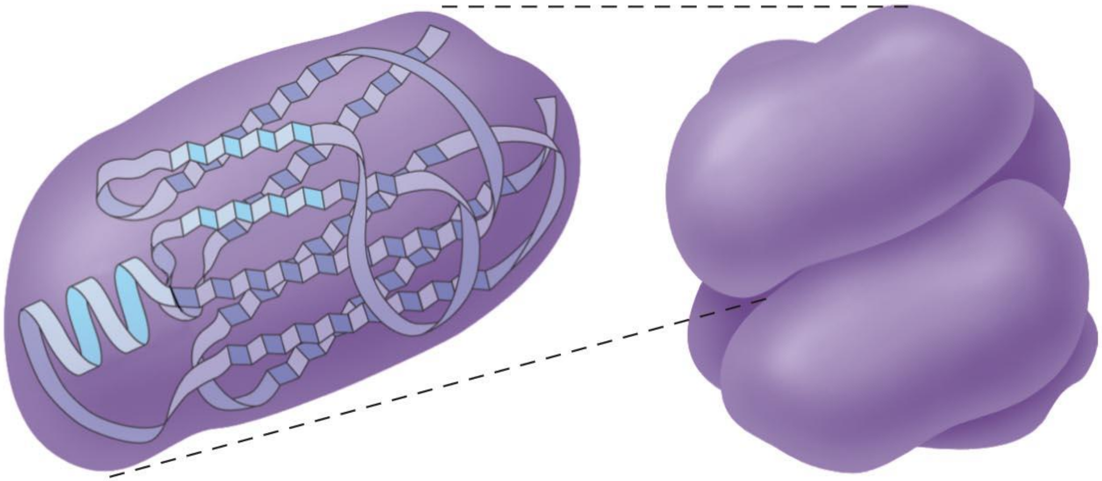
Quaternary Structure



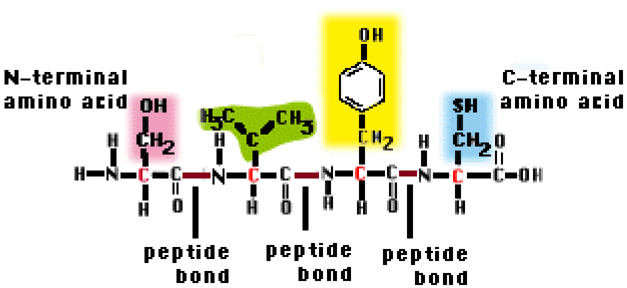
Tertiary Structure **Quaternary Structure**

'Proteins attain its structure through folding'

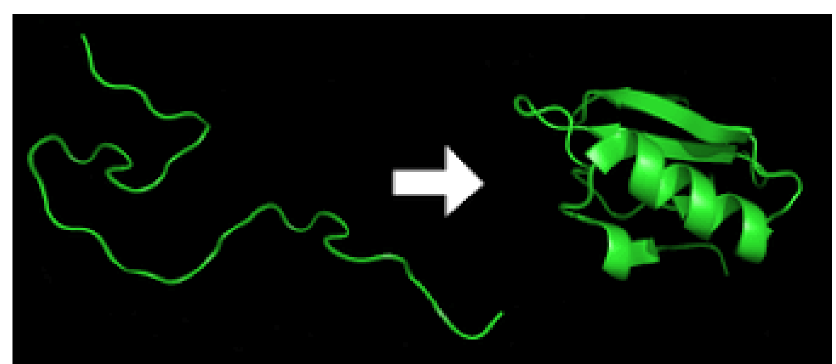
Coils or sheets due to R-group interactions

Protein subunits of an enzyme held together by hydrogen bonds, disulfide,Van der Waals forces, etc.

Protein folding is the physical process by which a protein chain acquires its native 3-D structure, a conformation, that is usually biologically functional, in an expeditious and reproducible manner.



Primary Sequence



Protein Folding: The Levinthal Paradox

- Too many different possible conformations for a protein to fold by a random search.
- Consider just for the peptide backbone, there are 3 conformations per amino acid in the unfolded state, For a 100 a.a. protein we have **3^{100} (5×10^{47}) conformations.**
- If the chain can sample 10^{12} conformations/sec (one per picosecond or 10^{-12} s to convert one conformation into another), **it takes 5×10^{35} sec (2×10^{28} year= 2 trillion trillion x 10^{4} yrs)**
- Actual folding time 0.1 to 1000 seconds
- Conclusion: Protein folding is not random, must have pathways.

Random search/sampling is Completely ruled out

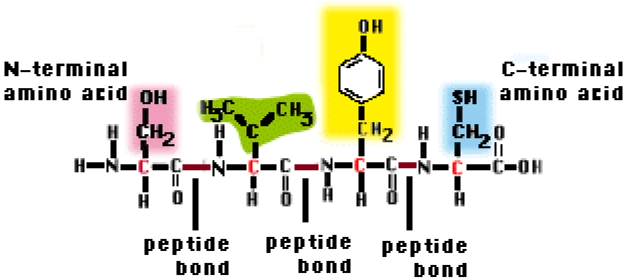
Cumulative selection:

How many key strokes would take a monkey poking randomly at a typewriter to reproduce a sentence **'Monkey is working'**. **$26^{15} = 1.6 * 10^{21}$**

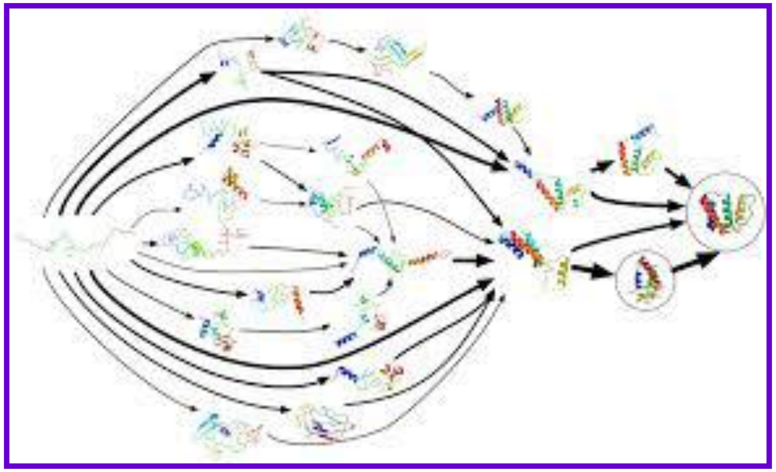
Preserved each correct character and allowed the monkey to retype only the wrong ones. On an average only few thousand keystrokes would be needed.

What are difference between above two cases ?

The essence of protein folding is the retention of partly correct intermediates like second case.



Primary Sequence



Protein misfolding and diseases

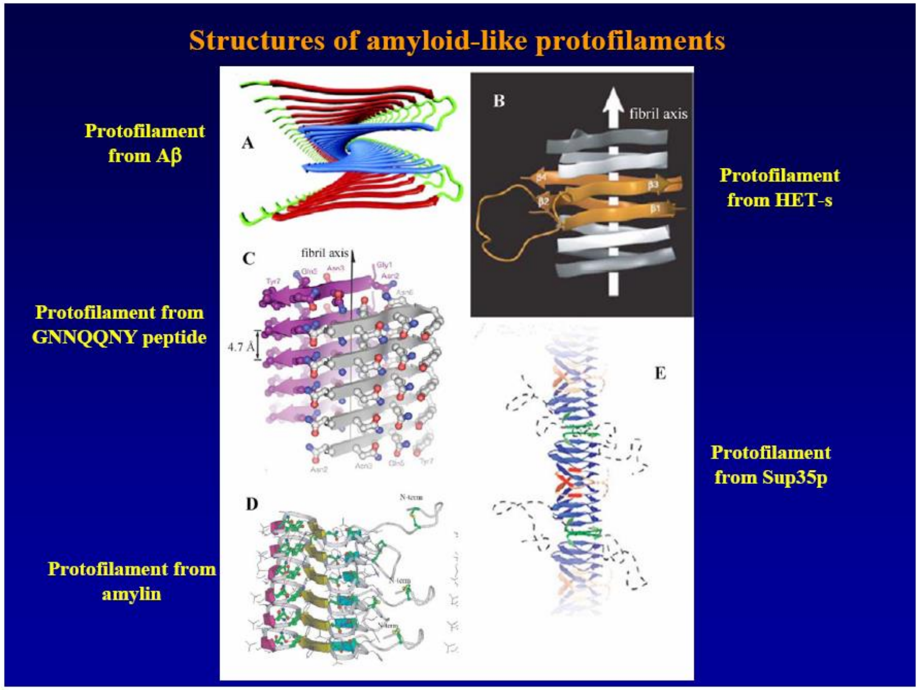
Misfolded proteins are associated with: Bovine spongiform encephalopathy **(mad cow disease),** Creutzfeldt–Jakob disease, Amyloid-related illnesses such as **Alzheimer's disease** as well as intracellular aggregation diseases such as **Huntington's and Parkinson's disease.**

