生物学导论

钟伟民

耶鲁大学
分子、细胞和发育生物学系

How to Investigate Life?

Imagination (creativity) is important for both scientists and artists,
but there are fundamental differences in how they imagine …

Biology: The Study of Living Things

- Are made up of a common set of chemical components
- Consist of one or more cells
- Contain genetic information
- Use genetic information to reproduce themselves
- Are genetically related and have evolved
- Can convert molecules obtained from their environment into new biological molecules
- Can extract energy from the environment and use it to do biological work
- Can regulate their environment

The cell theory: all life consists of cell, the basic unit of life,
and all cells come from preexisting cells

The theory of evolution: all living organisms are related to one another
through decent, and evolution by natural selection
is responsible for the diversity of adaptations found in living organisms

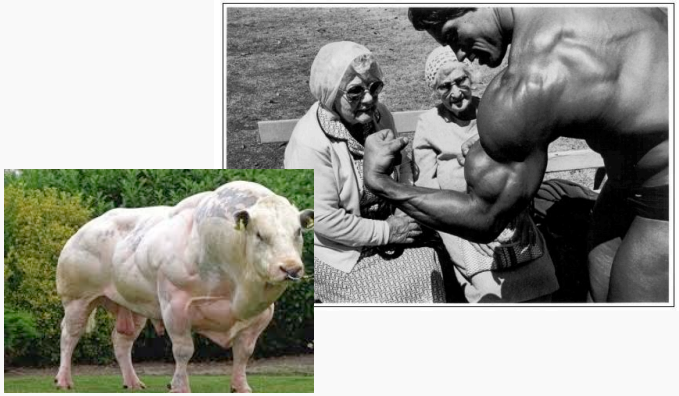
The Definition of Life

Viruses are infectious agents with genetic material (DNA or RNA)
& replicate by hijacking host cellular components

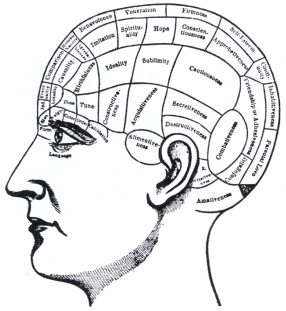
Prions are infectious proteins (no DNA or RNA)
& propagate by transmitting a mis-folded protein state
(inducing pre-existing normal forms into the rogue form)

How about viruses (病毒) and prions (朊病毒)?
(neither can propagate on their own)

How Does Our Brain Work?



How Does Our Brain Work?



Phrenology:
bumps on the head
Aggregated Field:
any part of the cortex can function
Distributed Processing:
one processing center to another

The cerebral cortex (the thin outer layer of the cerebral hemisphere) is concerned with cognitive functioning

Learning & Memory: The Case of H.M.

(the most important patient in the history of brain science)

Henry Gustav Molaison

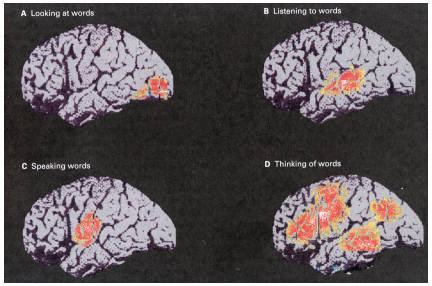
Part of his brain, including the hippocampus, was surgically removed in 1953 to treat seizures

For the next 55 years, each time he met a friend, each time he ate a meal, each time he walked in the woods, it was as if for the first time

We have two memory systems, declarative memory and motor learning, and they are handled by different parts of the brain

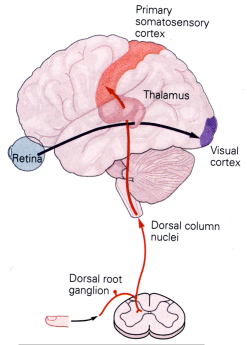
His identity was revealed only after his death on Dec. 2, 2008 at the age of 82 (it is essential to respect a subject's privacy when conducting research)

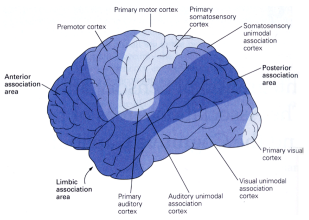
Regionalization of the Neocortex



Functional MRI
（功能性核磁成像）

Organization of the Nervous System





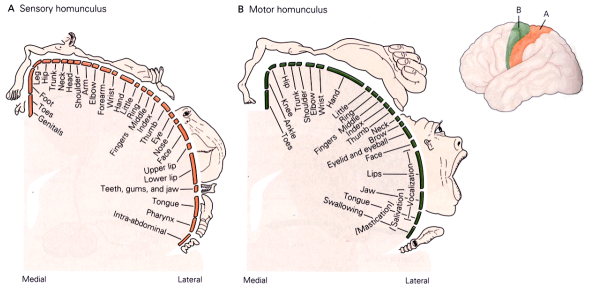
Topographical Map

Each part of the brain projects in an orderly fashion onto the next

Distributed Processing

Information passes serially from one processing center to another

Regionalization of the Neocortex



Topographical Map

“心想事成”

（结合生物学、工程学、计算机学以及数学和物理的知识）

BrainGate Pilot Clinical Trial
Drinking From a Bottle Using a Robotic Arm
Participant S3
Trial Day 1959 / 12 April 2011
Hochberg *et al.*, 2012

Caution: Investigational Device. Limited by Federal Law to Investigational Use.

LR Hochberg et al. *Nature* 485, 372-375 (2012)

How to Investigate Life?

Observe and speculate

Form hypothesis and make a prediction
(what else would be true if correct)

Design and conduct an experiment
(quantifiable data)

Analyze and interpret data
(statistical methods and alternative interpretations)

Ask new questions, re-examine the experiment, or revise hypothesis

一个好的实验也会证明假说是错的!

The Origin of Life

Is there a life force?

Disproving the idea of spontaneous generation of life
(or at least some simple forms of life)

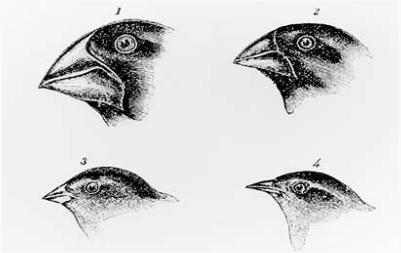
Francesco Redi: rotten meat and flies (17th century)

Louis Pasteur: microorganisms (19th century)

Life is not being generated from inanimate matter constantly
(at least life as we know it)

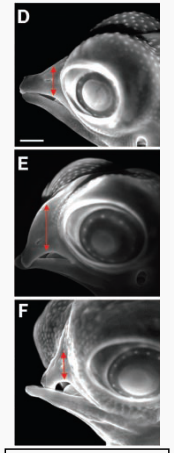
Genes, Development & Evolution Are Linked

Darwin's Finches



"Seeing this gradation and diversity of structure in one small, intimately related group of birds, one might really fancy that from an original paucity of birds in this archipelago, one species had been taken and modified for different ends…"

Charles Darwin (1845)



Abzhanov *et al*. (2004)
Science 305:1462-1465

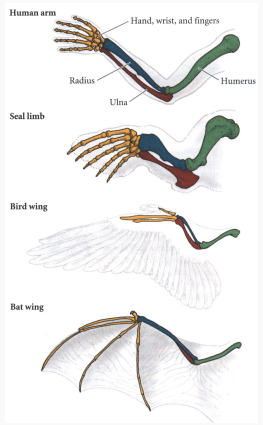
How Is All Life on Earth Related?

We share a common ancestor!

How Is All Life on Earth Related?

"Would it be too bold to imagine, that in the great length of time … before … mankind, that all warm-blooded animals have arisen from one living filament … possessing the faculty of continuing to improve by its own inherent activity, and of delivering down those improvements by generation to its posterity"

Erasmus Darwin, *Zoonomia* (1794)



How Is All Life on Earth Related?

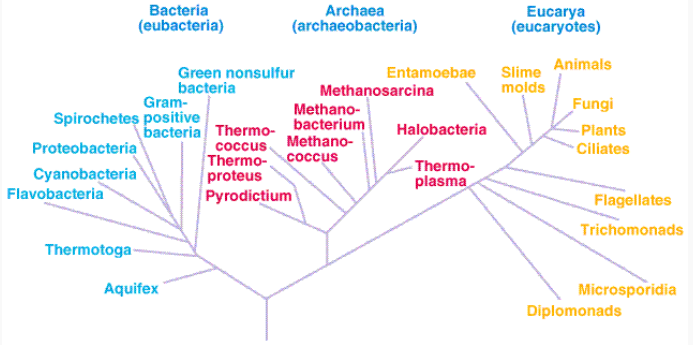
Phylogenetic tree (the tree of evolution) illustrates when populations split and evolved into new species and their relationships, using information based on:

- anatomical feature
- fossil record
- molecular evidence

Ribosomal RNAs (rRNAs) are particularly useful for evolutionary studies:

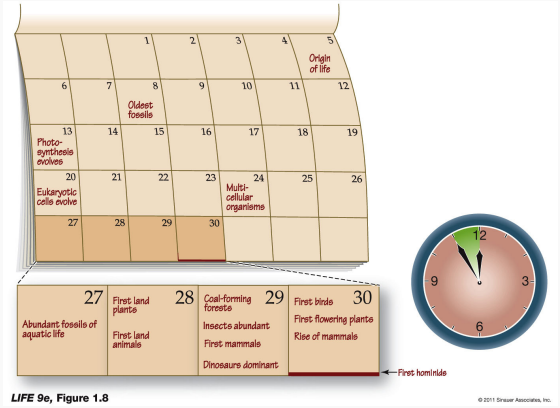
- evolutionarily ancient
- in all organisms
- function in the same way
- sequences change slowly (similarities between groups are easy to identify)

Three Domains of Life
(based on DNA comparisons)



Life on earth is one big extended family!

