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Phase Separation in Peptide Aggregation Processes – Multicanonical Study of a Mesoscopic Model

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We have performed multicanonical computer simulations of a small system of short protein-like heteropolymers and found that their aggregation transition possesses similarities to first-order phase separation processes. Not being a phase transition in the thermodynamic sense, the observed folding-binding behavior exhibits fascinating features leading to the conclusion that the temperature is no suitable control parameter in the transition region. More formally, for such small systems the microcanonical interpretation is more favorable than the typically used canonical picture.

1 Introduction

Folding-binding and docking processes between proteins are significant for catalysis, transport, and cell stabilization in biological systems. Also, gene replication and expression are impossible without defined binding mechanisms of molecules. However, the mutual influence of proteins on each other can also result in refolding of proteins (which often leads to the loss of their functionality and thus biological activity) or cluster formation. In the latter case, proteins self-assemble and form aggregates. The effects of plaque can be disastrous and cause heavy diseases: First, the assembled proteins lose their individual functionality and second, in the passive case, the aggregates hinder transport and signal exchange processes which are significant for the life of cells. In an active process, specific aggregates might be able to bind to cell membranes and to change the membrane morphology, e.g., by forming pores. In the amyloid hypothesis for the onset of Alzheimer's disease, for example, aggregates of Aβ proteins are believed to form pores in membranes of neuron cells, thus opening ion channels for neurotoxic calcium.[1]

We focus here on thermodynamic properties of the aggregation transition of small peptides. For this purpose, a simple hydrophobic-polar aggregation model is introduced and employed in a multicanonical study of a few short heteropolymers.[2,3]

2 Aggregation Model

For the aggregation study, we extend the AB model[4] by an additional interchain interaction between the M heteropolymers. As in the single-chain model, which has proven to be quite

useful in qualitative studies of tertiary folding behavior,[5] only two types of amino acids are considered: hydrophobic residues (A) which avoid contact with the polar environment and polar residues (B) being favorably attracted by the solvent. The single-chain energy of the μth heteropolymer ($\mu = 1, \ldots, M$) composed of N_μ monomers is given by[4]

$$E_{\mathrm{AB}}^{(\mu)} = \frac{1}{4} \sum_{i_\mu} (1 - \cos \vartheta_{i_\mu}) + \sum_{j_\mu > i_\mu + 1} \Phi(r_{i_\mu j_\mu}; \sigma_{i_\mu}, \sigma_{j_\mu}), \tag{1}$$

where $0 \leq \vartheta_{i_\mu} \leq \pi$ denotes the virtual bending angle between the monomers i_μ, $i_\mu + 1$, and $i_\mu + 2$. Not discriminating nonbonded interactions between monomers of the same or different polymers, our aggregation model reads[2]

$$E = \sum_{\mu} E_{\mathrm{AB}}^{(\mu)} + \sum_{\mu < \nu} \sum_{i_\mu, j_\nu} \Phi(r_{i_\mu j_\nu}; \sigma_{i_\mu}, \sigma_{j_\nu}), \tag{2}$$

where μ, ν label the M polymers interacting with each other, and i_μ, j_ν index the monomers of the respective μth and νth polymer. The nonbonded interresidue pair potential $\Phi(r_{i_\mu j_\nu}; \sigma_{i_\mu}, \sigma_{j_\nu}) = 4[r_{i_\mu j_\nu}^{-12} - C(\sigma_{i_\mu}, \sigma_{j_\nu}) r_{i_\mu j_\nu}^{-6}]$ depends on distance $r_{i_\mu j_\nu}$ and residue type $\sigma_{i_\mu} = A, B$. The long-range behavior is attractive for like pairs of residues [$C(A, A) = 1$, $C(B, B) = 0.5$] and repulsive otherwise [$C(A, B) = C(B, A) = -0.5$]. The length of all virtual peptide bonds is unity. In this short note, we focus on a system of two identical chains with the Fibonacci sequence $AB_2AB_2ABAB_2AB$, where the single-chain properties are known.[6] Our primary interest is devoted to the phase behavior of the system and for this purpose, the density of states $g(E)$ is a suitable quantity that we obtained by means of multicanonical computer simulations.[7]

