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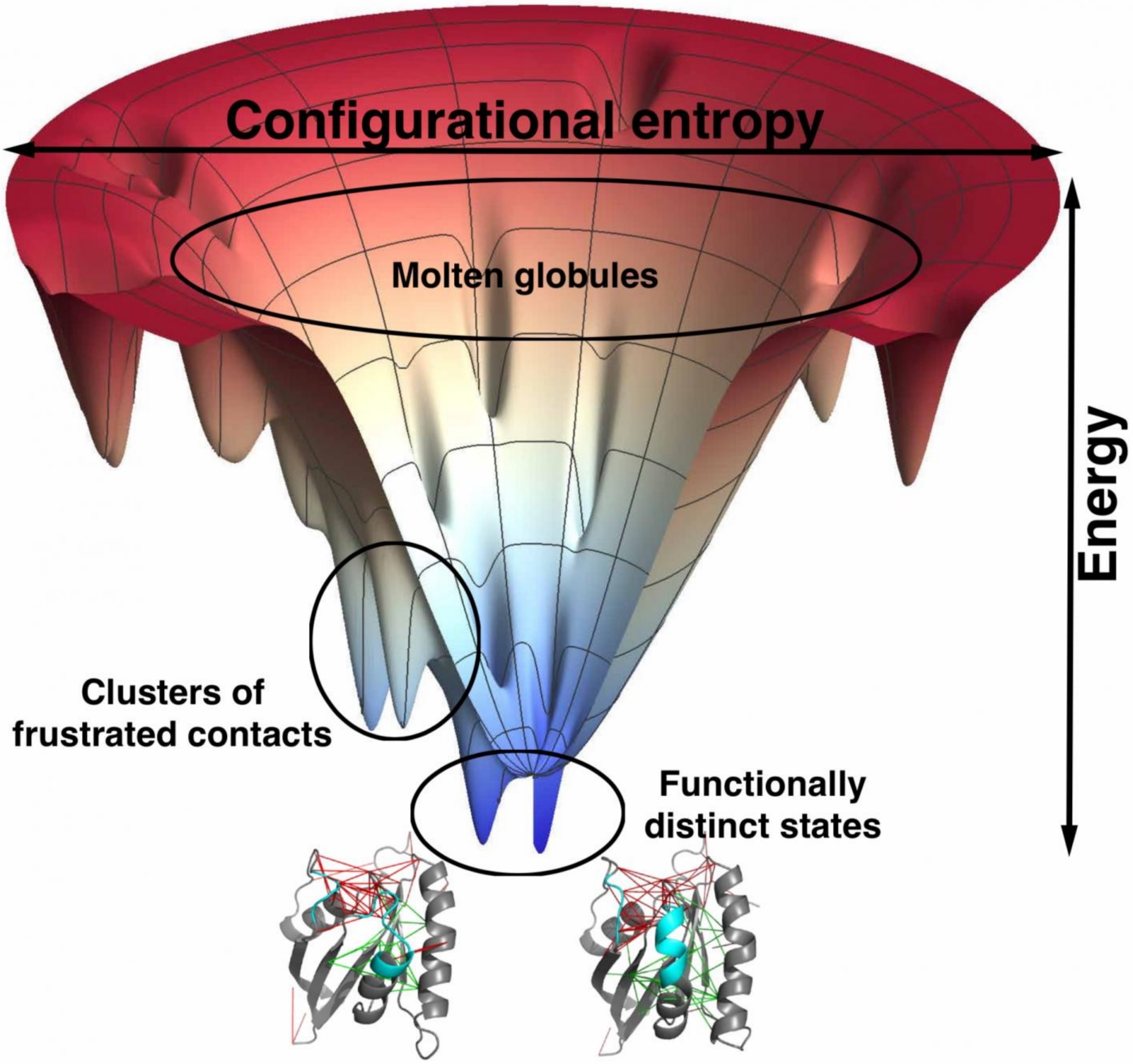