Life's Calendar
(the fossil and genetic records allow study of evolutionary relationships)



LIFE 9e, Figure 1.8

Percentage of Genes Conserved between Humans and Other Species

Organism	 CHIMP	 MOUSE	 CHICKEN	 FRUIT FLY
Gene Conservation with Humans (%)	99.5	88	75	60

The Chemistry of Life

The living world is composed of the same set of chemical elements as the rest of the universe

Life is based on chemistry and observes universal laws of chemistry and physics

But life has its unique molecules!

The Chemistry of Life

An atom contains electrons and a nucleus of protons and neutrons
- electrically neutral (electrons and protons same in number)
- the behavior of electrons determines chemical bonding and geometry

An element contains only one kind of atom
- each element has a different number of protons
- isotopes differ in the number of neutrons
- an unstable isotope is called a radioisotope

(spontaneously gives off energy from nucleus - α, β, γ radiation)

1 dalton (Da) = the mass of a single proton or neutron (1.7×10^{-24} grams)
(also called atomic mass unit or amu, the mass of electrons is tiny and can be ignored)

The atomic weight (mass) of an element is the average of the mass numbers of a representative sample of atoms of that element (including all isotopes in their naturally occurring proportions)

The Chemistry of Life

Atoms bond to form molecules

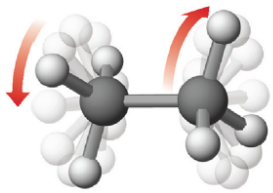
Covalent bond: sharing of electrons
Ionic bond: attraction of opposite charges
Hydrogen bond: sharing of H atom
Hydrophobic interaction: interaction of nonpolar substances in the presence of polar substances (especially water)
van der Waals interaction: interaction of electrons of nonpolar substances

Molecules vary in size
All molecules have a specific three-dimensional shape
Molecules are characterized by certain chemical properties that determine their biological roles

98% of the mass of all living organisms is composed of just six elements (C, H, N, O, P and S)

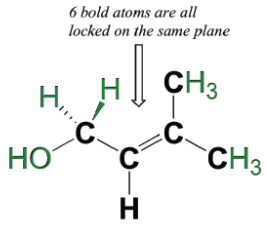
The Chemistry of Life

(some chemical bonds in a molecule can rotate freely)



CH_3-CH_3

Single bonds rotate freely

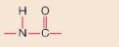
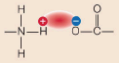
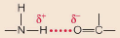
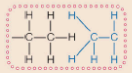
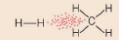


Double bonds do not rotate

The Chemistry of Life

(four types of non-covalent interactions cause macromolecules to fold into specific conformations)

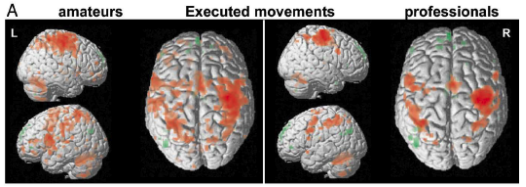
Chemical Bonds and Interactions

NAME	BASIS OF INTERACTION	STRUCTURE	BOND ENERGY[a] (KCAL/MOL)
Covalent bond	Sharing of electron pairs		50–110
Ionic bond	Attraction of opposite charges		3–7
Hydrogen bond	Sharing of H atom		3–7
Hydrophobic interaction	Interaction of nonpolar substances in the presence of polar substances (especially water)		1–2
van der Waals interaction	Interaction of electrons of nonpolar substances		1

[a]Bond energy is the amount of energy needed to separate two bonded or interacting atoms under physiological conditions.

The Musician's Brain

(Mozart's violin concerto in G major)

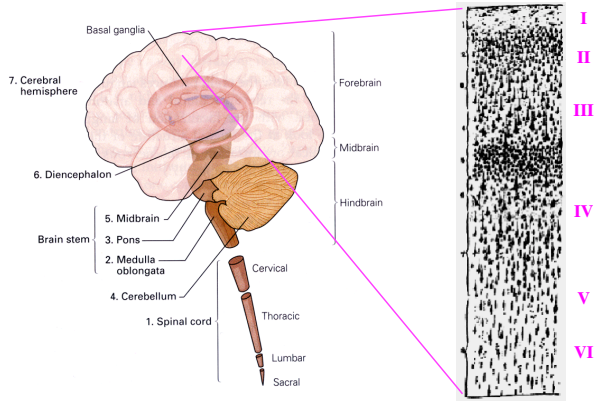


Functional changes within the brain due to behavioral modifications that accompany motor skill acquisition (Lotze et al., *NeuroImage* 20:1817-1829, 2003)

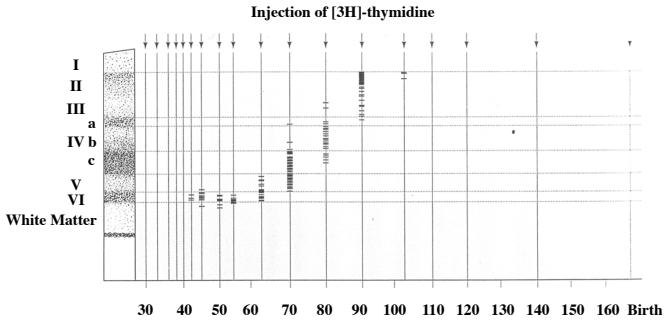
Functional MRI measures changes in blood flow and blood oxygenation that are linked to neural activity (oxygenated and deoxygenated hemoglobins respond differently to an externally applied magnetic field)

Taking advantage of the laws of chemistry and physics to study biology

The Neocortex Contains Six Layers of Neurons

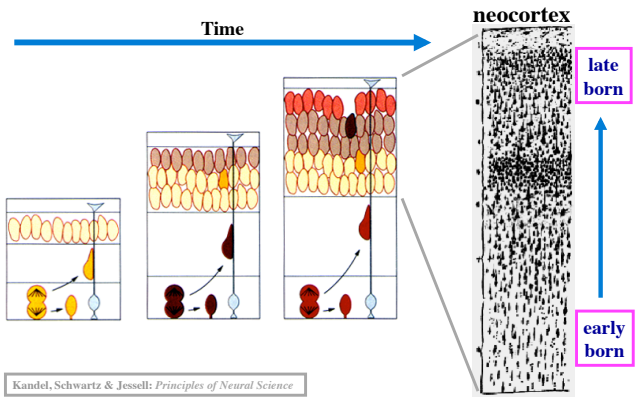


A Neuron's Birth Date Determines Its Laminar Fate



Taking advantage of the laws of chemistry and physics to study biology

Embryonic Development is Four-Dimensional
(Temporal Regulation of Neurogenesis)



The Chemistry of Life

The Molecules that Characterize Living Things

Nucleic Acids
Proteins
Carbohydrates
Lipids

All are polymers with the exception of lipids
They are macromolecules (> 1,000 grams per mole)

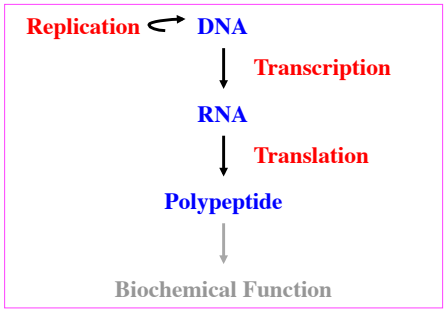
The chemical bonds can occur between molecules (intermolecularly) or within different parts of a single molecule (intramolecularly)

The Central Dogma of Molecular Biology

Colin M. MacLeod, Oswald T. Avery, Maclyn McCarty
(Francis Crick & James D. Watson)

Bacteria have genes like higher life forms, and the gene is DNA (*J Exp Med*, 1944)

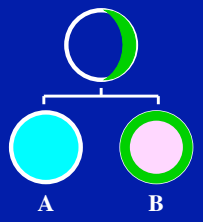
The Central Dogma of Molecular Biology

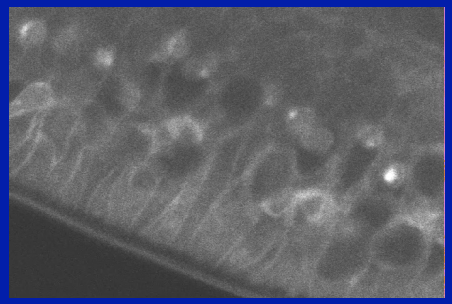


DNA stores genetic information

The Cell Theory

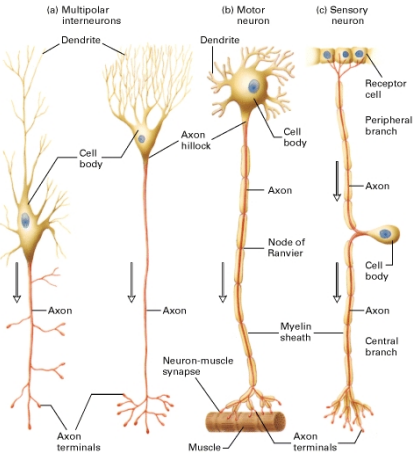
(all life consists of cell & all cells come from preexisting cells)





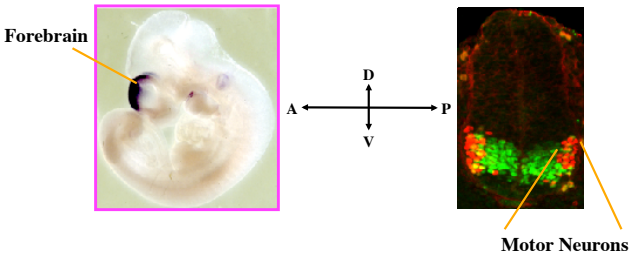
Courtesy of Bingwei Lu (Stanford University)

Structure of Typical Mammalian Neurons



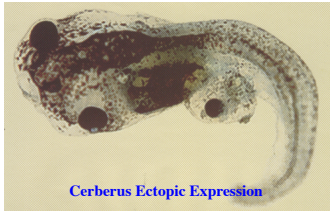
Molecular Cell Biology
4th edition
Lodish H, Berk A, Zipursky SL, et al.

