Biophysics and structural bioinformatics I

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Part 3

1. Conformational diseases

1.1. Loss of the protein activity

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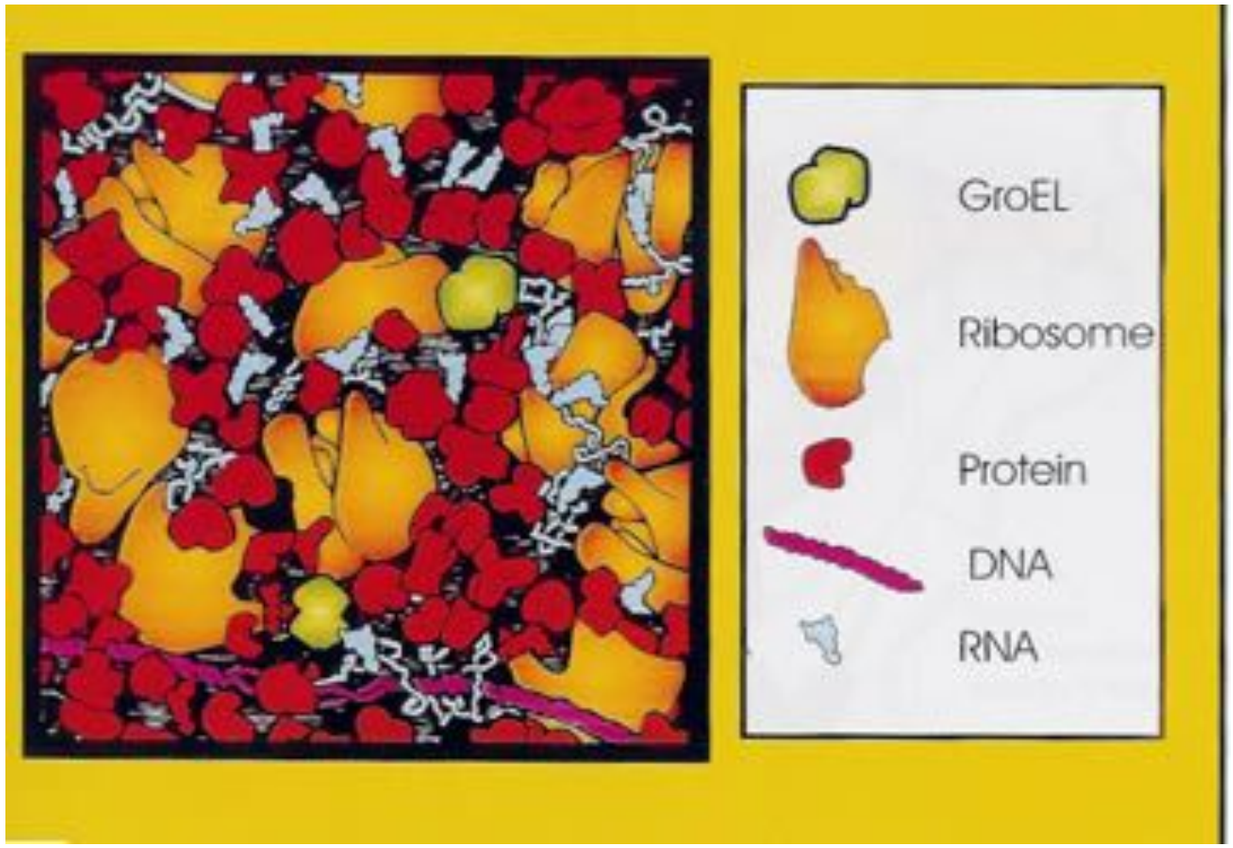
1. Conformational diseases

Conformational diseases are due to proteins that present a default in their structure or that are misfolded.

Some errors during the folding process are frequent, at least when the temperature is high or when the cell is “stressed”.

The cell medium present a high density of molecules, organites, ...



