From Collapse to Freezing in Random Heteropolymers

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We consider a two-letter self-avoiding (square) lattice heteropolymer model of \(N_H\) (out of \(N\)) attracting sites. At zero temperature, permanent links are formed leading to collapse structures for any fraction \(\rho_H = N_H/N\). The average chain size scales as \(R \approx N^{1/\nu} F(\rho_H)\) (\(d\) is space dimension). As \(\rho_H \to 0\), \(F(\rho_H) \sim \rho_H^\zeta\), with \(\zeta = 1/d - \nu = -1/4\) for \(d = 2\). Moreover, for \(0 < \rho_H < 1\), entropy approaches zero as \(N \to \infty\) (being finite for a homopolymer). An abrupt decrease in entropy occurs at the phase boundary between the swollen (\(R \sim N^{\nu}\)) and collapsed region. Scaling arguments predict different regimes depending on the ensemble of crosslinks. Some implications to the protein folding problem are discussed.

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The role of crosslinks in polymers have relevant applications for many kind of systems like proteins, DNA and other copolymers. Recently, it has been shown \([4]\) that random crosslinking of residues imposes stringent constraints in the protein folding kinetics. Assuming that there is one “correct” set of crosslinks resembling the native structure, it is found that the time needed for fast folding sequences to reach this state scales as \(N^\lambda\), where \(N\) is the number of monomers (or residues) in the chain and \(\lambda \approx 3\) (\(\lambda \approx 4\) at the onset). The model suggests that the size of the critical nucleus is on the order of the system size. Polymer crosslinking is also important for structure determination using NMR \([5]\). This technique determines a limited number of contacts in, say, proteins. Hence, one would like to understand how crosslinks constrain the possible conformations. Finally, we mention the process of vulcanization where concentrated solutions of crosslinked polymers become amorphous. These materials undergo a thermodynamic phase transition to a frozen phase if the number of crosslinks exceeds some critical value \([6]\).

For these reasons it is desirable to understand the role of internal constraints in polymers. Based on mean-field or ideal (random walk) polymer models, recent attempts to address this problem have given conflicting suggestions. Gutin and Shakhnovich \([7]\) found that the conformational entropy smoothly decreases as the number of crosslinks increases. These authors have hinted that these conclusions may depend on the ensemble of links. Bryngelson and Thirumalai \([8]\) found a threshold density \(\rho \approx N^{1/\nu}\) for self-avoiding walks (SAW). Accordingly, polymers collapse if the number of crosslinks scales as \(M \sim N^\phi\), with \(\phi \approx 1 - 1/d\nu\).

In this letter, we move beyond mean field to show that when links form freely among a random set of sites (annealed case) then polymers do not collapse to a compact state, unless the number of constraints scales linearly in \(N\). We should point out that in all likelihood the annealed case is a better model for real polymers. To reach this conclusion we analyze the whole sequence space of a two-letter heteropolymer model with \(N_H\) “hydrophobic” attracting sites and \(N_P\) “hydrophilic” (or “polar”) sites. The polymer chain is represented by a SAW of \(N = N_H + N_P\) sites on the square lattice with spacing \(a\). If two H sites are nearest neighbors, a short range attractive energy is assumed adding \(\epsilon < 0\) to the conformational energy of the chain. The only interaction, besides the aforementioned attraction between H sites, is self-avoidance which forbids two sites from occupying the same site. It should be mentioned that this model has been extensively used to study protein folding \([9,10]\), there a limited number of hydrophobic sites are believed to play a dominant role in the folding process. At zero temperature, \(H\) sites form permanent links. Using exact series enumeration \([10]\) of all possible crosslinked conformations, we obtain exact thermodynamic quantities for \(N \leq 20\). Analytically, we consider Flory’s affine network theory of rubber elasticity to generalize some of our conclusions to the problem of quenched random links. In what follows, we work in adimensional units with \(a, \epsilon = 1\).

It is well known that at some critical “theta” temperature \(T_\theta\) homopolymers undergo a coil-to-globular (or collapse) transition. Below \(T_\theta\) polymers collapse to an average radius of gyration \(\langle R_G \rangle\) scaling as \(N^{1/\nu}\). Above \(T_\theta\) polymers are swollen (or extended) with \(\langle R_G \rangle \sim N^{\nu}\), where \(\nu = 3/4\) and 0.592 for \(d = 2\) and 3 \([11]\), respectively. To analyze heteropolymers we proceed by computing the radius of gyration \(\langle R_G \rangle\), where the upper bar means average over sequence space, i.e. \(\langle N^{N_H} \rangle\) sequences for any given \(N\) and \(N_H\). Although the data shown in this letter corresponds to \(d = 2\), it is helpful theoretically.
to keep the symbols \(d\) and \(\nu\) in evidence.

