بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

Biochemistry

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture 3

Protein Structure Pt.3

Written by : Rand Alkhateeb
Jana Sawafta

Reviewed by : Lamar Khorma

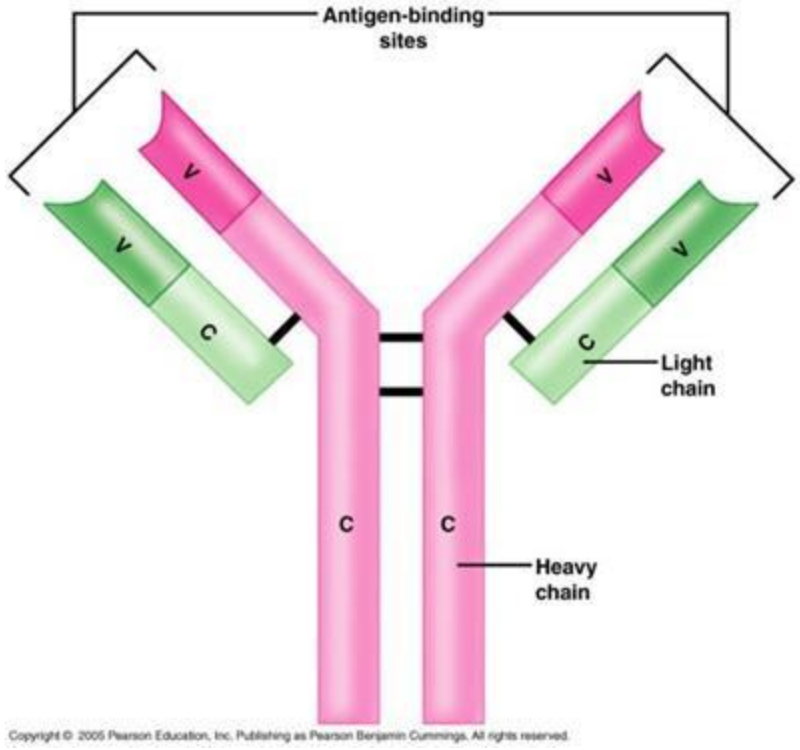
Color coding used in the modified:

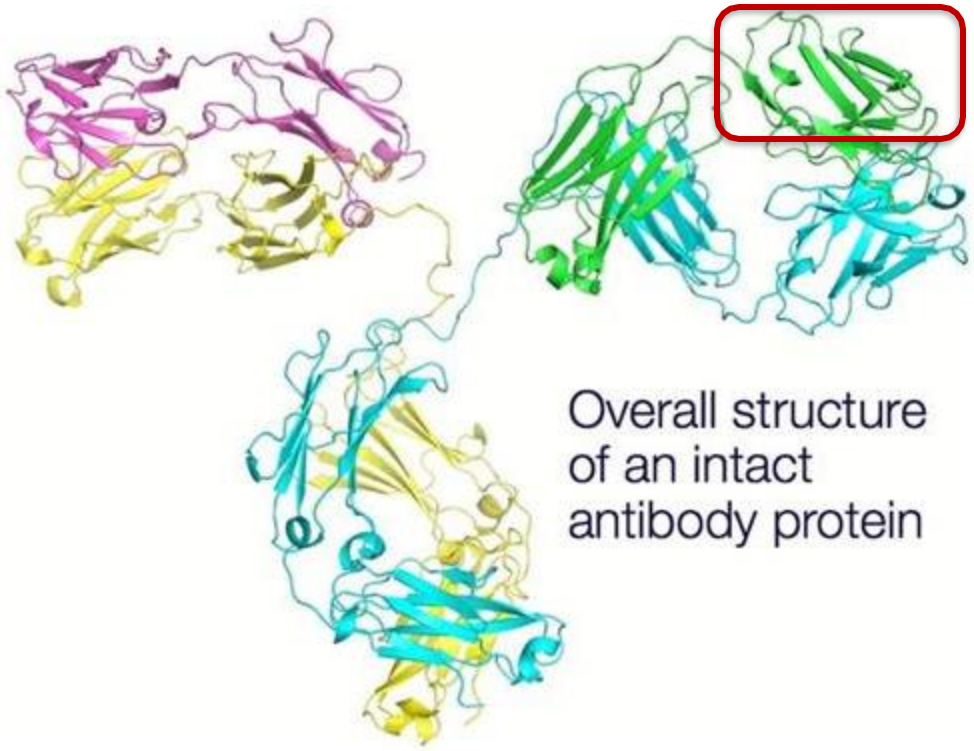
- *Black: the original slides*
- *Blue: the doctor's explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

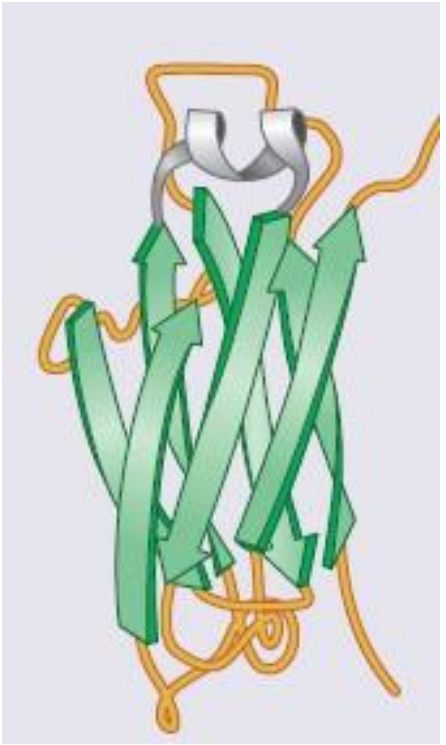
A more complex motif/domain/fold is...

