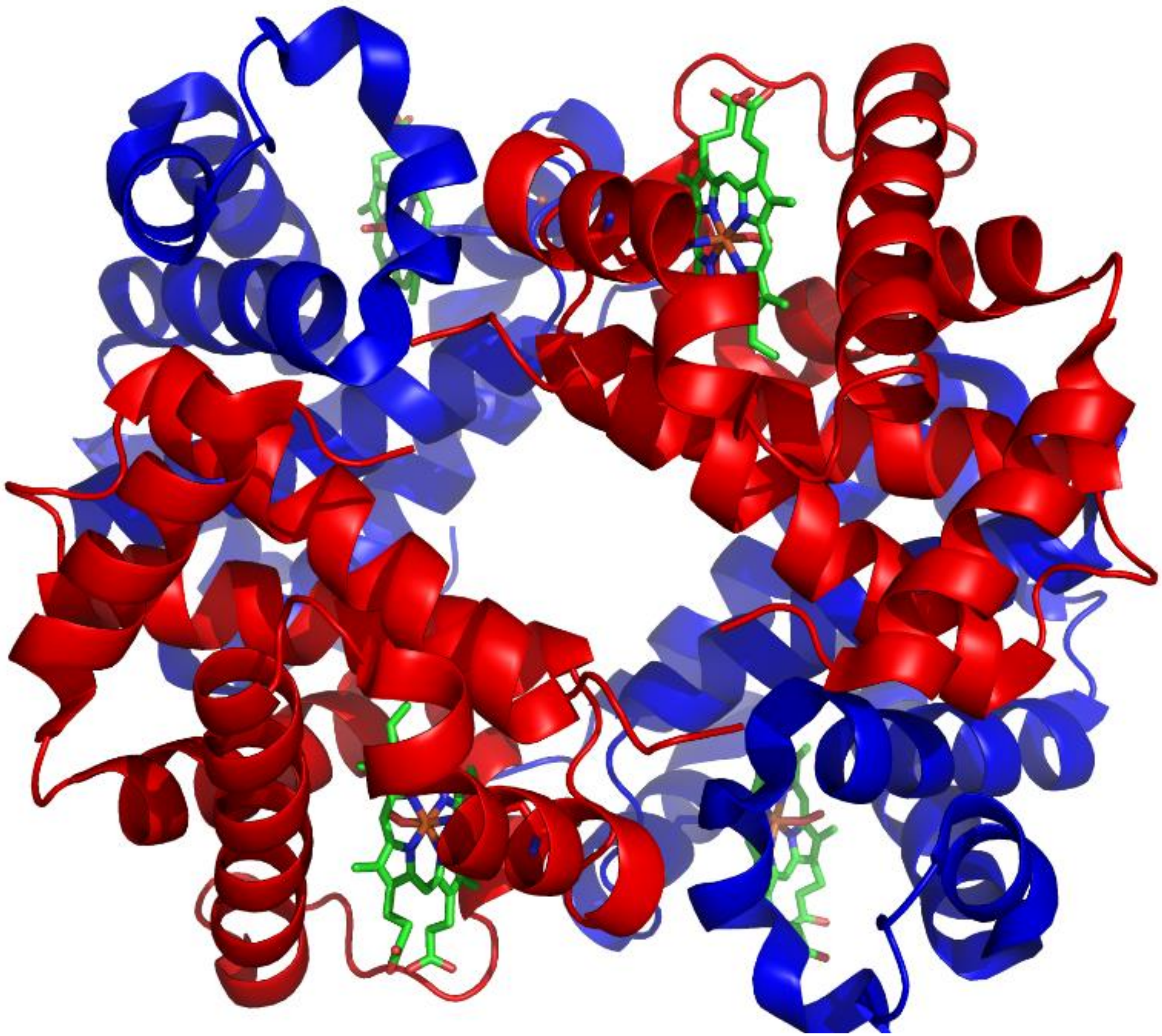
THE FOUNDATIONS OF BIOCHEMISTRY



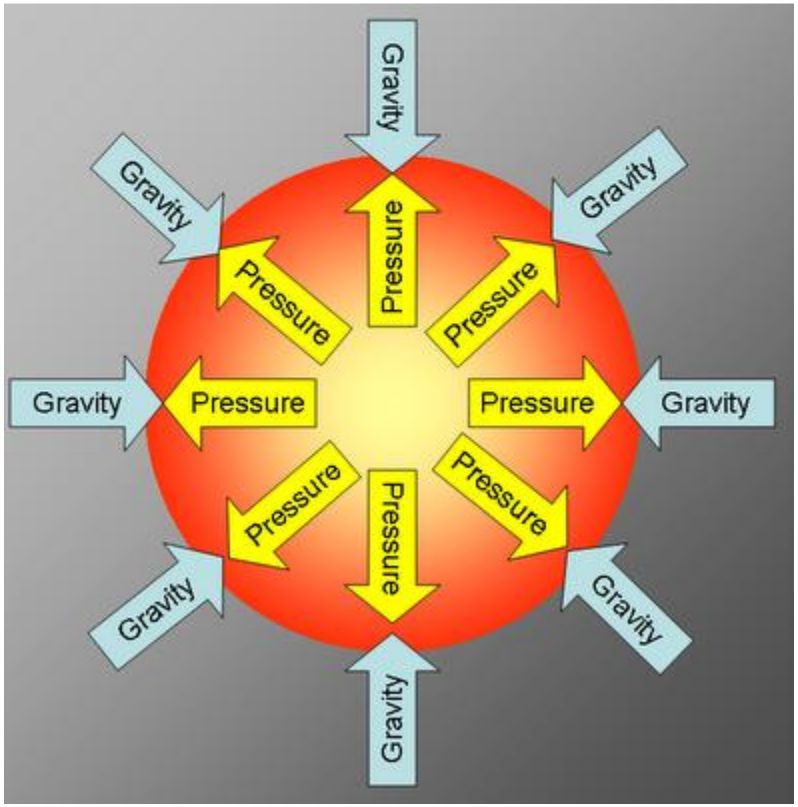
- About fourteen billion years ago, the universe arose as a cataclysmic eruption of hot, energy-rich subatomic particles.

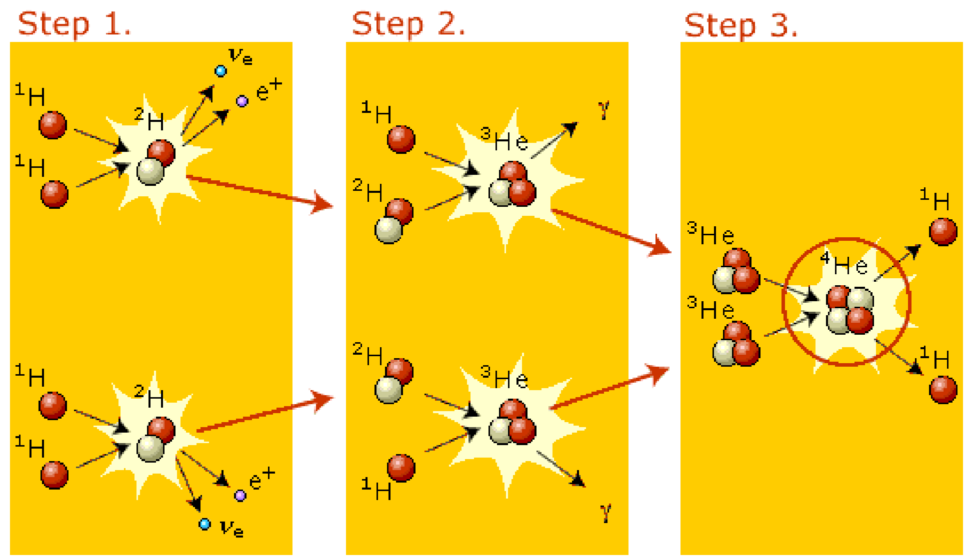
- Within seconds, the simplest elements (hydrogen and helium) were formed.

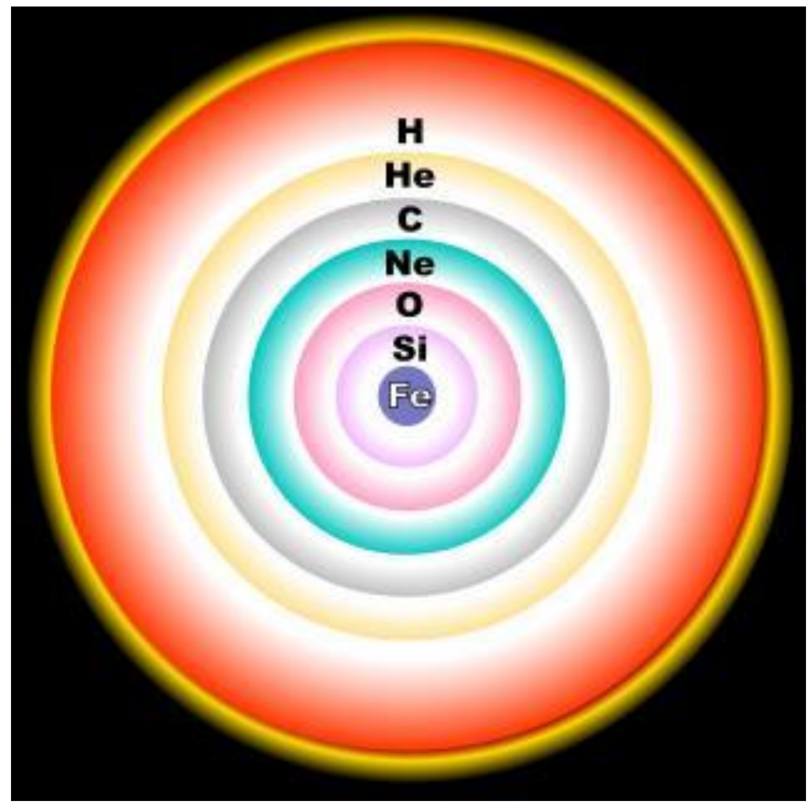
- As the universe expanded and cooled, material condensed under the influence of gravity to form stars.

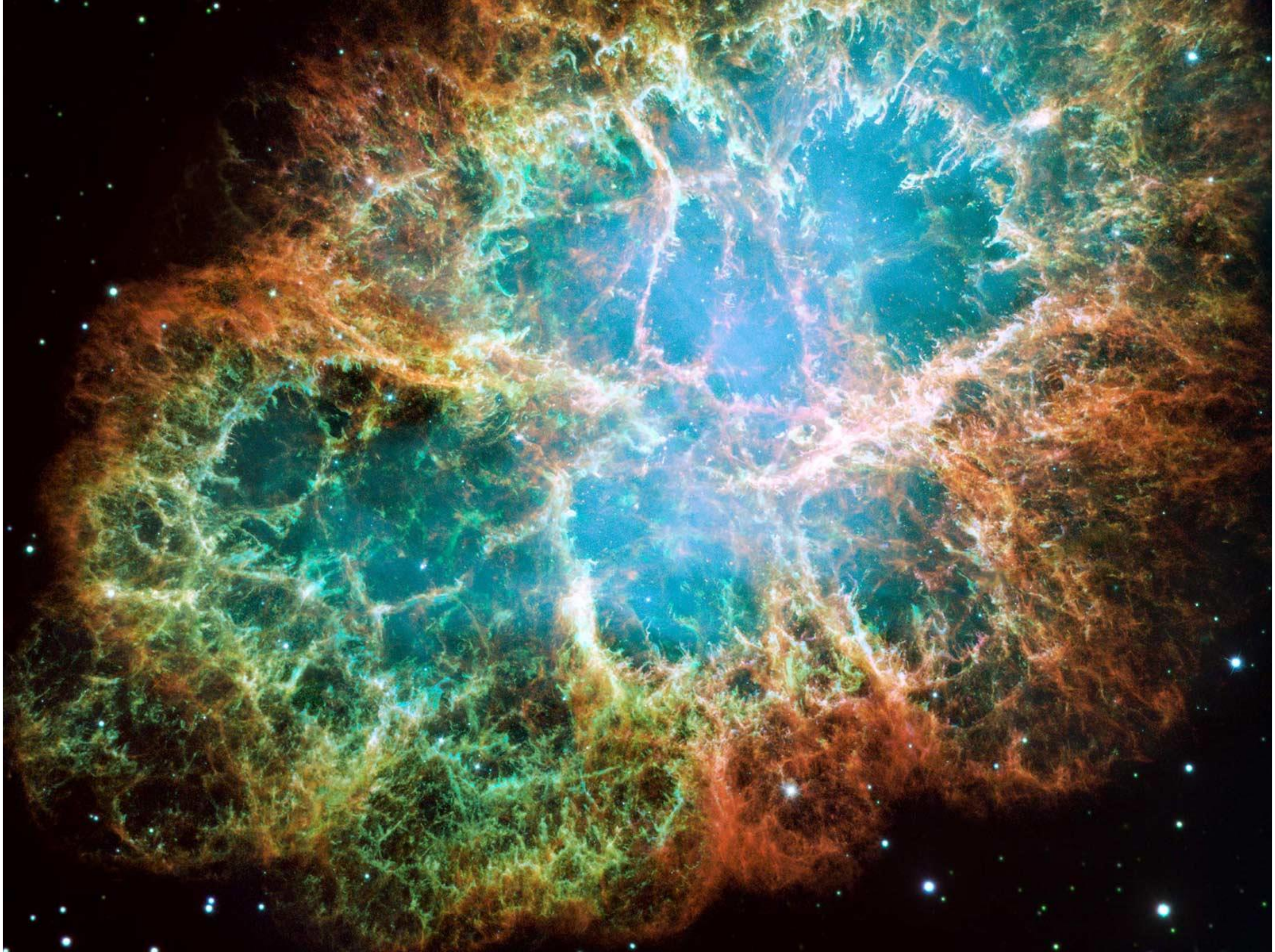
- Some stars became enormous and then exploded as supernovae, releasing the energy needed to fuse simpler atomic nuclei into the more complex elements.

- Thus were produced, over billions of years, the Earth itself and the chemical elements found on the Earth today.

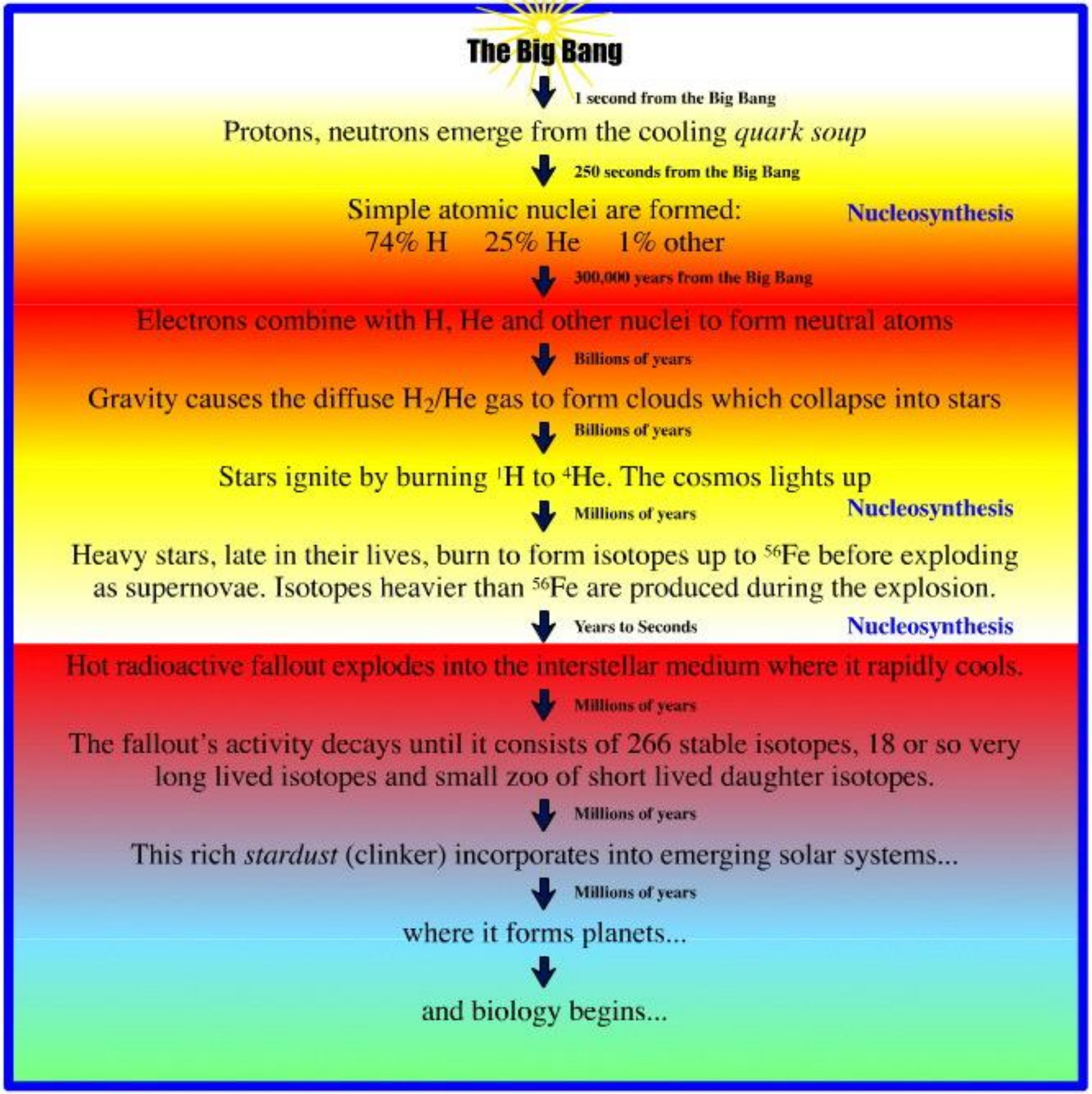


Gravity
Pressure


Step 1.
Step 2.
Step 3.
^1H
^2H
^3He
^4He
ν_e
e^+
γ


H
He
C
Ne
O
Si
Fe



Nucleosynthesis



❖About four billion years ago, life arose – simple microorganisms that extract energy and used it to make more complex biomolecules from the simple elements and compounds.

❖Biochemistry asks how the remarkable properties of living organisms arise from the thousands of different lifeless biomolecules.

❖Biochemistry describes in molecular terms the structures, mechanisms, and chemical processes shared by all organisms and provides organizing principles that underlie life in all its diverse forms, principles we refer to collectively as the molecular logic of life.

❖Although biochemistry provides important insights and practical applications in medicine, agriculture, nutrition, and industry, its ultimate concern is with the wonder of life itself.

❖The study of biochemistry shows how the collections of inanimate molecules that constitute living organisms interact to maintain and perpetuate life animated solely by the physical and chemical laws that govern the nonliving universe.

❖Yet organisms possess extraordinary attributes, properties that distinguish them from other collections of matter.

Distinguishing features of living organisms

- A high degree of chemical complexity and microscopic organization.
- Systems for extracting, transforming, and using energy from the environment.
- A capacity for precise self-replication and self-assembly
- Mechanisms for sensing and responding to alterations in their surroundings
- Defined functions for each of their components and regulated interactions among them.
- A history of evolutionary change.

Cellular Foundations

- Cells are the structural and functional units of all living organisms. Cells of all kinds share certain structural.

- The plasma membrane defines the periphery of the cell, separating its contents from the surroundings.

- It is composed of lipid and protein molecules that form a thin, tough, pliable, hydrophobic barrier around the cell.

- The membrane is a barrier to the free passage of inorganic ions and most other charged or polar compounds.

- Because the individual lipids and proteins of the plasma membrane are not covalently linked, the entire structure is remarkably flexible, allowing changes in the shape and size of the cell.

