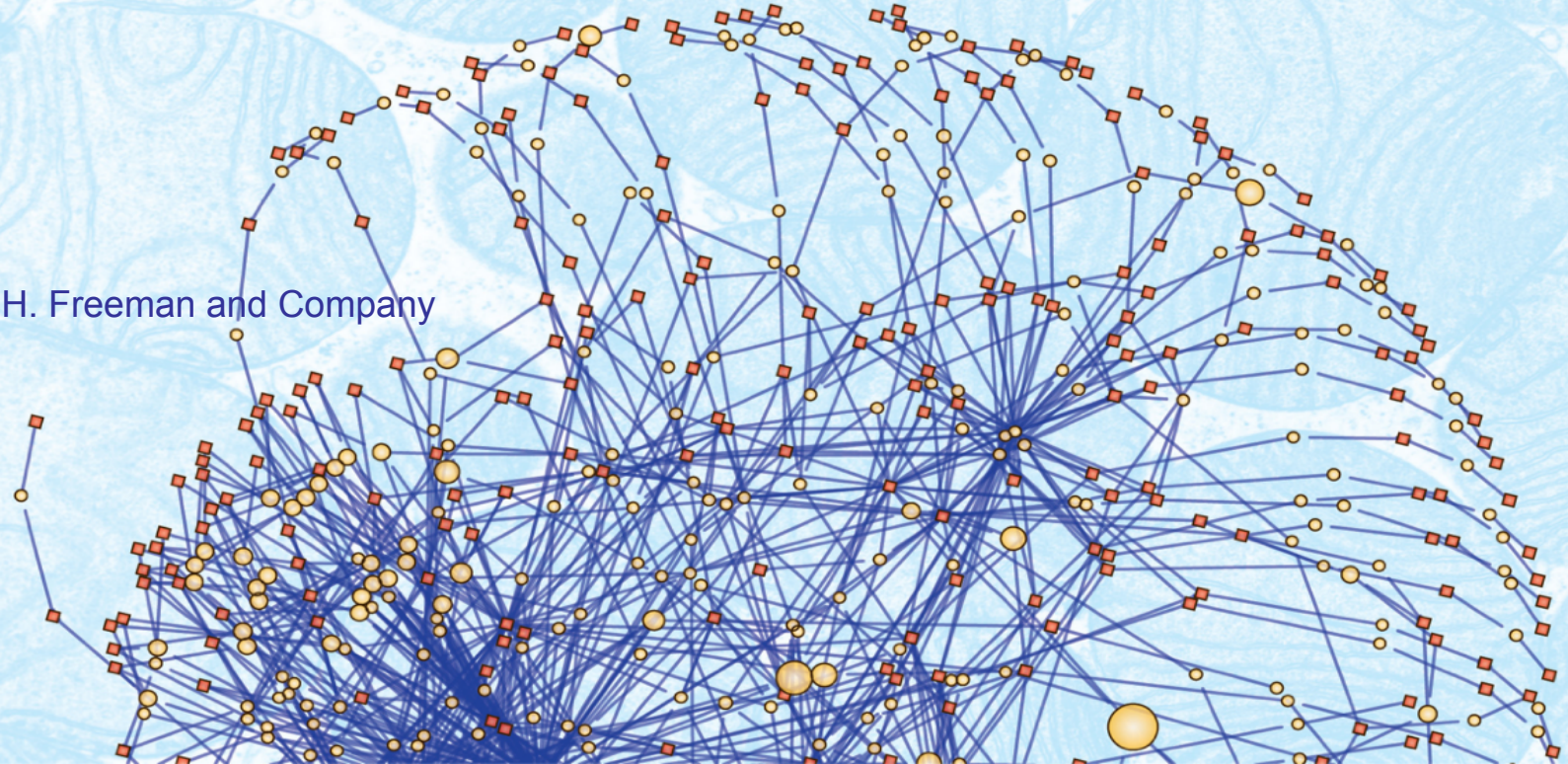
Lehninger

SIXTH EDITION

Principles of Biochemistry

David L. Nelson | Michael M. Cox

1 | Foundations of Biochemistry



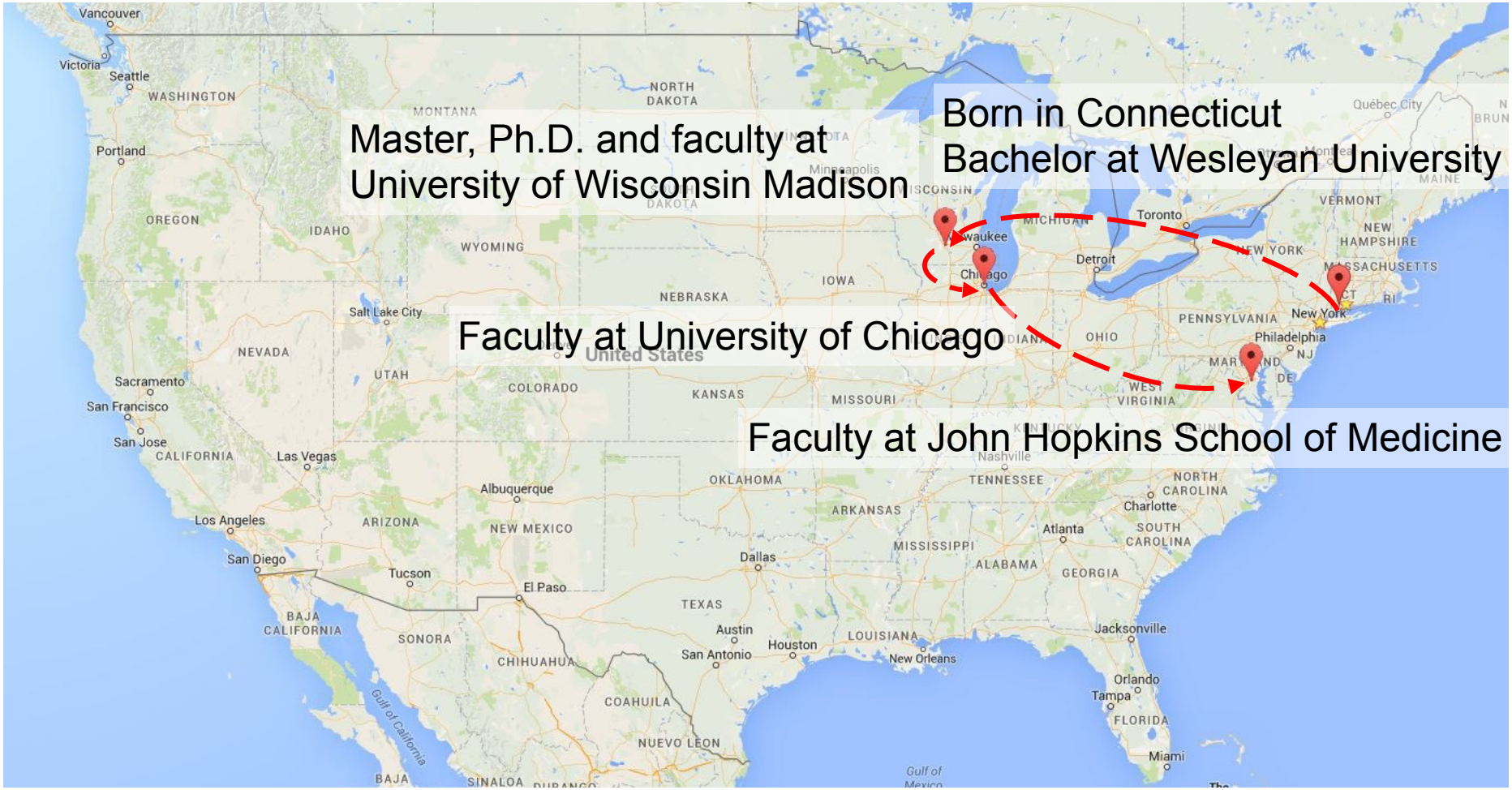
Albert Lehninger

- Born 02/17/1917 in Connecticut
- Bachelor (1939)
- Master (1940) and Ph.D. (1942)

- Citric acid cycle occurs in mitochondria
- Mechanism of oxidative phosphorylation
- Mitochondrial structure and function
- Bioenergetics

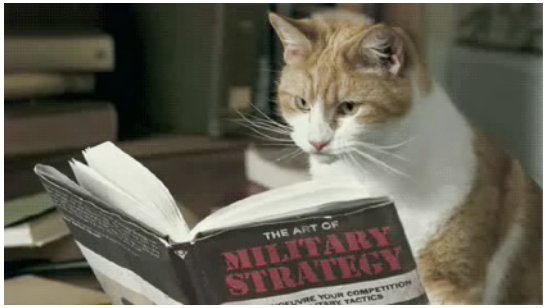
Albert L. Lehninger, 1917–1986

Albert Lehninger (1917–1986)



Biochemistry is the Chemistry of Living Matter

- What is living matter?
- Or, what are features of living organisms?
  - Able to run/walk/move?
  - Have emotions/feelings?
  - Able to read/learn?



Biochemistry is the Chemistry of Living Matter

Living Matter is characterized by:

- Complexity and organization
- Functions for components and regulated interactions
- Extraction, transformation and use of energy
- Sense and respond to alterations in surroundings
- Precise self-replication
- Allow changes for evolution

Biochemistry is the Chemistry of Living Matter

Living Matter is characterized by:

- Complex, organized and functional system

- Extraction, transformation and use of energy
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Biochemistry is the Chemistry of Living Matter

Living Matter is characterized by:

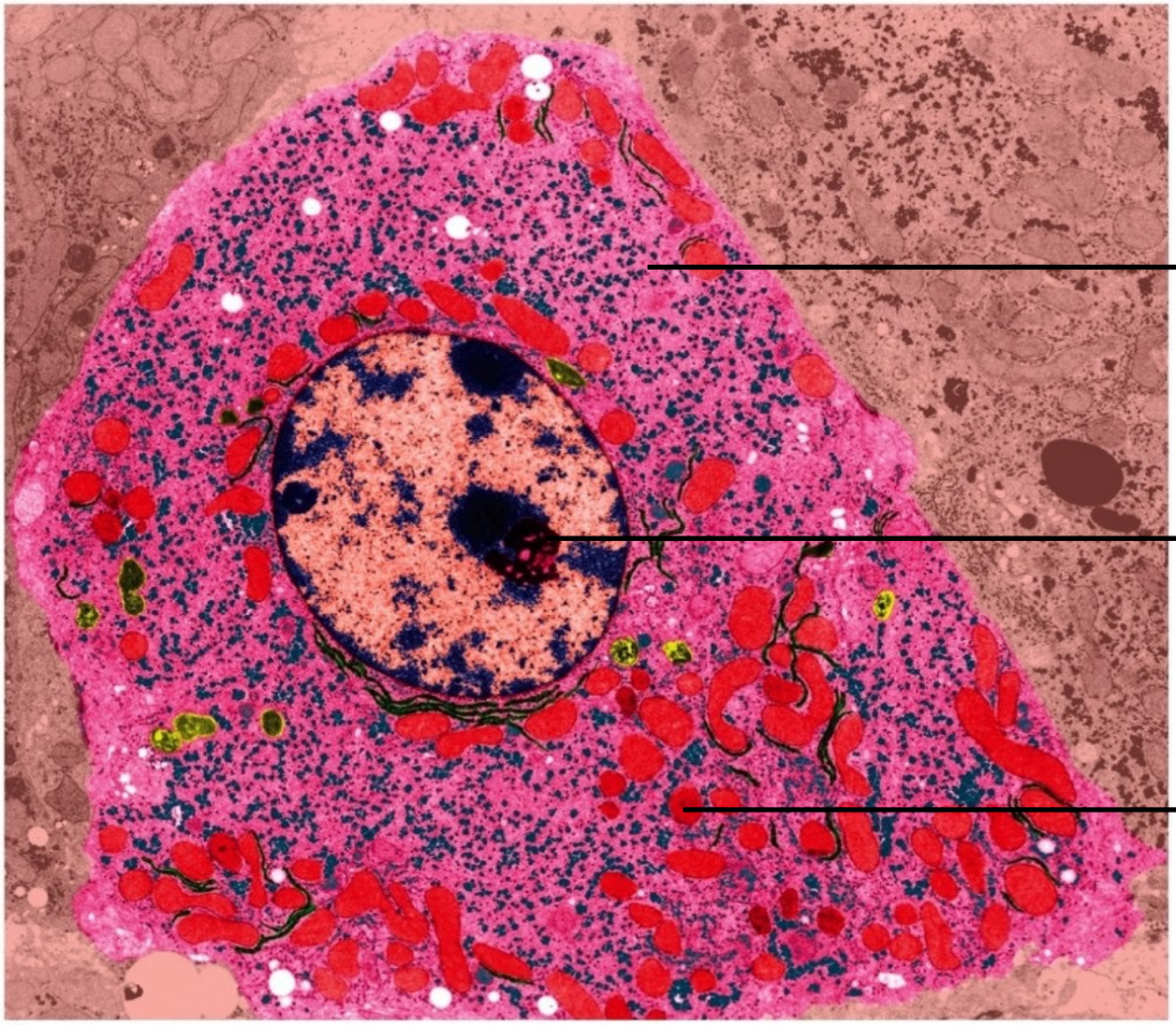
- Complex, organized and functional system
- Exchange energy and matter with surroundings
- Precise self-replication
- Allow changes for evolution

Biochemistry is the Chemistry of Living Matter

Living Matter is characterized by:

- Complex, organized and functional system
- Exchange energy and matter with surroundings
- Evolution

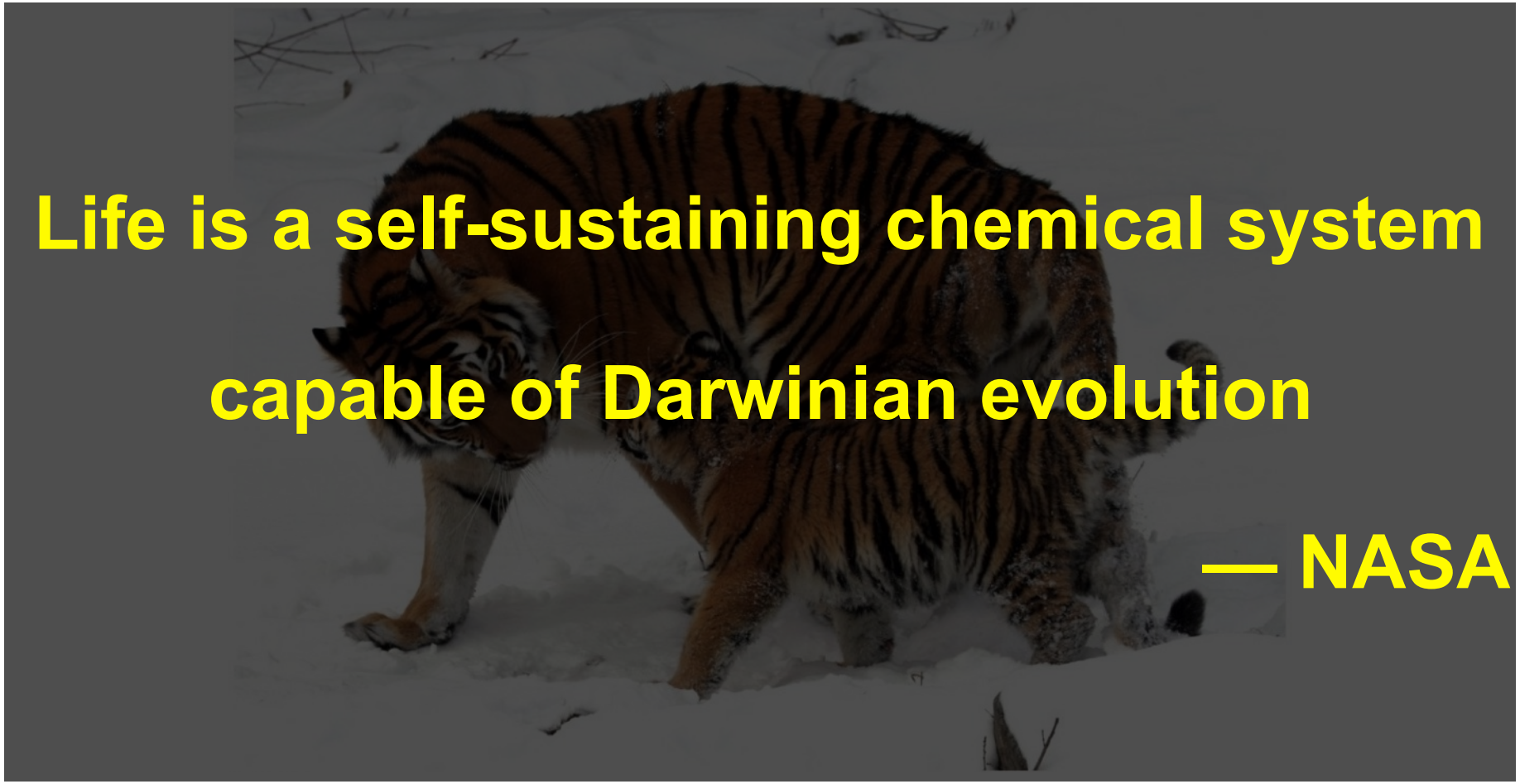
Complexity and Organization



Living organisms must intake nutrients

- A falcon acquires nutrients and energy by:
  - consuming a smaller bird.
- A sunflower acquires nutrients and energy from:
  - soil, air and sun.

Living organisms must accurately reproduce



Biological reproduction occurs with **near-perfect** fidelity.

Foundations of Biochemistry

Cellular foundations

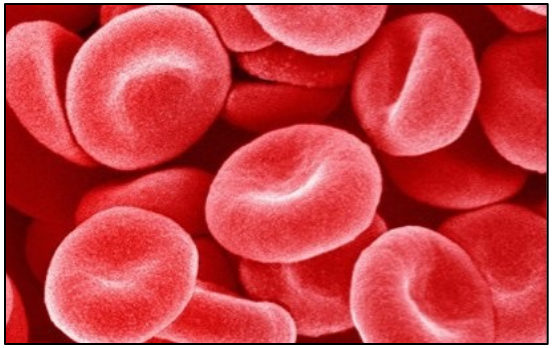
Chemical foundations

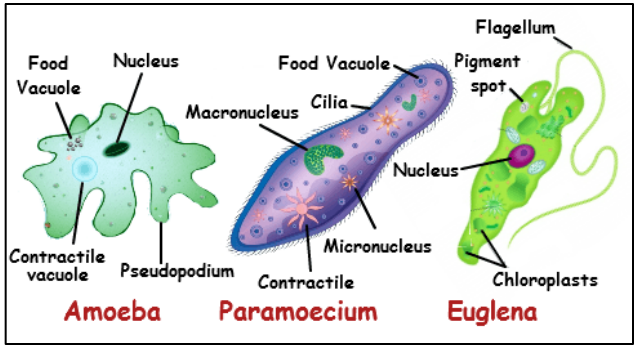
Physical foundations

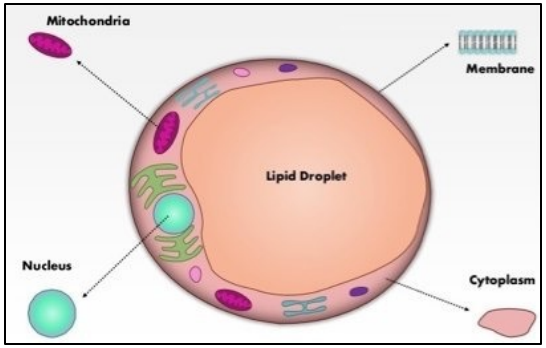
Genetic and evolutionary foundations

Cell: The Universal Building Block

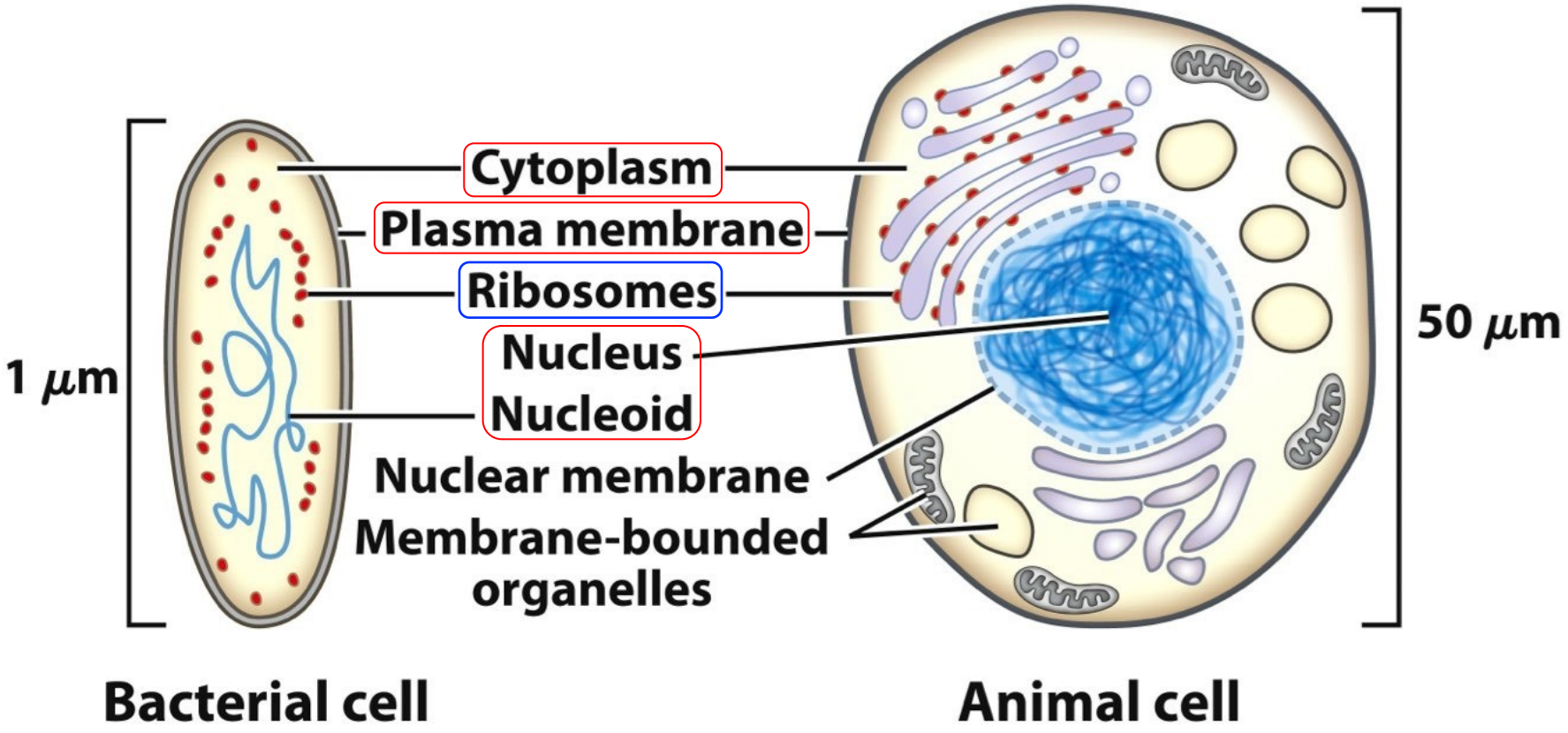
- Living organisms are made of cells
- Simplest living organisms are single-celled
- Larger organisms consist of many cells with different functions
- Not all of the cells are the same







