010, course # 20103142) ← Goes more deeply than most of the "similar" B.Sc courses
Network → System →	**Introduction to Neuroscience: Sensory-Motor and Memory Systems of the Brain** (yr 2010-2011)
System → Behavior →	**Introduction to Neuroscience: Behavioral Neuroscience** (yr 2009-2010, course # 20103151)

These Fundamental Courses are <u>highly recommended</u> for students interested in Neuroscience.

The four courses are independent of each other, and can be taken separately.

Introduction to Neuroscience:
From Neuron to Synapse

Lecture 1: Introduction to the course

Nachum Ulanovsky

Dept. Neurobiology, Weizmann Institute of Science

Course syllabus (by week)

1) Introduction: The structure and basic function of Neurons. (Ulanovsky)

2) The Ionic basis of the resting potential: Nernst equation, Goldman equation. Pumps. (Lampl)

3) Passive membrane properties. Equivalent electrical circuit. Cable theory: derivation, solutions, and implications for neuronal function. (Lampl)

4) Active membrane properties and the action potential. (Lampl)

5) Hodgkin-Huxley experiments and model. (Lampl)

6) Diversity of Ion Channels: Permeability, electrophysiology, single-channel recordings, channel structure. Ligand-gated ion channels (glutamate, GABA, glycine, serotonin, calcium...). Basic pharmacological tools. Clinical aspects of channel dysfunction. (Reuveny)

7) Synaptic Transmission - General overview: Transmitter release, vesicles, quantal release, presynaptic molecular mechanisms. (Reuveny)

Course syllabus (by week)

8) Models of synaptic transmission. Short-term synaptic depression and facilitation. Voltage-gated and ligand-gated transmission (including glutamate and GABA). The reversal potential. Synaptic integration in space and time. Chemical synapses versus electrical synapses. (Lampl)

9) Receptors: Molecular cascades, pharmacological manipulations. (Reuveny)

10) Neuronal Plasticity: NMDA versus AMPA receptors; Long-term potentiation (LTP) and beyond. (Segal)

11) The nervous system in numbers, temporal scales, and spatial scales. (Ulanovsky)

12) Historical overview and future outlook: Reflecting back on the great discoveries that were summarized in the current course, and then looking forward to novel emerging methodologies. (Lampl / Reuveny / Ulanovsky)

13) Solutions to Exercises & Preparation for exam. (Lampl & Reuveny)

Formalities

- Grading:
    - Final exam - Open material. The exam will comprise 90% of the final grade.
    - Exercises: 2-3 exercises will be given, and they will comprise 10% of the course's final grade.

- Bibliography:

- Purves *et al.*, Neuroscience, 3rd edition (2004).
- Kandel *et al.*, Principles of Neural Science, 5th edition (2008).

(PDF's of relevant chapters will be placed on the course website)

Differences from the Behavioral Neuroscience course

- Orderly thematic flow in this Cellular Neurophysiology course – as opposed to the more eclectic nature of our course (and all courses) on Behavioral Neuroscience. Hence it is *not* recommended to miss lectures. And if you missed – fill in !

- Math: Slightly more math than in the previous semester – it's an intrinsic part of the subject matter – but the math will be given at a very accessible level, and the most advanced math will be given as "Appendixes" on which we will not ask in the exam.

- No articles for final exam (since the old classical articles in Cellular Neurophysiology had different notations). But we highly recommend reading those papers for the interested and curious students.

A primer on neurons

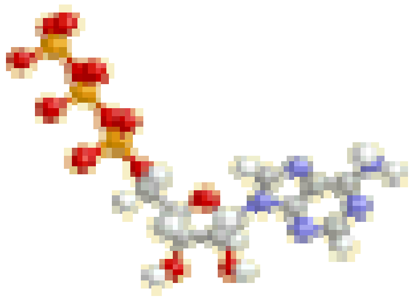
- **Biological molecules – an ultra-short overview for the non-biologists**
- **Structure of neurons**
- **Some history**

Biological Molecules

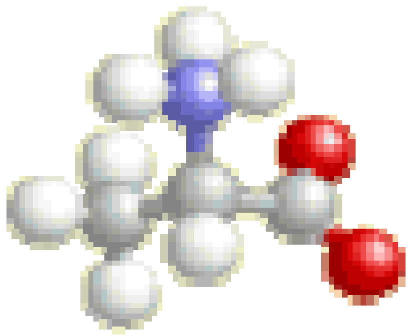
- ~70% of a cell's volume is water.
- Thousands of different kinds of molecules.
- Ions (Na^+, K^+,...) and other simple molecules.
- 4 major kinds of biological molecules:
  - Carbohydrates (saccharides)
  - Proteins
  - Nucleic acids
  - Lipids
- Carbohydrates, Proteins, Nucleic acids = Macromolecules.

I will talk today briefly only about Proteins and Lipids.
You will hear (a lot) about ions in subsequent weeks.

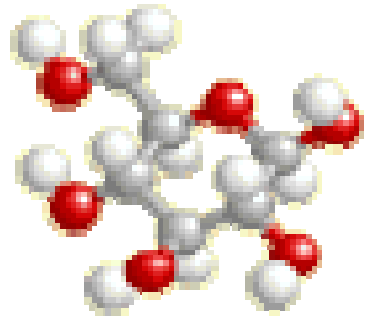
All macromolecules are chains constructed from a few simple compounds



Nucleotide



Amino acid



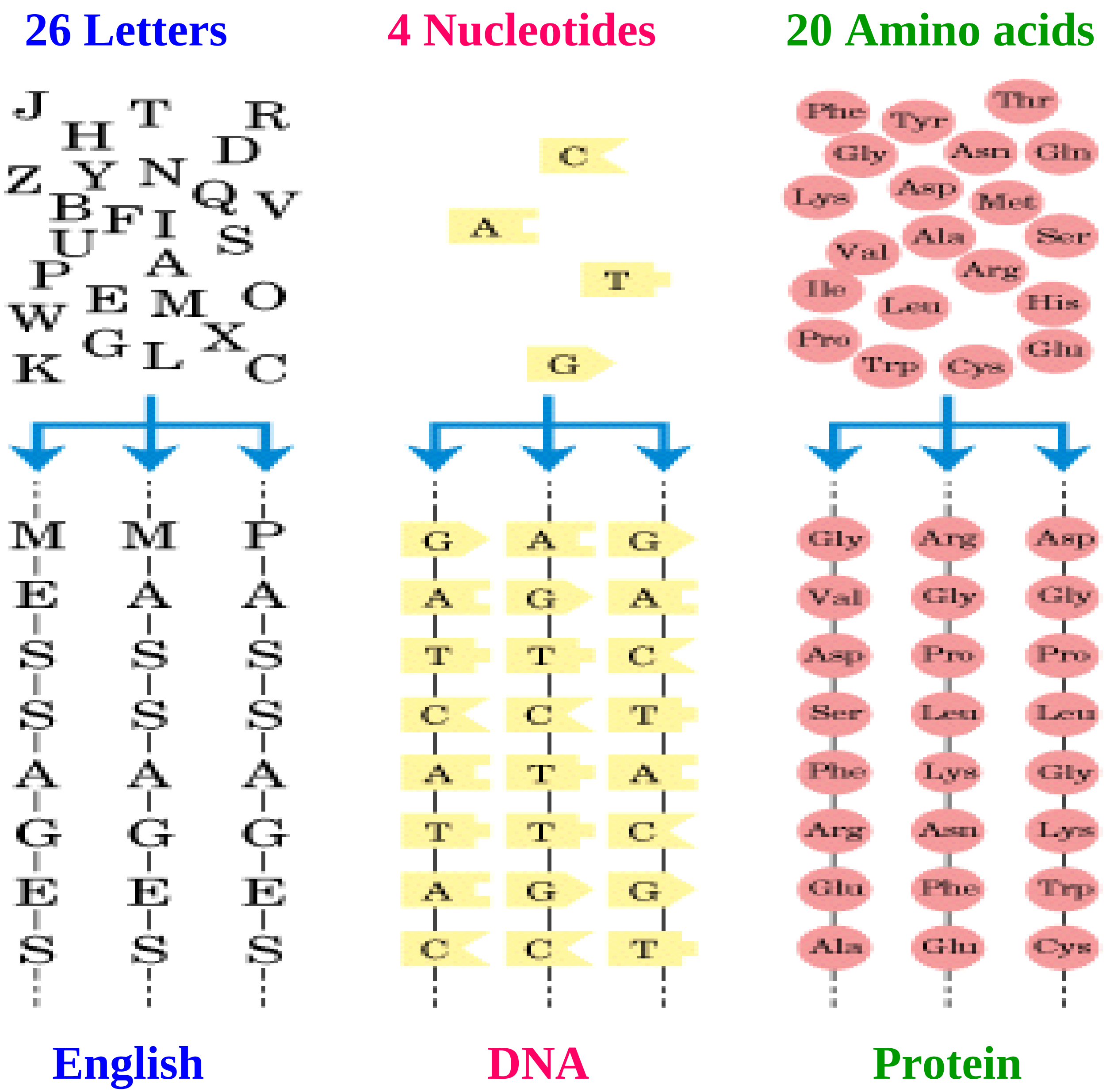
Monosaccharide (sugar)