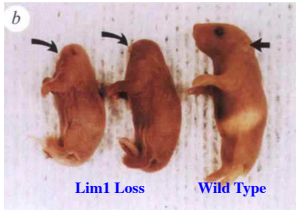
Cells Have Different Functions & Form Different Structures



- All cells come from preexisting cells
- Cells are both distinct entities and building blocks of more complex organisms
- All cells of a multicellular organism contains the same genome
- Differences in gene expression generate differences between cell types

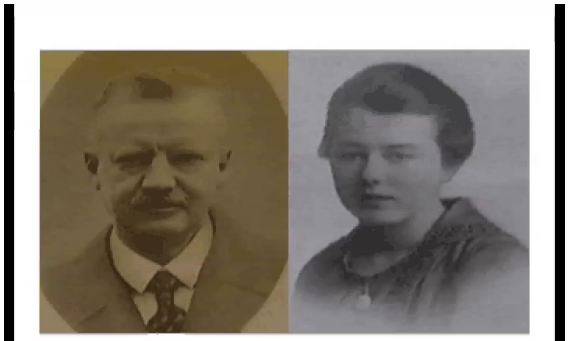
Gene Activity Change & Head Development





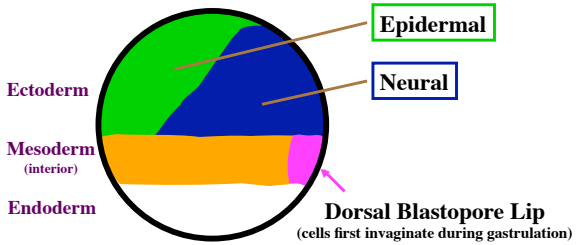
Bouwmeester et al., *Nature* 382:595-601, 1996; Shawlot & Behringer *Nature* 374:425-430, 1995

Grafting Experiments
(Spemann & Mangold, 1924)



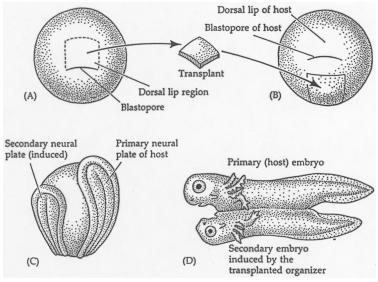
Noble Prize in Physiology or Medicine in 1935

Two Fate Choices for Ectoderm
(the nervous system originates from the ectoderm)



Endoderm: intestine, lung, liver, etc
Mesoderm: somites (vertebrae, dermis, muscle), genital ridge, kidney, etc
Ectoderm: skin and nervous system

Grafting Experiments
(Spemann & Mangold, 1924)



newt *(Triturus taeniatus and Triturus cristatus)*

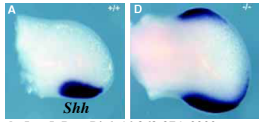
The concept of induction:
the dorsal lip induces and organizes a second body axis in neighboring cells

Zone of Polarizing Activity (ZPA) Is A Signaling Center Essential for Limb Patterning

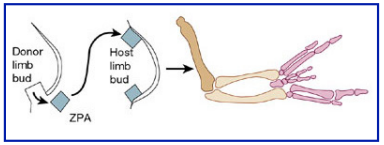
Human
(Polydactyly)

Mouse
(PPD Mutant)

Normal **PPD Mutant**



Blanc et al., *Int. J. Dev. Biol.* 46:969-974, 2002.



Discoveries in biology can be generalized!

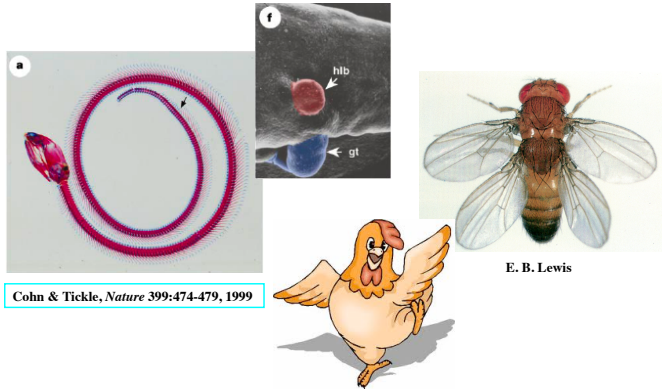
Evolution & Model Systems
(discoveries in biology can be generalized)

All organisms share a common genetic language for biological information
(all life is related by descent from a common ancestor)

A major unifying principle of biology is
change in the genetic makeup of biological populations through time

The power of using model systems to obtain knowledge
- bacteria (chemical reactions in cell)
- *Chlorella* (photosynthesis)
- *Arabidopsis thaliana* (plant development)
- sea urchins, round worms, fruit flies, zebrafish, frogs, chickens and mice
(animal development and human diseases)

Evolutionary Conservation & Differential Use of Developmental Pathways (Evo-Devo)



Cohn & Tickle, *Nature* 399:474-479, 1999

E. B. Lewis

Cellular Mechanisms of Learning & Memory
(the importance of model organisms)

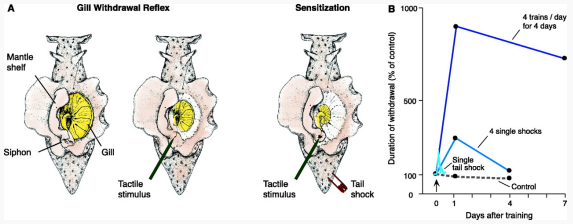
Eric Kandel

Aplysia californica
(a simple nervous system and large neurons)

Model Organisms & Studying Learning & Memory
(gill-withdrawal reflex of the sea slug *Aplysia californica*)

Evolution & Model Systems

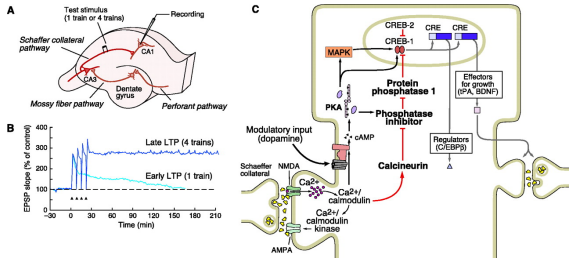
Aplysia and the Molecular Biology of Learning
(the ability of animals to modify behavior by learning)



E. R. Kandel Science 294, 1030 -1038 (2001)

Long Term Potentiation (LTP): a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously

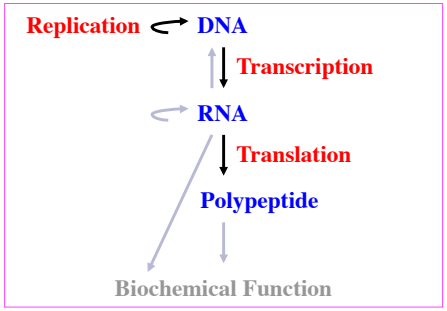
Evolution & Model Systems



E. R. Kandel Science 294, 1030 -1038 (2001)

LTP and Learning and Memory in the Hippocampus
(the ability of chemical synapses to change their strength)

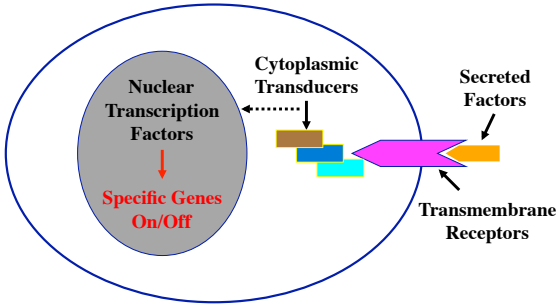
The Central Dogma of Molecular Biology



All cells of a multicellular organism contains the same genome, so how do macromolecules cooperate to make cells different?

How Do Macromolecules Cooperate?

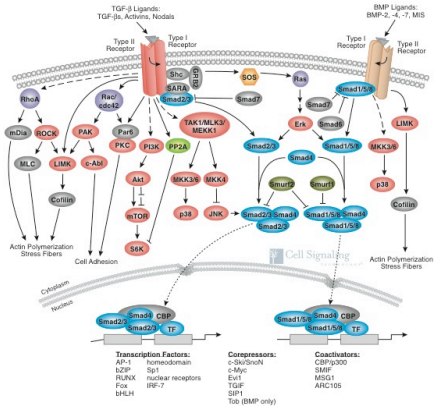
(signal transduction & cellular differentiation)



- Cells in our body have the same genetic make up (genes)
- Different cells express different subsets of the genes to perform specific functions
- Transcription factors bind to specific regulatory regions (promoters and enhances) of a gene to affect its expression

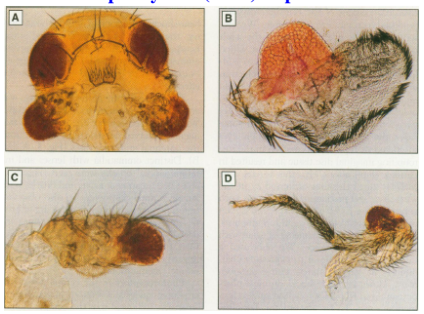
How Do Macromolecules Cooperate?

(signal transduction & cellular differentiation)



Data Mining & Mathematical Modeling

Ectopic Eyeless (Pax6) Expression



Genes and proteins don't work alone but act in a network!
(a need to understand how they interact with one another in each context)

The Origin of Life

The origin of small molecules of life
(amino acids, purines, pyrimidines and carbon sugars)
- from outside of the earth (meteorites like Murchison and ALH84001)
- synthesis from earth's early atmosphere

The origin of large molecules of life
- chemical changes (metabolism) first?
- replication first?
- RNA world?

The origin of first cells

Looking for Life Elsewhere

Has a unique structure and special properties
(e.g. large amount of hydrogen bonds, high specific heat and high heat of vaporization)
- ice floats!
- relative constancy of temperatures in oceans and large bodies of water
-cohesion and surface tension

Is an excellent solvent - the medium of life

Buffers minimize changes in pH to maintain internal homeostasis

Why is water so important?