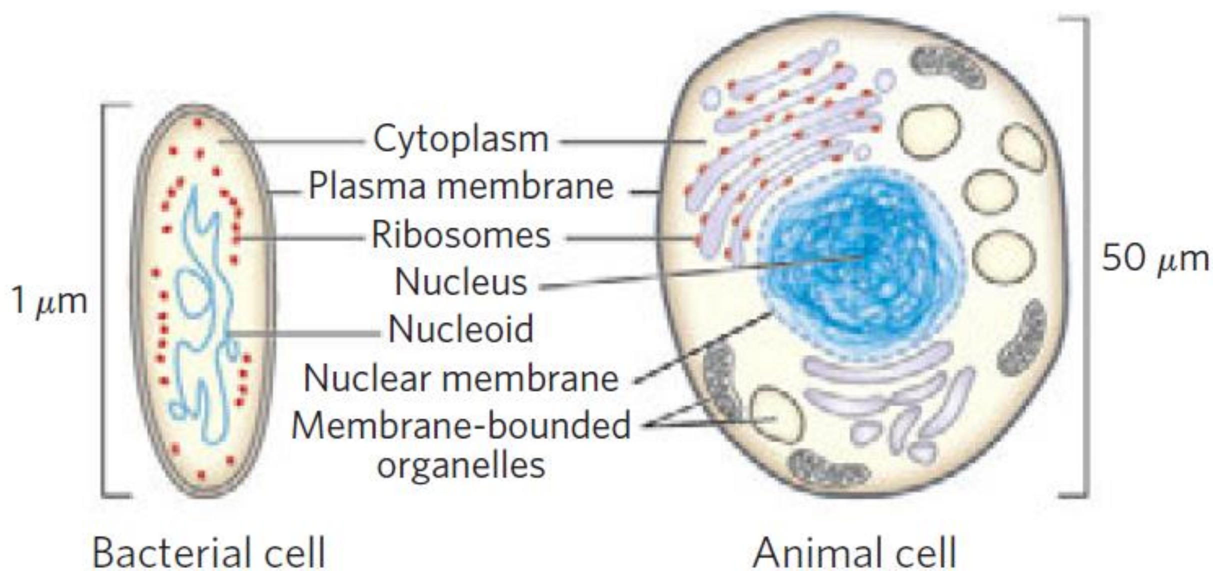
- The internal volume enclosed by the plasma membrane, the **cytoplasm**, is composed of an aqueous solution, the **cytosol**, and a variety of suspended particles with specific functions.

  - The cytosol is a highly concentrated solution containing **enzymes** and the **RNA molecules** that encode them;
  - the components (**amino acids** and **nucleotides**) from which these macromolecules are assembled;
  - hundreds of small organic molecules called **metabolites**, intermediates in biosynthetic and degradative pathways;
  - **coenzymes**, compounds essential to many enzyme-catalyzed reactions;
  - **inorganic ions**; and
  - **ribosomes**, small particles (composed of protein and RNA molecules) that are the sites of protein synthesis.

- All cells have, for at least some part of their life, either a **nucleus** or a **nucleoid**, in which the genome —the complete set of genes, composed of DNA—is stored and replicated.

- The nucleoid, in bacteria, is not separated from the cytoplasm by a membrane; the nucleus, in higher organisms, consists of nuclear material enclosed within a double membrane, the nuclear envelope.

- Cells with nuclear envelopes are called eukaryotes (Greek eu, “true,” and karyon, “nucleus”); those without nuclear envelopes—bacterial cells—are prokaryotes (Greek pro, “before”).



- All living organisms fall into one of three large groups (kingdoms, or domains) that define three branches of evolution from a common progenitor.

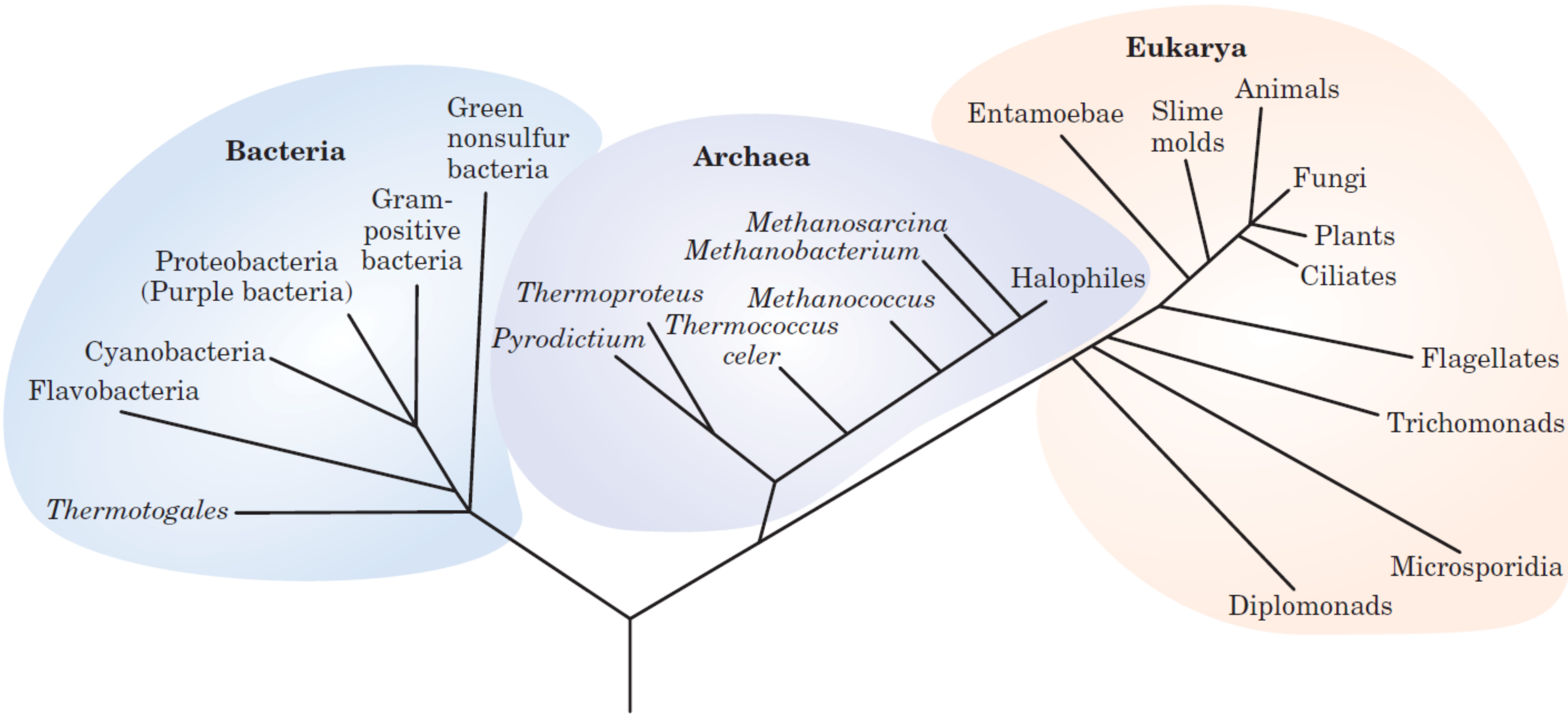
- Two large groups of prokaryotes can be distinguished on biochemical grounds: archaebacteria (Greek arche-, “origin”) and eubacteria (again, from Greek eu, “true”).

- Eubacteria inhabit soils, surface waters, and the tissues of other living or decaying organisms.

- The archaebacteria, more recently discovered, are less well characterized biochemically; most inhabit extreme environments—salt lakes, hot springs, highly acidic bogs, and the ocean depths.

- All eukaryotic organisms, which make up the third domain, Eukarya, evolved from the same branch that gave rise to the Archaea

Phylogeny of the three domains of life.

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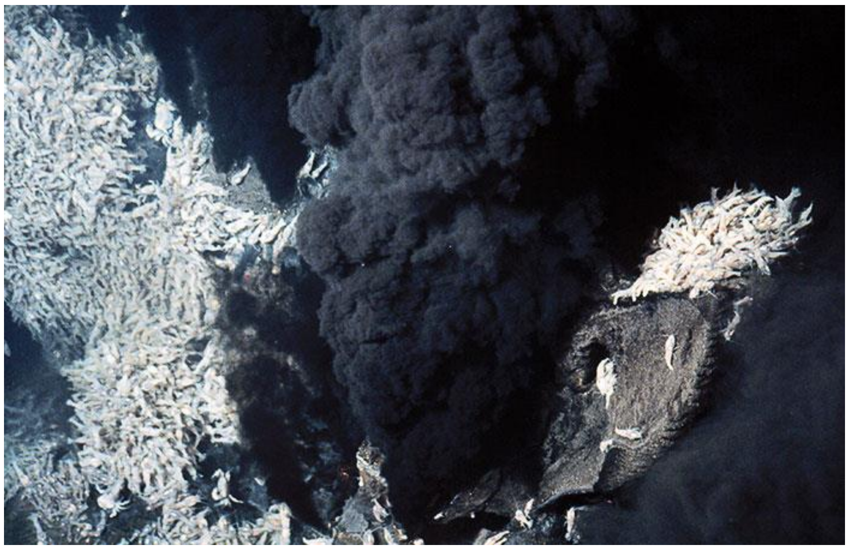
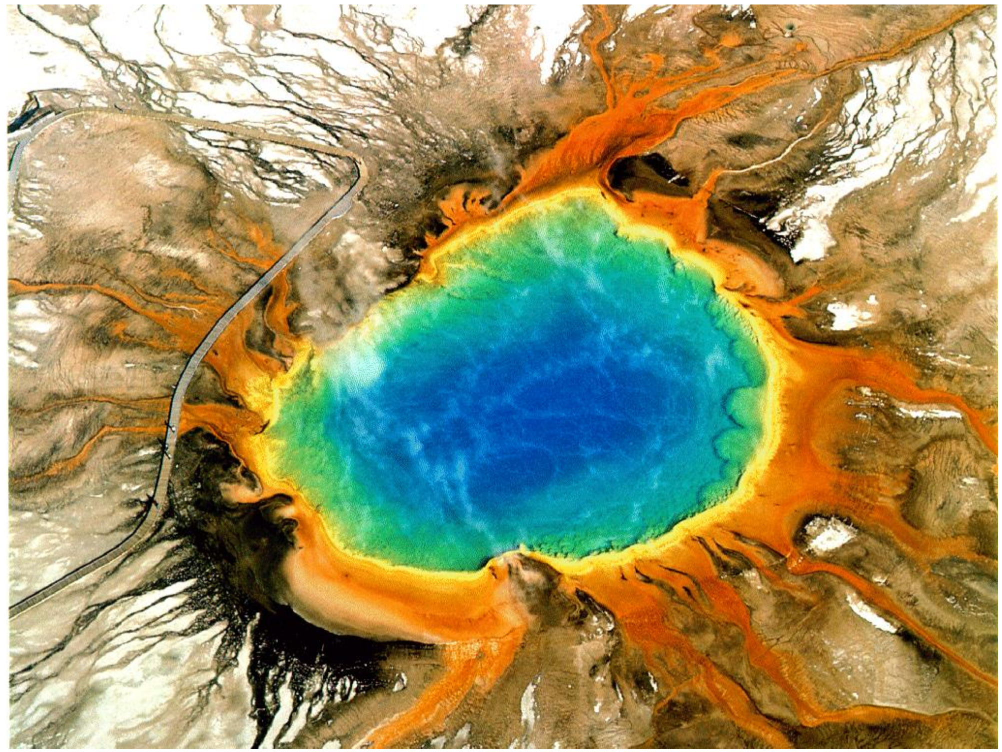




- Within the domains of Archaea and Bacteria are subgroups distinguished by their habitats.

- In **aerobic** habitats with a plentiful supply of oxygen, some resident organisms derive energy from the transfer of electrons from fuel molecules to oxygen within the cell.

- Other environments are **anaerobic**, virtually devoid of oxygen, and microorganisms adapted to these environments obtain energy by transferring electrons to nitrate (forming N_2), sulfate (forming H_2S), or CO_2 (forming CH_4).

- Many organisms that have evolved in anaerobic environments are obligate anaerobes: they die when exposed to oxygen.

- Others are facultative anaerobes, able to live with or without oxygen.

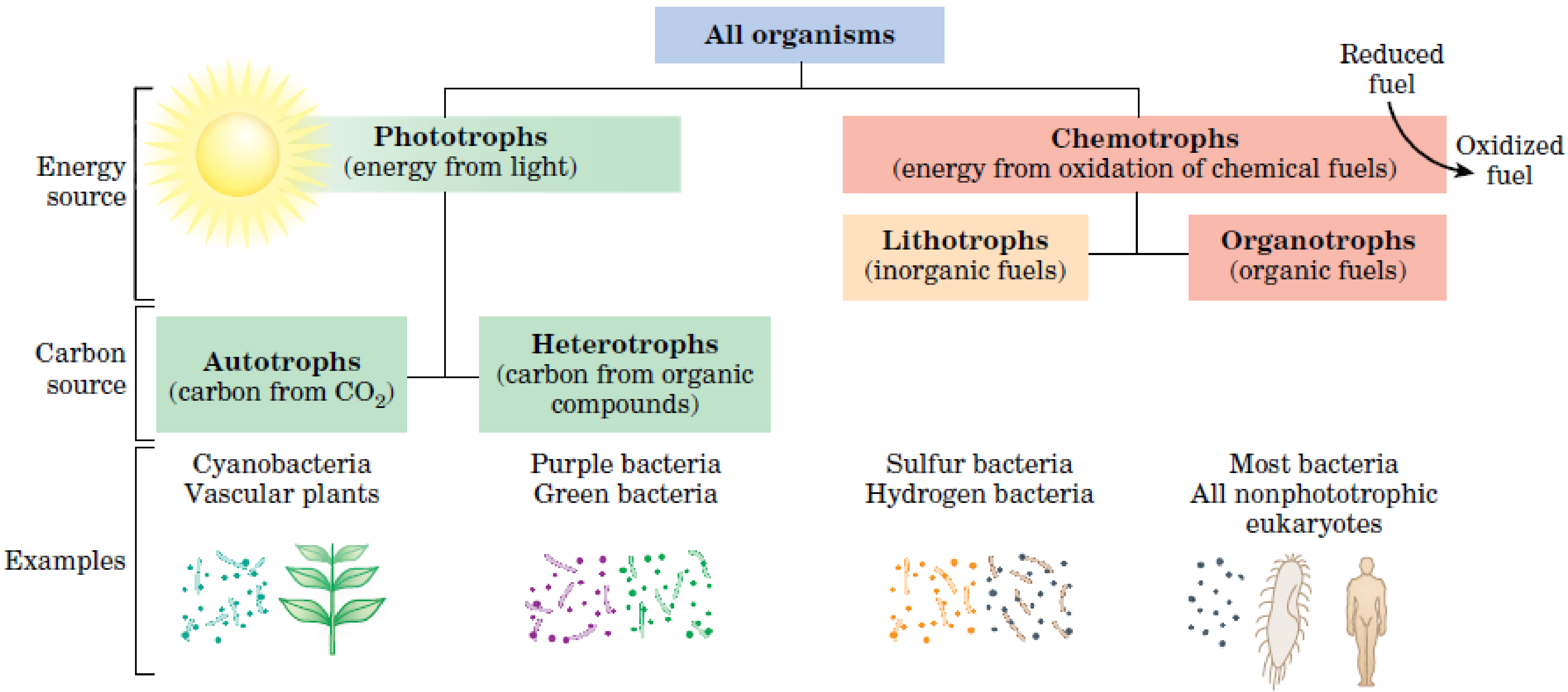
- We can classify organisms according to how they obtain the energy and carbon they need for synthesizing cellular material.

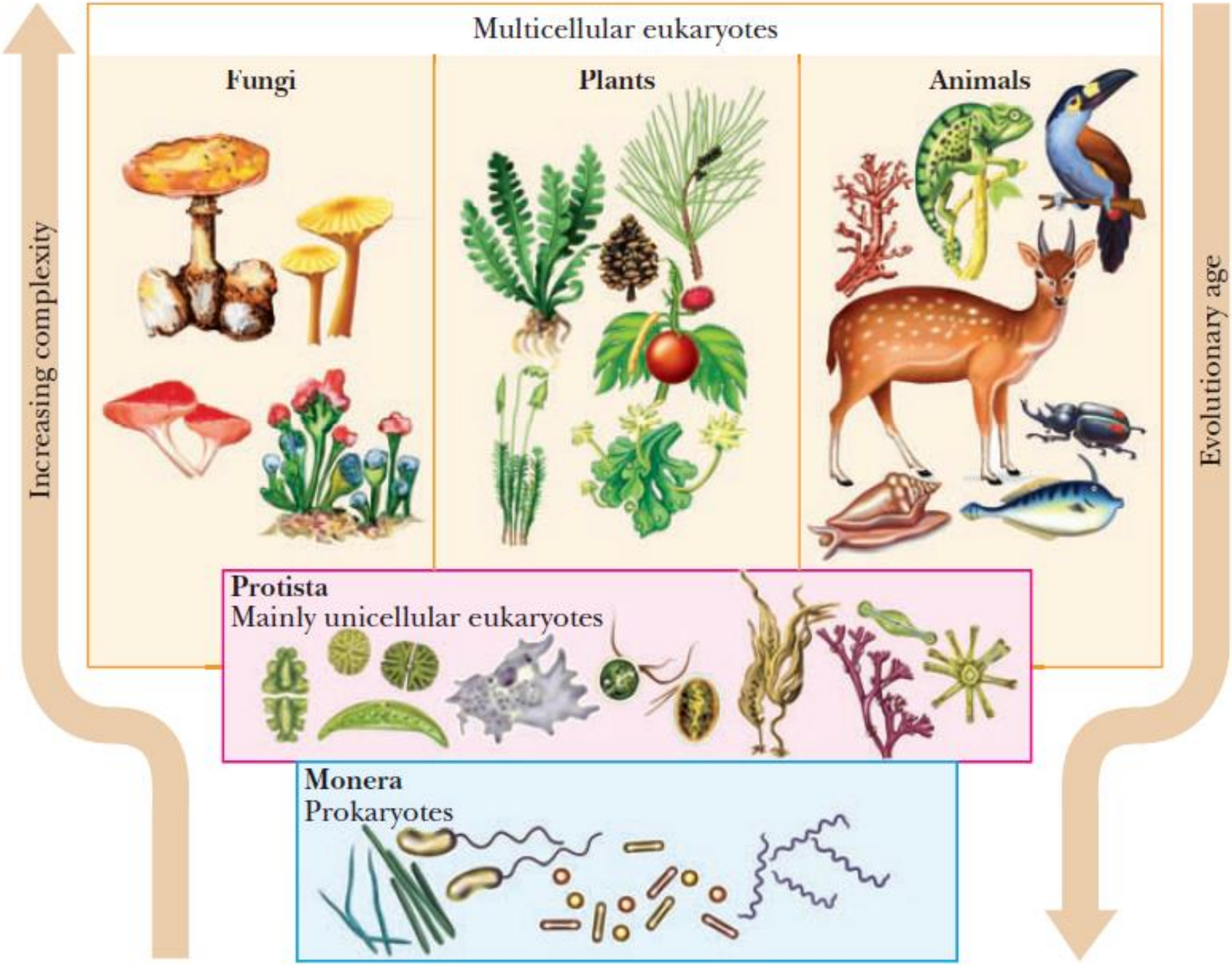
- There are two broad categories based on energy sources: phototrophs trap and use sunlight, and chemotrophs derive their energy from oxidation of a fuel.

- All chemotrophs require a source of organic nutrients; they cannot fix CO_2 into organic compounds.

- The phototrophs can be further divided into those that can obtain all needed carbon from CO_2 (autotrophs) and those that require organic nutrients (heterotrophs).

- No chemotroph can get its carbon atoms exclusively from CO_2 (that is, no chemotrophs are autotrophs), but the chemotrophs may be further classified according to a different criterion: whether the fuels they oxidize are inorganic (lithotrophs) or organic (organotrophs).