Monomeric subunits of macromolecules

↓ **Nucleic acids**

↓ **Proteins**

↓ **Polysaccharides**



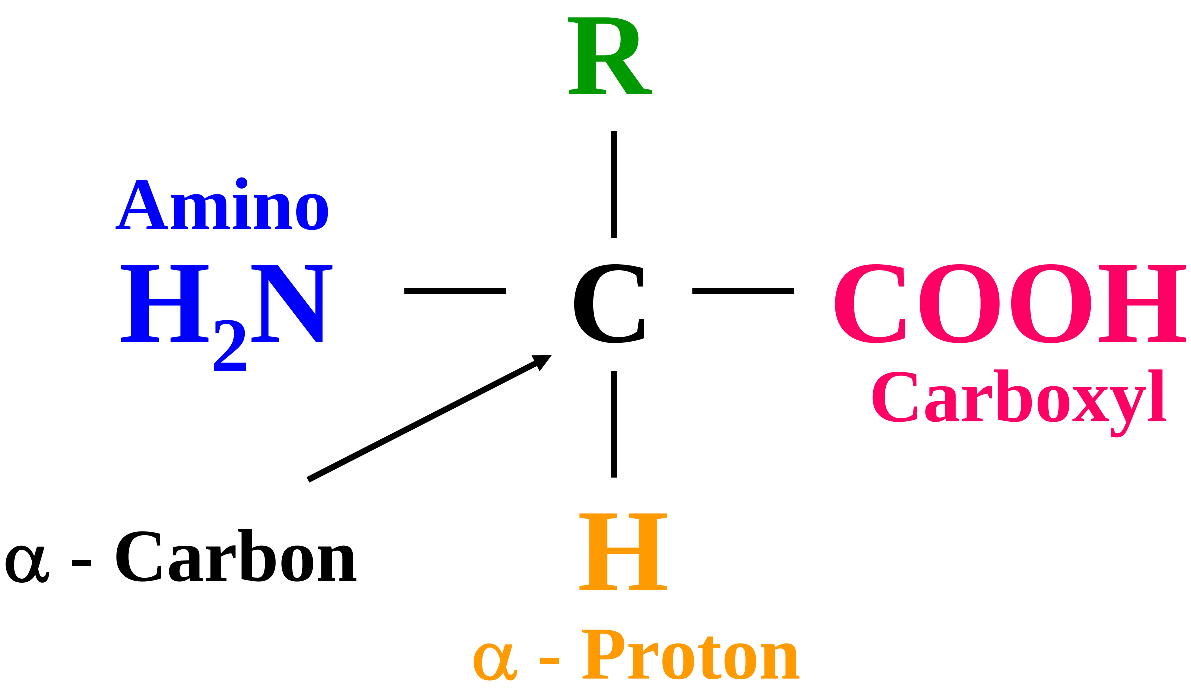
English – 26^n

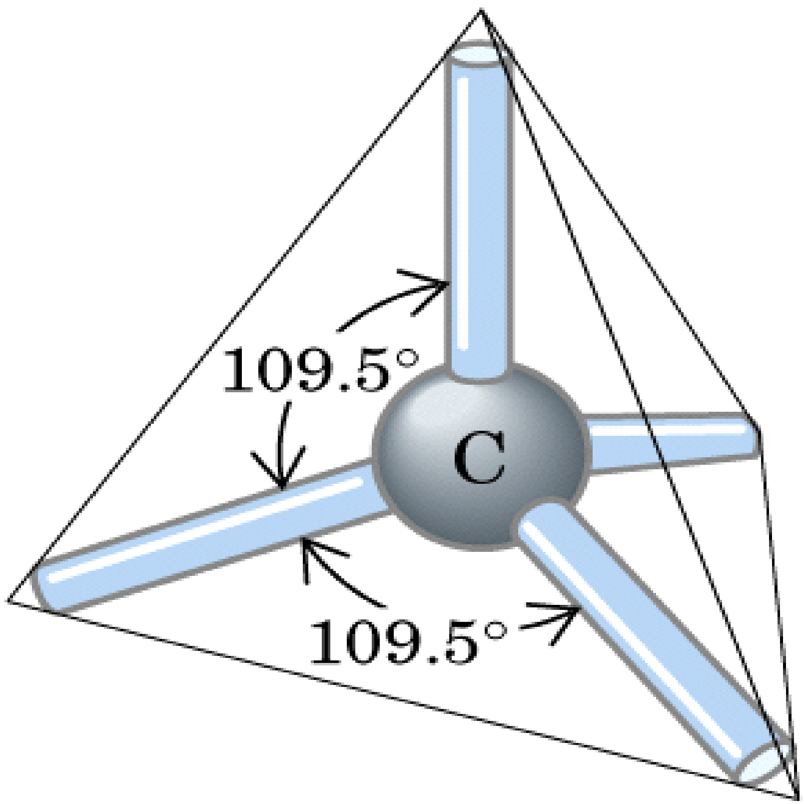
DNA – 4^n

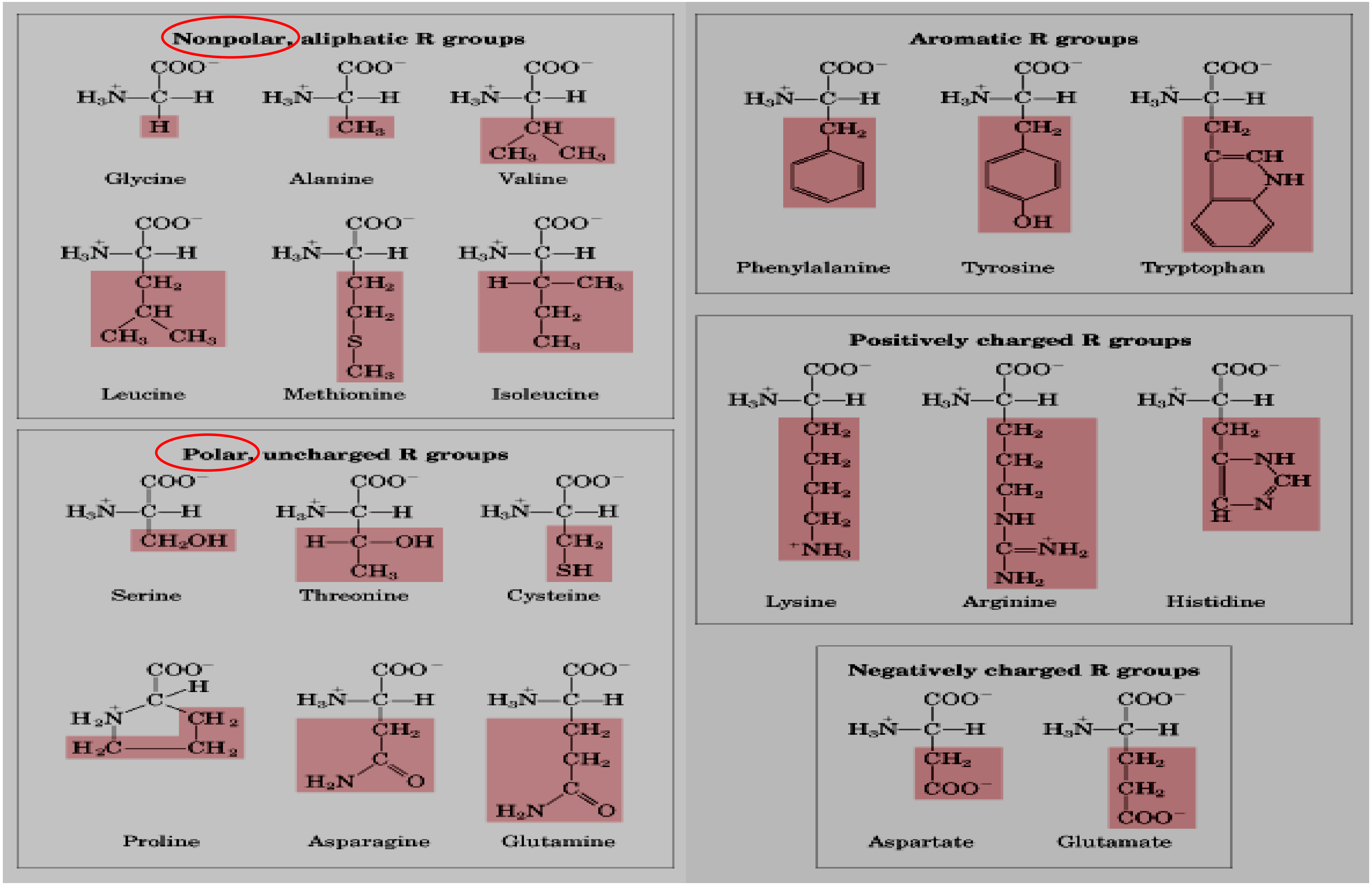
Protein – 20^n

Proteins

Amino acids **are the building blocks of proteins.**
All 20 natural amino acids have identical backbone structure:



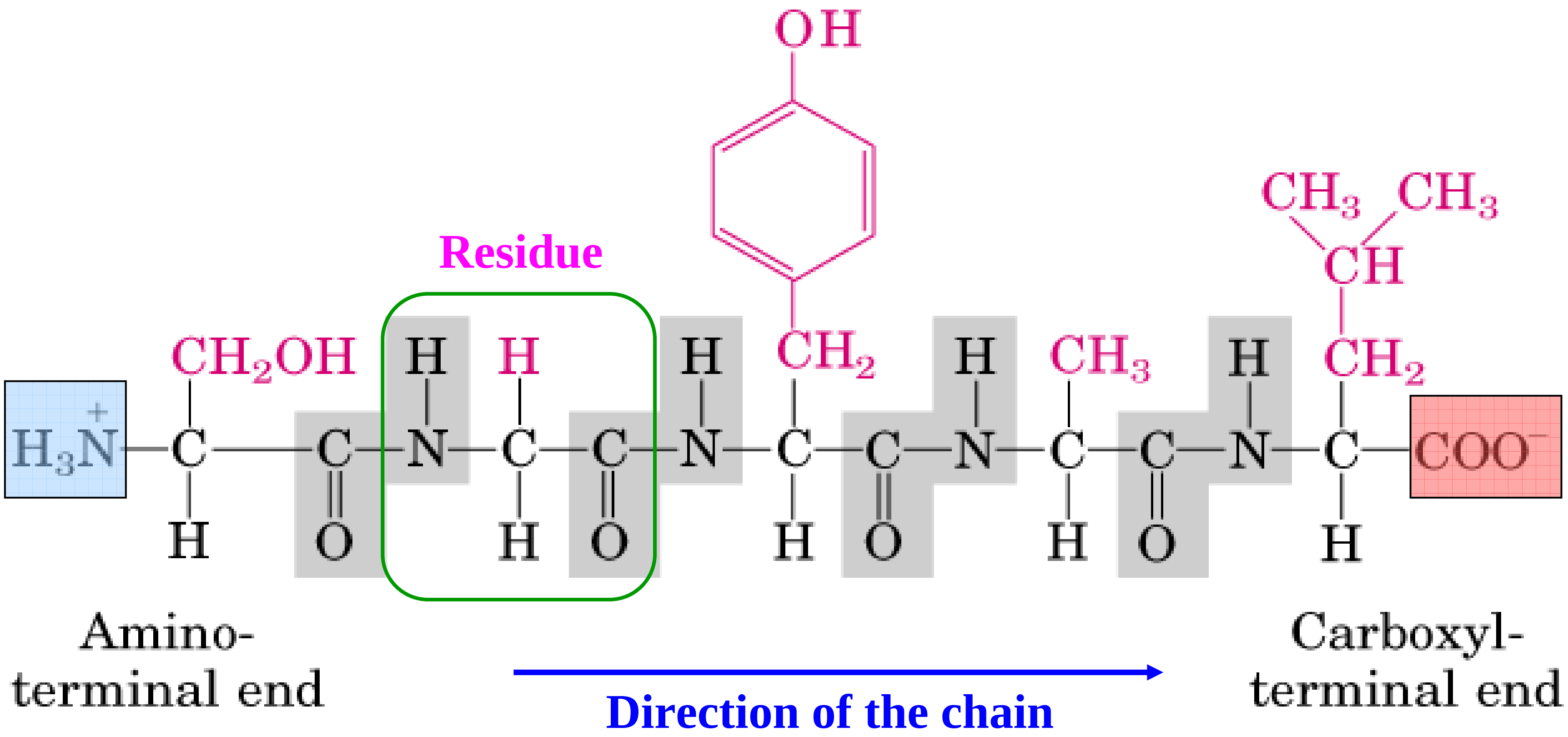



Nonpolar, aliphatic R groups
Glycine
Alanine
Valine
Leucine
Methionine
Isoleucine
Polar, uncharged R groups
Serine
Threonine
Cysteine
Proline
Asparagine
Glutamine
Aromatic R groups
Phenylalanine
Tyrosine
Tryptophan
Positively charged R groups
Lysine
Arginine
Histidine
Negatively charged R groups
Aspartate
Glutamate

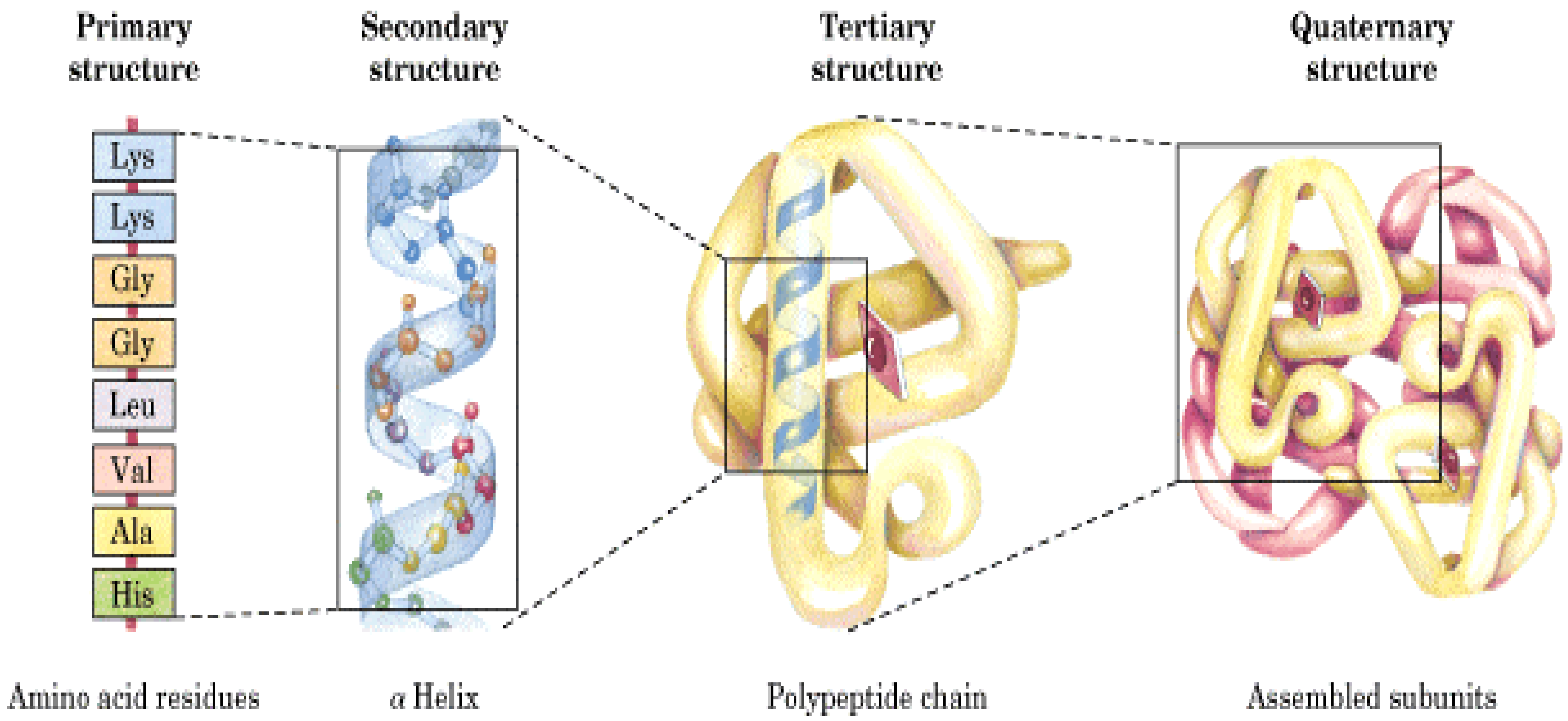
Polypeptide Chain:

Regularly repeating unit + **Variable part (Residue)**

Main chain (backbone) **Side chain**



Levels of structure in proteins



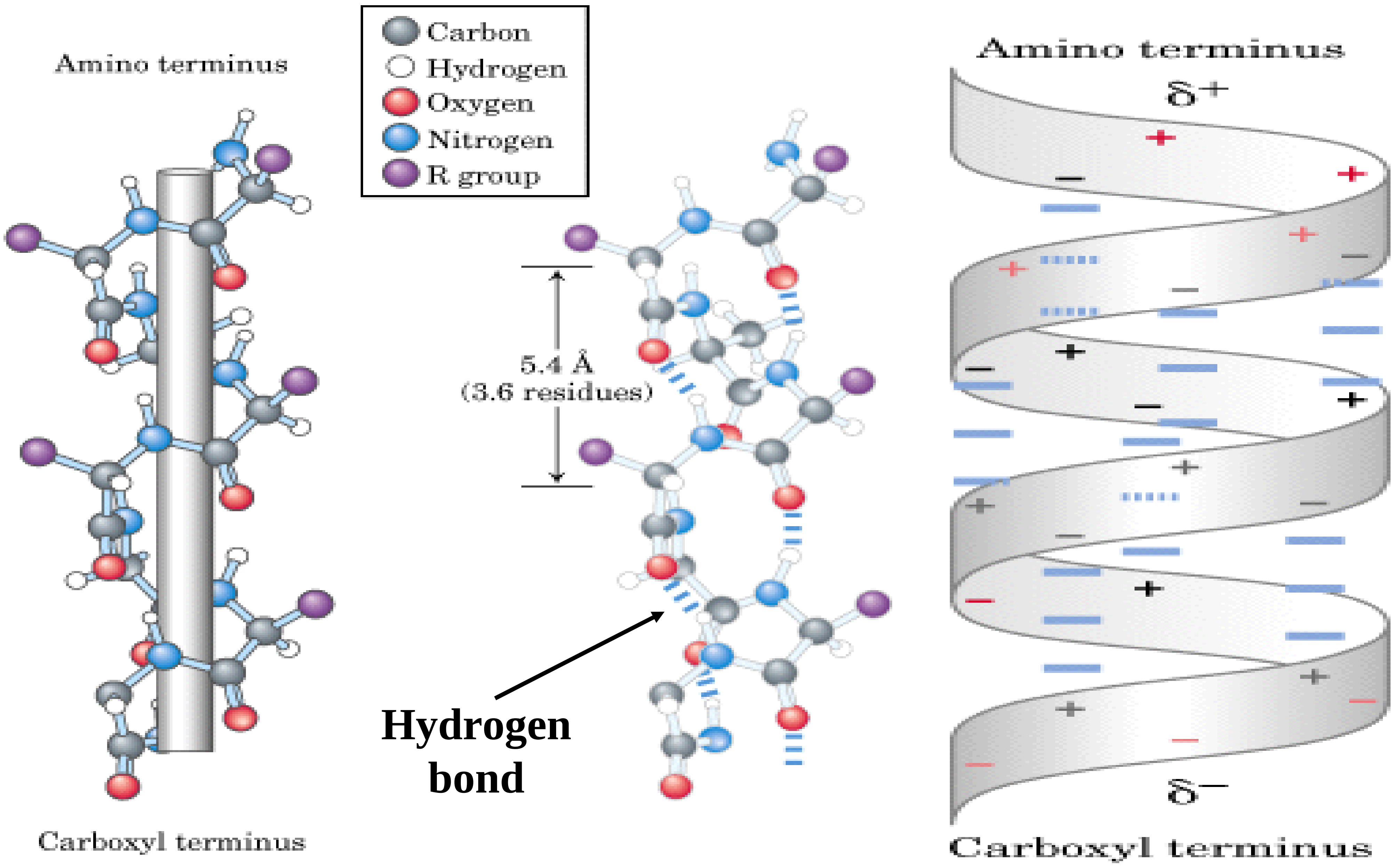
* **Primary structure** - sequence of amino acid residues