All cells share some common features



- Cell membrane separates self from non-self
- Nuclear envelope separates nucleus from cytoplasm

Cellular dimensions limited by diffusion

100 μm
- Human hair
- Paper thickness

10 μm
- Wool fiber
- Silk fiber
- Cotton fiber

5 μm
- Human sperm head
- Spider web silk

Human cell
50 μm

Bacterial cell
1 μm

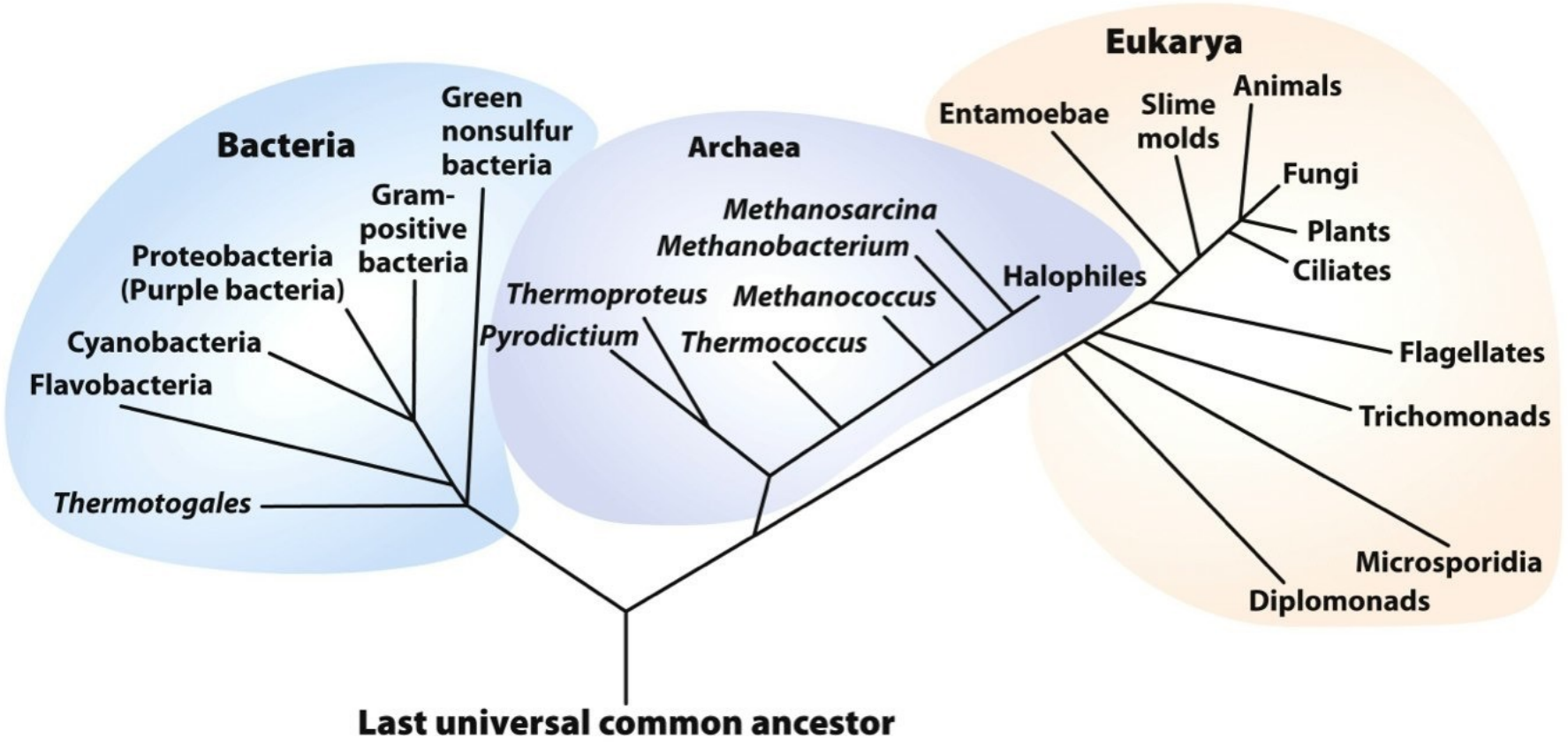
在大灾难到来前的一万七千年中，人类想尽了逃生的办法，其中最容易想到的是恒星际移民，但包括您这艘在内的所有方舟飞船都没有找到带有可居住行星的恒星。即使找到了，以大灾难前一个世纪人类的宇航技术，连移民千分之一的人类都做不到。另一个设想是移居到地层深处，躲过太阳能量闪烁后再出来。这不过是拖长死亡的过程而已，大灾难后地球的生态系统将被完全摧毁，养活不了人类的。

有一段时期，人们几乎绝望了。但某位基因工程师的脑海中闪现了一个火花：如果把人类的体积缩小十亿倍会怎么样？这样人类社会的尺度也缩小了十亿倍，只要有很微小的生态系统，消耗很微小的资源就可生存下来。很快全人类都意识到这是拯救人类文明惟一可行的办法。这个设想是以两项技术为基础的，其一是基因工程，在修改人类基因后，人类将缩小至10微米左右，只相当于一个细胞大小，但其身体的结构完全不变。做到这点是完全可能的，人和细菌的基因本来就没有太大的差别；另一项是纳米技术，这是一项在二十世纪就发展起来的技术，那时人们已经能造出细菌大小的发电机了，后来人们可以用纳米尺度造出从火箭到微波炉的一切设备，只是那些纳米工程师做梦都不会想到他们的产品的最后用途。

培育第一批微人类似于克隆：从一个人类细胞中抽取全部遗传信息，然后培育出同主体一模一样的微人，但其体积只是主体的十亿分之二。以后他们就同宏人（微人对你们的称呼，他们还把你们的时代叫宏纪元）一样生育后代了。

——节选自刘慈欣科幻小说《微纪元》

Three Distinct Domains of Life Defined by: Cellular and Molecular Differences



Archaea are evolutionarily more closely related to eukaryotes

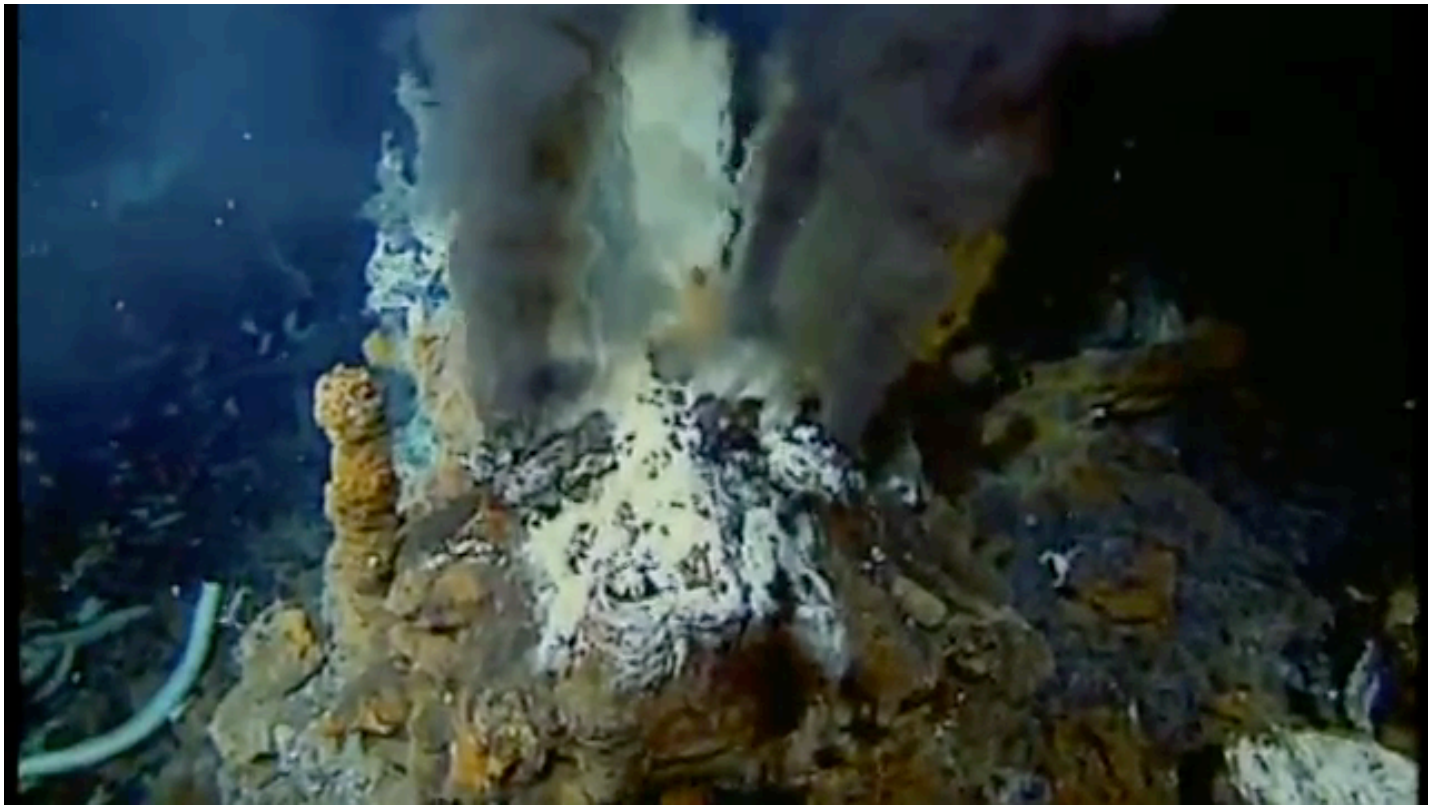
Discovery of Archaea

It was once believed there were **two** fundamental types of life on Earth:

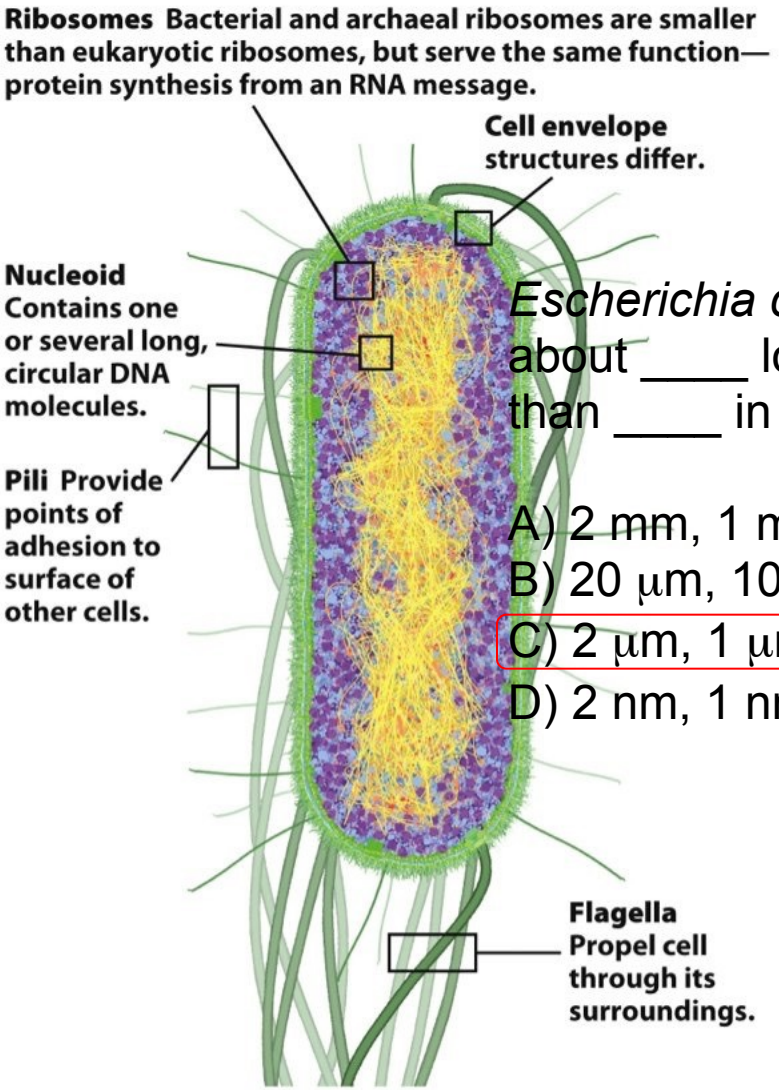
1. Bacteria - prokaryotes - DNA contained not within a nucleus
2. Everything else - eukaryotes - DNA enclosed within the nucleus

In 1977, Carl Woese found a **third** form of life - Archaea

- Able to live anywhere on the planet - the most extreme environment
  - hydrothermal vent on ocean floor (from freezing to 760℉ [400℃])
  - miles inside the Earth (lakes of acids)



Bacterial Cell Structure



Escherichia coli cell is an ovoid about ____ long and a little less than ____ in diameter.

A) 2 mm, 1 mm
B) 20 μm, 10 μm
C) 2 μm, 1 μm
D) 2 nm, 1 nm

Components of Bacterial Cell

Structure	Composition	Function
Cell wall	Peptidoglycan	Mechanical support
Cell membrane	Lipid + protein	Permeability barrier
Nucleoid	DNA + protein	Genetic information
Ribosome	RNA + protein	Protein synthesis
Pili	Protein	Adhesion, conjugation
Flagella	Protein	Motility
Cytoplasm	Aqueous solution	Site of metabolism

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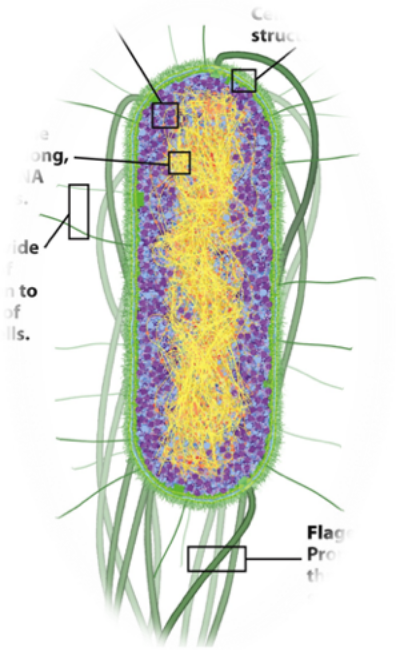
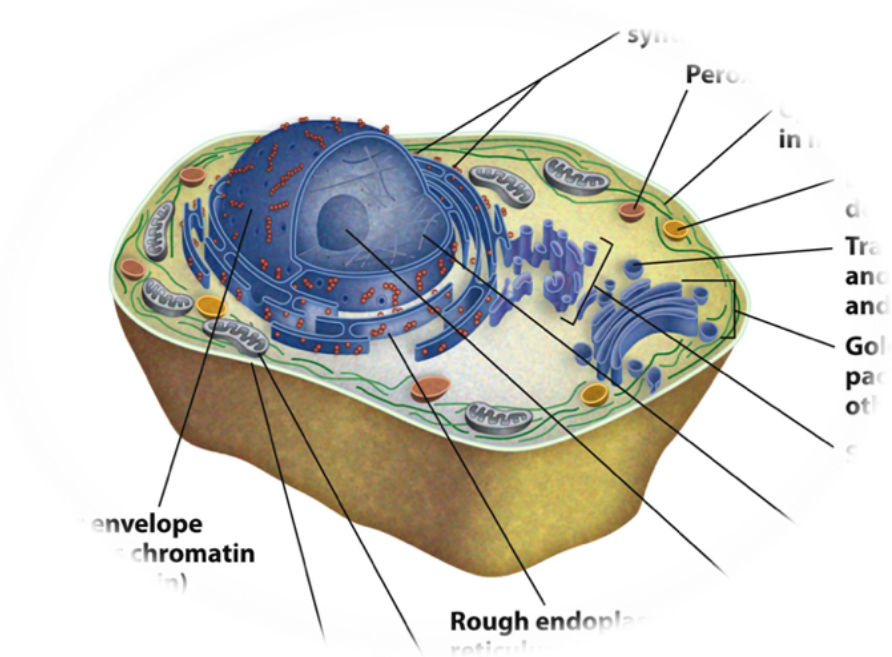
Eukaryote Cells: More Complexity

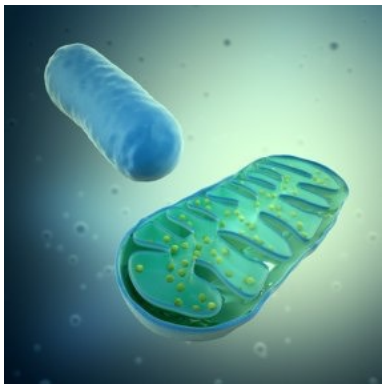
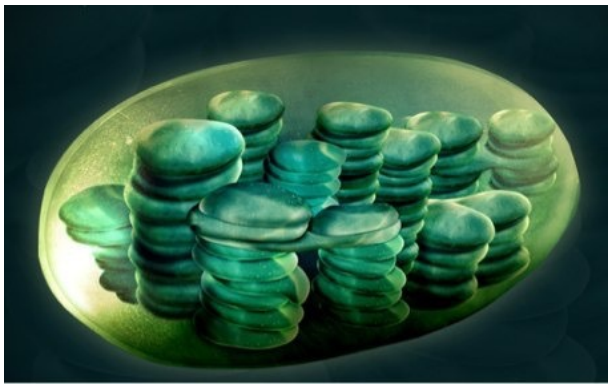
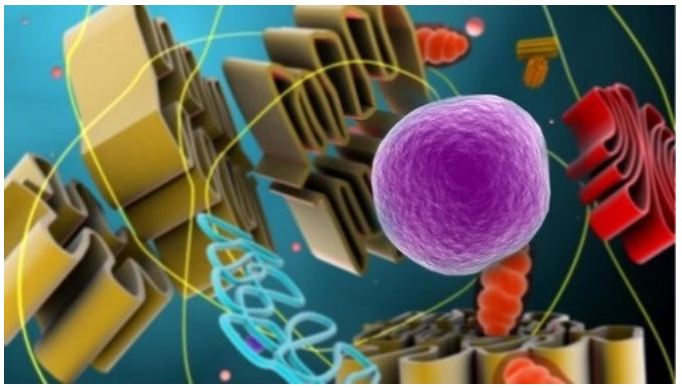
- Have nucleus by definition (bacteria are prokaryotes)
  - protection for DNA; site of DNA metabolism
  - selective import and export via nuclear membrane pores
  - some cells become anuclear (red blood cells)



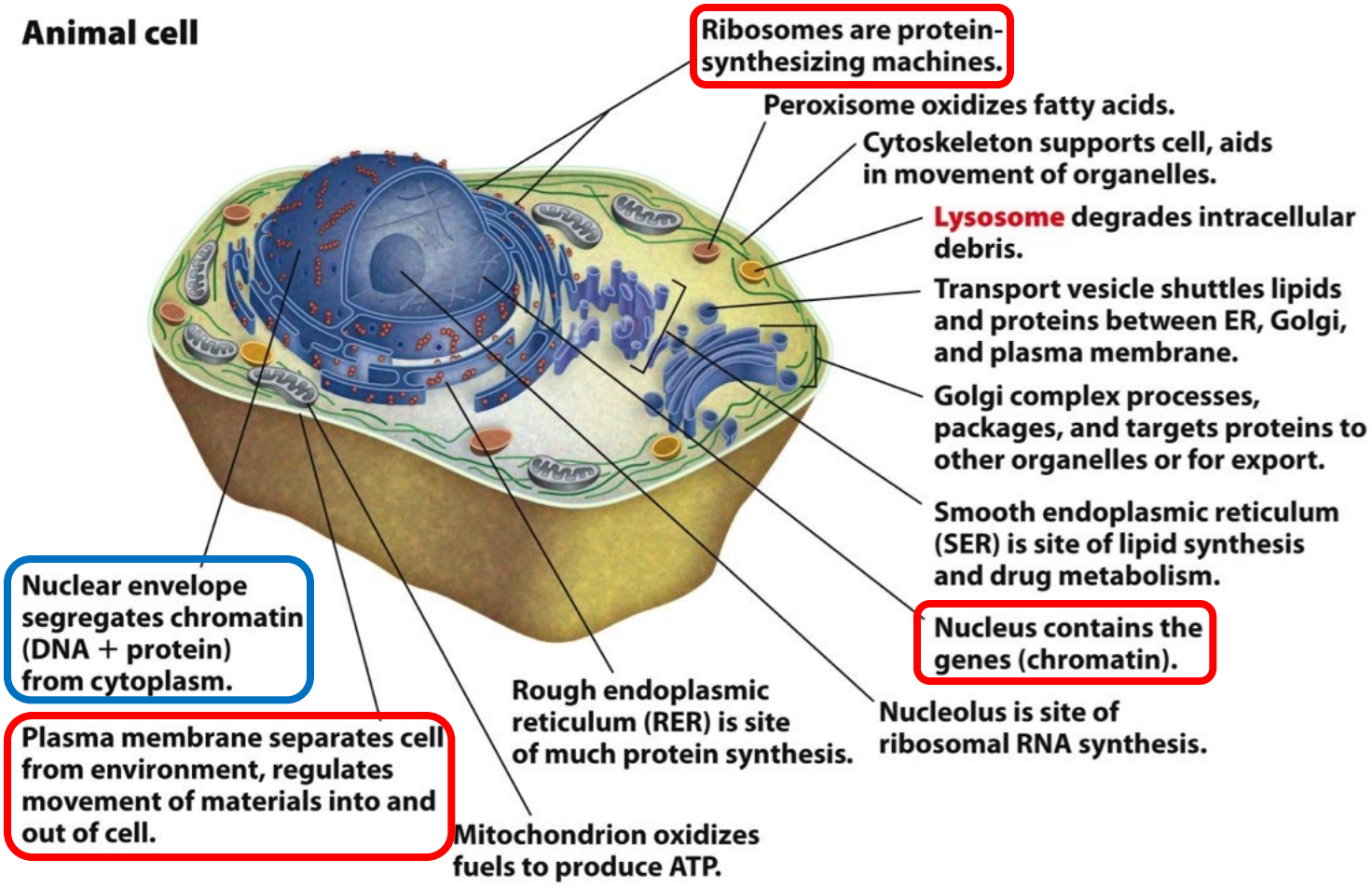


Eukaryote Cells: More Complexity

- Have membrane-enclosed organelles
  - Mitochondria for energy in animals, plants, and fungi
  - Chloroplasts for energy in plant
  - Lysosome for digestion of un-needed molecules
- **Spatial separation** of energy-yielding and energy-consuming reactions helps cells to maintain homeostasis and stay away from equilibrium