Revision to previous class

- The immunoglobulin fold that enables interaction with molecules of various structures and sizes.
  - Composed of multiple secondary structures
  - Could be relative to the primary structure, also there might be separated, primary structures that once folded they gather
  - Could be consecutive
  - For a protein that binds to the DNA : If it's primary structures belonged to the same gene that is transcripted into that protein are dissected, They can fold independently from the rest of each others onto their original structure , and yet each one can maintain its function







Revision to previous class

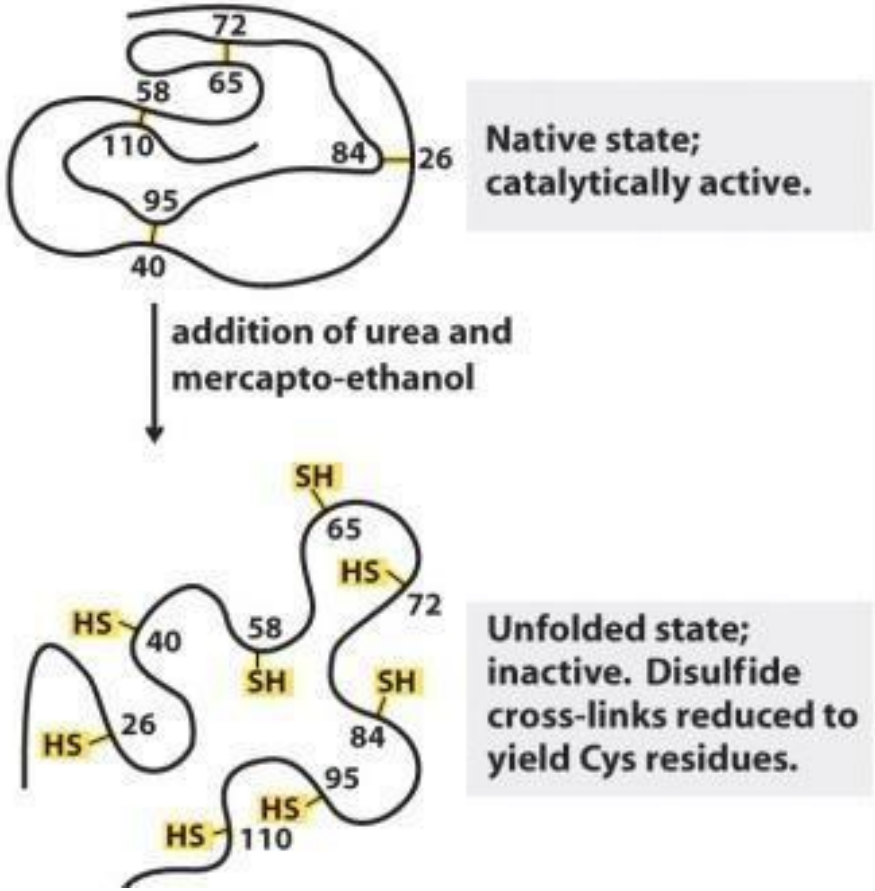
Properties of Proteins:

Denaturation and Renaturation

Revision to previous class

Denaturation

- Denaturation is the disruption of the native conformation of a protein via breaking the noncovalent bonds that determine the structure of a protein
- Complete disruption of tertiary structure is achieved by reduction of the disulfide bonds in a protein
- The denatured protein loses its properties such as activity and become insoluble.



Revision to previous class

Denaturing agents

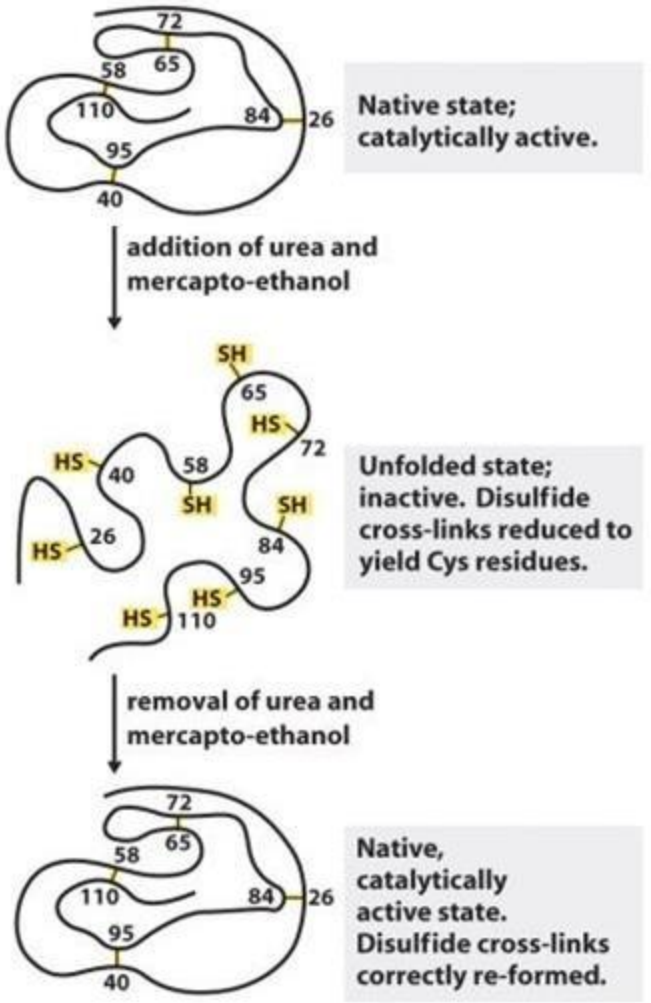
- Heat disrupts low-energy van der Waals forces in proteins
- mechanical agitation (as in blending eggs)
- Extremes of pH: change in the charge of the protein's amino acid side chains (electrostatic and hydrogen bonds).
- Detergents: Triton X-100 (nonionic, uncharged) and sodium dodecyl sulfate (SDS, anionic, charged) disrupt the hydrophobic forces.
  - SDS also disrupt electrostatic interactions.
- Urea and guanidine hydrochloride disrupt hydrogen bonding and hydrophobic interactions.

- Reducing agents: β-mercaptoethanol (β-ME) and dithiothreitol (DTT)
  - Both reduce disulfide bonds.

Revision to previous class

Renaturation

- Renaturation is the process in which the native conformation of a protein is re-acquired.
- Renaturation can occur quickly and spontaneously, and disulfide bonds are formed correctly.
- If a protein is unfolded, it can refold to its correct structure placing the S-S bonds in the right orientation (adjacent to each other prior to formation), then the correct S-S bonds are reformed.
- This is particularly true for small proteins.



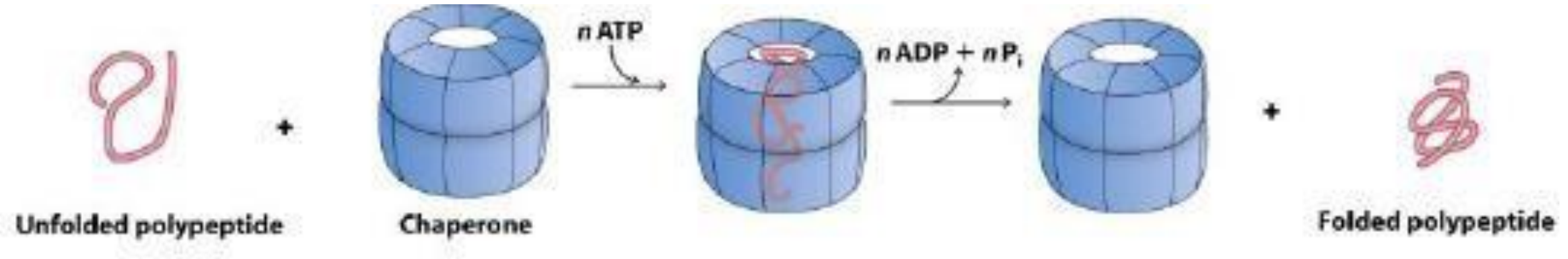
Revision to previous class

Factors that determine protein structure

- The least amount of energy needed to stabilize the protein. This is determined by:
  - The amino acid sequence (the primary structure), mainly the internal residues.
  - The proper angles between the amino acids
    - The different sets of weak noncovalent bonds that form between the mainly the R groups.
    - Non-protein molecules.

