Physica A 511 (2018) 154–165

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Cooperative fibril model: Native, amyloid-like fibril and unfolded states of proteins

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ARTICLE INFO

Article history:
Received 16 April 2018
Received in revised form 20 July 2018
Available online xxxx

Keywords:
Cooperative fibril model
Native structures
Unfolded structures
Amyloid-like fibril structures
Proteins
Thermostatistics

ABSTRACT

In this paper, we start by studying the cooperative model of Hansen et al. (1998) which describes folding and unfolding transitions of proteins. Analytical expressions for different thermodynamic quantities are derived, including the degree of thermodynamic cooperativity. This model is then extended to take into account proteins that can aggregate forming amyloid-like fibril structures. Changes to the model were guided by our current understanding of the thermodynamics of fibril formation. We provide analytical equations for different thermodynamic quantities of the modified model and we study its phase diagram as a function of temperature and the binding energy of the protein to the fibril $\varepsilon^{\star}$. We find that for positive $\varepsilon^{\star}$ values, fibrils are the most stable state at low temperatures. Moreover, the model predicts that fibrils can coexist with heat unfolded, native, or cold unfolded states.

1. Introduction

The different structures adopted by proteins at various conditions of temperature and solvation determine how these biomolecules contribute to the survival of cells [1]. At physiological conditions, proteins adopt ordered conformations known as native or folded state [2,3]. The adoption of these conformations is essential for proteins to function in the cell. At conditions in which entropic effects play an important role, e.g., high temperature, the unfolded state which comprises a large number of disordered conformations is favored [4,5]. Most proteins cannot function in the cell when unfolded. Proteins can also aggregate and form amyloid-like fibril structures when subjected to the right conditions [6–8]. For some protein sequences fibril-like structures have been associated with diseases [9]. A case in point are fibrils from the amyloid-β protein which are a main constituent of plaques in the brain of patients afflicted with Alzheimer's diseases [10,11]. Thus, a same protein sequence can contribute to the survival of cells or be responsible for diseases depending on the conformations it adopts [12]. The aim of this paper is to leverage on our thermodynamic understanding of proteins to provide insights into phase diagrams that includes native, unfolded, and fibril structures—see Fig. 1.

The transition between folded and unfolded states of proteins resembles a first-order phase transition whereby order parameters describing the degree of folding change abruptly as a function of external fields, e.g., temperature. This accounts for bimodal distributions of the order parameter at the transition temperature implying that proteins spend most of their time either in the native or in the unfolded state and almost no time at intermediate conformations [13]. This type of transition is also known as cooperative and it arise when the binding energy of a "native bond" (i.e., a bond in the native state) is reinforced by the existence of other native bonds in the system [14]. This scenario for the emergence of cooperativity

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https://doi.org/10.1016/j.physa.2018.07.045
0378-4371/

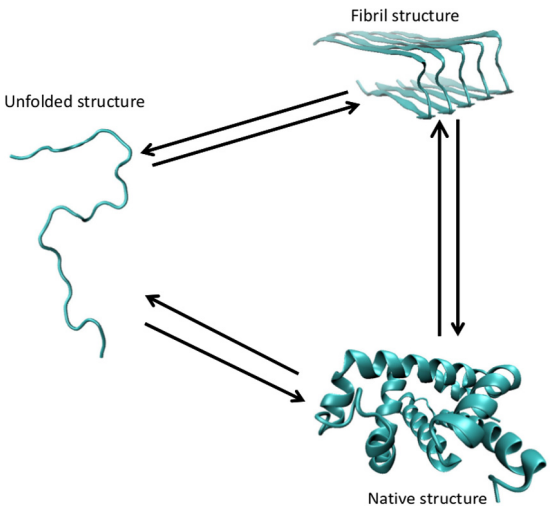

Fig. 1. Cartoon-like representation of native, unfolded and fibril structures. Arrows represent possible transitions between these states.

is consistent with the instability of many secondary structure of proteins (e.g., α-helix and β-sheet) in isolation that become stable when reinforced by non-local native contacts [15]. Thus, folding emerges from the concurrent formation of local and non-local bonds that give rise to secondary and tertiary structures of proteins, respectively [15]. However, the atomic origin of this reinforcement remains a question of debate [13]. Environmental-dependent hydrogen bonding [14], side-chain packing [16], and desolvation effects [17–19] are likely to contribute to increase folding cooperativity.