As shown in Fig. 1, we find that, at \(T = 0\), \(\langle R_0^2 \rangle\) is very well described by the scaling law

\[
\frac{\langle R_0^2 \rangle}{N^{2/3}} \approx F(\rho_H), \quad \text{with} \quad \rho_H = \frac{N_H}{N},
\]

where \(\rho_H = 1 - \rho_P\) corresponds to the fraction of \(H\) sites. We note that in general one should have allowed the scaling variable \(\rho\) to depend on a suitable crossover exponent, say, \(\rho_H = N_H/N^\phi\). Our results, however, indicate that \(\phi = 1\). Eq. 1 demonstrates that polymers collapse if and only if \(N_H\) scales as \(N\). This result is clearly not obvious. Namely, hydrophilic chains with a tiny, but finite, fraction of randomly distributed attracting sites are collapsed at \(T = 0\).

Furthermore, the scaling function \(F(\rho_H)\) is expected to have well defined asymptotic laws in both the hydrophilic \(\rho_H \to 0\), and the hydrophobic limit \(\rho_P \to 0\). For \(\rho_H \to 0\), one should recover the self-avoiding walk exponent (as a function of \(N\)). Hence,

\[
F(\rho_H) \approx A\rho_H^{2\zeta}, \quad \text{with} \quad \zeta = 1/d - \nu,
\]

This is in excellent agreement with the slope \(\zeta = -1/4\) observed in Fig. 1. At \(T = 0\), the chain ensemble corresponds to that of maximally crosslinked chains. Instead, we find \(\langle M \rangle \sim N_H^{[12]}\) suggesting the validity of (1) with a scaling variable \(\rho = M/N\) for \(M\) annealed random links. Based on (2), we predict \(\zeta \simeq -0.259\) for \(d = 3\). It is noteworthy that if one fixes \(N_H\) and \(N \to \infty\), then the transition between SAW behavior and the collapse regime occurs at \(\rho_H^* = 1 - \rho^*_P \simeq 0.61\) (see Fig. 1).

The hydrophobic limit is shown in the inset of Fig. 1. For \(\rho_P \to 0\), chains collapse, approaching a sphere of volume \(V \approx Na^d + O(N^{\sigma/d})\), where \(a^d\) is volume of lattice cell. Naively, we might expect \(\sigma\) to be a surface correction, i.e. \(\sigma = d - 1\). The data, however, shows

\[
\frac{\langle R_0^2 \rangle}{N^{2/3}} \approx R_0^2 + BP_{\rho_P}^{(d-\sigma)/d},
\]

where \(R_0^2 \equiv a^2/(2\pi)\), and \(\sigma = 0.7 \pm 0.1\) \((d = 2)\) is a novel universal exponent describing the approach to circularity of a collapsing chain. Interestingly, (3), is related to the longstanding problem of how many lattice points fit inside a sphere of volume \(V\), where \(\sigma\) is known to vary between 1/2 and (upper bound) \(7/11\) \((d = 3)\). The slope in Fig. 1 (inset) corresponds to the scaled version of this exponent. For \(d = 3\), \(R_0^2 \equiv (3a^3/4\pi)^{2/3}/5\) and \(\sigma < 2\) [13]. The apparent deviations from scaling at \(N_P \to 0\) are well known finite-size effects on the shape of collapsed lattice chains [13].

A similar analysis of the conformational entropy \(s_0(\rho_H) \equiv \ln \Omega(\rho_H)/N\), where \(\Omega\) is number of conformations, leads to the scaling plot shown in Fig. 2. In the hydrophilic region \(\rho_H \leq 0.6\), \(s_0(\rho_H) \approx G(\rho_H)/N^\chi\), with \(\chi = 0.43 \pm 0.04\). For \(\rho_H \geq 0.6\), entropy decreases even faster with \(N\). In the SAW limit \(\rho_H \to 0\), \(s_0\) approaches a constant yielding \(G(\rho_H) \sim \rho_H^{\chi}\). Scaling breaks down due to finite-size effects at \(\rho_P \sim O(N^{-1/d})\). At this point, hydrophilic sites rearrange on the surface of the structure and entropy approaches a constant — \(\tilde{s}_0(\rho_H = 1) = \ln q/c\), where \(q\) is the coordination number of the lattice [3]. Hence, in sharp contrast with the homopolymer cases \(\rho_H = 0\) and \(\rho_P = 0\), chains have zero entropy and are collapsed for any finite \(\rho_H < 1\) and \(N \to \infty\). Indeed, the internal network of permanent links formed for \(N_H \sim O(N) > N^{(d-1)/d}\) yields enough constraints to change the qualitative properties of polymers. We should mention that the entropy of maximally compact structures in heteropolymers have already been shown [8] to have a deep minimum around \(\rho_H \approx 0.6\).

