

The Protein Folding Problem : A Key To Understand Life

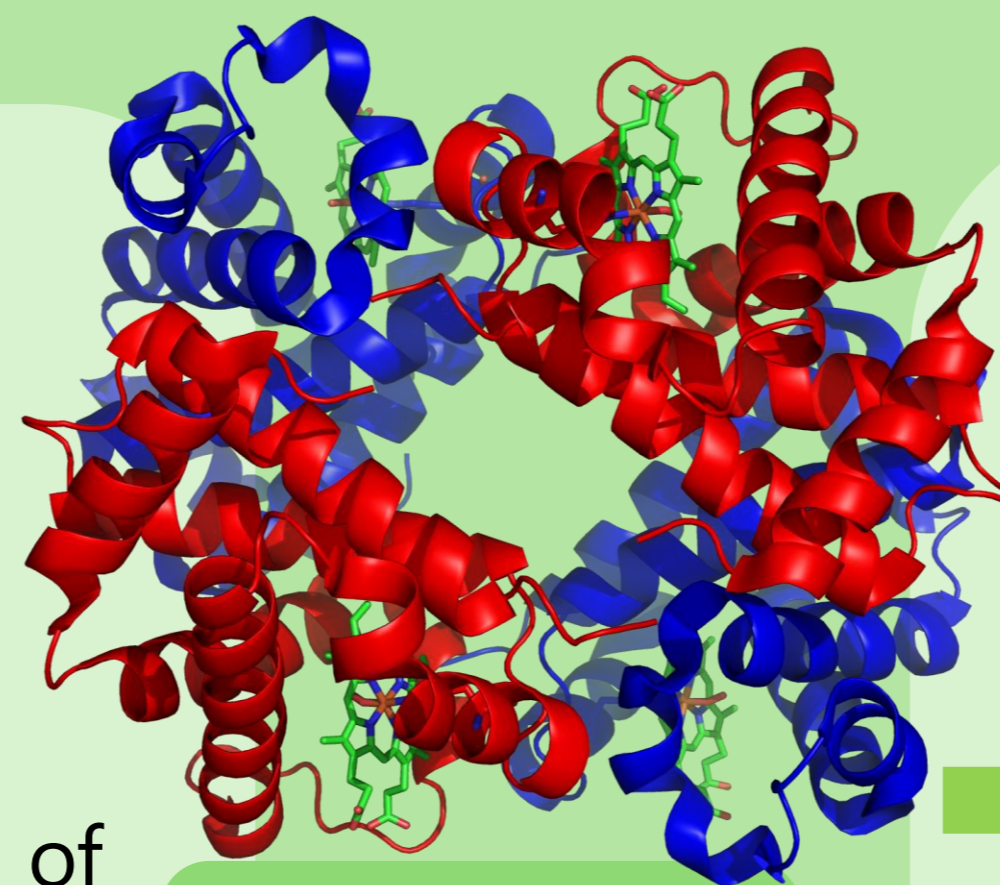


References

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Why is this problem important?

- Proteins: chains of amino acids which need to fold into a certain shape in order to perform their functions
- Proteins are essential to the functioning of the cell
- Misfolded proteins can aggregate, which can lead to diseases such as Parkinson's or Alzheimer's



Hemoglobin's folded form

AlphaFold

- Machine learning algorithm that predicts the folded shape of a protein from its amino acid sequence
- Fantastic tool to help structural biology and the design of new drugs
- Does not address the dynamics of folding, and cannot predict protein misfolding and aggregation
- Does not use physics principles, not clear why it works

Modelling the problem

- Biological systems try to maximize their entropy and minimize their energy
- In order to reach their native state, proteins follow the energy landscape defined by:

→ $G = H - TS$ Gibbs free energy

Levinthal's paradox
Why do proteins fold so fast compared to the huge number of possible configurations ?
→ Start to fold locally, number of configurations reduces exponentially

