Stoichiometry in Protein Folding?: Deeper Insights may be Useful

Understanding the mechanisms of protein folding has remained a mystery since many decades and there have been a number of models or views which have been proposed over the period of time (1-4). As of today, there has been a largely accepted statistical view of protein folding which suggests that a protein starts from an ensemble of unfolded states and folds through thousands of independent microscopic pathways, and finally converging to the native state (5-8). It has been widely believed and accepted that amino acids side chains play a very important role in the folding process through electrostatics, hydrogen bonding, hydrophobic interactions etc. Numerous experimental and theoretical reports are available to support this view as well (9-10). In fact preferential interactions between amino acids are the basis for introducing knowledge-based potentials, which in turn provide the underpinning for present day three-dimensional protein structure prediction by modeling and simulation (11-14 and references therein).

The authors of the paper “A Stoichiometry Driven Universal Spatial Organization of Backbones of Folded Proteins: Are there Chargaff’s Rules for Protein Folding?”, have made a fresh attempt to relook at this age old problem of protein folding with a completely different view point. In the paper published in this Journal (15), Mittal et al. bring forth the view that protein folding is a direct consequence of stoichiometric occurrences of amino acids, regardless of the size and fold of the protein. Mittal et al. also claim that the preferential interactions between amino acids do not drive protein folding. Going a step further, the authors also claim that the protein folding is a consequence of the interaction of the C-alpha atoms in backbone rather than the side chains. This obviously means that the side chains of the amino acids do not play any role in the protein folding process. This is contrary to the well accepted view that polar and non-polar amino acids are the primary driving force in the protein folding process.

This paper brings in a fresh insight into the protein folding problem, and adds another factor of “stoichiometry” into the numerous factors which govern the mechanisms of protein folding. Though stoichiometric based analysis seems interesting, there may be a few points which need to be addressed which may bring more light into this:

1. The authors have carried out an analysis of spatial distribution of amino acids in 3D space. The analysis has been carried out for a range between 0 to 9 Å and subsequently between 10 to 90 Å. The amino acids lying in this range have been defined as “contacts”. Since the distance of 90 Å is very large one needs to see how significant such interactions could be to affect the entire folding process. It would be more interesting to carry out the
analysis using “native contacts” which would be in the range 5 to 6 Å and which are well known to play an important role in protein folding. Having done an analysis of spatial distribution of amino acids, it would also be important to see the effects of crystal packing and symmetry on this analysis.

2. The plots of number of contacts versus neighborhood distances show a sigmoidal curve. One needs to explain why a sigmoidal curve is obtained in such an analysis. The analysis claims that a single amino acid independent spatial distribution is obtained for all cases. Does this necessarily mean that the amino acid side chains do not have any role to play in the folding process?

3. If the stoichiometric based hypothesis is true, it would be interesting to examine two proteins having different sequences but having the same stoichiometry. Do they have the same folding pattern? Such cases need to be examined and can be a proof for the hypothesis. To take things further, it would be good to experimentally synthesize such molecules and study their folding pattern.

4. Similarly, can one explain the phenomena of misfolding wherein the amino acid stoichiometry remains same but still the folding pattern changes? In a number of cases, it is well known that chaperones assist in protein folding process. If stoichiometry is the main factor in protein folding, then why does a protein require chaperones for folding?

5. Can we study cases of functional proteins like enzyme, wherein a mutation can change the entire conformation of an active site? It would be interesting to study the effect of a mutation on the protein fold, in one case which changes the stoichiometry and another which does not.

6. Lastly, can we formulate stoichiometric rules for formation of an alpha-helix, beta-sheet, coil etc., This, in my opinion would be the most interesting aspect of this work.

It may be possible that amino acid stoichiometry could be another important factor contributing to protein folding. The paper by Mittal et al. is very interesting and can add further value to our understanding of protein folding.

References