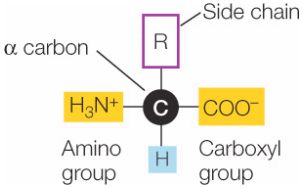
Three branches of life on earth:
BACTERIA, ARCHAEA & EUKARYA

Proteins & Enzymes

Proteins Play Very Diverse Roles

- Enzymes: catalytic proteins that speed up biochemical reactions
- Defensive proteins: recognize and respond to invading non-self substances
- Hormonal and regulatory proteins: control physiological processes
- Receptor proteins: receive and respond to molecular signals from inside and outside the organism
- Storage proteins: store chemical building blocks (amino acids) for later use
- Structural proteins: provide physical stability and movement (e.g. collagen)
- Transport proteins: carry substances within the organism (e.g. hemoglobin)
- Genetic regulatory proteins: regulate when, how, and to what extent a gene is expressed.

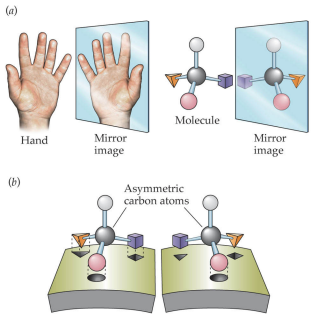
Proteins Are Amino Acid Polymers
(different proportions and sequences of 20 amino acids)



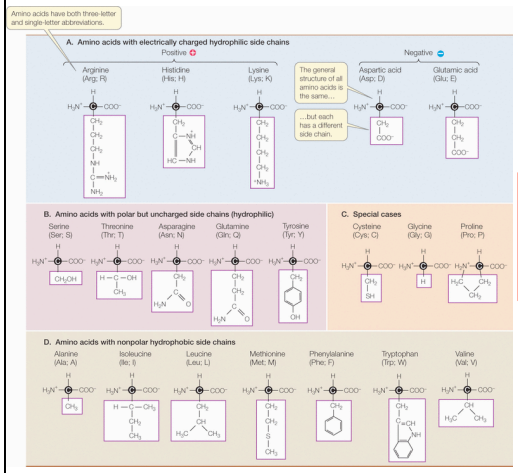
Monomers are linked by covalent bonds to form polymers
– synthesized through dehydration (condensation)
– broken apart via hydrolysis

The side chains contain functional groups important for determining the three-dimensional (3-D) structure and thus the function of the protein

Proteins Are Amino Acid Polymers
(different proportions and sequences of 20 amino acids as directed by genetic code)



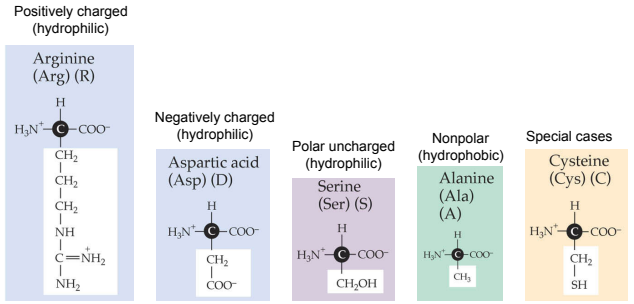
- Macromolecules like amino acids have handedness
- Only L-amino acids are more commonly found in proteins in most organisms



The 20 amino acids are distinguished by their side chains containing functional groups

Proteins Are Amino Acid Polymers

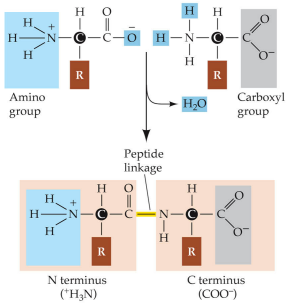
(different proportions and sequences of 20 amino acids as directed by genetic code)



Representative examples of each amino acid class

Peptide Linkages (Bonds) Form A Protein's Backbone

(have partial double bond character)

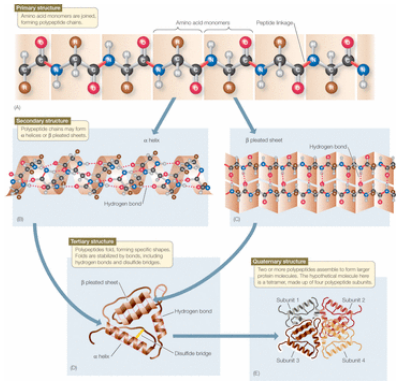


In the C—N linkage, the adjacent α carbons (αC—C—N—αC) are not free to rotate fully, limiting the folding of the polypeptide chain.

The oxygen bound to the carbon (C=O) in the carboxyl group carries a slight negative charge (δ^-), whereas the hydrogen bound to the nitrogen (N—H) in the amino group is slightly positive (δ^+). This asymmetry of charge favors hydrogen bonding within the protein molecule itself and with other molecules, contributing to both the structure and the function of many proteins.

The sequence of amino acids comprising the protein for the primary structure

There Are Four Levels of Protein Structure



Primary Structure:
amino acid sequence of polypeptide chain

Secondary Structure:
hydrogen bonding between atoms of the polypeptide "backbone" forming either β pleated sheets or α helices

Tertiary Structure:
interaction between the different amino acid side chains of the peptide

Quaternary Structure:
individual polypeptides associate through chemical bonding interactions to form larger molecules

Protein Folding

(determines shape or "conformation" responsible for activity or inactivity)

吴宪 (Hsien Wu)
(1893－1959)

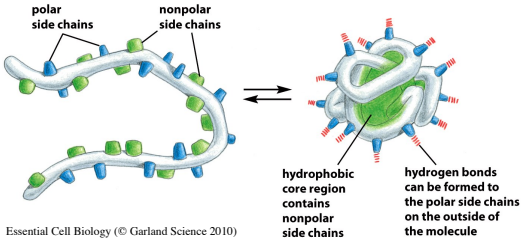
H. Wu. Studies on the denaturation of proteins, XIII. A theory of denaturation. *Chinese Journal of Physiology* 5:321-344 (1931)

"变性说"《中国生理学杂志》

"… in this paper of long ago, after years of work and thought, was (I believe) the first to grasp the fundamental relations between the native and the denatured state of protein molecules. Later workers have greatly enriched his picture, but his proposal still stands as a landmark in the field. Wu's paper is, I fear, unknown to many biochemists of today; and it should not be forgotten" (JOHN T. EDSALL)

Protein Folding

(determines shape or "conformation" responsible for activity or inactivity)



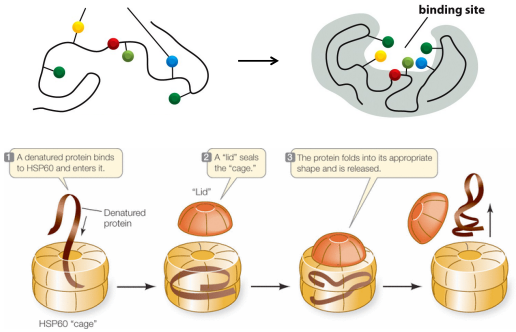
Essential Cell Biology (© Garland Science 2010)

Most proteins fold to a specific globular conformation

Physical stability of proteins in aqueous solution can be affected by temperature, pH, salt type, salt concentration, cosolutes, preservatives, and surfactants

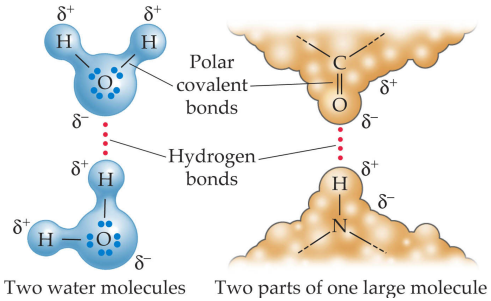
Chaperones & Protein Folding

(determines shape or "conformation" responsible for activity or inactivity)



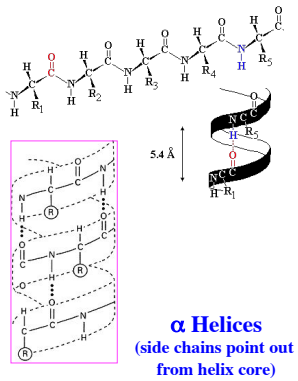
Chaperones like HSP60 take care of other proteins by folding them in a very specific way (just after a protein is made and following denaturation)

Hydrogen Bonds

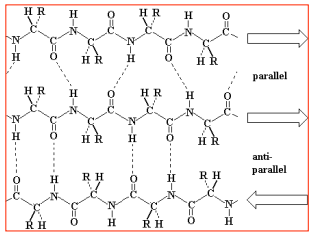


- Not a bond but an attraction between opposite partial charges of two polar molecules
- Very weak singularly but strong in large numbers

Hydrogen Bonds & Secondary Structure

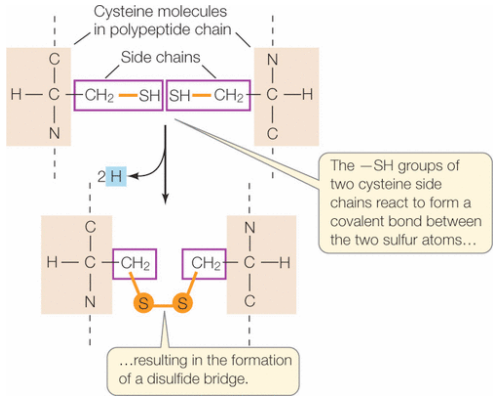


α Helices
(side chains point out from helix core)

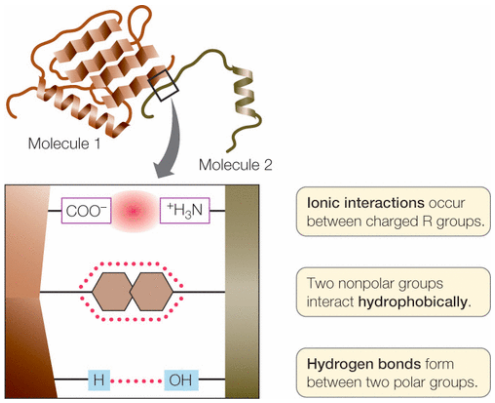


β-pleated sheets
(side chains alternate sticking above and blow sheet)

Disulfide Bridge & Tertiary Structure



Proteins Can Interact with Other Molecules

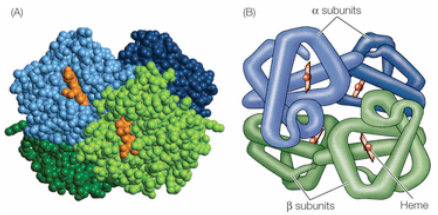


Ionic interactions occur between charged R groups.

