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Backbone Connectivity and Collective Aggregation Phenomena in Polymer Systems

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1. Introduction

A convenient theoretical entry to tackle the protein aggregation problems is to track on the origin of the aggregation phenomena from the viewpoint of polymer physics, enquiring how the underlying factors, such as the geometric packing, the topology and their mutual interplays in presence of solvent, play their roles in the processes. Such a view has been inspired by recent experiments [1, 2] and molecular dynamics simulations [3, 4] which suggest the ubiquitous presence of fibril formation [5] in various natural and laboratory prepared proteins or peptides. While the variety of amino acid sequences interferes with the occurrence of long-range structural ordering, a material-insensitive tendency of aggregation is observed [2, 3, 5]. By coarsening the sequence-sensitive details, the aggregation problem can be formulated in its minimal form as the clustering process of polymer chains [6, 7]. With such simplified models, the approach focuses more on the entropic effect caused by the constraint of chain connectivity [6–8], rather than on the material-dependent characteristics. In this chapter, we summarize our molecular dynamics simulation studies [6, 7] that reveal the relationship between the backbone connectivity of polymer chains and some benchmark features displayed in the aggregation processes of the model polymer chains.

In the model, the backbone connectivity of a polymer chain is realized by assigning a string of monomers with specific monomer-monomer two-body forces, perturbed with three-body and four-body angle dependent interactions [6], with their strengths measured by the parameters, k_{nn} , K_b and K_t , for the nearest neighbor (n.n.) interaction, the bending angle and the torsion angle potentials, respectively. In a collection of polymer chains, all the non n.n. pairs along a chain and those pairs on different chains are subject to Lennard-Jones (L-J) pair interactions. The presence of angle potentials, with significantly nonzero K_b or K_t values, breaks the isotropy surround the backbone. In such a system, the local inter-chain hindrance prevents the chains from clustering into ordered domains. The situation can, however, be reverted by reducing the values of K_b and K_t . We find that the formation of bundle-like domains (Fig. 1) is robust as soon as K_b and K_t are small enough. The observations are assured even if we introduce a small amount of dispelling background fluid molecules or impose a small fraction of impurity monomer sites.

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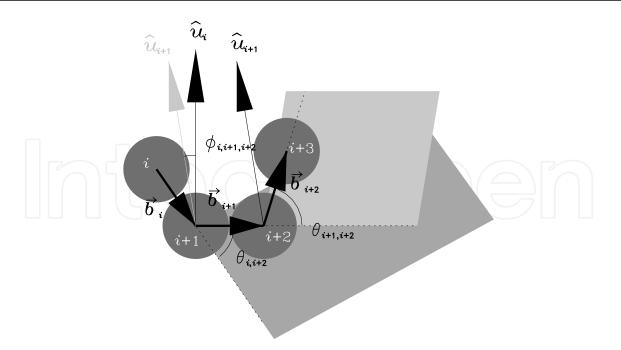


Fig. 2. Bending angle $\theta_{i,j,k}$ and torsion angle ϕ_{ijkl} extended by the consecutive monomers *i*, j = i + 1, k = i + 2 and l = i + 3 along a chain.

with its strength constant k_s , the $k_{nn} = 10^s$ multiple of the value k_0 (i.e. $k_s = k_{nn}k_0$) and balance length r_0 , for the five systems with s = 1, 2, 3, 4 (k_0 and r_0 are given below). They are labelled as I-s (I-1, ...,I-4, etc) systems in Table 1. The bead-rod chains in our model are chains with strict constant nearest neighbor bond lengths and are realized numerically by Lagrange's constraint forces using RATTLE numerical scheme [11]. The system is labelled as system I- ∞ in Table 1.

In all these model systems, the pair interactions between the non-neighboring monomers along a chain or between pairs in different molecules, *i* and *j* at a separation r_{ij} , are L-J potentials

$$V_{LI}(r_{ij}) = 4\epsilon ((r_{ij}/\sigma)^{-12} - (r_{ij}/\sigma)^{-6}).$$

In terms of the distance parameter σ and the strength parameter ϵ of L-J potential, we choose $k_0 = 1.5552 \times 10^5 \epsilon \sigma^{-2}$ and $r_0 = 0.357 \sigma$ [6, 12].

backbone anisotropy along the chains

In the second set (set II) of systems, the degrees of backbone anisotropy along the chains are introduced by perturbing bending potential,

$$\Theta(\theta_{i,j,k}) = K_{\rm b}c_{\rm b}(\cos\theta_{ijk} - \cos\theta_0)^2,$$

determined by the bending angle $\theta_{i,j,k}$ of three consecutive monomers *i*, *j* and *k* along a chain; and the torsion potential [13]

$$\Phi(\phi_{ijkl}) = K_{\mathsf{t}} \sum_{\iota=0}^{3} a_{\iota} (\cos\phi_{i,j,k,l})^{\iota}$$

as a function of the torsion angle ϕ_{ijkl} extended by four consecutive monomers *i*, *j*, *k* and *l* (see Fig. 2). The constants c_b , θ_0 [12]; and a_1 , a_2 and a_3 [13] are given so that a model polyethelyne