Problem solvers: chaperones

- These proteins bind to polypeptide chains and help them fold with the most energetically favorable folding pathway.
- Chaperones also prevent the hydrophobic regions in newly synthesized protein chains from associating with each other to form protein aggregates .

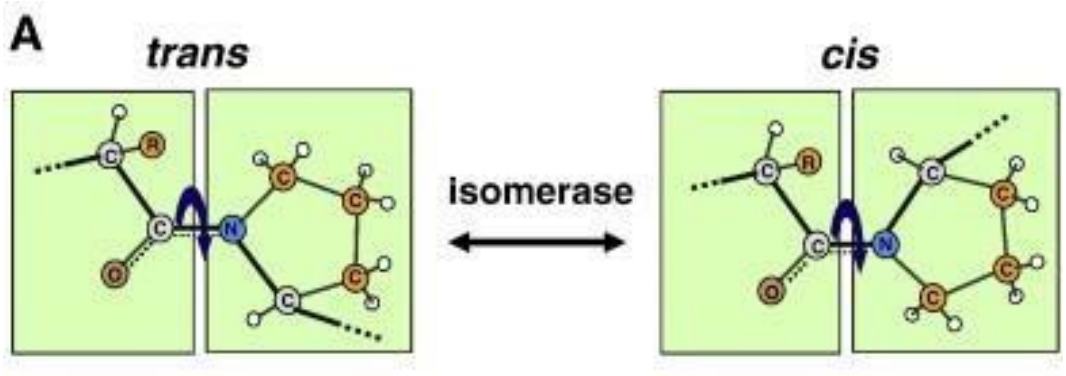


Many diseases are the result of defects in protein folding.

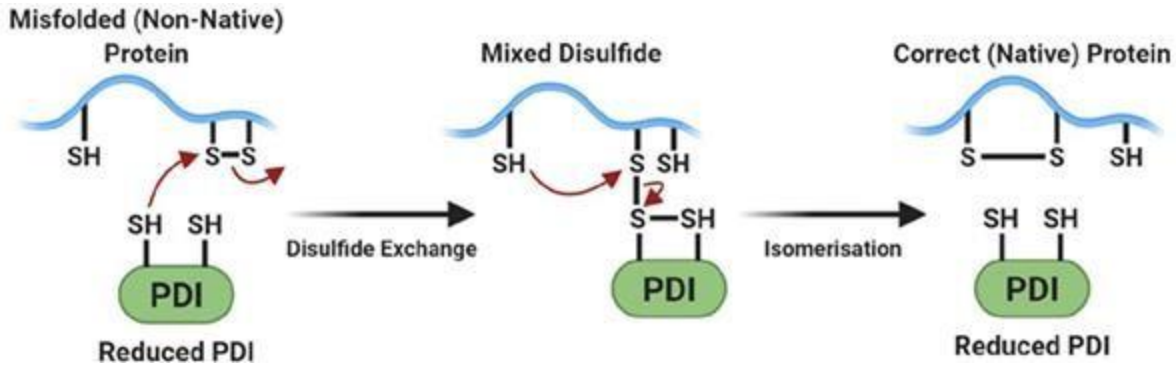
Other players These are enzymes

- A cis–trans isomerase converts a trans peptide bond preceding a proline into the cis conformation, which is well-suited for making hairpin turns.

Recall proline with a 50 cis : 50 trans ratio



- A protein disulfide isomerase, after the protein has folded, breaks and reforms disulfide bonds between the –SH groups of two cysteine residues.

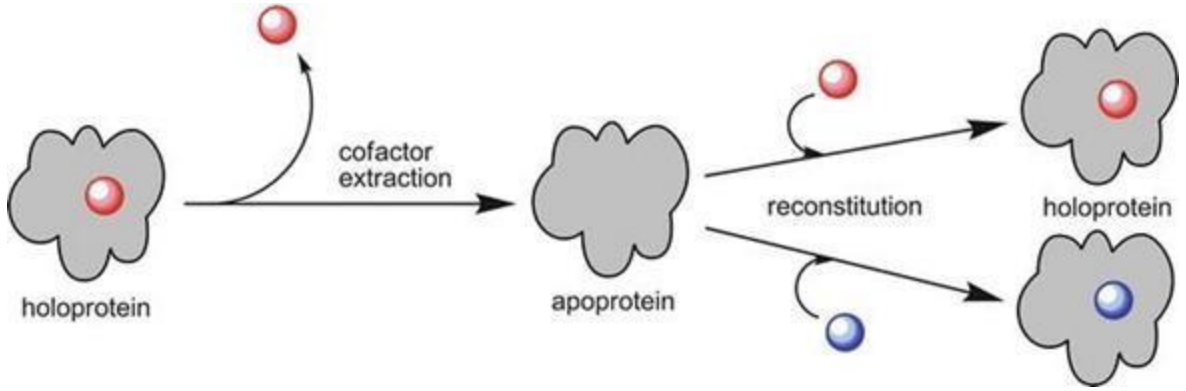


If the folding was unacceptable through the operation, the protein will hopefully degrade

Complex protein structures

Holo- and apo-proteins

- When a protein is conjugated to any associated non-protein components, such as prosthetic groups (organic molecules, like sugars & lipids) or metal ions, the protein is known as a **holoprotein** (also known as (AKA) a conjugated protein).
- If the non-protein component is removed, the protein is known as an **apoprotein**. Ex: apolipoproteins which the proteins that make the lipoprotein
  - In other words, it is the protein portion of a conjugated protein without the attached non-protein group.