Bacterial, animal, and plant cells are different



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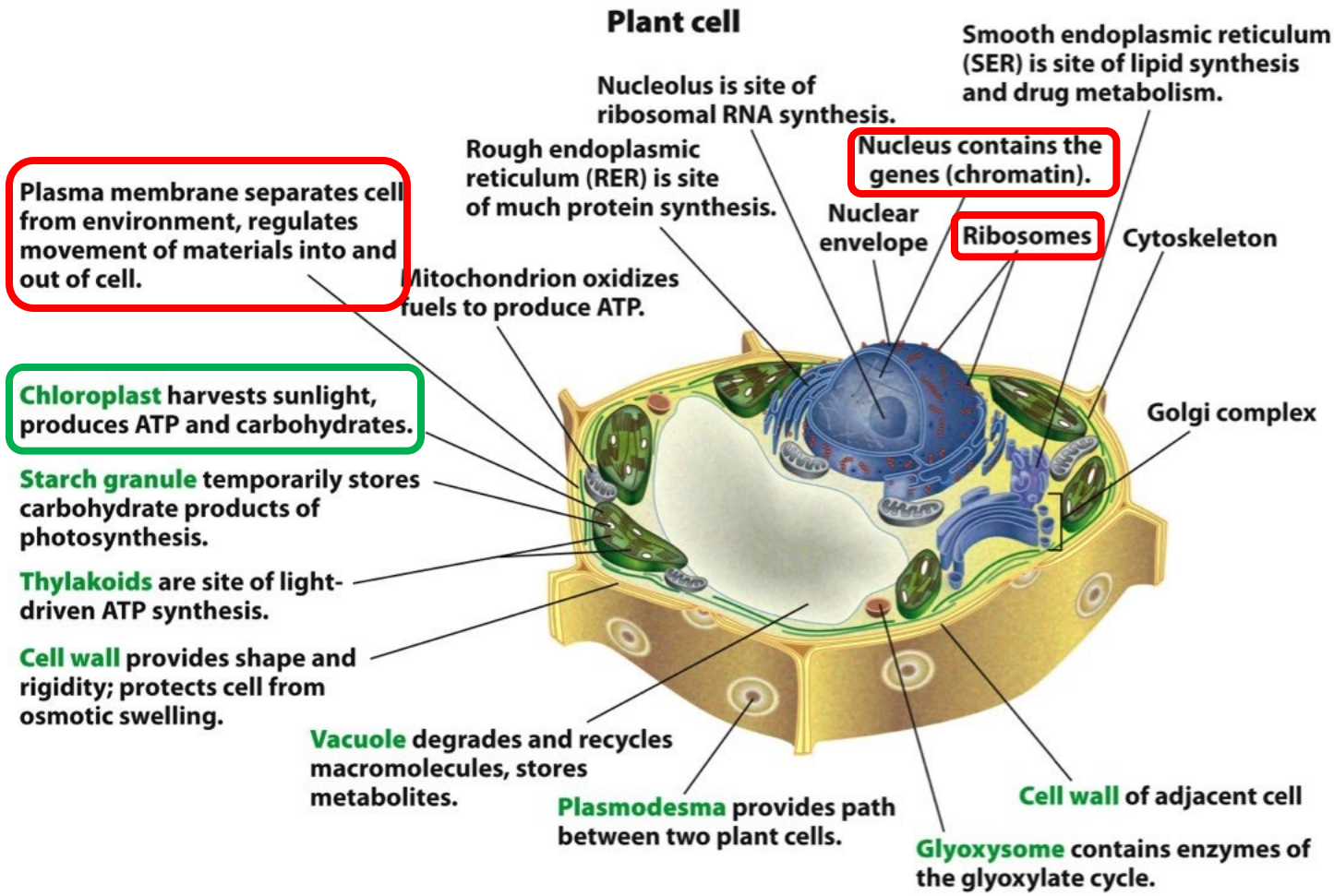
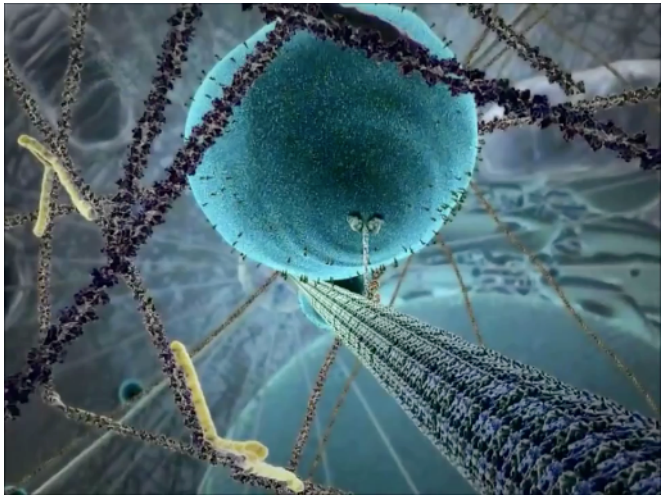
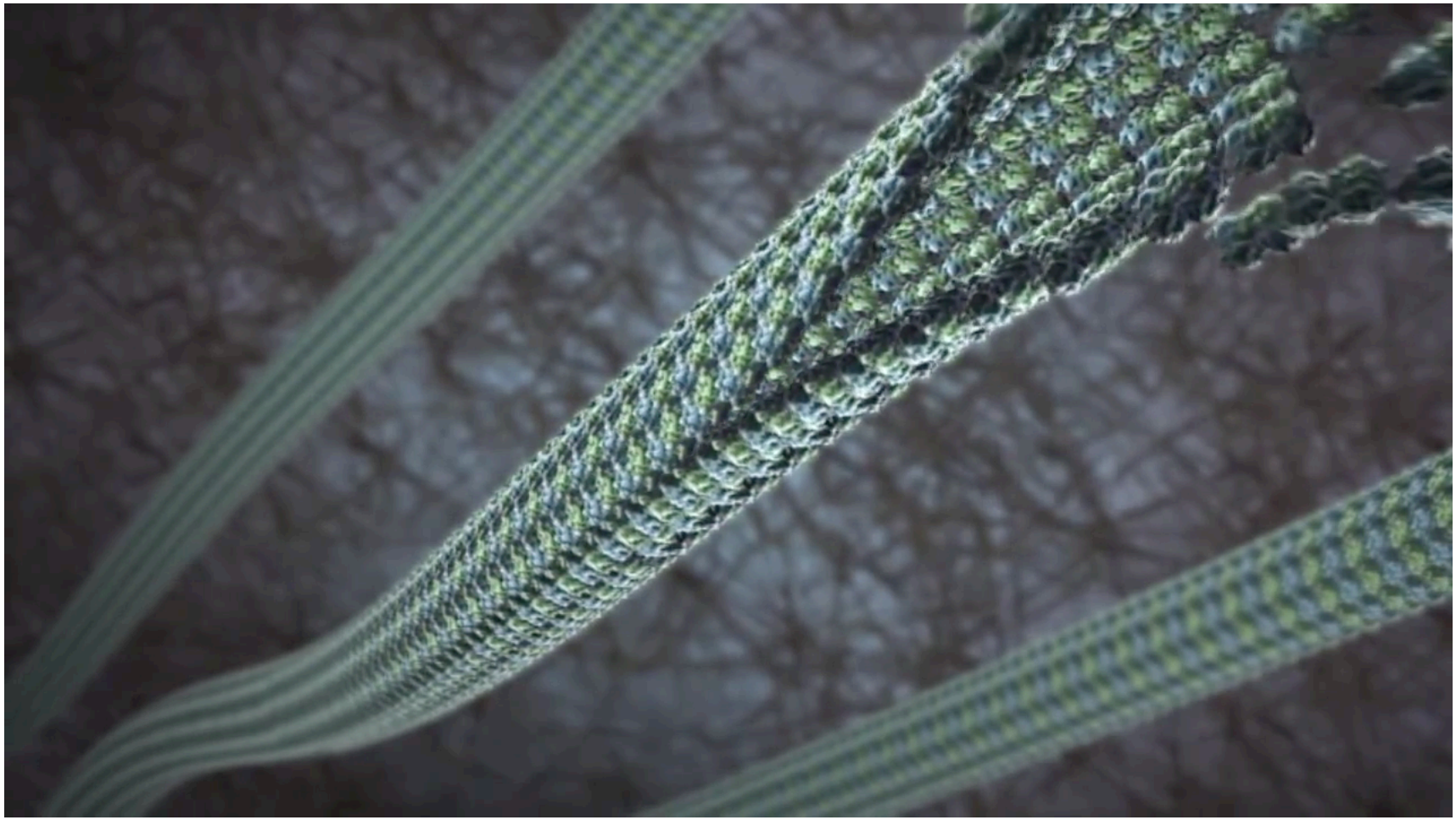


Cytoplasm and Cytoskeleton

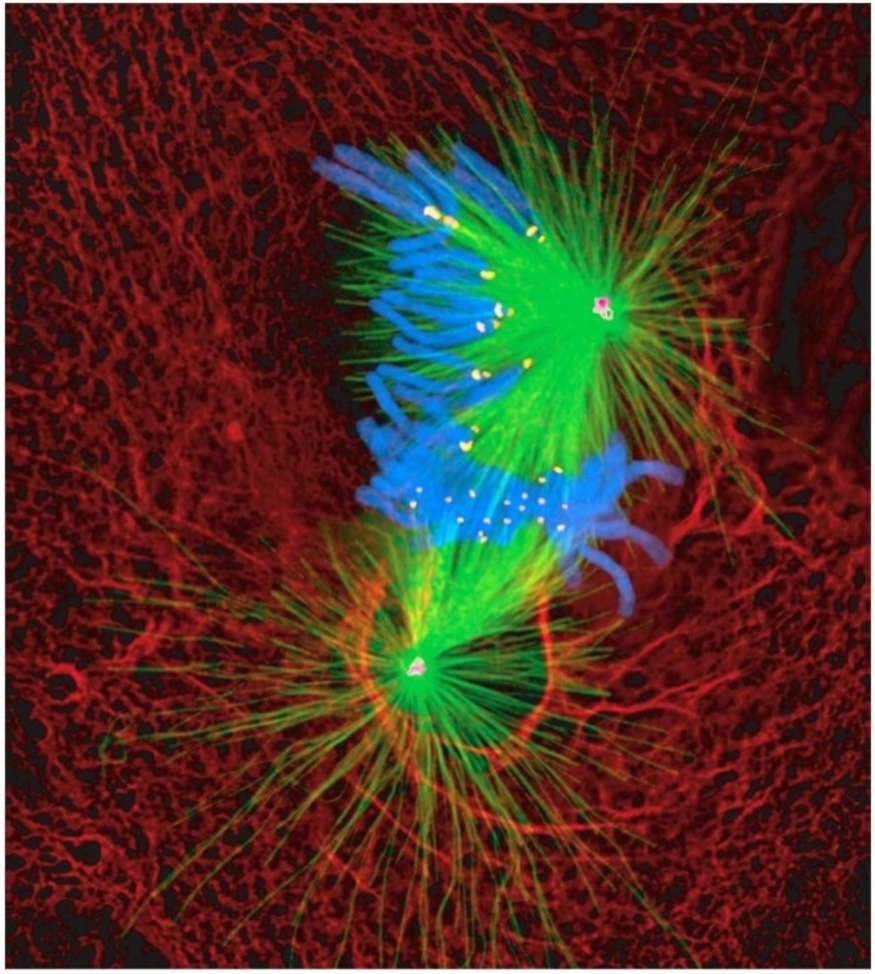
- Cytoplasm is highly **viscous** solution where many reactions take place
- Cytoskeleton consists of microtubules, actin filaments, and intermediate filaments
  - Cell shape
  - Intracellular organization
  - **Intracellular transport** paths
  - Cellular movement



Cytoskeleton undergoes constant disassembly-reassembly process

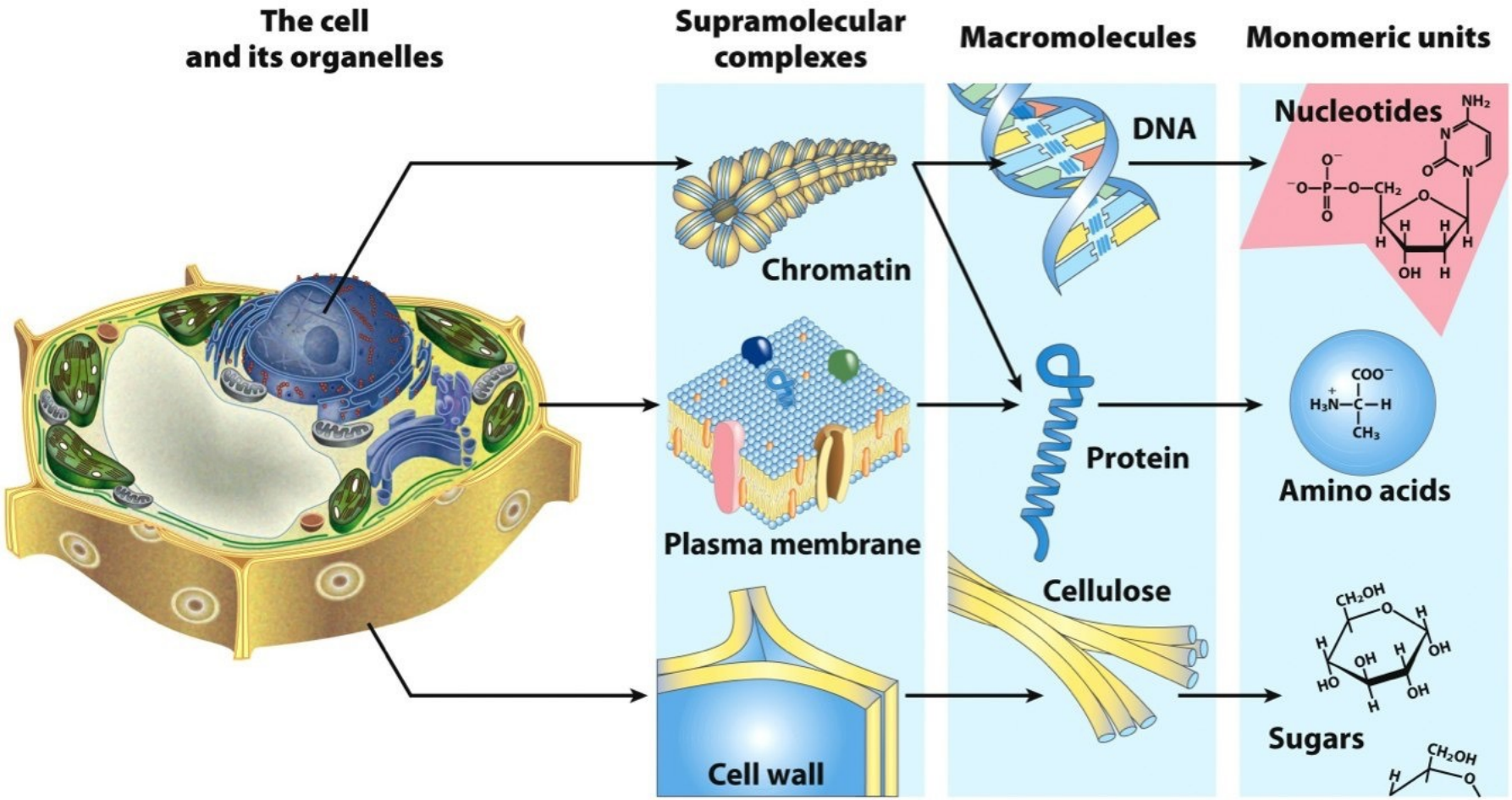


Cellular organization is dynamic, changing drastically at different stages



- **Microtubules (green)**
- Kinetochores (yellow)
- **Chromosomes (blue)**
- Centrosomes (magenta)
- Intermediate filaments (red)

Molecular Hierarchy of Structure



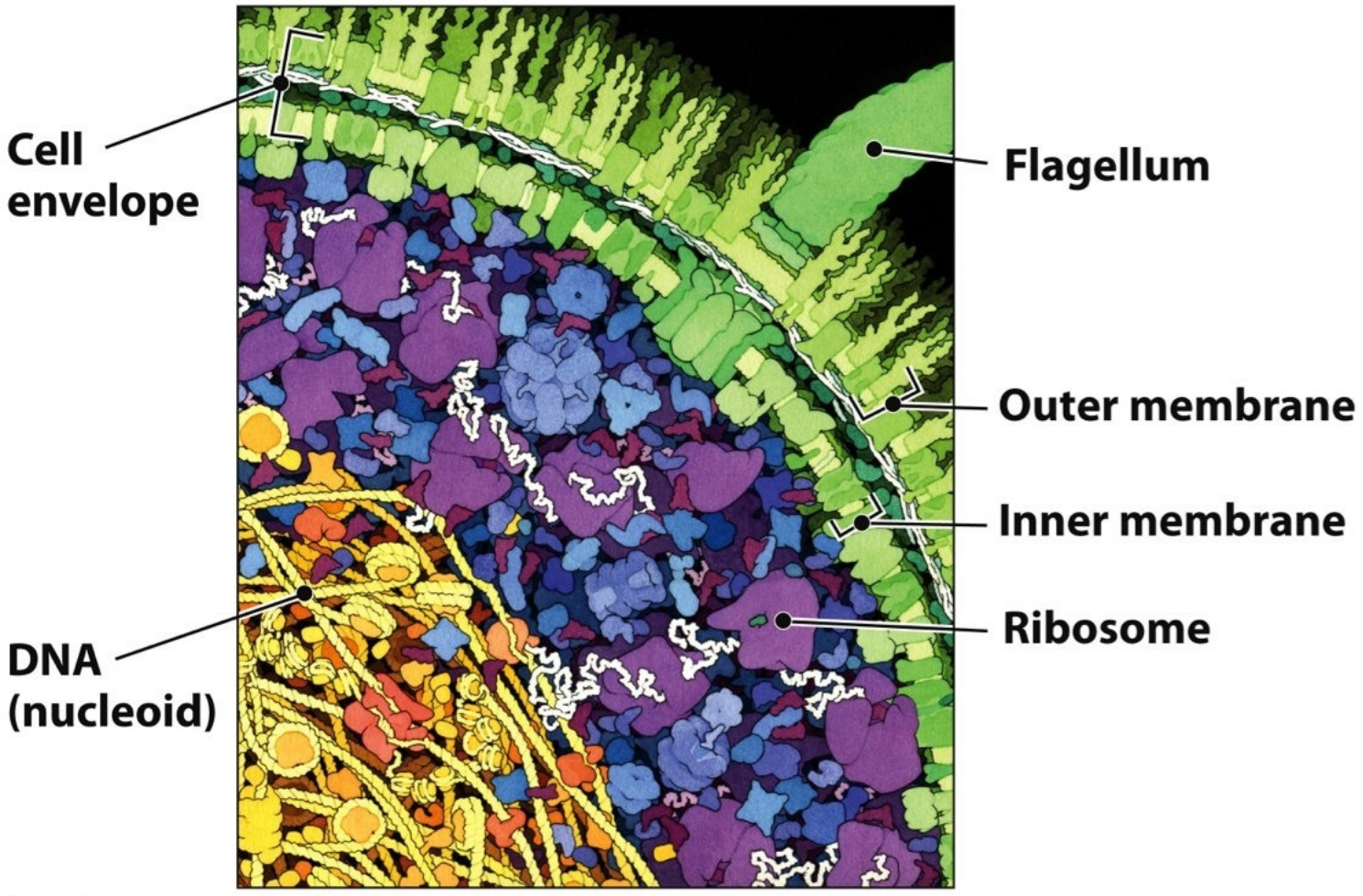
1000 nm, 1 μm
mitochondrion

20 nm
ribosome

5 nm
hemoglobin

0.5 nm
alanine

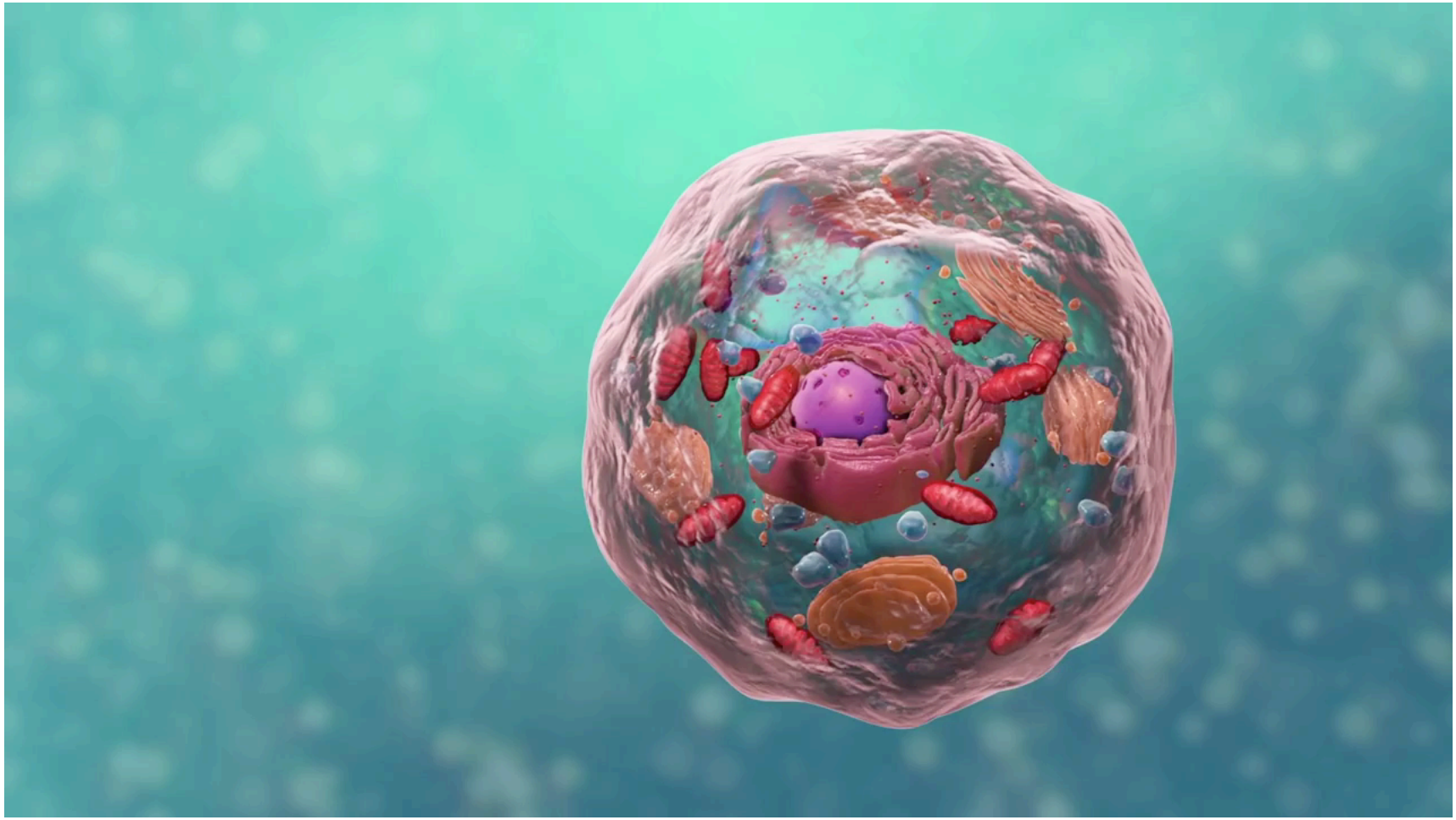
Cytosol is very crowded



Cellular Foundations Summary

- All cells are bounded by a plasma membrane
- In bacterial and archaeal cells, all components are contained within a cell envelope. Eukaryotic cells are multi-compartmented
- Cytoskeletal proteins give cells shape and rigidity, and serve as rails along which organelles move throughout the cell

