Biophysical aspect of coexistence of stability and flexibility of protein

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Introduction

The functional structure of proteins has the lowest energy levels with their most stable states.

Protein stability refers to their thermodynamic stability, which is related to the net balance of forces. Alongside this, the protein structure has remarkable flexibility that is critical for its function. Protein flexibility refers to concerted changes that affect a few degrees of freedom, modifying the overall structure without destroying it. Flexibility as a structural aspect or an extra structural dimension is undoubtedly encoded within the amino acid sequence of a protein, just like secondary, tertiary and quaternary structures are.

The relation between protein stability, flexibility and function remains one of the most challenging for scientists.

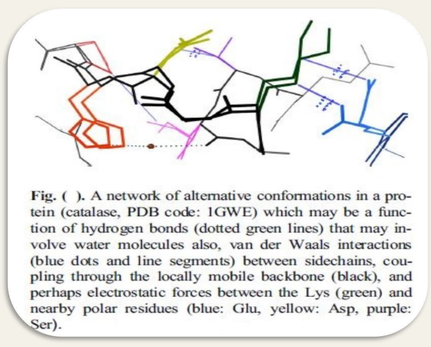
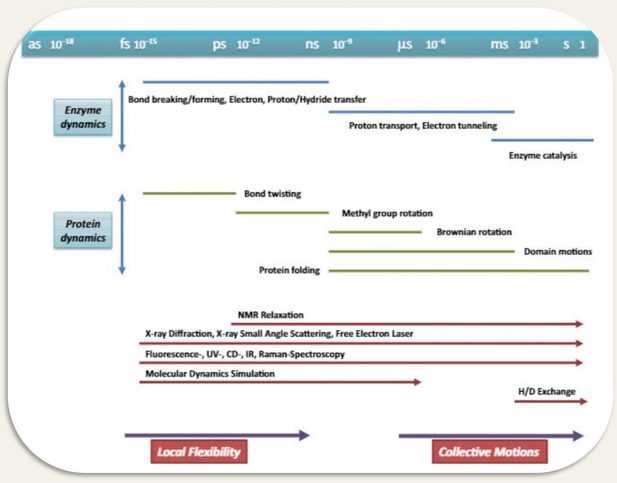


Fig. ( ). A network of alternative conformations in a protein (catalase, PDB code: 1GWE) which may be a function of hydrogen bonds (dotted green lines) that may involve water molecules also, van der Waals interactions (blue dots and line segments) between sidechains, coupling through the locally mobile backbone (black), and perhaps electrostatic forces between the Lys (green) and nearby polar residues (blue: Glu, yellow: Asp, purple: Ser).

Methods (I): flexibility

Each experimental or computational technique probes different temporal and spatial scales, ranging from picoseconds to milliseconds and minutes and from atomic positional fluctuations to conformational changes of large domains, respectively.

It is then inappropriate to rely on a single experimental technique for assessing flexibility in a complex macromolecule, because a protein can be rigid on a microscopic time scale and flexible on a longer time scale.

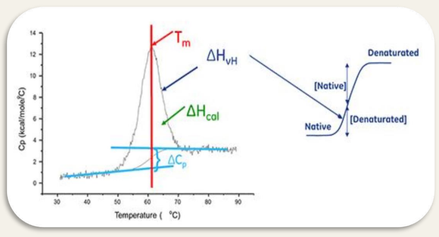


Methods (II): stability

Protein stability is measured by the difference in free energy between folded and unfolded states in equilibrium,

$\Delta G_{unf} = G_U(T) - G_F(T) = RT \ln(\langle U\rangle/\langle F\rangle)$, where R is the gas constant and $\langle U\rangle$ and $\langle F\rangle$ are the populations of the unfolded (U) and folded (F) states at a given temperature T.

For determining Protein Stability: Some of the Most Common Methods such as: Differential Scanning Calorimetry (DSC), Circular Dichroism (CD) Spectroscopy, Fluorescence-based Activity Assays, Pulse-Chase Method can be Used.



Result

There are several interesting results and hypotheses describing a possible role of rigidity and flexibility in protein function. Both theory and measurements show that active site residues tend to be locally less flexible/mobile than others. Moreover, active sites usually occur in global hinge centers indicating a low mobility. Analysis of protein structure networks and elastic network models indicate that active centers usually have non-redundant, unique connections, and often behave as 'discrete breathers' displaying a unique mobility pattern as compared to the rest of the protein. Discrete breathers occur at the stiffest regions of proteins, and may display a long-range energy transfer. On the contrary, increased flexibility of some activation segments may contribute to inactive, zymogen structures of protease enzymes, and differential flexibilities of the activation domains may also govern substrate-specific catalysis in the trypsin/chymotrypsin family of proteases.

Studies have shown that the function of some proteins is strongly affected by their flexibility, and with reduced flexibility, protein function also decreases. This is especially important for enzymes that have binding sites for the substrate.