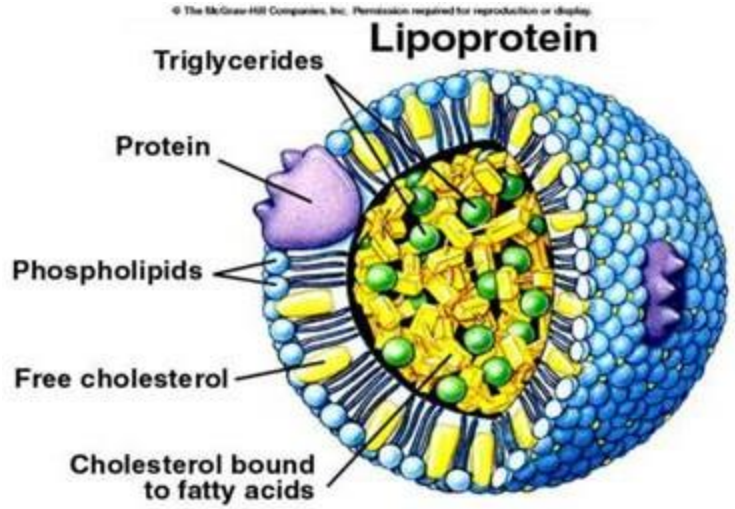


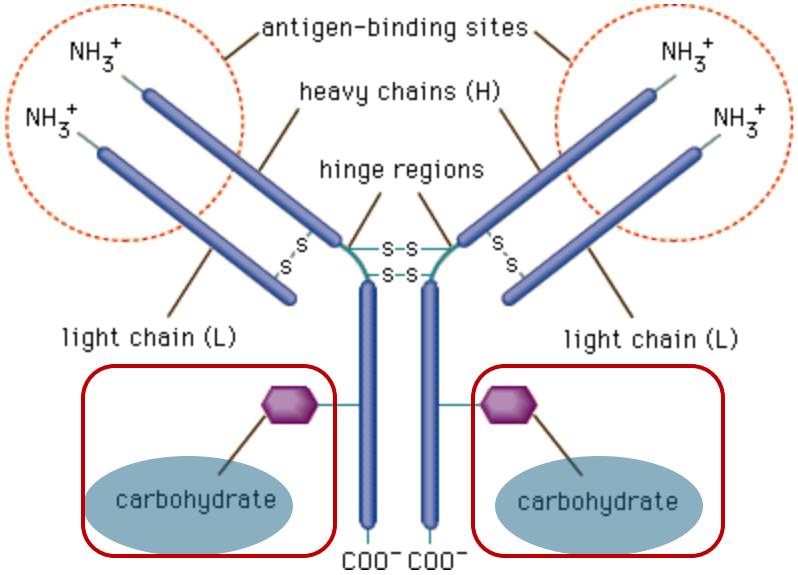
Coenzymes : complex organic molecules (the non-protein group) that assists enzymes in catalyzing biochemical reactions, they bind to proteins

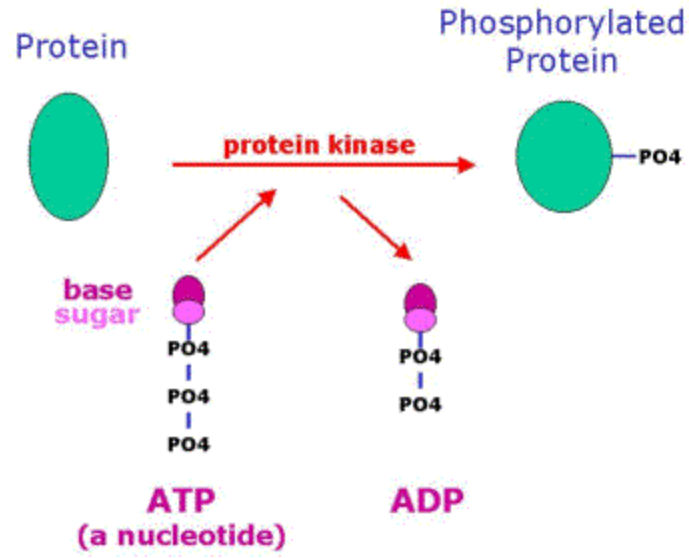
Prosthetic groups: coenzymes or metals that are tightly (covalently) bound to proteins like heme group

Other names of **conjugated proteins**

- Lipoproteins: Proteins associated with lipids
- Phosphoproteins: proteins that are phosphorylated
- Hemoproteins: proteins with heme
- Nucleoproteins: proteins with a nucleic acid
- Glycoproteins: proteins with carbohydrate groups