* **Secondary structure** - particularly stable arrangements of amino acid residues (structural patterns)

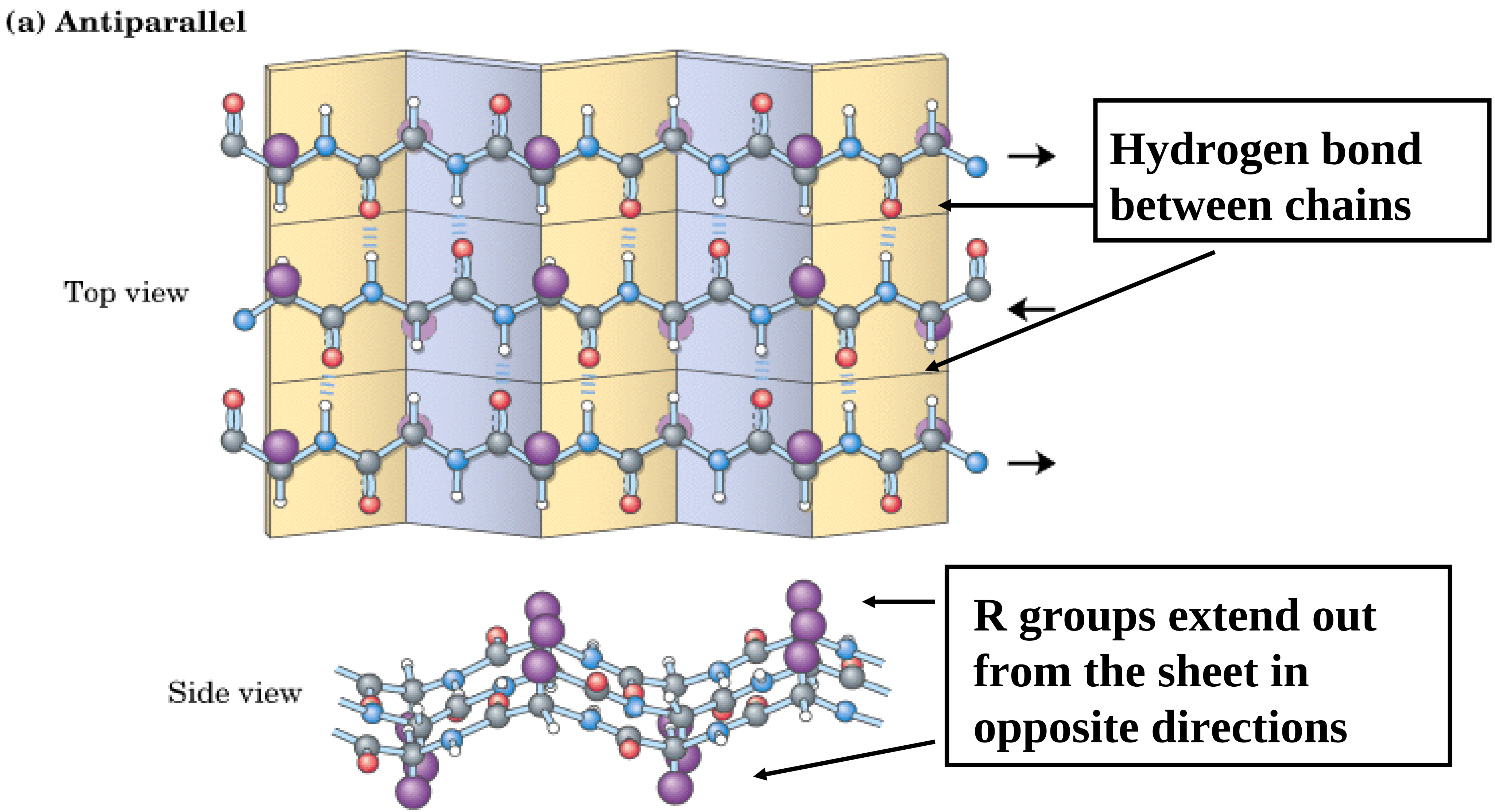
* **Tertiary structure** - three-dimensional folding of a polypeptide chain

* **Quaternary structure** - arrangement of several polypeptide subunits in space

The α Helix is a Common Protein Secondary Structure

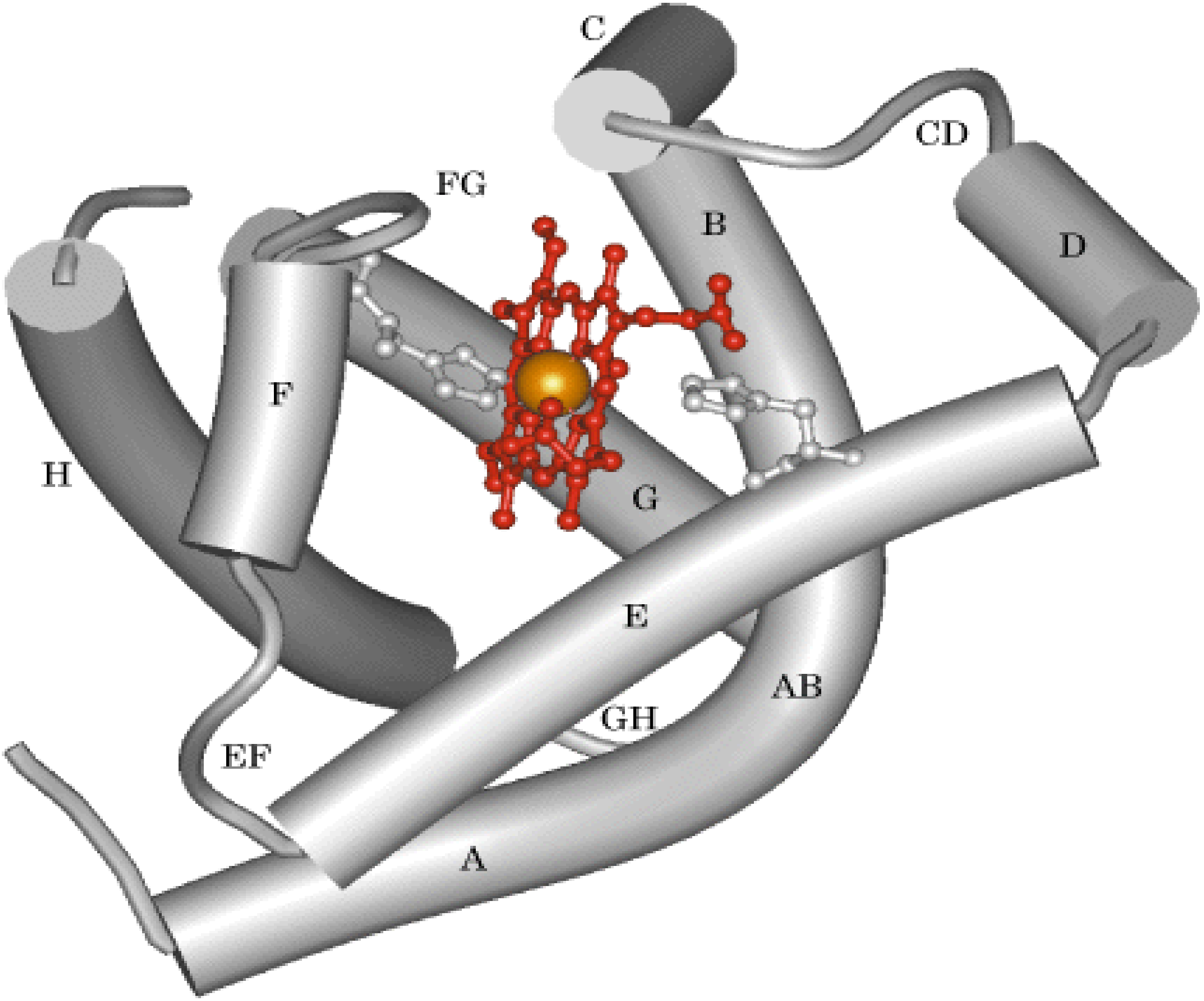


The β conformation organizes polypeptide chains into sheets

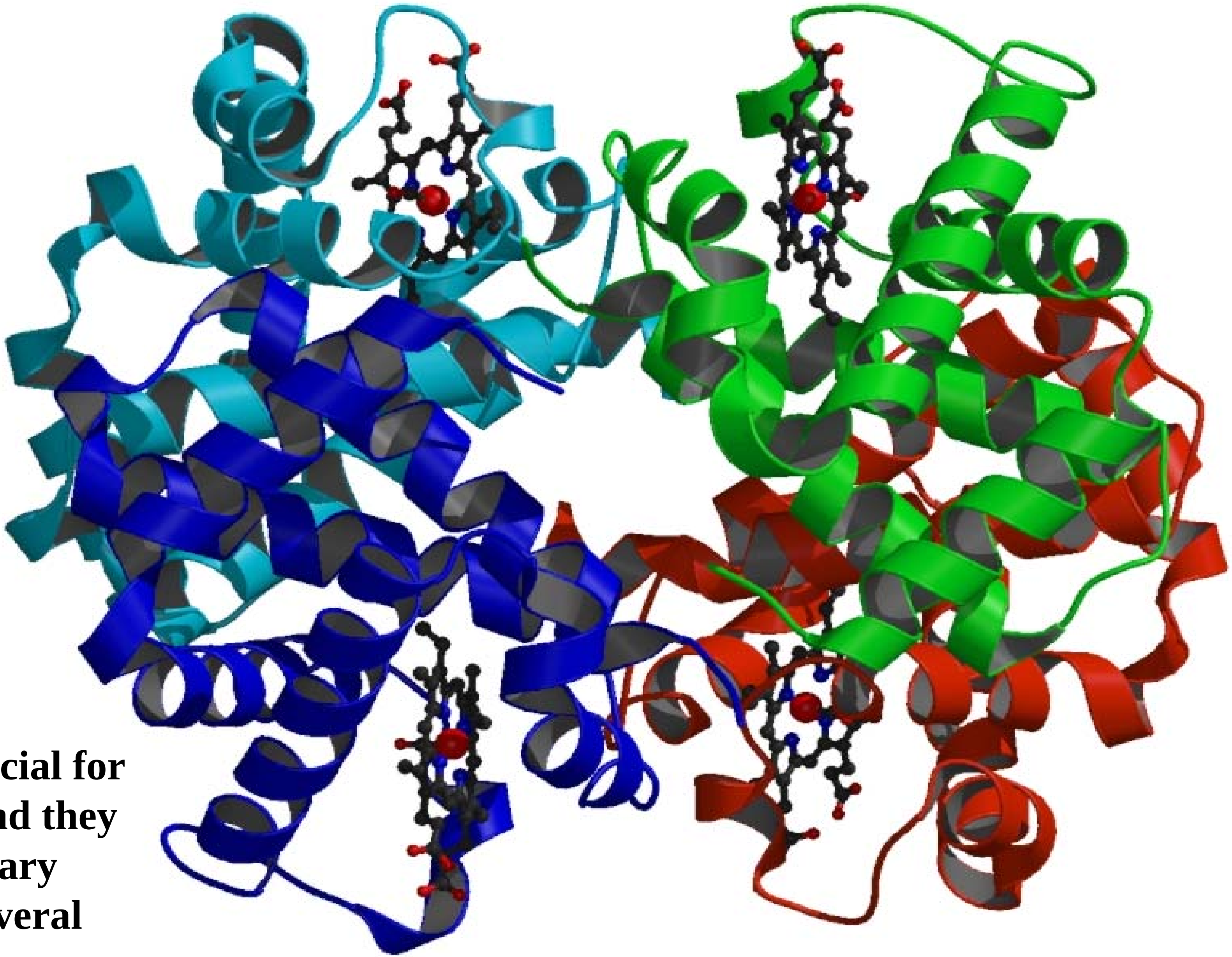


Tertiary structure

The protein Myoglobin is composed of 75% α Helix



Quaternary structure of Hemoglobin (4 polypeptide chains)