Aβ structure
Neuronal degeneration
associated with Alziemer's

(Tauopathy)
Amylin
(Peptide hormone)
Fibrillation

(Profilament)
Type 2 diabetes

- more **than 20 serious** human diseases are because of abnormal accumulation of amyloid fibrils



Model for prion that causes Creutzfeld-Jacob disease

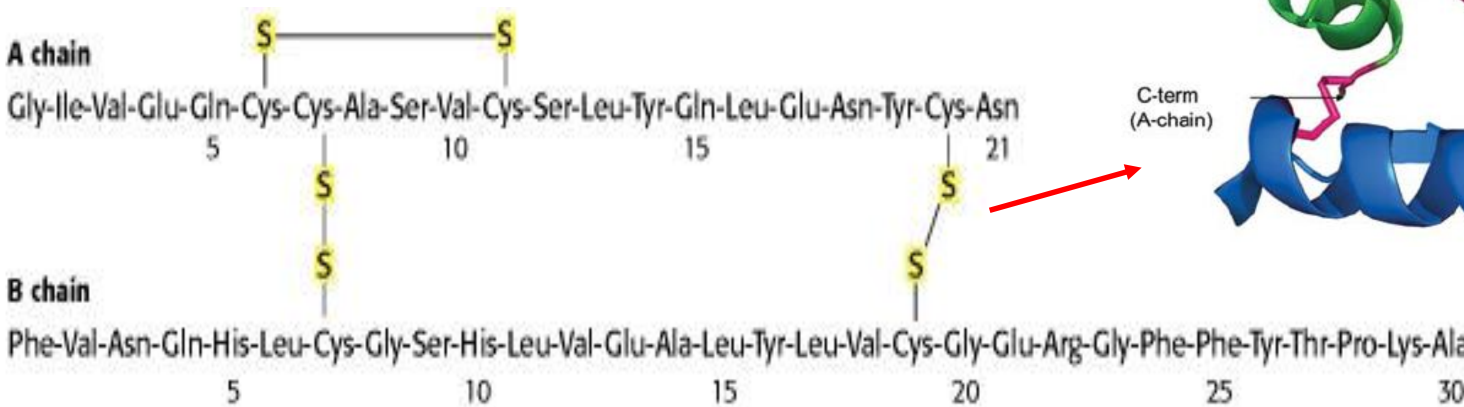
Aducanumab: Drug candidate against Alzheimer's disease:
Worth of Rs. 1,28,400 crore

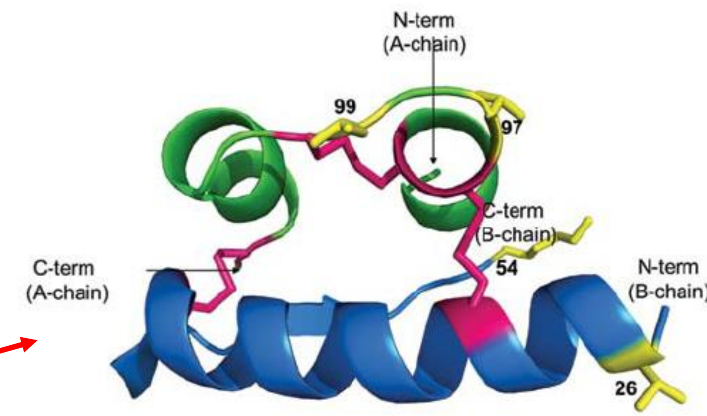
Protein stability and folding

The striking fact is that each protein has a unique, precisely defined amino acid sequence.

Protein folding is the process by which a **protein** structure assumes its functional shape or conformation.

Insulin

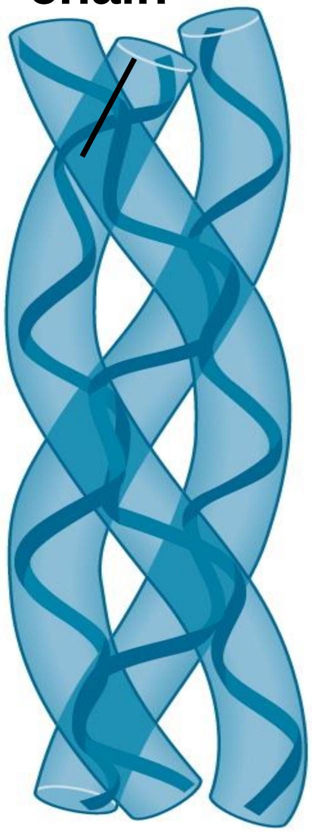




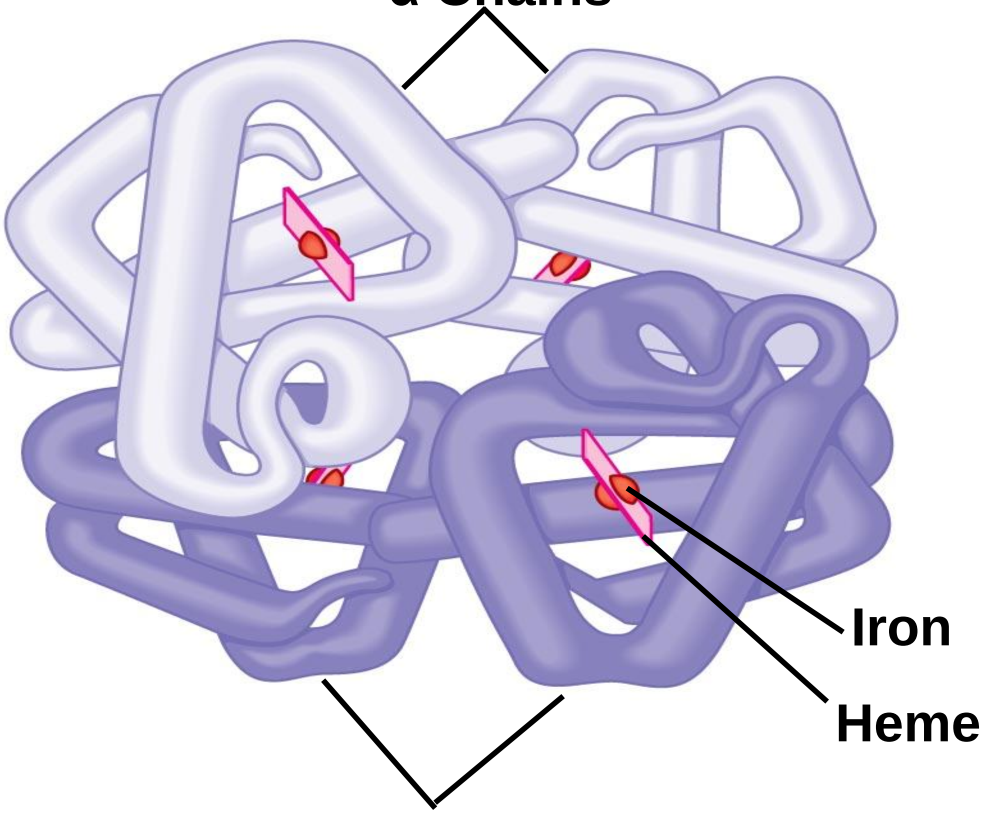
How many different kinds of polypeptides, each composed of 100 amino acids, could be synthesized using the 20 common amino acids?

$20^{100} = 1.26 \times 10^{30} = 1.26$ trillion $\times 10^{18}$!!!!!!!