All organisms
Reduced fuel
Oxidized fuel
Energy source
Phototrophs
(energy from light)
Chemotrophs
(energy from oxidation of chemical fuels)
Lithotrophs
(inorganic fuels)
Organotrophs
(organic fuels)
Carbon source
Autotrophs
(carbon from CO_2)
Heterotrophs
(carbon from organic compounds)
Examples
Cyanobacteria
Vascular plants
Purple bacteria
Green bacteria
Sulfur bacteria
Hydrogen bacteria
Most bacteria
All nonphototrophic eukaryotes


Multicellular eukaryotes
Fungi
Plants
Animals
Protista
Mainly unicellular eukaryotes
Monera
Prokaryotes
Increasing complexity
Evolutionary age

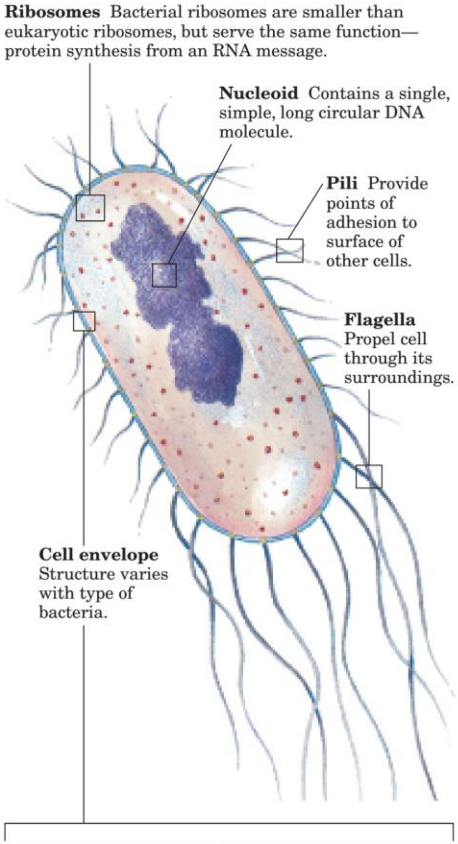
- The plasma membranes of bacteria consist of a thin bilayer of lipid molecules penetrated by proteins.

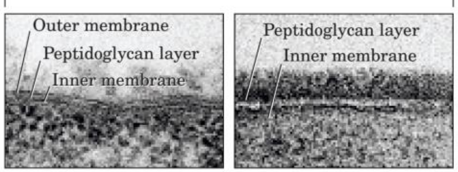
- Archaeal plasma membranes have a similar architecture, but the lipids can be strikingly different from those of bacteria.

- Some bacteria, called gram-positive because they are colored by Gram's stain (introduced by Hans Peter Gram in 1882), have a thick layer of peptidoglycan outside their plasma membrane but lack an outer membrane.

- Gram-negative bacteria have an outer membrane composed of a lipid bilayer into which are inserted complex lipopolysaccharides and proteins called porins.

- The structures outside the plasma membrane of archaea differ from organism to organism, but they, too, have a layer of peptidoglycan or protein that confers rigidity on their cell envelopes.



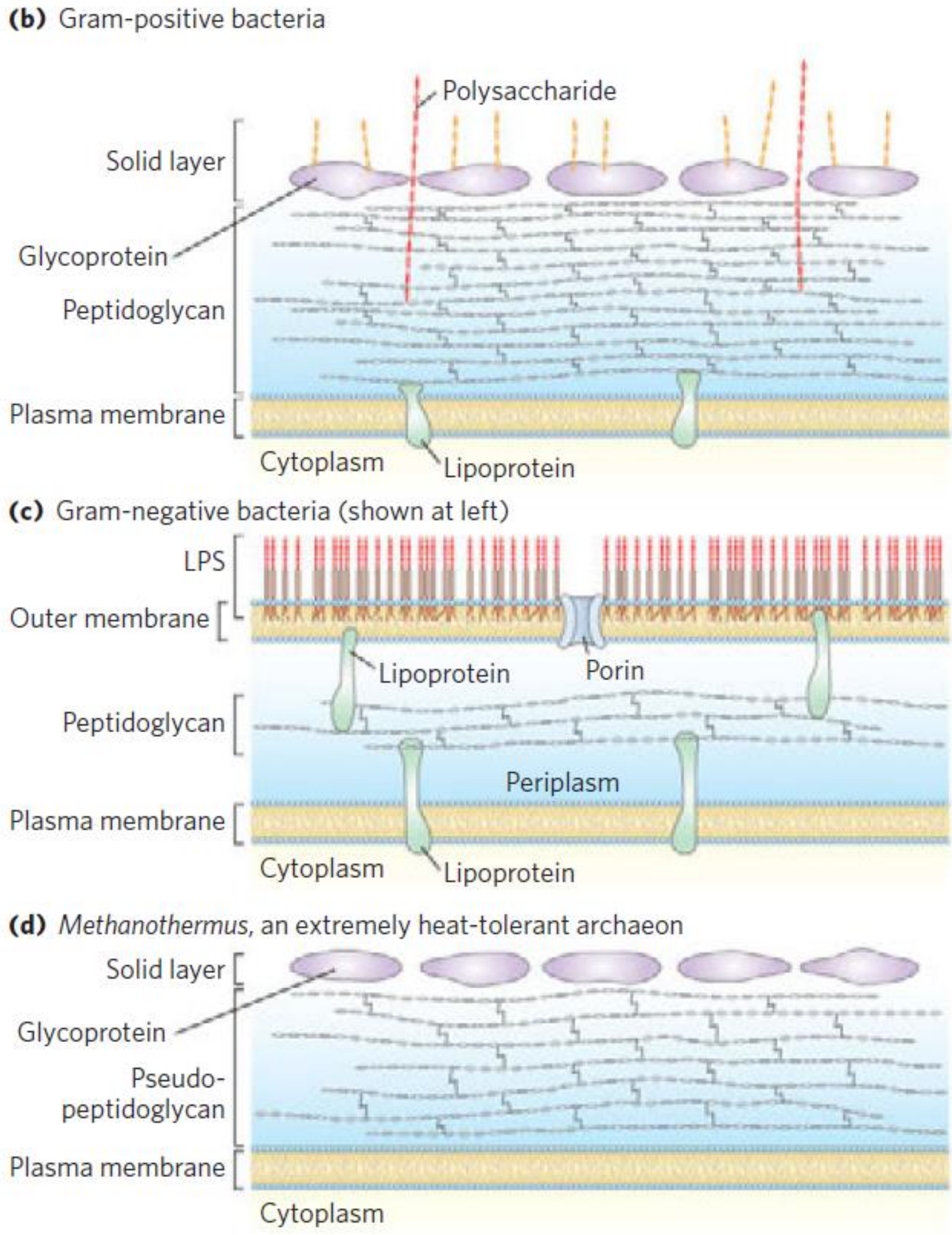


Gram-negative bacteria
Outer membrane; peptidoglycan layer

Gram-positive bacteria
No outer membrane; thicker peptidoglycan layer

Cyanobacteria
Gram-negative; tougher peptidoglycan layer; extensive internal membrane system with photosynthetic pigments

Archaebacteria
No outer membrane; peptidoglycan layer outside plasma membrane



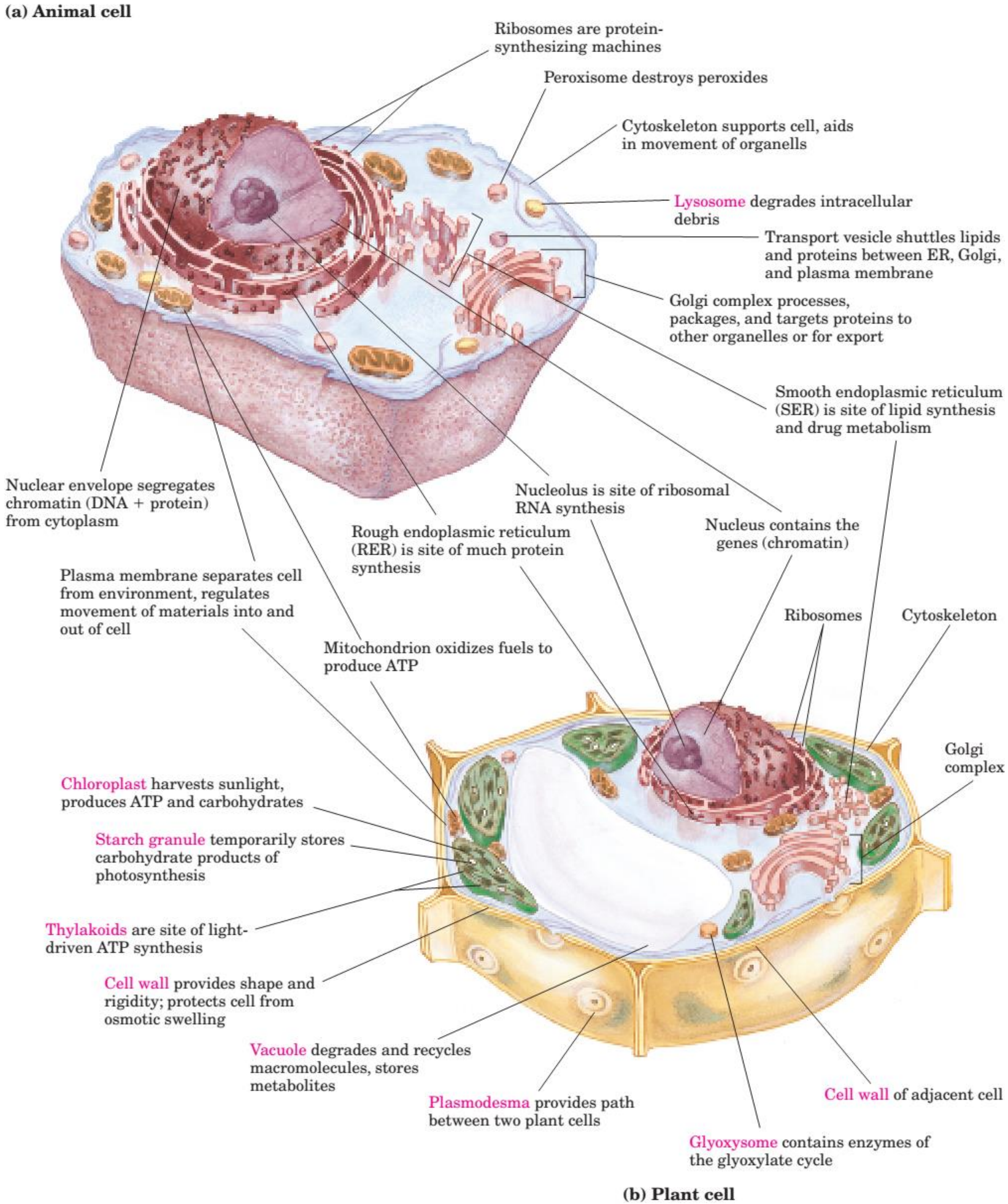
- Typical eukaryotic cells are much larger than, with cell volumes a thousand to a million times larger than those of bacteria.

- The distinguishing characteristics of eukaryotes are the **nucleus** and a variety of membrane-enclosed organelles with specific functions.

- These organelles include **mitochondria**, the site of most of the energy extracting reactions of the cell; the **endoplasmic reticulum** and **Golgi complexes**, which play central roles in the synthesis and processing of lipids and membrane proteins; **peroxisomes**, in which very long-chain fatty acids are oxidized; and **lysosomes**, filled with digestive enzymes to degrade unneeded cellular debris.

- In addition to these, plant cells also contain **vacuoles** (which store large quantities of organic acids) and **chloroplasts** (in which sunlight drives the synthesis of ATP in the process of photosynthesis.

- Also present in the cytoplasm of many cells are granules or droplets containing stored nutrients such as starch and fat.



ribosomes the sites of protein synthesis in all organisms, consisting of RNA and protein

cell membrane the outer membrane of the cell that separates it from the outside world

cell wall the outer coating of bacterial and plant cells

chloroplasts organelles that are the sites of photosynthesis in green plants

nucleus the organelle that contains the main genetic apparatus in eukaryotes

nucleolus a portion of the nucleus rich in RNA

mitochondrion an organelle that contains the apparatus responsible for aerobic oxidation of nutrients

endoplasmic reticulum (ER) a continuous single-membrane system throughout the cell

Golgi apparatus a cytoplasmic organelle that consists of flattened membranous sacs, usually involved in secretion of proteins

lysosomes membrane-enclosed organelles that contain hydrolytic enzymes

peroxisomes membrane-bounded sacs that contain enzymes involved in the metabolism of hydrogen peroxide (H_2O_2)

glyoxysomes membrane-enclosed organelles that contain the enzymes of the glyoxylate cycle

cytosol the portion of the cell that lies outside the nucleus and the other membrane-enclosed organelles

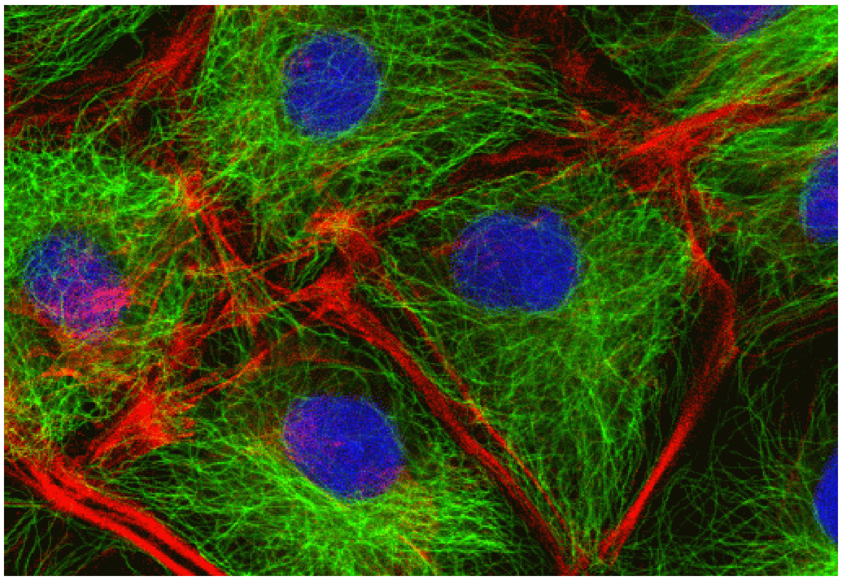
cytoskeleton (microtrabecular lattice) a lattice of fine strands, consisting mostly of protein, that pervades the cytosol

vacuoles cavities within the cytoplasm of a cell, typically enclosed by a single membrane, that may serve secretory, excretory, or storage functions

- Fluorescence microscopy reveals several types of protein filaments crisscrossing the eukaryotic cell, forming an interlocking three-dimensional meshwork, the cytoskeleton.

- There are three general types of cytoplasmic filaments—actin filaments, microtubules, and intermediate filaments, differing in width (from about 6 to 22 nm), composition, and specific function.

- All types provide structure and organization to the cytoplasm and shape to the cell. Actin filaments and microtubules also help to produce the motion of organelles or of the whole cell.

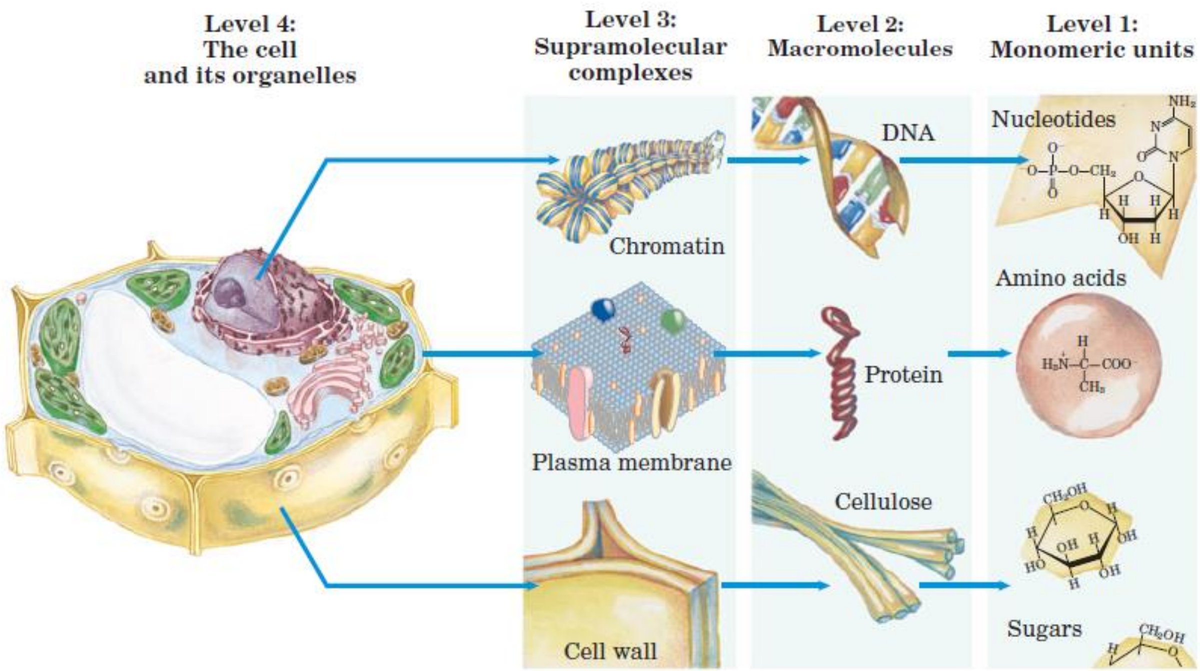


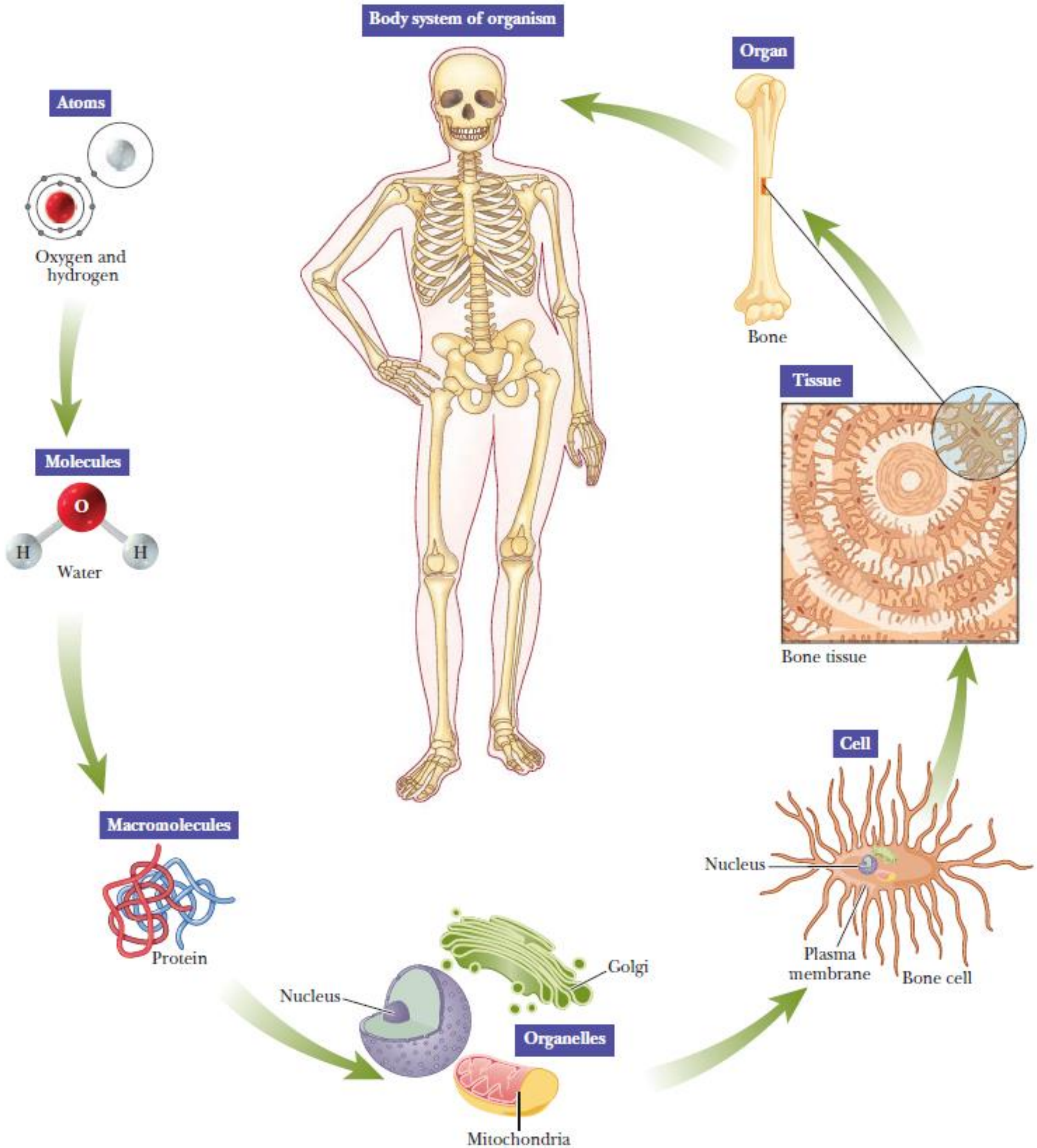
microtubules (green)
actin filaments (red)
the nucleus (blue).