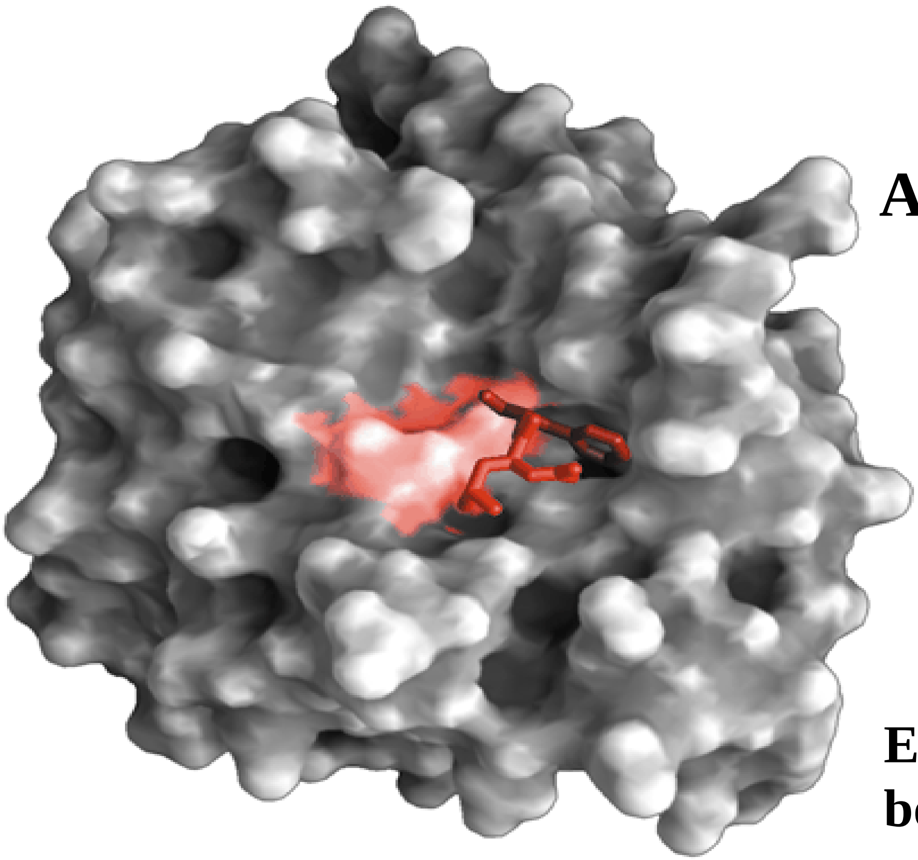


*** Ion channels are crucial for neuronal function – and they have complex quaternary structures, made of several subunits**

Enzymes are proteins that catalyze reactions

Catalytic power

Specificity

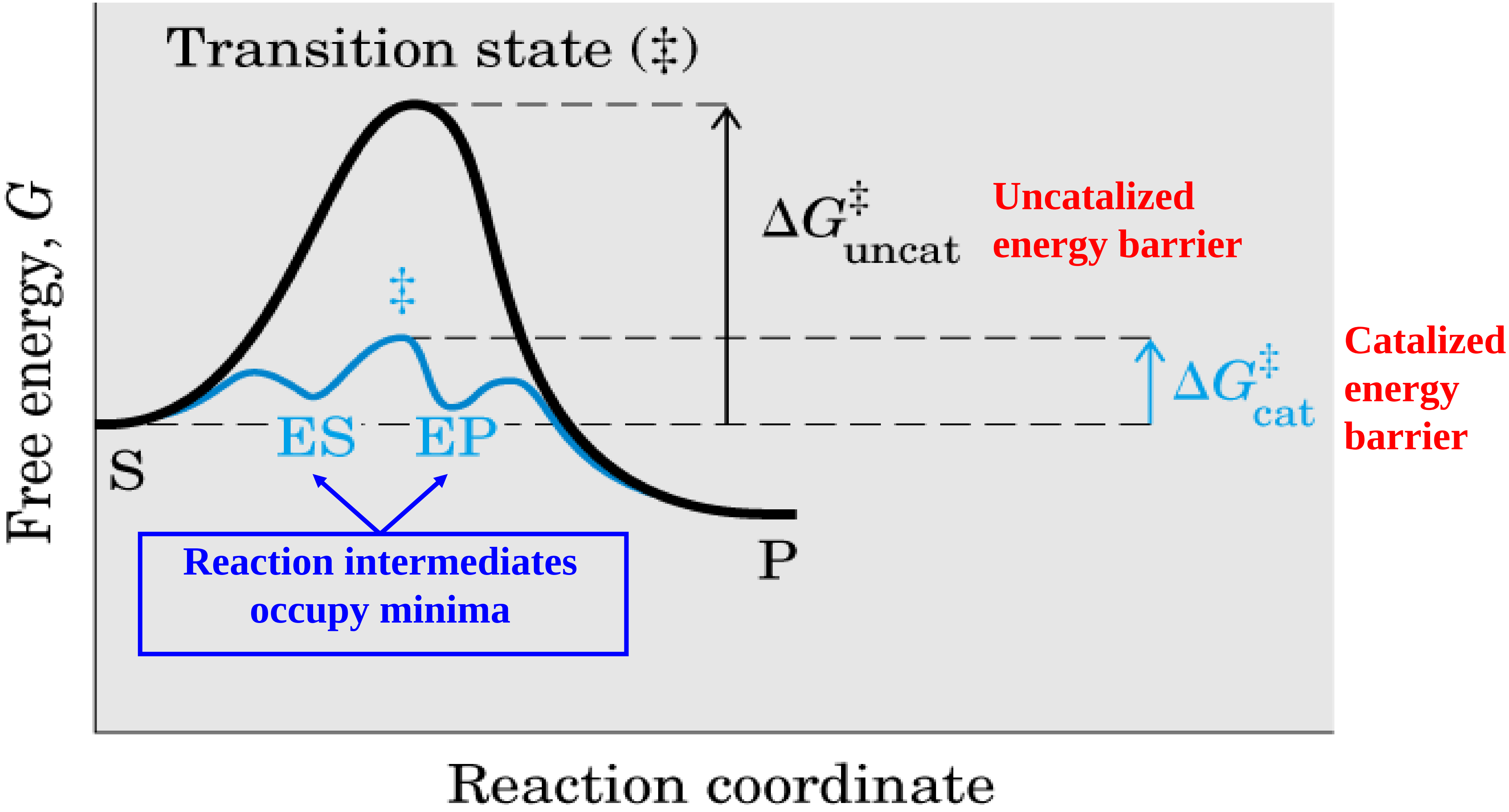


An enzyme-catalyzed reaction occurs at the active site

Enzyme *chymotrypsin* with the bound substrate

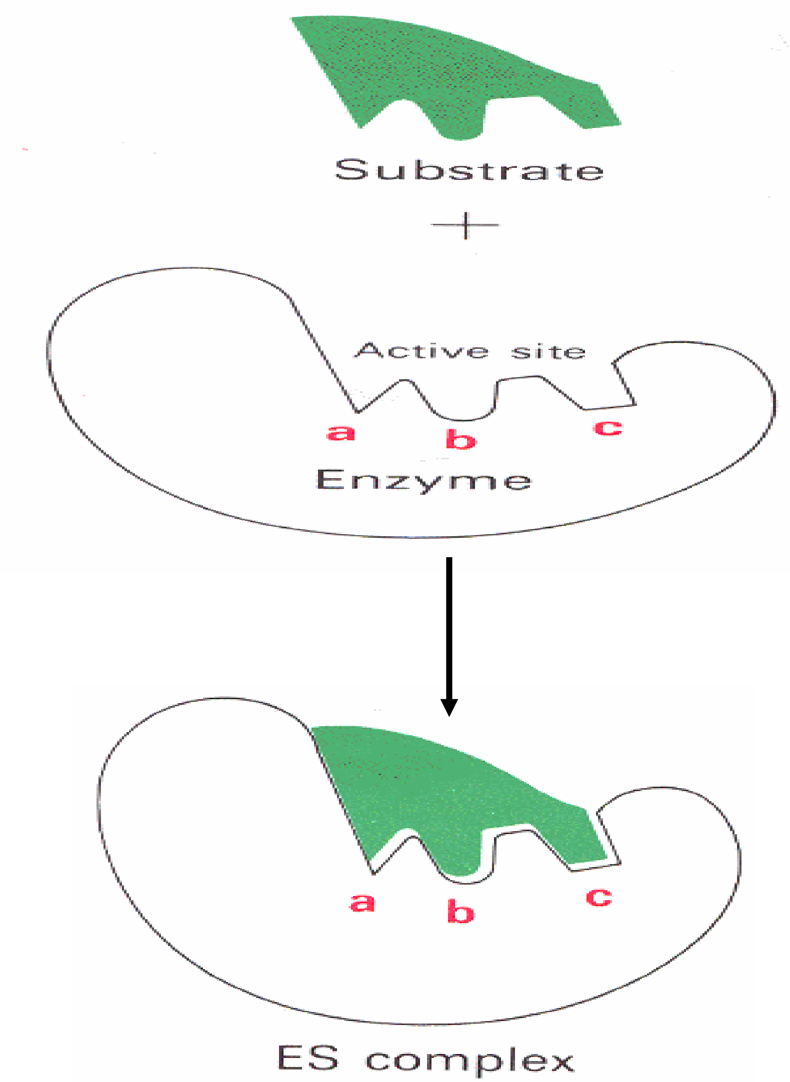
Catalytic power of Enzymes

$$E + S \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P$$

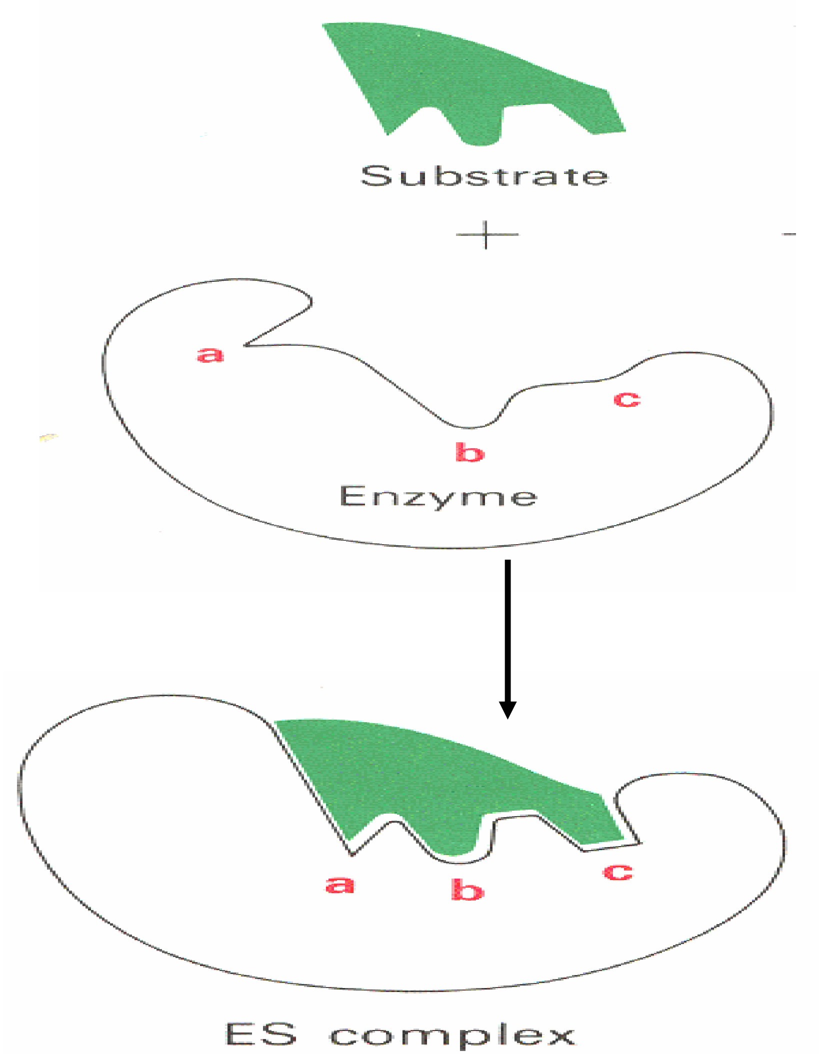


Specificity of Enzymes

Lock-and-key model (Fischer, 1890):

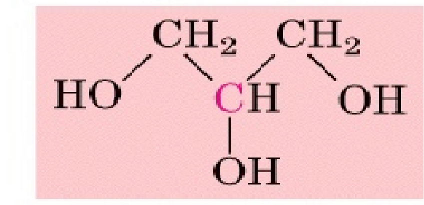


Induced fit model (Koshland, 1958):

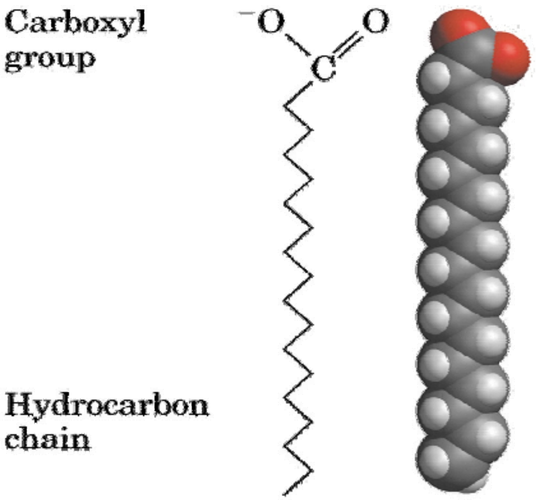


Lipids

- Insoluble in water, very hydrophobic
- Lower specific gravity than water
- Simple lipids are constructed from 2 or 3 fatty acids

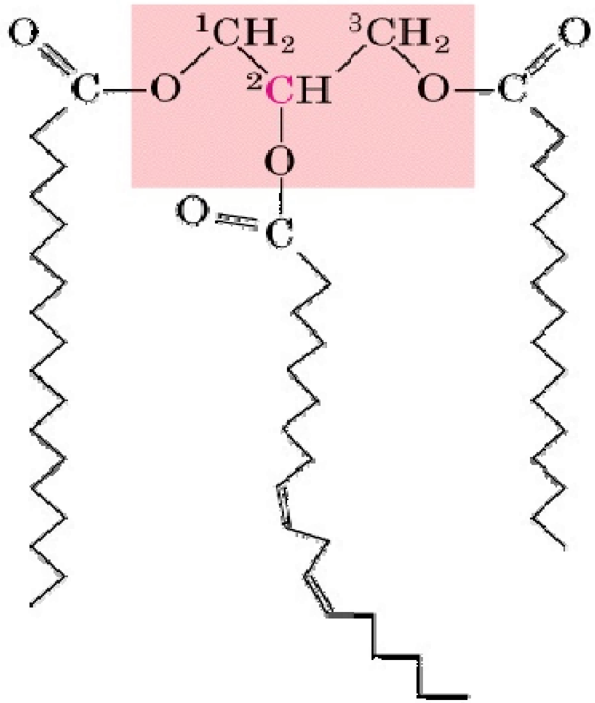


Glycerol



Fatty acid (saturated)