Cellular Foundations Summary



Foundations of Biochemistry

Cellular foundations

Chemical foundations

Physical foundations

Genetic and evolutionary foundations

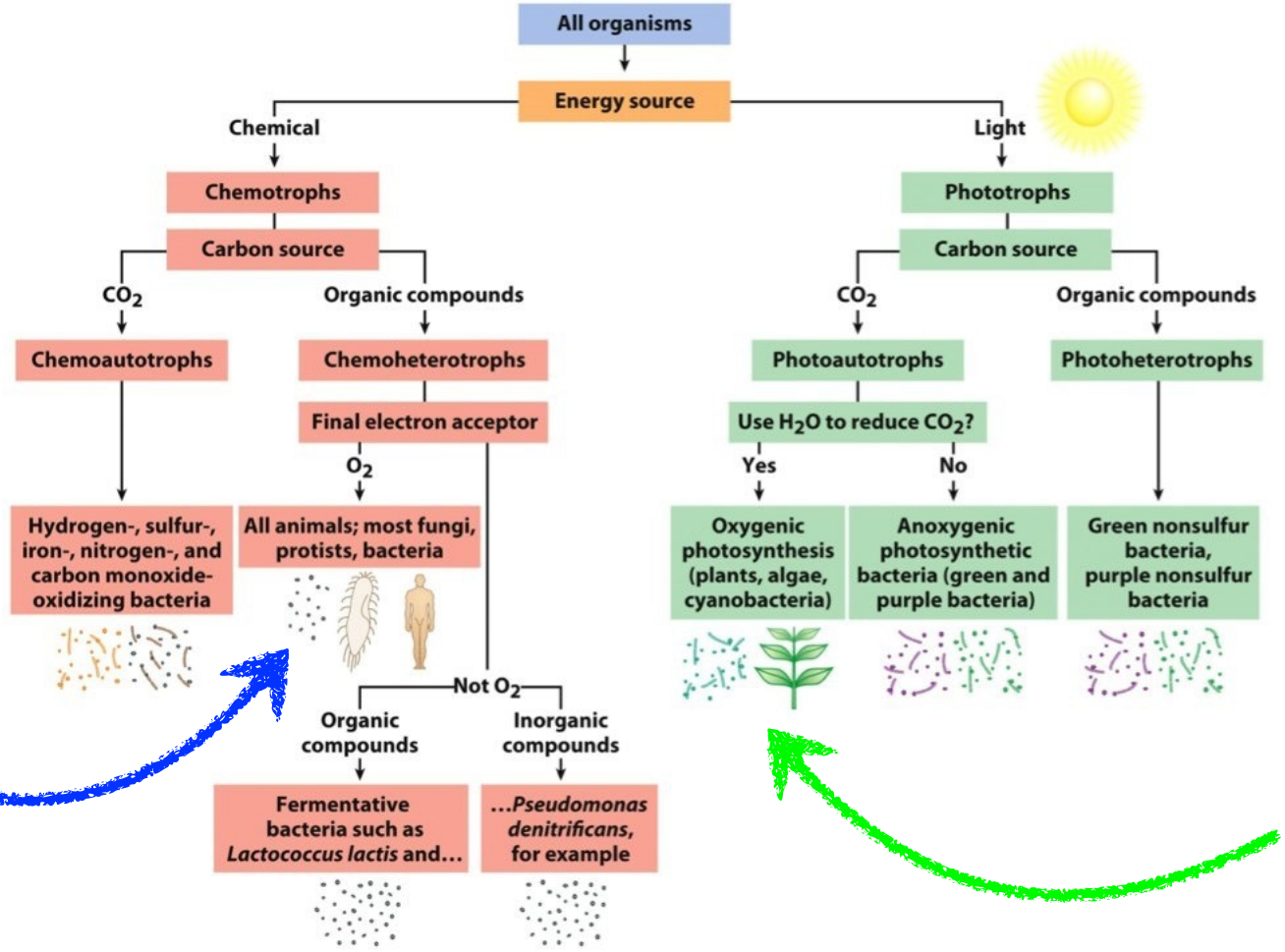
Biochemistry is the Chemistry of Living Matter

- The basis of all life is the chemical reactions that take place within the cell

Chemistry allows for:

- Complexity and organization
- Function and regulation
- Energy influx and transformation
- Respond to environment
- Replication and evolution

Organisms can also be classified by: different energy and carbon sources

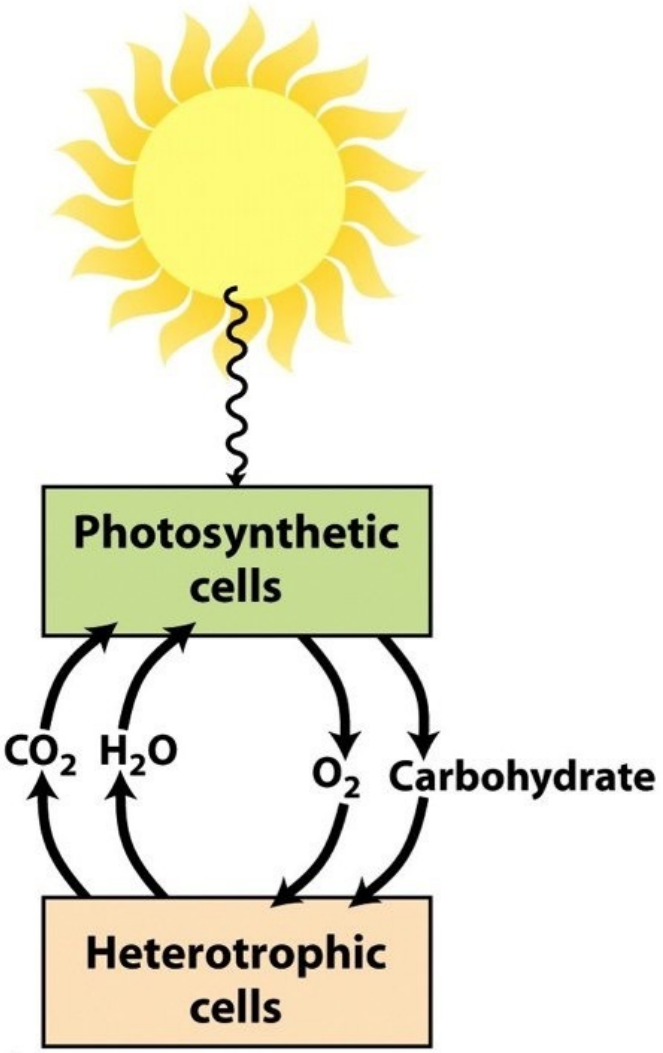


human and animals

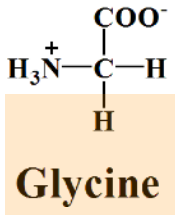
plants

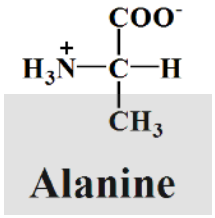
Living systems extract energy

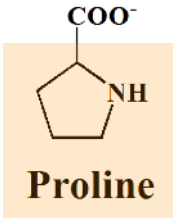
- Energy input is needed in order to maintain life
- From sunlight
  - plants
  - green bacteria
  - cyanobacteria
- From fuels
  - animals
  - most bacteria

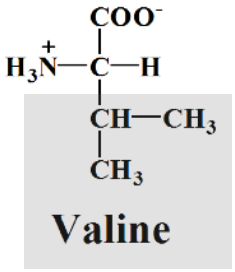


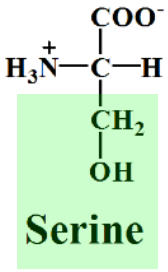
The ABCs of Life (amino acids)

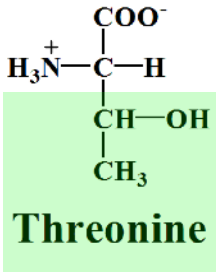


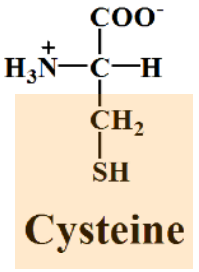


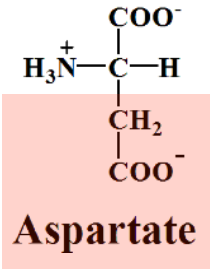


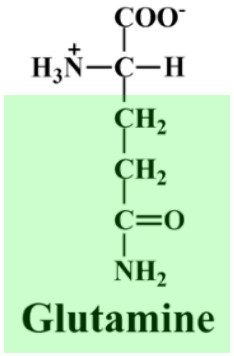


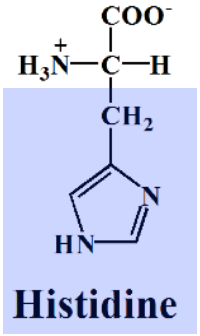


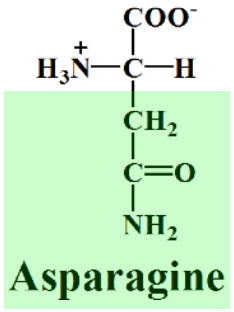


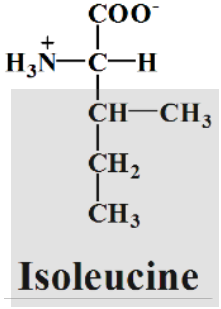


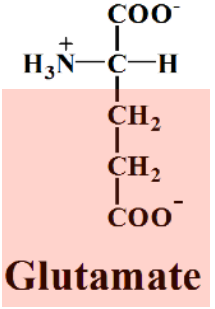


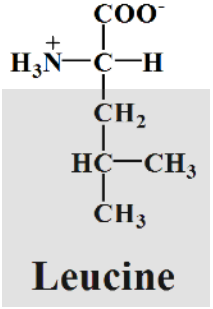


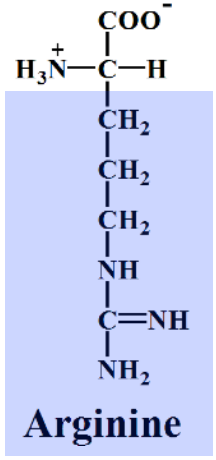


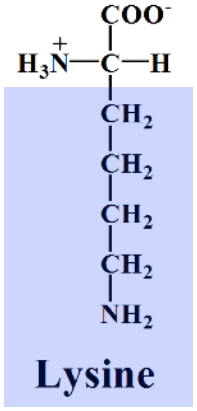


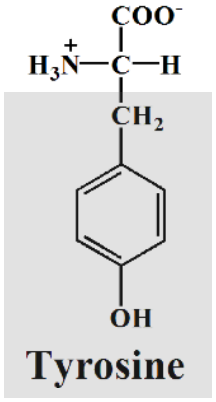


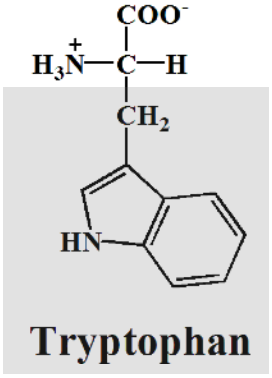


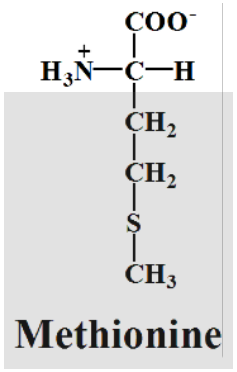


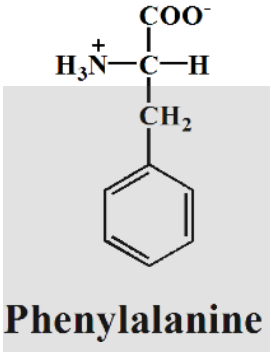






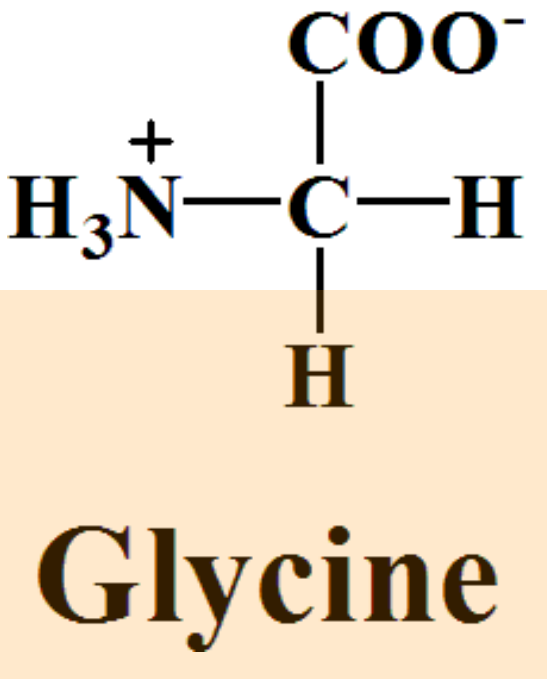


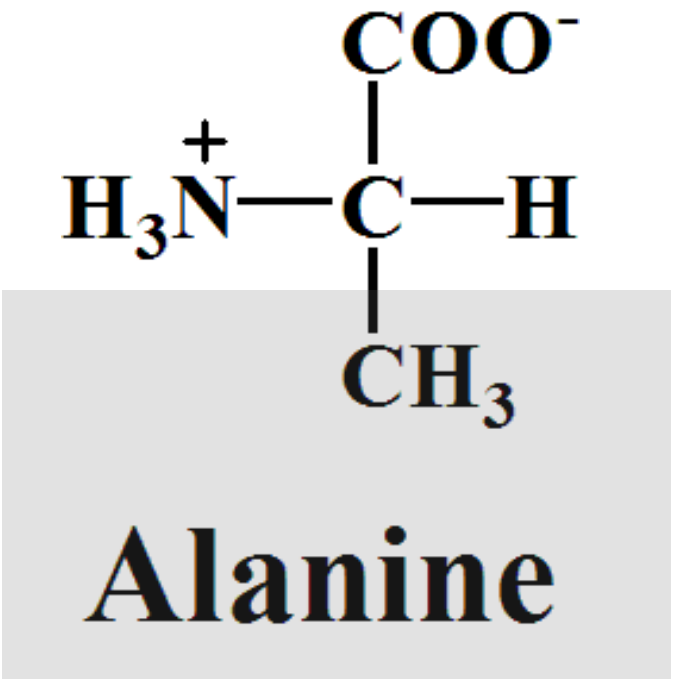




special
hydrophobic
uncharged
negative
positive

The ABCs of Life (amino acids)