- Macromolecules and their monomeric subunits differ greatly in size. An alanine molecule is less than 0.5 nm long.

- A molecule of hemoglobin, the oxygen-carrying protein of erythrocytes (red blood cells), consists of nearly 600 amino acid and associated in a structure 5.5 nm in diameter.

- In turn, proteins are much smaller than ribosomes (about 20 nm in diameter), which are in turn much smaller than organelles such as mitochondria, typically 1,000 nm in diameter.





Body system of organism
Organ
Atoms
Oxygen and hydrogen
Bone
Tissue
Molecules
O
H
H
Water
Bone tissue
Cell
Macromolecules
Nucleus
Plasma membrane
Bone cell
Protein
Golgi
Nucleus
Organelles
Mitochondria

Chemical Foundations

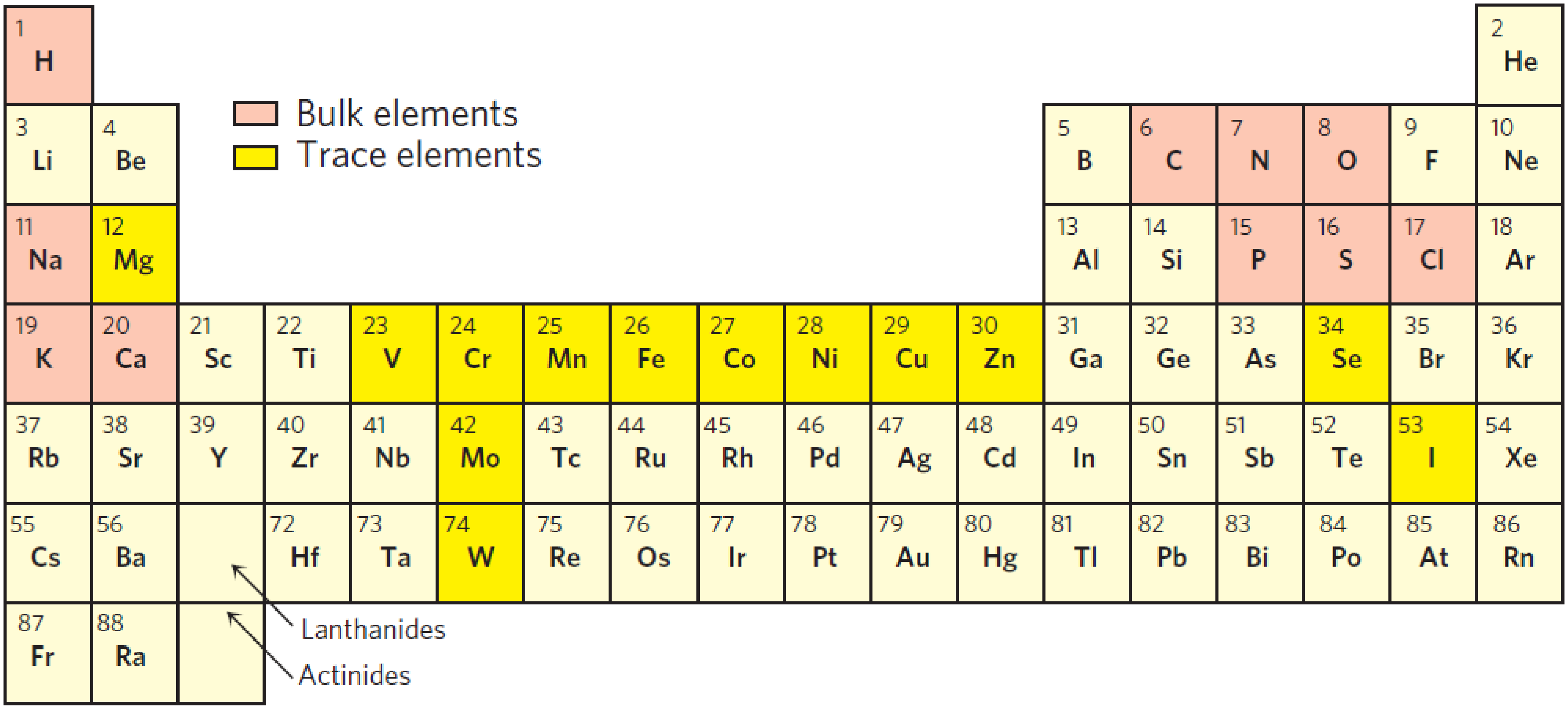
- Biochemistry aims to explain biological form and function in chemical terms.

- The four most abundant elements in living organisms, in terms of percentage of total number of atoms, are hydrogen, oxygen, nitrogen, and carbon, which together make up more than 99% of the mass of most cells.

- They are the lightest elements capable of forming one, two, three, and four bonds, respectively; in general, the lightest elements form the strongest bonds.

- The trace elements represent a miniscule fraction of the weight of the human body, but all are essential to life, usually because they are essential to the function of specific proteins, including enzymes.

Elements essential to animal life and health.



- The chemistry of living organisms is organized around carbon, which accounts for more than half the dry weight of cells.

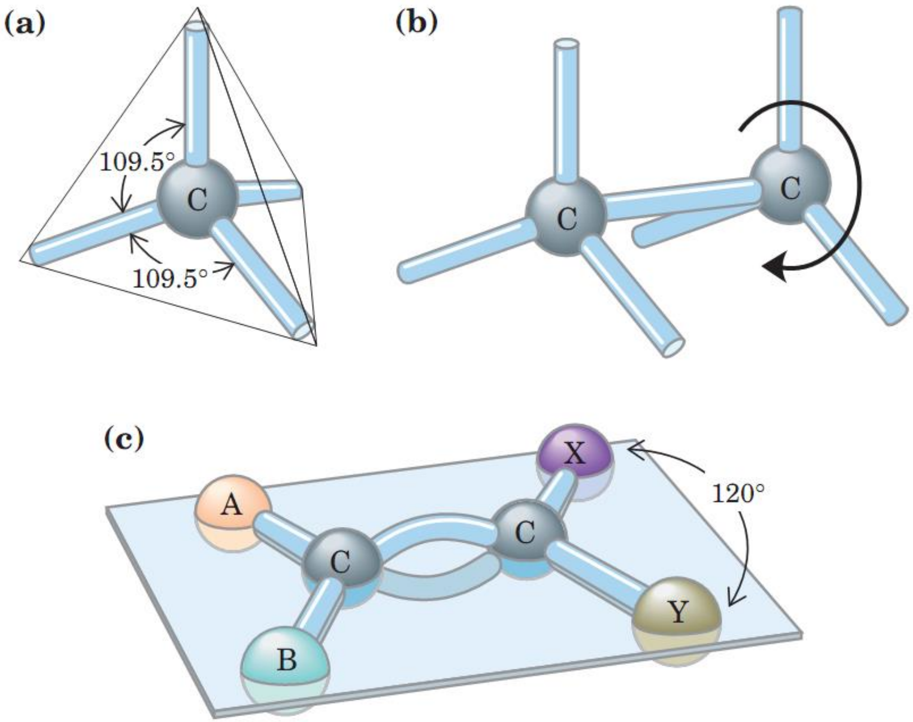
- Carbon can form single bonds with hydrogen atoms, and both single and double bonds with oxygen and nitrogen atoms.

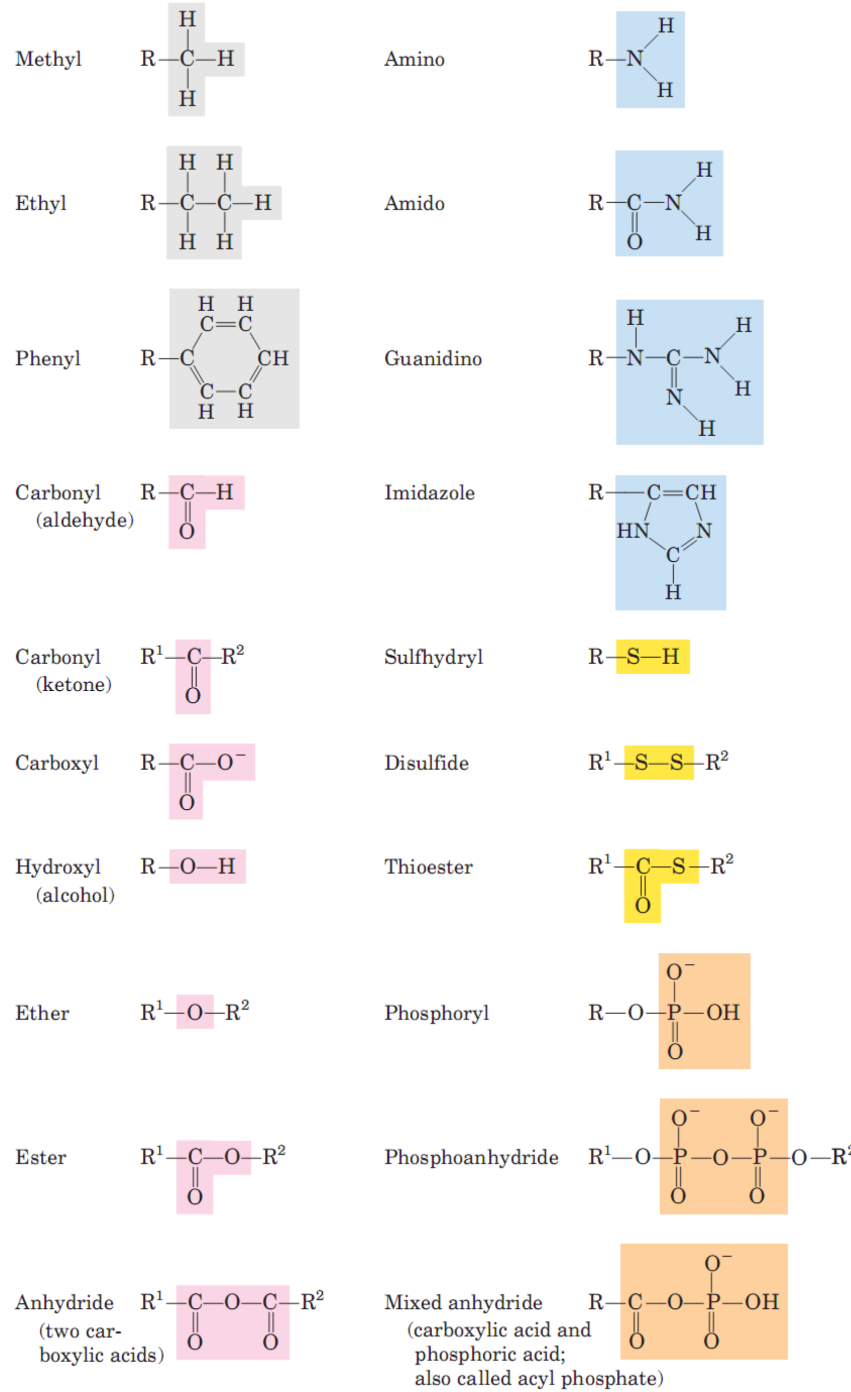
- Of greatest significance in biology is the ability of carbon atoms to form very stable carbon–carbon single bonds.

- Covalently linked carbon atoms in biomolecules can form linear chains, branched chains, and cyclic structures.

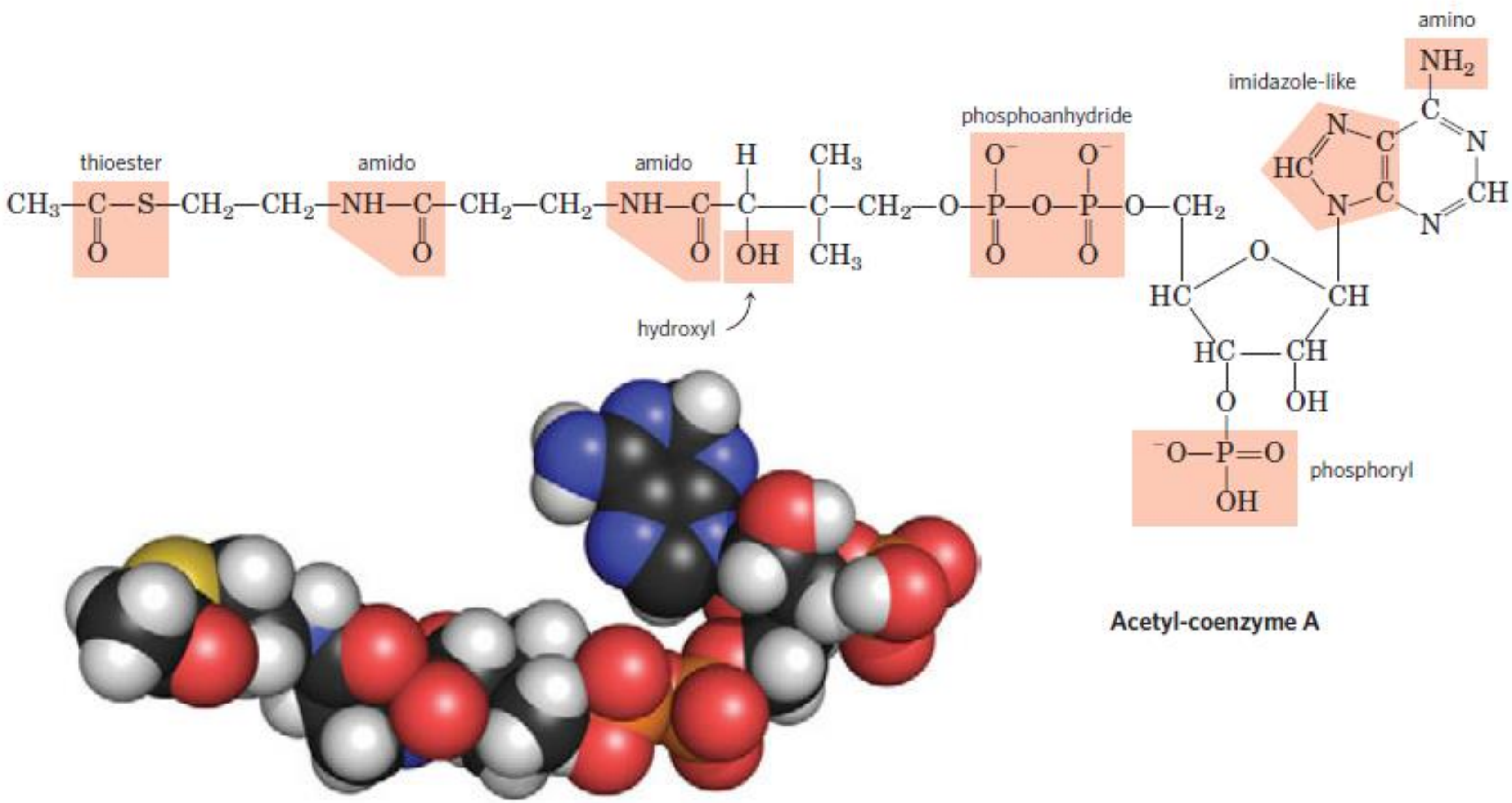
- It seems likely that the bonding versatility of carbon was a major factor in the selection of carbon compounds for the molecular machinery of cells during the origin and evolution of living organisms.

- Most biomolecules can be regarded as derivatives of hydrocarbons, with hydrogen atoms replaced by a variety of functional groups


(a)
109.5°
C
109.5°
(b)
C
C
(c)
A
X
120°
C
C
B
Y


Methyl
Ethyl
Phenyl
Carbonyl (aldehyde)
Carbonyl (ketone)
Carboxyl
Hydroxyl (alcohol)
Ether
Ester
Anhydride (two carboxylic acids)
Amino
Amido
Guanidino
Imidazole
Sulfhydryl
Disulfide
Thioester
Phosphoryl
Phosphoanhydride
Mixed anhydride (carboxylic acid and phosphoric acid; also called acyl phosphate)

Class of Compound	General Structure	Characteristic Functional Group	Name of Functional Group	Example
Alkenes	$RCH{=}CH_2$ $RCH{=}CHR$ $R_2C{=}CHR$ $R_2C{=}CR_2$	$C{=}C$	**Double bond**	$CH_2{=}CH_2$
Alcohols	ROH	$-OH$	**Hydroxyl group**	CH_3CH_2OH
Ethers	ROR	$-O-$	**Ether group**	CH_3OCH_3
Amines	RNH_2 R_2NH R_3N	$-N\lt$	**Amino group**	CH_3NH_2
Thiols	RSH	$-SH$	**Sulfhydryl group**	CH_3SH
Aldehydes	$R-C(=O)-H$	$-C(=O)-$	**Carbonyl group**	$CH_3C(=O)H$
Ketones	$R-C(=O)-R$	$-C(=O)-$	**Carbonyl group**	$CH_3C(=O)CH_3$
Carboxylic acids	$R-C(=O)-OH$	$-C(=O)-OH$	**Carboxyl group**	$CH_3C(=O)OH$
Esters	$R-C(=O)-OR$	$-C(=O)-OR$	**Ester group**	$CH_3C(=O)OCH_3$
Amides	$R-C(=O)-NR_2$ $R-C(=O)-NHR$ $R-C(=O)-NH_2$	$-C(=O)-N\lt$	**Amide group**	$CH_3C(=O)N(CH_3)_2$
Phosphoric acid esters	$R-O-P(=O)(OH)-OH$	$-O-P(=O)(OH)-OH$	**Phosphoric ester group**	$CH_3-O-P(=O)(OH)-OH$
Phosphoric acid anhydrides	$R-O-P(=O)(OH)-O-P(=O)(OH)-OH$	$-P(=O)(OH)-O-P(=O)(OH)-$	**Phosphoric anhydride group**	$HO-P(=O)(OH)-O-P(=O)(OH)-OH$



Acetyl-coenzyme A

- Dissolved in the aqueous phase (cytosol) of all cells is a collection of 100 to 200 different small organic molecules (Mr ~100 to ~500).

- The central **metabolites** in the major pathways occurring in nearly every cell—the metabolites and pathways that have been conserved throughout the course of evolution.

- This collection of molecules includes the common amino acids, nucleotides, sugars and their phosphorylated derivatives, and a number of mono-, di-, and tricarboxylic acids.

- There are other small biomolecules, specific to certain types of cells or organisms called as **secondary metabolites**, which play a role specific to organism.

- These metabolites include compounds such as morphine, quinine, nicotine, and caffeine.

- Macromolecules are the major constituents of cells.
- Many biological molecules are macromolecules, polymers of high molecular weight assembled from relatively simple precursors.
- Proteins, nucleic acids, and polysaccharides are produced by the polymerization of relatively small compounds with molecular weights of 500 or less.
- Shorter chains are called as oligomers.
- Synthesis of macromolecules is a major energy-consuming activity of cells.
- Macromolecules themselves may be further assembled into supramolecular complexes, forming functional units such as ribosomes.

