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## Microcanonical analysis of aggregation transitions in flexible polymer systems

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### Abstract

By means of extensive replica-exchange Monte Carlo simulations of a generic coarse-grained model, we examine systems consisting of up to 11 individual polymer chains with 5 monomers each. The application of microcanonical analysis methods reveals new details about the anatomy of aggregation transitions that were previously inaccessible via conventional canonical analysis. We find evidence for phase separation in the transition region and classify the transition as first order. Finally we show that the aggregation transition consists of a hierarchy of sub-phase transitions and discuss the implications of this finding.

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### 1. Introduction

Protein misfolding and aggregation are at the root of a number of pathological conditions such as Alzheimer’s and Parkinson’s diseases, cystic fibrosis, and type II diabetes [Selkoe (2003); Chiti and Dobson (2006)]. Recent studies indicate that under suitable conditions, where intermolecular, rather than intramolecular, interactions dominate the structure formation process, most proteins are able to form amyloid aggregate assemblies. This suggests that protein aggregation may be a generic property of polypeptide chains that does not necessarily depend on the specific amino acid sequences [Kayed et al. (2003); Thirumalai et al. (2003); Stefani (2004); Osborne et al. (2013)]. The essential properties of aggregation processes are preserved in simple coarse-grained models including the flexible and semi-flexible homopolymers and heteropolymers [Junghans (2009)]. Systematic and precise analyses of thermodynamic properties of structural phases and transitions in coarse-grained polymer models were only recently made possible by advances in sophisticated generalized-ensemble Monte Carlo algorithms. Among the most efficient contemporary simulation techniques are the generalized ensemble replica-exchange method [Swendsen and Wang (1986); Geyer

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(1991); Hukushima and Nemoto (1996)], the multi-canonical sampling methods [Berg and Neuhaus (1992)], and the Wang-Landau method [Wang and Landau (2001)]. The study of systems at the mesoscopic scale requires the explicit consideration and understanding of the finite-size effects which play an essential role in phase-separation and structure formation processes [Bachmann (2014)]. Systematic statistical analyses approaches beyond standard canonical methods are required to unravel the intricate interplay of entropy and energy in finite systems. Recently, a method based on microcanonical thermodynamics [Gross (2001)], the inflection point analysis of the microcanonical inverse temperature [Schnabel et al. (2011)] has been employed successfully in a variety of mesoscopic systems.

## 2. Model and methods

In this study, we examine a system of  $M$  interacting, elastic, flexible homopolymer chains, each consisting of  $N$  monomers, confined inside of a spherical volume at a constant density of  $\rho = 10^{-3}$  monomers per unit volume. The primary motivation for using this generic coarse-grained model is the combination of computational tractability and the presence of structural properties that are typically found in more complex models. The total energy of the system of  $M$  polymer chains of length  $N$  in a conformation  $\mathbf{X}^{(M)} = [(\mathbf{r}_1^{(1)}, \dots, \mathbf{r}_N^{(1)}), \dots, (\mathbf{r}_1^{(M)}, \dots, \mathbf{r}_N^{(M)})]$  is given by

$$E(\mathbf{X}^{(M)}) = \sum_{k=1}^M \sum_{i<j}^N U_{\text{LJ}}^{\text{trunc}}(r_{ij}^{(k)}) + \sum_{k=1}^M \sum_{i=1}^{N-1} U_{\text{FENE}}(r_{ii+1}^{(k)}) + \sum_{k<l} \sum_{i,j}^N U_{\text{LJ}}^{\text{trunc}}(|\mathbf{r}_i^{(k)} - \mathbf{r}_j^{(l)}|), \quad (1)$$

where  $r_{ij}^{(k)}$  is the distance between monomers  $i$  and  $j$  of the  $k$ -th chain. Intrachain and interchain pairwise non-bonded interactions are contained in the first and third terms, respectively, and are represented by a truncated and shifted Lennard-Jones (LJ) potential of the form

$$U_{\text{LJ}}^{\text{trunc}}(r_{ij}) = \begin{cases} U_{\text{LJ}}(r_{ij}) - U_{\text{LJ}}(r_c), & \text{if } r_{ij} \leq r_c, \\ 0, & \text{if } r_{ij} > r_c, \end{cases} \quad (2)$$

where

$$U_{\text{LJ}}(r_{ij}) = 4\epsilon \left[ \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^6 \right]. \quad (3)$$