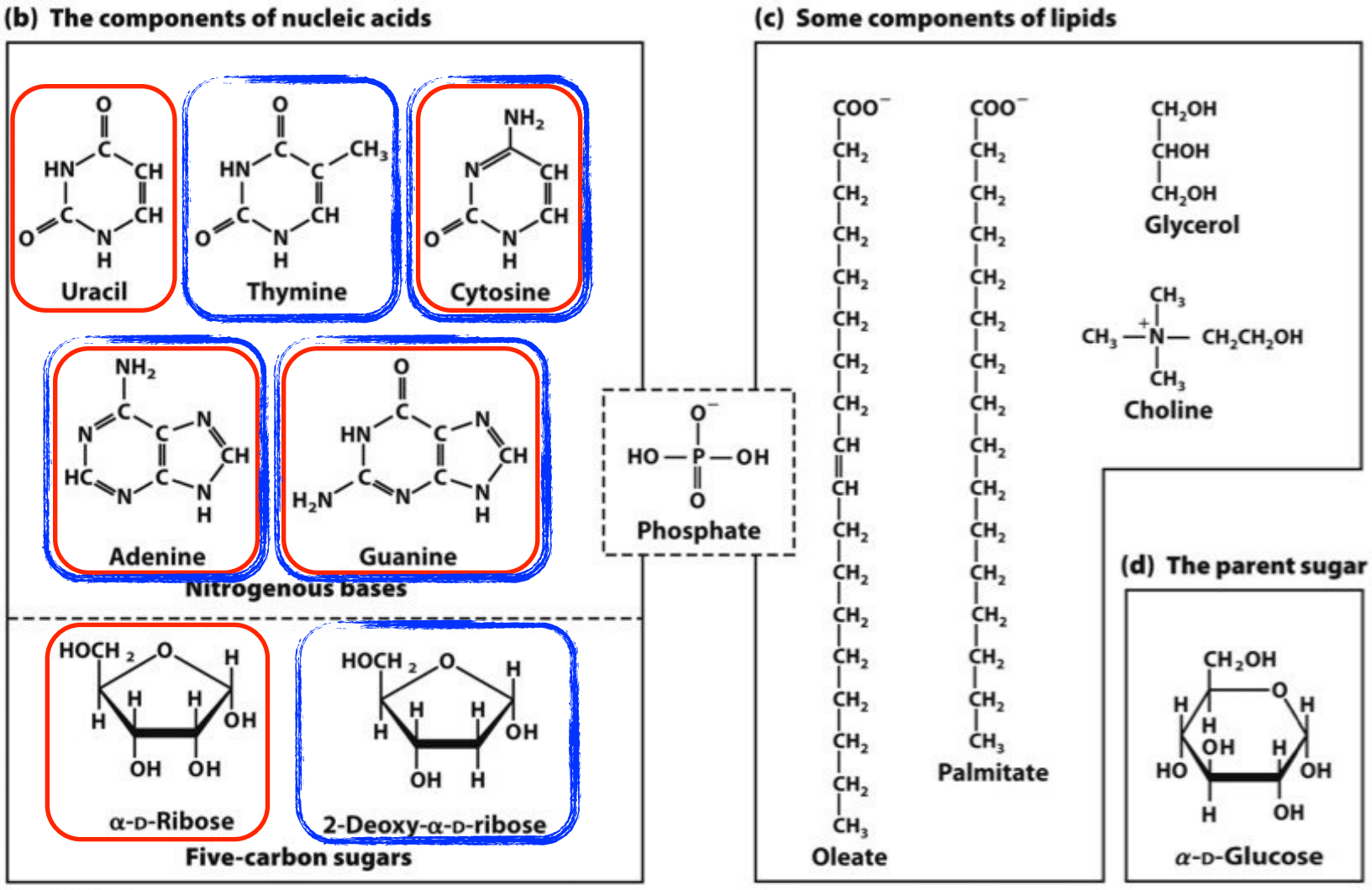




Gly, G **Ala, A**

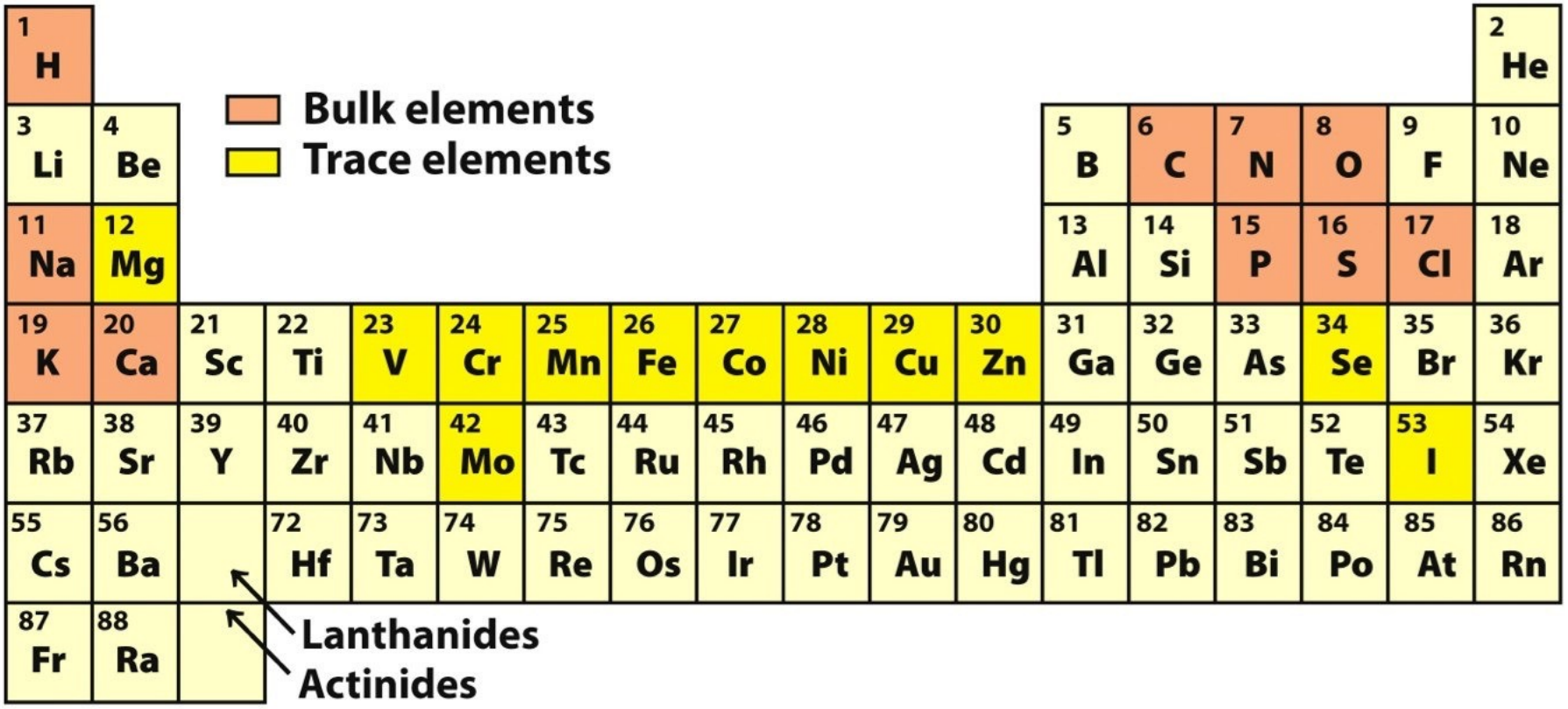
Amino acid for 1st week

The ABCs of Life

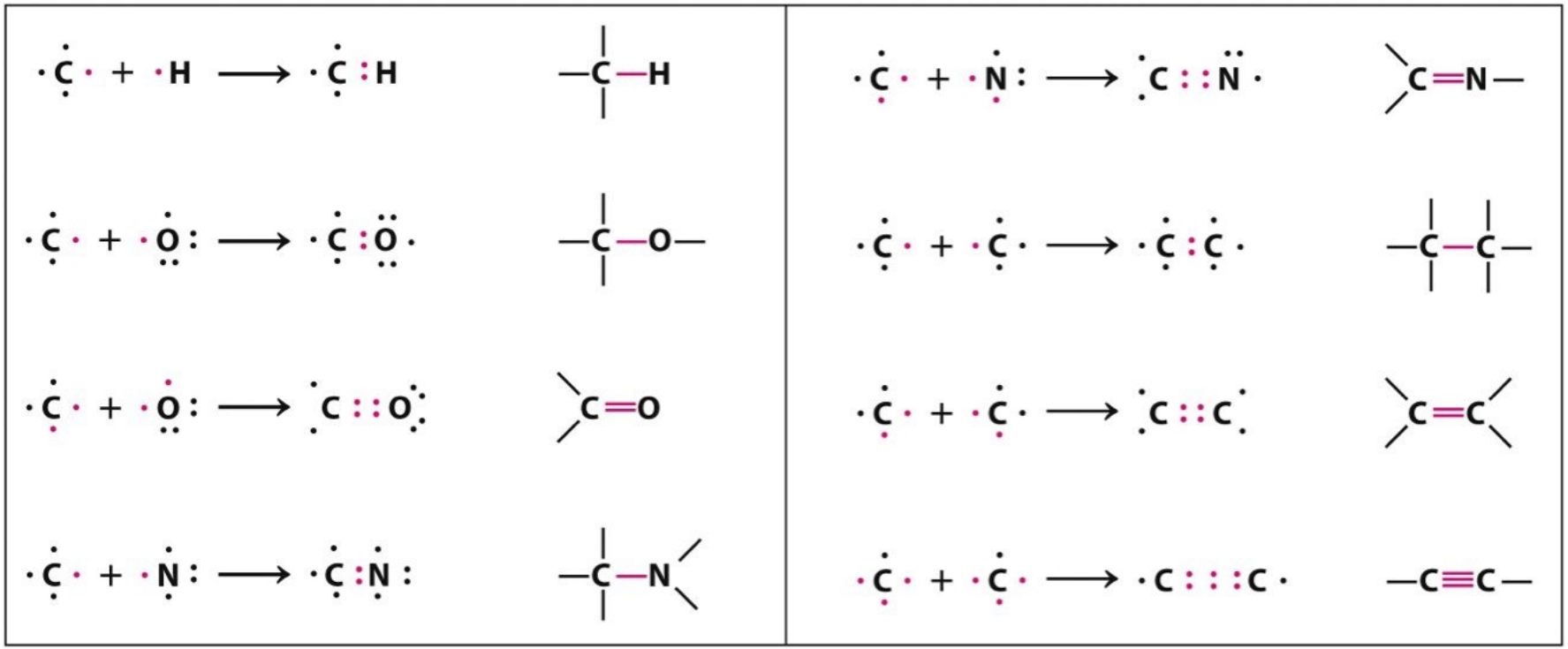


30 Elements Essential for Life

- Other than carbon, elements H, O, N, P, S are also common
- Metal ions (e.g., K^+, Na^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}) play important roles in metabolism

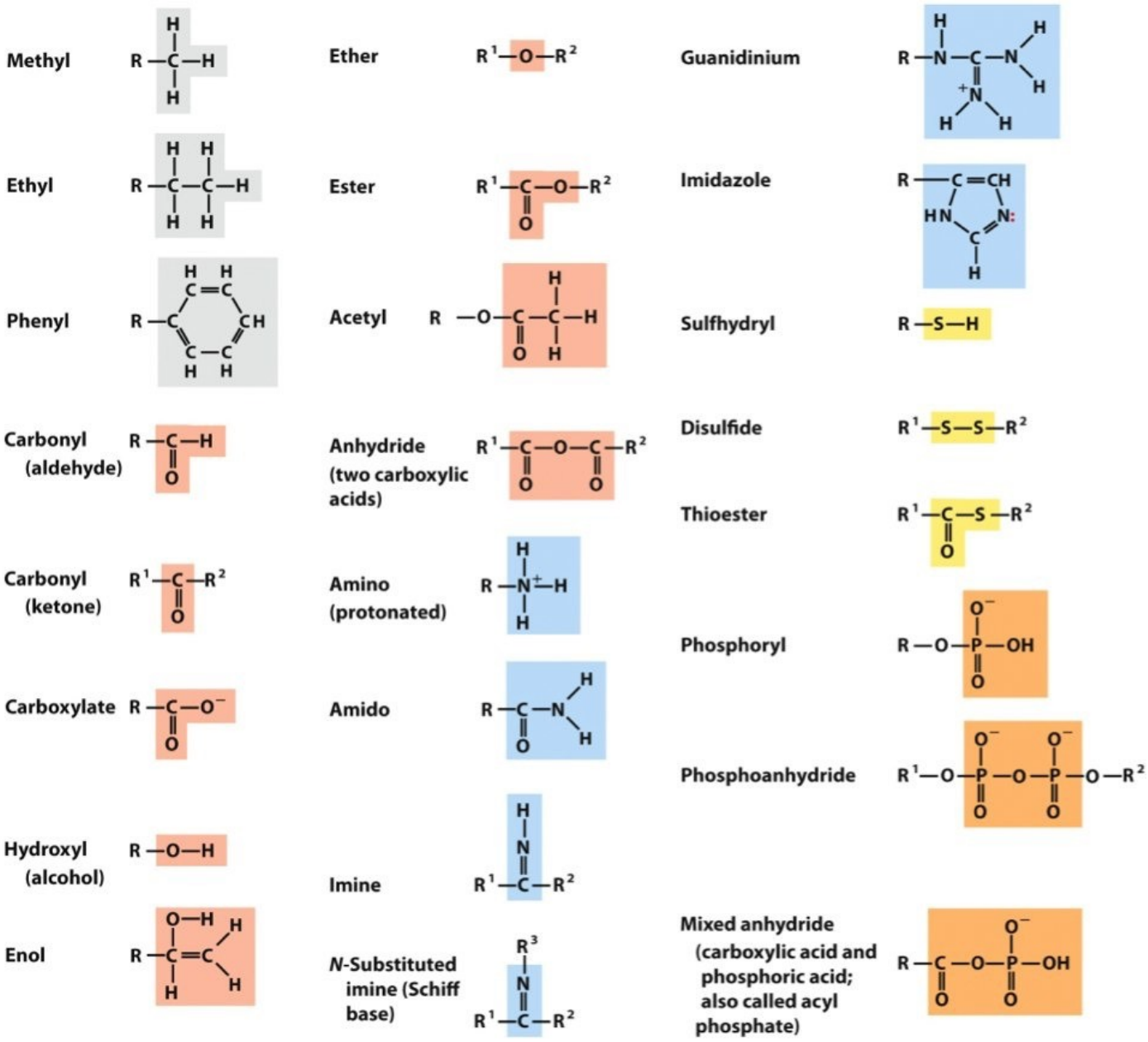


Biochemistry: Unique Role of Carbon

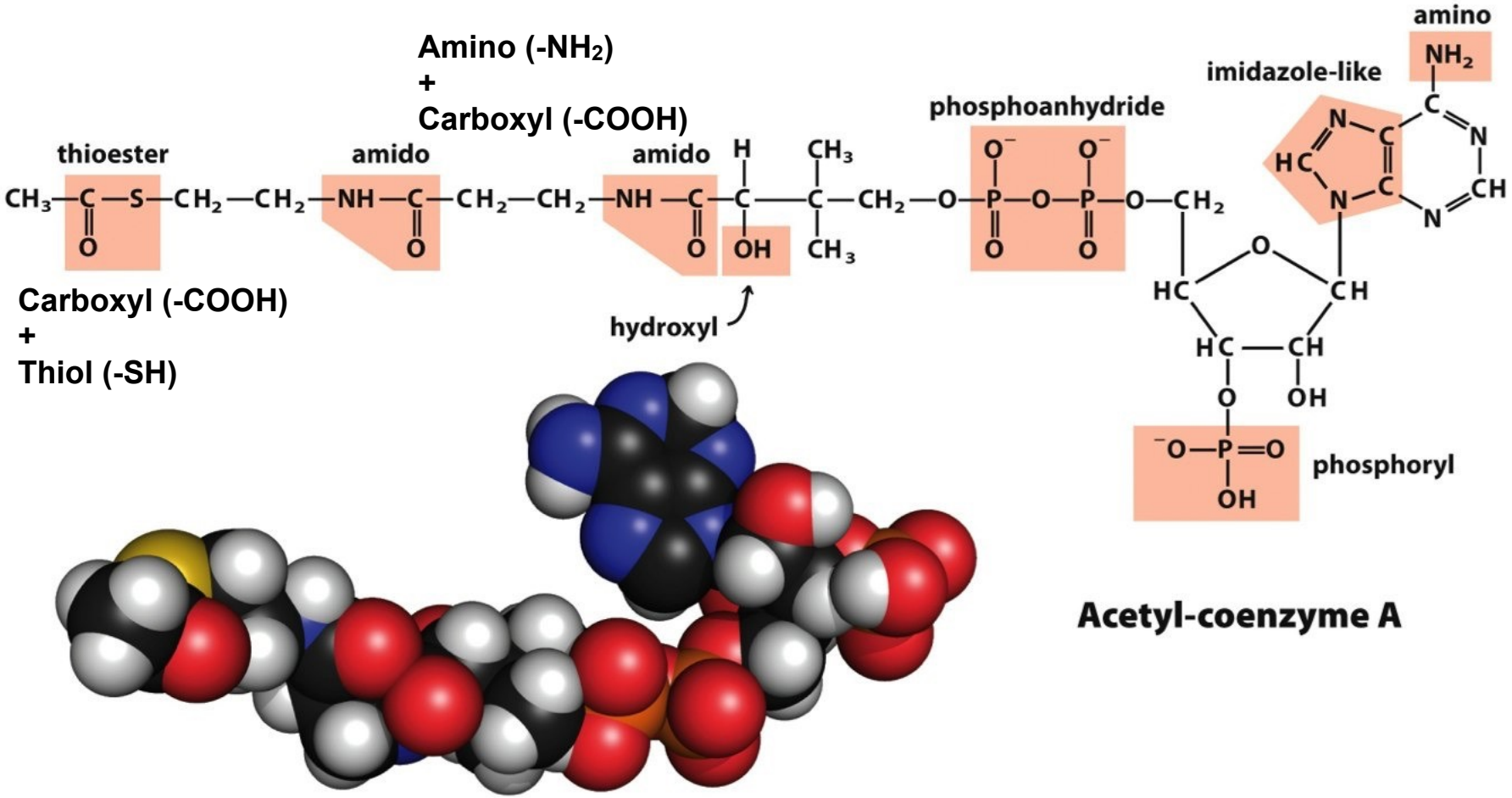


$^{\bullet}C\equiv N$	Name	Toxicity	Example
Inorganic	Cyanide ion	Highly toxic	NaCN, KCN
Organic	Cyano group	Less toxic	CH_3CN

Common Functional Groups of Biological Molecules



Biological molecules typically have several functional groups



Methamphetamine

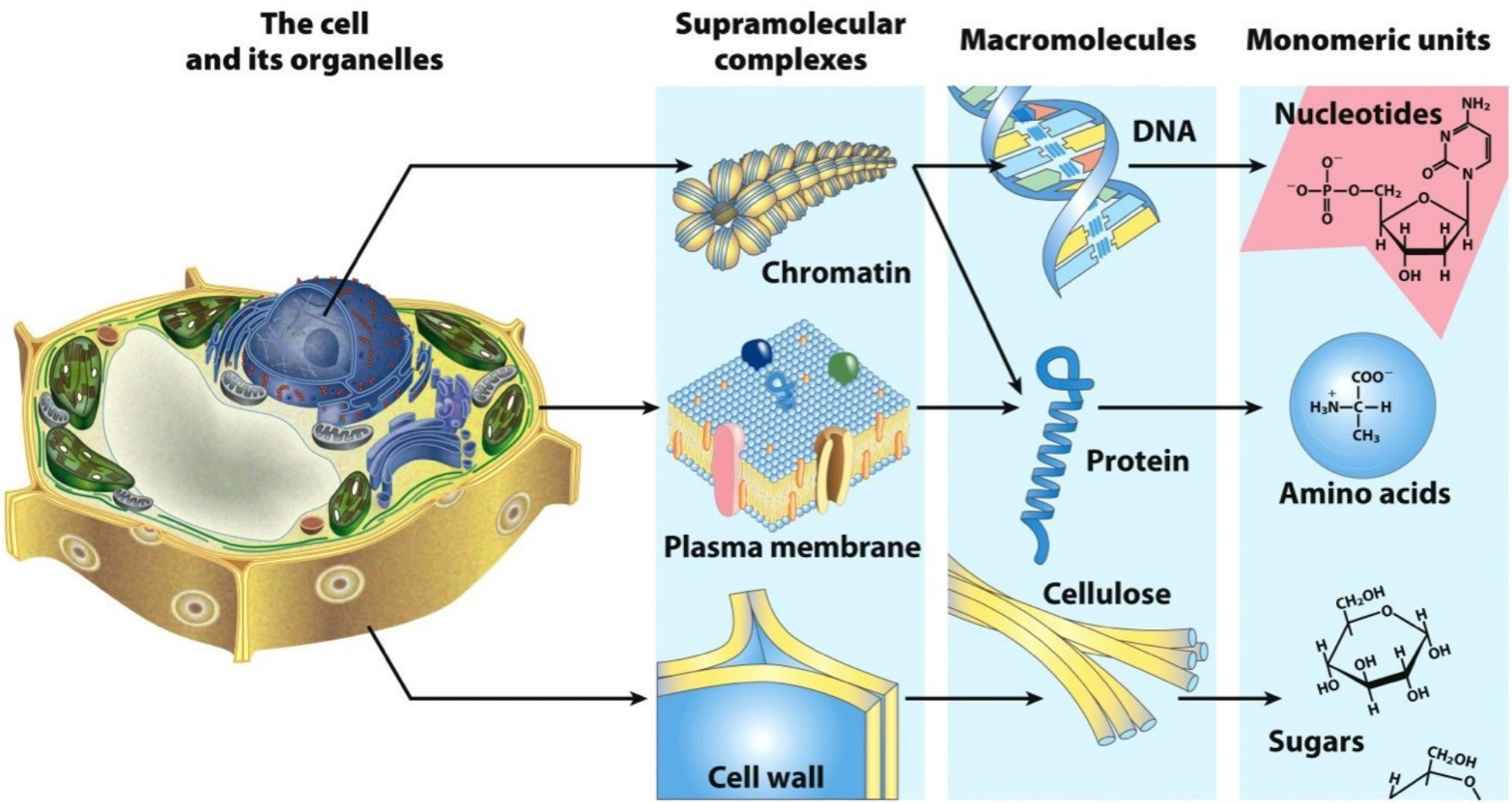
Ethylamine

Phenethylamine

Alpha-methylphenethylamine
Amphetamine

N-methyl-alpha-methylphenethylamine
Methamphetamine, meth, crystal meth

The Molecular Hierarchy of Structure



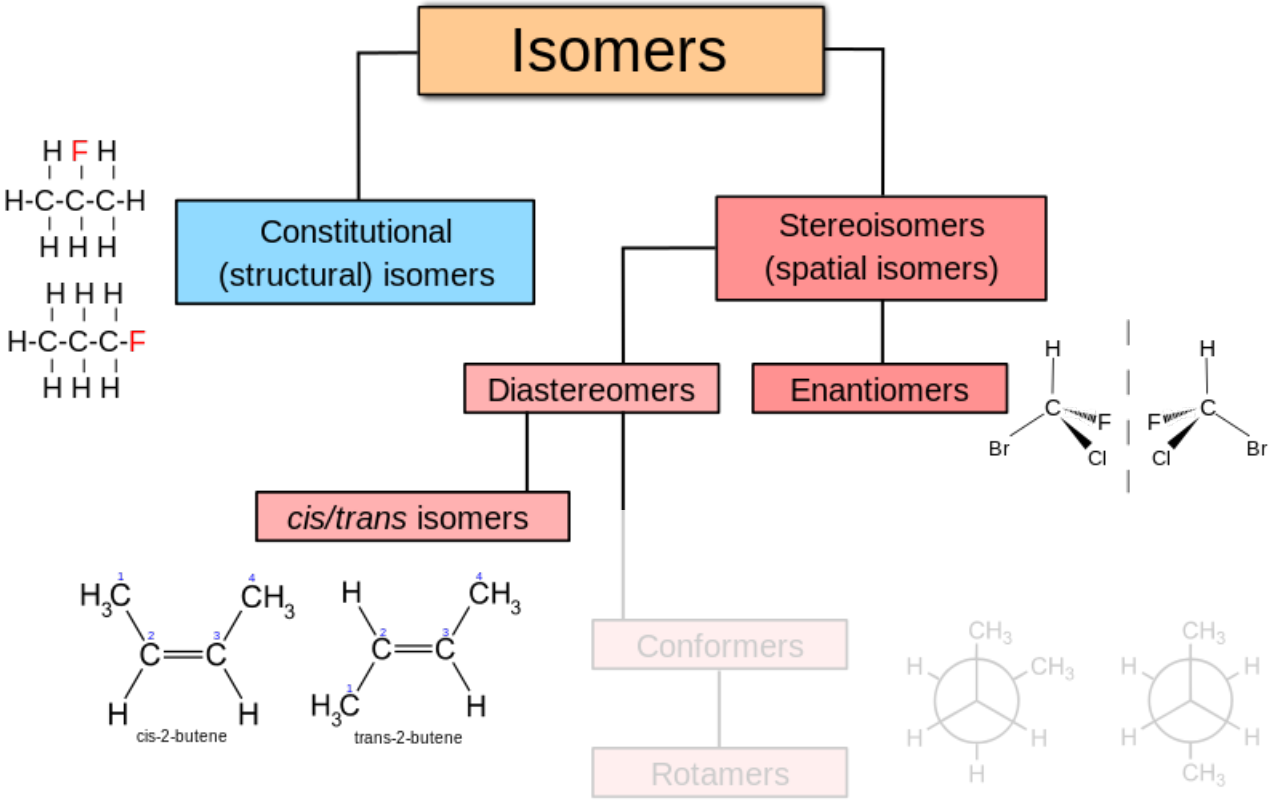
Macromolecules are made of basic monomeric subunits

Macromolecules are major constituents

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

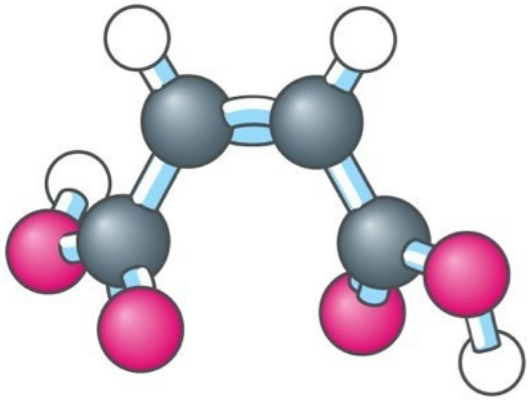
	Percentage of total weight of cell		Approximate number of different molecular species
Water	70	H, O	1
Proteins	15	C, H, O, N	3,000
Nucleic acids			
DNA	1	C, H, O, N, P	1–4
RNA	6		>3,000
Polysaccharides	3	C, H, O	10
Lipids	2	C, H, O	20
Monomeric subunits and intermediates	2		500
Inorganic ions	1		20

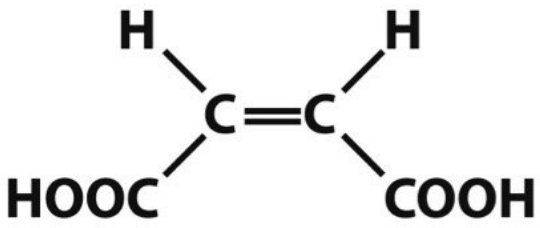
The function of molecules strongly depends on three-dimensional structure



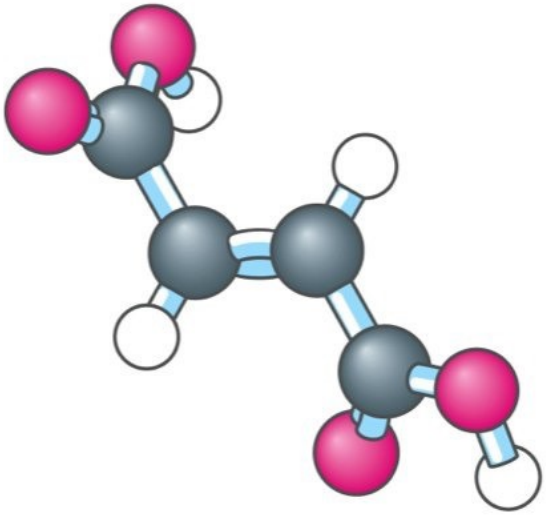
- Enantiomers (mirror images)
- Diastereomers (not mirror images)
  - Geometric Isomers (cis vs. trans)

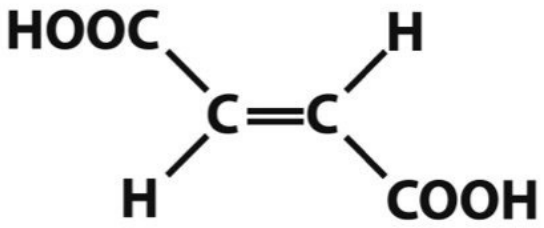
Cis vs. Trans (geometric isomers)