- Proteins, polynucleotides, and polysaccharides have large numbers of monomeric subunits and thus high molecular weights—in the range of 5,000 to more than 1 million for proteins, up to several billion for nucleic acids, and in the millions for polysaccharides such as starch.

- Individual lipid molecules are much smaller (Mr 750 to 1,500) and are not classified as macromolecules. But they can associate noncovalently into very large structures.

- Given their characteristic information-rich subunit sequences, proteins and nucleic acids are often referred to as **informational macromolecules**.

- Some oligosaccharides, as noted above, also serve as informational molecules.

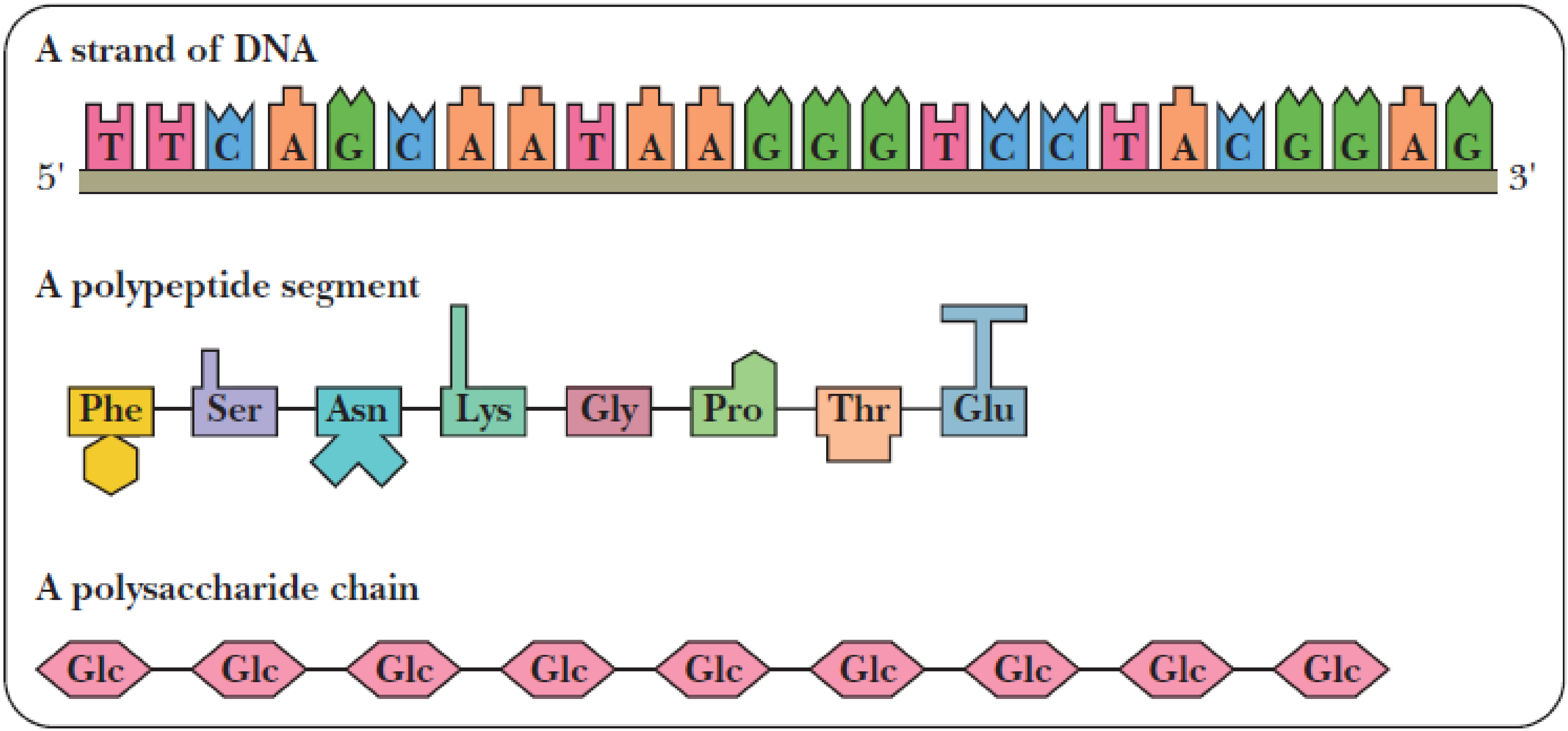

A strand of DNA
5'
T T C A G C A A T A A G G G T C C T A C G G A G
3'
A polypeptide segment
Phe Ser Asn Lys Gly Pro Thr Glu
A polysaccharide chain
Glc Glc Glc Glc Glc Glc Glc Glc Glc

TABLE 1–2 Molecular Components of an *E. coli* Cell

	Percentage of total weight of cell	*Approximate number of different molecular species*
Water	70	1
Proteins	15	3,000
Nucleic acids		
DNA	1	1
RNA	6	>3,000
Polysaccharides	3	5
Lipids	2	20
Monomeric subunits and intermediates	2	500
Inorganic ions	1	20

- The sum of all the proteins functioning in a given cell is the cell's **proteome**, and proteomics is the systematic characterization of this protein complement under a specific set of conditions.

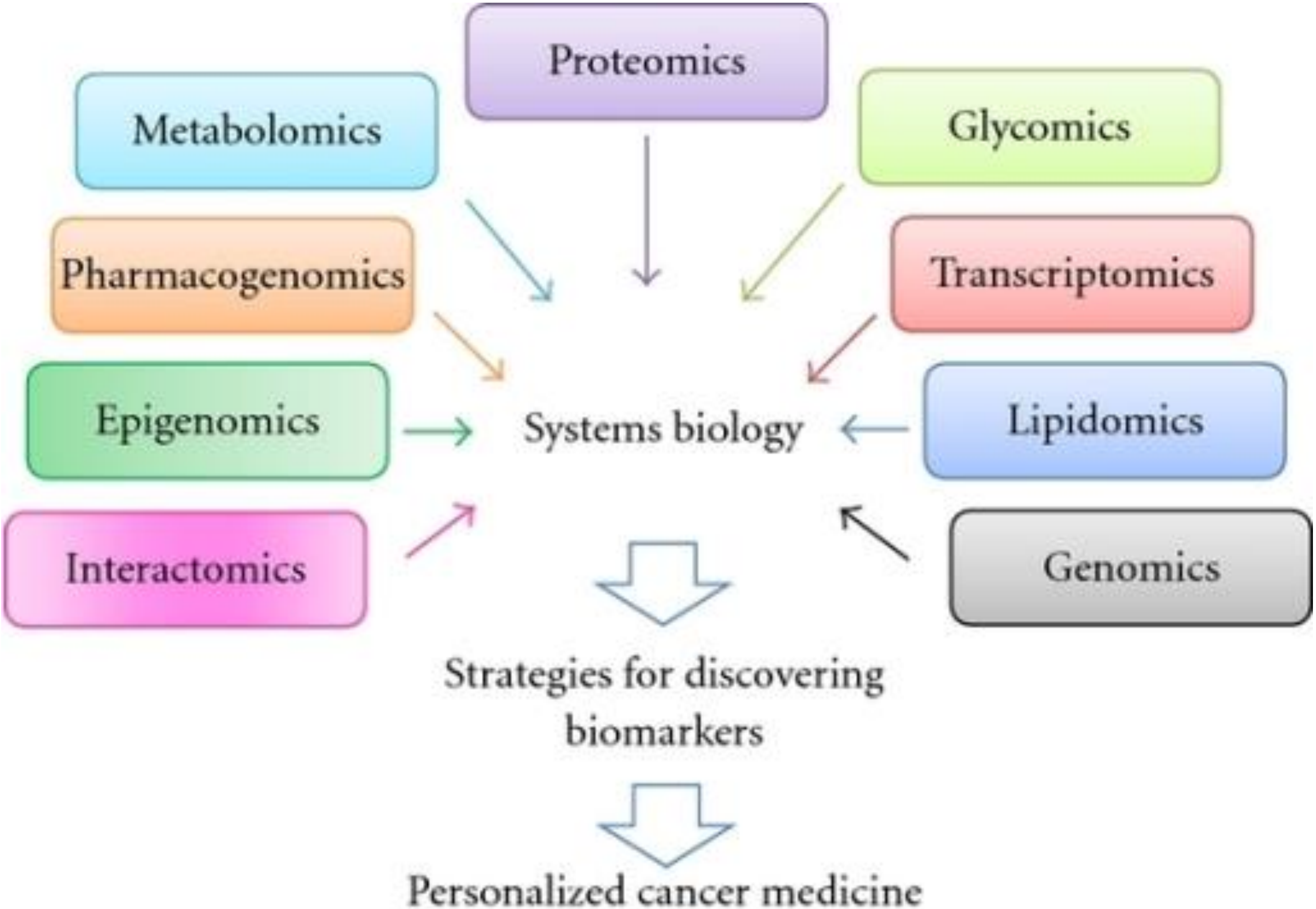
- The **genome** is the entire sequence of a cell's, and genomics is the characterization of the comparative structure, function, evolution, and mapping of genomes.

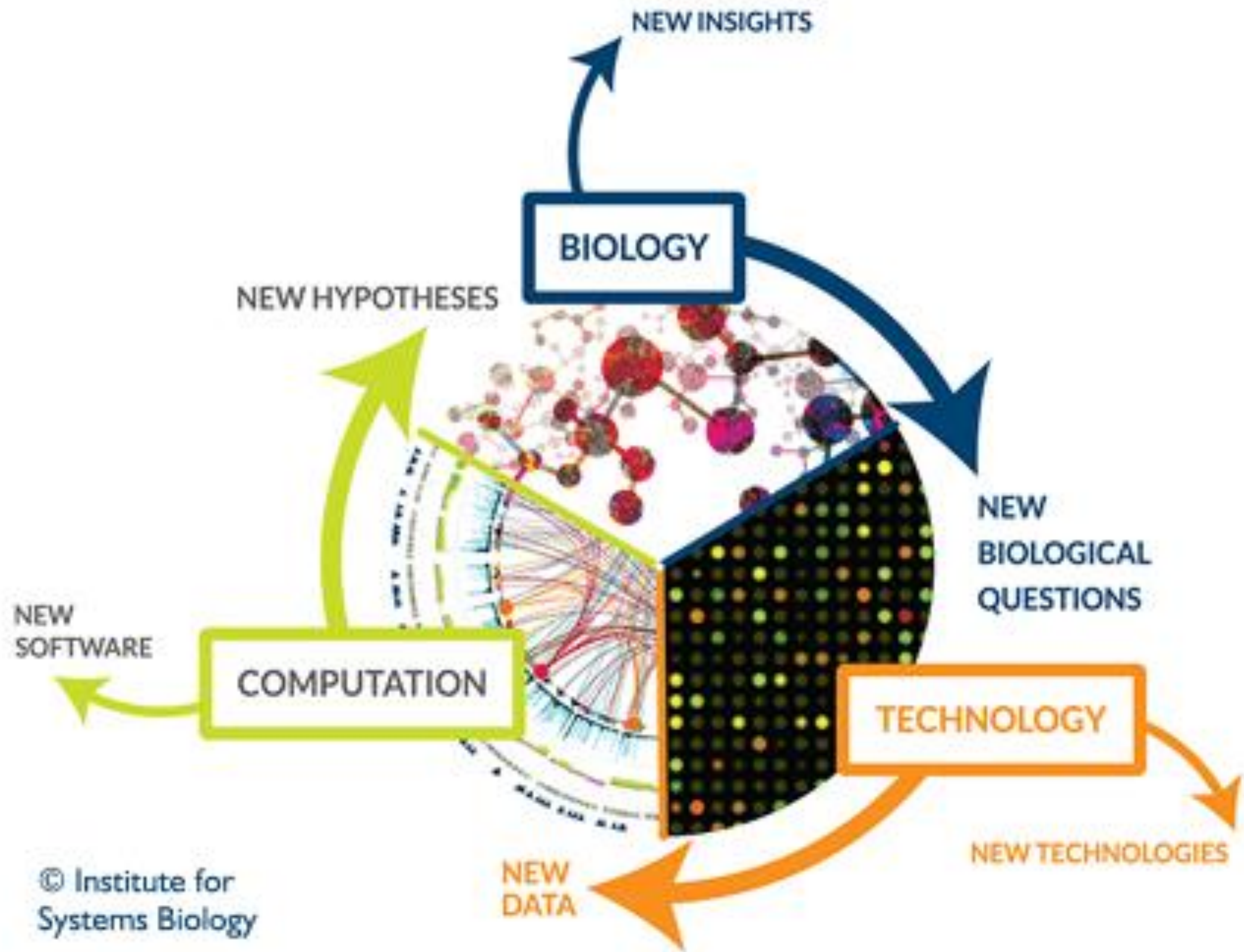
- A cell's **glycome** is all its carbohydrate-containing molecules.

- The lipid-containing molecules in a cell constitute its **lipidome**.

- With the application of sensitive methods it is possible to distinguish and quantify hundreds or thousands of these components.

- **Systems biology** is an approach that tries to integrate the information from genomics, proteomics, glycomics, and lipidomics to give a molecular picture of all the activities of a cell under a given set of conditions.

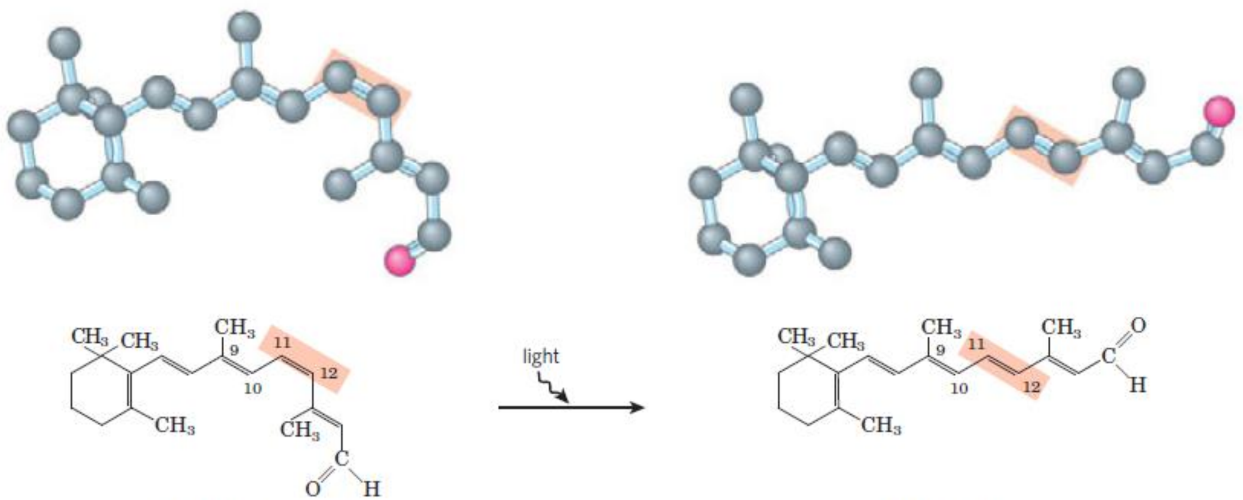

Proteomics
Metabolomics
Glycomics
Pharmacogenomics
Transcriptomics
Epigenomics
Systems biology
Lipidomics
Interactomics
Genomics
Strategies for discovering biomarkers
Personalized cancer medicine


NEW INSIGHTS
BIOLOGY
NEW HYPOTHESES
NEW
BIOLOGICAL
QUESTIONS
NEW
SOFTWARE
COMPUTATION
TECHNOLOGY
NEW TECHNOLOGIES
NEW
DATA
© Institute for
Systems Biology

- Three-dimensional structure is described by configuration and conformation

- A carbon-containing compound commonly exists as **stereoisomers**, molecules with the same chemical bonds but different stereochemistry—that is, different **configuration**, the fixed spatial arrangement of atoms.

- Interactions between biomolecules are invariably stereospecific, requiring specific stereochemistry in the interacting molecules



11-*cis*-Retinal

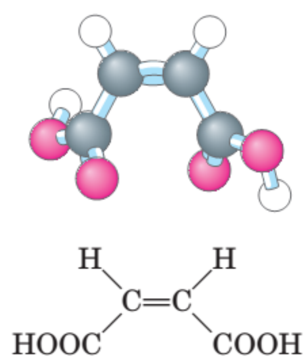
All-*trans*-Retinal

(b)

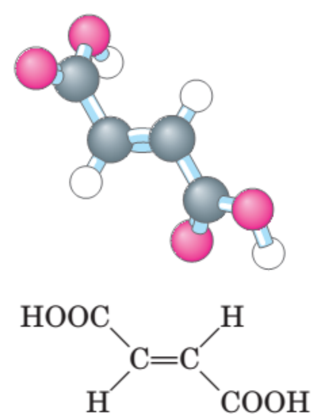
- Configuration is conferred by the presence of either (1) double bonds, around which there is little or no freedom of rotation, or (2) chiral centers, around which substituent groups are arranged in a specific orientation.

- The identifying characteristic of stereoisomers is that they cannot be interconverted without temporarily breaking one or more covalent bonds.

- The isomers of the first group are **geometric isomers**, or **cis-trans isomers**; they differ in the arrangement of their substituent groups with respect to the nonrotating double bond.



Maleic acid (cis)



Fumaric acid (trans)

- In the second type of configurational isomer, four different substituents bonded to a tetrahedral carbon atom may be arranged two different ways in yielding two stereoisomers with similar or identical chemical properties but differing in certain physical and biological properties.

- A carbon atom with four different substituents is said to be asymmetric, and asymmetric carbons are called **chiral centers**.

- A molecule with only one chiral carbon can have two stereoisomers; when two or more (n) chiral carbons are present, there can be 2^n stereoisomers.