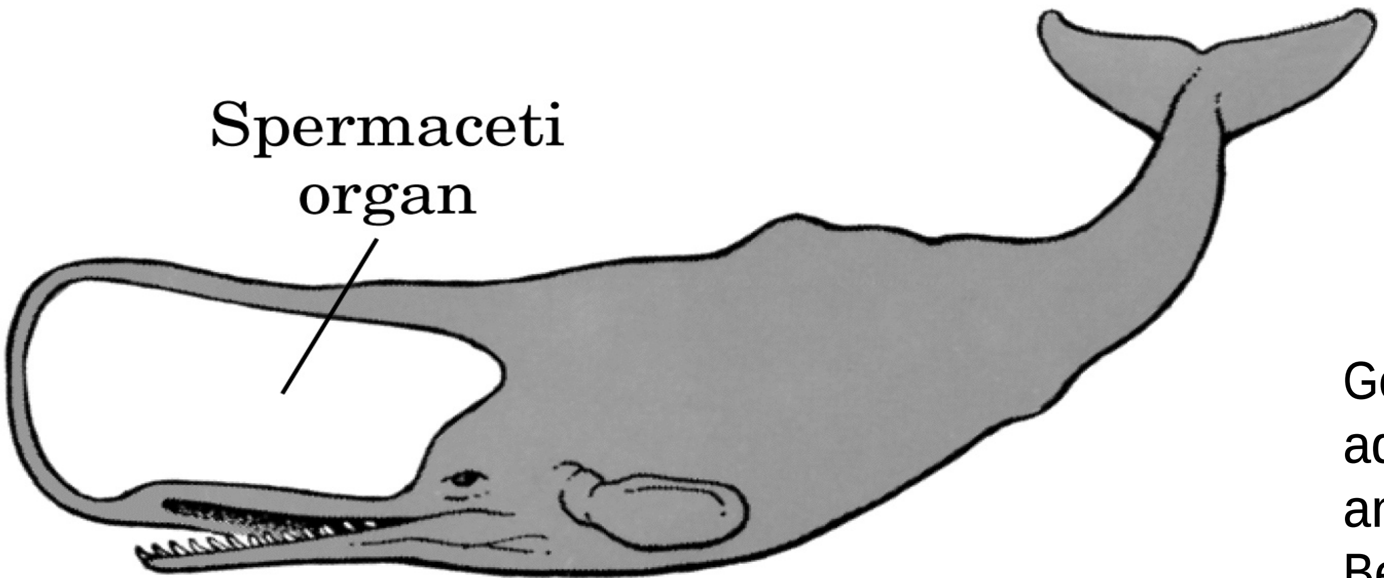
Lipid



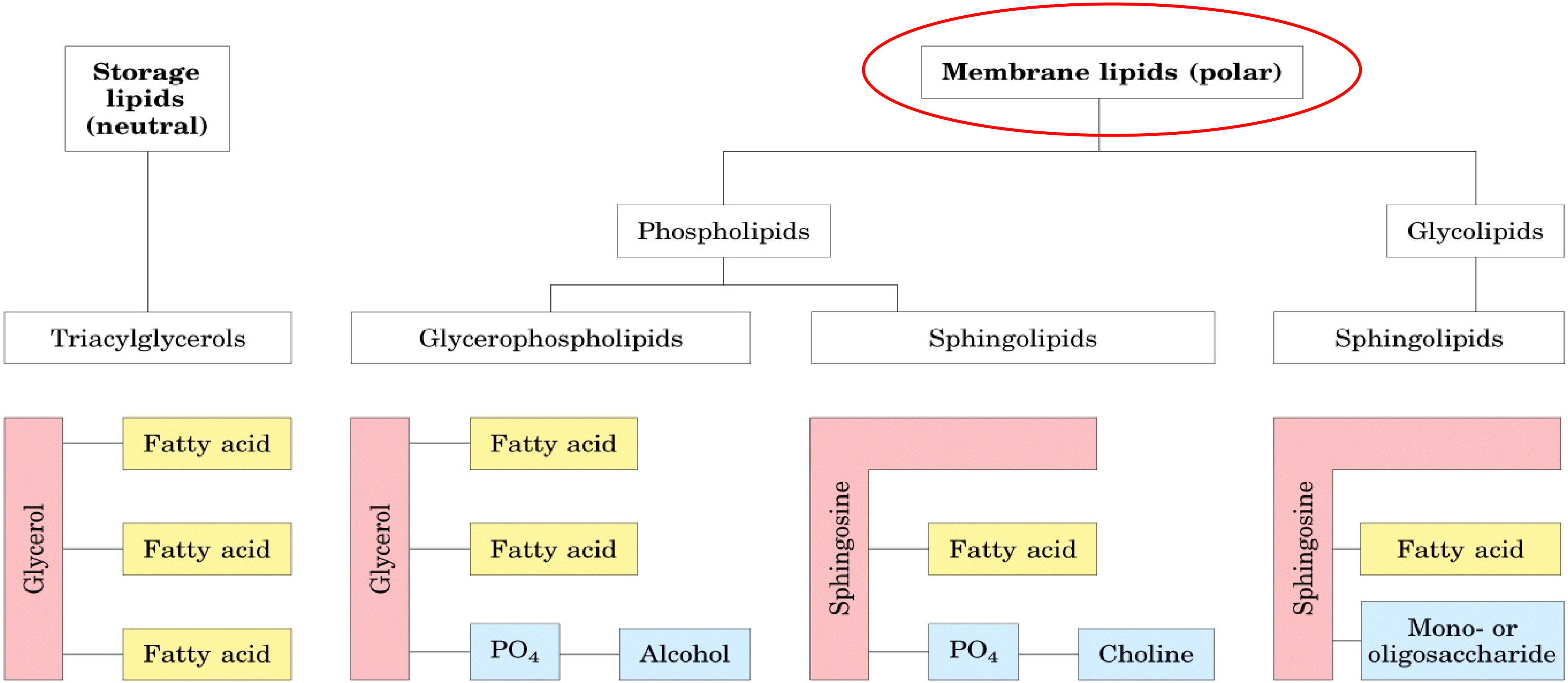
1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol

Functions of lipids:

- Structural elements of *membranes:* key components in all cells, including neurons
- Energy storage
- Insulation
- Hormones (e.g. steroids)
- Buoyancy and echolocation (*Spermaceti organ* – 18 tons of fat that control buoyancy and create a fatty *lens* in sperm whales, which is used to focus the sonar beam in whale echolocation; the *melon* is a similar lens structure in dolphins).

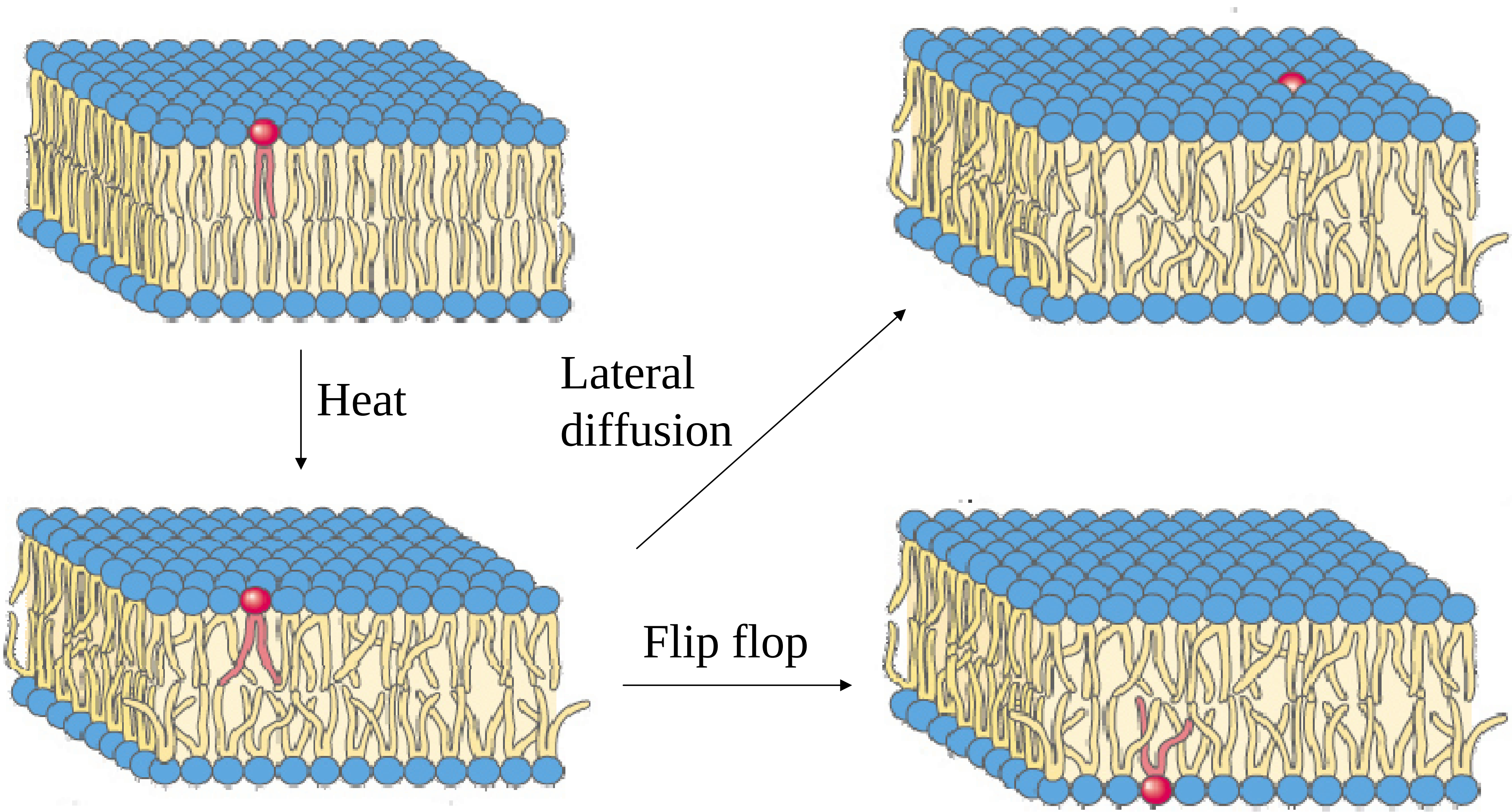


Go to the Vancouver aquarium to see the amazing melon of Beluga whales...



Storage lipids (neutral)
Membrane lipids (polar)
Phospholipids
Glycolipids
Triacylglycerols
Glycerophospholipids
Sphingolipids
Sphingolipids
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
PO4
Alcohol
Sphingosine
Fatty acid
PO4
Choline
Sphingosine
Fatty acid
Mono- or oligosaccharide

The lipid bilayer – held together by hydrophobic forces – is a 2 dimensional fluid



But membranes are much more than just a lipid bilayer

Membrane composition:

- Lipids
- Proteins
- Carbohydrates

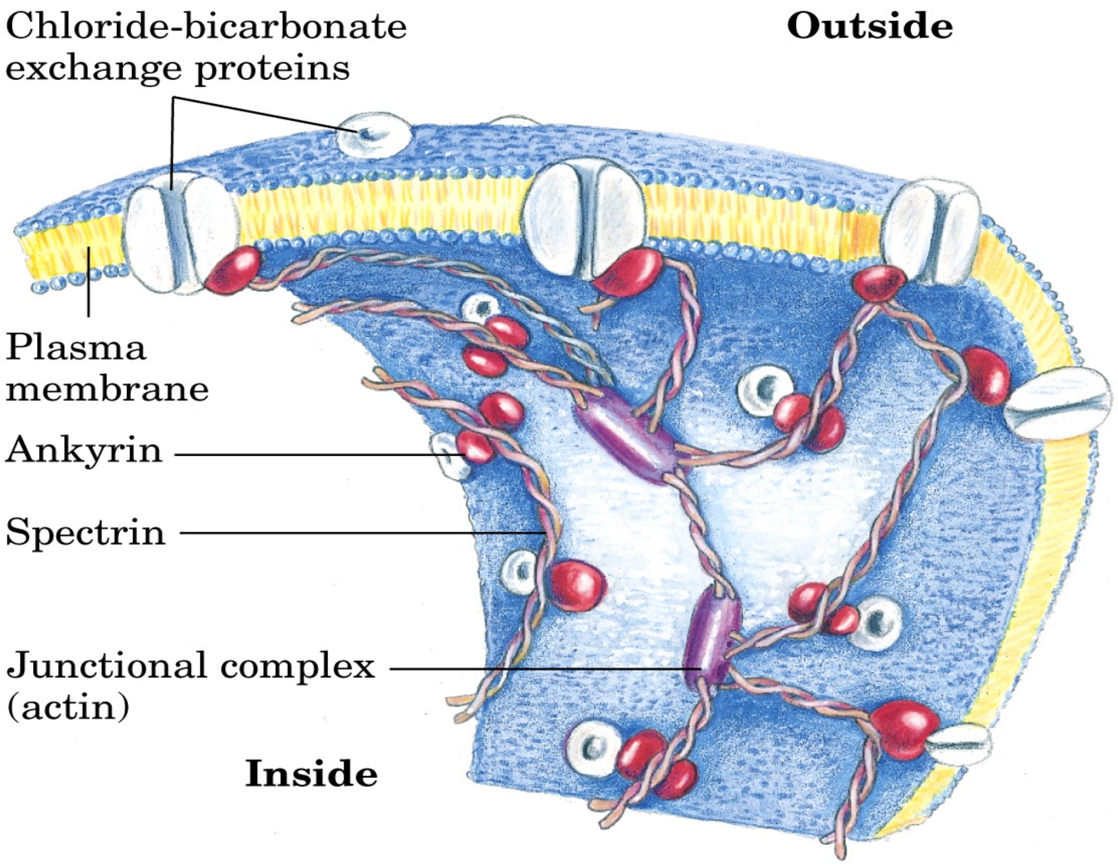
Major Components of Plasma Membranes in Various Organisms