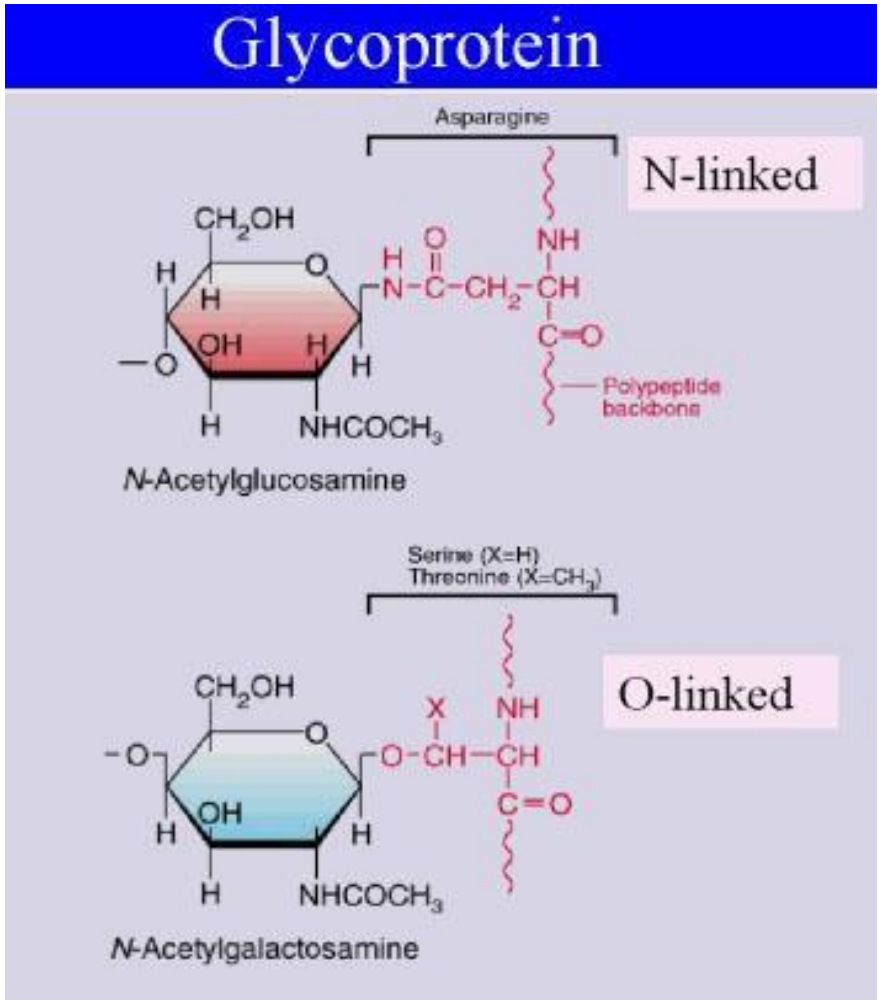






Classes of glycoproteins

- N-linked sugars (attach the anomeric carbon of sugar to the nitrogen (in the R group) of the amino acid)
  - The amide nitrogen of the R-group of **asparagine** NOT glutamine
- O-linked sugars (attach the anomeric carbon of sugar to the oxygen (in the R group) of the amino acid)
  - The hydroxyl groups of either **serine** or **threonine**
  - Occasionally to **hydroxylysine** such as in **collagen** the collagen is a glycoprotein

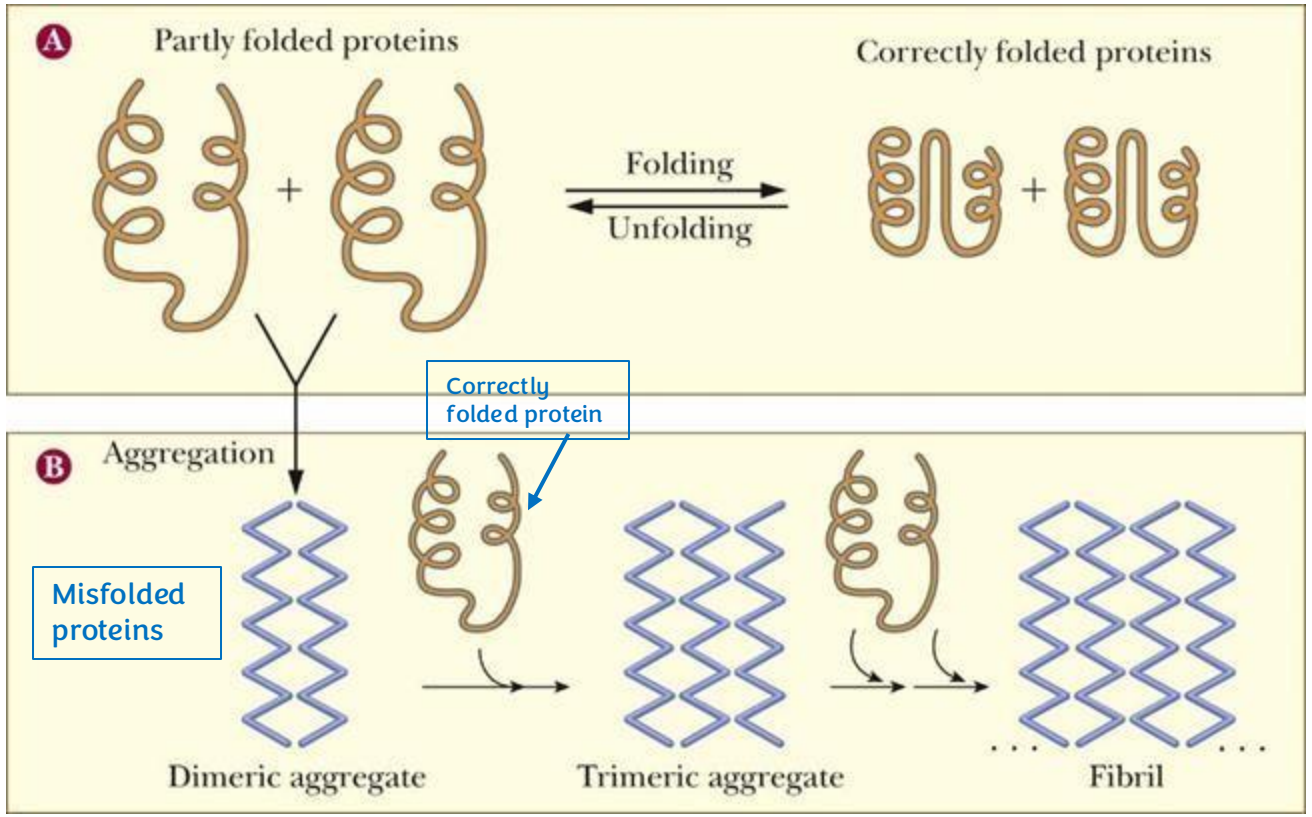


Note that both links are glycosidic linkages, which bound to the anomeric carbon of a sugar

Protein misfolding and diseases

The problem of misfolding

- When proteins do not fold correctly, (when the cell unfolds, then refold the protein again trying to fix it, but if it didn't get fixed , the protein will be degraded)
- their internal hydrophobic regions become exposed and interact with other hydrophobic regions on other molecules, and form aggregates.



The problem is when the proteins aggregate, they interact with other proteins and make them misfolded then they aggregate and make a protein cluster in the cell (cell damage)

Outcome of protein misfolding

- Partly folded or misfolded polypeptides or fragments may sometimes associate with similar chains to form aggregates.

- Aggregates vary in size from soluble dimers and trimers up to insoluble fibrillar structures (amyloid). Aggregate of misfolded proteins

- Both soluble and insoluble aggregates can be **toxic to cells**.

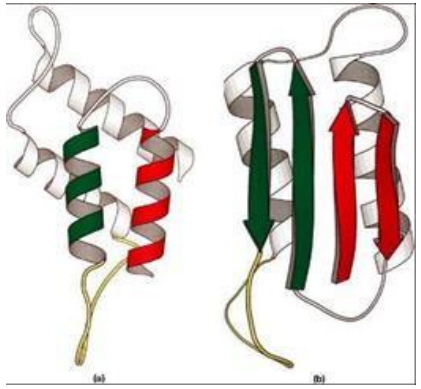
In general, diseases are caused by:
1. **infections** (microorganisms, viruses, and bacteria)
Most diseases, especially in third-world countries in Asia and Africa, are caused by infections because of poor Cleanliness, dirty water, and contact with animals. For example, animals can contaminate crops such as lettuce and tomatoes. If people eat contaminated food, they may get a bacterial infection that causes diarrhea and may need to go to the hospital. Therefore, bacterial infections are a common cause of disease in these countries.