The energy scale is set to  $\epsilon = 1$  and the length scale to  $\sigma = r_0/2^{1/6}$ , where  $r_0 = 0.7$  is the location of the LJ-potential minimum. We select a cut-off radius  $r_c = 2.5\sigma$  such that  $U_{\text{LJ}}(r_c) \approx -0.0163169\epsilon$ . Contained in the second term, bonded interactions are represented by the anharmonic FENE (finitely extensible nonlinear elastic) potential [Bird et al. (1987); Kremer and Grest (1990); Milchev et al. (2001)],

$$U_{\text{FENE}}(r_{ii+1}) = -\frac{K}{2} R^2 \ln \left[ 1 - \left( \frac{r_{ii+1} - r_0}{R} \right)^2 \right], \quad (4)$$

with parameter values  $K = 40$  and  $R_0 = 0.3$  as used by Gross et al. (2013). Importantly, intra- and interchain interactions are not distinguished energetically. In this study, we systematically investigate the aggregation behavior of up to 11 chains with  $N = 5$  monomers each.

The density of states  $g(E)$  is one of the most relevant system-specific quantities and is in most cases accessible only by computational methods. Here we use the replica-exchange Monte Carlo method known as parallel tempering, which is optimal for highly parallel computer architectures. As the output of the simulation, we obtain a set of canonical energy histograms ( $h(E; \beta_i)$ ,  $1 \leq i \leq N$ ). Each histogram provides an estimate for the density of states  $g_i(E) \sim h(E; \beta_i) \exp(\beta_i E)$ , and the estimator of the density of states  $g(E)$  can be obtained via the multiple-histogram reweighting method by Ferrenberg and Swendsen (1989).

A systematic approach towards the analysis of the density of states, which is capable of revealing the details of the finite-size effects on the structure formation and transitions in the system, is provided by the *microcanonical* analysis [Gross (2001)]. The major advantage of this method is the introduction of the inverse temperature as a *derived* quantity via

$$\beta(E) = \frac{dS(E)}{dE}, \quad (5)$$

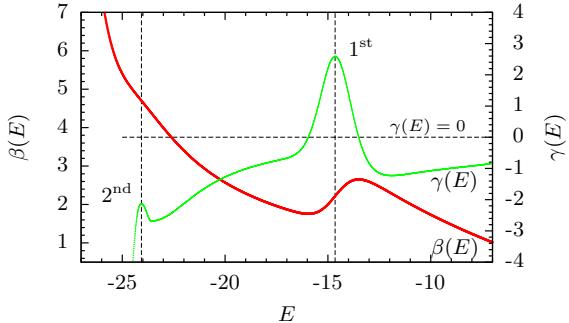


Fig. 1. A *first-order* transition occurs at  $E \approx -15$  as indicated by the positive-valued peak in  $\gamma(E)$ . Similarly, the negative-valued peak at  $E \approx -24$  indicates a *second-order* transition.

where  $S(E) = k_B \ln[g(E)]$  is the microcanonical entropy. Unlike its canonical counterpart, which is an external control parameter, the microcanonical temperature is an ensemble independent, intrinsic system property, and as such can be used to locate and classify all structural transitions of the system. In fact, a transition occurs when  $\beta(E)$  responds least sensitively to changes in energy; the basis for the inflection-point method [Schnabel et al. (2011)]. According to this scheme, a system undergoes structural transitions at the locations of the inflection points of  $\beta(E)$ . A transition is defined to be of *first order*, if  $\gamma(E) = d\beta/dE > 0$  at the inflection point. In the case of  $\gamma(E) < 0$ , the transition is defined to be of *second order* (Fig. 1).