	Components (% by weight)				
	Protein	**Phospholipid**	**Sterol**	**Sterol type**	**Other lipids**
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—

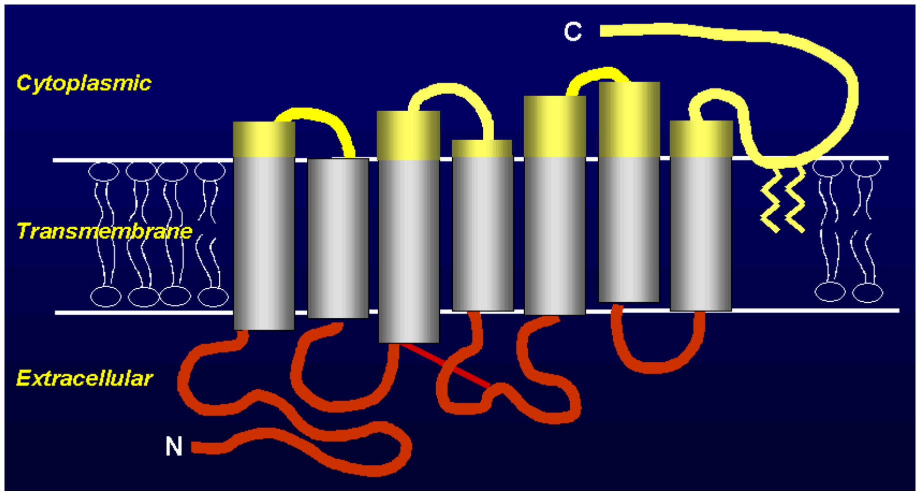
Membrane proteins:

- **Channels**
- **Pumps**
- **Receptors** (Signaling)

You will hear a lot in the course about the functions of proteins as channels, pumps and receptors.



Receptor

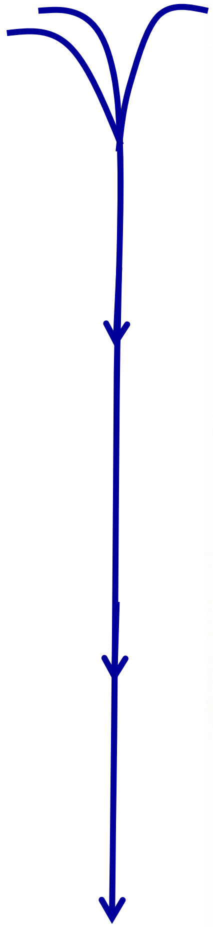


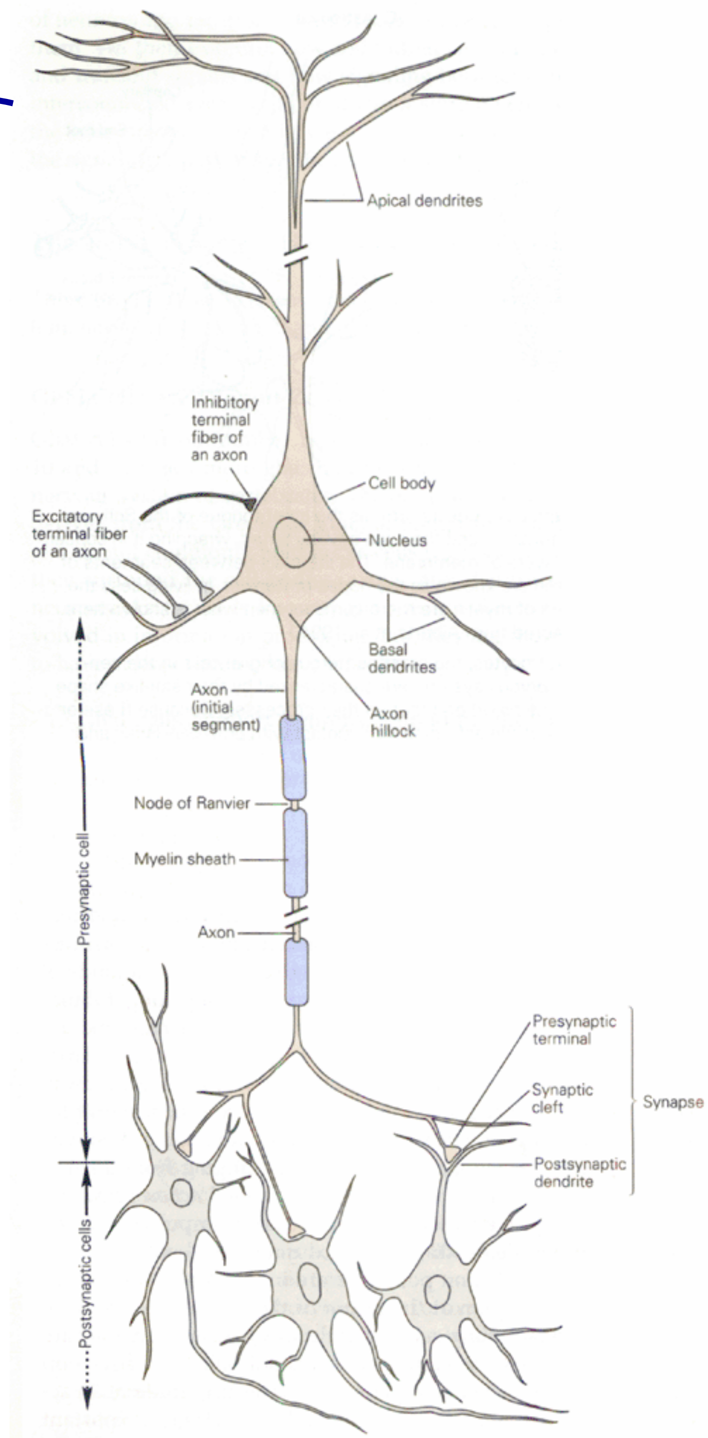
Many receptors (such as GPCRs – G-Protein Coupled Receptors, which you will hear a lot about later on) are 7-transmebmrane domain receptors, composed of 7 α-helixes crossing the membrane.

The structure of a neuron

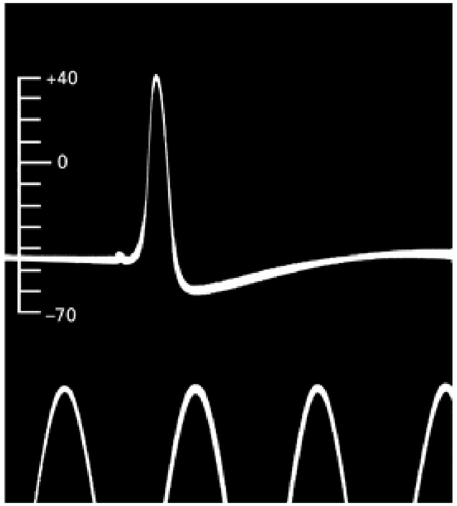
To a first approximation, electrical signals flow in neurons in a uni-directional fashion:

dendrites → soma → axon.





Neurons communicate with action potentials (spikes) *(with some exceptions in invertebrate brains)*



First published action potential (Hodgkin & Huxley 1939)

500 Hz sine wave (time marker)

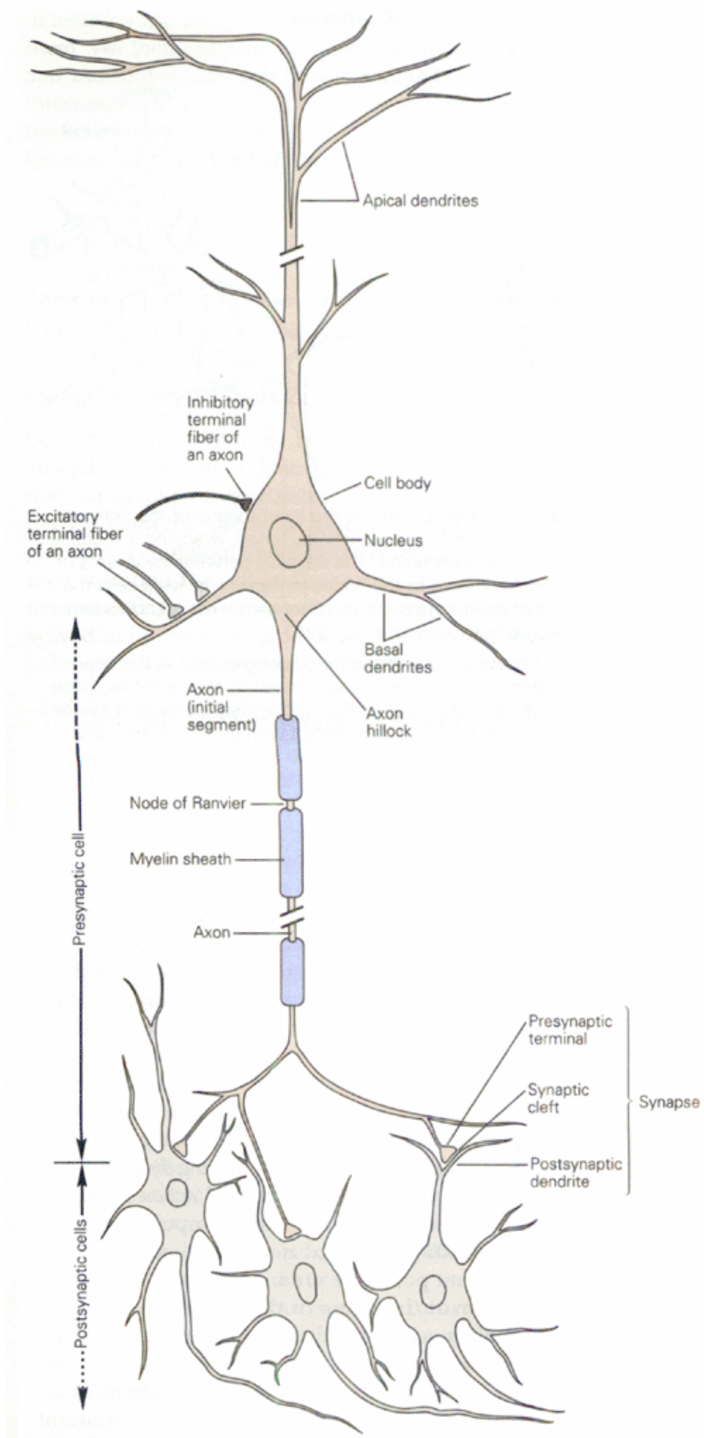
Some basic terms:

- Action potential (spike)
- Depolarization
- Hyperpolarization
- Propagation

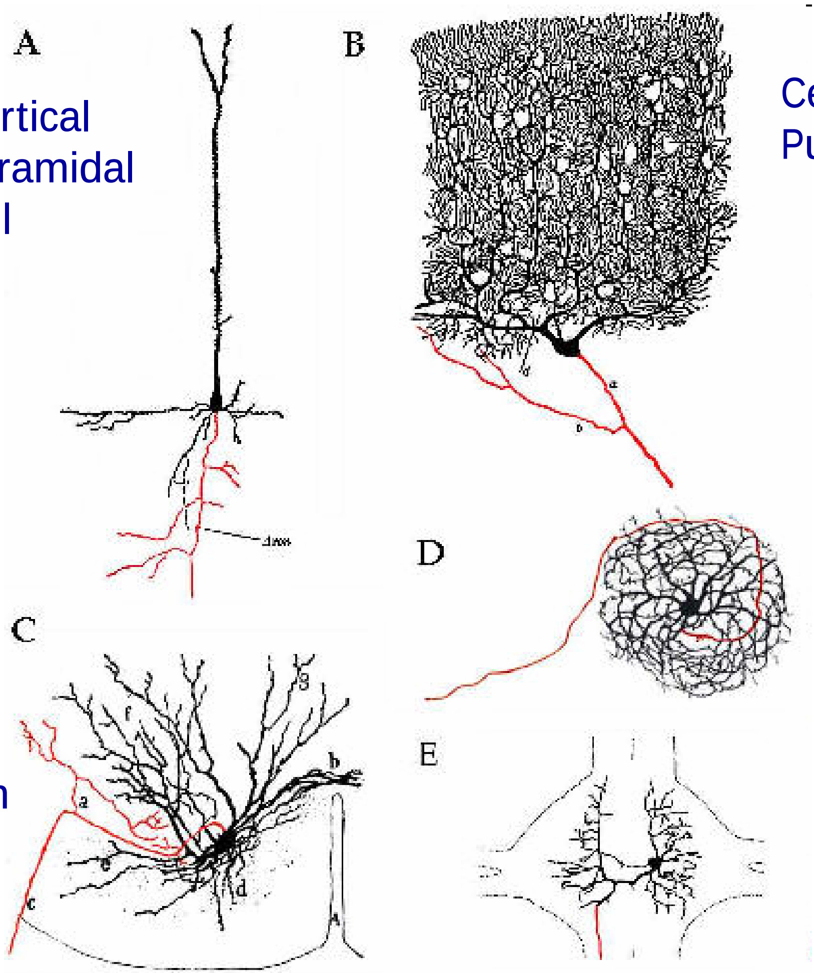
The structure of a neuron

Some basic terms:

- Membrane
- Cell body (soma)
- Dendrite
- Dendritic tree
- Axon
- Axon hillock
- Myelin Sheath & Nodes of Ranvier
- Action potential (spike)
- Synapse
- Anterograde, Retrograde



Heterogeneity of neuronal morphology is likely related to the different functions of different neurons