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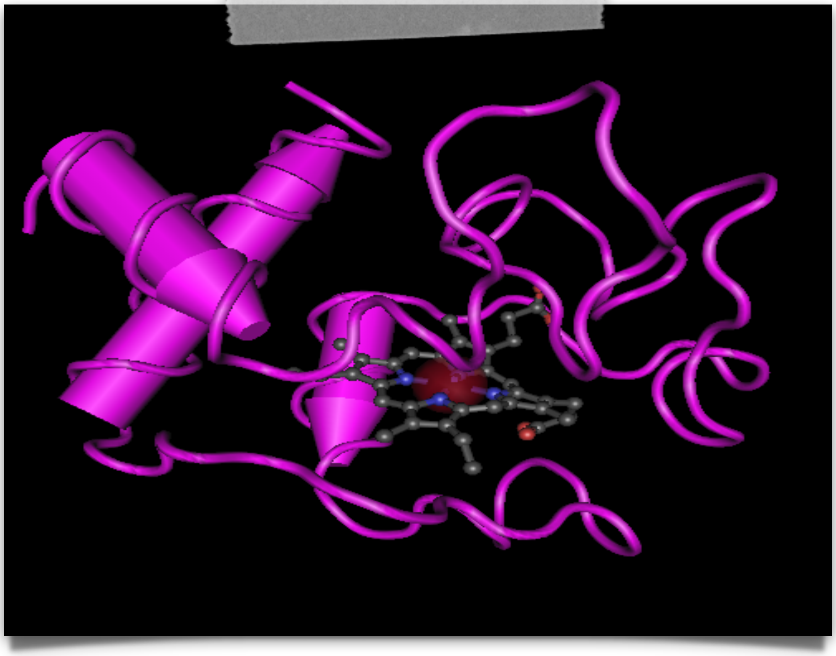

A JOURNEY OF PROTEIN FOLDING CONCEPTS FROM ANNALS TO CHRONICLES OF BIOCHEMISTRY

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DOWN MEMORY LANE

Almost 19 years back during my PG ship at Burdwan Medical College, myself and one of my fellow PGT was called upon by our the then Head of the Department of Biochemistry and guide, for a seminar presentation of one of the most stalwart and prolific personality of our discipline.

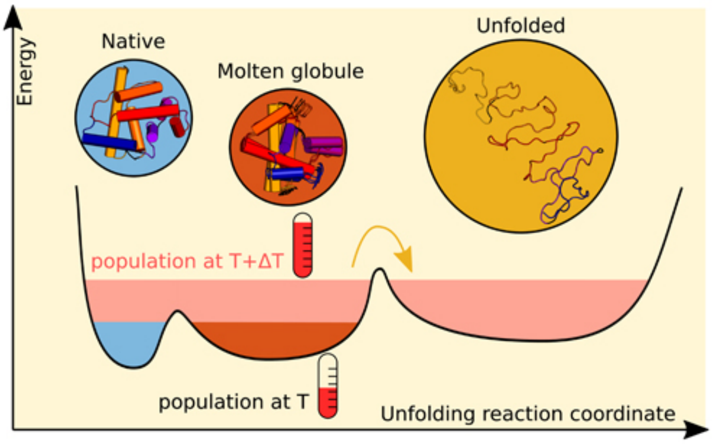
Topic was Protein Folding and diseases caused by Misfolding. We were at a soup and went through different books but couldn't find the proper one. Thereafter we came in contact with Annals of Biochemistry, which were already present in the department library of biochemistry. Hence we came in touch Annals of Biochemistry and its different editions dealing with theories of PROTEIN FOLDING during that time.

BACKGROUND

Recently, while coming across a journal in nature communication (Nat Commun 12, 3917 (2021) titled The architecture of the SARS-CoV-2 RNA genome inside virion) found a line in abstract "Using vRIC-seq data, we reconstructed the tertiary structure of the SARS-CoV-2 genome and revealed a surprisingly "Unentangled Globule" conformation." This uncommon nomenclature provoked us to get into the concept different from the older Molten globule conformation.

DISCUSSION

In previous years when we had a concept of Molten globule(MG) - which was a protein conformation, moderately compact but are lacking the specific tight packing of amino acid residues which creates the solid state like tertiary structure of completely folded protein (also termed- Equlibrium Globule). It was basically a third equilibrium state (or thermodynamically an intermediate one) different from the native denatured state.



