# Two views on the protein folding puzzle

Protein chain folding is a miracle. The protein chain is gene-encoded and initially has no structure (Fig. 1, left panel). Its intricate structure (Fig. 1, right), with every atom in its unique position, results from spontaneous folding.

This is as amazing as if a multicolored thread could produce a shirt itself!

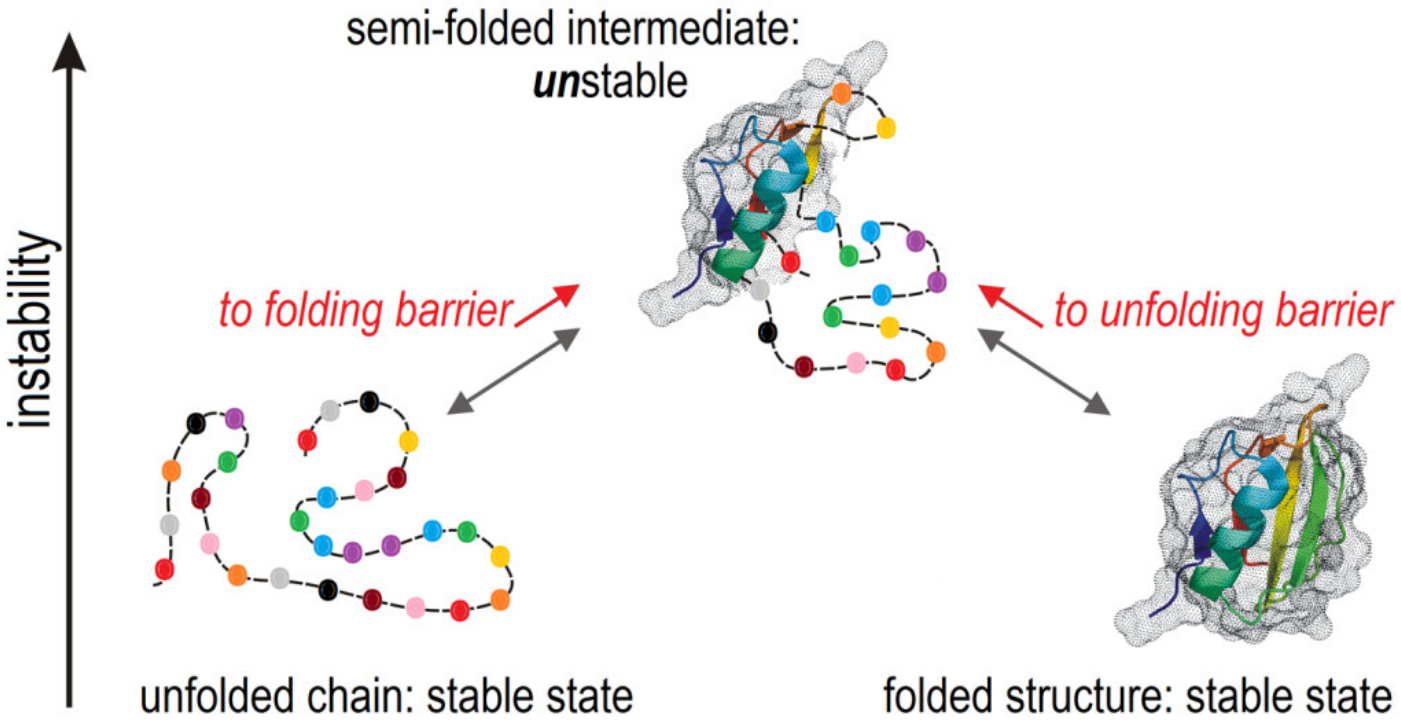


Fig. 1. Interconversion of two stable states of the protein chain via an unstable semi-folded intermediate. The colored helix, strands (strips) and loops (bold lines) show the chain fixed in the folded (right) or semi-folded (middle) structures; the globules are dotted. The broken line shows the structureless chain (left) and unfolded parts of the intermediate. The chain links (color beads) are gene-encoded. The most unstable semi-folded state acts as the free-energy barrier at the folding and unfolding pathways. Instability of the folding intermediatas, which is typical of proteins, results from the additional (by natural or artificial selection) reinforcement of the folded structures

The chain spontaneously finds its stable fold (Fig. 1: from left to right) within minutes or faster (both in vitro and in living cells), though much more than the entire life-span of the Universe would have been required to sample all possible chain structures in search for the most stable one. This is called "the Levinthal's paradox". To resolve it, various models of folding were proposed during decades.

However, these models fail to overcome the Levinthal's paradox *when* the globular structure stability is close to that of the unfolded chain and provide for no estimate of the folding rates (spaning over 11 orders of magnitude, Fig. 2).

The folding rate problem was solved using *unfolding* (not folding!) as the starting point, i.e., when the free-energy barrier between the globular and unfolded state (Fig. 1, middle) was viewed “from the globule side" (Fig. 1: from right to left).

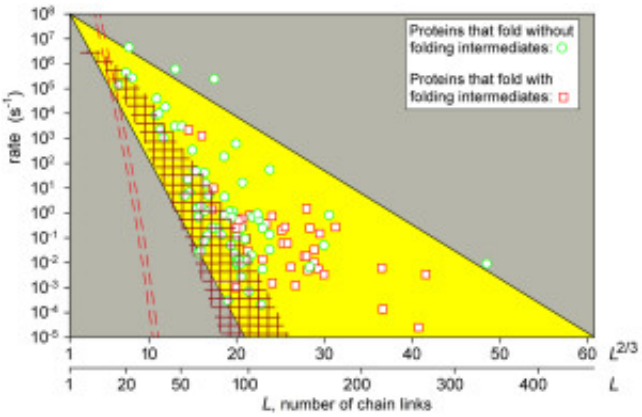


Fig. 2. Folding rates (circles and squares) of proteins, experimentally studied at equal stability of their folded and unfolded states. Yellow triangle shows the predicted (from consideration of unfolding!) range of these rates. The netted shading shows a recent theoretical estimate of the minimal rate of exhaustive sampling, at folding, of all possible packings of the protein secondary elements (helices and strands). The upper limit of the “Levinthal’s sampling time” is shown by the double dashed line.

The trick is that, firstly, the rates of the forward and reverse reactions coincide when the globular structure stability equals to that of the unfolded chain (according to the “principle of detailed balance” well-known in physics). Secondly, it is much easier to imagine – and investigate – how the thread unfolds than how it obtains a certain fold.

The validity of this theory (proposed two decades ago, when the experimental data were scarce) has been recently confirmed by all currently available experimental data (Fig. 2).

However, dissatisfaction felt because the *folding* problem has not been solved yet “from the viewpoint of the folding chain” (Fig. 1: from left to right) underlay further efforts made to estimate a volume of the necessary sampling in search for the most stable chain fold.

Recently, it has been shown that this volume, when considered at the level of formation and packing of the most strongly interacting protein structure elements (helices and strands, Fig. 1) is

by many orders of magnitude smaller than at the Levintal-considered level of separate chain links (beads in Fig. 1), and the rate of its sampling, at *folding*, become physically and biologically reasonable (and close to the unfolding-derived estimates, Fig. 2).

Thus, the protein folding puzzle is solved by viewing on it from two sides: the side of unfolding *and* the side of folding.

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## Publication

Reduction of the Search Space for the Folding of Proteins at the Level of Formation and Assembly of Secondary Structures: A New View on the Solution of Levinthal's Paradox.
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