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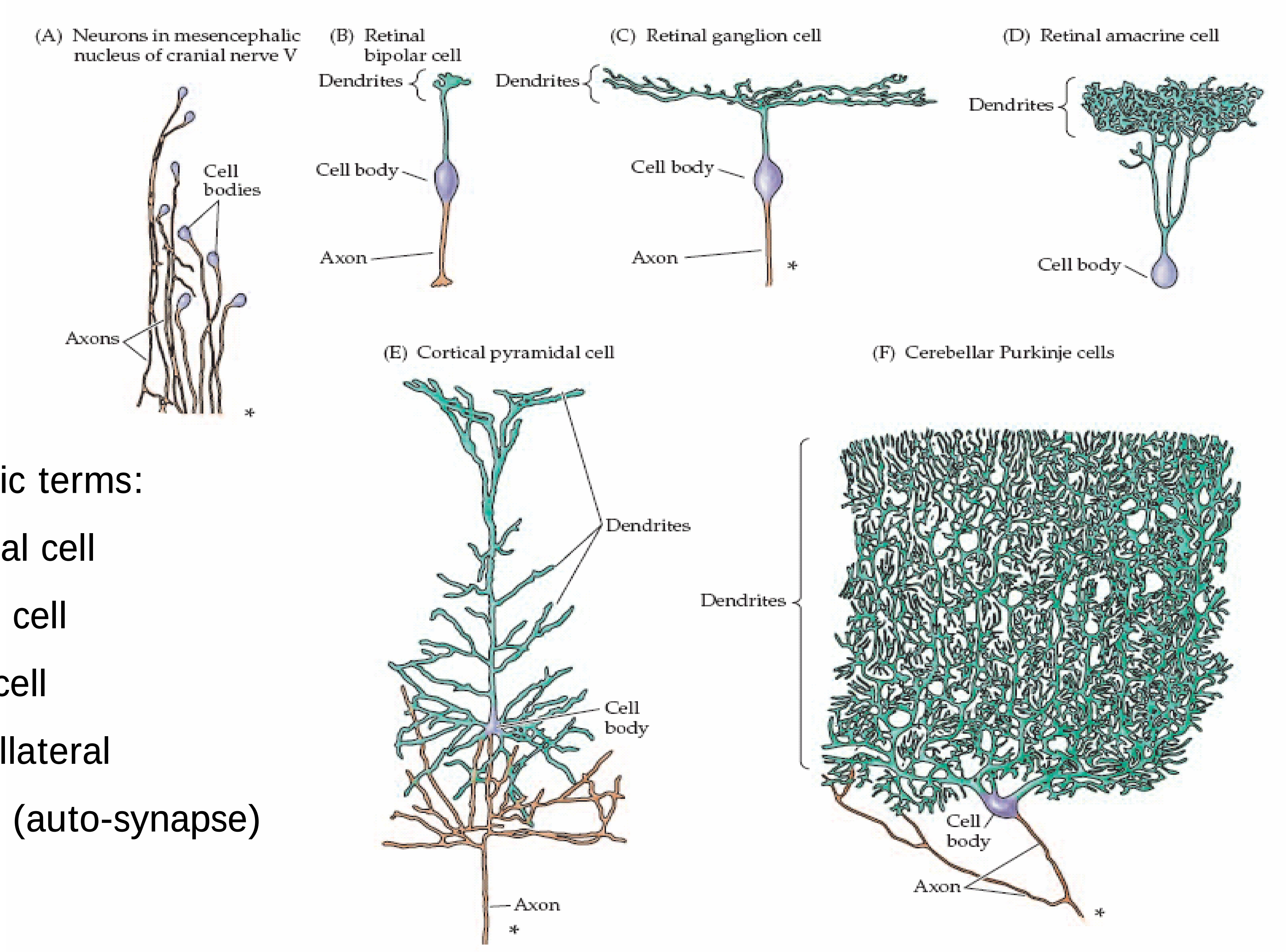
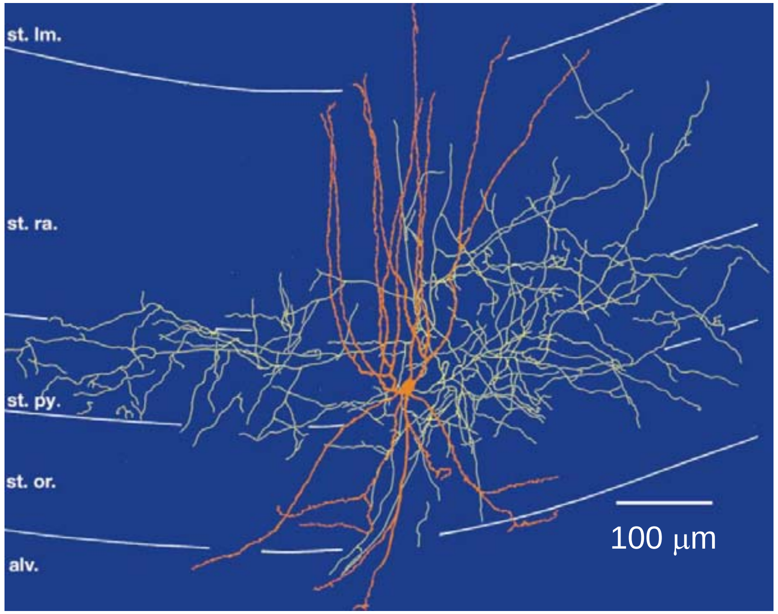


Some basic terms:

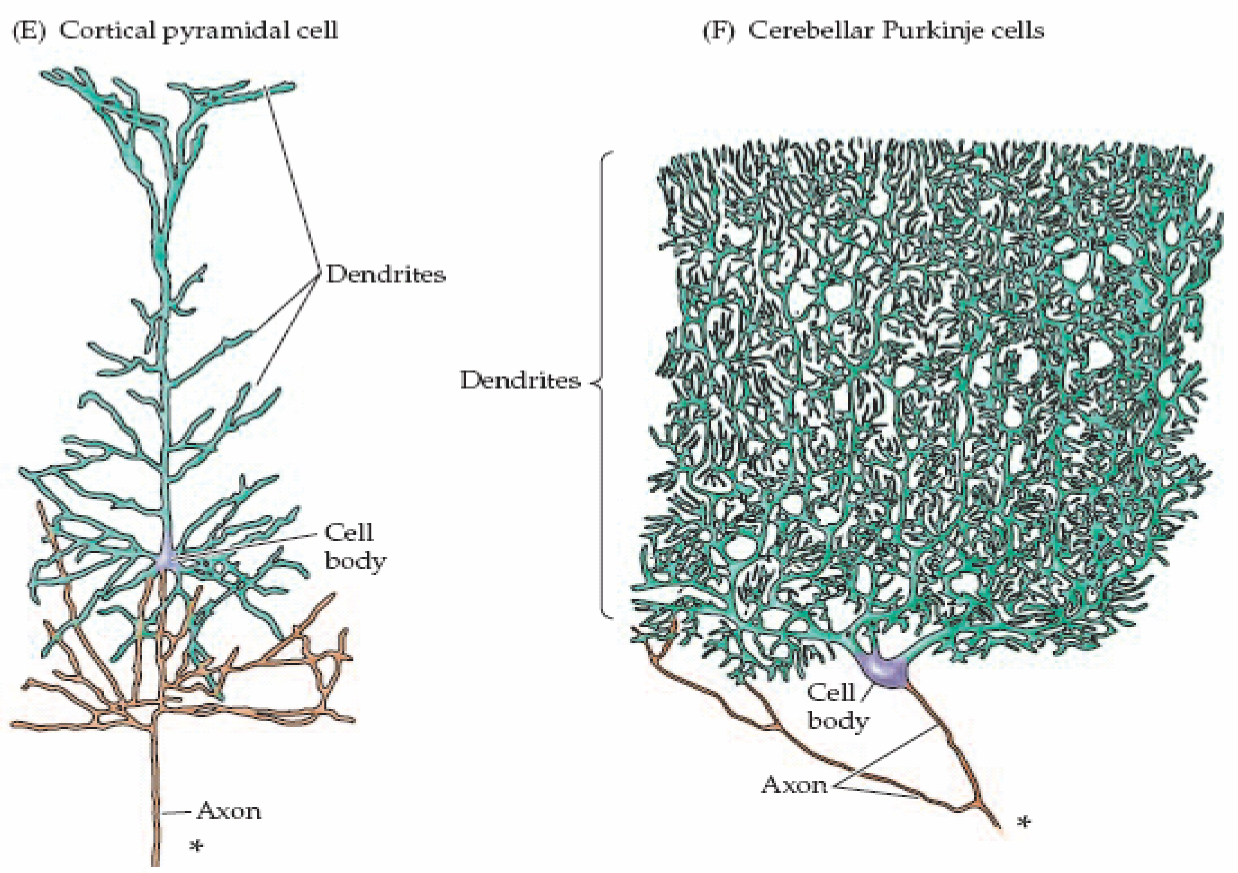
- Pyramidal cell
- Purkinje cell
- Bipolar cell
- Axon collateral
- Autapse (auto-synapse)

Some basic terms:

- <u>Projection neuron (principal cell)</u> – sends a long-range axon outside the local brain area (e.g., cortical and hippocampal pyramidal cells; cerebellar Purkinje cells, ...)
- <u>Interneuron</u> – a neuron that sends only *local* axons, i.e. does not project out of the local brain area (many many types of interneurons are known).



Hippocampal CA1 basket cell, showing soma & dendrites (red), axon (yellow) (Klausberger et al., *Nature* 2003)

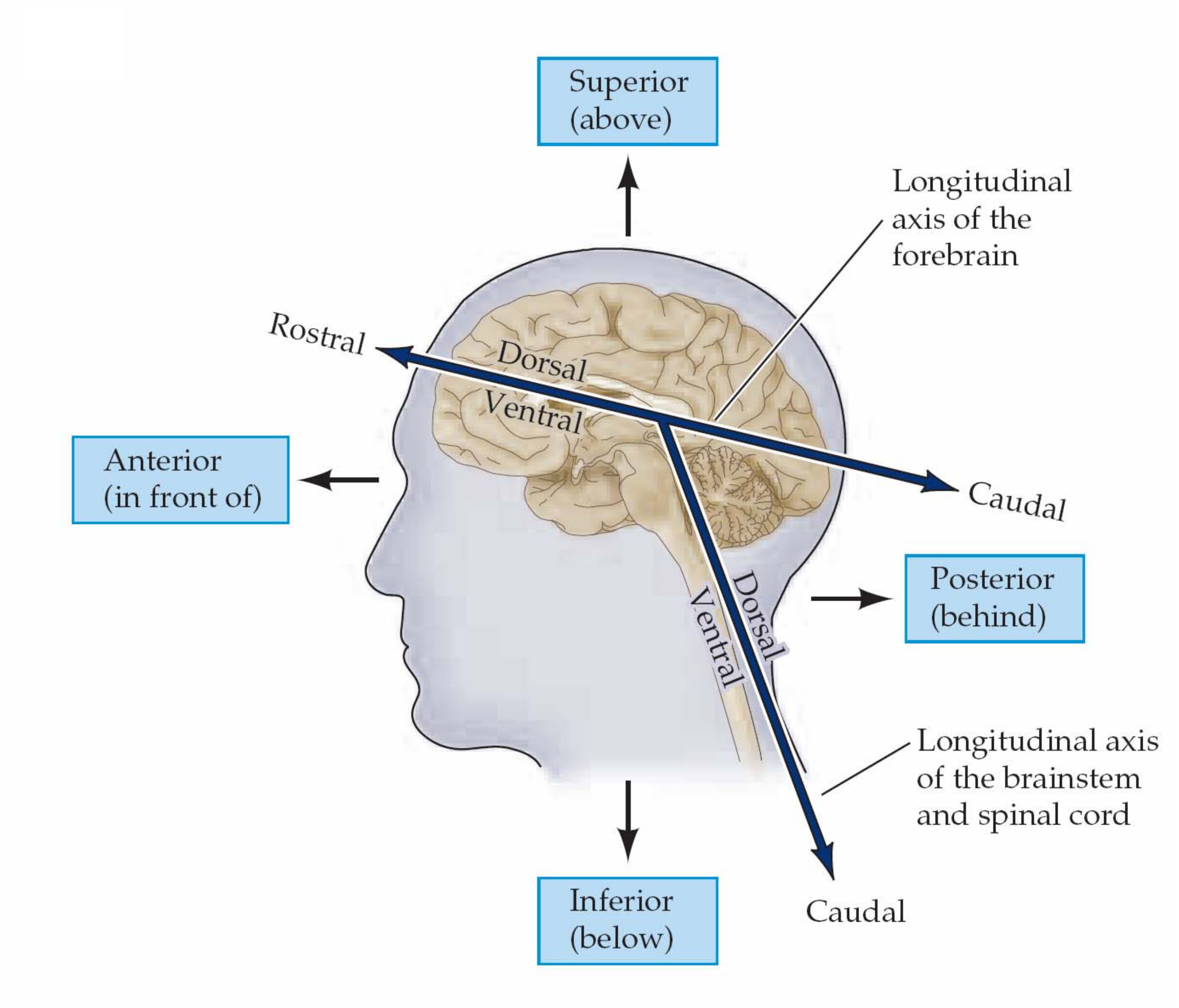


Glia (glial cells, neuroglia)