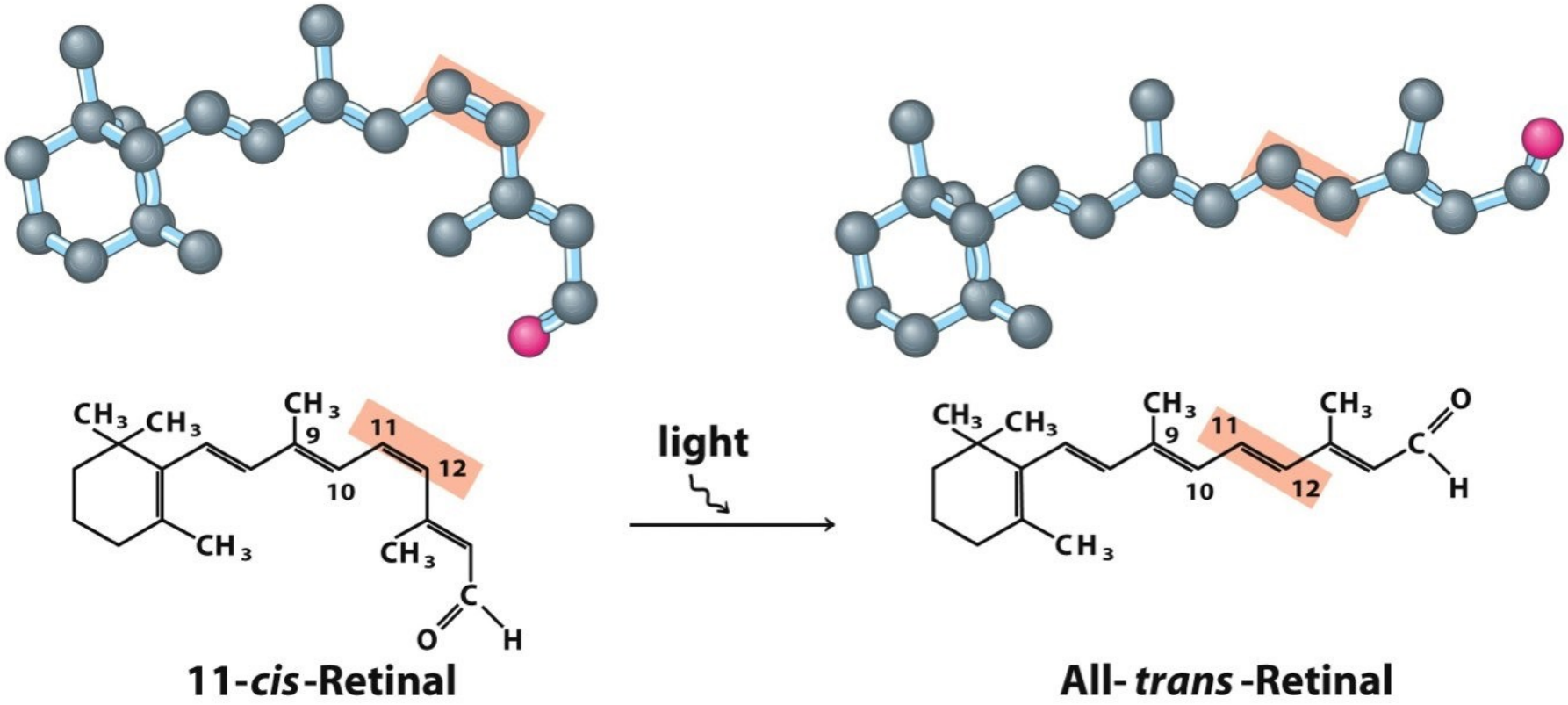
Maleic acid (cis)



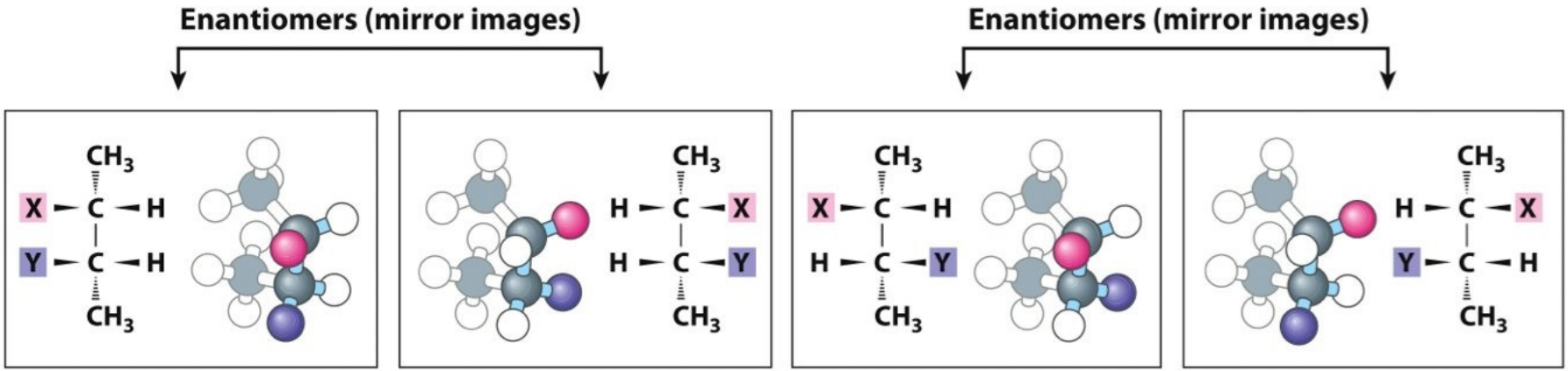


Fumaric acid (trans)

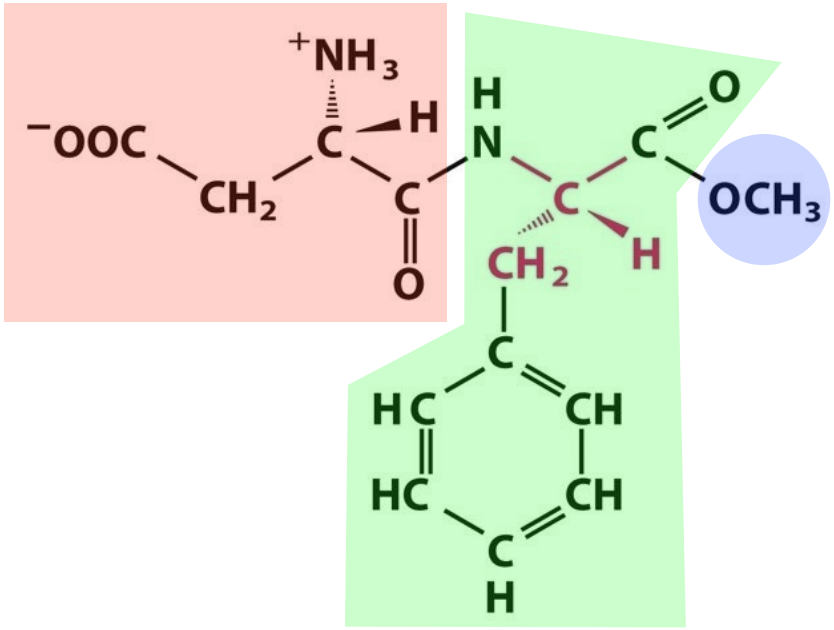
Cis vs. Trans (geometric isomers)



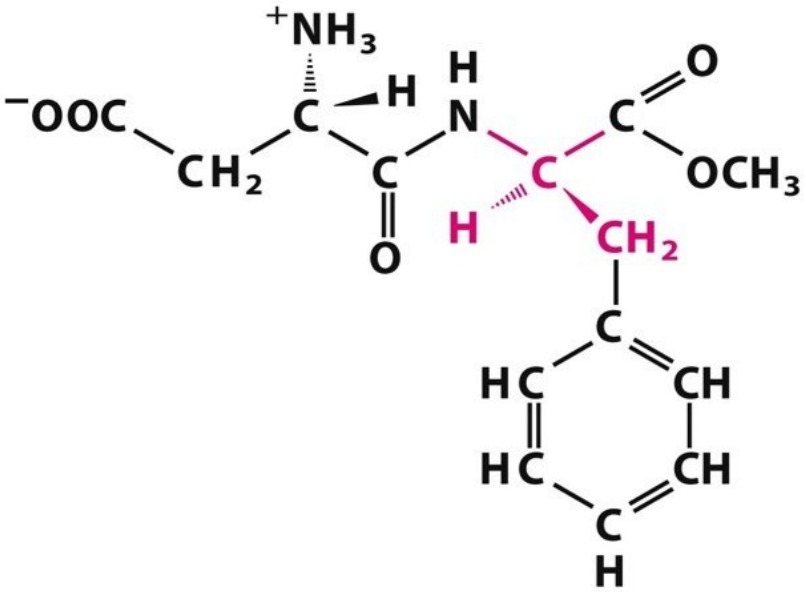
Enantiomers and Diastereomers



Enantiomers and Diastereomers



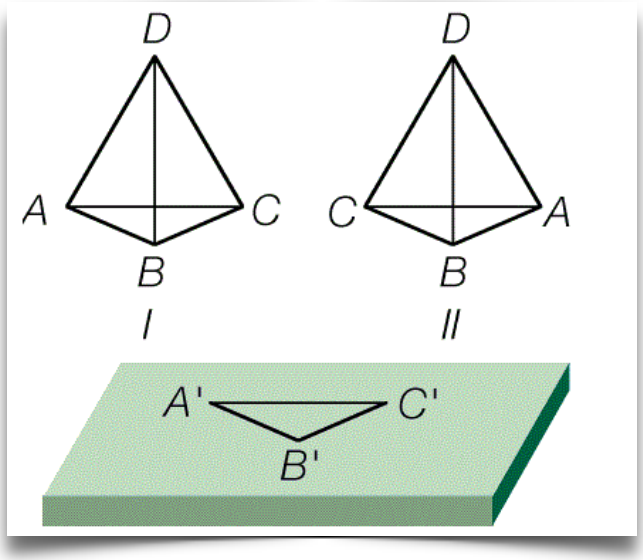
L-Aspartyl-L-phenylalanine methyl ester (aspartame) (sweet)



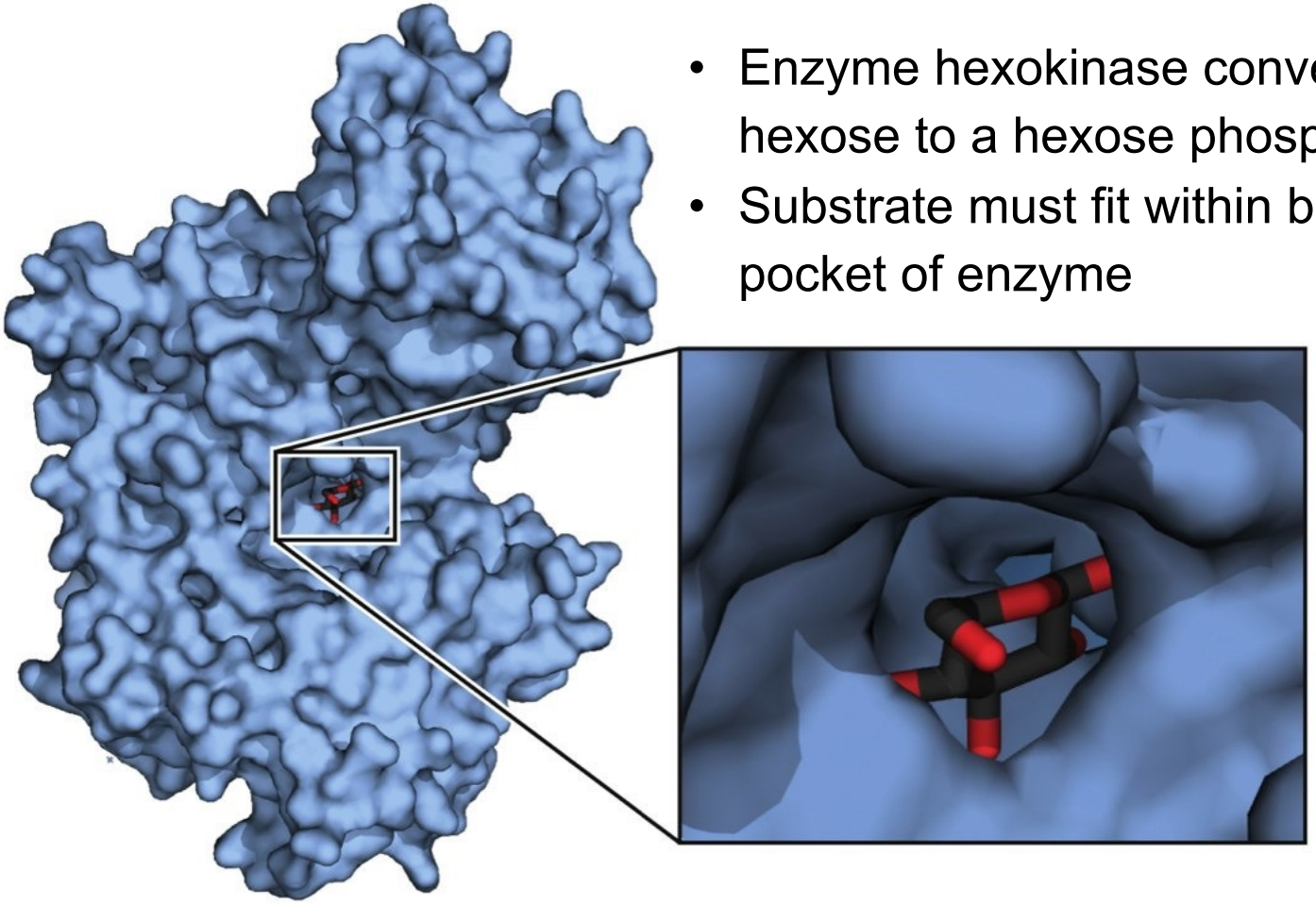
L-Aspartyl-D-phenylalanine methyl ester (bitter)

Interactions between biomolecules are specific

- Macromolecules have unique binding pockets
- Only certain molecules fit in well and can bind
- Binding of chiral biomolecules is stereospecific



Interactions between biomolecules are specific



- Enzyme hexokinase converts a hexose to a hexose phosphate
- Substrate must fit within binding pocket of enzyme

Chemical Foundations Summary

- Carbon-based life on Earth. Carbon is able to bond with hydrogen, oxygen, nitrogen and carbon itself
- Proteins and nucleic acids, linear polymers of simple monomeric subunits, are informational macromolecules
- Biological interactions are stereospecific

Foundations of Biochemistry

Cellular foundations

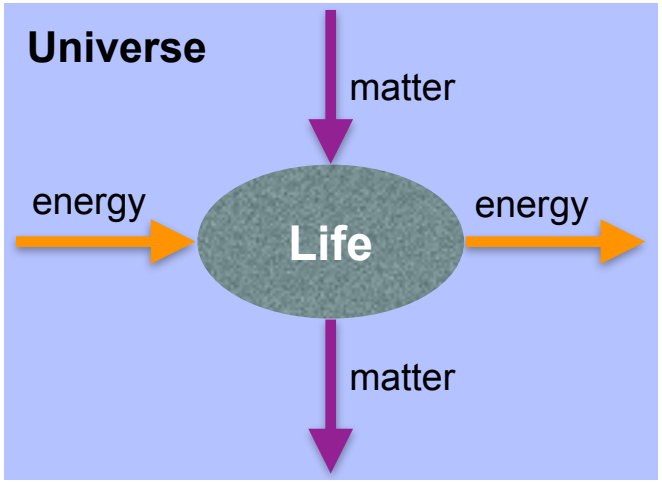
Chemical foundations

Physical foundations

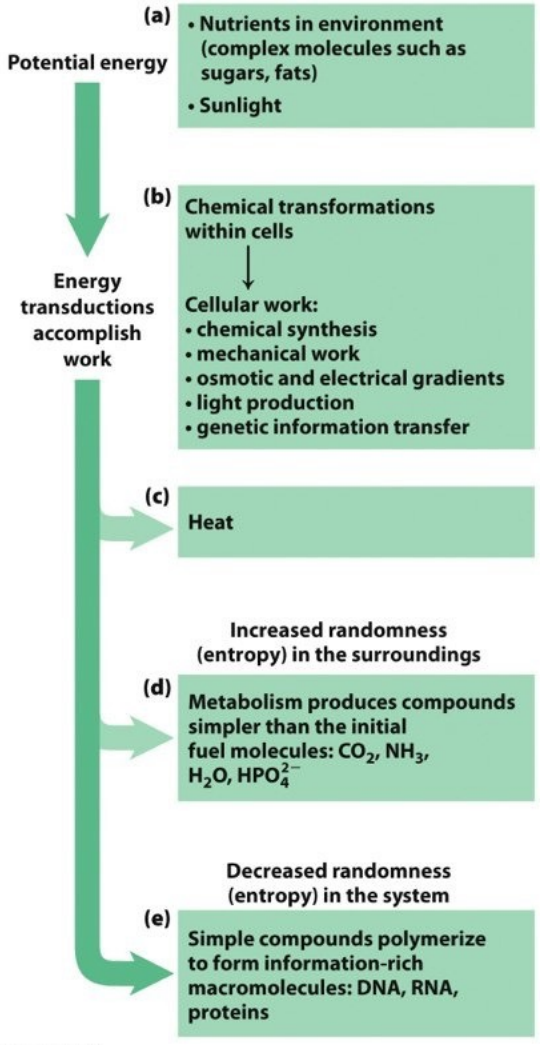
Genetic and evolutionary foundations

Lives exist in a dynamic steady state

- Different from surrounding
  - Kind and concentration
- Dynamic
  - Continuously synthesized and broken down
- Universe and system
  - Life is an open system (exchange energy and matter)
- First law of thermodynamics
  - Amount of energy remains constant, although form of energy may change



Organisms perform energy transductions to accomplish work to stay alive



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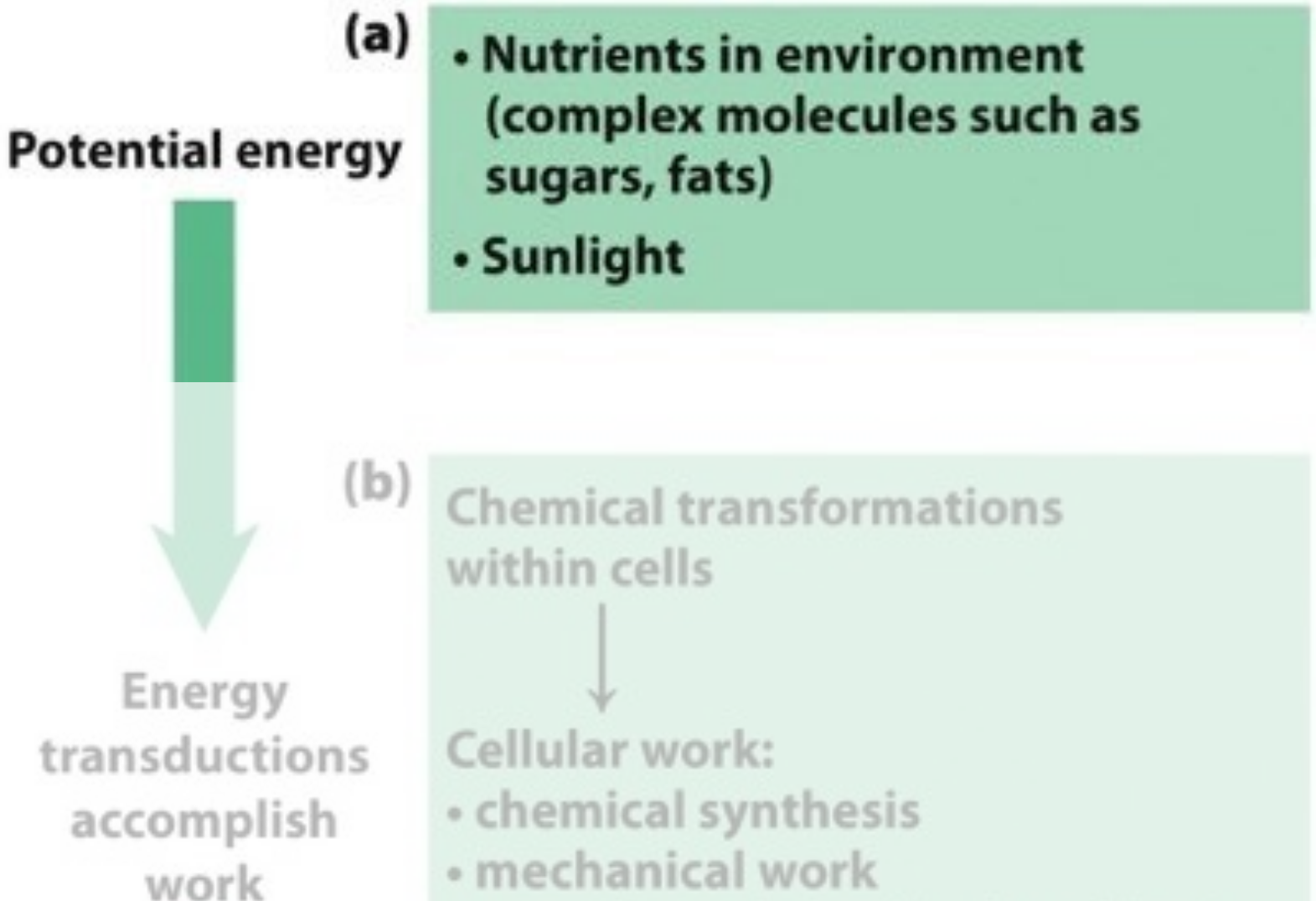

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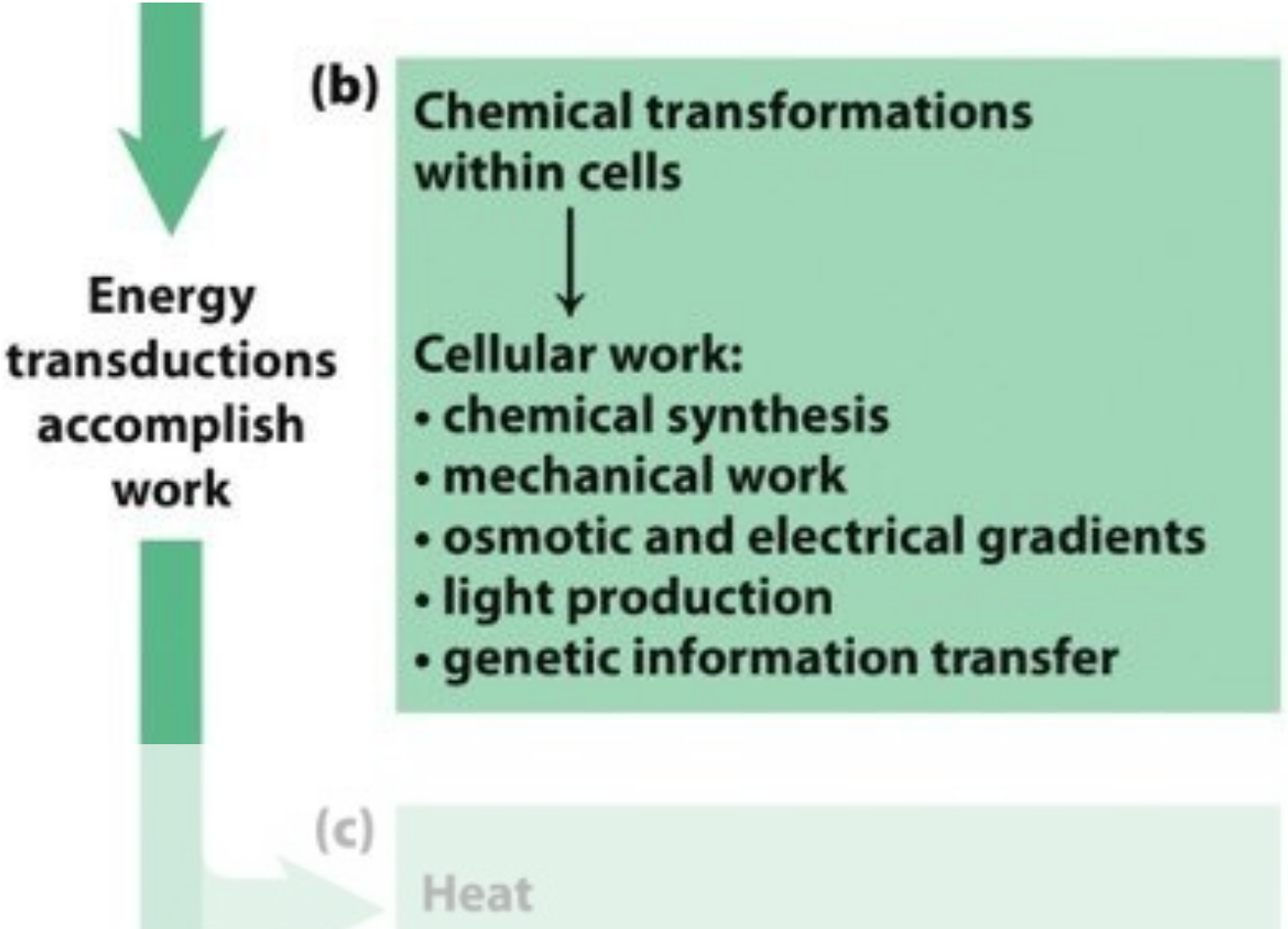