Misfolding: Life threatening diseases



Collagen

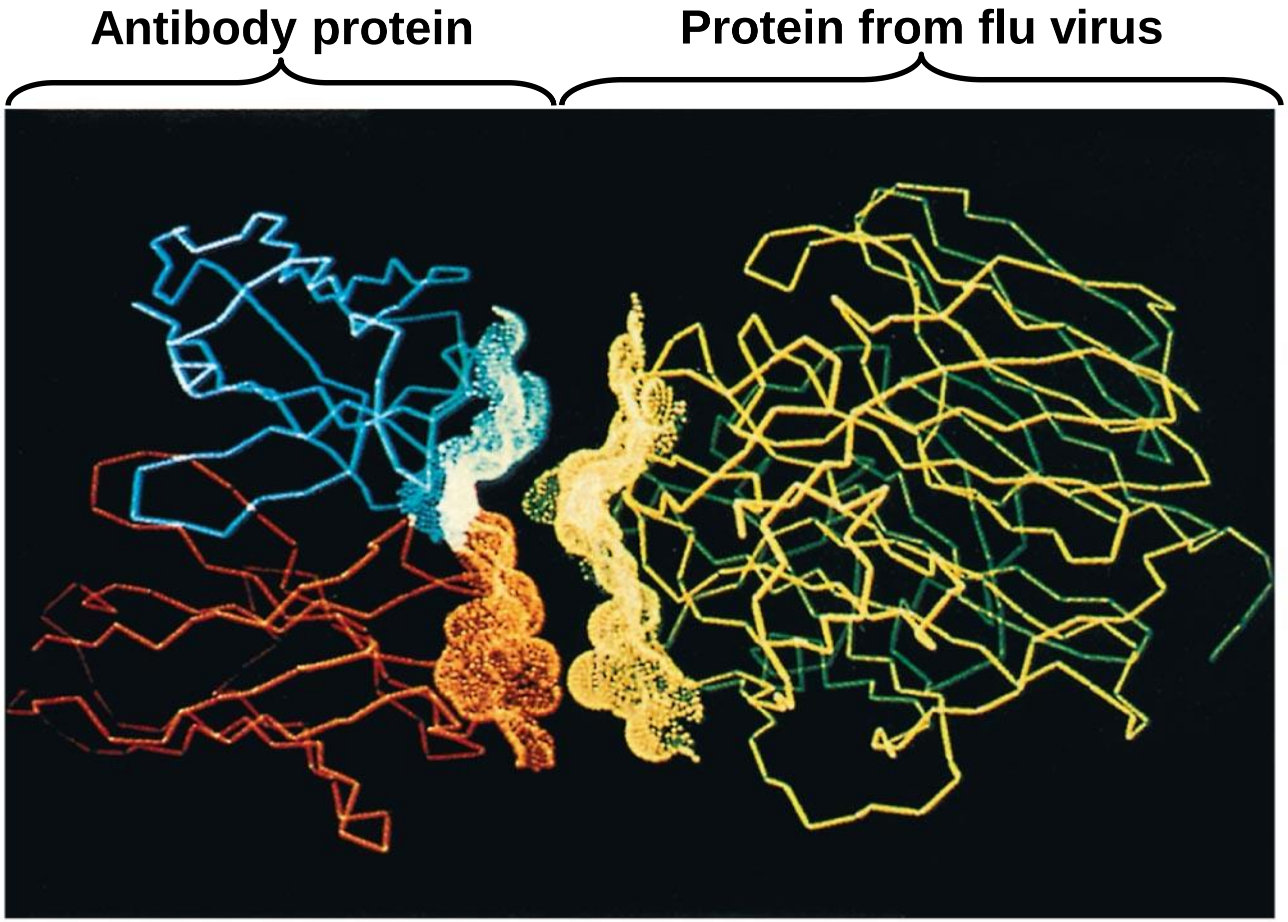


Hemoglobin

Collagen- fibrous protein made of three polypeptides coiled like a rope (fibrous protein)

Hemoglobin- globular protein made of four polypeptides: two alpha and two beta chains

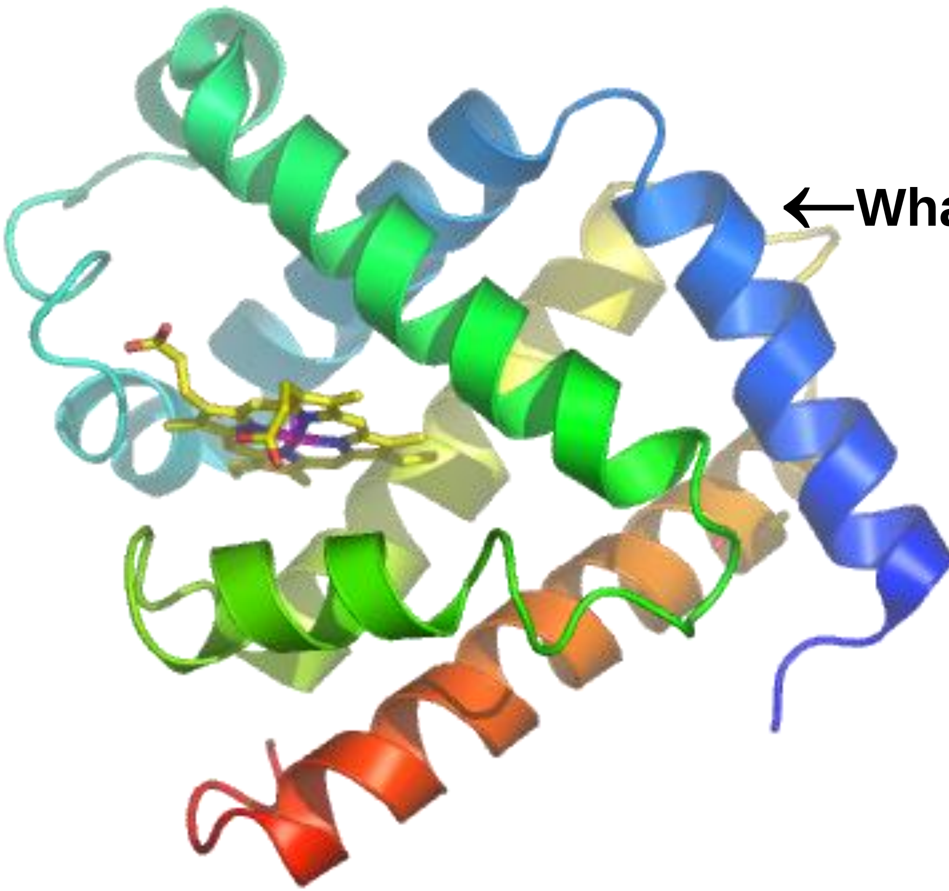
Protein Structure-Function



- Natural signaling molecules called **endorphins** bind to specific receptor proteins on the surface of the brain cells in humans, producing **euphoria** and relieving **pain**.
- **Morphine, heroine, and other opiate drugs mimics endorphins**

- **Thus, the function of a protein for instance, the ability of a receptor proteins to identify and associate with a particular pain relieving signal molecule.**

Overview of Protein Structure



Q:

←Whats this ribbon is?

A:

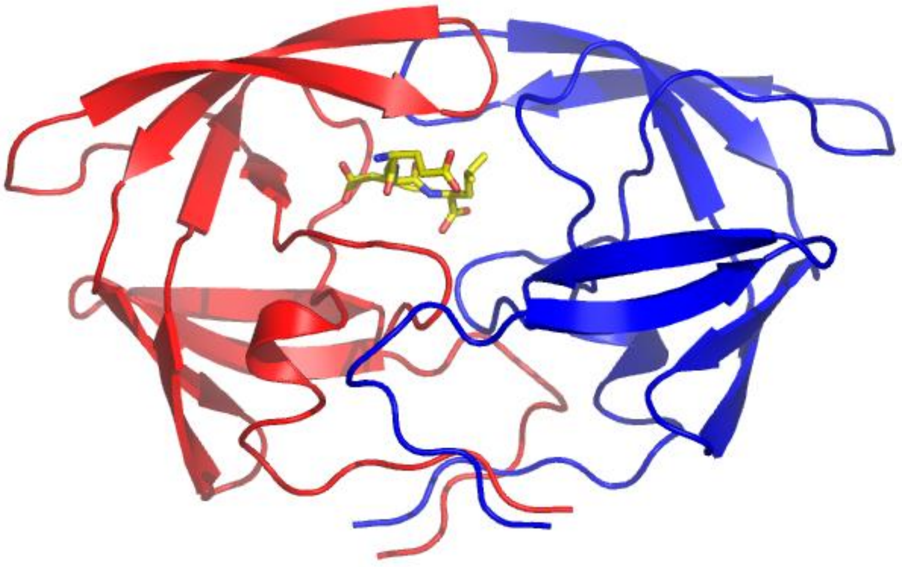
Something, got Noble prize for...

John Kendrew & Max Perutz 1962

Structures of myoglobin & hemoglobin

Why bother about Macromolecules (Proteins, Protein-Protein, Protein-DNA/RNA, DNA/RNA) structures?

- Gives you an visual image of how they look like.
- Study of these macromolecules allows to gain an insight into how really they accomplish their function.
- Drug design: Goldmine for pharmacological research
- Nobel prizes...



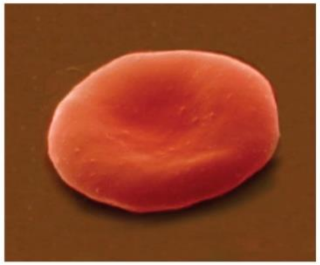
Sickle-Cell Disease: A Change in Primary Structure

Sequence-Structure-Function relationship

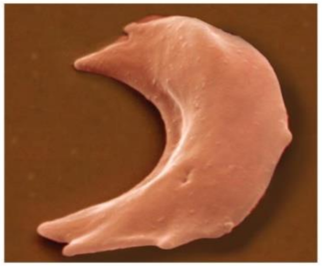
- Small changes in primary structure can affect protein structure and ability to function
- Sickle-cell disease, an inherited blood disorder, results from a single amino acid substitution in the primary structure of the hemoglobin

Normal red blood cells are full of individual hemoglobin molecules, each carrying oxygen.