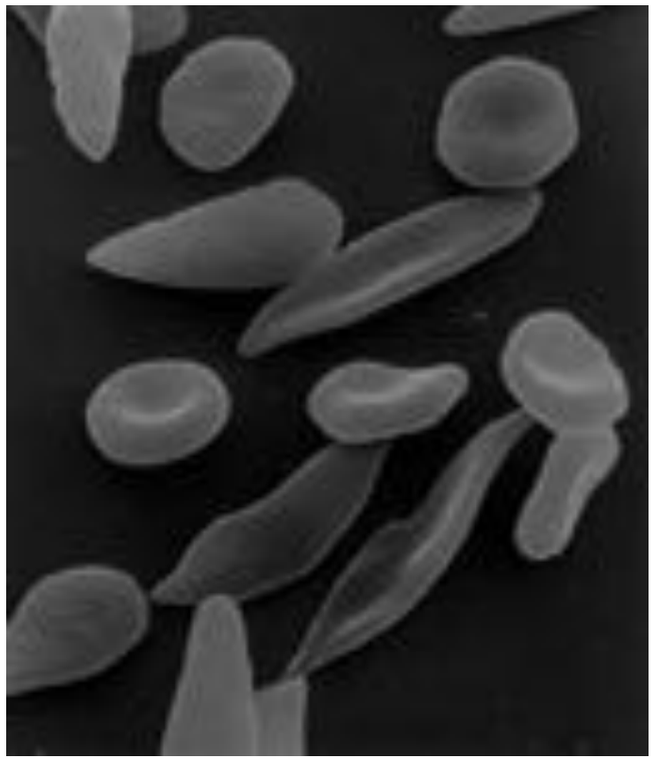
There are several types of diseases that are due to proteins:

- Diseases due to a loss of protein activity;
- Diseases that are related to amyloid aggregates;
- Diseases that are related to non-amyloid aggregates.

1.1. Loss of the protein activity

The pathology is related to the loss of the protein activity and/or to the accumulation of aggregates. For instance:

- Falciform anemia (sickle cell disease): this disease is characterized by abnormal red blood globules. This disease is due to the mutation Glu6→Val in hemoglobin. The conformational change after deoxygenation of hemoglobin leads to the exposure of an hydrophobic pocket. Val at position 6 can interact with this hydrophobic pocket and hemoglobin will aggregate. This aggregate will distort the red blood cells.



- The p53 protein is a transcription factor that plays an important role in apoptose of cells presenting DNA damages. Without p53, damaged cells will proliferate and the tumor risk is increased. p53 exists under several active and inactive forms ; some mutations block the protein in an inactive conformation.

◉ Conformational disorders involving inhibitors of serine protease (serpins). This family of inhibitors presents a loop that is recognized by the serine proteases. When the protease binds to this loop and cleave it, the inhibitor undergoes a conformational change, leading to the trap of the protease. Possible problem: aggregation due to the insertion of the loop into another serpin.