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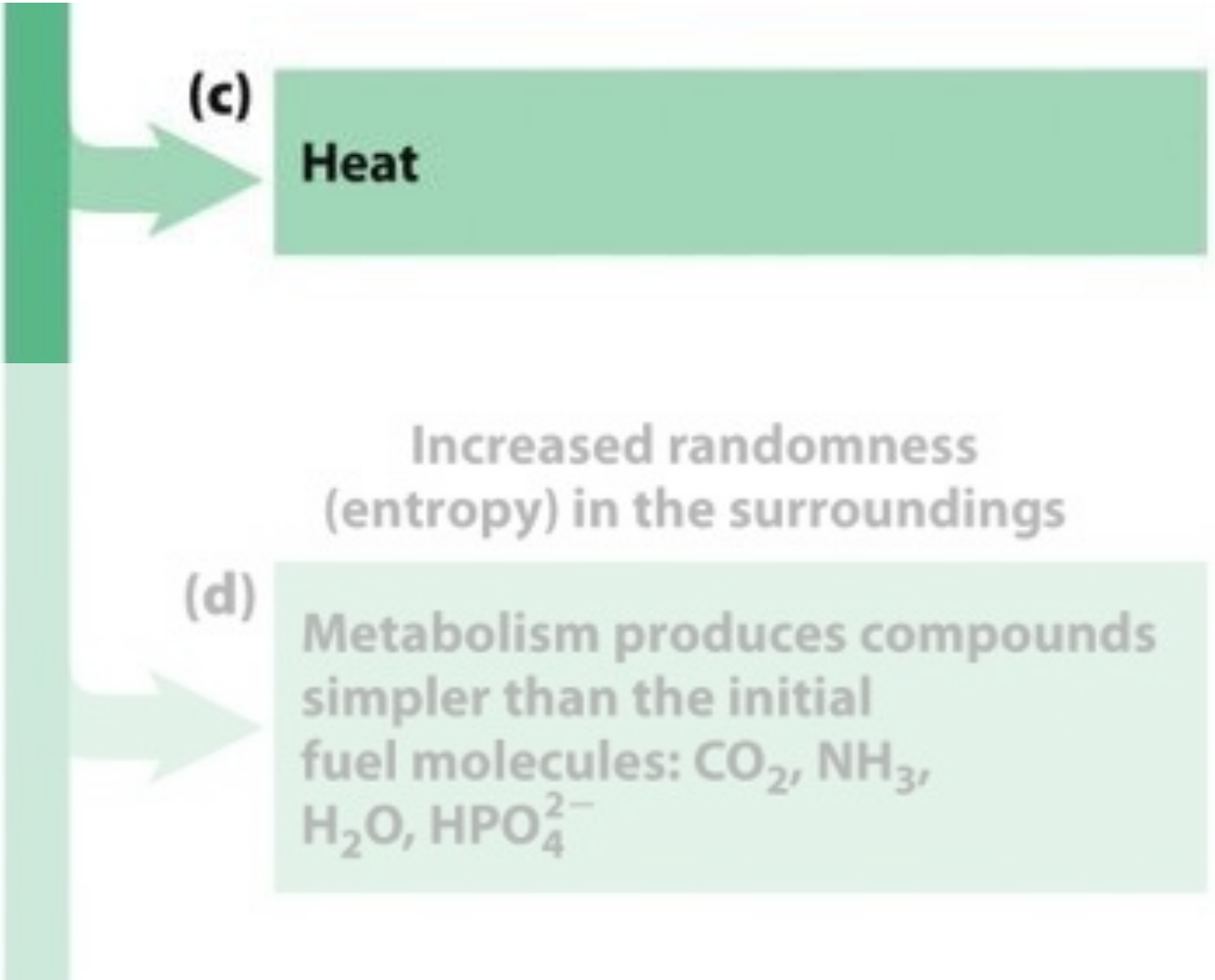

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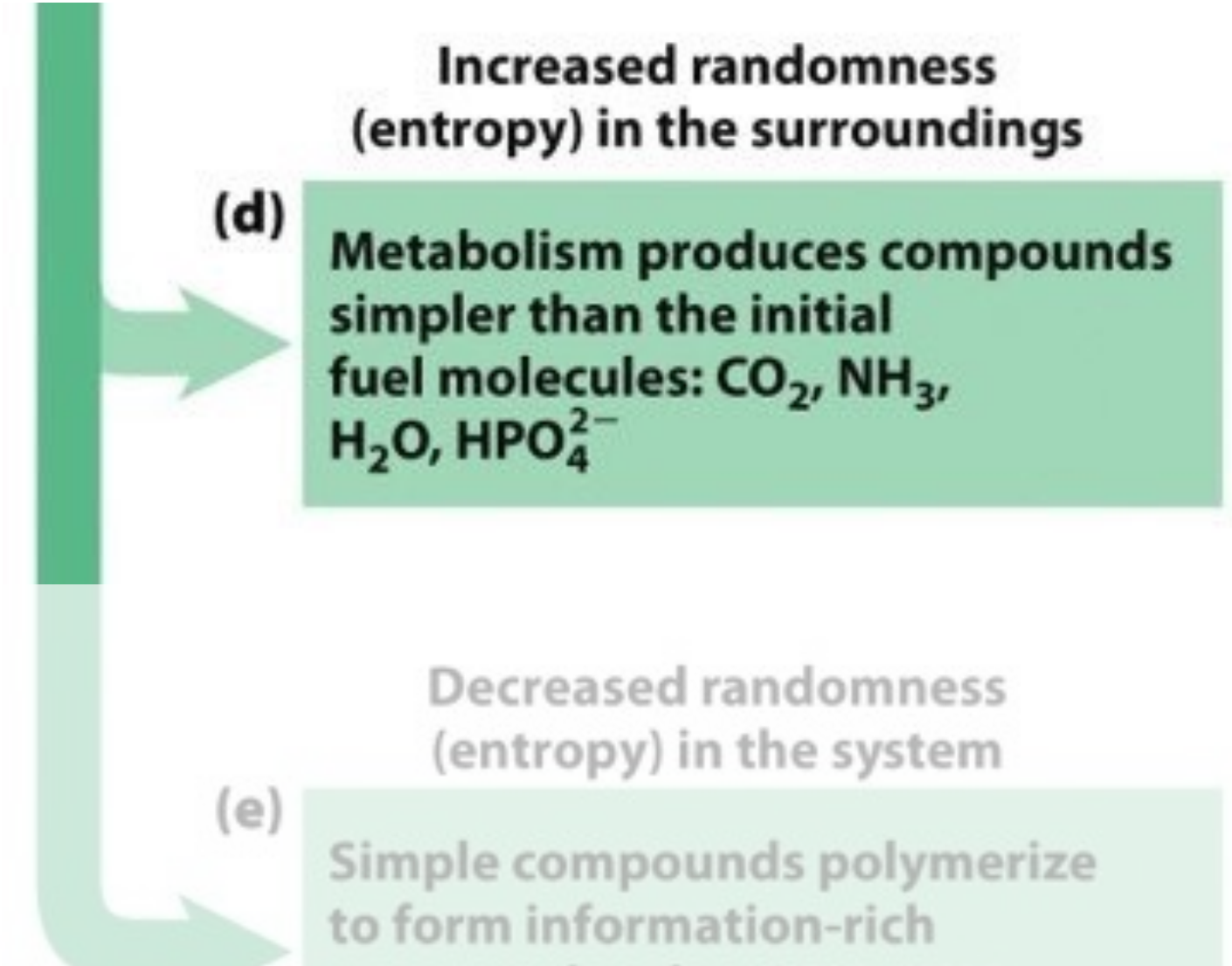
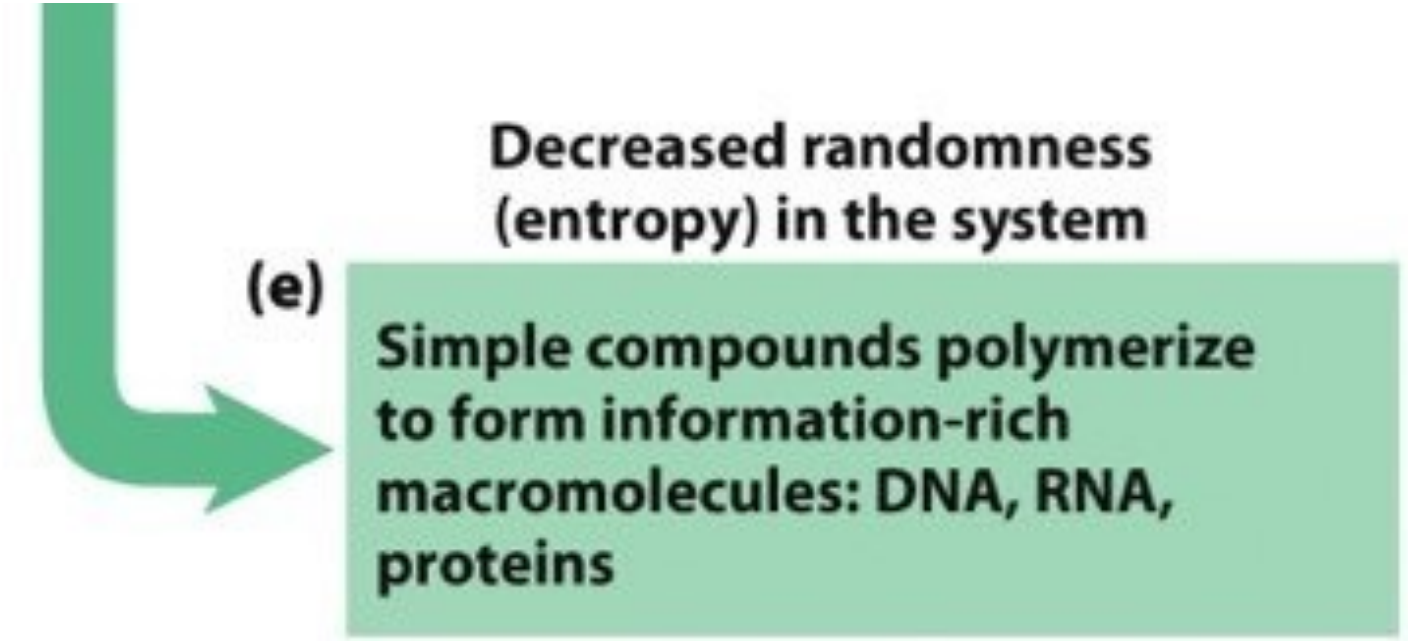
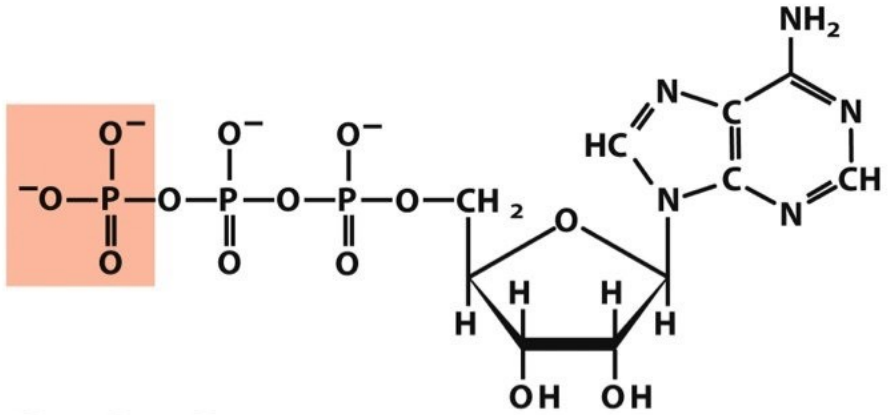


Organisms perform energy transductions to accomplish work to stay alive



ATP: Chemical Currency of Energy



How to speed reactions up

Higher temperatures

- Stability of macromolecules is limiting

Higher concentration of reactants

- Costly as more valuable starting material is needed

Change the reaction by coupling to a fast one

- Universally used by living organisms

Lower activation barrier by catalysis

- Universally used by living organisms

How to speed reactions up

Higher temperatures

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Change the reaction by coupling to a fast one

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Lower activation barrier by catalysis

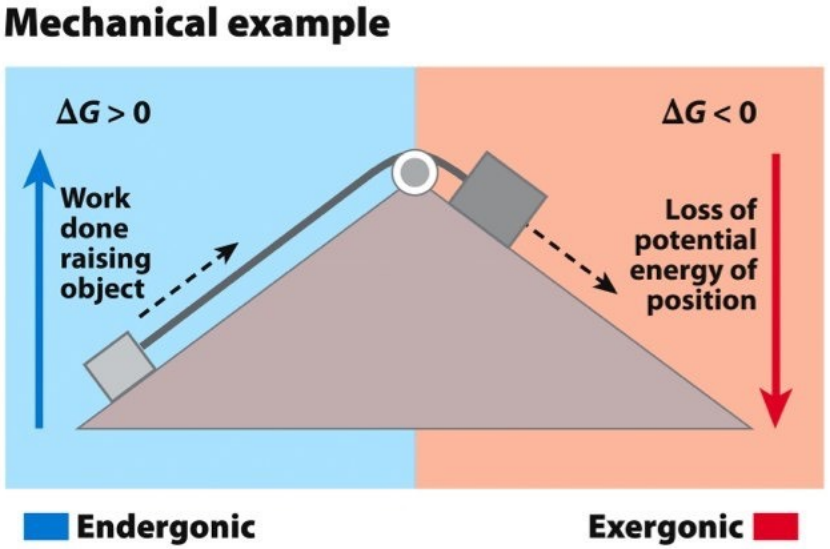
- Universally used by living organisms

Unfavorable and Favorable Reactions

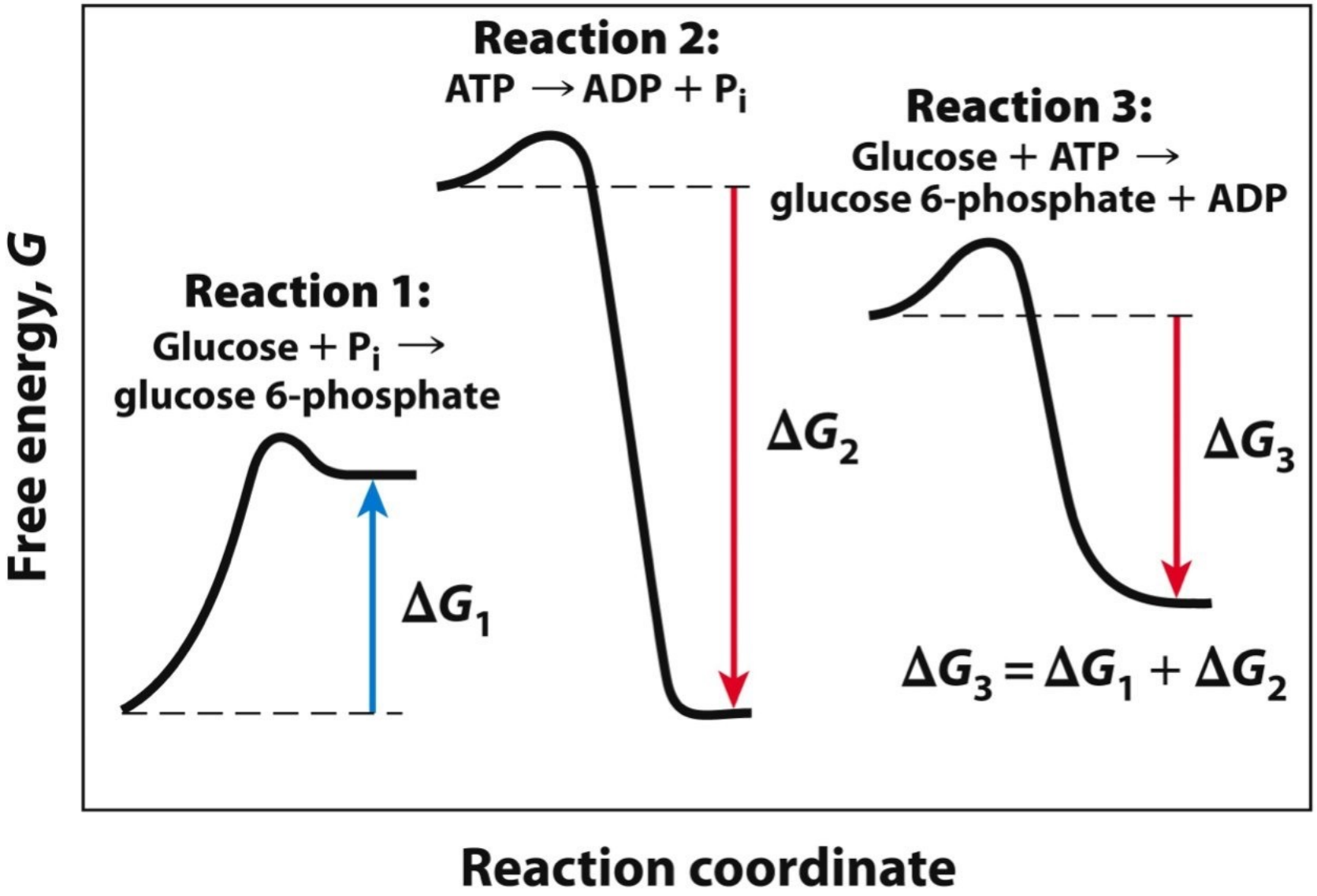
- Synthesis of complex molecules and many other metabolic reactions requires energy (endergonic)
  - A reaction might be thermodynamically unfavorable ($\Delta G° > 0$)
    - Creating order requires work and energy
  - Metabolic reaction might have too high energy barrier ($\Delta G^{‡} > 0$)
    - Metabolite is kinetically stable
- Breakdown of some metabolites releases significant amount of energy (exergonic)
  - Such metabolites (ATP, NADH, NADPH) can be synthesized using the energy from sunlight and fuels
  - Their cellular concentration is far higher than their equilibrium concentration

Energy Coupling

- Chemical coupling of exergonic and endergonic reactions allows otherwise unfavorable reactions
- The “high-energy” molecule (ATP) reacts directly with the metabolite that needs “activation”

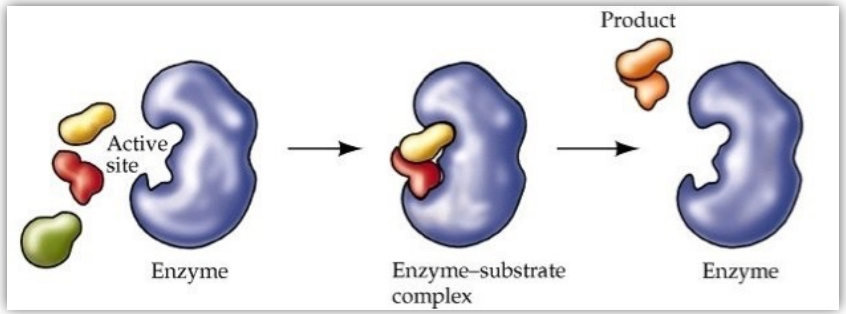


Chemical example



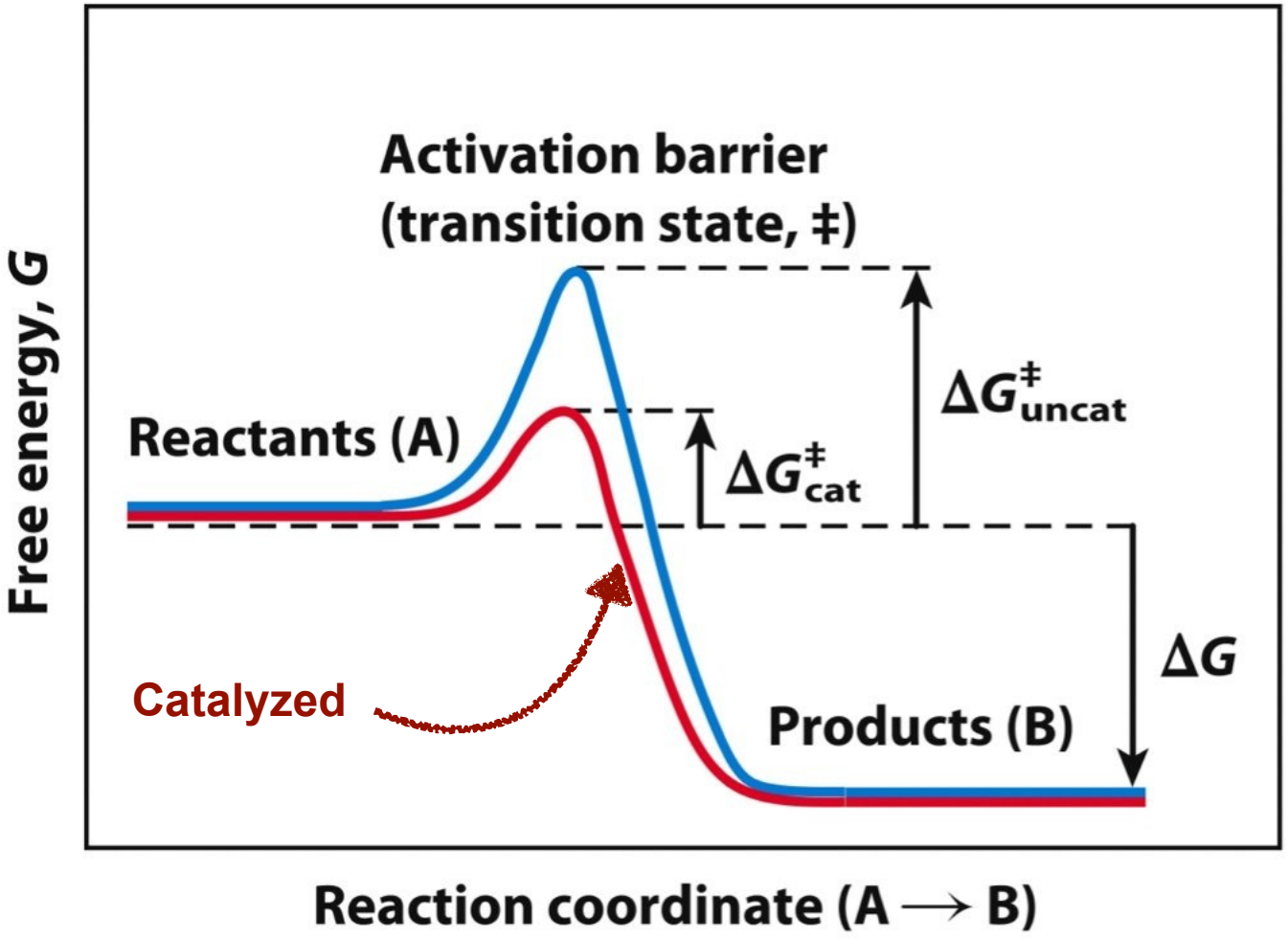
Catalysis

- A catalyst is a compound that increases the rate of a chemical reaction
- Catalysts lower the activation free energy $\Delta G^{\ddagger}$
- Catalysts do not alter $\Delta G°$
- Enzymatic catalysis offers:
  - acceleration under mild conditions
  - high specificity
  - possibility for regulation