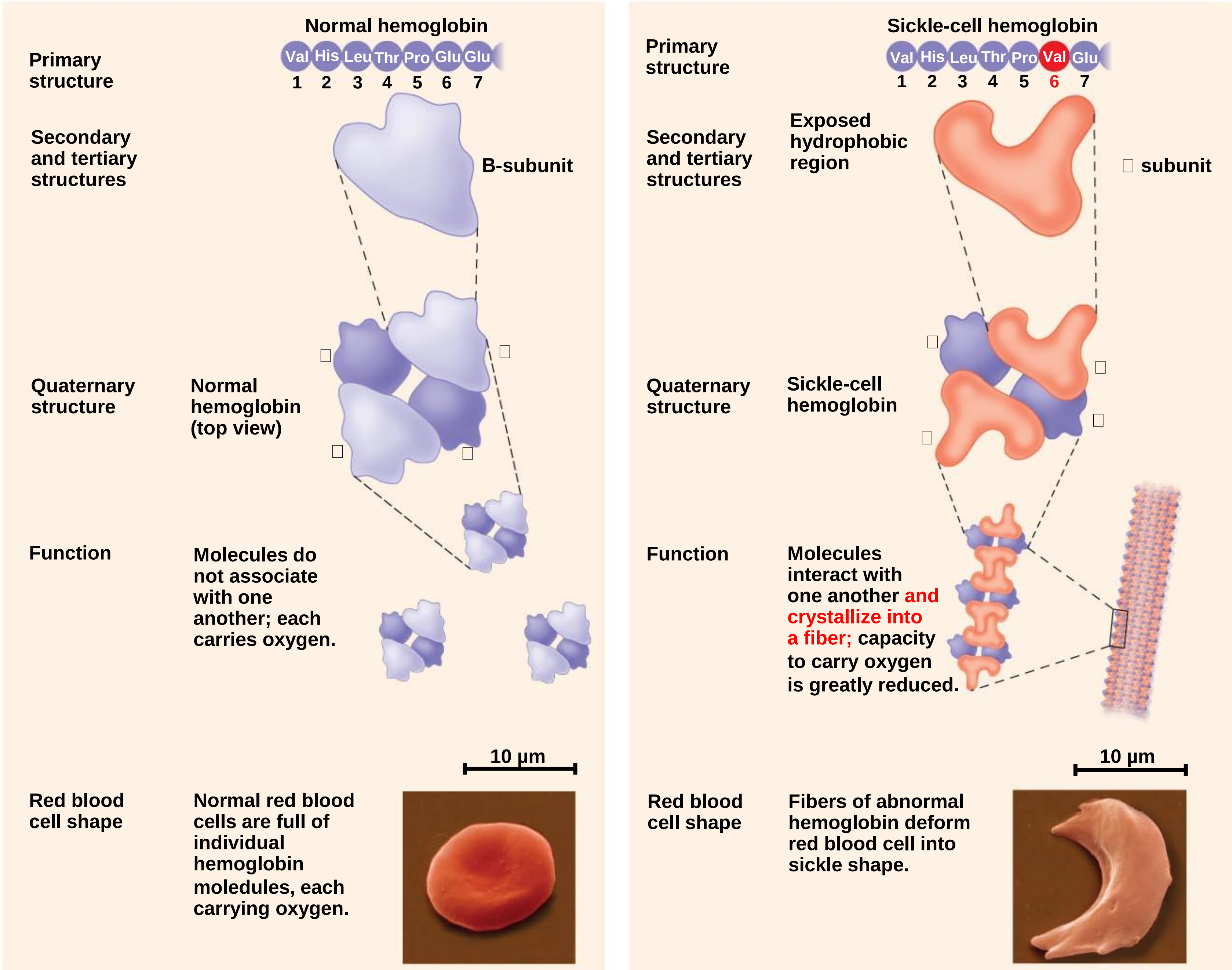
10 µm



10 µm



Fibers of abnormal hemoglobin deform red blood cell into sickle shape.


Normal hemoglobin
Primary structure
Val His Leu Thr Pro Glu Glu
1 2 3 4 5 6 7
Secondary and tertiary structures
B-subunit
Quaternary structure
Normal hemoglobin (top view)
Function
Molecules do not associate with one another; each carries oxygen.
10 µm
Red blood cell shape
Normal red blood cells are full of individual hemoglobin moledules, each carrying oxygen.
Sickle-cell hemoglobin
Primary structure
Val His Leu Thr Pro Val Glu
1 2 3 4 5 6 7
Secondary and tertiary structures
Exposed hydrophobic region
□ subunit
Quaternary structure
Sickle-cell hemoglobin
Function
Molecules interact with one another and crystallize into a fiber; capacity to carry oxygen is greatly reduced.
10 µm
Red blood cell shape
Fibers of abnormal hemoglobin deform red blood cell into sickle shape.

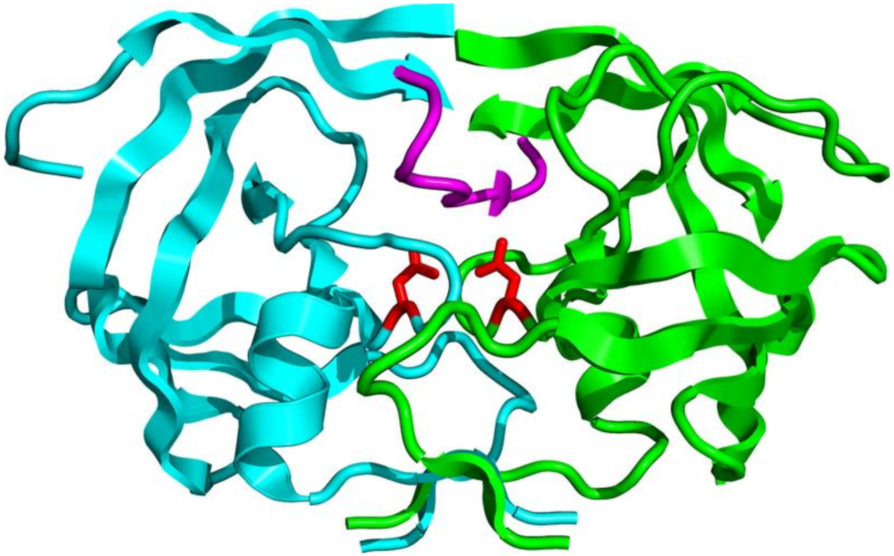
Computer-aided drug design

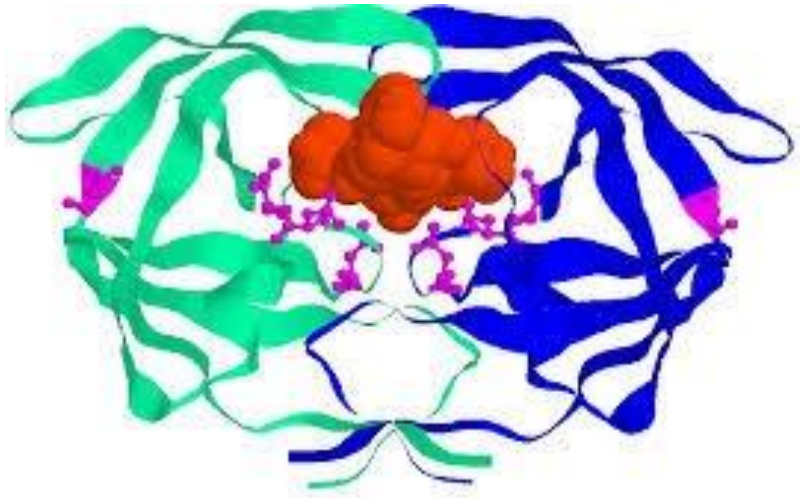
- Drug design is the inventive process of finding new medications for diseases based on the knowledge of a biological target.
- The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient.
- In the most basic sense, drug design involves the design of molecules that are **complementary in shape and charge to the bio-molecular target** with which they interact and therefore will bind to it.
- Drug design frequently relies on **computer modeling techniques**. This type of modeling is sometimes referred to as **computer-aided drug design**. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bio-molecular target is known **as structure-based drug design**.
- The ideal target macromolecule for **structure**-**based drug design** is one that is closely linked to human disease and binds a small molecule in order to carry out a function. The target molecule usually has a well-defined binding pocket.