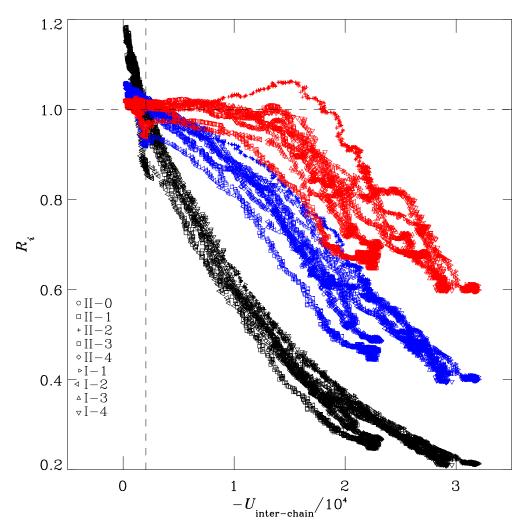


Fig. 3. R_0 (black), R_1 (blue) and R_2 (red) versus $-U_{inter-chain}$, for systems set I: I-1, I-2, I-3, I-4 and set II: II-0, II-1, II-2, II-3 and II-4, which contain chains with their nearest neighbor connected by spring forces (see Table 1).

chain is obtained by choosing $r_0 = 0.357\sigma$, and let the strength control parameters K_b and K_t be unity [12, 14]. With a range of values for K_b and K_t and a choice of bending angle parameter θ_0 , we are able to prepare chains with different degrees of local conformational hindrance [6, 15]. In our simulations, we prepare several systems, each composed of identical chains with $K_b = K_t$, which are allowed to have the value 0, 10^{-4} or 0.1 (see Table 1). The model mimics qualitatively the dispersed local conformational degrees of freedom that is present in those structured monomers, such as the amino-acids in protein molecules.

For systems in set II, the chains is further perturbed by randomly imposing a fraction of 5% monomers to have smaller sizes. In merging with monomer-repelling Lennard-Jones fluid atoms, the heterogeneity is further enhanced by rendering these 5% monomers to interact, in addition to the repulsive force, with an attractive part with the fluid atoms [6, 7]. Under the convention mentioned above, we label those systems as II-*s* (s = 0, 1, 2, 3, 4 or ∞) in Table 1, according to the exponent of the multiple ($k_{nn} = 10^s$ or ∞) of their nearest bonding strength $k_s = k_{nn}k_0$.

Three additional systems of pure ($N_F = 0$) homogeneous rigidly-bonded chains are also studied. Two of them that contain the same rigidly bonded chains, of shorter chain lengths

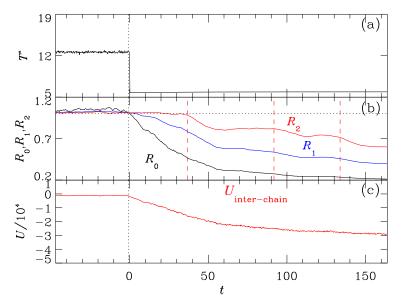


Fig. 4. Time evolutions of (a) instantaneous temperature T^* ; (b) the parameters R_0 (solid line), R_1 (dash dot line) and R_2 (dashed line); and (c) the inter-chain potential energy, for system I-4 (adapted from Ref. [6]).

(n = 25 and n = 50, respectively), are included in set I. They are used to underscore the effect of chain length. The other system consists of homopolymer chains to have the same backbone anisotropy ($K_b > 0$ and $K_t > 0$) as those in set II, but in absence of the 5% impurity monomers. We list this system as system III. Table I lists all the systems that are analyzed in this chapter. Each of them contains the same number $nN_p = 4000$ of monomers.

To show that the increased backbone anisotropy indeed hinders the ability to aggregate, we list the systems set IV in Table 1, which are different from their counterparts in set II, only in the 1000 times larger values in K_b and K_t (=0.1).

quenching

According to the scenario of clustering, the polymer chains aggregate when the temperature and the density of the systems fall within the coexistence region of the phase diagram. In the systems of polymer chains with rigid bonds, a quenching can be achieved by the numerical effect for the cases $K_b = K_t \le 10^{-4}$, that a convergence to satisfy holonomic constraints on bond lengths lead the dynamic system toward the low temperature attractor [7]. The system is, therefore, quenched spontaneously. With the bond constraints replaced by the confining of soft interaction potentials, on the other hand, the incoherence among the springs in different bonds does not favor a global numerical convergence. In order to lower the temperature of the polymer chains in this case, we have to control the simulated system manually by using a thermostat.