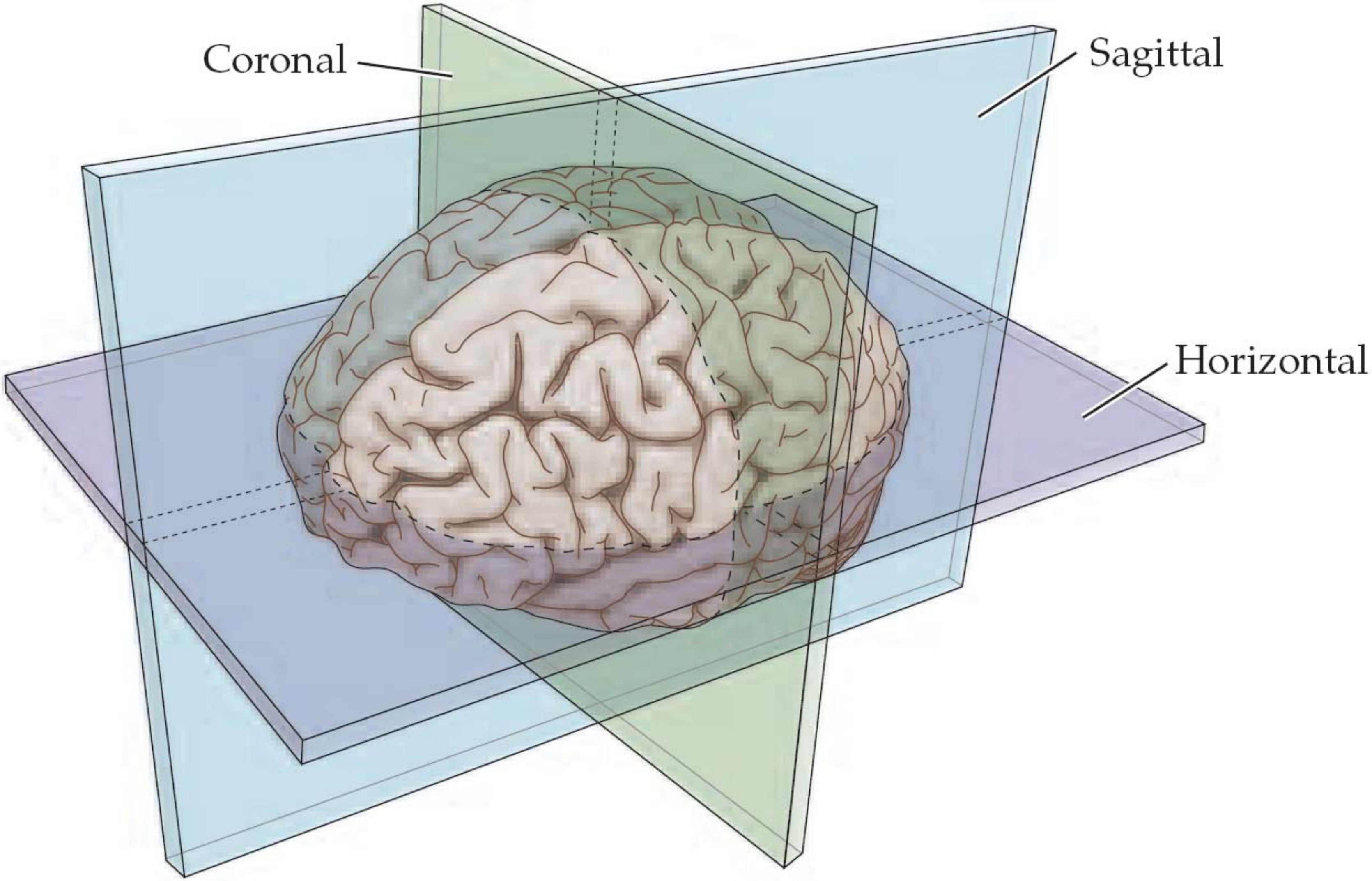
- **Microglia:** immune system cells in the CNS (central nervous system)
- **Macroglia**:
  - **Oligodendrocytes** (in CNS) and **Schwann cells** (in PNS) form the *Myelin Sheath* (insulation of axons) → faster action potential propagation
  - **Astrocytes** – (1) bring nutrients to neurons, (2) form the BBB (blood-brain barrier), (3) maintain extracellular potassium (K+) concentration, (4) uptake neurotransmitters**.**
  - A few other types of macroglia.
- Recent years provide increasing evidence that glia can directly modulate the function of neurons.

Glia are discussed in other courses, such as “Neuroimmunology” (last semester) and “Developmental Neurobiology”. In this course we will discuss only the function of neurons.

Getting oriented in the brain – directions



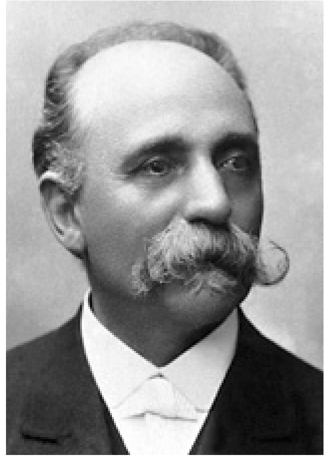
Getting oriented in the brain – planes of section



Some history: Ramón y Cajal vs. Golgi

Santiago Ramón y Cajal

Camillo Golgi



Shared the Nobel prize in 1906

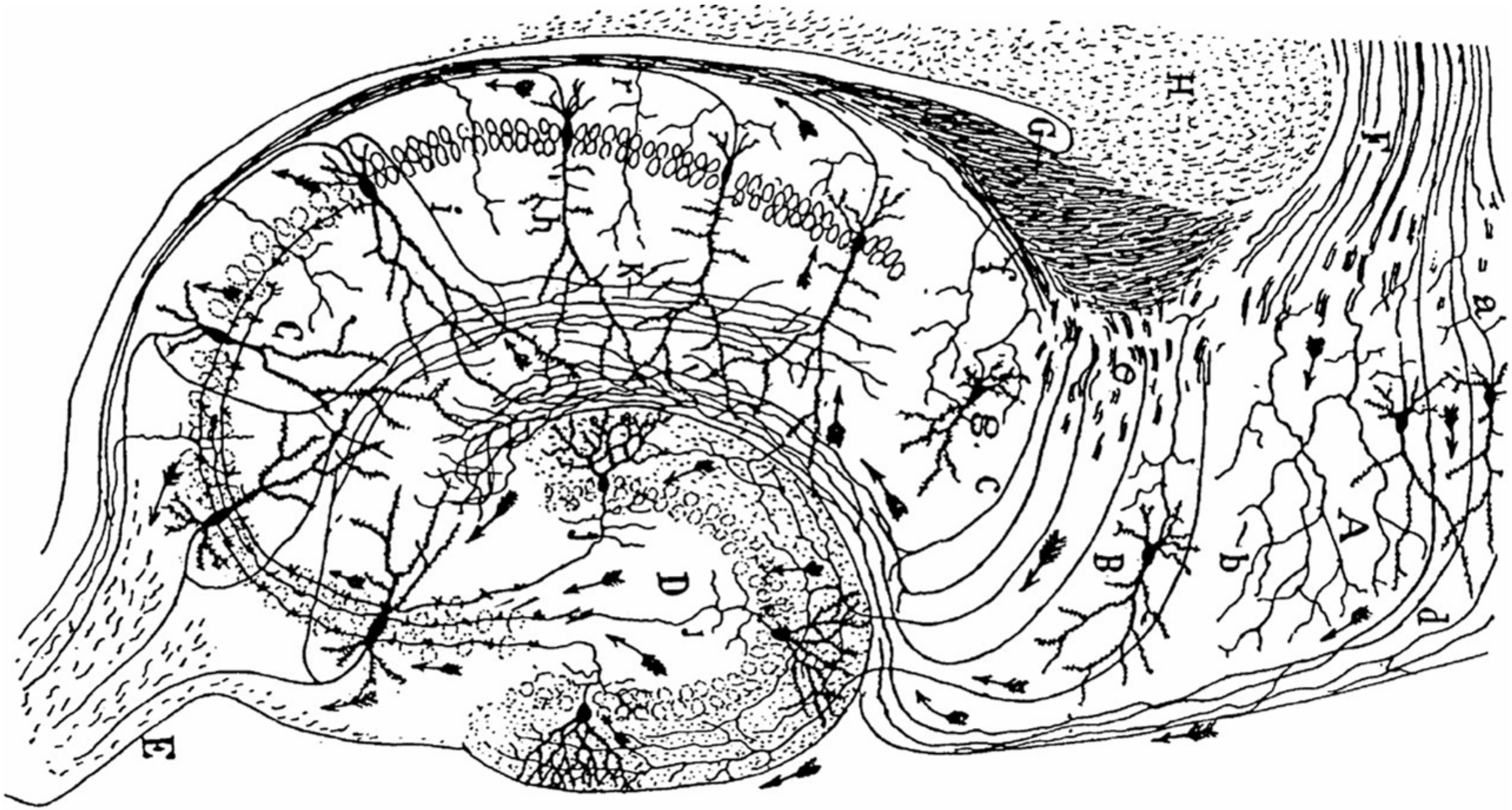
Provided key evidence for the **Neuron Doctrine**:

- The brain is composed of units (cells)
- Nerve cells are specialized in structure and function
- Nerve cells (neurons) are connected via sites of contact (later termed "synapses" by Sherrington)
- Dendrites and axons conduct electrical signals
- Law of Polarization: Neurons transmit information primarily uni-directionally (dendrites→soma→axon)
- and some other tenets that you'll learn in this course

Provided vast amount of anatomical data, and believed in the **syncytium theory**: namely, that nerve cells are connected through a *diffuse network*, interconnected cytoplasmatically; that is, they form a syncytium.

Some history: Ramón y Cajal vs. Golgi

Example: Drawing of the neurons, their interconnections, and flow in information in the rodent hippocampus (1911).

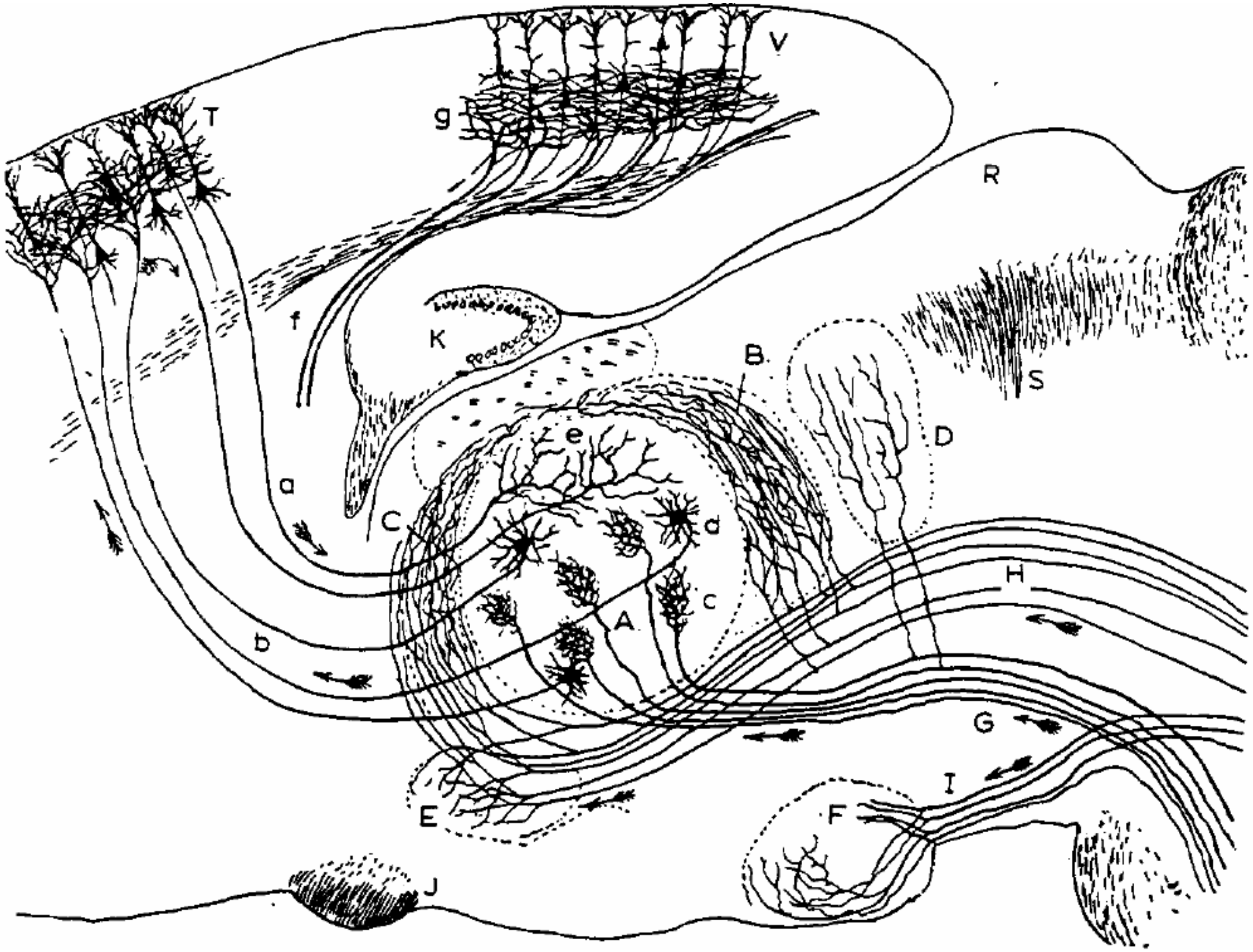


Some history: Ramón y Cajal vs. Golgi

Example: Drawing of the neurons, their interconnections, and flow in information in sensory nuclei of the thalamus (Nobel lecture, 1906).

Cortex →

Thalamus →



Some history: Ramón y Cajal vs. Golgi

This is how neurons stained with the Golgi method *actually* look (from the collections at Museo Cajal). Ramón y Cajal then artistically drew the neurons (and in later years, used also the *camera lucida* method).

Some history: Ramón y Cajal vs. Golgi

- Ramón y Cajal:
  - Mapped out the neural circuits of <u>many</u> brain areas in numerous animal species – vertebrates and invertebrates – including the neuron types in each brain area, and their inputs and outputs.
  - He did this in normal and pathological brains; and across developmental stages.
  - He mapped neural circuits based on structure alone – and *without* the use of *anterograde* or *retrograde tracers*, which were unknown at that time: A tour de force, and a classic example of inferring function from structure.
  - Ramón y Cajal is regarded by many as the founder of Neuroscience.
- Ironically, Ramón y Cajal contradicted Golgi's theory via extensive experimental studies which all used the Golgi staining method...
- But: The finding of *electrical synapses*, made of *gap junctions*, suggests that Golgi was not totally wrong, after all.