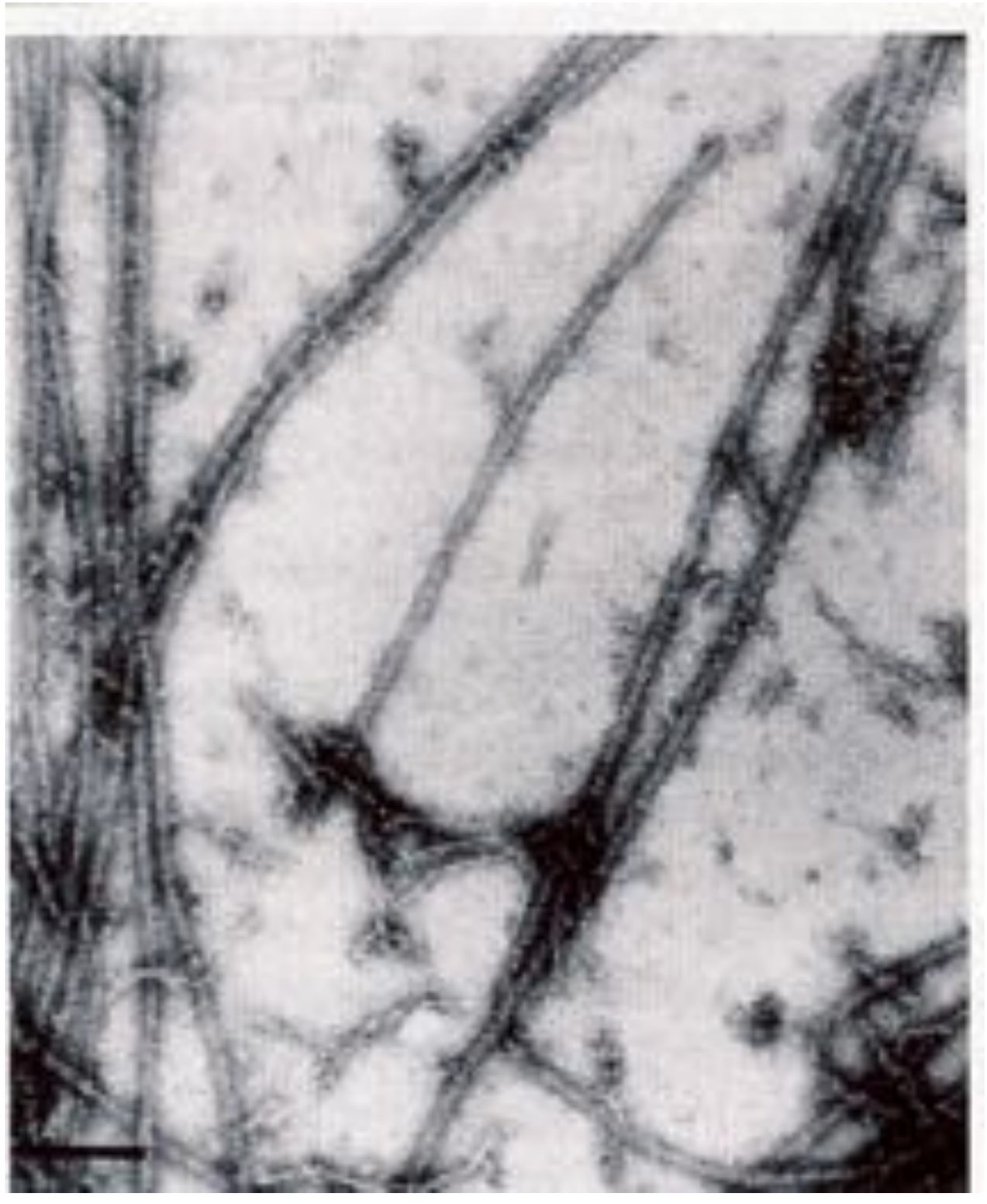
Example: α1-antitrypsine

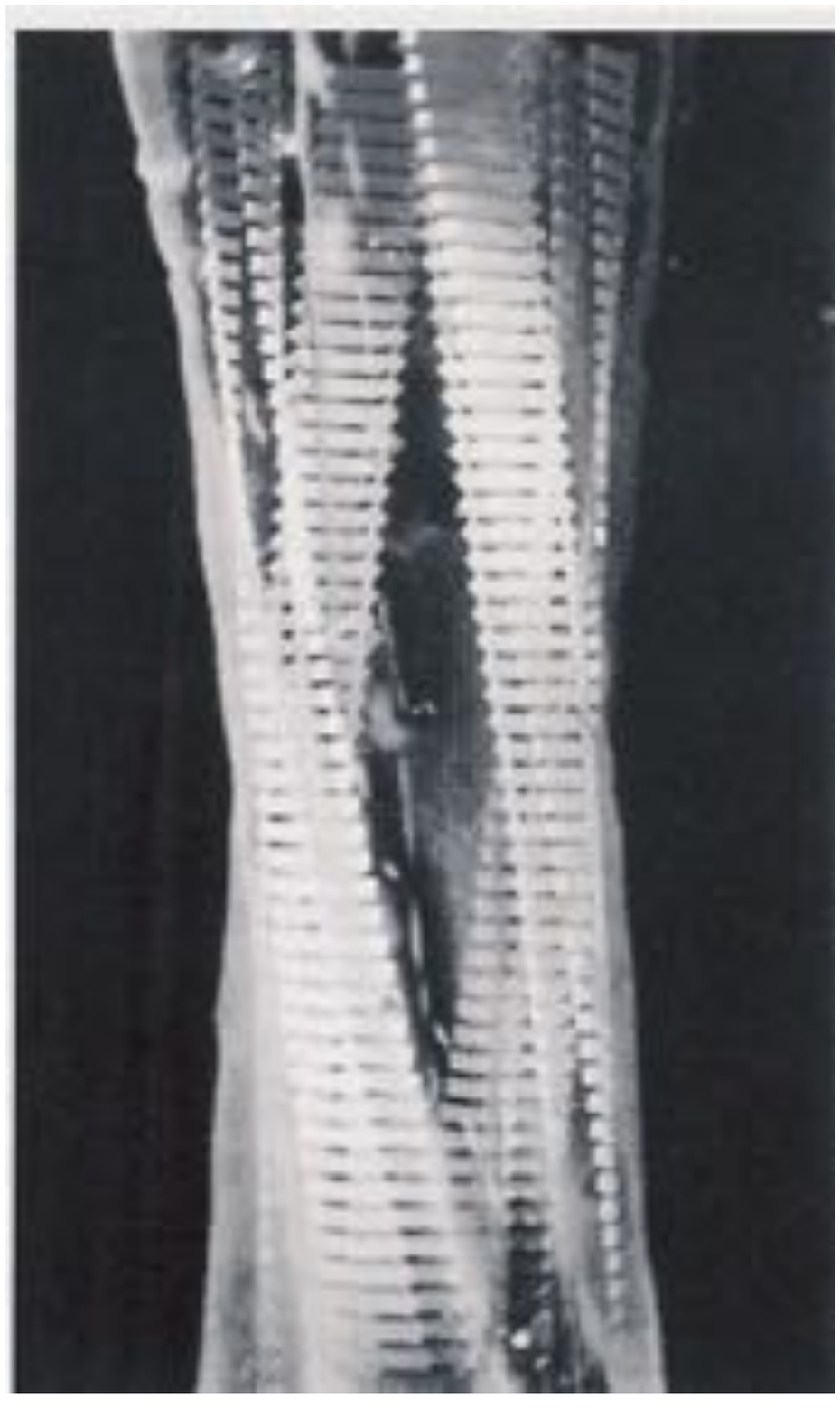
1.2. Amyloid aggregates

Amyloid fibers are a particular type of aggregate, that is highly organized. These fibers present a diameter about 100 Å, and they are linear. They are composed of at least 2 fibers of 25-35 Å diameter (protofibrils) which twist to form the mature fiber.

Amyloids correspond to β sheets, from different monomers, that gather. The β sheets are perpendicular to the axis of the fiber.

Several proteins and peptides are able to form amyloid fibers. However, the propensity to adopt a β strand conformation seems to be an important parameter.





◉ Alzheimer: fibrillar aggregates composed of the β-amyloid peptide (42 amino acids). The normal cleavage of the Amyloid Precursor Protein (APP) leads to a peptide of 40 amino acids; the β-amyloid peptide is due to a wrong cleavage of APP.

◉ Prion disease: aggregation of amyloid fibrils in the brain. These fibers are mainly composed of the prion protein (PrP). This protein presents two conformations:

a cellular form, with a high percentage of α helices (PrP^{c});

an amyloidogenic form, with a high percentage of β strands (PrP^{sc})