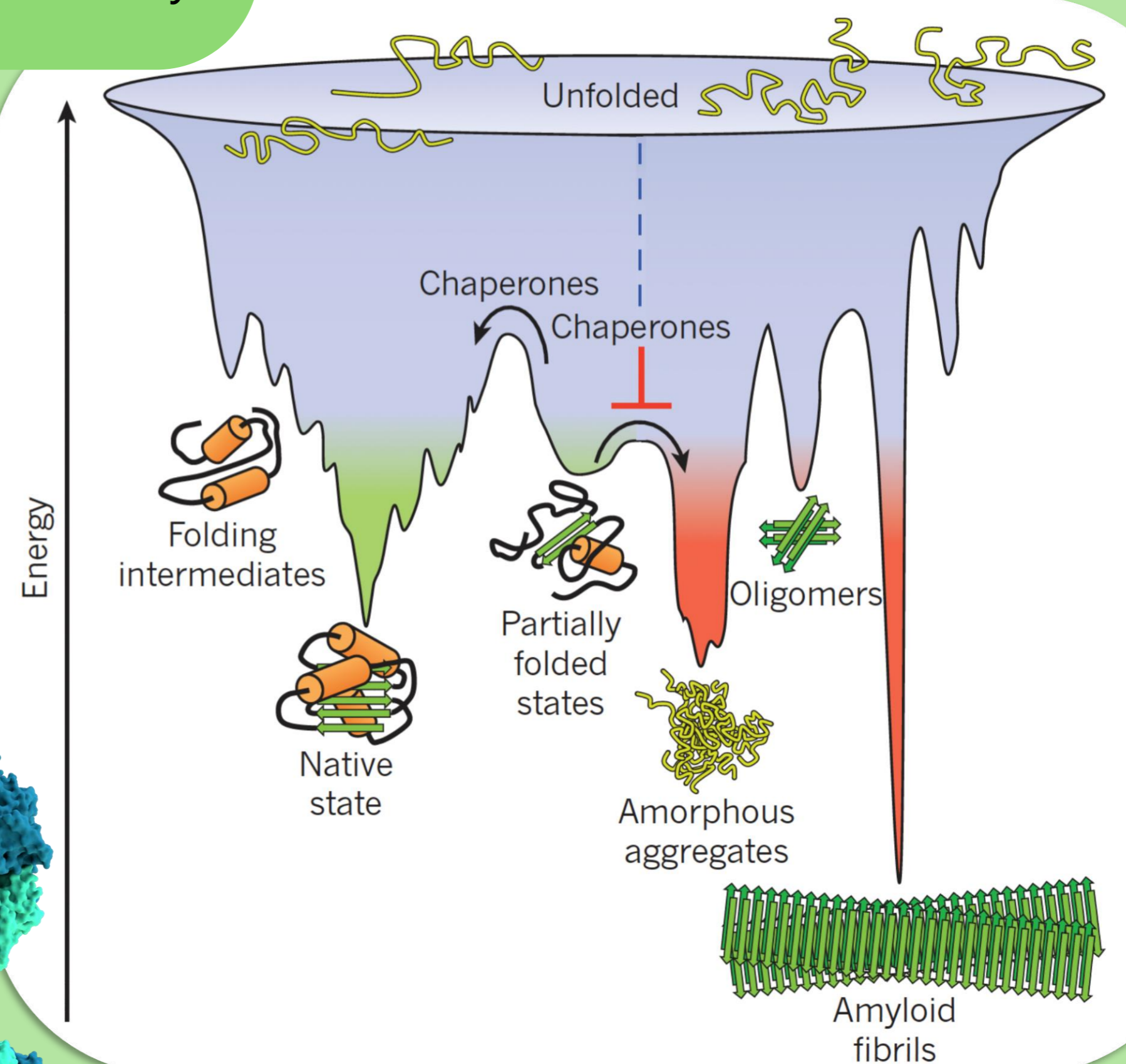
Native state : protein configuration in which it can perform its function

$$W(x^\mu; T) := -RT \ln \left(\int \exp[-\beta V(x^\mu, X^m)] dX^m \right)$$

- **Statistical mechanics** : treats problems which involve many interactions by considering the probability of being in a certain state

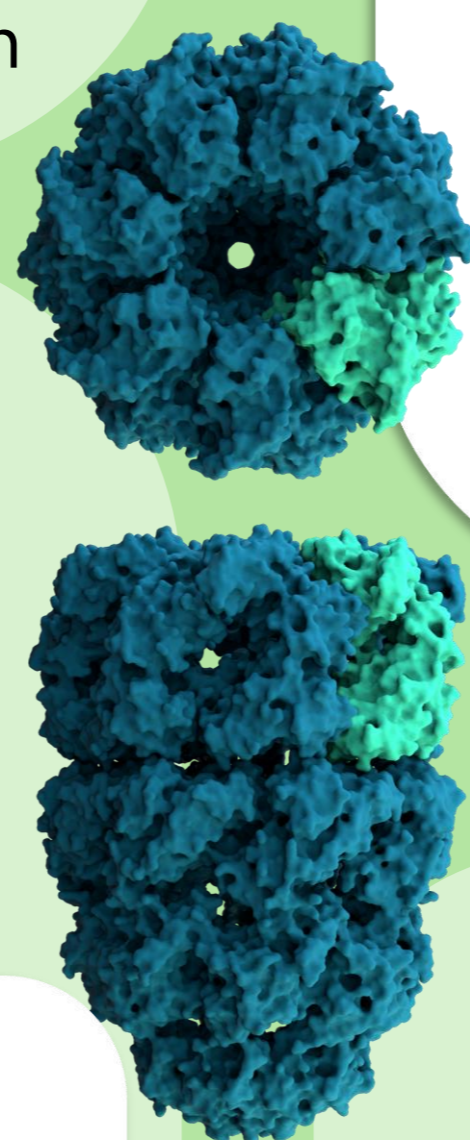
$$p(x^\mu) = \frac{1}{Z} \exp \left[\frac{-W(x^\mu)}{k_B T} \right]$$

Probability distribution of the position of the μ -atom of the protein



The role of chaperones

- Some proteins cannot fold alone and need chaperones to do it
- Chaperones prevent aggregation by unfolding a misfolded protein to help it fold correctly [1]



Example of energy landscape [1]

What is left to understand ?

- Difficulty in modelling and understanding all the interactions in a protein that determine how it folds
- Chaperones use ATP to do their work but we do not know the mechanisms involved
- The composition of our set of cellular proteins changes with ageing (may cause diseases) and we do not understand how