Since the distributions of the monomer velocities are known to deviate systematically from the standard Maxwell-Boltzmann with the increased strength of nearest neighbor bonding [16, 17] and are described by the Tsallis *q*-statistics [18], if the system reaches a "quasi-steady state", it is inappropriate to use the existing thermostating methods that would force the simulated system to converge to a state described by standard Maxwell-Boltzmann statistics. A naive choice without imposing presumed statistics is simply controlling *only* the mean value of the kinetic distributions. In the simplest version of the "velocity scaling" thermostate [19], we

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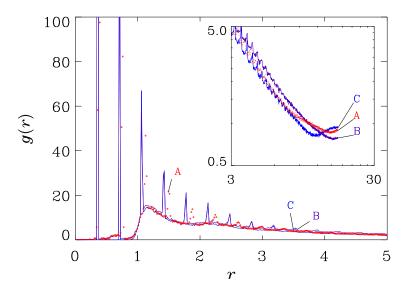


Fig. 8. (Color online) Monomer-monomer pair distribution functions for configurations in the systems II-0 (dots labeled as "A"), II-4 (solid line labeled as "B") and I-4 (solid line labeled as "C") at the onset time for fast falling R_2 . The inset shows the data in log-log plot (adapted from Ref. [6]).

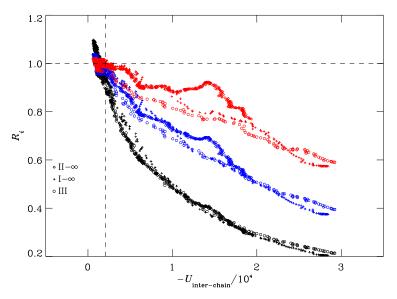


Fig. 9. Same as Fig. 3 for systems of rigidly-bonded chains.

An examination on the time evolutions (Fig 12 and Fig. 13) in these two systems, I-A and I-B, show also corresponding dynamic effects. Since the parameters R_0 , R_1 and R_2 feature the line-like, plane-like, and volume-like packed spatial structures, respectively, the returning of R_2 to a larger value in the later stage of evolution indicates the prevailing of three dimensional packing. The latter trend results in the larger values in volume. Figure 14 shows the R_0 and R_1 for n = 25 and n = 50 follow the decreasing trend in the growth processes, corresponding to reducing $U_{inter-chain}$ (or increasing $-U_{inter-chain}$) which is the same as those for systems of longer chains (the cases of n = 100 in Figs. 3 and 9), in contrast to the returning of R_2 to a larger value in the later stage. The latter trend is stronger for the shorter chains. The result strongly suggests the relevance of chain length on the structural formation in aggregation phenomena.

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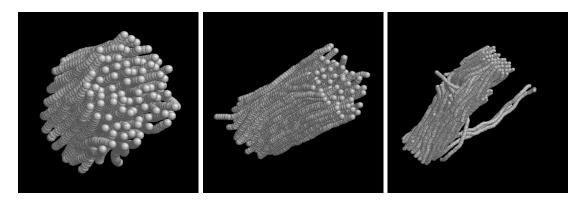


Fig. 10. Snapshots of the largest aggregated clusters for (left plot) n = 25, consisting of 81 chains, for (middle plot) n = 50), consisting of 51 chains, and for (right plot) n = 100, consisting of all 40 chains of the systems (adapted from Ref. [7]).

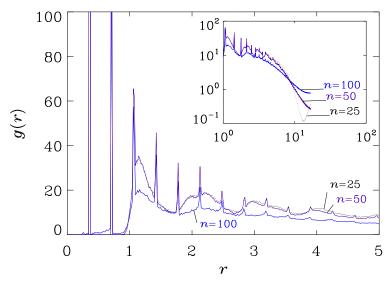
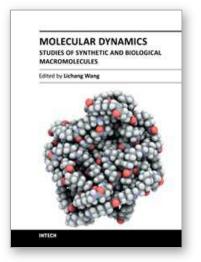


Fig. 11. (Color online) Comparison of monomer-monomer pair distributions of the aggregated configuration for n = 25 (blue line), n = 50 (red line) and n = 100 (black line) (adapted from Ref. [7]).

4. Growth hindered by backbone anisotropy

We have compared the aggregated structures between the systems with zero (system I-4) and with non-zero, but tiny angle potentials (system II-4),. While they both possess bundled clusters (Fig. 1), the non-zero tiny angle potentials break the symmetry to have a branched structure (right plot of Fig. 1). One more sensible question to solve is to ask if the bundled cluster can survive under even larger strengths in angle potentials. The simulations with chains having $K_b = K_t = 0.1$ (set IV in Table 1), which is 1000 times larger than those of the systems in set II have shown no cluster domains formed over time spans equivalent to or larger than those considered for systems in set II [6, 7]. The systems are brought to states at lower temperatures in a stepwise manner, with decreasing target temperature T_0^* at 8, 6 and 3, respectively, in three stages. We do observe the formation of local parallel conformations. But this local ordering can hardly extend to either the larger segment or to the gathering of more chains. The results indicate that the effect of frustration between the straight bundled packing and the local curvature imposed by the angle potentials prevent the aggregation. Such an observation is suggestive in considering more complicated material systems.



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