1.3. Non amyloid aggregates

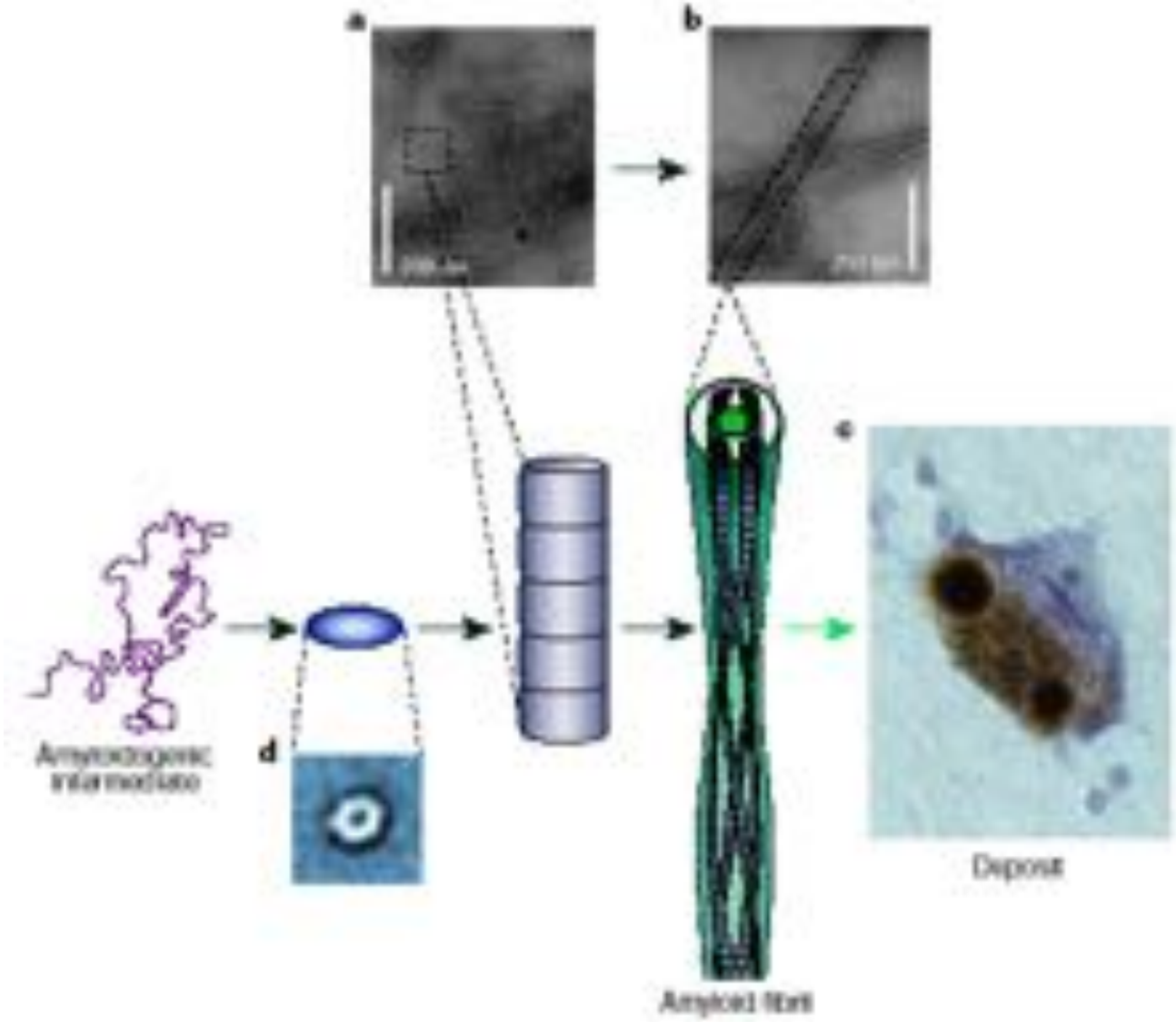
- Cataract: protein aggregates in the crystalline lens. Cells that form the crystalline lens present a large concentration in crystallins (proteins). There exist different crystallins. The eye lens is composed of a highly concentrated solution of different crystallins. Broken, unfolded or oxidized crystallins (due to age) can lead to opaque aggregates.

- Parkinson disease: the aggregation of some proteins occur in dopaminergic neurons.

In conclusion, there is a large number of diseases (non exhaustive list) that are due to protein aggregates.

