Influence of chain knotting on the rate of folding

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Addendum to

Rate of protein folding near the point of thermodynamic equilibrium between the coil and the most stable chain fold

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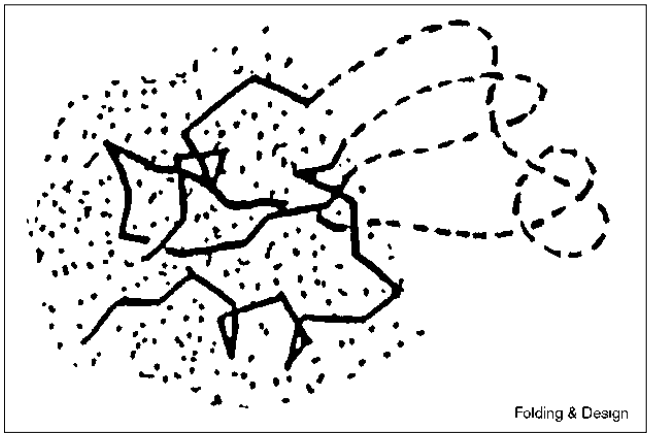
In our original paper [1], the time of achievement of the most stable chain was estimated (near the point of thermodynamic equilibrium between the fold and the coil) as:

$$\text{Folding time} \approx \exp[\lambda N^{2/3} \pm \chi N^{1/2}/2] \text{ nsec} \qquad (1)$$

where N is the number of residues in the chain, $\lambda \approx 1$ and $\chi \approx 1$. The term proportional to $N^{2/3}$ originates from the additional free energy of the surface of the folding nucleus (Figure 1) and the term proportional to $N^{1/2}$ originates from the heterogeneity of the chain links, which leads to a ruggedness of the folding pathway (compare with [2,3]). This estimate of achievement of the most stable chain fold is smaller by many orders of magnitude than the Levinthal estimate ([4]; folding time $\approx \exp[N]$) and explains why a chain of ~100 residues can find its most stable fold in a biologically reasonable time.

The estimate given by Equation 1 neglects the entropy of possible knotting of the disordered loops: as mentioned in [1], the entropy seems to be very small [5] when compared with the effects mentioned above. The estimate is correct only when the chain is not extremely long, however. Numerical experiments with polymers show that one can expect one knot for a chain region of roughly 100 chain links (see [5–7] and references therein). More precisely, in the most knotted chain it is one knot for a 27-link region and in a normally knotted coil it is one knot for 335 links if the chain is extremely thin (or for a much longer chain fragment if the chain is thick). When the native fold nucleus is formed, it must already have a 'correct' (i.e. as in the final structure) knotting of the disordered closed loops: their knotting cannot be changed without destruction of the nucleus fixing their ends, and subsequent folding of a wrongly knotted chain cannot bring it to the correct structure. The necessity of a correct chain knotting in the early folding steps (Figure 1) decreases the loop entropy in proportion to the expected number of knots (i.e. by ~0.01N) and thus introduces a multiplier of exp[~0.01N] in the above given estimate of the folding time. Folding simulations performed with chains of ~100 links [8,9] cannot reveal this multiplier, although it must dominate in any folding scaling law when N turns to infinity (for a review of the suggested laws, see [1–3,9]).

Figure 1



A folding intermediate consisting of the native-like nucleus (its mainchain is shown by solid line and the sidechain packing is shown by dots) decorated by disordered loops (dashed lines). Its successful folding to the final structure requires a correct knotting of the closed disordered loops.

Existence of such a multiplier brings us back to Levinthal's considerations [4] in which the number of chain links is substituted by the number of knots, which is about two orders of magnitude smaller. Thus, the exponential multiplier connected with knotting becomes really important only for chains of many thousands of residues, which is far above the normal size of protein chains.

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