Enzymes make reactions proceed on a biologically useful time scale

Enzymes lower the activation energy to increase the reaction rate

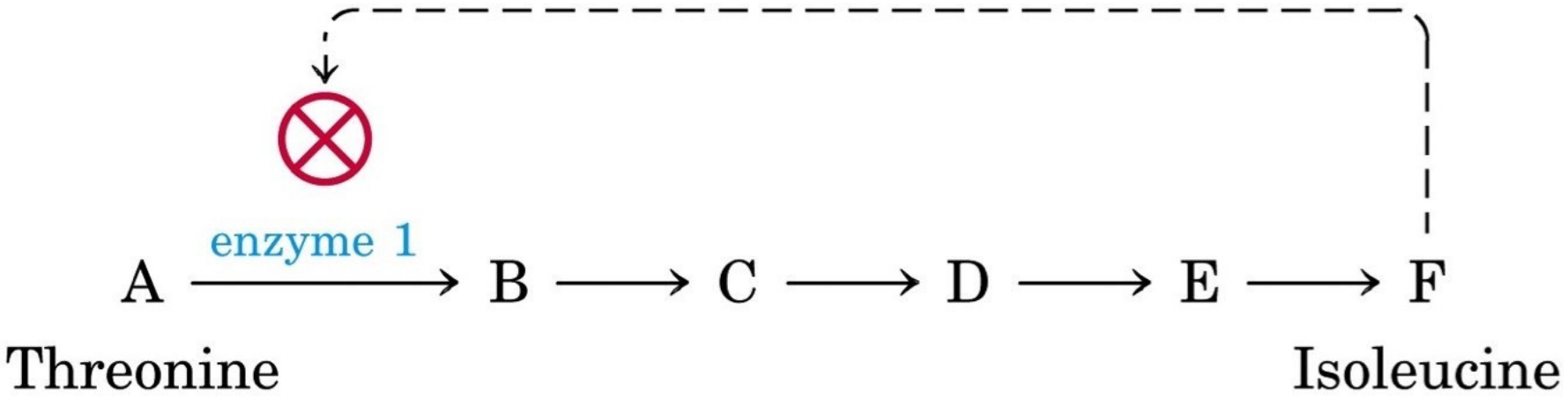


Series of related enzymatically catalyzed reactions forms a pathway

- Metabolic Pathway
  - produces energy or valuable materials

- Signal Transduction Pathway
  - transmits information

Pathways are controlled in order to regulate levels of metabolites



- Example of a negative regulation:
  - Product of enzyme 5 inhibits enzyme 1

Physical Foundations Summary

- Living cells are open systems, and maintain at a dynamic steady state far from equilibrium
- Many endergonic biochemical reactions are coupled to highly exergonic ATP hydrolysis
- Most cellular reactions proceed at useful rates only because enzymes are present to catalyze them

Foundations of Biochemistry

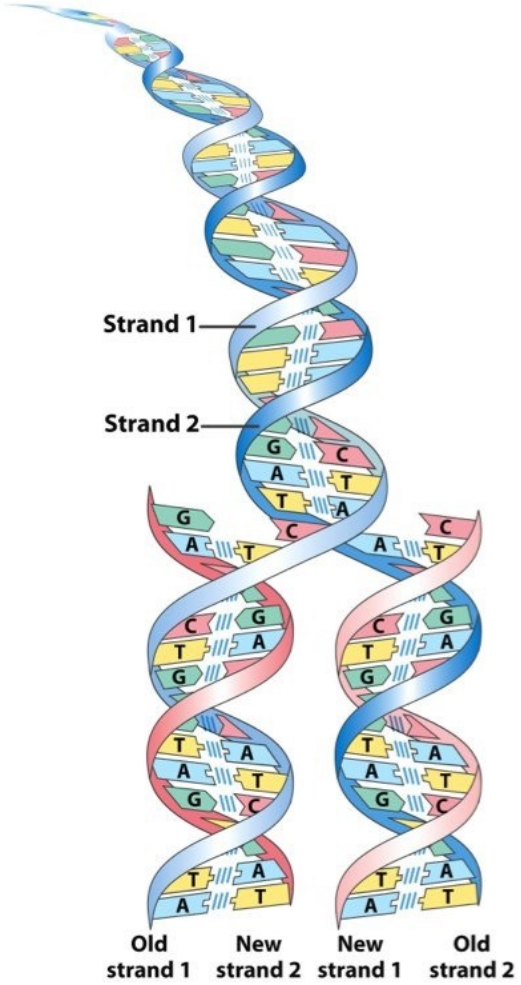
Cellular foundations

Chemical foundations

Physical foundations

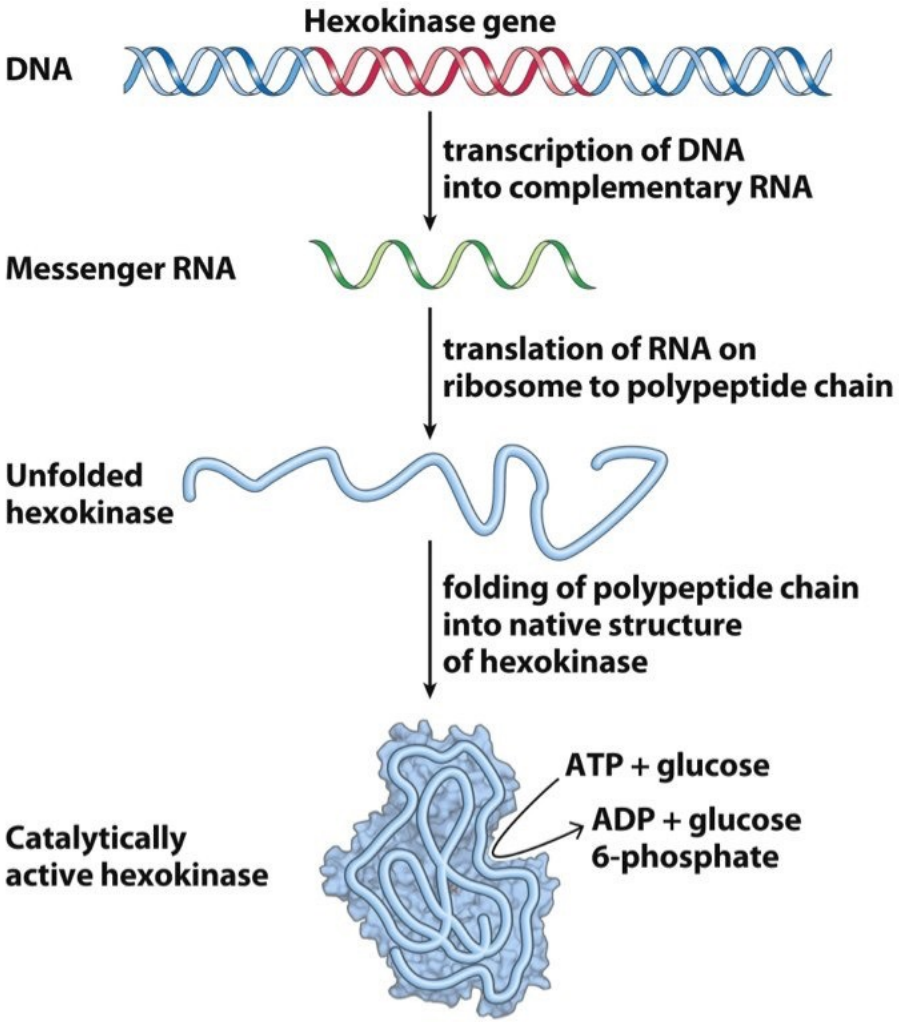
Genetic and evolutionary foundations

Complementarity in DNA allows for replication with near-perfect fidelity



The Central Dogma of Molecular Biology:

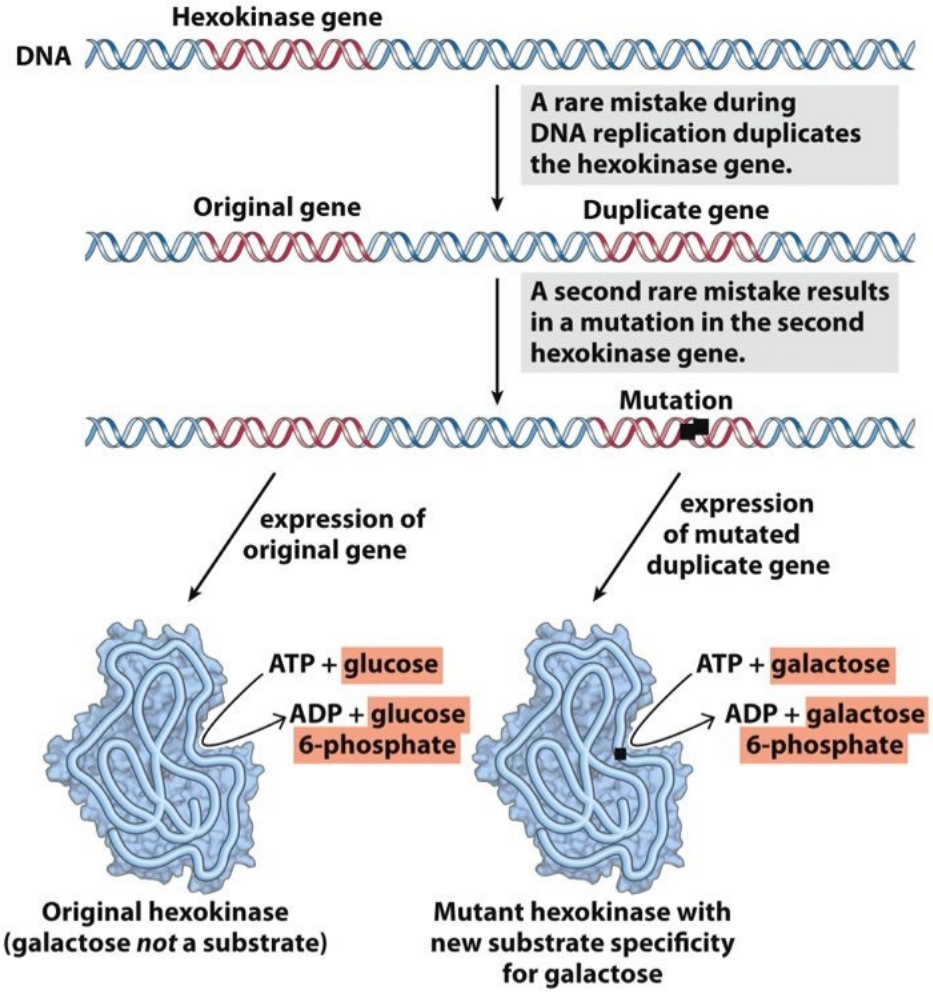
DNA → RNA → Protein



Natural selection favors some mutations

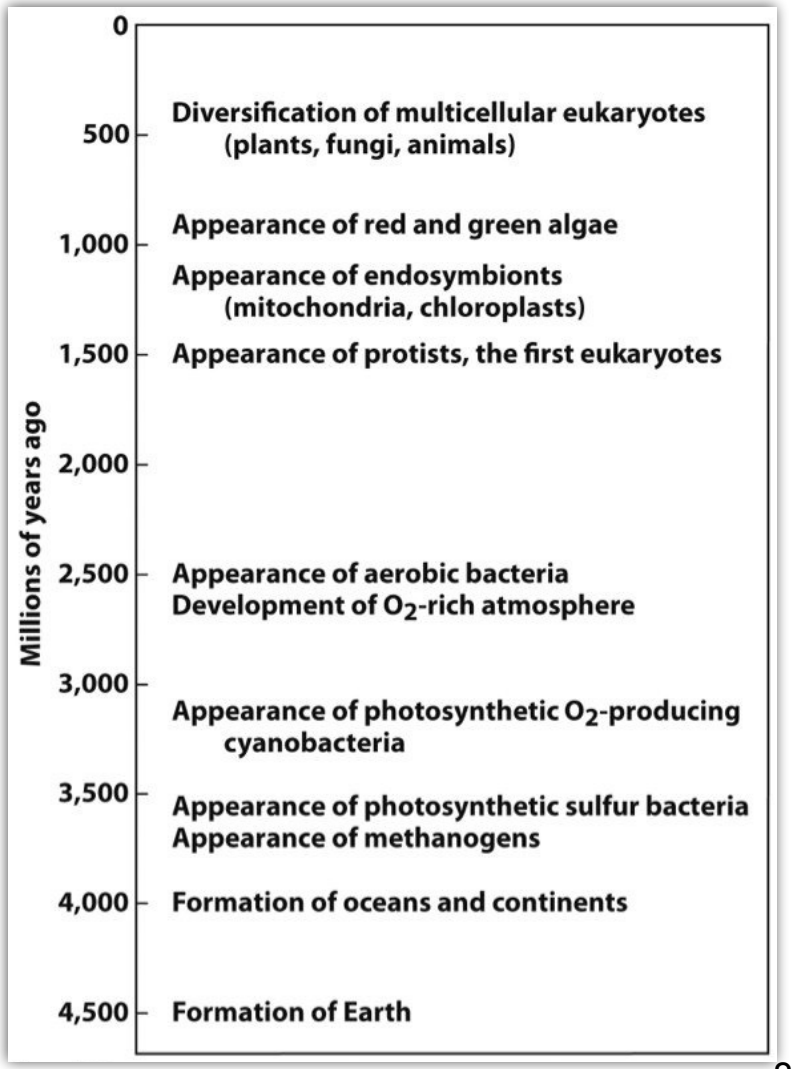
- Mutations occur more or less randomly
  - Balance between too many (below sustainability threshold) and too few (generate enough genetic variations)
- Mutations that give organisms an advantage in a given environment are more likely to be propagated
  - Natural selection (survival of the fittest)

Natural selection favors some mutations



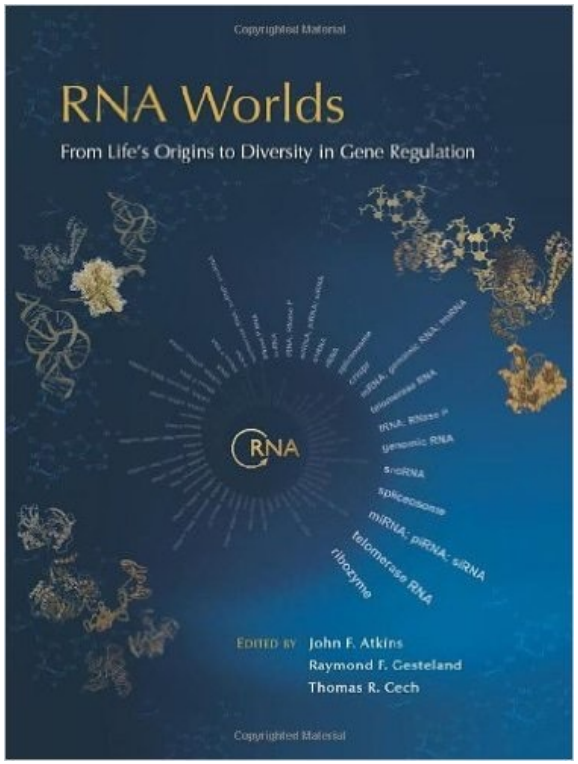
Genetic and Evolutionary Foundations

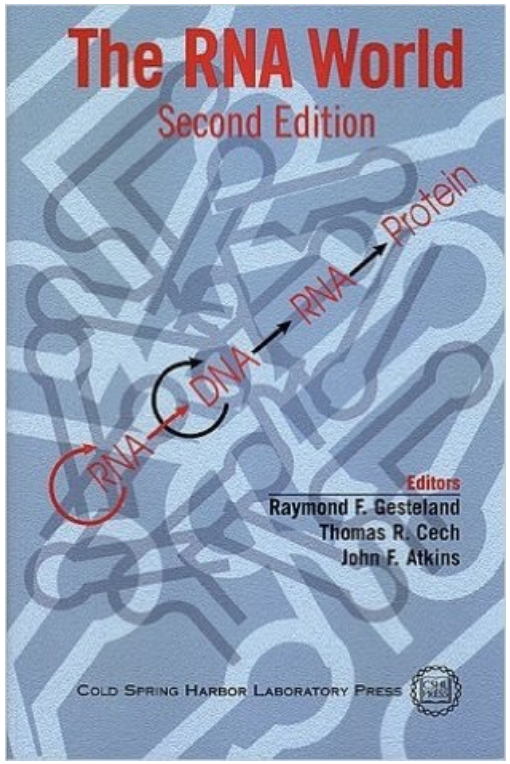
- Life on Earth arose 3.5-3.8 billion years ago.
- Formation of self-replicating molecules
- Could it be DNA?
- Could it be protein?

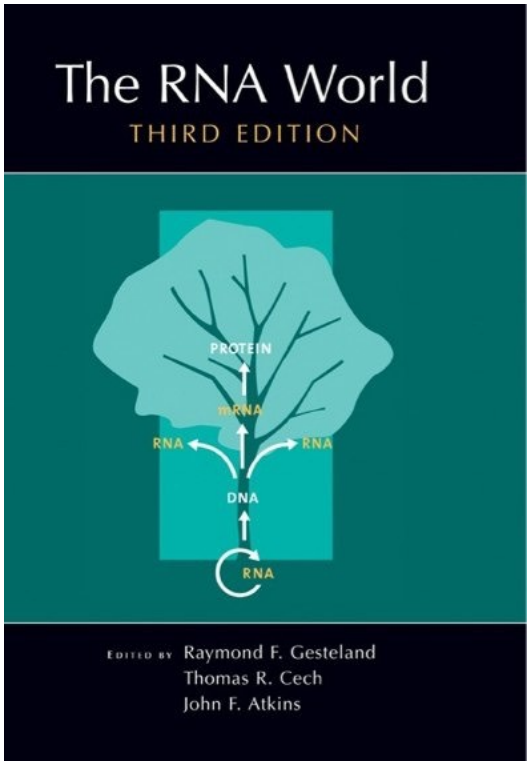


RNA World?

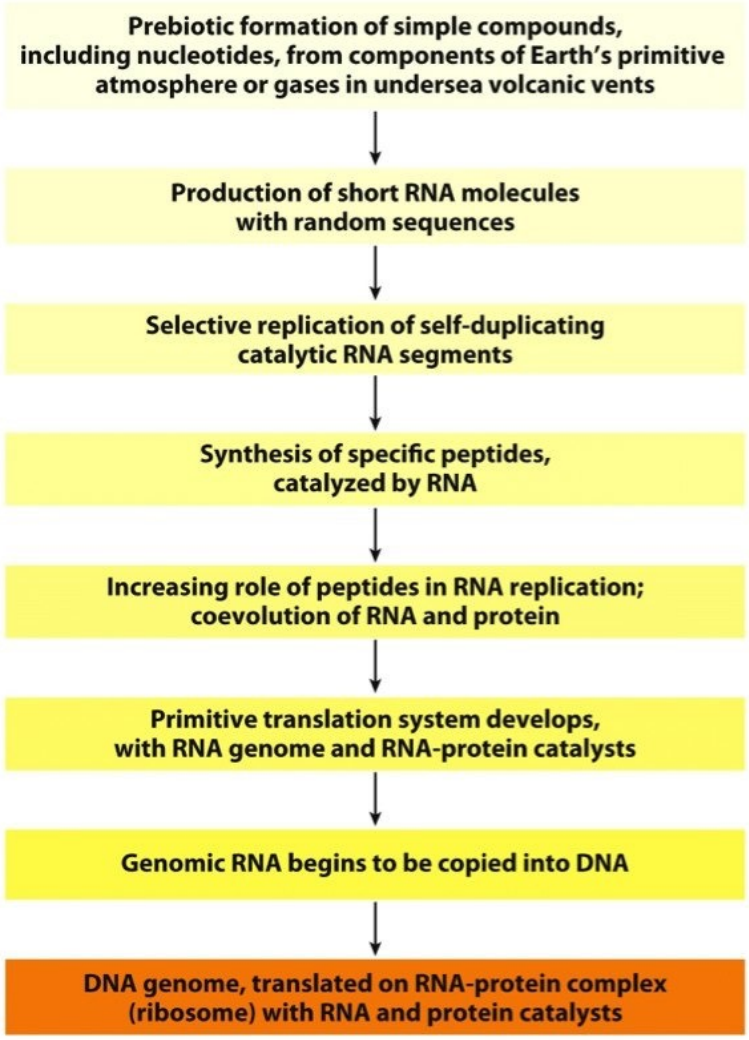
RNA can act both as the information carrier and biocatalyst







A possible RNA World scenario



Genetic & Evolutionary Foundations Summary

- Central dogma of molecular biology. Genetic information flows from DNA to RNA, and from RNA to protein
- Darwinian evolution. Random mutations lead to survival in an ecological condition
- Genetic and catalytic roles, possibly played by RNA, were taken over by DNA and proteins, respectively

Chapter 1: Summary

In this chapter, we learned:

- To understand what defines living organisms
- To relate structure and function of the cell
- To realize that the structure of biomolecules often gives them specific functions
- To grasp principles of bioenergetics
- To review the forces behind evolution