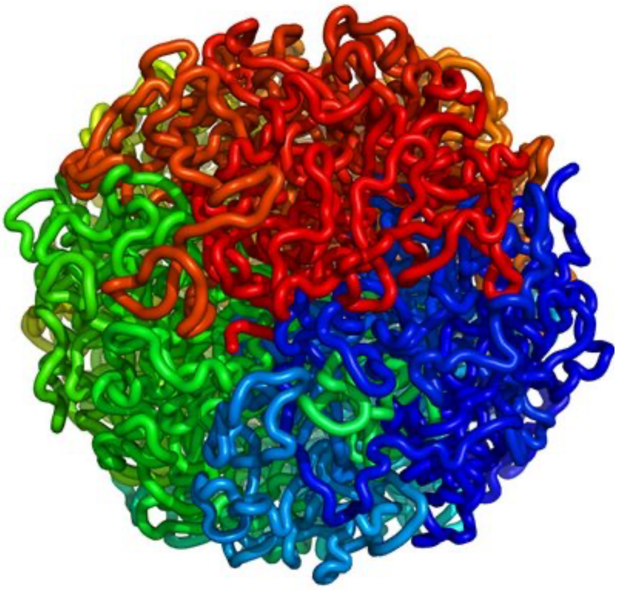
Under certain conditions like low pH, mild denaturation or high temperature this state collapse and form native secondary structure and also a dynamic tertiary structure mainly seen by CD (Circular dichroism) spectroscopy.

It can be a two state or a three state kinetic process to form molten globule from the denatured state because difference in native state of the protein and molten globule is that, MG lacks close packing of amino acid side chains.

The folding from the readily synthesized unfolded protein at ribosome to the native active state is remarkably fast despite the astronomical number of possible confirmation available to polypeptides. All the proposed mechanisms for protein folding i.e., the framework model, the diffusion collision model, the nucleation growth mechanism or the hydrophobic collapse model shows that when a polypeptide folds into its native states there is a progressive stabilization of partially structured folding intermediates in a hierarchical manner to prevent the polypeptide chains to go through all possible conformations.

The characterization of the intermediates on folding from the classical perspective of protein folding.

The MG state generally characterised by the presence of native-like secondary structure and compactness with highly labile side chain, corresponds to late folding intermediate. The equilibrium MG state was reported for the first time in cytochrome c (cyt c) under special conditions, such as low pH and high concentration of anions. MG states of a protein generated at low acidic and high alkaline pH have a wide range of structural and thermodynamic flexibility . However, nature and range of fluctuation of the MG states of a protein under physiological condition and the mechanism that stabilizes them are not well studied. Most importantly the MG state is important for protein function in living cells especially in protein-DNA and protein-protein interaction.



UNENTANGLE GLOBULE as confirmed by vRIC sequence data (RNA virus in situ confirmation sequencing data technology) got the name from CRUMPLE Globule THEN came → FRACTAL GLOBULE (which is basically unentangled)

Here the virion forms small crumples due to topological constraints, which are folded, that proceeds by the formation of a large crumple (thicker crumple) which confirmationally should be long lived. First it was postulated by Grosbug et. al (1988) ;it is referred to as Fractal Globule.

This fractal globule is space filling and it volume scales linearly with polymer lengths; the same way the molten globule does.

The fractal globule is unentangled as it contains no knots and maintains the topology of an open state .Only crumples (formed by interaction of molecular crosslinks) i.e., a condensed state is prevailing which can easily be opened. Whereas in Molten Globule or equilibrium globule it does not open up fully as it is trapped by multiple entanglements.

Such ability to rapidly unfold can be of great importance for gene activation (Hubner& Spector 2010; Muller et.al.2001) by modification or displacement of some components of

Advantage of this UNENTANGLED GLOBULE is that, it is stable and slowly it leads to the formation of equilibrium globule so that it can be slide through the energy funnel of folding.

It can have reversible and irreversible crosslinking of DNA by proteins or RNA molecules

Now in cases of SARS -COV 2 the structure was found to have long duplexes and higher order junctions (conformation by vRIC-seq data) which contribute to the sequential packaging of SARS -COV 2 genome.

CONCLUSION

Concepts changes from time to time due to newer technologies and expertise; so also different terminologies. It is just an overview of the protein folding concept which has encroached in chromatin remodelling also. Using the vRIC sequence data(it is a software based like bcl2fastq, STAR etc. and reference genome for SARS -COV 2) different conformational changes of PROTEIN FOLDING can be gathered henceforth.

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