3 Microcanonical vs. Canonical View

The Hertz definition of the microcanonical entropy is given by $\mathcal{S}(E) = k_B \ln \Gamma(E)$, where k_B is the Boltzmann constant ($k_B = 1$ in our simulations) and $\Gamma(E) = \int_{E_{\min}}^{E} dE'\, g(E')$ (where $E_{\min}$ is the ground-state energy) is the phase-space volume. In Fig. 1, $\mathcal{S}(E)$ is shown for our two-peptide system. Interestingly, in the energy region between E_{agg} and E_{frag} the entropy exhibits a convex behavior, which is a strong indication for surface effects within this small system.[8] Also shown in Fig. 1 is the corresponding concave hull $\mathcal{H}_{\mathcal{S}}(E)$, i.e., the Gibbs construction. The surface entropy, defined as $\Delta\mathcal{S}(E) = \mathcal{H}_{\mathcal{S}}(E) - \mathcal{S}(E)$ is maximal at the energy E_{sep}. The reason for the nonvanishing surface entropy is that the transition between the fragmented, i.e., separated chains, and the formation of a joint aggregate is a process with phase separation which is "delayed" due to steric surface effects reducing the entropy of the total system. Since entropy reduction is only achieved by additional energy consumption, the surprising side effect is that in the transition regime the aggregate becomes colder with increasing system energy. This is verified by considering the caloric temperature which is defined via $T^{-1}(E) = \partial\mathcal{S}(E)/\partial E$, also shown in Fig. 1. Actually, in the transition region, $T^{-1}(E)$ bends back with increasing energy.

Consequently, there is no unique mapping between temperature and energy in the transition region (or more precisely, within the bounds $T_<^{-1}$ and $T_>^{-1}$ indicated in Fig. 1). Thus the temperature should not be considered as a suitable external control parameter. From a statistical point of view this means that for transitions with phase separation in small

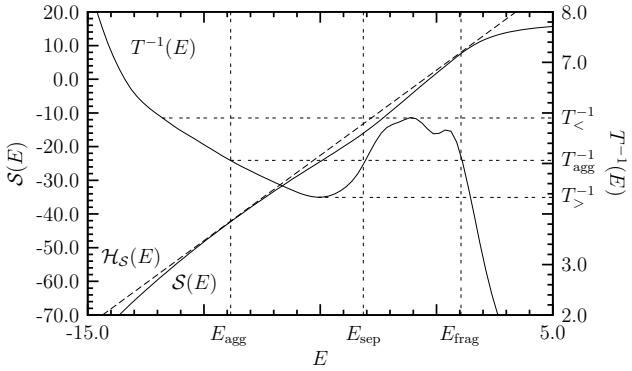

Figure 1. Microcanonical Hertz entropy $\mathcal{S}(E)$, concave Gibbs hull $\mathcal{H}_\mathcal{S}(E)$, and inverse caloric temperature $T^{-1}(E)$ as functions of energy. The phase separation regime is bounded by $E_{\rm agg}$ and $E_{\rm frag}$; the temperature region, where temperature is no suitable external control parameter and the canonical interpretation breaks down, ranges from $T_<^{-1}$ to $T_>^{-1}$. The slope of the Gibbs hull defines the aggregation temperature, $T_{\rm agg}^{-1} = \partial\mathcal{H}_\mathcal{S}(E)/\partial E = \text{const.}$

systems a microcanonical interpretation is preferred over the typically used canonical formalism. Since the backbending effect in the peptide aggregation process is a real physical effect, it should also be accessible to experimental verification, as it has indeed already been observed, for example, in experiments of sodium cluster formation processes.[9]

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