### 3. Results

The study of a single flexible homopolymer chain reveals the existence of three distinct structural phases, separated by the  $\Theta$  and the freezing transitions. Our results show that in multi-chain systems the aggregation and  $\Theta$  transitions are not separate processes, similar to what has been observed for heteropolymer systems by Junghans et al. (2010). In the low-temperature region, the thermodynamic properties of a multi-chain system become virtually indistinguishable from a single chain with equal number of monomers; hence the dynamics of the freezing transition are largely unaffected by chain segmentation.

The leftmost and rightmost intersection points of the Maxwell construction with the inverse temperature curves in Fig. 2 define the energetic boundaries of the transition region,  $e_{\text{agg}}$  and  $e_{\text{frag}}$ , respectively. The latent heat per monomer, defined as  $\Delta q = e_{\text{frag}} - e_{\text{agg}}$ , is positive, and increases with the number of chains in the system, as listed in Table 1 for various system sizes. In conjunction with the prominent back-bending features in the microcanonical inverse temperature curves, this supplies a strong evidence that the aggregation transition is a first-order phase-separation process even as the number of chains in the system becomes very large.

A closer inspection of Fig. 2 reveals that the number of oscillations in  $\beta(E)$  curve increases with the system size; an indication that the aggregation transition is in fact a composite process comprised of a hierarchy of separate sub-phase transitions. The energetic width of each oscillation corresponds to the latent heat associated with each sub-phase transition. With increasing system size, the amplitude of the back-bending oscillations decreases and the  $\beta(E)$  curve converges to the Maxwell construction in the thermodynamic limit.

In order to gain a deeper understanding of the complex structure of the aggregation transition, we now analyze the individual sub-phases which populate the phase-separation region. Here we restrict our investigation to systems consisting of very short 5-monomer chains for the reason that the relevant entropic surface effects and the consequent back-bending features in  $\beta(E)$  become less obvious with increasing chain length. In the energy region below  $e_{\text{agg}}$ , a single aggregate composed of all chains forms the dominant structure. Above  $e_{\text{frag}}$ , weak long-range interactions between individual polymer chains do not support the formation of aggregates, and the system is entirely fragmented. Intuitively, the individual sub-phases correspond to the possible groupings of  $N$  chains and their total number equals the number of partitions of a set with  $N$  elements. For a more quantitative analysis, we have implemented a cluster detection algorithm capable of identifying individual sub-phases, and collected separate statistical data for each indi-