Two nonpolar groups interact **hydrophobically**.

Hydrogen bonds form between two polar groups.

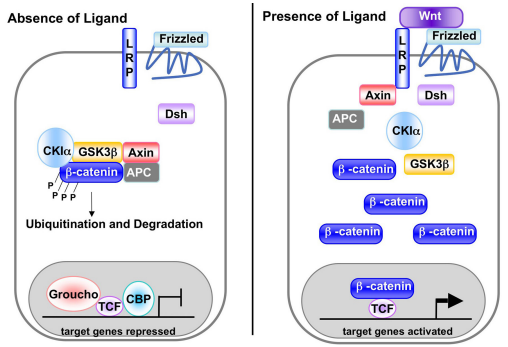
The Quaternary Structure of A Protein Consists of Subunits



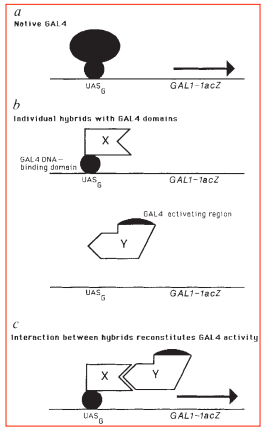
The subunits are hold together by hydrophobic interactions, van der Waals forces, hydrogen bonds, and ionic bonds

The weak nature of these forces permits small changes in the quaternary structure to aid the protein's function

Changes in Quaternary Structure Aid Function



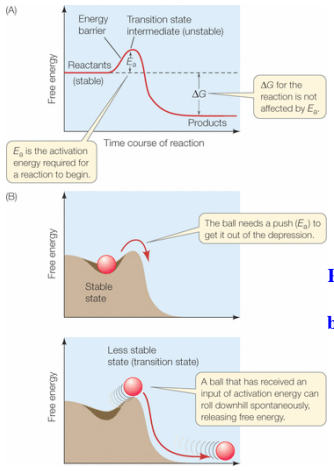
David M. Eisenmann, *Worm Book*



Taking Advantage of Quaternary Structure

A protein may assign different aspects of a function to different regions

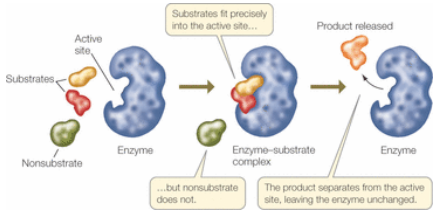
The Yeast Two-Hybrid System"
(Fields and Song, *Nature* 340:245-246, 1989)



Enzymes

Proteins that act as catalysts to speed up chemical reactions without themselves being permanently altered by lowing the energy barrier of a reaction

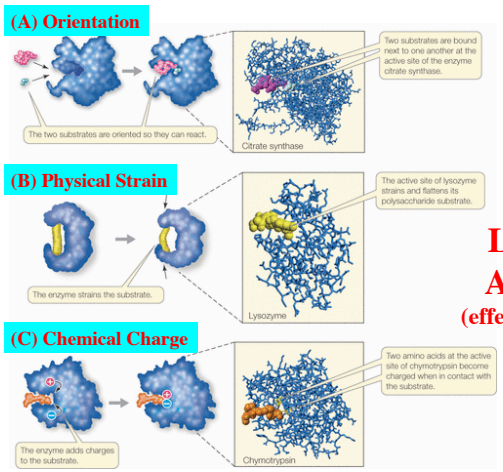
Enzymes



An enzyme–substrate complex (ES) is held together by one or more means (hydrogen bonding, electrical attraction, or temporary covalent bonding)

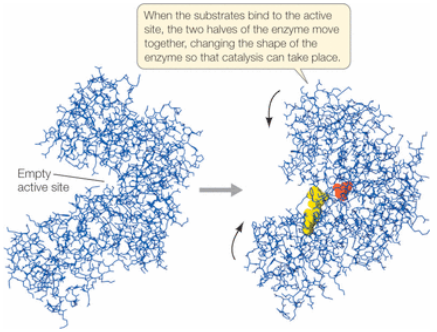
Most biological catalysts like enzymes are highly specific, recognizing and binding to only one or a few closely related substrates

The earliest biological catalysts likely are RNA molecules (ribozymes)



Life at the Active Site
(effect on substrates)

Life at the Active Site
(effect on enzymes)



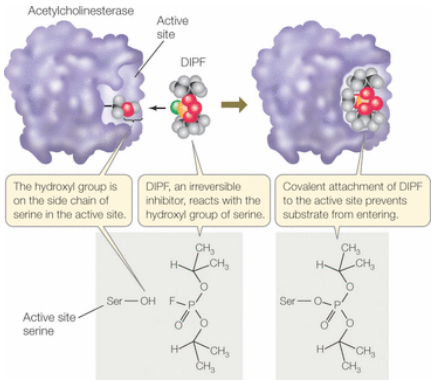
Some enzymes change shape after capturing the substrate

Some Enzymes Need Other Molecules
(nonprotein chemical "partner")

TYPE OF MOLECULE	ROLE IN CATALYZED REACTIONS
COFACTORS	
Iron (Fe^{2+} or Fe^{3+})	Oxidation/reduction
Copper (Cu^{+} or Cu^{2+})	Oxidation/reduction
Zinc (Zn^{2+})	Helps bind NAD
COENZYMES	
Biotin	Carries $-COO^{-}$
Coenzyme A	Carries $-CO-CH_3$
NAD	Carries electrons
FAD	Carries electrons
ATP	Provides/extracts energy
PROSTHETIC GROUPS	
Heme	Binds ions, O_2, and electrons; contains iron cofactor
Flavin	Binds electrons
Retinal	Converts light energy

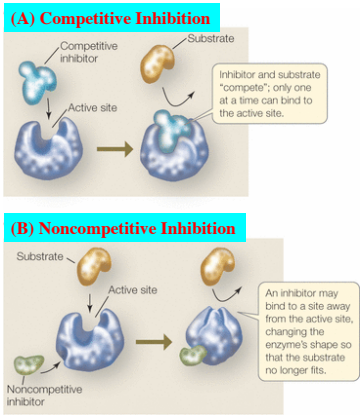
Regulation of Enzyme Activity
(irreversible, reversible and allosteric)

Irreversible



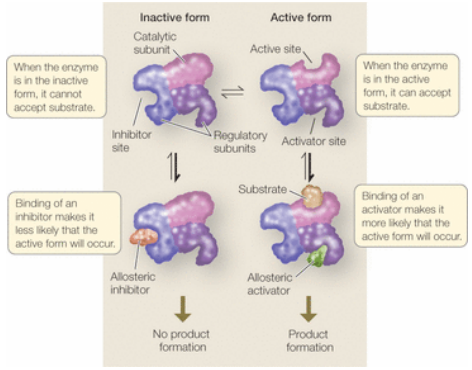
Regulation of Enzyme Activity
(irreversible, reversible and allosteric)

Reversible



Regulation of Enzyme Activity
(irreversible, reversible and allosteric)

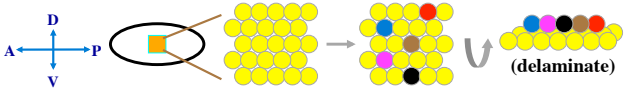
Allosteric



Like other proteins, enzymes are also affected by the environment (temperature and pH)

Specification of Neural Precursor Cells

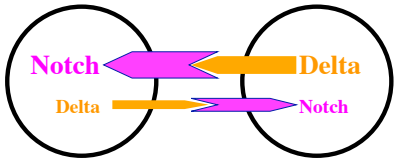
Each hemisegment: ~ 150 epithelial cells generate 30 unique neuroblasts



cell determined | group determined | cells equivalent

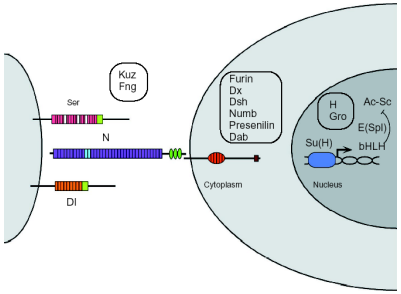
Doe et al. (1985) *Phil. Trans. R. Soc. Lond.*, B 312:67-81 (grasshopper)

Lateral Inhibition



single out cells to be neural precursor cells

Specification of Neural Precursor Cells



Notch ICD/Su(H)

↓

E(spl)

⊥

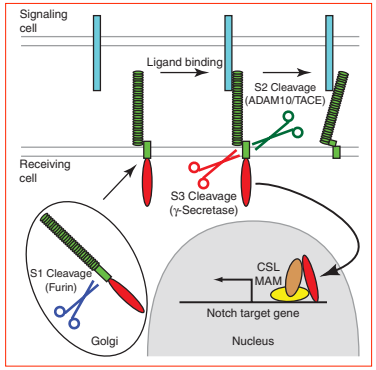
Ac-Sc

↓

Dl

Artavanis-Tsakonas et al. (1999) *Science*, 284:770-776

Notch Activation

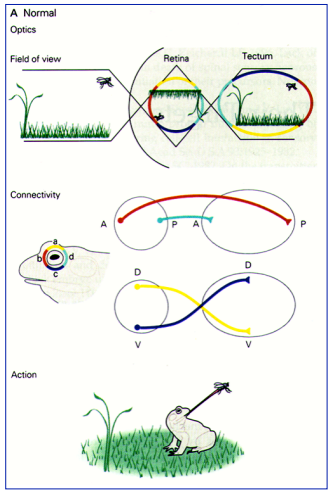


Carbohydrates & Biological Energy

Biochemical Transformation of Energy Is A Hallmark of Life

Energy is defined in physics as the capacity to do work, which occurs when a force operates on an object over a distance.