In addition, three types of relationship between protein stability and their function have been identified:

- Low correlation between stability and function

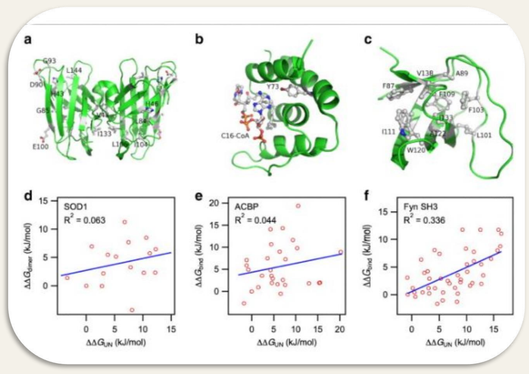


Fig A: Proteins with low correlations between protein stability and ligand affinity. Structures of a) SOD1 (PDB: 3h2p), b) the complex between ACBP and PCOA (PDB:1aca) and c) Fyn SH3 domain (PDB:3h0f).

- Negative correlation between stability and function

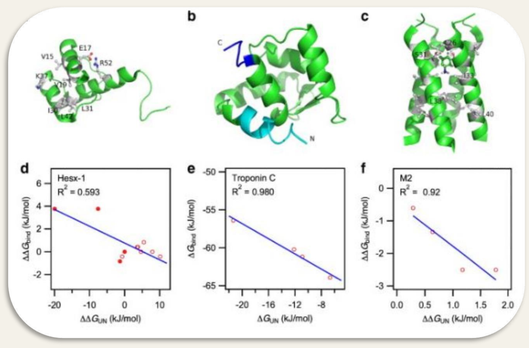


Fig B: Proteins with negative correlations between protein stability and ligand affinity. Structures of a) Hesx1, the stabilized variant R31L/E42L (PDB: 2k4o), b) troponin C (PDB:1zac) and c) M2 (PDB:3kqt).

- Positive correlation between local stability and function

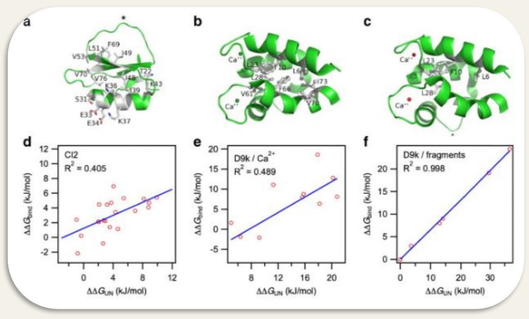
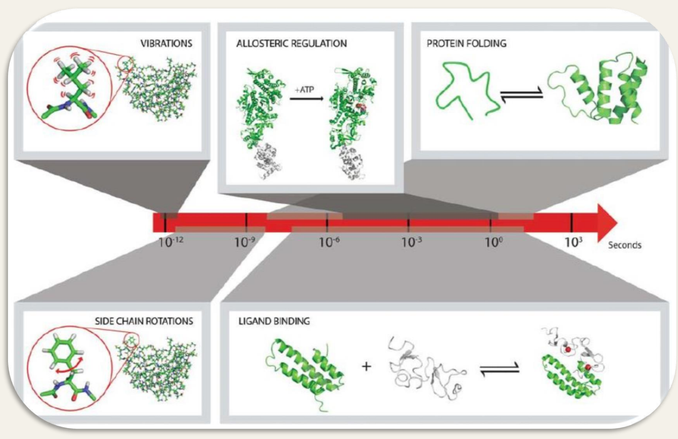


Fig C: Protein with positive correlations between protein stability and ligand affinity. Structures of a) CI2 (PDB:1coa), b) calbindin (PDB:4icb) and c) calbindin-fragments (PDB:4icb).

Result

From MD simulation method and experimental techniques we know the fastest events are vibrations of covalent bonds and fast side chain rotations on the picosecond to nanosecond timescale. At the other extreme of the timescale, protein–ligand dissociation and protein (un)folding may happen with time constants of hours.

This results indicates that flexibility along with stability is essential for protein function. Based on the results, it can be concluded that proteins are intrinsically dynamic macromolecules. But it should be noted that proteins are flexible as a consequence of their dynamics, yet their dynamics do not automatically result in flexibility. This also implies that a very dynamic protein may not necessarily be very flexible although this will often be the case.



Conclusion

- Flexibility is one of the factors that can cause proteins to be stabilized, however, they do not have negative effects on the stabilizing interactions .
- During the evolution, proteins in accordance with their biological functions have a certain amount of stability and flexibility. In fact, stability and flexibility are both adapted to protein function, so some proteins such as enzymes, flexibility is very effective and in proteins such as thermophilic proteins, the role of protein stability is more pronounced than its flexibility.
- **today**, there is a **flexible housing** discussion in architecture. It is not unexpected that in the near future, the information obtained from the flexibility - stability of proteins can be used in the stabilization of residential buildings by the architects.

Reference

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