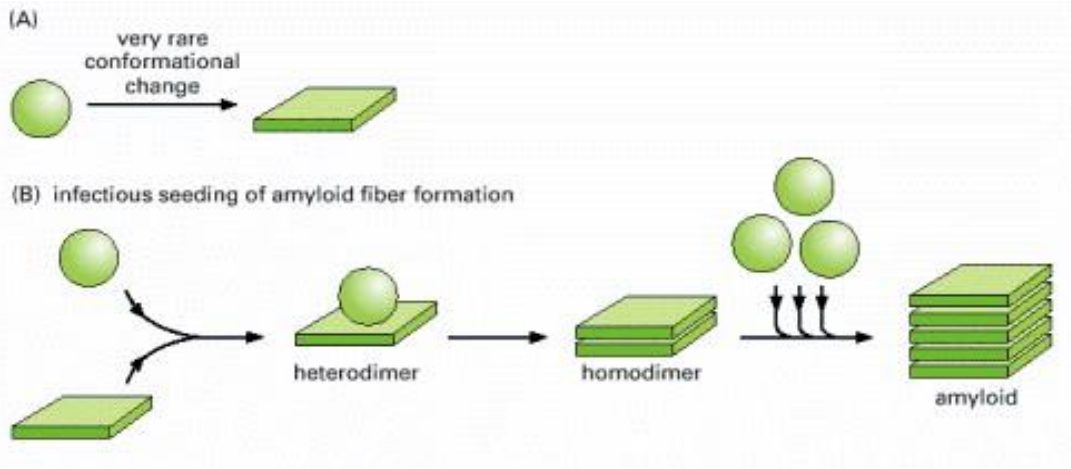
2.**Genetic mutations** can also cause disease. (they are caused by changes in DNA). This is one of the most important topics for us. They occur in Africa, Asia, Europe, and America.

3. 1960s, they discovered a strange disease that was **transmitted by Proteins.** It was something very unusual. They discovered what the protein was and called it the prion protein (a Protein in brain). Based on its name, the disease was called prion disease.

Prion disease

- Striking examples of protein folding-related diseases are prion diseases, It also occurs in animals and has different name, such as Creutzfeldt-Jacob disease (in humans), and mad cow disease (in cows), and scrapie (in sheep). However, they all have the same cause: a misfolded protein called the prion protein.
- Pathological conditions can result if a **brain** protein known to as prion protein **(PrP)** is misfolded into an incorrect form called **PrPsc**.
- PrPC has a lot of **α-helical conformation**, but PrPsc has **more β strands** forming **aggregates**.





The prion protein

- The misfolded prion protein affects all the other prion proteins in the brain.the prion protein, normally has alpha helices. For some unknown reason, these alpha helices turn into beta strands, leading to protein aggregation. One after another, they form amyloid, which consists of protein aggregates.
- The disease is caused by a transmissible agent
- Abnormal protein can be acquired by
  - Infection (If we eat meat from an infected cow, we may become infected)
  - Inheritance
  - Spontaneously (For unknown reason)

- **Mad Cow disease :**

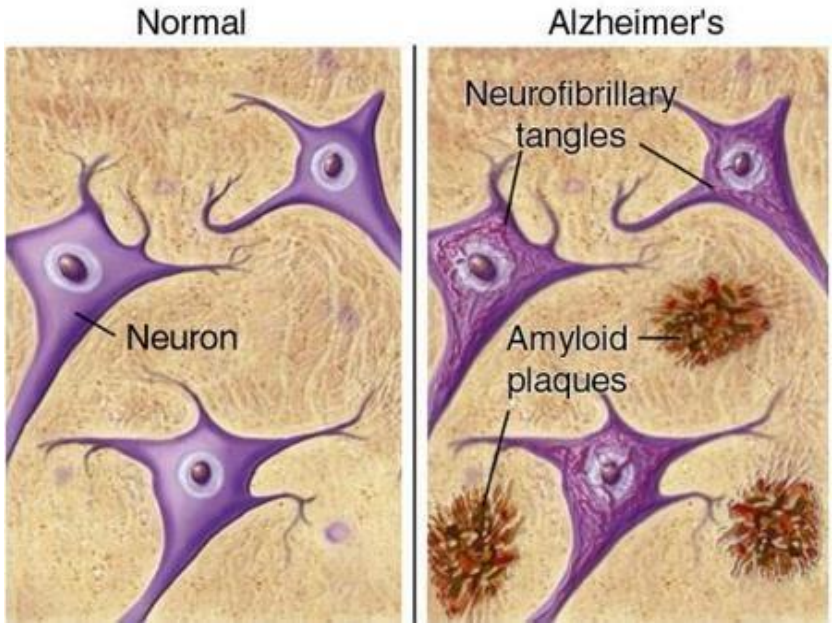
  The cows become "mad" and develop shaking in their legs. That is why, for example, if one country wants to damage another country's economy, all it has to do is spread a rumor that "your cattle have mad cow disease." This destroys the country's reputation because no one wants to buy meat from that country if it has mad cow disease.

  In the UK and brazil, about twenty years ago, mad cow disease actually spread. It was caused by a misfolded prion protein that affected the brain and damaged nerve cells. The disease caused massive economic damage, and thousands of cows had to be slaughtered to prevent the disease from spreading to humans.

Alzheimer's Disease

Alzheimer's disease has a similar idea. Alzheimer's disease is a type of **dementia**. Patients with Alzheimer's forget almost everything; they may not recognize things like eating or drinking, and they may not know when they need food or water.