Drugs derived from structure-based approaches

Nelfinavir in the active site of HIV-1 protease: Cleaves polyprotein

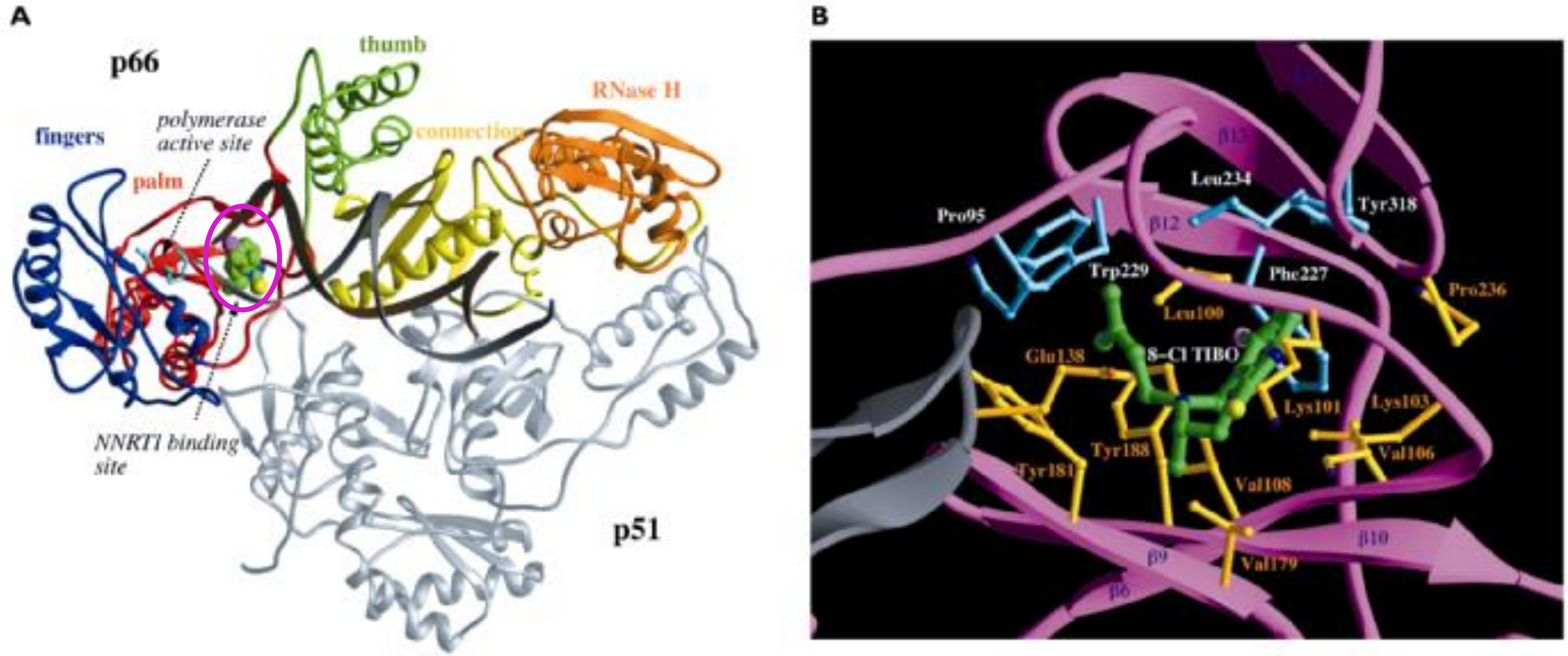
AIDS drug nelfinavir (brand name Viracept) is one of the drugs on the market that can be traced directly to structure-based methods.





Video

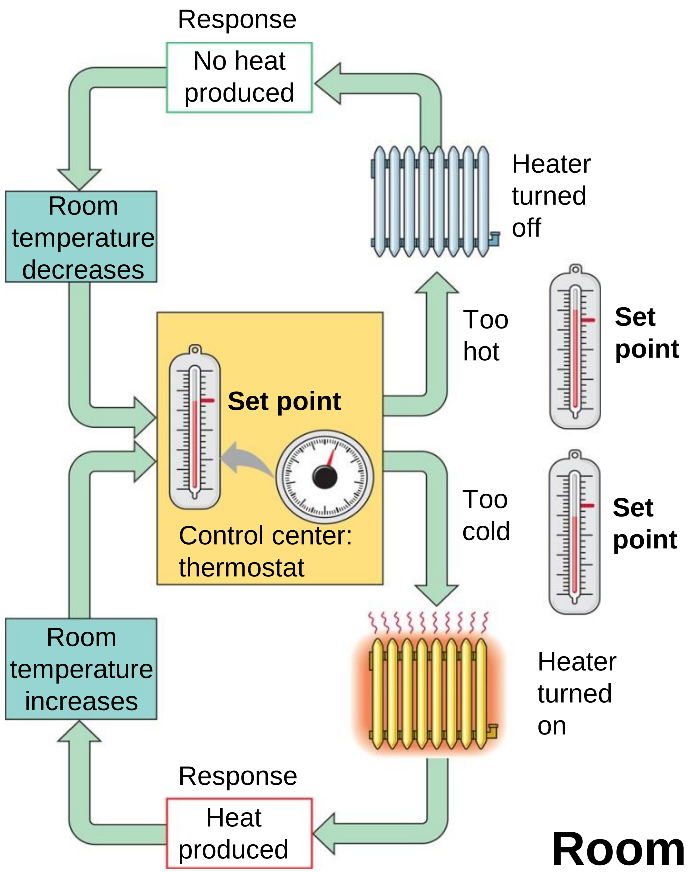
Reverse Transcriptase inhibitors on HIV and Hepatitis B



•Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudin, Abacavir, Emtricitabine, Entecavir, Apricitabine,

Homeostasis

- Any system in dynamic equilibrium tends to reach a steady state, a balance that resists outside forces of change. When such a system is disturbed, built-in regulatory devices respond to the departures to establish a new balance; such a process is one of feedback control.
- All processes of integration and coordination of function, whether mediated by electrical circuits or by nervous and hormonal systems, are examples of homeostatic regulation.
- If homeostasis is successful, life continues; if unsuccessful, disaster or death ensues.



A **receptor (thermometer)**, a **control center (thermostat)**, and **an effectors (heater)**

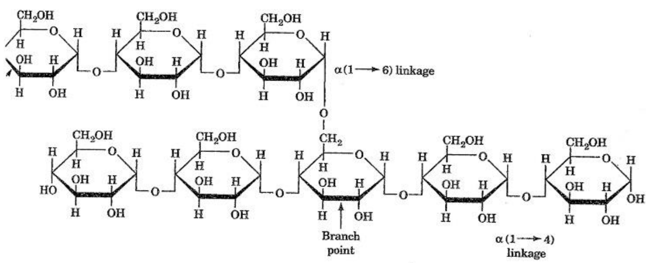
Negative feedback
Positive feedback

Room Heating System: Feed back loop

An animal can be **a regulator/conformers**

Glucose homeostasis and diabetes

(Insulin and Glucagon: Maintains Blood Sugar Level)