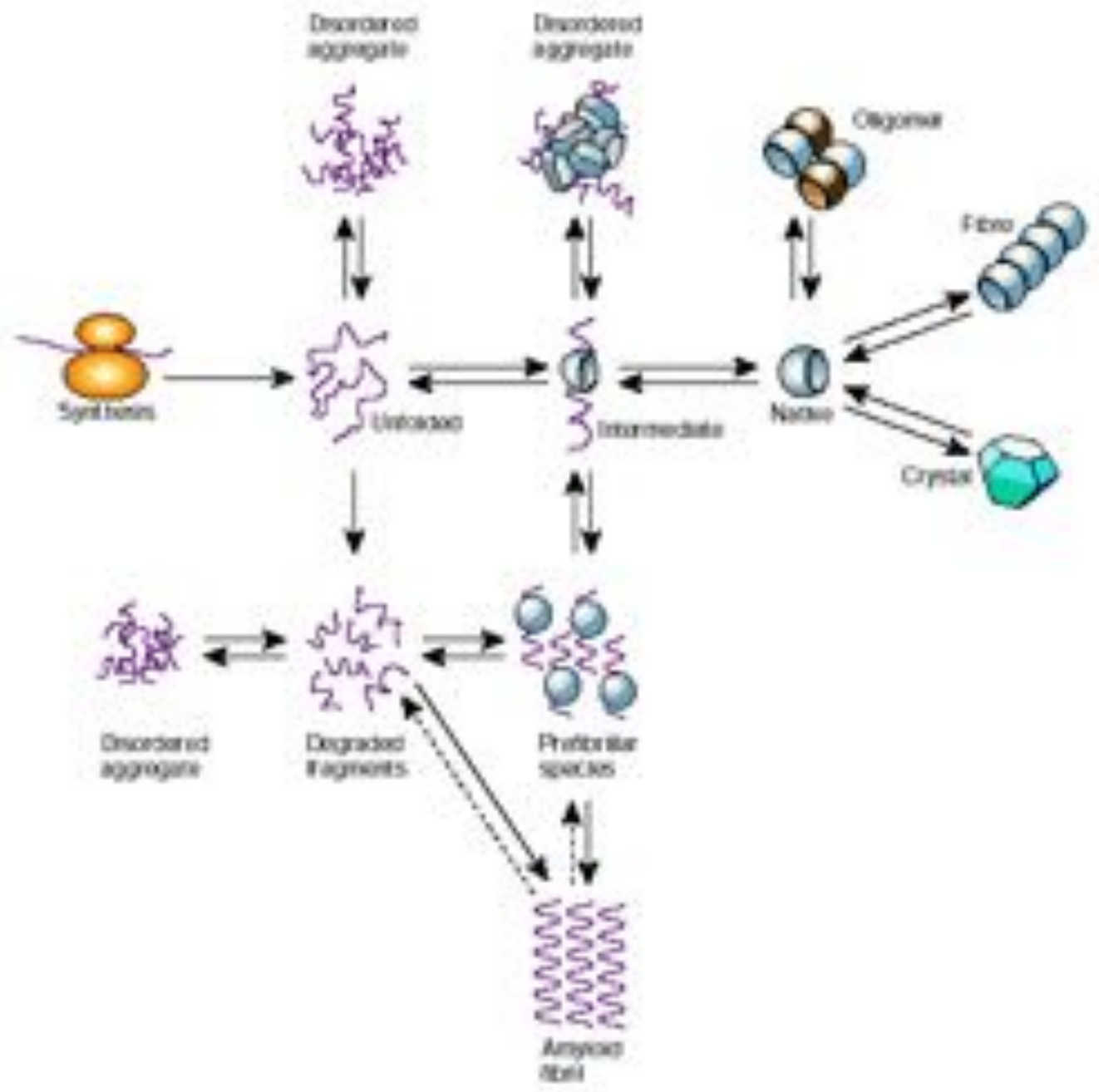
1.4. Ability of proteins to form amyloid fibers

In vitro, it is possible to form amyloid fibers with various proteins and peptides (using for instance non physiological conditions).



The ability to form amyloid structures seems to be general, but the propensity to form these fibers in given conditions depends on the sequence.

The relative aggregation rate of a large number of proteins and peptides correlate with some physico-chemical characteristics: the charge, the propensity to adopt an extended secondary structure, and the hydrophobicity.



The state of a protein depends on the thermodynamic stability of the conformations and on the kinetics of the transitions between these states. Some mutations can increase the population of a state and the propensity to aggregate.

Some studies suggest that aggregation is related to the presence of some amino acids that act as nucleus of the aggregation process. During evolution, the biological systems have become robust against aggregation. In addition to the optimisation of the protein sequence, molecular chaperones and degradation mechanisms control the state of a protein under given conditions.