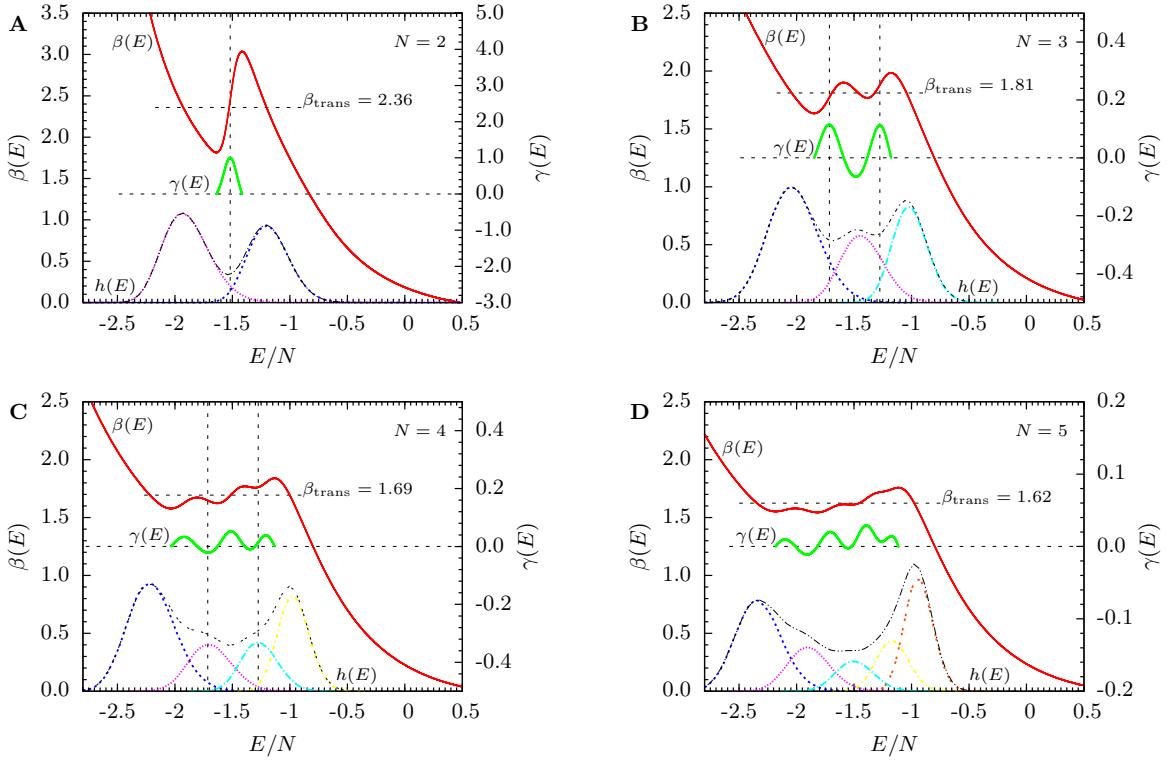


Fig. 2. Microcanonical inverse temperature  $\beta(E)$  as a function of energy per monomer in the aggregation transition region of systems with 2,3,4, and 5 polymer chains, respectively. The horizontal Maxwell lines mark the inverse aggregation temperatures  $\beta_{\text{agg}}$ , and the multiple peaks in  $\gamma(E)$  reveal the hierarchical nature of the transition. The microcanonical results are supplemented by canonical energy histograms obtained at the transition temperature, and corresponding to the distinct sub-phases in the transition region.

vidual sub-phase. The canonical histograms plotted in Fig. 2 reveal that at the transition temperature, the aggregate and the fragmented phases occur with the highest frequency, and are well separated energetically. In contrast, the intermediate sub-phases occur less frequently due to entropic suppression, and their energy distributions have a significant overlap. In systems with more than three chains, we detect fewer sub-phases than expected. As a result of extreme entropic suppression the missing sub-phases contribute only negligibly to the total density of states. In Table 1 we compare the theoretical values for the number of possible sub-phases ( $N_{\text{sub}}$ ) with the actual number of sub-phases ( $N'_{\text{sub}}$ ) that appear with non-negligible probability. It is apparent that only a small subset of possible sub-phases and respective sub-phase transitions consolidates the hierarchical structure of the aggregation transition. As a result, an aggregation transition in a system with  $M$  chains consists only of a sequence of  $M - 1$  sub-phase transitions. Whether this phenomenon is unique to aggregation transitions or is a generic property of a larger class of phase-separation processes will be a topic of future investigations.

#### 4. Summary

Combining an in-depth microcanonical analysis with the investigation of canonical energy histograms, we have unraveled the hierarchical nature of aggregation transitions in flexible homopolymer systems. Each oscillation in the microcanonical temperature curve indicates a single transition between two sub-phases which are adjacent in the energy space. The set of possible sub-phases increases rapidly with the number of chains. However, a powerful entropically driven selection mechanism ensures that only a small subset contributes to the overall aggregation process. With increasing number of chains, the number of oscillations in the microcanonical temperature increases linearly and the curve converges asymptotically to the Maxwell line.

Table 1. Inverse aggregation temperature ( $\beta_{\text{agg}}$ ), energy per monomer of the aggregate phase ( $e_{\text{agg}}$ ), energy per monomer of the fragment phase ( $e_{\text{frag}}$ ), latent heat per monomer ( $\Delta q$ ), theoretical number of sub-phases ( $N_{\text{sub}}$ ), and the number of sub-phases represented in the systems of various sizes ( $N'_{\text{sub}}$ ).