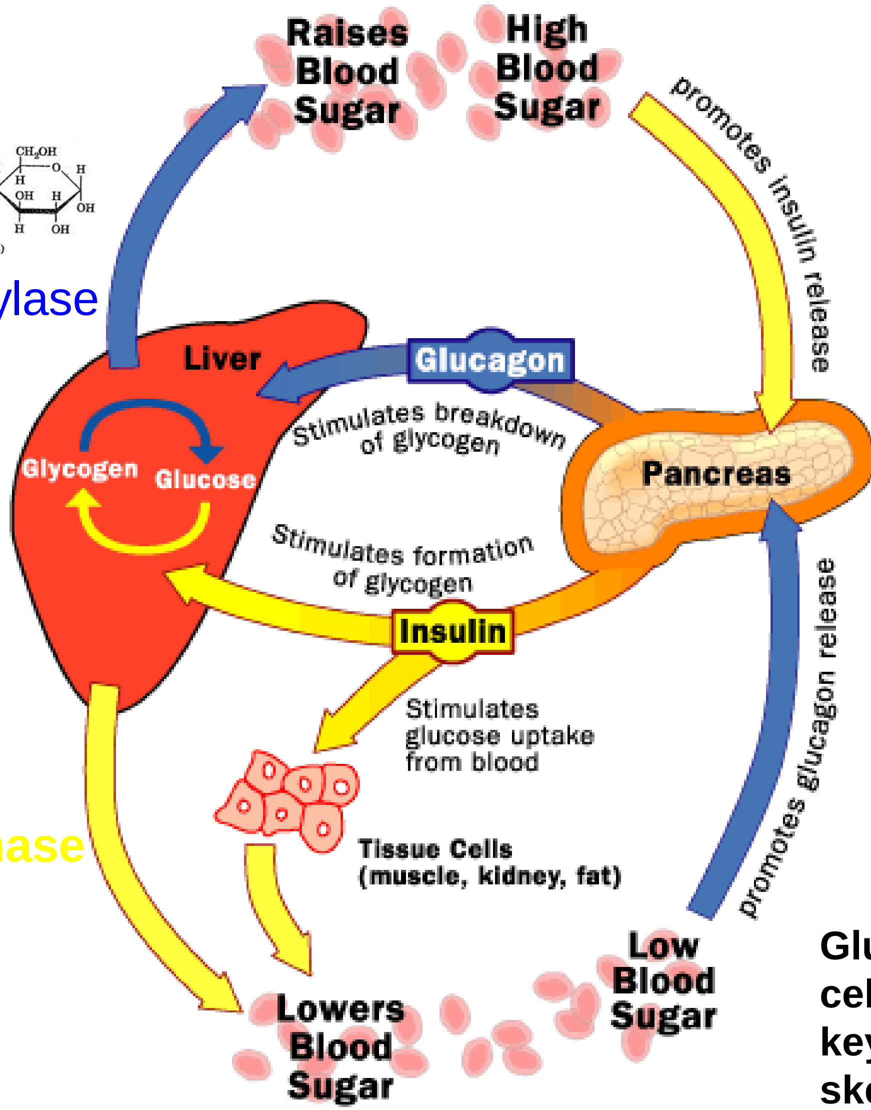
Glycogen phosphorylase

A **receptor**

Control center

Effectors

Glycogen synthase



Key

High Blood Sugar

Low Blood Sugar

70 to 100 mg/dL

1 dL = 100 mL

Glucose is major fuel for cellular respiration and a key source of carbon skeleton for biosynthesis

Maintenance of Glucose Homeostasis

What is Diabetes?

Excess glucose in the blood
(fasting level < 126 mg/dl)

After many years, diabetes can lead to serious problems with your eyes, kidneys, nerves, and gums and teeth. But the most serious problem caused by diabetes is heart disease. When you have diabetes, you are more than twice as likely as people without diabetes to have heart disease or a stroke.

Type 1 diabetes – Juvenile or insulin-dependent diabetes (β cells of pancreas do not make insulin because the body's own immune system has destroyed them)

Type 2 diabetes – Non insulin-dependent diabetes (NIDDM) (insulin is made, but not properly utilized by the cells)

Embroyonic stem cells can be used for generating β cells of pancreases

diabetes.niddk.nih.gov/dm/pubs/**type1**and**2**/index.htm

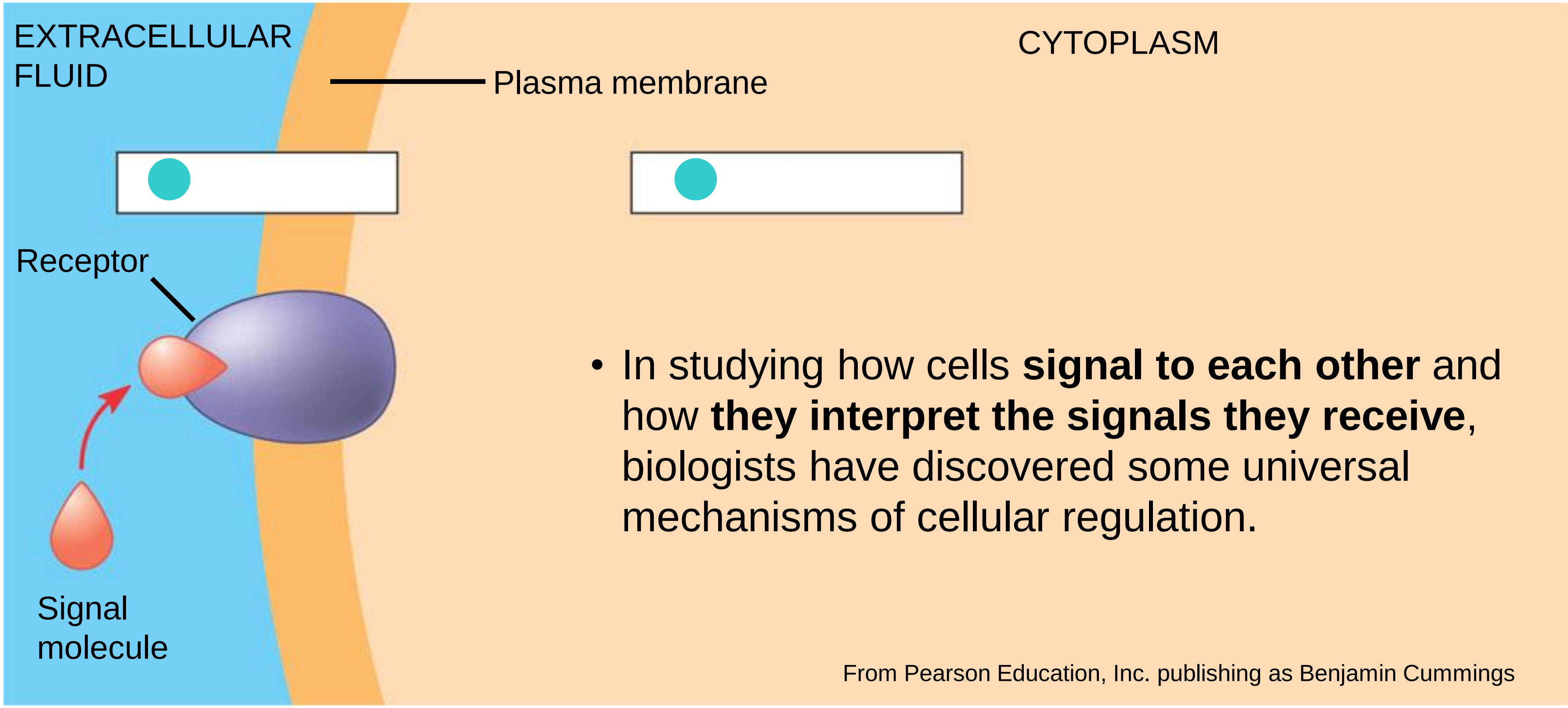
How does insulin act?

How insulin stimulates the release of Glycogen synthase or uptake of Glucose by the cell?

Insulin signaling

Although the details are not complete, insulin secreted by pancreatic β cells cause uptake of glucose by activating the **glucose transporter, GLUT**, in other cells

Pancreatic β cells <u>communicate</u> with other cells using insulin



- In studying how cells **signal to each other** and how **they interpret the signals they receive**, biologists have discovered some universal mechanisms of cellular regulation.

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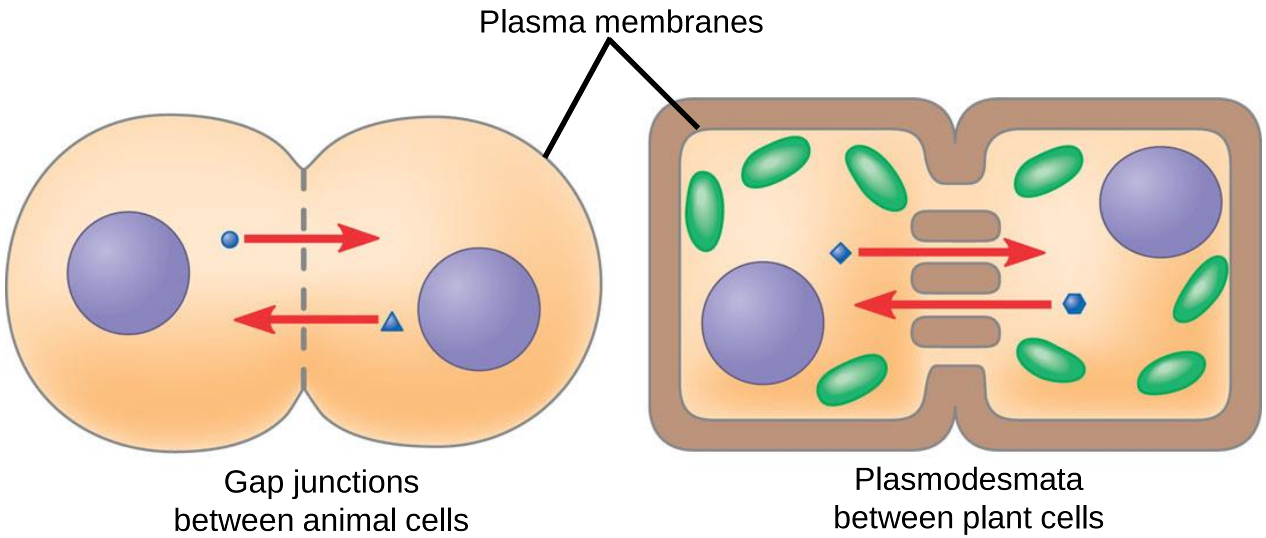
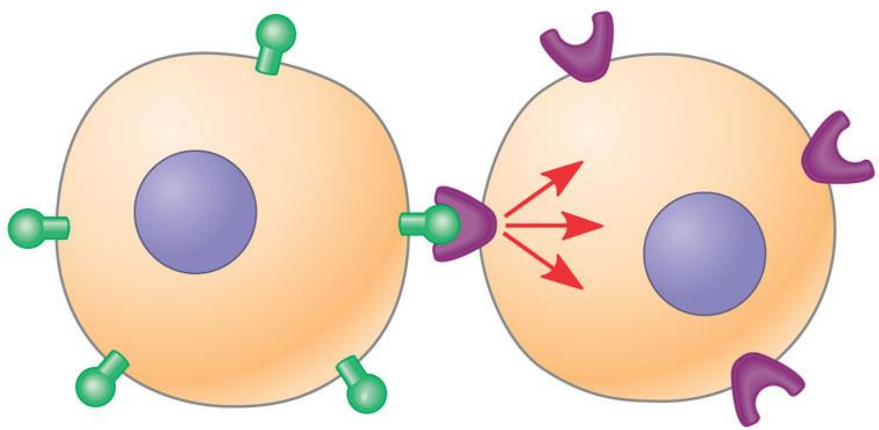
Communication by direct contact between cells

