Protein folding: coming to terms with cooperativity

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Most proteins fold in vitro under various renaturation conditions and in so doing, they create a gamut of local solvent environments. The conformation dependence of such environments arises since residues are clustered within a large-scale organization and polar and hydrophobic groups have distinctive ways of organizing solvent around themselves, shaping solvation hulls or cavities. Furthermore, the pairwise interactions of the peptide chain are inevitably sensitive to the environments the chain itself is creating [1-3]. This picture underscores what researchers have termed cooperativity, a central feature of the so-called hydrophobic collapse which suggests a concertedness of folding events requiring the participation of distant parts of the chain.

Nevertheless, in dealing with the rôle of cooperativity at the onset of large-scale organization, most approaches have so far avoided dealing with the wanton complexities involved in treating the solvent structure explicitly, let alone incorporating the conformation dependence of local solvent contexts [4-6]. On the other hand, in dealing with the protein folding problem by treating the solvent implicitly, theoreticians have based their analysis on intramolecular potentials which are pairwise additive: they seem reluctant to pay the price for circumventing the treatment of the solvent environment affecting the (i,j)-pair but not covalently bonded to either i or j. Thus, the protection—stabilization—of the (i,j)-interaction might easily compensate for the h-p mismatch between k and i. The reader should keep in mind that a hydrogen bond in a desolvated quasi in-vacuo environment is roughly ten times more stable than its “in bulk” counterpart [4].

This discussion makes it obvious that we must abandon the standard and widely used scheme: $U^{o} = \sum_{i,j} U^{o}_{ij}$, where $U^{o}$ is the context-insensitive in-bulk intramolecular potential energy and $U_{ij}^{o}$ the zeroth-order pairwise $(i,j)$-contribution; and replace it appropriately to incorporate the sensitivity to conformation-dependent environments.

In this regard, I propose the following Ansatz: the solvent environment affecting the $(i,j)$-contribution is articulated through third-body hydrophobic residues spatially close to the $(i,j)$-pair but not covalently bonded to either i or j. These third-body influences may be incorporated in the form of correlation factors which rescale the in-bulk $(i,j)$-term.

In a minimal model, at least two parameters would be needed: let $r^{*}$ be a critical distance to either i or j beyond which no influence is exerted by hydrophobic residue k, and let L be a parameter measuring the sensitivity of the pairwise interaction to the third-body presence. Within this frame we get:

$$U_{ij} = U^{o}_{ij} \times [\Pi L C(i, j, k)],$$  \hspace{1cm} (1)

where the correlation factor $C(i, j, k)$ is given by

$$C(i, j, k) = [1 + L \times h(r^{*},-d(i, k)) \times h(r^{*},-d(j, k))]^{C(i,j)}$$ \hspace{1cm} (2)

Here $h(x)$ is the Heaviside function ($h(x) = 1$ if $x > 0$ and $h(x) = 0$ if $x < 0$) and the exponent $g(i,j)$ is $+1$ if the favourable $(i,j)$-interaction ($U^{o}_{ij} < 0$) is further stabilized.
by desolvation, like a hydrogen bond or an attractive p-p interaction, or the h-p repulsion \((U^{o}_{ij} > 0)\) is further destabilized as the polar unit becomes progressively more buried, while \(g(i,j) = -1\) if the favorable \((i,j)\)-interaction is destabilized by desolvation, like a hydrophobic attraction \((U^{o}_{ij} < 0)\). In this way, the product of Heaviside functions ensures that only those third-body units within a critical distance from \(i\) and \(j\) will actually exert their influence, itself measured by the parameter \(L\). Thus, the cumulative effect of three-body correlations quantified in eqns (1) and (2) effectively models the solvent environment shaped by nearby hydrophobic groups.

This is a primitive Ansatz, but it seems to be the first to deal effectively with an emerging view which suggests that novel approaches to the folding problem should incorporate the dual role of hydrophobic residues which act not only as clustering elements, but also as backbone desolvators. This second role is paramount to understand cooperativity, the bête noire of the theory. Thus, the protein folding process may be regarded as a struggle for the survival of intramolecular hydrogen bonds. In this scenario, the protein chain organizes solvent as it folds onto itself and in so doing becomes an endogenous kosmotrope, making surrounding water molecules less prone to attack the intramolecular hydrogen bonds.

**REFERENCES**