- Some stereoisomers are mirror images of each other; they are called **enantiomers**. Pairs of stereoisomers that are not mirror images of each other are called **diastereomers.**

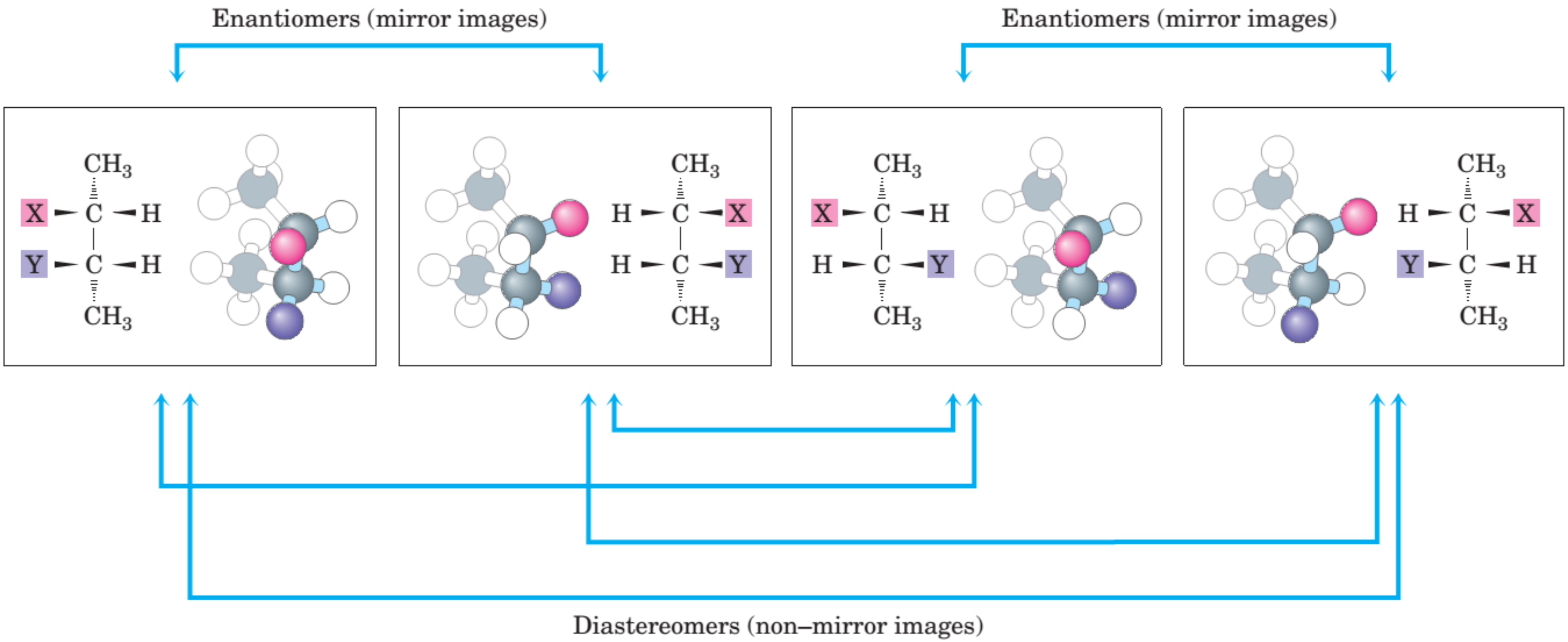


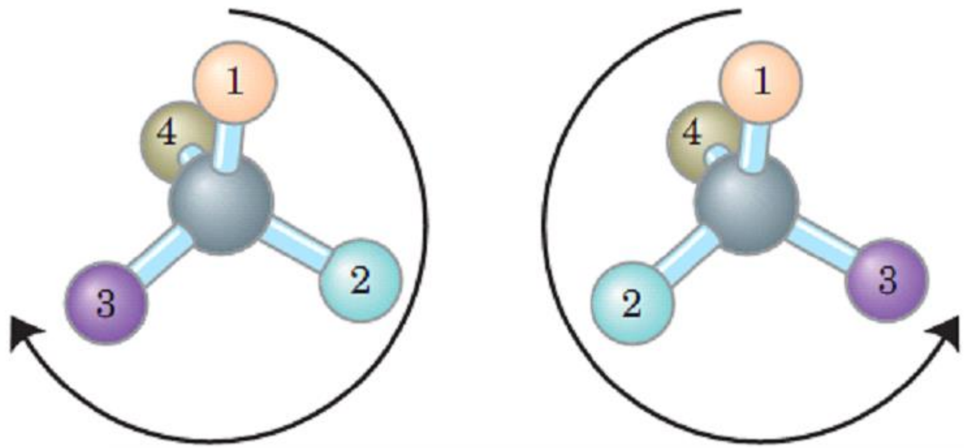
FIGURE 1–20 Two types of stereoisomers. There are four different 2,3-disubstituted butanes ($n = 2$ asymmetric carbons, hence $2^n = 4$ stereoisomers). Each is shown in a box as a perspective formula and a ball-and-stick model, which has been rotated to allow the reader to view all the groups. Some pairs of stereoisomers are mirror images of each other, or enantiomers. Other pairs are not mirror images; these are diastereomers.

❖ For compounds with more than one chiral center, the most useful system of nomenclature is the RS system. In this system, each group attached to a chiral carbon is assigned a priority.

❖ The priorities of some common substituents are;

$$—OCH_3 > —OH > —NH_2 > —COOH > —CHO > —CH_2OH > —CH_3 > —H$$

❖ For naming in the RS system, the chiral atom is viewed with the group of lowest priority pointing away from the viewer. If the priority of the other three groups (1 to 3) decreases in clockwise order, the configuration is (R).



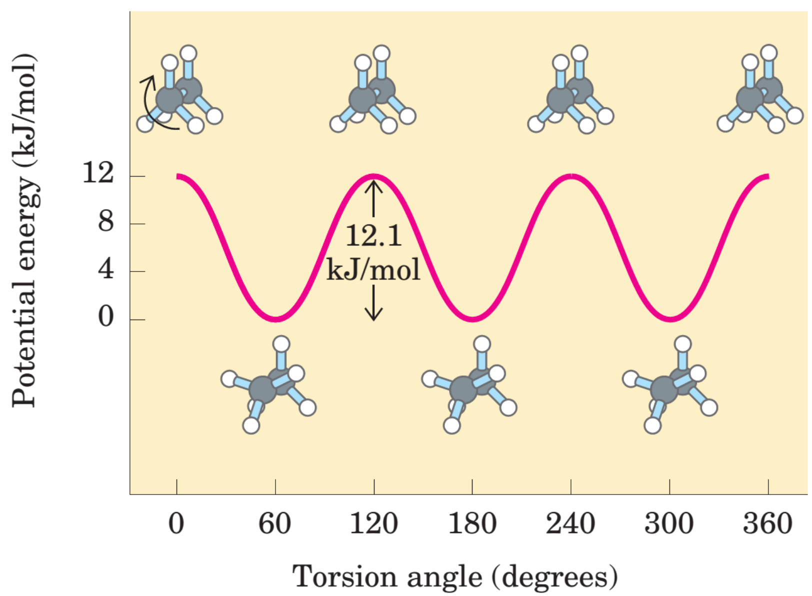
Saat Yönü
(*R*)

Saat Yönünün Tersi
(*S*)

- Distinct from configuration is molecular conformation, the spatial arrangement of substituent groups that, without breaking any bonds, are free to assume different positions in space because of the freedom of rotation about single bonds.

- In the simple hydrocarbon ethane, for example, there is nearly complete freedom of rotation around the COC bond.

- Many different, interconvertible conformations of ethane are possible, depending on the degree of rotation.

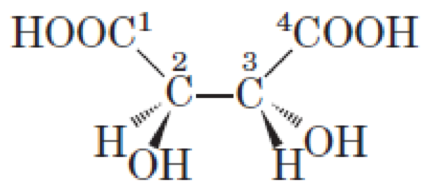


❖ Enantiomers have nearly identical chemical reactivities but differ in a characteristic physical property: their interaction with plane-polarized light.

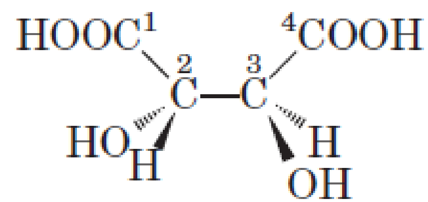
❖ In separate solutions, two enantiomers rotate the plane of plane-polarized light in opposite directions, but an equimolar solution of the two enantiomers (a **racemic mixture**) shows no optical rotation.

❖ Compounds without chiral centers do not rotate the plane of plane-polarized light.

Louis Pasteur,
1822-1895



(2*R*,3*R*)-Tartaric acid
(dextrorotatory)



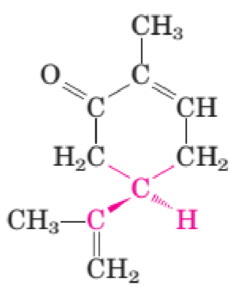
(2*S*,3*S*)-Tartaric acid
(levorotatory)

- Biological interactions between molecules are stereospecific: the "fit" in such interactions must be stereochemically correct.

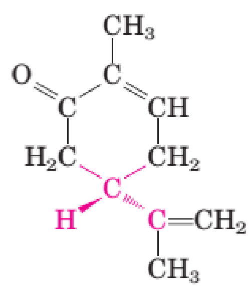
- In living organisms, chiral molecules are usually present in only one of their chiral forms.

- For example, the amino acids in proteins occur only as their L isomers; glucose occurs only as its D isomer.

- Living cells produce only one chiral form of biomolecules because the enzymes that synthesize them are also chiral.

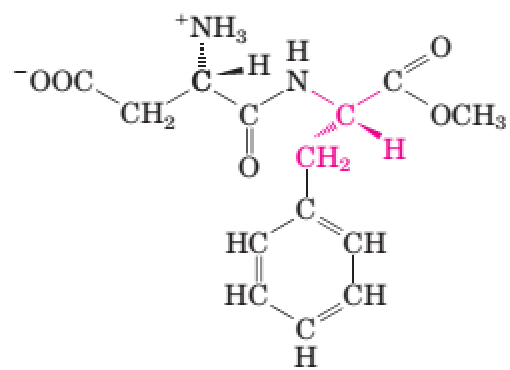


(*R*)-Carvone
(spearmint)

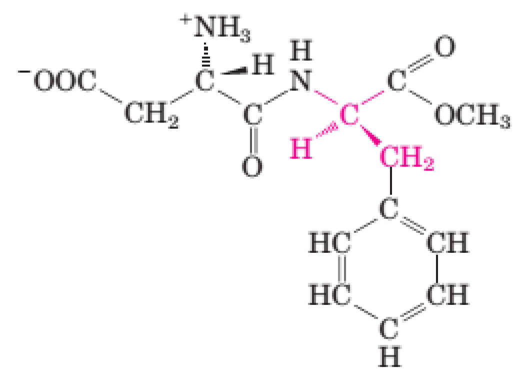


(*S*)-Carvone
(caraway)

(a)



L-Aspartyl-L-phenylalanine methyl ester
(aspartame) (sweet)



L-Aspartyl-D-phenylalanine methyl ester
(bitter)

(b)

Physical Foundations

- Living cells and organisms must perform work to stay alive and to reproduce themselves.

- The synthetic reactions that occur within cells, like the synthetic processes in any factory, require the input of energy.

- Although the characteristic composition of an organism changes little through time, the population of molecules within the organism is far from static.

- Small molecules, macromolecules, and supramolecular complexes are continuously synthesized and then broken down.

- The constancy of concentration is the result of a dynamic steady state, a steady state that is far from equilibrium.

- Maintaining this steady state requires the constant investment of energy; when the cell can no longer generate energy, it dies and begins to decay toward equilibrium with its surroundings.

Physical Foundations

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- The hemoglobin molecules carrying oxygen from your lungs to your brain at this moment were synthesized within the past month; by next month they will have been degraded and entirely replaced by new hemoglobin molecules.

- The glucose you ingested with your most recent meal is now circulating in your bloodstream; before the day is over these particular glucose molecules will have been converted into something else.

- The amounts of hemoglobin and glucose in the blood remain nearly constant because the rate of synthesis or intake of each just balances the rate of its breakdown, consumption, or conversion into some other product.

- The constancy of concentration is the result of a **dynamic steady state**, a steady state that is far from equilibrium.

- Maintaining this steady state requires the constant investment of energy; when the cell can no longer generate energy, it dies and begins to decay toward equilibrium with its surroundings.

- For chemical reactions occurring in solution, we can define a **system** as all the constituent reactants and products, the solvent that contains them, and the immediate atmosphere—in short, everything within a defined region of space.

- The system and its surroundings together constitute the **universe**.

- If the system exchanges neither matter nor energy with its surroundings, it is said to be **isolated**.

- If the system exchanges energy but not matter with its surroundings, it is a **closed** system; if it exchanges both energy and matter with its surroundings, it is an **open** system.

- A living organism is an open system; it exchanges both matter and energy with its surroundings.

- Living organisms derive energy from their surroundings in two ways: (1) they take up chemical fuels from the environment and extract energy by oxidizing them; or (2) they absorb energy from sunlight.

- **The first law of thermodynamics** describes the principle of the conservation of energy: *in any physical or chemical change, the total amount of energy in the universe remains constant, although the form of the energy may change*.

- This means that energy used by a system is converted from one form into another

- Cells are consummate transducers of energy, capable of interconverting chemical, electromagnetic, mechanical, and osmotic energy with great efficiency.

- DNA, RNA, and proteins are informational macromolecules; the precise sequence of their monomeric subunits contains information, just as the letters in a sentence do.

- The cell must invest energy to order the subunits in their correct sequence.

- It is extremely improbable that amino acids in a mixture would spontaneously condense into a single type of protein, with a unique sequence.

- This would represent increased order in a population of molecules; but according to the **second law of thermodynamics**, the tendency in nature is toward ever-greater disorder in the universe*: the total entropy of the universe is continually increasing*.

- To bring about the synthesis of macromolecules from their monomeric units, free energy must be supplied to the system

- The randomness or disorder of the components of a chemical system is expressed as **entropy**, S .

- Any change in randomness of the system is expressed as entropy change, ΔS, which by convention has a positive value when randomness increases.

- **Free-energy content**, G, of any closed system can be defined in terms of three quantities: **enthalpy**, H, reflecting the number and kinds of bonds; entropy, S; and the absolute temperature, T (in degrees Kelvin).

- The definition of free energy is $G = H - TS$.

- When a chemical reaction occurs at constant temperature, the free-energy change, G, is determined by the enthalpy change, ΔH, reflecting the kinds and numbers of chemical bonds and noncovalent interactions broken and formed, and the entropy change, ΔS, describing the change in the system's randomness:

$$\Delta G = \Delta H - T\,\Delta S$$

- A process tends to occur spontaneously only if ΔG is negative.

- Yet cell function depends largely on molecules, such as proteins and nucleic acids, for which the free energy of formation is positive: the molecules are less stable and more highly ordered than a mixture of their monomeric components.

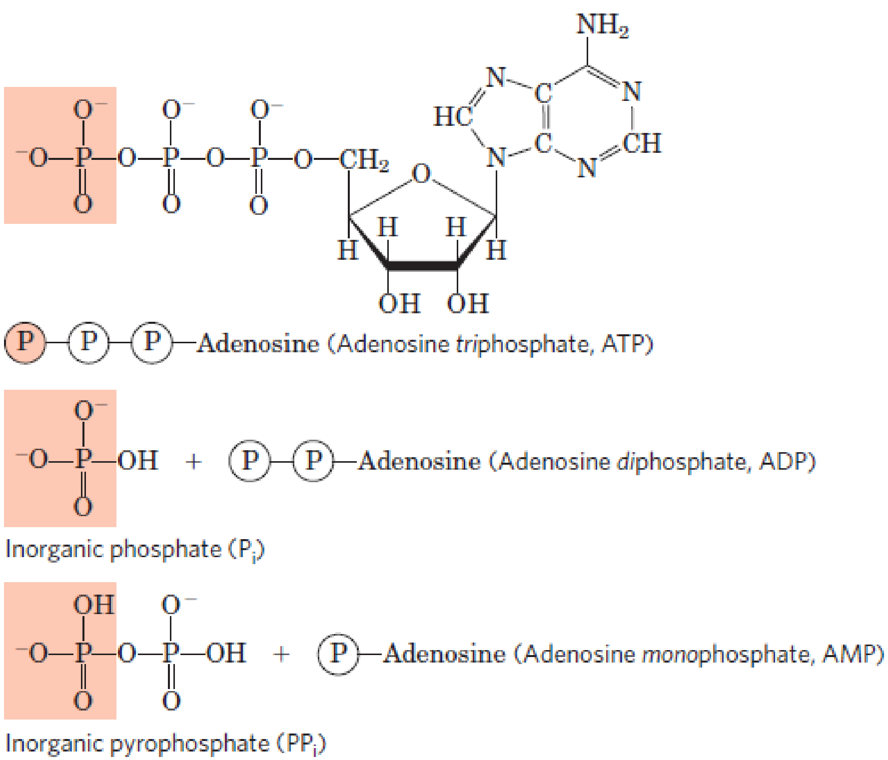
- To carry out these thermodynamically unfavorable, energy-requiring (**endergonic**) reactions, cells couple them to other reactions that liberate free energy (**exergonic reactions**), so that the overall process is exergonic: the sum of the free-energy changes is negative.

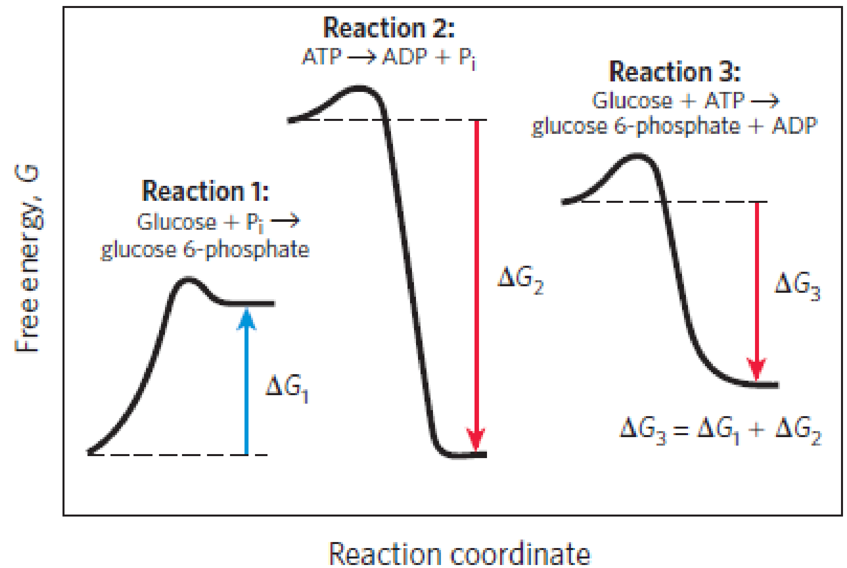
- In closed systems, chemical reactions proceed spontaneously until equilibrium is reached. When a system is at equilibrium, the rate of product formation exactly equals the rate at which product is converted to reactant. Thus there is no net change in the concentration of reactants and products; a steady state is achieved.

- The energy change as the system moves from its initial state to equilibrium, with no changes in temperature or pressure, is given by the free-energy change, ΔG.

- The magnitude of ΔG depends on the particular chemical reaction and on how far from equilibrium the system is initially.

❖ The usual source of free energy in coupled biological reactions is the energy released by breakage of phosphoanhydride bonds such as those in adenosine triphosphate





- The tendency of a chemical reaction to go to completion can be expressed as an equilibrium constant.

$$aA + bB \longrightarrow cC + dD \qquad K_{eq} = \frac{[C_{eq}]^c[D_{eq}]^d}{[A_{eq}]^a[B_{eq}]^b}$$

- A large value of Keq means the reaction tends to proceed until the reactants have been almost completely converted into the products.

- ΔG for any chemical reaction is a function of the standard free-energy change, ΔG° a constant that is characteristic of each specific reaction—and a term that expresses the initial concentrations of reactants and products:

$$\Delta G = \Delta G^\circ + RT \ln \frac{[C_i]^c[D_i]^d}{[A_i]^a[B_i]^b} \qquad \Delta G^\circ = -RT \ln K_{eq}$$

- We see that ΔG° is simply a second way (besides Keq) of expressing the driving force on a reaction.

- All biological macromolecules are much less thermodynamically stable than their monomeric subunits, yet they are kinetically stable.

- Virtually every chemical reaction in a cell occurs at a significant rate only because of the presence of biocatalysts, enzymes

- The breaking of existing bonds and formation of new ones generally requires, first, a distortion of the existing bonds to create a **transition state** of higher free energy than either reactant or product.

- The highest point in the reaction coordinate diagram represents the transition state, and the difference in energy between the reactant in its ground state and in its transition state is the **activation energy**, $\Delta G^{\ddagger}$.