As a function of temperature, from the homopolymer (theta) case, we start increasing \(\rho_P\) reducing the overall drive towards collapse. Then, as indicated in the phase diagram of Fig. 3, the collapse transition temperature \(T_x(\rho_P)\) —which divides the swollen from the collapsed region— goes down, and eventually to zero at \(\rho_P = 1\). Kantor and Kardar [12] have shown a related phase diagram for random “charges” in a \(d = 3\) chain. On a regime where both \(H\) and \(P\) sites attract each other, they found that chains collapse for \(|N_H - N_P|/N\) between 0 and 1. Note, however, that their model cannot sample the hydrophilic regime with less than 50% of attracting sites.

Entropy is \(\bar{s}(\rho_H, T) = (E - F)/TN\), where \(E\) and \(F\) are the energy and free energy, respectively. Upon crossing \(T_x(\rho_P)\), heteropolymer chains have a sharper decrease in entropy than homopolymers (see inset in Fig. 2). This sharpness appears to be higher than what would be expected for a critical transition. Moreover, the remanent entropy below \(T_x(\rho_P)\) decreases with system size, whereas above \(T_x(\rho_P)\) it remains constant. All these suggest that the nature of the transition changes from critical to 1st order at some tricritical point \(T_x(\rho_P^*)\) —from our limited data, we conjecture \(0 < \rho_P^* < 0.4\) (see Fig. 3).

Furthermore, one could also argue that given the first order jump in entropy at \(T = 0\) and \(\rho_P = 1\) \((N \to \infty)\), by continuity it is reasonable to expect a line of first order transitions beginning at \(T = 0\) and going to finite temperatures. Similar phase diagrams have been obtained for, say, the tricritical point in a dilute magnet [10]. The analogy here is diluting a “theta” polymer. It is also worth mentioning that a closely related model solved by Garel et. al. [14] shows that the nature of the collapse transition depends on the hydrophobic-hydrophilic content of the chain. In the hydrophilic regime, the transition is first-order. Whereas in the strong hydrophobic regime, the transition is continuous similar to an ordinary “theta” point. An impressive, and yet intriguing, result is that even if the collapse transition is continuous, the low temperature phase as no entropy (except at \(\rho_P = 0, 1\)).

In the hydrophilic regime \(\rho_H \lesssim \rho_H^*\) \((T = 0)\), the average number of conformations \(\Omega(\rho_H)\) grows exponen-
tially in $N$, changing to non-exponential growth only at $\rho_H \simeq 0.61 \pm 0.05$. The change in the scaling of $\Omega(\rho_H)$ is rather abrupt. Below $\rho_H$, $\ln \Omega(\rho_H)/N$ increases as $\sim (\rho_H - \rho_H^*)^\omega$, with $\omega \simeq 0.5 \pm 0.1$ [12]. Above $\rho_H^*$, $\ln \Omega(\rho_H)/N$ consistently decreases towards zero. This means that the structural localization in some few structures is particularly strong at and below $\rho_H^*$, see also Fig. 2. It is tempting to speculate that this special point $\rho_H^*$ is related to a rigidity percolation transition (see, e.g., [7]) from a rigid to a floppy structure, or to a “vulcanization” transition of a single chain. Certainly, these aspects of the model deserve further study.

For completeness, we assess the question: “What happens for crosslinks that can form arbitrarily apart along the backbone (quenched case)?” A general analysis of crosslinks in polymers can be made by means of Flory’s affine network theory of rubber elasticity. In this framework, the total free energy of a polymer of $N$ sites and $M_4$ crosslinks of functionality four can be constructed (see, e.g., [18]). By considering an elastic, repulsive and entropic energy term, plus an ideal gas as solvent, the typical size of a crosslinked polymer is found to be [12]

$$R \sim \rho^{-1/(d+2)} N^{2/(d+2)} \quad \text{with} \quad \rho = M_4/N.$$  

(4)

This expression is expected to be valid for $\rho \ll 1$. Strikingly, as $N \rightarrow \infty$, we automatically recover Flory’s exponent for a SAW with $R \sim N^{3/(d+2)}$. Moreover, for $d = 2$ the theory predicts the same scaling form and exponents as in Eqs. 1 and 2, with $R \sim \rho^{-1/4} N^{1/d}$.