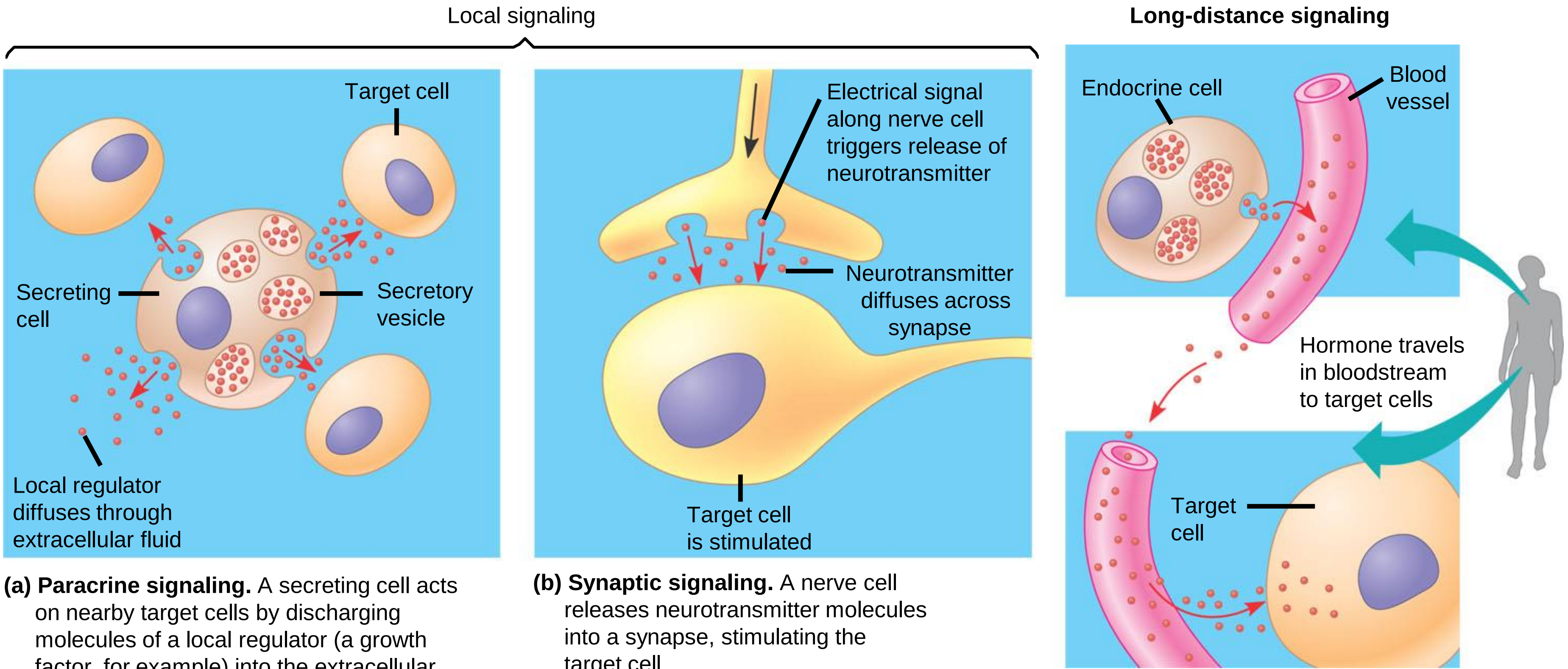


(a) Cell junctions. Both animals and plants have cell junctions that allow molecules to pass readily between adjacent cells without crossing plasma membranes.



(b) Cell-cell recognition. Two cells in an animal may communicate by interaction between molecules protruding from their surfaces.

Local and long-distance cell communication in animals



(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.

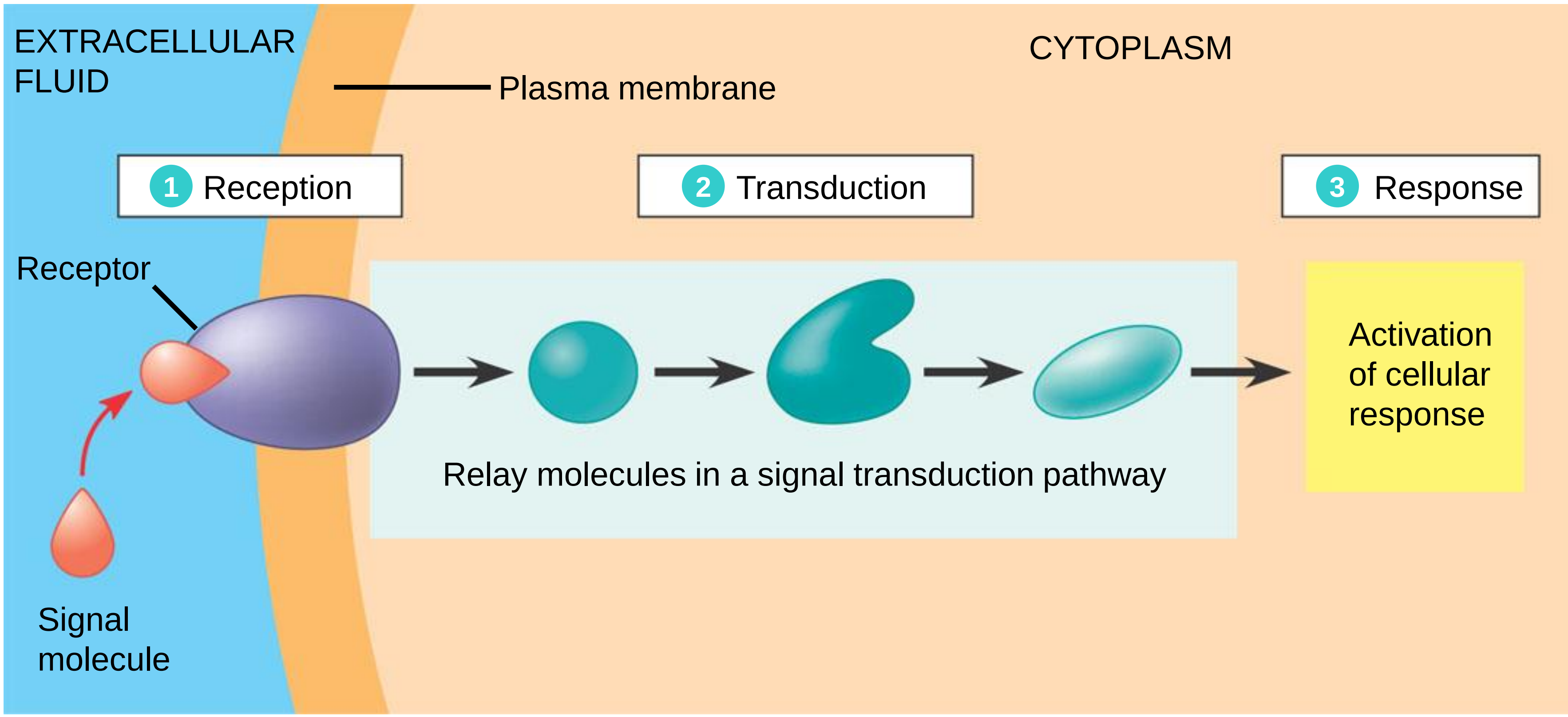
(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

(c) Hormonal signaling. Specialized endocrine cells secrete hormones into body fluids, often the blood. Hormones may reach virtually all body cells.

Snake Venom (Fasciculins)

A **hormone** is a class of regulatory **biochemical** molecules produced in **particular parts of organisms** by specific **cells, glands, and/or tissues** and then transported by the bloodstream to other parts of the body, with the intent of influencing a variety of **physiological and behavioral activities**, such as the processes of digestion, metabolism, growth, reproduction, and mood control.