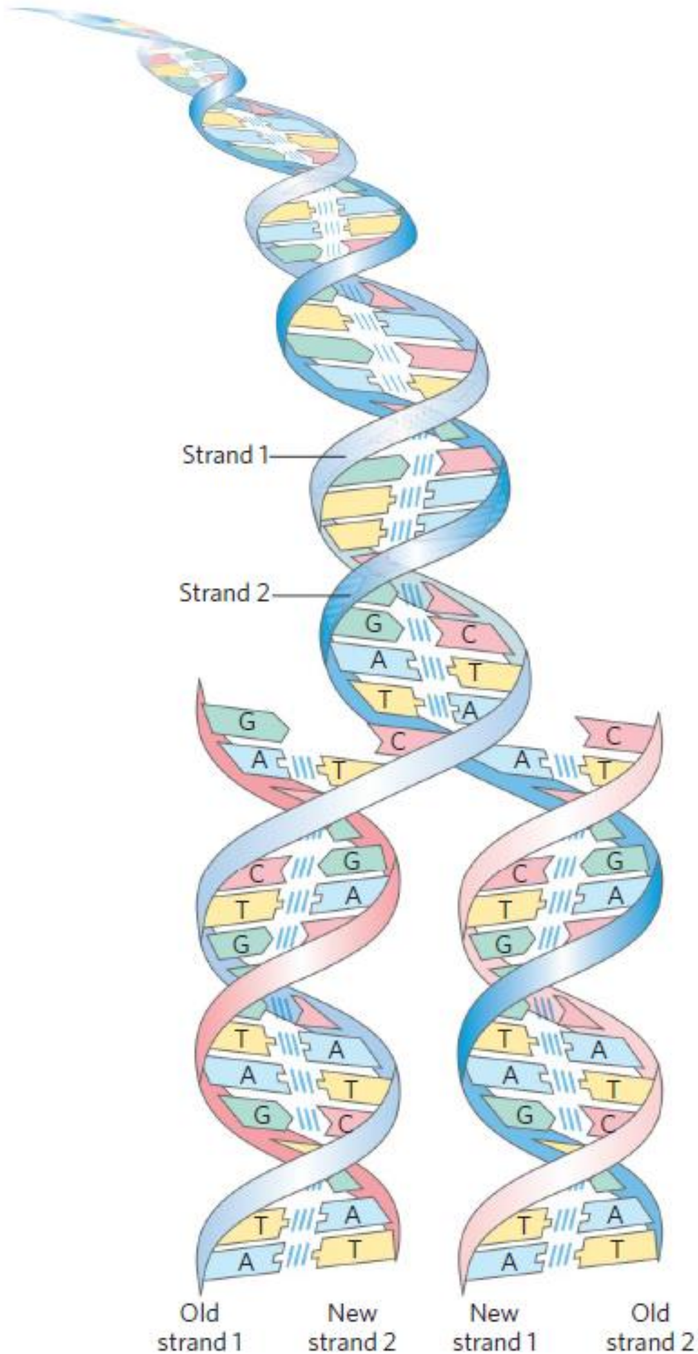
Genetic Foundations

- Perhaps the most remarkable property of living cells and organisms is their ability to reproduce themselves for countless generations with nearly perfect fidelity.

- This continuity of inherited traits implies constancy, over millions of years, in the structure of the molecules that contain the genetic information.

- The sequence of the monomeric subunits, deoxyribonucleotides, in **deoxyribonucleic acid, DNA** polymer encodes the instructions for forming all other cellular components and provides a template for the production of identical DNA molecules to be distributed to progeny when a cell divides.

- A human sperm or egg, carrying the accumulated hereditary information of billions of years of evolution, transmits this inheritance in the form of DNA molecules.


Strand 1
Strand 2
G
C
A
T
T
A
C
G
A
T
A
T
C
C
G
T
A
G
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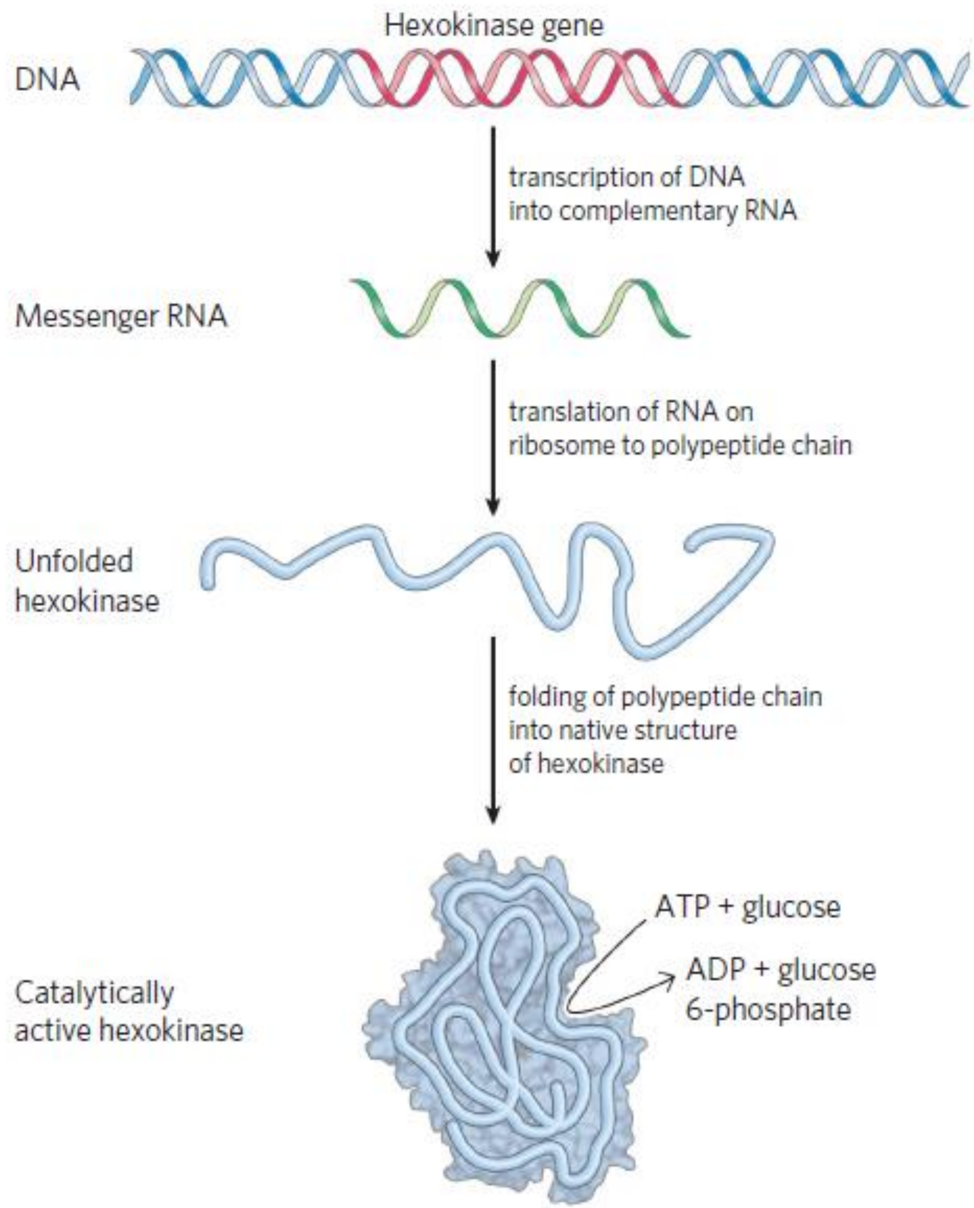
A
T
Old strand 1
New strand 2
New strand 1
Old strand 2


Hexokinase gene
DNA
transcription of DNA into complementary RNA
Messenger RNA
translation of RNA on ribosome to polypeptide chain
Unfolded hexokinase
folding of polypeptide chain into native structure of hexokinase
Catalytically active hexokinase
ATP + glucose
ADP + glucose 6-phosphate

- A linear sequence of deoxyribonucleotides in DNA codes (through an intermediary, RNA) for the production of a protein with a corresponding linear sequence of amino acids.

- The protein folds into a particular three-dimensional shape, determined by its amino acid sequence and stabilized primarily by noncovalent interactions.

- The precise three-dimensional structure, or **native conformation**, of the protein is crucial to its function.

- Once in its native conformation, a protein may associate noncovalently with other macromolecules (other proteins, nucleic acids, or lipids) to form supramolecular complexes such as chromosomes, ribosomes, and membranes.

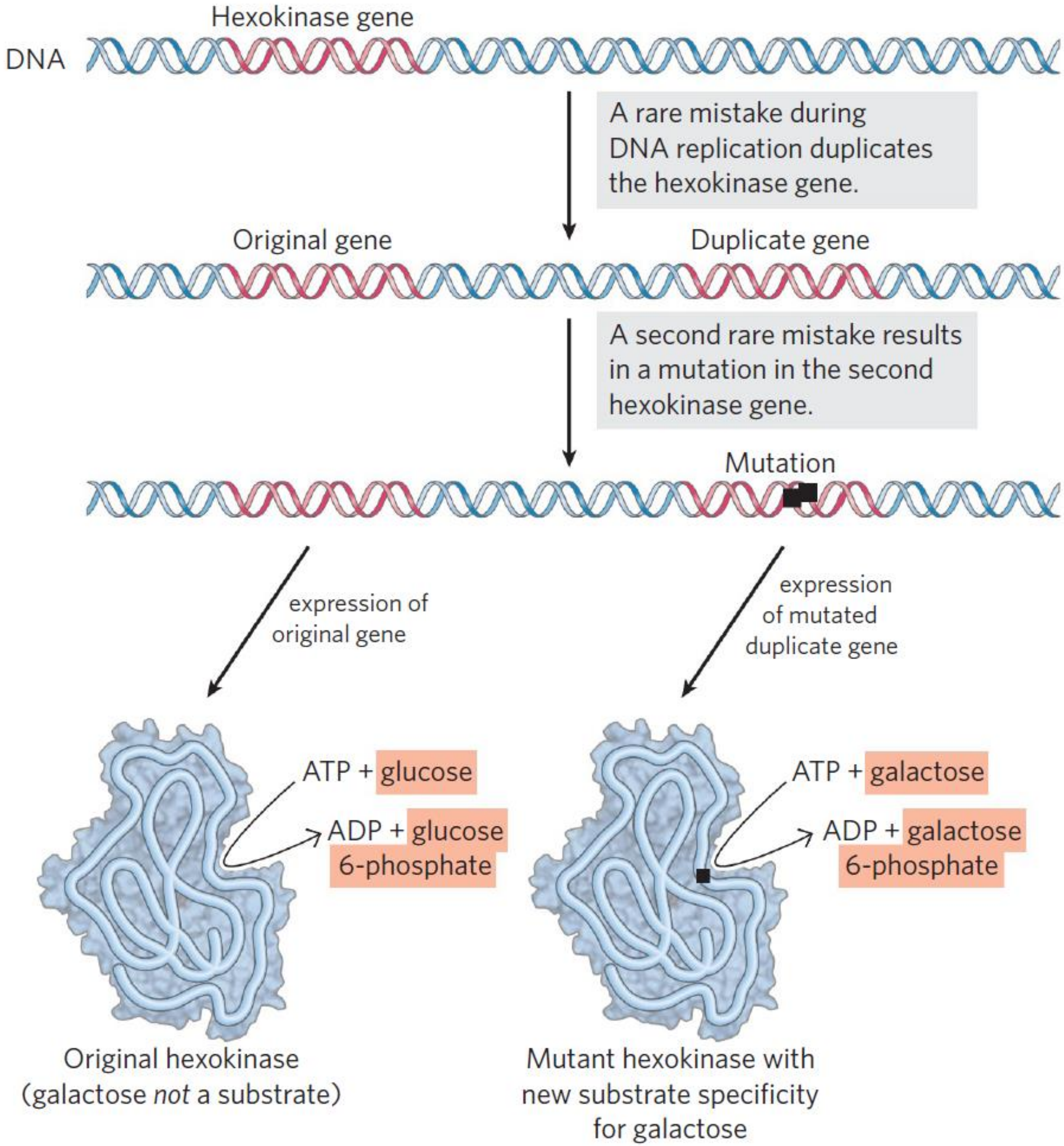
Evolutionary Foundations

- The remarkable similarity of metabolic pathways and gene sequences across the three domains of life argues strongly that all modern organisms are derived from a common evolutionary progenitor by a series of small changes (mutations), each of which conferred a selective advantage to some organism in some ecological niche.

- Infrequent unrepaired mistakes in the DNA replication process lead to changes in the nucleotide sequence of DNA, producing a genetic mutation.

- Mutations in the DNA handed down to offspring may be harmful or even lethal to the new organism or cell.

- Occasionally, however, a mutation better equips an organism or cell to survive in its environment



Hexokinase gene
DNA
A rare mistake during DNA replication duplicates the hexokinase gene.
Original gene
Duplicate gene
A second rare mistake results in a mutation in the second hexokinase gene.
Mutation
expression of original gene
expression of mutated duplicate gene
ATP + glucose
ADP + glucose 6-phosphate
ATP + galactose
ADP + galactose 6-phosphate
Original hexokinase (galactose *not* a substrate)
Mutant hexokinase with new substrate specificity for galactose

- The mutant enzyme might have acquired a slightly different specificity, for example, so that it is now able to use some compound that the cell was previously unable to metabolize.

- If a population of cells were to find itself in an environment where that compound was the only or the most abundant available source of fuel, the mutant cell would have a selective advantage over the other, unmutated (**wild-type**) cells in the population.

- The mutant cell and its progeny would survive and prosper in the new environment, whereas wild-type cells would starve and be eliminated.

- This is what Darwin meant by natural selection—what is sometimes summarized as "survival of the fittest."

- The DNA molecules of modern organisms are historical documents, records of the long journey from the earliest cells to modern organisms.

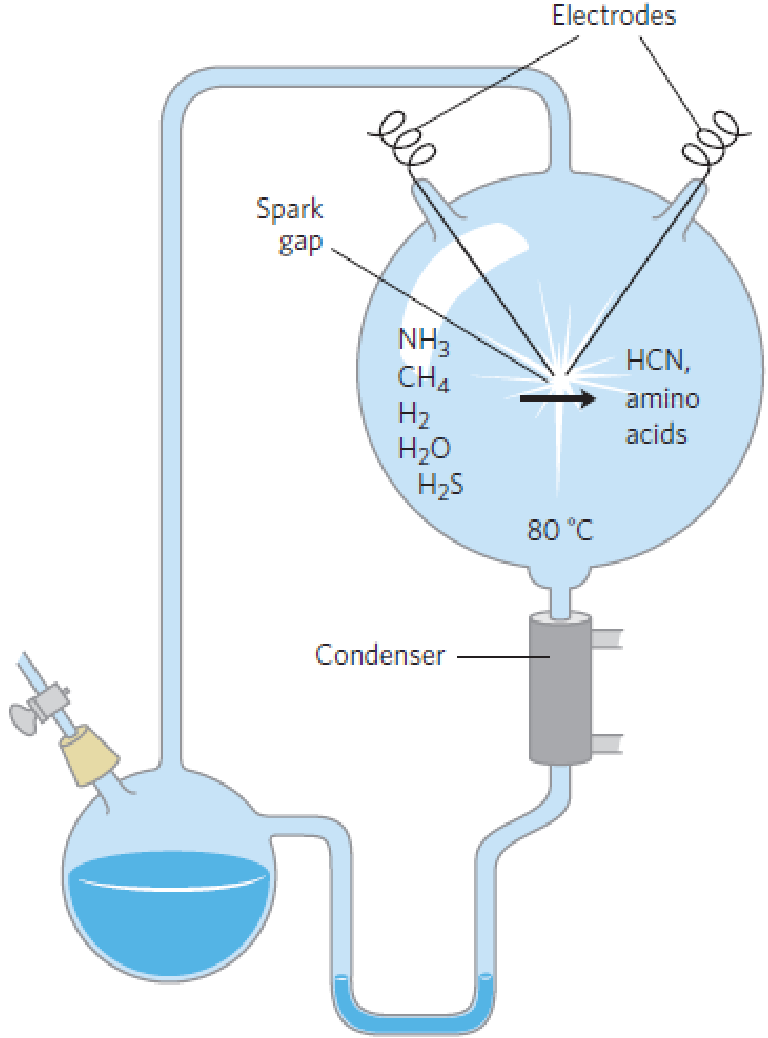
- The historical accounts in DNA are not complete, however; in the course of evolution, many mutations must have been erased or written over.

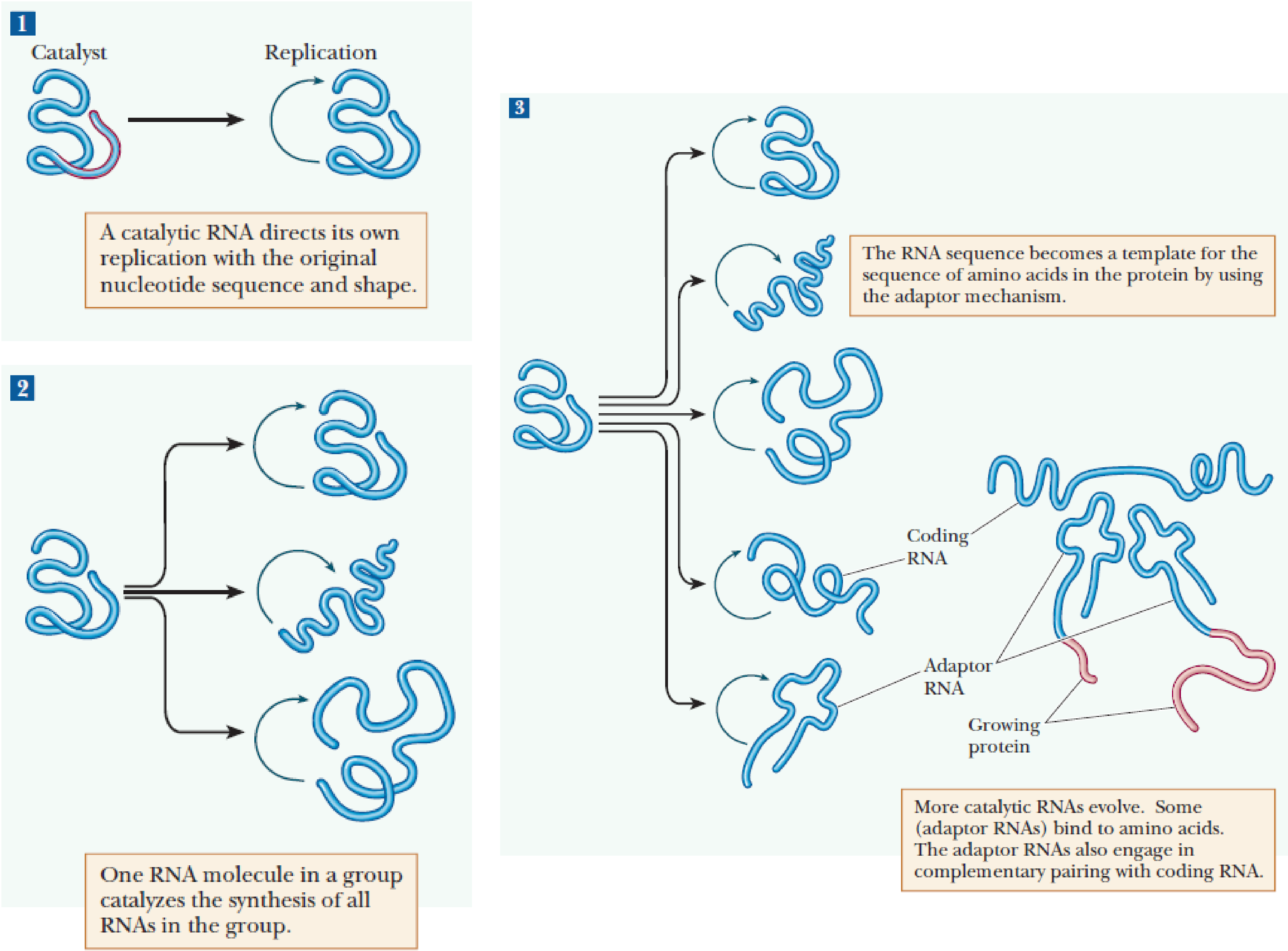
- But DNA molecules are the best source of biological history that we have.

