

## *The Anfinsen Postulate*

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The folded state of a protein, known as the native state, was said by Anfinsen to be determined *only* by amino acid sequence (1). The native state was said to be unique, stable, kinetically accessible and at a free energy minimum.

We believe that the Anfinsen model should be understood as an imprecise description of the essential nature of proteins. The essential nature of proteins is found in the self-complementarity of the backbone and in the dominance of cohesive-interactions of the backbone. In the interior of the native folded protein studied by Anfinsen, essentially all backbone hydrogen bond donors interact with backbone hydrogen bond acceptors, and vice versa. The intramolecular interaction space within Anfinsen's folded protein is dominated by cohesive-interactions of the backbone.

Anfinsen empirically described the behavior of an isolated protein under a specific set of non-denaturing conditions - in dilute solution. His model can correctly describe protein folding under those conditions. However, backbone cohesion dominates protein folding under *all* conditions. The Anfinsen model does not predict amyloids and appears to be partially falsified by their observation. Amyloids are protein assemblies composed primarily of  $\beta$ -sheets.  $\beta$ -sheet is the ancestral mode of polypeptide self-interaction (2, 3). Amyloids grow in part by inducing the conversion of  $\alpha$ -helices to  $\beta$ -sheets. Driven by assembly,  $\beta$ -sheets act as templates that direct the unwinding of a  $\alpha$ -helices. The free energy of  $\alpha$ -helix unfolding is compensated by formation of  $\beta$ -sheet during formation of hyperstable fibrils. Since monomers are forming multimers this process is dependent on concentration. At high concentrations,  $\beta$ -sheet is the default mode of self-interaction of the backbone of essentially any amino acid sequence (4, 5). Amino acid sequence should be considered a second order perturbation of cohesive backbone interactions. Amyloids and isolated globular proteins follow the same organizing principles; both demonstrate the dominance of cohesive backbone interactions under non-denaturing conditions.

### References.

1. Anfinsen CB, Haber E, Sela M, & White FH, Jr. (1961) The Kinetics of Formation of Native Ribonuclease During Oxidation of the Reduced Polypeptide Chain. *Proc Natl Acad Sci USA* 47:1309-1314.
2. Kovacs NA, Petrov AS, Lanier KA, & Williams LD (2017) Frozen in Time: The History of Proteins. *Mol. Biol. Evol.* 34(5):1252–1260.

3. Lupas AN & Alva V (2017) Ribosomal Proteins as Documents of the Transition from Unstructured (poly) Peptides to Folded Proteins. *J. Struct. Biol.* 198(2):74-81.
4. Fändrich M & Dobson CM (2002) The Behaviour of Polyamino Acids Reveals an Inverse Side Chain Effect in Amyloid Structure Formation. *The EMBO journal* 21(21):5682-5690.
5. Pedersen JS, Andersen CB, & Otzen DE (2010) Amyloid Structure—One but Not the Same: The Many Levels of Fibrillar Polymorphism. *The FEBS journal* 277(22):4591-4601.