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How native proteins aggregate in solution: A dynamic Monte Carlo simulation

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Abstract

Aggregation of native proteins in solution is of fundamental importance with regard to both the processing and the utilization of proteins. In the present work, a dynamic Monte Carlo simulation has been performed to give a molecular insight into the way in which native proteins aggregate in solution and to explore means of suppressing aggregation, using two proteins of different compositions and conformations represented by a two-dimensional (2D) lattice model (HP model). It is shown that the native HP protein with accessible hydrophobic beads on its surface is prone to aggregation. The aggregation of this protein is intensified when the solution conditions favor the partially unfolded conformation as opposed to either the native or fully unfolded conformations. In this case, the partially unfolded proteins form the cores of aggregates, which may also encapsulate the native protein. One way to inhibit protein aggregation is to introduce polymers of appropriate hydrophobicity and chain length into the solution, such that these polymer molecules wrap around the hydrophobic regions of both the unfolded and folded proteins, thereby segregating the protein molecules. Our simulation is consistent with experimental observations reported elsewhere and provides a molecular basis for the behavior of proteins in liquid environments.
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Keywords: Protein aggregation; Hydrophobic interaction; Polymer; Dynamic Monte Carlo simulation; HP model

1. Introduction

Protein aggregation in solution is a fundamental issue in relation to both the downstream processing of proteins, such as protein refolding [1], membrane separations [2–3], and preparative chromatography [4], as well as the utilization of proteins as biocatalysts [5] and pharmaceuticals [6]. While the amino acid composition and structure intrinsically determine the aggregation behavior of a protein, the effects of solution properties, including temperature, pH, salt type and concentration, co-solutes, preservatives, and surfactants, are also significant [7]. It has been shown [8–16] both experimentally and through simulations that aggregation starts from a partially unfolded conformation with more exposed hydrophobic regions as compared to its native counterpart. Current studies on protein aggregation are mainly concerned with protein folding where the protein is initially in the random coil conformation and efforts are directed towards delineating the competition between folding, misfolding, and aggregation [10,15,17–23]. Molecular descriptions of the aggregation of native protein in solution are not yet adequate, though the addition of water-soluble polymers is extensively applied to stabilize proteins in solution, selected examples of which are listed in Table 1.

Molecular simulation, as a powerful tool for exploring micro conformational transitions, has been widely used to study protein structural transitions. Dill et al. [31] proposed a two-dimensional lattice protein model (HP model), which highlights the hydrophobic interaction as the driving force for protein folding and aggregation, and which has since been widely used as a model protein. Istrail et al. [32] proposed a computer model for protein aggregation with competing productive folding, and were the first to present some background into the nature and significance of protein aggregation and the use of lattice Monte Carlo simulations in understanding other aspects of protein

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Table 1
Inhibition of protein aggregation during refolding by the addition of polymers

Polymer	Protein	Mechanism	References
PEG	Carbonic anhydrase B	Interaction of PEG with the first intermediate	[24–26]
	Lactate dehydrogenase	Preservation of α-helix with PEG	[27]
PNIPAAm	Carbonic anhydrase B	Formation of complexes with folded intermediates through hydrophobic interactions	[28]
	Lysozyme	Formation of PNIPAAm−lysozyme complex through hydrophobic interactions	[1,29,30]
Dextran	Aviscumine	Hydrogen-bonding interaction between protein and dextran molecules	[6]

folding. Leonhard et al. [33] proposed an interaction energy scale based on the Miyazawa−Jernigan forcefield to develop amino acid residue−solvent interactions for lattice Monte Carlo simulations of model proteins in water, and performed evaluations on a 27-mer 3D lattice model. Gupta and Hall [10,17,18,34,35] have subjected a 20-bead HP (HP20) protein model to a dynamic Monte Carlo simulation to study the folding pathway, the transition states of a single protein, and protein aggregation during the refolding process, starting from the fully denatured conformation. Bratko et al. [19], Costello et al. [20], Broglia et al. [15] and Cellmer et al. [36] have each used a 3D lattice model with Monte Carlo simulation to explore the competition between folding and aggregation. More computer simulation results on protein aggregation have been listed in a recent review by Cellmer et al. [37]. In a previous work, Lu et al. [38,39] performed dynamic Monte Carlo simulation of the refolding of HP20 protein assisted by surfactant and polymer molecules, and showed that the formation and dissociation of protein–surfactant or protein–polymer complexes facilitate the evolution from the partially folded conformation to the native conformation. In continuation of this work, Lu et al. [29] have proposed and demonstrated the idea of using a thermally responsive polymer to establish a transient environment that is in tune with the kinetics of folding during the collapse and rearrangement stage. All of these endeavors have confirmed the validity of the HP model in capturing the essential physical nature of protein folding versus aggregation, i.e., the formation of a hydrophobic core driven by intramolecular hydrophobic interactions as opposed to the formation of a molecular assembly driven by intermolecular hydrophobic interactions.

Describing the physical nature of protein aggregation in the context of protein stabilization, however, requires a different approach to those described above. Here, the starting state is the correctly folded native conformation rather than a fully denatured random coil conformation with fully exposed hydrophobic beads, which can thus interact with their neighboring counterparts leading to the formation of aggregates. The aims of the present study were to provide molecular insights into: 1) how the native protein aggregates in solution, and 2) how and to what extent the aggregation may be suppressed by adjusting the composition of the solution or introducing a weakly hydrophobic polymer. Simulations of protein stabilization have been focused on the interaction of the polymer with the native protein, the resulting polymer–protein complex, as well as how this impacts on: 1) protecting the native structure of the protein, and 2) inhibiting the formation of protein aggregate. However, these issues have not yet been adequately addressed.

For the present study, we used two different HP model proteins, namely 13-bead HP protein (HP13) and 20-bead HP protein (HP20), with a view to establishing a more comprehensive understanding of the aggregation of native protein as a function not only of the protein composition and structure, but also of its concentration, the solution composition, and the presence of different kinds of polymers. To mimic the aggregation that occurs

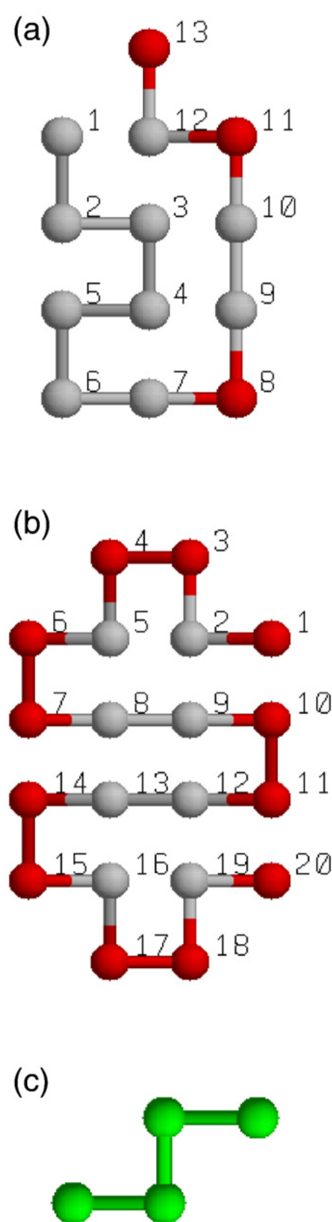

Fig. 1. Protein and polymer models: structures of native HP13 (a), native HP20 (b), and model polymer (c).

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