For $d = 3$, a new scaling behavior is predicted, namely $R \sim \rho^{-1/3} N^{2/5}$. For a given ratio $\rho$ conformations are not fully collapsed nor swollen [1]. This behavior has also been implied by Levin and Barbosa [3] in a study of phase transitions of neutral polyampholyte. The prediction is that polymers collapse if $M_4 \sim N^\phi$, with $\phi = 4/3$. However, if we also allow sites with functionality larger than four, then we get back to $\phi = 1$ as in (1). Hence, it is much harder to collapse a chain with two-particle links than with links that do not saturate.

In summary, the theoretical and numerical study of heteropolymers and random crosslinked chains has revealed a variety of different regimes, some with simple scaling behavior, others more complex and intriguing. For $d = 2$, we find that polymers collapse if and only if the number of mutually attracting monomers $N_H = N - N_P$ scales as the size of the system $N$. At zero temperature, novel universal exponents describe the limiting behavior for $\rho_H = N_H/N \rightarrow 0$ and 1. We expect the same conclusion to be valid for $d = 3$. For $d = 2$, the problem of annealed and quenched random links are predicted to have the same scaling properties. For $d = 3$, quenched (two-particle) links collapse a chain if $M \sim N^{4/3}$. The nature of the collapse transition changes from first to second order for some small enough density of non-interacting sites $\rho_P = N_P/N$. We note that almost simultaneously with collapse there is an abrupt decrease in entropy. Tracing this entropic change to a folding transition suggests a favorable scenario to find fast folding proteins [9]. In the thermodynamic limit ($T = 0$) random HP chains have zero entropy for any finite fraction $\rho_H < 1$. This entropic crisis and collapse is due to the network of internal constraints buried in the structure. This result has yet to be fully understood in the context of random heteropolymers with quenched disorder. Properties on the size, entropy, and number of conformations as a function of $\rho_H$ indicate the existence of a special point at $\rho_H^* \simeq 0.61$, most likely related to a rigidity percolation or vulcanization transition. Our results show that both structural determination and collapse require a relatively large number of constraints ($\gtrsim N$) suggesting that the thermodynamics and dynamics of crosslinking should play an important role in protein folding [1].

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FIG. 1. Scaling of squared radius of gyration averaged over sequence space as a function of fraction of hydrophobic (attracting) sites $\rho_H = N_H/N$, and of (inset) hydrophilic (non-interacting) sites $\rho_P = N_P/N$. Points with $N_H = 0$ and 1 are not shown as they correspond to unrestricted SAW. Symbols correspond to exact data for the square lattice. The limits for $\rho_H$ and $\rho_P \to 0$ are indicated by the dashed lines, i.e. $2\zeta = -1/2$ and $A = .132 \pm .001$ (2), and (inset) $\sigma = 0.7$ and $B = .036_{-4}^{+0.003}$ (3), respectively. (For $N \geq 18$, some data points with $\rho_H \sim 0.5$ are missing due to CPU constraints.)

FIG. 2. Entropy $\bar{s}_0(\rho_H)$ as a function of the scaling variable $\rho_H$, at $T = 0$. Same symbols as in Fig. 1. Inset, entropy $\bar{s}(T)$ as a function of temperature for $N = 15$ and $N_P = 0$ (dashed line) and $N_P > 0$ (solid lines). Values of $N_P$ are indicated in figure, see also dotted lines in Fig. 3. The collapse temperature $T_{c}(\rho_P)$ is indicated by the square symbols. The curves for $N_P = 7$ and 10 are indicative of a sharper transition than the $N_P = 0$ case.

FIG. 3. Schematic phase diagram of a heteropolymer. Square symbols show exact position of peak in the energy fluctuations $\Delta \bar{E} = \langle \bar{E}^2 \rangle - \langle \bar{E} \rangle^2$ for $N = 15$ and $N_P = 0$, $\cdots$, 13. Our data suggests the possibility of a first-order collapse transition (solid line) for hydrophilic chains changing to second-order (dashed line) for hydrophobic chains at some point $T_{c}(\rho_P)$, see text. A solid circle indicates the position of $\rho_P^*$. Curves in Fig. 2 are computed along dotted lines.