In biochemistry, it is more useful to consider energy as the capacity for change, and such changes are usually associated with changes in the chemical composition and properties of molecules.



Many Forms of Energy

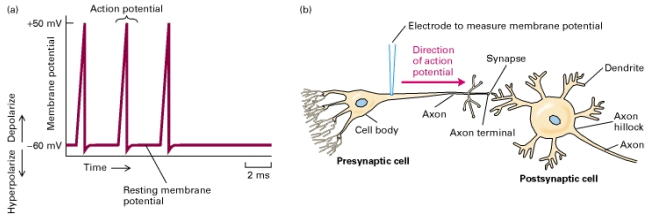
(chemical, electrical, heat, light, & mechanical)

Potential Energy (Stored Energy)
- the energy of state or position
- stored in chemical bonds, as a concentration gradient, an electric charge imbalance, etc

Kinetic Energy
- the energy of movement
- the type that does work and makes things change

Potential energy can be converted into kinetic energy and vice versa, and the form that the energy takes can also be converted.

Synapse: A Junction for Neuron to Pass An Electrical or Chemical Signal to Another Cell

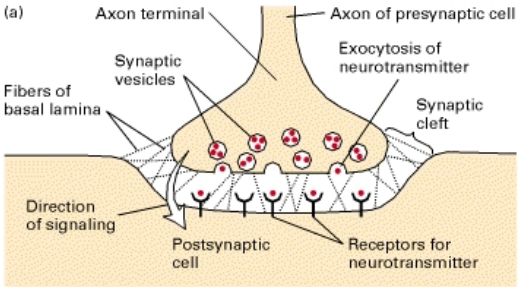


Molecular Cell Biology. 4th edition. Lodish H, Berk A, Zipursky SL, et al.

Biochemical transformation of energy is a hallmark of life

Chemical Synapse

(can be excitatory or inhibitory)

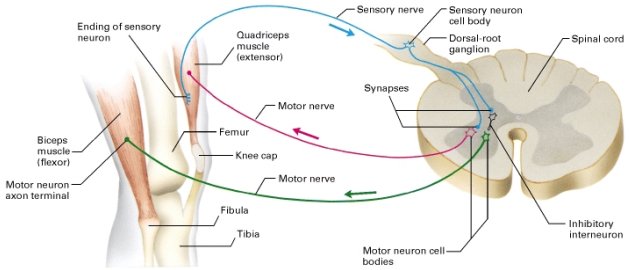


Molecular Cell Biology. 4th edition. Lodish H, Berk A, Zipursky SL, et al.

Biochemical transformation of energy is a hallmark of life

Neural Circuits

(the knee-jerk reflex arc)



Molecular Cell Biology. 4th edition. Lodish H, Berk A, Zipursky SL, et al.

Biochemical transformation of energy is a hallmark of life

The Laws of Thermodynamics

(energy cannot be created nor lost in a closed system)

The First Law of Thermodynamics

The total amount of energy before a transformation equals the total amount after a transformation

The Second Law of Thermodynamic

Within a closed system, the amount of energy available to work is always less than the original amount of energy; free energy decreases and unusable energy (disorder) increases (increase in entropy)

Not all energy can be used:

$G = H - TS$

We cannot measure G, H, or S absolutely but the change in each at a constant T:

$\Delta G = \Delta G_{products} - \Delta G_{reactants}$

H: enthalpy (the total energy, 焓); G: free energy (the usable energy that can do work);
S: entropy (the unusable energy, 熵); T: absolute temperature

Two Forms of Metabolism

Metabolism is the totality of chemical reactions in a living organism

- breakdown food to get energy and raw materials
- synthesize all needed molecules and store fuels
- use stored fuels when shortage occurs for energy and synthesize raw materials

Anabolic Reactions (Anabolism, 合成代谢)

- link simple molecules to form more complex
- require an input of energy and capture it in the chemical bonds formed

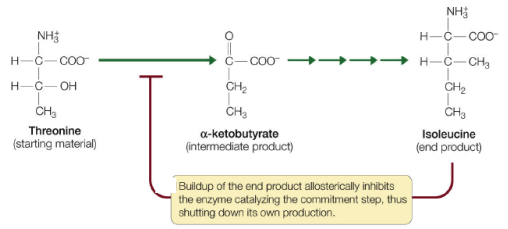
(may make a single, highly ordered substance from many smaller less ordered reactants)
(endergonic reactions: require or consume free energy)

Catabolic Reactions (Catabolism, 分解代谢)

- break down complex molecules into simpler ones
- release the energy stored in chemical bonds

(may break down an ordered reactant into smaller randomly distributed products)
(exergonic reactions: release free energy)

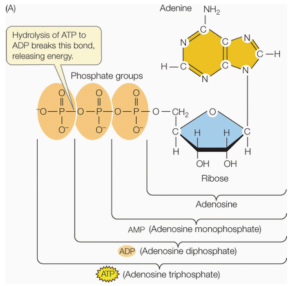
Metabolic Intermediates & Pathways



- Every chemical reaction proceeds to a certain extent, but not necessarily to completion (all reactants converted into products)
- Each reaction has a specific equilibrium point, which is related to the free energy released by the reaction under specified conditions
- Each enzyme catalyzes only a simple reaction, but string together, a set of enzymes can catalyze complex reactions, generating intermediates and forming pathways)
- Every pathway is regulated and the intermediates generated by each reaction within the pathway are shared by other pathways (network of pathways)

ATP and Biochemical Energetics

(cells rely on adenosine triphosphate for the capture and transfer of free energy)



A "currency" for Transferring Energy

(couples exergonic and endergonic reactions)

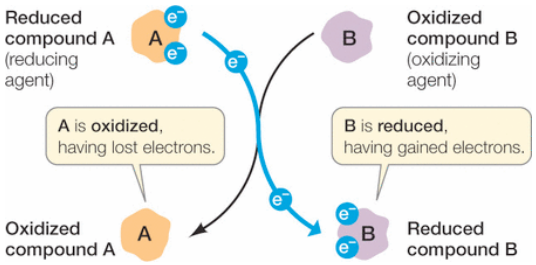
- Capture of free energy by generating ATP by using ADP and HPO_4^{2-} (Pi)
- Hydrolysis of ATP to release energy ($ATP + H_2O \rightarrow ADP + P_i$ + free energy)

A Building Block for Nucleic Acids

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + free energy (ΔG = -686 Kcal/mol)
ADP + Pi + free energy → ATP

The P-O bonds store a lot of free energy

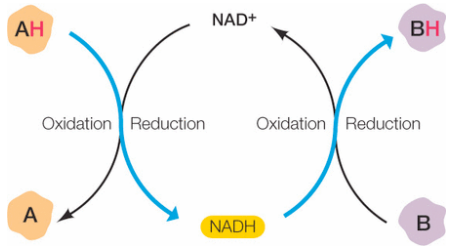
Redox Reactions Transfer Electrons and Energy



Oxidation and reduction always occur together!

Energy for Life

(the coenzyme nicotinamide adenine dinucleotide acts as an electron carrier in redox reactions)



Reduction: $NAD^+ + H^+ + 2\ e^- \rightarrow NADH$
Oxidation: $NADH + H^+ + \frac{1}{2}\ O_2 \rightarrow NAD^+ + H_2O$ (ΔG = -52.4 kcal/mol)

NADH, like ATP, can be thought of as a package of free energy
FAD (flavin adenine dinucleotide) is another electron transfer carrier during glucose metabolism

Carbohydrates

(similar in atomic composition but differ greatly in size)

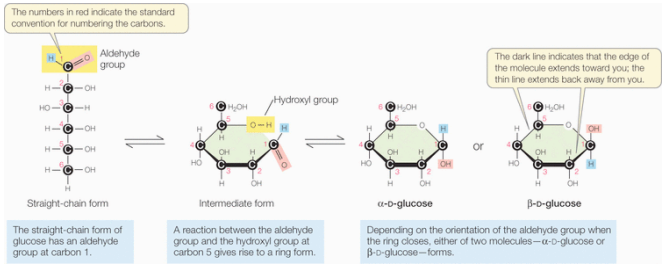
- **A source of stored energy that can be released in a form usable by organisms**
- **Used to transport stored energy within complex organisms**
- **Serve as carbon skeletons that can be rearranged to form new molecules**

There are four categories of biologically important carbohydrates:

- **Monosaccharides: simple sugars like glucose, ribose, and fructose that are the monomers from which the larger carbohydrates are constructed**
- **Disaccharides: two monosaccharides linked together by covalent bonds such as sucrose, which is made up of covalently bonded glucose and fructose molecules**
- **Oligosaccharides: made up of several (3–20) monosaccharides**
- **Polysaccharides: polymers made up of hundreds or thousands of monosaccharide such as starch, glycogen, and cellulose, are polymers**

Glucose

(the main energy source for living organisms)

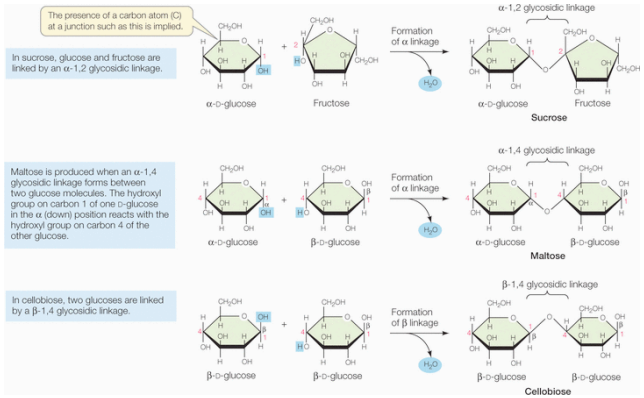


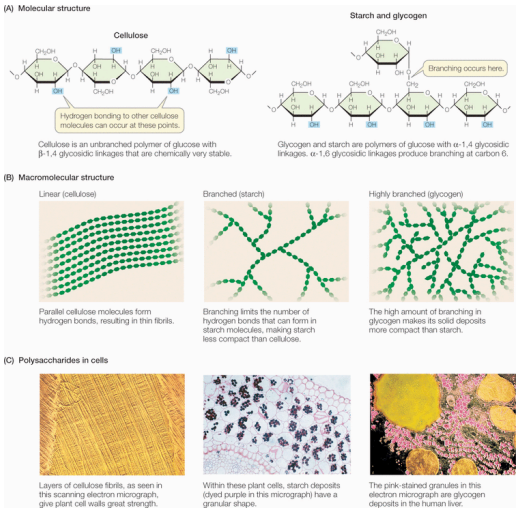
Glucose is a hexose, which also includes fructose, mannose and galactose

Glucose exists in straight chains and in ring forms.