System ( $M \times N$ )	$\beta_{\text{agg}}$	$e_{\text{agg}}$	$e_{\text{frag}}$	$\Delta q$	$N_{\text{sub}}$	$N'_{\text{sub}}$
2 × 5	2.361	-1.926	-1.202	0.724	2	2
3 × 5	1.811	-2.042	-1.044	0.998	3	3
4 × 5	1.694	-2.218	-1.002	1.216	5	4
5 × 5	1.624	-2.344	-0.975	1.369	7	5
11 × 5	1.423	-2.608	-0.887	1.721	56	11

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## References

- Selkoe, D.J., 2003. *Folding proteins in fatal ways*. Nature 425, 900–904.
- Chiti, F., Dobson, C.M., 2006. *Protein misfolding, functional amyloid, and human disease*. Annual Review of Biochemistry 75, 333–366.
- Kayed, R., Head, E., Thompson, J.L., McIntire, T.M., Milton, S.C., Cotman, C.W., Glabe, C.G., 2003. *Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis*. Science 300, 486–489.
- Thirumalai, D., Klimov, D.K., Dima, R.I., 2003. *Emerging ideas on the molecular basis of protein and peptide aggregation*. Current Opinion in Structural Biology 13, 146–159.
- Stefani, M., 2004. *Protein misfolding and aggregation: new examples in medicine and biology of the dark side of the protein world*. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1739, 5–25.
- Osborne, L., Bachmann, M., Strodel, B., 2013. *Thermodynamic analysis of structural transitions during GNNQQNY aggregation*. Proteins 81, 1141–1155.
- Junghans, Ch., Bachmann, M., Janke, W., 2010. *Statistical mechanics of aggregation and crystallization for semiflexible polymers*. EPL 87, 40002.
- Swendsen, R.H., Wang, J.S., 1986. *Replica Monte Carlo simulation of spin-glasses*. Physical Review Letters 57, 2607–2609.
- Geyer, C.J., 1991. *Computing Science and Statistics: Proceedings of the 23rd symposium on the interface*, E. M. Keramidas (editor), 156163.
- Hukushima, K., Nemoto, K., 1996. *Exchange Monte Carlo method and application to spin glass simulations*. Journal of the Physical Society of Japan 65, 1604–1608.
- Berg, B.A., Neuhaus, T., 1992. *Multicanonical ensemble: A new approach to simulate first-order phase transitions*. Physical Review Letters 68, 9–12.
- Wang, F., Landau, D.P., 2001. *Efficient, multiple-range random walk algorithm to calculate the density of states*. Physical Review Letters 86, 2050–2053.
- Bachmann, M., 2014. *Thermodynamics and statistical mechanics of macromolecular systems*, Cambridge University Press, Cambridge.
- Gross, D.H.E., 2001. *Microcanonical Thermodynamics*, World Scientific, Singapore.
- Schnabel, S., Seaton, D.T., Landau, D.P., Bachmann, M., 2011. *Microcanonical entropy inflection points: key to systematic understanding of transitions in finite systems*. Physical Review E 84, 011127(1–4).
- Bird, R.B., Curtiss, C.F., Armstrong, R.C., Hassager, O., 1987. *Dynamics of polymeric liquids* 2nd ed. Wiley, New York.
- Kremer, K., Grest, G.S., 1990. *Dynamics of entangled linear polymer melts: A molecular dynamics simulation*. The Journal of Chemical Physics 92, 5057.
- Milchev, A., Bhattacharya, A., Binder, K., 2001. *Formation of block copolymer micelles in solution: A Monte Carlo study of chain length dependence*. Macromolecules 34, 1881–1893.
- Gross, J., Neuhaus, T., Vogel, T., Bachmann, M., 2013. *Effects of the interaction range on structural phases of flexible polymers*. The Journal of Chemical Physics 138, 074905 1–8.
- Ferrenberg, A.M., Swendsen, R.H., 1989. *Optimized Monte Carlo data analysis*. Physical Review Letters 63, 1995–1998.
- Junghans, Ch., Janke, W., Bachmann, M., 2010. *Hierarchies in nucleation transitions*. Computer Physics Communications 182, 1937–1940.