Experimentally, the degree of cooperativity of folding/unfolding transitions can be quantified using calorimetric experiments [13,20] whereby the heat capacity C_p of proteins is measured as a function of temperature [21]. These experiments have also contributed to elucidate the main molecular forces driving protein folding [15]. In particular, the intrinsic increase in heat capacity upon unfolding, i.e., $\Delta C_p = C_p^{\text{unfolded}} - C_p^{\text{native}} > 0$, is ascribed to the solvation of hydrophobic residues that are buried in the native state and become exposed to the solvent [22,23]. Accordingly the magnitude of ΔC_p was shown to increase proportionally to the number of non-polar residues in the protein [24]. This relation between ΔC_p and non-polar residues remains an important argument in favor of hydrophobic interactions being a main force driving protein folding [15,22]. Calorimetric experiments can also be used to measure changes in enthalpy ΔH_o and entropy ΔS_o at the transition temperature T_o. These quantities, i.e., ΔC_p, ΔH_o, ΔS_o, and T_o, can be used to compute changes in the Gibbs free-energy upon unfolding, i.e., $\Delta G = G^{\text{unfolded}} - G^{\text{native}}$ [21,25–28]:

$$\Delta G(T) = \Delta H_o - T\Delta S_o + \Delta C_p\left[(T - T_o) - T\ln\left(\frac{T}{T_o}\right)\right]. \tag{1}$$

The curvature of the temperature dependence of ΔG in this equation is characterized by ΔC_p. Since ΔC_p is positive for proteins, this implies that proteins undergo phase transitions (when ΔG is equal to zero) at both high and low temperatures [29,30]. As a proof of concept, hydrophobic effects incorporated in coarse-grained models of proteins were shown to reproduce these transitions [31–37]. The "cooperative model" that will be modified in this work to account for fibrillization reproduces thermodynamic properties ($\Delta C_p > 0$) of folding/unfolding transitions as well as their high degree of cooperativity [38,39].

Only recently have experiments shown that fibrils can be exist in equilibrium with dissolved proteins [40,41]. In this equilibrium, proteins dissociate and are added to the fibril reversibly [40–43]. A few experiments have measured changes in thermodynamic quantities associated with the addition/dissociation of proteins into/from a matured fibril [40,41,44]. These experiments reported both positive and negative ΔC_p [45–49]. Currently, it is unclear how the sign of ΔC_p relate to the protein sequence, the structure of fibrils, and/or solvent condition. Recent all-atom molecular dynamics simulations computed ΔC_p for the dissociation of a non-polar fragment of the Amyloid-β protein (residues 16–21) [50]. This quantity was shown to be positive as expected for the solvation of non-polar residues but small (less than 1 kJ/mol/K). The latter is consistent with the lesser sensitivity of fibrils to temperature compared to the native state. This greater stability of fibrils to temperature can be related to increased hydrogen bonding formation in these structures compared to protein folding [51]. These hydrogen bonds form cooperatively in β-sheets structures and fibrils [52]. Cooperativity in amyloid-fibrils has also been observed as a function of protein concentration. Increasing the concentration of proteins in solution accounts for a cooperative increase in the average length of fibrils [53].

This work uses the cooperative model proposed by Hansen and co-workers [38,39] to describe protein folding transitions and the realization that protein addition to fibrils may be cooperative [52]. Accordingly, in this paper we study the cooperative model of protein folding and we provide analytical expressions for the temperature dependence of its different