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Express Communication

Loop Fold Structure of Proteins: Resolution of Levinthal's Paradox

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Abstract

According to Levinthal a protein chain of ordinary size would require enormous time to sort its conformational states before the final fold is reached. Experimentally observed time of folding suggests an estimate of the chain length for which the time would be sufficient. This estimate by order of magnitude fits to experimentally observed universal closed loop elements of globular proteins – 25-30 residues.

Key words: Levinthal's paradox, protein folding, chain conformation, closed loops, loop fold structure

In 1968 Levinthal in his report of which only brief summary is available (1) noted that reversibly denaturable proteins during transition from "random disordered state into a well-defined unique structure" have to go through conformational space with immense number of states, so that the time required for visiting all the states would also be very large. Indeed, (e.g. (2)) for a protein chain of length $L = 150$ (residues) with n = 3 alternative conformations for every residue, the time t required for sorting out all possible conformations of the chain is:

$$t = n^L \cdot \tau = 3^{150} \cdot 10^{-12}\ s = 10^{48}\ yrs \qquad [1]$$

($\tau = 10^{-12}\ s$ is time for elementary transition (2)). Observed values of t are in the range 10^{-1} to $10^3\ s$ (2), that is, the full sorting as above is impossible. Thus, protein folding has to proceed along a certain path that would avoid most of the conformational space. The path should somehow be directed by an as yet unknown sequence-dependent folding rule(s).

The size of the short chain for which the observed time span of 10^{-1} to $10^3\ s$ would be sufficient for trying every possible state can be calculated from [1], with the same assumptions, as $l_0 = \frac{\lg(t/\tau)}{\lg n} =$ 23 to 31 residues. In this case all conformations could be tried during the given time, and the lowest energy state(s) attended. Being logarithmic this estimate is rather insensitive to the choice of the values for n which according to various authors may change between 1.6 and 10 elementary conformations (3, 4). With these extreme values the above estimate spans the range $l_0 = 11$ to 74 residues. The l_0 value may, thus, serve as a rough estimate of the size of the units (chains or chain segments), which could attend all conformational states during observed time.

The estimated size of the hypothetical unit is identical to the optimum of loop closure for polypeptide chains, 20 to 50 residues (5), and to the observed size of recently discovered closed loop elements, 25-30 amino acid residues (5-7), of

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which globular proteins are universally built. One can hypothesize that the closed loops are also elementary folding units. In this case their linear arrangement within the protein folds (5, 8) would suggest a straightforward folding path: sequential formation of the closed loop units, along with their synthesis in the ribosome. If such successive formation of the stable folding units in the course of translation is assumed, it will require time proportional to the number of the units, that is, only several fold larger than required for a single unit. The above scenario is consistent with the typical rates of translation, 3 to 20 residues per second (9). Synthesis of the protein of length $L = 150$ takes, thus, 8 to 50 seconds, which is a fair match to the above range of folding rates. Thus, according to the estimates above the consecutive formation of the loop-like folding units of 25-30 residues is by the order of magnitude time-wise consistent with both folding and translational experiments.

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