Pentoses include the backbones of the nucleic acids (ribose and deoxyribose)

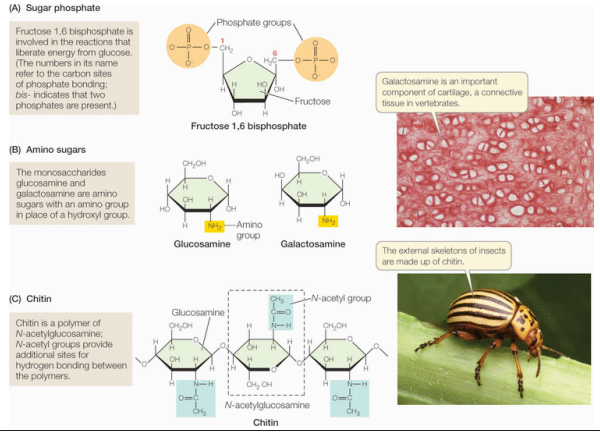
Glycosidic Linkage Bonds Monosaccharides

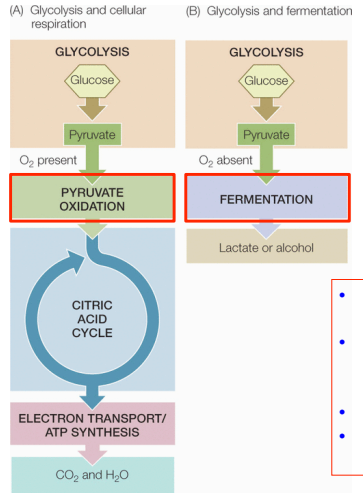




Polysaccharides
(less osmotic pressure)
(save energy for cells)

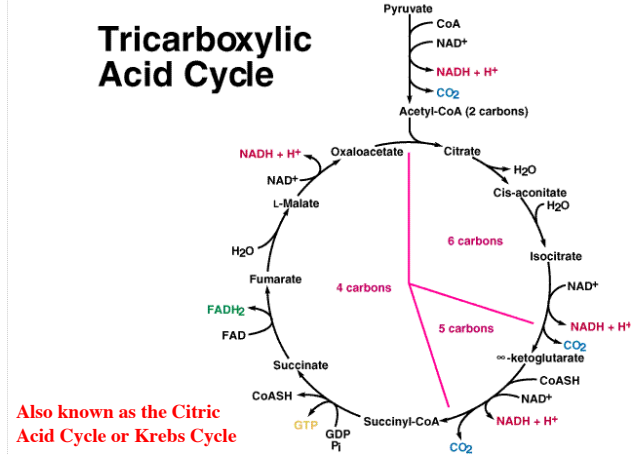
Carbohydrates Can Be Chemically Modified to Contain Additional Functional Groups



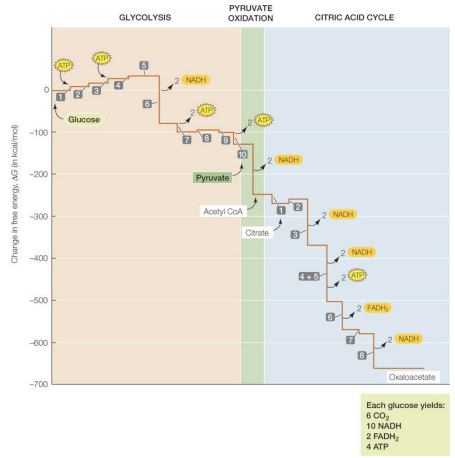


Energy Producing Metabolic Pathways

- **a series of separate reactions, each catalyzed by a specific enzyme**
- **each pathway is regulated by a key enzyme that can be inhibited or activated (the speed of reactions)**
- **most similar in all organisms**
- **occurring in specific organelles in eukaryotes**

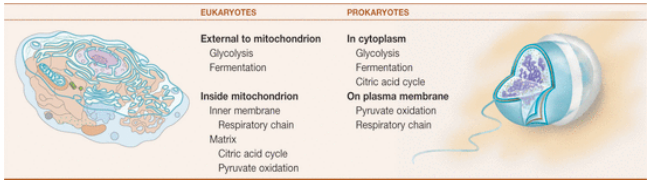


Also known as the Citric Acid Cycle or Krebs Cycle



Changes in Free Energy during Glycolysis and the Citric Acid Cycle

Energy Producing Metabolic Pathways



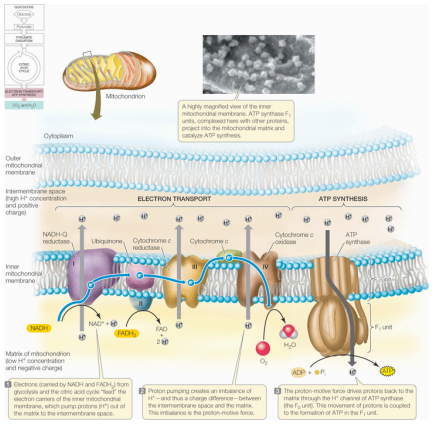
Oxidative Phosphorylation

ATP synthesis from the reoxidation of electron carriers in the presence of O_2
- Electron transport (electrons from NADH and FADH2 pass through the respiratory chain)
- Chemiosmosis (the protons diffuse back to into the mitochondria matrix through ATP synthase)

Substrate-Level Phosphorylation

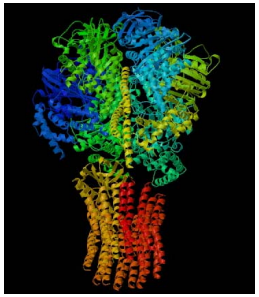
ATP production by directly transferring phosphate from a donor molecule onto ADP

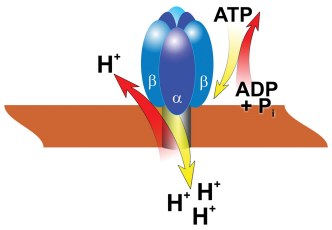
The Respiratory Chain & ATP Synthase Produce ATP



- Free energy stored in NADH is used to create a proton gradient across the inner mitochondrial membrane
- Lipid bilayer is not permeable to protons, which can only re-enter through the channel provided by the ATP synthase (a "turbine")
- The potential energy stored in the proton gradient (proton-motive force) is used to drive synthesis of ATP (chemiosmosis)

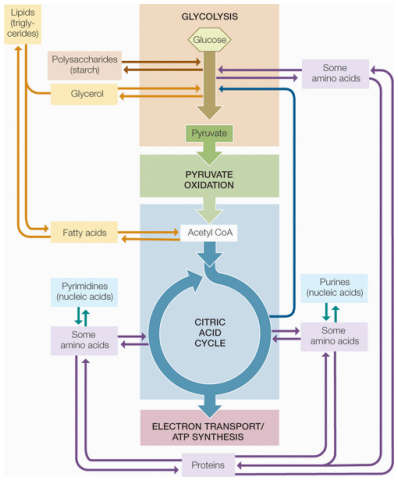
ATP Synthase & ATP Production





F1Fo ATP synthase is composed of a membrane-embedded portion, Fo, and a soluble central stalk, F1. Fo functions as a proton channel with a rotary motion that drives the coupled F1 to synthesize (red) or hydrolyze (yellow) ATP, depending on the rotational direction. F1 is composed of three α - subunits and three catalytic β - subunits alternatively arranged to form a hexagonal cylinder (Sulene et al. *Annals of Medicine* 2006, 38, 429-438)

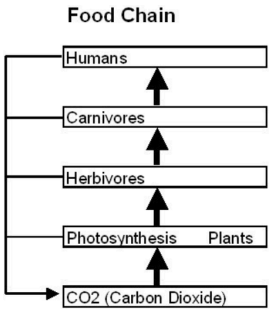
http://vcell.ndsu.nodak.edu/animations/atpgradient/movie-flash.htm

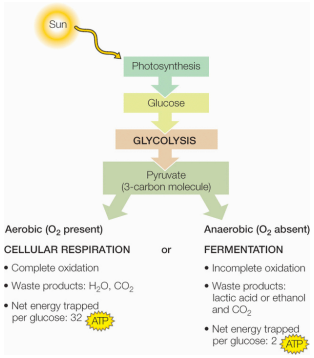


Polysaccharides, Lipids, and Proteins Can All Be Broken Down to Provide Energy

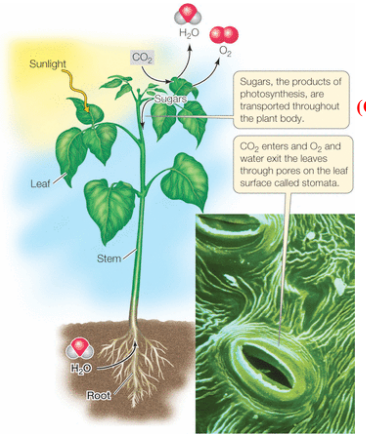
Many of the pathways can operate essentially in reverse