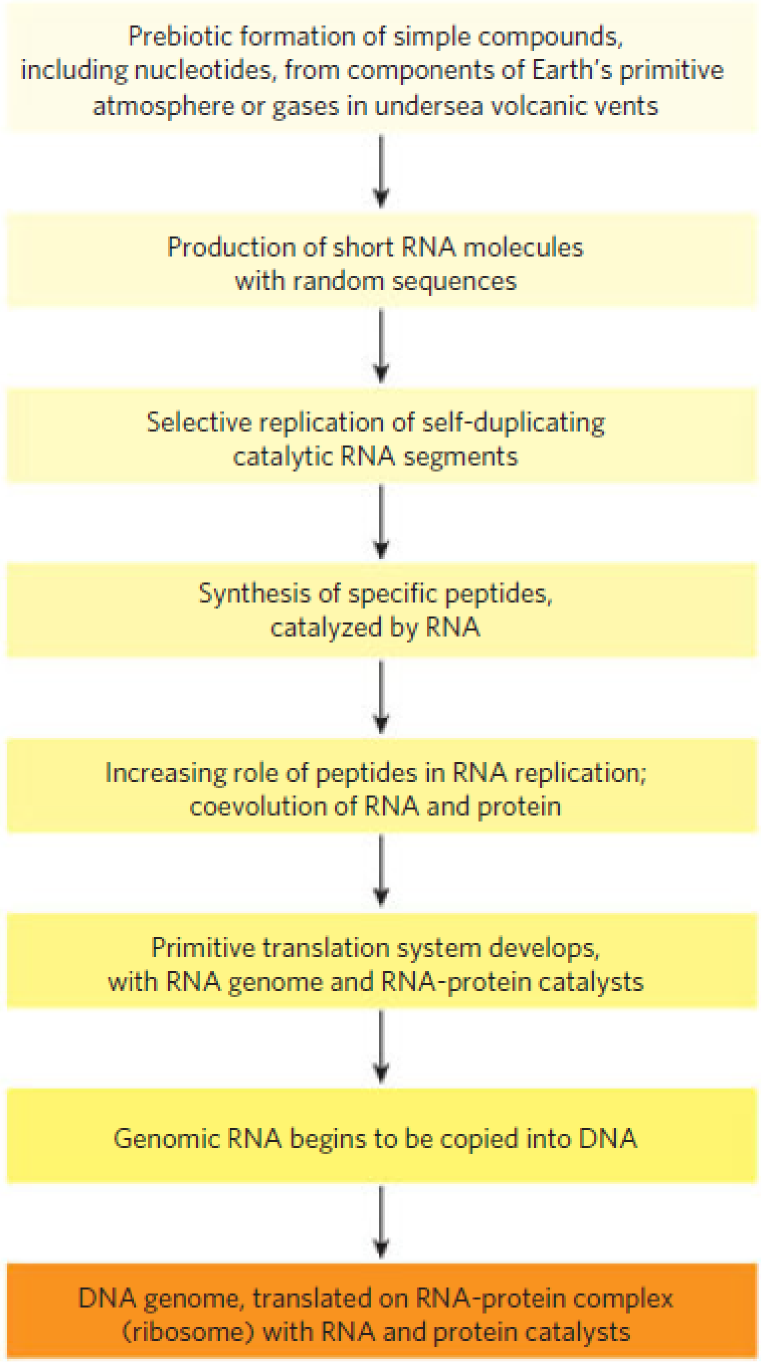
- Chance genetic mutations occurring in individuals in a population, combined with natural selection, have resulted in the evolution of the enormous variety of species we see today, each adapted to its particular ecological niche.

- How did the first living organisms acquire their characteristic organic building blocks?

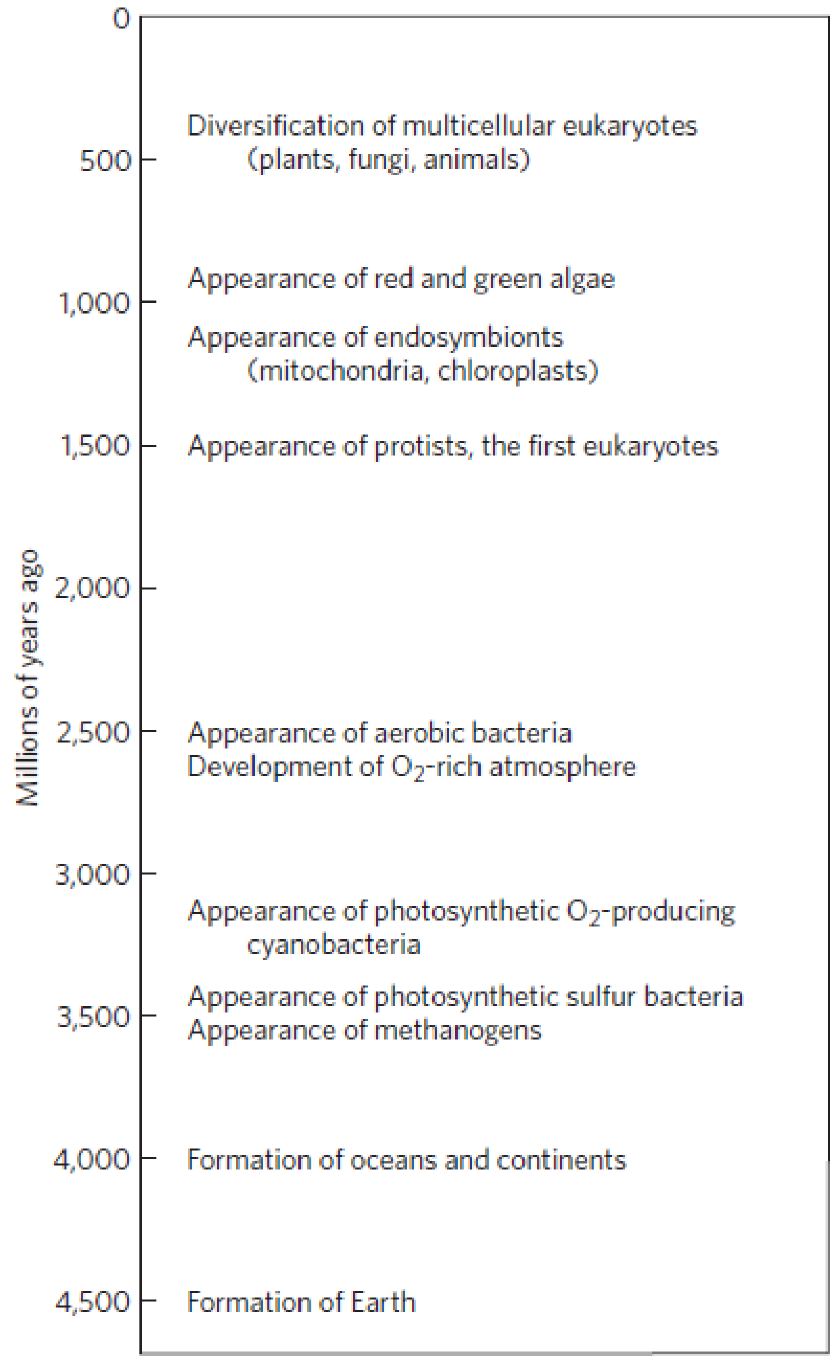
- According to one hypothesis, these compounds were created by the effects of powerful environmental forces—ultraviolet irradiation, lightning, or volcanic eruptions—on the gases in the prebiotic Earth's atmosphere, and on inorganic solutes in superheated thermal vents deep in the ocean.




1
Catalyst
Replication
A catalytic RNA directs its own replication with the original nucleotide sequence and shape.
2
One RNA molecule in a group catalyzes the synthesis of all RNAs in the group.
3
The RNA sequence becomes a template for the sequence of amino acids in the protein by using the adaptor mechanism.
Coding RNA
Adaptor RNA
Growing protein
More catalytic RNAs evolve. Some (adaptor RNAs) bind to amino acids. The adaptor RNAs also engage in complementary pairing with coding RNA.



Prebiotic formation of simple compounds, including nucleotides, from components of Earth's primitive atmosphere or gases in undersea volcanic vents
Production of short RNA molecules with random sequences
Selective replication of self-duplicating catalytic RNA segments
Synthesis of specific peptides, catalyzed by RNA
Increasing role of peptides in RNA replication; coevolution of RNA and protein
Primitive translation system develops, with RNA genome and RNA-protein catalysts
Genomic RNA begins to be copied into DNA
DNA genome, translated on RNA-protein complex (ribosome) with RNA and protein catalysts



Millions of years ago
0
500
1,000
1,500
2,000
2,500
3,000
3,500
4,000
4,500
Diversification of multicellular eukaryotes (plants, fungi, animals)
Appearance of red and green algae
Appearance of endosymbionts (mitochondria, chloroplasts)
Appearance of protists, the first eukaryotes
Appearance of aerobic bacteria
Development of O_2-rich atmosphere
Appearance of photosynthetic O_2-producing cyanobacteria
Appearance of photosynthetic sulfur bacteria
Appearance of methanogens
Formation of oceans and continents
Formation of Earth

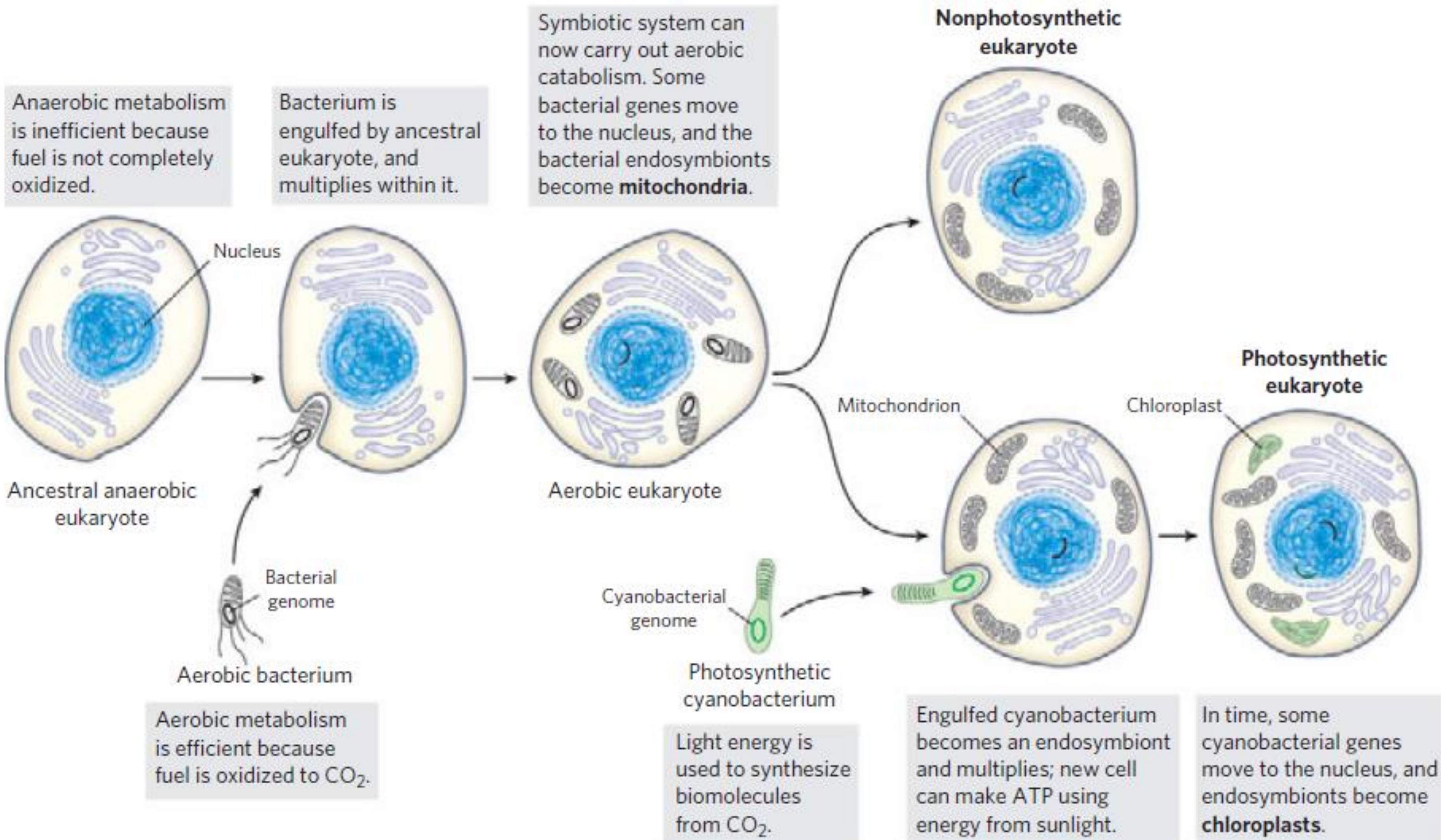
- Eukaryotic cells evolved from simpler precursors in several stages

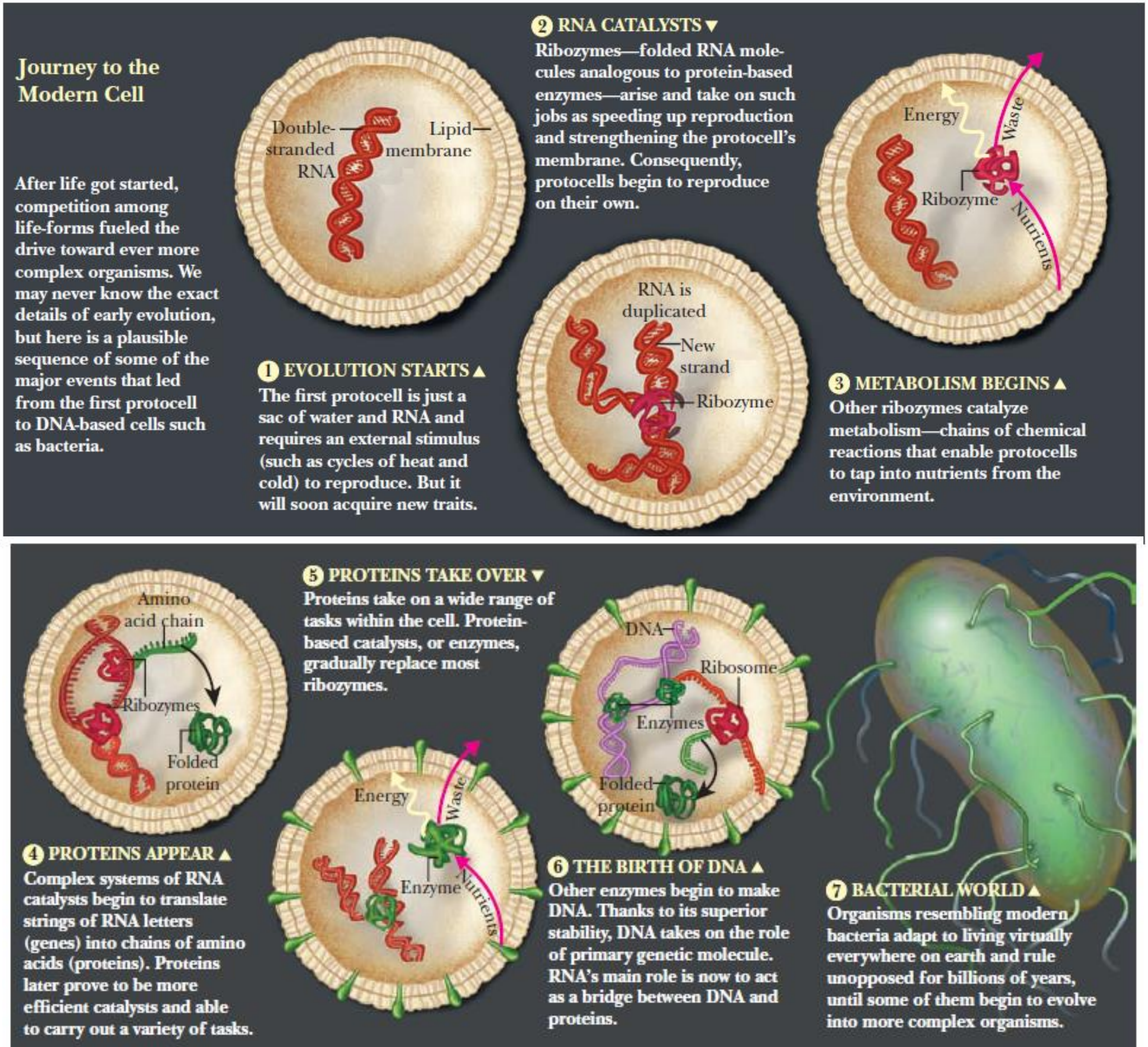
- Details of the evolutionary path from non-nucleated to nucleate cells can be deduced from the morphological and biochemical comparisons of modern organisms

- First, as cells acquired more DNA, the mechanisms required to fold it compactly into discrete complexes with specific proteins and to divide it equally between daughter cells at cell division became more elaborate.

- Second, as cells became larger, a system of intracellular membranes developed, including a double membrane surrounding the DNA.

- Finally, early eukaryotic cells, which were incapable of photosynthesis or aerobic metabolism, enveloped aerobic bacteria or photosynthetic bacteria to form **endosymbiotic** associations that eventually became permanent.


Anaerobic metabolism is inefficient because fuel is not completely oxidized.
Bacterium is engulfed by ancestral eukaryote, and multiplies within it.
Symbiotic system can now carry out aerobic catabolism. Some bacterial genes move to the nucleus, and the bacterial endosymbionts become **mitochondria**.
Nonphotosynthetic eukaryote
Nucleus
Ancestral anaerobic eukaryote
Aerobic eukaryote
Photosynthetic eukaryote
Mitochondrion
Chloroplast
Bacterial genome
Aerobic bacterium
Cyanobacterial genome
Photosynthetic cyanobacterium
Aerobic metabolism is efficient because fuel is oxidized to CO_2.
Light energy is used to synthesize biomolecules from CO_2.
Engulfed cyanobacterium becomes an endosymbiont and multiplies; new cell can make ATP using energy from sunlight.
In time, some cyanobacterial genes move to the nucleus, and endosymbionts become **chloroplasts**.


Journey to the Modern Cell
After life got started, competition among life-forms fueled the drive toward ever more complex organisms. We may never know the exact details of early evolution, but here is a plausible sequence of some of the major events that led from the first protocell to DNA-based cells such as bacteria.
Double-stranded RNA
Lipid membrane
1 EVOLUTION STARTS ▲
The first protocell is just a sac of water and RNA and requires an external stimulus (such as cycles of heat and cold) to reproduce. But it will soon acquire new traits.
2 RNA CATALYSTS ▼
Ribozymes—folded RNA molecules analogous to protein-based enzymes—arise and take on such jobs as speeding up reproduction and strengthening the protocell's membrane. Consequently, protocells begin to reproduce on their own.
RNA is duplicated
New strand
Ribozyme
Energy
Waste
Ribozyme
Nutrients
3 METABOLISM BEGINS ▲
Other ribozymes catalyze metabolism—chains of chemical reactions that enable protocells to tap into nutrients from the environment.
Amino acid chain
Ribozymes
Folded protein
4 PROTEINS APPEAR ▲
Complex systems of RNA catalysts begin to translate strings of RNA letters (genes) into chains of amino acids (proteins). Proteins later prove to be more efficient catalysts and able to carry out a variety of tasks.
5 PROTEINS TAKE OVER ▼
Proteins take on a wide range of tasks within the cell. Protein-based catalysts, or enzymes, gradually replace most ribozymes.
Energy
Waste
Enzyme
Nutrients
DNA
Ribosome
Enzymes
Folded protein
6 THE BIRTH OF DNA ▲
Other enzymes begin to make DNA. Thanks to its superior stability, DNA takes on the role of primary genetic molecule. RNA's main role is now to act as a bridge between DNA and proteins.
7 BACTERIAL WORLD ▲
Organisms resembling modern bacteria adapt to living virtually everywhere on earth and rule unopposed for billions of years, until some of them begin to evolve into more complex organisms.

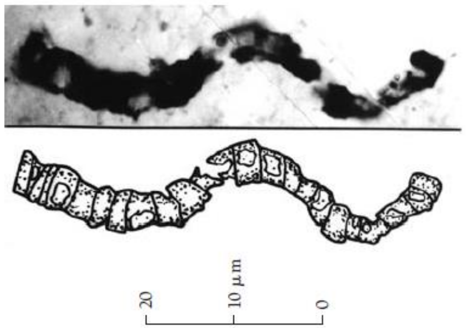


Figure 1-35 **Microfossil of what appears to be a cyanobacterium.** This fossil, shown with its interpretive drawing, is from ~3.5-billion-year-old rock from western Australia.