Overview of cell signaling: Signaling pathway: Cellular Internet



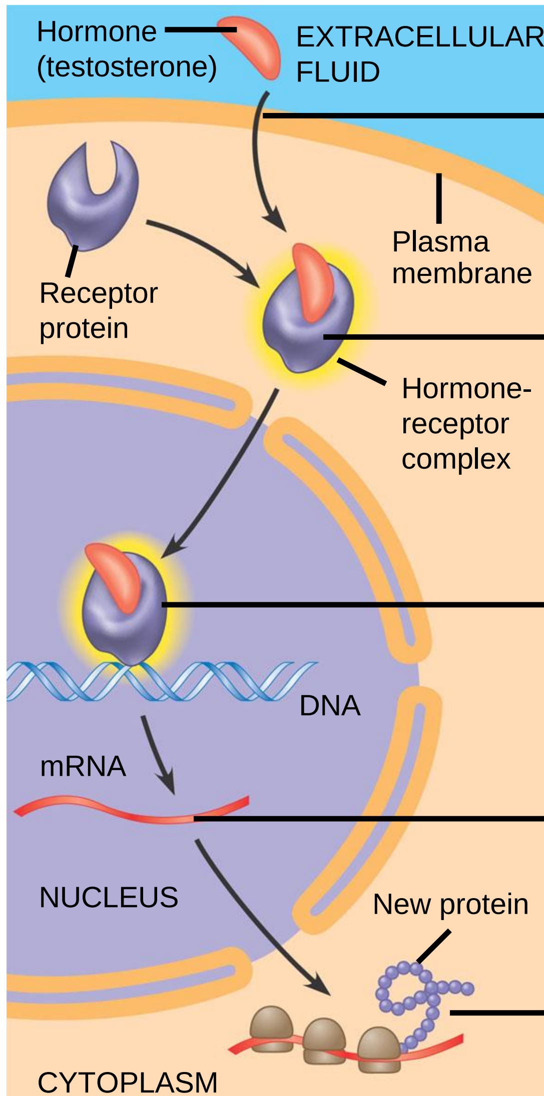
Signal from the environment: Like odor, touch, pathogen infection, Injury, smell, taste

Reception

Intracellular Receptors

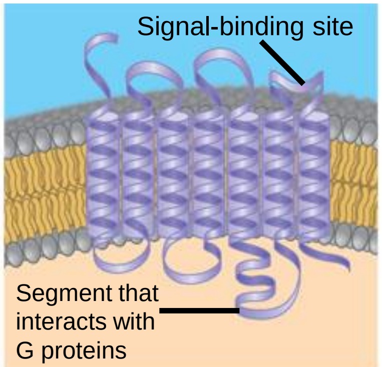
Membrane-bound Receptors

Intracellular receptors



1. The steroid hormone testosterone passes through the plasma membrane.
2. Testosterone binds to a receptor protein in the cytoplasm, activating it.
3. The hormone-receptor complex enters the nucleus and binds to specific genes.
4. The bound protein stimulates the transcription of the gene into mRNA.
5. The mRNA is translated into a specific protein.

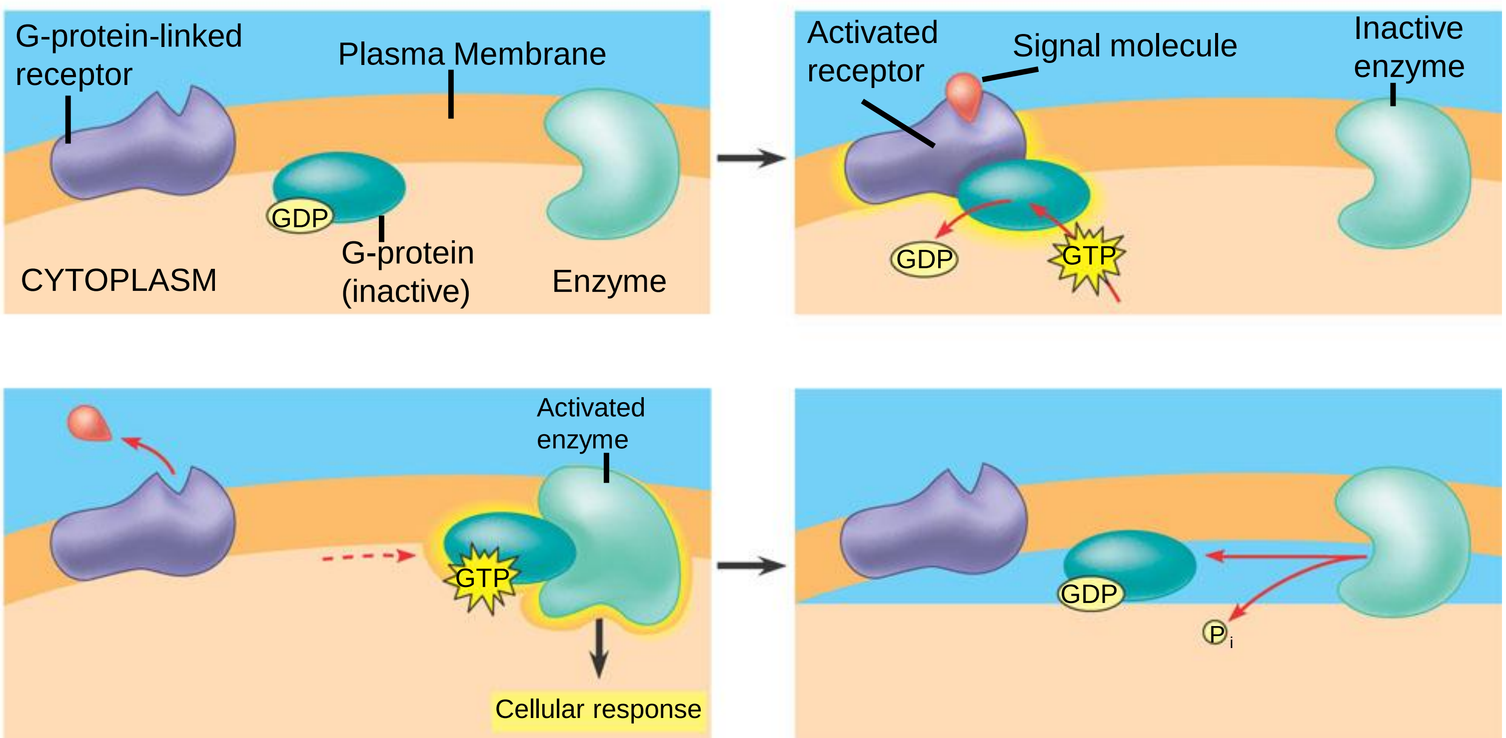
Membrane-bound Receptors



1. G-protein-linked
2. Tyrosine kinases
3. Ion channel

G-PROTEIN-LINKED RECEPTORS

- Herpesvirus: This virus causes Kaposi's sarcoma
- Pathogen toxins (cholera etc)



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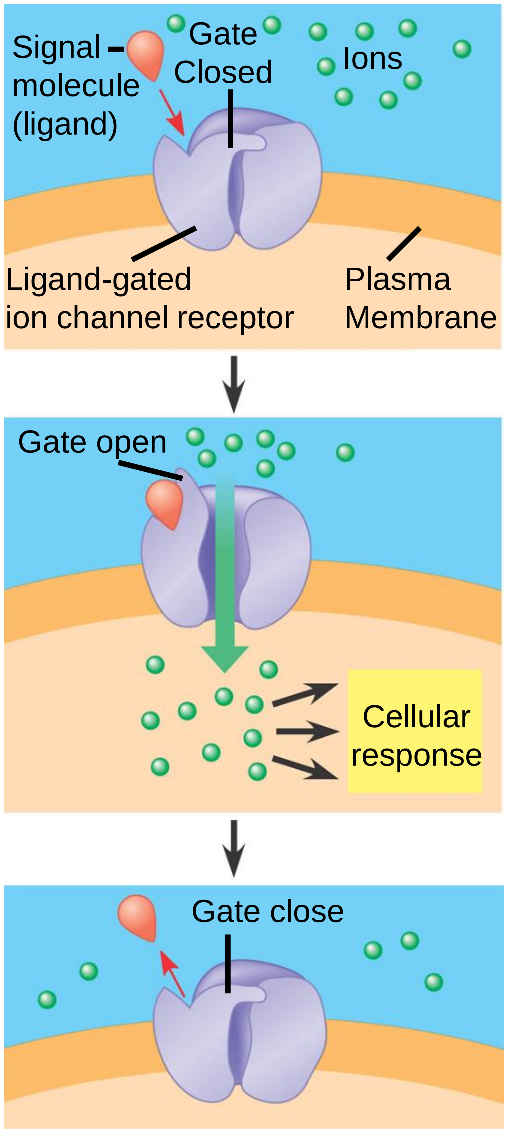
ION CHANNEL RECEPTORS: Nerrvous system



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