Energy for Life





Living organisms obtain their energy from the food compounds produced by photosynthesis by converting these compounds into glucose, which they metabolize to trap energy in ATP



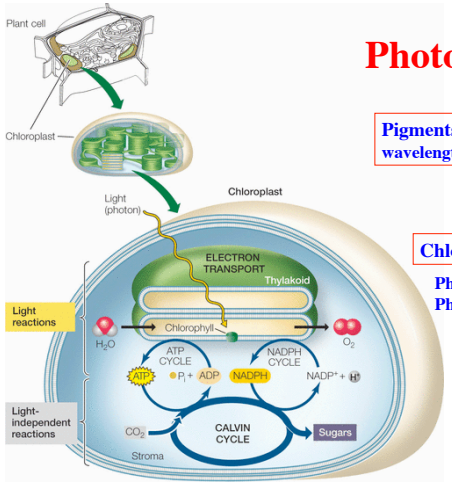
Photosynthesis

($CO_2 + H_2O \rightarrow O_2 +$ carbohydrates)

Water is the source of oxygen in photosynthesis

A metabolic process by which the energy of Sunlight is captured and used to convert carbon dioxide (CO_2) and water (H_2O) into carbohydrates ($C_6H_{12}O_6$) and oxygen gas (O_2)

Photosynthesis



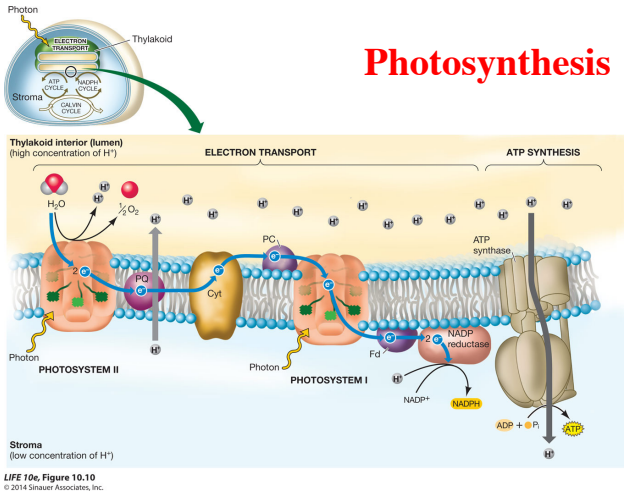
Pigments: molecules that absorb wavelengths in the visible spectrum

Chlorophylls: red and blue

Photosystem I (P_{700}, NADPH)
Photosystem II (P_{680}, ATP)

First product of CO2 fixation:
3PG (C3)
oxaloacetate (C4)

Photosynthesis



LIFE 10e, Figure 10.10
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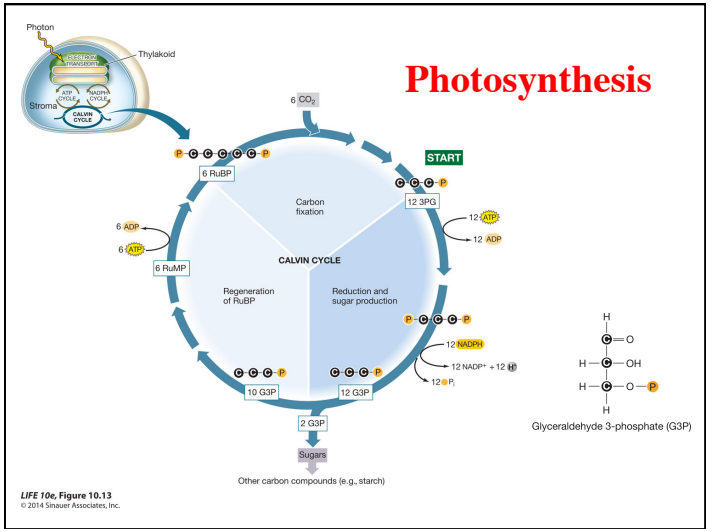
Photosynthesis



Glyceraldehyde 3-phosphate (G3P)

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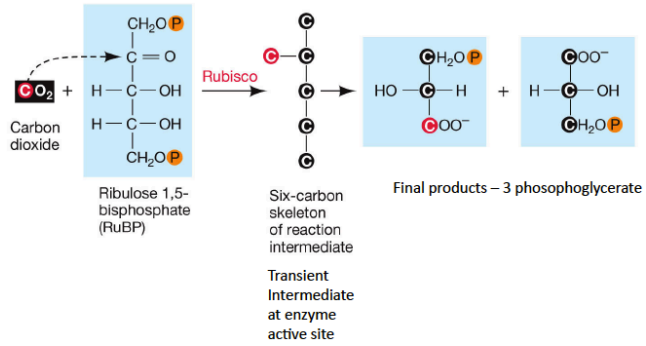
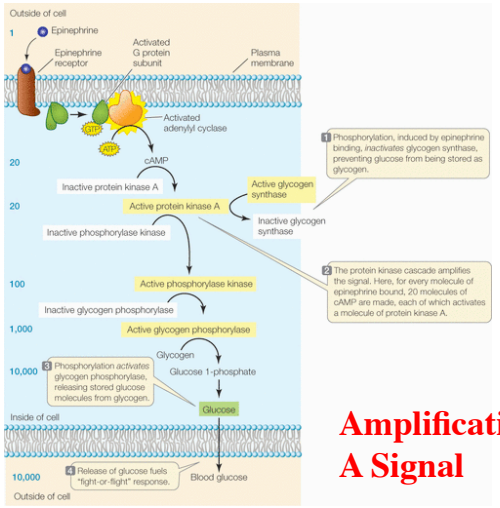
Photosynthesis

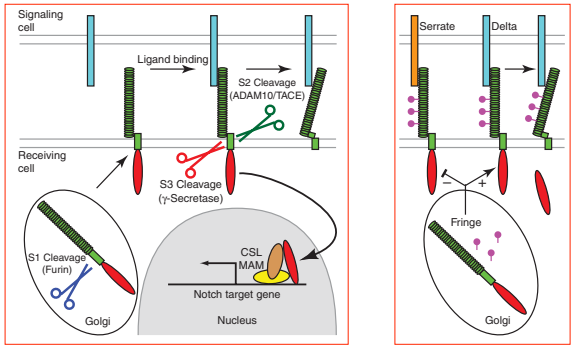
(Ribulose bisphosphate carboxylase/oxidase or Rubisco does the carbon fixation)



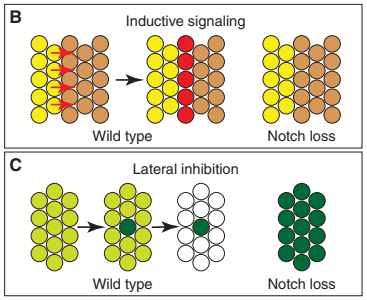


Amplification of A Signal

Glycosylation & Notch Activation



Glycosylation & Notch Activation



Requires Fringe

Does Not Requires Fringe

The enzyme O-fucosyl transferase adds fucose to the serine or threonine site in the Notch EGF-like repeats in the ER, and this is required for all Notch functions

The enzyme β1,3-N-acetylglucosaminyltransferase (Fringe) elongates the O-fucose site by adding an N-acetylglucosamine (GlcNAc) in the Golgi, but this is only required for some Notch functions

Key Concepts I

1. All life on Earth is related through evolutionary decent from a common ancestor, and cell is the basic unit of life.
2. Model organisms allow study of processes related to other organisms, including humans.
3. Scientific method is imperative to science and understanding.
4. The living world is composed of the same set of chemical elements as the rest of the universe, mostly made from six types of atoms.
5. Atoms form molecules through covalent bonds that have specific lengths and geometry, and three-dimensional structures of macromolecules determine their functions.
6. Biological macromolecules are often long chains with many freely-rotating single bonds to allow conformational flexibility.
7. Four types of non-covalent interactions cause macromolecules to fold into specific conformations and also allow them to reversibly bind specific substrates.

Key Concepts II

1. Proteins are linear chains of 20 types of amino acids connected by peptide bonds, with side chains giving different amino acid different physical properties for different interactions.
2. The primary structures of proteins are determined by amino acid sequences (encoded in DNA), which change over evolution and are altered in genetic disease.
3. Hydrogen bonding of the peptide backbone allow proteins to form secondary structures such as α helix and β sheet, which further fold up into a tertiary structure based mostly on the four types of non-covalent interactions between side chains.
4. Biological molecules spontaneously self assemble using the four interactions.
5. Proteins fold by finding their most energetically stable state, but some proteins require help from chaperones to find their most stably folded state.

Key Concepts III

1. All chemical reactions are slow under the mild conditions of life.
2. Every chemical reaction that occurs in biology needs to have $\Delta G<0$ and needs to be catalyzed by an enzyme.
3. Enzymes lower the activation energy to speed a reaction.
4. Enzymes are highly specific, just catalyzing one reaction by binding to specific molecules (substrates) to speed up their reaction with each other.
5. Enzymes can be turned on (activated) and off (inhibited).
6. Carbohydrates and lipids are both used to store energy.
7. Carbohydrates can build rigid structures.
8. Fuels are used in biology to generate the energy currency ATP.
9. ATP hydrolysis has $\Delta G<0$ and is coupled to reactions with $\Delta G>0$ so that the net process has $\Delta G<0$ and can go forward.

Key Concepts VI

1. All living things work in the same way at the molecular level
2. Energy from fuel oxidation in metabolism is initially captured in the reduced coenzyme NADH
3. Energy captured in NADH is transformed by electron transport into a proton gradient across the inner mitochondrial membrane
4. ATP synthase is a turbine in the inner mitochondrial membrane that spins to make ATP as protons pass through
5. Photosynthesis is the source of all the reduced carbon in the biosphere and of all the O2 in the atmosphere
6. The light reactions of photosynthesis generate ATP using a proton gradient and ATP synthase just as in mitochondrial ATP synthesis
7. The sole source of energy that enables the low entropy state in all biology is light captured by photosystems to excite electrons so they can reduce other molecules