- Not transmissible between individuals

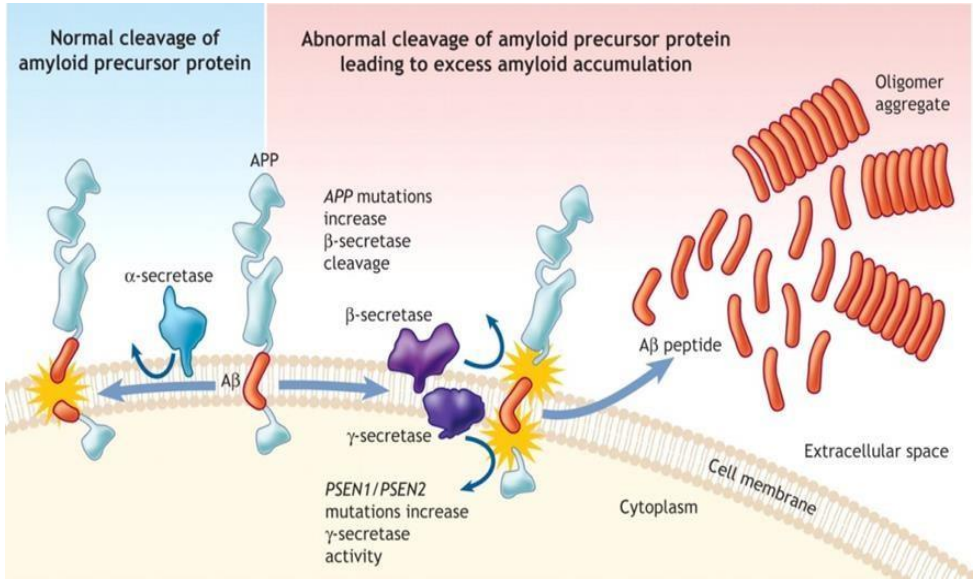


This disease is caused by protein aggregates,

Extracellular plaques of protein aggregates of a protein called tau and another known as amyloid peptides (Aβ) damage neurons (the word amyloid came from observing the accumulation of this protein in Alzheimer's disease.) The tau protein is found inside the cell, while the amyloid protein accumulates outside the cell, on the surface. Because of this aggregates, Alzheimer's patients develop amyloid plaques. Plaques are dark spots found in the tissue.

Formation of plaques

There are many theories about what causes the disease. **Normally**, proteins on the cell's surface undergo a process called turnover. Turnover means that old proteins are removed and replaced with new ones.



This process is called **shedding**, similar to how animals shed old skin (snacks) or hair (cats) to allow renewal.
However, in Alzheimer's disease -based on the theory-, shedding happens abnormally. This causes the release of **hydrophobic regions** of proteins. When many hydrophobic regions are released, they stick together and form amyloid plaques. These amyloid plaques damage the tissues and nerve cells, leading to Alzheimer's disease (dementia).

The exact cause is still unknown, but scientists are currently studying the process to understand it better.

Extra informations from the doctor

Recently, new research has been done on a disease called **fibromyalgia**. Several years ago, some people, especially women, were told that they were exaggerating their pain. However, researchers discovered that fibromyalgia is a real disease in which the pain threshold is lower. This means that normal sensations or small touches can be **amplified** and felt as stronger pain.

It can occur in males, but it is more common in females. Researchers performed large genetic studies, examining the DNA of around 2.5 million people with fibromyalgia to find common genetic mutations. They discovered 26 genes involved in this disease. These genes do not necessarily cause the disease directly, but they are related to it.
Now, we know that fibromyalgia is a disease related to the nervous system.

*Many diseases are caused by problems in one system, such as the immune system or muscles. However, some diseases involve multiple systems, including the central nervous system and muscles, and the exact cause may still be unknown.

Pharmacological (chemical) chaperones

Chaperones, in general, are proteins inside the body that are naturally present. They help proteins fold correctly. (slide 10)
Pharmacological/chemical chaperones are not natural; they are drugs.

Genetic mutations may cause defective protein folding resulting in the production of misfolded proteins, which are destined for degradation inside the cells.
They bind to the protein, and when the enzymes that are supposed to degrade the misfolded protein come, they prevent those enzymes from acting. As a result, they keep the misfolded protein present. This misfolded protein still has some activity; it is not 100% functional, but it does have activity. For example, it may have only 10% of the activity of the normal protein. It means it has residual activity. Therefore, the drug allows it to remain inside the cell and continue functioning.

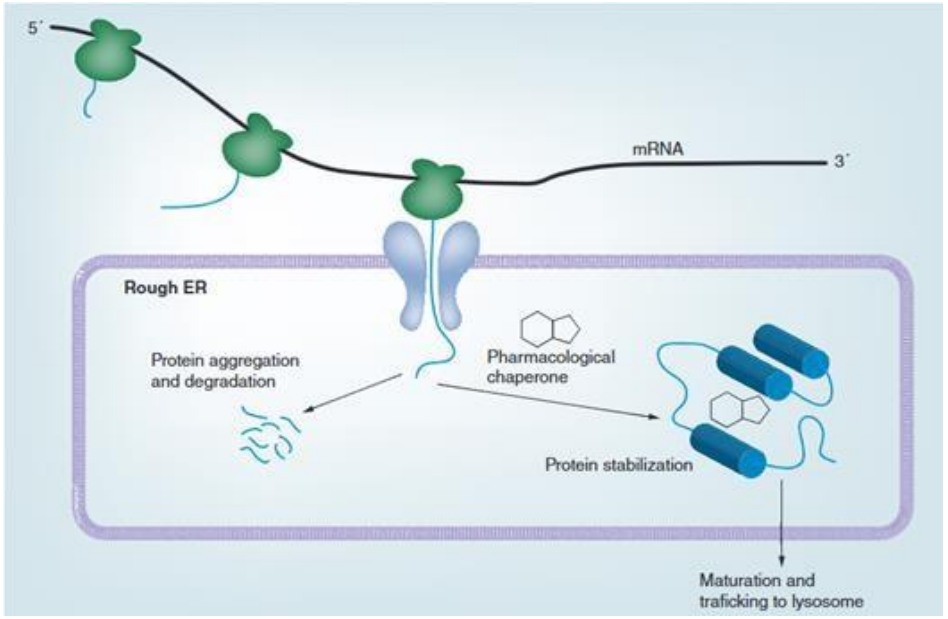
Humans usually have two copies of each gene, one from the father and the other from the mother.
If one of the genes stops working and the other copy of the same gene is still functional, this is not a disease because one gene is enough for the enzymes and proteins to function. So, if 10% of the proteins are not working, it's fine.

Even in tissues, muscular dystrophy disease affects the muscles, leading to the death of muscle cells. in mice, A few years ago, they were able to repair 10% of the cells in the muscles, and the disease disappeared. There is no need to repair every single cell. If we have functioning cells, the disease will go away. It is not necessary for all the cells to be functional. Ten percent is enough to protect the organism from the disease.

So, this mechanism prevented the misfolded protein or the partially folded protein from undergoing degradation. Since it still has some activity. It works a little better than not working at all.

Pharmacological (chemical) chaperones

- Genetic mutations may cause defective protein folding resulting in the production of misfolded proteins, which are destined for degradation inside the cells.
- Chemical chaperones are small-molecule drugs that work by:
  - Preventing the degradation of misfolded proteins that may still have some residual activity.
    - Sphingolipidoses (Singular: Sphingolipidosis, Sphingolipidosis is a disease that is connected to the metabolism of sphingolipids, which are mainly present in the central nervous system. Therefore, they affect the physiology and the growth of the brain.)
  - Binding to the mutated protein and, consequently, aiding in its folding.
    - Cystic fibrosis (is a disease that affects the lungs. Fibrosis tissue formation occur inside the lungs, causing difficulty in breathing properly. Usually, affected individuals die in their twenties.)

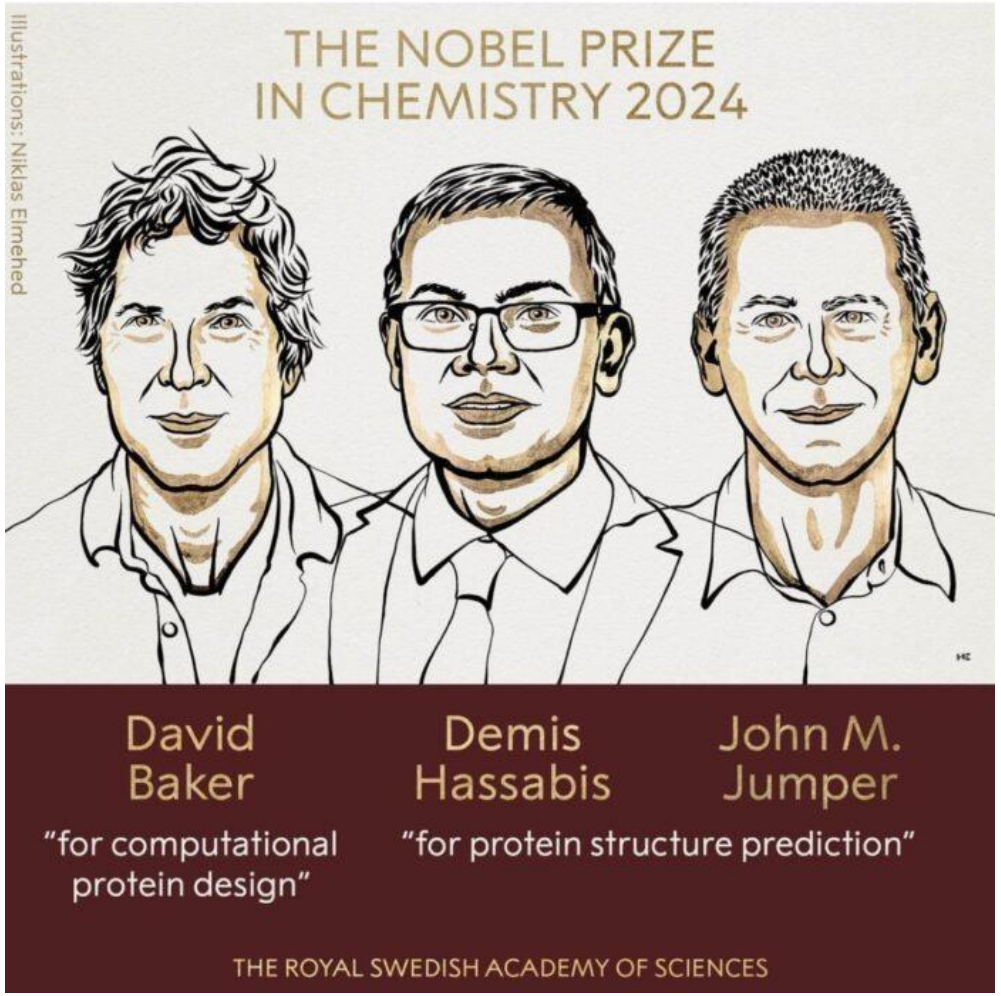


Extra informations from the doctor about AI and medicine

IBM one of the largest computer company at that time wanted to make a collection of protein structures, so we could know the amino acid sequence and the structure of the protein. Because if we know the structure, we can know the function, we can design treatments, and we can develop drugs. We can also know where we need to bind the drug, and we can understand the distances between atoms and amino acids. So, since the 1960s, they have been working on this project.

Tunyasuvunakool, K., Adler, J., Wu, Z. et al. Highly accurate protein structure prediction for the human proteome. Nature (2021). https://doi.org/10.1038/s41586-021-03828-1

In 2021, research papers in the two best scientific journals at the current time, Science and Nature, showed that they used AI to make predictions of protein structures. They said that the predictions were accurate.



Medscape Medical News

AI's Drug Revolution, Part 3: Making Proteins From Scratch

Sarah Amandolare
September 11, 2024

DECEMBER 5, 2024

Protein engineering research reveals the mysteries of life, enabling advances in pharmaceuticals

by Ula Chrobak, Stanford University

From the 1960s until the 2020s, they were trying to determine this information using very complicated methods.
It was successful, but it took a long time. During this period, they were able to determine the structures of around **one million** proteins from different organisms, including humans, mice, and others.
After this AI tool appeared, they were able to determine the structures of **500 million** proteins. As a result, they received the Nobel Prize within two years.
One of the Nobel Prize winners, Demis Hassabis, -not david baker as the doctor said- comes from a computer science background rather than biochemistry or medicine. Despite that, he was awarded the Nobel Prize in Chemistry.

Test yourself

Quiz

Additional Resources:

Reference Used:

Prof. Mamoun Ahram‘s live lecture

Extra References for the Reader to Use:

Marks’ Basic Medical Biochemistry

رسالة من الفريق العلمي:

يُصبح العبدُ ويُمسي غارقًا في بحارٍ من نعم الله، فيُعمي الشيطانُ بصرَه عنها، ويُعلِّق قلبَه ببلاءٍ واحد، حتى ينسى ما أفاض الله عليه من العافية والفضل.

وهكذا شأنُ النفس إذا غفلت، تُحصي ما فُقد، وتغفل عمَّا بقي، وتُعظِّم موضع الألم، وتنسى سعة النِّعم.

فاحذر أن يُنسيك بلاءٌ واحدٌ آلافَ النِّعم، فإن من عرف فضلَ الله، استحيا أن يشكو الكثير لأجل القليل، وحمد ربَّه على ما أبقى، قبل أن يتحسَّر على ما ابتلى.

قال تعالى: (وَآتَاكُم مِّن كُلِّ مَا سَأَلْتُمُوهُ وَإِن تَعُدُّوا نِعْمَتَ اللَّهِ لَا تُحْصُوهَا إِنَّ الْإِنسَانَ لَظَلُومٌ كَفَّارٌ)

لا تنسونا ووالدينا والأمة الإسلامية من صالح دعائكم، ولا تنسوا أهلنا في غزة والمسلمين في كل بقاع الأرض -نسأل الله أن يفرّج عنهم وينصرهم ويثبّت أقدامهم -

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 14	"… the terminal sugar is an amino sugar (sialic acid) "	This statement was told to be incorrect by the doctor We've added notes to tell the previous slides from the current ones
V1 → V2			